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Gut-Liver-Brain Axis and Alcohol Use Disorder: Treatment Potential of Fecal Microbiota Transplantation

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PURPOSE: Chronic alcohol use is a major cause of liver damage and death. In the United States, multiple factors have led to low utilization of pharmacotherapy for alcohol use disorder (AUD), including lack of provider knowledge and comfort in prescribing medications for AUD. Alcohol consumption has direct effects on the gut microbiota, altering the diversity of bacteria and leading to bacterial overgrowth. Growing evidence suggests that alcohol's effects on the gut microbiome may contribute to increased alcohol consumption and progression of alcohol-associated liver disease (ALD). This article reviews human and preclinical studies investigating the role of fecal microbiota transplantation (FMT) in ameliorating alcohol-associated alterations to the liver, gut, and brain resulting in altered behavior; it also discusses the therapeutic potential of FMT.
SEARCH METHODS: For this narrative review, a literature search was conducted in September 2022 of PubMed, Web of Science Core Collection, and Google Scholar to identify studies published between January 2012 and September 2022. Search terms used included "fecal microbiota transplantation" and "alcohol."
SEARCH RESULTS: Most results of the literature search were review articles or articles on nonalcoholic fatty liver disease; these were excluded. Of the remaining empirical manuscripts, very few described clinical or preclinical studies that were directly investigating the effects of FMT on alcohol drinking or related behaviors. Ultimately, 16 studies were included in the review.
DISCUSSION AND CONCLUSIONS: The literature search identified only a few studies that were directly investigating the effect of FMT on ALD or alcohol drinking and related behaviors. Largely proof-of-concept studies, these findings demonstrate that alcohol can alter the gut microbiome and that the microbiome can be transferred between humans and rodents to alter affective behaviors frequently associated with increased alcohol use. Other studies have shown promise of FMT or other probiotic supplementation in alleviating some of the symptoms associated with ALD and drinking. These results show that the implementation of FMT as a therapeutic approach is still in the investigatory stages.

KEYWORDS: alcohol; fecal microbiota transplant; alcohol-associated liver disease; gut-brain axis; gastrointestinal microbiome; microbiota; probiotics; behavior

Alcohol-associated liver disease (ALD) is a leading cause of morbidity and mortality in people with alcohol use disorder (AUD).[1] Alcohol exerts its effect on the liver through both direct and indirect pathways and can eventually lead to steatosis, steatohepatitis, fibrosis, hepatocellular carcinoma, and cirrhosis.[2] However, only approximately 10% to 20% of patients with ALD develop cirrhosis.[2] When decompensated cirrhosis develops, liver transplantation should be considered; however, a transplant may not be a feasible option for certain patients. Transplant eligibility is determined in a multidisciplinary fashion that includes a vigorous medical, psychosocial, surgical, and financial evaluation. Furthermore, the peri- and post-transplant periods can pose unique challenges to patients with underlying AUD. Individuals with chronic AUD are at risk for nutrient deficiencies, malnourishment, and sarcopenia.[3] As such, they can enter transplant in a frail state that can predispose patients to infection, impaired wound healing, and sarcopenia (loss of muscle mass and function). In addition, transplant committees often require that patients engage in post-transplant alcohol cessation programs. To obviate the need for liver transplants, efforts to treat AUD and reduce craving should begin earlier in the disease course. In the United States, currently approved pharmacologic therapies for AUD include disulfiram, acamprosate, and naltrexone.[4]

Although pharmacological treatments exist, the treatment gap for AUD is higher than for any other mental disorder,[5] and these treatments are prescribed only for a small percentage of patients with AUD. Several factors may contribute to the underuse of pharmacologic treatments for AUD, including lack of provider knowledge and comfort in prescribing these medications, low compliance with treatment among patients, and patient heterogeneity combined with the availability of only three approved medications. Thus, most patients with AUD—especially those with advanced AUD—are left untreated, and there is a need for additional, more effective therapies.

Newer therapeutic regimens include gut microbiome manipulation, which may modulate alcohol intake and drinking behavior.[2,6] Growing evidence suggests that alteration of intestinal microbiota—which include not only bacteria but also fungi and viruses—contributes to the progression of excessive alcohol consumption and ALD, and this may form a therapeutic target.[2,6] Alcohol consumption has both direct and indirect effects on the gut microbiota via alcohol metabolism, activation of inflammatory cascades, and alterations in the enteric nervous system.[2,6] This suggests that by altering the gut microbiota, alcohol consumption may be modulated, slowing the progression of ALD.[2,6]

The Impact of Alcohol on the Gut-Liver Axis

Gut-liver communication occurs both through the hepatic portal vein and the hepatic biliary system and can be influenced by the gut microbiota.[6] Dietary nutrients absorbed from the gut can be carried directly to the liver via the portal vein. However, if the gut microbiota composition or gut barrier function is disrupted, other mediators or toxins can take the same route to disrupt liver homeostasis.[7] The hepatic biliary system along with systemic circulation allows the liver to provide feedback to the gut via release of bile acids and other bioactive molecules.[6]

Alcohol consumption induces gut dysbiosis, an imbalance in gut microbiota, through several mechanisms. Chronic alcohol exposure decreases the production of mucus and antimicrobial peptides such as alpha-defensins and disrupts the intestinal barrier.[2,8,9] This allows for translocation of lipopolysaccharide (LPS) and other endotoxins into the liver via the portal vein.[10] LPS is produced by gram-negative bacteria and is one of the main factors in the pathogenesis of ALD. LPS activates toll-like receptors on the surface of Kupffer cells and induces pro-inflammatory signaling cascades, the release of cytokines, and, ultimately, hepatocyte damage.[6] People with ALD often show higher levels of circulating pro-inflammatory mediators, such as LPS, interleukin 8 (IL-8), and IL-17.[11] Pro-inflammatory circulating cytokines were found to positively correlate with scores of depression, anxiety, and alcohol craving in active drinkers.[12] Moreover, inflammation markers were found to correlate with ALD severity.[7,13]

Alcohol use could also alter gut microbiota by reducing production of short-chain fatty acids (SCFAs), which are beneficial fermentation products.[14] SCFAs have anti-inflammatory and immune-modulatory activity and help maintain the intestinal barrier.[6] Alcohol has been shown to decrease SCFA production, reflected in the fecal content of patients with alcohol-associated cirrhosis.[15] This alcohol-induced disruption of bacterial metabolites (such as SCFAs, and bile acids among others) is a consequence of altered gut microbiota composition.

Alcohol use has been shown to result in bacterial overgrowth and dysbiosis. In general, alcohol reduces *Bacteroidetes*, *Clostridia*, and *Verrucomicrobiae* and leads to increases in *Proteobacteria*, *Gammaproteobacteria*, and *Bacilli*.[16] Alcohol also has direct cytotoxic effect on hepatocytes; its metabolite acetaldehyde triggers pro-inflammatory signaling cascades and damages the epithelial barrier.[9]

The Impact of Alcohol on the Gut-Brain Axis

The gut microbiome also influences brain function and behavior through a variety of mechanisms and thus may be involved in the onset and severity of some psychiatric disorders, such as AUD.[6] Research has suggested that bacterial metabolites can cross the blood-brain barrier via sensory nerves that innervate the gut.[6] In patients with AUD, chronic low-grade inflammation leads to changes in pro-inflammatory mediators that can cross the blood-brain barrier to activate nuclear factor kappa B (NF-kB) in glial cells, leading to neuronal damage.[17] This concept was further confirmed in a study demonstrating that a single injection of LPS led to increases in tumor necrosis factor-alpha (TNF-alpha) in the liver and brain, promoted microglial activation, and induced degeneration of dopamine-secreting neurons.[17] Although some bacterial species can produce neurotransmitters, such as gamma-aminobutyric acid (GABA) and dopamine, it is debated whether these neurotransmitters can cross the blood-brain barrier.[6] It may be that signaling by the vagal nerve influences neurotransmitter production, which could impact behaviors associated with AUD, such as anxiety.[6] However, anti-inflammatory cytokines such as IL-10 have been shown to reverse anxiety-like behavior related to substance use.[18] Thus, multiple factors can influence the development of mood disorders. Vagal signaling may play a critical role in the onset and severity of AUD, as significant reduction in voluntary drinking was seen in rats that underwent vagotomy.[19]

Microbiota-derived ammonia can also impact the central nervous system.[6] Due to poor hepatic clearance, high levels of ammonia are seen in some patients with ALD, which can reach the brain and lead to astrocyte death, brain damage, and cognitive alterations. Another potential mechanism how gut microbiota may affect brain function is through the previously discussed alcohol-related decrease in levels of SCFAs, such as butyrate.[6] Butyrate is a potent inhibitor of histone deacetylases and thus can lead to epigenetic changes such as modulation of histone modifications.[20] Such epigenetic changes in the brain have the potential to impact current and future substance use by modulating addiction and reward networks.[21] One study reported correlations between the gut microbiome and behavioral and neurophysiological traits that define AUD, such as measures of impulsivity and augmentations in striatal dopamine receptor expression.[22]

This review presents the growing number of clinical and preclinical studies that are beginning to investigate the therapeutic role and mechanisms underlying fecal microbiota transplantation (FMT) in ALD and AUD (see Table 1). It is important to note that not all patients with AUD have dysbiosis and/or increased intestinal permeability; the reason for this is unclear. A literature search using the terms "fecal microbiota transplantation" AND "alcohol" found very few studies that directly investigated the effect of FMT on alcohol drinking behavior. In addition, only a small number of articles showed the impact of FMT on affective behaviors that are frequently associated with excessive alcohol use. Some studies have shown promise in using gut microbial manipulation for alleviating some of the symptoms associated with ALD. Using these studies, the review outlines the interplay between the modulation of the gut microbiome, the gut-liver-brain axis, and AUD. The article also discusses why microbiome manipulation may be a promising therapeutic for ALD and proposes future directions.

Search Methods

A September 2022 search of the PubMed database using the search terms "fecal microbiota transplantation AND alcohol, NOT review" identified 71 articles that were published between January 1996 and September 2022. Among these articles, 16 were preclinical studies that used alcohol in their model (e.g., animals treated with alcohol, or animals treated with FMT from alcohol-exposed subjects). Most of the excluded articles described studies of non–alcohol-associated liver disease. Of the 16 included preclinical publications, six assessed the effects of FMT or the modulation of the microbiome on ALD. Six other articles investigated the role of modulation of the gut microbiome on alcohol-associated behaviors (e.g., sociability, anxiety, and depression) or drinking behavior, with some reporting changes in gene or protein expression in the brains of recipient animals. The other four articles not directly discussed below were excluded for the following reasons: one article was a commentary, and three were focused on alcohol's role on innate and adaptive immunity or pulmonary infection, not the gut-liver-brain axis. The 71 identified articles included 11 human/clinical studies, but four were excluded because they were either not related to alcohol or were not focused on microbial therapeutics. The remaining seven articles were human/clinical studies related to alcohol or cirrhosis (see Table 1).

A similar search strategy was employed in the Web of Science Core Collection database and Google Scholar. These searches identified 32 publications, and these were also contained in the PubMed dataset. Of note, none of these publications were published prior to 2016.

Table 1: Summary of Preclinical and Clinical Studies Assessing the Effects of Fecal Microbiota Transplant (FMT) on Alcohol-Related Outcomes

Study*	Subjects	Model	Main Finding
Ferrere et al. (2017)[23]	Mice	Signs of ALD lesions after Lieber-DeCarli diet	FMT prevented the development of alcohol-induced liver lesions, but the effect depended on the host microbiome.
Wrzosek et al. (2021)[30]	Mice	Signs of ALD after FMT from SAH patients	Pectin-FMT beneficially reshaped the GM, in an AhR-dependent manner.
Yu et al. (2020)[31]	Mice	Signs of ALD lesions after Lieber-DeCarli diet with ethanol	FMT or LRP6-CRISPR improved GM diversity and composition to ameliorate ALD symptoms.
Yan et al. (2021)[32]	Mice	Signs of ALD lesions after Lieber-DeCarli diet with ethanol	TQE supplementation or TQE-FMT alleviated chronic alcohol-induced liver injury and markers of gut barrier dysfunction.
Yan et al. (2021)[33]	Mice	Signs of ALD lesions after Lieber-DeCarli diet with ethanol	UA had hepatoprotective effects and suppressed alcohol-induced oxidative stress and intestinal barrier disruption.
Guo et al. (2022)[34]	Mice	Acute ALD signs by ethanol lavage	Goji berries restored intestinal epithelial cell integrity and prevented acute liver injury induced by alcohol intake.
Xiao et al. (2018)[39]	Mice	FMT from noncontingent drinking mice	Alc-FMT transferred negative affective behaviors following withdrawal, altered brain gene expression, and reduced GM diversity.
Segovia-Rodriguez et al. (2022)[40]	Rats	FMT from ethanol-exposed rats (10 g/kg for 10 days)	Alc-FMT increased drinking and reduced locomotor activity, but this was dependent on antibiotics pretreatment.
Ezquer et al. (2022)[42]	Alcohol-preferring rats	Alcohol relapse drinking and LGG treatment	LGG modified the GM, reduced alcohol intake, and altered brain protein expression in a model of relapse drinking.
Bajaj et al. (2021)[56]	Humans	Patients with alcohol-associated cirrhosis and AUD	FMT reduced alcohol consumption and cravings and increased microbial diversity.
Philips et al. (2022)[58]	Humans	SAH hepatitis patients	FMT decreased alcohol relapse rates and increased time to relapse, increased beneficial GM diversity, and lowered rates of infections and hospitalizations with higher survival rates.
Philips et al. (2017)[59]	Humans	Open-label study of patients ineligible for steroid therapy	FMT recipients had higher transplant-free survival associated with reduction in pathogenic bacteria.
Sharma et al. (2022)[60]	Humans	Open-lab nonrandomized trial with severe alcohol-associated hepatitis with ACLF	FMT significantly reduced 28- and 90-day mortality and inflammatory cytokines.
Bajaj et al. (2017)[62]	Humans	Open-label randomized trial: outpatient men with cirrhosis and recurrent HE received FMT enema	Improved cognition along with increased microbial diversity.
Bajaj et al. (2019)[65]	Humans	Randomized, single-blind study: cirrhosis with recurrent HE receiving FMT capsules vs. placebo	FMT capsules were safe and improved duodenal mucosal diversity, dysbiosis, and objective measures of encephalopathy.
Philips et al. (2018)[68]	Humans	Comparative study between pentoxifylline, corticosteroid, nutritional therapy, and FMT	FMT had highest survival rates at 3-month follow-up by modulating GM composition and function and decreasing inflammatory pathways.
Zhao et al. (2020)[38]	Humans to mice	Cross-species Alc-FMT	Human to mouse Alc-FMT increased alcohol preference and negative affective behaviors and altered brain gene expression.
Wolstenholme et al. (2022)[41]	Humans to mice	Cross-species Alc-FMT and treated Alc-FMT	Alcohol preference and intake were reduced in patients with AUD after receiving FMT, and this behavior was transmissible to mice; liver, intestine, and brain gene expression was altered in mice.
Leclercq et al. (2020)[43]	Humans to mice	Cross-species Alc-FMT	Human-to-mouse Alc-FMT increased depression-like behavior and lowered sociability; brain neurotransmitter and myelin gene expression were altered.

*Studies are ordered by citation number within each subject type.

Note: ACLF, acute-on-chronic liver failure; AhR, aryl hydrocarbon receptor; Alc, alcohol; ALD, alcohol-associated liver disease; AUD, alcohol use disorder; CRISPR, clustered regularly interspaced short palindromic repeats; FMT, fecal microbiota transplant; GM, gut microbiota; HE, hepatic encephalopathy; LGG, *Lactobacillus rhamnosus* Gorbach-Goldin; LRP6, low-density lipoprotein-related protein 6; SAH, severe alcohol-associated hepatitis; TQE, *Thymus quinquecostatus* Celak extract; UA, ursolic acid.

Results

Gut Microbiome and ALD: Preclinical Studies

In one of the seminal preclinical studies to investigate whether manipulation of the intestinal microbiome can prevent the development of ALD, Ferrere et al. showed that factors other than alcohol exposure are involved in the development of ALD.[23] In this study that compared mice raised in two different institutions and that were fed the same Lieber-DeCarli diet—a liquid diet for rodents that contains all dietary and hydration needs as well as alcohol to induce the pathogenesis of early-stage ALD—mice consumed similar amounts of alcohol, had similar liver weights, and initially had similar fecal microbiota composition. However, mice from one facility developed early signs of ALD while mice from the other facility did not. Following 10 days of the Lieber-DeCarli diet supplemented with 5% ethanol, the animals exhibited specific microbiota profiles that were associated with susceptibility or resistance to ALD symptoms. In the ALD-sensitive mice, the alcohol diet induced a decrease of cecal *Bacteroidetes* and *Proteobacteria* and an increase of *Actinobacteria* and *Firmicutes*. Thus, the ALD-sensitive mice had 50% less *Bacteroides* than did the ALD-resistant mice at the end of the 10-day period. To prove that the microbiota were likely responsible for ALD sensitivity or resistance, the researchers performed FMT by transferring fecal matter from ALD-resistant mice to ALD-sensitive mice. FMT or pectin (complex heteropolysaccharides that can modulate the growth of gut microbiota) treatment protected the susceptible mice from alcohol-induced depletion of *Bacteroides*, and the microbiomes of FMT-treated mice were similar to the microbiomes of ALD-resistant mice. Moreover, FMT prevented the development of alcohol-induced liver lesions.[23] This study was an important first step in showing that the endogenous microbiome influences an individual's susceptibility to ALD and that manipulation of the intestinal microbiome can prevent the development of alcohol-induced liver lesions and may be a strong therapeutic treatment strategy.

Following this seminal study, additional research groups investigated whether probiotics or dietary supplements that alter the microbiome can also reduce ALD symptoms.[6,19,24-29] These studies generally demonstrated a positive outcome of treatment with probiotics on liver outcomes; however, as they did not use FMT, a detailed discussion is beyond the scope of this article. To mechanistically understand how pectin alters the intestinal microbiome and therapeutically treats ALD, mice received an FMT from patients with severe alcohol-associated hepatitis to establish alcohol-induced liver lesions in the context of the human microbiota.[30] The animals were then treated with pectin via FMT. Compared with control animals, pectin-treated mice showed a higher number of bacterial genes involved in carbohydrate, lipid, and amino-acid metabolism. Metabolomic analyses identified alterations in bacterial tryptophan metabolism and increased indole derivatives, suggesting activation of the aryl hydrocarbon receptor (AhR) signaling system. AhR agonists simulated the effects of pectin in liver tissue and reversed the signs of ALD. Conversely, knock-out of the AhR gene in mice reduced the effects of beneficial microbiota on alcohol-induced liver injury. Finally, the researchers found decreased level of AhR agonists in patients with severe alcohol-associated hepatitis, suggesting that AhR may be a new therapeutic target in ALD.[30] These findings indicate that pectin reshapes the microbiome in the context of the human microbiota and not only prevents, but reverses, alcohol-induced liver injury in mice.

In another study, Yu et al. directly compared FMT to clustered interspaced short palindromic repeats (CRISPR) inactivation of low-density lipoprotein receptor-related protein 6 (LRP6), a co-receptor of the canonical Wnt/beta-catenin pathway, in their ability to ameliorate ALD symptoms.[31] Knock-down of LRP6 by CRISPR, they hypothesized, would reduce Wnt signaling in hemopoietic stem cells to reduce their activation and, thus, improve the effects of liver fibrogenesis in their model of ALD. Rats fed an ethanol-containing Lieber-DeCarli diet to induce liver fibrosis and model early-stage ALD were then administered FMT from healthy rats or treated with LRP6-CRISPR. Histological and molecular assays revealed moderately improved liver histological markers in the FMT-treated rats that were accompanied by similar changes in fibrosis biomarkers. LRP6-CRISPR–treated mice showed similar improvements in liver histology and molecular markers, but with a greater effect size. Both LRP6-CRISPR and FMT treatment partially restored the composition of the gut microbiome and increased gut microflora diversity. Compared with untreated ALD-rats, LRP6-CRISPR and FMT both increased gut microbiota richness and diversity and resulted in a similar microbiota composition structure. Thus, principal coordinate analysis indicated that the gut microbiome of rats treated with LRP6-CRISPR and FMT overlapped and intersected with each other and with the control group. Specifically, LRP6-CRISPR and FMT each increased abundance of *Lactobacillus*. Thus, targeting the gut microbiome using samples from healthy rats or directly inactivating a member of the Wnt signaling pathway can improve the diversity and composition of the microbiome to ameliorate ALD symptoms.[31]

Three studies have used FMT procedures to show that gut microbiome remodeling may be a causal mechanism underlying the hepatoprotective effects and reductions in alcohol-induced liver injury of specific dietary enhancements, such as ursolic acid (UA) or Goji berries.[32-34] UA, a bioactive constituent in teas, fruits, edible plants, and herbs, also has hepatoprotective activity.[35-36] Using a model of chronic alcohol exposure to induce liver injury, Yan et al. showed that UA had not only hepatoprotective effects, but also suppressed alcohol-induced oxidative stress and intestinal barrier disruption.[33] An FMT study was performed to investigate the possible contribution

of gut microbiota manipulation in the beneficial effects of UA on alcohol-induced liver injury. Compared to mice receiving control-FMT, recipients of FMT from UA-consuming donors had a remodeled gut microbiome, less alcohol-induced gut dysbiosis, and reduced oxidative stress.[33] Alcohol-induced liver injury was also partly alleviated in UA-FMT recipient mice, suggesting the hepatoprotective activity of UA is transferable and can be partly attributed to gut dysbiosis correction.[33] Using a traditional Chinese medicinal plant, Goji berries, Guo et al. were able to restore the intestinal epithelial cell integrity and prevent acute liver injury induced by alcohol intake in mice.[34] To examine whether the Goji-modulated gut microbiota played a causal role on liver protection, an FMT experiment was performed in mice pretreated with antibiotics. FMT from donors that consumed Goji berries also protected against elevations in markers of acute alcohol-induced liver injury in recipient mice.[34] *Thymus quinquecostatus* Celak extract (TQE) is a species of thyme, widely used as food additive in Asia, that possesses hepatoprotective activity.[37] To investigate the mechanisms of TQE's liver protective effects in vivo, TQE supplementation alleviated chronic alcohol-induced liver injury and markers of gut barrier dysfunction in mice, likely through suppression of toll-like receptor 4-mediated inflammatory response and overproduction of reactive oxygen species.[32] FMT studies using material from TQE-exposed donors also counteracted the alcohol-induced gut dysbiosis and partially ameliorated liver injury in the recipient mice, suggesting a causal role of the gut-liver axis in the hepatoprotective effects of TQE.[32] Together, these studies show hepatoprotective effects of dietary supplements on acute or chronic alcohol-induced liver disease. FMT was used to show that these hepatoprotective effects can be transferrable and show causal role of the gut-liver axis in models of ALD.

Gut Microbiome and Alcohol Consumption: Preclinical Studies

Few studies have used preclinical models to directly investigate the role of the gut microbiome on alcohol drinking or alcohol-related phenotypes such as anxiety and depression.[38-43] Some of these studies used cross-species FMT to establish causality of the gut microbiome on alcohol drinking and related behavior.[38,40-42] Most of these six studies investigated the effect of microbiomes after alcohol exposure on similar outcomes and on gene or protein expression within the brain.[38,39,41-43] In one of the first studies directly assessing the ability of the gut microbiome to contribute to the development of alcohol-related behaviors, transplantation of gut microbiota from alcohol-fed mice facilitated the development of depressive-like behavior in alcohol-naïve recipients.[39] In this model of noncontingent voluntary alcohol consumption, 4 weeks of escalating ethanol concentrations in the drinking water did not alter bacterial abundance but did change gut microbiota composition. Alcohol-exposed mice displayed signs of negative affective behavior following alcohol withdrawal in two rodent models of depression (i.e., the forced swim and tail suspension tasks). Additionally, they exhibited decreased expression of the brain-derived neurotrophic factor (*Bdnf*) and corticotropin-releasing hormone receptor 1 (*Crhr1*) genes, as well as increased expression of the mu opioid receptor (*Oprm1*) gene in the hippocampus. Fourteen days of daily FMT from alcohol-drinking mice into alcohol-naïve recipients (Alc-FMT) increased their depression-like behavior, similar to that of the alcohol-drinking donors. These findings were interpreted as transference of behavioral signs of alcohol withdrawal-induced negative affect. Additionally, similar gene expression changes in *Bdnf*, *Crhr1*, and *Oprm1* found in alcohol-exposed mice were seen in the hippocampus of Alc-FMT mice. Finally, as seen in previous studies, both alcohol consumption and alcohol-FMT decreased the relative abundance of *Lactobacillus* and increased *Allobaculum* abundance.[39]

To investigate whether changes in the gut microbiome are a cause or a consequence of alcohol drinking, Segovia-Rodriguez et al. treated alcohol-naïve rats with FMT from rats exposed to high (10 g/kg) ethanol doses (Alc-FMT), control-FMT, or phosphate-buffered saline control for 10 days.[40] Antibiotic pretreatment was also tested in each group given the known effects of antibiotics on gut microbiome diversity and alcohol intake. Alc-FMT rats without antibiotic pretreatment increased their alcohol intake as compared to rats given control buffer via oral gavage, while control-FMT mice had decreased alcohol intake in the drinking in the dark multiple scheduled access model. The increased intake in Alc-FMT rats occurred 2 weeks after the last fecal transplant. The researchers suggested that this could be due to an interaction between the new Alc-FMT microbiota received and alcohol consumption, producing a synergistic effect that favored bacteria most benefited by alcohol consumption. Antibiotic pretreatment caused a significant reduction in alcohol consumption, and neither Alc-FMT nor control-FMT had an effect on intake. Additionally, spontaneous locomotor activity was reduced in the Alc-FMT mice, and antibiotic pretreatment abolished this effect.[40] The findings suggest that, similar to the study by Ferrere et al.,[23] alcohol preference may be dependent on the content of the gut microbiome since antibiotic pretreatment abolished the effects of both control-FMT and Alc-FMT.[40]

In another study not involving FMT, a dietary probiotic (*Lactobacillus rhamnosus* Gorbach-Goldin [LGG]) was used to modify the gut microbiota and assess alcohol intake in a rat model of alcohol relapse drinking.[42] Rats selectively bred for alcohol drinking consumed alcohol for 5 weeks before they were administered antibiotics followed by daily LGG during a forced deprivation period. Antibiotic treatment alone led to a reduction (30%–40%) of early alcohol relapse drinking (i.e., within 60 minutes of restored access to alcohol), which increased to a 20% decrease of relapse drinking with 24-hour access. LGG treatment inhibited relapse drinking by 66% to

80%, as did administration of *N*-acetylcysteine + acetylsalicylic acid (NAC+ASA), which inhibits the alcohol-induced hyperglutamatergic condition. However, the combination of LGG and NAC+ASA during the deprivation period showed additive effects and virtually suppressed (90% inhibition) binge-like drinking after renewed access to alcohol. The reductions in alcohol deprivation effect were accompanied by differential alterations in protein levels in the nucleus accumbens. LGG treatment increased dopamine transporters, while NAC+ASA increased glutamate transporter levels (xCT and GLT-1), suggesting these dietary supplements are acting through different mechanisms to reduce alcohol relapse.[42]

Role of Gut Microbiome in ALD: Clinical Studies

The gut microbiome—including bacteria, fungi, and viruses—has been implicated in the progression of liver disease in patients with underlying AUD; however, the few clinical studies that exist offer variable results.

Bacteria

A study by Maccioni et al. compared patients with ALD to healthy controls in an analysis of microbiota from feces and duodenal mucosa.[44] In this study, patients with hepatic inflammation and fibrosis had increases in potentially pathogenic bacterial taxa, including *Streptococcus*, *Shuttleworthia*, and *Rothia*. This supports the notion that alcohol exposure increases intestinal permeability and that this can potentially contribute to ALD development, though further studies are warranted. Patients with alcohol-associated cirrhosis exhibit an increase in oral microbial species (*Lactobacillus salivarius*, *Veillonella parvula*, *Streptococcus salivarius*, and *Bifidobacterium*) in stool compared to controls and patients with alcohol use disorder without cirrhosis.[45] Furthermore, pro-inflammatory bacteria such as *Enterobacteriaceae* were increased in patients with alcohol dependence, whereas butyrate-producing species (*Clostridiales*) were decreased.[45] Specifically, cirrhosis was significantly associated with the presence of *Bifidobacterium*. The *B. dentium* species, linked to alcohol-associated cirrhosis, has been shown to play an important role in GABA production.[4]

Another study analyzed microbiota in the colons of healthy controls as well as 48 patients with AUD with and without liver disease.[46] Mutlu et al. suggested that dysbiosis was worse in patients with alcohol-associated cirrhosis than in those with cirrhosis from other causes. Their study demonstrated that even in the early stages of ALD (without cirrhosis), changes in the gut microbiome occurred, such as reduced *Bacteroidetes* and increased *Proteobacteria*, and that levels of endotoxin were higher in patients who consumed alcohol.[46] Alcohol also has been shown to decrease commensal taxa in patients consuming alcohol, irrespective of their cirrhosis status.[47] It is suspected that increases in oral microbiota in the stool of patients with cirrhosis could be a result of the higher rate of oral infections, changes in salivary microbiome, and use of acid-lowering medications in this population. One study also suggested that increasing severity of liver disease is associated with a relative decrease in *Akkermansia muciniphila*.[48] Therefore, changes to the gut microbiome may be influenced by the severity of liver disease.

Fungi

Studies in people with ALD have identified an increase in *Candida* species and a decrease in *Epicoccum*, *Galactomyces*, and *Debaryomyces*. Lower fungal diversity was observed in patients with ALD compared to healthy controls. In addition, these changes to the intestinal mycobiota were consistent among patients with varying degrees of ALD.[49,50]

Viruses

The link between viruses and ALD is complex, and current knowledge is limited.[51,52] In patients diagnosed with alcohol-associated hepatitis, phages with hosts as varied as *Escherichia*, *Enterobacteria*, and *Enterococcus* were increased, as were viruses such as Parvoviridae and Herpesviridae. Specifically, the severity of ALD was associated with the presence of *Staphylococcus* phages and Herpesviridae.[52]

Effects of gut microbiota modulation

Several studies have assessed the effects of modulation of the gut microbiota on ALD. In a double-blind, placebo-controlled study, Amadieu et al. assigned a prebiotic (inulin) versus placebo for 17 days to 50 patients with ALD.[53] Patients receiving inulin had significantly higher markers of hepatic inflammation. In the subset of patients who had early ALD (as defined based on FibroScan and serum values), inulin administration was linked to an increase in *Bifidobacterium* and a decrease in *Bacteroides*, and again, higher levels of hepatic inflammation. These findings suggest that inulin may be able to alter the gut microbiome but not necessarily lead to clinically apparent changes to inflammation and that prebiotics may not be successful or beneficial for improvement in liver parameters. This study was limited, however, by sample size and a relatively short duration of inulin administration. Another study assessed the effects of LGG use in patients with moderately severe alcohol-associated hepatitis. LGG was associated with reduced short-term liver injury and reduction of alcohol consumption to abstinence levels at 6 months.[54]

The role of SCFAs also has been explored in patients with ALD. A metabolomics analysis of fecal specimens demonstrated changes in tetradecane, reduced antioxidant fatty alcohols, and reduced SCFAs.[55] These alterations promote an environment prone to oxidative stress and increased gut permeability.

Role of FMT in AUD Treatment

Another area of interest has been the role of FMT in AUD treatment. Bajaj et al. demonstrated the safety of FMT in patients with alcohol-associated cirrhosis.[56] They concluded that FMT was associated with reduced alcohol consumption

and craving, with higher SCFA and microbial diversity. There was also a nonsignificant trend toward abstinence in the FMT group. Wolstenholme et al. further explored these mechanisms in a cross-species FMT design, mentioned below.[41] A larger trial studying the clinical efficacy of FMT (NCT05548452) is currently enrolling.[57]

To extend these findings, Philips et al. treated patients with severe alcohol-associated hepatitis with FMT and prospectively analyzed stool samples.[58] During a follow-up period of up to 3 years, patients who underwent FMT had lower rates of ascites, encephalopathy, infections, and hospitalizations with higher survival rates. Moreover, the FMT group demonstrated decreased alcohol relapse rates and longer time to relapse when compared to the standard-of-care group. Regarding microbiota composition, the FMT group demonstrated an increase in *Bifidobacterium* and a decrease in *Acinetobacter*, thus favoring a nonpathogenic milieu.

In patients with severe alcohol-associated hepatitis refractory to steroid therapy, liver transplantation, with the limitations described above, typically is the next treatment option. To address this, an open-label study was conducted with eight patients who were ineligible for steroid therapy and were treated with nasojejunal FMT for 1 week.[59] Patients treated with FMT were found to have higher transplant-free survival, associated with reduction in pathogenic bacteria, as compared to historical patients with steroid-refractory alcohol-associated hepatitis (87% vs. 33%). Specifically, at the 1-year follow-up, patients treated with FMT had fewer *Proteobacteria* and more *Actinobacteria*. Furthermore, they exhibited a relative increase in nonpathogenic bacteria such as *Enterococcus villorum* and *Bifidobacterium longum*. Notably, there was coexistence of recipient and donor species at 6 and 12 months after FMT.[59]

The benefit of steroid treatments for severe alcohol-associated hepatitis is modest and limited to 28-day survival. Patients with alcohol-associated hepatitis have microbiota changes characterized by predominance of pathogenic species leading to immune dysregulation. Another study comparing FMT in 13 patients with standard of care (without steroids) in 20 patients reported a statistically significant increase in 90-day survival with FMT (54% vs. 25%, $p = 0.02$).[60] In an extension of these two studies,[59,60] Pande et al. compared the safety and efficacy of healthy-donor FMT versus prednisolone therapy in patients with severe alcohol-associated hepatitis in an open-label study; each group included 60 patients.[61] There was a statistically significant improvement in 90-day survival in the FMT group compared to the prednisolone group (75% vs. 57%, p = .044). Moreover, there were significantly fewer deaths related to infections in the FMT group, suggesting that FMT can be a safe alternative in patients with severe alcohol-associated hepatitis. However, further studies are needed with differing formulations.

FMT and Gut-Brain Axis Changes in ALD: Clinical Studies

A randomized controlled trial of FMT enema of men with cirrhosis and recurrent hepatic encephalopathy found that FMT increased microbiota diversity and improved cognition compared with standard of care.[62] Using a rationally derived stool donor that was enriched in SCFA-producing *Lachnospiraceae* and *Ruminococcaceae*, this open-label randomized controlled trial with a follow-up period of 5 months found that with antibiotic pretreatment and administration of an FMT enema, the FMT was significantly better tolerated than the standard of care treatment.[62] Whereas five patients in the standard of care group developed hepatic encephalopathy, none of the patients who had received FMT did. Other benefits associated with FMT included improved cognitive performance and changes in the microbiome, such as relative reduction in nonpathogenic taxa and increased microbial diversity.[62] A subanalysis of the data showed that improvement in microbial function was linked to cognitive improvement.[63] Long-term follow-up of participants in this trial showed a continued relative increase in *Burkholderiaceae* and decrease in *Acidaminococcaceae* in the FMT group.[64] Furthermore, the FMT group had decreased rates of liver-related hospitalizations and hepatic encephalopathy recurrence, suggesting that FMT could significantly improve the clinical course of patients with cirrhosis and have a positive impact on quality of life as well as reduce the economic burden of hospitalization.[64]

The effect of orally administered FMT on the gut-brain axis in cirrhosis also was studied in a phase I, randomized, placebo-controlled trial. Cognitive function improved after FMT, as measured by performance using the EncephalApp.[65] The study also confirmed the primary endpoint of safety and tolerability of the oral FMT capsules.[65] FMT also improved mucosal diversity, dysbiosis, and microbial function.[66]

Cross-species studies of microbiota and AUD

In one of the first cross-species studies, the gut microbiota from patients with AUD increased alcohol preference, induced changes in anxiety-like and depression-like behaviors, and altered brain gene expression of recipient mice.[38] The fecal microbiome of men hospitalized for AUD (Alc-FMT), enriched in *Firmicutes* and *Bacteroidetes*, or of the control group of men who had abstained from alcohol for at least a year (control-FMT) was transplanted over 13 days into male mice that had been pretreated with antibiotics. Alcohol intake and preference for 4% or 8% alcohol in a two-bottle choice model were increased in the Alc-FMT mice compared to control-FMT mice. Alc-FMT mice also showed decreased anxiety-like behavior (indicated by increased time in the open arms of the elevated plus maze or in the center of an open field), increased depression-like behavior (indicated by immobility in the tail suspension test), and fewer

social interactions compared to control-FMT mice. With respect to gene expression, Alc-FMT mice showed reduced expression of the metabotropic glutamate receptor 1 (*mGluR1*) and *PKCε* mRNA in the nucleus accumbens and reduced *Bdnf* and $GABA_A$ receptor (alpha-1$GABA_AR$) expression in the medial prefrontal cortex. Of note, antibiotic treatment prior to FMT modified some behaviors (e.g., decreased anxiety-like behavior) and increased locomotor activity in some tasks; however, social interactions and depressive-like behavior were not altered. Overall, the findings demonstrated that the gut microbiome of heavy drinkers can transmit some behavioral phenotypes similar to those seen in human drinkers.[38]

A separate study extended these cross-species findings by investigating the effects of an alcohol-FMT on addiction-associated behaviors such as sociability, anxiety-like and depression-like behavior; on brain functions such as myelination, neurotransmission, and inflammation; and on intestinal bacterial load and permeability.[43] Mice that received an FMT from patients with AUD with severe symptoms of gut dysbiosis; high depression, anxiety, and alcohol craving; and low sociability also displayed deficits in a social preference task and higher depressive-like behavior; however, no differences were found in models of anxiety-like behavior.[43] This was accompanied by increased corticosterone levels compared to mice that received control FMT. Within the brains of Alc-FMT mice, expression of several neurotransmitter subunits and myelin-associated genes was altered, but pro-inflammatory cytokines, chemokines, and markers of microglial activation were increased in the striatum, but not the prefrontal cortex, suggesting a local inflammatory response. Total bacterial load in the intestine was reduced in Alc-FMT mice, suggesting a lower bacterial count. The relative abundance of *Bacteroidetes* was decreased, while the abundance of *Firmicutes* was increased, similar to what is found in patients with AUD. This was accompanied by indicators of increased intestinal permeability, including decreased expression of markers of defense immune mechanisms, loss of intestinal homeostasis (reduced expression of *Reg3g* and *Lcn2*), modification of tight junction expression, and atrophy of the mucosal structure (reduced villous height and crypt depth in the ileum). Interestingly, the study suggested that the behavioral changes may not have been induced through a peripheral inflammatory response, but rather may have been a result of blood metabolite changes. Although the FMT-treated mice were not exposed to alcohol, increased portal vein ethanol concentrations were found in Alc-FMT mice. This suggests that the Alc-FMT mice likely were colonized by higher amounts of alcohol-producing bacteria such as *Clostridium*, *Lactococcus*, *Turicibacter*, and *Akkermansia*.

In a third study using a cross-species FMT design, changes in alcohol preference and intake that occurred in patients with AUD after receiving a fecal transplant were transmissible by FMT to germ-free mice (i.e., which had been treated to lack any microorganisms).[41] The study used fecal samples from a randomized clinical trial that demonstrated reduced alcohol craving and consumption after fecal transplantation in patients with severe AUD. Germ-free male mice then received either stool or sterile supernatants (the nonmicrobial buffer collected from around the stool pellet) collected from trial participants pre-/post-fecal transplant. Mice colonized with postfecal transplant stool but not supernatants exhibited reduced alcohol acceptance, intake, and preference compared with mice receiving prefecal transplant stool. Analyses of gene expression in the liver, intestine, and prefrontal cortex revealed that a majority of the differentially expressed genes—which were related to immune response, inflammation, oxidative stress response, and epithelial cell proliferation—occurred in the intestine rather than in the liver or prefrontal cortex.[41] These findings suggest a potential for therapeutically targeting gut microbiota and the microbial-intestinal interface to alter gut-liver-brain axis and reduce alcohol consumption in humans.

Conclusions and Future Directions

The studies reviewed here demonstrate the role of the gut microbiome in AUD and ALD. They suggest that the use of probiotics, prebiotics, or FMT warrants further investigation as therapeutic approaches for these conditions. In clinical and preclinical studies, excessive drinking or exposure to high levels of alcohol was associated with dysbiosis, intestinal permeability, and changes in immune response (see Table 1). Clinical studies have suggested that use of FMT in patients with AUD improved SCFA levels, which may reduce inflammation and aid in preventing additional liver damage.[56] FMT also has recently been used in preclinical models to manipulate the gut liver axis with certain dietary supplements to alleviate signs of acute or chronic alcohol-induced liver disease.[32-34]

Preclinical studies have used probiotics, prebiotics, or FMT from animals that had consumed those substances to improve alcohol-related behaviors such as alcohol consumption, providing evidence that gut microbiome manipulation may improve not only inflammation-related markers, but alcohol-related behaviors as well.[41,42] Several of the preclinical studies identified in this narrative review were proof-of-concept FMT studies to show that behaviors such as anxiety-like and depression-like phenotypes and alcohol drinking can be induced by FMT from a donor with a history of alcohol exposure.[38-40,67] However, the body of evidence in regards to FMT studies currently is still limited.

Clinical data suggest that with strict donor screening protocols, FMT appears to be safe, with low incidence of

reported adverse events; however, long-term prospective data are still lacking.[56] Currently, FMT only is indicated for recurrent *Clostridium difficile* infection, but the mounting evidence from preclinical and clinical studies suggests that it may be a therapeutic option for ALD as well.[47] Several challenges exist, however, including the need to define a healthy stool donor, determine the optimal route of FMT administration, and find effective ways to validate endpoints. Changes in the microbiome can lead to progression of ALD by maintaining a state of localized and systemic inflammation.[46] Also, although human studies support the role of healthy-donor FMT in improving transplant-free survival, reducing rates of infections, and even ameliorating craving for alcohol in patients with AUD, clinical data are limited by small sample sizes. Moreover, these studies often have focused on advanced ALD, and the benefit of FMT intervention on the liver and on psychological parameters in patients with less advanced forms of ALD remains unknown.

A study that compared pentoxifylline, corticosteroid, and nutritional therapy with FMT found that patients who received FMT via nasojejunal route had the highest survival rates of all groups at 3-month follow-up, suggesting a possible mortality benefit for FMT. FMT also led to improvement in clinical parameters while modulating and targeting inflammatory pathways such as LPS.[68] Therefore, when compared to other medical interventions such as steroids that have side effects, FMT could potentially serve as a relatively benign treatment modality. However, a major limitation to this study was inclusion of only male patients, which raises the question of generalizability.

Understanding of the role of the microbiome in progression of ALD is growing rapidly. However, questions remain regarding its exact role in the pathophysiology of liver disease and in therapeutic strategies. Although abstinence remains the cornerstone of therapy for AUD, the point at which abstinence can modulate changes at the microbiome level is poorly understood. Future studies should focus on the composition and function of the microbiome and its byproducts at the various stages of the ALD spectrum. This will require large, prospective clinical trials with a diverse population sample. Although preclinical studies have suggested that manipulation of the gut microbiome may alter drinking behavior, few clinical trials of microbiome-targeted interventions have assessed drinking behavior as an endpoint. Such studies would be important in assessing the impacts of FMT on AUD outcomes outside of ALD. The gut-brain axis also is known to play a critical role in AUD, as demonstrated by individuals with AUD having increased gut permeability that leads to higher rates of depression, anxiety, and alcohol craving after a short period of abstinence.[12] These observations suggest the microbiota can modulate cravings and other psychiatric comorbidities associated with addictive behaviors.

Dysbiosis occurs in some patients across the spectrum of liver disease severity, and changes in the microbiome are evident at the bacterial, viral, and fungal community level. Probiotics may address these changes; however, although probiotics have been associated with improvements in direct and indirect markers of disease severity in patients with ALD, most studies only had a small sample size, had a heterogeneous trial design, and were rarely reproduced. Targeting bacterial metabolites also could be promising, and given that patients with ALD have reduced levels of total fecal bile acids and SCFAs, addressing these changes could be a potential therapeutic target.

In summary, this review highlights the fact that, to date, few studies have evaluated FMT as a therapeutic option for reducing symptoms associated with excessive alcohol use. However, the number of such investigations is growing, and early studies have shown remarkable potential with a good safety profile. Although additional, larger clinical studies still are needed to determine whether FMT is an effective therapeutic strategy, evidence to date suggests that targeting the gut microbiome could be a promising treatment option for decreasing the risk of relapse in AUD patients and ameliorating the severity of ALD.

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NIAAA 50th ANNIVERSARY FESTSCHRIFT

Looking Back, Looking Forward: Current Medications and Innovative Potential Medications to Treat Alcohol Use Disorder

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I would like to acknowledge the support that NIAAA has provided for my work and say a wholehearted "Thank you and congratulations!" to NIAAA on their 50th anniversary, with best wishes for many more exciting advances and adventures in the treatment of AUD in the years to come. Appreciation is expressed to Sam Reed for his editorial assistance in the preparation of this manuscript.

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Dr. Mason is on the Scientific Advisory Board for Imbrium Therapeutics and on the Scientific Advisory Board for Awakn Life Sciences.

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This article is part of a Festschrift commemorating the 50th anniversary of the National Institute on Alcohol Abuse and Alcoholism (NIAAA). Established in 1970, first as part of the National Institute of Mental Health and later as an independent institute of the National Institutes of Health, NIAAA today is the world's largest funding agency for alcohol research. In addition to its own intramural research program, NIAAA supports the entire spectrum of innovative basic, translational, and clinical research to advance the diagnosis, prevention, and treatment of alcohol use disorder and alcohol-related problems. To celebrate the anniversary, NIAAA hosted a 2-day symposium, "Alcohol Across the Lifespan: 50 Years of Evidence-Based Diagnosis, Prevention, and Treatment Research," devoted to key topics within the field of alcohol research. This article is based on Dr. Mason's presentation at the event. NIAAA Director George F. Koob, Ph.D., serves as editor of the Festschrift.

KEYWORDS: alcohol; alcohol use disorder; treatment; medication; disulfiram; naltrexone; acamprosate

According to national surveys, more than 85% of U.S. adults have consumed alcohol at some point in their lifetime, and about 70% did so in the last year.[1] Most individuals drink responsibly and without adverse effects. However, a substantial proportion of people misuse alcohol.[1,2] Drinking patterns associated with alcohol misuse include binge drinking, heavy drinking, and high-intensity drinking. Binge drinking is typically defined as five or more drinks within a few hours for men and four or more drinks within a few hours for women. Heavy drinking is defined as four or more drinks per day or more than 14 drinks per week for men and more than three drinks per day or more than seven drinks per week for women. High-intensity drinking is defined as two or more times the gender-specific thresholds per day for binge drinking.[3] Moreover, according to the National Survey on Drug Use and Health, nearly 15 million people age 12 and older in the United States, or 5% of this age group, met the criteria for alcohol use disorder (AUD) in 2019.[1] Alcohol misuse and AUD exert a heavy toll on the individual, their families and communities, and society as a whole. Alcohol contributed to about 99,000 deaths in 2020, making it one of the leading preventable causes of death in the United States.[4] Additionally, alcohol misuse imposes a heavy economic burden on the nation.[5] Indeed, in many respects, alcohol misuse and its consequences are a substantially greater societal problem than the current opioid crisis, yet it generally receives less attention.[6-10] Therefore, the development and availability of effective treatments for AUD are of utmost importance.

Various treatment approaches have been identified for AUD, including pharmacological and nonpharmacological approaches. However, only a small proportion of people with AUD receive treatment. In 2019, only about 7% to 8% of these individuals were estimated to receive any treatment for AUD, and less than 2% reported using a medication approved by the U.S. Food and Drug Administration (FDA) for the treatment of AUD.[11] To date, only three medications—disulfiram, naltrexone, and acamprosate—have been approved by FDA for the treatment of AUD. Development of additional medications has largely been ignored by the pharmaceutical industry and instead is being driven by grants from the National Institute on Alcohol Abuse and Alcoholism (NIAAA) to academic scientists, as well as by work conducted by NIAAA's Clinical Investigations Group and Intramural Research Program. Numerous potential medications—including those currently used for other indications as well as newly developed medications—are being investigated and will hopefully help to increase the number of treatment options available to people with AUD and their health care providers. This article describes the characteristics, benefits, and risks of the FDA-approved medications for AUD; evaluates the benefits and risks of novel drugs repurposed for the treatment of AUD; and appraises novel drug targets that are in the pipeline.

FDA-Approved Medications

The three FDA-approved drugs to treat AUD have very different mechanisms of action, but they share some key characteristics:

- For AUD medications, the pivotal clinical trials conducted to gain FDA approval involved behavioral counseling for all the participants—both those receiving the active drug and those receiving placebo. In these pivotal trials, drinking outcomes were better for participants who received the medication plus counseling than for those who received placebo plus counseling, demonstrating an incremental benefit of using evidence-based medications combined with counseling beyond that shown by counseling alone.[12,13]
- All three medications are not to be used as a stand-alone treatment but as part of a comprehensive treatment plan based on a chronic care model, as suggested in the 2016 *Surgeon General's Report on Alcohol, Drugs, and Health*.[14] This comprehensive model includes medications and additional components such as behavioral therapies and recovery support services.
- Like behavioral counseling and other therapeutic approaches, the medications are a treatment for AUD but are not a cure. Moreover, they are not a treatment for alcohol withdrawal, which requires its own special type of medication.
- The medications do not substitute for alcohol—such as methadone does for opioids in the treatment of opioid use disorder—and they do not induce euphoria. Moreover, the drugs are not addictive; people taking them long term do not develop tolerance or experience withdrawal upon treatment discontinuation. Accordingly, these medications have no street value as illicit drugs.[15]

To obtain FDA approval for a medication to treat AUD, manufacturers must assemble a safety dossier that includes studies demonstrating that the medication itself has no misuse potential and does not harmfully interact with alcohol, for example, by further impairing awareness or coordination if a person consumes alcohol while taking the drug. Additionally, the medication must demonstrate efficacy in typically two pivotal trials—defined as randomized, double-blind, placebo-controlled, multicenter trials that ideally represent the four quadrants of the United States and have adequate representation of women and minority participants.[16] Pivotal trials typically are 6 months in duration, during which the medication is given in conjunction with behavioral counseling. Primary outcome measures used by FDA to determine efficacy generally are rates of days with no drinking or no heavy drinking (i.e., consumption of five or more drinks per day for men and four or more drinks per day for women).[15] To determine these outcomes, a standard "drink" is defined as the beverage volume that contains 0.6 oz. of pure ethanol, which corresponds to approximately 12 oz. of beer, 5 oz. of wine, or 1.5 oz. of distilled spirits.[17]

To determine participants' alcohol consumption in trials submitted for FDA approval, self-report instruments such as the Timeline Follow-back Interview capture the self-reported number of daily drinks consumed.[18] These self-reports are often combined with biochemical measures, such as breathalyzer readings, alcohol glucuronide urine dipsticks, or blood tests for the levels of the liver enzyme gamma-glutamyl transferase (GGT). Breathalyzer analyses only capture alcohol consumption at the time of the study visit whereas the alcohol glucuronide urine dipstick may reflect drinking up to 3 days before the study visit. Blood levels of GGT are an indirect marker of more distant alcohol consumption; they typically rise after heavy alcohol consumption that has continued for several weeks and may have occurred as long as 3 weeks prior to the study visit.[19] Smartphone apps for real-time drinking data collection and noninvasive transdermal wrist alcohol sensors are under development, but have not been used in regulatory studies.

Disulfiram

The first medication to be approved for AUD was disulfiram (Antabuse, now available in generic formulations), which entered the market in 1951—thus preceding even the inception of NIAAA. Its mechanism of action involves inhibition of the enzyme aldehyde dehydrogenase, which plays a central role in alcohol metabolism, converting the alcohol metabolite acetaldehyde into acetate. If an individual consumes alcohol while having disulfiram in their system, the drug will inhibit the acetaldehyde metabolism, resulting in rapid acetaldehyde accumulation that leads to a quick onset of flushing, nausea, palpitations, and other symptoms that can become quite severe and at times life-threatening. This mechanism of action acts as a psychological deterrent to any alcohol use.

Because of the rapid and potentially even fatal consequences of acetaldehyde accumulation after taking disulfiram, the medication should never be given to individuals with acute alcohol intoxication or without their full knowledge.[20] Additionally, individuals should be instructed to abstain from alcohol for at least 12 hours before taking disulfiram and be advised that reactions with alcohol can occur for as long as 14 days after discontinuing the medication. Disulfiram itself is associated with some hepatotoxicity; therefore, the patient's liver function should be measured before and during disulfiram treatment to ensure safety.

Disulfiram can only exert its effects if taken regularly. Studies found that outcomes are better in patients with high medication adherence who are strongly motivated to quit drinking, as well as in those patients who have a partner who is supportive of their recovery and will supervise the daily administration of disulfiram.[21,22]

Naltrexone

FDA originally approved naltrexone in 1984 for opioid addiction; for treatment of AUD, it was approved as an oral medication in 1994 (Revia and generic formulations) and as a long-acting injectable medication in 2006 (Vivitrol).[23-25] Naltrexone is a pure mu-opioid receptor antagonist that binds to the receptor, thereby blocking some of the rewarding effects of alcohol. Blunting the rewarding effects of drinking is thought to reduce alcohol consumption and thereby promote recovery from AUD. Consistent with this hypothesis, meta-analyses of numerous naltrexone studies have shown that, compared to placebo, the medication decreases heavy drinking.[12,13]

As with disulfiram, the efficacy of naltrexone is affected by adherence problems associated with oral dosing. To address these problems, a once-monthly, extended-release, intramuscular injection formulation has been developed.[25] Because naltrexone has such a specific mechanism of action, researchers have attempted to identify genetic predictors to determine which individuals with AUD might be most likely to respond to naltrexone treatment. To date, these investigations have not yielded reliable results; for example, initial findings of an association of different variants of the mu-opioid receptor gene *OPRM1* with response to naltrexone could not be replicated in other clinical trials.[26] However, the investigations into genetic predictors of naltrexone response are still ongoing.

Naltrexone treatment is generally considered safe. But because of the medication's effects on the mu-opioid receptor, it is important to rule out co-occurring illicit or prescribed opiate use prior to initiating treatment for AUD to avoid inducing acute opioid withdrawal. Also, like disulfiram, naltrexone itself is associated with some hepatotoxicity, particularly in higher doses. However, because alcohol itself is a hepatotoxin, naltrexone actually can improve liver functioning by reducing alcohol intake in individuals with AUD.[23]

Acamprosate

Disulfiram and naltrexone both aim to reduce drinking by making alcohol consumption a less pleasant experience, either by causing unpleasant effects after alcohol consumption or by reducing alcohol's stimulation of receptors in the brain's reward system. Acamprosate (Campral) takes a different strategy that is based on the observation that heavy drinking and withdrawal dysregulate the balance between the excitatory (glutamatergic) and inhibitory (primarily gamma-aminobutyric acid [GABA]-ergic) neurotransmitter systems in the brain. In particular, the excitatory system becomes hyperactive during early abstinence, and acamprosate has been shown to restore homeostasis in this system by reestablishing normal *N*-methyl-D-aspartate receptor tone in the glutamate system.[27,28]

Clinical studies lasting up to 1 year found that acamprosate treatment increased rates of abstinence relative to placebo.[12,15] Post-treatment follow-up studies found that these effects persisted for as long as 1 year after the last dose of medication.[12,15,28] Thus, unlike disulfiram and naltrexone, acamprosate seems to restore normal function in aspects of the brain's glutamatergic signaling system that can result in long-term AUD treatment effects. One additional component contributing to acamprosate's effectiveness may be its normalizing influence on alcohol-related sleep disturbances, which can be quite severe in early abstinence and precipitate relapse to drinking.[29,30]

Researchers at the Mayo Clinic have been seeking to identify predictors of patient response to acamprosate. They determined that a patient's serum glutamate concentrations at baseline could serve as a biomarker of treatment outcome, with high serum glutamate levels predicting a good response. Moreover, individuals who showed a response to acamprosate treatment showed the greatest reduction in serum glutamate levels from baseline to the end of treatment.[31]

Unlike disulfiram and naltrexone, acamprosate is not metabolized in the liver. Therefore, it is safe to use in patients with hepatic impairment. However, as acamprosate is excreted through the kidneys, it is important to ensure that patients do not have severe renal impairment. Acamprosate has low bioavailability, which necessitates that the medication be taken three times per day.[15]

U.S. Treatment Guidelines

In 2017, the American Psychiatric Association issued practice guidelines for the pharmacological treatment of patients with moderate to severe AUD.[20] These guidelines recommend use of acamprosate or naltrexone in patients who wish to cut down or quit drinking, who prefer medication or have not responded to nonpharmacological treatments, and who have no medical contraindications to use of these drugs. Disulfiram is not recommended as a first-line treatment for AUD, given (a) the potential risk of severe reactions and physiological consequences of drinking while taking the drug, and (b) the more robust evidence for efficacy in acamprosate and naltrexone. However, it may be used in patients who prefer disulfiram or are intolerant to or have not responded to naltrexone or acamprosate and who understand the risks of alcohol consumption while taking disulfiram.

The guidelines also recommend that antidepressant medications and benzodiazepines should not be used for the treatment of AUD unless the individual has been diagnosed with a concurrent disorder (e.g., depression, anxiety) for which these medications are indicated. Benzodiazepines can be used to manage acute alcohol withdrawal for up to 5 days; beyond that time, there is no support for the use of benzodiazepines in the treatment of AUD, especially because benzodiazepines themselves have misuse potential and are cross-tolerant with alcohol.[20]

Nalmefene—Widely Approved Outside the United States

A fourth medication, nalmefene, has been approved for treatment of AUD throughout the European Union, the United Kingdom, and other countries. In contrast to naltrexone, which mainly binds to the mu opioid receptor, nalmefene acts as a more potent antagonist at the mu, delta, and kappa opioid receptors.[32] Nalmefene's activity at the kappa opioid receptor is of interest because activation of this receptor is associated with increases in anxiety and dysphoria. Consequently, by blocking this array of receptors, nalmefene may diminish both the rewarding effects of alcohol as well as the anxiety and dysphoria associated with not drinking in individuals with AUD.

In contrast to oral naltrexone, disulfiram, and acamprosate, which must be taken daily, nalmefene is only taken 1 to 2 hours prior to anticipated drinking occasions. Follow-up studies of up to 1 year found that nalmefene treatment was associated with decreased drinking relative to placebo.[33-35] The European Medicine Agency based its approval on slightly different treatment outcome criteria than FDA, including a two-level reduction in World Health Organization (WHO) drinking risk levels.[36] (These risk levels—very high, high, medium, and low—are defined based on estimated mean daily ethanol consumption in grams in the previous 12 months.[37]) This level of reduction in alcohol consumption has been shown to be associated with improved mental health, particularly anxiety and depression; improved physical health (liver functioning); and improved overall quality of life.[38] Thus, both the FDA-approved drinking outcomes (i.e., rates of no drinking or no heavy drinking days) and the WHO risk level-based outcomes have broad clinical relevance for individuals with AUD.

Identifying New Medications for AUD

As described above, the currently approved medications for AUD largely focus on reducing the expected positive or rewarding effects of drinking. Disulfiram, naltrexone, and nalmefene all interrupt the binge intoxication phase, either by inducing negative responses after drinking or by reducing alcohol's rewarding effects, whereas acamprosate reduces craving in the preoccupation-anticipation phase in individuals in recovery (see Figure 1). Use of these anti-reward medications is based on the assumption that most people drink due to positive reinforcement—they want to experience alcohol's rewarding effects—and that taking away those effects will thereby discourage further drinking. However, as recent research has uncovered more information on alcohol's effects on the brain and the neurobiology of AUD, it has become clear that many people drink because of negative reinforcement—they want

to avoid the negative effects of not drinking.[39] In people with AUD, drinking cessation acts as a stressor because the brain has become used to the presence of certain alcohol levels. In these individuals, abstinence induces excessive activation of the brain stress systems, particularly in the central nucleus of the extended amygdala. This stress response includes the release of corticotropin-releasing factor (CRF), especially in early abstinence, which prompts symptoms of anxiety, dysphoria, irritability, and sleep disturbance that are characteristic of post-acute or protracted withdrawal.[39] At the same time, the brain's anti-stress systems often are depleted in early abstinence.[39] These observations have launched a new avenue of research in the quest for effective treatments for AUD focusing on the neuropeptides that have been shown to be dysregulated during early abstinence and which are associated with the symptoms of protracted withdrawal as potential drug targets for novel medications. The hope is that such treatments could interrupt the AUD cycle before reaching the craving and relapse/binge intoxication stage. Building on recent discoveries of the neurobiology of AUD—and particularly the role that the stress response has during early abstinence in driving the AUD cycle toward relapse—the goal is to normalize those systems to support recovery in a way that is safe and acceptable to patients.

To develop and study the effects of such medications, researchers, with support from NIAAA, developed parallel animal and human laboratory models of risk factors for relapse in protracted withdrawal.[40] The human model employed techniques already used for other purposes in the field. For example, the investigators used affective priming to induce some of the internal risk factors for relapse, such as the affective states mentioned above, by showing participants images associated with those mood states. Additionally, participants were exposed to external risk factors for relapse through visual and olfactory alcohol cue exposure (i.e., they were asked to view and smell a glass of their favorite alcoholic beverage but not drink it). The studies recruited non-treatment-seeking men and women with AUD who were required to remain abstinent for 3 days prior to testing while taking double-blind study medication. Thus, the volunteers were beginning to exhibit an activated stress response and were highly likely to be responsive to the alcohol beverage cues. The main goal of the experiments was to screen medications aimed at reducing the stress response associated with relapse risk in protracted withdrawal. The study participants were randomly assigned to the medication under investigation or placebo for a relatively short dosing period, based on the period needed to achieve steady-state or

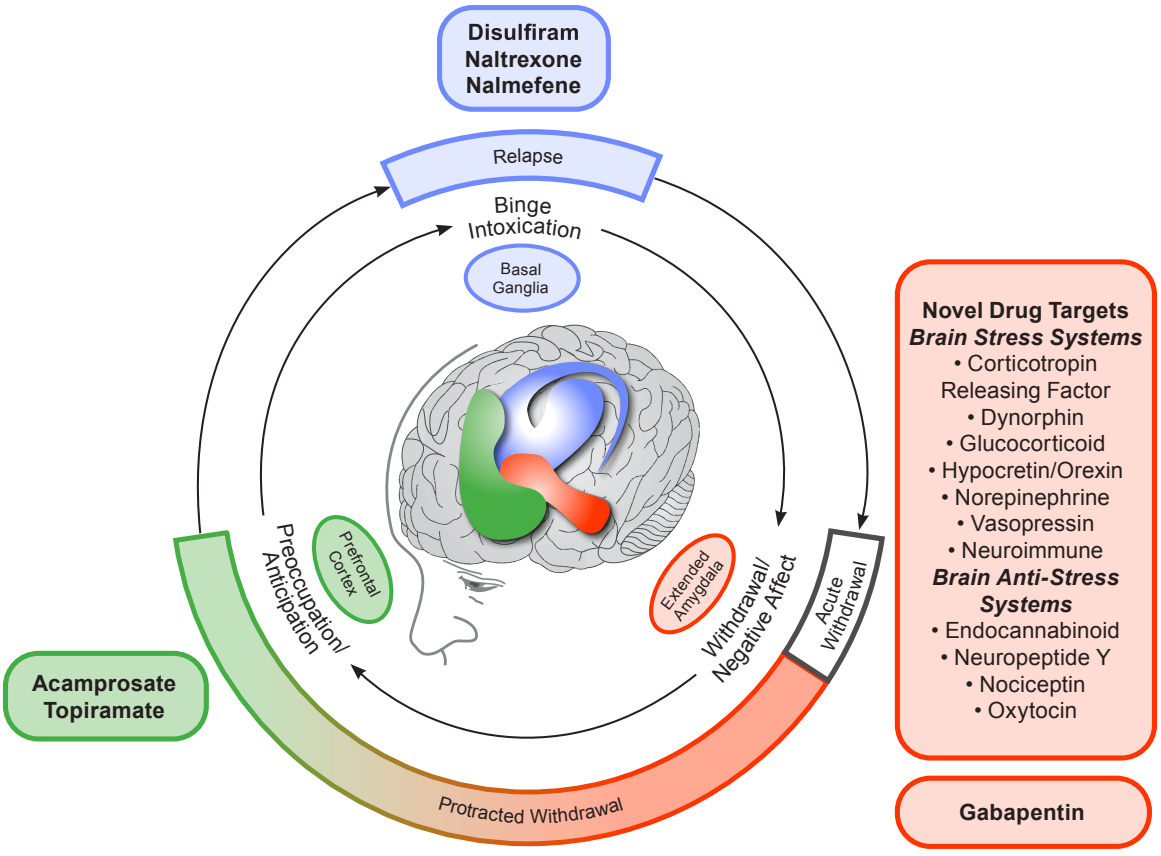

Figure 1. Conceptual framework for the effects of various medications on the three major stages of the alcohol addiction cycle and the clinical stages of alcohol use disorder. The outer ring relates to the clinical stages of alcohol use disorder; the inner ring relates to the three stages of the addiction cycle. *Note:* Adapted by permission from Springer Nature: *Neuropharmacology*, 35(1):217-238. Neurocircuitry of addiction. George F. Koob and Nora D. Volkow, 2010.[59]

maintenance dosing, which is typically between 1 and 2 weeks. Participants were then tested on the last day of dosing, using both subjective and objective measures of responsivity to alcohol as well as extensive analyses to evaluate how well tolerated and safe the studied drug was in individuals with AUD. This approach has been used to evaluate the effectiveness of several medication candidates.

Gabapentin

The first medication studied using this model was gabapentin, an oral anticonvulsant approved by FDA for the treatment of epilepsy and neuropathic pain. It acts by modulating GABAergic activity on voltage-gated calcium channels, which reduces postsynaptic excitability and decreases the release of excitatory neurotransmitters.[41] Because this activity also helps restore homeostasis in brain stress systems that become activated in early abstinence, gabapentin seemed to be a promising candidate for treatment of AUD. Moreover, several off-label clinical studies reported beneficial effects of gabapentin on symptoms associated with post-acute protracted withdrawal and risk of relapse, such as dysphoria, anxiety, and insomnia.[41] In fact, several studies reported that gabapentin was effective for treatment of insomnia, including alcohol-related sleep disturbance, indicating that it decreased stage 1 sleep and arousals while increasing slow-wave sleep and sleep efficiency.[41,42] Like acamprosate, gabapentin is not metabolized in the liver and has an acceptable safety and tolerability profile, further supporting its investigation in the treatment of AUD.[41]

To assess the efficacy of gabapentin in the treatment of AUD, Mason and colleagues conducted a human laboratory study in which they randomly assigned 33 volunteers with AUD to receive either 7 days of gabapentin (1,200 mg/d) or placebo and then tested them on the last day of dosing.[43] These analyses found that participants who were treated with gabapentin had significantly less craving, lower impulse to drink, and less feelings of loss of control over drinking than those who had received placebo. Gabapentin-treated participants also showed benefits compared with placebo across multiple dimensions of sleep, including sleep efficiency, sleep latency, and sleep quality. Moreover, individuals treated with gabapentin did not report next-day dysfunction or somnolence, which often occur after taking sleep medications.

Based on the findings of the initial study, the research team conducted a larger, double-blind, placebo-controlled, dose-ranging clinical trial of gabapentin in 150 outpatients seeking treatment for AUD.[44] Participants were randomized to 12 weeks of treatment with either the highest FDA-approved dose of gabapentin (1,800 mg/d), the lowest FDA-approved dose (900 mg/day), or placebo. All patients also received weekly abstinence-oriented counseling over the treatment period. Outcomes analyzed include rates of complete abstinence and no heavy drinking; drinking quantity and frequency; GGT levels as an objective indicator of recent alcohol use; as well as measures of craving, sleep disturbance, and negative affective symptoms.

Over the 12-week treatment period, participants who had received the highest dose of gabapentin had significantly less relapse to drinking and higher rates of complete abstinence compared with placebo; relapse and abstinence levels for participants treated with the 900 mg dose were intermediate. Similarly, participants receiving the high gabapentin dose had the highest proportion of individuals with no heavy drinking at about half the sample, which was about twice as much as among participants receiving placebo; the rate of heavy drinking in participants receiving the lower dose of gabapentin was again intermediate. Thus, both of these key outcomes showed significant linear dose effects. Similar results also were observed for quantity and frequency measures of drinking.[44]

Treatment with the 1,800 mg gabapentin dose also yielded the greatest effect on symptoms of protracted abstinence. Participants who had received this dose showed the greatest reduction in negative affective symptoms on the Beck Depression Inventory II; in craving as determined using the Alcohol Craving Questionnaire; and in sleep complaints as measured using the Pittsburgh Sleep Quality Index.[44] These results replicated the findings obtained in the earlier laboratory study.[42] Finally, gabapentin treatment was associated with significant reductions in GGT levels, indicating reduced recent alcohol use.[44] Together, the results supported the conclusion that gabapentin dose-dependently and significantly improved various parameters of AUD, including rates of complete abstinence and no heavy drinking; drinking quantity and frequency; as well as protracted withdrawal symptoms such as craving, sleep disturbance, and negative affect.

Gabapentin was well tolerated, with no serious or unexpected drug-related adverse events or evidence of misuse potential.[44] To date, numerous studies conducted in the United States and elsewhere have found no evidence of misuse potential for gabapentin in the treatment of AUD.[41] Bisaga and Evans demonstrated that gabapentin does not interact pharmacokinetically or pharmacodynamically with alcohol.[45] However, there have been reports that gabapentinoids, such as gabapentin and the newer drug pregabalin, have been misused by people with opioid use disorder who are in withdrawal, people who misuse prescription drugs recreationally, and people who are incarcerated, with self-administered doses greatly exceeding recommended doses.[41] Heightened monitoring for gabapentin misuse is warranted in these at-risk populations.

Based on these and other studies supporting the efficacy of gabapentin in treating AUD, the American Psychiatric Association has included gabapentin and another anticonvulsant, topiramate, in its 2017 *Practice Guideline for the Pharmacological Treatment of Patients With Alcohol Use Disorder.*[20] These guidelines recommend that gabapentin or topiramate be used in patients who have a goal of decreasing or quitting drinking, who prefer

gabapentin or topiramate, who are intolerant to or have not responded to acamprosate or naltrexone, and who have no contraindications to the use of gabapentin or topiramate.

Mifepristone

Mifepristone is a medication approved by FDA for Cushing's syndrome that shows promise as a repurposed medication for the treatment of AUD and acts upon the protracted withdrawal phase of the AUD cycle.[46] Mifepristone is a mixed glucocorticoid/progesterone receptor antagonist that has been hypothesized to normalize the altered activity of the hypothalamic-pituitary-adrenal axis. As previously mentioned, heavy alcohol consumption and subsequent withdrawal have an impact on the body's stress response, with heavy alcohol use blunting activity of the hypothalamic-pituitary-adrenal axis and the stress associated with subsequent abstinence driving CRF release in the amygdala, which contributes to protracted withdrawal symptoms.[47,48] Consequently, administration of mifepristone to people with AUD following acute withdrawal was hypothesized to normalize the individual's stress response and CRF dysregulation, thereby protecting against relapse during protracted withdrawal.

To investigate this hypothesis, Vendruscolo and colleagues evaluated the effects of mifepristone on people with AUD in a laboratory model of risk factors for relapse.[46] Participants were randomly assigned to mifepristone (600 mg/d) or matched placebo for 7 days, with testing conducted on the last day of dosing. The analyses found that participants treated with mifepristone not only exhibited significant reductions in craving and response to alcohol cues, but they also had significantly lower levels of drinking than did those who had received placebo, both during the week of treatment and at 1-week follow-up. Moreover, participants receiving mifepristone showed a significant reduction from baseline in GGT levels, the marker of liver function that is sensitive to alcohol intake, as well as in two other measures of liver function (i.e., aspartate transaminase and alanine transaminase levels).[46]

Looking Ahead in Medication Development for AUD

The clinical studies of both gabapentin and mifepristone showed reductions in craving and alcohol consumption, as well as improvements in liver function tests compared to placebo, suggesting that both medications have therapeutic potential for AUD.[43,44,46] Additionally, both medications were well tolerated and triggered no concerns regarding safety, medication adherence, or misuse potential, including rebound craving or alcohol use after medication discontinuation, in these samples of individuals with AUD. These findings provide clinical validation of earlier preclinical studies of protracted withdrawal, in which the medications reduced reinstatement of ethanol seeking and ethanol intake. They also lend support to the role that medications targeting abstinence-related dysregulation in brain stress systems can play as a novel treatment approach for AUD. Such medications may reduce the negative affect and insomnia associated with early abstinence and thereby both increase medication adherence and reduce the misery of early abstinence.

In addition to these studies, which were largely funded by NIAAA, the institute itself has an active research program. The NIAAA Clinical Investigations Group conducts multicenter trials that have shown positive results for two medications relevant to protracted abstinence—varenicline (Chantix), a partial alpha(4)beta(2) nicotinic acetylcholine receptor agonist that FDA has approved as a treatment for smoking cessation, and an investigational vasopressin antagonist.[49,50] The NIAAA Intramural Research Program also has been active in studying molecules that may be relevant to treating protracted abstinence, including ghrelin receptor antagonists[51] and mineralocorticoid receptor antagonists,[52,53] and a molecule that may show efficacy for both AUD and alcohol-associated liver disease.[54] These are just a few examples of the many hundreds of drugs that have been evaluated, with NIAAA support, for efficacy in the treatment of AUD.

What characteristics should medications to treat AUD have? Ideally, they should be small molecules that can cross the blood-brain barrier and target the brain regions and systems that are dysregulated by chronic heavy alcohol consumption in a way that is relevant to treating AUD. They should not have misuse potential, nor should they interact with alcohol. This is important so that, in case of relapse, the medication does not exacerbate alcohol's effects, such as impaired alertness and motor coordination. Additionally, medication candidates should have a good safety profile, particularly no hepatotoxicity; they should show good tolerability with only mild to moderate adverse events that do not prompt treatment discontinuation; they should have good patient acceptability in terms of the route of administration, which is typically oral; and the dosing regimen should be acceptable to the patients and adaptive to their lifestyle.

Another consideration in developing medications for AUD is the potential for sex differences as well as racial differences in drug metabolism, as exemplified by a greater prevalence of the flushing response in certain East Asian populations. Such differences in drug metabolism may affect drug efficacy or safety. Therefore, it is important to have diversity, equity, and inclusion among participants in clinical trials of medications to treat AUD. Sex differences have not been studied systematically for disulfiram and naltrexone; however, although sex does not affect the pharmacokinetics of the long-acting formulation of naltrexone, only men responded to the medication in the pivotal

trial, whereas women did not.[25] The reasons underlying these differences are not fully understood. Sex differences have been comprehensively analyzed for acamprosate in a meta-analysis of individual records obtained from more than 1,300 women and nearly 4,800 men who participated in 22 acamprosate clinical trials.[55] The meta-analysis found a significant effect of acamprosate relative to placebo on both rates of abstinence and rates of no heavy drinking, and these effect sizes did not differ between men and women. Similarly, the side effect and tolerability profile of acamprosate, including the number, type, and severity of adverse events, did not differ between men and women. Moreover, despite a history of significantly more anxiety, depression, suicide attempts, drug misuse, interpersonal loss, and greater liver impairment at baseline in women than in men, women responded comparably well to acamprosate treatment of AUD.[55]

Another issue to consider in AUD treatment is the age of the patient, as it is never too early (or too late) to treat AUD. In the United States, drinking is illegal for people under age 21, although some in this age group do meet the criteria for AUD. A small, double-blind, placebo-controlled clinical trial of disulfiram conducted in teens found good tolerability and higher rates of abstinence with the medication compared to placebo.[56] At the other end of the age spectrum, some people older than age 65 have been included in some trials of disulfiram,[57] naltrexone,[25] and acamprosate;[58] however, the numbers were not sufficient to analyze differences in safety and efficacy from younger patients. AUD is a serious concern in older adults because some of its common effects may have more serious consequences in this population, such as the increased risk of falls. Closer monitoring with medication treatment may be necessary if an older person is at increased risk for liver, kidney, or cardiac problems, or uses additional medications to treat other disorders; however, unless there is a medical contraindication, medication treatment is indicated in this age group.

Overall, however, it is clear that new medications to treat people with AUD are urgently needed and that the use of the existing medications must be significantly expanded to support people recovering from AUD. Effective treatments for AUD—both pharmacological and nonpharmacological—are available, but they can only help if they are actually being used. The fact that only 7% to 8% of individuals with AUD report receiving any treatment is a clear indication that much remains to be done in this respect. To support both patients and treatment providers in ensuring that people with AUD receive the appropriate care, NIAAA has created the *NIAAA Alcohol Treatment Navigator* (www.alcoholtreatment.niaaa.nih.gov). This online tool outlines the features of evidence-based AUD treatment, describes the varied routes to recovery, and provides a strategy to help people find practitioners in their area that provide evidence-based treatments, whether behavioral or pharmacological, for AUD.

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Alcohol Use Disorder: The Role of Medication in Recovery

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The misuse of alcohol in the United States continues to take a large toll on society, resulting in the deaths of about 88,000 Americans per year. Moreover, it is estimated that nearly 14.6 million Americans currently meet diagnostic criteria for current alcohol use disorder (AUD). However, very few individuals receive treatment, with an even smaller portion receiving medications approved by the U.S. Food and Drug Administration (FDA) for the treatment of AUD, despite scientifically rigorous evidence showing the benefits of combining medication approved for treating AUD with evidence-based behavioral therapy. These benefits include higher rates of abstinence and less risk of relapse to heavy drinking, with associated improvements in medical and mental health and in quality of life. This review provides an overview of FDA-approved medications and "off-label" drugs for the treatment of AUD. The article emphasizes that AUD medical advice and prescription recommendations should come from professionals with training in the treatment of AUD and that treatment plans should consider medication in conjunction with evidence-based behavioral therapy. Finally, this review notes the limited number of medications available and the continued need for the development of new pharmacotherapies to optimize AUD recovery goals.

KEY WORDS: disulfiram; acamprosate; naltrexone; gabapentin; medication-assisted treatments; alcohol use disorder; alcohol; drug therapy

INTRODUCTION

It is estimated that nearly 14.6 million Americans currently meet the diagnostic criteria for alcohol use disorder (AUD)[1] included in the *Diagnostic and Statistical Manual of Mental Disorders,* 5th edition (*DSM-5*),[2] and approximately 88,000 die from alcohol-related causes in the United States each year.[3] An older term, "alcohol dependence," is equivalent to the *DSM-5* criteria for AUD of moderate or greater severity.[4] This is the stage of AUD severity for which pharmacotherapy is generally indicated. Effective intervention can decrease drinking

and the likelihood of subsequent relapse, thereby significantly improving an individual's health and reducing the negative consequences of AUD that are most likely to burden society.[5]

This paper provides an overview of the medications for AUD that are currently available for use by the recovery community, as well as a brief introduction to potential medications under development. Throughout, this review emphasizes that (1) all AUD medical advice and prescription recommendations should come from professionals (or in consultation with professionals) who have specific training in the treatment of AUD; (2) physical examination and laboratory testing are recommended before treatment is initiated and may help with subsequent monitoring of treatment response and adverse events; (3) medications are not "stand-alone" treatments for AUD, but rather are an element in a comprehensive treatment plan; (4) clinical trial data show drinking outcomes and recovery are significantly better when behavioral interventions are combined with AUD medication rather than given without AUD medication; and (5) there is a critical need for research on potential modifiers of response—including potential differences in drug metabolism due to sex hormones, race or ethnicity, and pharmacogenetic and pharmacometabolomic markers—to identify individuals most likely to respond or have significant side effects to specific AUD pharmacotherapies. The U.S. Food and Drug Administration (FDA) uses drinking outcomes of abstinence from alcohol and/or cessation of heavy drinking (males, five or more drinks per day; females, four or more drinks per day) in determining its approval of a candidate drug. Additionally, measures of improved medical and mental health and of quality of life are associated with these operational measures of recovery but often are not reported in the clinical trial literature given the relatively short duration of clinical trials (generally 6 months or less). Given that FDA approval is associated with drinking-specific outcomes and that these outcomes have been linked to improvement in measures of medical and mental health and quality of life, there is reason to believe that by alleviating problems associated with AUD, the use of AUD medications may bestow other positive contributions to recovery.[6,7] The final section briefly reviews new pharmacological approaches and potential medications under development for the treatment of AUD.

CURRENT FDA-APPROVED MEDICATIONS TO TREAT AUD

To date, the FDA has approved three medications for the treatment of AUD. These alcohol-specific pharmacotherapies are the oral alcohol-aversive drug disulfiram (Antabuse), introduced more than half a century ago in 1951; the opioid antagonist naltrexone, approved in 1994 as an oral formulation (Revia) and in 2006 as a long-acting injectable formulation (Vivitrol); and the oral centrally acting taurine analog, acamprosate (Campral), approved in 2004. In other countries, the European Medicines Agency approved the opioid antagonist nalmefene (Selincro) in 2013 for the treatment of alcohol dependence throughout the United Kingdom and European Union. Nalmefene is similar to naltrexone, but it binds more potently to a broader range of opioid receptor subtypes. The FDA-approved medications act via widely different mechanisms but share some key features relevant to recovery and highlight the complex nature of AUD. More specifically, these medications are aimed at restoring normal functioning in alcohol-altered neurophysiological processes or act to blunt or punish the reinforcing properties of alcohol.

Treating AUD with a prescribed drug can appear counterintuitive or concerning to those aspiring to a drug-free recovery. Therefore, such overarching concerns must be addressed before delving into the details of a specific medication. All drugs (prescribed, herbal, and

over-the-counter) have a potential for harm. FDA has evaluated the drugs approved to treat AUD and found the safety profile to be acceptable, particularly given the potentially lethal harms of ineffectively treated AUD of moderate or greater severity. None of these prescribed medications are mood-altering, habit-forming, or addictive. They do not produce euphoria or other subjective experiences associated with misuse potential, nor do they have "street value" as do illicit drugs. None are "substitution" drugs for alcohol, as is methadone for heroin. Tolerance, or a need to increase the dose, does not develop with continued use, nor does rebound craving or drinking occur when medication is discontinued.

All AUD medical advice and prescription recommendations should come from professionals (or in consultation with professionals) who have specific training in the treatment of AUD. This training is critical because the efficacy of drug treatment may be influenced by an individual's unique characteristics, including comorbid conditions, severity and complexity of AUD, state of sobriety at the onset of treatment, medication adherence, any side effects, and motivation to recover from AUD. Treatment outcomes in a large acamprosate trial were significantly better in individuals motivated to a treatment goal of abstinence.[8] Therefore, a detailed understanding of these factors and available treatment options, obtained in partnership and communication with the individual, may optimize treatment selection and recovery. In addition, and perhaps more important, the time course for recovery is quite variable and subject to myriad environmental changes. Therefore, a trained professional is in the best position to respond to these changes in real time and adjust treatment accordingly.

People in recovery from AUD may need to take medications for other medical or psychiatric disorders, in conjunction with medication for AUD. Physician members of Alcoholics Anonymous (AA) have developed a thoughtful guide to the appropriate use of such non-AUD medications, with the aim of minimizing risk of their misuse and undermining recovery. Both treatment providers and persons in recovery can refer to and access the guide online (https://www.aa.org/pages/en_US/aa-member-medications-and-other-drugs). AA does not offer medical advice, but strongly recommends seeking out physicians who are experienced in the treatment of AUD. Persons in recovery are urged to communicate openly with their prescribing doctor if they skip doses or take extra medication, have a desire to take more medication, or experience side effects that make them feel worse, as well as to be sensitive to changes in their own behavior and mood when starting a new medication or when a dose is changed. Such reactions could signal an increased risk of drug misuse or relapse. AA stipulates that its members do not "play doctor"; all medical advice and prescriptions should come from a qualified provider.

EFFICACY CRITERIA FOR MEDICATIONS TO TREAT AUD

Comprehensive meta-analyses of randomized controlled trials of FDA-approved medications to treat AUD have shown a significant benefit on rates of abstinence and/or cessation of heavy drinking in studies that were typically 6 months in duration (see Table 1). It is critical to appreciate that those clinical trials included either the nonpharmacological treatment routinely provided for AUD in a given setting or protocol-specific behavioral treatments for all participants. Therefore, the medication (plus behavioral treatment) demonstrated a significant benefit over placebo (plus behavioral treatment) on drinking outcomes.

These rigorous, evidence-based findings have two important implications:

Table 1 Summary of Treatment Parameters for Medications Approved by the FDA for Alcohol Use Disorder

Parameter	Disulfiram* *(oral)*	Naltrexone* *(oral)*	Naltrexone* *(injectable)*	Acamprosate* *(oral)*
Primary evidence-based outcome	No drinking Double-blind trials, n.s.[25] Open-label trials, moderate effect size[25] Supervised administration trials, large effect size[25]	No heavy drinking NNT = 12[14] NNT = 8.6[15]	Heavy drinking days WMD = -4.6%[14]	No drinking NNT = 12[14] NNT = 7.5[15]
Median trial duration	6.5 months[25]	3 months[14]	6 months[20]	6 months[14]
Dosing	500 mg daily, Weeks 1-2; 250 mg daily thereafter	One 50 mg tablet, daily	One 380 mg injection, monthly	Two 333 mg tablets, 3x daily
Cost per month†	$48	$33	$1,308	$142
Abstinent baseline	≥ 12 hours (mandatory)‡	≈ 4 days[15]	7 days[20,‡]	≈ 6 days[15]
Medical contraindications‡	Use of metronidazole, paraldehyde, alcohol-containing preparations Severe myocardial disease or coronary occlusion Psychosis	Opioid dependence, withdrawal, or use Acute hepatitis or liver failure	Opioid dependence, withdrawal, or use within 7-10 days Acute hepatitis or liver failure	Severe renal impairment (creatinine clearance ≤ 30mL/min)
Adverse events	Neuritis, neuropathy‡ Hepatitis, hepatic failure‡ Psychosis‡ Drowsiness, fatigue‡ Impotence‡ Headache‡ Acne, allergic dermatitis‡ Metallic, garlic aftertaste‡	Dizziness NNH = 16[14] Nausea NNH = 9[14] Vomiting NNH = 24[14]	≥ 5% and 2x placebo‡ Vomiting, nausea Injection site reactions Muscle cramps Dizziness, syncope Somnolence, sedation Decreased appetite	Diarrhea 17% (placebo 10%)‡

*Review each drug's package insert for full prescribing information.

†Monthly cost estimates provided by local discount pharmacy (Costco) and are based on generic formulations when available.

‡Information derived from package inserts.

Note: FDA, U.S. Food and Drug Administration; NNH, a statistical estimate of the number needed to harm for the specified adverse event to occur in one individual; NNT, a statistical estimate of the number needed to treat to achieve the specified outcome in one individual; n.s., not significantly different than placebo; WMD, weighted mean difference.

1. Medications are not "stand-alone" treatments for AUD, but rather an element in a comprehensive treatment plan that includes behavioral therapy.
2. Drinking outcomes are significantly better when behavioral interventions are combined with AUD medication than when they are given without AUD medication.

Clinical trials of AUD medications typically incorporate a derivation of motivation enhancement or cognitive-behavioral treatment manuals developed for Project MATCH (https://pubs.niaaa.nih.gov/publications/projectmatch/matchintro.htm); the manual used in the multicenter U.S. acamprosate study is available at http://www.pearsoncenter.org/therapistmanual.

Given the incremental gains in recovery found when AUD medications are used in combination with behavioral treatment, recovery strategies should consider medications as an option in the treatment plan for AUD. For individuals with AUD, recovery historically has been viewed as a lifestyle of voluntary abstinence from alcohol and nonprescribed drugs.[9] In addition to complete abstinence, FDA has identified "no heavy drinking" as a clinically relevant outcome for assessing a drug's efficacy for AUD, given the relationship between alcohol-related harms and heavy drinking. Chronic heavy drinking is defined in women as routinely drinking more than three drinks per day or more than seven drinks per week, and in men as routinely drinking more than four drinks per day or more than 14 drinks per week.[10] These two FDA-recognized outcomes can be reported as the percentage of individuals having no drinks or no heavy drinking days over the course of treatment, which is typically 6 months in duration (see Table 1).

A third potential regulatory outcome for approval of a drug for treatment of AUD has recently been proposed. The proposed outcome involves a reduction of one or two in the World Health Organization (WHO) risk levels of alcohol use (measured in grams of alcohol consumed per day).[11] The European Medicines Agency used this outcome in its evaluation of nalmefene for the treatment of AUD.[12] Of note, unlike other oral AUD medications, nalmefene is not taken daily, but rather 2 hours prior to an anticipated heavy drinking situation. The 6-month duration of the majority of clinical trials for AUD may be too brief and the sample sizes too small to measure alcohol-related harms, such as driving under the influence or impaired quality of life. However, secondary analyses of larger data sets have shown that a reduction in WHO risk drinking levels is associated with significantly fewer alcohol-related consequences (e.g., less anxiety and depression, lower blood pressure and liver enzyme levels, improved quality of life).[6,7] Taken together, these findings suggest that the significant benefits of FDA-approved medications on reduced alcohol consumption also may have wide-ranging emotional and physical health benefits for individuals with AUD.

INTEGRATING MEDICATION INTO AN AUD TREATMENT PLAN

Given the scope of benefits associated with pharmacotherapy combined with evidence-based behavioral treatment for AUD, it is perplexing that a nationwide pharmacy survey suggests that fewer than 9% of eligible individuals have ever been provided with a prescription for a medication to treat AUD; psychiatrists provided the majority of these prescriptions.[13] Recent large-scale meta-analyses have reported that either acamprosate or naltrexone combined with counseling has superior efficacy for increasing rates of abstinence or of no heavy drinking relative to counseling administered in conjunction with placebo.[14,15] Recognizing the incremental gain typically achieved when medication is incorporated into the treatment plan, the American Psychiatric Association (APA) recently developed a practice guideline for the pharmacological treatment of individuals with AUD.[16] This guideline suggests that acamprosate or naltrexone be used in individuals with moderate to severe AUD who wish to cut down or quit drinking, who prefer medication or who have not

responded to nonpharmacological treatments, and who have no contraindications to the use of these medications. APA further suggests that disulfiram should not be selected as an initial treatment for AUD, given the physiological consequences of drinking in combination with this medication. In addition, this guideline recommends that antidepressant medications should not be used for the treatment of AUD, unless there is a comorbid disorder for which these treatments are indicated.[16] Furthermore, the medications approved to treat AUD are not treatments for alcohol withdrawal and should be initiated only following detoxification and/or after abstinence has been established. Acute withdrawal involves primarily symptoms of autonomic hyperactivity that may last up to 5 days, and although most cases (85%) do not require medication, severe alcohol withdrawal can be life-threatening if untreated.[17] Benzodiazepines are a standard treatment for clinically significant acute alcohol withdrawal symptoms, with the understanding that they are not an accepted treatment of AUD per se because of misuse potential.[16]

In its first report on alcohol, drugs, and health, the Office of the Surgeon General proposes a chronic care management approach to AUD that includes evidence-based behavioral and pharmacological treatments; social support services; and clinical monitoring of adverse events, medication adherence, and symptoms of relapse at every follow-up visit.[18] The report notes the importance of working collaboratively with the individual and their social support system; communicating the risks and benefits of each treatment option relative to the individual's recovery goals, drug costs, and dosing schedule; and ensuring that the individual comprehends this information. This again serves to highlight the importance of specific training in the treatment of AUD, given the need to explain complex information using clearly understood language. A written information sheet providing details about the prescribed medication can be taken home by the individual for future reference. It is recommended that the provider contact the individual a few days after an AUD medication is prescribed to address any concerns, to assess medication adherence and side effects, and to facilitate successful medication initiation.

SAFETY AND SIDE EFFECTS OF AUD MEDICATIONS

The well-being and safety of the individual is always the highest concern. Each AUD medication has a label or package insert that contains FDA-approved statements about the drug's indication (or purpose), dosing, side effects, and any warnings or contraindications. The label can be accessed by typing "[drug name] label" in an online search engine. Safety is optimized by heeding the recommended dose and the cautions and contraindications on the drug label. Ideally, the provider would have access to a complete and detailed medical history of the individual to optimize safety. Physical examination and laboratory testing are recommended before treatment is initiated and may help with subsequent monitoring of treatment response and adverse events. These lab tests could include alcohol breath/blood concentration, alcohol glucuronide testing, urine drug screen, liver function tests (i.e., gamma glutamyl transferase [GGT], alanine transaminase, aspartate transaminase), complete blood count, testing for vitamin deficiencies, renal function tests (standard panel for urea [blood urea nitrogen], electrolytes, and serum creatinine), and a pregnancy test for women of childbearing potential. Furthermore, measures of hepatic function and creatinine clearance may be critical in determining the choice of drug treatment. For example, baseline liver function tests may detect clinically significant hepatic impairment that would mitigate against treatment with disulfiram and naltrexone as well as severe impairment in creatinine clearance that would contraindicate the choice of acamprosate. A baseline urine drug screen may also be useful, as it may provide information about otherwise undisclosed drug use, including opioid use, which would rule out naltrexone treatment of AUD.

Individuals also should be assessed for any comorbid disorders, including depression and

other drug use disorders. Comorbid conditions may significantly influence AUD outcome if left untreated. Risk of suicide may be elevated in individuals with AUD, and it is recommended that the individual be screened and monitored for suicidality at baseline and throughout treatment to identify increased suicide risk that requires further intervention.

As with all medications, the FDA-approved pharmacotherapies for the treatment of AUD have common side effects (e.g., dizziness, nausea, diarrhea). Usually mild and associated with treatment initiation, these side effects resolve quickly. Individuals should be advised to avoid driving a car or operating heavy machinery until they are reasonably certain that the drug does not affect their ability to engage in such activities. Individuals should be given emergency phone numbers and instructed to call immediately if suicide ideation or depression develops, or if symptoms of acute hepatitis or liver failure emerge (in the case of naltrexone and disulfiram). As a precaution, it is highly recommended that individuals carry a card in their wallet listing all current medications in the event of a medical emergency. For example, anesthesia and pain management may need to be adjusted in individuals taking naltrexone. Furthermore, the presenting medical emergency may be the result of an interaction between alcohol and disulfiram.

Medication nonadherence will negatively impact treatment outcomes. Individuals can be instructed to bring the container for their oral medication to follow-up visits to be assessed for unused drug. Noncompliance can result from adverse side effects, inconvenience, the perception that the drug is no longer needed (i.e., "I feel fine"), and/or a return to drinking. It is therefore critical to understand the reason(s) for treatment noncompliance. First, treatment providers need to determine if adverse events (e.g., medication side effects) are undermining medication adherence, and intervene accordingly. In terms of convenience, long-acting injectable naltrexone was developed to offset the adherence problems noted with daily oral naltrexone dosing. Given that acamprosate has a dosing schedule of three times daily, it is recommended that patients keep their medication in a weekly pill organizer with day and time indicated for each dose. Patients are also advised to link commonly missed doses with an activity of daily living such as eating meals or brushing teeth as a reminder to take their medication at that time. Monitoring medication compliance is paramount to successful treatment outcomes.

MEDICATION INITIATION AND DURATION

The early days of abstinence are a period of heightened vulnerability for relapse and a critical time for healing neural processes associated with negative affect and impaired executive function.[19] Medications for AUD can have the greatest impact on reducing relapse risk when initiated immediately after a 4- to 7-day detoxification period.[15,20]

The patient's pattern of alcohol misuse should be established as a baseline, preferably using quantitative self-report and biochemical measures, against which treatment effects can be tracked. In addition, harmful effects of alcohol on the individual's health, functioning, and legal status should be documented and incorporated into a personalized treatment plan.

There is little scientific evidence to guide the optimal duration of pharmacological treatments of AUD. Decisions about treatment duration should reflect the individual's history of relapse, the severity of AUD at baseline, and the individual's clinical response and side effects to the medication. This should be discussed with the individual if they express a desire to discontinue treatment before a stable recovery has been achieved.

In situations where there is no response to treatment, the provider may consider switching to an alternative AUD medication. This decision is more difficult in situations where a partial response is observed. For example, an individual may have reduced their drinking by half from baseline, but continues to have episodes of heavy drinking. In these situations, the provider may consider the use of combined treatments on a case-by-case basis.

Some data lend support to the safety of acamprosate combined with naltrexone or disulfiram,[21-23] but efficacy data are insufficient to support a general recommendation for combined use as a first-line treatment approach to AUD.[16]

FDA-APPROVED MEDICATIONS FOR AUD

Disulfiram

In 1951 disulfiram (Antabuse; now in generic formulations) was the first drug approved for the treatment of AUD by the FDA. Pharmacologically, disulfiram inhibits the enzyme aldehyde dehydrogenase. Even small amounts of alcohol can cause acetaldehyde to quickly accumulate, resulting in a rapid onset of flushing, nausea, and vomiting. The resulting acute physical distress serves to reduce drinking and break the cycle of binge intoxication (see Figure 1). In severe reactions, there is the possibility of multiple cardiac and respiratory symptoms that could result in death. The intensity of the interaction varies across individuals but is generally proportional to the amounts of disulfiram and alcohol ingested and can last from 30 to 60 minutes to several hours, or as long as there is alcohol in the blood. Individuals should be instructed to abstain from alcohol for at least 12 hours before taking disulfiram and be advised that reactions with alcohol can occur up to 14 days after discontinuing disulfiram.

The therapeutic action of disulfiram is punitive, resulting in acute physical distress when taken with alcohol. Therefore, it should never be given to an individual in a state of alcohol intoxication or without their full knowledge. When taken as prescribed, disulfiram is typically well tolerated,[24] but more serious adverse events were found with disulfiram than with comparison treatments.[25] The psychological threat (fear) of the interaction between disulfiram and alcohol may be the primary mechanism of disulfiram's deterrent effect, as opposed to the drug's pharmacodynamic properties.[25] Therefore, consideration of disulfiram may be warranted only in individuals who have a clear goal of complete abstinence, are capable of understanding the risks of an interaction between alcohol and disulfiram, have not responded to acamprosate and naltrexone, and have no medical contraindications.[16] Given the drug's potential for hepatotoxicity, it is recommended that individuals taking disulfiram have bilirubin and liver function tests at baseline and 2 weeks, once a month for the next 6 months, and every 3 months thereafter. Medication nonadherence is a common problem with disulfiram,[26] and outcomes are optimized with supervised administration.[27]

Naltrexone

Naltrexone is a pure opioid receptor antagonist that the FDA approved first for opioid dependence (in 1984), and later for alcohol dependence (as an oral medication in 1994 and as a long-acting injectable in 2006). The therapeutic action of opioid receptor antagonism is to blunt the rewarding effects of alcohol. In our conceptual model (shown in Figure 1), blunting the rewarding effects of alcohol can reduce drinking and break the cycle of binge intoxication. Although side effects are generally mild (initial nausea, vomiting, and dizziness), a recent meta-analysis found a higher risk for discontinuation due to adverse events with naltrexone relative to placebo.[14] This meta-analysis, which included the results of 53 randomized controlled trials (involving 9,140 patients) of oral naltrexone (50 mg/d) for the treatment of AUD, showed that naltrexone significantly decreased the likelihood of a return to heavy drinking and, to a lesser extent, a return to any drinking.[14] This replicated the results from an earlier meta-analysis that reported a decreased risk of a return to heavy drinking and that also assessed moderators of naltrexone treatment response.[15] Maisel et al. (2013) found that 4 days of abstinence prior to beginning treatment significantly improved naltrexone treatment response and that having treatment goals other than abstinence was associated with a larger effect size on reducing heavy drinking than having the goal of complete abstinence.

Naltrexone, like disulfiram, is pharmacologically effective primarily while present in the system, but induces no long-term changes in the brain.

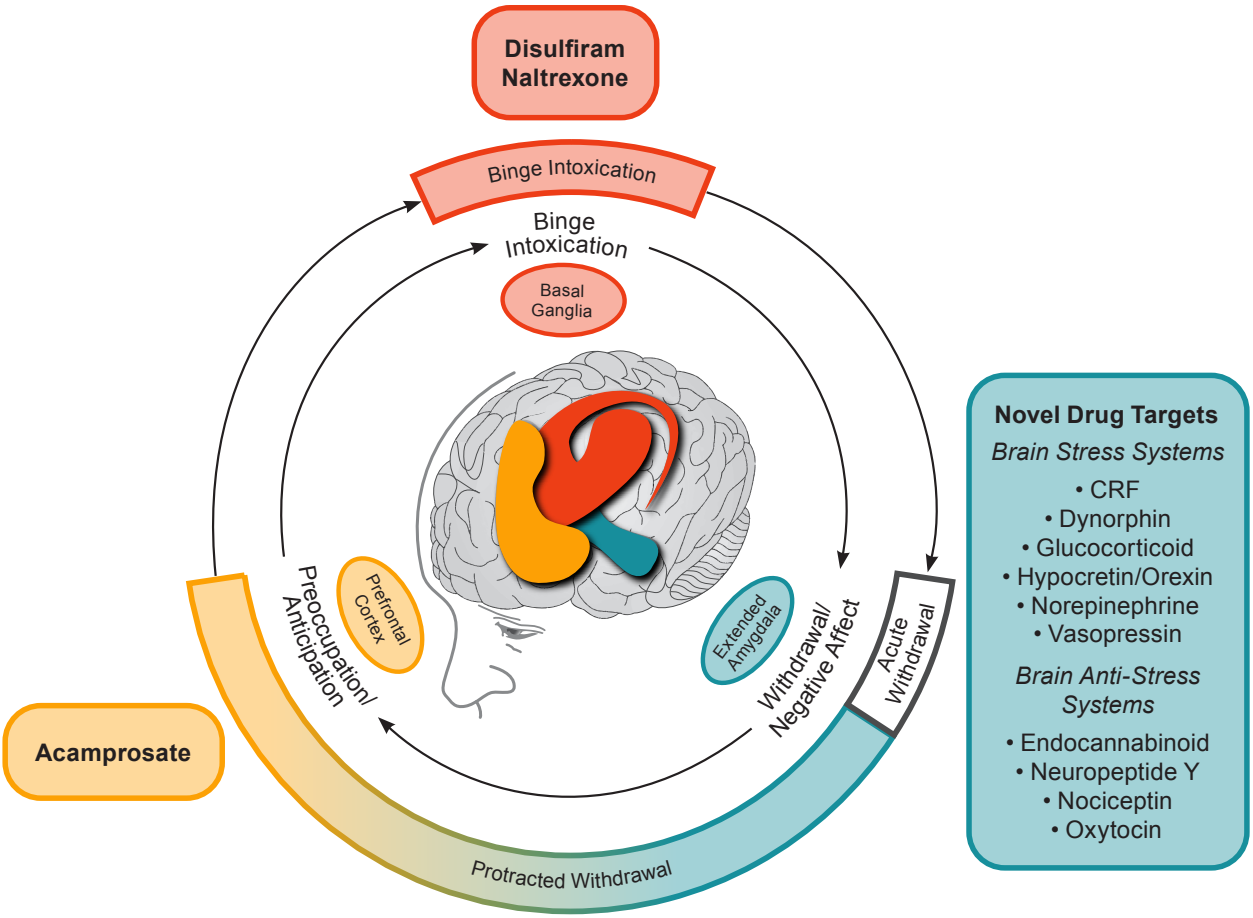

Figure 1 Conceptual framework for the effects of various medications on the three major stages of the alcohol addiction cycle and the clinical stages of alcohol use disorder (AUD). The outer ring relates to clinical stages of AUD. The inner ring relates to three stages of the addiction cycle. Acute withdrawal relates to physiological and emotional effects that are opposite to those of alcohol and includes activation of the extended amygdala brain stress systems. Acute withdrawal is a time-limited process (up to only 5 days in duration). Protracted withdrawal is characterized by continued hyperactivation of the brain stress systems. The overexpression of brain stress neuropeptides is hypothesized to mediate the anxiety, dysphoria, irritability, and sleep disturbances of post-acute (i.e., protracted) withdrawal that may persist for an indefinite duration. Protracted withdrawal/negative affect helps drive craving in the preoccupation/anticipation stage, for which acamprosate is the only available treatment. *Note*: CRF, corticotropin-releasing factor. Adapted by permission from Springer Nature: Nature Neuropsychopharmacology, 35(1):217-38, Neurocircuitry of addiction, George F. Koob and Nora D. Volkow, 2010.[31]

This is important in understanding the duration of treatment effects of naltrexone and disulfiram. For example, follow-up studies of patients in two 3-month naltrexone studies showed that treatment effects were no longer significant relative to placebo by 1 to 3 months posttreatment.[28,29] Pairing naltrexone with a form of cognitive behavior therapy focused on relapse prevention coping skills, therefore, may offer an optimal treatment strategy.[29]

Regarding route of administration, there have been no head-to-head comparisons of the efficacy of oral versus injectable naltrexone to date. A meta-analysis of drinking outcomes from 1,926 participants in two trials of different formulations of injectable naltrexone found no significant effects of treatment on return to any drinking or to heavy drinking, but did find a reduction in the number of heavy drinking days. The trial conducted in

support of FDA approval found a similar effect of naltrexone (Vivitrol) 380 mg per injection, but only in men and only in those with 7 days of abstinence prior to randomization.[20]

Any form of naltrexone treatment for AUD is contraindicated in individuals who have current physiologic dependence on opioids, who are in opioid withdrawal, who have used prescribed or illicit forms of opioids within the past 7 to 10 days, or who have a urine drug screen positive for opioids. This avoids unintended precipitation of opioid withdrawal through administration of an opioid antagonist. Of note, naltrexone can cause hepatocellular injury when used in higher than recommended doses and is contraindicated in individuals with acute hepatitis or liver failure.

Acamprosate

Acamprosate was developed in France in the 1980s and approved by FDA for the maintenance of abstinence in detoxified patients with alcohol dependence in 2004. The pharmacological action of acamprosate is complex. The chemical structure is similar to that of the endogenous amino acid homotaurine, which is a structural analog of the amino acid neurotransmitter gamma-aminobutyric acid (GABA) and the amino acid neuromodulator taurine. Repeated cycles of heavy drinking and withdrawal have been shown to dysregulate the balance between neuronal excitation (e.g., glutamatergic) and inhibition (e.g., GABAergic).[30] It has been hypothesized that this glutamatergic hyperactivity is associated with alcohol craving and the preoccupation/anticipation phase of protracted withdrawal—an effect that is ameliorated by acamprosate (see Figure 1).[31] Therefore, it suggested that the pharmacotherapeutic action of acamprosate in AUD works by restoring homeostasis in *N*-methyl-D-aspartate (NMDA)–mediated glutamatergic neurotransmission.[32,33] Acamprosate requires approximately 1 week to reach steady-state levels in the nervous system, and its effects on drinking behavior have been shown to persist in studies of up to 1 year after the treatment is completed, consistent with its role in restoring persisting homeostasis in brain glutamatergic activity.[33]

A meta-analyses of 27 randomized controlled trials of acamprosate (typically 6 to 12 months in duration) found that acamprosate was significantly more likely than placebo treatment to prevent a return to any drinking.[14] This finding replicates the results from an earlier meta-analysis that found a significantly higher rate of complete abstinence associated with acamprosate.[15] Detoxification or required abstinence prior to acamprosate administration was associated with increased efficacy.[15] A separate meta-analysis using individual records from more than 6,000 participants in 22 acamprosate studies found the medication to have a significant gain in the rate of complete abstinence and no heavy drinking over the study duration,[34] with no differences in the rate of discontinuation due to adverse events or severity or type of adverse event. Acamprosate was also associated with significantly higher rates of treatment completion and medication compliance than placebo. Posttreatment follow-up studies have shown the effects of acamprosate to be sustained for periods of up to 1 year after the last dose.[33] Acamprosate also has been reported to reverse alcohol-related insomnia and changes in sleep architecture.[35,36] This added benefit may improve treatment outcomes in individuals with comorbid psychiatric disorders characterized by sleep disturbance, such as post-traumatic stress disorder, anxiety, and depressive disorders.

Acamprosate is not metabolized by the liver and is not associated with hepatotoxicity. moreover, acamprosate does not interact with medications commonly prescribed for individuals with AUD, including disulfiram, antidepressants, anxiolytics, or hypnotics. pharmacokinetic studies found that coadministration with naltrexone increased the rate and extent of acamprosate absorption without compromising its tolerability.[22,23] As noted previously, acamprosate is taken three times a day, due to low bioavailability. This dosing schedule may be supported by placing a 1-week supply of medication in a commercially available pill organizer with day and time indicated for each dose.

Acamprosate is well tolerated with minimal side effects (e.g., mild to moderate diarrhea, typically at the start of treatment). The results of a meta-analysis found acamprosate to have no increase in the risk of withdrawal from treatment due to adverse events compared with placebo.[14]

"OFF-LABEL" MEDICATIONS TO TREAT AUD

Given that existing pharmacotherapies are underutilized and limited in scope, there is a continued need for the development of new medications to treat AUD safely and effectively. One avenue to discovery involves the repurposing of existing medications. This is the most expeditious route given that these drugs have FDA approval for use as treatments in other medical conditions and known safety profiles. However, once a drug is in generic formulations, there is little financial incentive for a pharmaceutical company to incur the cost of the additional research required for FDA approval of AUD as a new indication. Thus, the use of such drugs to treat AUD is considered "off label." Two generic drugs, topiramate and gabapentin (both originally developed as antiepileptic medications), have shown therapeutic potential for AUD and have been included in APA's practice guideline.[16] The guideline recommends the use of topiramate or gabapentin in individuals who have a goal of decreasing or quitting drinking and who are intolerant to or have not responded to acamprosate and naltrexone.[16] Co-occurring disorders, concomitant medications, side effect profiles, and contraindications for use are additional factors that may guide the selection of topiramate or gabapentin.

Topiramate

Topiramate (Topamax and generics) is currently approved by the FDA for the treatment of epilepsy and for the prophylaxis of migraine, and has been extensively studied for the treatment of AUD. A meta-analysis of randomized controlled trials of 3 months duration and target doses of 200 to 300 mg/d in outpatients with AUD found topiramate to be associated with fewer drinking days, fewer heavy drinking days, and fewer drinks per drinking day, compared with placebo.[14] Although promising, topiramate has a number of warnings and precautions. Safety monitoring recommends baseline and periodic measures of serum bicarbonate to detect treatment-emergent metabolic acidosis; baseline tests of renal function, as creatinine clearance of less than 70 mL/min requires a dose adjustment to half the starting and maintenance dose; and baseline tests of hepatic function, as topiramate plasma concentration is increased in hepatic impairment. In addition, it has been reported that individuals with AUD who were treated with topiramate had a higher risk of cognitive dysfunction, paresthesia, and taste abnormalities than did individuals treated with placebo. The cognitive dysfunction—including confusion; psychomotor slowing; attention, concentration, and memory impairment; and speech or language problems—was commonly associated with treatment discontinuation.[37] Individuals should be gradually withdrawn from topiramate to minimize the potential for seizures. An individual's current medications should be reviewed prior to considering topiramate, which interacts pharmacokinetically with some antiepileptic drugs, central nervous system depressants, oral contraceptives, metformin, lithium, and carbonic anhydrase inhibitors.

Gabapentin

Gabapentin (Neurontin and generics) is used "off label" for the treatment of AUD and is included in APA's practice guideline.[16] It is a synthetic GABA analog approved by FDA for the treatment of epilepsy and postherpetic neuralgia.[38] The authors hypothesize that gabapentin acts in AUD to break the cycle of negative affect given its effects on mood and sleep and on electrophysiological results showing that it acts like a corticotropin-releasing factor (CRF) receptor antagonist in the central nucleus of the amygdala (CeA)[38] (see Figure 1). A recent review found the efficacy of gabapentin for treatment of AUD supported by five of six single-site treatment studies reporting drinking

outcomes.[39] The efficacy of gabapentin has been reported to be dose dependent. More specifically, a 12-week trial of 0, 900, and 1,800 mg/d of gabapentin showed significant linear dose effects on rates of abstinence and absence of heavy drinking; number of drinks per week; number of drinking days per week; GGT; and standardized measures of craving, negative affect, and insomnia,[40] with the 1,800 mg/d dose associated with greatest efficacy. Similar to acamprosate, six of eight AUD studies reported a significant beneficial effect of gabapentin on alcohol-related sleep disturbance.[39] Moreover, gabapentin-related decreases in negative affect have been reported.[39] These clinical findings are consistent with basic research suggesting gabapentin may support recovery by restoring homeostasis (a stable equilibrium) in brain stress systems that become dysregulated in the protracted withdrawal/negative affect phase of AUD.[38] Research suggesting that gabapentin may be most effective in individuals with acute alcohol withdrawal symptoms was challenged because individuals with clinically significant acute alcohol withdrawal were systematically excluded from participation in this research.[41] Gabapentin should not be considered a standalone treatment for severe acute alcohol withdrawal because of its ineffectiveness in suppressing seizures related to alcohol withdrawal.[39] The APA practice guideline recommends the use of gabapentin for the treatment of AUD, not alcohol withdrawal.[16] Note that relative to other AUD medications, gabapentin shows unique evidence for treating the mood and sleep disturbance of the protracted withdrawal phase.

There are no contraindications to gabapentin, other than known hypersensitivity to the medication. Gabapentin is not metabolized in the liver and is eliminated from systemic circulation by renal excretion as unchanged drug. As such, a baseline test of creatinine clearance is indicated, with dose adjustments indicated in individuals with reduced renal function (creatinine clearance < 60 mL/min). Alcohol was not found to interact meaningfully with gabapentin in a pharmacokinetic/pharmacodynamic (PK/PD) study.[42] The lack of appreciable hepatic metabolism is a PK advantage of gabapentin, as chronic heavy drinking is often associated with liver injury. There were no reported safety concerns among the 655 individuals with AUD treated with gabapentin in clinical studies (≤ 1,800 mg/d), and any adverse events tended to be mild to moderate and to not differ from placebo.[39] These common adverse events included headache, insomnia, fatigue, muscle aches, and various gastrointestinal complaints at equivalent rates in both gabapentin- and placebo-treated outpatients with AUD. Taken together with patient experience for approved pain and epilepsy indications, gabapentin is considered to have a good safety and tolerability profile. As with any centrally active drug, individuals should be advised not to drive motor vehicles or operate heavy machinery until they have ascertained that the drug does not affect their performance.

Antiepileptic drugs, including gabapentin and topiramate, have been shown to increase the risk of suicidal thoughts or behavior in about one in 500 patients, irrespective of disorder. Further, abrupt withdrawal from gabapentin and topiramate can increase the risk of precipitated seizures and status epilepticus, and drug dose should be tapered gradually when discontinuing treatment. Reports of misuse of gabapentinoids, such as gabapentin and pregabalin, are increasingly documented in high-risk populations, notably among those who misuse opioids and prescription drugs. Gabapentin is not a controlled or scheduled substance. There was no evidence of tolerance to gabapentin dose or rebound with titration off drug, nor evidence of misuse potential, in studies of individuals with AUD. However, patients undergoing opioid withdrawal, those who misuse prescriptions recreationally, and prison populations may be at increased risk to misuse gabapentin, with self-administered doses often far exceeding the therapeutic range.[43,44] Hence, patients with risk histories should be monitored for potential gabapentinoid misuse or diversion.

Baclofen

Baclofen is a selective gamma-aminobutyric acid-B (GABA-B) receptor agonist; see de Beaurepaire et al., 2019, for review.[45] Baclofen has been used to

treat muscle spasticity, secondary to neurological conditions. It has been hypothesized that the pharmacotherapeutic action of baclofen in AUD may be to suppress the ventral tegmental area (VTA) dopamine system and blunt reinforcement, serving to reduce drinking and thereby breaking the cycle of binge intoxication (see Figure 1). Initial reports were positive in 39 male participants with AUD, showing that treatment with baclofen 30 mg/d increased the percentage of individuals who achieved and maintained abstinence as well as the number of abstinent days, and decreased the number of drinks per drinking day as well as anxiety levels.[46] However, these results have not been consistently observed in subsequent studies.[45] In addition, the use of baclofen remains controversial, in part because of uncertainty regarding dosing and efficacy, along with concerns about safety. Individuals should be told to avoid drinking while taking the drug as the sedative properties of both drugs may potentiate each other. Individuals should not drive motor vehicles or operate heavy machinery until they have ascertained that the drug does not affect their performance. Individuals also should be advised of the risk of overdose. Side effects range in severity, from nonsevere to more dangerous types, including seizures, respiratory depression with sleep apnea and potentially coma (in case of intoxication), severe mood disorders (mania or depression, with the risk of suicide), and mental confusion or delirium. Baclofen is mostly (~ 80%) eliminated from systemic circulation by renal excretion as unchanged drug. Therefore, baseline and repeated tests of renal function are recommended given that renal problems can lead to an accumulation of baclofen, which may result in mental confusion. Baclofen treatment should start and end slowly as there is a withdrawal syndrome associated with abrupt cessation of treatment; withdrawal symptoms may include confusion, agitation, seizures, and delirium and may be confused with alcohol withdrawal.[47] More research is needed to clarify the potential efficacy and safety of baclofen in AUD.

SEX DIFFERENCES IN AUD AND RESPONSE TO AUD PHARMACOTHERAPIES

To date, very few publications have examined sex differences in pharmacotherapies for AUD. This is surprising given that 5.6 million American women (~4%) met criteria for AUD in a recent survey by the Substance Abuse and Mental Health Services Administration.[48] Furthermore, it has been reported that women generally experience liver damage and other health problems after consuming less alcohol than men.[49,50] For example, among women, chronic consumption of more than two drinks per day is associated with increased risk of mortality, breast cancer, hypertension, stroke, and reproductive problems;[49] and binge drinking (e.g., consuming four or more drinks in a row) may incur increased risk of accident, rape, assault, and unprotected sex.[51] Given the significant disease burden of AUD in women, early intervention and effective treatment options are imperative.

There is a clear need for women to be represented in clinical trials of AUD, because sex may be associated with differential drug efficacy. The majority of clinical trials of disulfiram have been conducted primarily in men; women comprised less than 10% of all patients included in a recent meta-analysis.[25] A clear example of sex differences was reported in a pivotal multicenter trial for AUD where long-acting injectable naltrexone (Vivitrol) showed efficacy in men but not in women.[20] The reason for the sex difference in Vivitrol efficacy is not understood, as the pharmacokinetics of the drug do not differ between men and women. Additionally, oral naltrexone did not differ from placebo in the only trial exclusively studying women.[52]

Conversely, no sex differences were found in a sex-specific meta-analysis of individual records obtained from 1,317 women and 4,794 men who participated in 22 acamprosate clinical trials.[34] A significant effect of acamprosate relative to placebo on rates of abstinence and absence of heavy drinking was found in both men and women. The side effect and tolerability profile of acamprosate

was comparable to that of placebo and did not differ between women and men. Acamprosate was associated with significantly higher rates of treatment completion and medication compliance than placebo among both women and men.

Systematic evaluation of potential differences in drug metabolism due to race, ethnicity, or sex hormones, and of consequent effects on drug efficacy or safety, is essential for all medications to treat AUD, and clinical trials require adequate representation of women and individuals from diverse racial and ethnic backgrounds. An additional concern is that the prevalence of AUD is highest among women in the prime childbearing years (ages 18 to 29), with associated risk of fetal alcohol spectrum disorders.[53] Women with childbearing potential who do not use a reliable method of birth control or who are pregnant or lactating must be excluded from medication trials to avoid exposing the fetus or newborn to medication. There are no adequate and well-controlled studies of pharmacotherapies for AUD in pregnant women. Therefore, it is recommended that these medications not be used during pregnancy.

PHARMACOGENETIC AND PHARMACOMETABOLOMIC PREDICTORS OF RESPONSE

Pharmacogenetic and pharmacometabolomic predictors have the potential to inform clinical care by identifying individuals likely to respond to or have significant side effects to a specific medication, thereby personalizing AUD treatment. For example, a number of pharmacogenetic studies have focused on the moderating effects of a variant in the mu-opioid receptor gene OPRM1 on response to naltrexone. However, a comprehensive review of the literature concluded that inconsistent findings across studies and a lack of translation of findings from human laboratory studies to clinical trials do not yet support this application of pharmacogenetics in AUD clinical practice.[54]

Recent studies using pharmacometabolomics offer insights into optimizing acamprosate treatment. For example, elevated baseline serum glutamate was found to be a biomarker of response to acamprosate in alcohol-dependent patients,[55] with responders showing significantly higher baseline serum glutamate levels. Interestingly, this study reported that serum glutamate levels of responders were normalized after acamprosate treatment, whereas there was no significant glutamate change in nonresponders; this provides further support for the hypothesis that acamprosate works to restore homeostasis in the brain glutamate system. By developing such predictors, it may be possible to improve patient treatment matching and the overall success rate of acamprosate—and, to that end, any pharmacotherapy used in the treatment of AUD.

CONCLUDING REMARKS AND FUTURE DIRECTIONS

The recent surge in understanding of the neurocircuitry and neuropharmacological mechanisms that are involved in AUD have provided abundant targets for future medication development for treating AUD.[31] However, most previous work on medications has focused on blocking the rewarding effects of drugs in the binge intoxication stage of the AUD cycle. A clear role for drug targets in the protracted withdrawal phase is indicated by persisting negative emotional states that drive drinking relapse, such as anxiety, dysphoria, irritability, and insomnia (see Figure 1). To this end, medication development for AUD can benefit from the use of a framework for stages of the AUD cycle that is linked to neurocircuitry and that includes protracted withdrawal/negative affect.[56] Indeed, dysregulation in the brain reward and stress systems that results in the symptoms associated with the protracted withdrawal/negative affect and preoccupation/anticipation stages of the AUD cycle is a neglected focus for AUD drug development. Both repurposed drugs (e.g., gabapentin and mifepristone, a glucocorticoid receptor antagonist)[57] and new molecular entities (e.g., a vasopressin V1b receptor antagonist)[58] are all selective for restoring homeostasis in brain stress systems that drive symptoms of protracted withdrawal, and they show promise as emerging new treatments for AUD.

Medications can help restore normal brain functioning, reduce relapse risk, and decrease symptoms of protracted withdrawal (e.g., craving, mood, sleep disturbance), thereby facilitating better engagement in behavioral treatment. Behavioral therapies, in turn, enhance pharmacotherapy response by modifying attitudes and behaviors related to alcohol, increasing healthy life skills, and helping people to stay engaged in recovery.

The Alcohol Treatment Navigator website (https://alcoholtreatment.niaaa.nih.gov) was created by the National Institute on Alcohol Abuse and Alcoholism to assist individuals in locating clinicians who provide evidence-based behavioral and/or pharmacological treatments for AUD. Combining evidence-based pharmacological and behavioral treatments for AUD may increase the likelihood of individuals with AUD meeting their goals for recovery.

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The Role of the Family in Alcohol Use Disorder Recovery for Adults

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Alcohol use disorder (AUD) and family functioning are inextricably bound, and families are impacted negatively by AUD, but families show substantial improvements with AUD recovery. Family members can successfully motivate a person with AUD to initiate changes in drinking or to seek AUD treatment. During recovery, family members can provide active support for recovery. Several couple- or family-involved treatments for AUD have been developed and tested in rigorous efficacy trials. Efficacious treatments based in family systems theory or cognitive behavioral approaches focus on the concerned family member alone, or they engage the couple or family as a unit in the treatment. However, most treatments have been studied in fairly homogeneous, heterosexual, White, non-Hispanic populations, limiting the potential generalizability of these treatments. Substantial gaps remain in our understanding of family processes associated with the initiation and maintenance of AUD recovery among adults. This review outlines the existing literature and describes opportunities for future research to address knowledge gaps in understanding the mechanisms by which these treatments are efficacious, use of family-based treatments with diverse populations, integration of pharmacotherapies with family-involved treatment, role of families in recovery-oriented systems of care, and how to improve treatment development and dissemination.

KEY WORDS: alcohol; adult; alcohol treatment; couples; family therapy; recovery

It is almost axiomatic that alcohol use disorder (AUD) and the family are inextricably bound. AUD harms individual family members and the functioning of the family as a whole, and family members' actions may exacerbate problematic drinking. Conversely, families play a key role in recovery from AUD, and recovery has a positive impact on family members and family functioning. Scientific research to understand the interrelationships between drinking and family functioning began in the early 1900s, and treatment models that address both drinking and family functioning have been developed and tested for close to 75 years. This article reviews the conceptual and empirical literature on the impact of AUD on families, the role of the family in recovery from AUD, the role of family-involved treatment in fostering recovery, and issues related to specific populations. The review concludes with suggested future directions for research. When discussing families, we are using the term broadly to refer to a broad range of kinship relationships. When discussing couples, we are referring to couples in intimate relationships regardless of marital or co-habiting status, and using the term "partner" to refer to either individual in the intimate relationship. However, where research findings apply to a more limited group (e.g., spouse versus partner) we use the correct term to delimit the population studied. Given the limitations of current research findings, we are referring to different-sex couples unless otherwise specified.

THE IMPACT OF AUD ON FAMILIES

AUD affects the functioning of families: Family members take on additional household and childcare responsibilities, social events are disrupted, and families may experience significant financial difficulties.[1] Individual members of these families suffer as well. Spouses and children of adults with AUD or other substance use disorder (SUD). experience psychological distress as well as health and behavioral problems. For example, women with a male partner who has AUD and is actively drinking reported elevated levels of depression, anxiety and psychosomatic complaints, and disruptions to work and social/leisure activities, and they utilize more health care resources.[2-4] Similarly, children who have a parent with AUD experience a variety of psychological, behavioral, and school problems.[5,6]

Research also has demonstrated a reciprocal relationship between drinking, AUD, and the quality of intimate relationships. For example, longitudinal studies of engaged different-sex couples have found that the husband's drinking prior to marriage is a strong predictor of the wife's drinking a year into marriage,[7] that the female partner's drinking influences the male partner's drinking in the next year,[8] and that relationship distress and AUD are strongly related.[9] A recent meta-analysis of 17 studies (N = 10,553 couples) focused on different-sex couples found that partners influence one another's drinking, although the magnitude of effects was modest. The extent to which women influenced men's drinking ($\beta = .19$) was slightly greater than the extent to which men influenced women's drinking ($\beta = .12$).[8] Results from clinical and nonclinical samples also reveal a close association between heavy drinking and the perpetration of intimate partner violence.[10] Couples with at least one partner with AUD have high rates of intimate partner violence, regardless of the sex of the partner with AUD,[11] and drinking is common during episodes of interpersonal violence.[12] Most typically, interpersonal violence is bidirectional in these couples.

Orford and his colleagues have proposed that the functioning of family members of those with AUD is best understood within a stress-strain-coping-support (SSCS) framework.[13] The SSCS model assumes that living with a family member with AUD is a stressful circumstance, putting family members at risk of a variety of psychological and physical health problems. Within this model, families are seen as engaging in a variety of behaviors to cope with this chronic stressor, some of which are more effective in helping families to cope with and to influence the drinker's behavior, and others that are less effective. The SSCS framework has informed much of contemporary research on AUD and the family.

THE ROLE OF THE FAMILY IN RECOVERY FROM AUD

There are strong connections between family functioning and drinking outcomes. Family behaviors can contribute to changes in drinking, and, conversely, changes in drinking can contribute to more positive family functioning. For example, in early studies, Moos and colleagues examined the longitudinal course of functioning in families of men receiving treatment for AUD. At 2-year follow-up, they compared family functioning for men who were in recovery to men who had relapsed. Wives of men in recovery, compared to wives of men who relapsed, drank less, were less depressed and anxious, had fewer negative life events, and had higher family incomes.[14] Similarly, the children of the men in recovery showed fewer symptoms of emotional distress.[15] As a whole, families of men in recovery had greater family cohesion, greater expressiveness, a higher orientation toward recreational activities, and greater agreement in how they viewed the overall environment of their families, compared to families of men who had relapsed.[16] These studies highlight the positive impact of recovery on families.

Families may play a key role in fostering the initiation of recovery. Although popular literature and 12-step mutual help groups for families, such as Al-Anon (https://al-anon.org/), emphasize detachment for family members and empirically supported interventions for families, such as Community Reinforcement and Family Training (CRAFT),[17] it has been found that family behavior can increase the probability that an individual will seek help for AUD.[18] Key family behaviors that support the initiation of change include ignoring behaviors associated with using alcohol or drugs, reinforcing positive or desirable behaviors related to sobriety or help-seeking, allowing the drinker to experience the naturally occurring negative consequences of drinking, and making specific and positive requests for changes in behavior related to drinking, such as reducing consumption or seeking help.[17]

Families and other members of the social network of persons with AUD also play an important role in supporting successful changes in drinking.[19] Although the scientific literature is limited on specific family behaviors that facilitate and support successful recovery from AUD, there is evidence that active partner coping predicts positive outcomes. Specific types of active partner coping that support successful change include (a) decreasing negative or controlling behaviors that serve as antecedents to drinking; (b) increasing supportive and problem-solving communication; (c) reinforcing positive behavior change by the partner with an alcohol problem; (d) increasing shared positive activities; and (e) reducing family member drinking behavior to support changes in the drinking of the person with AUD.[20]

Families also may make recovery more difficult. For example, individuals with AUD perceive relationship problems as significant relapse precipitants,[21] and believing that one's partner also has AUD predicts poorer drinking outcomes compared to individuals who did not believe that their partners have AUD.[22] Specific family behaviors associated with relapse include negative attitudes, emotional responding, and low levels of distress tolerance.[19]

THE ROLE OF FAMILY-INVOLVED TREATMENT IN FOSTERING RECOVERY

Knowledge of the impact of AUD on families has led to the development of family-engaged treatments. Considerable research has focused on the development and testing of these family-engaged treatments to foster recovery from AUD. These treatments have focused on the role of the family in the initiation of help seeking, initiation of change, and maintenance of long-term change. The following sections describe and review treatments for affected family members in their own right, and as a way to help effect change in the identified individual with AUD. This is then followed by a review of the array of interventions influenced by cognitive behavioral therapy (CBT) and family systems models. Table 1 provides a summary of key elements in each of the treatments reviewed.

Table 1 Family Interventions for AUD

Intervention	Number of Sessions	Target Population	Key Interventions
5-Step Method[23]	Variable/ as needed	Family members	Explore sources of stress/strain Provide psychoeducation Identify ways of coping Identify social supports Address other family needs
Community Reinforcement and Family Training (CRAFT)[17]	12 or more	Family members	Decrease behaviors protecting from negative consequences Increase self-care Increase positive responses to changes in drinking Enhance self-care Protect from domestic violence Enhance communication skills
A Relational Intervention Sequence for Engagement (ARISE)[24]	3 or more	Family members	Level 1: telephone coaching to invite person with AUD to a meeting Level 2: face-to-face coaching with family Level 3: coaching family to set limits and consequences
Significant Other engagement in Motivational Interviewing (SOMI)[26]	1	Couples	Single session of motivational interviewing Partner skills to enhance motivation to change drinking Partner skills to support drinking reductions
Alcohol Behavioral Couple Therapy (ABCT)[20]	12 (weekly)	Couples	Cognitive behavioral therapy interventions to change drinking Partner skills to support change Partner skills to decrease antecedents to drinking Couple skills to manage drinking situations Enhance positive couple interactions Enhance couple communication skills
Behavioral Couples Therapy (BCT)[31]	12–20 (weekly)	Couples	Implement daily recovery contract Enhance positive couple interactions Enhance couple communication skills
Brief Family-Involved Treatment (B-FIT)[41]	3 (weekly)	Family member and person with AUD	Increase positive interactions Implement recovery contract Enhance family communication skills
Brief Strategic Family Therapy (BSFT)[43]	12–16 (weekly)	Whole families	Influence maladaptive family interactions, alliances, and boundaries Decrease scapegoating
Multidimensional Family Therapy (MDFT)[44]	40–48 (twice weekly for 5 to 6 months)	Whole families	Develop multiple therapeutic alliances Restructure family functioning
Multisystemic Therapy (MST)[45]	Approximately 20	Whole families; youth involved with juvenile justice system	Individual treatment Family intervention School-based intervention Peer-based intervention Community-based intervention

Treatments for Affected Family Members

The 5-Step Method, a systematic intervention based on the SSCS model, is designed to help families cope more effectively with the AUD of a family member. The focus of the intervention is on the families in their own right, rather than on the relationship between family behaviors and outcomes for the person with AUD. The 5-Step Method helps families explore sources of stress and strain in their lives, provides psychoeducation about the SSCS model, helps them identify effective ways of coping with these sources of stress, assists them in identifying sources of social support for themselves, and assists with other needs that family members might have. The 5-Step Method has been tested with families in primary care as well as specialty care settings, with results supporting the effectiveness of the approach in reducing family-related harm in terms of both physical and psychological symptoms.[23]

Two treatments focus on providing family members with skills to help a family member to seek AUD treatment. CRAFT helps concerned family members to change contingencies for drinking by decreasing behaviors that protect the drinker from naturally occurring consequences of drinking, increasing positive family responses to changes in drinking, learning self-care and protection from intimate partner violence, and learning how to communicate positive requests for change and/or help seeking.[17] Compared to Al-Anon, CRAFT results in significantly greater rates of help seeking, and comparable rates of improvement in family members' depression and anxiety. The ARISE method (A Relational Intervention Sequence for Engagement) provides a series of steps that family members may use to encourage their loved one to seek treatment; ARISE also is effective in encouraging persons with AUD to seek treatment.[24] In addition to treatments for the affected family member alone, there are several treatment models and approaches that involve both the affected family members and the individual with AUD. Treatments with strong empirical support have drawn largely from cognitive behavioral and family systems concepts; the following sections review these approaches.

Cognitive Behavioral Approaches

Cognitive behavioral therapy (CBT) approaches view alcohol use as a learned behavior, cued by environmental stimuli and maintained by the positive consequences of alcohol use. Family-engaged CBT approaches view family behaviors as potential cues for drinking, as providing positive consequences of drinking, and as having the potential to provide positive consequences for changes in drinking behavior.

Adding partner-assisted components to individual treatment might involve partners assisting the person with AUD with accurate self-monitoring of alcohol intake and contributing to functional analysis of drinking patterns to help identify high-risk situations in which craving and alcohol consumption are likely to present a challenge. Psychoeducation is also common to help the partner more clearly understand the treatment needs and program of recovery for the person with AUD. Partner involvement might provide additional benefits such as helping the partner without AUD to develop new skills to reinforce changes in drinking and minimize behaviors that might contribute to maladaptive couple and family interactions. One recent study exemplifying this approach found support for integrating romantic partners into individual motivational interviewing interventions to improve individual AUD outcomes.[25,26]

Several manual-guided conjoint couple therapies incorporate cognitive behavioral techniques that have proven useful in individual treatments along with couple-focused interventions. One such modality with strong empirical support for both men and women with AUD is Alcohol Behavioral Couple Therapy (ABCT).[20] ABCT is a 12-week, cognitive behavioral treatment that has demonstrated efficacy in reducing alcohol consumption, enhancing relationship functioning, and improving partners' skills to facilitate reductions in drinking.[27] Core components of ABCT include (a) CBT interventions to help the person with AUD change his or her drinking,

(b) psychoeducation for the intimate partner to learn how to support changes in the behavior of their partner with AUD and to decrease behaviors that might serve as triggers for drinking, (c) interventions to teach the couple how to deal more effectively with drinking situations and drinking urges, (d) behavioral couple therapy interventions to increase positive interactions and improve communication skills, and (e) couple-focused relapse prevention. Figure 1 summarizes the hypothesized mechanisms by which ABCT impacts drinking outcomes. Recent ABCT literature indicates a strong association between partner participation in treatment and AUD outcomes. Reductions in drinking have been associated with increases in partner coping, conflict resolution skills, relationship satisfaction, and support behaviors.[28] Greater relationship quality before treatment predicted abstinence and alcohol consumption posttreatment.[29] Greater relationship satisfaction also is associated with fewer drinking urges and greater reduction in drinking urges during ABCT.[30] One notable strength of ABCT is that it results in positive outcomes for couples presenting with poor relationship functioning and high levels of psychiatric comorbidity, and it is equipped to treat couples in which one or both partners have AUD.[27]

A second well-researched approach to couple-involved therapy is behavioral couples therapy (BCT) for AUD and other SUD.[31] BCT is a 12- to 20-session intervention that lasts 3 to 6 months. The core components of BCT include (a) a daily "recovery contract" to encourage abstinence from substance use, (b) interventions to increase positive couple behaviors, and (c) training in behavioral communication skills. Participants with SUD also complete weekly urine drug screens, and progress is monitored in a calendar-assisted approach (similar to the Timeline Follow-Back procedure).[32]

Like ABCT, BCT is suitable to implement alongside 12-step groups such as Alcoholics Anonymous (https://aa.org/) and individual AUD treatments. Data from randomized controlled trials suggest that BCT has excellent feasibility, participant acceptability, and efficacy.[33,34,35]

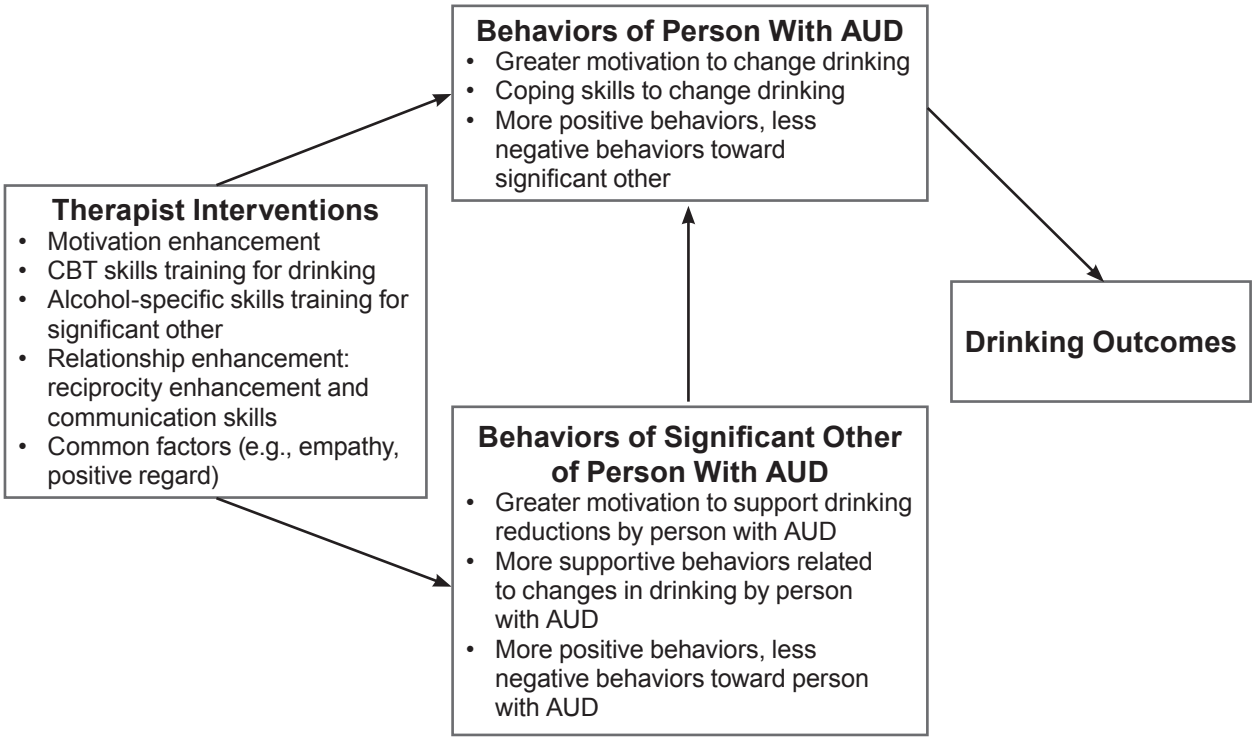

Figure 1 Hypothesized mechanisms of change in Alcohol Behavioral Couple Therapy. *Note:* AUD, alcohol use disorder; CBT, cognitive behavioral therapy.

BCT also has the ability to reduce maladaptive couple conflict behaviors such as intimate partner violence[36] and has been tested for use among military veterans with positive outcomes[37] and with couples in which both partners have AUD.[38] However, findings from one recent trial indicate that a group adaptation to BCT to treat multiple couples simultaneously did not perform as well as when couples were treated separately.[39]

Brief family-involved treatment (B-FIT) is a three-session intervention that aims to improve family functioning, increase family-related incentives associated with reduced alcohol consumption, and implement proven techniques for family treatment of AUD to achieve and maintain long-term abstinence.[40] Specifically, B-FIT incorporates adaptations such as (a) involving any concerned family member rather than romantic partners only, (b) implementation within a patient's multifaceted program of recovery, (c) targeting the key components of ABCT in an accelerated manner, and (d) leveraging behavioral contracting techniques to increase treatment efficiency.[41] B-FIT was recently examined in a pilot randomized controlled trial ($N = 35$ couples) with promising outcomes.[42]

Family Systems Approaches

Treatment models based in family systems theory assume that the actions of individual family members affect all other members of the family, and that families have typical and repetitive ways of interacting that maintain dysfunctional behavior patterns of the family as a whole and of individuals within the family. Thus, these models focus on change in the structure and functioning of the family to effect change in dysfunctional behaviors, such as alcohol or drug use, in individual family members. Three major approaches in family systems therapy have evidence supporting their efficacy and should be noted, although most of the controlled trials of these treatments have been conducted primarily with adolescents with AUD or other SUD.

Brief strategic family therapy (BSFT) combines interventions from structural and strategic family therapies and assumes that substance use as well as other behavioral problems are symptoms of family dysfunction. Thus, the treatment focuses on influencing maladaptive patterns of family interaction, alliances, boundaries, and scapegoating of individual family members. Data reported from multiple studies support that BSFT is efficacious in decreasing adolescent substance use a year after treatment, that changes in family functioning mediate the relationship between BSFT and outcomes, and that parents receiving BSFT also decreased their drinking after treatment.[43]

Multidimensional family therapy (MDFT) views adolescent problems as multidimensional and addresses factors on multiple levels (i.e., individual, family, environment) that may be contributing to the adolescent's problem behaviors. The treatment involves establishing multiple relationships between the therapist and the adolescent, family, and other systems, and it uses a range of interventions to restructure family and individual functioning. Data suggest that MDFT is more effective than comparison treatments,[43] although it is more costly to deliver. However, when the associated costs of delinquency are considered, the cost-effectiveness of MDFT is comparable to cognitive behavioral interventions.[44]

Multisystemic therapy (MST), developed as a family intervention for youth involved with the juvenile justice system, intervenes in multiple systems, including the individual, family, school, peer, and community. The primary focus of MST has been on antisocial behaviors, but data also suggest that, compared to community treatment as usual, MST leads to positive substance use outcomes.[43] Combined with interventions to strengthen families with parental AUD and child maltreatment, MST has been found to decrease child negative symptoms, parental substance abuse, and instances of child maltreatment.[45]

Summary of Family-Involved Treatments

Efficacious treatments drawn from cognitive behavioral and family systems theories have been developed both for family members alone and for

family members together with the individual with AUD. Most controlled trials of these treatments have compared either the family-involved treatment to treatment without the family member, or variations on the specific treatment (e.g., ABCT with or without involvement in Alcoholics Anonymous). Thus, the research literature to date does not provide guidance to clinicians about selecting a treatment from among those with empirical support.

SPECIFIC POPULATIONS

A great deal has been learned to date regarding efficacious family and couple treatment models. However, the empirical literature is also clear that AUD is a condition characterized by a great deal of heterogeneity in etiology, course, and factors influencing treatment outcomes. The following section describes treatment considerations for populations that might require tailored treatment considerations and adaptations to optimize outcomes.

Military and Veteran Families

Rates of hazardous and harmful alcohol use and AUD are high among active duty military and veteran populations. Compared to age- and sex-matched civilian samples, both women and men in active duty and veteran populations consume alcohol more frequently and heavily as well as incur a nearly fivefold greater risk for experiencing harmful alcohol-related health outcomes and developing AUD. Toward the goal of improving the health of the U.S. armed forces, their partners, and their families, emerging research has examined existing or adapted behavioral treatment approaches to determine their appropriateness in military and veteran populations, including couple therapy and treatment for families of veterans with AUD. For example, one recent open-label trial examined an adaptation of ABCT for returning military veterans ($N = 44$ couples).[46] This study utilized a 15-session format and incorporated relevant topics for combat veterans, including intimate partner violence, depression, post-traumatic stress disorder (PTSD), and traumatic brain injury, which are all known to co-occur at high rates with heavy drinking and to affect military populations disproportionately. Similarly, BCT has demonstrated efficacy among veterans with AUD and co-occurring PTSD. More recently, a novel integrated approach that combines BCT with Cognitive Behavioral Couples Therapy for PTSD (Couple Treatment for AUD and PTSD) has shown promise in a preliminary open-label pilot study ($N = 13$ couples).[37] Given that military culture places heavy emphasis on marriage and family, this population is ripe with opportunities to advance dyadic alcohol research to better understand how veteran and active duty families cope with and encourage recovery from AUD, and how the family as a whole changes as the person with AUD recovers. In addition, more attention is needed to address the unique challenges to implementing dyadic treatment in active duty and veteran treatment settings (e.g., frequent relocations, extended deployments).

Women

Women with AUD experience different challenges than men with AUD in general and particularly in terms of intimate relationships. Data from longitudinal research suggest that husbands' drinking patterns prior to marriage strongly predict women's drinking in the first year of marriage, and male partners of women with AUD are more likely than wives of men with AUD to have AUD as well.[47] Women with AUD see relationship problems and the male partner's drinking as important antecedents to relapse, and they use alcohol to cope with relationship problems. Male partners of women with AUD tend to avoid confrontation as a way to cope with the woman's drinking.[48]

The efficacy of ABCT and BCT has been tested with women with AUD and their male partners.[47,49,50] In all three studies, ABCT or BCT led to better alcohol use outcomes for the women compared to the control condition. McCrady and colleagues also found that women who entered treatment with higher levels of relationship distress and women who presented with another clinical and personality disorders had greater improvements in drinking with BCT than individual therapy.[47]

However, if given the choice, women with AUD prefer individual rather than conjoint therapy, citing as reasons their desire to work on individual problems, their perception of a lack of support from their partner, and logistical challenges to attending treatment together.[51]

Racial and Ethnic Minority Populations

Race and ethnicity play a significant role in family and couple relationship structure and functioning for many persons with AUD, thereby influencing the complex role of the family in AUD treatment seeking and recovery trajectories. To develop the knowledge base regarding the mechanisms by which race and ethnicity influence AUD recovery in families, dyadic AUD research must improve diversity within samples and must focus on treatment development adaptations for specific diverse populations. The existing literature demonstrates that substantial differences exist in alcohol consumption patterns, etiology, and risk factors associated with developing AUD as well as treatment engagement and outcomes in different racial and ethnic groups.[52] Racially and ethnically diverse minority populations are persistently underrepresented as participants in randomized controlled trials focused on alcohol use. AUD research on families and couples faces a similar constraint that currently limits the generalizability of current findings.

Cultural constructs and institutional marginalization are likely to impact AUD recovery among racial and ethnic minority groups in varying ways. Furthermore, the complex intersectionality of various cultural and institutional factors is likely to influence drinking and recovery. Among other factors, gender roles, socioeconomic status, health care access, employment status, immigration status, involvement with the criminal justice system, religion, and language barriers are likely to manifest in separate but overlapping ways among families who belong to racial and ethnic minority groups.[53,54] Some research suggests that acculturation and "traditional" family structures more often identified in non-White, non-Hispanic families might prevent the onset of AUD and facilitate effective treatment seeking and change in racial and ethnic minority groups.[52,55] Conversely, stigma and cultural beliefs related to AUD and help seeking, as well as couple and family therapy specifically, might negatively influence AUD recovery processes for some members of racial and ethnic minority groups. However, these mechanisms have not been well tested in the context of couple or family treatment for AUD.

Socioeconomic Status

Socioeconomic status (SES) is defined by many variables, including educational access and level, occupational status, housing access, neighborhood factors, and income.[56] Although AUD occurs among individuals and families from all socioeconomic backgrounds, the direct association between socioeconomic status, AUD, and alcohol-related harms is complex.[57] However, research indicates that families with lower SES (based on factors such as income and educational level) might incur increased negative physical and mental health sequelae of AUD, encounter barriers to accessing treatment, and confront more barriers to successful treatment outcomes, compared to families with higher SES.[53,54,57,58] Minimal research has been conducted regarding socioeconomic barriers to accessing couple therapy for AUD specifically; thus, research is necessary to identify potential socioeconomic disparities and pathways to mitigating them. One study of access to general couple therapy was conducted among couples living in neighborhoods with at least 30% of households below the poverty threshold. Results showed that when couples in this sample obtained access to treatment, they utilized couple therapy services and derived positive gains.[59] Thus, research is needed to better understand AUD recovery among families with different socioeconomic advantages or disadvantages. Studies investigating effective methods to increase access to low-cost treatment options—including those with technological adaptations to increase treatment availability—are warranted. Leveraging existing study data and using qualitative data collection techniques to identify barriers and methods to overcoming barriers are also needed.

Sexual and Gender Minority Populations

Individuals identifying as sexual and gender minorities are more likely to consume alcohol and have higher rates of AUD than individuals identifying as heterosexual.[60] Some accruing research suggests connections between alcohol use, AUD, and relationship functioning in this population. For example, in same-sex male couples, poorer relationship functioning appears related to higher rates of alcohol problems;[60] in same-sex female couples, higher levels of verbal aggression and physical violence are associated with higher levels of alcohol use;[61] and differences in alcohol use in same-sex female couples are associated with poorer relationship functioning (e.g., poor conflict resolution, poor satisfaction).[62] However, research on intimate or family relationships and recovery in sexual minority groups is very limited. One qualitative study of gay men in recovery examined familial and other social network influences on recovery.[63] Family and other social network factors cited as important to their recovery included acceptance of their sexual orientation and a sense of social connectedness. Conversely, although the men indicated that they continued to look to their families for support, many continued to experience family rejection of their sexual orientation and perceived this as a stressor that made recovery more difficult.

Engaging Communities in AUD Treatment

A crucial shift emerging in the AUD treatment community is the recognition that treatment approaches need to be adapted to accommodate families from diverse backgrounds, rather than expecting individuals and families to adapt to current treatment methods. To achieve this goal, research is needed on how to modify current approaches to reduce pervasive barriers to identification of AUD, how to develop evidence-supported approaches to treatment access and engagement relevant to diverse populations, and how to include diverse communities in the scientific process (as both participants and investigators). Increasing partnerships between research and AUD provider teams with health systems and community representatives serving racial and ethnic minority families, families with limited economic resources, and sexual minority populations might reveal pathways to achieve this goal. Community-based participatory research is an approach that provides one framework for developing research through true community partnerships.[64]

FUTURE DIRECTIONS FOR RESEARCH

During the past several decades, the empirical literature has expanded significantly to develop a critical foundation of knowledge and advance the implementation of family and couples-based approaches to AUD treatment. This section reviews promising areas for future research to further advance the state of the science in this area and to inform clinical best practices to optimize the AUD recovery process by incorporating family members.

Understanding Couple and Family Support in Recovery

Data are limited on the role of couple and family support in AUD recovery processes outside of treatment; most of our knowledge to date has come from clinical trials of specific couple- or family-involved treatments or from studies using patients in treatment programs. A related question that warrants attention in the literature is learning about the circumstances under which partners and family members are well suited versus possibly inappropriate for conjoint therapies. Clinical guidelines for couple therapy for AUD suggest that conjoint therapy should not be attempted for couples with intimate partner violence that has resulted in physical harm or fear of retaliation or for couples in which one partner is planning to leave the relationship.[20] Gaining a clearer understanding of the specific couple and family behaviors that support or are detrimental in AUD recovery, as well as the mechanisms by which these behaviors influence

AUD recovery, is crucial to improve alcohol prevention and treatment efforts. For example, studies examining family-specific interactive behaviors that increase or mitigate known precipitants to drinking and relapse risk, such as heightened craving, are warranted. Similarly, this literature can be improved by examining thoughts, behaviors, and emotions that acutely predict both positive and negative AUD treatment outcomes, including those that occur within and between treatment sessions.

Exploring Partner and Family Integration in Recovery-Oriented Systems of Care

Although the majority of the current review has focused on manual-guided and single-episode treatment approaches, it is widely recognized that more integrated and sustainable resources often are warranted to initiate and maintain AUD recovery across populations. During the last two decades, research focused on recovery-oriented systems of care (ROSC) has demonstrated positive findings.[65-69] ROSC is defined as "networks of organizations, agencies, and community members that coordinate a wide spectrum of services to prevent, intervene in, and treat substance use problems and disorder."[65] Identifying pathways to integrate partners and family members, where appropriate, into ROSC models holds promise, but has not been investigated thoroughly. Future research directed at examining facilitators and barriers—at the patient, provider, and system levels—to inviting family members into AUD treatment under this model is necessary. For example, some individuals engaged in ROSC might be facing obstacles such as homelessness or incarceration that might make it more challenging to identify and engage a supportive peer, partner, or family member. Under these circumstances, an adjunctive approach to developing or strengthening nonfamilial social support relationships could be explored. It also is possible that improved training in existing couple and family theory and treatment modalities could facilitate greater accessibility and treatment outcomes.

Role of Partners and Family in AUD Resilience

The existing literature can be improved by developing a better understanding of couple- and family-level factors promoting AUD resilience, with a particular focus on individuals, couples, and families who choose to change their drinking behaviors without engaging formal treatment resources. Recent literature has begun to expand the knowledge base regarding individual-level behavioral and neurobiological factors associated with greater likelihood of sustained recovery. However, less research has focused on the specific roles of partner and family members in changing drinking behaviors, neurobiological functioning associated with recovery-related cognitions and behaviors, and recovery when formal treatments are not engaged.[70-72] Extending this area of the literature might be particularly useful for diverse populations with disproportionate risk for developing AUD or disparities and barriers to accessing formal or traditional AUD treatment resources.[73,74]

Specific Populations

Couples and families from diverse backgrounds differ in their values, the structure and functioning of the families, gender roles within these relationships, how family members influence and support each other, and the role of alcohol use and AUD in the family. Although awareness of diversity in family functioning among different racial and ethnic groups, socioeconomically challenged populations, sexual and gender minorities, and veteran populations is increasing, the specific associations between alcohol use, AUD, family functioning, and AUD recovery have not been studied. Future research needs to focus on developing a more nuanced understanding of family structure and function around AUD in diverse populations to develop effective family-engaged treatments and dissemination of knowledge of effective practices to support recovery for these populations.

Expanding Couple and Family Treatment for AUD

Technology

One new direction for dyadic AUD treatment is the integration of existing and emerging modalities with electronic and technologically based adaptations (e.g., smartphone/online access, e-health [electronic health], m-health [mobile health]). Such adaptations hold promise to facilitate treatment access and engagement, enable accuracy in assessment, reduce participant burden, and streamline delivery of treatment content.

Among individual participants, technology-assisted and fully technology-based interventions are rapidly proliferating in the alcohol field. Technology-based approaches have proven utility to inform novel treatment development efforts, and they focus existing interventions on key components that are most likely to yield significant impacts on alcohol-related cognitions and behavior. Studies conducted among individuals consistently find that technology-assisted modalities are highly feasible and acceptable among participants. They show promise to increase participant access, engagement, and outcomes; to improve reach and cost-effectiveness; and ultimately to provide a viable AUD treatment option for individuals in a variety of populations.[75,76] An emerging body of literature is examining technology-based, e-health, or mobile interventions for couples with AUD. Findings from the limited emerging literature on technology-based couple interventions are encouraging. For example, one recent study tested a mobile support system to facilitate family communication among families affected by AUD ($N = 9$).[77] Another study examined the feasibility and acceptability of a novel, four-session, web-based AUD intervention for military and veteran couples ($N = 12$) with promising outcomes.[78] As remote telehealth (e.g., using telephone and/or videoconferencing) approaches are evolving in the AUD treatment field, an emerging literature suggests that telehealth implementation of couple and family therapy is also feasible and acceptable.[79] Recent research on a brief, in-person, home-based couple intervention found positive results for enhancing accessibility and efficacy.[80] Creating a home-based family telehealth intervention model of recovery has the potential to improve treatment access for individuals in AUD recovery and their partners and families.

A recently completed Small Business Innovation Research Phase 1 development project created a novel e-health intervention for families to reduce driving while intoxicated (DWI) and DWI recidivism.[81] The intervention, B-SMART, was designed to help reduce risk for DWI reoffending by leveraging environmental support (e.g., family support) known to reinforce and thus increase the likelihood of alcohol abstinence and simultaneously reduce harmful drinking outcomes. Participants ($N = 32$) were family members of individuals with a recent DWI arrest and an interlocking ignition device installed on their vehicle, who rated the useability of the smartphone app. A Small Business Technology Transfer Phase 2 grant is underway to develop additional intervention modules and to conduct a randomized trial of the efficacy of the intervention.[82] Overall, a great deal more research is needed to adapt existing dyadic AUD treatment modalities to incorporate technology such as mobile or online assessment monitoring, telehealth sessions, or self-guided online interventions.

Pharmacological treatment of AUD for couples and families

Combining pharmacological interventions with evidence-based behavioral treatments has the potential to optimize and sustain AUD treatment outcomes.[83-85] However, few studies have examined the role of pharmacological interventions in trials of conjoint or family treatments for AUD. Research aimed at examining the role of medication utilization and compliance in dyadic and family modalities is needed. More specifically, medication-enhanced psychotherapy for AUD, in which medications and behavioral interventions are designed to work synergistically within or between sessions, is a promising new direction for couples. As new medications for AUD are being developed specifically with the goal of

targeting brain stress and social reward systems (e.g., intervening in the withdrawal/negative affect and preoccupation/anticipation stages of AUD), medications to simultaneously maximize AUD outcomes and enhance relationship functioning could optimize AUD and relationship functioning outcomes among couples.[86-91] One such medication, intranasal oxytocin, is currently being examined among couples with AUD for that purpose.[92] Phase II trials of 3,4-methylenedioxymethamphetamine (MDMA) also are being conducted for a variety of psychiatric conditions, including among couples, and could hold promise to augment dyadic intervention for AUD.[93]

Neurobiological underpinnings of AUD

Current AUD research has a heavy emphasis on understanding the neurobiological and behavioral underpinnings of AUD and interactions between them. Such approaches have proven utility in novel treatment development efforts. However, advanced neurobiological measures and techniques, which have proven useful in treatment development efforts with individuals, have not yet been applied to couples. For example, clinically relevant AUD biomarkers are rarely examined in epidemiological or treatment research with couples. Similarly, although functional magnetic resonance neuroimaging is widely used in laboratory and treatment research in the alcohol field, there is a scarcity of literature examining resting state or task-related neural functioning in romantic couples. Some novel directions include hyperscanning, in which two participants are scanned simultaneously in response to shared stimuli, and adapting imaging paradigms to address relational behaviors relevant to AUD.[94,95] Preliminary evidence from a small sample of couples with relationship distress and substance misuse suggests that intimate partner violence in the relationship might exacerbate neural stress responses associated with couple conflict cues.[96] When applied to either mechanistic or treatment development efforts, this emerging line of literature might help to develop neural prognostic and diagnostic indicators of positive AUD treatment outcomes, risk for AUD relapse, and short- and long-term correlates of AUD relapse risk.

Another area of potential for future research is applying the existing literature on dyadic physiological and neuroendocrine co-regulation to the alcohol field, an effort that has begun but needs to be extended. Data collected from samples of couples experiencing relationship distress and who enrolled in treatment trials for problems other than AUD indicate that discordant dyadic autonomic dysregulation is associated with acute and more severe couple conflict,[97] whereas synchrony in autonomic functioning is indicative of constructive couple therapy processes such as working alliance and improved health outcomes.[98] As biofeedback intervention approaches continue to evolve in the AUD field, these emerging data can help to inform the development and refinement of remote and in-person dyadic biofeedback to support recovery efforts among families affected by AUD.

Involvement of partners and family members in AUD therapies in the context of co-occurring mental health conditions

Identifying pathways to successfully treat AUD and co-occurring conditions among individual participants remains an area of intense scientific inquiry. However, far less attention has been dedicated to understanding how partners and family members might contribute to adjunct or conjoint therapies. One preliminary pilot study found promising feasibility and acceptability outcomes when examining a novel integrated approach that combines BCT with Cognitive Behavioral Couples Therapy[99] for PTSD ($N = 13$ couples).[37] Research also suggests that ABCT is more efficacious than individual CBT for women with AUD and co-occurring clinical and personality disorders.[47] A great deal more research is needed to identify dyadic pathways to treating AUD and commonly co-occurring conditions such as PTSD and depression.

Dissemination and implementation

Despite the abundance of rigorously conducted studies and findings supporting the efficacy of

dyadic AUD treatment, evidence-based couple and family therapies are rarely applied in frontline treatment settings. Literature identifying barriers to provider uptake and patient utilization is also limited. The scant data available suggest that a lack of familiarity with modalities such as BCT among treatment providers and administrators of treatment clinics are among the most commonly cited challenges.[100] Additional challenges include (a) logistical and time-related barriers to scheduling sessions with both members of a couple; (b) a lack of clarity regarding insurance reimbursements available for couple therapies (and whether reimbursements are greater than for individual sessions); (c) lack of formal training in couples therapies for AUD; and (d) perceived increase in the difficulty of implementing dyadic treatment compared to treating individuals with AUD.[100] As a result, dissemination and implementation efforts are needed to identify more clearly provider and administrative barriers to uptake across various treatment settings (e.g., community clinics, Veterans Affairs clinics, academically affiliated clinics), to develop accessible provider education models, and ultimately to develop a more robust and diverse pipeline of capable and confident providers.

The majority of individuals with AUD who change successfully do so on their own, without any formal treatment.[101] As knowledge accrues about the most effective ways for families to motivate persons with AUD to change and to support change efforts, models to disseminate this knowledge in provider training programs and outside of treatment settings are needed. Community-based studies of these dissemination efforts also are needed to advance provider education and training efforts and to promote utilization of the full scope of couple and family treatments for AUD that are both available and efficacious.

Mechanisms of Treatment Response

Although efficacious couple and family treatments for AUD have been developed and tested, knowledge regarding behavioral mechanisms of action underlying treatment response largely remains untested. It is possible that both individual and relational mechanisms specific to family and couple interactions might facilitate improved treatment outcomes, maintenance of recovery programs and sobriety, and long-term health. Thus, studies examining the mechanisms of action underlying effective couple and family treatments for AUD—as well as secondary analyses of extant data sets and studies combining data sets from multiple randomized controlled trials—are warranted. One avenue to addressing this gap in the literature is the use of observational coding schemes to examine within-session behaviors indicative of treatment response. A recent study examined the association between pronoun utilization (i.e., "I" versus "we") within ABCT sessions and found that greater "we" language utilization was associated with greater alcohol abstinence at end of treatment and follow-up.[102] Recent analyses based on coding of within-session language in ABCT sessions have found that contemptuousness by individuals with AUD toward their partners predicts poorer drinking outcomes[103] and that within an ABCT treatment session there is a complex interaction among client and partner change language and positive and negative relationship behaviors.[104] This line of research can be expanded to further improve our understanding of within-session behaviors relevant to AUD recovery among couples and families, given that several reliable and valid observational coding systems (i.e., the Rapid Marital Interaction Coding System [RMICS]; System for Coding Couple Interaction in Therapy–Alcohol [SCCIT-A]) have been developed and are widely used among couples in laboratory settings.

One specific mechanistic aspect of this literature that has not been thoroughly explored is the role of specific conflict behaviors and dyadic processes (both adaptive and maladaptive) in influencing alcohol craving as well as risk for lapse and relapse in AUD. The daily process and micro-longitudinal research designs and methods that have proven essential to understand some individual and dyadic mechanisms linking alcohol with couple conflict behaviors, such as intimate partner violence, have not been extended to nonviolent dyadic processes and recovery-related cognitions

and behaviors. This literature could be advanced through innovative intersections of multi-method approaches that link laboratory, neurobiological, and naturalistic data, such as incorporating traditional clinical trial designs with micro-longitudinal and remote assessment methods. Such data might be used to inform novel and accessible adjunct interventions and tailored treatment modifications to insulate people with AUD and their families from high-risk situations.

Leveraging Representative Samples

Future large-scale and multisite studies examining nationally representative samples (such as the National Epidemiologic Survey on Alcohol and Related Conditions [NESARC] data set,[105] etiological processes (such as the Adolescent Brain Cognitive Development study [ABCD]),[106] and treatment development (such as the Combined Pharmacotherapies and Behavioral Interventions for Alcohol Dependence [COMBINE study])[107] have the ability to leverage rich infrastructures and diverse resources, often in a longitudinal fashion, to measure dyadic and family functioning using reliable and valid measures. To date, measurement of partner- and family-related variables has been limited in existing efforts. Increased collaboration between investigators and treatment providers with dyadic and family expertise pertaining to AUD is warranted in future integrated and large-scale efforts. As brief and empirically sound measurement approaches become more widely available, such collaborative efforts have the potential to reduce existing silos between fields of expertise within the AUD research community and ultimately to provide critical new information to drive the AUD field forward.

SUMMARY AND CONCLUSIONS

The existing literature suggests that families play a key role in motivating persons with AUD to recognize the need to change, providing support for change, and supporting long-term recovery and that AUD recovery is good for families. Most of our current knowledge, however, has come from studies of relatively small clinical samples or from treatment studies. The lack of community-based research, multisite randomized controlled trials, research on integration of partners and family members in recovery-oriented systems of care, conduct of AUD treatment-specific meta-analyses, and the exclusion of couple- and family-level variables in large-scale longitudinal studies of the onset and course of AUD remain important areas for future research. Similarly, the lack of research on the role of the family in AUD recovery in diverse populations is a major gap in the current literature.

The existing literature from treatment studies suggests that integrating partners and family members into AUD treatment is a highly effective way to maximize positive treatment outcomes and to facilitate long-term AUD recovery and health of individuals with AUD and their families. Several manual-guided approaches have proven efficacy, but efforts to improve provider education and increase uptake of evidence-supported couple- and family-based AUD treatment modalities are needed to improve access and maximize the reach of available interventions. Challenges also might emerge if social relationships are persistently strained, if it is not safe or appropriate to include partners and family members in these modalities, or if individuals with an alcohol problem are navigating additional challenges such as incarceration or homelessness that are likely to influence day-to-day social contact and implementation of currently available modalities. There is an abundance of new opportunities to integrate emerging novel scientific methods—such as multimodal, multidisciplinary assessment and intervention approaches—into research focused on couples and families with a family member with AUD. The literature also is clear that improved access to AUD treatments among diverse populations is needed. It is crucial to improve synergy between existing alcohol research and the treatment community as well as the vast population of individuals in need of AUD treatment and their partners and families. Progress toward meeting these goals can be facilitated through increased collaboration with community partners

to develop culturally informed modifications to research inclusion, AUD assessment, and intervention. Increased collaboration between investigators, administrators, and clinical providers to maximize existing federal funding investments in couple and family AUD treatment and recovery processes also holds potential to reduce treatment barriers and improve long-term outcomes for couples and families.

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Racial/Ethnic Disparities in Mutual Help Group Participation for Substance Use Problems

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Mutual help groups are a ubiquitous component of the substance abuse treatment system in the United States, showing demonstrated effectiveness as a treatment adjunct; so, it is paramount to understand whether they are as appealing to, and as effective for, racial or ethnic minority groups as they are for Whites. Nonetheless, no known comprehensive reviews have examined whether there are racial/ethnic disparities in mutual help group participation. Accordingly, this study comprehensively reviewed the U.S. literature on racial/ethnic disparities in mutual help participation among adults and adolescents with substance use disorder treatment need. The study identified 19 articles comparing mutual help participation across specific racial/ethnic minority groups and Whites, including eight national epidemiological studies and 11 treatment/community studies. Most compared Latinx and/or Black adults to White adults, and all but two analyzed 12-step participation, with others examining "self-help" attendance. Across studies, racial/ethnic comparisons yielded mostly null (*N* = 17) and mixed (*N* = 9) effects, though some findings were consistent with a racial/ethnic disparity (*N* = 6) or minority advantage (*N* = 3). Findings were weakly suggestive of disparities for Latinx populations (especially immigrants, women, and adolescents) as well as for Black women and adolescents. Overall, data were sparse, inconsistent, and dated, highlighting the need for additional studies in this area.

KEY WORDS: race/ethnicity; African American; Hispanic; Native American; mutual help; self-help; alcohol

INTRODUCTION

Racial/ethnic minority groups comprise a large proportion of the U.S. population and evidence a substantial need for treatment of substance use disorder (SUD). Analysis of the most recent, reliable data available—the 2018 National Survey on Drug Use and Health (NSDUH)[1]—found that the prevalence of past-year SUD among those age 12 and older was higher among some racial/ethnic minority groups than Whites. Compared to Whites (with a prevalence rate of 7.7%), the prevalence of past-year SUD was 31% higher among American Indians or Alaska Natives (10.1%), 21% higher among Native Hawaiians or Other Pacific Islanders (9.3%), and 16% higher among multiracial U.S. residents (8.9%). The prevalence rate for Whites was similar to those for Hispanic or Latino populations (7.1%) and Black or African American populations (6.9%). Prevalence among Asians was low overall (4.8%), though other studies suggest that substance use problems may be elevated in some ethnic subgroups (e.g., Koreans) and in Asian American young adults.[2-4] Parallel patterns emerged for alcohol and illicit drug use disorders, revealing elevated rates among American Indians or Alaska Natives, Native Hawaiians or Other Pacific Islanders, and multiracial respondents in both cases.

Participation in mutual help groups (also known as self-help groups), including 12-step groups such as Alcoholics Anonymous (AA), is an integral and nearly ubiquitous component of the U.S. SUD treatment system[5-7] and a typical constituent of mandated treatment.[8] Moreover, 12-step participation—in conjunction with specialty SUD treatment (i.e., formal SUD treatment, such as that delivered in outpatient or residential treatment programs)—is also highly effective in treating SUD for typical treatment populations overall.[9-14] Indeed, 12-step facilitation (TSF) interventions, which are designed to enhance involvement by (for example) explaining 12-step principles and culture, have repeatedly, if not universally, achieved better substance use outcomes than both usual treatment alone and gold standard treatments, such as cognitive behavioral therapy.[15] Emerging studies also have examined, and found support for, the effectiveness of abstinence-based, secular mutual help alternatives to the 12-step approach.[16-18] For instance, one recent study compared the effectiveness of 12-step groups and several abstinence-based alternatives—namely, Women for Sobriety, Self-Management and Recovery Training (SMART Recovery), and LifeRing Secular Recovery (LifeRing)—among current attendees with alcohol use disorder (AUD) over 1 year. Results indicated equally strong relationships between higher involvement and better substance use outcomes regardless of mutual help group choice and, unexpectedly, higher group cohesion and satisfaction in Women for Sobriety, SMART Recovery, and LifeRing versus 12-step groups.[17,18]

Together, the prevalence and effectiveness of mutual help groups highlight a critical need to understand the nature and extent of racial/ethnic disparities in mutual help group participation for substance use problems. Given that mutual help groups are a key resource for supporting recovery, any racial/ethnic disparity in mutual help participation connotes a potential health disadvantage for racial/ethnic minority groups that is worthy of investigation.[19] Investigation of disparities in mutual help group participation is particularly valuable because there are reasons to believe that racial/ethnic minority groups (and especially immigrants) experience unique barriers to mutual help participation (e.g., racial/ethnic discrimination) as well as more barriers to help-seeking generally, described below. Accordingly, the present study offers a comprehensive review of empirical research on racial/ethnic disparities in mutual help group participation, addressing research on individuals with alcohol and/or drug problems. Although others have summarized the literature on racial/ethnic disparities related to mutual help groups,[10,20,21] this study is the first known comprehensive review. Attention is focused predominantly on racial/ethnic disparities related to 12-step groups (and especially AA) because these groups have been the dominant focus of existing literature; however, the review also discusses alternatives to 12-step groups. Results will inform attempts to maximize SUD treatment effectiveness among racial/ethnic minority groups as well as future research aiming to understand

recovery and pathways for recovery among racial/ethnic minority populations.

UNIQUE BARRIERS TO PARTICIPATION IN MUTUAL HELP GROUPS

Several qualitative studies on the experiences of racial/ethnic minority individuals in 12-step groups/AA have concluded that these individuals may face unique barriers to full mutual help group participation and benefit. For example, Jilek-Aall suggested that AA can be off-putting to American Indians because attending AA may be equated with rejection of one's Indian identity and culture; because AA's worldview and practices (e.g., focus on confession-like speeches and Christian religiosity) are not consistent with those of American Indians; and because of miscommunication, barriers to trust, and discrimination by Whites.[22,23] Venner and colleagues' more recent, qualitative study likewise concluded that American Indians may avoid AA because they see it as "for White men," because aspects of the program are not consistent with their beliefs and preferences, and because they feel scrutinized in AA.[24] For some of the same reasons, others have argued that mainstream AA can be a poor fit for Black[25-27] and Latinx[28] people with substance use problems.

This literature broadly illuminates three distinct mechanisms that may create discomfort for racial/ethnic minority individuals in the context of mutual help groups. Racial/ethnic minority individuals may (a) perceive that their people and culture are not well represented within a given mutual help group's founding, history, membership, and/or leadership, generating concern and mistrust; (b) perceive that a given mutual help group's philosophy, values, and practices run counter to those of their own culture; and (c) experience challenging, current social contexts within a given mutual help group, such as heightened scrutiny, prejudice, and discrimination. These barriers could influence racial/ethnic minority individuals to avoid meetings and/or to participate in circumscribed ways that limit the benefits of participation, such as avoiding talking, avoiding sensitive disclosures, and failing to seek a 12-step sponsor. Although not a focus of the above studies, language barriers also could diminish or preclude participation for racial/ethnic minority groups, especially recent immigrants and those with low acculturation to U.S. society.

Counter to these arguments, some evidence suggests that such differences can be at least partially overcome. In principle, 12-step groups are open to adaptation,[29,30] and they have proliferated (in sometimes adapted form) in many countries throughout the world, suggesting the potential for wide if not universal appeal.[31] Furthermore, 12-step groups have been culturally adapted specifically for American Indian and Alaska Native,[22,23,32,33] Black,[26,27] and Latinx[28,34,35] populations. For American Indians and Alaska Natives, the Medicine Wheel and 12 Steps program blends Native American traditional teachings with the 12 Steps of Alcoholics Anonymous to provide culture-specific recovery assistance for Native Americans.[32] In this program, each step may be worded differently from its AA wording, and the steps are presented in a circle rather than as a straight-line listing to ensure cultural appropriateness. Also, this program states that being "in recovery" requires a further journey to wellness by going beyond "clean and sober," by pursuing a journey of healing and balance—mentally, physically, emotionally, and spiritually. This highlights that racial/ethnic minority individuals may have distinct concepts of recovery that should (and can) be addressed in cultural adaption.

Nonetheless, appropriately adapted meetings may not be available and accessible to all racial/ethnic minority groups and subgroups. For example, Asian Americans may face especially serious barriers to 12-step participation given the prohibitions common to many Asian cultures against publicly acknowledging addiction[36,37] and given the heterogeneous composition and small number of Asian Americans in the United States, which may inhibit the growth of culturally adapted meetings. Racial/ethnic minority individuals living outside of major metropolitan areas or ethnic enclaves also may be at a disadvantage, due to their restricted access to culturally adapted meetings;[29] and recent immigrants and others low on acculturation may

struggle with cultural mismatch regardless of the availability of culturally adapted meetings, as adapted meetings in the United States still may fail to adequately reflect their cultures of origin.[28]

GENERAL BARRIERS TO HELP SEEKING

Quantitative and qualitative studies also suggest that racial/ethnic minority groups face greater barriers to seeking help for SUD more generally, which likewise could influence mutual help group participation and benefits. Multiple studies conducted with U.S. national samples have reported lower rates of specialty SUD treatment utilization among Latinx (vs. White) individuals with SUD,[38-44] with studies suggesting particularly limited utilization among foreign-born and Spanish-speaking Latinx subgroups.[45-47] National studies in the United States also have reported disparities in specialty SUD treatment utilization among Asian Americans (vs. Whites)[4,48] and lower SUD treatment retention among both Black and Latinx (vs. White) individuals.[49,50] These studies provide compelling evidence of racial/ethnic disparities in treatment utilization and retention because they used nationally representative samples, restricted analysis to those with an SUD, and often controlled for problem severity.

A parallel evidence base has addressed general barriers to seeking help for an SUD, focusing mostly on Latinx and Black populations.[42,47,51-55] Studies (most addressing multiple barriers simultaneously) have described increased barriers facing Latinx and Black populations in several categories, including logistic barriers (e.g., difficulties with finding treatment, paying/qualifying for treatment, obtaining transportation, handling family and work responsibilities), attitudinal barriers (e.g., lack of perceived treatment need, lack of perceived treatment effectiveness), social and legal barriers (e.g., lack of social support/pressure for treatment seeking, stigma, concerns about deportation, concerns about retaining child custody), and cultural barriers (e.g., lack of culturally adapted treatments, lack of racial/ethnic minority group representation among clients and staff).

Although parallel studies have not been conducted to explore barriers to mutual help group participation per se, many of the above barriers could plausibly affect mutual help group participation. Logistic barriers may be especially salient for recent immigrants and economically disadvantaged groups. For example, recent immigrants and impoverished members of racial/ethnic minority groups may face particular challenges in locating appropriate meetings, obtaining transportation to meetings, and handling competing responsibilities. That said, impacts of certain logistic and legal barriers to help seeking in general terms may be somewhat mitigated when considering mutual help group participation specifically. This is because 12-step meetings are widely available (i.e., located in accessible community settings), free, and independent of governmental institutions.

A last point worthy of attention is that disparities in treatment utilization and retention among Latinx, Black, and Asian populations may themselves constitute barriers to mutual help group participation among affected groups because specialty treatment constitutes a major route to mutual help group involvement (and especially 12-step involvement). Referral to meetings by treatment staff is perhaps the predominant route to 12-step participation, so those who do not attend (or attend less) treatment may be less likely to participate in 12-step groups. Toward this point, 32% of respondents to the 2014 AA Membership Survey reported direct referral from a treatment facility, and 59% reported receiving some treatment/counseling related to their drinking before coming to AA; among the latter, 74% said this experience played an important part in directing them to AA.[8] Referral to 12-step by medical and mental health professionals is also common,[8] which may similarly disadvantage Latinx and Black individuals because they are less likely than Whites to regularly access primary care and mental health care.[56-59]

The discussion above paints a complex picture of the potential for racial/ethnic disparities related

to mutual help groups. It suggests that, although any racial/ethnic minority individual could experience multiple barriers to mutual help group participation, mitigating factors may alter the impacts of these barriers. In lieu of study hypotheses, this review therefore offers two questions:

1. What is the extent and nature of quantitative research on racial/ethnic disparities in mutual help group participation?
2. Do existing studies suggest racial/ethnic disparities in mutual help group participation, and for whom?

In addressing the second question, the review initially examines national studies and treatment/community studies separately, given their differences in rigor and sampling strategies. However, in view of the limited evidence base, results from both study types are synthesized to formulate overarching conclusions.

METHODS

Approach and Search Strategy

The current review employed a narrative review strategy strengthened by incorporation of key aspects of systematic reviews, including systematic search procedures and study coding. To locate relevant publications, PubMed and PsycINFO were searched using the following search terms and combinations thereof: mutual help, self-help, mutual aid, Alcoholics Anonymous, Narcotics Anonymous, Cocaine Anonymous, Marijuana Anonymous, 12-step, twelve-step, SMART Recovery, LifeRing, Women for Sobriety, alcohol, substance, drug, Black, African American, Latino, Hispanic, Asian American, American Indian, Native American, Alaska Native, race, and ethnicity. Reference lists of relevant articles and related-citation links also were examined.

Focal Variables and Study Inclusion and Exclusion Criteria

This review examined associations between racial/ethnic self-identification (the independent variable) and mutual help participation (the outcome), defined as meeting attendance and/or participation in key activities. The review included only original, quantitative articles describing the results of U.S. studies; published in English-language, peer-reviewed journals; and analyzing the presence or extent of mutual help participation across two or more specific racial/ethnic groups with SUD treatment need—as indicated by the presence of an alcohol problem and/or drug use/a drug problem. The review included studies on both adults and adolescents, using no publication date restrictions. Studies were excluded from review if they (1) analyzed only one racial/ethnic group; (2) compared Whites to a combined sample of racial/ethnic minority groups; (3) omitted statistical tests of racial/ethnic differences in mutual help group participation or data sufficient for such tests; or (4) presented results for subsamples of racial/ethnic minority groups where data for the larger racial/ethnic populations were published elsewhere.

Analysis and Summary of Findings

Where statistical comparisons were not provided, this review's lead author conducted bivariate comparisons (i.e., Pearson chi-square tests) using raw, published data. Study characteristics and relevant results were summarized in two descriptive tables. A third table was used to summarize the main results for each racial/ethnic subgroup separately. This table coded results for racial/ethnic comparisons across all mutual help participation outcomes for a given study, but relative only to a specific racial/ethnic group (e.g., coding results for Latinx-White comparisons on all study measures of mutual help group participation at all time points). Results were coded as null, mixed, entirely consistent with lower minority-group participation (a disparity), or entirely consistent with higher minority-group participation (a minority advantage); results were coded as "mixed" when they differed across outcomes, data sources, and/or subgroups (e.g., genders). Marginally significant results (i.e., $.05 < p < .10$) were coded as significant, not null, for this purpose.

RESULTS

National, Epidemiological, Cross-Sectional Studies

Table 1 presents the characteristics and key results of identified national epidemiological studies examining racial/ethnic differences in mutual help group participation; all were cross-sectional ($N = 8$ studies).[38-42,60-62] Data sources were the 1995–2010 National Alcohol Survey (NAS) series, the 1991–1992 National Longitudinal Alcohol Epidemiologic Survey (NLAES), the 2001–2002 and 2004–2005 National Epidemiologic Surveys on Alcohol and Related Conditions (NESARC), and the 2001–2013 NSDUH series, yielding six unique data sets. No studies addressed adults over the past decade. As shown in Table 1, key racial/ethnic subgroups were relatively large (all $N > 100$), excepting those for Asian American/Native Hawaiian/Pacific Islander ($N = 99$) and Native Hawaiian/Pacific Islander ($N = 68$) groups. All but two studies targeted Latinx and/or Black populations, and only one targeted adolescents. All but two studies[40,42] aggregated across nativity and gender when examining racial/ethnic differences. However, all studies including Latinx respondents, excepting the NLAES, reported providing Spanish-language interviews, allowing participation of those not fluent in English. Half targeted those with AUD only, with the others targeting other drug use disorders also or exclusively. All eight studies analyzed AA/12-step or "self-help" attendance and were limited to a measure of any versus no attendance, most using a lifetime time frame. Five conducted multivariate analyses.

Results were quite mixed, with three studies providing at least some evidence of disparities (i.e., Cummings et al., 2011;[39] Mancini et al., 2015;[40] Zemore et al., 2014[42]); three showing at least some evidence of a minority advantage (i.e., Chartier et al., 2011;[38] Perron et al., 2009;[61] Wu et al., 2016[62]); and two reporting entirely null results (i.e., Schmidt et al., 2007;[41] Kaskutas et al., 2008[60]) for racial/ethnic differences in mutual help group participation. (See also Table 3.)

Treatment and Community Studies

Table 2 presents the characteristics and key results of identified treatment- and community-based studies examining racial/ethnic differences in mutual help group participation ($N = 11$ studies).[29,63-72] Studies represent 10 unique data sources, many dated—especially for Latinx-White and Black-White comparisons. Seven of the 11 reported total *samples* of less than 100 for key racial/ethnic subgroups. All but two studies targeted Latinx and/or Black populations exclusively, and all but one targeted adults. All 11 studies aggregated across nativity and gender groups for analysis, and no studies sampling Latinx respondents reported the use of Spanish-language interviews. Five targeted individuals seeking alcohol-related services (the remainder studying populations seeking SUD services), and all studied AA/12-step participation. Contrasting with the epidemiological studies, most (six) captured level of (vs. any/no) participation, at least in addition to any/no participation, and several examined activity participation as well as attendance at meetings. Most (eight) conducted only bivariate analyses or analyses controlling for treatment condition or time alone.

Results were again mixed, with three studies providing at least some evidence of disparities (i.e., Arroyo et al., 1998;[65] Tonigan et al., 1998;[66] Tonigan, 2003[69]); three showing at least some evidence of one or more minority advantages (i.e., Humphreys et al., 1991;[63] Kingree et al., 1997;[64] Tonigan et al., 2013[72]), one reporting countervailing results (i.e., Kaskutas et al., 1999[67]), and four reporting entirely null results (i.e., Humphreys and Woods, 1993;[29] Hillhouse and Fiorentine, 2001;[68] Goebert and Nishimura, 2011;[70] Krentzman et al., 2012[71]). (See also Table 3.)

Overall Summary of Results

Table 3 summarizes the findings of Tables 1 and 2 separately for comparisons involving Latinx; Black; American Indian or Alaska Native; Asian American, Native Hawaiian, or Other Pacific Islander; and multiracial respondents. As noted in the Methods, this summary table simultaneously codes results for comparisons across all mutual

Table 1 National, Epidemiological, Cross-Sectional Studies of Racial/Ethnic Differences in Mutual Help Group Participation ($N = 8$)

Authors	Analytic Sample (All Mixed-Gender)	Data Source	Use of Spanish Interviews	Mutual Help Group Participation Outcome	Analysis	Results
Schmidt et al., 2007[41]	1,885 White, 704 Latinx, and 627 Black respondents	Adults with a lifetime AUD in the combined 1995 and 2000 NAS	Yes	AA attendance (yes vs. no) in one's lifetime	Bivariate only	In the total sample, analyses showed no racial/ethnic differences.
Kaskutas et al., 2008[60]	1,029 White, 103 Latinx, 120 Black, and 73 Other respondents	Adults who attended a 12-step group in their lifetime (and prior to the past year) for an alcohol problem in the 2001–2002 NESARC	Yes	12-step attendance (yes vs. no) in the past year	Bivariate only	In the total sample, analyses showed no racial/ethnic differences.
Perron et al., 2009[61]	2,682 White, 595 Latinx, and 610 Black respondents	Adults with a lifetime DUD in the 2001–2002 NESARC	Yes	12-step attendance (yes vs. no) in one's lifetime	Bivariate and multivariate; controls were demographics and presence of other lifetime psychiatric disorders	Among those reporting any lifetime help seeking for a drug problem, both bivariate and multivariate analyses showed a significantly higher rate of 12-step attendance among Black vs. White respondents; Latinx and White respondents were equivalent. Among the total sample, bivariate analyses* similarly revealed a significantly higher rate of 12-step attendance among Black vs. White respondents.
Chartier et al., 2011[38]	For the NLAES, 6,016 White, 395 Latinx, and 598 Black respondents; for the NESARC, 8,011 White, 1,677 Latinx, and 1,579 Black respondents	Adults with a lifetime AUD in the 1991–1992 NLAES and the 2001–2002 NESARC	Yes for the NESARC, not stated for NLAES	12-step attendance (yes vs. no) in one's lifetime	Bivariate and multivariate; controls were survey, demographics, insurance status, and alcohol severity	In the NLAES, bivariate analyses* showed no racial/ethnic differences. In NESARC, bivariate analyses* showed a significantly higher rate of 12-step attendance among Black vs. White respondents; Latinx and White respondents were equivalent. In pooled survey data, multivariate analyses showed a significantly higher rate of 12-step attendance among Latinx vs. White respondents; Black and White respondents were equivalent. A significant interaction indicated that the Latinx-White difference was diminished or reversed at higher levels of AUD severity.

Authors	Analytic Sample (All Mixed-Gender)	Data Source	Use of Spanish Interviews	Mutual Help Group Participation Outcome	Analysis	Results
Cummings et al., 2011[39]	8,506 White, 2,004 Latinx, 1,051 Black, 325 American Indian/Alaska Native, 181 Asian American, 68 Native Hawaiian/Pacific Islander, and 499 Multiracial respondents	Adolescents with past-year SUD in the combined 2001–2008 NSDUH	Yes	Self-help attendance (yes vs. no) in one's lifetime	Bivariate and multivariate; controls were demographics, insurance status, any mental health treatment, type of SUD, and self-rated health	In the total sample, both bivariate and multivariate analyses showed significantly lower rates of self-help attendance among both Latinx and Black vs. White respondents; no other differences emerged.
Zemore et al., 2014[42]	3,788 White, 949 Latinx, and 738 Black respondents	Adults with lifetime AUD in combined 2000, 2005, and 2010 NAS	Yes	12-step attendance (yes vs. no) in one's lifetime	Bivariate and multivariate; controls were survey, demographics, and dependence severity (as in Model 3)	Among men, both bivariate and multivariate analyses showed a lower rate of 12-step attendance among Latinx vs. White respondents (though the difference was marginally significant in bivariate analyses); Black and White respondents were equivalent. Among women, both bivariate and multivariate analyses showed lower rates of 12-step attendance among Latinx and Black vs. White respondents.
Mancini et al., 2015[40]	5,754 White, 743 U.S.-born Latinx, and 280 Latinx immigrant respondents	Adults with lifetime drug use in the 2001–2002 and 2004–2005 NESARC (using variables from both)	Yes	12-step attendance (yes vs. no) in one's lifetime	Bivariate and multivariate; controls were demographics, parental drug use history, and lifetime mood and anxiety disorders	In the total sample, both bivariate* and multivariate analyses showed a significantly lower rate of 12-step attendance among Latinx immigrant vs. White respondents; U.S.-born Latinx and White respondents were equivalent.
Wu et al., 2016[62]	4,361 White, 799 Hispanic, 459 Black, 141 American Indian/Alaska Native, 99 Native Hawaiian/Pacific-Islander/Asian American, 266 Multiracial respondents	Respondents age 12 and older reporting past-year OUD in the combined 2005–2013 NSDUH	Yes	Self-help attendance in the past year	Bivariate only	Among those reporting past-year use of any alcohol/drug services, analyses showed a significantly higher rate of self-help attendance among American Indian vs. White respondents; no other differences emerged.

Note: AA, Alcoholics Anonymous; AUD, alcohol use disorder; DUD, drug use disorder; NAS, National Alcohol Survey; NESARC, National Epidemiologic Survey on Alcohol and Related Conditions; NLAES, National Longitudinal Alcohol Epidemiologic Survey; NSDUH, National Survey on Drug Use and Health; OUD, opiate use disorder; SUD, substance use disorder.*Analyses conducted on raw data by this review's lead author.

help participation outcomes for a given study, but relative only to a specific racial/ethnic group. This table reveals a lack of strong support for broad racial/ethnic differences in mutual help group participation. Of 35 comparisons between specific racial/ethnic minority groups and Whites on measures of mutual help group participation in a given study, nearly half ($N = 17$) yielded null results; only six comparisons yielded unequivocal support for racial/ethnic disparities, whereas nine yielded mixed results and three yielded unequivocal support for a minority advantage in mutual help group participation.

Nonetheless, it may be possible that results signify disparities for particular Latinx subgroups, as no results indicated a Latinx-White minority advantage and four results indicated Latinx-White disparities. Also, two of the three results coded as "mixed" reveal some disparities: Mancini et al. (2015) reported disparities in lifetime 12-step attendance among immigrant (but not U.S.-born) Latinx adults with lifetime drug use in a national sample,[40] and Tonigan et al. (1998) reported disparities in AA attendance at the 12-month follow-up exclusively among Latinx adults with AUD in Project MATCH (with Latinx-White differences being nonsignificant at prior follow-ups).[66] Black-White comparisons seem more consistent with null effects, with exceptions, as they yielded a range of results including many null results and several results suggesting a minority advantage. Data were very sparse for other racial/ethnic groups, with no evidence of disparities emerging.

DISCUSSION

Question 1: Extent and Type of Research on Disparities

The present review identified 19 studies addressing racial/ethnic disparities in mutual help group participation among those with SUD treatment need. This set includes eight national, epidemiological, cross-sectional studies that were generally well powered, incorporated Spanish-language interviews (allowing inclusion of Spanish speakers), and incorporated multivariate analyses with some adjustment for potential confounds. Also in this set were 11 treatment/community studies, strengths of which included consideration of level of mutual help group participation, as well as any or none, and analysis of multiple outcomes (including participation over time). Almost all studies used strong measures of SUD treatment need (i.e., SUD/AUD status), and rigorously conducted studies were included among both types.

Despite some strengths, the reviewed studies evidenced multiple design limitations, as follows.

- **Studies were generally dated and not optimally designed to assess racial/ethnic differences, with many studies showing inadequate power.** All but four studies analyzed data collected partially or entirely more than a decade ago. U.S. demographics are in constant flux—for example, recent years have witnessed rapid growth of racial/ethnic minority populations and shifts in Latinx settlement patterns[73,74]—so older findings may not represent current conditions in the United States. Existing analyses also seemed to be largely secondary analyses, and most treatment/community studies were underpowered for detecting differences in mutual help group participation across racial/ethnic groups. Even assuming bivariate analysis and a continuous outcome, tests require at least 99 participants per group to detect a small-to-medium effect size (Cohen's $d = .40$) with adequate power ($\beta = .80$);[75] power is even more limited given multivariate analysis and a dichotomous outcome.
- **Studies provided limited data on racial/ethnic minority groups other than Latinx and Black populations, and on important racial/ethnic subgroups including immigrants, women, and adolescents.** Identified studies included just two or three studies each on American Indian or Alaska Native, Asian American, and Native Hawaiian and Other Pacific Islander populations. One study examined immigrants (Mancini et al., 2015),[40] one study examined women separately (Zemore et al., 2014),[42] and two studies examined adolescents (Cummings et al., 2011;[39] Krentzman et al., 2012[71]). Yet, all of the studies focusing on

Table 2 Treatment and Community Studies of Racial/Ethnic Differences in Mutual Help Group Participation ($N = 11$)

Authors	Analytic Sample (All Mixed-Gender)	Data Source and Analytic Design	Use of Spanish Interviews	Mutual Help Group Participation Outcome	Analysis	Results
Humphreys et al., 1991[63]	201 total with 115 Black respondents at follow-up; precise breakdown not provided	Adults with SUD recruited from 19 public SUD treatment programs (11 outpatient, 8 residential) in Michigan; longitudinal (follow-up rate 63%)	N/A	12-step attendance (any vs. no) between treatment end and 6-month follow-up	Bivariate only	In the total sample, analyses showed a significantly higher rate of 12-step attendance among Black vs. White respondents.
Humphreys & Woods, 1993[29]	267 White and 233 Black respondents at follow-up	Adult "substance abusers" (SUD status unclear) recruited from 22 SUD treatment programs in Michigan; longitudinal (follow-up rate 71%)	N/A	12-step attendance (any vs. no) in the prior 30 days at 12-month follow-up	Bivariate only	In the total sample, analyses* showed no racial/ethnic differences.
Kingree et al., 1997[64]	22 White and 78 Black respondents at follow-up	Adults with SUD recruited from a 120-day, 12-step–oriented addiction treatment program serving indigent poly-drug users, most with cocaine as drug of choice; longitudinal (follow-up rate 56%)	N/A	Scores on the AAAS and endorsement of specific AA-related behaviors and experiences, assessed 60 days post-baseline	Bivariate only	In the total sample, analyses showed marginally higher scores on the AAAS and a significantly higher rate of "sharing in meetings" among Black vs. White respondents; no other differences emerged.
Arroyo et al., 1998[65]	62 White and 46 Latinx respondents at baseline	Adults with AUD recruited from intake at the University of New Mexico's outpatient, publicly funded SUD treatment program; longitudinal (follow-up rates 91% to 97%)	None described	Proportion days AA meeting attendance over the follow-up interval at 2, 4, and 6 months post-baseline	Multivariate only; controls were gender, education, and baseline AA attendance	In the total sample, analyses showed significantly fewer days of AA attendance among Latinx vs. White respondents collapsing across follow-ups.
Tonigan et al., 1998[66]	For outpatient sample, 735 White, 111 Latinx, and 52 Black respondents; for aftercare sample, 592 White, 27 Latinx, and 112 Black respondents at baseline	Project MATCH: Adults with AUD recruited from a broad range of SUD outpatient and residential treatment sites, assigned to one of three interventions; longitudinal (follow-up rates > 90%)	None described	AA attendance (yes vs. no) over the prior 3 months at 3, 6, 9, and 12 months post-baseline	Multivariate only; control was intervention condition	Among outpatients, analyses showed no racial/ethnic differences. Among aftercare patients, analyses showed significantly fewer days of AA attendance among both Latinx and Black vs. White respondents at the 12-month follow-up only; no other differences emerged.

Authors	Analytic Sample (All Mixed-Gender)	Data Source and Analytic Design	Use of Spanish Interviews	Mutual Help Group Participation Outcome	Analysis	Results
Kaskutas et al., 1999[67]	538 White and 253 Black respondents at baseline	Epidemiological Laboratory (EpiLab) Study: Adults recruited from (a) 10 alcohol programs representative of public, HMO, and for-profit programs in northern California ($N = 926$) and (b) the general population of alcohol-dependent and problem drinkers ($N = 672$); analysis uses only sample (a); baseline analysis	N/A	AA and NA/CA attendance (yes vs. no); scores on a composite measure of AA involvement; and endorsement of specific AA-related behaviors/experiences, all for the pretreatment period and assessed at baseline	Bivariate and multivariate (the latter conducted only for AA attendance); controls were demographics, ASI Alcohol Severity, ASI Drug Severity, prior SUD treatment, and any prior NA/CA attendance	In the total sample, bivariate analyses showed significantly higher rates of both AA and NA/CA attendance among Black vs. White respondents. However, multivariate analyses showed no racial/ethnic differences in AA attendance. Among those reporting any AA attendance, there were no racial/ethnic differences in overall AA involvement, but significant differences emerged for specific AA-related behaviors/statuses: Black respondents were more likely to report that they were AA members, had had a spiritual awakening, and did service/volunteer work in the last year (vs. White respondents); White respondents were more likely to currently have a sponsor and to have read the AA literature (vs. Black respondents).
Hillhouse and Fiorentine, 2001[68]	76 White, 72 Latinx, and 110 Black respondents at follow-up	Adults (SUD status not specified) recruited from 26 outpatient SUD treatment programs in the Los Angeles area; only those in treatment for at least 8 weeks included; longitudinal (follow-up rate 74%)	None described	Pattern of 12-step participation (i.e., classification as persister, initiate, dropout, or nonattender) 24 months post-baseline	Bivariate only	In the total sample, analyses showed no racial/ethnic differences.
Tonigan, 2003[69]	1,380 White, 141 Latinx, and 168 Black respondents at baseline	Project MATCH: Adults with AUD recruited from a broad range of SUD outpatient and residential treatment sites, assigned to one of three interventions; baseline analysis	None described	Proportion days AA meeting attendance prior to treatment (period undefined), assessed at baseline	Bivariate only	In the total sample, analyses showed significantly fewer days of AA meeting attendance among both Latinx and Black vs. White respondents.

Authors	Analytic Sample (All Mixed-Gender)	Data Source and Analytic Design	Use of Spanish Interviews	Mutual Help Group Participation Outcome	Analysis	Results
Goebert and Nishimura, 2011[70]	71 "Euro" American, 31 Asian American, and 90 Native Hawaiian respondents at baseline	Adults (SUD status not specified) recruited from intake at two major residential SUD treatment programs in Hawaii; baseline analysis	N/A	AA attendance (yes vs. no) prior to treatment (period undefined), assessed at baseline	Bivariate only	In the total sample, analyses showed no racial/ethnic differences.
Krentzman et al., 2012[71]	124 White and 41 Black respondents at baseline	Adolescents with SUD recruited from intake at the largest adolescent residential treatment provider in a central Midwestern region; longitudinal (follow-up rate 90%)	N/A	12-step helping behaviors and 12-step work in past month/90 days, as measured by Service to Others in Sobriety and General AA Tools of Recovery (GAATOR) scales, assessed 2 months post-baseline	Bivariate and multivariate; controls were baseline value of the outcome, demographics, total number of substance use diagnoses, prior SUD treatment, religiousness, readiness for change, and sexual abuse history	In the total sample, both bivariate and multivariate analyses showed no racial/ethnic differences.
Tonigan et al., 2013[72]	133 White and 63 American Indian respondents	Data merged from two studies recruiting adult participants in early AA affiliation and residing in large southwestern city; longitudinal (follow-up rates not specified)	N/A	Proportion days AA meeting attendance (period undefined), AA meeting attendance (yes vs. no), and 12-step work (assessed using GAATOR) at baseline and at 3, 6, and 9 months post-baseline	Multivariate only with time as the only covariate	In the total sample, analyses showed no racial/ethnic differences in AA attendance or 12-step work from baseline through follow-ups. However, analyses showed a significantly lower decline in any AA attendance over time among American Indian vs. White respondents.

Note: AA, Alcoholics Anonymous; AAAS, AA Affiliation Scale; ASI, Addiction Severity Index; AUD, alcohol use disorder; CA, Cocaine Anonymous; GAATOR, General AA Tools of Recovery; HMO, health maintenance organization; NA, Narcotics Anonymous; N/A, not applicable; SUD, substance use disorder. *Analyses conducted on raw data by this review's lead author.

immigrants, women, and adolescents reported disparities, underlining the importance of studying these populations.

- **Regardless of racial/ethnic group focus, treatment/community studies sampled a restricted range of populations, further limiting generalizability.** Although most national studies provided Spanish-language interviews, none of the treatment/community studies did so. Hence, these studies presumably excluded all those not fluent in English, who differ widely from English speakers on substance use and help-seeking patterns.[58-60,76] Treatment/community studies also focused on a small set of predominantly urban samples. This is an important limitation because, as discussed, geography may moderate racial/ethnic disparities in mutual help group participation and benefits, with those living outside of ethnic enclaves likely to show increased disparities.
- **Studies focused predominantly on respondents with AUD, and all studies examined AA/12-step participation or global "self-help" participation.** Very few studies focused on populations with a drug use disorder (DUD), and none examined 12-step alternatives such as SMART Recovery, a rapidly growing recovery resource. Consequently, findings cannot be confidently generalized to populations with DUD—comprising large proportions of those with SUD treatment need[77,78]—or to 12-step alternatives.

Studies also showed limitations associated with their measures and analysis.

- **Studies often relied on crude, dichotomous measures of 12-step participation (especially in national samples).** Most problematic, national studies relied completely on any/no (usually lifetime) measures of mutual help participation. Although power considerations may preclude use of more detailed measures, this means that national data cannot speak to potential disparities in involvement patterns, such as a tendency for Latinx people to discontinue 12-step involvement more frequently than Whites. Most studies also neglected to measure activity participation, though much of the effectiveness of 12-step participation can be attributed to activity involvement, such as obtaining a sponsor.[79]
- **Studies relied quite heavily on bivariate analyses, and they neglected potential confounds.** Even where multivariate analyses were conducted, very few controlled for differences in SUD severity. Neglect of SUD severity is particularly concerning: Where SUD severity is not controlled, any findings may be distorted by an association between race/ethnicity and problem severity, as higher SUD severity has been consistently associated with greater 12-step participation[80 83] (and indeed implies greater treatment need). These limitations should be addressed in future research.

Question 2: Findings for Racial/Ethnic Disparities

As a whole, studies did not provide strong evidence of racial/ethnic disparities for any racial/ethnic group. Still, six studies revealed some evidence of Latinx-White disparities in mutual help group participation, including national, epidemiological studies using NSDUH, NESARC, and NAS data (Cummings et al., 2011;[39] Mancini et al., 2015;[40] Zemore et al., 2014[42]) and treatment/community studies analyzing data from a New Mexico outpatient SUD treatment program and Project MATCH (Arroyo et al., 1998;[65] Tonigan et al., 1998;[66] Tonigan et al., 2003[69]). Results of a NESARC analysis by Mancini et al. (2015) are particularly notable, showing a sizeable disparity among Latinx immigrants (vs. Whites) reporting drug use across bivariate and multivariate analyses; analyses revealed significantly lower odds of lifetime 12-step attendance among Latinx immigrants vs. Whites (multivariate $OR = 0.39$).[40] Results call for cautious interpretation because, in addition to targeting any/no participation, analyses considered all those with any drug use and did not control for drug use severity. Still, similar results emerged in a within-group (noncomparative) study of Latinx respondents with lifetime AUD interviewed for the 2000–2010 NAS,[60] which reported significantly greater lifetime

Table 3 Summary of Results for Racial/Ethnic Disparities in Mutual Help Group Participation Across Studies

Comparison	Null Results	Mixed Results	Lower Minority Participation (Disparity)	Higher Minority Participation (Advantage)
Latinx vs. White	5 studies *Table 1*: Schmidt et al., 2007;[41] Kaskutas et al., 2008;[60] Perron et al., 2009;[61] Wu et al., 2016;[62] *Table 2:* Hillhouse and Fiorentine, 2001[68]	3 studies *Table 1:* Chartier et al., 2011;[38] Mancini et al., 2015;[40] *Table 2:* Tonigan et al., 1998[66]	4 studies *Table 1:* Cummings et al., 2011;[39] Zemore et al., 2014;[42] *Table 2:* Arroyo et al., 1998;[65] Tonigan et al., 2003[69]	0 studies
Black vs. White	6 studies *Table 1:* Schmidt et al., 2007;[41] Kaskutas et al., 2008;[60] Wu et al., 2016;[62] *Table 2:* Humphreys and Woods, 1993;[29] Hillhouse and Fiorentine, 2001;[68] Krentzman et al., 2012[71]	5 studies *Table 1:* Chartier et al., 2011;[38] Zemore et al., 2014;[42] *Table 2:* Kingree et al., 1997;[64] Tonigan et al., 1998;[66] Kaskutas et al., 1999[67]	2 studies *Table 1:* Cummings et al., 2011;[39] *Table 2:* Tonigan et al., 2003[69]	2 studies *Table 1:* Perron et al., 2009;[61] *Table 2:* Humphreys et al., 1991[63]
American Indian or Alaska Native vs. White	2 studies *Table 1:* Cummings et al., 2011;[39] *Table 2:* Goebert and Nishimura, 2011[70]	1 study *Table 2:* Tonigan et al., 2013[72]	0 studies	1 study *Table 1:* Wu et al., 2016[62]
Asian American, Native Hawaiian or Other Pacific Islander vs. White*	2 studies *Table 1:* Cummings et al., 2011;[39] Wu et al., 2016[62]	0 studies	0 studies	0 studies
Multiracial vs. White	2 studies *Table 1:* Cummings et al., 2011;[39] Wu et al., 2016[62]	0 studies	0 studies	0 studies
Total Results	17 studies	9 studies	6 studies	3 studies

Note: Results coded as "mixed" when differing across outcomes, data sources, and/or subgroups (e.g., genders); marginally significant results coded as significant and not null.
*Comparisons were between Asian Americans vs. Whites and Native Hawaiians/Pacific Islanders vs. Whites[39] and between Native Hawaiians/Pacific Islanders/Asian Americans vs. Whites.[62]

12-step attendance among those interviewed in English vs. Spanish (multivariate *OR* = 3.20) despite comprehensively controlling for severity. As this review's Introduction suggests, multiple studies[58-60] likewise have found diminished use of specialty treatment (and AUD services broadly) among Latinx immigrants and those speaking predominantly Spanish. In general, Latinx immigrants may tend to use fewer services, including mutual help groups, and/or prefer services not fully captured in the literature, such as services in their countries of origin and/or nontraditional services in the United States. For example, literature has documented some use among Latinx populations of *anexos,* which are community-based recovery homes that draw on AA principles and provide care to primarily male Latinx migrants and immigrants.[84,85] Regardless, these disparities raise questions as to whether existing recovery-related services are sufficient to support recovery for Latinx populations.

Also notable, studies reported substantial Latinx-White disparities in analyses targeting women (Zemore et al., 2014)[42] and adolescents (Cummings et al., 2011),[39] again across bivariate and multivariate analyses. These studies are notable because they analyzed large, national data sets and employed multivariate analyses. Moreover, the pattern of effects in each was similar across multiple outcomes, and results were not undermined by findings for null or contrary results in other studies. Using NAS data, Zemore et al. (2014) reported significantly lower odds of lifetime 12-step attendance among Latinx versus White women with lifetime AUD (multivariate *OR,* Model 3 = 0.30).[42] Findings also revealed large disparities in 12-step attendance among Latinx versus White men and Black versus White women, along with the same pattern of disparities for specialty treatment, perhaps implying general obstacles to help seeking among all Latinx individuals and Black women. Using NSDUH data, Cummings et al. (2011) reported substantially lower rates of 12-step attendance among both Latinx and Black (vs. White) adolescents, again in both bivariate and multivariate models; they also found the same pattern of disparities for any SUD treatment and treatment in medical settings.[39] Cummings et al. speculated that these disparities may be explained by lack of SUD services in Latinx and Black neighborhoods; low acculturation among Latinx adolescents; and racial/ethnic differences in stigma, attitudes, and cultural beliefs concerning behavioral health problems and treatment.[39] It is also possible that there are detrimental, cumulative effects of being both young and belonging to a racial/ethnic minority group, such as intensified stigma and difficulties with "fitting in" in treatment and mutual help group settings.

Otherwise, findings for Latinx-White disparities in the general population and among treatment/community samples were quite mixed. Existing data are not sufficient to confidently establish those factors driving variation in results across studies, but variation across national epidemiological studies may at least partially reflect differences in how studies obtained respondents from racial/ethnic minority groups. For example, at the time data relevant to this review were collected, the NSDUH did not oversample racial/ethnic minority groups; the NESARC oversampled racial/ethnic minority groups, although information on oversampling methods could not be located; and the NAS targeted high-minority-density areas. The NAS approach apparently yielded the strongest representation of Latinx respondents low on acculturation, with 45% of Latinx respondents interviewed in Spanish across the pooled 1995–2005 NAS[60] (vs. 16% in the 2001–2002 NESARC[86] and a weighted 23% in the 2001–2013 NSDUH[87]). If disparities are strongest for Latinx populations low on acculturation, as seems evident, this may explain why Zemore et al. (2014) reported Latinx-White disparities for both men and women,[42] and other national studies did not.

Meanwhile, respondents' geographic context—and specifically, access to racial/ethnic minority–inclusive and culturally adapted meetings in the community—may have contributed to variation in results for the treatment/community studies. Humphreys and Woods (1993) have argued that geography and race/ethnicity interact to affect mutual help group participation, and specifically that people with SUD may prefer to attend meetings

in areas where their own race/ethnicity is well represented.[29] In fact, their study of treatment seekers with SUD found that Black participants were more likely to attend a mutual-help group if they resided in a predominantly Black area; similarly, White participants were more likely to attend a mutual help group if they resided in a predominantly White area. Accordingly, the inconsistent results for treatment/community studies may reflect differences in the samples' access to minority-inclusive and culturally adapted meetings. This seems a plausible explanation for the null findings reported for Latinx-White differences in mutual help group participation in the diverse Los Angeles metropolitan area (i.e., Hillhouse & Fiorentine, 2001),[68] versus other studies reporting Latinx-White disparities with samples drawn from less metropolitan areas (i.e., the Arroyo[65] and Tonigan[66,69] studies). Future studies of racial/ethnic disparities that explicitly consider the acculturation status of respondents and access to minority-inclusive and culturally tailored meetings will be needed to better evaluate these possibilities.

Regarding Black populations, studies produced little evidence for disparities in mutual help group participation, and several studies reported evidence of greater mutual help group participation among Blacks than Whites (i.e., Perron et al., 2009;[61] Humphreys et al., 1991;[63] Kingree et al., 1997;[64] Kaskutas et al., 1999[67]). (Exceptions are the notable studies targeting women and adolescents described above.) Several factors could explain the relatively strong participation rates among Black people with SUD treatment need overall. As noted above, studies generally did not control for SUD severity, so they may have missed disparities that would arise when accounting for intensity of treatment need. Another possibility is that prevalent religiosity/spirituality among Black populations[88,89] may make 12-step groups particularly appealing, counteracting any obstacles to participation. Other explanatory factors may include the higher rate of SUD treatment coercion among Black versus White populations,[90] which can include coercion to 12-step group participation, and differences in program emphasis on 12-step principles and participation within programs serving predominantly Blacks vs. Whites.[29] The mixed findings for Black-White differences may reflect chance, geographic factors, and sample characteristics (e.g., proportion with DUD, as those with DUD may be more likely than those with AUD to experience coercion). Findings from the few studies of American Indian, Alaska Native, Asian American, Native Hawaiian, and Other Pacific Islander populations provided no indication of disparities, but the sparse data preclude strong conclusions.

Future Research Needs and Clinical Implications

The sparse and inconsistent evidence base described above highlights a need for additional research on racial/ethnic disparities in mutual help group participation. In particular, current epidemiological studies are needed to better investigate potential disparities, ideally using sophisticated measures of mutual help involvement and accounting for potential differences in clinical severity. NSDUH data would be especially well suited for examination of current disparities in rates of mutual help group participation. Well-powered treatment/community studies are also important to address the potential for racial/ethnic disparities in mutual help group involvement patterns over time, including involvement in key activities such as sponsoring relationships. Both epidemiological and treatment/community studies should pay particular heed to individual and contextual factors—such as gender, age, acculturation level, and access to minority-inclusive and culturally tailored meetings—that may affect participation in mutual help groups. Meanwhile, qualitative studies would be useful to capture the self-perceived needs and barriers of racial/ethnic minorities regarding mutual help groups. Studies might focus particularly on Latinx, American Indian, Alaska Native, Asian American, Native Hawaiian, and other Pacific Islander populations as well as racial/ethnic minority immigrants, women, and adolescents.

Studies also might address a wider range of mutual help groups as recovery resources for racial/ethnic minority individuals, such as SMART Recovery. SMART is the largest known alternative to 12-step groups with more than 2,200 meetings in the United States. SMART's philosophical

focus on empowerment (vs. surrender) may be especially appealing and appropriate for racial/ethnic minority individuals, who are likely to face disenfranchisement by the majority culture. Similarly, research is needed to examine the use of online mutual help meetings and resources among racial/ethnic minority groups. Many mutual help options, including 12-step groups, have online meetings and forums,[17,91] and aspects of these resources (e.g., their greater anonymity and ease of access) may be particularly appealing to racial/ethnic minority individuals. Importantly, online meetings have the potential for substantial cultural tailoring because they are geographically unlimited: A given meeting might be tailored to a very specific subgroup and draw attendees from around the globe. Online recovery resources have become an especially salient target for research in recent times because they offer ongoing, peer-based support during periods of social distancing.

Finally, studies are needed to address racial/ethnic disparities in the relationship between mutual help group participation and benefits. Few studies have addressed whether mutual help group participation is equally beneficial for racial/ethnic minority groups, with existing studies relying on a limited set of data sources.[65,69,72,92,93] A key question is whether Spanish-language 12-step groups are effective among Spanish-speaking Latinx individuals, as 12-step participation may be a more accessible form of treatment than specialty care for disadvantaged Latinx populations, with Spanish meetings available in many urban centers (though the extent of foreign-language meetings in the United States has not been well documented).[94,95] Broadly, it would be valuable to address the effectiveness of all prevalent mutual help group options and participation modes (i.e., in-person, online) for sustaining recovery among racial/ethnic minority individuals.

Together, the directions discussed above have the potential to advance the field not only by better describing existing disparities, but also by improving referral practices and interventions. Ultimately, studies might support the development and dissemination of new mutual help resources for racial/ethnic minority groups (e.g., culturally adapted meetings), which may be particularly important for those who underutilize specialty treatment and/or experience the heaviest burden of problems.

Limitations of This Review

The current review may have omitted relevant studies because inclusion criteria were limited to published studies indexed in PubMed and PsycINFO. The review's search strategy assumed that the vast majority of relevant studies would be indexed in these databases, but other databases may have yielded additional articles. Further, to be expeditious, this review drew upon, but did not fully adopt, guidelines from the PRISMA Group (Preferred Reporting Items for Systematic Reviews and Meta-Analyses).[96] Future reviews may benefit from more formalized review procedures. Last, because the review was limited to U.S. studies, results cannot be generalized to other countries. (For international studies of AA, see Makela, 1996.[97])

FINAL CONCLUSIONS

Mutual help groups are a foundational and an effective component of the SUD treatment system in the United States, so it is critical to understand whether they are as appealing and effective for racial/ethnic minority groups as they are for Whites. Further, there are reasons to believe that racial/ethnic minorities (and especially immigrants) experience elevated barriers to participation in such groups, including barriers to mutual help group participation specifically and help seeking generally. Nonetheless, this comprehensive review found existing data to be insufficient to fully evaluate racial/ethnic disparities in mutual help group participation. Findings provided very tentative evidence for Latinx-White disparities, particularly among certain subgroups (i.e., immigrants, women, adolescents), as well as for disparities among Black women and adolescents. However, identified studies showed numerous limitations. Conclusions emphasize the need for additional research addressing the limitations of existing studies and targeting new and understudied questions, such as widening the lens to examine neglected mutual help group options and modes of participation.

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Impact of Continuing Care on Recovery From Substance Use Disorder

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Continuing care is widely believed to be an important component of effective treatment for substance use disorder, particularly for those individuals with greater problem severity. The purpose of this review was to examine the research literature on continuing care for alcohol and drug use disorders, including studies that addressed efficacy, moderators, mechanisms of action, and economic impact. This narrative review first considered findings from prior reviews (published through 2014), followed by a more detailed examination of studies published more recently. The review found that research has generally supported the efficacy of continuing care for both adolescents and adults, but the picture is complex. Reviews find relatively small effects when results from individual studies are combined. However, continuing care of longer duration that includes more active efforts to keep patients engaged may produce more consistently positive results. Moreover, patients at higher risk for relapse may benefit to a greater degree from continuing care. Several newer approaches for the provision of continuing care show promise. These include incentives for abstinence and automated mobile health interventions to augment more conventional counselor-delivered interventions. Primary care can be used to provide medications for opioid and alcohol use disorders over extended periods, although more research is needed to determine the optimal mix of behavioral treatments and other psychosocial services in this setting. Regardless of the intervention selected for use, the status of most patients will change and evolve over time, and interventions need to include provisions to assess patients on a regular basis and to change or adapt treatment when warranted.

KEY WORDS: substance use disorder; treatment; continuing care; review; recovery; alcohol

As the substance use disorder (SUD) treatment system has evolved, the term "continuing care" has come to have two meanings.[1-4] As originally conceptualized, continuing care was a period of lower-intensity treatment following a more intensive initial period, such as residential care or an intensive outpatient program (IOP).[2,4] As such, continuing care was synonymous with "aftercare" or "stepdown care." In this model, the goals of continuing care were to solidify and sustain the gains made in the initial phase of treatment, to establish abstinence if it was not already achieved, and to prevent subsequent relapses from worsening to the point that further acute treatment was necessary. In addition, disease management models of SUD treatment, sometimes delivered via primary care or via regular checkups, have attempted to improve outcomes by managing patients over extended periods. These models also can be seen as continuing care approaches.[1,3]

Due to the recognition that substance use disorder can be a chronic, long-term disorder, there has been an increase in research on how to improve the effectiveness of continuing care. The purpose of this review is to provide an update on the latest research on SUD continuing care, including newer approaches such as incentives, primary care–based clinical management, measurement-based care, adaptive treatment models, and mobile health components. The review begins with a brief summary of prior reviews (published through 2014) of SUD continuing care research. First, however, this review presents a conceptual model of continuing care and its principal goals with regard to the promotion of extended recovery.

CONCEPTUAL MODEL

A return to substance use following a period of abstinence involves a number of distal and proximal factors, as outlined by Witkiewitz and Marlatt in their dynamic model of relapse.[5] Factors such as family history of SUD, social support, self-efficacy, craving, and outcome expectancies account for level of general vulnerability to relapse. When high-risk situations are encountered, these factors—along with current affective state and the degree to which an effective coping behavior is performed—determine whether relapse occurs. Long-term recovery is a function of a number of factors, including characteristics of the individual's relapse vulnerability as described in the Witkiewitz and Marlatt model, type and duration of treatment received including continuing care, and a variety of non-treatment factors experienced during and after formal treatment.[1,2,6] These factors include participation in mutual help organizations, other forms of social support, and engagement in organizations and activities that promote recovery.

The important functions of continuing care in the recovery process involve maintaining abstinence/initial treatment gains; addressing relapse/non-response, including limiting the severity of relapses; connecting patients to other sources of support; and addressing other recovery issues, including employment, recreation, housing, and involvement in meaningful and/or enjoyable activities. Many of these functions are included in Wagner et al.'s chronic care model,[7] which features interventions to increase self-confidence and skill levels, a focus on goal setting, identification of barriers to achieving goals, methods to overcome such barriers, support for patient self-management, and links to community resources.

Two important challenges faced during the continuing care phase of treatment are patient dropout and changes in the patient's clinical needs over time. Therefore, effective clinical care must include elements that facilitate better retention and must be flexible enough to adapt to the changing needs of individuals. This review examines strategies that address these two issues, including active outreach to patients, use of incentives, measurement-based care, and adaptive treatment.

METHODS USED IN THE REVIEW

PubMed and PsycINFO were used to identify prior reviews of the continuing care research literature

as well as articles published after 2014 that were not included in these reviews. The search terms included substance use disorder, addiction, drug use disorder, alcohol use disorder, continuing care, aftercare, stepped-care, treatment outcome, efficacy, effectiveness, and cost-effectiveness. Studies without control groups were excluded from the review, with the exception of one study on the first evaluation of an intervention based on a package of services formerly offered only to pilots and doctors. Studies were not excluded for other methodological reasons or for country of origin.

PRIOR REVIEWS OF CONTINUING CARE

Adult Participants

One of the first reviews of continuing care included studies of continuing care versus no continuing care or minimal continuing care as well as studies comparing two or more active continuing care interventions.[2] This review reported mixed results, with approximately half the interventions producing positive effects. Compared to studies with negative findings, the studies that generated positive effects tended to feature continuing care interventions with longer planned durations (at least 12 months), more active efforts to engage and retain patients, and weaker control conditions. A subsequent meta-analysis focused on 19 randomized trials published through 2010 that compared continuing care for SUD with minimal or no continuing care.[8] The results of this study indicated a small but significant benefit for continuing care on SUD outcomes at the end of the interventions ($g = .19$, $p < .001$) and at post-treatment follow-up ($g = .27$, $p < .01$). (Hedges' g and Cohen's d are roughly equivalent measures of effect size.)

A systematic review of six methodologically rigorous trials of continuing care for alcohol use disorder found similarly mixed results.[9] The trials tested multimodal interventions based on the chronic care model following initial treatment in more intense addiction and psychiatric programs. The interventions included a range of active outreach techniques, from telephone calls to follow-up by nurses, and various forms of individual or couples counseling. Four of the six trials found that patients receiving continuing care supplemented by active outreach interventions had significantly better drinking outcomes than patients receiving usual continuing care. In summary, prior reviews on the adult SUD continuing care literature found on average relatively small positive effects, which appeared to mask a fair amount of heterogeneity in results across studies.

Adolescent Participants

Studies of continuing care for adolescents were reviewed by Passetti and colleagues.[10] This review identified six studies with randomized designs, and four of these studies evaluated assertive continuing care (ACC).[11] ACC consists of home visits, linkage to other services, transportation to services or other pro-recovery activities, advocacy to access services, and provision of the evidence-based adolescent community reinforcement approach (A-CRA).[12] In three of the four studies of ACC, this intervention produced significantly better SUD outcomes than the continuing care provided as treatment as usual (TAU).[11,13,14] A second intervention, active aftercare, whether delivered via in-person or telephone sessions, was found to be more effective than no aftercare (control condition).[15] Finally, the effects of A-CRA versus continuing care with enhanced cognitive behavioral therapy (CBT) for adolescents who did not achieve abstinence in the initial phase of treatment were studied by Kaminer and colleagues.[16] There were no differences in retention or abstinence rates between the two treatment conditions. It should be noted that three of these studies also were included in the review by Blodgett et al.[8] In summary, prior reviews of continuing care for adolescents with SUD generally found favorable results, particularly for ACC.

CONTINUING CARE STUDIES NOT INCLUDED IN PRIOR REVIEWS

A number of continuing care studies were not included in these reviews, primarily because they were published after 2010.

Mindfulness-Based Relapse Prevention

Mindfulness-based relapse prevention (MBRP), an intervention that combines mindfulness practices and CBT relapse prevention (RP), was evaluated in a study by Bowen and colleagues.[17] Participants who had successfully completed the first phase of treatment were randomly assigned to aftercare—MBRP, RP, or TAU (12-step programming and psychoeducation)—and followed for 12 months. Participants in MBRP and RP had lower rates of relapse to substance use and heavy drinking than did those in TAU. Moreover, among participants with some substance use, those in MBRP and RP had fewer days of substance use and heavy drinking than did those in TAU. RP was superior to MBRP in time to first drug use. Conversely, MBRP produced fewer days of reported substance use and heavy drinking at 12 months than did RP and TAU. These findings suggest that MBRP may be at least as effective as RP.

Telephone-Based Continuing Care

Efficacy and effectiveness analyses

McKay and colleagues have published results from three additional telephone-based continuing care studies that were not included in earlier reviews.[2,8,9] The first of these was conducted among participants with cocaine use disorder who had participated in an IOP for 2 to 4 weeks.[18] About 40% of the sample also had current co-occurring alcohol use disorder (AUD). Participants were randomly assigned to IOP (TAU); IOP plus telephone monitoring and counseling (TMC), which consisted of up to 39 calls provided on a titrated schedule over 24 months; or IOP plus TMC with incentives for completed continuing care sessions (i.e., $10 gift coupons for each continuing care session attended in the first year), and followed for 24 months. The primary outcome was a composite measure that considered cocaine use, other drug use, and heavy alcohol use. There were no significant treatment main effects in this study. However, among participants who continued to use cocaine or drink alcohol in the first 3 weeks of IOP, TMC had significant positive effects on the primary outcome compared with TAU with IOP. Although the incentives almost doubled the number of continuing care sessions that were attended, substance use outcomes in the TMC plus incentives condition were slightly worse than those in TMC.

A second study, also focused on IOP patients with cocaine use disorder, evaluated an augmented version of TMC plus incentives for attendance that was provided to patients from the beginning of IOP, rather than only to those patients who had been attending IOP for several weeks.[19] This 12-month version of TMC also included more vigorous outreach efforts when patients stopped completing calls, and more active efforts to link patients to recovery services in the community. Results of this randomized study indicated that this intervention actually produced worse results than the comparison condition, IOP only, over the 12-month follow-up, as indicated by the composite measure described above and cocaine urine toxicology. The authors speculated that providing such an intensive continuing care intervention in parallel with IOP may have overburdened and possibly confused patients in the study. Finally, 12-month outcomes from an ongoing study examining a 12-month version of TMC and a smartphone recovery program indicated that patients randomized to TMC had better outcomes on measures of status and frequency of alcohol use and heavy alcohol use than did those randomized to TAU.[20]

The impact of telephone continuing care on criminal justice outcomes was examined by combining patients with cocaine use disorder from three continuing care studies[8,21,22] and comparing outcomes among those randomized to IOP plus

TMC and those randomized to IOP only.[23] The outcome measure was criminal convictions in the 4 years after admission to treatment. Controlling for a criminal sentence in the year prior to baseline, gender, age, and continuing care study, people with cocaine use disorder randomized to an IOP plus a telephone-based continuing care intervention had 54% lower odds of a criminal conviction and sentence in the 4 years after enrollment into the continuing care study, compared to those randomized to an IOP alone.

A 12-week version of the TMC protocol described in the studies above also was evaluated by Timko and colleagues.[24] Patients (90% male) with co-occurring SUD and a psychiatric disorder who were receiving treatment in an inpatient psychiatric facility were randomized to receive 12 weeks of TMC or standard continuing care. Outcomes obtained for up to 12 months post–continuing care indicated that TMC did not improve substance use outcomes or increase attendance at self-help programs compared to standard care. The authors speculated that the intervention may have been too brief and not intensive enough to improve outcomes in what was already a fairly comprehensive program. In addition, work by McKay and colleagues has indicated that TMC may be more effective for women than for men.[25,26]

Economic analyses

Two investigations of the economic impact of TMC also have been published. The first study[27] examined the 12-week version of TMC that was evaluated by McKay and colleagues.[21] The study found that TMC was less expensive per client ($569) than treatment as usual aftercare with group counseling ($870) or than individual RP ($1,684). TMC also was more effective, with an abstinence rate of 57% compared to 47% for TAU. Thus, relative to TAU, TMC produced a highly favorable negative incremental cost-effectiveness ratio (-$1,400 per abstinent year). TMC also proved favorable under a benefit-cost perspective.

The second study[28] examined the 24-month version of TMC evaluated by McKay and colleagues.[18] The study evaluated the cost-effectiveness of TMC with and without incentives as a continuing care protocol for individuals with cocaine use disorder. Results suggest that, for the average client, TMC is a cost-effective strategy for reducing substance use, particularly if society is willing to pay more than $30 per day of abstinence. TMC plus incentives, on the other hand, was less cost-effective than TAU and was slightly less effective and more costly than TMC alone.

The results are reinforced by the societal cost analysis, which indicated that TMC generated the greatest reduction in societal costs overall ($1,564 on average). However, the TMC plus incentives condition had very high net savings ($2,138 from provider perspective, and $1,343 from societal perspective) for those patients who had a poor initial response to IOP as indicated by continued substance use. This finding illustrates that, from an economic perspective, it is advantageous to monitor substance use early in treatment and to tailor continuing care on the basis of whether initial abstinence is achieved. Continued substance use early in IOP could flag higher-risk individuals who are more likely to require more extensive and expensive interventions such as TMC plus incentives to achieve good outcomes over longer periods of time. The results of this study suggest that for such individuals, increased societal benefit will more than offset the added costs of the more expensive continuing care intervention.

Mediation effects

In the McKay et al. study, the positive effects of telephone continuing care relative to TAU (group counseling) over a 2-year follow-up were mediated by self-help involvement during continuing care as well as self-efficacy and commitment to abstinence 3 months after treatment.[21] Scores on these measures were higher in the telephone condition relative to TAU, the measures predicted subsequent substance use outcomes, and analyses indicated significant mediation effects.[29]

Summary

Telephone continuing care appears to improve outcomes consistently for individuals with AUD. The findings for individuals with drug use disorders are more varied, with some studies generating no effects or even negative effects and others yielding positive effects in the full sample or in higher-risk subsamples. In addition, telephone continuing care has been found to be cost-effective and cost-beneficial compared to TAU, and to reduce the risk of criminal convictions in the 4 years following treatment intake.

Recovery Management Checkups

Efficacy and effectiveness analyses

Recovery management checkups (RMC) is a continuing care intervention that provides individuals who have entered treatment for SUD with long-term monitoring of their substance use and active attempts to reengage them in treatment when needed.[30-33] In RMC, an in-person clinical assessment is provided every 3 months by using standardized instruments as well as urine testing for substance use. When the clinical assessment indicates a need for active treatment, individuals are transferred to a linkage manager, who uses motivational interviewing techniques to help them recognize and acknowledge their resumption of substance use and need for additional treatment. Formal barriers to reentering treatment are discussed and addressed, and scheduling and transportation to treatment are arranged.

Three randomized trials comparing the RMC intervention with TAU have found positive effects on substance use outcomes.[30-33] The first study in this series assigned 448 adults with chronic substance use to receive RMC plus standard treatment for 2 years or standard treatment alone.[30,32] More than 90% of those randomized to RMC were seen at each quarterly assessment; these adults received the intervention if they were designated as in need of treatment, as indicated by "out of control" use in the prior 90 days. In intent-to-treat analyses, patients assigned to the RMC group, compared to those who received standard treatment alone, had fewer quarterly assessments in which they were found to be in need of SUD treatment. However, there were no significant differences between the two groups in substance-related problems per month or in total days of abstinence.

A second study randomly assigned 446 adults with chronic substance use disorder to receive RMC plus standard treatment for 4 years or standard treatment alone.[31] In intent-to-treat analyses, patients assigned to the RMC group had fewer quarters in which they were found to be in need of SUD treatment, fewer substance-related problems per month, and more total days of abstinence (1,026 vs. 932 days) compared with patients in the control group who got assessments only.

A third trial randomly assigned 480 female offenders referred from incarceration to community-based SUD treatment to TAU versus TAU plus RMC provided for 3 years.[33] Results indicated that RMC was beneficial for women who were not on probation. For example, among women not on probation, those who received RMC, compared with those who received TAU alone, were more likely to receive any days of SUD treatment (9% vs. 5%), less likely to engage in weekly alcohol and drug use (47% vs. 60%), and less likely to engage in any HIV-risk behavior (66% vs. 73%). Conversely, there were no significant positive effects for RMC in women on probation, possibly because they were already closely monitored.

Economic analyses

Cost-effectiveness was examined in the study in which 446 adults with chronic SUD were randomized to receive RMC for 4 years or quarterly assessments only.[31] Over the 4-year trial, RMC cost on average $2,184 more than conducting quarterly assessments only. The incremental cost-effectiveness ratio for RMC was $23.38 per day abstinent and $59.51 per reduced problem related to excessive substance use. When additional costs to society were factored into the analysis, RMC was less costly and more effective than quarterly assessment only.[34]

Summary

RMC has consistently produced better substance use outcomes and quicker reentry into treatment during relapses than have assessments without intervention. Results also have indicated that RMC is a cost-effective and potentially cost-saving intervention.

Continuing Care Based on Physician Health Programs

The model of continuing care used to treat physicians and pilots features intensive treatment initially, combined with extended continuing care for 5 years or more, and frequent random drug testing over that period. The active ingredients of the intervention are thought to be rapid detection of relapse to facilitate outreach, accountability, and social support. Several residential programs have developed continuing care interventions based on this model. One of these programs, My First Year of Recovery (MyFYR), was recently evaluated in a single-group observational study with no control group.[35] MyFYR consists of random urine toxicology tests, recovery coaching, and a web-based application that links important individuals in the patient's life (e.g., spouse, employer, other family members, provider) and supplies updates to these individuals on the patient's urine testing compliance and results.

This evaluation found that patients who received MyFYR provided 70% of the scheduled urine samples over a 12-month period, for an average of 16.4 urine samples per patient.[35] As determined by urine toxicology and client and family reports, 54% of the patients had some use of alcohol or drugs during the follow-up period. Of these relapsed patients, 71% were retained or re-engaged in MyFYR. Of these retained or re-engaged patients, 50% were able to re-establish abstinence for 2 months or more, as documented by multiple negative urine toxicology results. These results suggest that continuing care based on physician health programs also may be effective for individuals who are not motivated to participate in order to regain or maintain a professional license and a high-paying job. However, randomized studies with proper control conditions are needed before any conclusions are drawn about the effectiveness of this approach.

CARE MANAGEMENT IN PRIMARY CARE

Clinical trials have been conducted to determine whether management of SUD, including ongoing continuing care, is feasible in primary care. Fiellin and colleagues randomized primary care patients with opioid use disorder to standard medical management with once-weekly dispensing of buprenorphine–naloxone, standard medical management with thrice-weekly dispensing, or enhanced medical management with thrice-weekly dispensing.[36] All treatments were provided for 24 weeks. Results indicated that there were no differences between the three conditions on any of the primary substance use or retention measures.

In a second study, 563 patients with alcohol or drug use disorders who were completing medically supervised detoxification were randomly assigned to chronic care management for substance use disorder in primary care or to usual care for these disorders in primary care.[37] The chronic care management intervention was delivered by an interdisciplinary team consisting of a nurse care manager, a social worker, an internist, and a psychiatrist with addiction expertise. At the 1-year follow-up, the chronic care management group and the control group did not differ on abstinence from heavy drinking, opioids, and stimulants (40% vs. 42%). There were no significant differences in other outcomes except fewer alcohol problems were reported by those with alcohol use disorder in the chronic care management group, a small effect of questionable clinical significance. Moreover, a follow-up analysis from this study also found no positive effects for subsets of patients in the chronic care management group with co-occurring major depression or post-traumatic stress disorder.[38]

A third clinical trial randomly assigned 82 women with a history of homelessness and alcohol use problems to a 6-month chronic care intervention or to usual care from primary care

doctors without specialized training in alcohol interventions.[39] The chronic care intervention consisted of brief intervention by a primary care doctor, referral to alcohol treatment services, and ongoing support from a case manager. Both conditions significantly reduced their alcohol consumption. There were no differences between the groups in reductions in drinking, housing stability, or mental or physical health.

In a fourth clinical trial, 163 patients with a DSM-IV diagnosis of alcohol dependence treated in primary care were randomly assigned to 26 weeks of alcohol care management or to referral for standard treatment in a specialty outpatient addiction treatment program.[40] The care management program, which was provided in person and by phone, focused on the use of pharmacotherapy and psychosocial support. Compared with patients in the standard treatment group, patients receiving care management attended clinic visits more frequently, were more likely to receive naltrexone (12% vs. 66%), and had a smaller proportion of heavy drinking days per month. Overall abstinence did not differ between groups.

These studies generated little evidence on how to improve the treatment of patients with a drug or alcohol use disorder in primary care. However, offering alcohol care management to patients in primary care who have AUD does appear to be more effective than referring them to specialty care.

USE OF MOBILE HEALTH TECHNOLOGY IN CONTINUING CARE

There are three potential roles for mobile health technology such as smartphone and texting programs in the delivery of continuing care. First, the technology could be used in conjunction with other behavioral interventions to provide automated support between therapy sessions and to convey information on a patient's status back to the provider. For example, the A-CHESS (Addiction–Comprehensive Health Enhancement Support System) smartphone program has a number of supportive functions that can be accessed 24/7, including a chat room populated by others using the app, a library of materials on how to handle risky situations and other stressors, relaxation aids, and rapid connections to specified social supports.[41] In addition, the app sends out daily and weekly assessments to patients using the system, and the patients' responses are available in a dashboard that can be accessed by providers. The system also can be set to automatically send emails to providers when a patient reports worrisome information. Second, apps and SMS (short message service) could be used as stand-alone continuing care, perhaps for individuals who have limited access to more traditional clinic-based continuing care and for those further along in recovery. Finally, mobile heath can be an option for individuals who prefer virtual rather than in-person treatment.

So far, the apps and SMS programs that have been developed for individuals with SUD tend to fall into two main types.[42] Several programs provide simplified versions of complex evidence-based behavioral interventions, such as CBT and the community reinforcement approach. These programs include CBT4CBT[43] as well as reSET and reSET-O by Pear Therapeutics. Others, such as A-CHESS,[41] do not attempt to provide manualized therapy interventions such as CBT to users. Rather, they have a range of other features designed to support recovery, such as self-monitoring, information on dealing with high-risk situations, tools for relaxation or distraction, and ways of connecting with peers or treatment providers. Most of these interventions have not been developed specifically for continuing care, but could potentially be used in that role. However, A-CHESS and two texting interventions were designed for the provision of continuing care.

In a controlled trial of A-CHESS, patients with alcohol use disorder ($N = 349$) who had completed residential treatment were randomized to receive A-CHESS for 8 months or standard continuing care only.[41] The participants continued to use the A-CHESS system throughout the 8-month period during which it was provided. At 8 months, 70% of subjects were using A-CHESS at least

weekly, compared to 92% at 1 month. Overall, participants used the system on 40% of the days they had access to it. Although frequency of reported alcohol use was low in both conditions during follow-up, patients receiving A-CHESS reported 49% fewer days with risky drinking in the prior 30 days at the 4-, 8-, and 12-month follow-up as compared to those in TAU. Rates of alcohol abstinence within the prior 30 days were higher in A-CHESS than in TAU at the 8-month follow-up (78% vs. 67%) and the 12-month follow-up (79% vs. 66%). A secondary analysis found that the positive effects of A-CHESS were mediated by increases in participation in outpatient treatment but not by increases in attendance at mutual health groups.[44]

A second trial of continuing care for patients with AUD found that providing A-CHESS, a smartphone, and a data plan for 12 months significantly reduced days of alcohol use and heavy alcohol use over that period relative to patients who did not receive A-CHESS.[20] However, a condition that combined both A-CHESS and TMC in an integrated package did not produce superior alcohol use outcomes to A-CHESS or TMC alone.[20]

The efficacy of a recovery support program with mobile texting, called Educating and Supporting inQuisitive Youth in Recovery (ESQYIR), was evaluated by Gonzales and colleagues.[45] The intervention consisted of 12 weeks of daily text messages about disease management, which included monitoring, feedback, reminders, education, and support. Monitoring texts were sent out every afternoon, along with feedback texts tailored on the basis of responses to the monitoring texts. In the study, 80 youths who had completed an initial phase of treatment were randomized to aftercare as usual (referral to self-help programs) or to ESQYIR. At 6- and 9-month post-aftercare follow-up, youths randomized to ESQYIR were less likely than those in TAU to test positive for their primary drug. They also reported significantly higher self-efficacy and were more likely to participate in recovery-oriented activities. Secondary analyses found that the positive effect of the intervention was mediated by increased involvement in pro-recovery activities other than Alcoholics Anonymous (AA) or Narcotics Anonymous (NA), but not by participation in AA or NA.[46]

A randomized study in Switzerland evaluated a continuing care intervention using text messaging to monitor self-selected drinking goals. The intervention also provided motivational text messages and telephone calls when participants failed to achieve goals or asked for support.[47] Participants in the SMS condition responded to 88% of the SMS prompts, and 44% sent at least one request for help. Compared to standard continuing care, the intervention reduced the rate of at-risk drinking from 42% to 29%, a nonsignificant decrease.

Finally, Rose and colleagues developed an automated continuing care intervention that is delivered by telephone via interactive voice response (IVR).[48] Participants call into the system once per day to report on 16 factors, including substance use, mood states, craving, self-efficacy, risk situations, sobriety support, substance-free recreation, and coping. When participants are judged to be at risk based on this assessment, tailored feedback is provided. Other features include CBT skills encouragement, coping skills review, and coping skills practice. Each month, participants also receive a personalized voice message from a counselor, which includes comments on progress and suggestions. The IVR system was evaluated in a study in which individuals with AUD who had completed 12 weeks of CBT were randomized to 4 months of the IVR system or of usual care, and followed for 12 months.[48] Most primary analyses indicated no differences in drinking outcomes between the two conditions. However, a group x time interaction on drinking days per week favored the IVR condition. In addition, in participants who were abstinent at the end of the 12-week initial CBT intervention, outcomes on any drinking at the 2- and 4-month follow-up and any heavy drinking at the 4-month follow-up favored IVR over usual care.[48] However, given the large number of analyses performed, these positive results should be interpreted cautiously.

Most of these studies testing continuing care with mobile health interventions have yielded positive effects on substance use outcomes. However, despite the initial promise of mobile health interventions, significant challenges remain in the provision of continuing care via mobile health apps and SMS. A recent systematic review found rapidly declining rates of smartphone use in most studies of interventions for mental health problems.[49] This has sometimes been the case with mobile health interventions for addiction.[20,42] Also, potential users must have access to a smartphone and data plan, or a telephone with SMS capabilities for texting-based interventions.

INCENTIVES FOR ATTENDANCE AND ABSTINENCE

Several studies have examined the impact of providing incentives either for attendance at continuing care or for drug abstinence during continuing care. In one study, patients with cocaine use disorder who had completed 2 to 4 weeks of an IOP were randomized to receive additional individual CBT for 5 months (yes/no) and to receive monetary incentives for cocaine abstinence over 12 weeks (yes/no) in a 2 x 2 design.[50] In the group that received both CBT and incentives for abstinence, participants were eligible for the incentives only if they were attending CBT sessions. Results over an 18-month follow-up found a significant positive main effect for abstinence incentives, and the best outcome was obtained in the group that received both incentives and CBT.[50] Kirby and colleagues compared the standard 12-week contingency management for cocaine abstinence protocol with an extended 36-week protocol in methadone-maintained adults with cocaine use disorder, and found that the extended protocol produced significantly longer durations of continuous cocaine abstinence during weeks 1 through 24 and higher rates of cocaine-free urine samples during weeks 24 through 36.[51] A third study examined the impact of providing $10 as an incentive for each continuing care session attended in the first year of a 2-year intervention for IOP patients with cocaine use disorder.[18] The incentive almost doubled the number of continuing care sessions attended, but had no effect on cocaine use outcomes or on overall drug and alcohol use. Finally, Lash and colleagues found that adding social reinforcement of abstinence to an intervention that included attendance contracts and prompts improved aftercare attendance and abstinence outcomes compared to contracts and prompts only.[52] These studies have found strong evidence of the efficacy of providing incentives for abstinence during continuing care. However, there is no evidence that providing incentives for continuing care attendance improves outcomes.

ADAPTIVE TREATMENT AND CONTINUING CARE

There is a great deal of heterogeneity in how individuals respond to SUD treatment, including continuing care.[4] Even with the most effective interventions, a significant percentage of patients will not exhibit a strongly positive response. Therefore, it is important to be able to adapt, or adjust, treatment when patients are not getting better.[53] Moreover, there can be considerable heterogeneity within individuals in how their recovery is progressing over time. For example, a patient may do well in the first phase of treatment and in the first few months of continuing care, but then relapse and have a difficult time regaining abstinence. In a number of other areas in medicine—such as infectious diseases, hypertension, and cancer—algorithms have been developed to aid physicians in selecting optimal "plan B" treatments when the initial treatment offered does not work well.

In the treatment of SUD, less is known about how to best address heterogeneity of response between patients and within patients. However, some initial progress has been made. RMC addresses within-patient heterogeneity in response over extended periods of time by providing assessments every 3 months, with a protocol to

transition individuals back into SUD treatment if they return to heavy alcohol or drug use.[30-33] The research on TMC found that this extended intervention was most helpful for patients who did not do well in the first month of IOP, as evidenced by continued substance use,[18] poor social support,[25] or low motivation for recovery.[25] Results over a 24-month follow-up period identified several subgroups for which adding TMC to IOP was particularly effective relative to IOP only: participants with poor social support, those with less motivation for recovery, and those with more prior treatment experiences.[25] In addition, TMC was more beneficial for women participants than for male participants in two studies.[25,26]

One study with adolescents sought to determine the kind of continuing care that was best for those who had a poor response to outpatient treatment.[16] Adolescents who did not achieve abstinence after 7 weeks of outpatient treatment were randomized to 10 weeks of individual CBT or A-CRA. Of these patients, 37% completed continuing care and 27% achieved abstinence. However, there were no differences in outcome between the two continuing care conditions.

These findings suggest that assessments conducted prior to and during continuing care provide data that can be used to improve outcomes by triggering changes to treatment.[4,54] Ideally, these assessments should address recent or current substance use as well as other factors that are linked to relapse. For example, current depression, craving poor social support, and lack of commitment to abstinence all have predicted subsequent relapse in multiple studies. Even if a patient remains abstinent during continuing care, it may be important to modify the intervention in some way if craving or depression increases.[4]

RESEARCH ASSESSMENT EFFECTS

There is evidence that research follow-up can have a positive effect on alcohol and drug use outcomes in treatment studies. Clifford and colleagues found that study participants who received more follow-ups had significantly better alcohol use outcomes.[55] In a second study, participants were randomly assigned to one of four research assessment follow-up schedules that varied by frequency and duration. Those assigned to the infrequent and brief assessment condition had worse drinking outcomes (i.e., higher frequency, greater quantity), higher negative consequences of drinking, and worse drug use outcomes than did those assigned to more frequent and longer assessments.[56] Other studies in this area have produced more mixed results.[57] Although the mechanisms of action are not well understood, the process of being asked about substance use may increase its salience for the participant, or may be therapeutic in some other way.

MEDICATIONS

The U.S. Food and Drug Administration (FDA) has approved several medications for AUD and opiate use disorder. With regard to medications for AUD, there is no convincing evidence to date that longer periods of use produce better drinking outcomes than do shorter periods, or that using the medications in the context of continuing care produces better outcomes. However, this is largely because little research in this area has been done; most studies have evaluated only 12- or 24-week courses of medication. In one exception to this general trend, a study with male veterans with chronic, severe alcohol addiction found no differences between placebo, naltrexone for 3 months, and naltrexone for 12 months conditions in frequency of drinking or number of drinks per drinking day at 1-year follow-up.[58] Conversely, there is good evidence that longer periods on medications for opiate use disorder produce better outcomes than shorter periods, and at this point, detoxification is not recommended.[59] There are no FDA-approved medications for stimulant or cannabis use disorder. More research is needed to determine if longer durations on medications for AUD are beneficial, and to identify successful strategies to increase long-term use of effective medications.

CONCLUSIONS

At this point, continuing care is widely believed to be an important component of effective treatment for substance use disorder, particularly for those individuals with a problem severe enough to require specialty care treatment. The research base generally has supported the efficacy of continuing care for both adolescents and adults, but the picture is complex. Reviews have found relatively small to moderate effects when results from individual studies are averaged or combined in some way.[2,8] However, there is some evidence that continuing care of longer duration that includes more active efforts to keep patients engaged may produce more consistently positive results.[2,13] Moreover, patients at higher risk for relapse—by virtue of continued substance use in the first phase of care, or poor social support or low motivation early in treatment—may benefit to a greater degree from continuing care than those patients with a better prognosis.[18,25,26]

Several new approaches show promise for the provision of continuing care. These include incentives for abstinence; use of automated mobile health interventions to augment more conventional counselor-delivered interventions; and extended treatment and monitoring programs that, until very recently, have been provided only to pilots and doctors. There is also evidence that primary care can be used to provide medications for opioid and alcohol use disorders over extended periods; however, more research is needed to determine the optimal mix of behavioral treatments and other psychosocial services in this setting. Regardless of the intervention selected for use, it is clear that the status of most patients with SUD will change and evolve over time, and interventions need to include provisions to assess patients on a regular basis and to change or adapt treatment when warranted.[4,25,26,54] More research is needed to develop evidence-based protocols for adapting continuing care interventions over time and addressing nonresponse. In addition, to promote higher rates of stable, long-term recovery, additional work is needed to develop methods to integrate continuing care interventions more effectively with other supports available in the community and to promote greater involvement in rewarding activities that provide enjoyment and a sense of meaning and purpose.[6]

The field is also starting to move toward more specific guidelines regarding the characteristics of high-quality continuing care. A recent review of evidence-based guidelines and quality indicators derived 13 specific quality indicators, including the provision of information on self-help, relapse prevention strategies, involvement of family members, provision of both behavioral interventions and medications, minimum of 3 months of follow-up, and patient involvement in development of continuing care plans.[60] The development of evidence-based clinical practice guidelines to facilitate wider implementation of effective continuing care would be a major advance for the field. As discussed here, these guidelines likely will need to include information on adapting continuing care over time at the individual level to achieve optimal outcomes. For example, higher-risk patients likely will benefit from continuing care interventions with longer durations, and some patients may have preferences for particular approaches or modalities (e.g., mobile health vs. clinic-based care).

Finally, although the efficacy of specific continuing care interventions is certainly important, the crucial roles played by providers who deliver these interventions have not received sufficient attention. Some providers are simply better than others, but the individual characteristics and training that facilitate greater success as a continuing care provider have received little attention. Intriguing work in this area has been done by Karno and Longabaugh, who conducted an elegant series of studies on the impact of continuing care therapist counseling style, and the interaction between counseling style and patient characteristics, on drinking outcomes.[61,62] This work has involved the careful coding of therapist and patient behaviors during continuing care treatment sessions for factors such as focus on emotional material and directness.

In one study, patients with clinically elevated depression scores had better drinking outcomes if their therapists had a *low* focus on painful emotional material, and worse outcomes when the therapist was more focused on such material.[61] Therapist focus on emotional material did not predict drinking outcomes in patients who were not depressed. A second study looked at therapist directiveness, or the degree to which the therapist employed confrontation, interpretation, and closed-ended questions; addressed in-session resistance; initiated topics; and provided information.[62] Results indicated that higher therapist directiveness predicted worse drinking outcomes in high-anger patients, and better drinking outcomes in low-anger patients. Therefore, in addition to proceeding with the further development and evaluation of innovative continuing care interventions and methods of intervention delivery, much more attention should be devoted to improving the therapeutic skills of providers and studying the process of change within continuing care sessions.

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Alcohol Screening, Brief Intervention, and Referral to Treatment (SBIRT) for Girls and Women

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Females ages 12 and older are the fastest growing segment of alcohol consumers in the United States, with the past decade showing a 16% increase in alcohol use per 12-month period and a 58% increase in high-risk drinking (i.e., > 3 drinks in a day and/or > 7 drinks in a week) per 12-month period. The increase in alcohol use and risk drinking poses unique and serious consequences for women. Women have a more rapid progression to alcohol-related problems and alcohol use disorders (AUD) than men, and if pregnant, women can potentially expose the fetus to alcohol. Screening, brief intervention, and referral to treatment (SBIRT) is an evidence-based, integrated public health approach used to identify and address risky alcohol use among women in a variety of health and social service settings. This article presents the current status of SBIRT among girls ages 12 and older, women of childbearing age, and older women. Screening instruments, brief interventions, and implementation issues specific to women of all ages are described. Through this review of the current literature, care providers can determine best practices for the prevention and treatment of risk drinking in women of all ages presenting in health care settings.

KEY WORDS: brief intervention; risk; alcohol; SBIRT; screening; women; female adolescents

INTRODUCTION

Alcohol is the most commonly consumed substance among Americans ages 12 and older, and women are the fastest growing segment of alcohol consumers in the United States.[1,2] Female alcohol consumption that meets criteria for risk drinking, defined as more than three drinks in a single day or more than seven drinks per week, has the potential to negatively affect the health and well-being of women across their life spans.[3] Evidence indicates converging patterns of alcohol consumption between men and women resulting from recent increases in female alcohol

use behaviors.[2,4,5] For instance, data collected in the past decade reveal that among U.S. women, alcohol use increased by 16% per 12-month period, high-risk drinking increased by 58% per 12-month period, and diagnoses of alcohol use disorder (AUD)—as defined in the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders*—increased by 84% per 12-month period.[2] These increases have unique and serious consequences for women given that they experience a more rapid progression—at lower consumption levels—to alcohol-related problems and AUD than men.[6,7]

This recent increase in female alcohol consumption underlines a need for additional research and clinical efforts to address alcohol use among girls and women.[2,4] Because risky drinking poses unique and detrimental consequences to all women, age and life circumstances should not preclude any subset of girls or women from research or clinical efforts to address this growing public health concern. Indeed, risky alcohol use is prevalent among young girls;[8,9] pregnant and postpartum women;[10,11] victims of child abuse,[12] sexual trauma,[13] and intimate partner violence;[14] female veterans;[15] incarcerated girls and women;[16] sexual-minority women;[17] and older women.[5] Due to alcohol's nondiscriminatory nature towards varying groups of women, universal screening, brief intervention, and referral to treatment (SBIRT) appears to be an appropriate, evidence-based public health approach capable of identifying and addressing risky alcohol use among females in a variety of health and social service settings.[18] This article presents a review of the literature regarding the role of SBIRT in addressing risky alcohol consumption among girls (ages 12 to 18), women of childbearing age (i.e., ages 18 to 44), and older women (i.e., ages 65 and older). There is a general lack of currently available research data specific to women ages 45 to 64, but other than risk of pregnancy associated with women ages 18 to 44, the role of SBIRT is similar for women ages 45 to 64 to that for younger women. Databases used for this review include PubMed, Cochrane Library, Google Scholar, and Academic Search Complete. The reference lists of selected articles and texts were also explored.

SBIRT

The current SBIRT model is based on a recommendation from the National Academy of Medicine (previously called the Institute of Medicine) to develop integrated service systems that bridge the gap between primary prevention and treatment services for individuals with problematic alcohol and/or illicit drug use.[19] In 2003, the Substance Abuse and Mental Health Services Administration (SAMHSA) established an initial SBIRT grant program, with the intent of integrating behavioral health services into settings where individuals who engaged in risky substance use behaviors could be identified and offered an appropriate level of intervention and care.[20] Findings from this initiative suggest that SBIRT is associated with improvements in alcohol use outcomes.[20,21]

The U.S. Preventive Services Task Force (USPSTF), an independent entity consisting of experts in preventive medicine, recently updated its recommendation for care providers. This update recommends that care providers screen all adults ages 18 and older, including pregnant women, for risky alcohol use and provide brief behavioral counseling interventions, when appropriate, to reduce unhealthy alcohol use.[22] Screening adolescents younger than age 18 was not included in the updated recommendation; the USPSTF concluded that there is insufficient evidence to properly assess the benefits versus risks for alcohol screening and brief interventions (BI).[22] The American Academy of Pediatrics (AAP), however, has recommended the practice of screening and providing BI to adolescent alcohol users, citing low cost, minimal potential for harm, and emerging evidence of the benefit that SBIRT may have among adolescent alcohol users.[23]

SBIRT is intended to identify, reduce, and prevent problematic alcohol use behaviors and is made up of three key components: screening, brief intervention, and referral to treatment. Ideally, the first step of the SBIRT process is to administer a validated prescreen

instrument to all presenting individuals in a practice setting, as part of the routine intake procedure, to identify those who are drinking at or above risky levels.[24,25,26] When prescreen instruments detect consumption at risk levels, measured by standard drinks (14 grams or 0.6 fluid ounces of pure alcohol) consumed, a more comprehensive assessment can be conducted to gauge the severity of alcohol use and inform BI and/or treatment options.[3] For example, the National Council for Behavioral Health recommends that a symptom checklist or other validated assessment be used to obtain alcohol-related symptoms from individuals whose prescreen indicates risky consumption.[26] If it is determined that an individual is consuming alcohol at moderate risk levels (i.e., above NIAAA threshold for low-risk consumption but not at a level indicative of AUD), then the second step in the SBIRT process is to complete a BI protocol. BIs are often based on principles of motivational interviewing (MI) and aim to increase awareness of alcohol-related risks and consequences and to encourage motivation for change. If an individual is identified to be drinking at levels that are suggestive of AUD, then referral to specialized treatment for further assessment and care is recommended.[27]

SCREENING

SBIRT begins with universal screening, the goal of which is to identify individuals who have, or are at risk of developing, alcohol-related problems.[27] Universal screening that is adherent to SBIRT standards, and described in multiple SBIRT practice guides, involves the administration of a validated prescreen instrument that has been limited to a few questions needing only simple responses.[24,26,28,29] Ideal screening instruments have high sensitivity and specificity ratings, with cutoff scores designed to maximize both ratings in order to minimize false positives and false negatives.[30] However, for prescreen instruments that are intended to be universally administered, priority is often given to sensitivity over specificity so that individuals in large clinical populations (e.g., women in primary or reproductive care settings who consume alcohol while pregnant) are appropriately identified for further assessment.[30,31]

This article classifies screening instruments into prescreen and screen categories. The purpose of prescreening is to assess an individual's frequency and quantity of alcohol use to determine whether the person is drinking at age-specific risk levels, whereas the purpose of screening is to elicit alcohol-related symptoms from those that have been identified as drinking at risk levels. Prescreens and screens should work in succession, and because many instruments are capable of serving both screening purposes, this dual process is sometimes consolidated into a single step within clinical practice settings.

Universal prescreening and screening efforts must be conducted using valid, age-appropriate instruments with cutoff scores that are tailored to a population's sex and age (see Table 1).[32] Following is an overview of screening practices and instruments that have been validated for use within specified age groups of girls and women.

Adolescents

NIAAA, SAMHSA, and AAP recommend that care providers screen all adolescents and young adults ages 12 to 21 for alcohol and substance use behaviors using validated screening instruments on a yearly basis and, as needed, during acute care visits.[33] There are currently three prescreen options that are applicable to adolescents: the two age-specific questions found in NIAAA's *Alcohol Screening and Brief Intervention for Youth: A Practitioner's Guide*;[29] the first three questions of the Screening to Brief Intervention (S2BI); and the three-item Alcohol Use Disorders Identification Test–Concise (AUDIT-C).[33] The two age-specific questions found within NIAAA's guide ask about an adolescent's personal alcohol use as well as that of their friends and is appropriate for children and adolescents between the ages of 9 and 18. This AAP-endorsed guide includes elementary, middle, and high school age-appropriate variations of these two questions, which allow for accurate correlation of patient responses to current or potential risky alcohol consumption.[29] The S2BI instrument screens

for alcohol, tobacco, marijuana, and illicit drug use by asking a single frequency-of-use question per substance. This screener is highly sensitive and specific at discerning among various risk categories, from no use to severe substance use disorder (SUD). Although not a formal diagnostic instrument, the S2BI has been shown to closely correspond with the likelihood of current SUD.[34] The AUDIT-C, validated for use with young people ages 12 to 19, has three questions to identify the quantity and frequency of alcohol consumption.[32,35,36]

When adolescents score positive on a prescreen instrument, indicating some level of risky alcohol consumption, they are asked to respond to additional, more specific screening questions to determine whether a BI or referral to treatment is appropriate. Screening instruments that have been validated for use with adolescents and can be used to inform next steps include the 10-item Alcohol Use Disorders Identification Test (AUDIT); the Brief Screener for Tobacco, Alcohol, and Other Drugs (BSTAD); and the Car, Relax, Alone, Forget, Friends, Trouble (CRAFFT) screening instrument.[23,32,37] The AUDIT is the most widely tested alcohol screening instrument and is commonly used to assist in the early identification of individuals engaging in risky drinking behaviors.[22] Furthermore, the AUDIT has been validated for use among young people,and evidence suggests a lack of gender bias between female and male adolescents.[32,35] The BSTAD, an adaptation of the questions found within NIAAA's guide includes questions on alcohol, tobacco, and drugs, and has been shown to be highly sensitive and specific at identifying risky past-year alcohol use among adolescents ages 12 to 17.[38] Recommended by both NIAAA and AAP, the CRAFFT has been validated across pediatric settings to identify risky substance use behaviors among adolescents.[18,39] Interestingly, the CRAFFT was able to detect preconception substance use in a small cohort of pregnant adolescents and young women between ages 17 and 25.[33,40] The CRAFFT has many advantages, including a short administration time and high sensitivity and specificity.[33] It also shows no evidence of gender bias.[36]

Screening adolescents for risky alcohol use can be incorporated into psychosocial approaches. For example, the home environment, education and employment, eating, peer-related activities, drugs, sexuality, suicide/depression, and safety from injury and violence (HEEADSSS) and the strengths, school, home, activities, drugs/substance use, emotions/depression, sexuality, safety (SSHADESS) tools are interview frameworks specifically designed for use with adolescents in health care settings.[23,33] The HEEADSSS interview is a practical, complementary strategy that establishes rapport by asking less threatening questions at the beginning of the encounter before transitioning to more personal or potentially intrusive topics such as substance use.[33] The SSHADESS interview covers the same life areas as the HEEADSSS, but it also underscores adolescents' resiliency by identifying their perceived and realized strengths before asking questions related to environmental context or risky behaviors.[23]

A caveat is that an assurance of confidentiality is needed to improve the accuracy of adolescent screening responses. Because most adolescents are not comfortable discussing topics like alcohol use and sexual activity in the presence of a parent or guardian, clinicians are encouraged to create scripts or other procedures to excuse the accompanying adult from a portion of the health exam.[33] For example, asking the adult to leave the room during the physical exam portion validates the adolescent's developmental need for privacy and creates space for a confidential discussion concerning alcohol and other potentially risky behaviors.[33] Federal and state privacy laws entitle adolescents to privacy regarding substance use treatment, so adolescents may further benefit from a script ensuring that what is disclosed to the provider will not be shared with their caregiver unless an immediate risk of injury to oneself or another is divulged.[33]

Women of Childbearing Age

For women of childbearing age, the USPSTF supports the use of brief prescreening instruments for alcohol with 1 to 3 items—such as the

AUDIT-C or the NIAAA-recommended Single Alcohol Screening Question (SASQ), also referred to as the "single binge drinking question"—to quickly identify women who may be at risk.[22,41,42] The use of a single binge drinking question has also been recommended as a first step to effectively and efficiently identify women who are likely to be at risk of an alcohol-exposed pregnancy (AEP).[43] For example, a single binge drinking question was found to correctly identify 99% of women, from two countries and cultures, who had been identified as at risk of an AEP.[43] The Quick Drinking Screen (QDS) is another brief instrument that is efficacious at initially identifying women at risk of an AEP.[44] Items from the QDS were measured against data collected from a 90-day timeline followback (TLFB) assessment among a sample of women already determined to be at risk of an AEP. The results found that the women's answers to QDS items were highly similar to their 90-day TLFB responses.[43]

Once a brief prescreening measure identifies a woman who is likely to be at risk for alcohol misuse and/or an AEP, it is recommended that a more comprehensive instrument be administered.[22,43] For example, the 10-item AUDIT is an efficacious measure that has been validated for use with this population.[45] There are also several assessments designed specifically for women of childbearing age, including pregnant women and women at risk of an AEP. It is recommended that universal prescreening among women of childbearing age be used to identify and assess women at risk of an AEP.[45,46] Screening this population provides the opportunity for early intervention among women who may have consumed alcohol prior to becoming aware of their pregnancy. Screening also alerts care providers of consumption levels indicative of AUD so that they can refer these women for specialized treatment.

The Tolerance, Annoyed, Cut Down, Eye-Opener (T-ACE) questionnaire was the first validated screening instrument developed to identify drinking among pregnant women. It is often used in reproductive settings, including maternity care and gynecological clinics.[25,31] In comparison to the AUDIT, the four-item T-ACE has shown slightly higher sensitivity at detecting current alcohol consumption among pregnant women.[31] In addition, the T-ACE accurately identifies varying levels of alcohol consumption and is acceptable for use among culturally diverse obstetric populations.[31] The five-item Tolerance, Worried, Eye-Opener, Amnesia, K/Cut Down (TWEAK) screening instrument is another validated questionnaire for identifying drinking among women, including those who are pregnant and those at risk of an AEP.[25,31,45] Although the TWEAK questionnaire appears to be highly sensitive at identifying heavy patterns of alcohol consumption, primarily among white women, it is less sensitive at detecting lower levels of drinking that could still be considered at risk.[25,47]

In addition to the T-ACE and TWEAK, the USPSTF also recommends the Normal Drinker, Eye-Opener, Tolerance (NET), and the Parents, Partner, Past, Present Pregnancy (4P's Plus) as screening measures capable of assessing alcohol use among pregnant women.[22,47,48] Nonetheless, the T-ACE and TWEAK reportedly perform best among pregnant women and do not appear to have a significant advantage over one another, because both are well-validated screening measures that can be quickly administered in a variety of women's health settings.[18]

Older Women

Older women are often missed by screening efforts because their alcohol-related symptoms are often mistaken for signs of aging.[49] For this reason, systems must be put into place to ensure universal screening on a recurring basis in settings that care for older women.[50] Alcohol screening should take place any time new mental or physical health symptoms arise, before prescribing a new medication, in response to major life changes (e.g., retirement, death of a spouse), and on a yearly basis as part of routine physical and mental health services.[50,51] Providers should be aware that a history of risky alcohol use among older adults often predicts future increases in drinking.[50] Prescreening questions like "During your lifetime,

have you ever used alcohol?" followed by "During the past year, have you had four or more drinks on a single occasion?" help to determine whether more comprehensive assessments are warranted.[51,52] The AUDIT-C and the two-item Substance Use Brief Screen (SUBS) are also prescreen options available for use with this population.[53-55]

Several screening instruments have been validated for use with older adults. Measures like the AUDIT include screening questions on lifetime problems to assess current alcohol-related risk.[54,56] Other screening tools include the Cut Down, Annoyed, Guilty, Eye-Opener (CAGE), the Michigan Alcoholism Screening Test—Geriatric Version (MAST-G), the Short MAST-G, and the Comorbidity Alcohol Risk Evaluation Tool (CARET).[54,57] All of these instruments gather information about the level of consumption and offer decision support for care providers.[50,54] In general, alcohol screening and assessment instruments among older women should contain questions about the frequency and quantity of alcohol use, experiences with drinking-related consequences, medication use, and feelings of depression.[50]

SCREENING RECOMMENDATIONS

There are very few studies on alcohol screening specific to adolescent females and older adult females beyond childbearing age, with a majority of information coming from mixed-gender studies. The largest body of evidence on screening women is for those of childbearing age, likely due to the added risks and harms associated with prenatal alcohol exposure. Nonetheless, universal screening should begin in early adolescence and be repeated at regular intervals across settings that provide health care and social services to girls and women. However, although alcohol screening instruments elicit important information about an individual's level of risk and alcohol-related symptoms, these tools are not a replacement for a complete substance use assessment. Because these instruments are brief and, in many cases, can be self-administered, it is often recommended that care providers use them as decision support aids to guide additional steps based on the preliminary level of risk indicated by these alcohol screening instruments.

The successful implementation of a screening protocol depends on the setting in which it is delivered. For example, settings with access to interdisciplinary professionals may find that longer, more thorough assessment instruments are practical, whereas settings with fewer resources are likely to benefit from utilizing brief instruments like the AUDIT, which has been validated for use across age groups.[32,35,56] Additionally, questions or measures may be added to assessment protocols to identify other factors known to be associated with female alcohol use behaviors (e.g., age of onset, depression and anxiety, childhood and/or intimate partner abuse, co-occurring substance use behaviors) to better inform BI and referral to treatment practices.[13,16,58,59] Moreover, care providers need to remain mindful regarding the language they use to describe alcohol-related concerns so as not to further stigmatize female populations.[60] For example, some women may be sensitive to language such as "alcoholic," "addict," or "abuser"; the use of such language may dissuade women from providing relevant information pertaining to their alcohol use behaviors. Therefore, care providers are advised to use medically accurate terms throughout their discussions regarding alcohol and substance use behaviors.[55,60]

BRIEF INTERVENTIONS

BIs are evidence-based practices that are short, targeted conversations between women and clinicians that follow screening results indicative of risky alcohol consumption. The overall goal of BIs is to help adolescent girls and women who are at risk of alcohol-related consequences by increasing their awareness about the ways alcohol use may put them at risk and encouraging their self-motivation for change.[27,61] Common components of BIs include conversations on standard drink sizes, low- versus high-risk drinking limits, and potential health effects and

social consequences of drinking.[3,62] Another common element of BIs is providing personalized normative feedback, with evidence supporting the use of gender-specific feedback for women.[63,64,65] BIs can be delivered by professionals with different backgrounds and expertise, and they can take place in face-to-face settings, over the phone, or through electronic means.[61,66] How effective BIs are can depend on the number of sessions and length of time allotted for each session. For example, systematic reviews and meta-analyses have found that very brief (i.e., ≤ 5 min) and brief single-contact interventions (i.e., 6 to 15 min) tend to be less effective than brief multicontact interventions (i.e., each contact ≤ 15 min), which evidence shows is the most effective across populations and outcomes.[18,63,67] Additionally, one meta-analysis found that extended BIs (defined by the author as BIs that required several visits, or multicontact interventions) resulted in significant change in alcohol consumption for women but not men.[68]

BIs for risky alcohol use are often based on the principles of MI. Using this collaborative, client-centered approach, providers help females explore and resolve their ambivalence toward changing unhealthy behaviors (e.g., alcohol consumption at risk levels).[69] A core tenet of MI is the use of nonconfrontational techniques to allow individuals to guide themselves toward change without feeling the need to defend their choices.[69]

Adolescents

AAP recommends basing the degree of intervention delivery for youth on the level of risk identified at the time of screening. When no alcohol use is reported, clinicians are encouraged to provide positive verbal reinforcements to motivate continued abstinence. Evidence suggests that even a few positive words from a health care provider may delay alcohol use initiation, and thus extend time for adolescent brain maturation.[23] These positive reinforcements may be critical for female adolescents to receive, especially girls at risk of early alcohol initiation,[7,58] because of the detrimental effects of alcohol on the female developing brain.[70] When infrequent alcohol use is endorsed by female adolescents, such as when an S2BI result indicates alcohol use of one to two times the previous year, it is recommended that care providers advise adolescents to abstain. This advice may combine information on negative health consequences with recognition of personal strengths and positive attributes.[23]

BIs are recommended when an adolescent screens positive for drinking at risky levels. Evidence from a recent meta-analysis of 185 studies examining the effects of alcohol-related BIs for adolescents and young adults found that the interventions effectively reduced drinking and alcohol-related consequences, with effects lasting up to 1 year and showing no demographic variance.[65]

BIs that utilize MI have been found to be effective with substance-using adolescent populations. Much of the research supporting this view falls into the harm-reduction continuum: that is, adolescents do not move directly into abstinence but rather gradually decrease their risky behavior.[71,72] In addition to the effectiveness of MI techniques within this population, a systematic review and meta-analysis conducted by Carney and Myers also found that adolescents showed a preference for individualized interventions (i.e., compared with a group format) conducted over multiple sessions (i.e., compared with a single event).[67]

In alignment with the USPSTF finding of there being insufficient evidence to evaluate the utility of BIs among alcohol-using adolescent populations, evidence specific to adolescent females who receive brief alcohol interventions is also lacking and warrants future investigation. In a recent systematic review and meta-analysis of the literature on brief alcohol interventions for adolescents and young adults, Tanner-Smith and Lipsey found a limited number of studies with boy-only or girl-only samples that reported little to no evidence of differential effectiveness based on gender.[65] There is some evidence, however, suggesting that BIs for alcohol use may be particularly effective for adolescent girls, especially when the provider is also female and the information is delivered in the context of an ongoing provider–patient relationship.[73]

Women of Childbearing Age

There is strong evidence supporting the use of BIs among pregnant and nonpregnant women of childbearing age as a means of reducing levels of alcohol consumption and risks associated with AEPs.[18,62,74] For example, in one large multisite trial, approximately 69% of women who, at intake, were drinking at risky levels and not using effective contraceptive methods reduced their risk of an AEP at the 9-month follow-up after receiving an intervention incorporating MI. The women in this study achieved risk reduction by abstaining from alcohol or drinking below risky levels, by using effective contraceptive methods every time they had vaginal intercourse with a fertile male, or both.[75] A number of randomized controlled trials with pregnant women have also reported significant reductions in alcohol use and improved newborn outcomes following the facilitation of BIs.[62]

In addition to previously mentioned common components of BIs (e.g., personalized normative feedback), interventions with women of childbearing age often also include feedback on the potential effects of alcohol on fetal and child development.[25,64] It is recommended that postpartum women receive information on infant exposure to alcohol through breastmilk and that contraceptive use should be incorporated into BIs with nonpregnant women who are at risk of an AEP.[25,64]

Efficacious prevention and intervention programs have been developed for use with women of childbearing age. One example is the CHOICES program and its adaptations: BALANCE, EARLY, and CHOICES Plus.[76,77,78] CHOICES is an established AEP prevention program based on the principles of MI and designed to provide nonpregnant women of childbearing age with information to help them make informed choices on ways to avoid an AEP.[43] The CHOICES protocol has been widely disseminated across health and social service settings (e.g., primary care facilities, jails, sexually transmitted disease clinics).[75,78,79] Also, as a result of meeting rigorous peer-review criteria, the CHOICES program was included in SAMHSA's Evidence-Based Practices Resource Center (https://www.cdc.gov/ncbddd/fasd/choices-importance-preventing-alcohol-exposed-pregnancies.html).

Older Women

Although limited, studies on BIs with older adults suggest that BIs are effective at reducing risky alcohol consumption, with sustained reductions ranging from 2 to 18 months.[80,81,82] The content and format of most BIs are similar, as are the recommendations, whether delivered to younger or older cohorts. For example, providers are advised to use nonstigmatizing and nonjudgmental language when discussing screening results and any potential alcohol-related health consequences with women.[55] Regarding older women, some experts suggest that providers may find that incorporating the women's family and friends into various parts of the BI process may prove successful.[51]

Other BIs

Multiple BI models have been created to aid in the facilitation of BI conversations.[25,27] A systematic review of BIs for risky drinking in primary care settings reported that a majority are arranged according to the SAMHSA-endorsed Feedback, Responsibility, Advice, Menu of strategies, Empathy, Self-efficacy (FRAMES) model.[33,64] Other BI models that are endorsed by SAMHSA include the Feedback, Listen, Options (FLO) model, the Brief Negotiated Interview (BNI) Steps, and the BNI and Active Referral to Treatment: Provider Training Algorithms.[27] All of these models serve as useful guides for delivering BIs and are presumed to be equally efficacious regardless of age or gender. Practitioners should choose the model that best suits their work setting.

In summary, BIs are valuable tools for reducing alcohol consumption and its associated risks (e.g., AEPs). It is vital to consider that despite a number of randomized controlled trials suggesting similar efficacy for brief alcohol interventions among women and men,[83,84] women have been less likely to receive BIs in practice. As such, lending attention to this issue is critical considering that the prevalence rates for alcohol use among women are rising.[85]

REFERRAL TO TREATMENT

Referral to treatment is a process designed to assist women with accessing specialized treatment, selecting facilities, and navigating barriers that may prevent treatment engagement.[27] Treatment options for women with AUD may include residential treatment, outpatient psychological therapy (e.g., family, group, conjoint, individual), medication-assisted treatment, self-help or support group programs (e.g., 12-step programs such as Alcoholics Anonymous), harm reduction approaches, use of a recovery coach, or any combination of these. There are also treatment options that cater exclusively to women, such as the Women for Sobriety program and women-only Alcoholics Anonymous groups. Specialized alcohol treatment should be personalized to the woman, taking into account her medical, social, and cultural needs. Providers should be aware of local treatment options in order to conduct warm handoffs—referrals facilitated in the presence of the patient to encourage communication and partnership between the patient and treatment team—when needed. Providers should also pay special attention to the treatment selection for pregnant and postpartum women to ensure that appropriate medical care and social support options are available.[25] Providers may also choose to access SAMHSA's online resource guide, which includes samples of scripts, procedures, and links to treatment locator websites.[27] Other referral resources include NIAAA's online Alcohol Treatment Navigator tool (https://alcoholtreatment.niaaa.nih.gov) and NIAAA's publicly available resource guides, with information specific to referrals: *Alcohol Screening and Brief Intervention for Youth: A Practitioner's Guide*[29] and *Helping Patients Who Drink Too Much: A Clinician's Guide*.[28]

Referral to treatment is a critical, yet often overlooked, component of SBIRT. Although some studies have found it effective to link individuals to specialty treatments,[86,87] evidence from many others suggests that it is often difficult to link individuals in need of alcohol-related specialized care to substance use treatment services. For example, a meta-analysis of nine studies found no evidence that brief alcohol interventions were efficacious for increasing the use of alcohol-related services.[88] Referral to treatment is further compounded by gender-specific barriers to treatment that impact women's ability to engage in services. In general, women are less likely than men to initiate alcohol treatment services, and when they do, research suggests that women often contend with stigma, negative staff attitudes, lack of affordable or safe childcare options, and concerns over child custody.[89] When they do access treatment services, more women than men present with histories of trauma and abuse, psychological distress and mental health concerns, interpersonal and family-related issues, and financial constraints.[90] Barriers on a systemic level include lack of treatment options because of geographic isolation and lack of awareness among care providers regarding local treatment options that are capable of addressing the unique needs of adolescent girls and women in treatment settings.[89]

BARRIERS AND FACILITATORS TO SBIRT IMPLEMENTATION

A number of health and social service providers (e.g., physicians, nurses, social workers, psychologists, midwives) are qualified to effectively implement SBIRT across a variety of patient and client settings. However, studies of SBIRT implementation reveal that few providers feel comfortable doing so, with the lowest screening and counseling rates seen among young adult and women's reproductive care providers.[18] For example, one study found that one-third of women who endorsed alcohol consumption in women's health clinics were not asked how much they drank and that a majority of women drinking at risk levels did not receive advice on low-risk limits.[91] Another study concluded that approximately half of women at risk of an AEP did not receive information pertaining to this risk from their health care providers.[91] These findings corroborate national survey data of family planning clinicians, which found that of these clinicians,

approximately one-third used a validated screening measure and one-fifth provided a referral that consisted of more than a list of treatment options.[92]

Qualitative analyses conducted among health care providers have revealed several common barriers to implementing SBIRT, including time constraints, competing priorities, cost, and privacy and confidentiality concerns.[93-96] Barriers that pediatric providers cited include concerns regarding the willingness of adolescents to return for follow-up, limited access to and knowledge of adolescent treatment programs or local expertise, and confidentiality concerns.[94] Additional SBIRT barriers that prenatal care providers identified included lack of rapport between providers and women presenting for an initial prenatal consultation; providers' misperception that there is a low prevalence of alcohol use by pregnant women; providers' lack of skills, training, and follow-up protocol; women's underreporting or false disclosure of alcohol consumption; and providers' concerns over creating guilt and anxiety among pregnant women.[95,96]

Many of these provider-identified barriers should be considered in combination with, and resulting from, U.S. state policies mandating that health care providers report perinatal substance use to child welfare agencies.[97,98] For instance, in 2017, Jarlenski and colleagues conducted a systematic content analysis that identified 24 states with statutes around reporting perinatal substance use by health care providers. Twenty of the states identified had mandatory reporting statutes, while 11 states specified a penalty capable of resulting in a misdemeanor charge for health care providers who failed to report known perinatal substance use.[98] Furthermore, some state statutes allow for involuntary commitment and custody loss solely as a result of prenatal substance use, thus creating an ethical and moral dilemma for prenatal care providers because this violates the principles of patient autonomy and beneficence.[99] This issue was further complicated for prenatal care providers by updated recommendations from the American College of Obstetricians and Gynecologists and the Centers for Disease Control and Prevention, which advise providers to conduct universal screening at initial prenatal appointments.[46,98]

In addition to the barriers faced by prenatal care providers, pregnant women engaged in substance use behaviors often face their own barriers to receiving care, such as fear of stigmatization and legal consequences. This may result in a lack of engagement in prenatal care altogether, thus eliminating the potential for SBIRT implementation and posing significant risks to the health of both mother and child.[60]

Older women also face unique barriers to alcohol intervention and treatment efforts. These include financial limitations and lack of mobility and transportation. Older women also report higher rates of stigma, shame, and guilt than younger women, which may lead to an increased prevalence of isolation, anxiety, and depression.[51]

Approaches to Facilitating SBIRT Implementation

In response to the many recognized barriers, research has begun to identify approaches that facilitate successful SBIRT implementation. So far, evidence suggests that having a practice champion, utilizing an interprofessional team, communicating the details of each SBIRT step, developing relationships with referral partners, instituting ongoing SBIRT training for sustainability, aligning SBIRT practices with the organization's flow, and integrating SBIRT into electronic health records are all ways to facilitate ongoing SBIRT efforts.[24] Additionally, a study of ongoing SBIRT facilitation compared usual care and two adolescent SBIRT delivery modalities (pediatrician-only and pediatrician with an embedded behavioral clinician) and found that although substance use outcomes did not differ between pediatrician-only and embedded behavioral clinician groups, adolescents in the embedded group reported fewer depression symptoms at follow-up.[100] The inclusion of a

behavioral clinician in pediatric settings may be especially beneficial to adolescent girls in light of recent evidence that higher levels of depression severity among girls ages 13 to 16 predicted alcohol use in the following year.[59]

Technology

The use of technology is an additional option for overcoming SBIRT barriers in clinical settings that lack available staff and time resources for ongoing face-to-face implementation.[101] Technology is increasingly being used to facilitate various SBIRT components, with preliminary evidence observed among adolescent girls and women looking promising.[74,102,103] A recent systematic review of women's experiences with technology-based screening found that the perception of anonymity made it easier to divulge potentially stigmatizing information compared to in-person, face-to-face screening methods. Therefore, technology-based screening has the potential to increase disclosure rates and intervention receipt.[104] Studies also suggest that women feel less embarrassed and less afraid of judgment when they participate in technology-based interventions, and the flexibility offered by some technology-based treatments may also be appealing to women who are not willing or able to participate in more formal treatment programs because of family and societal roles.[104]

Nevertheless, whether electronic SBIRT can be effective as a stand-alone entity has yet to be established. One recent study demonstrated successful implementation of a technology-based alcohol intervention (i.e., sans personnel) among women of childbearing age;[66] however, interaction findings from other studies suggest that various female groups may have other intervention needs.[105] For example, Choo and colleagues reported that although female victims of intimate partner violence were receptive to electronic screening and advice, they also desired empathy and compassion from human interaction provided during intervention delivery.[105] Still, evidence has suggested that electronically delivered SBIRT components are mutually beneficial to both women and providers.[103,106] In the future, the use of electronic approaches could also assist in the translation of research findings into routine care settings by standardizing intervention delivery methods while maintaining wide applicability across health and social service settings.[107]

FUTURE DIRECTIONS

More research is needed to evaluate the effectiveness, efficacy, and feasibility of SBIRT practices among females, primarily those in younger and older cohorts, and those at risk of AEPs.[4,10,59,64] Recent reports showed increases in alcohol use among adolescent girls, with evidence suggesting a reversal from traditional male excess to slight female excess in 8th grade, and by 12th grade, 35% of girls reported past-month alcohol use, corresponding to a 250% increase from 8th grade.[9,102] Age of alcohol use initiation is particularly worrisome among adolescent females, given that early initiating females drink more than all male adolescents from ages 12 to 17.[8] Additionally, the association between depression severity and alcohol use appears to be more salient for early adolescent girls than for boys of the same age, with observations suggesting that alcohol use both predicts and is a consequence of depression.[59] Research is also needed to address alcohol use among older women due to population increases. Given the aging of the baby-boom generation, population projections estimate that by 2040, the proportion of women to men ages 65 or older will be 127 to 100.[51,108]

SBIRT is essential for the ongoing identification and intervention of risky alcohol use behaviors among adolescent girls and women. As the prevalence rate of female alcohol use increases, so too should the implementation of SBIRT. These prevention and intervention efforts can help promote lifelong health and well-being among women, with special attention paid to younger and older cohorts, and those at risk of an AEP.

Table 1 Alcohol Screening Instruments

Instrument	No. of Items in Instrument	Approx. Time to Administer (min)	Applicable Population	Scoring That Indicates Risk and Statistical Performance (Sensitivity; Specificity)	Copyright, Source(s), and Cost‡‡	Link(s)
NIAAA *Alcohol Screening and Brief Intervention for Youth: A Practitioner's Guide*[29]	2 to 3 depending on severity	~2	Adolescents ages 9 to 18	Elementary or middle school adolescents (≤ 15 years old) reporting any alcohol use (0.89; 0.91)[33] High school adolescents (≥ 16 years old) reporting ≥ 6 days of past-year alcohol use (0.88; 0.81)[33]	Copyright: N/A Source: N/A Cost: Free online	Publicly available NIAAA guide containing screening questions (page 8): https://www.niaaa.nih.gov/sites/default/files/publications/YouthGuide.pdf
Screening to Brief Intervention (S2BI)[34*]	3 (additional 4 if past-year use indicated)	~2	Adolescents ages 12 to 17	Adolescents reporting alcohol use *once or twice* in the past year (0.96; 0.92) Adolescents reporting alcohol use *monthly* in the past year (0.79; 0.96) Adolescents reporting alcohol use *weekly or more* in the past year (1.00; 0.88)	Copyright: N/A Source: N/A Cost: Free online	Publicly available NIDA link to online version with options for patient or clinician administration: https://www.drugabuse.gov/ast/s2bi/#/
Brief Screener for Tobacco, Alcohol, and Other Drugs (BSTAD)[38*]	6 (additional 3 to 11 if past-year use indicated)	~2	Adolescents ages 12 to 17	≥ 2 days of past-year alcohol use (0.96; 0.85)	Copyright: N/A Source: N/A Cost: Free online	Publicly available NIDA link to web-based instrument with options for patient or clinician administration: https://www.drugabuse.gov/ast/bstad/#/
Alcohol Use Disorders Identification Test (AUDIT)	10	~2 to 3	Adolescent girls ages 12 to 19, adults,§ pregnant women, older adults	Positive score indicating risk: Adolescent girls: ≥ 5 (0.95; 0.77)[32] Adults: ≥ 8 (0.38–0.73; 0.89–0.97)[18]** Pregnant women: > 0[18] Older adults: ≥ 5 (0.86; 0.87)[54]	Copyright: 1989, Thomas Babor and the World Health Organization Sources: World Health Organization, Division of Mental Health & Prevention of Substance Abuse, 1211 Geneva 27, Switzerland Email: Publications@who.int Thomas F. Babor, Alcohol Research Center, University of Connecticut, Farmington, CT Cost: Core questionnaire can be reproduced without permission; test and manual are free; training module costs $75	Publicly available link to self-report instrument: https://cde.drugabuse.gov/sites/nida_cde/files/AUDIT-SelfReport_v1.0_2014May20.pdf

Instrument	No. of Items in Instrument	Approx. Time to Administer (min)	Applicable Population	Scoring That Indicates Risk and Statistical Performance (Sensitivity; Specificity)	Copyright, Source(s), and Cost‡‡	Link(s)
Alcohol Use Disorders Identification Test-Concise (AUDIT-C)	3	~1	Adolescent girls ages 12 to 19, adult women,† pregnant women, older adults	Adolescent girls: ≥ 3 (0.96; 0.65)[32] Adult women: ≥ 3 (0.73–0.97; 0.34–0.89)[18] Pregnant women: > 0 (NR‡)[18] Older adults: ≥ 4 (0.94; 0.80)[54]	Copyright: N/A Source: N/A Cost: Free online	Publicly available SAMHSA link: https://www.integration.samhsa.gov/images/res/tool_auditc.pdf
Car, Relax, Alone, Forget, Friends, Trouble (CRAFFT)[37]*	4 (additional 5 if past-year use indicated)	~2 to 3	Adolescents ages 12 to 21	≥ 1 (0.94; 0.74)[30,39] Optimal cutoff score indicating heightened risk for SUD: ≥ 2 (0.79; 0.97)[39]	Copyright: 2001, Boston Children's Hospital Source: The Center for Adolescent Substance Abuse Research, Children's Hospital, 300 Longwood Ave., Boston, MA 02115 Phone: 617-355-5433 Email: crafft@childrens.harvard.edu Cost: N/A	Publicly available SAMHSA link which states that the CRAFFT may be reproduced in [this] exact form for use in clinical settings courtesy of the Center for Adolescent Substance Abuse Research at the Boston Children's Hospital: https://www.integration.samhsa.gov/clinical-practice/sbirt/CRAFFT_Screening_interview.pdf Link from Boston Children's Hospital with additional information: http://crafft.org/
NIAAA Single Item Alcohol Screening Questionnaire (SASQ)[52]	1	~1	Adults	≥ 1 (0.82; 0.79)[18]	Copyright: N/A Source: N/A Cost: N/A	Publicly available SAMHSA link to NIAAA's *Helping Patients Who Drink Too Much: A Clinician's Guide,* which includes NIAAA SASQ (page 4): https://www.integration.samhsa.gov/clinical-practice/Helping_Patients_Who_Drink_Too_Much.pdf Publicly available USPSTF Final Recommendation Statement: *Unhealthy Alcohol Use in Adolescents and Adults: Screening and Behavioral Counseling Interventions,* includes NIAAA SASQ question: https://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/unhealthy-alcohol-use-in-adolescents-and-adults-screening-and-behavioral-counseling-interventions

Instrument	No. of Items in Instrument	Approx. Time to Administer (min)	Applicable Population	Scoring That Indicates Risk and Statistical Performance (Sensitivity; Specificity)	Copyright, Source(s), and Cost‡‡	Link(s)
Quick Drinking Screen (QDS)[44,109]	3	~1	Adults	Scoring based on presence of NIAAA defined at-risk drinking (i.e., more than 3 drinks on any day or 7 drinks per week for adult women) in past 90 days[43††]	Copyright: 2003, Sobell & Sobell Source: Linda C. Sobell, PhD, ABPP, Center for Psychological Studies, Nova Southeastern University, 3301 College Ave., Fort Lauderdale, FL 33314 Email: sobelll@nova.edu Cost: Free	Publicly available link that states that this screener can be freely used as it is in the public domain: https://www.nova.edu/gsc/forms/quick_drinking_screen.pdf
Tolerance, Annoyed, Cut Down, Eye Opener (T-ACE)[31]	4	~1	Women of childbearing age	≥ 2 (0.69–0.88; 0.71–0.89)[25]	Copyright: 1989, Harcourt Health Sciences; permission needed to publish Sources: S. Martier, Ob/Gyn, 4707 Saint Antoine, Detroit, MI 48201 Permissions Department, Mosby, Inc. (a division of Elsevier), 6277 Sea Harbor Dr., Orlando, FL Phone: 407-345-3994 http://www.us.elsevierhealth.com/ Cost: N/A	Publicly available NIAAA link containing copyright information: https://pubs.niaaa.nih.gov/publications/t_ace.htm Publicly available NIAAA link containing T-ACE questions: https://pubs.niaaa.nih.gov/publications/arh28-2/78-79.htm
Tolerance, Worried, Eye Opener, Amnesia, K-Cut Down (TWEAK)[31]	5	~2	Pregnant women	≥ 2 (0.71–0.91; 0.73–0.83)[25]	Copyright: None Source: Marcia Russell Prevention Research Center, 1995 University Avenue, Suite 450, Berkeley, CA 94704 Phone: 510-883-5703 Email: russell@prev.org Cost: Free	Publicly available NIAAA link with more information: https://pubs.niaaa.nih.gov/publications/assessingalcohol/instrumentpdfs/74_tweak.pdf
Normal Drinker, Eye-Opener, Tolerance (NET)[47]	3	~1	Pregnant women	≥ 2 (0.61; 0.87)[47]	Copyright: 1989, Lippincott Williams & Wilkins Source: Lippincott Williams & Wilkins Permissions Department, 351 West Camden St., Baltimore, MD 21201 Phone: 410-528-4050 Email: permissions@lww.com http://www.lww.com/permissions/index.htm Cost: N/A	Not publicly available
Parents, Partner, Past, Present Pregnancy (4P's Plus)[48]*	5	~1	Pregnant women	≥ 1 (0.87; 0.76)[48]	Copyright: The National Training Institute/NTI Upstream Source: NTI Upstream, 180 N. Michigan Ave., Suite 700, Chicago, IL 60601 Cost: Licensing fees may apply	Publicly available link with more information: https://www.ntiupstream.com/4psabout

Instrument	No. of Items in Instrument	Approx. Time to Administer (min)	Applicable Population	Scoring That Indicates Risk and Statistical Performance (Sensitivity; Specificity)	Copyright, Source(s), and Cost‡‡	Link(s)
Substance Use Brief Screen (SUBS)[53*]	4	~1	Adults	Any response other than "never" on alcohol binge question: (0.85; 0.77)	Copyright: N/A Source: N/A Cost: N/A	Publicly available NIH publication with more information: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4475501/
Cut Down, Annoyed, Guilty, Eye-Opener (CAGE)[57]	4	~1	Adults	≥ 2 (0.14–0.39; 0.97)	Copyright: None Source: N/A Cost: Freely available as it is in the public domain and no permission is necessary unless used in a profit-making endeavor	Publicly available SAMHSA link: https://www.integration.samhsa.gov/clinical-practice/sbirt/CAGE_questionaire.pdf
Michigan Alcohol Screening Test–Geriatric Version (MAST-G)[57]	24	~5 to 10	Older adults	≥ 5 (0.70–0.91; 0.81–0.85)	Copyright: 1991, The Regents of the University of Michigan Source: Frederick C. Blow, PhD, University of Michigan Alcohol Research Center, 400 E. Eisenhower Parkway, Suite A, Ann Arbor, MI 48104 Phone: 313-998-7952 Cost: Free online	Publicly available NIH link to SAMHSA's *Substance Abuse Among Older Adults: Treatment Improvement Protocol No. 26* (page 55): https://www.ncbi.nlm.nih.gov/books/NBK64419/pdf/Bookshelf_NBK64419.pdf
Short Michigan Alcohol Screening Test–Geriatric Version (SMAST-G)[57]	10	Not reported	Older adults	≥ 2 (0.52; 0.96)	Copyright: 1991, The Regents of the University of Michigan Source: N/A Cost: N/A	Publicly available link provided by The Hartford Institute for Geriatric Nursing, New York University, Rory Meyers College of Nursing: https://consultgeri.org/try-this/general-assessment/issue-17.pdf
Comorbidity Alcohol Risk Evaluation Tool (CARET)	10	~2 to 5	Older adults	A positive response in any of the seven risk categories (0.92; 0.51)[54]	Copyright: N/A Source: N/A Cost: N/A	Not publicly available

NIAAA = National Institute on Alcohol Abuse and Alcoholism; NIDA = National Institute on Drug Abuse; NIH = National Institutes of Health; SAMHSA = Substance Abuse and Mental Health Services Administration.

* Instrument screens for alcohol and other substances.

† Recommended AUDIT-C cutoff score is different for adult women (≥ 3) and men (≥ 4).[18]

‡ Not reported.

§ Recommended AUDIT cutoff score is the same for adult women and men (≥ 8).[18]

** Several U.S.-based studies show more optimal balances of sensitivity and specificity at lower AUDIT cutoffs (e.g., 3, 4, 5); preliminary findings from the USPSTF 2018 updated evidence report and systematic review indicates that lower cutoffs may be preferred.[18]

†† Sensitivity and specificity are not reported for this instrument.

‡‡ N/A, information was not available or retrievable. None, the instrument explicitly states that no copyright is held. Cost: N/A, no information was found regarding cost. Free/free online, the information pertaining to the instrument explicitly states that it is available to the public.

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Treatment Interventions for Women With Alcohol Use Disorder

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Women with alcohol use disorder (AUD) experience more barriers to AUD treatment and are less likely to access treatment than men with AUD. A literature review identified several barriers to women seeking help: low perception of a need for treatment; guilt and shame; co-occurring disorders; employment, economic, and health insurance disparities; childcare responsibilities; and fear of child protective services. Women entering treatment present with more severe AUD and more complex psychological, social, and service needs than men. Treatment program elements that may reduce barriers to AUD treatment include provision of childcare, prenatal care, treatment for co-occurring psychological problems, and supplemental social services. Research has suggested that outcomes for women are best when treatment is provided in women-only programs that include female-specific content. To date, research on treatments tailored to the individual needs of women is limited, but research on mechanisms of change has suggested the importance of targeting anxiety and depression, affiliative statements in treatment, abstinence self-efficacy, coping skills, autonomy, and social support for abstinence. Future research should focus on early interventions, linkages between primary care or mental health clinics and AUD treatment settings, and integrated treatments for co-occurring AUD and other disorders. Further research should also explore novel treatment delivery approaches such as digital platforms and peer support groups.

KEY WORDS: alcohol use disorder; barriers; mechanisms of change; outcomes; treatment; women

INTRODUCTION

Historically, women with alcohol use disorder (AUD) have been an underserved population. In the United States, more than 5 million adult women, or 4.2% of the adult female population, meet criteria for current AUD.[1] Although this percentage is half that of adult men (8.4%), among adolescents, more females than males meet criteria for current AUD (2.7% vs. 2.3%),[1] and recent research has suggested that the gender gap in alcohol use and alcohol-related harm is narrowing.[2] Heterogeneity in rates of AUD is found among different racial/ethnic groups, with higher rates among Black and Hispanic women than among White women,[3] and rates of AUD among gender minority women also are higher than among heterosexual women.[4]

A smaller proportion of women than men received AUD treatment both in the past year[1] (7.9% of adult women vs. 9.2% of adult men; 4.6% of adolescent females vs. 7.4% of adolescent males) and in their lifetime[5] (15.0% of women and 22.0% of men with AUD who are younger than age 45). Utilization rates for treatment services by women and men do not differ across different racial/ethnic groups.[5] Given the increasing rates of AUD among women and the lower rates of treatment utilization among women, a rethinking of AUD treatment for women is in order. The purpose of this article is to describe the barriers to treatment entry experienced by women with AUD, the unique characteristics and presenting concerns of women with AUD who do seek treatment, and the current knowledge about effective treatments. Sources of information for this review included a comprehensive review published in 2013,[6] articles identified in a search in PsycINFO® using the search terms "women," "alcohol," and "treatment," and articles identified through selective reviews to identify key publications on trauma-informed treatment and substance use disorder (SUD) in female veterans.

WOMEN SEEKING AUD TREATMENT

Women seeking AUD treatment differ from men in their sociodemographic characteristics and psychological profiles. They experience some unique barriers to accessing treatment and present to treatment with some needs that differ from men in AUD treatment.

Characteristics of Women With AUD at Treatment Entry

Women seeking AUD treatment vary along a number of dimensions that may impact their access to treatment, treatment needs, and treatment response.

Sociodemographic characteristics and substance use

Women who present to AUD treatment often have markedly different characteristics and backgrounds than men in these treatment settings. Such distinctions among women include younger age, more severe alcohol and drug use histories, less education, lower income, higher unemployment, more housing needs, more children living at home, and higher parental stress.[6] In terms of substance misuse, rates differ among subgroups. For example, non-Hispanic White and American Indian/Alaska Native women are more likely than women of other racial/ethnic groups to identify alcohol as their primary substance of use when entering treatment for SUD.[7] Among pregnant women entering treatment for SUD, approximately 18% identified alcohol as their primary substance of use.[7] In a study of women veterans with SUD, researchers found that entry into and engagement with treatment were associated with having a co-occurring psychological disorder and receiving services at facilities offering women's treatment.[8]

Psychological co-occurrences

Compared to men, women who enter AUD/SUD treatment generally report higher levels of physical and mental health concerns. Rates of co-occurring disorders vary with the treatment setting and population. Epidemiologic data suggest that compared with men with AUD, women with AUD have a higher prevalence of co-occurring DSM-IV Axis I disorders (84.2% vs. 75.5%),

a similar prevalence of other drug dependence (15.2% vs. 14.3%), a higher prevalence of mood and anxiety disorders (53.1% vs. 29.1% and 44.3% vs. 26.2%, respectively), and a similar prevalence of personality disorders (36.5% vs. 33.3%).[9] A recent nationwide study of veterans with AUD found that women veterans had more psychological and substance use comorbidities than men.[10] In addition, women in SUD treatment have a much higher prevalence (up to 80.0%) of lifetime physical, sexual, and/or emotional abuse and trauma, and concerns about current domestic violence are common.[11] Rates of current post-traumatic stress disorder (PTSD) among women in SUD treatment range from 25.0% to 55.0%.[12]

Barriers to Treatment

Women who do not receive AUD treatment have some sociodemographic difference from women in AUD treatment. For example, a sample of women with AUD who were not in treatment but perceived a need for treatment were less educated, had a family income less than $75,000, and were more likely to use psychotropic medications compared to those who did not perceive a need for treatment.[13] Women experience both internal and external barriers to AUD treatment. These barriers may partially explain the gender discrepancy in treatment initiation rates and include low perception of need for treatment; guilt and shame stemming from the discrepancy between traditional gender expectations and societal views of women with AUD; depression and other co-occurring disorders; greater employment, economic, and health insurance disparities relative to men; childcare responsibilities; and fear of child protective services.[6]

Recent research has suggested that traditional gender expectations and lay beliefs about AUD may contribute to lower AUD treatment utilization among women. Lale and colleagues found that compared to men, women were more likely to attribute AUD to "bad character" and less likely to attribute AUD to genetics.[14] Women also worry that they will be perceived as "bad mothers" and potentially lose custody of their children if they disclose having an alcohol problem.[7] Relatedly, women are more likely than men to experience feelings of embarrassment, to experience fear, to have the belief that no one can help, and to have the belief that their problem is not serious enough to require AUD treatment.[15] In addition to these intrapersonal barriers, women may experience less social support to enter AUD treatment than men do. Women with AUD are more likely than men to be in an intimate relationship with a partner who also has AUD,[16] and women tend to have less spousal and family support for recovery.[17] Further, women generally report more logistical barriers to treatment utilization, including greater difficulties with transportation, lack of available childcare, and inadequate insurance coverage.[17]

Compared to men, women are more likely to seek AUD treatment through a general versus substance use-specific health care sector[18] or in the context of treatment at a general mental health clinical setting,[19,20] and less likely to be court mandated to treatment.[21] Women with AUD also generally report stressful life events and nonsubstance-related mental health concerns as their primary reasons for seeking treatment.[22] Welfare, child welfare, and legal systems provide additional portals through which some women enter AUD treatment.[21] Primary care physicians, gynecologists, and psychiatrists may benefit from focused training in identification and referral of women with AUD to offset the gender discrepancy observed in women's entry into AUD treatment. Relatedly, women have shown a preference for AUD treatment settings that offer childcare.[23] Thus, more easily accessible, children-friendly treatment centers with wide availability are also likely to improve treatment utilization among women with AUD.

AUD TREATMENT SERVICES FOR WOMEN

Treatment Retention

In general, the literature is mixed regarding AUD treatment attrition and gender differences.[6] Previous studies have found that women tend to have longer inpatient stays and that longer inpatient

stays are associated with an increase in sustained abstinence for women but not for men.[22,24] Bravo and colleagues reported that women engaged in outpatient AUD treatment longer and discontinued treatment at a lower rate than men.[25] In a comprehensive review, Greenfield and colleagues concluded that although there are no gender differences in attrition, predictors and mediators of treatment retention differ by gender.[23] Predictors of better treatment retention among women include demographic variables, such as lower psychiatric impairment, higher socioeconomic status, and greater social support and stability,[23] and program variables, such as female-specific treatment and facilities that allow children to stay with their mothers.[6] A recent investigation of 1.8 million individuals who received SUD treatment at federally funded facilities found that, across treatment settings, women and men did not differ in rates of early discharge.[26] However, when treatment settings were stratified by type (detoxification, residential, and ambulatory), women were more likely than men to leave detoxification treatment prematurely. The authors suggested that lower rates of female-specific services and higher rates of psychiatric co-occurring disorders within detoxification settings might have accounted for this gender difference.

Treatment Outcome

In general, studies of mixed-gender treatment programs have found few gender differences in short-term outcomes for AUD across a range of interventions, samples, and sites, despite women at baseline generally presenting with more severe clinical issues.[6] For example, in their analysis of five randomized clinical trials (RCTs) of intensive outpatient contingency management for AUD and SUD, Rash and Petry found no differences between men and women's abstinence rates during the 3-month treatment period, although women initially presented with more financial, family/social, and psychiatric problems.[27] Likewise, a study of a large outpatient AUD treatment cohort in Spain found no differences between men and women in alcohol consumption 1 year posttreatment, despite women presenting with more symptoms of dependence at baseline.[25]

Results have been more mixed regarding women's long-term outcomes compared to men.[6] In the same study from Spain described above, women had superior drinking outcomes compared to men at 5, 10, and 20 years posttreatment.[25] Conversely, Litt and colleagues found that women had worse drinking outcomes than men in the 2 years following outpatient AUD treatment.[28] These poorer outcomes may have been due to the nature of the active treatment, which focused on altering the participant's social network to gain more support for abstinence; women in the study had less abstinence-supportive social networks and more difficulty altering these networks.

Historically, gender has typically not been taken into consideration in psychopharmacologic treatment for AUD, and women have been underrepresented in AUD medication trials.[29] However, research has begun to improve in this area. A review by Agabio and colleagues found that too few studies of disulfiram had included women to test potential gender differences in response to this medication.[30] There were a sufficient number of studies on acamprosate and naltrexone, which showed that both medications were generally efficacious for women; however, results of gender comparisons were too variable to draw firm conclusions. Canidate and colleagues conducted a systematic review of seven studies on naltrexone for the treatment of AUD among women.[31] Among this limited number of studies, naltrexone was found to have a modest effect on drinking quantity and time of relapse but not on the overall frequency of drinking among women. The authors concluded that the effect of naltrexone on women is currently understudied. This Canidate article highlights the need to continue to use rigorous research designs to study differences in the efficacy of naltrexone on women versus men.

Reducing Barriers to Treatment for Women

A comprehensive review identified six major elements of SUD treatment programs for women

that reduce barriers to treatment and/or address women's unique needs.[32] These include the provision of childcare, prenatal care, women-only treatment, treatment for co-occurring mental health problems, a comprehensive approach to treatment, and supplemental services that address women-focused topics. Each of these elements was linked to favorable treatment outcomes. In a qualitative meta-synthesis of programs that included women and their children, several treatment processes were identified by different stakeholders (clients, clinicians, and program administrators) as instrumental to positive outcomes: developing a sense of agency, giving and receiving social support, engaging with program staff, fostering self-disclosure, recognizing self-destructive patterns of behavior, setting goals, and feeling motivated by the presence of children.[33] Although some of these processes are common to any AUD treatment, it is necessary to recognize the unique blend of common and specific treatment processes that are effective for women in treatment with their children. Although studies have repeatedly identified the importance of including children-supportive services in women's SUD treatment programs, a 2018 Substance Abuse and Mental Health Services Administration (SAMHSA) survey found that only 5.8% of SUD treatment facilities provided childcare and only 2.6% of residential programs provided beds for clients' children.[34]

Guiding Principles for Women's AUD Treatment

Recognizing the unique treatment needs of women with AUD and SUD, SAMHSA published a set of evidence-based principles to guide gender-responsive treatment for women.[7] These guidelines include several recommendations. For example, they recommend developing cultural competence to frame women's AUD symptoms and treatment in their socioeconomics contexts (e.g., employment, income, housing). They suggest that providers acknowledge the unique significance of women's relationships and attend to the "caregiver roles that women often assume throughout the course of their lives." Relatedly, the guidelines address stigma by noting the importance of "recognizing that ascribed roles and gender expectations across cultures affect societal attitudes toward women who abuse substances." Other recommendations state that SUD treatments for women adopt a trauma-informed approach, which often emphasizes women's strengths, and address "women's unique health concerns" through "an integrated and multidisciplinary approach." The SAMHSA guidelines conclude that clinical treatment services (e.g., screening, mental health services), clinical support services (e.g., parenting education, job training), and community support services (e.g., childcare, transportation) would work collaboratively to facilitate comprehensive AUD treatment for women of diverse backgrounds.[7]

Advances and Gaps in Treatment Development for Women

With increasing recognition of the unique clinical profiles of women with AUD has come increasing attention to whether AUD treatment programs are serving the needs of women. The 2018 SAMHSA annual survey of substance use treatment programs found that 49% of programs surveyed provided special programs or groups for women and 23% provided services for pregnant or postpartum women.[34] In contrast, data from the Veterans Health Administration (VHA) revealed that most VHA facilities offered SUD services to women but that most of these services were generic rather than female-specific (85% vs. 30%).[35]

The need for specialized services for women has both an empirical and a clinical rationale. As reviewed earlier in this article, compared to men, women are less likely to seek AUD treatment, have different social contexts, present with different profiles of co-occurring disorders, and have a unique and complex set of service needs that may not be addressed in a standard, mixed-gender AUD treatment program.[9,36] Thus, treatment programs and researchers have been seeking to create and evaluate services intended to attract women to AUD treatment and improve

outcomes. AUD services for women vary along two dimensions—whether they are provided in a mixed-gender or women-only treatment setting and whether the content of the treatment is generic or tailored specifically to women's clinical and other service needs.[37] Thus, delivery of AUD treatment to women may occur in (a) mixed-gender programs with no female-specific programming, (b) mixed-gender programs with female-specific programming, (c) single-gender (women-only) programs with no female-specific programming, or (d) single-gender (women-only) programs with female-specific programming.

Mixed-gender versus single-gender treatment

Single-gender treatment services seem appealing because they have the potential to provide an environment in which women may feel more comfortable sharing emotional and personal information. For instance, it is possible that among women who have a history of trauma or abuse from men, single-gender treatment might be preferable because of the possibility that participation in a mixed-gender program could trigger trauma-related symptoms. In addition, given the broader literature on the relative interactional dominance of men in mixed-gender groups, women may have more opportunities to participate when in women-only groups.[38] However, research on women's treatment preferences yields a more nuanced picture. Although some research suggests that women prefer women-only groups,[23] a narrative analysis of interviews with women with a range of SUD treatment experiences found that the women reported concerns and anxiety about being in women-only treatment because of their own history of dysfunctional relationships with women and their greater comfort in being with men.[39] However, women in the study reported positive experiences once they entered women-only services.

Few studies have compared women's outcomes from mixed-gender versus women-only programs that were not adapted with female-specific content. In one early study, Bride compared the outcomes for women who were in a mixed-gender program to the outcomes for women who later participated in the same program that had become a women-only program with no female-specific content.[40] Outcomes were similar between the two samples.

More extensive research has compared mixed-gender to single-gender programs that incorporate female-specific themes, services, or content. For example, interviewed providers of services for female veterans with SUD identified five female-specific themes and services that they viewed as key to treatment: a focus on safety; scheduling that accommodates women's work and family responsibilities; flexibility in the resources provided; staff trained in serving women's clinical needs; provision of on-site childcare; and a positive, supportive, nonconfrontational treatment environment.[41] Although some of these treatment elements may be relevant to treatment for any patient with SUD, the combination of these elements was seen as key to successful treatment for the female veteran population. In addition to treatment elements, female-specific content has focused on clinical issues of particular significance to women, such as trauma, physical abuse, relationships, parenting, assertiveness, and treatment of co-occurring disorders.

One of the earliest studies of women-only treatment with female-specific content was the Early Treatment of Women with Alcohol Addiction (EWA) study.[42] A 2-year follow-up of women found better clinical outcomes in the EWA than mixed-gender treatment, and a long-term study of mortality revealed lower mortality rates for younger women who participated in the EWA program than the mixed-gender treatment.[43] A later study of a large sample of women in women-only versus mixed-gender residential SUD treatment found that women were twice as likely to complete the women-only treatment and that higher retention was associated with higher rates of abstinence posttreatment.[44,45] More recent studies have found that (a) treatment retention and entry to aftercare were enhanced by gender-specific services in an intensive treatment program that also provided transitional housing, particularly for women who completed residential treatment;[46] (b) women-only treatment predicted

better legal and drug outcomes but no differences in alcohol use outcomes;[47] and (c) women in the single-gender treatment had significantly less substance use (participants were primary stimulant users) and less criminal activity than those in the mixed-gender treatment.[48] In contrast, Kaskutas and colleagues found that a mixed-gender, comprehensive, hospital-based treatment resulted in better alcohol abstinence outcomes than women-only treatment and was superior to generic, community-based, mixed-gender treatment.[49]

Single-gender treatment with no female-specific programming

Some empirically supported treatments have been tested in female samples with any adaptation of the treatment to women's treatment needs. Two studies compared behavioral couple therapy to individual treatment for women with AUD and their male partners.[50,51] O'Farrell and colleagues compared behavioral couple therapy to individual treatment for women with SUD and their male partners.[52] All three studies found that the behavioral couple therapy led to positive changes in alcohol or drug use, with better alcohol or drug use outcomes for the women receiving couple therapy. In their study, McCrady and colleagues found that women presenting with higher levels of relationship distress and women with co-occurring Axis I or II disorders had greater improvements in drinking.[50] Note, however, that couple therapy is a modality available to only a small proportion of the population of women with AUD. Notably, when given the choice, even women with male partners indicated a preference for individual rather than couple therapy, stating that they wanted to work on their own problems, did not see their partners as supportive, or thought the logistics of scheduling couple sessions was too difficult.[53]

Chronic care models for persons with serious mental illness and SUD are another empirically supported approach that has been tested in female samples without female-specific programming. These models have been developed and tested with homeless women who have AUD. The chronic care model emphasizes availability of a primary care provider, care management, education about alcohol, and referral to addiction services. Compared to women who received treatment as usual in a health care clinic for homeless women, women who participated in the chronic care program engaged with more SUD treatment services in the 3 months after starting the program.[54]

Single-gender treatment with female-specific programming

There has been substantial research on women-only treatment with female-specific content. For example, Polcin and colleagues compared intensive, nine-session motivational interviewing (MI) for women with standard one-session MI.[55] For the intensive treatment, therapists were trained to use MI to focus on alcohol use as well as female-specific themes—such as personal relationships, issues related to parenting, abuse, and barriers to treatment—and other psychological concerns, such as low self-esteem or co-occurring disorders. Compliance with the treatment was high (80% of heavy drinkers completed at least seven sessions), and women receiving intensive MI reduced their drinking more than women receiving standard MI. Connors and Walitzer developed and tested an intervention to help heavy-drinking, nonalcohol-dependent women reduce their drinking.[56,57] The intervention focused on skills to reduce drinking and other life skills believed to be relevant to women, such as problem-solving, communication and assertiveness, and strategies to enhance their social support system. Compared to treatment focused only on drinking, women who also received the life skills interventions and booster sessions had outcomes that were more positive.

Another single-gender treatment with women-specific programming was developed by Epstein and colleagues. The outpatient, female-specific cognitive behavioral treatment (FS-CBT) was an adaptation of a the gender-neutral cognitive behavior therapy manual-guided treatment for AUD.[58] The FS-CBT manual (a) highlighted two clinical themes meaningful to women, self-care and autonomy; (b) included female-specific

interventions focused on coping with negative emotions and developing/enhancing women's social network supportive of abstinence; and (c) provided women-specific examples throughout to personalize the material to each woman's issues, such as dealing with heavy drinkers in the social network, parenting, life-stage transitions, trauma, self-esteem, and relationships.[59] In an RCT comparing FS-CBT to an evidence-based, gender-neutral CBT for AUD, Epstein and McCrady found that women in both treatment conditions were highly engaged, reported a high level of satisfaction with the treatment, significantly reduced their drinking, and improved in other areas of life functioning such as depression, anxiety, autonomy, and sociotropy.[58] There were no treatment condition effects, and the FS-CBT treatment was equally effective as the gender-neutral one. In a subsequent RCT, Epstein and colleagues tested the individual modality FS-CBT treatment versus a new group therapy format of the same contents in a "pure comparison" design.[60] Both FS-CBT treatment modalities (individual and group therapy) resulted in significant positive changes in drinking, depression, anxiety, coping skills, self-confidence, interpersonal functioning, and self-care even though treatment attendance and therapeutic alliance were greater in the individual FS-CBT condition. Cost-effectiveness analyses favored the group format.[61]

In a pilot study, Greenfield and colleagues tested a women-only Women's Recovery Group (WRG, $n = 16$) for SUD against mixed-gender Group Drug Counseling (GDC, $n = 7$ women, 10 men).[62] WRG included cognitive behavioral and relapse prevention elements, as well as "repair work" relevant for women (repairing SUD-related damage to relationships and self, and learning to enjoy life without substances).[63] GDC was a traditional mixed-gender treatment program focused on substance-related topics with no gender-specific content. During treatment, the groups did not differ in substance[62] or psychiatric improvement;[64] however, women in WRG continued to reduce substance use in the 6 months posttreatment, and also reported higher satisfaction with the treatment they received.

In a subsequent, larger RCT,[65] with a similar design except that the WRG groups offered rolling admission, outcomes of 52 women in WRG were compared with those of 48 women in GDC (with 58 men in GDC). All participants had SUD or AUD. Women in both treatments reduced drinking, and there were no treatment condition differences in within- or posttreatment drinking outcomes. Because WRG had both a women-only group composition and female-specific content compared to GDC, which had both a mixed-gender format and no female-specific content, it is unclear whether study results were linked to group composition, female-specific content, or both, but both the pilot and the larger RCT demonstrated that WRG is at least comparable to a typical "treatment-as-usual" such as a mixed-gender GDC in community settings. The authors also noted that the WRG in the larger trial was delivered on a rolling admissions basis and suggested that the revised format may have diluted the impact of the WRG.

In a series of three studies on putative mechanisms of change in WRG, secondary analyses of the pilot and/or larger RCT data from studies just described here above, showed that more affiliative statements were made in WRG than GDC[66,67] and that more affiliative statements were associated positively with women's drinking outcomes during and 6 months after treatment, particularly in the WRG condition.[68] Sugarman and colleagues created and piloted (for feasibility, acceptability, and satisfaction) a web-based, gender-specific individual psychoeducation intervention based on WRG content.[69] The gender-specific modules might ultimately comprise a female-specific component of care to be delivered in a mixed-gender setting.

Najavits and colleagues reported an RCT comparing the A Woman's Path to Recovery (WPR) model to the gender-neutral 12-Step Facilitation (TSF) model for women veterans with SUD, the majority of whom (i.e., more than 74%) had current AUD.[70] The WPR model is based on cognitive behavioral, interpersonal, and emotive therapy methods, and theory on gender differences in addiction and recovery. The "exploration" phase of the treatment highlights five themes:

"body and sexuality, stress, relationships, trauma and violence, and thrill-seeking."[70(p211)] The "healing" section covers "recovery methods in four domains—relationships, beliefs, actions, and feelings."[70(p211)] Both WPR and TSF were single-gender groups, facilitated by women clinicians, and provided compensation to offset potential childcare costs or other financial barriers to participation. The treatments resulted in similar improvements in alcohol and drug use, coping skills, and psychiatric functioning. The authors noted that female-specific treatment content might be less relevant to veterans than to their civilian counterparts because male-dominated military culture may diminish traditional gender experiences for women.

In summary, several forms of empirically supported treatments have been tested and found to be efficacious with women, and several women-only treatments with female-specific content have been tested in rigorous RCTs. Overall, most of these studies have found limited evidence for superior alcohol use outcomes, but several of these studies have found greater satisfaction with the female-specific format and treatment content. Because these programs are appealing to women, they may increase women's utilization of AUD treatment, and enhance both engagement and retention in AUD treatment.

Treatment for Co-occurring Disorders

Treatment for co-occurring disorders may be indicated for the many women with AUD who present with additional mental health concerns. Interventions that address the co-occurrence of AUD with trauma and PTSD, mood disorders, and borderline personality disorder may be especially relevant for women.

Trauma

Given the highly elevated rates of trauma among women with AUD/SUD, SAMHSA has suggested that treatment for this population may benefit from adopting principles of trauma-informed care.[7] A trauma-informed approach recognizes the prevalence and impact of trauma in women with AUD and adjusts treatment accordingly, even if clients do not meet diagnostic criteria for PTSD. Trauma-informed AUD treatment does not need to target trauma explicitly, but rather may consider trauma in the assessment and planning phases of treatment. For example, SAMHSA recommends that AUD treatment providers should assess women at intake for trauma histories and PTSD symptomatology and refer clients with severe symptomatology to providers who have experience working with traumatized populations (i.e., if they lack such experience themselves). Another recommendation is to "avoid triggering trauma reactions or re-traumatizing women." For example, violating a client's trust or disregarding a client's emotions or experiences may trigger trauma reactions. SAMHSA also recommends that programs should "adjust staff behavior" and modify the treatment environment "to support clients' coping capacities and safety concerns." Specific strategies may include ensuring that urine specimens are collected in a private setting and establishing consistency in the treatment program's routines and enforcement of rules. In addition, AUD treatment providers should "allow survivors to manage their trauma symptoms" in a manner conducive to AUD treatment engagement and success. For example, allowing clients to express strong feelings without facing judgment and explicitly addressing trauma only when a client is ready are considered trauma-informed approaches. Finally, SAMHSA recommends that trauma-informed AUD treatment for women should "emphasize skills and strengths, interactive education, growth, and change beyond stabilization." Specific skills to incorporate into treatment may include assertiveness training and relaxation techniques.

Covington developed the Helping Women Recover program for the treatment of SUD.[71] Following the principles of trauma-informed care, this treatment aims to provide a "healing" (i.e., safe, empowering, relational) environment that emphasizes strengths and is sensitive to cultural and gender issues. Treatment modules include topics hypothesized to be essential to women's recovery: a focus on self and the integration of roles with feelings, thoughts, and attitudes;

healthy interpersonal relationships; sexuality; and spirituality. Covington also developed the Beyond Trauma: A Healing Journey for Women treatment program, which teaches women how to identify trauma and other forms of abuse, helps them understand typical reactions to trauma and abuse, and fosters the development of coping skills.[72] In an RCT with incarcerated women, 77% of whom were primary stimulant users, Messina and colleagues integrated the Helping Women Recover and Beyond Trauma protocols into a gender-responsive treatment (GRT) program.[73] GRT was compared to a standard prison-based therapeutic community (TC), which, like GRT, was single-gender and targeted SUD, but unlike GRT did not focus on gender-specific issues or trauma histories. Both conditions improved women's psychological well-being and alcohol use outcomes, but women in GRT also had more favorable outcomes for drug use, length of aftercare treatment engagement, and rate of reincarceration in the year following release from parole. A subsequent analysis showed that women with physical/sexual abuse histories had significantly better posttreatment depression and substance use outcomes following GRT than TC.[74]

An extension of trauma-informed care is treatment for co-occurring SUD and PTSD. In general, this co-occurrence is complex and difficult to treat because SUD and PTSD are reciprocally functional and often exacerbate each other.[75,76] Drinking or drug use often functions to self-medicate PTSD symptoms and enable avoidance of remembering traumatic events. Reducing substance use may initially intensify PTSD symptoms and thus predispose the client to relapse. An increasing focus has emerged on targeting PTSD and SUD concurrently.[75,76] This integrated focus is particularly relevant to women who present to SUD treatment and often have elevated rates of trauma history and PTSD.[12]

Recently, integrated models of treatment for PTSD and SUD have been developed and tested with mixed results. For instance, Najavits developed Seeking Safety (SS), a CBT-based treatment model that aims to reduce co-occurring PTSD and SUD by enhancing coping skills.[77] SS emphasizes themes of establishing safety, taking back power, being honest, setting boundaries, practicing compassion, healing from anger, grounding, creating meaning, and increasing self-care. Hien and colleagues tested the efficacy of SS and another active treatment condition Relapse Prevention against a treatment-as-usual control condition.[78] Women in SS and relapse prevention had comparable posttreatment reductions in both PTSD and SUD symptoms, and both treatments were superior to the control condition. Likewise, a study conducted through the National Institute on Drug Abuse Clinical Trials Network found no differences in PTSD or SUD outcomes between an abbreviated version of SS and a health education control condition, both delivered as adjuncts to standard SUD treatment.[79]

Morrissey and colleagues studied another integrated treatment approach for women with SUD.[80] The researchers used a quasi-experimental design to examine a large cohort treated across nine sites. Participants were mostly of low socioeconomic status and had serious mental and/or physical health problems as well as an interpersonal trauma history. The integrated treatment was associated with lower substance use and improved general mental health but not with reduced PTSD symptoms. Overall, it remains unclear whether integrated treatments for PTSD and AUD/SUD in women are superior to stand-alone SUD treatments. Widespread methodological limitations in the current literature warrant continued investigation of integrated treatments, including outcomes that may be specific to women with AUD.[75,76]

Mood disorders

Another promising area of treatment development for women is integrated behavioral therapy for SUD and depression. Treating depression and AUD concurrently may be important because negative affect is a particularly salient trigger for drinking among women. In turn, regular heavy drinking may inhibit recovery from mood disorders. Further, more women than men with AUD have a co-occurring mood disorder, and

there is an elevated suicide risk among women with AUD.[6] However, research on integrated AUD and mood disorder treatments for women is limited. For example, in a pilot study, researchers tested 8 sessions of interpersonal psychotherapy as an adjunct to outpatient AUD treatment for 14 women with co-occurring AUD and major depression.[81] The study found that women were highly engaged and satisfied with the adjunct treatment and reported follow-up reductions in drinking, depressive symptoms, and interpersonal problems. A study of men and women with depressive symptoms and hazardous drinking compared the effects of integrated alcohol-depression treatment, alcohol-only treatment, and depression-only treatment.[82] The integrated treatment generally produced the best alcohol and depression outcomes for both women and men. In the nonintegrated treatments, women's drinking and depressive symptoms improved more in the depression-only treatment, whereas men improved more in the alcohol-only treatment. These findings highlight the unique benefit of treating depression among women with co-occurring AUD and suggest the need for more RCTs targeting this co-occurrence in women.

Given that drinking and antidepressant use are generally contraindicated adds to the significance of concurrent treatment of AUD and depression to maximize the effectiveness of psychotropic medications.[6] One RCT tested the effect of citalopram plus naltrexone and clinical case management for men and women with AUD and depression.[83] Compared to placebo, citalopram did not produce greater improvements in drinking or mood with one exception: women (but not men) on citalopram had a higher percentage of abstinent days. These findings point to the potential for tailoring antidepressant treatment to maximize treatment benefits for women with co-occurring AUD and depression.

Borderline personality disorder

Research has demonstrated elevated rates (i.e., of approximately 18%) of borderline personality disorder (BPD) in women seeking treatment for AUD.[84] Dialectical behavior therapy (DBT) is an empirically supported treatment for BPD that has been successfully adapted for co-occurring SUD.[85] A systematic review found that DBT has shown positive potential for the treatment of women with co-occurring SUD and BPD,[86] leading to reductions in substance use, suicidal/self-injurious behaviors, treatment attrition, and social functioning problems. No studies that tested DBT specifically with women who have co-occurring AUD and BPD have been found.

Mechanisms of Change: How Change Occurs

The goal of understanding moderators and mechanisms of change in treatment is to identify how patient characteristics interact with treatments, identify variables key to successful change, and then develop or modify treatments to target those variables more efficiently in treatment. Currently, there are relatively limited data on moderators and mechanisms of change in alcohol use during and after AUD treatment for women. Moderators are defined as "specification variables" that impact the association between two other variables,[87] for instance, the effect of baseline major depressive disorder on treatment outcome of female-specific versus gender-neutral treatment for AUD. A mediator is an "intervening variable" that "transmits the effect of the independent variable on the dependent variable";[87] for instance, cognitive behavioral treatment of AUD has its effect on drinking outcome in part by increased use of effective coping skills among clients.

Research on moderators of outcome has elucidated the need for heterogeneity in samples and helped to refine female-specific treatments.[87] For example, findings that anxiety pretreatment and depression pre- and posttreatment predicted poorer drinking outcomes for women[88] suggest the value of including interventions to alleviate depression and anxiety in female-specific AUD treatment. Recent and more sophisticated research has studied the interaction of moderators and mediators of treatment response. For instance, Holzhauer and colleagues combined a moderator

analysis with testing the intensity and timing of reductions in drinking after specific outpatient treatment sessions that targeted depression and anxiety in female-specific AUD treatment.[89] Three moderators assessed at baseline—depression, anxiety, and self-efficacy to remain abstinent in negative affect situations—predicted sudden gains (i.e., a steep decrease in drinking) after Session 5 or 6, which included interventions to attenuate negative affect. The results suggest that women who enter treatment struggling with negative affect may respond well to very specific, targeted interventions for those problems.

Hallgren and colleagues examined three hypothesized mechanisms of change—abstinence self-efficacy, coping skills, and therapeutic alliance—in outpatient AUD treatment for women.[90] These authors used daily data from the individual versus group female-specific parent study[60] and sophisticated longitudinal statistical modeling to quantify rates of change around initiation of abstinence for each participant in outpatient FS-CBT. They also tested time-linked change in mediators before each of the 12 therapy sessions. Data on daily drinking and craving were available for the baseline, in-treatment, and 12-month follow-up periods. Results focused on two subgroups of women: those who had initiated abstinence before treatment and those who initiated abstinence during treatment. Those who initiated abstinence during treatment showed marked improvements in two key hypothesized mechanisms of change (abstinence self-efficacy and coping skills) during the week that they initiated abstinence. Women who were abstinent at the start of treatment maintained higher abstinence self-efficacy and coping skills throughout treatment. Previously, Hallgren and colleagues had found that daily-rated alcohol craving (a different mediator) decreased in relation to initiation of abstinence in men and women in outpatient CBT for AUD.[91]

Using Network Analysis, a novel statistical approach that uses multilevel vector autoregression estimation for multiple time series data to simultaneously examine change among several hypothesized mechanisms of change, Holzhauer and colleagues compared pathways to drinking reduction among women in gender-neutral versus FS-CBT.[59,92] Across treatments, women changed their drinking via increased coping skills, abstinence self-efficacy, and increased autonomy. For women in FS-CBT, change in drinking also occurred through decreases in sociotropy and increases in social support for abstinence. Surprisingly, change in depression was linked to better drinking outcomes for women in gender-neutral CBT.

Going forward, continuing moderated mediation studies that examine the response of gender-specific moderators of response to medications or behavioral interventions for AUD, and the mechanisms by which these treatments operate for specific subpopulations, will help guide the development of personalized medicine for addiction.[30] A moderated mediation approach can facilitate examination of individual differences and sample heterogeneity that are linked to drinking outcomes and help to identify gender differences in pathways to successful treatment outcomes.

CONCLUSIONS AND RECOMMENDATIONS

Since the National Institutes of Health mandate in 1994 that biomedical research include female participants in clinical research,[93] a substantive body of literature emerged describing the unique aspects of AUD among women, which led to an accelerated development of treatments targeting women's unique clinical presentation. In 2006, the National Institute on Alcohol Abuse and Alcoholism (NIAAA) identified women as an understudied population in treatment research and prioritized research to better understand the mechanisms by which treatments for AUD effect change in drinking.[94,95] Findings that drinking outcomes of female-specific and gender-neutral treatments may be similar does not mean that the development of female-specific treatments should not be pursued. First, there is evidence that mechanisms of women's response to treatment

(i.e., pathways to change) may differ from that of men, and identification of these gender-specific pathways can guide the development of efficient, gender-differentiated active ingredients in treatment. Second, there may be greater benefits of women-specific (vs. gender-neutral) treatment for secondary outcomes, such as psychosocial well-being, psychiatric health, pregnancy outcomes, and HIV risk reduction. Third, further study is needed on whether the availability of women-specific and women-only treatments enhances treatment access and engagement for women with AUD.

Gaps in knowledge remain; however, increasingly sophisticated research approaches are available to continue to tackle the questions of how and which treatments work best for whom. The contemporary focus on personalized medicine[96,97] extends to women with AUD; the end goal is not only to provide an array of specialized treatment options specifically tailored to enhance women's treatment access and engagement but also to provide science-based treatment elements and options uniquely matched to various common clinical presentations among women with AUD.

A critical problem to resolve is treatment access and utilization. Only 15% of women with lifetime AUD ever seek treatment for it, and women experience multiple individual-based barriers to accessing treatment. In addition, systemic barriers to AUD treatment for women need attention, as a minority of substance use treatment services in the United States offer gender-segregated or female-specific programming. Extant literature suggests that women may prefer gender-segregated treatment for AUD but also suggests this treatment offers no added benefit in the absence of female-specific programming content. Thus, widespread availability of female-only treatment settings that include evidence-based female-specific interventions and content is likely to increase treatment utilization and enhance outcomes for women with AUD. In order to populate female-only treatment settings with female-specific programming, we need to develop an array of evidence-based options. A number of RCTs have yielded newly available, evidence-based female-specific treatment protocols for AUD and SUD treatment that are at least equivalent in positive outcomes to evidence-based control treatments.[59,60,62,70,74,79] Outcomes for secondary (non-AUD) patient problems, such as depression and anxiety,[59,60] trauma symptoms,[69] cardiovascular function,[98] health behaviors, drug use, and quality of life[99,100] from these female-specific treatments also have been positive. NIAAA's focus on implementation studies in conjunction with the study of mechanisms of change[101] should accelerate testing the incorporation of female-specific interventions into community settings—not just addiction specialty clinics but also primary care and general mental health settings. These interventions should ultimately lead to algorithms for optimal personalization of treatment components to individuals' clinical presentation. In the meantime, since most women currently receive treatment in gender-neutral settings, it is important to address women's specific needs even in the context of mixed-gender, gender-neutral[102] clinical programming. Research to address unresolved gaps in the knowledge base is needed. For example, does the availability of female-specific programming, whether in female-segregated or mixed-gender settings, increase AUD treatment utilization by women? In addition, there is a dearth of rigorous RCTs comparing female-only versus mixed-gender treatment formats that contain female-specific programming to test differential treatment engagement and positive outcomes.

Notable areas of additional needed research on women and AUD treatment follow.

Prevention

Women who enter treatment for AUD present with greater addiction and more severe psychosocial issues than men. Secondary prevention research has focused on engaging women in treatment as well as on providing alcohol psychoeducation earlier in women's problem drinking careers, which may help arrest the telescoped trajectory to AUD and SUD and the corresponding psychosocial decline.

Setting

Women are more likely to self-identify as having an alcohol problem and enter AUD treatment through a medical or mental health portal than a substance use specialty clinic. For instance, women may obtain AUD treatment in the course of seeking treatment for a co-occurring psychiatric disorder, such as PTSD or depression, in a general mental health setting.[19,20] Also, brief interventions in primary care settings have been found to be promising in reducing drinking among less complex cases of women with low co-occurrence,[103] but no studies have examined the co-location of more intensive outpatient female-specific AUD treatments in primary care or women's medical clinic settings.

Treatment Silos

Increasing rates of drug use among women point to a need for integrated AUD and SUD female-specific treatments. Although some evidence-based treatments are available,[103] the net can be cast even wider to include a range of health behaviors such as nutrition, sleep, exercise, smoking cessation, and use of benzodiazepines. Framing AUD treatment for women in the context of a general health and wellness approach that addresses other health behaviors may increase appeal, reduce stigma, and enhance utilization.

Digital Delivery Platforms

Testing telehealth platforms for individual and group AUD treatments may help reduce barriers to use among women. Likewise, testing ancillary smartphone applications that link women to in vivo coping skills training and social network support could enhance outcomes of existing in-person programs or serve as stand-alone aids for women who face insurmountable treatment entry barriers.

Female-Specific, Coping-Skills-Based, Peer Support Groups

Female-specific, coping-skills-based, peer support groups are not widely available. The evidence base for women's Alcoholics Anonymous meetings needs to be established. In addition, the recent positive development of a recovery coach industry may help with in vivo social support especially for women, but research is necessary to establish an evidence base.

Medications

Research on medications for women with AUD as one treatment element should continue. A precision medicine approach testing gender, genetic profiles, and specific medications is an important avenue to pursue.

Mechanisms of Change Research

Research on mechanisms of change is crucial to untangle whether similar drinking outcomes of women and men with AUD are achieved via gender-specific pathways to change and to identify active ingredients and mediators of treatment change best suited for women with only AUD and for women with specific types of co-occurring disorders. New methodologies in statistics, neuroscience, and research design are helping to clarify these questions; however, additional research is needed to streamline and personalize optimally efficient treatment components for every woman seeking care for AUD.

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Integrating Treatment for Co-Occurring Mental Health Conditions

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Given the high co-occurrence between alcohol use disorder (AUD) and mental health conditions (MHCs), and the increased morbidity associated with the presence of co-occurring disorders, it is important that co-occurring disorders be identified and both disorders addressed in integrated treatment. Tremendous heterogeneity exists among individuals with co-occurring conditions, and factors related to both AUD and MHCs, including symptom type and acuity, illness severity, the chronicity of symptoms, and recovery capital, should be considered when recommending treatment interventions. This article reviews the prevalence of co-occurring AUD and MHCs, screening tools to identify individuals with symptoms of AUD and MHCs, and subsequent assessment of co-occurring disorders. Types of integrated treatment and current challenges to integrate treatment for co-occurring disorders effectively are reviewed. Innovative uses of technology to improve education on co-occurring disorders and treatment delivery are also discussed. Systemic challenges exist to providing integrated treatment in all treatment settings, and continued research is needed to determine ways to improve access to treatment.

KEY WORDS: **alcohol use disorder; integrated treatment; mental health condition; screening; treatment setting**

Introduction

Given the high co-occurrence between alcohol use disorder (AUD) and mental health conditions (MHCs),[1] and the increased morbidity associated with the presence of co-occurring disorders,[2] it is important to identify the co-occurring disorders and to address both disorders in treatment to improve treatment outcome. Treatment that addresses both disorders concurrently with the same provider or treatment team is called integrated treatment. As integrated treatments continue to be developed, evaluated, and implemented, the heterogeneity associated with co-occurring AUD and MHCs needs to be acknowledged, since it can affect individual functioning and prognosis. Factors that

contribute to heterogeneity among individuals with co-occurring AUD and MHCs include acuity of symptoms, severity of illness, chronicity of symptoms, co-occurring drug use, physical health, cognitive impairment, and recovery capital (Table 1). Recovery capital is a newer dimension to consider, which includes the amount of available resources a person has to support stabilization of AUD and the transition into recovery.[3]

Table 1 Factors That Affect Functioning and Prognosis for Individuals With Co-Occurring AUD and MHCs

Factor	Examples
Acuity of Symptoms	• Symptoms of alcohol withdrawal that require urgent medical management • Active suicidal ideation that requires inpatient psychiatric admission • Current symptoms of disorder only • Lifetime history of disorder
Severity of Illness	• Severe AUD • Serious mental illness: schizophrenia, bipolar disorder, treatment-resistant major depressive disorder, or anxiety associated with agoraphobia
Chronicity of Symptoms	• Recent onset of symptoms • Chronic symptoms with minimal periods of recovery
Co-Occurring Drug Use	• Injection drug use • Substances (e.g., cocaine) associated with psychiatric symptoms (e.g., anxiety and psychosis)
Physical Health	• Malnutrition or liver cirrhosis related to chronic alcohol use • Physical disability • Infectious disease: HIV or hepatitis C • Pregnancy and family planning
Cognitive Impairment	• Substance related • Low IQ • Head trauma
Recovery Capital	• Employment • Education • Finances • Living situation • Social networks

This article provides a background on the prevalence of AUD and co-occurring MHCs, discusses screening tools to identify individuals with symptoms of problematic alcohol use and an MHC, and discusses subsequent assessment of co-occurring disorders. Patient placement considerations and types of integrated treatment are also covered. The article concludes with a discussion of the challenges of integrating treatment for co-occurring disorders effectively and the recent innovations in education and treatment delivery that address some of these challenges.

Background

Over the past 30 years, there has been increasing awareness that AUD frequently co-occurs with MHCs. The high rate of co-occurring AUD and MHCs is not surprising, since research has demonstrated that young people with a history of an MHC, when compared to peers with no MHC history, are at increased risk to initiate alcohol use, transition to regular use, and subsequently develop AUD.[4] Furthermore, co-occurrence begins to emerge early. One study found that adolescents with an MHC had onset of alcohol use, regular alcohol use, and AUD at median ages of 12.2 years, 13.8 years, and 14.3 years, respectively.[4]

Individuals with AUD, when compared to individuals with MHCs, have a higher prevalence of co-occurring disorders. More specifically, among adults in the United States in 2017, an estimated 14.1 million had AUD, and 46.6 million had an MHC.[1] Within these two groups, 5.9 million adults had current, co-occurring AUD and MHCs, which represents 41.8% of individuals with current AUD and 12.7% of individuals with a current MHC. In adults, AUD has been associated with an increased lifetime risk for major depressive disorder (adjusted *OR* of 1.3), anxiety disorder (adjusted *OR* of 1.3), and bipolar I disorder (adjusted *OR* of 2.0), as well as with antisocial and borderline personality disorders (adjusted *OR*s of 1.9 and 2.0, respectively).[5] For MHCs, a history of childhood attention deficit hyperactivity disorder, oppositional defiant disorder, or conduct disorder has been associated with an increased risk for developing AUD,[6] and bipolar I disorder, antisocial personality disorder, and psychotic spectrum illness have been associated with substantially higher rates of lifetime and current AUD.[7,8]

Co-occurring AUD and MHCs have been associated with poorer outcomes, such as increased rate of relapse,[9] use of psychiatric services, and use of emergency services,[2] when compared to each disorder separately. Although treatment interventions

have been developed specifically for individuals with AUD, most treatment is provided in clinical settings that treat both AUD and other drug use disorders, hereafter called substance use disorder (SUD) treatment.

Until the increased recognition of co-occurring disorders in the 1980s and 1990s, patients who presented for SUD or mental health treatment often were not evaluated for a co-occurring disorder, or their treatment plan did not address the co-occurring disorder. Since neither disorder is likely to show sustained improvement if one disorder is treated without acknowledging the presence or influence of the co-occurring disorder,[10-13] different treatment approaches were developed to address co-occurrence, including sequential, parallel, and integrated treatments. In sequential treatment, one disorder is assessed and treated before addressing the other disorder. In parallel treatment, different providers or treatment teams address each disorder separately. In integrated treatment, the same provider or treatment team addresses both disorders concurrently.

If one treatment team provides care, the providers work in the same setting and coordinate care. Colocation of treatment and coordinated care helps providers give patients a consistent message regarding treatment and recovery.[14] Integrated treatment is considered the standard of care regardless of the treatment setting (SUD or mental health) a patient presents to first.[15]

To support the dissemination of integrated treatment, the Substance Abuse and Mental Health Services Administration (SAMHSA) released the Integrated Treatment for Co-Occurring Disorders Evidence-Based Practices Kit in 2009, which remains publicly available.[16] Since then, SAMHSA and the Health Resources and Services Administration established a Center for Integrated Health Solutions to support the development of integrated primary and behavioral health care for MHCs, SUD, and physical health conditions such as hypertension, obesity, and cardiovascular disease. These efforts are needed, since most individuals with co-occurring SUD and MHCs do not receive integrated treatment. For example, in 2017, only 8.3% of adults with an MHC and co-occurring SUD received mental health and SUD services, whereas 38.2% received mental health services only, 4.4% received SUD treatment only, and 49% received no treatment.[1]

Screening and Assessment

One factor contributing to low rates of integrated treatment for individuals with co-occurring AUD and MHCs is poor identification of the presence of a co-occurring disorder. Like other health conditions for which routine screening occurs at certain ages (e.g., breast cancer screening for women beginning at age 40) or in certain settings (e.g., screening for hyperlipidemia in primary care settings), screening for both the presence of AUD and for other MHCs can be efficiently conducted. This screening, however, may be rare in practice, especially among certain subgroups. One review found that adolescents, individuals from low socioeconomic backgrounds, and racial/ethnic minorities often are not identified as having a co-occurring disorder, despite having both disorders.[17] Routine, standardized screening is necessary to identify problematic alcohol use and mental health symptoms and to assess for co-occurring disorders.

Screening for alcohol and other substance use in the medical setting has become the standard of care because of the demonstrated efficacy of screening, brief intervention, and referral to treatment (SBIRT) in the primary care setting for reducing problematic alcohol use.[18] Over the past 15 years, emphasis on implementing SBIRT in other health care settings, such as emergency departments and inpatient medical settings, has increased.[19] Given the relationship between AUD and MHCs, these medical settings present opportunities for incorporating screening for mental health symptoms with screening for problematic alcohol use, and further research is needed on how to do this. Likewise, more research is needed on the effectiveness of SBIRT in the mental health treatment setting, since most individuals with co-occurring MHCs and AUD receive mental health treatment only. Table 2 lists representative examples of screening tools that assess for problematic alcohol use and other substance use. Screening for symptoms of an MHC in an SUD treatment setting is also necessary. Table 3 includes examples of screening tools for MHCs.

In addition to detecting the presence or absence of co-occurring AUD or MHCs, understanding the nature, scope, chronicity, and effect of the primary disorder and the co-occurring ones is critically

Table 2 AUD and SUD Screening and Assessment Tools for the Primary Care Setting

Tool	Description
AUD	
Alcohol Screening and Brief Intervention for Youth: A Practitioner's Guide[20]	• Clinician-administered screening • Developed for youth ages 9 to 18 • Two questions about patient and peer alcohol use • Developmentally specific questions for patients in elementary school, middle school, and high school
Alcohol Use Disorders Identification Test (AUDIT)[21]	• Clinician- or patient-administered screening • Developed for adults • Ten questions about alcohol use, three questions in abbreviated version (AUDIT-C)
AUD and SUD	
Screening to Brief Intervention (S2BI)[22] Brief Screener for Tobacco, Alcohol, and Other Drugs (BSTAD)[23]	• Clinician- or patient-administered screening • Developed for adolescents • Three initial questions about tobacco, alcohol, and marijuana use in the past year • Four additional questions about other types of drugs if adolescent replied yes to any of the three initial questions • For S2BI, four choices for frequency of use over the past year • For BSTAD, number of days of use over the past year
Tobacco, Alcohol, Prescription Medication, and Other Substance Use (TAPS)[24]	• Clinician- or patient-administered screening and assessment • Developed for adults • Four initial questions about tobacco, alcohol, illicit drugs, and nonmedical use of prescription drugs in the past year • Additional questions to assess risk level if patient replied yes to initial questions
National Institute on Drug Abuse (NIDA) Quick Screen[25]	• Clinician-administered screening and assessment • Developed for adults • Four initial questions about frequency of tobacco, alcohol, illicit drug, and nonmedical prescription drug use in the past year • Clinician intervention guided by patient response
Alcohol, Smoking and Substance Involvement Screening Test (ASSIST)[26]	• Clinician-administered screening and assessment • Developed for adults • Questions about lifetime and past 3-month use of tobacco, alcohol, and seven other drugs • Assessment of frequency, desire to use, and associated substance use problems if patient endorsed substance use in the past 3 months • Questions about injection drug use, concern from friends or relatives, and difficulty with decreasing substance use if patient endorsed lifetime substance use

Table 3 MHC Screening Tools

Screening Tool	Description
Pediatric Symptom Checklist (PSC)[27]	• Parent- or child-administered screening for emotional or behavioral problems • Developed for children and adolescents ages 6 to 16 seen in primary care • Seventeen or 35 questions that assess psychosocial functioning
Patient Health Questionnaire (PHQ-9)[28]	• Patient-administered screening for depression • Developed for adults seen in primary care • Nine questions
Generalized Anxiety Disorder (GAD-7)[29]	• Patient-administered screening for generalized anxiety disorder • Developed for adults seen in primary care • Seven questions
Mental Health Screening Form III[30]	• Clinician- or patient-administered screening to identify psychiatric co-occurrence • Developed for adults receiving treatment for SUD • Eighteen questions

important for formulating an effective treatment and recovery plan. Typically, this process is called the assessment, in contradistinction to the initial screening. Longer comprehensive assessment tools for SUD that also assess for problems related to an MHC have been used in clinical trials and in the community. These tools include the semistructured Addiction Severity Index (ASI),[31] the Global Appraisal of Individual Needs (GAIN),[32] and the American Society of Addiction Medicine (ASAM) Criteria.[33] The psychiatric scales from the ASI have been shown to be an effective tool for identifying individuals with a co-occurring MHC, but further assessment is needed to determine which co-occurring disorder is present.[34] The GAIN assesses for symptoms of specific psychiatric disorders, including internalizing disorders such as depression, anxiety, trauma, and suicide, as well as externalizing disorders such as attention deficit hyperactivity disorder and conduct disorder.[32] The ASAM Criteria was designed to help clinicians determine the recommended treatment setting and level of care for patients with SUD, but it includes a brief mental health symptom assessment that can be used to identify acute psychiatric safety concerns and symptoms that need further assessment.[33]

One challenge to screening and assessing for co-occurring MHCs in individuals with AUD is that problematic alcohol use is associated with changes in mood, sleep, concentration, and anxiety. Initially, it may be unclear if someone suffers from a co-occurring MHC that is independent of alcohol or drug use and that warrants focused attention, or if symptoms or the apparent disorder will dissipate with alcohol or drug abstinence. To address this challenge, the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) includes the diagnosis "alcohol-induced mental disorders" to describe symptoms of a temporary MHC only observed during severe alcohol intoxication or during withdrawal from alcohol.[35] Therefore, comprehensive screening and assessment of co-occurring MHCs should not be done when an individual is intoxicated or is experiencing withdrawal symptoms. Generally, in addition to screening for symptoms of an MHC during an individual's initial engagement in treatment, clinicians should reassess mental health symptoms later during treatment to confirm the diagnosis and severity of the MHC and to plan for treatment.

Although there should be no "wrong door" for treatment when an individual with AUD and a co-occurring MHC presents for care, until integrated treatment of both disorders is more commonplace, clinicians need to consider the severity and effects of each disorder when recommending treatment settings. The quadrant model is a tool that can be used to help clinicians make these recommendations. The quadrant model has four treatment categories based on the severity of the SUD and MHC: the primary health care setting, the SUD setting, the mental health system, and specialized co-occurring disorder programs.[36] This model has been adopted by national addiction and mental health treatment administrators,[37] has been validated as effective at categorizing patients with co-occurring disorders, and has been associated with appropriate service utilization.[38]

The quadrant model can also help clinicians assess whether a patient would benefit from referral to a different treatment program to expedite symptom stabilization and maximize treatment efficacy. However, the quadrant model assumes comprehensive screening and assessment of substance use and mental health symptoms. Thus, continued efforts are needed to improve screening for both disorders to facilitate a thorough assessment and subsequent referral to appropriate treatment. Most patients and families do not know or understand the differences between treatment settings, so more research is needed on how to facilitate treatment referrals so patients remain engaged in care.

Types of Integrated Treatment

Regardless of the treatment setting, behavioral therapy, pharmacotherapy, and recovery support in the patient's community should be considered in treatment plans for patients with co-occurring AUD and MHCs. Because of the heterogeneity among co-occurring AUD and MHCs, individualized treatment plans should account for the severity of each disorder and for patient preference regarding interventions. Also, although not typically assessed, the amount of available resources a person has for stabilization and recovery needs to be included in the assessment to inform the treatment plan.

These resources often are called "recovery capital," a dimension[3] that recently developed tools can assess.[39,40] Two clinically identical patients can have different levels of recovery capital in terms of employment, education, finances, living situation, and social networks, all of which can affect clinical interventions and, ultimately, the likelihood of remission and long-term recovery.

Behavioral therapy

Behavioral therapies, such as motivational enhancement therapy, cognitive behavioral therapy, contingency management, and 12-step facilitation, are the standard of care for individuals with AUD and are a key part of a treatment plan for individuals with co-occurring AUD and MHCs.[41] As such, behavioral therapy for AUD, which is commonly motivational enhancement therapy or cognitive behavioral therapy, is provided to all participants in most randomized controlled trials that evaluate pharmacotherapy for individuals with AUD and an MHC. Although less commonly discussed, AUD-focused therapies delivered to individuals with MHCs may need to be adapted to account for the MHC. For example, Levin and colleagues modified the delivery of cognitive behavioral therapy for SUD when working with individuals who had co-occurring attention deficit hyperactivity disorder.[42] The researchers allowed in-session time for completing homework assignments, checked in with participants after presenting any new paradigm for understanding drug use behavior, and used visual diagrams to help with skills training.

Other behavioral therapies designed to address MHCs, such as cognitive behavioral therapy for depression or anxiety and dialectical behavioral therapy for mood dysregulation, can be integrated into the treatment plan for individuals who have co-occurring disorders. For example, integration of modules from cognitive behavioral therapy for individuals with AUD and depression may include introducing skills to address each disorder at alternating sessions. Increasingly, co-occurring disorders are being addressed simultaneously in a single session. Examples include integrated group therapy for adults with bipolar disorder and SUD,[43] integrated individual cognitive behavioral therapy for depression and SUD,[44] integrated cognitive behavioral therapy for post-traumatic stress disorder and SUD,[45] and "seeking safety," a group therapy for individuals with a history of trauma and SUD.[46]

These integrated protocols appear to be promising. Researchers that conducted a meta-analysis of studies that combined cognitive behavioral therapy and motivation interviewing to treat individuals with depression and AUD found that integrated treatment, when compared to usual care, was associated with small but clinically significant improvements in depressive symptoms and alcohol use.[47] Another review of integrated treatments for individuals with SUD and trauma experiences also found that integrated treatment was associated with improvement in both SUD and symptoms of post-traumatic stress disorder, but no clear benefit was found for integrated treatment when it was compared to nonintegrated treatment.[48] Further research is needed to compare the efficacy, cost, and patient satisfaction associated with integrated versus nonintegrated behavioral treatment of AUD and MHCs.

Pharmacotherapy

Pharmacologic trials for co-occurring AUD and MHCs have focused primarily on treating the MHC with a medication that has demonstrated efficacy for treating the MHC in the absence of co-occurring AUD.[49-51] This type of trial includes, for example, using an antidepressant medication to treat an individual who has AUD and major depressive disorder. On average, these pharmacologic trials have shown modest improvements in the MHC, with limited improvement in the co-occurring AUD.[52,53] Likewise, clinical trials that used medication effective at treating AUD alone have shown some improvement in the AUD, with limited improvement in the co-occurring MHC.[50,54] Importantly, in the studies that evaluated the effectiveness of AUD medication for co-occurring AUD and MHCs, most participants were also simultaneously receiving medication for the MHC, which may have affected study outcome.[54,55]

Pharmacologic trials for co-occurring disorders have been limited by small sample sizes, which reflects difficulty recruiting and retaining participants in these trials. Given these challenges, studies using registries or electronic medical record databases may be an alternative for evaluating outcomes associated with available pharmacologic treatments. For

example, one recent quasi-experimental study used public databases to examine the effect of medication treatment for AUD among adults involved in the criminal justice system.[56] These participants had alcohol dependence (per the DSM-IV classification) and serious mental illness (i.e., schizophrenia, bipolar disorder, or major depressive disorder). Although details on abstinence, heavy-drinking days, and symptoms of the MHC were not accessible through the public databases used in this study, the databases allowed investigators to identify a large sample (N = 5,743) and use information on functional outcomes, which served as a proxy for traditional outcomes used in a randomized controlled trial. In this study, individuals who received medication for AUD were less likely at the 1-year follow-up to have been hospitalized for a psychiatric condition or to have used the emergency department. They also were more likely to have adhered to their psychotropic medication regimen than participants who were not taking these medications.

The overall literature on pharmacotherapy for co-occurring AUD and MHCs suggests medication without other treatment interventions may not be adequate to stabilize both conditions.[52,57] Nonetheless, medication is a treatment option that should be discussed with patients who have co-occurring disorders. For more serious mental illness, specifically bipolar disorder and psychotic disorders, disorder-specific medication is necessary for initial stabilization and maintenance.[37] For other MHCs, such as depression and anxiety with mild to moderate impairment and AUD with mild impairment, when each disorder is considered separately, treatment guidelines suggest medication or therapy as options for first-line treatment, although medication is more strongly indicated for individuals who have greater impairment.[58-60] More research is needed to determine if medication should be more strongly indicated for co-occurring AUD and MHCs causing mild impairment, given the more complicated course of illness when these disorders co-occur.

Recovery support in the community

Peer-led mutual help organizations can be another component of a treatment plan for individuals with co-occurring AUD and MHCs. Beginning in the 1980s, mutual help organizations for individuals with SUD and an MHC were formed, including Dual Recovery Anonymous, Double Trouble in Recovery, and Dual Diagnosis Anonymous.[61] These groups all follow the 12 phases or traditions of 12-step organizations, but they have modifications addressing the co-occurring MHC. Relative to 12-step organizations for AUD alone, such as Alcoholics Anonymous, mutual help groups for individuals with co-occurring disorders are less common, and less research exists that evaluates the relationships among group attendance, mental health symptoms, and alcohol use. In one study of individuals with psychotic disorders (schizophrenia or schizoaffective disorder) and AUD and/or cocaine use disorder, in which a majority of the participants were African American, investigators found that regular attendance at Double Trouble in Recovery was associated with fewer psychiatric symptoms, increased rates of abstinence, and greater adherence to psychiatric medication.[62]

Because of their greater national presence, mutual help organizations for AUD or MHCs are much more accessible than those for co-occurring disorders. Among the mutual help organizations for AUD, Alcoholics Anonymous is the largest, with approximately 61,000 meetings serving 1.3 million members in the United States.[63] Also, Alcoholics Anonymous has been the mutual help organization most thoroughly evaluated for the effect of participation, both for individuals with AUD and for those with co-occurring AUD and an MHC. A recent systematic review and meta-analysis of patients with AUD and co-occurring MHCs found that AUD improved with Alcoholics Anonymous attendance, and the patients with co-occurring AUD and an MHC benefited from engagement with Alcoholics Anonymous as much as patients with no co-occurring MHC.[64]

Mutual help organizations for individuals with MHCs have greatly expanded over the past 30 years as part of an overall emphasis on including peers in the recovery process. Whether participation in these groups provides benefit has been less clear,[65] and research in this area has been complicated by a lack of standardization across groups. Substantial variability exists regarding services provided by these groups, which can include telephone support hotlines, social and recreational activities, and advocacy, in addition to face-to-face meetings. Also, research evaluating the efficacy of these groups

has not examined differences between individuals who have an MHC with a co-occurring AUD and those with no co-occurring AUD. Further research is needed to determine the ways individuals with co-occurring AUD and MHCs might benefit from participation in a mutual help organization that is focused on alcohol and other substance use versus a group focused on symptoms of the MHC.

In addition to in-person peer support, individuals who have AUD and/or MHCs are increasingly seeking support through online support groups and social media.[66,67] Research is ongoing to determine the effectiveness, important characteristics (e.g., synchronous, such as chat rooms; asynchronous, such as forums; and level of monitoring from moderators), and risks of online peer support. Because of the heterogeneity associated with co-occurring AUD and MHCs, people with similar illness experiences may be geographically far apart, and online peer support could help them connect.

Comprehensive integrated treatment for serious mental illness and AUD

Evidence-based practices for integrated treatment programs for individuals with substantial impairment and low functioning because of AUD and a serious mental illness, such as schizophrenia or bipolar disorder, include incorporating interventions that match an individual's stage of readiness for treatment engagement[68] and involve assertive outreach, motivational interventions, and counseling to build cognitive and behavioral skills. Evidence-based practices also include strengthening an individual's connection with social supports that encourage recovery, a comprehensive approach that addresses AUD and MHCs in all aspects of the program, including social services, and takes a long-term, community-based perspective on recovery. Cultural sensitivity and competence are also crucial aspects of integrated treatment programs.

One example of a comprehensive integrated treatment is integrated dual diagnosis treatment, which incorporates these evidence-based practices and integrates all components of a treatment plan, including psychological, pharmacological, educational, and social interventions.[69] Assertive community training and intensive case management are two other treatments that have been adapted for individuals with serious mental illness and co-occurring AUD.[37] These two treatments both involve intensive case management, skills training, and individual counseling.

The research supporting superior efficacy associated with integrated treatment remains limited. However, in a systematic review of randomized controlled trials of long-term integrated psychosocial interventions for individuals with SUD and serious mental illness, when the researchers compared integrated intervention with usual care, they found no significant differences in participant alcohol or substance use, functioning, or life satisfaction.[70] The investigators noted that their systematic reviews of the existing literature were limited by differences in study design and the outcomes used to evaluate intervention efficacy, as well as by low rates of subject retention, longitudinally.

Challenges in Implementing Integrated Treatment

Although integrated treatment is considered the standard of care for individuals with co-occurring AUD and MHCs, implementing it in both SUD and mental health treatment centers has been difficult. Some of the implementation challenges relate to the independent development of the public mental health and SUD treatment systems, which have differences in workforce training (e.g., coursework and clinical rotations), licensure requirements, and reimbursement.

Training and licensure requirements for providers delivering the same type of treatment vary among specialties. For example, behavioral therapies are commonly delivered by psychologists, social workers, counselors with primary training in MHCs, or alcohol and drug counselors. The programs that train these providers have different accreditation bodies that oversee the educational requirements during training. The programs also have different state licensure requirements. In 2009, the Council for Accreditation of Counseling and Related Educational Programs revised its standards to emphasize that mental health counselors need to have exposure to coursework specific to substance use.[71] When mental health counseling programs were surveyed in 2013, 69% required this coursework, and 13% offered it as an elective.[72] In contrast, the Council on Social Work

Education has no emphasis on coursework specific to substance use, and the same survey found only 2% of master's degree programs in social work required this coursework, and only 64% offered it as an elective.

For alcohol and drug counselors, training traditionally has emphasized clinical rotations, but more recently it has been shifting toward incorporating more formalized coursework.[73] Unlike other behavioral therapy providers, alcohol and drug counselors have no national accreditation system to guide their training for MHCs, and training programs are more influenced by state licensure requirements. Differences in training and licensure may affect the dissemination and implementation of newer evidence-based practices, such as integrated treatments. Standardized training and licensure requirements could provide a mechanism for monitoring training, and it could potentially encourage dissemination of newer practices through continuing education requirements.

However, requiring that all providers receive training in both SUD and MHCs does not guarantee they will receive didactic and clinical training in both conditions or training in integrated treatment. Training experiences for these disorders generally occur separately. In part, separate training experiences occur because integrated services may not have been developed to serve as a clinical training site, and because many educators lack training and expertise in the management of co-occurring disorders.

For example, although graduate medical education for psychiatry requires that trainees be exposed to addiction psychiatry, concerns have been raised that the current training does not produce psychiatrists who are well-prepared to manage SUD, or co-occurring SUD and MHCs, in practice.[74] When training directors of general psychiatry were surveyed to identify barriers to adequate training in addiction, the two most commonly identified barriers were limited faculty and staff with expertise, and limited faculty and staff time to supervise clinical experiences.[74] This survey also found that in 2017, only 15% of general psychiatry training programs had board-certified faculty in addiction psychiatry, and only 37% of programs had board-certified faculty in addiction medicine.

Since no formal training paths offer training in integrated treatment, providers generally need to pursue training in each field to be prepared to provide this type of care. Few incentives exist for pursuing additional training, because within the SUD and mental health treatment systems, additional reimbursement is not provided for delivering integrated treatment services. Reimbursement inequities also exist for each type of care. Historically, insurance benefits for mental health treatment have been greater than the benefits for substance use treatment.[75]

The federal Mental Health Parity and Addiction Equity Act of 2008 was enacted to address this inequity. Despite the legislation, integrated treatment delivery is still limited by restrictive diagnostic and billing criteria that generally assess service eligibility based on one disorder only.[76] Often, the criteria do not account for the complexity added to either disorder when a co-occurring disorder is present. Furthermore, integrated care often requires frequent communication among providers to effectively coordinate care, but coordination of care is not a reimbursable service in fee-for-service insurance models. SAMHSA continues to work to address these barriers, and it is possible that as health care financing transitions from fee-for-service to population-based care, funding to support integrated treatment programs may become more flexible.

Innovative Models

One example of an innovative model for improving education is the Extension for Community Healthcare Outcomes program for primary care providers, called Project ECHO (https://echo.unm.edu). This program uses a simultaneous video link to connect specialists and primary care providers in different regions of a state for regular case-based discussions. In New Mexico, one focus of Project ECHO has been a weekly meeting about addictions and psychiatry. A review of the program suggests that this type of learning opportunity helped New Mexico increase the number of physicians who have waivers to prescribe buprenorphine in underserved areas at a much faster rate relative to other states in the country.[77]

Innovative models also have been developed to address some of the challenges associated with implementing integrated treatment, particularly the shortage of providers in the addiction treatment setting who are trained in both SUD

and MHCs. When two transdiagnostic and not disorder-specific interventions for MHCs were evaluated among individuals with AUD and co-occurring anxiety disorders, the interventions showed encouraging preliminary results.[78,79]

Unified protocol therapy is an emotion-focused, cognitive behavioral therapy treatment that has been shown to be effective for a range of different MHCs, including anxiety, depression, and bipolar disorder. In an 11-week study, 81 individuals who had AUD and an anxiety disorder were randomized to 4 conditions, and the group that received the unified protocol therapy was the only group to have a significant reduction in heavy-drinking days when compared to the other groups.[78]

Acceptance and commitment therapy is a mindfulness-based form of behavioral therapy that has been shown to be effective for anxiety and depression, as well as for SUD. In a 12-week, uncontrolled pilot study of acceptance and commitment therapy, which included 43 veterans with AUD and post-traumatic stress disorder, researchers found that 67% of the veterans completed the protocol.[79] Improvements in alcohol use, anxiety, depression, and quality of life were also reported. More research is needed to evaluate the efficacy of these transdiagnostic interventions for co-occurring AUD and MHCs. Currently, five clinical trials registered on clinicaltrials.gov are investigating these two transdiagnostic interventions for co-occurring disorders.

Another strategy for addressing implementation challenges has been to leverage technology to help providers who have no prior specialized training deliver cognitive behavioral therapy for anxiety disorders. For example, in the coordinated anxiety learning and management (CALM) intervention for addiction recovery, individuals with SUD and an anxiety disorder receive a group-based, computer-assisted, but therapist-directed, treatment for anxiety disorders that has been adapted for individuals with co-occurring disorders. In a randomized controlled trial, individuals who received the CALM intervention had less anxiety and less substance use through 6-month follow-up when compared to those who received the usual care.[80]

Future Directions

Although integrated treatment for co-occurring AUD and MHCs makes intuitive sense, the evidence base supporting integrated treatment, particularly for co-occurring anxiety and depression, is less mature. To address the heterogeneity among individuals with co-occurring disorders, more research is needed on the types of services, service providers, and treatment settings that are best for which groups of individuals. Also, in the evaluation of a treatment's efficacy, it is important to include individual strengths, such as recovery capital, that may moderate or mediate response to treatment. Recruiting participants who have AUD and MHCs for randomized controlled trials to evaluate the effectiveness of treatment can be challenging, and increasing measurement-based practice[81] within current treatment structures could help clinicians determine which patients are struggling and prompt re-evaluation of treatment plans.

Furthermore, a limited amount of staff and faculty with expertise in integrated treatment for individuals with SUD and MHCs has been identified as a barrier to improving education and subsequent delivery of care for co-occurring disorders. Therefore, it is imperative that educators and policy makers consider increasing virtual and multidisciplinary training opportunities that focus on addiction, MHCs, and integrated treatment. Increasing multidisciplinary training opportunities includes streamlining continuing education accreditation so an educational program developed for one group of providers can easily be shared with other providers who could benefit from the same information and who also need continuing education credits for their specialty.[81]

Finally, continued innovation is needed to use promising technologies, such as computerized interventions, to treat co-occurring disorders in settings that have limited expertise. Although some preliminary projects have evaluated adapting computerized interventions for MHCs for delivery in the SUD treatment setting, no trials of computerized interventions for SUD have been adapted for delivery in the mental health treatment setting. Since most individuals with co-occurring SUD and MHCs receive care in the mental health

setting, this is an important setting for evaluating these types of interventions.

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Pharmacotherapy for Co-Occurring Alcohol Use Disorder and Post-Traumatic Stress Disorder

Targeting the Opioidergic, Noradrenergic, Serotonergic, and GABAergic/Glutamatergic Systems

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Alcohol use disorder (AUD) and post-traumatic stress disorder (PTSD) are highly comorbid, and treatment outcomes are worse in individuals with both disorders. Several neurobiological systems have been implicated in the development and maintenance of AUD and PTSD, and pharmacologic interventions targeting these systems for singular diagnoses of AUD or PTSD have proven effective. However, there are no established treatments for co-occurring AUD and PTSD, and relatively few studies have examined potential pharmacotherapy for treating symptoms of both AUD and PTSD in comorbid populations. This review provides a brief overview of the studies to date on pharmacotherapeutic treatment interventions for comorbid AUD and PTSD and highlights future directions for promising targets that have potential in the treatment of individuals with this dual diagnosis. Clinical implications of these findings are also discussed. While current medications targeting the opioidergic, noradrenergic, serotonergic, and GABAergic/glutamatergic brain systems are only modestly efficacious in improving symptoms in individuals with comorbid AUD and PTSD, novel targets within these neurobiological systems may be clinically useful for treating alcohol use outcomes and PTSD symptom severity. More work is needed to optimize pharmacologic treatment strategies that target both alcohol-motivated behavior and PTSD-related symptoms in individuals with co-occurring AUD and PTSD.

KEY WORDS: **alcohol; alcohol use disorder (AUD); comorbidity; pharmacotherapy; post-traumatic stress; post-traumatic stress disorder (PTSD)**

Introduction

Over the past decade, 12-month alcohol use, high-risk drinking, and alcohol use disorder (AUD) have increased by 11.2%, 29.9%, and 49.4%, respectively, in the United States.[1] In addition to increasingly high prevalence rates of AUD and the severe health and economic consequences associated with the disorder,[2] AUD is also highly comorbid with other psychiatric illnesses. One such comorbidity is post-traumatic stress disorder (PTSD). PTSD is a chronic and disabling disorder and is characterized by intrusive or distressing thoughts, persistent avoidance of stimuli related to the traumatic event, negative alterations in cognition or mood, and symptoms of arousal following exposure to a traumatic event. Lifetime and 12-month prevalence of PTSD in the general population are 6.1% and 4.7%, respectively.[3] This percentage is larger in certain populations, such as veteran populations, where lifetime prevalence ranges from 6.9% in U.S. veterans to 37.3% in war-specific cohorts.[4] Previous estimates suggest that individuals with PTSD are more likely to have comorbid AUD, as much as 42% of individuals within the general population[5] and 55% of veterans.[4] This is consistent with recent epidemiologic findings demonstrating a reciprocal relationship between the two disorders, such that the odds of having PTSD are significantly greater in individuals with lifetime AUD.[6]

Individuals with both AUD and PTSD typically exhibit worse outcomes, ranging from social consequences and psychological problems to treatment responses, when compared with individuals with either diagnosis alone.[7] Individuals with comorbid AUD and PTSD tend to have more severe PTSD symptoms, increased alcohol-related problems, increased risk of relapse, more frequent hospitalizations, increased emotional dysregulation, and increased odds of additional psychiatric comorbidity and suicide attempts than individuals with either disorder alone.[8,9] Other difficulties in this comorbid population include increased unemployment and homelessness. To further complicate the picture, only 19.8% and 59.4% of those with singular diagnoses of lifetime AUD and PTSD, respectively, ever seek or receive treatment,[3,6] and treatment-seeking rates in individuals with comorbid AUD and PTSD are very low.[8] Treatment adherence and response are also poorer in individuals with both disorders, compared with individuals with a singular diagnosis.[9]

The neurobiology underlying AUD and PTSD is complex and not fully understood. While not comprehensive of all systems, the opioid, norepinephrine, serotonin, gamma-aminobutyric acid (GABA), and glutamate neurotransmitter systems are independently implicated in the pathophysiology of the development and maintenance of both AUD and PTSD.[9,10] Extensive research has focused on the opioidergic system specifically for AUD[11] and to a lesser extent for PTSD.[12] More recent attention has focused on the importance of the role of brain stress systems in both drinking behavior[13] and PTSD symptomology,[14] highlighting the importance of the noradrenergic system. "Feed-forward" mechanisms within the stress systems may mediate exaggerated stress responses in individuals with AUD and PTSD. In brief, corticotropin-releasing hormone stimulates the release of norepinephrine in response to stress.[15] Increased levels of norepinephrine are thought to play an important role in arousal, drug-motivated behaviors, withdrawal, and PTSD. Further, norepinephrine release and stress can lead to the release of serotonin,[15] which is commonly associated with anxiety disorders and depression but also PTSD. Recent evidence suggests that GABAergic and glutamatergic pathways may also be linked to AUD and PTSD. GABA and glutamate work synergistically and are important in neural plasticity, memory consolidation, fear learning, anxiety, and drug craving,[16] lending support for these systems in the maintenance of AUD and PTSD. Targeting alcohol responses and stress reactivity within these systems to treat comorbid AUD and PTSD represents a niche area of research and warrants further investigation.

Although several thorough reviews on interventions for comorbid AUD and PTSD have been published recently,[16] this review aims to discuss pharmacotherapy for comorbid AUD and PTSD in terms of five neurobiological systems: the opioidergic, noradrenergic, serotonergic, GABAergic, and glutamatergic systems. While not comprehensive of all systems that may be dysregulated by both AUD and PTSD, most of the existing work examining pharmacologic treatments in individuals with comorbid AUD and PTSD have focused on these neurobiological systems. To date, there are 12

studies, including randomized controlled trials, small open-label trials, and retrospective studies, that have examined pharmacotherapy targeting opioidergic, noradrenergic, serotonergic, and GABAergic/glutamatergic systems for the treatment of co-occurring AUD and PTSD. These studies, reviewed in this article, indicate that there is limited to modest efficacy in reducing both alcohol use outcomes and symptoms associated with PTSD in individuals with a dual diagnosis. Because effective pharmacologic treatments remain elusive, finding novel treatment targets or pharmacotherapeutic treatment strategies for comorbid AUD and PTSD is critical.

The purpose of this review is to provide an overview of current clinical trials and human experimental studies examining pharmacotherapy for comorbid AUD and PTSD. For each neurobiological system discussed, we provide potential candidates that could be examined in future studies on effective treatment targets. Finally, we provide future research directions and suggestions that have potential to advance the field toward improvements in clinical treatment options for individuals with both AUD and PTSD. While there is a rich literature on behavioral treatments for comorbid AUD and PTSD, behavioral interventions are beyond the scope of the present review (see Simpson, Lehavot, and Petrakis for a review of behavioral clinical trials).[17]

Agents Acting on the Opioidergic System

Naltrexone, a nonselective opioid antagonist that is one of four U.S. Food and Drug Administration (FDA)-approved medications to treat AUD, was approved based on two randomized controlled trials that demonstrated reductions in alcohol craving, drinking days, and risk to alcohol relapse.[10] Few studies have examined naltrexone for PTSD without comorbidity, and results are mixed and limited by small sample sizes.[12] To date, three studies have examined oral naltrexone for treating co-occurring AUD and PTSD,[18-20] demonstrating modest efficacy on alcohol use outcomes and craving and limited efficacy for improving some PTSD symptoms. In veterans with comorbid AUD and PTSD, naltrexone, when compared with placebo, effectively reduced the percentage of heavy-drinking days and increased consecutive days of abstinence.[18] But in a separate study of veterans with comorbid AUD and PTSD, naltrexone given in addition to paroxetine or desipramine, serotonin and norepinephrine reuptake inhibitors, respectively, decreased alcohol craving but did not influence drinking outcomes.[19] Both studies used 50 mg/day naltrexone, and the latter study did not examine naltrexone alone.

One other study examined 100 mg/day naltrexone in both civilians and veterans with comorbid AUD and PTSD.[20] In that study, naltrexone, relative to placebo, decreased alcohol craving and the percentage of drinking days. PTSD symptom severity declined over the course of all three studies, but there was no advantage of naltrexone over placebo. Further, in an exploratory analysis, Foa and colleagues demonstrated that individuals treated with naltrexone and prolonged exposure therapy were more likely to have a clinically meaningful reduction in PTSD symptom severity at 6-month follow-up, compared with the other three treatment conditions: placebo plus prolonged exposure therapy, naltrexone plus supportive counseling, or placebo plus supportive counseling.[20] It should be noted that these studies were conducted with veterans and civilians who had a dual diagnosis of AUD and PTSD, suggesting efficacy across multiple populations.

Other Opioidergic Medications

Naltrexone was efficacious in reducing alcohol use outcomes but did not consistently or robustly improve PTSD symptoms in individuals with AUD and PTSD. Other medications targeting the opioidergic system show promise in reducing symptoms associated with singular diagnoses of AUD or PTSD, but these medications have yet to be tested in individuals with AUD and PTSD comorbidity. For alcohol, randomized controlled trials demonstrate that nalmefene, a combined mu-opioid receptor antagonist and partial kappa-opioid receptor agonist, is effective in reducing a number of alcohol use outcomes, compared with placebo, in individuals with AUD (see Mann et al. for a review).[21] Older studies have also evaluated nalmefene for PTSD, with some indication that nalmefene reduces emotional numbing, nightmares, flashbacks, intrusive thoughts, and other PTSD-associated symptoms.[22] However, to date, no studies

have examined nalmefene for comorbid AUD and PTSD.

Other findings suggest that signaling at primarily kappa-opioid receptors plays a role in alcohol-motivated behaviors. Preclinical studies suggest that the kappa-opioid receptor antagonists JDTic and nor-binaltorphimine (nor-BNI) attenuate alcohol self-administration and cue-induced reinstatement of alcohol-seeking in rodents, with some indication that kappa-opioid receptor antagonists are more effective in alcohol-dependent versus nondependent animals.[23] Kappa-opioid receptors are also thought to play a role in regulating stress and anxiety, and they have been suggested for use as pharmacologic agents for the treatment of stress-related psychiatric disorders.[24] Because kappa-opioid receptor antagonists have the ability to reduce persistent hyperarousal and improve alterations in cognition, characteristic symptoms of PTSD, they may be useful for this clinical indication. Unfortunately, not many studies have examined these pharmacologic treatments for AUD or PTSD alone or for their comorbidity. Targeting kappa-opioid receptors may be a promising avenue for individuals with AUD and PTSD, especially for individuals with severe AUD, as JDTic was more effective in alcohol-dependent rodents than in nondependent rodents.

Agents Acting on the Noradrenergic System

Prior studies evaluating the efficacy of prazosin, an alpha$_1$-adrenergic antagonist, for separate indications of AUD[25,26] and PTSD[27] have demonstrated promising results in reducing alcohol- and PTSD-related outcomes, respectively. However, to date, only two studies have evaluated prazosin for co-occurring AUD and PTSD, with mixed results. In the first study, a 6-week, placebo-controlled trial of 16 mg/day of prazosin was effective in reducing percent drinking days per week and percent heavy-drinking days per week in civilians and veterans with comorbid AUD and PTSD.[28] Results also showed a trend toward reduced alcohol craving. In the second study, the same dose of prazosin (16 mg/day) was not advantageous over placebo in reducing drinking in veterans with comorbid AUD and PTSD, although drinking did decline over the course of the 12-week study overall.[29] This study was conducted at two different Veterans Health Administration (VHA) outpatient sites, and alcohol use outcomes were confounded by a site difference, such that better outcomes were demonstrated at the VHA site providing sober housing during treatment. In both studies, prazosin was not more effective than placebo in improving PTSD symptoms or symptom severity.

One other study examined the noradrenergic antidepressant desipramine, a norepinephrine reuptake inhibitor, among veterans with comorbid AUD and PTSD.[19] In this clinical trial, which did not include a placebo-only control group, desipramine, versus the serotonergic antidepressant paroxetine, decreased the number of drinks per drinking day and the percentage of heavy-drinking days. Like the two prazosin studies, there was a decrease in PTSD symptoms over time but no significant differences between medications.

Other Noradrenergic Medications

Of the two studies that evaluated prazosin for co-occurring AUD and PTSD, only one found an effect on drinking behavior,[28] and neither found an effect on PTSD outcomes.[28,29] While this is discouraging, a recent human laboratory study indicated that doxazosin, another alpha$_1$-adrenergic antagonist, was effective in reducing alcohol consumption in individuals with AUD who had a strong family history of alcohol problems.[30] Studies on doxazosin for PTSD also indicate that the drug may be effective in reducing some PTSD symptoms.[31] Doxazosin is also currently being studied in individuals with comorbid AUD and PTSD. Doxazosin may be more advantageous than prazosin for the treatment of either indication alone, or their comorbidity, due to the long-acting nature of the drug. Doxazosin has a half-life of approximately 18 hours, whereas prazosin has a half-life of approximately 2 to 4 hours. Thus, medication adherence and study retention may improve due to a once-daily dosing schedule of doxazosin compared with multiple prazosin doses throughout the day.

Like prazosin and doxazosin, propranolol also targets the noradrenergic system, but at beta-adrenergic receptors, and it may be a treatment option for individuals with comorbid AUD and PTSD. While limited, studies in humans have shown

that propranolol reduces alcohol craving and somatic symptoms associated with alcohol withdrawal,[32] and previous literature has demonstrated the efficacy of propranolol in reducing intrusive traumatic memories and flashbacks associated with PTSD.[33]

More recently, there has been interest in the ability of propranolol to disrupt drug-related memory reconsolidation, which may be effective in reducing rates of drug relapse. In rodents, repeated propranolol administration disrupted the memory for alcohol-cue associations, such that animals reduced responding for alcohol,[34] but results have not been consistent.[35] In humans, propranolol decreased drug craving when administered before memory reactivation through a script detailing a personalized drug-taking experience.[36] However, like the preclinical findings, studies in humans have had mixed results regarding propranolol's ability to disrupt drug-associated memory reconsolidation.[37] Also, to our knowledge, propranolol has not yet been tested specifically in humans for alcohol-associated memories.

Propranolol has also been tested for its ability to disrupt trauma-related memories. Evidence suggests that propranolol effectively reduces physiologic reactivity, fear-rated memories associated with trauma, and PTSD severity, if given soon after a traumatic event,[38] and it may be used as a strategy to reduce the development or severity of PTSD.[39] Because propranolol demonstrates efficacy in reducing alcohol-motivated behavior, attenuating PTSD symptoms, and disrupting both drug- and trauma-associated memory reconsolidation, propranolol may also be effective in reducing alcohol use outcomes and PTSD symptom severity in individuals with comorbid AUD and PTSD, providing another potential avenue for treatment and clinical improvement.

Agents Acting on the Serotonergic System

Selective serotonin reuptake inhibitors (SSRIs) have been the first-line of treatment for PTSD, with only two SSRIs FDA-approved to treat PTSD—sertraline and paroxetine.[40] However, the efficacy of SSRIs in treating PTSD and associated symptoms is limited, with less than 20% to 30% of patients achieving full remission.[41] Similarly, findings on SSRIs for the treatment of AUD or associated symptoms are limited.[42] To date, few studies have examined the effect of SSRIs on comorbid PTSD and AUD conditions. In the 1990s, Brady and colleagues conducted a small open-label pilot study of 200 mg/day of sertraline in individuals with comorbid PTSD and AUD.[43] Participants self-reported alcohol consumption, and the researchers found that sertraline effectively reduced PTSD symptoms and the average number of drinks consumed, and it increased the number of days of alcohol abstinence. Following these positive preliminary findings, larger trials generally have been less successful at using sertraline to treat alcohol-motivated behavior and have had only modest success using sertraline to treat PTSD.[44,45] In these trials, individuals with comorbid AUD and PTSD demonstrated decreases in drinking behavior, but sertraline was no more effective than placebo at influencing alcohol use outcomes.

Regarding PTSD, Brady and colleagues demonstrated a trend such that sertraline decreased PTSD symptom severity and the cluster symptoms of hyperarousal and intrusion to a greater degree than placebo.[44] Supporting these findings, Hien and colleagues demonstrated greater reductions in PTSD symptoms at the end of treatment for the sertraline-treated group compared with the placebo group,[45] and this effect was sustained at 6- and 12-month follow-up. Interestingly, when treated with sertraline, a subgroup of individuals with early-onset PTSD and less severe AUD had more improvement in alcohol use outcomes than individuals treated with sertraline who had late-onset PTSD and more severe AUD.[44] Further, a subsequent secondary data analysis concluded that improved PTSD symptoms, particularly hyperarousal, were associated with improved alcohol-related symptoms,[46] possibly suggesting that treatments targeted at reducing hyperarousal or hyperreactivity may be more beneficial in reducing symptoms of both AUD and PTSD in this comorbid population.

Another study examined an FDA-approved medication for the treatment of PTSD in veterans with a dual diagnosis of AUD and PTSD.[19] Paroxetine was not better than desipramine in reducing percent heavy-drinking days or drinks per drinking day, but paroxetine was comparable to desipramine in reducing PTSD symptoms. As previously discussed, naltrexone in addition

to paroxetine or desipramine reduced alcohol craving, but there was no significant additive effect of naltrexone in combination with paroxetine or desipramine on drinking or PTSD symptoms.

Finally, although not an open-label or randomized controlled trial, a retrospective study evaluated the efficacy of quetiapine, an atypical antipsychotic with antagonist effects at serotonin 5-HT_2 receptors, among veterans with AUD, of whom 90% were diagnosed with PTSD.[47] These veterans had been treated with quetiapine for sleep disturbances, as older and more recent work has shown that quetiapine is effective in reducing disturbed sleep and other symptoms associated with PTSD.[48,49] This retrospective study aimed to target alcohol use outcomes, thus changes in PTSD symptom severity were not reported. Quetiapine, when compared with placebo, decreased the number of times admitted for detoxification, increased the total number of days abstinent from alcohol use, and trended toward increasing time to relapse. While quetiapine reduced alcohol craving and alcohol consumption in individuals with AUD in preliminary human laboratory, open-label, and retrospective studies, it was not efficacious in reducing drinking outcomes in a large, multisite clinical trial.[50]

Other Serotonergic Medications

As previously mentioned, sertraline and paroxetine are the only two FDA-approved medications to treat PTSD, and evidence suggests that these medications target PTSD symptom severity, versus the overall reduction or remission of PTSD symptoms, in individuals without AUD and PTSD comorbidity.[51] Further, based on findings in this review, sertraline yields mixed results in comorbid populations regarding the reduction of alcohol use outcomes and PTSD symptoms. Trazodone, a second-generation antidepressant and antagonist at serotonin 5-HT_2 and alpha$_1$-adrenergic receptors, is prescribed off-label for singular AUD or PTSD and may be an effective second-line treatment for individuals with co-occurring AUD and PTSD. Likely due to trazodone's anxiolytic- and sedative-like properties, early studies demonstrated that trazodone improved sleep disturbances associated with AUD and alcohol withdrawal.[52] However, in a study of alcohol detoxification patients, the trazodone-treated group increased alcohol consumption following cessation of the medication.[53]

Regarding PTSD, older studies demonstrated that trazodone decreased PTSD symptoms and dysregulated sleep associated with PTSD.[54] In individuals with co-occurring substance abuse and anxiety symptoms, including PTSD symptoms, trazodone decreased alcohol consumption and reduced anxiety symptoms.[55] While trazodone has not yet been investigated in individuals with comorbid AUD and PTSD, and recently published studies on the efficacy of trazodone for either indication remain elusive, there is some evidence suggesting that trazodone may be clinically useful for treating sleep disturbances associated with both AUD and PTSD and possibly their comorbidity. However, results should be interpreted with caution until further studies can establish the safety and efficacy of trazodone in AUD and PTSD populations.

Further, 3,4-methylenedioxy-methamphetamine (MDMA) has shown promise for treatment-resistant and chronic PTSD.[56,57] MDMA, a derivative of methamphetamine, primarily acts to increase the net release of serotonin, although it may stimulate the release of other monoamine neurotransmitters (dopamine and noradrenaline) as well. Pilot studies and a long-term follow-up study demonstrated that MDMA-assisted psychotherapy reduced PTSD symptoms and increased self-reported improvement in individuals with resistant, chronic PTSD.[58] While these results are encouraging for PTSD, to our knowledge, MDMA has not been investigated as a treatment for AUD or comorbid AUD and PTSD. The abuse liability of MDMA may make it less desirable as a medication for the treatment of any substance use disorder (SUD), including AUD.

Agents Acting on the GABAergic and Glutamatergic Systems

There is promising evidence suggesting that the GABA and glutamate systems may be targets for treating comorbid AUD and PTSD.[59] While not FDA-approved for the treatment of AUD, topiramate, an anticonvulsant with action at both GABA and glutamate receptors, has demonstrated efficacy in reducing alcohol consumption in humans and is recommended as a second-line treatment.[10]

Furthermore, other studies suggest that topiramate may be effective in treating PTSD.[60] Contributing to the framework for studying topiramate in this comorbid population, an 8-week, open-label pilot study assessed the effect of topiramate among veterans with PTSD.[61] These veterans did not have co-occurring AUD and PTSD, but the authors examined the effect of topiramate on alcohol use and PTSD symptoms. In this study, topiramate was effective in reducing drinking behavior in individuals with high-risk drinking patterns, as well as reducing nightmares and sleep disturbances associated with PTSD. Because the results from this pilot trial and other research demonstrated the efficacy of topiramate for either AUD or PTSD, Batki and colleagues conducted the first randomized controlled trial of topiramate among veterans who have comorbid AUD and PTSD.[62] Topiramate, when compared with placebo, was effective in decreasing alcohol craving and the percentage of drinking days, and topiramate trended toward decreasing PTSD symptom severity and hyperarousal. It should be noted that there were significant cognitive effects of topiramate on learning and memory in this study, but these cognitive deficits improved by the end of treatment.

Other GABAergic and Glutamatergic Medications

Zonisamide is an anticonvulsant agent similar to topiramate, but it may have fewer side effects. This may be due to the more indirect effect of zonisamide on GABA and glutamate activity, compared with topiramate.[63] A small study evaluating the efficacy of zonisamide in the treatment of AUD showed that zonisamide was well-tolerated and reduced heavy-drinking days, drinks per week, and alcohol urges,[63] and a small pilot study suggests its safety in comorbidity (I. L. Petrakis, personal communication, 2018).

Gabapentin and pregabalin, other FDA-approved anticonvulsants exerting action on GABA synthesis in the brain, have been studied to a moderate extent for their potential in treating AUD and alcohol withdrawal syndrome.[64] In individuals with AUD, gabapentin effectively reduced heavy drinking and alcohol craving, and it improved rates of abstinence,[65] although results are mixed, with some findings indicating that gabapentin is more efficacious in individuals with a history of alcohol withdrawal.[66] Pregabalin is more potent than gabapentin and also has positive effects on alcohol craving and withdrawal.[67] Because of the anxiolytic properties of both drugs, including their role in reducing generalized anxiety, these agents may hold promise in diminishing symptoms associated with PTSD. Some case reports and retrospective studies confer an advantage of gabapentin over placebo in reducing flashbacks, nightmares, and other sleep disturbances.[68,69] In a randomized controlled trial and case report, pregabalin, when administered in addition to standard medication, also improved PTSD symptom severity, hyperarousal, and sleep disturbances in individuals with combat-related PTSD or sexual trauma.[70,71] While these anticonvulsants have modest efficacy in reducing drinking behavior and PTSD symptoms independently, they should not be ruled out as secondary treatment options for individuals with co-occurring AUD and PTSD who are unresponsive to first-line treatments, especially for individuals who have alcohol withdrawal syndrome or sleep problems associated with PTSD.

Recent evidence also suggests a role for the metabotropic glutamate receptor 5 (mGluR5) in the pathophysiology of PTSD and AUD. Preclinical studies indicate that mGluR5 activity may mediate fear conditioning[72] and regulate alcohol-related behavior.[73] Indeed, antagonists at mGluR5 sites, such as 2-methyl-6-(phenylethynyl)-pyridine (MPEP), block the acquisition of fear and decrease alcohol self-administration and reinstatement in rodents.[73,74] In humans, new positron emission tomography (PET) neuroimaging results demonstrate higher mGluR5 availability and positive correlations between mGluR5 availability and avoidance symptoms in individuals with PTSD.[75] This makes sense, considering that the preclinical literature indicates that mGluR5 receptors are involved in the regulation of fear and stress-related behaviors.[72] Likewise, hyperactivity at glutamatergic receptors is associated with chronic alcohol misuse,[76] and PET studies have demonstrated alterations in mGluR5 availability in individuals with AUD, including those who are abstinent.[77]

Taken together, blocking mGluR5 sites may be beneficial in reducing both PTSD-related symptoms

and alcohol use outcomes in individuals with both disorders. Although not yet empirically tested, mGluR5 antagonism could provide another new approach for treating comorbid AUD and PTSD. It should be noted that there may be unwanted effects associated with GABAergic or glutamatergic medications, namely cognitive impairment.[62,76] Therefore, treatment approaches involving drugs targeted at the GABA or glutamate neurotransmitter systems may be warranted only in individuals unresponsive to other treatment options.

Other Targets

Neurokinin-1 receptors have also been targeted as having an effect on alcohol-motivated behavior because of their role in the stress response, with results indicating efficacy in reducing alcohol craving and cortisol reactivity in humans[78] and in blocking stress-induced reinstatement of alcohol-seeking in rodents.[79] However, in a human experimental study of individuals with co-occurring AUD and PTSD, aprepitant, a neurokinin-1 receptor antagonist, demonstrated no advantage over placebo in decreasing alcohol craving, subjective responses to stress or alcohol cues, or PTSD symptom severity.[80]

Other treatment targets may include the antioxidant *N*-acetylcysteine, the novel vasopressin 1b receptor antagonist ABT-436, and the neuropeptide oxytocin. A recent pilot trial examined the effect of *N*-acetylcysteine or placebo in veterans with comorbid PTSD and SUD and found *N*-acetylcysteine to be more effective than the placebo in reducing drug craving and PTSD symptoms.[81] Preclinical work has shown that *N*-acetylcysteine reduced alcohol-seeking and reacquisition of alcohol self-administration in rodents.[82] Another recent clinical trial examined the effect of ABT-436 in individuals with AUD only and found that ABT-436, when compared with placebo, increased days of abstinence.[83] Importantly, in a subgroup analysis, individuals with higher baseline levels of stress demonstrated better ABT-436 treatment responses for drinking outcomes. Thus, individuals with AUD and high stress may benefit most from vasopressin 1b antagonism, likely indicating that ABT-436 may be an effective, promising pharmacologic treatment option for individuals with comorbid AUD and PTSD.

Because of its anxiolytic properties,[84] oxytocin also presents as a potential candidate for the treatment of PTSD[85] and AUD.[86] In patients with PTSD, oxytocin decreased total PTSD symptoms provoked by exposure to a traumatic script, the intensity of recurrent thoughts about trauma, subjective anxiety and tension, and amygdala reactivity to emotional faces.[87] Oxytocin also reduced alcohol withdrawal in patients with AUD,[88] and it may moderate cue-induced alcohol craving in a subset of individuals who have anxiety and AUD.[89] To our knowledge, oxytocin has yet to be tested in a comorbid population. These avenues should be explored in future investigations.

Combination Pharmacotherapies

Combination pharmacotherapy may be another viable treatment option for co-occurring AUD and PTSD, as the clinical efficacy of monotherapy is limited to modest in treating both alcohol use and PTSD symptoms in this comorbid population. In preclinical studies, prazosin, naltrexone, and propranolol all singularly reduced responding for alcohol and decreased alcohol self-administration, but these drugs also reduced other palatable, oral reinforcers.[90] Subthreshold dosing combinations can be used on the basis that a combination of already efficacious medications can target multiple neural systems. Or, combined medications can target one neural system but affect different receptor subtypes that may be dysregulated in each disorder, thus addressing different symptoms or aspects of behavior. Similarly, medications with different mechanisms of action can be used in combination and in a lower dose range to potentially minimize side effects associated with higher doses of one drug alone, possibly improving medication compliance and study retention.[91]

Work in rodents confirms that combination pharmacotherapy may be a promising treatment approach for AUD. When administered in combination, prazosin and propranolol, two drugs targeting different receptor subtypes within the same neural system, were more effective than either drug alone in decreasing alcohol intake.[90,92] Further, prazosin in combination with naltrexone, two drugs targeting different neural systems, was more effective

in reducing alcohol-seeking and consumption than either drug alone.[90,93]

This combination approach has also been proposed as a treatment strategy for PTSD to optimize treatment response and prevention.[33] Medications within the noradrenergic system but with differing mechanisms of action have been shown to treat separate symptoms of PTSD. For example, prazosin, the alpha$_1$-adrenergic receptor antagonist, reduces combat-related nightmares and insomnia; whereas propranolol, the beta-adrenergic receptor antagonist, decreases flashbacks and traumatic memories associated with PTSD. As such, Shad and colleagues postulated that prazosin in combination with propranolol may lead to significant clinical improvement of PTSD by treating a broader spectrum of PTSD-related symptoms, an effect not demonstrated with monotherapy.[33]

Further, a fairly recent case report suggests that prazosin in combination with naltrexone was effective in reducing alcohol craving and PTSD-related flashbacks within 4 days of treatment, with complete remission of alcohol craving and flashbacks in 2 to 4 weeks.[94] It should be noted that these findings were from a single male subject diagnosed with AUD, PTSD, and bipolar II disorder who was taking lithium concurrently with prazosin and naltrexone. To our knowledge, combination pharmacotherapy targeting the noradrenergic system has not yet been tested in human laboratory studies or pilot trials of individuals with co-occurring AUD and PTSD and may be one possible direction to guide optimal and novel clinical treatment approaches for this vulnerable comorbid population.

Clinical and Research Implications

To date, only 12 studies have examined pharmacologic treatment for co-occurring AUD and PTSD. Three studies targeted mainly the opioidergic system, two targeted the noradrenergic system, four targeted the serotonergic system, two targeted the GABAergic and glutamatergic system, and one targeted the neurokinin-1 receptor. Consistent with conclusions from the recent comprehensive review by Petrakis and Simpson,[16] there are contradictory findings within each neurobiological system targeted. Overall, findings within the opioidergic system demonstrated a modest reduction in alcohol use outcomes. Prazosin, a target within the noradrenergic system, yielded mixed results regarding alcohol use, and neither of the two studies found an effect on PTSD outcomes. Serotonergic medications also yielded mixed results on alcohol use outcomes but tended to improve PTSD symptoms overall. Topiramate, acting at both GABA and glutamate receptors, reduced drinking behavior and improved PTSD symptoms. While topiramate may stand out as the most promising medication for comorbid AUD and PTSD, larger studies need to be conducted to evaluate its safety and efficacy, especially given the cognitive side effects of the drug. Future work should consider investigating lower doses of topiramate to decrease side effects and improve personalized medicine.[95]

Several factors may contribute to the overall mixed results. Sample sizes were relatively small for half of the studies. While some studies included women, others examined only men or few women. This gender gap could be problematic, as recent research indicates that medication response may differ by gender for naltrexone, some serotonergic medications, and noradrenergic targets. For example, in one study, women's responsiveness to naltrexone varied across the menstrual cycle, and, during the luteal and early follicular phases, treatment with naltrexone increased serum cortisol,[96] which may have implications for stress reactivity in both AUD and PTSD. Other research suggests that women have better treatment responses to SSRIs, including sertraline, and have fewer associated adverse events.[97]

Recent evidence also suggests that noradrenergic targets for tobacco dependence may differentially attenuate stress reactivity in women and nicotine-related reinforcement in men.[98] It is plausible that noradrenergic compounds may also preferentially target gender-sensitive systems for AUD and may be more effective in treating women with post-traumatic stress. Further, recent findings suggest that the prevalence of drinking has increased among women over the past decade,[1] and women have higher rates of PTSD than men.[3] Thus, it is important to consider sample size and the ability to detect gender differences in medication response when examining pharmacotherapies for comorbid AUD and PTSD, especially given that many studies were conducted primarily in males.

Another challenge in treating comorbid AUD and PTSD may be related to the type of trauma endured

prior to the onset of PTSD. For example, half of the studies examining pharmacotherapy for co-occurring AUD and PTSD reviewed in this article investigated treatment effects in veterans, and many of them had combat-related trauma. The other half examined treatment effects in civilian populations with traumas resulting from childhood experiences, sexual assault, physical assault, witnessing death, and natural disasters. To further complicate treatment, at least one study demonstrated that the severity and order of the development of comorbidity may be related to treatment efficacy. Sertraline was more effective in reducing drinking outcomes in individuals with early-onset PTSD and less severe AUD than in those with late-onset PTSD or more severe AUD.[44] Thus, further research on personalizing treatment to reflect diagnostic onset and trauma type may be a relevant approach when examining novel targets or strategies for co-occurring AUD and PTSD.

Given the high rates of comorbidity for these two psychiatric disorders, it is somewhat surprising that so few studies have examined effective pharmacologic treatment options. This could be due to the complexity associated with psychiatric comorbidity and the difficulties of conducting research among this population. Treatment studies tend to focus on the effect of medication on one disorder, often excluding for comorbidity. However, real-world clinical populations often include comorbid conditions, further emphasizing the urgent need to examine better pharmacotherapies for improving co-occurring AUD and PTSD in a clinically meaningful way.

Promising targets within each system have demonstrated efficacy in treating independent diagnoses of both AUD and PTSD. For example, nalmefene, doxazosin, propranolol, trazodone, gabapentin, and pregabalin have all been found to reduce alcohol- and PTSD-related outcomes, but they have not yet been tested in comorbid populations. Further, subthreshold combination pharmacotherapy in animal models has been efficacious in reducing alcohol-motivated behavior, and may be an effective strategy for individuals who are unresponsive to first-line treatments or for those who are sensitive to adverse events associated with higher doses of a singular drug.

There is a rich literature on behavioral treatments for comorbid AUD and PTSD that is beyond the scope of the current review.[17] However, future research should also consider examining behavioral interventions in combination with these novel pharmacotherapies to better manage alcohol use outcomes and PTSD symptoms in this comorbid population. Human laboratory studies provide an efficient, cost-effective avenue for evaluating the effects of potential medications on psychiatric disorders. This method has been used effectively to screen medications for drug use disorders.[99] When examining treatments for co-occurring AUD and PTSD, investigators are encouraged to use promising treatment targets or their combinations. Also, researchers can use human laboratory paradigms to screen these potential medications in an effort to optimize the clinical utility of pharmacotherapeutic treatments for comorbid AUD and PTSD.

Conclusion

Pharmacotherapeutic treatment options for co-occurring AUD and PTSD are limited. To date, only 12 studies have examined pharmacologic interventions in this comorbid population, and most demonstrated only modest efficacy, but results are mixed. While not comprehensive of all neurobiological systems that may be dysregulated by alcohol use and post-traumatic stress, the existing literature has focused on the opioidergic, noradrenergic, serotonergic, and GABAergic/glutamatergic systems. Targeting other promising, efficacious medications within these neurobiological systems, or combining medications within the same system or across systems, may be an important and promising next step in treating comorbid AUD and PTSD, especially among individuals who are unresponsive to first-line treatments. Future studies need to urgently address this critical literature gap in order to advance pharmacotherapeutic treatment options in special populations with co-occurring AUD and PTSD.

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Behavioral Treatments for Alcohol Use Disorder and Post-Traumatic Stress Disorder

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Alcohol use disorder (AUD) and post-traumatic stress disorder (PTSD) are highly prevalent and debilitating psychiatric conditions that commonly co-occur. Individuals with comorbid AUD and PTSD incur heightened risk for other psychiatric problems (e.g., depression and anxiety), impaired vocational and social functioning, and poor treatment outcomes. This review describes evidence-supported behavioral interventions for treating AUD alone, PTSD alone, and comorbid AUD and PTSD. Evidence-based behavioral interventions for AUD include relapse prevention, contingency management, motivational enhancement, couples therapy, 12-step facilitation, community reinforcement, and mindfulness. Evidence-based PTSD interventions include prolonged exposure therapy, cognitive processing therapy, eye movement desensitization and reprocessing, psychotherapy incorporating narrative exposure, and present-centered therapy. The differing theories behind sequential versus integrated treatment of comorbid AUD and PTSD are presented, as is evidence supporting the use of integrated treatment models. Future research on this complex, dual-diagnosis population is necessary to improve understanding of how individual characteristics, such as gender and treatment goals, affect treatment outcome.

KEY WORDS: **alcohol use disorder; comorbidity; integrated treatment; post-traumatic stress disorder**

Overview

Alcohol use disorder (AUD) and post-traumatic stress disorder (PTSD) are chronic, debilitating conditions that commonly co-occur.[1] The high rates of disability, physical and mental health problems, and health care utilization associated with co-occurring AUD and PTSD pose a tremendous economic burden in the United States and worldwide.[2-14] Previous reviews of treatment options for comorbid AUD and PTSD

indicate that effective treatments are scant, and there is substantial room for improvement.[4-9] Furthermore, individuals with co-occurring AUD and PTSD suffer a more complicated course of treatment and less favorable treatment outcomes, when compared with individuals who have either disorder alone.[15-19] Therefore, identifying effective interventions to treat co-occurring AUD and PTSD is a national public health priority. This review describes evidence-supported interventions targeting AUD and PTSD individually and in the context of co-occurrence.

Behavioral Treatments for AUD

Behavioral interventions are a primary component of the treatment of AUD and can be used as freestanding treatments or as part of a more comprehensive treatment plan that includes pharmacotherapies. Behavioral interventions for AUD include providing psychoeducation on addiction, teaching healthy coping skills, improving interpersonal functioning, bolstering social support, increasing motivation and readiness to change, and fostering treatment compliance.

Cognitive behavioral therapies (CBTs) are some of the most commonly used and empirically supported behavioral treatments for AUD.[20,21] Over the past 30 years, numerous meta-analyses and systematic reviews have demonstrated that CBT is an effective treatment for AUD.[20,22-25] For substance use disorders, small but statistically significant treatment effects have been observed for various types of CBT.[24] CBT interventions typically are designed as short-term, highly focused treatments that can be implemented in a wide range of clinical settings. These interventions are flexible and can be applied in individual or group therapy formats. CBTs for AUD focus on the identification and modification of maladaptive cognitions and behaviors that contribute to alcohol misuse.[21] Behavioral treatments for people with AUD also target motivation for change and improvement of specific skills to reduce the risk for relapse.

Although most behavioral interventions are designed as short-term treatments (e.g., 8 to 20 sessions), many people struggling with AUD require long-term treatment. Depending on the severity of the AUD, history of treatment attempts, family history, and other risk factors, some individuals will remain in various stages of treatment for years to maintain sobriety. Furthermore, many individuals with AUD will complete several rounds of treatment and engage in several different types of treatment simultaneously (e.g., CBT and 12-step engagement). In this section, we briefly review several empirically supported behavioral interventions for AUD. (Higgins and colleagues provide more information on behavioral interventions for substance use disorders.[26])

Relapse prevention

For the past 30 years, relapse prevention[27] has been one of the prevailing empirically supported CBTs for AUD.[20] Relapse prevention is designed to help people with AUD identify high-risk situations for relapse (e.g., negative emotional states and alcohol-related cues) and develop effective coping strategies.[21,28] This intervention encourages behavioral strategies such as avoiding or minimizing exposure to cues that trigger cravings, engaging in pleasant activities, and attending self-help groups. In addition, individuals receiving this treatment learn to recognize warning signs that typically precede a relapse and create a relapse management plan (i.e., an emergency plan for what to do if a relapse occurs). Relapse prevention also focuses on strategies for challenging relapse-related cognitions (e.g., "A few drinks won't hurt"). In a review of 24 randomized controlled trials, relapse prevention was associated with reductions in relapse severity and with sustained and durable effects.[29] Evidence from the review suggests that relapse prevention is most effective for those who have negative affect, more severe substance use disorder, and greater deficits in coping skills.

Contingency management

Contingency management is a behavioral therapy that employs the basic behavioral principles of positive and negative reinforcement to promote the initiation and maintenance of abstinence or other positive behavior changes.[30,31] The most thoroughly researched form of contingency management involves monetary-based reinforcement, in which money or vouchers can be earned and exchanged for prizes, contingent on meeting therapeutic goals.[32] Often, the primary goal is abstinence, but other goals

may include therapy attendance, prosocial behaviors, or compliance with medications.[21,26] Contingency management is designed to help promote initial abstinence of substance use. This intervention can be particularly helpful when the individuals receiving treatment have little or no internal motivation, or if they lack natural reinforcers, such as family relationships.[26,33] Numerous studies show that contingency management can increase abstinence, clinic attendance, and medication compliance.[32,34-37]

Motivational enhancement

Motivational enhancement therapy is an intervention designed to enhance internal motivation for change and engagement in the change process.[38,39] This therapy stemmed from the recognition that many individuals with AUD are ambivalent about changing their behavior, unmotivated, or not ready for change. Motivational enhancement therapy can be used as a stand-alone treatment or in combination with other behavioral interventions.[21,40] Based on the principles of motivational interviewing,[41] this therapeutic technique is collaborative, empathetic, and nonconfrontational. It helps individuals with AUD resolve ambivalence about quitting or reducing their alcohol intake, increase their awareness of the negative consequences of drinking alcohol and the positive benefits of abstinence, and resolve values discrepancies (e.g., valuing physical health is incompatible with alcohol misuse). Motivational enhancement therapy has been shown to be particularly effective for individuals who have AUD, for those who use nicotine, and for participants who have substance use disorder and a problem with anger.[25,40,42-45]

Couples therapy

Alcohol behavioral couple therapy[46] and behavioral couples therapy for alcoholism and drug abuse[47] are manual-guided (also known as manualized) treatments for AUD that incorporate participation of a significant other or romantic partner. Most effective AUD treatments target individuals, but these two therapies also target relationship functioning, which is an important mechanism in the etiology, course, and treatment of AUD.[8,9] Both of these therapies involve 12 weekly, 60- to 90-minute sessions that focus on psychoeducation and cognitive behavioral interventions. The interventions target relationship skills and skills related to reducing AUD severity. Alcohol behavioral couple therapy uses motivational interviewing techniques and focuses on harm reduction, and behavioral couples therapy for alcoholism and drug abuse emphasizes attaining and maintaining abstinence.

Twelve-step facilitation

Twelve-step facilitation is a manual-guided intervention for AUD that is based on the 12 steps of Alcoholics Anonymous.[48] Twelve-step facilitation is designed to help with early recovery and to help people engage with a local Alcoholics Anonymous or other 12-step therapy group in the community.[21] This therapy focuses on acceptance of addiction as a chronic and progressive illness, acceptance of the loss of control over drinking, surrendering to a higher power, lifelong abstinence from alcohol, and fellowship through a group. Participants are encouraged to obtain a sponsor who will serve as a source of practical advice and support during recovery. Data from the National Institute on Alcohol Abuse and Alcoholism project Matching Alcoholism Treatment to Client Heterogeneity (Project MATCH) found that individuals who received 12-step facilitation, compared to cognitive behavioral or motivational enhancement therapies, were significantly more likely to be abstinent at follow-up visits during the 3 years after treatment.[25] In addition, in the Project MATCH study, 12-step facilitation was found to be particularly helpful for participants whose social networks included other people who had substance use disorders.

Community reinforcement

The community reinforcement approach is a CBT designed to enhance social, recreational, and vocational skills.[21] Participants learn conflict resolution skills, ways to foster healthy relationships, and how to develop a new social network.[26] This approach is different from other CBT interventions in that it targets a person's reinforcers (e.g., family, friends, work, and hobbies) and helps reconnect that person with these sources of reinforcement.[21] Community reinforcement is often combined with contingency management approaches to deliver external reinforcers (e.g., money) during the initial

treatment period, to be followed by more natural sources of reinforcement (e.g., family and recreation) in the later stages of treatment.[26] Treatment with disulfiram is offered as part of the community reinforcement approach to help decrease alcohol use. In addition to increasing abstinence, this approach has been shown to reduce the time spent drinking and the time spent being unemployed, away from family, and institutionalized.[26]

Mindfulness

More recently, several mindfulness-based interventions have been developed for the treatment of substance use disorders. In general, mindfulness practices seek to redirect attention to the present moment and strengthen the development of nonattached acceptance of both pleasant and aversive experiences. One such intervention, mindfulness-based relapse prevention, builds on traditional relapse prevention.[49] This intervention typically is delivered in an 8-week group format and includes psychoeducation regarding mindfulness and relapse, breath-focused awareness, body-scan exercise, and yoga mindfulness exercise. In one study, a mindfulness-based relapse prevention intervention resulted in reductions in heavy drinking, when compared with standard relapse prevention.[50] The same researchers reported that the mindfulness-based approach may have yielded more enduring effects than standard relapse prevention, as evidenced by a significantly lower probability of heavy drinking at a 12-month follow-up for the participants who received the mindfulness-based intervention. However, a recent meta-analysis of nine randomized controlled trials found no differences in relapse between mindfulness-based relapse prevention and comparable interventions, such as relapse prevention.[51]

Another intervention, mindfulness-oriented recovery enhancement, is a group intervention delivered over 8 to 10 sessions.[52] This intervention includes mindfulness training, cognitive restructuring, and savoring strategies designed to enhance positive emotions and salience of naturally occurring rewards. Less research has been conducted using this intervention, but one study found that mindfulness-oriented recovery enhancement resulted in reduced cravings and negative affect and improved positive affect.[53]

Behavioral Treatments for PTSD

Behavioral intervention is considered a first-line approach in the treatment of PTSD. Several empirically supported behavioral interventions have been disseminated across populations and treatment settings. As with treatments for AUD, various treatment modalities for PTSD have been studied. Comprehensive analysis of the literature on this topic is challenging because of the diversity of inclusion and exclusion criteria of participants, the heterogeneous nature of PTSD symptoms, high treatment dropout rates, and symptoms that persist after treatment.[54-58] Meta-analytic reviews of these treatments indicate that prolonged exposure therapy, cognitive processing therapy, and eye movement desensitization and reprocessing are among the most frequently and rigorously examined treatment options. In randomized clinical trials, these treatments all have similar levels of effectiveness.[59-62] CBTs for PTSD are based on prevailing empirically supported etiological theories that suggest PTSD results from learned and exacerbated fear reactivity and disrupted cognitive and affective responses to trauma exposure.[63] Targeting these processes in cognitive behavioral interventions typically results in substantial improvement in PTSD symptom severity[60,64] and in various domains of functioning, when compared with unstructured interventions or usual treatment conditions.[65-67] Treatment guidelines indicate that exposure-based psychotherapies have sufficient empirical evidence to be deemed effective PTSD treatments.[60-68] These and other emerging therapies are described in this section.

Prolonged exposure

Prolonged exposure is a manual-guided CBT consisting of 10 weekly, 60- to 90-minute individual therapy sessions.[54] The central therapeutic component of prolonged exposure is based on Pavlovian learning theory. The treatment involves repeatedly presenting a conditioned stimulus (e.g., a trauma reminder) in the absence of an unconditioned stimulus (e.g., the traumatic event). This is accomplished through imaginal exposure during therapy sessions and through in vivo exposure in the environment. On average, prolonged exposure demonstrates robust symptom severity improvement.[69]

Cognitive processing

Another manual-guided cognitive behavioral modality that has received strong empirical support for the treatment of PTSD is cognitive processing therapy.[70] Cognitive processing therapy consists of 12 weekly, 60-minute individual sessions. This therapy involves creating and discussing written narratives describing the thoughts and emotions related to the traumatic event. Participants receive homework assignments designed to identify and challenge the maladaptive thought patterns that are central to the development and maintenance of PTSD symptomatology. A modified, group therapy version of cognitive processing therapy was designed and tested, with promising results.[65] Evidence also supports the effectiveness of cognitive-only cognitive processing therapy,[71] which includes psychoeducation about PTSD, cognitive skill-building, and learning cognitive restructuring skills. The cognitive-only therapy does not employ written narratives, and the most recent treatment manual recommends the cognitive-only therapy as the first-line version, with written narratives as an optional modification.[72]

Eye movement desensitization and reprocessing

For the treatment of PTSD, eye movement desensitization and reprocessing has received empirical support[73] and is one of the therapies that has received endorsement in recent U.S. Department of Veterans Affairs and U.S. Department of Defense treatment guidelines. Eye movement desensitization and reprocessing is one of the three most-studied treatments for PTSD.[59] This therapy incorporates a variety of techniques, including prolonged exposure and cognitive restructuring, but it differs in that it applies these techniques in conjunction with guided eye movement exercises.

Narrative exposure

Narrative exposure therapy is a manual-guided psychotherapy developed to treat PTSD among individuals seeking asylum from political or organized violence.[74] In this technique, which also includes psychoeducation about PTSD, participants narrate their relevant developmental memories in chronological order and narrate details of their trauma exposures as they were experienced over time. Typically, the sessions are 60 to 120 minutes, approximately once a week for 4 to 10 weeks.

Present-centered therapy

Present-centered therapy is a time-limited intervention that includes a psychoeducation component, skill development to manage daily stressors and challenges, and homework to solidify the new skills developed in sessions.[75,76] This therapy has demonstrated efficacy in a variety of populations and is commonly used in randomized controlled trials as a comparator for new or adapted PTSD treatments.[77]

Cognitive behavioral conjoint therapy

Cognitive behavioral conjoint therapy for PTSD is a manual-guided, 15-session CBT.[78] This intervention is designed to improve PTSD symptoms and relationships at the same time. Research in this area is critical, as dyadic distress and dysfunction are saliently associated with poor individual PTSD treatment outcomes. Cognitive behavioral conjoint therapy involves psychoeducation on PTSD and relationships, learning communication skills to address avoidance related to PTSD and relationship problems, and challenging trauma-related beliefs.

Other interventions

Additional interventions that integrate cognitive behavioral and other therapeutic approaches include emotion-focused therapy[79] and brief eclectic psychotherapy.[80] The empirical literature on these approaches is limited, but the research demonstrates promising findings.

Behavioral Treatments for Comorbid AUD and PTSD

Problems with alcohol use have been included in the *Diagnostic and Statistical Manual of Mental Disorders* since its original 1952 edition, but PTSD was not introduced as a psychiatric diagnosis until the third edition in 1980.[81] Since 1980, behavioral

treatments for comorbid AUD and PTSD often have been conducted sequentially, with alcohol-first treatments being more prevalent than PTSD-first treatments. Theoretically, achievement of abstinence facilitates development of cognitive skills such as impulse control and emotion regulation. These skills are subsequently useful in trauma-focused therapies, and they help minimize the risk of alcohol use as a means of avoiding trauma processing. However, individuals with comorbid AUD and PTSD often request integrated treatment or are unwilling to stop drinking alcohol. Opponents of PTSD-first and integrated treatments voice concern that AUD symptoms will worsen if skills promoting abstinence are not well-developed first, and that PTSD symptomatology will also worsen overall.[82-84]

Irrespective of the theoretical debate, epidemiologic evidence suggests that integrated treatments are not yet widely used in substance use disorder treatment centers.[8,84] Data from the Substance Abuse and Mental Health Services Administration (SAMHSA) *National Survey of Substance Abuse Treatment Services (N-SSATS): 2016* indicate that although 77% of the responding facilities at least "sometimes" offered some form of trauma-related counseling, only 38% reported "always or often" using this approach.[85] This percentage has improved slightly since SAMHSA's 2009 N-SSATS report, when 67% of respondents reported "sometimes, often, or always" offering trauma-focused treatment. In 2012, Capezza and Najavits noted that additional studies about "the content of trauma counseling currently offered by facilities" and "whether the treatment is informed by the evidence" would be useful.[86]

To better understand why integrated treatments are not used as often as sequential treatments, Gielen and colleagues conducted a qualitative study of health care provider views on treating PTSD in patients with co-occurring substance use disorder.[87] The researchers reported that health care providers underestimate the prevalence of the comorbid conditions. Given that only 50% of substance use disorder treatment centers endorse providing a comprehensive mental health assessment, it is likely that PTSD is not systematically identified in many initial diagnostic assessments. Only 66% of substance use disorder treatment centers report offering any form of mental health treatment not related to substance misuse.[85]

Gielen and colleagues noted that health care providers frequently appreciate that comorbid AUD and PTSD are associated with more severe symptomatology and worse treatment outcomes.[87] They also found that health care providers frequently expressed the belief that integrated treatment of AUD and PTSD would worsen cravings and reduce AUD treatment retention and efficacy. When studying the effectiveness of integrated treatments, researchers consistently use standardized therapies. However, at community substance abuse treatment centers, these therapies may not be routinely available because providers may not be trained in these approaches. Also, in some settings, providers may not be familiar with validated, standardized methods of PTSD screening. SAMHSA's 2016 N-SSATS report did not comment on staff training levels at substance abuse treatment centers. Identifying methods to address the need for standardized treatments is an important area for future research.

Despite health care provider concerns about implementing integrated behavioral treatments for comorbid AUD and PTSD, a growing evidence base indicates that integrated treatments are safe, feasible, well-tolerated, and effective.[9,88-94]

In a recent review, Simpson and colleagues evaluated 24 randomized clinical trials (N = 2,294) from studies of behavioral treatments for comorbid PTSD and substance use disorder.[9] The trials were grouped into three categories: (1) exposure-based treatments, (2) coping-based strategies, and (3) addiction-focused interventions. No significant differences in treatment retention were found across the three groups.

However, it is important to note that for the 24 trials, treatment retention measures varied widely.[9] For example, one trial measured treatment retention as attendance at 12 out of 12 sessions, but another trial calculated the average number of sessions attended and determined that treatment was completed if participants finished at least 6 out of 25 sessions. Another trial evaluated retention based on participant provision of a urine sample at the end of 12 weeks.

Accounting for these measurement differences, participant retention for trauma-focused studies was approximately 51%.[9] Retention was about 50% for nontrauma-focused studies and about 44% for studies that focused on substance use disorders. The

trials' control conditions had more retention than the experimental conditions, with 72% participant retention for trauma-focused studies, 53% for nontrauma-focused studies, and 31% for studies that focused on substance use disorders.

The analysis conducted by Simpson and colleagues included only a small number of studies, and more research on this topic is needed, as treatment retention among individuals with co-occurring PTSD and substance use disorder has significant room for improvement.[9] Overall, the data indicate that trauma-focused treatments are an effective approach for reducing PTSD severity. Thus, integrated trauma-focused treatments are recommended for individuals with comorbid AUD and PTSD.[7,9]

Furthermore, many people report that they prefer integrated models of treatment to sequential models.[95] Integrated treatments are linked with the self-medication hypothesis, which suggests that substances are often used as a means to manage distress associated with PTSD symptoms. Thus, integrated treatments for AUD and PTSD comorbidity have the advantages of acknowledging the interplay between AUD and PTSD symptoms and of targeting both conditions simultaneously with one health care provider and one treatment episode. The integrated model is further supported by studies indicating that PTSD symptom improvement influences subsequent AUD symptom improvement more than AUD symptom changes influence subsequent PTSD symptoms.[18,96]

Integrated Behavioral Treatments

Treatment of comorbid AUD and PTSD presents substantial challenges to providers across disciplines and treatment settings. Individuals who have both AUD and PTSD demonstrate high-risk behaviors more often than those who have only one diagnosis; consequently, they require high levels of monitoring and intervention.[84,97] Thus, developing effective integrated behavioral interventions to treat comorbid AUD and PTSD is a public health priority. Trials of integrated treatments demonstrate that substance use and PTSD severity decrease with the use of trauma-focused interventions, and these effects are largely maintained at 3-, 6-, and 9-month follow-ups.[98-100]

Seeking safety

The seeking safety approach, a 25-session CBT focused on developing strategies to establish and maintain safety, is one of the most widely studied integrated treatments.[101] Originally, seeking safety was designed as a group intervention, but it has also been studied as an individual format. The intervention has been shown to reduce symptoms of AUD and PTSD for a range of populations (e.g., women, men, veterans, and people who are incarcerated).[102-105] Some studies showed that participants who received the seeking safety approach had better substance use outcomes than those who received treatment as usual. However, other studies found no treatment group differences for substance use or PTSD severity.[106]

The seeking safety approach, like most of the integrated treatments, does not include discussions of trauma memories or events, primarily because providers have concerns about using exposure-based practices in a group format and with people who have comorbid substance use disorder and PTSD.[107] However, given the abundance of literature documenting the efficacy of prolonged exposure in the treatment of PTSD, development of exposure-based interventions for the treatment of comorbid AUD and PTSD has increased. A number of studies now demonstrate the safety and feasibility of employing exposure-based interventions among individuals who have PTSD and comorbid substance use disorders.[9,90,91,93,108]

Concurrent treatment of PTSD and substance use disorders using prolonged exposure (COPE)

A manual-guided, integrated therapy that has demonstrated efficacy in treating comorbid AUD and PTSD is concurrent treatment of PTSD and substance use disorders using prolonged exposure.[109] This therapy is a 12-session, individual intervention that synthesizes empirically validated, cognitive behavioral treatment for AUD with prolonged exposure therapy for PTSD.[110] Several randomized controlled trials conducted in the United States and internationally demonstrate that this treatment significantly reduces AUD and PTSD severity.[96,100,111]

Other treatments

Another cognitive behavioral approach to integrated treatment for comorbid AUD and PTSD is integrated cognitive behavioral therapy, which is a manual-guided intervention with preliminary, but growing, empirical support.[99,112] This treatment consists of 8 to 12 weekly sessions for the individual and focuses on psychoeducation, mindful relaxation, coping skills, and cognitive flexibility.

Other interventions include the trauma recovery and empowerment model, which was designed for women, and a version of the same therapy designed for men.[113] These interventions are group-based, focus on recovery skills, and have demonstrated reductions in substance use.[114] Also, couple treatment for AUD and PTSD, a 15-session couple therapy adapted from Monson and Fredman's cognitive behavioral conjoint therapy for PTSD,[78] has promising preliminary empirical support.[115]

Other treatments with limited or preliminary empirical support are "transcend," a 12-week partial hospitalization program that integrates cognitive behavioral and other theoretical approaches;[116] the addictions and trauma recovery integrated model, an individual approach that focuses on reconstructing trauma memories;[117] and trauma adaptive recovery group education and therapy, a group intervention designed to enhance emotion regulation.[118] (See Table 1 for brief descriptions of the integrated treatments discussed in this section.)

Future Research

Over the past few decades, important advances have been made in behavioral treatments for comorbid AUD and PTSD. The most notable area of progress is the development of trauma-informed, manual-guided, integrated, cognitive behavioral treatments that concurrently address symptoms of both conditions. Before these developments, sequential treatment was the only form of behavioral intervention employed. Now, individuals with comorbid AUD and PTSD, as well as their health

Table 1 Empirically Supported Integrated Treatments for AUD and PTSD

Treatment	Content	Number of Sessions
Individual Only		
Concurrent Treatment of PTSD and Substance Use Disorders Using Prolonged Exposure[109]	Relapse prevention and coping skills integrated with prolonged exposure	12
Individual or Group		
Integrated Cognitive Behavioral Therapy[112] (initially individual, then group)	Mindful relaxation, flexible thinking skills (e.g., cognitive restructuring and behavioral functional analysis)	8 to 12
Seeking Safety[101]	Coping skills, interpersonal relationship skills, self-development skills	25
Trauma Adaptive Recovery Group Education and Therapy[118]	Emotion regulation, mental focusing, executive function skills, mindfulness, interpersonal engagement and interaction skills	4 to 14
Couples		
Couple Treatment for AUD and PTSD[115]	Coping and relapse prevention skills, interpersonal relationship skills	15
Group Only		
Transcend[116]	In first half of sessions, coping skills only; trauma processing added in second half of sessions	12
Trauma Recovery and Empowerment Model[113]	Gender specific; cognitive restructuring, coping skills training, social support, communication skills	18 to 29

care providers, have additional treatment options available.

For future research, it will be important to continue to advance and optimize integrated treatments and to address which individuals are ideal candidates for integrated therapies. Despite the established efficacy of integrated treatments and reported preferences for this type of therapy, treatment retention and dropout rates remain an important area of concern in this dual-diagnosis population.[99,100] Further study that directly compares sequential and integrated treatment outcomes is necessary. One ongoing study addresses this gap in the literature by assessing whether retention rates between sequential and integrated treatments differ.[119]

Studies that compare other outcomes related to treatment retention and symptom improvement, such as sleep, mood symptoms, somatic medical conditions, and safety profiles (including violence and suicidality), would also be helpful. The literature currently lacks studies that examine the association between premorbid functioning and the ability to engage in manual-guided, evidence-supported therapies. Also needed is examination of how adding PTSD-focused treatment to AUD treatment will be feasible in terms of treatment costs, training requirements, and staff workload. The overlap of AUD with other substance use disorders is highly prevalent. Studies examining outcomes of integrated treatments among people with comorbid AUD and PTSD, when compared with people who have PTSD and substance use disorder involving multiple substances, is necessary to identify and target specific alcohol-related treatment needs. Finally, given the heterogeneous nature of AUD[120] and the complex etiology, course, and treatment of both AUD and PTSD, studies that examine commonalities underlying effective behavioral treatments are essential.

Gender is another important consideration in the development of effective treatments for comorbid AUD and PTSD. Critical psychosocial and neurobiological differences between men and women have been demonstrated through research on the connection between stress (e.g., exposure to sexual trauma) and substance use disorder in the context of complex comorbidities.[121,122] Also, gender may be a factor in the utilization of treatment for these conditions.[123]

Finally, individual preference is a critical consideration when matching people with treatment modalities. Emerging literature suggests that many people who have both PTSD and substance use disorder symptoms perceive a strong link between them, and they prefer integrated versus sequential treatment.[124,125] Also, individuals receiving treatment might have a goal to reduce substance use rather than attain or maintain abstinence.[126] Investigations that consider these individual and contextual factors are necessary to effectively match treatment approaches with individual needs and to maximize treatment development research for comorbid PTSD and AUD.

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Development, Prevention, and Treatment of Alcohol-Induced Organ Injury

The Role of Nutrition

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Alcohol and nutrition have the potential to interact at multiple levels. For example, heavy alcohol consumption can interfere with normal nutrition, resulting in overall malnutrition or in deficiencies of important micronutrients, such as zinc, by reducing their absorption or increasing their loss. Interactions between alcohol consumption and nutrition also can affect epigenetic regulation of gene expression by influencing multiple regulatory mechanisms, including methylation and acetylation of histone proteins and DNA. These effects may contribute to alcohol-related organ or tissue injury. The impact of alcohol–nutrition interactions has been assessed for several organs and tissues, including the intestine, where heavy alcohol use can increase intestinal permeability, and the liver, where the degree of malnutrition can be associated with the severity of liver injury and liver disease. Alcohol–nutrition interactions also play a role in alcohol-related lung injury, brain injury, and immune dysfunction. Therefore, treatment involving nutrient supplementation (e.g., with zinc or S-adenosylmethionine) may help prevent or attenuate some types of alcohol-induced organ damage.

Key words: Alcohol consumption; alcohol use, abuse, and disorder; heavy alcohol consumption; alcohol–nutrition interactions; organ injury; tissue injury; intestine; nutrition; nutrients

The effect of alcohol on organ health and injury is complex and influenced by a host of different factors, such as dose of alcohol consumed; duration and pattern of drinking (e.g., binge drinking); and, as reviewed in this article, potential interactions with nutrition. The *2015–2020 Dietary Guidelines for Americans* (U.S. Department of Health and Human Services and U.S. Department of Agriculture 2015) highlight the concept of the standard drink and the fact that if alcohol is consumed, it should be in moderation (i.e., up to 1 drink per day for women and 2 drinks per day for men in adults of legal drinking age). It is becoming increasingly accepted that this moderate form of drinking may have health benefits that seem to lessen many types of organ injury. This concept was popularized in 1991, when Morley Safer presented information on the television show *60 Minutes* related to the "French paradox"—that is, the observation that the French seemed to have lower rates of heart attacks despite higher fat consumption. This outcome was postulated as possibly resulting from the beneficial effects of wine consumption by the French. Subsequent studies have shown that all forms of alcohol, when consumed in moderation, seem to lower the risk of coronary artery disease (Yang et al. 2016). The beneficial effect can be represented by a J-shaped curve, in which low alcohol consumption has protective effects compared with abstention, whereas excessive alcohol consumption is harmful. Moderate drinking also may have

beneficial effects on several other organs and organ systems, including the following:

- Decreased risk of ischemic stroke (Sacco et al. 1999);
- Protection against type 2 diabetes (Conigrave et al. 2001);
- Decrease in rheumatoid arthritis (Di Giuseppe et al. 2012);
- Improved cognition (Anstey et al. 2009);
- Decreased progression of liver disease to fibrosis in obese individuals (Thomson et al. 2012); and
- Improved renal function (Koning et al. 2015).

Indeed, moderate alcohol consumption may be associated with an overall modest survival benefit (Ford et al. 2011).

Moderate alcohol consumption also has been shown to decrease biomarkers of inflammation, such as C-reactive protein, and reduced inflammation could be one unifying mechanism underlying alcohol's protective effects (Imhof et al. 2004). On the other hand, long-term heavy alcohol abuse can cause organ injury, which may, at least in part, result from alcohol–nutrient interactions and alcohol-related nutrient deficiencies. As described in this article, people who abuse alcohol frequently consume large amounts of alcohol, which may contribute to the displacement of needed nutrients (see figure 1). Indeed, recent analyses of nutritional status and alcohol consumption in people with alcohol use disorder (AUD) who were admitted to a rehabilitation program demonstrated that the participants generally had a normal body mass index, were not overtly malnourished, and did not have clinical evidence of alcohol-induced organ injury. However, these people were consuming, on average, 14 drinks per day, which would amount to about 2,000 calories per day or more consumed as alcohol (Vatsalya et al. 2016). Considering that the participants had a normal body mass index, this suggests that they replaced normal nutrients with alcoholic beverages, resulting in potential nutrient deficiencies. Nutritional supplementation may either help ameliorate such deficiencies or have pharmacologic effects.

Alcohol and nutrition can interact at multiple levels. For example, alcohol metabolism can result in the generation of reactive oxygen species, which can deplete endogenous nutritional antioxidant stores and contribute to oxidative stress. Heavy alcohol consumption also can cause poor intestinal absorption of certain nutrients (e.g., zinc) or increase nutrient losses (e.g., by

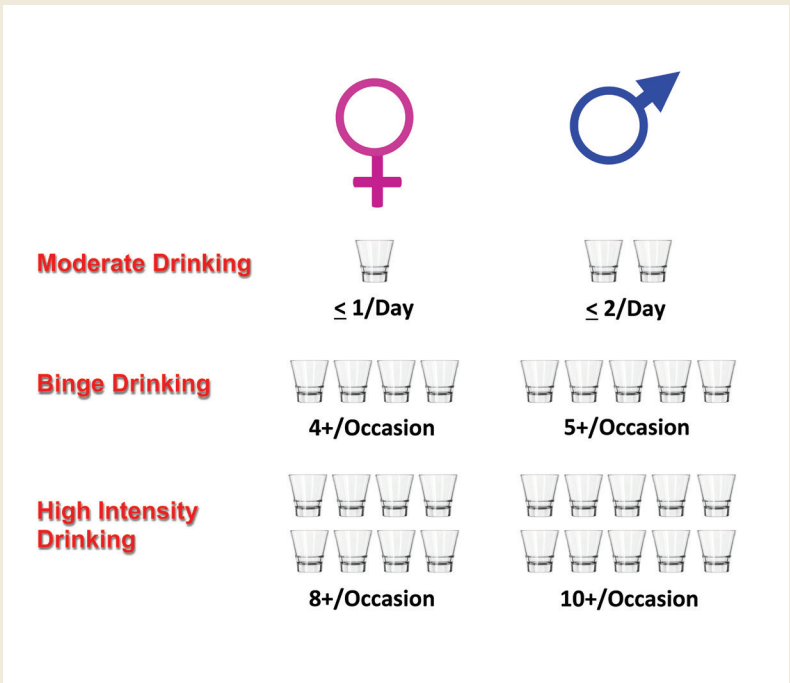

Figure 1 Drinking levels and their consequences. In the United States, drinking levels are expressed in terms of standard drinks consumed—that is, the number of alcoholic beverages drunk, each containing about 0.6 fluid ounce or 14 grams of pure alcohol. The *Dietary Guidelines for Americans 2015–2020* defines moderate drinking as consuming up to 2 drinks/day for men and up to 1 drink/day for women. The Substance Abuse and Mental Health Services Administration defines binge drinking as consuming 5 or more (for men) or 4 or more (for women) alcoholic drinks on the same occasion on at least 1 day in the past 30 days (National Institute on Alcohol Abuse and Alcoholism 2016). High-intensity drinking refers to drinking at levels far beyond the binge threshold, resulting in high peak blood alcohol concentrations. Some studies define high-intensity drinking as two or more times the gender-specific binge drinking thresholds (Patrick et al. 2016); others use a higher threshold (Johnston et al. 2016). Some individuals drink considerably more than this. For example, one study found that patients admitted to a National Institutes of Health treatment facility with a diagnosis of alcohol use disorder consumed the equivalent of 13 drinks per day (Vatsalaya et al. 2016). In these drinkers, the metabolic effects of alcohol and altered nutrient intake may set the stage for alcohol–nutrient interactions and organ injury.

increasing zinc and magnesium excretion in the urine). Moreover, nutrition can have a far-reaching impact through altering epigenetic mechanisms, such as methylation and acetylation of DNA and associated proteins. Finally, the degree of alcohol-related malnutrition can be associated with the severity of organ injury (e.g., alcoholic hepatitis). This article reviews how nutritional alterations may predispose to alcohol-induced organ injury and how nutritional supplementation may prevent and/or treat alcohol-induced organ injury. The article specifically highlights the effects of certain alcohol–nutrient interactions, with a focus on zinc and linoleic acid, and their impact on epigenetics and selected organ injury.

Nutrition and Nutritional Alterations Following Alcohol Use/Abuse

Alcohol: Nutrition Overview

From a nutrition perspective, alcohol is a significant source of calories, but these can be considered "empty" calories—that is, they contain few micronutrients, such as vitamins and minerals, normally found in most food sources (Antonow and McClain 1985). The main site of beverage alcohol (i.e., ethanol) metabolism is the liver, where ethanol is converted to carbon dioxide and water, with an energy yield of 7 kcal/g of alcohol. Regular alcohol intake can be a major source of calories, because beer has approximately 150 kcal per 12-ounce can and bourbon or scotch with a mixer has approximately 125 kcal per drink. Thus, a person can easily consume 200 to 500 calories or more per day by consuming 2 to 3 drinks. For people attempting weight reduction, alcohol consumption therefore can be considered a source of unwanted and empty calories. Moreover, when alcohol intake is combined with fructose-containing sugared drinks, the intake of empty calories increases even further, enhancing the opportunity for alcohol-induced organ injury. Finally, alcohol can be an expensive source of calories compared with traditional foods, and this may become a major problem for people with limited incomes.

The issue of alcohol as a nutrient becomes more prominent when dealing with people with AUD and those with alcohol-induced organ injury. Analyses of the nutritional status of people with AUD admitted to treatment programs found that these individuals often consumed 35 to 50 percent of their total calories as alcohol, and some exhibited inadequate micronutrient intake and micronutrient serum levels (Antonow and McClain 1985). However, most had little or no evidence of protein-calorie malnutrition and loss of muscle mass. In contrast, patients admitted to hospitals for severe alcoholic hepatitis who also consumed 50 percent of their total calories as alcohol not only regularly showed depletion of certain micronutrients but also loss of muscle mass (Mendenhall et al. 1995*a*). The following sections focus on the micronutrient zinc, which may be deficient or have altered metabolism with heavy alcohol consumption, and a macronutrient (i.e., dietary fat) that may play a role in alcohol-induced organ injury. Some of the other micronutrients for which heavy alcohol intake may cause deficiency states or altered metabolism are listed in the table.

Zinc

Zinc is an essential trace element required for normal cell growth, development, and differentiation, including such processes as DNA synthesis, RNA transcription, and cell division and activation. It is a critical component of many proteins/enzymes, including zinc-dependent transcription factors. Zinc deficiency or altered zinc metabolism is frequently observed in heavy alcohol drinkers and may result from decreased dietary intake, increased urinary excretion, abnormal activation of certain zinc transporters, and induction of hepatic metallothionein (Mohammad et al. 2012). Zinc deficiency may manifest itself in many ways in alcoholics, ranging from raised, crusting skin lesions around the eyes, nose, and mouth (figure 2) to impaired wound healing or liver regeneration, altered mental status, or altered immune function (Mohammad et al. 2012). Importantly, oxidative stress (e.g., resulting from ethanol metabolism) may cause release of zinc from critical zinc-finger proteins and cause loss of DNA-binding activity. Specifically, oxidative stress causes modification of certain amino acids (i.e., cysteine residues) that hold the zinc in place in zinc-finger proteins such as hepatocyte nuclear factor 4 (HNF4), a transcription factor that is essential for liver development.

Zinc supplementation has been documented to block or attenuate experimental organ injury and dysfunction in the gut, liver, lung, and brain through multiple pathways. Thus, zinc may

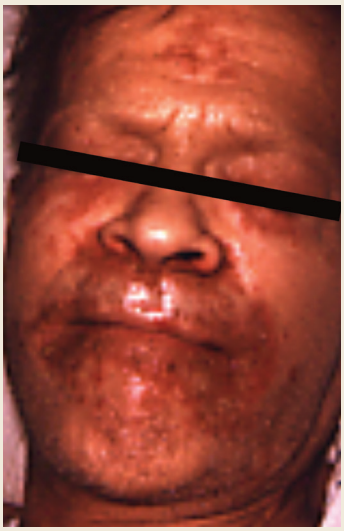

Figure 2 Chronic alcohol user who had been consuming large amounts of beer before admission. Note classical skin lesions of zinc deficiency around the eyes, nose, and mouth.

strengthen the integrity of the intestinal wall by stabilizing tight junctions, reduce transfer of toxic bacterial molecules (e.g., endotoxin) into the blood, lower the levels of metabolic toxins such as ammonia in the blood, decrease production of inflammation-promoting (i.e., proinflammatory) cytokines, reduce oxidative stress, and attenuate apoptotic cell death (Zhong et al. 2010, 2015) (figure 3). The dose of zinc used for treatment of alcohol-induced organ injury such as liver disease usually is 50 mg of elemental zinc taken with a meal to decrease the potential side effect of nausea. Intake of greater than 50 mg of elemental zinc per day can cause dose-related side effects, such as copper deficiency resulting from reduced copper absorption.

Table Types of Nutrient Deficiency Caused by Heavy Drinking and the Associated Signs and Symptoms

Selected Nutrient Deficiency	Signs/Symptoms
Magnesium	Insulin resistance, muscle cramps
Selenium	Myopathy, cardiomyopathy
Vitamin B1/Thiamine	Wernicke-Korsakoff syndrome, neurologic symptoms
Vitamin B2/Riboflavin	Glossitis, cheilitis, and lingual papillae atrophy
Vitamin A/Retinol	Abnormal dark adaptation, rough skin
Vitamin C	Scurvy with purpura and petechiae
Vitamin D	Altered bone metabolism, altered gut barrier/immune function
Vitamin E	Oxidative stress
Niacin	Skin photosensitivity, confusion, pellagra
Folate, S-Adenosylmethionine	Anemia, altered methylation, epigenetic effects

Dietary Fats

The critical role for specific types of dietary fat (i.e., saturated versus unsaturated fats) in intestinal and liver injury has been demonstrated and extensively studied in preclinical animal models of alcohol feeding using various sources of dietary lipids. Experimental evidence has shown that dietary saturated fats (SFs) attenuated, and unsaturated fats (USFs) enhanced, alcohol-induced liver damage (Nanji and French 1989). Thus, in contrast to the general assumption that SFs are less healthy than USFs, in this situation SFs had a protective effect and USFs had a harmful effect.

Further analyses focused on the role of different types of dietary polyunsaturated fatty acids (PUFAs) in alcohol-induced gut and liver injury. There are two major families of dietary PUFAs—omega-6 [ω-6] and omega-3 [ω-3] PUFAs—each of which includes numerous related metabolites. It has been demonstrated that linoleic acid, an ω-6 PUFA [18:2ω-6], is required for the development of experimental alcohol-induced intestinal and liver injury and that the severity of alcoholic liver disease (ALD) is correlated with the amount of linoleic acid in the diet (Nanji and French 1989; Ronis et al. 2004). Conversely, fish oil (a rich source for ω-3 PUFAs) or purified ω-3 PUFAs (e.g., eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA], which are known to be important in brain development) may be beneficial in ALD. For example, in mice, prior ingestion of fish oil, specifically tuna fish oil, in amounts that provided 30 percent of the total caloric intake, resulted in reduced hepatic fat accumulation caused by a single dose of ethanol administration. This effect was mediated, at least in part, through marked reductions in the expression of the hepatic enzyme stearoyl-CoA desaturase-1 and in the activity of the transcription factor sterol regulatory element–binding protein (Wada et al. 2008). Mice supplemented with highly purified DHA also had significantly decreased alcohol-induced liver steatosis, inflammation, and injury (Huang et al. 2013). The beneficial role of ω-3 PUFAs in experimental ALD also has been supported by the observation that when rhesus monkeys who had free access to an ethanol solution were fed a diet that was generally nutritionally adequate (including the linoleic acid amount), but with a low ω-3 PUFA content (i.e., a very low concentration of α-linolenic acid), the animals developed hepatic steatosis and fibrosis (Pawlosky and Salem 2004). The ω-3 PUFAs also are precursors to factors that resolve injury and inflammation, such as resolvins (e.g., E- and D-series resolvins generated from EPA and DHA, respectively), and a high dietary ω-6/ω-3 PUFA ratio may be disadvantageous to resolving inflammation (Serhan and Petasis 2011). Thus, emerging evidence suggests that dietary fats can play a role in both initiation and treatment of alcohol-induced organ injury in the gut and liver as well as in the brain (which will be discussed later in this article).

Nutrition–Alcohol Interactions and Epigenetics

In virtually every cell type, epigenetic mechanisms—that is, modifications to the genetic material that do not alter the DNA sequence—play a critical role in both the physiologic and pathologic regulation of gene expression. These mechanisms, which involve chromatin remodeling initiated by posttranslational modifications of

histones and changes in DNA methylation status, can activate or deactivate gene transcription. The proteins that are involved in posttranslational histone modifications and DNA methylation changes require a variety of cofactors, including acetyl coenzyme A, S-adenosylmethionine (SAM), nicotinamide adenine dinucleotide, and zinc (Moghe et al. 2011). A person's nutritional status can significantly influence the availability of these cofactors and, consequently, epigenetic mechanisms, gene expression, and disease pathogenesis. Chronic alcohol consumption is known to affect nutritional status at many levels, including nutrient intake, absorption, utilization, and excretion, causing nutritional disturbances and deficiencies in these cofactors. Research has determined that alcohol-induced nutrient fluctuations can impact transcriptional activity and expression of genes by modulating epigenetic parameters, including histone modifications and DNA methylation (Moghe et al. 2011; Zakhari 2013). Hence, in people with AUD, the combined effects of alcohol metabolism and compromised nutrition are likely to influence epigenetic mechanisms, gene expression, and disease pathogenesis involving intestinal barrier dysfunction, immune suppression, and organ injury.

Alcohol's Effects on Histone Acetylation and Methylation

It is becoming increasingly evident that histone-associated epigenetic modifications, such as histone acetylation and methylation, play a significant role in the regulation of gene expression and development of alcohol-induced organ pathology, such as liver disease and immune dysfunction (Moghe et al. 2011). In particular, histone acetylation in promoter regions is a key regulator of gene expression and is associated with enhanced transcriptional activity, whereas deacetylation typically is associated with transcriptional repression. Steady-state levels of acetylation result from the balance between the opposing activities of two groups of enzymes—histone acetyltransferases and histone deacetylases. The expression and activities of both types of enzymes can be influenced by alcohol and cofactors, such as nicotinamide adenine dinucleotide and zinc (Ghare et al. 2014; Moghe et al. 2011). Taken together, epigenetic histone modifications provide a likely link between alcohol-mediated nutrient alterations in gene expression and disease pathogenesis.

Alcohol's Effects on DNA Methylation

Investigation of the dietary influences on epigenetic processes has revealed a direct link between SAM, which serves as the primary biological methyl donor, and DNA methylation changes that epigenetically influence gene expression (McCabe and Caudill 2005). In general, DNA hypermethylation at DNA sequences called CpG islands in gene promoters leads to transcriptional silencing, whereas DNA hypomethylation allows for transcription to occur.

Excessive alcohol consumption can decrease SAM levels via multiple mechanisms, such as reduced folate levels and inhibition of key enzymes in one-carbon metabolism. The reduced SAM levels lead to aberrant DNA methylation patterns and pathogenic alterations in gene expression (Varela-Rey et al. 2013). Importantly, alcohol-induced perturbations in global and regional DNA methylation have been linked with diverse pathological conditions, including ALD, carcinogenesis in various organs, alcohol dependence, and fetal alcohol spectrum disorders

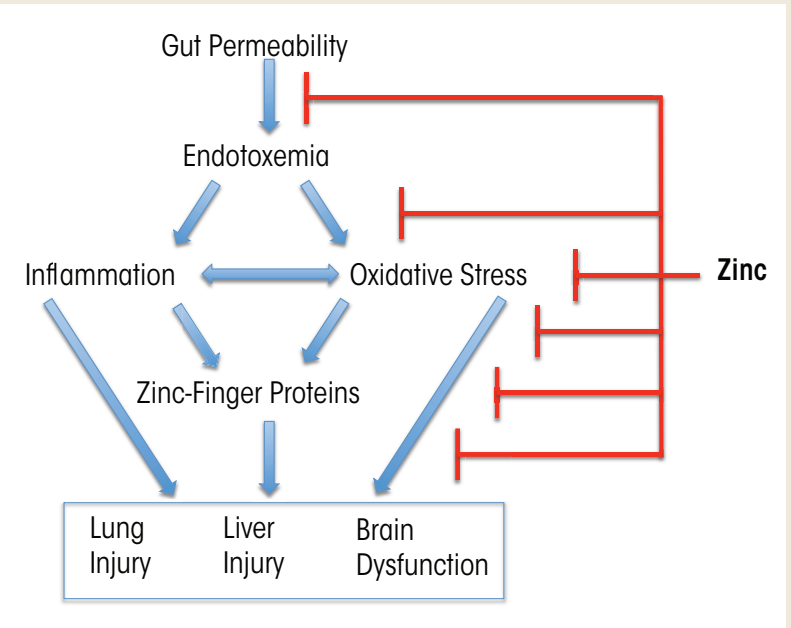

Figure 3 Zinc therapy positively affects multiple mechanisms of alcohol-induced organ injury. Thus, zinc enhances the gut barrier and tight junctions, thereby reducing gut permeability and the risk of transfer of bacterial endotoxin into the blood (i.e., endotoxemia). In addition, zinc decreases proinflammatory cytokine production and oxidative stress and ensures proper functioning of important zinc-dependent regulatory proteins (e.g., zinc-finger proteins). Through these and other mechanisms, zinc supplementation can improve liver injury and may attenuate lung and brain dysfunction.

(FASD), to name only a few. Clearly, further research is needed to detail the alcohol–nutrient interactions that influence epigenetic mechanisms underlying pathogenic changes in gene expression and disease progression, with the goal of developing nutrient-based therapies.

Examples of Nutrition–Alcohol Interactions in Alcohol-Induced Organ/Tissue Injury

Intestine

The intestinal mucosa plays a critical role in preventing passage of toxins from the intestine into the bloodstream, as well as in immune function, detoxification, and metabolism. The importance of the gut in alcohol-mediated multiorgan pathology is becoming increasingly recognized. Clinical and experimental data have demonstrated that the gut-derived bacterial product, lipopolysaccharide, also referred to as endotoxin, plays a crucial role in the development and progression of alcohol-induced organ injuries, including ALD. Significantly increased endotoxin levels in the blood (i.e., endotoxemia) have been found in patients with different stages of ALD, including fatty liver, hepatitis, and cirrhosis (Parlesak et al. 2000).

Multiple mechanisms contribute to alcohol-associated endotoxemia, including alcohol-mediated alterations in the composition of the bacterial population of the gut (i.e., gut microbiome) (Mutlu et al. 2009) and increased lipopolysaccharide translocation as a result of disruption of intestinal barrier integrity. Recent studies in mice have demonstrated that the type of dietary fat consumed can influence alcohol-induced changes in the gut microbiome composition (and, therefore, function), intestinal injury/inflammation, and intestinal barrier function (figures 4 and 5). Specifically, when comparing animals that were fed either dietary USFs or SFs plus ethanol (EtOH),[1] the studies found the following:

[1] The diet containing USFs was rich in corn oil, whereas the diet containing SFs was rich in medium-chain triglycerides.

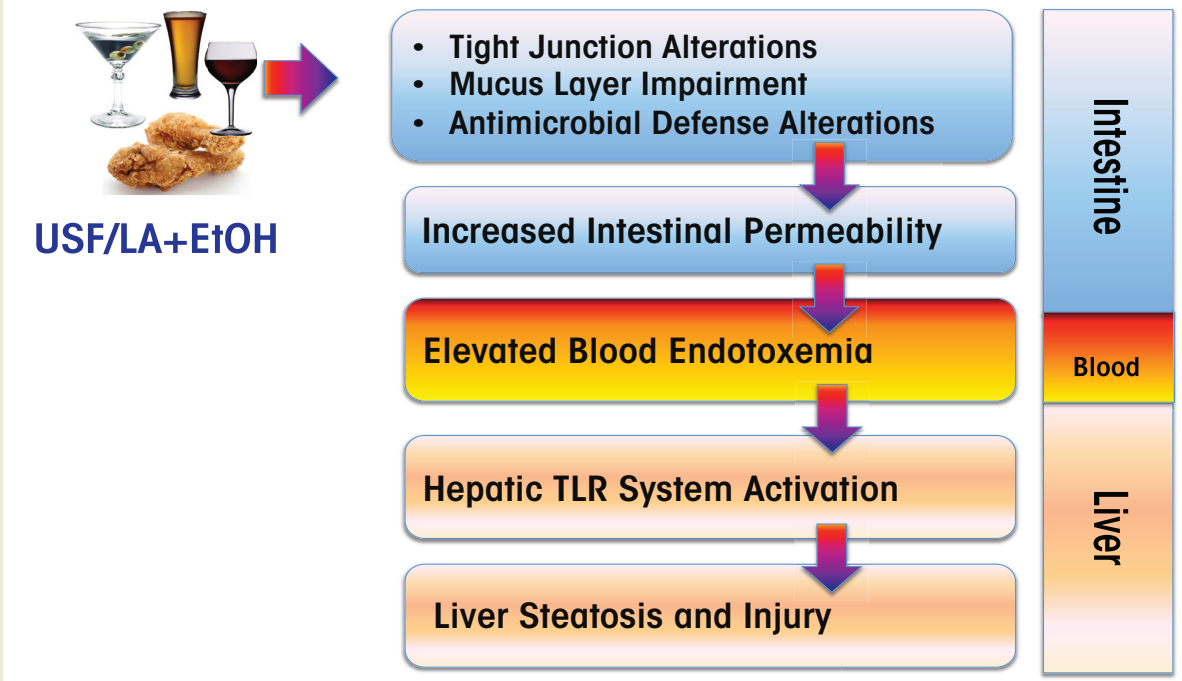

Figure 4 Alcohol (EtOH) consumption combined with dietary intake of unsaturated fatty acids (USFs) (e.g., linoleic acid [LA]) can have numerous deleterious effects on the intestine, blood, and liver. In the intestine, this combination changes the bacterial composition (microbiome) and interferes with various aspects of the body's defense systems, thereby increasing intestinal permeability. This leads to endotoxemia and liver injury.

NOTE: TLR = toll-like receptor.

- The animals that received EtOH+USF showed increased gut permeability and elevated endotoxemia compared with those that received EtOH+SF (Kirpich et al. 2012) (figure 5A).

- Compared with EtOH+SF, a chronic EtOH+USF diet triggered an intestinal proinflammatory response characterized by increased levels of several cytokines, including tumor necrosis factor-α and monocyte chemoattractant protein-1. In addition, the intestinal mucus layer and antimicrobial defenses were altered (Kirpich et al. 2013).

- Intestinal inflammation was positively correlated with the EtOH+USF-triggered disruption of the intestinal tight junctions (figure 5B). Even in the absence of alcohol, a USF diet resulted in downregulation of intestinal expression of tight-junction protein mRNA compared with an SF diet. Alcohol further suppressed tight-junction proteins in animals receiving EtOH+USF, but did not affect intestinal tight junctions in the EtOH+SF group (Kirpich et al. 2013) (figure 5B).

- Unlike EtOH+SF, dietary EtOH+USF caused alterations in gut microbiota (Bull-Otterson et al. 2012; Kirpich et al. 2016) (figure 5C).[2] The observed microbiota and intestinal barrier changes were associated with significant liver steatosis, inflammation, and injury in EtOH+USF-fed mice (figure 5D). These adverse effects of ethanol on the liver were markedly attenuated by a SF diet containing medium-chain triglycerides.

[2] The EtOH+USF-induced changes in gut microbiota were characterized by the decrease of certain bacteria (i.e., the *Bacteriodetes* phylum) with a proportional increase in others (i.e., gram-negative *Proteobacteria* and gram-positive *Actinobacteria* phyla). The bacterial genera that showed the biggest expansion were the gram-negative, alkaline-tolerant *Alcaligenes* and gram-positive *Corynebacterium* (Bull-Otterson et al. 2013).

Thus, it is clear that the interactions of dietary fat and alcohol are important in mediating alcohol-induced intestinal and liver injury.

Similarly, in mice, zinc deficiency associated with chronic alcohol intake led to markedly decreased tight-junction proteins and increased endotoxemia. Zinc supplementation corrected these effects through multiple mechanisms, including zinc-finger function and epigenetic mechanisms (Zhong et al. 2015). In summary, an important component of alcohol-induced organ inflammation/injury arises in the gut and may be modified by nutrition.

Liver Injury

Patients with severe alcoholic hepatitis almost invariably demonstrate some form of malnutrition. Probably the most detailed information concerning malnutrition in ALD comes from two large studies from the Veterans Health Administration (VA) Cooperative Studies Program in patients with alcoholic hepatitis (Mendenhall et al. 1984, 1986, 1995*a,b*). In these studies, almost 50 percent of the patients' energy intake was derived from alcohol. Although they frequently showed no inadequate calorie intake, the patients often exhibited insufficient intake of protein and critical micronutrients. The severity of liver disease generally correlated with the severity of malnutrition. During treatment, the patients received a balanced 2,500-kcal hospital diet (monitored by a dietitian) that they were encouraged to consume. Investigators found that voluntary oral food intake correlated in a stepwise fashion with 6-month mortality data. Thus, patients who voluntarily consumed more than 3,000 kcal per day had virtually no mortality, whereas those who consumed less than 1,000 kcal per day had a 6-month mortality of more than 80 percent (Mendenhall et al. 1995*a*). Moreover, the degree of malnutrition correlated with the development of serious complications, such as encephalopathy, ascites, and hepatorenal syndrome (Mendenhall et al. 1995*a*).

Initial interest in nutrition therapy for ALD was stimulated by Patek and colleagues (1948) who demonstrated that a "nutritious diet" improved the 5-year outcome of patients with alcoholic cirrhosis compared with historic control subjects. Subsequently, nutritional supplementation through a feeding tube was shown to significantly improve liver function in inpatients with ALD compared with inpatients who ate a hospital diet (Kearns et al. 1992). Probably the most important data supporting nutrition therapy came from a multicenter study by Cabré and colleagues (2000), who randomly assigned patients with severe alcoholic hepatitis to receive either the glucocorticoid prednisone (40 mg daily) or a liver-specific formula containing 2,000 calories per day through a feeding tube.[3] The 1-month mortality was the same in both groups, but the 1-year mortality was significantly lower in the enteral-nutrition group than in the glucocorticoid group, mainly because they experienced fewer infectious complications. This study clearly documented the importance of enteral nutrition in severe alcoholic hepatitis. Oral/enteral nutrition is preferable over parenteral nutrition because of lower costs, risk of sepsis from the parenteral nutrition line, preservation of the integrity of the gut mucosa, and prevention of bacterial translocation and multiple-organ failure.

Enteral nutrition supplements also have been shown to improve nutritional status and immune function in outpatients with alcoholic cirrhosis as well as to reduce hospitalization. The concept of an outpatient late-evening snack (prior to bedtime) was established after studies demonstrated altered energy metabolism in people with liver cirrhosis. These patients exhibit depleted hepatic glycogen stores, which force the body to depend on fat and protein stores, leading to catabolism during an overnight fast.

[3] This polymeric enteral solution was enriched in branched-chain amino acids, energy dense (1.3 kcal/ml), and low in fat and sodium.

A randomized controlled trial demonstrated that provision of a late-evening nutritional supplement (compared with daytime supplements) over a 12-month period could improve body protein stores in patients with cirrhosis. The nighttime snack resulted in body protein accrual equivalent to about 2 kg of lean tissue sustained over 12 months, whereas this benefit was not observed with daytime snacks. Thus, late-evening snacks are valuable nutritional interventions in outpatients with alcoholic cirrhosis (Plank et al. 2008).

Many types of nutritional supplements have yielded positive effects in animal models of ALD, especially antioxidants. However, human studies using specific nutrients or combination therapy are limited and generally have shown equivocal or negative results. Larger, well-designed studies are required.

Lung Injury

Chronic alcohol abuse alters the phenotype of the lung and makes it more susceptible to subsequent challenges, such as bacterial infection and acute lung injury. One of the mechanisms that contribute to increased susceptibility to infection and injury is alcohol-induced oxidative stress. Oxidative

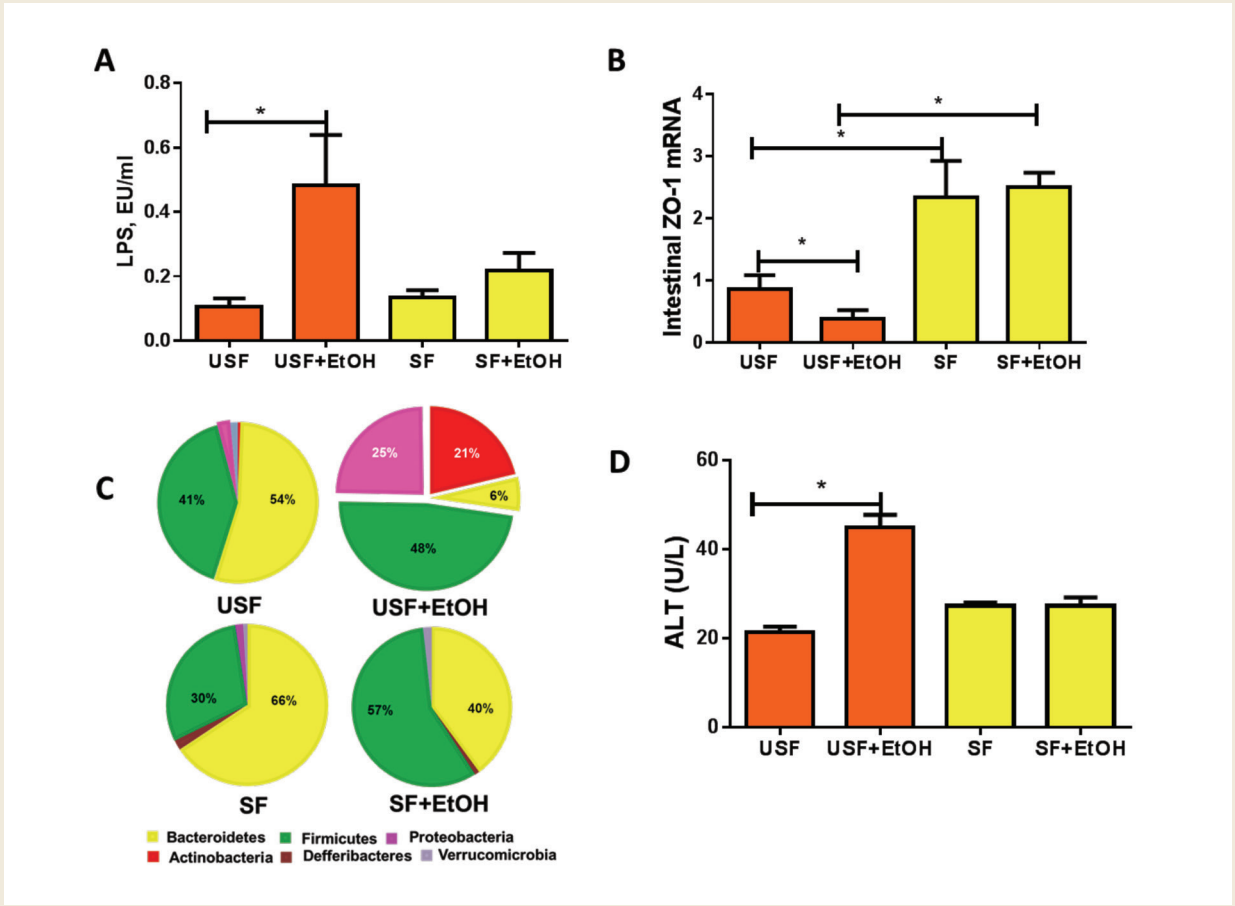

Figure 5 Effects of saturated fat (SF) and unsaturated fat (USF) diets on endotoxemia, intestinal tight junctions, gut microbiome, and liver injury in response to chronic alcohol (EtOH) feeding. **(A)** Plasma endotoxin levels assessed by plasma lipopolysaccharide (LPS) measurement. Alcohol feeding significantly increases LPS levels in the plasma when combined with a USF diet. **(B)** Levels of the mRNA for the tight-junction protein zonula occuldens-1 (ZO-1) in the intestine. Animals receiving a USF diet showed greater disruption of tight junctions (i.e., lower ZO-1 levels) than animals receiving a SF diet; this effect was exacerbated with alcohol feeding. **(C)** Comparative analysis of the relative abundance of different phyla of gut bacteria in mice fed ethanol and different types of dietary lipids. The phyla abundance is indicated by the color bars. **(D)** Liver injury was evaluated by plasma alanine aminotransferase (ALT) activity. In animals receiving a USF diet, but not in those receiving a SF diet, alcohol feeding caused significant liver injury.

NOTE: Horizontal bars indicate statistically significant differences.

stress is defined as an imbalance between oxidants and antioxidants, and the way cells sense and respond to such an imbalance is a key determinant of disease initiation/progression or resolution. Oxidant-sensing and -signaling pathways rely primarily on proteins with reactive thiol-containing cysteine residues. The reactivity of a given protein thiol can be fine tuned by its local redox environment—that is, by the ratio of reduced versus oxidized molecules in the cell. This redox environment largely is controlled by two low-molecular-weight thiol-disulfide redox couples: one composed of the amino acid cysteine (Cys), which is the reduced partner of the pair, and its disulfide cystine (CySS), which serves as the oxidized partner. The other redox pair comprises glutathione (GSH) as the reduced partner and its disulfide GSSG as the oxidized partner. The two pairs are related but have different roles. Cys is one of the three component amino acids making up GSH, so it is not surprising that they share similar chemical properties. However, these redox control systems are compartmentalized; GSH/GSSG provides control mechanisms within cells and in the lung-lining fluid, whereas Cys/CySS predominates in the extracellular fluids of plasma and interstitium. The extracellular Cys/CySS redox state has been shown to have a direct effect on the production of two important proinflammatory cytokines, namely production of transforming growth factor β by lung fibroblasts (Ramirez et al. 2007) and interleukin-1 β by monocytes (Iyer et al. 2009).

Accumulating evidence suggests that the Cys/CySS and GSH/GSSG redox couples can be controlled by the diet. Dietary supplementation with the cysteine precursors N-acetylcysteine or procysteine has been used extensively to counteract the effects of oxidative stress. Although the effects of these cysteine precursors usually are attributed to enhanced GSH synthesis, they also are effective even when given in combination with a GSH-synthesis inhibitor (e.g., buthionine sulfoximine) (Lailey et al. 1991). Recent studies showed that supplementing the diet with a combination of cysteine and methionine could prevent oxidation of the plasma Cys/CySS redox couple and decrease circulating levels of proinflammatory interleukin-1 β in endotoxin-challenged mice (Iyer at al 2009). Similar diets also can alter the plasma Cys/CySS redox state in humans (Jones et al. 2011). It will be interesting to determine whether this type of dietary intervention can protect against lung injury in chronic alcoholics.

Zinc deficiency, particularly within immune cells in the lungs (i.e., alveolar macrophages), also contributes to increased susceptibility to bacterial infection in chronic alcoholics (Mehta et al. 2011). Studies in rats showed that chronic alcohol feeding decreased bacterial clearance from lung and oxidized Cys/CySS in the alveolar space. Dietary zinc supplementation blocked both of these effects (Mehta et al. 2011).

Brain Injury

Prenatal alcohol exposure can result in a range of detrimental effects, including damage to the developing brain, that are collectively known as FASD. Early autopsy studies, as well as more recent magnetic resonance imaging studies in both animal models and humans have revealed a variety of brain abnormalities, including reduced brain size (i.e., microcephaly) and anomalies of specific brain structures (e.g., the cerebrum, cerebellum, hippocampus, basal ganglia, and corpus callosum) after prenatal alcohol exposure (Lebel et al. 2011; Lipinski et al. 2012). These ethanol-induced brain insults contribute to the learning deficits, impairment in memory, difficulties with motor planning, and problems in regulating emotions and behavior observed in children with FASD.

Alcohol can damage the developing embryo through multiple mechanisms. Oxidative stress seems to play an important role in ethanol-induced programmed cell death (i.e., apoptosis) and morphological abnormalities (Chen et al. 2013). In addition, accumulating evidence suggests that changes in epigenetic regulation are involved in the pathogenesis of FASD. For example, in animal studies, prenatal alcohol exposure increased the proportion of offspring with an unusual coat color by inducing hypermethylation of a specific gene, *Avylocus (*Kaminen-Ahola et al. 2010). Moreover, recent studies demonstrated that microRNA 125b can prevent ethanol-induced apoptosis of certain embryonal cells (i.e., neural crest cells) by targeting two specific genes called *Bak1* and *PUMA* (Chen et al. 2015).

It also is well known that nutritional deficiencies contribute to the pathogenesis of FASD and to ethanol-induced damage to the developing brain. Heavy maternal alcohol consumption results in deficiency in nutrients that are critical for fetal development and maternal health, including vitamins A and D, thiamin, folate, and zinc (Dreosti 1993). Moreover, as in adult brains, DHA deficiency occurred in the developing brain of animals prenatally exposed to ethanol. Finally, studies have shown that diets low in nutrients exacerbate alcohol-induced brain damage in the offspring (Nacach et al. 2009).

Maternal nutrient supplementation may decrease the risk of FASD and serve as a potential intervention for FASD. Some nutritional interventions target oxidative stress. For example, antioxidant supplements, such as vitamins C and E, can reduce oxidative stress, cell death, and behavioral impairments in animals prenatally exposed to ethanol. Studies in the adult brain have demonstrated that ethanol-induced neuro-inflammation and degeneration can be countered by dietary DHA. Similarly, an ω-3-enriched diet that contains 24.6 percent DHA has been shown to reduce ethanol-induced oxidative stress in the developing brain (Patten et al. 2011), consistent with the relationship between dietary fat and organ injury discussed earlier. Other nutritional

Glossary

Ascites: Accumulation of fluids in the abdominal cavity.

Cardiomyopathy: A condition of the heart muscle wherein it becomes enlarged, thick, or rigid. In rare cases, the muscle tissue in the heart is replaced with scar tissue.

Cell-Mediated Immunity: Part of the immune response that involves the activation of phagocytes, antigen-specific cytotoxic T-lymphocytes, and the release of various *cytokines* in response to a foreign molecule (i.e., antigen).

Cheilitis: Inflammation affecting the lips; this inflammation may include the skin around the mouth (i.e., perioral skin), the vermilion border, and/or the labial mucosa.

CpG Islands: Short DNA sequences that contain high levels of the normally rare cytosine–guanine sequence among the nucleotide sequence; they are targets of *DNA methylation* and are involved in the regulation of gene transcription.

Cytokines: A broad and loose category of small proteins (~5–20 kDa) that are important in cell signaling. Their release has an effect on the behavior of cells around them. They can be either proinflammatory or anti-inflammatory in their effects.

DNA Methylation: Epigenetic mechanism of regulation of gene expression, in which a strand of DNA is modified by addition of a methyl group (CH_3) to any cytosine located directly before a guanine.

Encephalopathy: A syndrome of overall brain dysfunction that can have many different organic and inorganic causes.

Enteral Nutrition: Delivery of nutrients in liquid form directly into the stomach or intestine.

Epigenetic: Heritable or nonheritable changes in phenotype or gene expression caused by mechanisms other than changes in the underlying DNA sequence; epigenetic changes can alter the appearance and structure of the DNA or the histone proteins around which the DNA is wound (e.g., *DNA methylation, histone acetylation*), thereby influencing gene expression.

Glossitis: Inflammation of the tongue.

Glycogen: Large, branched carbohydrate molecule consisting of glucose residues; constitutes the major carbohydrate reserve of animals and is stored primarily in liver and muscle.

Hepatorenal Syndrome: Functional kidney failure, but without pathological changes to the kidneys that is associated with cirrhosis and *ascites*.

Histones: Protein structures around which DNA strands are wrapped.

Histone Acetylation: *Epigenetic* modification of *histones* that involves the addition of an acetyl group.

Humoral Immunity: Immunity mediated by proteins called antibodies.

Interstitium: The space between cells in a tissue or organ.

Metallothionein: Cysteine-rich proteins that can bind to heavy metals (e.g., zinc) through the *thiol* groups of their cysteine components. They participate in the uptake, transport, and regulation of zinc and can help control *oxidative stress*.

Methionine: An essential amino acid that can supply methyl groups for various metabolic reactions.

Micronutrient: Any essential dietary element required only in small quantities (e.g., trace minerals).

Myopathy: Muscular disease in which the muscle fibers do not function for any one of many reasons, resulting in muscular weakness.

Oxidative Stress: An imbalance between oxidants (e.g., free radicals) and antioxidants that can lead to excessive oxidation and cell damage.

Parenteral Nutrition: Intravenous administration of nutrients.

Pellagra: A clinical niacin deficiency syndrome characterized by dermatitis, inflammation of the mucous membranes, diarrhea, and psychic disturbances (e.g., depression, irritability, anxiety, disorientation, or hallucinations).

Glossary *(continued)*

Petechiae: Small, nonraised, perfectly round, purplish red spots caused by bleeding in the skin layer or beneath the mucous membranes.

Purpura: Any of a group of conditions characterized by small hemorrhages in the skin, mucous membranes, or serous membranes.

Redox Environment: The balance between oxidants and antioxidants in a cell or organ; often used to describe the balance of oxidized and reduced nicotinamide adenosine dinucleotide (NAD and NADH) in a biological system such as a cell or organ.

S-adenosylmethionine (SAM): Common co-substrate involved in methyl group transfers, transsulfuration, and aminopropylation. Although these anabolic reactions occur throughout the body, most SAM is produced and consumed in the liver.

Scurvy: Condition caused by vitamin C deficiency and characterized by weakness, anemia, spongy gums, and bleeding from the mucous membranes.

Steatosis: Abnormal accumulation of lipids in the functional cells of various tissues (e.g., in the liver).

Thiol: Any organic compound containing a thiol (-SH, or sulfhydryl) group; often have strong odors resembling garlic or rotten eggs.

Tight Junction: An intercellular junction between epithelial cells, at which the adjacent cell membranes are joined tightly together, forming a belt-like seal; these junctions limit the passage of small molecules and ions between cells.

Zinc-Finger Protein: A protein containing a small structural motif that is characterized by the coordination of one or more zinc ions in order to stabilize the fold.

interventions may work through epigenetic modulations. Supplementation with nutrients that act as methyl donors, including folic acid and choline, may modulate epigenetic profiles and alter the expression of genes important for neurodevelopment. Thus, prenatal folic acid supplementation attenuated ethanol-induced malformations, growth retardation, and neuronal loss (Wang et al. 2009), whereas prenatal and postnatal supplementation with choline reduced ethanol-induced malformations and behavioral impairment (Thomas et al. 2010). Furthermore, recent studies have shown that sulforaphane, a chemical that is abundant in broccoli sprouts and which can inhibit enzymes involved in epigenetic modifications (i.e., DNA methyltransferase and histone deacetylases), can diminish ethanol-induced apoptosis in neural crest cells through induction of nuclear factor (erythroid-derived 2)-like 2 (Nrf2) (Chen et al. 2013). These findings highlight the potential of nutrient supplementation in preventing or attenuating brain damage associated with FASD, improving cognitive function in children with FASD, and attenuating brain damage in adults.

Immune Dysfunction

Excessive alcohol consumption has deleterious effects on the immune system. Several clinical and experimental studies have suggested that long-term alcohol use can lead to the dysregulation of both cell-mediated and humoral immunity (Barve et al. 2002). Epidemiologic studies have documented that alcohol-induced impairment of the immune system leads to increased susceptibility to opportunistic infections and development of certain tumors (Barve et al. 2002). Although many types of immune cells are affected by alcohol, including neutrophils, natural killer cells, and monocytes/macrophages, several observations suggest that the major effect of ethanol involves the impairment of thymus-derived lymphocytes (T lymphocytes or T cells). Because a subgroup of T-lymphocytes (i.e., CD4+ T cells) are the central regulators of the immune system, including cell-mediated and humoral immunity, loss of their survival and function constitutes a critical part of alcohol-induced immune dysfunction.

A number of experimental animal models of ethanol abuse have established that chronic alcohol administration decreases the absolute numbers of CD4+ T cells in the thymus, spleen, lymph nodes, and periphery, as well as the immune function of these cells (Barve et al. 2002). Similarly, patients with AUD exhibit significantly reduced numbers of CD4+ T cells (Barve et al. 2002). Although other clinical complications in alcoholic patients can negatively influence the immune system, recovery of the CD4+ T-cell count was noted after alcohol withdrawal in several studies, suggesting that ethanol can directly affect CD4+ T-cell survival (Barve et al. 2002). Moreover, experimental and clinical studies have documented that alcohol intake can cause depletion of CD4+T cells, and the mechanisms underlying this effect are only beginning to be understood. Research has indicated that ethanol

can potentially act as a cofactor and exacerbate clinical conditions that cause CD4+ T-cell depletion by enhancing activation-induced, fatty acid synthase–mediated apoptosis (Ghare et al. 2014). In addition to affecting CD4+ T-cell numbers, ethanol also has a major effect on T-cell function by decreasing the production of the cytokine, interleukin-2, which is critical for the clonal expansion of CD4+ T cells (Ghare et al. 2011).

In subjects with AUD, the combined effects of alcohol metabolism and compromised nutrition led to major nutrient disturbances, including deficiency of the critical nutrient metabolite, SAM. Studies found that levels of SAM as well as of methionine adenosyltransferase (MAT II), the enzyme that converts methionine to SAM, were markedly reduced in cultured CD4+ cells exposed to alcohol. This resulted in a significant upregulation of expression and activity of several enzymes involved in apoptosis, leading to increased apoptotic cell death (Hote et al. 2008). Moreover, restoration of intracellular SAM levels via SAM supplementation considerably attenuated this apoptotic death in T cells, implying a causal/protective role for SAM in T-cell survival (Hote et al. 2008).

Overall, these findings have begun to provide critical molecular insights into epigenetic mechanisms underlying the alcohol- and nutrient (SAM)-status–induced immunotoxicity in human CD4+ T cells. Because there currently is no Food and Drug Administration–approved therapy for the treatment of immune suppression associated with chronic alcohol abuse, these findings have the potential to facilitate the development of nutrient (SAM)-based therapy in alcoholic patients.

Conclusions

Alterations in nutrition and nutrient metabolism are common in chronic alcoholics and may contribute to alcohol-induced organ injury. Conversely, nutritional supplementation may prevent the development or attenuate the progression of alcohol-induced organ injury. Nutritional supplements may alleviate a nutrient deficiency or act as pharmacologic agents. Such nutrients also may have epigenetic effects. Nutritional supplementation as a therapy is especially attractive because there are currently no Food and Drug Administration–approved therapies for most forms of alcohol-induced organ injury and nutrient supplements are readily available.

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The authors declare that they have no competing financial interests.

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Alcoholic Liver Disease: Pathogenesis and Current Management

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Excessive alcohol consumption is a global healthcare problem. The liver sustains the greatest degree of tissue injury by heavy drinking because it is the primary site of ethanol metabolism. Chronic and excessive alcohol consumption produces a wide spectrum of hepatic lesions, the most characteristic of which are steatosis, hepatitis, and fibrosis/cirrhosis. Steatosis is the earliest response to heavy drinking and is characterized by the deposition of fat in hepatocytes. Steatosis can progress to steatohepatitis, which is a more severe, inflammatory type of liver injury. This stage of liver disease can lead to the development of fibrosis, during which there is excessive deposition of extracellular matrix proteins. The fibrotic response begins with active pericellular fibrosis, which may progress to cirrhosis, characterized by excessive liver scarring, vascular alterations, and eventual liver failure. Among problem drinkers, about 35 percent develop advanced liver disease because a number of disease modifiers exacerbate, slow, or prevent alcoholic liver disease progression. There are still no FDA-approved pharmacological or nutritional therapies for treating patients with alcoholic liver disease. Cessation of drinking (i.e., abstinence) is an integral part of therapy. Liver transplantation remains the life-saving strategy for patients with end-stage alcoholic liver disease.

Key words: Alcohol consumption; heavy drinking; alcohol effects and consequences; abstinence; alcoholic liver disease; liver injury; hepatic lesions; steatosis; hepatitis; fibrosis; cirrhosis; treatment; pharmacological therapy; nutritional therapy; liver transplantation

Excessive alcohol consumption is a global healthcare problem with enormous social, economic, and clinical consequences, accounting for 3.3 million deaths in 2012 (World Health Organization 2014). Excessive drinking over decades damages nearly every organ in the body. However, the liver sustains the earliest and the greatest degree of tissue injury from excessive drinking because it is the primary site of ethanol metabolism (Lieber 2000). After a brief overview of alcohol metabolism in the liver, this article will summarize the mechanisms through which excessive alcohol consumption contributes to the development of various types of alcohol-induced liver damage. It also will review modifiers of alcoholic liver disease (ALD) and discuss currently used treatment approaches for patients with ALD.

Hepatic Alcohol Metabolism

Beverage alcohol (i.e., ethanol) is chiefly metabolized in the main parenchymal cells of the liver (i.e., hepatocytes) that make up about 70 percent of the liver mass (Jones 1996). These cells express the highest levels of the major ethanol-oxidizing enzymes, alcohol dehydrogenase (ADH), which is located in the cytosol, and cytochrome P450 2E1 (CYP2E1), which resides in the

smooth endoplasmic reticulum (ER) (figure 1). Hepatocytes also express very high levels of catalase, an enzyme that inhabits peroxisomes. Catalase normally carries out the detoxification of hydrogen peroxide (H_2O_2) to water and oxygen. However, when ethanol is present, catalase has an accessory role in ethanol metabolism by using H_2O_2 to oxidize ethanol to acetaldehyde. Ethanol oxidation by catalase is a relatively minor pathway in the liver, but has a larger ethanol-oxidizing function in the brain (Aragon et al. 1992).

ADH is the most catalytically efficient ethanol-metabolizing enzyme. It reaches its half-maximal velocity when circulating ethanol levels are about 5 to 10 milligrams per deciliter, well below levels that cause intoxication.[1] ADH-catalyzed ethanol oxidation uses nicotinamide adenine dinucleotide (NAD^+) as a cofactor, generating reduced NAD^+ (NADH) and acetaldehyde. The latter compound is highly reactive and toxic. It can covalently bind to proteins (Donohue et al. 1983), lipids (Kenney 1982), and nucleic acids (Brooks and Zakhari 2014) to form acetaldehyde adducts, which, in turn, can disrupt the structure and function of these macromolecules (Mauch et al. 1986). One way that hepatocytes minimize acetaldehyde toxicity is by rapidly oxidizing it to acetate using the enzyme aldehyde dehydrogenase 2 (ALDH2) inside mitochondria. The ALDH2 reaction is another oxidation–reduction step that generates NADH and acetate, the latter of which can diffuse into the circulation to be utilized in other metabolic pathways. The enhanced generation of NADH by both ADH- and ALDH2-catalyzed reactions decreases the normal intrahepatocyte NAD^+/NADH ratio, called the cellular redox potential. This change causes significant metabolic shifts from oxidative metabolism toward reductive synthesis, favoring the formation of fatty acids, which contribute to fatty liver development (Donohue 2007).

[1] People are legally inebriated when their blood alcohol levels reach 80 milligrams per deciliter.

CYP2E1 is the other major hepatic enzyme that catalyzes ethanol oxidation to acetaldehyde. Although the catalytic efficiency of CYP2E1 is considerably slower than that of ADH, CYP2E1 has a 10-fold higher capacity for binding ethanol, becoming half-saturated at 46 to 92 milligrams per deciliter. Also important is that CYP2E1 is an inducible enzyme; its hepatocellular content rises during chronic ethanol consumption (Dilger et al. 1997; Lieber and DeCarli 1968). Ethanol interacts directly with the CYP2E1 protein, causing it to assume a conformation that resists degradation by the ubiquitin-proteasome system and resulting in the accumulation of CYP2E1

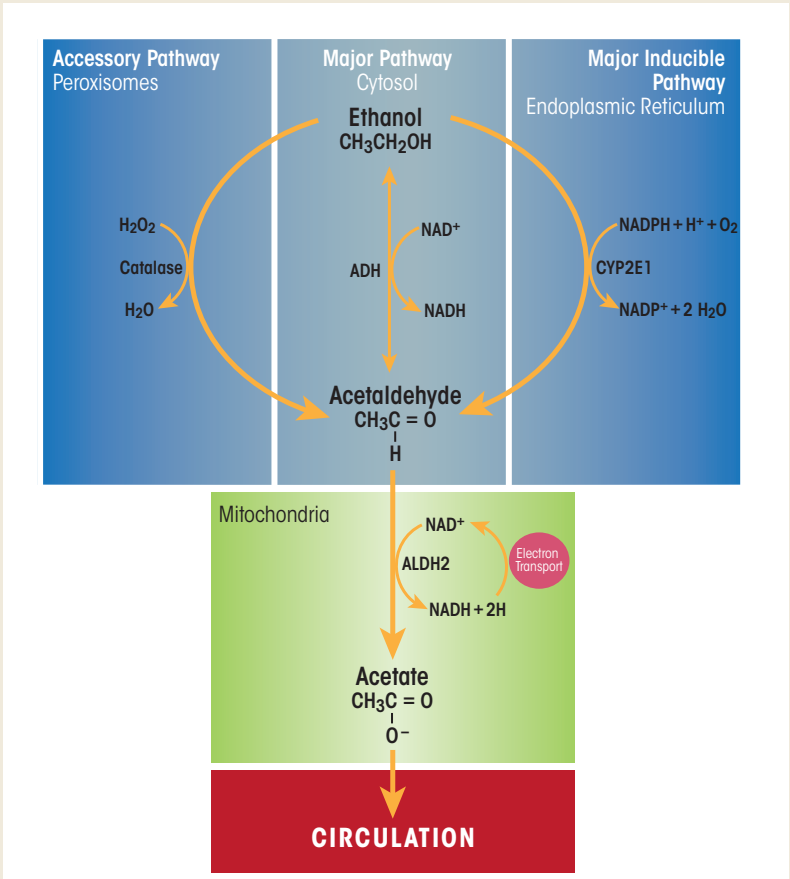

Figure 1 Major and minor ethanol-oxidizing pathways in the liver. Ethanol (i.e., ethyl alcohol) is oxidized principally in hepatocytes of the liver. **(Middle panel)** Alcohol dehydrogenase (ADH), a major enzyme in the cytosol, and aldehyde dehydrogenase 2 (ALDH2), which is located in the mitochondria, catalyze sequential oxidations that convert ethanol to acetate, producing two mole equivalents of reduced nicotinamide adenine dinucleotide (NADH). **(Right panel)** Cytochrome P450 2E1 (CYP2E1) is a major inducible oxidoreductase in the endoplasmic reticulum that oxidizes ethanol, in the presence of molecular oxygen (O_2), to acetaldehyde and converts reduced NAD phosphate (NADPH) to its oxidized form, generating water. **(Left panel)** Peroxisomal catalase is a minor hepatic pathway of ethanol oxidation that uses hydrogen peroxide (H_2O_2) to oxidize ethanol to acetaldehyde and water.

SOURCE: Figure adapted from Zakhari and Li 2007.

molecules (Roberts et al. 1995). CYP2E1 induction has several major effects in heavy drinkers: First, because more CYP2E1 oxidizes ethanol, drinkers develop a "metabolic tolerance"—that is, they need to drink more alcohol to reach a level of intoxication that they formerly achieved after drinking less alcohol. Second, accelerated alcohol metabolism by higher levels of CYP2E1 puts liver cells in metabolic peril, because more CYP2E1 not only produces more acetaldehyde, but the induced enzyme also generates greater amounts of various other reactive oxygen species (ROS), including hydroxyethyl radicals (i.e., free-radical forms of ethanol), superoxide anions (O_2^-) and hydroxyl radicals (·OH). Continuous generation of these reactive molecules in problem drinkers eventually creates the condition known as oxidant stress or oxidative stress. Under these conditions, the rate of ROS generation exceeds the liver's capacity to neutralize them with natural antioxidants, such as glutathione and vitamins E, A, and C, or to remove them using antioxidant enzymes, including those listed in table 1 (Fang et al. 2002). Animal studies have revealed that chronic ethanol consumption decreases the activities and/or amounts of several antioxidant enzymes, which worsens the hepatocytes' oxidant burden (Chen et al. 1995; Dong et al. 2014; Zhao et al. 1996). Oxidant stress further is exacerbated when the generated ROS undergo secondary reactions with proteins and unsaturated lipids. The latter reactions result in the generation of lipid peroxides, which themselves interact with proteins and with acetaldehyde to form bulkier adducts (e.g., malondialdehyde-acetaldehyde [MAA] adducts) that are capable of generating an immune response (Tuma et al. 1996). Finally, because of CYP2E1's broad substrate specificity, increased levels of the enzyme also accelerate the conversion of excess amounts of substrates other than ethanol, such as the analgesic and antipyretic medication acetaminophen. Following CYP2E1 induction by heavy drinking, acetaminophen is converted to a more toxic, reactive intermediate. This places the chronic drinker at substantial risk for liver disease or acute liver failure, especially after an acetaminophen overdose (Schiodt et al. 2002).

Alcohol's Effects on Other Liver Cell Types

Although hepatocytes comprise most of the liver mass, nonparenchymal cells, including Kupffer cells (KCs), sinusoidal endothelial cells, hepatic stellate cells (HSCs), and liver-associated lymphocytes make up the remaining 15 to 30 percent of the liver mass. These nonparenchymal cells interact with hepatocytes and with each other via soluble mediators and by direct cell-to-cell contact. Each liver cell type plays a specific role not only in normal hepatic physiology but also in initiating and perpetuating liver injury.

Spectrum of ALD

Heavy ethanol consumption produces a wide spectrum of hepatic lesions, the most characteristic being fatty liver (i.e., steatosis), hepatitis, and fibrosis/cirrhosis (see figure 2). Steatosis is the earliest, most common response that develops in more than 90 percent of problem drinkers who consume 4 to 5 standard drinks per day over decades (Ishak et al. 1991; Lieber 2004). (A standard drink is defined as the amount of alcoholic beverage that contains approximately 0.5 fluid ounces, or about 14 grams, of pure alcohol [figure 3]). However, steatosis also develops after binge drinking, defined as the consumption of 4 to 5 drinks in 2 hours or less. Steatosis was formerly considered a benign consequence of alcohol abuse. It is characterized by the deposition of fat, seen microscopically as lipid droplets, initially in the hepatocytes that surround the liver's central vein (i.e., perivenular hepatocytes), then progressing to mid-lobular hepatocytes, and finally to the hepatocytes that surround the hepatic portal vein (i.e., periportal hepatocytes). If the affected individual ceases drinking, steatosis is a reversible condition with a good prognosis. However, patients with

Table 1 Hepatic Enzymatic Defenses Against Free-Radical Attack

Enzyme	Abbreviation	Cellular Location	Function	Effect of Chronic Ethanol Administration	References
Copper–Zinc-Superoxide Dismutase	Cu/Zn-SOD	Cytosol	Converts superoxide to H_2O_2	Decreases activity and content	Chen et al. 1995; Zhao et al. 1996
Manganese-Superoxide Dismutase	Mn-SOD	Mitochondria	Converts superoxide to H_2O_2	Decreases activity and content	Chen et al. 1995; Zhao et al. 1996
Catalase	Catalase	Peroxisomes	Converts H_2O_2 to H_2O	Increases activity	Chen et al. 1995
Glutathione Peroxidase	GSH peroxidase	Cytosol/ mitochondria	Scavenges peroxides and free radicals	Unaffected	Chen et al. 1995
Glutathione Reductase	GSSG reductase	Cytosol	Regenerates reduced GSH from GSSG	Decreases activity	Dong et al. 2014
Glutathione-S-Transferase	GST	Nuclei, cytosol, mitochondria	Transfers sulfur to acceptor molecules	Increases activity	Chen et al. 1995

chronic steatosis are more susceptible to fibrotic liver disease (Teli et al. 1995), because the presence of fat likely represents a greater risk for lipid peroxidation and oxidative damage.

Alcoholic hepatitis is a more severe, inflammatory type of liver injury characterized by swollen, dying hepatocytes (i.e., ballooning degeneration), neutrophilic infiltration, and the development of tangled aggregates of insoluble proteins called Mallory-Denk bodies within hepatocytes. Central to hepatitis development is the activation of KCs, the resident liver macrophages.

Fibrosis and its terminal or late stage, cirrhosis, refer to the deposition of abnormal amounts of extracellular matrix proteins, principally by activated HSCs. Patients initially exhibit active pericellular fibrosis, which may progress to cirrhosis, the late stage of hepatic scarring. However, some degree of hepatitis likely is always present in cirrhotic patients, whereas hepatic fat usually is not prominent in these individuals. The World Health Organization's (2014) *Global Status Report on Alcohol and Health* estimates that 50 percent of all deaths caused by cirrhosis were attributable to alcohol abuse.

The following sections provide a detailed description of the mechanisms involved in the development of these major lesions.

Mechanisms Involved in Alcoholic Steatosis

As the preceding section on ethanol metabolism stated, ethanol and acetaldehyde oxidations generate higher levels of NADH, which alters the cellular redox potential and enhances lipid synthesis (i.e., lipogenesis). However, ethanol-induced redox change alone does not fully explain why the liver rapidly accumulates fat. More recent studies now strongly support the notion that ethanol-induced steatosis is multifactorial as discussed below (see figure 4).

Alcohol Accelerates Hepatic Lipogenesis

Enhanced lipid synthesis results from a higher expression of lipogenic enzymes and cytokines (see table 2) that are encoded by genes regulated by two transcription factors, sterol regulatory element binding protein-1c (SREBP-1c) and early growth response-1 (Egr-1). SREBP-1c belongs to a family of transcription factors that control hepatic cholesterol metabolism. However, in heavy drinkers, ethanol oxidation short-circuits hepatic lipid metabolism, converting the liver from a lipid-burning to a lipid-storing organ. Thus, hepatic SREBP-1c is relatively inactive in hepatocytes of abstinent people, residing mostly in the ER. However, in a person who binges or habitually drinks, hepatic ethanol oxidation triggers the translocation of SREBP-1c from the ER to the Golgi apparatus, where it

Table 2 Lipogenic Enzymes Regulated by SREBP-1c

Enzyme	Abbreviation	Function
Fatty Acid Synthase	FAS	Synthesizes fatty acids from acetyl coenzyme A (CoA) and palmitate
Acyl CoA Carboxylase	ACC	Synthesizes malonyl CoA from acetyl CoA
ATP Citrate Lyase	ACL	Converts citrate and CoA to acetyl CoA
Stearoyl CoA Desaturase	SCD	Synthesizes unsaturated fatty acids (oleate) from saturated fatty acids (stearate)
Malic Enzyme	ME	Generates reducing equivalents (NADPH) for triglyceride synthesis

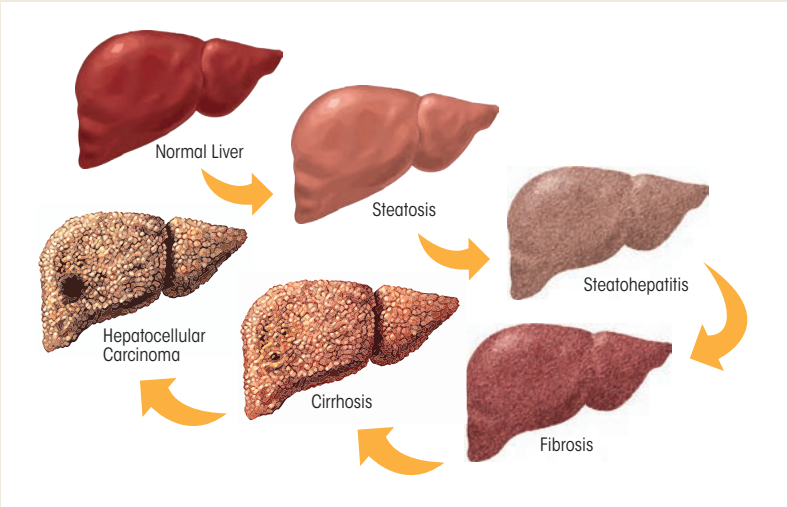

Figure 2 Spectrum of alcoholic liver disease. Heavy ethanol consumption produces a wide spectrum of hepatic lesions. Fatty liver (i.e., steatosis) is the earliest, most common response that develops in more than 90 percent of problem drinkers who consume 4 to 5 standard drinks per day. With continued drinking, alcoholic liver disease can proceed to liver inflammation (i.e., steatohepatitis), fibrosis, cirrhosis, and even liver cancer (i.e., hepatocellular carcinoma).

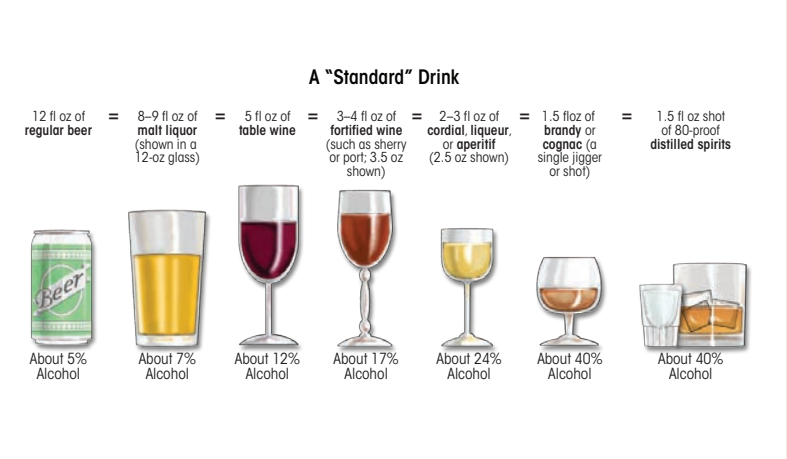

Figure 3 Illustration of "standard drinks" in order of increasing ethanol content among currently available alcoholic beverages. According to the National Institute on Alcohol Abuse and Alcoholism, the amount of beverage containing approximately 14 g of pure ethanol is defined as a standard drink. The percent of pure alcohol, expressed as alcohol by volume (alc/vol), varies by beverage. Thus, 12 ounces (360 mL) of beer at 6 percent alc/vol, 5 ounces (150 mL) of wine at 12 percent alc/vol, or 1.5 ounces (45 mL) of distilled spirits at 40 percent alc/vol each are equivalent to a standard drink. Although the standard-drink amounts are helpful for following health guidelines, they may not reflect customary serving sizes. In addition, although the alcohol concentrations listed are typical, there is considerable variability in actual alcohol content within each type of beverage.

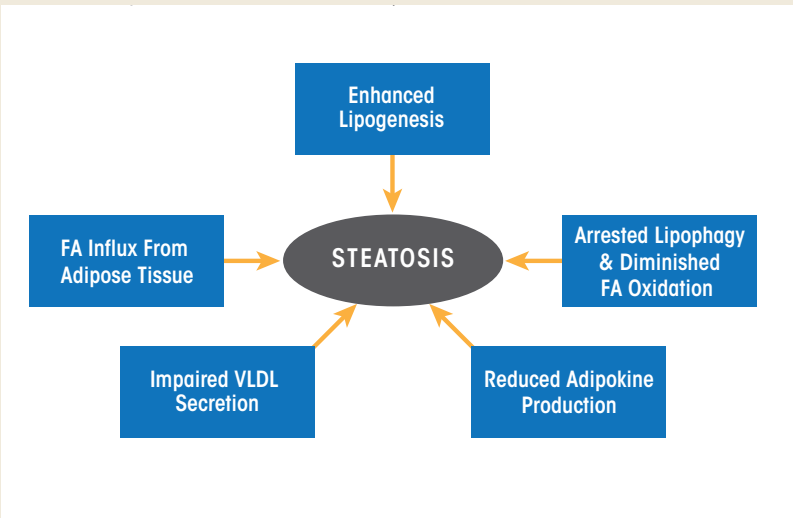

Figure 4 Hepatic and extrahepatic mechanisms that contribute to the development of alcoholic fatty liver (i.e., steatosis).

NOTE: FA = fatty acid; VLDL = very low density lipoprotein.

undergoes proteolytic maturation to its active form, generating a transcriptionally active SREBP protein fragment that enters the nucleus and enhances lipogenic gene expression (see table 2). Egr-1 controls the expression of genes that respond to cellular stress. It binds to gene promoter regions that are relevant to alcohol-induced liver injury and steatosis. The most notable of these is tumor necrosis factor alpha (TNFα), a lipogenic cytokine. Additionally, because Egr-1 is activated very early after ethanol administration (Donohue et al. 2012), it also regulates the expression of the SREBP-1c gene (Thomes et al. 2013). Figure 5 shows the postulated scheme of transcriptional control that contributes to enhanced lipogenesis in the liver.

In addition to enhanced hepatic lipogenesis, fat (i.e., adipose) tissue contributes to the development of steatosis. Adipose tissue normally is an important energy depot, storing excess calories derived from food consumption as fat. When necessary, high-energy fat then can be used to fulfill energy requirements during times of low nutrition (e.g., fasting) or high calorie utilization (e.g., exercise). Research with rodents subjected to chronic alcohol feeding has shown that ethanol consumption reduces adipose tissue mass by enhancing fat breakdown (i.e., lipolysis) in adipose tissue (Kang et al. 2007; Wang et al. 2016; Wei et al. 2013). The free fatty acids released from adipose tissue are taken up by the liver and esterified into triglycerides, thereby exacerbating fat accumulation in the liver (Wei et al. 2013). Clinical studies also have demonstrated that people with alcohol use disorder who have fatty liver have significantly lower body weight, body mass index, and body-fat mass content than control subjects (Addolorato et al. 1997, 1998).

Alcohol Decelerates Hepatic Lipid Breakdown

Because most lipids in hepatocytes are stored in lipid droplets, these organelles must first be degraded to extract

the lipids for their subsequent oxidation. Breakdown of lipid droplets is accomplished by lipophagy, a specialized form of the intracellular process that degrades cytoplasmic components (i.e., autophagy). During lipophagy, lipid droplets are engulfed within double-membrane–bound vacuoles called autophagosomes. These vacuoles transport the lipid-droplet cargo to lysosomes, where they are degraded by lipid-digesting enzymes (i.e., lipases), releasing free fatty acids that then undergo β-oxidation inside mitochondria. The rates of autophagy reportedly are retarded by chronic ethanol consumption, at least in part because ethanol is thought to cause faulty lysosome biogenesis. This results in fewer, more defective lysosomes (Kharbanda et al. 1995, 1996), thereby slowing the breakdown of lipid droplets in the steatotic liver.

It also is quite clear that once fatty acids are released from lipid droplets, heavy alcohol consumption reduces their rates of β-oxidation. There are several reasons for the slowdown: First, the enhanced generation of NADH by ethanol oxidation inhibits mitochondrial β-oxidation. Second, metabolically generated acetaldehyde inactivates the peroxisome proliferator activated receptor alpha (PPAR-α), a transcription factor that acts in concert with the retinoid X receptor (RXR) and governs expression of genes that regulate fatty-acid transport and oxidation. Acetaldehyde likely inactivates PPAR-α by covalently binding to the transcription factor (Galli et al. 2001), thereby blocking its ability to recognize and/or bind PPAR-α promoter sequences. Third, both acute and chronic ethanol oxidation cause mitochondrial depolarization, impairing their abilities to generate energy (i.e., adenosine triphosphate [ATP] molecules), and causing their outer membranes to leak, resulting in inefficient fatty-acid import and lower rates of β-oxidation (Zhong et al. 2014). Fourth, ethanol consumption reduces the production of the hormone adiponectin, which is secreted by fat cells (i.e., adipocytes). One study demonstrated that the restoration of adiponectin to alcohol-fed animals re-establishes fatty-acid oxidation to normal (Xu et al. 2003). In addition, adiponectin appears to reduce the production of the cytokine TNFα, and there is evidence that TNFα also may regulate adiponectin production (You and Crabb 2004).

Alcohol Causes Defective Hepatic Lipid Export

It is well known that the liver exports triglycerides and cholesterol only as constituents of very low density lipoprotein (VLDL) particles; any impairment in either the synthesis or export of VLDL particles therefore contributes to fat accumulation within hepatocytes. VLDL assembly is regulated by the availability of triglycerides (which make up more than 50 percent of the VLDL lipids) stored in cytoplasmic lipid droplets. Up to 70 percent of the triglycerides in VLDLs are derived from the pool of triglycerides stored in lipid droplets that first undergo lipolysis and then are re-esterified to constitute VLDL triglycerides. Although earlier reports implicated altered VLDL secretion in the development of alcoholic steatosis (Venkatesan et al. 1988), exactly how alcohol impairs lipolysis of triglyceride stores in lipid droplets for assembly of VLDL and its subsequent secretion is unknown. However, studies have shown that alcohol-impaired VLDL secretion is caused by a decreased synthesis of an essential constituent of VLDL (Kharbanda et al. 2007, 2009) as well as by reduced activity of an essential protein for its assembly (Shearn et al. 2016; Sugimoto et al. 2002).

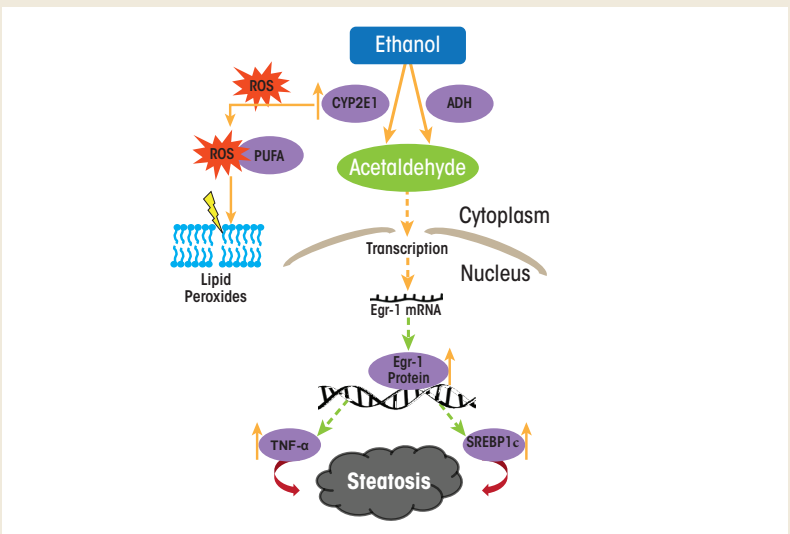

Figure 5 Proposed mechanism by which ethanol oxidation regulates early growth response-1 (Egr-1) and sterol regulatory element binding protein-1c (SREBP-1c) to enhance lipogenesis. Alcohol dehydrogenase (ADH) and cytochrome P450 2E1 (CYP2E1) each catalyze ethanol oxidation, producing acetaldehyde. This aldehyde enhances Egr-1 gene transcription by activating the Egr-1 promoter, thereby increasing the levels of Egr-1 mRNA and, subsequently, nuclear Egr-1 protein. It is believed that nuclear Egr-1 protein regulates transcription of SREBP-1c and tumor necrosis factor (TNF) genes to initiate ethanol-induced lipogenesis and fatty liver (i.e., steatosis).

NOTE: PUFA = polyunsaturated fatty acid; ROS = reactive oxygen species.
SOURCE: Figure adapted from Thomes et al. 2013.

Mechanisms Involved in Alcoholic Hepatitis

Alcoholic hepatitis occurs in about 30 to 40 percent of individuals reporting chronic alcohol abuse. It represents the most serious form of ALD and is associated with high short-term mortality. Ballooning degeneration of hepatocytes containing Mallory-Denk bodies, infiltrating neutrophils, and fibrosis are characteristic pathologic findings indicative of hepatitis (Lefkowitch 2005). Central to the progression of alcoholic hepatitis are resident and infiltrating immune cells called macrophages, which have important roles in inducing liver inflammation. KCs, the resident macrophages in the liver, represent up to 15 percent of liver cells and 50 percent of all macrophages in the body. They reside in the liver sinusoids and provide the first line of defense, serving as potent innate immune cells. In contrast, infiltrating macrophages are recruited as immature cells from the bone marrow, and their differentiation into macrophages in the liver only occurs during inflammation.

The ability of macrophages to regulate inflammation depends on their polarization—that is, their ability to develop into one of two different functional states, namely M1 (i.e., proinflammatory) or M2 (i.e., anti-inflammatory) macrophages. The polarization to either phenotype depends on the microenvironment, including circulating growth factors, cytokines, and pathogen-associated molecular pattern (PAMP) as well as damage-associated molecular pattern (DAMP) molecules. Because the liver is exposed to countless antigens, pathogens, and toxic substances that come from the intestine via the portal circulation, it must be protected from developing an immune response to such exposure. As a result, KCs usually have tolerogenic properties, meaning that they do not respond to all antigens with an immune response. However, excessive alcohol exposure can switch KCs to a proinflammatory M1 phenotype. Usually, ALD progression from liver steatosis to inflammation requires a second insult in addition to the alcohol exposure, such as another toxic insult, nutritional factor, or viral infection (Tsukamoto et al. 2009). More importantly, KCs can regulate the development of inflammation, depending on their ability to either induce or suppress proinflammatory changes. These effects are related to the stage and severity of the alcoholic hepatitis; in severe cases, KCs differentiate to the proinflammatory M1 phenotype, whereas in mild forms, KCs switch to the anti-inflammatory M2 phenotype. As inducers of inflammation, KCs release multiple proinflammatory cytokines, including TNFα, interleukins, and chemokines that attract inflammatory cells from circulation. KCs also are an abundant source of ROS that exacerbate oxidative stress in the liver.

What factors trigger KC activity in patients with alcohol use disorder? One major factor is endotoxin, also called lipopolysaccharide (LPS), a cell-wall component of Gram-negative bacteria that translocates from the gut lumen into the portal circulation to reach the liver (figure 6). Accumulating data demonstrate that excess ethanol intake induces endotoxemia through two main mechanisms—by stimulating bacterial overgrowth and by increasing intestinal permeability (Bode and Bode 2003). Animal studies have revealed that increased circulating endotoxin levels correlate with the severity of liver disease (Mathurin et al. 2000). LPS is sensed by two types of receptors—CD14 and toll-like receptor 4 (TLR4)—

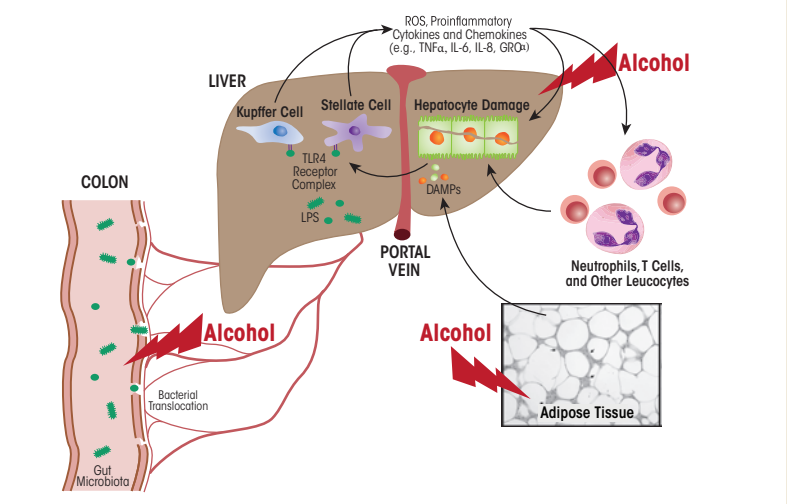

Figure 6 The gut–liver axis. A major factor in the initiation of the inflammatory response by resident macrophages of the liver (i.e., Kupffer cells) is endotoxin or lipopolysaccharide (LPS), a cell-wall component of Gram-negative bacteria that translocates from the gut lumen into the portal circulation to reach the liver. Enhanced circulating endotoxin levels in alcoholic hepatitis are caused by alcohol-induced qualitative and quantitative changes in the bacteria that inhabit the gut (i.e., gut microbiota) and increased gut leakiness. In the liver, LPS activates Kupffer cells and hepatic stellate cells by interacting with toll-like receptor 4 (TLR4). These cells produce reactive oxygen species (ROS) as well as proinflammatory cytokines and chemokines that together with alcohol contribute to hepatocyte damage. Other factors contributing to hepatocyte damage include alcohol-induced activation of various immune cells (i.e., neutrophils, T cells, and other leukocytes) as well as alcohol's effects on the fat (i.e., adipose) tissue, which results in the production of damage-associated molecular pattern (DAMP) molecules.

on the KC surface (Suraweera et al. 2015). These receptors activate KCs to produce proinflammatory cytokines and promote free-radical formation via induction of the reduced nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and CYP2E1. The resulting reactive oxygen and nitrogen species promote the release of pro-inflammatory cytokines, which in turn increase inflammasome activation in KCs and the release of chemokines that attract circulating immune cells to the liver. Inflammasomes are innate immune-system sensors that regulate the activation of caspase-1 and induce inflammation in response to microbial/viral pathogens, molecules derived from host proteins, and toxic insults (e.g., alcohol exposure).

Other factors can exacerbate liver inflammation. Prominent among these are MAA adducts that are produced in alcohol-exposed hepatocytes. These adducts are taken up by scavenger receptors on KCs (Ambade and Mandrekar 2012), further promoting the proinflammatory response. Also, because macrophages metabolize ethanol via CYP2E1, the induction of oxidative stress by alcohol exposure activates macrophage-dependent release of proinflammatory cytokines, including TNFα. Although hepatocytes normally are resistant to TNFα, alcohol exposure sensitizes them to the cytokine, causing their death via apoptosis. The resulting release of small vesicles (i.e., exosomes) from dying hepatocytes provides activation signals to KCs (Nagy et al. 2016). Apoptotic hepatocytes are engulfed by KCs, thereby switching their phenotype to M1, which exacerbates inflammation. Inflammation-associated release of chemokines, in turn, attracts circulating macrophages, T-cells, and neutrophils (an additional source of oxidative stress) to the liver. These immune cells, by releasing proinflammatory cytokines and chemokines with direct cytotoxic effects, further promote hepatocyte cell death and the persistence of alcoholic hepatitis.

Recently, it was reported that HSCs also play a dual (i.e., stage-dependent) role in the regulation of liver inflammation (Fujita et al. 2016). An important function of HSCs is to transmit signals from sinusoid cells to the liver parenchyma. The proinflammatory cytokines and chemokines produced by activated KCs stimulate the production of proinflammatory cytokines by HSCs. In addition, LPS also can directly activate HSCs through TLR4 to promote the secretion of proinflammatory cytokines. The functions of HSCs are regulated by KCs. The dual role of KCs in the regulation of inflammation is not only related to production of proinflammatory substances. At the stage of the resolution of inflammation, KCs produce anti-inflammatory substances, such as prostaglandin D2, which is sensed by HSC receptors. Prostaglandin D2 programs HSCs to switch their production to anti-inflammatory factors, including transforming growth factor-β1 (TGF-β1), which promotes fibrogenesis. The role of KCs and HSCs in promoting alcohol-induced inflammatory changes and progression to fibrosis/cirrhosis is schematically presented in figure 7.

Mechanisms Involved in Fibrosis/Cirrhosis

HSCs are the key players in the development of fibrosis. These cells normally

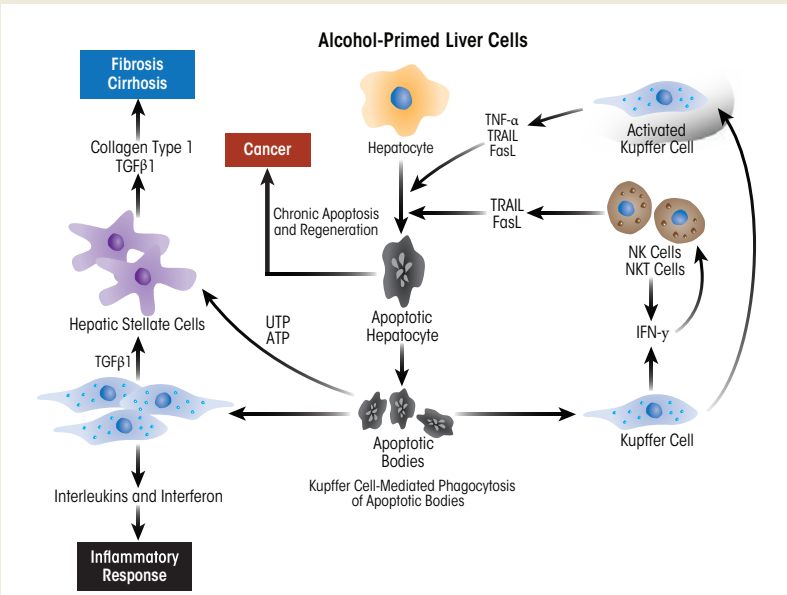

Figure 7 Schematic depiction of the role of Kupffer cells (KCs) and hepatic stellate cells (HSCs) in promoting alcohol-induced inflammatory changes and progression to fibrosis and cirrhosis. Injury begins with alcohol-induced hepatocyte damage and death (apoptosis), which generates apoptotic bodies that stimulate KCs to secrete inflammatory factors, such as tumor necrosis factor alpha (TNFα), interferon gamma (IFN-γ), tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), and Fas ligand (FasL). These factors attract immune cells (e.g., natural killer [NK] cells and natural killer T cells [NKT cells]) to the liver to exacerbate the inflammatory process. Activated HSCs secrete abundant extracellular matrix proteins (e.g., collagen type 1), forming scar tissue (fibrosis) that can progress to cirrhosis. In this condition, the scar tissue forms bands throughout the liver, destroying the liver's internal structure and impairing the liver's ability to regenerate itself and to function.

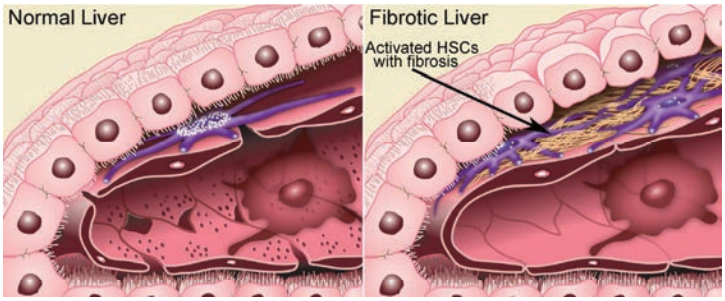

Figure 8 Hepatic stellate cells (HSCs) are key players in the development of fibrosis. HSCs normally reside in the space of Disse as quiescent, lipid (retinyl-ester)-storing cells. Chronic ethanol consumption initiates a complex activation process that transforms these quiescent HSCs into an activated state. Activated HSCs secrete copious amounts of the scar-forming extracellular matrix proteins. This, in turn, contributes to structural changes in the liver, such as the loss of hepatocyte microvilli and sinusoidal endothelial fenestrae, ultimately causing the deterioration of hepatic function.

SOURCE: Figure adapted from Friedman 2000.

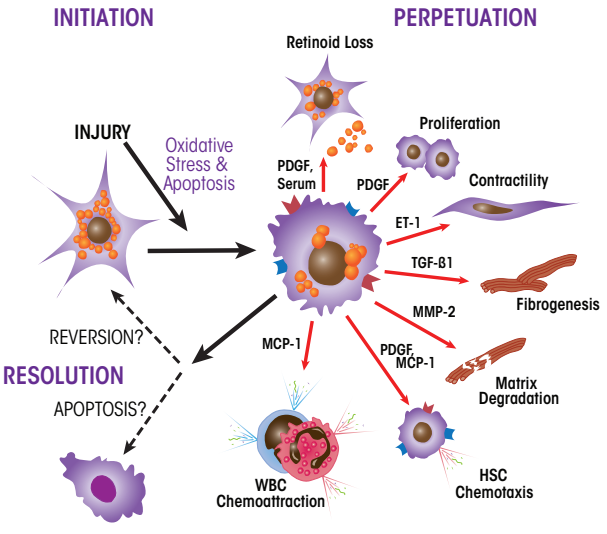

Figure 9 Pathways of hepatic stellate cell (HSC) activation. Following hepatic injury, HSCs undergo a complex activation process involving numerous signaling molecules that is characterized by loss of retinoids, increased proliferation, contractility, and chemotaxis. These activated cells are the principal cell source of increased and irregular deposition of extracellular matrix components, which characterize fibrosis. Activated HSCs also contribute to the inflammatory response by coordinating the recruitment and stimulation of white blood cells (WBCs) by releasing chemokines and proinflammatory cytokines, as well as expressing adhesion molecules.

NOTE: ET-1 = endothelin-1; MCP-1 = monocyte chemoattractant protein-1; MMP-2 = matrix metalloproteinase-2; PDGF = platelet-derived growth factor; TGF-β1 = transforming growth factor-beta1.
SOURCE: Figure adapted from Friedman 2000.

reside in the space of Disse as quiescent, lipid (retinyl-ester)-storing cells (figure 8). Following hepatic injury, HSCs undergo a complex activation process (figure 9) and become the principal source for the increased and irregular deposition of extracellular-matrix components that characterize fibrosis. Activated HSCs also contribute to the inflammatory response, coordinating the recruitment and stimulation of leukocytes by releasing chemokines and proinflammatory cytokines as well as expressing adhesion molecules. The leukocytes, in turn, not only attack and destroy hepatocytes, but also activate quiescent and activated HSCs, thereby exacerbating the fibrogenic response (Friedman 2008).

Hepatic fibrosis is a transient and reversible wound-healing response, which may be restored to normal in some patients if alcohol intake ceases. However, if drinking continues, chronic inflammation and sustained fibrogenesis progress, resulting in the substitution of liver parenchyma by scar tissue that severely compromises the liver's vascular architecture. The main pathological feature of cirrhosis is the formation of regenerative nodules of hepatic parenchyma surrounded by fibrous septa. Cirrhosis development progresses from a compensated phase, in which part of the liver remains undamaged and functionally compensates for the damaged regions, to a decompensated phase, in which scar tissue fully envelops the organ. The latter is characterized by development of portal hypertension and/or liver failure.

Modifiers of ALD Risk

Among problem drinkers, only about 35 percent develop advanced liver disease. This is because modifiers, as listed below, exist that exacerbate, slow, or prevent ALD disease progression.

- *Pattern of Consumption and Beverage Type.* The most important factors determining the progression

of liver disease are the beverage type consumed and the amount and pattern of drinking (e.g., outside mealtime or binges). Intake of 40 to 80 grams ethanol/day by males and of 20 to 40 grams/day by females for 10 to 12 years is a general predictor of more severe cases of ALD, including alcoholic steatohepatitis, fibrosis, and cirrhosis (Becker et al. 1996).

- *Gender.* Epidemiologic data show that women are more susceptible to alcohol-related liver damage than men. This appears to be related to higher blood alcohol concentrations in women than in men who ingest the same amount of alcohol, resulting from a lower proportion of body water in females compared with males of equal weight (Mumenthaler et al. 1999). There also are reports that women possess a lower capacity than men to oxidize ethanol in the gut, a process called first-pass metabolism (Frezza et al. 1990). This deficit in women allows greater quantities of ethanol into the portal circulation, thereby exposing their livers to higher ethanol concentrations. Further, gender-based differences in the sensitivity of KCs to endotoxins and hepatic inflammatory responses have been related to higher susceptibility to ALD progression in females than in males (Frezza et al. 1990).

- *Age.* It is not completely clear how age modifies ALD progression. It is, however, a predictor for ALD (Masson et al. 2014), because older adults (i.e., ages 65 and up) are more vulnerable to and show greater degrees of ethanol-induced impairments than younger people (Meier and Seitz 2008).

- *Race/Ethnicity.* Ethnicity is a major factor affecting the age at and severity of presentation of different subtypes of ALD (Levy et al. 2015). The

Glossary

Ascites: Accumulation of fluid in the abdominal cavity.

Autophagy: The breakdown of organelles (e.g., lipid droplets) and macromolecules (e.g., proteins and lipids) in lysosomes for maintenance of cell homeostasis.

β-Oxidation: The main metabolic process by which fatty acids are broken down in the cell.

Chemokine: Any of a group of small signaling proteins that are released by a variety of cells to stimulate the movement of *leukocytes* and attract them to the site of an immune response.

Cytokine: Any of a group of small, hormone-like proteins secreted by various cell types that regulate the intensity and duration of immune responses and mediate cell-to-cell communication.

Depolarization: Reduction in the difference in electrical charge across a membrane (e.g., between the inside and outside of a cell or a cell compartment, such as a mitochondrion), which can affect numerous cellular functions.

Encephalopathy: Any disorder of the brain; syndrome of overall brain dysfunction that can have many different organic and inorganic causes; for example, advanced liver cirrhosis can cause hepatic encephalopathy.

Endoplasmic Reticulum (ER): An organelle found in eukaryotic cells that forms an interconnected network of membrane-enclosed sacs or tube-like structures and is connected with the outer membrane of the cell nucleus; the ER serves many functions, including the folding and transport of newly produced proteins that are then delivered to the *Golgi apparatus*.

Epigenetic: Pertaining to the regulation of gene expression without altering the DNA sequences; can include chemical modifications of the DNA or of the proteins (i.e., histones) around which the DNA is wound.

Golgi Apparatus: Membrane-enclosed organelle with tube-like structures that plays a role in the transport of newly produced proteins to their destination within the cell or out of the cell; the Golgi apparatus receives proteins packaged into small membrane-enclosed vesicles from the *endoplasmic reticulum* and transports them to their final destinations.

Hepatic Stellate Cell (HSC): Cell type found in the liver with several long protrusions that wrap around the *sinusoids.* HSCs play an important role in liver fibrosis; in normal liver, the HSCs are in a resting state but become activated upon liver damage, resulting in cell proliferation and secretion of collagen scar tissue.

Hepatorenal Syndrome: The occurrence of kidney failure in patients with liver disease.

Kupffer Cell (KC): Specialized immune cells (i.e., macrophages) that reside in the liver and are part of the immune system, particularly inflammatory responses; they play a central role in early stages of alcoholic liver disease.

reason(s) for these differences are not clear.

- *Genetics.* Both genetic and epigenetic influences govern the initiation and progression of ALD. Genome-wide association studies have identified specific genetic markers (i.e., single-nucleotide polymorphisms) in genes encoding alcohol-metabolizing enzymes, cytokines, and antioxidant enzymes that are related to the progression of ALD (Stickel and Hampe 2012). Most recently, an allele of patatin-like phospholipase domain-containing protein 3 (PNPLA3 I148M), a triglyceride-degrading enzyme, was identified as an independent risk factor for alcoholic cirrhosis (Anstee et al. 2016; Burza et al. 2014).

- *Nutritional Factors.* Dietary fat is a macronutrient and dietary modifier for ALD. In rodents, dietary saturated fat seems to protect against alcohol-induced liver damage, whereas dietary unsaturated fat that is enriched in linoleic acid reportedly promotes such damage (Kirpich et al. 2016).

- *Drugs.* Alcohol and other drugs (including prescription medications, over-the-counter agents, and illicit drugs) interact to enhance hepatotoxicity. For example, as described earlier, acetaminophen hepatotoxicity can be exacerbated by alcohol abuse.

- *Obesity.* Population-based studies have indicated a significant correlation between the risk of liver damage and alcohol consumption in people with a high body mass index (Ruhl and Everhart 2005).

- *Smoking.* Cigarette smoking can adversely affect certain hepatic functions and is associated with higher risk of alcoholic cirrhosis in humans (Klatsky and Armstrong 1992).

Glossary *(continued)*

Leukocytes: White blood cells that make up the immune system; they are found throughout the body and include five main types, one of which are the monocytes/*macrophages*.

Lipophagy: The selective *autophagy* of lipid droplets.

Macrophage: A type of *leukocyte* that act as phagocytes—that is, they ingest and destroy bacteria, foreign particles, and dead or diseased cells or other degenerating material in the body; they also release signaling molecules involved in the immune response.

Parenchymal Cells: The distinguishing or specific cells of an organ or gland that are contained in and supported by the connective tissue; parenchymal cells of the liver are the hepatocytes.

Peroxisome: A membrane-enclosed organelle found in many eukaryotic cells that contains various enzymes needed for the formation and degradation of hydrogen peroxide (H_2O_2); plays a role in breaking down fatty acids and detoxifying various molecules.

Portal Hypertension: Elevated blood pressure in the blood system supplying the liver (i.e., portal system); occurs in cirrhosis and other conditions that cause blockage of the portal vein.

Promoter: A region of DNA located in front of a gene that regulates and marks the starting point for gene transcription.

Proteolytic: Pertaining to or causing the breakdown of proteins (i.e., proteolysis).

Reactive Oxygen Species (ROS): Highly reactive chemical molecules containing oxygen, such as hydrogen peroxide or superoxide, that are formed as natural byproducts of various metabolic reactions but whose levels can increase during times of environmental stress; excess levels of ROS can damage macromolecules (e.g., proteins or DNA).

Sinusoid: A small, thin-walled blood vessel characterized by open pores between the cells lining the vessel, allowing small and medium-sized proteins to readily enter and leave the bloodstream; in the liver, *Kupffer cells* are located inside the sinusoids.

Space of Disse: In the liver, the small space that separates the walls of the *sinusoids* from the *parenchymal cells* (i.e., the hepatocytes).

Ubiquitin-Proteasome System: A system comprising multiple components that identifies and degrades unwanted proteins in all cells; is involved in cell growth and differentiation, cell death (i.e., apoptosis), and stress and immune responses.

Vacuole: A clear space within a cell that may surround an engulfed foreign particle and may degrade or digest that particle.

- *Viral Infections.* The course of hepatitis C (HCV) and hepatitis B (HBV) viral infections is worsened in alcohol-abusing patients, causing rapid progression to fibrosis, cirrhosis, and even hepatocellular carcinoma (Szabo et al. 2006). Several common mechanisms of viral infection and alcohol-induced damage have been suggested (Zakhari 2013); however, the exact mechanisms for this rapid disease progression are not completely understood. Because viral infections such as HCV or HBV affect more than 170 million people worldwide (Gitto et al. 2014), the following section will describe this topic in greater detail.

HCV and Alcohol

HCV and alcohol are the two most widespread causes of liver disease worldwide. Almost all patients with a history of both HCV infection and alcohol abuse develop chronic liver injury. Some studies report that 16.9 percent of HCV-infection cases progress to liver cirrhosis, which is twice the prevalence of cirrhosis from alcoholic liver disease. In HCV-positive alcohol abusers, cirrhosis prevalence is even higher at 27.2 percent (Khan and Yatsuhashi 2000). A daily intake of 80 grams of alcohol increases liver-cancer risk 5-fold over that of non-drinkers, whereas heavy alcohol use by HCV-infected individuals increases cancer risk by 100-fold over uninfected heavy drinkers.

There are multiple mechanisms by which alcohol potentiates HCV-infection pathogenesis. For example, HCV proteins induce oxidative stress by binding to the outer membranes of mitochondria, stimulating electron transport and increasing the generation of cellular ROS (e.g., superoxide) (Otani et al. 2005). Coupled with the ethanol-induced depletion of the antioxidant glutathione and ROS-induced suppression of proteasome activity, this compromises cell viability (Osna et al. 2008), causing hepatocyte apoptosis (Ganesan et al. 2015; Siu et al. 2009). Ethanol-induced oxidative stress also causes mutations in the HCV genome that increase resistance to interferon (IFN) treatment, the former standard of care for HCV (Seronello et al. 2011). Only 9 percent of HCV-infected people with alcohol use disorder respond to IFNα therapy. There currently is little information on whether heavy drinking affects the outcomes of HCV treatment with the new generation of antiviral agents (Keating 2015).

Ethanol metabolites appear to stimulate HCV replication. CYP2E1-positive hepatoma cells exposed to ethanol show an increase in HCV RNA (McCartney et al. 2008). However, this rise is only temporarily sustained (Seronello et al. 2007), because these heavily infected cells eventually die by apoptosis (Ganesan et al. 2015). The resulting cell fragments (i.e., apoptotic bodies) contain infectious HCV particles that spread the virus to uninfected cells, causing the production of proinflammatory cytokines by phagocytosing KCs (Ganesan et al. 2016). In addition to apoptotic bodies, another type of cell-derived vesicles (i.e., exosomes) that leak from dead cells enhances intracellular HCV replication in neighboring cells through an exosomal microRNA (miRNA 122). Because ethanol exposure also increases hepatic miRNA 122 levels (Bala et al. 2012), HCV replication in problem drinkers likely is augmented (Ganesan et al. 2016).

Innate immunity is the first line of antiviral protection in the liver. HCV commandeers this line of defense, and ethanol metabolism potentiates its takeover. For example, activation of antiviral IFNβ production in liver cells occurs via the interferon regulatory factor 3 pathway, which requires participation of a protein called mitochondrial antiviral signaling protein (MAVS). HCV evades this innate-immunity protection by cleaving MAVS (Gale and Foy 2005), and ethanol metabolism further enhances this cleavage. There are other published examples of how ethanol consumption interferes with the immune response to HCV infection (Ganesan et al. 2015; Siu et al. 2009). Thus, HCV and ethanol synergize in thwarting protective mechanisms that include both innate and adaptive immunity by increasing oxidative stress in liver cells, thereby accelerating the onset of cell death and facilitating the spread of the virus.

Current Management of ALD

There are no FDA-approved therapies for treating patients with ALD. The following therapies currently are used for optimal ALD management.

Abstinence

Drinking cessation is considered the most effective therapy in patients with ALD. Abstinence from alcohol not only resolves alcoholic steatosis but also improves survival in cirrhotic patients (Sofair et al. 2010). The effectiveness of abstinence is enhanced when it is combined with lifestyle modifications (e.g., behavioral interventions and dietary alterations) that are supervised by a nurse, primary care physician, or gastroenterologist/hepatologist (Addolorato et al. 2016; Pavlov et al. 2016).

Natural and Artificial Steroids

Corticosteroid treatment, including the use of prednisolone, has been the most extensively used form of therapy, especially for moderate to severe alcoholic hepatitis, based on their ability to suppress the immune response and proinflammatory cytokine response (Mathurin et al. 1996, 2013; Ramond et al. 1992). However, outcomes with steroids have been variable (Thursz et al. 2015). Current guidelines suggest discontinuation of therapy if there is no indication of a decrease in bilirubin levels by day 7 of treatment (European Association for the Study of the Liver 2012).

Nutritional Supplements

Nearly all patients with severe alcoholic hepatitis and cirrhosis are malnourished

and their degree of malnutrition correlates with disease severity and complications, such as variceal bleeding, ascites, infections, encephalopathy, and hepatorenal syndrome (Halsted 2004; Mendenhall et al. 1995; Stickel et al. 2003). Deficiencies in micronutrients (e.g., folate, vitamin B6, vitamin A, and thiamine) and minerals (e.g., selenium, zinc, copper, and magnesium) often occur in ALD and, in some instances, are thought to be involved in its pathogenesis (Halsted 2004). According to the current guidelines of the American Association for the Study of Liver Diseases, all patients with alcoholic hepatitis or advanced ALD should be assessed for nutritional deficiencies and treated aggressively with enteral nutritional therapy. A protein intake of 1.5 grams per kilogram bodyweight and 35 to 49 kcal per kilogram bodyweight per day is recommended for ALD patients (Frazier et al. 2011). Micronutrient supplementation should be considered if deficiencies are detected. Supplementation with one such micronutrient, zinc, has been shown to be therapeutic in animal models of alcoholic liver injury. Mechanistic studies have revealed that its protection is mediated by blocking or attenuating most mechanisms of liver injury, including increased gut permeability, oxidative stress, increased TNF production, and hepatocyte apoptosis (Mohammad et al. 2012). The few clinical studies conducted to date suggest that zinc supplementation could be an effective therapeutic approach for humans because liver function of ALD and HCV patients improved with 50 mg of elemental zinc (Mohammad et al. 2012).

Liver Transplantation

This procedure remains the standard of care for patients with end-stage liver disease. Some patients with ALD are not listed for the replacement of their own liver by a donor organ (i.e., orthotopic liver transplantation) for reasons such as continued alcohol consumption, improvement in liver function after abstinence, and a higher incidence of cancers of the upper airways and upper digestive tract. As a result, transplantation candidates with ALD often are screened for common malignancies and must undergo a formal medical and psychiatric evaluation. They also must abstain from alcohol for 6 months before being considered for liver transplantation. Data show that fewer than 20 percent of patients with histories of alcohol use as the primary cause of end-stage liver disease receive liver transplants (Lucey 2014). However, patient and organ survival is excellent in this patient population, with considerable improvement in their quality of life (Singal et al. 2012, 2013). Following transplantation, ALD patients return to consuming alcohol at rates similar to those transplanted for other reasons, although ALD patients may consume greater amounts (Bergheim et al. 2005). Because all transplant recipients exhibit increased levels of alcohol use over time, post-transplant interventions are deemed extremely valuable in supporting patients to maintain abstinence (Donnadieu-Rigole et al. 2017).

Unconventional and Herbal Remedies

Patients often turn to natural and herbal therapies based on their potential for hepatoprotection. A U.S. survey revealed that 41 percent of patients with liver disease used some form of complementary and alternative medicine. An extract of milk-thistle seeds (silymarin) and garlic were reported as the most commonly used herbs for liver disease, followed by ginseng, green tea, gingko, echinacea, and St. John's wort (Strader et al. 2002). As indicated in a recent review (Kim et al. 2016), these and other natural medicines, including betaine, curcumin, fenugreek seed polyphenol, LIV-52, vitamin E, and vitamin C, have shown efficacy in experimental models of alcoholic liver injury but must pass the rigors of large randomized, controlled clinical trials.

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Nature and Treatment of Comorbid Alcohol Problems and Post-Traumatic Stress Disorder Among American Military Personnel and Veterans

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Many service members and veterans seeking treatment for alcohol problems also have post-traumatic stress disorder (PTSD). This article considers the effectiveness of treating alcohol problems and PTSD simultaneously. The authors begin by summarizing the extent of excessive alcohol use among military service members and veterans. They then explore the relationship between combat exposure and subsequent alcohol use; identify and briefly describe evidence-based treatments for alcohol problems and PTSD, separately; and review research on the effects of single treatments for both PTSD symptoms and alcohol use.

Key words: Alcohol use, abuse and dependence; problematic alcohol use; post-traumatic stress disorder; stress; military; veterans; combat exposure; treatment

Many service members and veterans seeking treatment for alcohol problems have experienced the life-threatening stress of combat, many have post-traumatic stress disorder (PTSD), and many service members and veterans seeking treatment for PTSD have alcohol or other substance problems. Sensitivity to these issues can influence how a therapist relates to the patient and also has possible implications for developing a treatment strategy (U.S. Department of Veterans Affairs [DVA] 2010). Historically, clinicians have been concerned that patients need to reduce or resolve substance abuse before PTSD treatment can be successful. But research is showing that both disorders can be treated simultaneously. Here, we assess the scope of the problem and examine treatments that can be effective for treating each disorder individually as well as in tandem.

Alcohol Problems in Active-Duty Military Personnel and Veterans

For more than 30 years the Department of Defense (DoD) has conducted recurrent surveys to determine rates of excessive alcohol use among active-duty personnel. The most recent of these (DoD 2013) revealed wide prevalence of "binge" drinking, defined as consuming 5 or more drinks for males or 4 or more drinks for females on a single occasion. An analysis of this survey by Bray and colleagues (2013) found that across the U.S. Armed Services 33 percent of personnel reported binge drinking during the 30 days preceding the survey, with considerable variation in rates across military departments (Army, 34 percent; Navy, 38 percent; Marines, 49 percent; and Air Force, 24 percent). Twenty percent of male and female active-duty personnel engaged in heavy drinking, which was defined as binge drinking at least once a week during the past 30 days (Bray et al. 2013).

Less is known about alcohol use problems among veterans. One analysis examined results from the National Survey on Drug Use and Health from 2004 through 2010 (Golub et al. 2013). The study compared veterans ages 21 to 34 with non-veteran peers matched on age and gender. The two groups were quite similar in their rates of alcohol use disorder (AUD) in the past year (15 percent); "binge" drinking (44

percent), defined as consuming 5 or more drinks on at least one occasion during the past 30 days; and heavy drinking (14 percent), defined as binge drinking on 5 or more days during the past 30 days (Golub et al. 2013).

Combat Stress and Alcohol Misuse

As of September 30, 2013, 2.6 million service members had been deployed to Operation Enduring Freedom, Operation Iraqi Freedom, and Operation New Dawn since 2001 (DVA 2013). Due to high rates of combat and blast exposure, healthcare providers within the DOD and the U.S. Departments of Veterans Affairs (VA) are offering services to increasing numbers of veterans and active-duty personnel returning with complex mental and physical health problems (Hoge et al. 2004, 2008).

PTSD is the most common mental health diagnosis for the nearly 1 million U.S. veterans who served in Iraq and Afghanistan between October 1, 2001, and September 30, 2013, and who accessed services through the Veterans Health Administration (VHA) (DVA 2013). Nineteen percent of those who have served in Iraq and Afghanistan develop PTSD within a year of their return to the United States (Tanielian and Jaycox 2008).

Symptom clusters for PTSD as defined by the *Diagnostic and Statistical Manual of Mental Disorders* (DSM–5) are illustrated in the accompanying textbox (American Psychiatric Association 2013). Based on the previous DSM–IV criteria (American Psychiatric Association 1994), rates of PTSD in returning service members vary somewhat as a function of the method for collecting data, with results from screening instruments suggesting a range of 10 to 20 percent (Milliken et al. 2007; Seal et al. 2007; Sundin et al. 2010). Structured clinical interviews yield a somewhat lower but still disconcerting PTSD rate of 7 to 10 percent (Erbes et al. 2007). Among individuals with a history of traumatic brain injury, rates of PTSD seem to escalate to 33 to 39 percent (Carlson et al. 2011). An analysis of VA healthcare statistics from October 7, 2001, to March 31, 2008, showed that PTSD was the most prevalent psychiatric diagnosis, affecting approximately 21.5 percent of patients (Cohen et al. 2010). As of 2014, VA public health data suggest that 30 percent of veterans of military service in Afghanistan and Iraq seeking VA care have PTSD.

Substance use disorders (SUDs) are another common reason for seeking mental health services. PTSD and substance use disorder frequently co-occur (McCauley et al. 2012). As illustrated by the figure, a consistently increasing percentage of veterans who have received VHA care, regardless of when they served in the military, have

DSM–5 Post-Traumatic Stress Disorder Symptom Clusters

Re-experiencing

- Recurrent, intrusive, and distressing memories, images, thoughts, and/or perceptions
- Recurrent distressing dreams
- Dissociative reactions (flashbacks)
- Marked psychological and/or physiological response to cues that symbolize or resemble the event

Avoidance

- Of memories, thoughts, or feelings about the event
- Of reminders of the event

Negative Alterations in Cognitions and Mood

- Inability to recall an important aspect of the event
- Persistent, exaggerated negative beliefs or expectations about self, others, or the world
- Persistent negative emotional state
- Diminished interest/participation in significant activities
- Detachment/estrangement
- Persistent inability to experience positive emotions

Marked Alterations in Arousal and Reactivity

- Irritability/outbursts or anger
- Reckless or self-destructive behavior
- Hypervigilance
- Exaggerated startle response
- Difficulty concentrating
- Difficulty falling or staying asleep or restless sleep

been diagnosed as having comorbid PTSD and SUD. In fiscal year 2013, 26.5 percent of VA patients with a diagnosis of PTSD also had SUDs. It is also worth noting that the number of veterans with both conditions has increased by 76 percent since fiscal year 2008, a rate exceeding the increase in prevalence for PTSD (52.3 percent) or for SUD (33.1 percent) alone (Program Evaluation and Resource Center, VA Medical Center, Palo Alto, CA. January 2014, personal correspondence).

Individuals with AUD and PTSD tend to have greater risks for other psychiatric disorders, respond less favorably to interventions for the AUD, and are at increased risk of relapse to problematic drinking (Torchalla et al. 2012).

Relationship between PTSD and Substance Misuse

Citing data from the National Comorbidity Survey (Kessler et al. 1995), Jacobsen and colleagues (2001) observed that, when they exclude nicotine dependence, the psychiatric condition most likely to co-occur among men with PTSD was alcohol abuse/dependence. Among women with PTSD, alcohol abuse/dependence was the second most common mental health combination, with depression or anxiety being the most common. Study investigators proposed two reasons for this association. For one, PTSD may follow alcohol misuse, because people who misuse alcohol may tend to place themselves in situations that involve increased risk for trauma and subsequent PTSD; alcohol may also sensitize them to developing a PTSD reaction in response to trauma. Second, alcohol misuse may follow PTSD by playing a "self-medication" role to dampen the hyperarousal component of PTSD. Interestingly, Jacobsen and colleagues further comment that the neuronal arousal associated with alcohol withdrawal may be augmented by PTSD-linked hyperarousal and may make individuals with PTSD more likely to return to drinking than those who need only cope with the arousal associated with acute drinking cessation.

A study of patients receiving treatment for SUD indicated that improvements in PTSD symptoms over 2-week periods during the 26-week study were associated with decreases in cocaine and opioid use and possibly reductions in alcohol use (p=.056) (Ouimette et al. 2010). These findings support the theory that people with PTSD use drugs and alcohol to self-medicate. However, the study sample was small and consisted solely of patients currently in treatment. Hence, the finding may not generalize well to a random sample of people with both conditions.

Combat and Subsequent Alcohol Misuse

Milliken and colleagues (2007) conducted the largest study of combat's influence on mental health

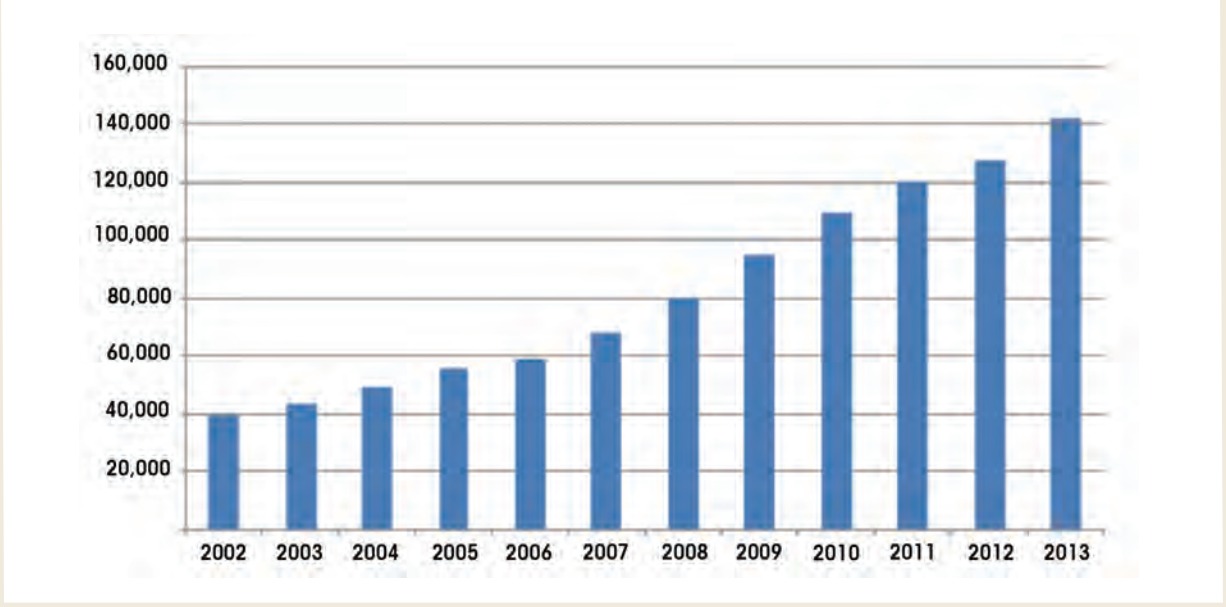

Figure Veterans receiving care in the Veterans Health Care Administration for comorbid PTSD and substance use disorder by year.

SOURCE: Program Evaluation and Resource Center, VA Medical Center, Palo Alto, CA. January 2014, personal correspondence.

functioning of service members. They analyzed responses on the Post Deployment Health Reassessment (PDHRA), a clinical and self-report measure that includes questions related to combat stress and alcohol problems. Soldiers completed the survey 3 to 6 months after redeployment to combat service in Iraq. More than 88,000 soldiers completed both this survey and a related-content survey administered to them at redeployment. Nearly 70 percent of respondents reported traumatic combat experiences, and around 50 percent of active personnel and reserve component personnel reported that at some time they feared that they would be killed. Nine percent of active-duty respondents and 14 percent of U.S. Army Reserve and National Guard soldiers endorsed at least three of four PTSD screening items. The PDHRA also included a two-item screen for alcohol problems; 12 percent and 15 percent, respectively, of the active duty and reserve component respondents endorsed at least one such item. Yet only 0.4 percent of the sample reported having been referred to substance abuse treatment.

Data from the large-scale Air Force Community Assessment Survey conducted in the spring of 2008 demonstrated a relationship between the total number of deployments and cumulative time deployed with the subsequent likelihood of an Air Force member becoming a problem drinker. Each additional year of deployment increased the risk of becoming a problem drinker by 23 percent, and each additional deployment period increased the risk by 14 percent. Interestingly, the risk of becoming a problem drinker was not associated with how recently a soldier was deployed (Spera et al. 2011).

Another survey (Santiago et al. 2010) given to soldiers 3 to 4 months after returning from deployment to Iraq found that 27 percent scored positive for alcohol misuse, as shown by endorsement of at least one of two screening items on the Two-Item Conjoint Screen. Soldiers exposed to more intense combat were also more likely to score positive on the alcohol misuse screen. Another study found that deployments involving combat exposure also were associated with post-deployment heavy weekly drinking, binge drinking, and alcohol-related problems among active duty and reserve component personnel (Jacobson et al. 2008).

Alcohol problems among military personnel exceed those of civilian populations in part because of demographic differences in age, gender balance, and education level among military populations. However, other factors contribute to the risk of alcohol misuse among service members, including deployment stress, combat exposure, and PTSD. Reflecting this, an increasing number of veterans are being treated by the VHA for comorbid SUDs and PTSD. The challenge is to implement treatments found to be effective for both conditions, as well as to continue to develop more effective interventions.

Effective Alcohol Treatments

Psychotherapies

Several psychosocial interventions for treating alcohol problems have shown strong evidence for effectiveness. The VHA's policy is that patients with alcohol problems have access to at least two of the following:

- *Cognitive–Behavioral Therapy for Relapse Prevention,* which assists patients in identifying internal and external stimuli that prompt drinking, and in learning skills and alternative ways of thinking to cope with these cues and avoid alcohol use.
- *12-Step Facilitation,* which promotes participation in Alcoholics Anonymous and working the steps of the program. It employs a treatment manual with activities and homework assignments and is conducted in a one-on-one counseling relationship.
- *Community Reinforcement Approach,* which helps patients establish a strong environmental support system to help sustain sobriety.
- *Substance Use Disorder–Focused Behavioral Couples Counseling/Family Therapy,* which emphasizes the participation of significant others in treatment. Sessions focus on improvements in communication and interactional patterns of the couple or family, especially as they relate to drinking.
- *Motivational Enhancement Therapy,* which builds on principles of motivational interviewing. It employs treatment processes that reflect the patient's level of readiness for change.

For detailed descriptions of these treatments, see Finney and Moos (2002).

Pharmacotherapies

The *VA/DoD Clinical Practice Guideline for Management of Substance Abuse Disorders* (DVA and DoD 2010) offers the following recommendations for the pharmacological management of alcohol dependence:

- Oral naltrexone should be routinely considered in conjunction with addiction counseling.
- Injectable naltrexone is effective in conjunction with addiction counseling when the patient is willing to accept monthly injections.
- Acamprosate should routinely be considered in conjunction with addiction counseling as an alternative to naltrexone.
- Disulfiram should only be used when the goal is abstinence.

A recent meta-analysis reinforces the value of pharmacological treatment for alcohol abuse (Jonas et al. 2014). The analysis found that both acamprosate and oral naltrexone were associated with reductions in how often patients returned to drinking with no significant differences between the two drugs in controlling alcohol consumption. The authors emphasize that less than one-third of people with AUD receive treatment, and only a small percentage of these patients (less than 10 percent) receive medications to assist in reducing alcohol consumption. A companion editorial by Bradley and Kivlahan (2014) emphasizes the importance of integrating psychopharmacological and psychosocial interventions in treating AUD and of integrating these treatments into primary care services.

Effective PTSD Treatments

Psychotherapies

In 2008, the Institute of Medicine conducted a comprehensive review of outcomes on existing PTSD treatments. The report determined that "evidence is sufficient to conclude the efficacy of exposure therapies in the treatment of PTSD" (chapter 4, p. 97). Shortly thereafter, the VHA began promoting the use of two trauma-focused, manualized cognitive–behavioral psychotherapies (Karlin et al. 2010): Prolonged Exposure (PE; Foa et al. 2007) and Cognitive Processing Therapy (CPT; Resick and Schnicke 1992). Both interventions demonstrated efficacy in randomized controlled trials with civilians (Foa et al. 1999, 2005; Resick et al. 2002) and veterans (Monson et al. 2006; Schnurr et al. 2007). Evidence for both psychotherapies for veterans and active duty service members has continued to accumulate (Chard et al. 2010; Goodson et al. 2013; Rauch et al. 2009; Tuerk et al. 2011; Walter et al. 2014). Treatment effectiveness seems to persist following treatment (Resick et al. 2012). The goals of both interventions are to reduce avoidant coping; purposefully confront traumatic memories; and modify maladaptive, trauma-related thoughts. Nevertheless, the rationales and procedures of the two treatments differ significantly.

PE includes four essential elements: psychoeducation, in-vivo exposure, imaginal exposure, and in-session discussion following imaginal exposures to facilitate emotional processing and corrective learning (Foa et al. 2007). In the initial phase of treatment, therapists present information about common reactions to trauma, factors that maintain PTSD symptoms, conceptual bases for interventions, and breathing retraining. They reinforce this information with standardized handouts. In-vivo exposure procedures require patients to progressively confront situations and stimuli (including sights and sounds) that they previously avoided, because they associated the situations and stimuli with their traumatic memory. Imaginal exposure asks patients to verbally revisit their traumatic memory and emotionally process the experience to bring about corrective learning and habituation in later treatment sessions. Imaginal exposure begins in the third session and is followed by a collaborative "processing" discussion, typically involving support, normalization of experience, and discussion about key perceptions linked with the traumatic experience. In the mid-to-later phases of PE, imaginal exposure focuses on the most distressing aspects of the index trauma, or "hotspots." Patients typically complete 90-minute sessions once a week, with most patients requiring 8 to 15 sessions for treatment completion. Clinicians audiotape sessions and require patients to review the tapes between appointments.

CPT (Resick 2001) consists of 12 treatment sessions that include cognitive interventions in either a group or individual format. During the initial sessions, patients receive psychoeducation about PTSD and underlying information processing frameworks, complete written assignments to clarify the personal significance of traumatic experiences, and identify problematic trauma-related beliefs or "stuck points." During the middle stages of CPT, patients learn to use a variety of worksheets to identify linkages between events, thoughts, and feelings; to produce and repeatedly read detailed accounts of their most traumatic experience(s), with an emphasis on experiences associated with traumatic events; and to begin challenging their stuck points with support and assistance from the therapist. Therapists use Socratic questioning to teach patients to examine and modify relevant maladaptive cognitions that maintain PTSD symptoms. They assign patients daily worksheets for home practice. In the final phases of the treatment, therapists aim to modify beliefs in five key domains: safety, trust, power/control, esteem, and intimacy. Patients consolidate their treatment gains in the concluding session.

Pharmacotherapies for PTSD

A wide range of psychotropic medications have been explored for treating PTSD. *VA/DoD Clinical Practice Guidelines for the Management of Post-Traumatic Stress* (DVA and DoD 2010) most strongly recommend selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs). The high blood pressure medication, prazosin, has been increasingly used to treat PTSD, but the *VA/DoD Guidelines* only recommend this as an adjunctive therapy for nightmares associated with the disorder.

Treating Co-Occurring PTSD and AUD

Psychosocial Treatments

Few well-controlled studies have assessed the efficacy of trauma-focused, cognitive–behavioral treatments, such as PE or CPT, in patients dually

diagnosed with PTSD and SUD or AUD. This likely reflects a bias toward excluding patients with dual diagnosis from clinical trials because of traditional clinical concerns that concurrent misuse of substances could diminish the benefits of PTSD treatment (Riggs et al. 2003), or that exposure-based interventions might lead to relapse or to escalation of substance misuse (Hien et a. 2004; McGovern et al. 2009).

Taken in concert, the literature on treatments for co-occurring PTSD and AUD indicates that dually diagnosed patients can tolerate and benefit from psychotherapies specifically formulated to address trauma and PTSD. In fact, a forthcoming meta-analytic *Cochrane Review* that consolidates outcomes from over 1,400 participants (Roberts et al. 2012) concludes that combined, trauma-focused interventions meant to address both PTSD and AUD or SUD perform as well as or better than usual treatments in reducing symptoms of both disorders. Nonetheless, there is room for much improvement in this area, and debate continues about how best to engage and treat this complex population (Foa et al. 2013*b*; Najavits 2013). Additional research also is needed to determine optimal methods for assisting veterans or service members with co-occurring conditions and retaining them in treatment.

Several descriptions and reports also have been published on the use of present-focused, skills-based psychotherapies specifically targeted to the needs of dually diagnosed patients. Of these, Seeking Safety, a manualized cognitive–behavioral treatment that can be delivered to individuals or groups, has received the greatest attention (Najavits and Hein 2013; Najavits et al. 1998). Each session includes components for reducing the effects of trauma ("safety") and diminishing substance use and follows the same structure: a "check-in" where therapists gather information on maladaptive or "unsafe" behaviors and coping skills among patients; a review of a quotation that captures the essence of the current session's topic; a review of handouts to facilitate discussion and skills practice linked with the topic; and a "check-out" asking patients to commit to between-session skills implementation. The full protocol includes sessions dealing with 25 different topics, including promoting safety, taking back power from PTSD, healing from anger, creating meaning, and detaching from emotional pain or grounding. The protocol does not include any exposure-based exercises.

Although participants have generally accepted Seeking Safety and 22 reports have found mostly beneficial outcomes with PTSD-related symptoms and alcohol or substance use (Najavits and Hien 2013), the largest controlled trial evaluating this treatment found null results when contrasted with a health education control protocol. There is also a high rate of attrition among patients receiving Seeking Safety (Hien et al. 2009). The few studies of Seeking Safety conducted with veterans have included small sample sizes of not more than 25 patients each (Cook et al. 2006; Norman et al. 2010). Seeking Safety also has often failed to outperform control conditions on outcome measures for PTSD (Boden et al. 2012) or substance use (Desai et al. 2008). It thus remains uncertain whether this treatment should be considered a treatment of choice for veterans or military service members with co-occurring PTSD and AUD. However, for those who do not choose to begin trauma-focused therapy, Seeking Safety can be an effective engagement strategy that may be sufficient to reduce symptoms for some and to act as an effective preparation for trauma-focused treatment for others.

Psychopharmacologic Treatments

Less is known about the clinical value of combining pharmacological treatments with psychosocial treatments for co-occurring PTSD and alcohol dependence (Ravelski et al. 2014), but an article from Foa and colleagues (2013*a*) suggests that combining prolonged exposure therapy and oral naltrexone may be effective in reducing the percentage of drinking days in this population.

There are no direct contraindications to prescribing patients with PTSD any of the pharmacotherapeutic agents recommended in the *VA/DoD Clinical Practice Guidelines for the Management of Substance Use Disorders* (DVA and DoD 2009) for the treatment of AUD. However, certain other conditions commonly associated with PTSD and alcohol dependence may preclude use of some pharmaceuticals. For example, if patients have sustained significant liver damage subsequent to co-existing PTSD and alcohol dependence, they should avoid naltrexone and disulfiram. In addition, intravenous substance abuse may contribute to renal disease, which may complicate the use of naltrexone or acamprosate. Findings that PTSD itself may predispose patients to coronary artery disease (Edmondson et al. 2013) suggest that a careful cardiac evaluation be performed before prescribing disulfiram. Finally, chronic pain frequently co-occurs with both PTSD and substance abuse, and naltrexone may interfere with currently effective pain control regimens that rely on opioid agents.

Benzodiazepines are an effective treatment for relieving symptoms of alcohol withdrawal. However, the VA/DoD PTSD guidelines (DVA and DoD 2010) raise concerns about using benzodiazepines to treat PTSD, because these agents have not been shown to be effective as single-channel treatments for PTSD and might even complicate PTSD's course. Although this is not an absolute contraindication to the acute use of benzodiazepines for alcohol detoxification, it does call for careful monitoring of any ongoing benzodiazepine use. Along these same lines, clinicians should consider the severe physiological stress that can be associated with future states of intoxication and withdrawal when they choose a treatment for patients with

combined PTSD and alcohol dependence who are prone to withdrawal. For example, use of a tricyclic antidepressant to treat PTSD (not a top recommendation in the VA/DoD PTSD guidelines (DVA and DoD 2010), but a treatment that can be effective for PTSD) may lower seizure threshold in a patient prone to cycles of alcohol relapse and withdrawal. Also, prazosin, which was originally marketed as an antihypertensive, could cause hypotension in medically unstable patients, including during states of dehydration or in patients in alcohol withdrawal.

Although the 2010 VA/DoD Clinical Practice Guideline for the Management of Post-Traumatic Stress lists topiramate as having no demonstrated benefit for PTSD, a pilot study suggests that this anticonvulsant may have some value for treating both PTSD and AUD (Batki et al. 2014). However, topiramate cannot be recommended currently as a first- or second-line treatment for either disorder.

Conclusion

AUD and PTSD are common and severe problems in veterans and military service members and merit intervention. Fortunately, a number of psychological treatments and medications have been demonstrated as effective for each problem and should be incorporated into clinical practice whether the conditions occur independently or together. When AUD and PTSD occur in the same patient, they should generally be addressed simultaneously, either in closely coordinated or integrated care. Contrary to earlier clinical concerns that substance abuse should be reduced or resolved before treatment for PTSD, it seems that for most patients the treatments can be performed simultaneously with good results. In fact, clinical experience and emerging research suggests that it is best to combine modalities and targets within a comprehensive treatment plan. As in other areas of clinical practice, clinicians should systematically and frequently monitor patient progress to determine if some modification may be needed in the treatment protocol. It also is important to assess the patient's medical status before prescribing pharmacotherapies. In many cases, especially those involving alcohol dependence, adjunct medications will prove useful.

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Advances in Substance Abuse Prevention and Treatment Interventions Among Racial, Ethnic, and Sexual Minority Populations

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Substance abuse research among racial, ethnic, and sexual minority populations historically has lagged behind that conducted with majority samples. However, interesting and potentially important advances in prevention, brief interventions, and treatment have been made in the last few years, at least among some minority populations, such as American Indian youth. New prevention efforts have focused on point-of-sale interventions for alcohol, as well as on family-unit interventions designed with subpopulation cultural values in mind. In addition, previously established evidence-based and culturally relevant interventions are being combined with computer technology. Empirical data support using brief interventions with patients of color in medical settings, capitalizing on teachable and reachable moments during a physical trauma or other health crisis. Finally, use of empirically supported treatment may be helpful, with a caveat that these interventions must appropriately match cultural traditions and respect the values of the clients. More research clearly is needed, especially among certain minority populations in the United States. A greater emphasis should be placed on developing novel, culturally grounded interventions in partnership with communities, in addition to adapting existing mainstream interventions for use by other cultures.

Key words: Alcohol use, abuse, and dependence; alcohol research; race; ethnicity; minorities; ethnic minorities; sexual minorities; prevention; intervention; treatment; point of sale intervention; family intervention; computer technology; cultural traditions; culturally grounded intervention

Historically, prevention and treatment intervention research rarely has been conducted with racial and ethnic or sexual minorities as its principal focus; this also holds true for the alcohol and other drug abuse field. The lack of credible research has been one source of the disparities in substance abuse and its consequences found among many of these groups. Fortunately, advances recently have been made in preventing, intervening in, and treating substance abuse among traditionally underserved racial, ethnic, and sexual minority subpopulations. This article reviews some of these advances, focusing on alcohol abuse but also including abuse of other drugs or substance abuse in general, as appropriate. The article also will suggest next steps for research in this area.

Challenges in Addressing Prevention and Treatment for Minority Populations

Many minority populations in the United States face well-documented challenges, such as higher-than-average rates of poverty, homelessness, and incarceration, which may contribute to increased rates of alcohol use disorder as well as other substance use disorders. A less concrete factor influencing prevention and treatment is that minorities often face stereotypes in the general population. Such stereotypes foster biased behavior toward minority groups, which may promote alcohol and other drug abuse and create greater levels of anxiety among group members themselves (Blume et al. 2012). Such factors also are likely to affect whether members of minority groups decide to seek treatment and how they experience treatment if they do (for a review of access to treatment studies, see Schmidt in this issue).

Cultural background also figures into how minority populations respond to treatment and prevention efforts. Differences in worldviews, cultural traditions, and upbringing mean that not all groups may respond to an intervention that has demonstrated success in the general population (Taylor 2003). Certain groups also face specific challenges. For treatment to be effective, providers need to identify those challenges and offer appropriate interventions. For example, American Indian (AI) and Alaska Native (AN) populations face high rates of alcohol abuse among youth (SAMHSA 2014), and relatively easy access to alcohol may be one of the contributing factors. Thus, in one study (Lynne-Landsman et al. 2015) about 75 percent of all outlets tested sold alcohol to young-appearing AI buyers at least once. Other research confirmed that underage AI youth may obtain alcoholic beverages from stores both on and near reservations either directly through illegal sales to minors or indirectly through purchases by adult friends (Lee et al. 2015). Prevention efforts aimed at lowering sales of alcohol to minors therefore could be effective for these groups. For example, Moore and colleagues (2013) demonstrated that a reward-and-reminder underage drinking prevention program in convenience stores could reduce alcohol sales to minors near rural reservations.

Recent research focused on prevention and treatment efforts for minorities has suggested that feeling safe in the environment both inside and outside of treatment centers plays a pivotal role in the success of interventions. As is discussed below, when a group's basic needs are met, group members are more likely to cut back on drinking (Larimer et al. 2009). Furthermore, when they feel secure—that is, understood culturally and not threatened—they express deeper satisfaction with treatment or prevention programs and may be more likely to continue participating (Guerrero 2013). In some cases, adapting empirically proven treatment methods is sufficient in helping clients feel safe; but in others, novel, culturally centered approaches may prove useful.

Advances in Understanding the Treatment Environment

Various studies have highlighted the importance of a safe environment for positive treatment outcomes among clients from racial, ethnic, and sexual minority groups. The groundbreaking Housing First study demonstrated that a safe housing environment alone was sufficient to improve substance-use outcomes and reduce public health costs in people with severe alcohol problems, including many homeless people of color (Larimer et al. 2009). A more recent data analysis found that motivation to change predicted improved alcohol-use outcomes 2 years after the Housing First intervention, whereas attending abstinence-based treatment did not (Collins et al. 2012).

The prevention and treatment environment also affect substance abuse treatment outcomes through the therapeutic working alliance—that is, the working relationship that clients believe they have with their therapists. Positive working alliances have been found to predict successful treatment engagement and completion (Meier et al. 2005). Davis and Ancis (2012) pointed out that most studies investigating the working alliance in treatment have been conducted with predominately White patient samples. However, they did identify three important factors that affect the working alliance among clients of color. First, culturally responsive treatment has been positively associated with improvements in

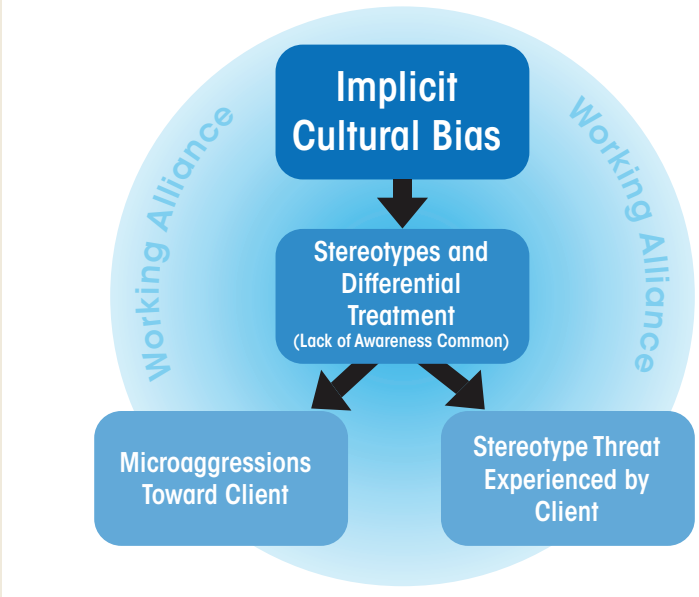

Figure 1 Implicit bias and its threat to working alliance. All people, including treatment professionals, are affected by implicit biases transmitted within our culture that may escape our personal awareness. Implicit bias makes the commission of microaggressions by staff and the experience of stereotype threat by minority clients more likely. This potentially harms the working alliance and undermines treatment outcomes.

the working alliance. Second, in their interactions with both counselors and other treatment staff, clients of color encounter biased beliefs and attitudes, which often are the result of stereotyping. Third, poor working alliances frequently are a function of how often a client in therapy experiences microaggressions—commonly experienced insults, put-downs, or messages of exclusion stemming from stereotypes associated with minority-group membership—and of a client's perceptions of a therapist's low cultural competence.

Microaggressions correlate with alcohol abuse and greater anxiety (Blume et al. 2012). Thus, they may foster an environment conducive to alcohol problems and also may undermine the treatment environment and the working alliance. Microaggressions occur in the context of culturally implicit bias—that is, cultural biases ingrained in the social order that perpetuate stereotypes and prejudices often expressed automatically and without awareness by members of the social order (figure 1). Mental health professionals may direct microaggressions toward their clients automatically and unwittingly. Microaggressions also may result from programmatic or institutional cultural insensitivity toward clients (Sue et al. 2007). Interestingly, clients of color interpret the common lack of discussion in treatment concerning bias and prejudice and their links to substance-use behavior as a microaggression (Burris 2012).

Stereotyping also may influence substance-use and treatment outcomes by increasing the risk of stereotype-threat situations, in which minority members find themselves at risk for fulfilling a commonly held group-based stereotype (e.g., African Americans in academic situations where they are expected to perform poorly) (Steele and Aronson 1995). These situations place significant stress on minority-group members that can affect both physiological responses (e.g., blood pressure) (Blascovich et al. 2001) and cognitive function, including in substance abusers (Cole et al. 2006; Looby and Earleywine 2010). As an example, AI/AN clients often are stereotyped by the firewater myth, a belief that Native Americans cannot tolerate or regulate the ingestion of alcohol and will lose behavioral control if they drink any alcohol. AI/AN clients could experience stereotype- threat situations that may adversely affect treatment outcomes when treatment programs or professionals (perhaps unwittingly) communicate an understanding of addiction that aligns with the assumptions of the firewater myth.

The therapist is only one source of stereotyping and microaggression. The working alliance transcends the client–therapist relationship and includes the positive or negative impacts of institutional climate on clients. Indeed, discussions concerning prejudice and homophobia and their links to substance abuse have largely been ignored until very recently.

Research also has demonstrated that the cultural climate of treatment is a critical factor influencing treatment outcomes. Thus, increased cultural competence among treatment-center staff has been shown to contribute to higher rates of treatment retention (Guerrero 2013). Similarly, improved cultural sensitivity among treatment-program managers has been positively associated with higher rates of retention and less time on waitlists before treatment admission (Guerrero and Andrews 2011). Increasing the cultural competence of treatment administrators, counselors, and treatment-center staff who interact with clients seems to be one method for improving treatment outcomes, perhaps by making it less likely that clients will experience microaggressions and stereotype-threat situations.

Matching and Molding Prevention and Treatment Interventions

In addition to evaluating the impact of the treatment environment, investigators have focused on determining which alcohol-related interventions facilitate success for minority clients. Recent studies in both prevention and treatment show that some mainstream interventions may be effective when matched with certain population subgroups in culturally appropriate ways. Moreover, their success often improves when adapted for use in different cultures.

Moving beyond such adaptations, some research suggests that creating new prevention and treatment methods with the participation of minority-group members can foster the success of interventions even more (Bermúdez Parsai et al. 2011; De las Nueces et al. 2012; Stacciarini et al. 2011; Tapp et al. 2013). Community-based participatory research (CBPR) methods, a research model that respects minority-community authority, needs, and values in the conduct of research, makes community stakeholders equal partners with scientists during all phases of project development, implementation, and dissemination. CBPR can be used to create novel interventions specifically tailored for racial and ethnic minority communities. The following sections focusing on prevention and treatment studies, respectively, demonstrate that all three approaches—matching existing methods in culturally relevant ways to the values and needs of the communities being served, adapting existing methods to different cultures, and creating new strategies with the participation of the target community—are demonstrating success in addressing alcohol problems among minority clients.

Advances in Prevention

Over the last few years, researchers have begun developing and sometimes adapting prevention programs aimed at addressing problems specific to target populations and testing the programs empirically. One promising intervention targeted the availability of alcohol to underage purchasers near AI reservations in California. The reward-and-reminder program

enlisted young-looking confederates who attempted to purchase alcohol without showing proper identification. When convenience-store clerks requested identification, they were rewarded with gift cards; when they did not, they were sent reminder letters concerning State laws about liquor sales. After two cycles of rewards and reminders, stores were completely in compliance when assessed (Moore et al. 2012).

Culturally relevant prevention programs that focus on the family rather than on individuals have been successful, because they acknowledge beliefs held by many minority cultures concerning the importance of the family (rather than the individual) as the principal unit of function (figure 2). This family-oriented approach stresses the value of interdependence and the commonly held tenet that families work together to solve the problems of individual members. These interventions generally involve family members and parent–youth dyads working in unison on various family-building strategies (e.g., family communication) and substance-use prevention program components (e.g., parental monitoring). Other approaches include completing the more traditional individualized prevention components, such as parent training (for adults) or drink-refusal skills (for youth).

One family-oriented intervention, for example, targeted mother–daughter dyads through a Web-based delivery system. The investigators found reduced substance use, improved child–parent relationships, and increased self-efficacy and refusal skills among female adolescent African Americans, Asian Americans, and Latinas (Fang et al. 2010; Schinke et al. 2011). Other examples include the Familias Unidas program with Latino youth in the juvenile justice system and their primary caretakers, which led to a drop in substance abuse as well as in high-risk sex (Prado et al. 2012). The Strong African American Families and Adults in the Making programs resulted in slower increases in alcohol consumption and intoxication (i.e., slower alcohol-use escalation) among African-American youth compared with control subjects (Brody et al. 2010, 2012).

Skill-based interventions that incorporate traditional practices to strengthen the bonds of youth to their communities and cultures also are under investigation. Komro and colleagues (2015) are conducting a promising screening, brief intervention, and referral to treatment (SBIRT) prevention trial that includes a culturally centered approach to intervention targeting the youth environment within the Cherokee Nation. A computer-based intervention that incorporates developmentally appropriate gaming and video clips to prevent substance use (Project HAWK) also is being tested among AI youth (Raghupathy and Go Forth 2012). Researchers have not yet evaluated the efficacy of these new methods. Think Smart, another school-based program that develops both traditional and mainstream cultural competence among AI participants in the later elementary school grades, was associated with lower student inhalant abuse but showed null results for other substance use (Johnson et al. 2009).

Both Project HAWK and the Think Smart program were derived from the evidence-based State-wide Indian Drug Prevention Program that features skills training to increase bicultural competence and resilience among at-risk AI youth (Schinke et al. 2000). Use of innovative skills-training interventions is a fruitful area for improving prevention programs for other groups as well. For example, the REAL skills groups that focus on various refusal skills and a group-based social-norms approach have improved outcomes in the culturally

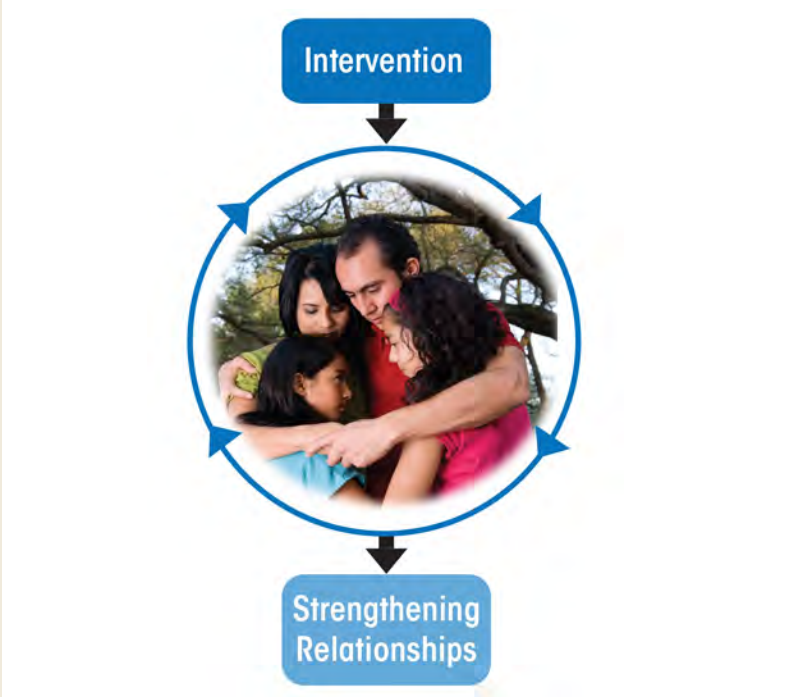

Figure 2 Family-oriented interventions. Recent advances in effective prevention programs among subpopulations have focused on family-level interventions consistent with the strong cultural values about the importance of family in collectively addressing the needs of a family member.

based prevention program for Latino youth called Keepin' It Real, especially when used with youth around the seventh grade (Marsiglia et al. 2012).

Beyond such adaptations of existing programs, other communities are experimenting with new methods developed in cooperation with minority groups themselves. For example, the Cherokee Talking Circle school-based intervention program, a uniquely Cherokee-centered strategy that includes the use of talking-circle groups as a culturally relevant approach to solving problems together, was associated with reduced substance use among AI youth. Those randomly assigned to the Cherokee Talking Circle intervention had significantly better outcomes with respect to total symptom severity, substance use, general life problems, and internal and external behavior at 3 months post-intervention than those assigned to a mainstream school-based substance abuse education program (Lowe et al. 2012).

Such CBPR among racial and ethnic minority populations has demonstrated the ethical and practical necessity of adaptive interventions that tend to evolve during the course of a research study. This can be done while preliminary outcomes are analyzed by researchers and community stakeholders and used to modify interventions (Henry et al. 2012). At the same time, some researchers have voiced concerns about overemphasizing the process of culturally adapting empirically validated mainstream interventions to the exclusion of other methods. One experienced AI research team (Whitbeck et al. 2012) urged a paradigm shift away from adapting Western best practices and toward development of novel evidence-based and culturally relevant interventions in partnership with Native communities. They suggested such a shift because interventions developed for Western populations sometimes do not align with Native worldviews and traditions. Moreover, many Native communities harbor a lingering deep distrust of Western-oriented practices because of historical abuses by researchers (Whitbeck et al. 2012).

Advances in SBIRT and Motivational Interventions

Although novel, culturally based treatments ultimately may be considered ideal, mainstream SBIRT has been used successfully in racial and ethnic populations. One report (Madras et al. 2009) pooled data from multiple medical care settings (including emergency departments, primary care, and other institutions) for a study funded by SAMHSA to evaluate SBIRT, with the majority of the participating patients being people of color. The investigators found that, across the sites, patients experienced improved outcomes for substance-use and functional status 6 months post-intervention. Unfortunately, the types of brief interventions were not consistent across sites and there were no control groups, although all participating sites seemed to foster the spirit of motivational interviewing.

Brief motivational interventions with African Americans and Latinos in trauma centers also have been associated with reductions in alcohol use at 6 and 12 months post-intervention (Field et al. 2010). Ethnic matches between Latino clients and interventionists seemed to improve outcomes (Field and Caetano 2010), potentially supporting other research on the importance of the working alliance. Positive outcomes also did not depend on whether the subject subsequently attended treatment (Field et al. 2013).

Research from the National Institute on Drug Abuse (NIDA) Clinical Trials Network found that motivational enhancement therapy was particularly effective among African-American participants with higher readiness-to-change scores (Burlew et al. 2013). In a multisite randomized controlled trial, motivational enhancement therapy also was effective with and personally appealing to Spanish-speaking Latino adults who primarily misused alcohol, but less effective for those who used other drugs (Carroll et al. 2009). In another pilot study, culturally adapted motivational interviewing was well received by Latino immigrant participants (Lee et al. 2011).

Other Advances in Treatment

Research studies have demonstrated empirical support for mindfulness-based relapse prevention as a substance-use intervention among women of color (Amaro et al. 2014; Witkiewitz et al. 2013; see sidebar "Religious Affiliation and Spiritual Practices: An Examination of the Role of Spirituality in Alcohol Use and Alcohol Use Disorder"). Although interest in using mindfulness as a substance-use intervention among racial and ethnic minorities has increased substantially, some researchers have raised questions about the cultural relevance of such interventions. For example, Hall and colleagues (2011) expressed concerns that mindfulness interventions may be highly Westernized. These strategies are not particularly helpful for certain racial and ethnic minority groups unless they are aligned with traditional cultural values and traditions.

Drink-refusal skills also have been identified as potentially helpful for African-American clients. In an examination of Project COMBINE data, African-American participants who completed drink-refusal skills training had significantly more positive treatment outcomes compared with those who did not complete the skills-training component. The positive outcomes were demonstrated up to 1 year post-intervention (Witkiewitz et al. 2011).

Communities also have collaborated with researchers using CBPR methods to create novel treatment interventions, just as they have done with prevention programs. One recent and promising example is the development of Drum-Assisted Recovery Therapy, which uses traditional Native American drumming and singing as well as talking circles to help AI/AN treatment

clients with recovery from substance abuse (Dickerson et al. 2012). Researchers used qualitative methods and key community stakeholder involvement to develop and refine the culturally grounded therapy protocol that bears little resemblance to traditional treatment methods or mainstream therapies.

Interventions for Sexual Minorities

Sexual minorities have been relatively overlooked in prevention and treatment intervention research, perhaps because of substance abuse stigma and homophobia. For sexual-minority clients of color, there also are the added dimensions of racial- and ethnic-based prejudice and bias. Sexual minorities experience elevated risk for substance abuse, but intervention research with this particular subpopulation is sorely lacking (Green and Feinstein 2012). However, researchers have found that in general, sexual-minority clients prefer to seek alternative rather than mainstream forms of treatment, especially if they do not closely identify with mainstream heterosexual beliefs (Dillworth et al. 2009).

Real Men Are Safe is a group-based program that emphasizes motivational enhancement, didactics, and skills training targeting high-risk sexual behavior among men in substance abuse treatment. It has been associated with modest improvements in safe-sex practices among sexual-minority men of color in substance abuse treatment. The program was culturally adapted by a qualitative examination of data collected from an expert panel of professionals who conducted research among ethnic sexual minorities that was then used to revise and enhance program content. Some evidence also suggests that the adapted Real Men Are Safe may have been more culturally relevant for African Americans and Latinos than for other groups (Calsyn et al. 2012, 2013). The results are promising and suggest that mainstream treatment can be culturally adapted for sexual-minority clients in ways that may reduce other risk behaviors.

Advances in Pharmacologic Treatment

Beyond advances in psychotherapy, pharmacological approaches have been investigated in minority populations as well. In one randomized placebo-controlled trial with a rather high dropout rate, naltrexone use was associated with fewer alcohol-related consequences and greater percentage of days abstinent among AN clients in isolated rural areas of Alaska (O'Malley et al. 2008; see also Greenfield and Venner 2012).

However, two other studies found null results for naltrexone's efficacy among African-American clients—one from Project COMBINE that examined alcohol-dependent participants (Ray and Oslin 2009) and another that investigated social drinkers under laboratory conditions (Plebani et al. 2011). Few pharmacotherapy studies have been conducted with minority population samples large enough to produce meaningful results. More investigation is needed to assess the efficacy of specific drugs, including naltrexone, among various subpopulations.

Conclusions and Future Directions

Exciting new programs for prevention, brief opportunistic intervention, and treatment have been successfully developed and tested with racial, ethnic, and sexual minority populations—groups often at risk for substance abuse and with well-documented disparities. Recent interventions have combined computer- or Web-based technologies with culturally relevant adaptations, including a focus on the family as the unit of intervention, as well as culturally grounded and informed measurement (see Allen and Mohatt 2014). In addition, empirically supported skills-based approaches seem helpful for certain subpopulations, with the caveat that the interventions may require appropriate cultural alignment of the intervention with the beliefs and traditions of the group being targeted. Recent studies continue to demonstrate that when appropriate CBPR methods are used, evidence-based interventions can be used in culturally appropriate ways to benefit some racial, ethnic, and sexual minority populations.

However, given the vast heterogeneity of some minority groups (e.g., AI/AN) (Etz et al. 2012), some minority communities likely will reject existing interventions as culturally insensitive or not reflecting their beliefs and values (Whitbeck et al. 2012). In addition, some studies using culturally adapted interventions based on empirical evidence have found null or inconsistent outcomes (e.g., Carroll et al. 2009), suggesting that other approaches are needed. Thus, although such interventions can be helpful for some minority groups, a prudent strategy would involve simultaneously developing novel and culturally specific interventions using rigorous CBPR strategies for communities where other interventions may not work well (Etz et al. 2012; Whitbeck et al. 2012).

Intervening at the level of the treatment environment to improve outcomes for racial, ethnic, and sexual minority clients also is an exciting new development that holds particular promise for improving the working alliance, a consistent predictor of treatment outcomes independent of intervention modality. Above all, more can be done to improve the climate of prevention and treatment programs. Such efforts could reduce the likelihood of microaggressions and risk of stereotyping and stereotype threats that may negatively affect client outcomes following interventions.

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Recent Developments in Alcohol Services Research on Access to Care

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In the United States, only about 10 percent of people with an alcohol or drug use disorder receive care for the condition, pointing to a large treatment gap. Several personal characteristics influence whether a person will receive treatment; additionally, many people with an alcohol use disorder do not perceive the need for treatment. The extent of the treatment gap differs somewhat across different population subgroups, such as those based on gender, age, or race and ethnicity. Recent health care reforms, such as implementation of the Patient Protection and Affordable Care Act of 2010, likely will improve access to substance abuse treatment. In addition, new treatment approaches, service delivery systems, and payment innovations may facilitate access to substance abuse services. Nevertheless, efforts to bridge the treatment gap will continue to be needed to ensure that all people who need alcohol and drug abuse treatment can actually receive it.

Key words: Alcohol use disorder; alcohol services research; health care disparities; health care financing; treatment; substance abuse treatment; treatment access; access to care; parity; socioeconomic disparity; special populations; gender; age; race; ethnicity; health care reform; Patient Protection and Affordable Care Act

Of the more than 18 million Americans who need treatment for alcohol use disorder (AUD), less than 10 percent actually receive care (Substance Abuse and Mental Health Services Administration [SAMHSA] 2013). This problem, often referred to as the substance abuse treatment gap, is a longstanding concern for alcohol services research. Studies suggest that many factors contribute to the treatment gap, ranging from inadequate treatment capacity to organization and financing policies, negative attitudes on the part of potential treatment seekers, and inequities in the distribution of care. However, today, the landscape of alcohol treatment is shifting with health care reform, the advent of new treatment modalities, and secular changes in the populations needing care. In light of these trends, the research and treatment communities are seeking new answers to old questions: What is the current scope and nature of the treatment gap? Which subpopulations are the most underserved? How are major policy changes affecting access to alcohol treatment? And how can the newest treatments become available to a wider segment of the population in need?

Understanding the Treatment Gap

Recent analyses of the U.S. population buttress claims that there exists a considerable unmet need for substance abuse treatment—enough to warrant serious, sustained attention by policymakers. It is safe to say that the substance abuse treatment gap in the United States is somewhere close to 90 percent. In other words, only about 10 percent of people with a current alcohol or drug use disorder receive care for the condition. This conclusion is based on a thorough national analysis that estimated the treatment gap using a wide range of possible metrics (Schmidt 2007*a*). The analysis found that even after using diverse measurement approaches, estimates of the treatment gap tended to cluster within a relatively narrow range of 8 percent to 12 percent. More recently, the 2014 National Survey on Drug Use and Health (NSDUH) found that approximately 18 percent of people needing treatment for alcohol and other drug use problems actually received any care in the previous year, and about 11 percent received specialty care (SAMHSA 2015). These estimates of the change in treatment gap pale in comparison to the magnitude of the problem they quantify.

The substantial gap between those who need treatment and those who actually get treatment has, in fact, been a longstanding issue in alcohol

services research. In the 1980s, researchers began trying to understand what distinguished people who receive treatment from those who do not (Weisner 1988). What began as an effort to simply describe the problem evolved into a wide-ranging research enterprise seeking to explain why so many Americans fail to obtain needed care. Further analyses demonstrated that a cluster of factors robustly predict the likelihood of receiving substance abuse treatment, including the client's age, gender, marital status, perceived need for treatment, and prior use of services (Weisner et al. 2002).

It also is clear that people who meet the criteria for an AUD often do not see a need for professional care. According to the 2014 NSDUH, only 6.3 percent of people diagnosed with substance use disorder or treated for substance use problems in a specialty treatment facility felt that they needed treatment (SAMHSA 2015), and the majority did not make an effort to seek care (SAMHSA 2015). Respondents cited several reasons for not seeking or receiving treatment, including not being ready to stop substance use, lack of health care coverage or means to afford treatment, fear of problems at work or stigmatization by others, and not knowing where to go for treatment. Others may question the efficacy of treatment (SAMHSA 2002). However, the reaction of family and friends to a person's drinking problem can motivate care seeking, even when the affected individual is hesitant, and social support also can influence responses to treatment (Worley et al. 2015).

Some investigators have examined the "thresholds of severity" at which individuals with a drinking problem will perceive a need for care (Schmidt 2007*a*). These studies found that a person who is experiencing symptoms of mental distress, in addition to having problems with substance use, is much more likely to see a need for treatment than is a person without those symptoms. Once again, perceptions by others in the problem drinker's life are critical factors in seeking care. Experiencing family, work, and legal problems also significantly increase the likelihood that people would see a need for care and eventually get there.

Who Lacks Care? Uneven Access Across Subpopulations

Not all subgroups in the U.S. population are equally affected by the treatment gap. To better understand the causes and extent of the treatment gap for people with AUD, it is useful to look separately at different subpopulations based on gender, age, race and ethnicity, and other variables.

Gender

During the 1980s, women were underrepresented in addiction treatment programs by a one-to-four ratio compared with men. Therefore, researchers prodigiously investigated the reasons contributing to this underrepresentation, finding that women largely sought care from other types of providers, such as mental health providers, to avoid the stigma of substance abuse treatment (Weisner and Schmidt 1992). Since then, the gender gap has substantially narrowed (Steingrímsson et al. 2012). Although almost twice as many men than women received any substance use treatment in 2014 (Center for Behavioral Health Statistics and Quality 2015), the prevalence of substance abuse and dependence similarly was about twice as high among men as it was among women.[1] The narrowing of this gender gap has led researchers to focus on other underserved populations.

Age

A significant concern today is the disproportionately low rate of treatment utilization, and particularly specialty treatment, among adolescents and young adults in the United States. According to the 2014 NSDUH, about 1.3 million adolescents ages 12–17, and 5.8 million young adults ages 18–25, needed treatment for substance use problems (SAMHSA 2015). However, only 8.5 percent of these adolescents and 8.0 percent of young adults received treatment at a specialty facility, compared with 13.2 percent of adults ages 26 and older who needed treatment (SAMHSA 2015). The need for treatment appears similar among male and female adolescents, as indicated by a similar prevalence of substance abuse and dependence, but females are more likely to receive care from professionals specially trained in substance abuse treatment (Center for Behavioral Health Statistics and Quality 2015).

Looking at the other end of the age spectrum, studies point to a treatment gap for elderly people with alcohol and illicit drug problems, albeit a narrower one. According to the 2014 NSDUH, more than 1.1 million people ages 65 and older needed treatment for a substance use disorder, but only about 234,000 people in this age group (or about 21 percent) received treatment (Center for Behavioral Health Statistics and Quality 2015). This treatment gap may, at least in part, result from difficulties with the identification and diagnosis of substance use problems in this population (Blow et al. 2002).

Race and Ethnicity

The debate about racial and ethnic disparities in health care access reached national prominence in 2002, with the publication of the watershed Institute of Medicine report *Unequal Treatment: Confronting Racial and Ethnic Disparities in Health Care* (Smedley et al. 2002). The report delivered a scathing view of gross inequities in access to, and the quality of, health care for America's racial and ethnic minority groups. Although it seemed almost inevitable that substance abuse researchers would uncover similar evidence of disparities, by and large,

[1] According to the 2014 NSDUH, the prevalence of abuse or dependence among men was 3.4 percent for illicit substances, 8.5 percent for alcohol, and 10.7 percent for illicit drugs or alcohol, compared with 1.9 percent, 4.4. percent, and 5.7 percent, respectively, among women (Center for Behavioral Health Statistics and Quality 2015).

those observed in the wider health care system appear far more pronounced.

Studies in the substance abuse field show more modest and subtle variations in treatment access by race and ethnicity (Schmidt et al. 2006). African Americans and Hispanics—the two groups most commonly studied—tend to experience more health and social consequences for a given level of drinking than their White counterparts. The higher incidence of negative social consequences among minorities could result from stress associated with discrimination or from differences in how various racial and ethnic communities respond to risky drinking and how the wider society responds to drinking within these communities (Mulia et al. 2009). With respect to treatment use, few differences exist between Whites, African Americans, and Hispanics, at least in those who experience alcohol problems on the less severe end of the spectrum. With increasing problem severity, however, African Americans and Hispanics have lower odds of entering treatment compared with Whites (Chartier and Caetano 2010; Schmidt et al. 2007*b*). In addition, when members of different ethnic groups do seek help for an alcohol problem, they tend to obtain different types of care. Hispanics receive less specialty care than do Whites (Schmidt et al. 2007*b*). Finally, although treatment retention is similar across ethnic groups, White patients receive more types of clinical services than Hispanics or African Americans, with the exception that African Americans receive more employment services (Niv et al. 2009).

One potential contributor to ethnic disparities in treatment access is geographic variation in the availability of treatment slots. In an interstate comparison of the alcohol treatment supply, McAuliffe and Dunn (2004) found that the Southern and Southwestern regions of the United States—regions with disproportionately large minority populations—are the most underserved. Surveys suggest that long wait times resulting from limited treatment capacities are a primary reason for unmet treatment need (Andrews et al. 2013). In national surveys, African Americans were disproportionately more likely to report lengthy wait times as a reason for not entering care (Schmidt et al. 2006). Individuals referred to treatment by the criminal justice system, who are more likely to belong to a minority group, also experience longer wait times (Andrews et al. 2013).

Who Pays? Health Care Reform, Parity, and Access to Care

Lack of or insufficient insurance coverage may be one of the barriers that prevents people with alcohol problems from entering treatment. Accordingly, recent health care reforms are expected to have a significant impact on access to substance abuse treatment. In the late 1990s and early 2000s, mental health and substance abuse spending was growing at a slower rate than the gross domestic product and shrinking as a share of all health care spending (Mark et al. 2011). Indications are that this could change dramatically under health care reform. Approximately 25 million individuals will become newly insured as a result of the Patient Protection and Affordable Care Act of 2010 (ACA), known colloquially as "Obamacare" (Mark et al. 2015). Even before that, reforms under the Mental Health Parity and Addiction Equity Act of 2008 (MHPAEA) required commercial health plans, as well as Medicaid managed-care plans, to cover substance abuse treatment services at comparable levels to medical and surgical services. The ACA expands access to health insurance through Medicaid, further promotes insurance parity, and encourages new models of payment and service delivery. Although the MHPAEA and the ACA do not guarantee parity coverage for all Medicaid recipients, they offer a variety of mechanisms by which States may do so at their discretion (Burns 2015). (For more information on the influence of these health care reforms on treatment access, see the sidebar "Parity, the Affordable Care Act, and Access to Treatment.")

It is notable, however, that empirical studies prior to these reforms did not identify insurance coverage as one of the most significant predictors of entering alcohol treatment (Schmidt and Weisner 2005). Because addiction treatment is heavily subsidized by a separate stream of federal block grant funding, uninsured individuals often appeared to have better access to alcohol treatment than some groups of insured people. The MHPAEA and ACA may be changing this by expanding access to health insurance, deepening mandates for parity, and offering unprecedented opportunities for service growth and delivery-system reform. Under the ACA, overall funding for substance abuse services is increasing (Buck 2011). Before the health care reforms, Medicaid was not a major funder of substance abuse treatment, but this now is changing (Andrews et al. 2015*b*).

The State of Massachusetts, which created the blueprint for the ACA, presents a window into the potential long-range impacts of the federal reforms. This State's experience paints a cautiously optimistic picture for the Nation. Since the State's health care reforms, treatment capacity in Massachusetts has expanded to accommodate a growing number of people seeking alcohol services. Treatment admissions increased by 17.1 percent, and daily censuses of patients in substance abuse treatment increased by 4.7 percent. However, the reforms in Massachusetts appear to be having somewhat mixed effects on the quality of care, and uninsured people continue to face challenges (Maclean and Saloner 2015).

In nationwide studies carried out since the passage of the ACA and the MHPAEA, having Medicaid or private insurance was associated with a higher likelihood of receiving substance abuse treatment among people

who perceived a need for it (Ali et al. 2015; Mechanic 2012). Moreover, national studies of health plans suggest that the 2008 MHPAEA parity law has met its goal of putting coverage for behavioral health care on par with coverage for medical and surgical care (Horgan et al. 2015). For people with commercial insurance, the MHPAEA has had modest effects on reducing out-of-pocket costs and increasing access to outpatient services (Haffajee et al. 2015). Federal parity also is associated with an increased probability of out-of-network visits and increased average spending on substance abuse treatment (McGinty 2015). Many predicted that, under parity laws, health plans would more aggressively manage utilization, for example, through more stringent requirements on prior authorization for services. However, a national survey of health plans found that only 5 percent of plans require prior authorization for outpatient substance abuse treatment (Merrick et al. 2015).

Although the evidence to date is promising, a variety of limitations in the implementation of the new laws suggest that it could take many years to realize the promise of federal parity and health care reform. Twenty States have completely opted out of the ACA's

Parity, the Affordable Care Act, and Access to Treatment

Although having insurance coverage is not the most important factor influencing access to substance abuse treatment, the ways in which insurance coverage works do affect treatment availability and influence people's decisions about seeking care. Recent health care reforms present both fresh opportunities and new barriers affecting treatment access.

The Mental Health Parity and Addiction Equity Act of 2008 requires group health plans offering mental health and addiction services to cover such services at the same levels that they cover other medical and surgical services. The law applies to Medicaid managed-care plans as well as to private plans, but exempts health plans with fewer than 50 employees. Parity technically means that all aspects of coverage are comparable to those covering medical and surgical care, including deductibles and copayments, limitations on the frequency of treatment, and methods of determining whether treatment is necessary. Coverage for alcohol treatment offered by insurance plans therefore becomes more generous under this reform. However, the law does not require that plans cover addiction treatment at all, nor does it require that all areas of addiction be covered. Because of this, there are concerns that companies previously offering some addiction treatment benefits may choose to drop coverage in response to the parity law (Stewart and Horgan 2011).

The Patient Protection and Affordable Care Act of 2010 (ACA) extends insurance coverage to more Americans by expanding Medicaid eligibility and requiring individuals to obtain insurance coverage. Because private insurance plans still are not required to furnish substance abuse coverage, the focus of discussions about access to alcohol and other substance treatment revolves primarily around the effects of the expanded Medicaid benefits. The ACA also includes ideas for health care delivery and payment reforms that are likely to help providers deliver a wider range of behavioral health services. It encourages the use of preventive services, continuity of care, and substance abuse education. It also allows providers treating mental illness to pay more attention to substance abuse problems and provides pathways for incorporating evidence-based treatments. As poor continuity and coordination of care accounted for part of the substance abuse treatment gap and problems with treatment access, the ACA may offer tools to address these issues (Mechanic 2012).

These two pieces of legislation seem to have an impact on the treatment gap. For example, insured people who heretofore ran into caps or limits on their substance abuse coverage may benefit from the parity requirement. In addition, some people who previously could not afford insurance will now be able to obtain coverage (Mark et al. 2011). However, although the ACA does not allow States to reduce Medicaid enrollment, they still can cut health care services funded through general State funds. Because substance abuse treatment relies heavily on non-Medicaid public funds through block grants, treatment and ancillary services remain especially vulnerable to funding cuts during State budget shortfalls (Mark et al. 2011).

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Medicaid expansion program, thus substantially limiting its national impact. There are further concerns that treatment systems may lack the capacity and manpower to treat the swelling numbers of newly covered individuals (Ghitza and Tai 2014; Weil 2015). One survey of State agencies found that fewer than half were helping providers to modernize care or had technical support to maximize insurance participation (Andrews et al. 2015*a*). Similarly, a study of public treatment programs in Los Angeles County found them ill prepared to align their programs with the new realities of health care reform (Guerrero et al. 2015).

Access to What? New Treatments and Service Delivery Systems

Services research has demonstrated that access to new treatment modalities and service-delivery forms is in flux under health care reform. Service delivery and payment innovations introduced by the ACA could facilitate access to services that have not previously been reimbursable, including comprehensive care management, care coordination, social support, transition care, collaborative care, and other evidence-based interventions. The ACA also has ushered in a trend toward integrating addiction and primary health care under the auspices of "patient-centered medical homes" (PCMH) and Medicaid "health homes" (Starfield and Shi 2004). Health homes target chronic-disease comorbidities prevalent in alcohol treatment populations, and almost all participating States include substance abuse in their qualifying conditions.

The PCMH model originated in private health plans as a strategy to lower costs while improving the quality and continuity of care. Under this model, substance abuse services are linked to primary care through strong referral networks using electronic medical records, or they may be "co-located" under one roof in efforts to more deeply integrate care (Rittenhouse and Shortell 2009). Early evaluations—mostly in large, integrated delivery systems—show that this model improves quality, with savings in total health care costs (Crabtree et al. 2011). To a more limited extent, PCMH applications have shown positive outcomes for accessibility and continuity of care in safety-net populations, where substance abuse treatment need is disproportionately high (Rittenhouse et al. 2012).

Health care reform further appears to be catalyzing a longstanding structural shift toward the use of screening and brief interventions (SBIs) delivered in mainstream medical care settings, most notably primary care and hospital settings (Babor and Higgins-Biddle 2000). SBIs may help close the treatment gap by expanding capacities within mainstream medical care settings. An SBI can be as brief as 5 to 10 minutes and can be particularly effective when performed by a primary care physician. It begins with an assessment of the patient's alcohol use; patients screening positive for an alcohol problem then are advised to cut down or abstain and may be referred for further professional help. Studies have long shown that SBI offers an evidence-based, cost-effective approach for reducing patients' drinking (Fleming and Barry 1991). Introducing SBI programs into settings such as Federally Qualified Health Centers,[2] schools, workplaces, and criminal justice settings could broaden their reach and also help more disadvantaged populations (Mulia et al. 2014). Health services researchers are developing and testing more streamlined Web-based approaches to training health care providers in SBI skills, which could increase the system's capacity to provide this form of care (Stoner et al. 2014). Electronic versions of SBI and "guided self-change" approaches also hold promise for allowing efficient self-treatment for people with moderately severe substance use disorders (Sinadinovic et al. 2014; Wagner et al. 2014). However, a 2010 national survey of health plans found that only 18 percent of insurance products required screening for alcohol- and drug-abuse problems in primary care (Garnick et al. 2014).

A related challenge is promoting the adoption of even newer evidence-based treatments, most notably pharmaceutical approaches. "Second-generation" medications, such as acamprosate and regular and extended-release naltrexone, are clinically efficacious during detoxification and recovery from alcohol abuse. A national survey of health plans found that 96 percent of insurance products included coverage for addiction medications (Horgan et al. 2014). However, for patients, difficulties in gaining health plan authorization and covering high copayments may be barriers to using addiction medications. Providers also face challenges ordering and obtaining licenses to administer certain medications.

Initiatives such as Advancing Recovery and the Medication Research Partnership have been effective in working with the public and private sectors to facilitate adoption of pharmacotherapies for AUD. These organizational-change initiatives bring payers and providers together into collaboratives that test organizational changes supporting the increased use of medications through brief, experimental "change cycles." Implementation strategies that work are quickly scaled up through sharing across members of the collaborative. Demonstrations suggest that supported partnerships such as these can achieve a wider adoption of evidence-based treatment practices more rapidly and effectively (Ford et al. 2015; Schmidt et al. 2012).

Bridging the Treatment Gap: A Continuing Agenda

As seen through the lens of health services research, problem drinkers face better prospects for treatment in

[2] Federally Qualified Health Centers are community-based organizations that offer comprehensive primary care and preventive care, including substance abuse services, to people of all ages, regardless of their ability to pay or health insurance status. They are therefore an important part of the health care safety net.

the current landscape, characterized by the expansion of insurance coverage under health care reform and parity laws, as well as rapid clinical innovations and service-delivery-system reforms. But it also is a landscape in which the need for care still far outstrips the supply of treatment—one in which waiting lists for care are long as the alcohol field looks to the wider health care system to build greater capacity. Above all, today's health services researchers describe a treatment system that is moving toward closer alignment with the wider health care system. This can be seen in the movement toward more integrated models of service delivery through the PCMH and Medicaid health homes. It also is evident in the push toward parity in insurance coverage, and in the scaling-up of SBI programs in primary care and other medical care settings. Finally, alignment with the greater health care system can be observed in the promotion of pharmaceutical therapies, most notably the new second-generation pharmaceuticals for treating addiction. Deepening collaboration between alcohol treatment and mainstream health care systems will likely lead to further—undoubtedly controversial—changes in services for people with alcohol problems. But this may very well be the field's best hope for solving what is arguably its greatest challenge: reaching a greater proportion of the population in need of care.

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Neuroplasticity in Human Alcoholism

Studies of Extended Abstinence with Potential Treatment Implications

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Alcoholism is characterized by a lack of control over excessive alcohol consumption despite significant negative consequences. This impulsive and compulsive behavior may be related to functional abnormalities within networks of brain regions responsible for how we make decisions. The abnormalities may result in strengthened networks related to appetitive drive—or the need to fulfill desires—and simultaneously weakened networks that exercise control over behaviors. Studies using functional magnetic resonance imaging (fMRI) in abstinent alcoholics suggest that abstinence is associated with changes in the tone of such networks, decreasing resting tone in appetitive drive networks, and increasing resting tone in inhibitory control networks to support continued abstinence. Identifying electroencephalographic (EEG) measures of resting tone in these networks initially identified using fMRI, and establishing in longitudinal studies that these abstinence-related changes in network tone are progressive would motivate treatment initiatives to facilitate these changes in network tone, thereby supporting successful ongoing abstinence.

Key words: Alcoholism; alcohol use, abuse, and dependence; neuroplasticity; brain; brain networks; appetitive drive networks; appetitive drive; behavior control; inhibitory control networks; functional magnetic resonance imaging; abstinence; electroencephalographic; treatment

A person with alcoholism engages in risky or dangerous drinking despite experiencing serious negative physical and social consequences. Such persistence in pursuing damaging behaviors suggests that the short-term "appetitive" results of drinking (such as intoxication and losing one's inhibitions) have greater control over the alcoholic's behavior than do the negative consequences. From a neurobiological perspective, this pattern implies weak "top-down"—or knowledge-driven—executive control over impulsive and compulsive urges to consume alcohol and a strong "bottom-up"—or stimulus-driven—appetitive drive to consume alcohol, both impulsively and compulsively.

Research using functional magnetic resonance imaging (fMRI) has identified networks of disparate brain regions involved in executive control and others involved in appetitive drive. Studies in alcoholics have demonstrated differences in activity in these networks compared with nondrinkers, implying that the networks can contribute to the poor decisionmaking and risky behaviors seen among alcoholics. This article reviews fMRI evidence that, compared with non–substance-abusing control subjects (NSACs), brain executive control networks are weakened or "tuned down" and appetitive drive networks are strengthened or "tuned up" in active alcoholism. Further, alcoholism correlates with changes in synchrony, or how well the brain regions within each network operate in concert. We also present cross-sectional fMRI data showing that abstinence maintenance is associated with compensatory changes in synchrony in these networks, such that the executive control network has greater synchrony and the appetitive drive network has reduced synchrony both in comparison to NSACs. The article proposes that electroencephalographic (EEG) analogs of these alcohol-related network differences exist and should be characterized. EEG could reveal different properties of these brain networks, such as timing of event processing, and may be more amenable than

fMRI to active interventions such as neurofeedback. The article reviews a wide literature that supports the potential efficacy of an EEG neurofeedback intervention to mimic or augment the network changes seen in long-term abstinence. Finally, it presents a prototype showing that such neurofeedback is technically feasible.

Brain Network Activity in Alcoholics

To understand what brain changes underlie behavior seen in alcoholism, researchers have focused on two networks believed to influence whether a person acts to fulfill a desire or to govern or control the desire when faced with a choice. These two networks are the appetitive drive and executive control networks (see sidebar, "Brain Regions and Their Contributions to Behavior"). During its early stages, alcohol consumption is a goal-directed behavior, initiated and executed by regions within the executive control network (such as the dorsolateral prefrontal cortex and anterior cingulate cortex), with its rewarding effects processed by appetitive drive regions (such as the nucleus accumbens). After a person repeatedly consumes alcohol, consumption may become more automatic (with more involvement of appetitive drive regions such as the caudate and putamen) and less voluntary (with less involvement of executive control regions) (Everitt and Robbins 2005). Alcohol consumption shifts to a more habitual mode, particularly to avoid withdrawal symptoms. The behavioral fate of repetitive actions, such as compulsive alcohol consumption, seem to be instantiated in mesostriatocortical networks (Graybiel 1998; Volkow et al. 2013). An individual with alcohol dependence seeks alcohol compulsively—a behavior associated with increased activity of appetitive drive regions when presented with an alcohol cue—and experiences a lack of engagement of prefrontal regions, which under normal circumstances inhibit or stop a maladaptive behavior such as excessive alcohol consumption.

To determine how activity in these brain regions looks among alcoholics compared with control subjects, researchers use fMRI. fMRI measures brain activity by detecting the blood-oxygen-level–dependent (BOLD) contrast related to neural activity. Most fMRI experiments examine task-related patterns in the location and magnitude of the BOLD response, that is, the task activation of the brain. Many differences in activation in the executive control and appetitive drive networks have been observed in alcohol use, abuse, and dependence, suggesting that these networks and the multiple brain regions they encompass can contribute to the poor decisionmaking and risky behaviors seen in alcoholism (for a review, see Camchong et al. 2014).

For example, increased activity in the amygdala and insula, which are associated with inflexible, poor decision-making (Xiao et al. 2013), appears in binge drinkers. Lower activity in the dorsolateral prefrontal cortex (DLPFC) occurs among short-term abstinent alcoholics during inhibition tasks (Li et al. 2009) and in those with a family history of alcoholism during response inhibition (Norman et al. 2011) or when they are asked to make risky versus safe decisions (Cservenka and Nagel 2012). Further, lesser activation of prefrontal executive control regions compared with control subjects has been observed in alcoholics during spatial and verbal working-memory tasks (see the textbox on "Brain Regions and Their Contributions to Behavior") (Cservenka and Nagel 2012; Desmond et al. 2003; Pfefferbaum et al. 2001). Active drinkers show enhanced BOLD activation in the ventral striatum when presented with visual alcohol cues, which also supports the notion of a stronger appetitive and reward drive in people with current alcohol dependence (Ihssen et al. 2011; Myrick et al. 2004, 2008). Active drinkers with a diagnosis of alcohol dependence compared with active drinkers without alcohol dependence show higher activity in their DLPFCs when performing a delayed-reward decision task (Amlung et al. 2012). This increased activity may reflect increased demand that alcoholics (vs. NSAC) place on the executive control network when required to make decisions to delay behavior ruled by appetitive drive.

These studies demonstrate that excessive alcohol use and even the genetic vulnerability to alcoholism (observed prior to initiating alcohol use) is associated with activation patterns different from those of control subjects in brain regions that are part of the executive control and appetitive drive networks. More recently, scientists have taken fMRI studies a step further to examine differences in how well such brain regions work together. Such work suggests that faulty co-activation or synchrony within brain networks, or an imbalance between opposing brain networks, is important in alcoholism.

Synchrony in Brain Networks

Various methodologies for detecting brain activity demonstrate that more than one region becomes activated at a time, both during task performance and while at rest. Imaging studies now have begun to parse how the regions work together and whether disturbances within networks are associated with identifiable patterns of behavior. Early fMRI studies primarily focused on changes in the magnitude of the BOLD response, assessing activation and de-activation of brain regions during a task. More recently, studies have shifted to using fMRI to probe the similarity or synchrony of the BOLD response across spatially disparate regions, especially while the brain is at rest. The work builds upon the EEG literature that long ago established the existence of spontaneously oscillating brain networks. EEG measures brain electrical activity. Oscillations detected with EEG at characteristic frequencies, or bands, represent the

summed activity of thousands of neurons. Synchrony of oscillatory activity between brain regions is thought to support neural communication and plasticity (for review, see Fell and Axmacher 2011). For example, electrophysiological studies suggest that gamma band (higher than 30 Hz) synchronization is responsible for the integration of brain regions involved in specific aspects of stimulus processing. Synchrony of gamma oscillations enhances neural communication between regions, and lack of synchronization actually may prevent neural communication between cell assemblies. Scientists also have proposed that synchronization facilitates neural plasticity by enabling spike-field coherence that promotes the induction of long-term potentiation in neurons (see Glossary). Supporting this idea, studies show higher phase synchronization during encoding of information that a subject remembers than during encoding of information that the subject does not remember. Thus, scientists typically interpret high correlation or synchrony as representing a more integrated and responsive network and a low correlation or synchrony as representing a dysfunctional network or one with impaired communication. Network synchrony often is referred to in the literature as "functional connectivity."

Researchers largely agree that cortical oscillations evident in the EEG are related to the BOLD signal detected in fMRI, although the precise relationship is an area of active research (Thompson et al. 2014*a*,*b*; Whitman et al. 2013). This relationship suggests that changes in synchrony of the BOLD response may prove analogous to changes in synchronous EEG oscillations that reflect network integrity. Measuring network synchrony using fMRI can provide more precise information about the locations of brain regions acting together than EEG can capture.

Studies of the synchrony of the fMRI BOLD response during rest have gained in popularity, leading to the identification of several networks that are intrinsic to the brain's function (for review, see Lee et al. 2013). The most widely studied network is perhaps the default mode network (DMN), which is a group of brain regions that are active at rest but de-activated during cognitive tasks and which exhibits a highly synchronous low frequency (lower than 0.1 Hz) BOLD signal at rest. Many other networks that are highly synchronous at rest have been identified, including the somatosensory, visual, auditory, language, attention, and executive control networks. Networks identified during rest are robust, reliably detected in most people, and remain intact during task performance, although task synchrony may differ from synchrony observed during rest (Wilcox et al. 2011). The success of using synchrony measures in resting state fMRI has led to increased interest in measuring the synchrony of regions of activation in more traditional task-related fMRI studies. This work, in turn, has led to the identification of synchronous networks related to appetitive drive, cue salience, or behavior (Lee et al. 2013), which are key to studies of addiction.

Resting-State fMRI Synchrony Studies

Studies in Active Users and Very Early Abstinence

Because synchrony seems to represent the health of a network, it may be affected in certain networks by—or it may affect—alcoholism. Some recent work has examined resting-state fMRI synchrony in multiple brain networks in individuals with current alcohol use disorder (AUD) (Weiland et al. 2014). The fMRI time series measures of synchrony (i.e., average within-network correlations of BOLD signal magnitude across the network's nodes) were computed for 14 networks in each of 422 individuals with active AUD and in 97 control subjects. In this study, top-down executive control is reflected by the left and right executive control networks (LECN and RECN, respectively). The anterior salience network (composed of nodes including bilateral middle frontal gyrus, middle cingulate gyrus, and insula) reflects bottom-up appetitive drive. Network strength, a global measure of the fMRI time-series synchrony within each network, on average for all networks was lower for subjects with AUD than for control subjects. Tests of single networks showed lower synchrony in subjects with AUD versus control subjects for the LECN, consistent with the model that poor top-down executive control contributes to alcohol dependence. In addition, lower synchrony within the sensorimotor, basal ganglia, and primary visual networks in AUD versus control subjects may reflect alcohol's damaging effects on other networks that contribute to addiction. For the LECN alone, lower synchrony was associated with greater alcoholism severity and more years of drinking.

A study of fronto-striatal functional connectivity in cocaine use disorders supports the model that a strong bottom-up appetitive drive network is active in addiction (Wilcox et al. 2011). Fourteen subjects with chronic cocaine abuse or dependence (92% with comorbid alcohol abuse or dependence) in very early abstinence (but unlikely to be in significant acute withdrawal) had their resting-state fMRI recorded and compared with that of 16 healthy controls. Patients with chronic cocaine use exhibited increased synchrony between the ventral striatum and orbitofrontal cortex, key regions of the reward and appetitive drive network.

Studies in Long-Term Abstinence

The above section suggests that current dependence and abuse is associated with exaggerated bottom-up and compromised top-down neural network functioning. The question then becomes whether abstinence from alcohol changes that neural network

picture. Existing task studies suggest that compensatory mechanisms appear in long-term abstinence from nicotine and alcohol that may exert control over reward seeking and attenuate appetitive drive (Beck et al. 2009; Grüsser et al. 2004; Nestor et al. 2011; Wrase et al. 2007). To study brain network tone associated with long-term abstinence (LTAA), the authors examined resting-state fMRI synchrony in 23 LTAA subjects (8 women, ages 48.5 ± 7.1 years, abstinent 7.91 ± 7.80 years) and 23 NSAC subjects (8 women, ages 48.0 ± 6.7 years) (Camchong et al. 2013*b*). They used bilateral nucleus accumbens (NAcc) seeds (i.e., the fMRI time-series generated by the left and right NAcc) to probe the reward and appetitive drive network by identifying regions with synchronous fMRI responses, and a subgenual anterior cingulate cortex (sgACC) seed to probe the executive control network. All subjects also performed the intra-/extradimensional set shift task (IED; Cambridge Cognition 2006) outside of the scanner, and the study correlated their performance with the synchrony of the neural networks at rest. The IED assesses cognitive flexibility by examining an individual's ability to change a learned behavior with changing response contingencies.

Compared with NSAC subjects, LTAA subjects showed (1) decreased synchrony of limbic reward regions (e.g., caudate and thalamus) with both bilateral NAcc and sgACC seeds (figure 1) and (2) increased synchrony of bilateral NAcc seeds with left DLPFC (suggesting greater inhibitory control) and between the sgACC seed and right DLPFC (consistent with greater emotion regulation) (figure 2). The synchrony of bilateral NAcc seeds and left DLPFC was positively correlated with IED task performance outside of the scanner, suggesting that subjects with greater synchrony in the executive control network were better able to inhibit a learned response when a new rule was introduced. Additionally, duration of abstinence in LTAA was negatively correlated with the synchrony between sgACC and right DLPFC.

The lower synchrony of the limbic reward network in LTAA may reflect an ongoing compensatory effort to lower the induction of brain activity in regions known to be involved in reward processing. Increased synchrony between the NAcc and left DLPFC is consistent with literature showing that DLPFC input to the NAcc is involved in inhibition of behavior (Ballard et al. 2011; McClure et al. 2004), as is the correlation of this synchrony measure with IED performance.

LTAA subjects with a shorter duration of abstinence had higher synchrony between sgACC and right DLPFC. The authors suggest that individuals with shorter duration of abstinence are more vulnerable to relapse than individuals with longer abstinence and thus may need more vigilant emotional regulation (reflected here by increased synchrony between sgACC and right DLPFC) to manage emotional situations and successfully avoid relapse. On the other hand, individuals with longer abstinence, who are at lower risk for relapse, may have a lower need for regulating emotion; hence, lower synchrony between sgACC and DLPFC in LTAA subjects was associated with longer (multiyear) abstinence durations. In total, the results here support the existence of compensatory mechanisms in LTAA subjects that are evident during rest, in which enhanced synchrony within the executive control networks and attenuated synchrony within appetitive drive networks may facilitate the behavioral control required to maintain abstinence.

Studies of Comorbid Stimulant Dependence

To determine whether network synchrony abnormalities also underlie stimulant dependence, we examined LTAA subjects with comorbid stimulant dependence (LTAAS subjects; n = 35; 20 women, ages 47.9 ± 7.3 years; averaging 5.67 ± 4.80 years of abstinence), comparing them with 23 LTAA subjects without comorbid drug dependence (Camchong et al. 2013*a*) and 23 NSAC subjects. An earlier finding in this population shows that reduced activity in the insula (see sidebar, "Brain Regions and Their Contributions to Behavior") in stimulant addicts during decisionmaking (Paulus et al. 2005) or attention tasks (Clark et al. 2012) may predict subsequent relapse. Also, the insula has reciprocal connections with both the executive control (sgACC) and appetitive drive seeds (NAcc) (Craig 2009; Kelly et al. 2012), and accumulating evidence indicates insula involvement in behavioral aspects of addiction such as stress coping, decisionmaking, or cue responsiveness (Naqvi and Bechara 2010). The authors therefore examined synchrony of sgACC and NAcc seeds with insular activity in all three groups. The results showed commonalities in LTAA and LTAAS network synchrony. Compared with NSAC subjects, both groups showed enhanced executive control synchrony and enhanced synchrony between NAcc and midposterior insula. However, differences appeared as well. LTAAS subjects showed no attenuation of their appetitive drive network synchrony, with appetitive drive synchrony presenting higher in LTAAS subjects than LTAA subjects. LTAAS subjects also had enhanced synchrony between sg-ACC and the anterior or mid-insula compared with NSAC subjects. These findings implicate insula involvement in the top-down and bottom-up network adaptive synchrony phenomena in alcohol abstinence, especially in individuals with comorbid drug dependence. These results suggest common as well as specific targets for treatment to support abstinence in chronic alcoholics with, versus without, comorbid stimulant dependence. The results do not speak to possible similar effects in drug addicts without comorbid alcohol dependence, but suggest that studying

such individuals with the paradigms presented here may prove fruitful.

Studies in Short-Term Abstinence

Differences in synchrony observed among abstinent alcoholics compared with control subjects may reflect actual changes that the brain goes through to support abstinence or they may preexist in certain individuals and help those people to achieve and maintain abstinence. If the enhanced executive control network synchrony and suppressed appetitive drive network synchrony observed in LTAA subjects truly represent adaptive network changes during extended abstinence, then similar but smaller magnitude effects on network synchrony should appear in short-term abstinence. The authors investigated whether resting-state fMRI synchrony patterns found in LTAA subjects can be identified in short-term abstinent alcoholics (STAA subjects, abstinent 72.59 ± 18.36 days) (Camchong et al. 2013*c*). Using the same methodology as before (Camchong et al. 2013*b*), they examined network synchrony in 27 STAA subjects, and compared them with the 23 LTAA and 23 NSAC subjects from the previous study. They found synchrony effects ordered in magnitude from NSAC to STAA subjects and then to LTAA subjects within both the appetitive drive and executive control networks. Abstinence duration was associated with progressively lower synchrony of the appetitive drive network (NSAC subjects had higher appetitive synchrony than STAA subjects, who in turn had higher synchrony than LTAA subjects) and higher synchrony of the executive control network (NSAC subjects had lower executive synchrony than STAA subjects, while LTAA subjects demonstrated the highest level of executive control synchrony) (see figures 1 and 2). A significant positive correlation also appeared in STAA subjects between strength of synchrony between NAcc and left DLPFC and IED performance. Finally, the researchers saw a significant positive correlation in STAA subjects between strength of limbic reward network synchrony and current antisocial symptoms (i.e., antisocial behavior). These findings suggest that abstinent alcoholics experience adaptive differences in synchrony patterns compared with control subjects, and the magnitude of the difference increases with duration of abstinence.

Summary of Resting-State fMRI Synchrony Studies

These studies indicate that active alcoholics exhibit lower top-down executive control network synchrony and higher bottom-up reward and appetitive drive network synchrony, and that these phenomena are more than reversed with successful abstinence. The observed "overcompensation" in network synchrony—that is, the greater executive control network synchrony observed in STAA and LTAA subjects compared with control subjects—may be necessary in order to inhibit the habitual response to alcohol. This is consistent with the authors' 2013 paper showing that antisocial disposition does not change with long-term abstinence but that antisocial behavior is inhibited, with antisocial symptoms approaching zero in LTAA subjects (Fein and Fein 2013). Given this earlier observation of no change in antisocial disposition (or antisocial thinking) in LTAA subjects, it is not surprising that alcoholics need a very strong inhibitory control system to inhibit antisocial behavior (including drinking).

Task-Related fMRI Synchrony Studies

Several fMRI task studies have demonstrated altered executive control network activation and connectivity in alcoholism, implying that the resting-state fMRI synchrony differences observed are present during task processing. Research to determine the association between resting state fMRI network synchrony and network performance during tasks that involve appetitive drive and executive control would help demonstrate how the brain's readiness alters the brain's response to a task. For example, in nicotine addicts, a modified Stroop task (which tests the time it takes a subject to respond to a question about an image that contains nicotine versus neutral cues) has been used to assess appetitive drive and executive control networks (Nestor et al. 2011). The study provides evidence that higher executive control network activation when viewing nicotine cues occurs in former versus current smokers (i.e., higher executive control network activation appears with longer nicotine abstinence).

Jazmin Camchong developed an alcohol-cue analog of this task (see figure 3). In a pilot study, she tested five LTAA and two NSAC subjects who had demonstrated resting-state fMRI synchrony differences from each other. She found an alcohol-cue interference effect in LTAA subjects (i.e., longer reaction times to alcohol versus neutral cues) as well as higher synchrony of executive control regions in LTAA versus control subjects when viewing alcohol cues. These pilot results suggest that synchrony within the executive control network is higher in LTAA subjects both at rest and during task performance.

Task studies, which can isolate elements of complex behaviors, could help show not only whether synchrony influences behavior but what synchrony changes mean in relation to what scientists know about how alcoholism disrupts normal functioning. For example, one way of conceptualizing the core problem in alcoholism and other addictions is that reinforcements consequent to behavior—such as becoming sick or hungover after drinking—do not appropriately guide future behavior. Adaptive learning involves computation by the brain of reward prediction errors (PEs), which reflect the difference between expected

Brain Regions and Their Contributions to Behavior

Alcoholic behaviors represent a shift away from regulation of behavior by the brain's control and management functions (i.e., executive control) and toward influence by functions that process reward (i.e., appetitive drive). Parts of the brain's complex anatomy involved in each of these functions are spread far apart from one another. Nevertheless, they can act in concert to direct behaviors, and the balance between them turns out to have a profound impact in addiction and recovery. In the human brain, the appetitive drive and reward network—that is, the areas involved in forming and responding to appetites, drives, and desires—comprises mesocortico-limbic regions that mediate aspects of drug addiction such as responses to rewarding stimuli (e.g., the ventral tegmental area and nucleus accumbens), memory of rewarding stimuli (e.g., the amygdala and hippocampus), and regulation of emotion and executive function (e.g., the prefrontal and anterior cingulate cortices) (Everitt and Robbins 2005). The striatum (including the nucleus accumbens, ventral putamen, and ventral caudate) and orbitofrontal cortex are key regions mediating appetitive drive and behavior toward seeking reward (Elliott et al. 2010; Everitt and Robbins 2005; Taha and Fields 2006).

The subgenual anterior cingulate cortex (sgACC), a subdivision of the anterior cingulate cortex, plays a central role within the predominantly frontal cortical network underlying executive control (Botvinick et al. 2001). The ACC has widespread connections with the lateral prefrontal cortex and limbic structures (including the hippocampus, amygdala, and anterior thalamus) that are involved in emotional responsiveness and the regulation of behavior in the context of rewarding and punishing outcomes (Drevets et al. 1997; Kelly et al. 2009; Phan et al. 2005). A compromised top-down executive control network may underlie the poor regulation of behavior and emotion that has been considered primary in relapse (Berking et al. 2011; Cooper et al. 1995; Fox et al. 2008).

Here, images of the brain are labeled with some of the regions most important to the executive control and appetitive drive networks. The behaviors with which the regions are associated are also listed.

Appetitive Drive Network

Amygdala: *See* limbic system.

Caudate: Part of the striatum that influences goal-directed actions or behaviors.

Hippocampus: *See* limbic system.

Insula: Implicated in inflexible, poor decisionmaking. Also involved in stress coping and cue responsivity, which are behavioral aspects of addiction.

Nucleus Accumbens: Part of the striatum with roles in reward and reinforcement learning as well as fear, impulsivity, and addiction.

Orbitofrontal Cortex: Involved in motivational behavior as well as emotion and social behavior. It receives and responds to primary sensory information. It is involved in the detection and processing of consequences of behavior, including the attachment of emotional valence to the negative consequences of behavior.

Posterior Cingulate Cortex: Part of the default mode network (see Glossary) and possibly involved in human awareness. Also involved in pain and episodic memory retrieval and in intrinsic control networks.

Prefrontal Cortex: Involved in planning cognitive behavior, regulation of emotion, and executive function. Also part of the executive control network.

Putamen/Ventral Putamen: Part of the striatum involved in mediating appetitive drive. The putamen regulates movement and has influence on habits and on learning related to stimulus response.

Thalamus: *See* limbic system.

Ventral Tegmental Area: Involved in response to rewarding stimuli.

Executive Control Network

Basal Ganglia: Connected with the cerebral cortex, thalamus, and brain stem. Involved in the control of voluntary movement, procedural learning, habits, cognition, and emotion.

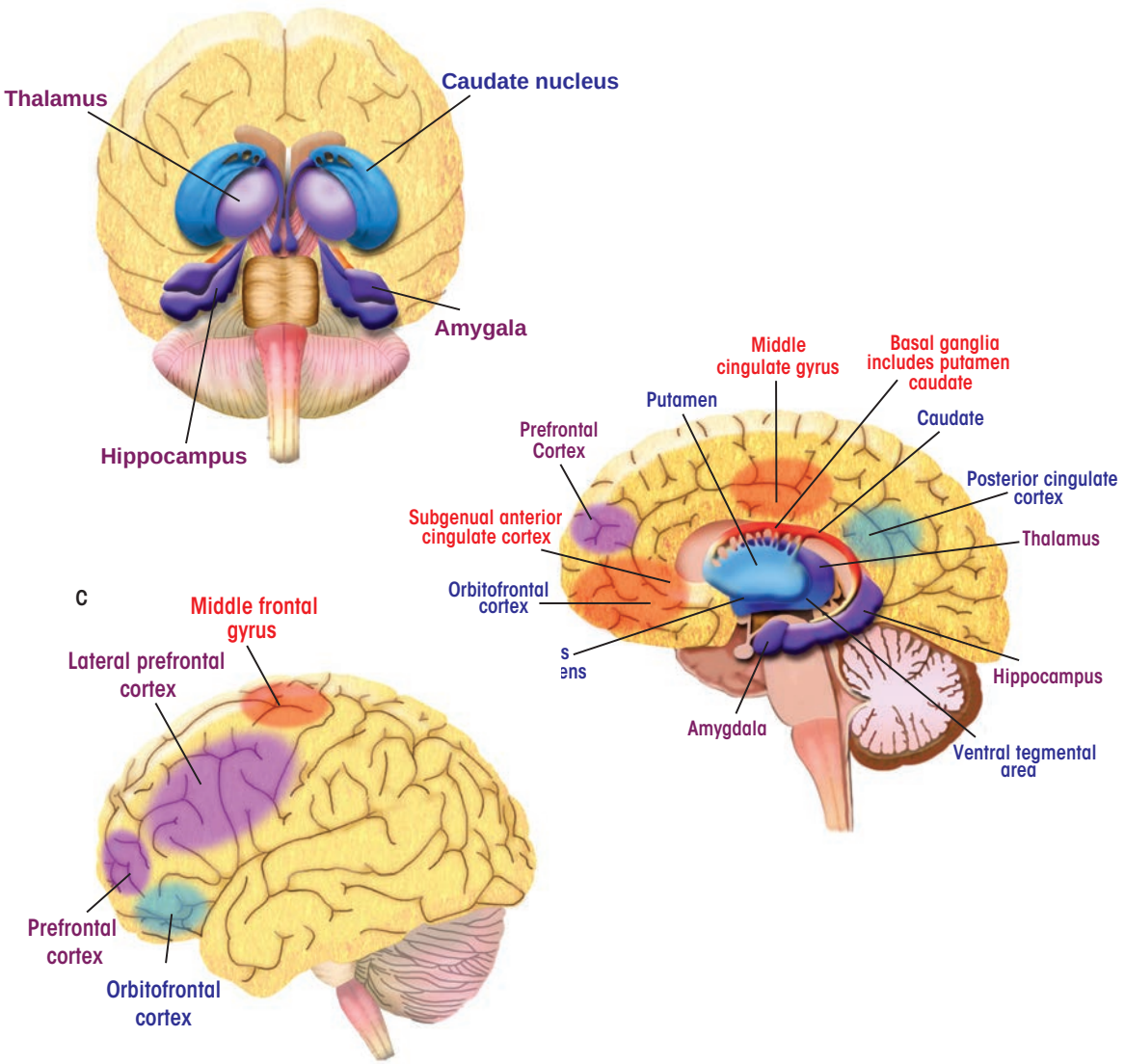
Bilateral Middle Frontal Gyrus/Middle Cingulate Gyrus: Parts of a salience network, a key mechanism by which the brain picks out details in its environment to focus on. Involved in learning and attention.

Lateral Prefrontal Cortex: Involved in goal-directed behavior. Includes the dorsolateral prefrontal cortex (a functional distinction), involved in executive functions such as working memory, cognitive flexibility, planning, inhibition, and abstract reasoning.

Limbic System: Encompasses the hippocampus, amygdala, and anterior thalamus. Implicated in both appetitive drive and executive control networks. An emotion, behavior, and motivation center.

continued

Brain Regions and Their Contributions to Behavior *(continued)*



Red–Executive Control Blue–Appetitive Drive Purple–Both Executive Control and Appetitive Drive

Locations of brain regions involved in executive control and appetitive drive. **(A)** Front Brain View: A frontal image of the brain showing internal structures involved in appetitive drive and in both appetitive drive and executive control networks. Though spread far apart in the brain's anatomy, the regions (shown here and in the other two brain illustrations) operate in concert to form these networks. **(B)** Side Brain View: A side view of the brain showing internal structures and locations of regions associated with either executive control or appetitive drive or, in many cases, with both networks. **(C)** External Brain View: An external view of the brain showing regions associated with the appetitive drive and executive control networks.

Brain Regions and Their Contributions to Behavior *(continued)*

continued

Subgenual Anterior Cingulate Cortex (sgACC): Connected with the lateral prefrontal cortex and with limbic system regions. Involved with emotion processing, learning, and memory.

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and actual outcomes. Normally, the PEs affect behavior by influencing higher-order executive functioning of the DLPFC, a region involved in goal-directed behavior. Park and colleagues (2010) tested models of the decision-making deficits in alcoholics and the networks underlying these deficits. They examined striatal PEs and functional connectivity between the striatum and DLPFC. A total of 20 male alcoholics in early abstinence (average 16.9 days abstinent) and 16 male healthy control subjects were studied using fMRI during a reward-guided decision-making task with changing response–outcome contingencies, which assesses how readily the subject learns. Alcoholics needed significantly more trials than did control subjects to meet learning criteria. In both groups, the PE from each stimulus presentation correlated significantly with the BOLD midbrain signal, and there were no differences between groups in the striatal PE signal. However, the influence of the striatal PE signal on the DLPFC was markedly attenuated in the alcoholics, suggesting that although the PE signal was being generated, it did not influence learning in the expected way. Moreover, striatal–DLPFC connectivity correlated significantly with learning during the task and was strongly negatively correlated with craving, especially in alcoholics.

In another study, 20 non–treatment-seeking problem drinkers underwent fMRI during a stop-signal task (SST) to assess response inhibition, a subject's ability to inhibit his own response to a stimulus (Courtney et al. 2013). Weaker functional connectivity between frontal regions and the striatum correlated with the severity of alcohol dependence, although SST behavioral performance was uncorrelated with severity, suggesting that the BOLD signal is more sensitive to alcohol's effects than task performance. The researchers concluded that as alcoholism progresses, the fronto-striatal pathway is weakened, leading to less inhibitory control as part of executive functioning.

Other studies of network functioning in alcoholics during active tasks have also revealed abnormalities in networks other than the executive control and appetitive drive networks. For some tasks, alcoholics seemed to recruit additional brain regions (vs. controls) to accomplish a task, perhaps to overcome strong appetitive signals, or physical or functional degradation of brain networks used by controls for task performance. Within the DMN, for example, abstinent alcoholics show less resting-state synchrony between the posterior cingulate and cerebellar regions compared with control subjects but show greater left posterior cingulate-cerebellar synchrony during a spatial working-memory task. The finding suggests that alcoholics need more integration of inputs from multiple brain regions to achieve comparable task performance to controls (Chanraud et al. 2011). In addition, higher connectivity among nodes of the DMN was associated with better task performance in both alcoholics and control subjects and also associated with longer abstinence in the alcoholics.

In later work (Chanraud et al. 2013), researchers observed that

compared with control subjects, recovering alcoholics recruited two additional fronto-cerebellar networks during a spatial working-memory task. In another study, lower fronto-cerebellar fMRI synchrony during a motor task also was observed in chronic alcoholics who were abstinent 5 to 7 days versus control subjects (Rogers et al. 2012). These results reinforce the idea that people generally require synchronous brain activity from disparate regions to respond appropriately to a stimulus and that alcoholics may need to marshal more brain regions to complete a task. The finding also provides evidence for improved network communication with extended sobriety.

A study of 18 abstinent alcoholics and 17 healthy control subjects acquired fMRI data during an attentional Stroop task (Schulte et al. 2012) and revealed abnormal synchrony in networks in the brains of abstinent subjects that may mediate between the top-down executive control and bottom-up appetitive drive networks. Using midbrain or posterior cingulate cortex (PCC) seeds (regions showing significant group-by-task activation contrasts in the fMRI analysis), the authors observed lower synchrony in alcoholics versus control subjects between the PCC and middle cingulate cortex, which they interpreted as reflecting difficulty in adapting functional network activity to executive task demands. They also observed greater synchrony between the midbrain and the middle cingulate cortex and striatal regions. They believe this suggests that alcoholics rely on greater integration of inputs from multiple brain regions as a compensatory mechanism to support task performance.

Task-related fMRI studies also may help identify characteristics of brain connectivity that can help predict whether or how readily an alcoholic will achieve abstinence. A cue-reactivity fMRI experiment with alcohol-associated and neutral stimuli was used to study 46 detoxified alcohol-dependent patients (19.74 ± 22.66 days abstinent) and 46 control subjects (Beck et al. 2012). Three months following scanning, 30 patients had relapsed and 16 had maintained alcohol abstinence. The study compared fMRI results of the subsequent relapsers with those of the abstainers. When presented with alcohol-associated versus neutral stimuli, abstainers had demonstrated stronger functional connectivity than those who had relapsed between midbrain (including the ventral tegmental area and subthalamic nuclei) and left amygdala and between midbrain and

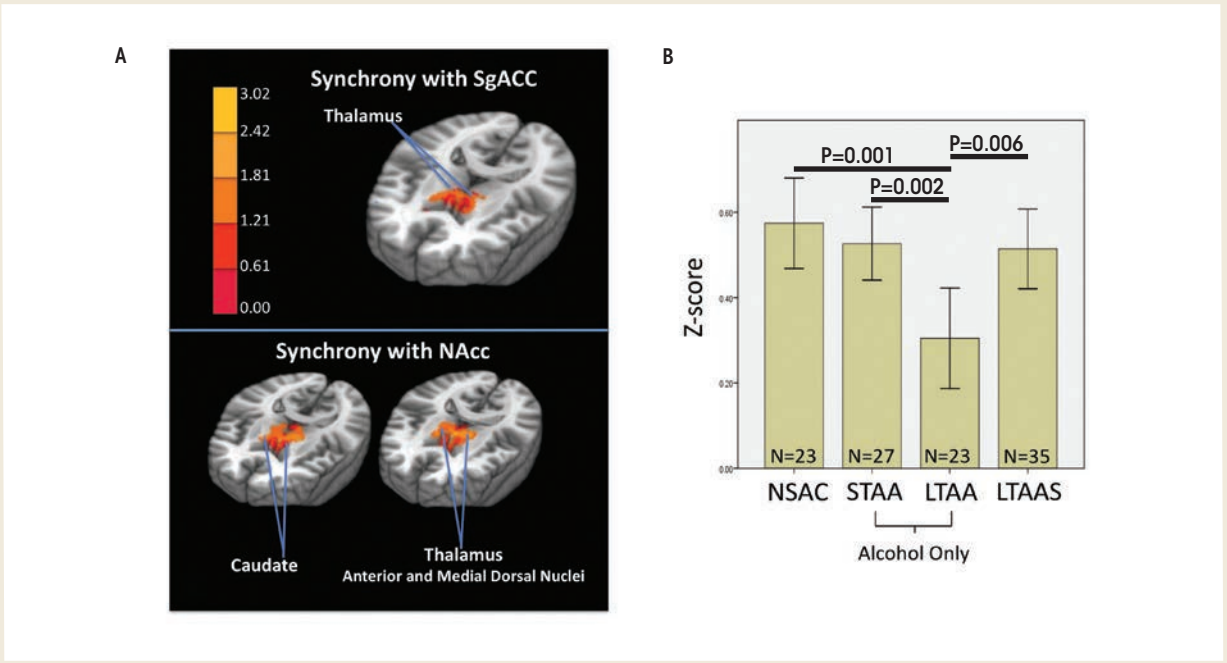

Figure 1 fMRI resting-state synchrony within the appetitive drive network is shown. **(A)** The voxels with activity synchronous to the subgenual anterior cingulate cortex (sgACC) and nucleus accumbens (NAcc) seeds are overlaid in red/yellow. These regions of the thalamus and caudate are crucial in bottom-up appetitive drive. (**B**) The average Z-scores indexing synchrony between the SgACC and NAcc seeds and the colored regions shown in the left panel are shown for non–substance-abusing control subjects (NSAC), short-term abstinent alcoholics (STAA), long-term abstinent alcoholics (LTAA), and stimulus-dependent long-term abstinent alcoholics (LTAAS). The LTAA show significantly less synchrony than NSAC, STAA, and LTAAS, with STAA and LTAAS synchrony midway between NSAC and LTAA.

left orbitofrontal cortex. These are brain regions associated with the processing of salient or aversive stimuli. The increased synchrony in abstainers between the midbrain and amygdala may mediate an enhanced aversive reaction to alcohol stimuli, which may then act as a warning signal (through stronger midbrain-frontal cortex synchrony) to help maintain abstinence.

In summary, fMRI functional connectivity or synchrony studies provide ample evidence that altered network synchrony exists in alcoholism and that plastic changes in network synchrony occur with abstinence. However, from cross-sectional studies alone, one cannot distinguish between brain synchrony actually changing in long-term abstinence (Camchong et al. 2013*b*,*c*), versus selective survivorship (i.e., individuals with such synchrony differences are more likely to achieve abstinence, and individuals with the largest differences from NSAC are more likely to achieve protracted abstinence), or a combination of the two. Only longitudinal studies can determine whether the observed cross-sectional findings indeed reflect adaptive changes in network synchrony with extended abstinence.

Applying Synchrony Findings to Treatment

Scientists understand little of how successful treatments such as behavioral therapies or 12-step programs work. They also understand little of the neurological mechanisms underlying reduction or cessation of drinking. Data reviewed here point to one such possible mechanism. They reveal network synchrony changes detected using fMRI that are graded with abstinence duration, suggesting that achieving and maintaining abstinence is associated with adaptive brain network synchrony changes that support reductions in bottom-up appetitive drive and increases in top-down executive inhibitory control. If longitudinal studies can confirm that the degree of the changes in the appetitive drive and executive control networks is associated with and predictive of successful abstinence, then such changes may underlie the success of behavior therapies. In addition, interventions that directly augment the network changes

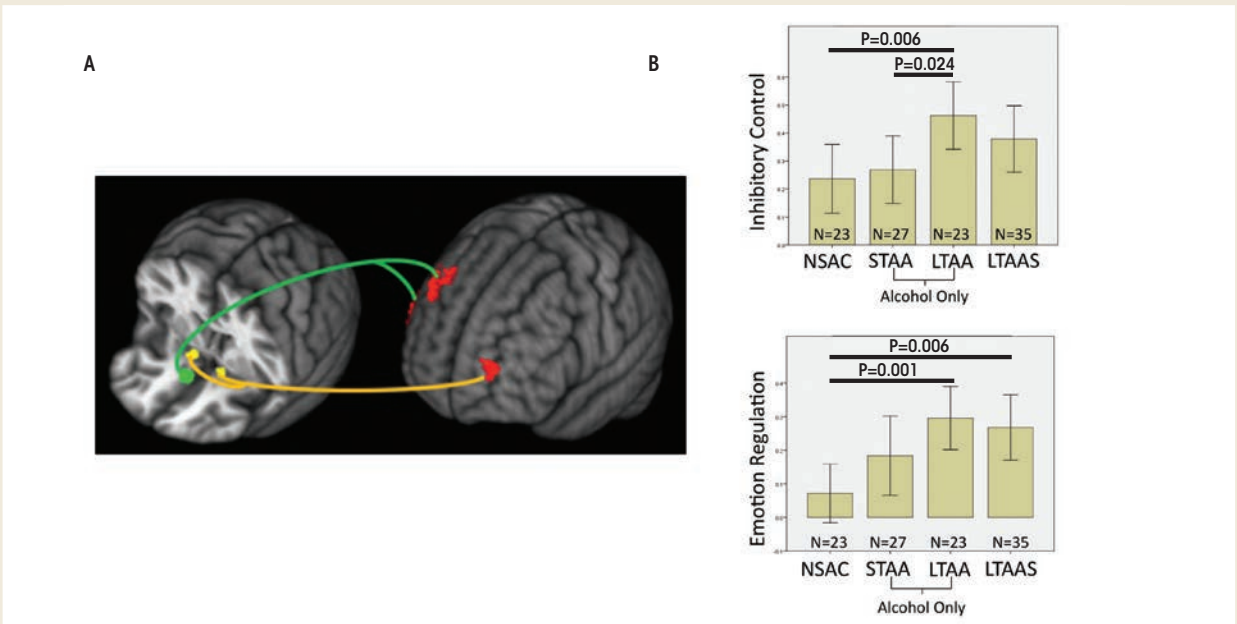

Figure 2 fMRI resting-state synchrony within the executive control network is shown. **(A)** The voxels with activity synchronous with the subgenual anterior cingulate cortex (sgACC, shown in green on the left brain image) are located in the right dorsolateral prefrontal cortex (DLPFC) and are overlaid in red on the right brain image. The voxels with activity synchronous with the bilateral nucleus accumbens (NAcc, shown in yellow) are located in the left DLPFC and are overlaid in red on the right brain image. The right DLPFC is associated with emotion regulation, and the left DLPFC is associated with inhibitory control. **(B)** The average Z-scores indexing synchrony between the NAcc and left DLPFC (top) and between the sgACC and right DLPFC (bottom) are shown for non–substance-abusing control subjects (NSAC), short-term abstinent alcoholics (STAA), long-term abstinent alcoholics (LTAA), and stimulus-dependent long-term abstinent alcoholics (LTAAS). The LTAA show significantly greater synchrony than NSAC and STAA, with STAA and LTAAS synchrony values slightly greater than NSAC, between inhibitory control brain regions. Both LTAA and LTAAS show significantly greater synchrony than NSAC, with STAA values midway between NSAC and LTAA, between emotion regulation brain regions.

may provide another tool in the treatment toolbox.

The idea of modifying brain network synchrony to promote abstinence is bolstered by the literature on using transcranial direct-current stimulation (tDCS) or repetitive transcranial magnetic stimulation (rTMS) to treat alcohol craving. These noninvasive treatments are thought to reduce craving by modulating the activity and connectivity of brain networks. Boggio and colleagues (2008) showed that tDCS of the DLPFC decreased alcohol craving compared with sham treatment. In later work, Mishra and colleagues (2010) studied 45 alcohol-dependent patients administered rTMS of the DLPFC and found significant decreases in a craving measure within the group that received rTMS compared with the sham group. One interpretation is that these treatments resulted in increased DLPFC activity and better executive control over craving.

A case study by De Ridder and colleagues (2011) provides further evidence that brain functions in alcoholism can be trained or influenced using relatively noninvasive techniques. The researchers used rTMS targeting the anterior cingulate cortex in an attempt to reduce craving and promote abstinence in a woman with a long history of alcohol dependence and treatment. Before treatment, the patient showed increased EEG synchrony between the ACC and PCC, and fMRI showed activation of regions of the appetitive drive network (NAcc, ACC, and PCC) in response to cue-induced worsening of craving. Following successful rTMS, fMRI-detected activation of NAcc, ACC, and PCC disappeared, and the patient's synchrony pattern normalized. When rTMS treatment became ineffective and relapse occurred, activity and synchrony within the appetitive drive network returned. Although their effect was not permanent, the rTMS treatments seem to have altered network synchrony and reduced craving.

Direct currents and magnetic waves applied transcranially thus seem to influence brain synchrony and may help reduce symptoms such as craving in alcoholism. At the same time, people can achieve abstinence without them. A technique such as neurofeedback might help people with addictions directly strengthen the tone of their inhibitory networks or weaken the tone of their appetitive drive networks. Neurofeedback is a method built upon the idea that the mind and body are one, and that by training the mind or brain to achieve particular states indexed by some measured neurobiological signal (such as the BOLD response or EEG), the body will react in a more optimal way in order to improve emotional, cognitive, physical, and behavioral experiences. Neurofeedback that "feeds back" an auditory or visual signal that corresponds to the strength of brain network synchrony may promote network synchrony adaptations that support abstinence. For example, a neurofeedback protocol may instruct a patient to try to raise the pitch of a tone. A low-pitched tone is played when network synchrony is low, and the pitch increases with network synchrony. As the patient works to raise the tone, synchrony in the target network improves, training the network.

Relating fMRI to EEG

Some technical challenges stand in the way of neurofeedback. First, it is neither practical nor economically feasible to use neurofeedback to modify fMRI-detected network synchrony directly. Furthermore, fMRI's BOLD response cannot provide the time resolution necessary to allow real-time feedback to a patient about synchrony changes occurring in his or her brain. In contrast, EEG provides precise time resolution and generally is a more economical and efficient tool for use in treatment than fMRI.

Since research on brain networks involved in alcoholism has used fMRI to date, scientists need to find EEG results that are analogous to the relevant fMRI-detected network phenomena to make EEG useful in neurofeedback. Fortunately, converging evidence suggests that the fMRI BOLD response reflects the summed neural activity of several oscillatory EEG networks (for review, see Whitman et al. 2013). These EEG networks may oscillate out of phase (i.e., the peak of oscillation does not coincide across nodes of the network) at multiple frequencies (e.g., theta, alpha, or gamma), and the activity of separate networks may vary as a function of cognitive states lasting only a few hundred milliseconds. fMRI networks detected in response to task processing are likely to comprise multiple oscillatory EEG networks reflecting both evoked (i.e., time-locked to the task) and induced (i.e., not time-locked) EEG responses and including responses that derive from phase alignment within EEG networks, wherein the summed activity creates a large, detectable signal (Burgess 2012). Because of the more complex nature of EEG measures of brain activity that change at the same pace as cognitive processes, EEG networks representing executive control and appetitive drive could potentially reveal more about the mechanisms underlying the processing and inhibition of alcohol cues that contribute to the maintenance of abstinence. Such EEG networks also could serve as neurofeedback targets.

Neurofeedback of EEG Network Synchrony

EEG network connectivity analysis is in its early stages, but pursuit of the identification of EEG networks that change with abstinence is crucial given the possibility of a neurofeedback intervention to facilitate abstinence. Preliminary data show that resting EEG coherency carries information that differs between LTAA and NSAC subjects, and that correlates with resting-state fMRI executive control network synchrony. Further study could identify reliable EEG executive control and appetitive drive network

synchrony measures as neurofeedback targets.

Roberto Pascual-Marqui's keynote address at the International Society for Neurofeedback and Research in 2011 presented a model for examining brain network synchrony from scalp-recorded EEGs. Using low-resolution electromagnetic tomography (LORETA) (Pascual-Marqui 2002, 2007) to estimate cortical EEG sources and independent components analysis (ICA) to identify synchronous source activity, he demonstrated EEG networks involving similar cortical regions to those identified by resting state fMRI from the literature. More recent work used EEG to study the effect of acute alcohol intake on the brain's resting state network in social drinkers. It examined the coherence between the activity of certain cortical areas within different frequency bands (Lithari et al. 2012) to construct brain networks. The work demonstrates that network synchrony changes occur over a short period of time (within 25 minutes of alcohol consumption) and are reflected in the scalp-recorded EEG, which can then be attributed to brain locations for network analysis. These results support the idea that EEG brain network synchrony could provide a neurofeedback target.

History

EEG neurofeedback in the treatment of substance use disorders dates to 1975 (for review, see Sokhadze et al. 2008) and was based on an alpha-theta training protocol, aimed at increasing the proportion of alpha (8 to 13 Hz) and theta (4 to7 Hz) band activity in the ongoing EEG to promote a state of profound relaxation similar to a meditative state. Although early studies were uncontrolled and abstinence rates were not reported, results suggested that biofeedback-induced alpha/theta states promoted insight and attitude changes in alcoholics, and that these changes enhanced recovery (Twemlow and Bowen 1976, 1977; Twemlow et al. 1977). Peniston and Kulkosky (1989) conducted the first randomized controlled studies of alpha-theta EEG neurofeedback. Of 10 alcoholic patients (who had formerly failed hospital treatment for alcoholism) who underwent neurofeedback training, 8 remained generally abstinent for at least 3 years, and they showed persistent changes in alcoholic personality variables. A case study (Fahrion et al. 1992) further described neurofeedback treatment in an 18-month-abstinent alcoholic who was experiencing craving and a fear of relapse. It concluded that neurofeedback was a useful intervention for reducing craving even in abstinent alcoholics. Later work also reported sustained abstinence in a group of alcoholic depressed patients who were treated with alpha-theta neurofeedback (Saxby and Peniston 1995). Critics deem alpha-theta neurofeedback no more effective than suggestion or meditation techniques. However, the fact that feedback of a single electrode measuring alpha and theta—which affords a limited view of the complex interaction of brain networks involved in alcohol abuse and dependence—works as well as it does, encourages the notion that feedback of EEG signals reflecting the functioning of the executive control and appetitive drive networks would yield even more impressive results.

To examine this idea that neurofeedback learning would be improved if activity from specific brain regions related to the desired outcome behavior was monitored, Congedo and colleagues (2004) pioneered neurofeedback using LORETA with a protocol

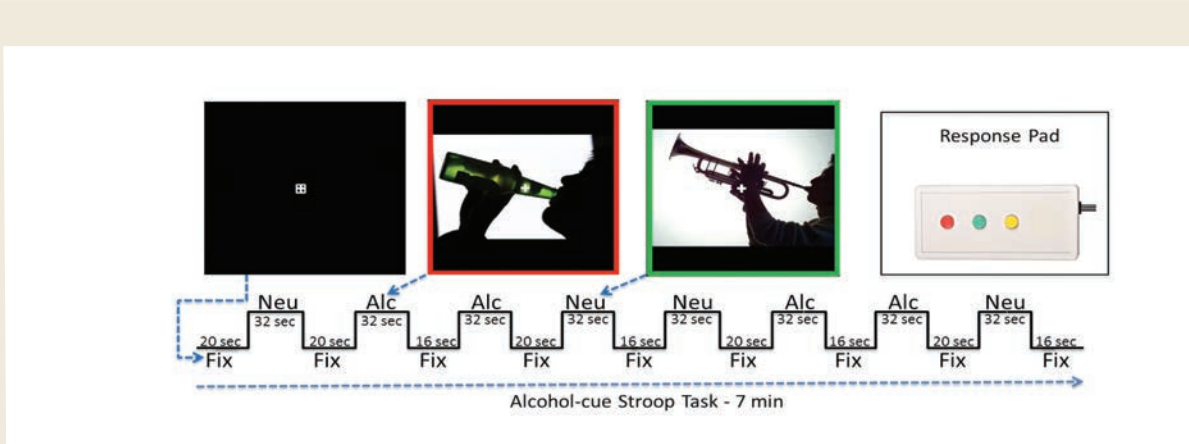

Figure 3 Alcohol-cue Stroop task. During the fixation (Fix) blocks, subjects keep their eyes fixated on the cross. During the neutral (Neu) and alcohol (Alc) blocks, subjects are instructed to keep looking at the fixation cross in the middle, while they notice the color of the picture's border, and respond by pressing the corresponding colored button on the response pad.

designed to improve sustained attention. Alpha and beta band current densities were estimated for an anterior cingulate region of interest using LORETA based on 19 scalp electrodes, and the power ratio between bands was used to drive feedback signals. They demonstrated that the current density power ratio increased over multiple neurofeedback sessions and that subjects could willfully increase that ratio. Scientists subsequently used LORETA neurofeedback to train eight healthy individuals to increase their low-beta power activity (moving the EEG frequencies in a direction opposite to alpha/theta feedback) for an anterior cingulate ROI in an effort to improve alertness and attention (Cannon et al. 2007). The subjects increased their beta power within the target ROI after neurofeedback, and these changes were associated with behavior change. Furthermore, beta power increases also were observed within ROIs that encompassed the left and right prefrontal cortex and the right post central gyrus, demonstrating parallel modifications in regions of the executive control network, although training targeted only a single anatomical node. More recent work has explored the feasibility of neurofeedback using a LORETA-derived anatomical source in clinical populations (Cannon et al. 2008) and has explored the utility of measuring EEG network synchrony using LORETA-derived sources (Cannon et al. 2012; Coben et al. 2014).

EEG Neurofeedback

The authors propose that EEG neurofeedback promoting increased inhibitory control network synchrony and reduced appetitive drive network synchrony would result in a "resting-state brain" that can more appropriately deal with the challenges of maintaining abstinence. The design of such an EEG neurofeedback protocol requires identification of EEG networks that change with abstinence and correspond to the

Cognitive Testing Tools

Alcoholism affects an array of cognitive functions that involve different brain regions. Asking a patient or subject to perform tasks that isolate specific cognitive processes from each other provides an essential tool for imaging studies, because the tasks induce measurable activity in the specific brain regions required to perform them. Researchers can compare activity patterns seen among alcoholics with those seen among abstainers and healthy control subjects. Tests referred to in this article are described here:

Delayed Reward Task: This tests a subject's ability to resist the temptation of an immediate reward in favor of waiting for a later reward. The task involves impulse control and self-control.

Intra/Extradimensional Set Shift Task: This tests the subject's ability to learn a rule through trial and error and then reverse it in favor of a new rule. The task requires attention and flexible thinking.

Motor Task: The task tests a subject's ability to learn and voluntarily produce intentional movements to proficiently perform a goal-oriented task. Motor tasks require considerable cognitive input.

fMRI Reward-Guided Decision-Making Task: This assesses a subject's learning rate by letting the subject look at different stimuli and choose one that is associated with a positive outcome (e.g., a smiley face). Each time the subject chooses an item and receives negative feedback (e.g., a frowning face), a prediction error is generated. The learning rate counts the number of trials the subject goes through to figure out which stimulus leads to a positive outcome.

Spatial and Verbal Working-Memory Tasks: Working memory actively holds multiple pieces of information in the mind where they can be manipulated. It includes subsystems that store and manipulate both visual images and verbal information. Tasks that test working memory require a subject to manipulate information as part of a goal-directed action while also being presented with distractions. The cognitive processes required to accomplish the task include executive control and attention, among others.

Stop-Signal Task: Here, a subject is asked to respond as quickly as possible to a particular feature of a stimulus (e.g., color, shape, or location). In some instances, however, the stimulus is followed by another signal—such as an auditory tone—that tells the subject to withhold her planned response. This tests the subject's ability to inhibit responses.

Stroop Task: This assesses whether a subject experiences interference in reaction time for completing a task. The classic Stroop test example involves looking at the names of colors spelled out in ink that is not the same color as the word (e.g., the word "red" spelled in blue ink). The subject is asked to name the color of the ink, and reaction time can indicate whether a person has problems with selective attention, cognitive flexibility, or processing speed.

appetitive drive and executive control networks previously identified using fMRI. Given the success of LORETA for estimating EEG network synchrony (Cannon et al. 2012; Coben et al. 2014; De Ridder et al. 2011) and the active research in the estimation of EEG sources and source synchrony (Chiang et al. 2009; Cook and Koles 2006; Gramfort et al. 2013; Sekihara et al. 2001), these networks likely can be identified and used as neurofeedback treatment targets for abstinence maintenance.

Technical challenges are inherent in a real-time EEG brain network synchrony neurofeedback system. However, the authors' prototype for an EEG neurofeedback system uses a quad-core Intel i5 computer to acquire EEG and estimate network synchrony based on comparing the EEG of each possible pair of electrodes, and a second computer to display a movie as the feedback signal. Although the best estimates of EEG network synchrony likely will be derived from intracranial source estimates, the prototype has computational demands greater than those required to estimate intracranial source connectivity and thus is more than adequate to establish the feasibility of a future EEG network synchrony neurofeedback system. The prototype records 64 channels of scalp EEG, estimates pairwise cross-coherencies, and computes the contribution of the independent components (IC) that index executive control or appetitive drive network synchrony. First, the subject's baseline network synchrony is estimated for use during training. During neurofeedback training, the system continuously records 64 channels of scalp EEG and analyzes the EEG to estimate network synchrony in real time. The real-time synchrony is compared with the subject's baseline synchrony and the target distributions of synchrony for NSAC, STAA, and LTAA subjects. A degraded video stimulus feeds back to the subject if there is a large difference between the real-time estimate of synchrony and the target synchrony, whereas a clear video signal appears when the real-time synchrony estimate approaches the target synchrony. The prototype is fast enough to update the neurofeedback to the patient 10 times per second despite a computationally intensive method of reflecting EEG network synchrony. It is likely that a much simpler algorithm will sufficiently index EEG network synchrony once research clarifies which signals best represent key aspects of brain network synchrony in recovering alcoholics. For example, neurofeedback systems could eventually use cross-correlation of selected electrode pairs within one or two frequency bands, or correlation of estimated source activity or power between a small number of anatomical sources. The central research task that would enable development of an EEG neurofeedback system to treat alcoholism remains identifying the EEG measures of network function that change with abstinence and that correspond to the appetitive drive and inhibitory control fMRI networks.

Conclusions

Alcoholism is characterized by a lack of control over excessive alcohol consumption despite significant negative consequences, a pattern of behavior that implies weak top-down executive control over impulsive and compulsive urges to consume alcohol, and a strong bottom-up appetitive drive that produces those urges. fMRI studies have identified multiple brain regions that contribute to the poor decisionmaking and risky behaviors seen in alcoholism. This chapter reviews fMRI network synchrony, or functional connectivity, studies suggesting that faulty coactivation or synchrony of multiple brain regions comprising networks, or an imbalance between opposing brain networks, is important in alcoholism. fMRI network studies in active alcoholics suggest that impulsive and compulsive behaviors are related to the ineffectiveness of brain networks, characterized by decreased synchrony in top-down executive control network and increased synchrony in the bottom-up appetitive drive network. Repeated high-volume alcohol exposure may compromise network integrity, as suggested by the relationship between synchrony and the severity and duration of alcohol use. Continued abstinence following alcoholism displays a different synchrony pattern. A series of studies in short- and long-term abstinent alcoholics observed decreased synchrony in appetitive drive networks and increased synchrony in inhibitory control networks, suggesting that the alcohol-induced imbalances in brain networks are reversed, helping individuals achieve and maintain abstinence by inhibiting behavior and reducing appetitive drive. Longitudinal studies of abstinent alcoholics at rest and during task performance would definitively establish whether plastic changes in the synchronous activity in brain networks reflects a crucial brain mechanism underlying the behavior changes in alcoholics that result in extended abstinence. Furthermore, the identification of EEG measures analogous to fMRI-executive control and appetitive drive network synchrony could potentially reveal the sequence and timing of mechanisms underlying the processing and inhibition of the brain's response to alcohol cues that contribute to the maintenance of abstinence. Confirming the progressive network synchrony changes with longitudinal studies of abstinent alcoholics—together with identifying EEG networks—would support the treatment potential of interventions to augment these network changes. Neurofeedback of EEG alpha and theta rhythms has been a successful component of alcoholism treatment in some subjects, and feedback of a signal that indexes synchrony in specific brain networks holds great promise as an alcoholism treatment. A prototype for neurofeedback to alter measures of EEG network synchrony demonstrates the technical feasibility of this treatment approach. If longitudinal studies

Glossary

Default mode network (DMN): A network of defined brain regions that is active when a person is not focused on the outside world but is awake. It is characterized by neural oscillations (see electroencephalography [EEG], below) and is deactivated when a person focuses on a task or action.

Electroencephalography (EEG): Records electrical activity along the scalp. EEG measures voltage fluctuations resulting from activity in the neurons of the brain. It can detect neural oscillations, which reflect the naturally occurring rhythmic, repetitive neural activity that occurs in the central nervous system. When many neurons act together, the synchronized activity results in the oscillations. Different synchronized activity between neurons gives off oscillations at different, characteristic frequencies. These frequencies have been aggregated into bands that have been named with Greek letters (e.g., alpha, theta, gamma, etc.).

Functional Magnetic Resonance Imaging (fMRI): A technique for assessing brain activity by measuring changes in blood flow that occur in response to neural activity (also called the BOLD response). MRI uses an electromagnet to align atomic nuclei, which then give off a measurable signal. MRI measures the magnetic signal from hydrogen nuclei in water. When neurons increase their activity, their demand for oxygen increases and blood flow increases to the area, allowing the system to determine what brain regions are active versus others.

fMRI Seeds: Signals from very precise locations in the brain region or structure of interest. Seeds can be a single fMRI volume element or a "region of interest" or ROI. Seeds are used to calculate correlations with the activity of all other locations, which appear as connections "growing" from the "seed," resulting in detailed data on connectivity in brain areas.

fMRI Task-Related Studies: Record and measure activation of brain regions while a subject is asked to complete a task, such as looking at a picture, that elicits a specific cognitive response in the brain. Studies can be designed so that the process of interest can be measured separately from other processes (see textbox).

Low-Resolution Electromagnetic Tomography (LORETA): A method for determining the location of electrical activity in the brain using multiple channel electroencephalography recordings.

Neurofeedback: Biofeedback that uses real-time displays that are a function of brain activity—including electroencephalography—to teach self-regulation of brain function.

Phase Synchronization: Occurs when a certain characteristic of an oscillation—the phase—is aligned in separate brain regions. When oscillations are in phase or synchronized, they reinforce each other.

Repetitive Transcranial Magnetic Stimulation (rTMS): Uses precisely targeted magnetic pulses to stimulate areas of the brain.

Spike-Field Coherence: Measures neuronal synchronization across brain areas by comparing spikes—electrical signals that occur when a neuron "fires" or emits an action potential—with the surrounding field potential, which is the compound activity of a large pool of neurons that may oscillate at different frequencies. Spikes may be synchronized or "coherent" at some frequencies that contribute to the local field potential, but may have no phase relation to other frequencies.

Synchrony: Oscillatory activity of physically distant brain regions occurring at the same time (or coinciding). Synchronization has been linked to cognitive functions.

Transcranial Direct Stimulation (tDCS): Uses constant, low current to stimulate a brain region, delivered to the brain region through scalp electrodes.

confirm that the adaptive changes in brain functional organization summarized in this article support ongoing abstinence, then EEG treatment to augment these changes is feasible and should be pursued.

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The authors declare that they have no competing financial interests.

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Advances in Diagnosis and Treatment of Fetal Alcohol Spectrum Disorders

From Animal Models to Human Studies

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Prenatal alcohol exposure can cause a number of physical, behavioral, cognitive, and neural impairments, collectively known as fetal alcohol spectrum disorders (FASD). This article examines basic research that has been or could be translated into practical applications for the diagnosis or treatment of FASD. Diagnosing FASD continues to be a challenge, but advances are being made at both basic science and clinical levels. These include identification of biomarkers, recognition of subtle facial characteristics of exposure, and examination of the relation between face, brain, and behavior. Basic research also is pointing toward potential new interventions for FASD involving pharmacotherapies, nutritional therapies, and exercise interventions. Although researchers have assessed the majority of these treatments in animal models of FASD, a limited number of recent clinical studies exist. An assessment of this literature suggests that targeted interventions can improve some impairments resulting from developmental alcohol exposure. However, combining interventions may prove more efficacious. Ultimately, advances in basic and clinical sciences may translate to clinical care, improving both diagnosis and treatment.

Key words: Fetal alcohol spectrum disorders; prenatal alcohol exposure; fetal alcohol effects; developmental alcohol exposure; developmental disorder; diagnosis; treatment; intervention; human studies; clinical studies; animal models; literature review

Alcohol consumption during pregnancy can interfere with both embryonic and fetal development, producing a wide range of outcomes that fall under the rubric of fetal alcohol spectrum disorders (FASD). FASD is the nondiagnostic umbrella term used to refer to the full range of effects that can occur following prenatal alcohol exposure. Such exposure can produce a variety of effects, including physical birth defects, growth retardation, and facial dysmorphism, but the most profound effects are on the developing brain and accompanying cognition and behavior. The disabilities associated with prenatal alcohol are variable, influenced by numerous factors, and can have a lifelong impact. Therefore, early diagnosis and intervention are essential for improved clinical outcomes (Streissguth et al. 2004).

Animal models have played a critical role in research on FASD, including studies confirming that alcohol is indeed a teratogen and those providing insights into the mechanisms by which alcohol exerts its teratogenic effect. Researchers have used a wide variety of organisms to model the effects of prenatal alcohol exposure, which mimic both the physical and the behavioral alterations seen in human FASD (Wilson and Cudd 2011). These models allow researchers to experimentally control factors, including alcohol dose, pattern and timing of exposure, nutritional status, maternal factors, and genetics, that are known to influence and contribute to variability in clinical outcomes. Animal models also can help identify better strategies for diagnosing and treating FASD. This review will not directly compare the animal and human data because previous reviews have done this (Schneider et al. 2011). Rather, it will highlight and integrate translational research that might lead to advancements in the diagnosis and treatment of FASD. Furthermore, several psychosocial, academic, and

behavioral interventions for FASD that recently have been discussed elsewhere (Paley and O'Connor 2011) are difficult to model in animals and thus will not be reviewed here. Instead, this review focuses on recent pharmacological, nutritional, and exercise interventions that have shown promise in preclinical studies and are progressing toward translation to the clinic.

Identification and Diagnosis

To obtain an accurate estimate of FASD prevalence and provide early intervention for affected individuals, it is critical to identify infants prenatally exposed to alcohol. Identification is less problematic on the severe end of the spectrum—where fetal alcohol syndrome (FAS) lies—because it is characterized by obvious growth retardation, central nervous system (CNS) dysfunction, and a specific pattern of craniofacial anomalies (see figure 1A). However, many, if not the majority, of individuals affected by prenatal alcohol exposure do not meet criteria for FAS (Bertrand et al. 2005), yet have significant neurobehavioral impairments (Mattson et al. 2013). These cases are referred to as alcohol-related neurodevelopmental disorders (ARND) and are often difficult to identify because they lack the characteristic facial features and growth retardation seen in FAS. In fact, an ARND diagnosis requires confirmation of prenatal alcohol exposure, which often is unavailable or unreliable (see Riley et al. 2011 for a comparison of various diagnostic schemas for FAS and ARND). Finding novel ways to identify at-risk individuals for disabilities along the spectrum is critical, as is identifying effective interventions to mitigate these cognitive and behavioral effects.

The routine use of objective, validated, and highly specific markers of prenatal alcohol exposure would help improve FASD identification, which currently is hampered by a lack of good information. For example, a recent study (May et al. 2014*a*) found that only 33 percent of the mothers of children given a diagnosis of FAS provided information about their alcohol consumption. In addition, a large number of children with FASD are in adoptive situations or foster care, and there may be little knowledge of their alcohol exposure. Several indirect and direct markers of alcohol exposure (see figure 2A) exist and have been described at length elsewhere (Bakhireva and Savage 2011). Fatty acid ethyl esters, ethyl glucuronide, ethyl sulphate, and the alcohol-derived phospholipid phosphatidylethanol are among several promising metabolic biomarkers. All of these are byproducts of alcohol metabolism, and each is limited by how long after alcohol exposure they are detectable. Another newly identified marker may persist longer than these metabolic markers. As shown in a sheep model, unique circulating microRNAs (miRNA) may help identify individuals consuming alcohol and, importantly, those exposed to alcohol in utero. An initial study

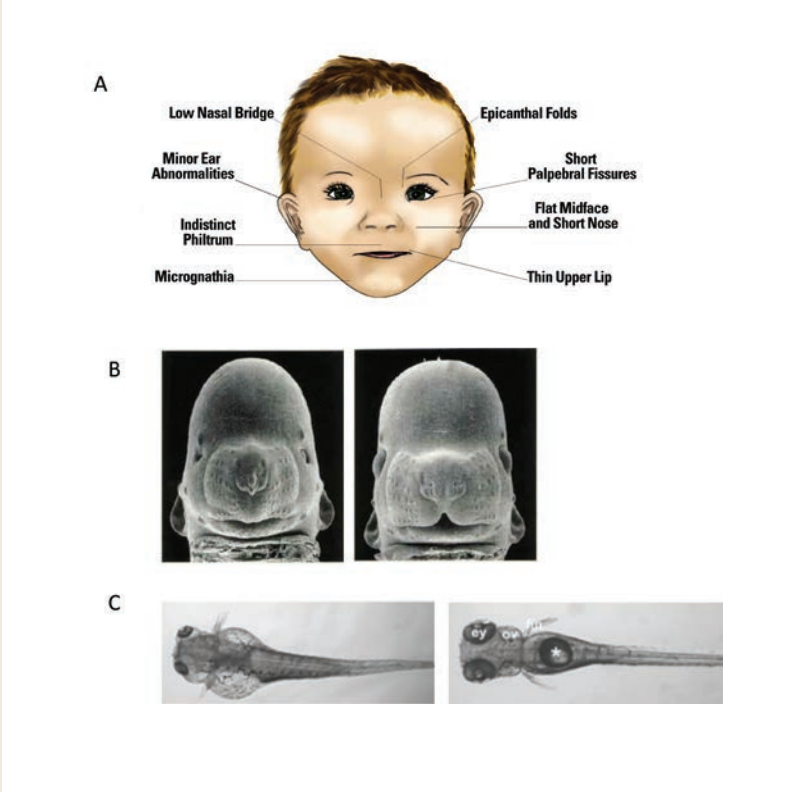

Figure 1 Craniofacial anomalies associated with alcohol exposure during development. **(A)** An illustration of a child with facial features of fetal alcohol syndrome (FAS). **(B)** Left figure shows a mouse with gestational day 7 alcohol exposure: Note small head, small eyes, and lack of a cleft under the nose compared with the control mouse on the right. **(C)** Zebrafish with embryonic alcohol exposure on the left compared with a control on the right. Again notice the small eyes, the smaller head, and the malformed body cavity and fin displacement resulting from alcohol exposure.

SOURCE: Figure 1A: Warren et al. 2011.
Photos in B are courtesy of Dr. Kathleen Sulik, University of North Carolina at Chapel Hill.
Photos in C were taken from Marrs et al. 2010.

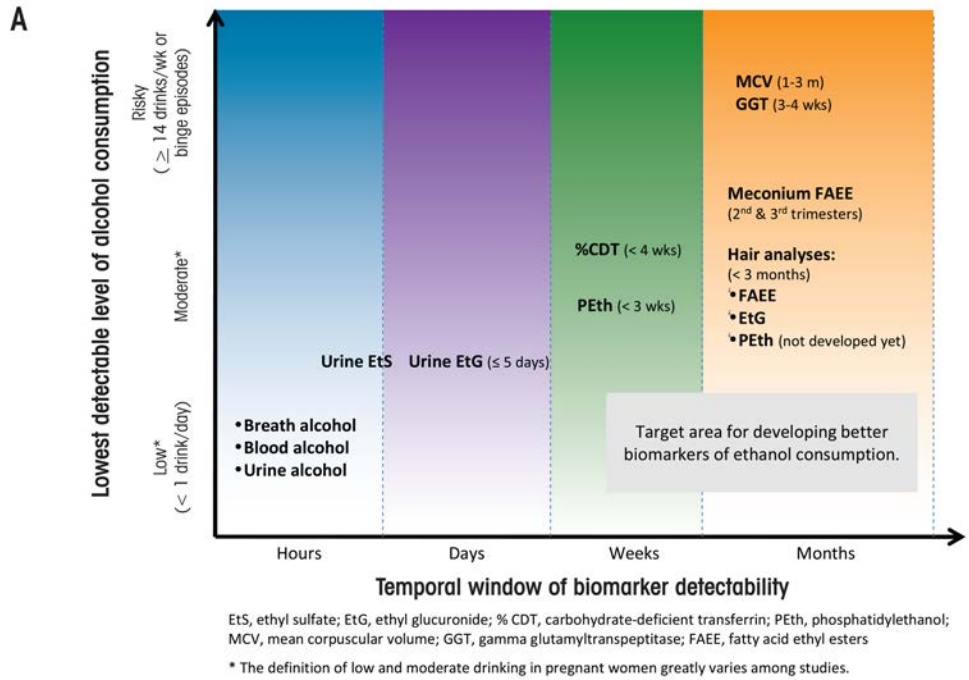

Figure 2 Indirect and direct markers of alcohol exposure. **(A)** Ideally, biomarkers could be both sensitive and specific to alcohol exposure and also indicate the timing and amount of alcohol exposure. This figure shows the period of time, or detection window, during which alcohol consumption can be detected and the lowest levels of alcohol consumption detectable by current alcohol biomarkers. For example, fatty acid ethyl esters are detectable in a variety of biological samples, such as neonatal hair and meconium, for several months after exposure. **(B)** MicroRNAs (miRNAs) may serve as potential biomarkers. Using a sheep model, Dr. Rajesh Miranda has identified several miRNAs that are modified by ethanol. As shown in this panel, miR-9 expression was significantly increased in plasma from the ethanol-exposed pregnant female compared with the control female but significantly decreased in plasma from neonatal lamb compared with controls. Alterations in miR-9 may be indicative of alcohol exposure in the mother, but also may serve as a marker of alcohol-induced injury in the neonate.

SOURCE: Figure 2(A): Bakhireva and Savage 2011. Figure 2(B): Modified from Balaraman et al. 2014.
NOTE: * = significantly different from control.

suggests that several microRNAs (miRNAs), including miR-9, -15b, -19b, and -20a, are potentially sensitive indices of alcohol exposure in both the pregnant ewe and newborn lamb (Balaraman et al. 2014) (see figure 2B). Researchers are conducting miRNA studies in humans to confirm the sheep findings. If they succeed, miRNAs may provide a new tool to identify alcohol-exposed pregnancies/infants, similar to their use as diagnostic biomarkers in a variety of other disease states (Weiland et al. 2012).

Other novel FASD diagnostic techniques include ways to identify potential at-risk individuals based upon subtle, subclinical facial features. In particular, researchers have developed a computerized method for detecting facial features using three-dimensional facial imaging and computer-based dense-surface modeling (see figure 3). Hammond and colleagues (Suttie et al. 2013) compared this approach with a standard dysmorphology exam for diagnosing FAS and found a high degree of agreement. The researchers used sophisticated mathematical techniques to characterize the facial features of heavily exposed individuals who did not have facial features that would have led to a diagnosis of FAS using traditional measures. They categorized participants as having facial features that were either "more similar to those with FAS" or "more similar to unexposed controls." Importantly, the heavily exposed children with FAS-like faces performed at a level similar to the FAS group on neurobehavioral tests, whereas those with more control-like faces exhibited behavioral profiles similar to control subjects. These data were collected on a homogenous ethnic group in South Africa and therefore need to be replicated in other populations. Still, they provide preliminary evidence that this approach may constitute a means to identify at-risk individuals based upon subtle, sub-clinical facial features.

Developing truly accurate and specific methods for identifying individuals with FASD requires an understanding of the full spectrum of alcohol-related consequences and clarification of the various factors, both protective and permissive, that influence outcome variability. Animal models have provided information on the mechanisms by which alcohol affects facial development and the factors that may make a fetus more susceptible to these facial changes (see figure 1B and C for examples of craniofacial defects in the mouse and zebrafish). In the mouse, for example, alcohol administration on gestational

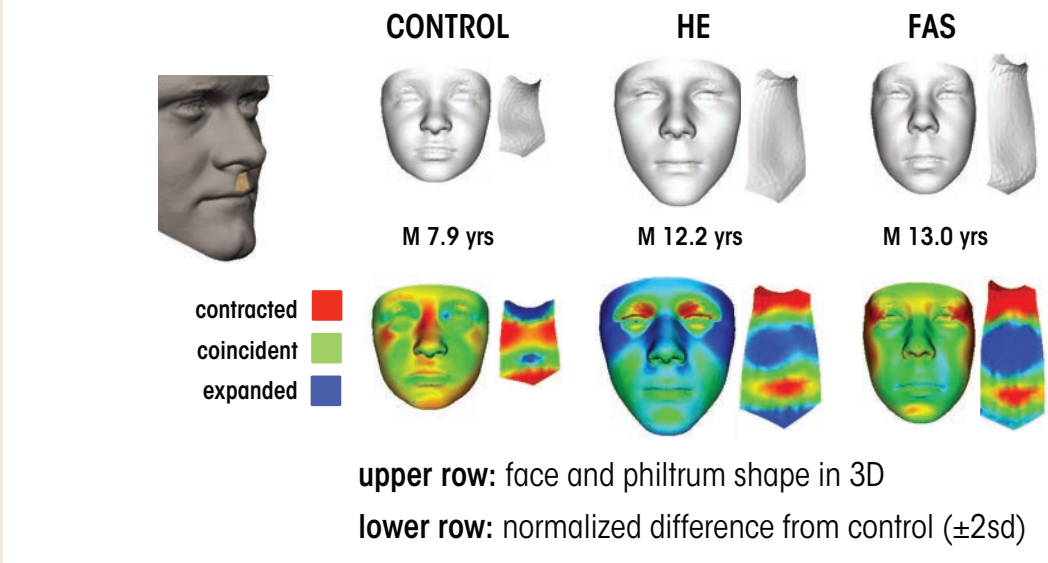

Figure 3 Three-dimensional facial imaging used to detect the effects of prenatal alcohol exposure. Each case shows face and philtrum (ridge under nose) shape as well as heat maps indicating significant regions of difference from age- and sex-matched control subjects. The control case shows an unexposed individual with some flattening across the nasal bridge, a small jaw and a strongly grooved philtrum. The heavily exposed (HE) case is an individual with known exposure without clinically recognized fetal alcohol syndrome (FAS). The overall face size is average or larger and the upper part of philtrum is smooth. The FAS case shows a reduced face size and philtrum smoothness, best revealed in the philtrum heat map; red at outer canthi (outer edge of eye) identifies narrow palpebral fissures.

day (GD) 7, equivalent to approximately week 3 postfertilization in a human pregnancy, produces a constellation of facial malformations similar to those seen in FAS. Defects include severe midfacial hypoplasia, shortening of the palpebral fissures, an elongated upper lip, and deficient philtrum (Godin et al. 2010). However, alcohol exposure delayed a day and a half to GD 8.5 produces a distinctly different pattern of malformations, with mild hypoplasia and shortening of the palpebral fissures and upper lip but a preserved philtrum (Lipinski et al. 2012) (see figure 4A and B). These data suggest that maternal alcohol consumption, even before many women are aware that they are pregnant, can cause significant and selective facial alterations in their offspring. The distinctive facial phenotype of FAS depends on the timing of exposure, and other facial characteristics resulting from alcohol exposure during different critical periods are possible.

As with facial dysmorphology, basic science models illustrate that the timing of alcohol administration also produces differing patterns of brain malformations, which again may account for the variability in outcomes. O'Leary-Moore and colleagues (2011) recently reviewed the different brain changes following a single day of alcohol exposure during early fetal development in the mouse using magnetic resonance imaging (MRI). Alcohol exposure on GD 7 was particularly damaging to medial forebrain regions, with relative sparing of mesencephalic and rhombencephalic regions (Godin et al. 2010). The morphological changes induced by alcohol exposure on GD 8 included disproportionate volume reductions in the olfactory bulbs, hippocampus, and cerebellum and relative sparring of the pituitary and septal regions (Parnell et al. 2009). GD 9 exposure produced reductions in cerebellar volume, ventricle enlargement, and shape deviations in the cerebral cortex, hippocampus, and right striatum (Parnell et al. 2013). In contrast, offspring exposed to alcohol on GD 10 displayed enlarged ventri-

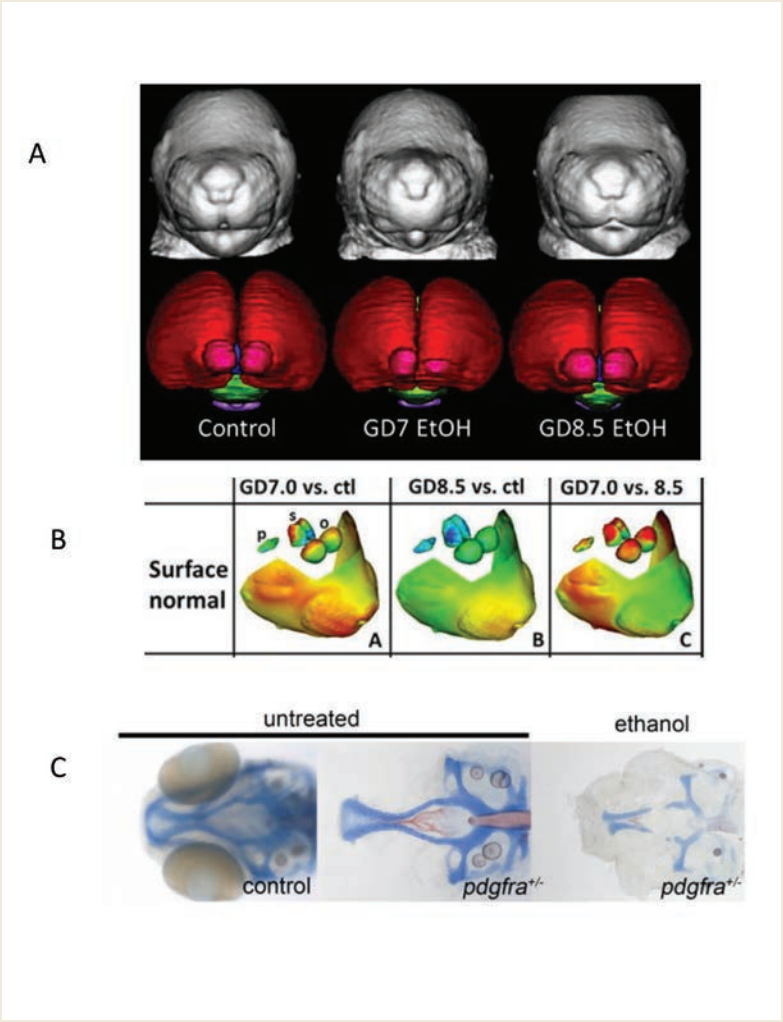

Figure 4 Magnetic resonance imaging (MRI) images showing the differential effect of different timing of exposure on face shape and brain morphology. **(A)** The left panel shows a control, whereas the two other panels show animals exposed on gestation day 7 and gestation day 8.5. The different timing produces differential effects on face and brain. **(B)** An illustration of how the shape analysis shown in figure 3 can be applied to the mouse images. The left panel shows the difference between an animal exposed on gestation day 7 versus a control. Red areas indicate a reduction in size. The middle panel shows gestation day 8 exposure versus control, note the absence of many red areas. The right panel shows the difference between the two exposure times. **(C)** Ethanol interacts synergistically with the *PDGFRA* gene. The two left most figures show an intact embryo and the dissected neurocranium of a stained *PDGFRA* heterozygote displaying normal morphology of the neurocranium. The right most panel shows how ethanol severely disrupts development of the anterior neurocranium and palate of the zebrafish. The homozygote, -/-, (not shown) is even more affected.

SOURCE: Photos in A and B are courtesy of Dr. Kathleen Sulik, University of North Carolina at Chapel Hill. Photos in C are courtesy of Dr. Johann Eberhart, University of Texas at Austin.

cles and disproportionate reductions in cortical volume (O'Leary-Moore et al. 2010). Brain-imaging studies in humans with FASD also find morphological alterations in many of these brain structures (see Moore et al. 2014 for review), which may vary depending on the specific timing of alcohol exposure. These exposure timing–dependent brain changes likely produce different behavioral outcomes, contributing to the variability in impairment seen clinically. Ultimately, understanding the relationship between alcohol exposure parameters and variability in outcome, including different behavioral phenotypes, may improve detection of individuals with FASD.

Recent studies also suggest that the interaction of alcohol with specific genes involved in brain development and the development of facial features may affect the FASD phenotype. A study in zebrafish, for example, examined the interaction of alcohol with the gene for platelet-derived growth factor receptor alpha (Pdgfra) (McCarthy et al. 2013). This gene is involved in cellular migration and proliferation and is necessary for proper migration of neural crest cells, which contribute to the formation of diverse structures, including the face. The researchers found that pdgfra interacts with alcohol to protect against severe craniofacial defects. Specifically, more than 60 percent of zebrafish heterozygous for the pdgfra gene showed cranial facial defects after alcohol exposure compared with only about 10 percent of the alcohol-treated wild-type embryos (figure 4C). A genome-wide genetic scan, using single nucleotide polymorphisms (SNPs), in humans with FASD supports these findings, showing that craniofacial phenotypes seen in FASD are linked to the *PDGFRA* gene (McCarthy et al. 2013). A more recent

Glossary

Apoptosis: A process of programmed cell death.

Brain-derived neurotrophic factor (BDNF): A protein secreted in the brain to support the survival of neurons; it plays a role in the growth, differentiation, and maintenance of these cells.

Cerebellum: An area of the brain important for coordinating motor function, as well as playing a role in simple learning and attention.

Corpus callosum: A wide bundle of fibers that connects the left and right hemispheres of the brain.

Cortex: The outer layer of the brain that is composed of folded gray matter and associated with perception, voluntary movement, and integration of information to support cognitive functions such as memory, language, and abstract thinking, among others.

cAMP response element–binding protein (CREB): A protein that binds to certain stretches of DNA and influences activation of genes.

Epigenetics: The study of factors that affect gene expression without directly changing the DNA.

Epigenome: Chemical changes to the DNA and histone proteins that affect gene expression.

Ethyl glucuronide: A byproduct of alcohol metabolism formed in the body after alcohol consumption.

Ethyl sulphate: A byproduct of alcohol metabolism formed in the body after alcohol consumption.

Fatty acid ethyl esters: The products of a reaction between ethanol and fatty acid cells.

NMDA receptors: A receptor in the brain activated by the neurotransmitter glutamate. Among its many roles, NMDA receptors help control synaptic plasticity (the ability of the brain to change and evolve), learning and memory.

Oxidative stress: When there is an imbalance between the body's production of reactive oxygen species (free radicals), and antioxidants, which defend against reactive oxygen species.

Pallidum: Refers to the globus pallidus, a subcortical brain structure involved in the regulation of voluntary movement.

Palpebral fissures: The opening between the upper and lower eyelids; length is measured as the distance between the inner to outer eye corners.

Peptide: Chains of 10 to 50 amino acids.

Philtrum: The typically vertical groove between the upper lip and nose.

Phosphatidylethanol: A metabolite of alcohol, created when phospholipase D interacts with alcohol.

Teratogen: A substance that interferes with development and causes birth defects.

Thalamus: A part of the vertebrate brain made up of two symmetrical halves deep in the middle of the brain. Among other roles, it is involved in relaying sensory and motor signals to the cerebral cortex, and regulating consciousness, sleep, and alertness.

study in zebrafish found that a gene involved in the development of the embryonic axis, *vangl2,* interacts strongly with alcohol (Swartz et al. 2014). This finding provides another potential gene target to help identify significant sources of variance in terms of susceptibility to the facial characteristics and perhaps changes in brain seen in FASD (see McCarthy and Eberhart 2014 for a recent review of genetic factors involved in FASD).

Basic research in people with FASD also is providing new methods for assessing alcohol's clinical effects. Studies have identified several relationships between facial measurements and brain structure in FASD (reviewed in Moore et al. 2014). For example, shorter palpebral fissures predict volume reductions in the bilateral ventral diencephalon, a thinner anterior corpus callosum, and a thicker right inferior frontal cortex. The smoothness of the philtrum predicts volumetric reductions in the thalamus and the left pallidum. Facial measures also predict brain maturation patterns: Children with greater facial dysmorphia displayed a linear pattern of cerebral cortex growth, at least from childhood through adolescence, rather than the developmentally appropriate inverted U-shaped trajectory. Continued research examining the relationship between face, brain, and behavioral outcomes resulting from prenatal alcohol eventually may lead to the identification of specific patterns of anomalies that can be used to better identify FASD and improve diagnosis. Moreover, patterns of outcomes may illuminate mechanisms by which alcohol disrupts developmental processes, which can inform treatment strategies. It must be cautioned, however, that the utility of these findings will largely depend on their sensitivity and specificity to alcohol.

Treatment Strategies

Although no specific treatments exist that are unique for FASD, the similarity between the cognitive and behavioral characteristics of FASD and other disorders provides a framework for treatment development. For example, estimates indicate that anywhere from around 50 percent to over 90 percent of individuals with FASD who have been clinically referred meet diagnostic criteria for attention deficit/hyperactivity disorder (ADHD) (Bhatara et al. 2006; Fryer et al. 2007). One approach would be to treat individuals with FASD with medications, such as stimulants, that have been successful in treating ADHD. However, mixed results have been found with stimulant treatment in clinical studies on FASD. For example, treatment with stimulant medications may reduce hyperactivity, with little evidence for beneficial effects on attention (e.g., Doig et al. 2008). Other studies have noted variable and unpredictable effects (O'Malley and Nanson 2002) or even poorer outcomes (Frankel et al. 2006) in FASD. Animal studies find that perinatal alcohol exposure leads to hyperactivity and that treatment with stimulants later in life increases, rather than attenuates, animals' spontaneous locomotor behaviors (Hannigan and Berman 2000). Atomoxetine (Strattera), a nonstimulant medication for ADHD, also is often used in the treatment of attention problems in FASD and a clinical trial of its effectiveness in FASD is under way.

Researchers are using their knowledge of the mechanisms underlying alcohol's toxic effect on the fetus to design preclinical models that test the efficacy of a number of pharmaceutical agents to mitigate alcohol-related impairments (Idrus and Thomas 2011). For example, prenatal alcohol exposure results in deficient activation of cyclic-AMP response element–binding protein (CREB), which can impair brain plasticity, a process of neural change important for brain development, learning, and memory. The pharmaceutical vinpocetine, a vasodilator and anti-inflammatory agent, inhibits the enzyme phosphodiesterase type 1, an action that prolongs CREB activation and thereby strengthens synaptic connections. Studies in animal models find that vinpocetine attenuates alcohol-related impairments in cortical plasticity and reduces learning and memory deficits associated with developmental alcohol exposure (Medina 2011). Clinical trials in humans with dementia have shown some promise and no serious adverse consequences, although results with other disorders, such as ischemic stroke remain inconclusive (Medina 2011). Clinical studies to evaluate this drug in humans with FASD are an important next step.

Preclinical models of FASD also have used neuroprotective peptides to mitigate neuropathologies and behavioral impairments resulting from developmental alcohol exposure. Originally, researchers administered the neuroactive peptides NAP and SAL concurrently with alcohol to pregnant rodents in an attempt to prevent alcohol-induced damage in the offspring. Subsequently, researchers have administered the peptides to adolescent rodents exposed to alcohol prenatally and found that they can reduce deficits in behavioral tasks, such as a T-maze and a Morris water maze (Incerti et al. 2010). The peptides also reversed alcohol-related changes in NMDA receptors in the hippocampus and cortex. These peptides are being developed to treat a number of neurodegenerative diseases and may prove useful in the treatment of FASD.

Nutritional Interventions

Research clearly shows that nutritional factors influence alcohol's damaging effects on the fetus. Moreover, it is possible that postnatal nutrition also might influence physical and behavioral outcomes in individuals with FASD.

Prenatal Nutritional Interventions

Some studies suggest that women who drink during pregnancy have nutritional deficits relative to control subjects. In one study, for example, May and colleagues (2014*b*) examined the

nutritional status of a group of South African mothers who gave birth to children with FASD compared with a group of mothers who gave birth to children without FASD. The mothers of children with FASD were more likely to be deficient in several vitamins, including vitamins A, B6, choline, C, D, and E; minerals, including calcium, iron, and zinc; and omega-3 fatty acids. Deficiencies in these micronutrients during pregnancy can contribute to abnormal fetal development (Nyaradi et al. 2013) and may further exacerbate the damaging effects of alcohol on the developing embryo and fetus. In animal models, maternal nutritional deficiencies (e.g., zinc or iron) during pregnancy increase the detrimental effects of prenatal ethanol on brain development and subsequent behavior in offspring. For example, the combined insults of prenatal alcohol exposure and iron deficiency resulted in increased cerebellar apoptosis (cell death), reduced myelin content, and greater impairments in cerebellar-dependent classical eyeblink conditioning compared with either insult alone (Rufer et al. 2012).

Research also finds that nutritional supplementation during pregnancy may attenuate ethanol's teratogenic effects. In one relatively small study (Avalos et al. 2011), low to moderate alcohol consumption during pregnancy resulted in a twofold increase in small-for-gestational-age infants relative to mothers who abstained. However, the offspring of women who consumed alcohol and reported taking nutritional supplements during pregnancy were no different on these measures than the offspring of abstainers (Avalos et al. 2011). The study reported similar results for preterm births. In a study of pregnant women currently being conducted in the Ukraine, researchers compared the birth outcomes of women given vitamin supplements with those not given supplements. Both groups included women who were consuming alcohol. Although the researchers still are analyzing the results, preliminary reports indicate that the women consuming alcohol and taking micronutrient supplements have a lower rate of babies with FASD than women in the nonsupplement group (Chambers et al. 2013).

Other nutritional interventions target oxidative stress. Alcohol increases oxidative stress, which in turn can initiate a cascade of events that eventually lead to widespread CNS cell loss during development (Brocardo et al. 2011). In rodent models of FASD, pregnant females given nutrients high in antioxidant properties (e.g., vitamin C, vitamin E, omega-3 fatty acids) during the time they also are given alcohol, give birth to offspring with reduced oxidative stress and cell loss, and fewer behavioral impairments (Brocardo et al. 2011; Patten et al. 2013*a*). Although antioxidant treatments in animal models are encouraging, researchers prematurely terminated a clinical trial utilizing high doses of vitamins C and E in women with alcohol-exposed pregnancies because of safety concerns (Goh et al. 2007).

Other studies are examining the role of nutritional supplements on gene transcription. Animal models of FASD demonstrate that prenatal alcohol exposure significantly affects gene transcription through epigenetic modifications (Ungerer et al. 2013). Specifically, alcohol-induced changes in DNA methylation, histone modification, and noncoding RNAs may alter the expression patterns of numerous genes important for neurodevelopment and behavior. Nutrients such as choline, betaine, folic acid, methionine, and zinc can influence these epigenetic profiles and can potentially attenuate alcohol-induced changes to the epigenome. For example, supplemental choline in rats exposed to alcohol during development alters alcohol-related changes in global DNA methylation in the hippocampus and prefrontal cortex (Otero et al. 2012) and significantly attenuates ethanol-induced hypermethylation of genes in the hypothalamus (Bekdash et al. 2013). Additionally, access to a diet supplemented with nutrients that act as methyl donors normalized changes to DNA methylation patterns in embryonic tissue following a single binge exposure to alcohol in early gestation (Downing et al. 2011). These nutrient-induced changes to the epigenome may contribute to the behavioral and cognitive improvements seen in alcohol-exposed rodents following supplementation (see below).

Additional preclinical research indicates that supplementation with beta-carotene (provitamin A), nicotinamide (the amide of vitamin B3), and zinc all may reduce alcohol's effects on fetal development, including cell loss, fetal dysmorphology, and cognitive impairments (reviewed in Idrus and Thomas 2011). These animal studies highlight the protective effects that nutrient supplementation can have on development during alcohol exposure. Improving the nutritional status of pregnant women, especially those who consume alcohol, will likely result in improved outcomes in offspring.

Postnatal Nutrient Interventions

Nutritional status also can affect cognitive development throughout childhood (Bryan et al. 2004). Recent studies have examined the nutritional intake of children with FASD. Based on their dietary habits, many children with FASD are not consuming adequate or daily-recommended amounts of omega-3 fatty acids, vitamin D, and choline (figure 5A) (Fuglestad et al 2013; Werts et al. 2014). Although these studies have some limitations—including low sample sizes, comparison with national data rather than a local control group, and relying on self-reports—they do indicate that individuals with FASD ingest inadequate levels of certain nutrients and therefore may benefit from nutrient supplementation. In rodent models, administering these micronutrients during or shortly following developmental alcohol exposure significantly mitigated ethanol-induced impairments on brain and behavior (figure 5B) (Idrus and Thomas 2011; Patten et al. 2013*b*). For example, animal

models have shown that choline can attenuate ethanol's adverse effects on both brain and behavioral development when administered postnatally, long after alcohol exposure has ceased (Ryan et al. 2008).

Clinical studies currently are underway to examine the effectiveness of choline supplementation in children with FASD. Preliminary results from a study examining choline supplementation in children with FASD aged 2.5–4.9 years suggest that supplemental choline is both feasible and tolerable, with few side effects being reported (Wozniak et al. 2013). The results on behavioral measures should be available soon. In addition to nutrient supplementation, at-risk populations may benefit from better access to food naturally high in nutrients found to improve outcomes in animal studies.

Exercise Interventions

Exercise has many beneficial effects on brain and behavior outcomes. Reports in both human and rodents indicate that exercise improves learning and memory; increases circulating proteins that support brain function, such as brain-derived neurotrophic factor (BDNF); and, in rodents, increases generation of new neurons in the adult hippocampus (Voss et al. 2013). In addition, clinical studies show beneficial cognitive effects following exercise in normal aging, Alzheimer's disease, and Parkinson's disease (reviewed in Yau et al. 2014). No published studies to date have implemented an exercise intervention to improve cognitive and behavioral outcomes in individuals with FASD, but preliminary data and preclinical results are promising, as described below.

Studies suggest that running may enhance learning and memory in rodents prenatally exposed to alcohol. Rodents will run multiple kilometers per day when they have access to a running wheel, making it ideal for an exercise intervention. Indeed, access to a running wheel significantly attenuates spatial learning and memory impairments in adult rats exposed to alcohol during development (Christie et al. 2005; Thomas et al. 2008). In addition, these improvements in cognitive function following exercise are associated with exercise-induced enhancements in BDNF and adult hippocampal neurogenesis, both of which are influenced by developmental alcohol exposure (Gil-Mohapel et al. 2010).

However, the long-term effects of short periods of exercise may be limited. For example, increases in BDNF return to normal levels within 2 weeks following exercise (Gil-Mohapel et al. 2010). That said, the benefits of exercise may be prolonged through additional environmental experiences, such as those provided by raising animals in an enriched, stimulating environment. In fact, Hamilton and colleagues (2014) have found that the combination of wheel running followed by enrichment significantly increases adult neurogenesis relative to wheel running alone in alcohol-exposed rats. Similarly, exercise plus enrichment mitigates alcohol-induced impairments on behavioral tasks, such as trace eyeblink conditioning and contextual fear conditioning. Behavioral improvement was associated with increases in adult neurogenesis

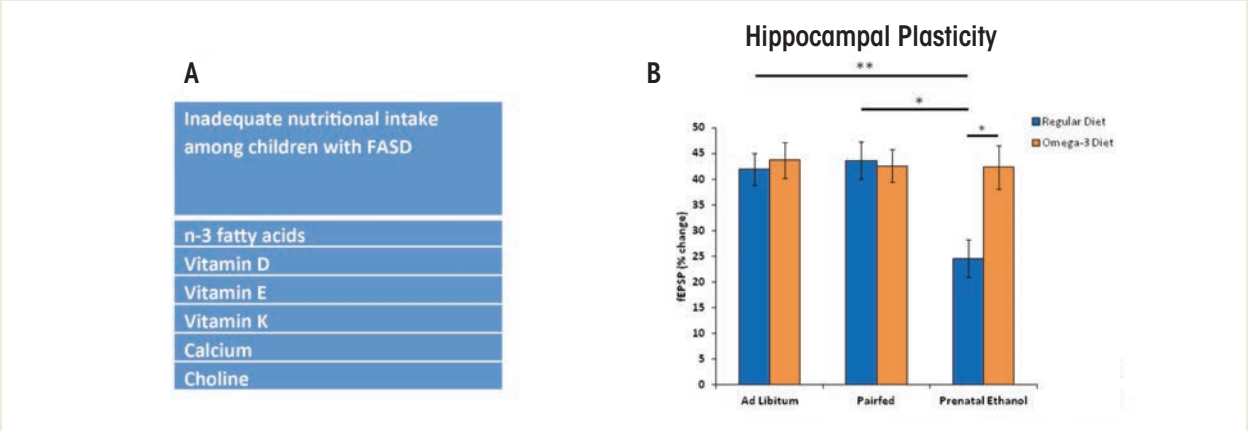

Figure 5 **(A)** Many children with fetal alcohol spectrum disorder (FASD) are not consuming adequate or recommended levels of nutrients (Fuglestad et al. 2013). **(B)** Rodent models have shown that postnatal supplementation with various nutrients, including vitamin D, choline, and omega-3 fatty acids can reduce the severity of FASD. As shown in B, prenatal alcohol exposure in a rodent model impaired hippocampal plasticity, as measured by reduced long-term potentiation (blue bars = normal diet), an effect attenuated with postnatal supplementation with omega-3 fatty acids (orange bars = omega-3 supplemented diet) (Patten, et al. 2013*b*). Such studies illustrate how preclinical and clinical studies may inform one another in the development of effective interventions for FASD.

NOTE: * = significant group differences at $p \leq 0.05$; ** = significant group differences at $p \leq 0.01$)

(Hamilton et al. 2014). In addition, specific motor training can have beneficial effects on the structure and function of the cerebellum among rodents exposed to alcohol prenatally (Klintsova et al. 2000).

In translating these preclinical findings to human studies, researchers may need to tailor their exercise interventions to accommodate some of the motor impairments evident in FASD. A recent meta-analysis of motor skills in children and adolescents with FASD reported impairments in balance, motor coordination, and ball skills (Lucas et al. 2014).

A number of clinical research programs are using these findings to develop motor training and/or exercise interventions and investigate their efficacy in individuals with FASD. None have published results yet, except in abstract form. The following are two promising examples:

- Researchers at the University of Washington are using sensorimotor training via a virtual-reality system to try to improve motor deficits. Participants stand on a moveable surface, wearing virtual-reality goggles as the program attempts to train them to use sensory information for balance (Jirkowic et al. 2014).

- Researchers at the University of the Fraser Valley are using strength-based interventions in an attempt to improve motor skills and cognitive function in FASD. In this intervention, clinicians create a physical activity and motor skills program based on an individual child's strengths, with the hope that such training may generalize to some aspects of executive functioning, attention, and visuospatial processing in children with FASD (Keiver et al. 2014).

Conclusion

FASD can be difficult to treat for a number of reasons. First, identifying individuals with prenatal alcohol exposure can be a challenge. Although the characteristics of FAS are well defined, alcohol-affected children who do not meet the criteria for FAS or for whom exposure histories are unknown are more difficult to ascertain. Children who are diagnosed earlier have improved clinical outcomes (Streissguth et al. 2004), highlighting the need for early identification. Although there are methodological and ethical concerns that must be addressed, sensitive and specific biomarkers of exposure or effect would improve identification. Continued research examining the interrelations among alcohol-induced face and brain malformations and neurocognitive outcomes using both human and animal models may yield novel means for identification and/or novel specific targets for interventions.

Overall, studies with animal models of FASD demonstrate a wide array of benefits of pharmacological, nutritional, and environmental interventions to both brain structure/function and behavior. However, relatively few clinical studies have evaluated such treatments in FASD. There are some important potential limitations to these treatments. First, many of the treatments have very specific targets and consequences, whereas the range of deficits in FASD is quite varied. For example, in animal models of FASD, nutritional supplementation with choline has a greater positive effect on hippocampal function compared with cerebellar function; in contrast, motor training may be better able to target cerebellar effects in this population. Interventions that use multiple intervention strategies (e.g., nutrition and exercise) as well as more traditional interventions (educational, speech, occupational and/or physical therapies) may mitigate a wider range of cognitive impairments when translated to clinical cases of FASD. Given the numerous successes in identifying potential interventions in preclinical research, the upcoming years should increase translation of these findings to clinical research and eventually to health care settings.

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Cognitive Neuroscience Approaches to Understanding Behavior Change in Alcohol Use Disorder Treatments

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Researchers have begun to apply cognitive neuroscience concepts and methods to study behavior change mechanisms in alcohol use disorder (AUD) treatments. This review begins with an examination of the current state of treatment mechanisms research using clinical and social psychological approaches. It then summarizes what is currently understood about the pathophysiology of addiction from a cognitive neuroscience perspective. Finally, it reviews recent efforts to use cognitive neuroscience approaches to understand the neural mechanisms of behavior change in AUD, including studies that use neural functioning to predict relapse and abstinence; studies examining neural mechanisms that operate in current evidence-based behavioral interventions for AUD; as well as research on novel behavioral interventions that are being derived from our emerging understanding of the neural and cognitive mechanisms of behavior change in AUD. The article highlights how the regulation of subcortical regions involved in alcohol incentive motivation by prefrontal cortical regions involved in cognitive control may be a core mechanism that plays a role in these varied forms of behavior change in AUD. We also lay out a multilevel framework for integrating cognitive neuroscience approaches with more traditional methods for examining AUD treatment mechanisms.

Key words: Alcohol use, abuse, and dependence; alcohol use disorder; neuroscience; cognitive neuroscience; brain; cognition; neural mechanisms; pathophysiology; behavior change; behavioral intervention; relapse; abstinence; treatment

Understanding the mechanisms that underlie recovery from alcohol use disorder (AUD) is critical to advancing AUD treatment science (Huebner and Tonigan 2007; National Institute on Alcohol Abuse and Alcoholism [NIAAA] 2009). Scientific progress over the last three decades has led to the development of a number of effective behavioral and pharmacological AUD interventions (Dutra et al. 2008). However, even evidence-based treatments are only modestly effective. For example, reported rates of nonresponse to treatment interventions in major AUD treatment studies have ranged from 30 percent to 85 percent (Anton 2006; Johnson et al. 2007; McKay 2009; Project MATCH Research Group 1997). There is a general consensus that improving AUD behavioral intervention outcomes requires an understanding of the mechanisms that underlie behavior change in effective treatments (Magill and Longabaugh 2013; Morgenstern and McKay 2007). Thus, building a strong foundation for AUD treatment science includes answering the question of how, not just whether, a treatment is effective (Kazdin 2007).

To date, research on the mechanisms of effective AUD treatments that underlie behavior change have made limited progress, suggesting the need for major revisions in the theory and methods used for this work. Cognitive neuroscience may provide the tools for those revisions. Indeed, the pathophysiological processes that maintain AUD, such as craving, relapse, and withdrawal, are increasingly being understood in terms of the functioning of specific neural systems. As such, any psychosocial treatment for AUD that effectively changes behavior must interact at some level with these processes and, therefore, must influence these same neural systems. This article will review what cognitive neuroscience can tell us

about the neural bases of AUD and the mechanisms by which psychosocial treatments may function to elicit behavior change in AUD patients.

Psychosocial Treatment Mechanisms Research in AUD

There is a relatively large research literature on AUD behavioral treatment mechanisms (Huebner and Tonigan 2007; Longabaugh et al. 2013). This research largely represents an extension of assumptions and methods used to test treatment efficacy (Kazdin and Nock 2003; Morgenstern and McKay 2007; Wampold 2001). It has tested the treatment theories that guide evidence-based treatments using a set of mediation analysis procedures embedded within a clinical trials framework (Nock 2007). Stated succinctly, treatment theories postulate that the treatments work via some unique ingredient, often referred to as a specific effect—that is not present in other treatments (Morgenstern and McKay 2007). For example, theories postulate that motivational interviewing (MI) increases patients' motivation to change their behavior (Miller and Rose 2009) and that neither a weak control condition like psychoeducation nor even a bona fide effective treatment like 12-step facilitation affects a patient's motivation to change (Slaymaker and Sheehan 2013). Unfortunately, reviews of this literature generally conclude that there is limited support for most AUD treatment theories (Apodaca and Longabaugh 2009; Morgenstern and McKay 2007; Longabaugh et al. 2013). Indeed, most effective evidence-based AUD behavioral interventions yield equivalent outcomes even among subgroups where one would expect to find a difference. For example, MI typically has not proven superior to other AUD treatments among individuals with low motivation to change (Morgenstern and McKay 2007).

Even in instances where tests do not involve comparing treatments, it has often been difficult to establish seemingly straightforward links between treatment mediators and outcome. For example, Kelly and colleagues (2014) examined whether changes in peer networks mediated improved outcomes in 12-step treatment for young adults. Findings indicated that peer networks changed in the expected direction: posttreatment participants had fewer friends who used substances and more friends who abstained. Both greater affiliation with self-help organizations and changes in peer networks predicted improved outcome. However, contrary to prediction, the link between greater self-help affiliation and improved outcome was not mediated by changes in social networks. The authors concluded that more needs to be understood about how affiliation with self-help works to improve outcomes among youth with AUD.

It is important to note that some AUD treatment mediation studies have yielded important positive findings. For example, Moyers and colleagues (2009) found that improved outcomes in MI were mediated by increases in client motivational statements during treatment sessions. In addition, studies have consistently found that expected mediators such as motivation to change, self-efficacy, and social support for abstinence predict treatment outcome as well as improve during treatment, even though support for full mediation or specific effects generally has been absent. Overall, mediation analysis research has yielded less insight than expected about how AUD behavioral treatments work (Longabaugh et al. 2013). Given the relatively limited progress to date, it seems likely that major revisions in the theory and methods used to understand mechanisms of behavior change in AUD will be needed to advance this critical area of inquiry.

A major challenge to improving the informative value of AUD treatment mechanisms research is identifying the right measures to index the psychological processes that are hypothesized to mediate behavior change. Most of the conceptual frameworks and methods used to examine AUD treatment processes have not been revised to incorporate recent major conceptual and methodological advances for understanding the motivational, cognitive, affective, and, ultimately, neural processes that promote behavior change (Morgenstern et al. 2013). For example, constructs such as "motivation for change," "peer networks," or "coping skills" are very complex, and self-report measures designed to index them may encompass multiple psychological processes, some of which may relate to behavior change and others which may not. Furthermore, behavior change may depend upon psychological processes that are largely outside of conscious awareness and therefore not accessible by self-report measures. Moreover, such constructs may be difficult to relate to the underlying pathophysiology of addiction, which is understood increasingly in terms of highly specific affective, motivational, cognitive and neural processes. Cognitive neuroscience may hold the key to allowing researchers to use all of the processes to examine psychosocial treatment mechanisms.

Why Use Cognitive Neuroscience Approaches?

There are several reasons why understanding psychosocial treatment mechanisms at the neural level will be critical for advancing AUD treatment. Any psychosocial treatments for AUD that are effective at changing behavior must interact at some level with the pathophysiological processes that maintain AUD, which themselves are being understood increasingly in terms of the functioning of specific neural systems. Indeed, identifying neural systems that play a role in behavior change in psychosocial treatments can help researchers hone current treatments and develop more effective ones. For example, it can

facilitate more effective integration of behavioral treatments with medications, a goal that so far has proven elusive using purely clinical approaches (Combine Study Research Group 2006). In addition, measuring the functioning of brain systems involved in behavior change in a given treatment, especially when combined with genetic biomarkers, may be used to identify patients who are likely to respond to that treatment, another goal that has been elusive using purely clinical approaches (Project MATCH Research Group 1997). Other mental disorders that commonly co-occur with AUD, such as mood and anxiety disorders, also are now being understood in terms of the functioning of specific neural systems.

Among neuroscience approaches, cognitive neuroscience approaches have the most value for understanding psychosocial treatment mechanisms. Cognitive neuroscience approaches include a number of different methods aimed at understanding the relationship between relatively complex behaviors such as memory, attention, language, emotion and decisionmaking, and the structure and function of large-scale neural systems over relatively brief time periods (seconds). At a pragmatic level, cognitive neuroscience methods, such as structural and functional magnetic resonance imaging, allow for the noninvasive study of neural functioning in human subjects, which is critical in patient-oriented translational research. Also, compared with molecular or cellular approaches, the constructs addressed by cognitive neuroscience are nearer to the clinical phenomenology of AUD, as well as to the psychological constructs that have thus far been used to explain mechanisms of behavior change in AUD treatment.

Although cognitive neuroscience approaches may address certain clinically relevant questions that may improve the efficacy of psychosocial treatments, there is nothing inherently more valid or true about the neural level of understanding treatment mechanisms. A framework that integrates across multiple levels of analysis—social, interpersonal, behavioral, cognitive, and neural—will ultimately yield the most clinically useful understanding of behavior change. This would bring AUD research in line with the overall shift in mental health research to understand mental disorders and their treatments using a multilevel framework that includes neuroscience approaches (National Institute of Mental Health 2013).

Neurocognitive Models of Addiction Pathophysiology

Arguably, more is known about the pathophysiology of AUD and other substance use disorders than of any other mental disorders. This is in large measure attributed to the development of highly valid animal models of drug and alcohol addiction that mimic the basic elements of human addiction, including drug self-administration, conditioned-place preference, and cued relapse. Researchers have coupled these animal models with invasive methods for measuring and manipulating neural function with a high degree of spatial and temporal localization in order to provide a detailed picture of the neural mechanisms that maintain addiction. The consensus that has emerged from this extensive body of work, reviewed at length elsewhere (Everitt and Robbins 2005; Koob and Le Moal 2001; Robinson and Berridge 2008), is that drugs and alcohol trigger dopamine-induced sensitization within incentive neural systems, in particular the ventral striatum, which normally motivate and guide the seeking of natural rewards but, after being sensitized, come to motivate and guide the seeking of drugs and alcohol.

In parallel with this animal literature, a large number of functional imaging studies in patients with substance use disorders have revealed neural systems whose activity is increased by exposure to drug and alcohol cues. Schacht and colleagues (2013) conducted a recent meta-analysis of functional magnetic resonance imaging (fMRI) studies in which AUD patients were exposed to alcohol-related cues. Their analysis showed that, consistent with animal models, alcohol cues reliably elicit neural activation in the ventral striatum. It also showed that alcohol cues elicit activation in cortical regions involved in decisionmaking, cognitive control, and emotional experience, such as the ventromedial prefrontal cortex, the anterior cingulate cortex, and the insula. Importantly, the analysis found that the ventral striatum was the region in which activity was most consistently related to behavioral and self-report measures of alcohol seeking, such as craving, and in which treatment most consistently reduced activity.

More recent work has examined the role of prefrontal cortical systems in various inhibitory, cognitive control, and decisionmaking functions that moderate or shape alcohol-seeking motivation in the service of long-term goals and the avoidance of negative consequences. A number of studies have shown that AUD is associated with structural and functional abnormalities in the prefrontal cortex (Goldstein et al. 2004; Volkow et al. 1994), along with neuropsychological impairments in a variety of executive functions mediated by the prefrontal cortex (Sullivan et al. 1993, 1997). Bechara and colleagues (2000), for example, have found a critical role for the ventromedial prefrontal cortex in the successful performance of behavioral tasks that require the forgoing of short-term, but certain, rewards to avoid long-term, but uncertain, negative consequences. Subsequently, they demonstrated that AUD patients show impairments on these same behavioral tasks, similar to impairments seen in patients with ventromedial prefrontal cortex damage (Bechara and Damasio 2002; Bechara et al. 2002). The decisions in these tasks resemble an AUD patient's decision to abstain or relapse, which is a decision

to obtain a short-term reward (alcohol) without regard to a variety of uncertain, long-term negative consequences. Additionally, fMRI studies have linked dysfunction in the dorsolateral prefrontal cortex to impaired inhibitory control in AUD (Li et al. 2009). One study (Field et al. 2007) has linked AUD with impairments in delayed discounting and executive attention functions, both of which depend upon prefrontal cortical regions. A more recent study (Naqvi et al. 2015) finds that, compared with social drinkers, AUD patients are less able to reduce cue-induced craving by thinking about long-term negative consequences of alcohol use. This ability is a cognitive regulation function that fMRI studies in cigarette smokers show depends upon functional interaction between the dorsolateral prefrontal cortex and the ventral striatum (Kober et al. 2010).

Together, this work suggests that AUD is maintained by the interaction of two neural adaptations that arise as a result of chronic alcohol use:

- The dopamine-induced sensitization of the ventral striatum to alcohol and alcohol-related cues, leading to enhanced emotional and behavioral reactivity to these stimuli; and

- Impairments in prefrontal cognitive control functions, leading to an inability to regulate emotional and behavioral hyperreactivity to alcohol and alcohol-related cues that are driven by a sensitized ventral striatum.

These neural adaptations make it difficult for AUD patients to control alcohol use in the face of negative consequences, a hallmark of AUD. If this model is correct, then effective treatments for AUD should either directly downmodulate the ventral striatum reactivity to alcohol and alcohol-related cues, or they should enhance the prefrontal cortex's ability to regulate ventral striatal reactivity to alcohol and alcohol-related cues according to long-term goals and consequences.

Neurocognitive Predictors of Relapse

If AUD patients remain abstinent after they stop drinking, it suggests that the behavior change mechanisms of their treatment worked. Conversely, if they relapse after a period of abstinence, it suggests that the same behavior change mechanisms failed. Thus, it may be possible to infer mechanisms of behavior change by identifying neural measures that predict relapse and abstinence. One of the first studies to do this, by Wrase and colleagues (2008), measured regional brain volumes in several reward-related brain regions in detoxified AUD patients. They found that the volume of the amygdala was lower in patients who relapsed to heavy drinking by 6 months, compared with those who abstained. Subsequently, Cardenas and colleagues (2011; Durazzo et al. 2011) showed that, compared with patients who abstained, patients who relapsed by 8 months posttreatment had relatively smaller total volume in the orbitofrontal cortex. Similarly, Rando and colleagues (2011) showed that patients with a smaller volume of gray matter in medial prefrontal regions, including the anterior cingulate cortex, relapsed more quickly and were more likely to drink heavily during relapse than patients with larger gray-matter volumes. What is not clear from these studies is whether a reduction in volume represents a loss of function, which would tend to increase relapse risk in the case of prefrontal cognitive control systems that regulate alcohol seeking, or whether the reductions represent a gain of function, which would tend to increase relapse risk in the case of incentive motivational systems that promote alcohol seeking.

These limitations may be addressed by functional imaging studies that examine how neural activity measured under various conditions predicts relapse. Several of these studies have been completed to date:

- Seo and colleagues (2013) measured neural activity during alcohol cue exposure, stressful imagery, and neutral imagery. They found that activity in the ventromedial prefrontal cortex and anterior cingulate cortex during neutral imagery predicted relapse within 3 months.

- In a small study, Braus and colleagues (2001) showed that alcohol cue–elicited activity in the ventral putamen predicted relapse within 3 months.

- Grusser and colleagues (2004) showed that alcohol cue–elicited activity in the putamen, anterior cingulate, and adjacent medial prefrontal cortex predicted relapse at 3 months.

- Heinz and colleagues (2007) failed to show a correlation between alcohol cue–elicited neural activity and relapse within 6 months but did show that neural activity elicited by positive emotional pictures within the thalamus and ventral striatum predicted abstinence.

- Camchong and colleagues (2013) showed that lower resting-state connectivity between "reward" and "executive control" regions during early abstinence predicted relapse within 6 months. They also found that resting-state connectivity between these systems was negatively correlated with poor inhibitory control in an affective go/no-go task.

Many of these functional imaging studies did not address patients' engagement in informal treatments such as 12-step groups during the follow-up period. This limitation makes it unclear whether neural activity was predictive of "intrinsic" abstinence capabilities,

or of the capacity to respond to these informal treatments. That said, together, these structural and functional imaging studies point toward neural systems that promote abstinence that already has been initiated. As such, they may not be generalizable to understanding the neural mechanisms by which actively drinking AUD patients reduce their alcohol use. This may bear upon the distinction between treatments intended to prevent relapse and treatments intended to initiate abstinence or to moderate alcohol use. Moreover, it is not clear whether results of studies examining predictors of abstinence and relapse in nontreatment samples can even be generalized to understand behavior change that results from effective treatments. This will require studies that examine neural functioning in treatment-seeking AUD patients both prior to and after completing treatment.

Neurocognitive Mechanisms of Existing, Evidence-Based AUD Treatments

A small number of studies have attempted to examine the specific neurocognitive mechanisms by which existing effective behavioral interventions change behavior, a concern that is central to mechanisms of behavior change initiation (MOBC) research (NIAAA 2009). In one study, Vollstädt-Klein and colleagues (2011) used fMRI to examine changes in neural activity elicited by alcohol-related cues both before and after participants received nine sessions of cue-exposure treatment (CET), which was added to supportive outpatient treatment. The researchers compared these patients with patients who received supportive outpatient treatment alone. They found that patients receiving CET showed a greater reduction in cue-elicited activity in the ventral and dorsal striatum, the anterior cingulate cortex, the precentral gyrus, the insula, and several prefrontal regions. This finding is consistent with a reduction in the rewarding interoceptive effects of alcohol as a result of CET.

DeVito and colleagues (2012) used fMRI to examine changes in neural activity related to the Stroop color–word interference task, which engages cognitive control and executive attention functions, in patients with substance use disorders that included AUD. Patients performed the Stroop task during fMRI both before and after receiving treatment. Half of the patients received treatment as usual from an outpatient drug treatment program along with 8 weeks of biweekly computerized cognitive behavioral therapy (CBT). The other half only received treatment as usual. Study authors found that patients receiving CBT improved their performance on the Stroop task and had decreased task-related activity in the anterior cingulate cortex (ACC), inferior frontal gyrus, and the midbrain. This is consistent with the theory that CBT improves general cognitive control functions. The study did not examine whether CBT changed neural activity related to alcohol-specific cognitive control functions, such as performance on an alcohol-specific Stroop task or cognitive regulation of alcohol craving, which would speak more specifically to the mechanisms of changing alcohol use behavior, as opposed to general self-regulatory mechanisms. Furthermore, this study did not examine AUD specifically but rather grouped patients with AUD with patients with other substance use disorders.

In another fMRI study, Feldstein Ewing and colleagues (2011) compared neural responses with alcohol cues during exposure to "change talk" and "counterchange talk," which are linguistic/semantic constructs hypothesized to mediate behavior change in MI. Study participants were AUD patients seeking treatment. The study found that exposing patients to alcohol-related cues while they listened to counterchange talk elicited activity in the ventral striatum, orbitofrontal cortex, and insula, whereas none of these areas showed any activity during change talk. These regions all play a role in representing the incentive value of rewards. This suggests that change talk may downmodulate the neural representations of the incentive value of alcohol-related cues. The study did not examine how these responses changed over the course of MI treatment, which would be necessary to infer whether this mechanism actually plays a role in this particular treatment.

These studies are important first steps; however, they possess a number of limitations. For example, none of them reported drinking outcomes after the interventions, which limits the ability to infer whether changes in neural functioning due to the interventions drive behavior change. Also, the control interventions were not themselves effective treatments that were missing only the hypothesized behavior change mechanism. This is important because existing evidence-based AUD treatments are complex, with multiple psychological components, many of which potentially affect behavior. This makes it necessary to examine neural mechanisms of behavior in existing treatments in a "top-down" fashion by decomposing complex intervention-specific constructs, such as change talk and coping skills into specific neurocognitive functions, such as reversal learning, cognitive control, emotion regulation, and response inhibition, both as they relate to alcohol and as they relate to general reward functions.

Novel AUD Treatments Derived From Neurocognitive Mechanisms

An alternative approach to understanding behavior change in AUD involves constructing novel interventions based upon our current understanding of the neurocognitive mechanisms of AUD pathophysiology and behavior change. As discussed above, AUD is associated with impairments in a number of executive functions that require regulation of subcortical reward-related and automatic processes by

prefrontal regions, including working memory, inhibitory control, reward learning, and craving regulation. Thus, interventions targeted at remediating these impairments should lead to reductions in alcohol use behavior. This provides both a new set of effective treatments and also indirectly tests hypotheses about the role of cognitive functions that are being remediated and, by extension, their neural substrates, in behavior change.

In a study by Houben and colleagues (2011*b*), non–treatment-seeking heavy drinkers completed 25 daily sessions of general working-memory training, including tasks designed to improve digit span, letter span, and visual-spatial working memory, all with progressively increasing difficulty. A heavy-drinking control group performed similar tasks that did not increase in difficulty. Participants in the active intervention group had improved working-memory function and, more importantly, significantly reduced the number of drinks they drank per week, compared with participants in the control group. This effect persisted for more than a month. The researchers also collected data on participant performance on an implicit alcohol association test, which measures the automaticity of processing alcohol-related information. They found that changes in working-memory capacity mediated the effects of working-memory training on reduction in alcohol use and that baseline performance on the implicit association test moderated this relationship. These findings provide circumstantial evidence that working-memory training reduced drinking by increasing control over automatic alcohol-related processing.

In another study, Houben and colleagues (2011*a*) examined the effect of a different cognitive task on non–treatment-seeking heavy drinkers. In a single session, one group of participants learned to provide "go" responses to non–alcohol-related cues and "no-go" responses to alcohol-related cues. Another heavy drinking group completed a version of the task requiring "go" responses to alcohol cues and "no-go" responses to nonalcohol cues. The researchers found that subjects in the no-go alcohol group significantly reduced their drinking in the week after the task, whereas subjects in the go alcohol group increased their drinking. Performance on this kind of go/no-go paradigm depends upon inhibitory control as well as reward-learning functions, suggesting that such functions may play a role in behavior change in AUD. However, this study did not provide a direct test of this model.

Both of these studies were relatively small and were undertaken in non–treatment-seeking heavy drinkers, as opposed to treatment-seeking patients diagnosed with AUD. Therefore, it is not known if these interventions would have similar effects in more severe, treatment-seeking AUD populations, who generally have more severe drinking problems and are likely to have a higher level of dysfunction in the neurocognitive functions being addressed by these interventions. It also is possible that the effects of these interventions were small, compared with potential effects of entering into a formal treatment with a high level of motivation for change, as is the case with many treatment seekers.

A larger study by Wiers and colleagues (2011) addressed these limitations. The study examined the effect of cognitive-bias modification (CBM) given to AUD patients prior to entering inpatient rehabilitation. CBM involved training patients to push a joystick away (an avoidance movement) whenever they saw an alcohol cue. This intervention is similar to the go/no-go task in that it involves repeatedly assigning a negative value (in this case a movement with intrinsic negative valence) to alcohol. Participants in the control groups received either no training or a training condition in which they had to make equal numbers of avoidance movements to alcohol cues and nonalcohol cues. The researchers followed patients for a year after they completed inpatient rehabilitation. The results showed that patients who received CBM prior to entering inpatient rehabilitation were somewhat less likely to relapse. And although the effect was just below the threshold for statistical significance, it provides circumstantial evidence that such implicit forms of reappraisal of alcohol's value may affect behavior change.

Summary and Limitations of Cognitive Neuroscience Approaches

A theme that emerges from the disparate lines of research reviewed here is that effective treatments for AUD serve to increase prefrontal cortex function and downmodulate the function of reward systems, especially the ventral striatum. Given the role of functional interactions between the prefrontal cortex and the ventral striatum in a variety of self-regulation processes (Ochsner et al. 2012), it is likely that increased functional interaction between these regions may serve as a critical behavior change mechanism that is shared by a number of different effective psychosocial treatments. In other words, findings from cognitive neuroscience predict that effective treatments increase prefrontal cortical function, decrease ventral striatal function, and increase functional connectivity between these two regions, especially during the processing of alcohol-related information (figure 1). Although a number of the studies cited here provide circumstantial evidence for this mechanism, no studies have tested it directly.

Another important theme that emerges from this literature is whether behavior change mechanisms related to AUD are specific to alcohol use or more general cognitive changes. AUD is associated with deficits in a number of general cognitive functions, especially executive and cognitive control functions, as well as specific "gains of function," with respect to the incentive and rewarding effects of alcohol and related cues. Thus, it is important to understand whether a given intervention changes alcohol use behavior

because it influences general cognitive functions or because it influences functions that are specific to the processing of alcohol-related information. For example, it is possible that interventions aimed at reducing the incentive salience of alcohol cues, such as cue-exposure therapy, and interventions aimed at increasing the ability to specifically regulate this incentive salience, such as cognitive bias modification and cognitive regulation of craving, are mediated by the specific mechanism of prefrontal executive/cognitive control regions modulating the processing of alcohol's incentive value by subcortical reward-related regions. Concurrently, interventions aimed more generally at improving prefrontal cortex functions, such as working-memory training, may facilitate the more specific interventions because these general functions play a part in alcohol-specific regulation functions.

Although cognitive neuroscience approaches provide a window into AUD treatment mechanisms that aligns with our current understanding of AUD pathophysiology, there are limitations to cognitive neuroscience approaches that affect the ability to infer AUD treatment mechanisms. A major limitation of all functional imaging studies is that they are essentially correlational. Merely showing that a given psychological process is associated with increased activity within a specific neural system does not by itself prove that this neural system is critically necessary for the psychological process. By extension, merely showing that neural activity within a brain system changes as a result of a treatment does not demonstrate that this treatment must affect this brain system to elicit behavior change. When examining disease pathophysiology, it is difficult to know whether differences between patients and healthy controls in brain structure and function play a causal role in disease pathology, whether they are merely parallel phenomena, or whether they pre-exist disease development. This issue may be addressed in prospective studies in at-risk individuals (see Ersche et al. 2012 for an example of this approach applied to structural brain abnormalities in addiction). Such limitations are not specific to AUD treatment research; they are inherent in all translational neuroimaging studies that aim to examine pathophysiology and treatment mechanisms.

Future Directions

Using cognitive neuroscience approaches to study behavior change in psychosocial treatments for AUD is a young field.

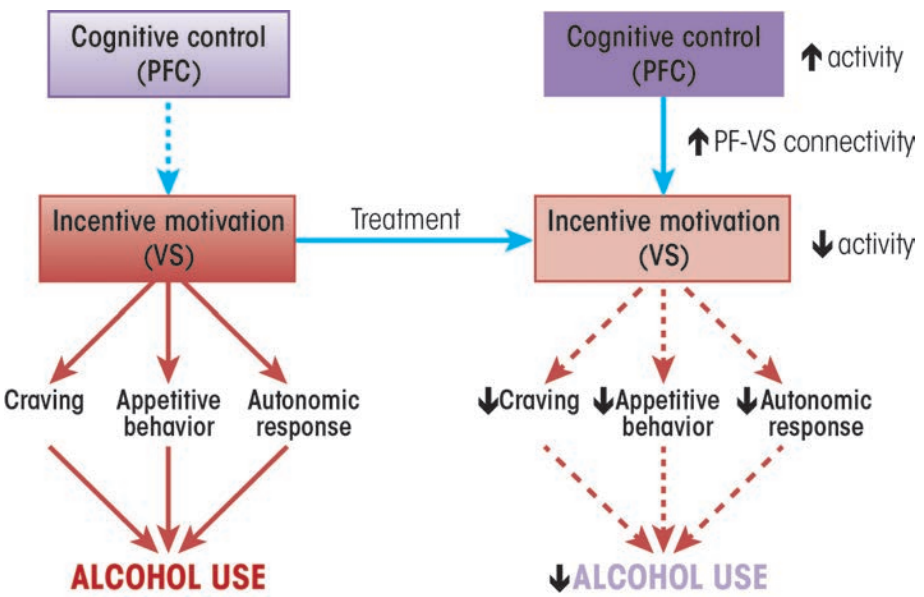

Figure 1 A potential common mechanism for alcohol use disorder (AUD) treatments. A number of studies suggest that AUD treatments elicit behavior change by increasing the regulation of brain regions that mediate incentive motivation, such as the ventral striatum, by prefrontal cortical regions that mediate cognitive control. Arrows denote expected changes in specific neural, behavioral, psychophysiological and clinical outcome measures, given this hypothesized treatment mechanism. PFC = prefrontal cortex. VS = ventral striatum.

Future studies can address some of the current weaknesses of this field by integrating cognitive neuroscience approaches with the conceptual and methodological approaches that already have proven useful for examining AUD treatment mechanisms. The first step in such an approach is to identify specific cognitive, affective, and behavioral processes that are hypothesized to mediate behavior change in a given treatment. The next step is to operationalize these processes using relatively simple paradigms that can be implemented in functional imaging experiments. This also should include appropriate control tasks that are ideally the same as the experimental tasks, minus the psychological processes under study. There should be preliminary data showing which neural parameters (i.e., activity measures in specific brain systems, along with measures of connectivity between brain systems) are changed by this task, compared with the control task, and how this relates to behavioral measures acquired during the functional imaging experiments. There should also be a clear set of a priori hypotheses about which of these neural parameters relate to behavior change in the treatment and which do not. The clinical population should be well characterized using self-report measures of AUD severity and or psychological processes that have already been studied as mediators of behavior change in the treatment under study. Patients should be randomly assigned to receive the active treatment or an equally effective control treatment that is hypothesized to not depend upon the processes under study. Functional imaging data, along with self-report measures, should be acquired both prior to and then immediately following the treatments. Appropriate clinical outcome measures should be specified.

What kind of results would be necessary to support the role for a specific neural system in the mechanism of a treatment? First, it would be necessary to show that the active treatment, but not the control treatment, changed the functioning of this neural system as it relates to the specific psychological process under study. Second, it would be necessary to show that the relationship between the treatment and the clinical outcome was statistically mediated by the effect of treatment on the functioning of this neural system. Third, it would be useful to relate changes in neural function from pre- to posttreatment to changes in self-report measures indexing psychological processes already known to mediate behavior change in the

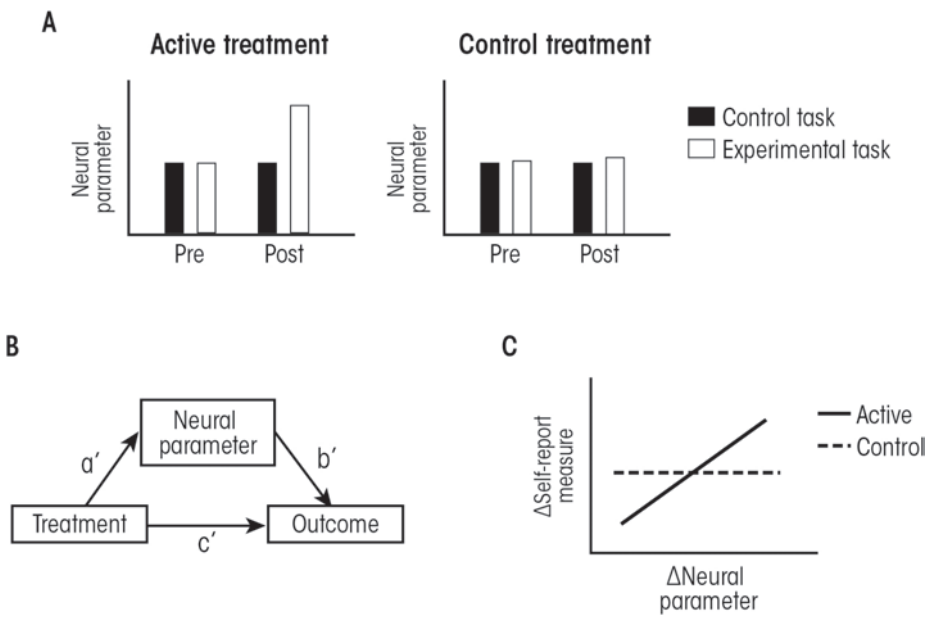

Figure 2 Predicted results from experiments directed at addressing the role of neural systems in alcohol use disorder (AUD) treatment mechanisms. **(A)** An active treatment should increase the neural parameters that index the functioning of these systems as it relates to a specific psychological process of interest (the experimental task). There should be no effect of the control treatment on these neural parameters. **(B)** The effects of a treatment on the neural parameter should mediate the effects of the treatment on clinical outcome. **(C)** Changes (Δ) in the neural parameters from pre- to posttreatment should correlate with corresponding changes in self-report measures that index psychological processes already known to drive behavior change.

treatment. This would help to clarify whether the neural system plays a role in psychological processes already known to be involved in behavior change, or whether neural systems impact some other, as yet unknown, psychological processes that drive behavior change. This approach is illustrated in figure 2.

Once a neural system is identified as playing a role in behavior change in a specific treatment, additional studies can use "interventional" approaches, such as transcranial magnetic stimulation, to examine how noninvasively disrupting or enhancing the functioning of this neural system impedes or augments behavior change during the treatment. Additionally, researchers can add medications that are known to target this neural system to the treatment, and observe the effect on behavior change. Researchers also can seek out AUD patients who acquire brain damage in the neural system—for example from a stroke—and examine whether the brain damage reduces the efficacy of the treatment as a result of impairments in the psychological processes mediated by the damaged neural system. These approaches would provide direct tests of the role of the neural system and the psychological processes it mediates in behavior change, as opposed to the correlational evidence provided by functional neuroimaging.

Although such an approach attempts to relate changes in neural parameters acquired in functional imaging experiments to changes in behavior, it is important to note that the neural parameters by themselves do not constitute a mechanism. Rather, they are measurements of the functioning of specific neural systems that are involved in psychological processes that drive behavior change. In this way, the approach must integrate across multiple levels of analysis. Such an integrative approach does not place a higher value on neural measures compared with psychological or clinical measures. Instead, the approach depends on several levels of analysis in order to arrive at a coherent, clinically useful understanding of how currently effective treatments change behavior, one that can ultimately facilitate the development of novel, more effective treatments.

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Advances in Medications and Tailoring Treatment for Alcohol Use Disorder

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Alcohol use disorder (AUD) is a chronic heritable brain disorder with a variable clinical presentation. This variability, or heterogeneity, in clinical presentation suggests complex interactions between environmental and biological factors, resulting in several underlying pathophysiological mechanisms in the development and progression of AUD. Classifying AUD into subgroups of common clinical or pathological characteristics would ease the complexity of teasing apart underlying molecular mechanisms. Genetic association analyses have revealed several polymorphisms—small differences in DNA—that increase a person's vulnerability to develop AUD and other alcohol-related intermediate characteristics, such as severity of drinking, age of AUD onset, or measures of craving. They also have identified polymorphisms associated with reduced drinking. Researchers have begun utilizing these genetic polymorphisms to identify alcoholics who might respond best to various treatments, thereby enhancing the effectiveness of currently tested medications for treating AUD. This review compares the efficacy of medications tested for treatment of AUD with and without incorporating genetics. It then discusses advances in pre-clinical genetic and genomic studies that potentially could be adapted to clinical trials to improve treatment efficacy. Although a pharmacogenetic approach is promising, it is relatively new and will need to overcome many challenges, including inadequate scientific knowledge and social and logistic constraints, to be utilized in clinical practice.

Key words: Alcohol use disorder; alcoholism; brain disorder; medications; treatment; environmental factors; biological factors; genetic factors; pathophysicological mechanisms; molecular mechanisms; genetic polymorphisms; pharmacogenetics

Despite decades of research on various methods for treating alcohol use disorder (AUD), AUD remains prevalent throughout the world, making it critical to develop a more comprehensive approach to address the issue. Heavy drinking is the third largest risk factor for global disease burden, leading to enormous social and economic decline (World Health Organization 2014). Each year, alcohol misuse is attributed to approximately 88,000 deaths in the United States and 2.5 million deaths worldwide (Centers for Disease Control and Prevention 2014). Many individuals who drink are able to consume small amounts of alcohol without progressing into heavy drinking that often leads to AUD. However, in the United States alone, approximately 13 percent of those who drink meet criteria for AUD (Friedmann 2013). Despite community education programs on the consequences of harmful drinking, only about 15 percent of those who have an AUD seek treatment, citing reasons that include social stigma, expense, skepticism about treatment efficacy, lack of knowledge on available treatment options, and lack of treatment facilities (National Institute of Alcohol Abuse and Alcoholism 2014).

Finding treatments that successfully help people regulate their drinking or stop drinking altogether is a primary goal of AUD treatment researchers. Along with psychosocial treatments, researchers have been developing and testing pharmaceuticals that can help people with AUD reach their treatment goals. To date, multiple compounds have been tested in pre-clinical studies and phase ll clinical trials. However, the U.S. Food and Drug Administration (FDA) has only approved three specifically for treating AUD (Litten et al. 2014): oral and long-acting injectable naltrexone,

acamprosate, and disulfiram. Some European countries have approved nalmefene and sodium oxybate for AUD treatment. Several other drugs, including ondansetron, topiramate and gabapentin, which are drugs approved to treat nausea (ondansetron) and seizures (topiramate and gabapentin), also have shown promise for treating AUD (Johnson et al. 2003; Mason et al. 2012, 2014; Sellers et al. 1994). All of these medications, except disulfiram (see textbox), modulate the neuronal pathways governing the urge or propensity to drink, withdrawal-related symptoms, or maintaining abstinence.

Although naltrexone and acamprosate are used to treat patients, they have not shown strong effects in achieving abstinence or non–heavy-drinking levels in phase II clinical trials (Cochrane Primary Care 2013*a*,*b*). In an effort to develop more effective medications, researchers increasingly are focusing on two goals: (1) improving the efficacy of existing medications and (2) discovering new drug targets. To improve the efficacy of existing medications, researchers are trying to identify subgroups of AUD patients with common underlying pathophysiology who are more likely to respond to certain medications. Such an approach would control for physiological and environmental variations that play a major role in people's vulnerability to AUD and their response to medication. The challenge is finding ways to specifically and accurately identify subgroups. For example, clinical presentation can vary widely, and there is little consensus as to what constructs should be used to delineate subgroups (Johnson 2010). Genetics holds more promise. The traits that encompass the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM–IV) diagnosis of alcohol addiction and misuse are highly heritable (Goldman et al. 2005), with some but not all of the seven DSM–IV diagnostic criteria having a genetic predisposition (Kendler et al. 2012). In addition, genetic association analyses suggest that several clinical subtypes, including age of onset of problem drinking, severity of drinking, patterns of drinking, alcohol withdrawal, and other comorbid psychiatric conditions, share specific genetic differences, known as polymorphisms. Therefore, employing these clinical subtypes that are intermediate to disease diagnosis, and the genes associated with the disease, seem to be a more plausible and comprehensive approach to identifying treatment responders. Perhaps focusing on the diagnostic criteria that are controlled by genetic factors will afford greater statistical power to mine underlying genetic factors associ-

Disulfiram

Disulfiram (Antabuse) was the first medication available for the treatment of alcohol use disorder, and it remains the most widely prescribed medication in some countries. Disulfiram inhibits the low Km alcohol metabolism enzyme aldehyde dehydrogenase 2 (ALDH2) in the liver and the brain, increasing the downstream acetaldehyde levels (Vasiliou et al. 1986). If a person taking disulfiram drinks alcohol, the resulting acetaldehyde levels cause an aversive reaction that is characterized by nausea, vomiting, headaches, a flushed face and neck, and sometimes rare symptoms that include vertigo, blurred vision, hypotension, and syncope (McMahon 1980). Because of this very unpleasant experience, patients often lack motivation to remain compliant. In the United States, disulfiram is rarely prescribed because of its potentially serious side effects.

In the brain, where catalase is the primary ethanol-metabolizing enzyme, ALDH2 is expressed in very low levels. Acetaldehyde produced in the ventral tegmental area (VTA) of the brain by catalase was shown to be rewarding (Karahanian et al. 2011), but it is not clear whether disulfiram affects acetaldehyde levels generated via catalase. Recent evidence from various groups also has demonstrated that disulfiram's mechanism of action is more complex and, in addition to ALDH, may target other proteins such as dopamine catabolizing enzymes, particularly, dopamine beta-hydroxylase (Gaval-Cruz et al. 2008; McCance-Katz et al. 1998). Furthermore, the primary metabolite of disulfiram, diethyldithiocarbamate, is active and has many protein targets, including transcription factor nuclear factor kappa-B (NF-κB) that can impact many neurotransmitter systems simultaneously. To date, there have been no pharmacogenetic studies conducted using disulfiram.

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ated with AUD pathophysiology. Additionally, the genetic variations in genes encoding enzymes that determine the bioavailability of a medication, receptor binding and uptake sites, and enzymes involved in a medication's elimination also could determine individual's variable responses to medications. This article will first present an overview of recent findings in AUD pharmacogenetic research, followed by a discussion on how preclinical genetic research can be adopted to improve the current status of the pharmacogenetics of AUD.

Pharmacogenetic Studies for Improving Efficacy of Current Medications

Researchers have conducted pharmacogenetic trials for improving the efficacy of four drugs to treat AUD: naltrexone and acamprosate as well as two off-label medications, ondansetron and topiramate. Although gabapentin shows promise for reducing heavy drinking and increasing abstinence (Mason et al. 2012, 2014), to date no one has conducted pharmacogenetic trials on this drug. The pharmacogenetic studies of naltrexone, acamprosate, ondansetron, and topiramate are discussed at length below, and table 1 compares their effect sizes when studied using a pharmacogenetic approach and a nonpharmacogenetic approach.

Naltrexone

The FDA approved oral naltrexone to treat AUD in 1994. It is relatively safe and well tolerated, with only a few reported nonspecific adverse effects (Chochrane 2010). At typical dosages, commercially available naltrexone, known as levo-naltrexone, primarily inhibits μ-opioid receptors (MOR) (Ziauddeen et al. 2013). The idea behind using naltrexone for AUD came from studies showing that some alcohol-dependent individuals have an endogenous opioid deficiency (Oslin et al. 2003). Both rodent models and human imaging studies show an acute increase in endogenous opioid released upon alcohol ingestion, which instigates its reinforcing effects (Gianoulakis 1996). Phase l/ll human laboratory trials conducted prior to FDA approval showed that naltrexone reduced alcohol cravings and reduced relapse to heavy drinking (O'Malley et al. 1992; Volpicelli et al. 1992).

The majority of clinical trials conducted in the United States to

Table 1 Effect Sizes in Pharmacogenetic and Nonpharmacogenetic Phase II AUD Treatment Trials

	Effect Size	
Medication and End-point Variable	**Nonpharmacogenetic Trials**	**Pharmacogenetic Trials Effect Size (Gene Tested)**
Naltrexone		
Relapse to heavy drinking	0.247 (Del Re et al. 2013)	
Percent days abstinent	0.143 (Del Re et al. 2013)	
Good clinical outcome	Not measured	>0.8 in carriers of rs1799971:G allele (Anton et al. 2008)
Ondansetron		
Drinks per drinking day	NS; ondansetron vs. placebo main effects (Correa et al. 2013; Johnson et al. 2000, 2011)	0.87 in carriers of any one or more of the following genotypes → rs1150226:AG, rs1176713:GG, and rs17614942:AC; 0.59 when carriers of SLC6A4:LL and rs1042173: TT are added to the above group (Johnson et al. 2013)
% heavy drinking days	NS; ondansetron vs. placebo main effects (Correa et al. 2013; Johnson et al. 2000, 2011)	0.78 in carriers of any one or more of the following genotypes → rs1150226:AG, rs1176713:GG, and rs17614942:A; 0.42 when carriers of SLC6A4:LL and rs1042173: TT are added to the above group (Johnson et al. 2013)
% abstinent days	NS; ondansetron vs. placebo main effects (Correa et al. 2013; Johnson et al. 2000, 2011)	0.68 in carriers of any one or more of the following genotypes → rs1150226:AG, rs1176713:GG, and rs17614942:AC; 0.43 when carriers of SLC6A4:LL and rs1042173: TT are added to the above group (Johnson et al. 2013)
Topiramate		
Drinks per drinking day	0.45 (Johnson et al. 2003, 2007*a*; Rubio et al. 2009)	
% heavy drinking days	0.62 (Johnson et al. 2003, 2007*a*; Kranzler et al. 2014; Rubio et al. 2009)	Effective only in rs2832407:CC carriers but not in carriers of rs2832407:AC/AA (Kranzler et al. 2014)
% abstinent days	0.46 (Johnson et al. 2003, 2007*a*; Kranzler et al. 2014; Rubio et al. 2009)	Effective only in rs2832407:CC carriers but not in carriers of rs2832407:AC/AA (Kranzler et al. 2014)

All effect sizes are given in Cohen's *d*. NS: Nonsignificant.

compare the efficacy of naltrexone to a placebo have shown that the drug is more effective in reducing drinking severity than promoting abstinence (Litten et al. 2013). In addition, although a recent multivariate meta-analysis of 41 single- and multisite pharmacotherapy trials conducted from 1992 to 2009 found that the effect size for naltrexone was modestly higher than placebo, its clinical success for promoting abstinence and reducing heavy drinking has declined steadily since the earliest single-site studies (Del Re et al. 2013). This failure of chronic treatment with naltrexone may, in part, be explained by the finding by Gelernter and colleagues (2007) that chronic exposure to opioid antagonists results in upregulation of cell-surface MOR density and function.

Studies into whether there are genetic markers that predict whether certain people respond better than others to naltrexone mostly have focused on a polymorphism of the *OPRM1* gene, which encodes for MOR subtype 1. The single nucleotide polymorphism (SNP), called rs1799971, is the most extensively studied *OPRM1* polymorphism in alcoholism research. It results from the substitution of an A nucleotide with a G nucleotide in exon 1 of *OPRM1* (Anton et al. 2008). The resulting allele is called A118G or Asn40Asp. The allelic differences are associated with both altered binding capacity and expression levels of MOR subtype 1 across species. Specifically, the G allele is associated with increased binding capacity for β-endorphin in cultured oocytes (Bond et al. 1998) and reduced mRNA and protein expression levels (Mague et al. 2009; Zhang et al. 2005), suggesting a relative baseline deficit of MOR subtype 1.

The first pharmacogenetic trial to study the use of naltrexone for treating AUD (Oslin et al. 2003) examined whether differences in rs1799971 influenced outcome. The retrospective, exploratory study used a double-blind, placebo-controlled 12-week treatment trial, with 141 alcohol-dependent individuals of European descent. The results indicated that people who carried at least one copy of the G allele and received naltrexone relapsed to heavy drinking at lower rates and took longer to do so than people who did not carry the G allele and received naltrexone. Although the results are intriguing, the study combined two disparate clinical trials and did not find a statistically significant interaction between naltrexone and the genotypes.

Since then, several other groups also have investigated whether rs1799971 affects drinking severity in naltrexone-treated individuals. By far the largest was conducted by Anton and colleagues (2008), using a subset of genetic samples from participants in the Combined Pharmacotherapies and Behavioral Interventions for Alcohol Dependence (COMBINE) study. The researchers analyzed the effectiveness of naltrexone in 604 Caucasians recruited at 11 academic sites across the United States. All of the study participants met criteria for DSM–IV alcohol dependence upon entering the study and were recently abstinent. The study found that participants who carried the rs1799971:G allele who also received naltrexone had fewer days of heavy drinking, defined as more than five standard drinks for men and four standard drinks for women, after 16

Table 2 Frequencies of Pharmacogenetic Markers in Ethnic/Racial Populations

Medication	Pharmacogenetic Marker (Gene-Polymorphism: Genotype)	African	Caucasian	East Asian	South Asian
Naltrexone	OPRM1-rs1799971:GG/GA	0.023	0.292	0.622	0.693
Ondansetron	HTR3A-rs1150226:AG	**0.470**	0.134	Fixed	0.023
	HTR3A-rs1176713:GG	**0.113**	0.088	0.048	0.136
	HTR3B-rs17614942:AC	0.077	**0.097**	Fixed	0.023
	SLC6A4-5HTTLPR:LL	**0.582**†	0.334††	0.109‡	0.191‡‡
	SLC6A4-rs1042173:TT	**0.736**	0.283	0.042	0.216
Topiramate	GRIK1-rs2832407:CC	0.019	**0.354**	0.205	0.273

All frequency data are from HapMap, unless specified otherwise. Highest population frequencies are in boldface letters.

† Douglas et al. 2011; Gelernter et al. 1998; Herman et al. 2011; Kraft et al. 2007; Roy et al. 2007.

†† Biederman et al. 2009; Douglas et al. 2011; Foley et al. 2004; Frisch et al. 1999; Geijer et al. 2000; Gerra et al. 2005; Gonda et al. 2010; Gokturk et al. 2008; Grabe et al. 2012*a,b;* Hallikainen et al. 1999; Herman et al. 2011; Illi et al. 2011; Iordanidou et al. 2010; Kronenberg et al. 2008; Landaas et al. 2010; Merenakk et al. 2011; Michaelovsky et al. 1999; Minelli et al. 2011; Mrazek et al. 2009; Mujakovic et al. 2011; Noskova et al. 2008; Pivac et al. 2009; Polito et al. 2011; Stoltenberg et al. 2012; van der Zwaluw et al. 2010; Volf et al. 2009.

‡ Choi et al. 2006; Chong et al. 2000; Chu et al. 2009; Gelernter et al. 1997; Hong et al. 2003; Katsuyama et al. 2008; Kim et al. 2006, 2007; Kweon et al. 2005; Li et al. 2007; Matsushita et al. 2001; Narita et al. 2001; Shin et al. 2010; Yamakawa et al. 2005; Yu et al. 2002.

‡‡ Banerjee et al. 2006; Guhathakurta et al. 2006; Vijayan et al. 2009, Kumar et al. 2007, 2012; Margoob et al. 2008; Sikander et al. 2009, Tibrewal et al. 2010.

weeks of treatment. Interestingly, the G-allele carriers in the group that received only naltrexone without cognitive behavioral treatment had significantly more abstinent days during the 16-week treatment period (P = 0.01 to 0.03) than all other genotype-by-treatment groups.

Along with the traditional measures of treatment effectiveness, the authors constructed an outcome measure called "rates of good clinical outcome." They defined this as the following:

> *"abstinent or moderate drinking without problems, a maximum of 11 (women) or 14 (men) drinks per week, with no more than 2 days on which more than 3 drinks (women) or 4 drinks (men) were consumed, and 3 or fewer alcohol-related problems endorsed on the Drinker Inventory of Consequences scale during the last 8 weeks of treatment"* (Anton et al. 2008, p. 138).

The authors found that the naltrexone-treated G-allele carriers were more than five times more likely to have rates of good clinical outcomes than all other treatment-by-genotype groups combined. The fact that all significant findings were present only in those who did not receive psychotherapy in addition to naltrexone—a finding which the authors explained as the pharmacological effects of naltrexone that were not masked by psychotherapy—has attracted caution in interpreting these findings.

Results from numerous subsequent studies have failed to replicate the predictive ability of rs1799971 (Arias et al. 2014; Coller et al. 2011; Foulds et al. 2015; Oslin et al. 2015) for improving naltrexone treatment response. Negative findings in these smaller statistically underpowered studies likely indicate that rs1799971 has a modest effect on naltrexone's effectiveness. Given that rs1799971 alleles are more prevalent in Caucasian and Asian populations (table 2), naltrexone likely would be most beneficial in these populations (Ray et al. 2012). Supporting this argument, a few human laboratory trials have demonstrated that both European and Asian male and female heavy social drinkers carrying rs1799971:G, who were treated with naltrexone, had reduced craving for alcohol compared with people who received the placebo (Ray et al. 2010, 2012).

Acamprosate

The FDA approved acamprosate to treat AUD in 2004, but it mainly is used in Europe for maintaining abstinence presumably by reducing craving, especially after alcohol detoxification (Cochrane 2011). Contrary to these findings, some studies suggest that acamprosate prevents relapse, not through altered craving (Umhau et al. 2011) but rather by reducing central nervous system hyperexcitabilty (Dahchour et al. 1998) and by causing a negative affective state during alcohol withdrawal (Cole et al. 2000).

Acamprosate consists of two acetyl-homotaurine molecules linked by a calcium salt (Kalk and Lingford-Hughes 2014) with a chemical structure similar to the amino acid neurotransmitters gamma-aminobutyric acid (GABA), glutamate, glycine, aspartate, and taurine. It is thought that acamprosate stabilizes the chemical balance in the brain that would be disrupted by alcohol withdrawal. However, the molecular mechanisms involved are unclear. Many studies have shown that acamprosate has dose-dependent agonistic effects at $GABA_A$ receptors and weak antagonistic effects at N-methyl-D-aspartate (NMDA) receptors and metabotropic glutamate receptor 5 (mGLuR5) (Krystal et al. 2006; Pierrefiche et al. 2004). A more recent study by Spanagel and colleagues (2014) showed that acamprosate's antirelapse effects are, in fact, exerted via calcium that is incorporated in its formulation, rather than through effects of acetylhomotaurine on GABA and glutamate receptors (Spanagel et al. 2014).

Researchers working in European populations have found a few genetic polymorphisms that predict treatment response to acamprosate. Ooteman and colleagues (2009), for example, examined a polymorphism found in a $GABA_A$ receptor gene called *GABRB2*. They found that alcohol-dependent patients carrying the TT genotype of the *GABRB2* C1412T polymorphism had reduced physiological responses (measured by decreased heart rate) to alcohol cues than patients carrying the C allele (Ooteman et al. 2009). Another study examined a polymorphism associated with a gene called *GATA4*, which encodes a transcription factor for atrial natriuretic peptide and has been associated with alcohol addiction (Kiefer et al. 2011). The SNP, called rs13273672, has an A allele and a G allele. The study found that study participants who carried the A allele had improved abstinence levels after 90 days of acamprosate treatment compared with patients carrying the G allele (Kiefer et al. 2011). This study also showed that patients carrying two copies of the A allele had increased plasma levels of atrial natriuretic peptide, providing a biological mechanism for the statistical association with treatment outcome. In another study, Spanagel and colleagues (2005) examined polymorphisms in a gene called *Per2,* which is associated with circadian cycles. The researchers demonstrated that mice with a mutation in *Per2,* known as $Per2^{Brdm1}$ mutant mice, reduced their drinking following acamprosate treatment (Spanagel et al. 2005). Additional biochemical examination showed that the $Per2^{Brdm1}$ mutant mice had a deletion in the PAS domain of the Per2 protein that resulted in reduced glutamate transporter Eaat1 expression levels and in turn increased synaptic glutamate levels. The same study examined alcohol intake in a population of Caucasian individuals treated with acamprosate and found that those who carried a protective allele located within a regulatory region of *PER2* intron 3 had lower alcohol intake (less than 300 g/day) than those who did not carry the allele. These findings need to be repli-

cated in independent studies to validate their pharmacogenetic relevance in acamprosate treatment.

Ondansetron

The FDA has approved ondansetron to treat postoperative and chemotherapy-induced nausea. The drug attaches to a number of receptors, dampening their ability to respond. It shows a low affinity to 5-HT_{1A}, 5-HT_2, adrenergic α1 and α2, dopamine receptor subtype 2, muscarinic M2, μ opioid receptor, benzodiazepine, and histamine H_1 receptors. But it has a much larger affinity for 5-HT_3 receptors, which have been associated with alcohol consumption. 5-HT_3 receptors are ligand-gated ion channels that mediate the fast depolarization of neurons. They regulate dopamine release and are located densely in the brain's mesocorticolimbic region. Alcohol stimulates 5-HT_3, enhancing dopamine release and thereby increasing the risk of alcohol misuse. Selectively blocking 5-HT_3 receptors attenuates dopamine release. Indeed, two studies showed that, in mice, alcohol intake had an inverse relationship with the expression levels of 5-HT_3 receptors in the amygdala (Ciccocioppo et al. 1998; Hensler et al. 2004). Further characterizing the relationship between alcohol drinking and 5-HT_3 receptors, Hodge and colleagues (2004) demonstrated that drinking behavior in mice is mediated specifically by the 5-HT_{3A} subunit of the 5-HT_3 receptor complex. Another study found that mice with high compulsive-like alcohol-seeking behavior had lower levels of CpG methylation in the promoter region of the *HTR3A* gene, which codes for 5-HT_{3A} (Barker et al. 2014). These mice required higher doses of ondansetron to reduce their compulsive-like alcohol-seeking behavior, suggesting that higher expression levels of the 5-HT_{3A} subunit are associated with compulsive alcohol-seeking tendencies.

Findings from rodent models (Kostowski et al. 1994; Meert 1993) and subsequent human laboratory studies conducted with alcoholic individuals showed that ondansetron was able to reduce drinking (Sellers et al. 1994). One study suggested that it reduced drinking only in people with a biological predisposition to develop alcoholism before age 25 (Johnson et al. 2000). By testing a 16-fold dose range, this study also found that the most effective dose (4 μg/kg of body weight) is about 1,000 times smaller than the commercially available form for its FDA-approved indication. Independent replication studies have not all found the same link between age of onset and ondansetron's treatment efficacy (Kranzler et al. 2003), and even Johnson and colleagues (2011) failed to find a significant effect of ondansetron, combined with cognitive–behavioral therapy, in reducing drinking among early-onset alcoholics (Johnson et al. 2011).

To examine whether certain subgroups respond better to ondansetron, Johnson and colleagues (2011) tested ondansetron in two subgroups of alcoholics based on their genotype for the serotonin transporter gene *SLC6A4*-promoter region functional polymorphism 5-HTTLPR (L/S). They found that patients treated with ondansetron who carried the LL genotype (5-HTTLPR:LL) drank about 1.5 fewer standard drinks on a drinking day and had 10 percent more abstinent days, compared with all other treatment by genotype groups (Johnson et al. 2011). A unique strength of this pharmacogenetic study was that the researchers randomly assigned participants to receive treatment (ondansetron plus CBT or placebo plus CBT) based on their 5-HTTLPR genotypes, which provided ample statistical power to detect the genetic effects. The researchers also further refined the 5-HTTLPR:LL group by adding another functional polymorphism in *SLC6A4* (SNP rs1042173[T/G]) that researchers had shown alters mRNA expression levels (Seneviratne et al. 2009). Adding this refinement markedly increased patients' response to ondansetron: Carriers of both 5-HTTLPR:LL and rs1042173:TT genotypes who received ondansetron drank about 2.6 fewer drinks on a drinking day, and the percentage of abstinent days within the 3-month treatment period increased to 15.5 percent, compared with all other treatment by genotype groups. Only a small human laboratory trial has been reported so far to support the findings of the above pharmacogenetic trial. In a human laboratory trial, Kenna and colleagues (2014) demonstrated that alcohol-dependent individuals with 5-HTTLPR:LL genotype significantly reduced their alcohol consumption in response to 0.5 mg/day ondansetron treatment both in a naturalistic and a human laboratory environment under a self-administration model.

Johnson and colleagues (2011) selected the two SLC6A4 functional polymorphisms to personalize ondansetron in the above-mentioned study, because the serotonin transporter is the main modulator of serotonergic signaling. However, ondansetron does not bind to the serotonin transporter. Its primary target is the 5-HT_3 receptor and, more specifically, the 5-HT_{3A} subunit. When a serotonin molecule binds to a 5-HT_{3A} subunit, a signal is propagated along the postsynaptic neuron, and this signal is blocked by ondansetron. The 5-HT_{3A} subunits heteromerize with 5-HT_{3B} subunits to form functionally efficient 5-HT_3 receptors. Hence, in a secondary analysis, Johnson and colleagues (2013) re-analyzed the sample from their 2011 study to include polymorphisms from the two genes encoding 5-$HT_{3A/B}$ subunits—*HTR3A* and *HTR3B* (Johnson et al. 2013). They found that genotypes across *HTR3A* and *HTR3B* were better able to identify subgroups of alcoholic individuals who would respond to ondansetron treatment compared with the two *SLC6A4* polymorphisms. The specific *HTR3A* and *HTR3B* predictive genotypes identified in this study were rs1150226–AG, rs1176713–GG and rs17614942–AC,

respectively. When all individuals carrying any one or more of these three genotypes, along with the previously identified SLC6A4:LL/TT genotypes, were pooled together into one group, they predicted the number of drinks per drinking day, percentage of abstinent days, and heavy drinking days with larger effect sizes (table 1). The major drawback of this exploratory study is the small sample size. Large multisite randomized trials are needed to validate the findings of both pharmacogenetic trials by Johnson and colleagues (2011 and 2013).

Topiramate

Researchers have tested topiramate as a promising agent to treat AUD in several clinical trials. Topiramate "decreases alcohol reinforcement and the propensity to drink (Johnson et al. 2007*a*, p. 4)" by facilitating GABA-A receptors and antagonizing AMPA and Kainate glutamate receptors (Angehagen et al. 2005; Braga et al. 2009; Poulsen et al. 2004; Simeone et al. 2011), which, in turn, reduce dopamine levels in mesocorticolimbic systems (Johnson et al. 2007*a*).

Johnson and colleagues (2003) conducted the first randomized, placebo-controlled trial (RCT) with topiramate for treating AUD. They tested a daily dose of up to 300 mg per day over a period of 12 weeks in a relatively small heterogeneous population of men and women. They reported a moderate to high effect size (0.7) for reducing heavy drinking by about three standard drinks on a drinking day, and a comparable effect size (0.76) for improving abstinence by about 27 percent. Follow-up studies (see table 1) carried out in larger populations with similar doses of topiramate have found it effective over a placebo, albeit with smaller effect sizes for reducing heavy drinking or improving abstinence (table 1). Several other RCTs also have reported no effect of topiramate on treating AUD (Kampman et al. 2013; Likhitsathian et al. 2013). A recent meta-analysis (Blodgett et al. 2014), performed with data from seven RCTs conducted between 2003 and 2014, supported a small to moderate effect for topiramate. Table 2 displays the effect sizes of topiramate on three drinking measures common to four of the seven RCTs. Although topiramate was reported to be more effective than other medications tested for AUD, higher rates of adverse effects observed in RCTs are a concern limiting its use. The most common adverse effects include cognitive dysfunction (Johnson et al. 2003), paresthesias (Kampman et al. 2013), and taste abnormalities (Johnson et al. 2008).

Pharmacogenetic tests of topiramate have focused on an SNP for a gene encoding one of topiramate's primary receptor targets: the kainite Gluk1 receptor. The SNP, called rs2832407, is on a gene called *GRIK1*, and is an intronic substitution of nucleotides C-to-A. Kranzler and colleagues (2009) found that the minor allele A is associated with alcohol dependence. In a study examining whether the alleles influenced the effectiveness of topiramate, Ray and colleagues (2009) reported that patients treated with 300 mg of topiramate and who carry at least one copy of the A allele (AC or AA) had an increased risk for adverse events compared with patients with two copies of the C allele (CC). In an RCT that separated European participants by their genetic profile (CC, AA, or AC), Kranzler and colleagues (2014) compared the effectiveness of 200 mg topiramate with a placebo. They found that topiramate only decreased heavy drinking and increased abstinence rates in participants carrying two C alleles. For participants carrying AC or AA alleles, placebo and topiramate had similar effects on both drinking measures. If replicated in larger populations, this finding may facilitate the successful use of topiramate at a lower dose, reducing the adverse events that have restricted its use.

Other Notable Genetic Polymorphisms

In recent years, researchers have compiled several large-scale genomic datasets that they have used to identify a handful of genetic variants that seem to influence the development of DSM-IV–defined alcohol dependence. Prospective clinical trials conducted in treatment-seeking populations will be critical to translating these findings into pharmacogenetics or improving medication efficacy and safety.

The strongest findings from genome-wide association studies (GWAS) to date are observed for the genes encoding the alcohol-metabolizing enzymes aldehyde dehydrogenase (ALDH) and alcohol dehydrogenase (ADH). Identifying genetic variations in these alcohol-metabolizing enzymes may have significant implications on pharmacological effects of some potential and currently used AUD medications. For example, oral naltrexone, ondansetron, sertraline, finasteride, and olanzapine all undergo significant first pass metabolism in the liver. Converging effects of these medications and genetic variations on alcohol metabolism should be considered as potential pharmacogenetic markers to personalize AUD treatment.

To date, the most consistently replicated polymorphism associated with alcohol metabolism is the SNP rs671 in the *ALDH2* gene, which is mapped to chromosome 12q24.2 and encodes the mitochondrial ALDH isozyme ALDH2. The SNP rs671 arises from a G to A allele transition. Researchers consistently have found that the rs671:A allele protects Asians against developing alcoholism (Tan et al. 2012) and is associated with slower metabolism of acetaldehyde, which leads to an aversive disulfiram-like reaction (Liu et al. 2005). The rs671:A allele is not reported in African and European populations (National Center for Biotechnology Information, 2015). However, researchers have found that another polymorphism, called ALDH1A1*2 in the ALDH1A1

gene, is associated with greater risk for alcoholism in African populations (Moore et al. 2007; Spence et al. 2003) but not in Asian populations (Otto et al. 2013).

Another SNP associated with alcoholism-related traits and gastrointestinal tract cancers in Asian and European populations is called rs1229984 and is found in the *ADH1B* gene that encodes the β subunit of ADH1 (McKay et al. 2011; Park et al. 2013; Wu et al. 2013). It consists of an A allele and a G allele. Bosron and Li (1986) found that the A allele increases the capacity of ADH to oxidize alcohol into acetaldehyde by several-fold. A variant of one of the other two ADH1 subunits—the A allele of the *ADH1C* gene, called SNP rs698—also increases the capacity of ADH to oxidize alcohol into acetaldehyde by several-fold (Bosron and Li 1986).

Characterizing Treatment Effects at the Molecular Level by Examining Gene Expression

Changes in drinking patterns or adverse events associated with a treatment, which typically are used to measure "treatment response" are, in fact, on some level determined by changes in the expression of multiple genes involved in drinking behavior that result from an extremely complex combination of environmental factors and the strength and duration of treatment.

Several studies have examined how alcohol alters gene expression patterns in postmortem humans, as well as in rodent brains and in vitro cell cultures. These studies have looked both at candidate genes and at a global genome-wide level. Especially with the advancement of gene expression technologies, new data have emerged not only on differentially expressed genes but also on underlying mechanisms of expression changes. Table 3 presents notable findings from human postmortem studies with potential pharmacogenetic implications that have not yet been investigated.

Studying gene expression mechanisms in living humans is understandably daunting. Nevertheless, exploring gene expression alterations is essential in clinical trials that aim to understand how medications work to change drinking behavior. In fact, researchers can examine gene expression using

Table 3 Potential Pharmacogenetic Targets Detected in Human Postmortem Brain Studies in Alcohol-Dependent Subjects and Animal Studies

Potential Medication Targets	Altered Genes (Reference)	
	Human Postmortem Studies	Animal Studies
Acamproate	↑NMDA subunit genes *GRIN2B* and *GRIN2D* in hippocampus (Enoch et al. 2014); ↓*GRIN2D* in the central amygdala (Jin et al. 2014); ↓*GRIN2A* in caudate n. (Bhandage et al. 2014)	↓*GRIN1* with chronic ethanol use in dorsolateral prefrontal cortex and ↑*GRIN1-1* isoform and ↓*GRIN1-2* isoform in OFC of male cynomolgus monkeys (Acosta et al. 2010).
Topiramate	↑*GRIA4* and *GRIK3* in hippocampus (Enoch et al. 2014); ↓*GRIA1, GRIA4, GRIK2,* and *GABRA2* in the central amygdala (Jin et al. 2014)	*GRIA2* flop mRNA levels in OFC and *GRIA3* flip and flop and *GRIA4* flop mRNAs in DLPFC positively correlated with daily ethanol intake in male cynomolgus monkeys (Acosta et al. 2011).
Ondansetron (for association with QT interval prolongation)/ Topiramate	↓*SCN4B* in PFC (Farris et al. 2014)	↑*SCN4B* in limbic areas in mice (Mulligan et al. 2006, Tabakoff et al. 2008)
Ondansetron/SSRIs	↑*TPH2* expression in dorsal and median raphe nuclei (Bach et al. 2014)	
Baclofen	↓*GABBR1* in cortex through intron 4 alternative mRNA splicing (Lee et al. 2014) and hippocampus (Enoch et al. 2012)	↓*GABBR1* in hippocampus in P rats (Enoch et al. 2012)
Naltrexone	↑*PDYN* and *PDYN* in dorsolateral-PFC, *OPRK1* in OFC and *PDYN* in hippocampus (Bazov et al. 2013)	↓synaptosomal *OPRK1* receptor expression in mesolimbic brain regions (Nizhnikov et al. 2014) in Sprague-Dawley rats; ↑*POMC, PDYN* and *PENK* in nucleus accumbens in rats (Bordner and Deak 2015); ↑*PDYN* amygdala and nucleus accumbens in rats (D'Addario et al. 2013; Lam et al. 2008)
Canabinoid	↑*CNR1* in PFC of suicidal alcoholics (Erdozain et al. 2014)	↓*CNR1* in caudate-putamen, ventromedial nucleus of the hypothalamus, hippocampus and ↑ in dentate gyrus (Ortiz et al. 2004); ↓*CNR1* in whole brain (Stringer et al. 2013)
Olanzapine	↓*DRD2* receptor protein levels in carriers of Taq1A polymorphism in the caudate nuclei (Noble et al. 1991)	↓*DRD2* in the nucleus accumbens and the hippocampus (Bice et al. 2008; Thanos et al. 2004)

↑ upregulated genes; ↓ downregulated genes; OFC—orbitofrontal cortex; DLPFC—dorsolateral prefrontal cortex; PFC—prefrontal cortex.

easily obtainable peripheral tissue, such as blood, combined with neuroimaging techniques to clarify how changes seen in the blood correlate with what is happening in the brain.

The clinical trial of odansetron by Johnson and colleagues (2011) reported preliminary data that shed light on their finding that patients carrying the SLC6A4:LL genotype responded better to ondansetron. Specifically, they found that study participants carrying the LL genotype were more likely than other participants to have an increase in SLC6A4 gene expression in blood cells (Seneviratne and Johnson 2012). As a future direction, it would be equally important to investigate the length of time the gene expressions persist during a medication-free follow-up period and whether the reversal of expression to premedication state would lead to relapse.

A newer technology for studying gene expression in living people is the creation of what is called induced pluripotent stem cells (iPSC) from tissues such as skin, allowing researchers to obtain cell cultures consisting of neurons and glia (Johnson et al. 2007*b*; Takahashi and Yamanaka 2006). The iPSC technology still is in its infancy, and only a few studies have used this relatively expensive technology in psychiatric research. In the drug addiction field, the only reported study to use iPSC-derived neural cells is a study by Lieberman and colleagues (2012) that examined the effects of alcohol on gene expression of NMDA receptors and their function. They found that expression levels of the NMDA receptor genes *GRIN1*, *GRIN2A*, and *GRIN2D* increased following cell cultures exposed to alcohol for 7 days. These findings corroborate earlier reports from human postmortem brain studies and findings from animal research and support using iPSC as a potential minimally invasive method to study molecular mechanisms in neurons. However, several challenges to this technology remain before it is ready for wider use in preclinical research, including high cost, inefficiency in producing mature cell types with realistic functionality, and difficulty developing cultures enriched with mature (desired) cells and without undifferentiated (undesired) cell types that retain the potential for tumor formation in vivo.

Conclusion

In the past few years, many studies have focused on scrutinizing genetic polymorphisms that alter a person's vulnerability to develop AUD. Association of these polymorphisms in shaping response to medications, or pharmacogenetics, only has begun recently. And although only a handful of published studies address AUD pharmacogenetics, those that have demonstrate a clear advantage over prescribing a common pill to all.

That said, several crucial steps are needed prior to applying these findings to clinical practice. First, the findings from published studies must be validated in larger, independent, preferably phase III, randomized placebo-controlled clinical trials. It also is widely accepted that the genetic architecture of different racial or ethnic groups tends to differ, although 99 percent of the human genome is shared among all races. This raises the possibility that what works for one ethnic population may not be optimal for another. The pharmacogenetic trials discussed above were conducted in predominantly Caucasian populations. Intriguingly,

Glossary

Allele: A fragment of DNA that can differ among individuals of the same species at a specific location of a chromosome. The difference can be just a single nucleotide or several nucleotides.

Exon: Genes are made up of segments of DNA called introns and exons, where the exon represents that part of the gene that is used to create the mature form of RNA, which is then translated into amino acids and make up a protein molecule.

Intron: Genes are made up of segments of DNA called introns and exons. The introns are parts of the DNA that are transcribed into the immature form of RNA but are spliced out before the RNA is translated into a protein.

Nucleotides: The subunits of nucleic acids, such as DNA and RNA, consisting of a nitrogen base (adenine [A], thymine [T], guanine [G], and cytosine [C]), a five-carbon sugar (deoxyribose or ribose, respectively), and at least one phosphate group.

Polymorphism: Differences in DNA sequences found within different individuals of the same species at the same location in the chromosome.

Single nucleotide polymorphism (SNP): A consistent change in a single nucleotide (A, T, C, or G) in a DNA sequence that can be found within members of a population at the same location in the chromosome. For example, the same fragment of DNA from two individuals may have the sequence, TCAGGT and TCAAGT, with a difference in a single nucleotide.

as shown in table 2, all of the genetic markers found to alter treatment efficacy of naltrexone, ondansetron, and topiramate in the few published phase II clinical trials show a significant variation in their prevalence among different racial groups. For example, pharmacogenetic markers for efficacy of ondansetron, which were found in a study of alcoholics of European descent (Johnson et al. 2011), are more prevalent in individuals with African ancestry and rare to nonexistent in East Asians. Furthermore, other genetic polymorphisms that modulate the function of the reported genetic markers also may vary among racial populations, rendering them inconsequential in nontested ethnic populations. Thus, only studies conducted in separate racial populations could decipher the clinical use of pharmacogenetic markers discovered in alcoholics of European ancestry.

Second, all pharmacogenetic trials conducted to date have used a candidate polymorphism approach. The tested genetic polymorphisms have proven to predict efficacy successfully over the conventional treatment approach. Nevertheless, much more comprehensive analyses are needed to explore the existence of other more predictive genetic markers of treatment efficacy. One approach would be to sequence the entirety of genes that include the selected polymorphisms. Another approach would be to conduct a GWAS with samples collected from a treatment trial, rather than a population-based genetic study, designed to detect genetic associations of disease vulnerability. This is especially important as treatment response and disease vulnerability may not necessarily share common polymorphic associations with the same magnitude of effects. Indeed, a GWAS analysis requires a large population of more than 1,000 participants completing the trial, which only can be obtained in multicenter trials. One solution to achieving such an ambitious task would be to require collection of genetic material, for future testing, from all National Institute on Alcohol Abuse and Alcoholism–funded AUD medication treatment trials. It also is important to note challenges with conducting prospective stratified studies. These studies are strengthened if researchers can study equal numbers of people with different versions of the marker under investigation. This design allows researchers to compare directly treatment response between groups carrying the marker and those not carrying the marker. However, it also is more challenging to enroll participants into genotype groups if the minor allele is rare in the population. Under such circumstances, a treatment by genotype group for people carrying a major allele would fill out much quicker than the treatment-by-genotype group for people carrying the minor allele. This could lead to potential selection bias, which is not a concern in randomized controlled clinical trials where the genetic samples are analyzed retrospectively.

Third, a genetic marker, predictive of greater treatment response or adverse events to a medication, ideally should be a surrogate for a pathophysiological process underlying AUD and/or a physiological alteration caused by the medication itself. Genetic markers detected in statistical association analyses should be tested for their functionality and response to both the medication and alcohol. This requires a more vigorous collaborative effort from clinical, translational, and basic science researchers. In addition to the scientific challenges, a number of practical issues such as privacy and confidentiality, provider training, and access to genetic testing facilities warrant consideration for the clinical application of pharmacogenetics. Despite these challenge, the pharmacogenetics approach is by far the most promising advancement in AUD treatment.

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The Promises and Pitfalls of Digital Technology in Its Application to Alcohol Treatment

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Individuals seeking to change their alcohol use form a heterogeneous group with varied treatment goals—including moderation and abstinence—that therefore requires flexible treatment options. The availability of alcohol in the United States, and the pervasive social pressure to drink, warrant treatments that support individuals outside the treatment environment and that foster coping and self-regulation in the face of these demands. Emerging digital technologies show promise for helping both to hone therapies to clients' individual needs and to support clients in settings beyond the clinic. In the broader health care arena, digital health technologies (DHTs) are transforming how health professionals assess, prevent, and treat both physical and mental health problems. DHTs include assessments and interventions delivered via computer, Internet, mobile phone, and wireless or wearable device technologies. The emerging literature examining within-treatment and mobile DHTs highlights an opportunity to create personalized alcohol treatments for every person seeking care. Despite the promises DHTs may hold, however, there still are many potential risks to using them and a number of challenges regarding how to integrate them into treatment successfully. This article will review the current and potential advantages of DHTs in alcohol treatment and the technological, personal, organizational, and systemic limitations of integrating various technology-based assessment and intervention programs into care.

Key words: Alcohol use, abuse, and dependence; treatment; assessment; intervention; technology; digital technology; electronic health technology; computer technology; Internet; telecommunication; literature review

Using methods like the Network for the Improvement of Addiction Treatment (NIATx) that identify the strengths and weaknesses of current treatment processes (Karlsson et al. 2010), treatment providers can identify the components of care in which DHTs may have the most and least impact, as well as the obstacles that arise when attempting DHT integration. This article's initial section will review some of the emerging trends and promises of DHTs inside and outside of alcohol treatment, including consumer-based DHTs, DHTs for treatment initiation and intake, DHTs to enhance alcohol treatment services and services for comorbid conditions, DHTs to extend care beyond the clinic and increase salience of the therapeutic environment, mobile assessment and just-in-time interventions, combining DHTs with in-person support, and finally DHT acceptability from the perspective of the client.

The Promise of DHTs

Direct-to-Consumer DHTs

Ample evidence shows that the majority of individuals who could benefit from alcohol treatment never seek care, suggesting a need to expand the reach and accessibility of treatment. Thus, the proliferation of DHTs that increase people's awareness of how much they drink or their relationship with drinking could meet this need. To date, the development and implementation of digital health services marketed directly to consumers has largely occurred outside of the traditional professional in-person treatment community. These technologies use both brief, one-time computer-based screening and brief interventions and multimodular long-term Internet programs (see table) (Brendryen et al. 2013; Carey et al. 2009; Cunningham et al. 2011; Hester et al. 2013). Such self-guided interventions have typically targeted a lower-severity population than those who tend to seek treatment for alcohol use disorders (AUDs), extending the reach of available options for individuals along the broader problem-drinking spectrum. The rise of mobile-phone applications has produced a large number of alcohol-specific mobile programs available directly to the consumer outside of care, ranging from blood alcohol content (BAC) calculators to coping-skills programs. However, almost no research exists to support the efficacy of these applications beyond their face validity (Cohn et al. 2011). For individuals in recovery, there also are numerous Web-based programs and mobile applications such as online video support meetings, 12-step meeting-finder apps, virtual sponsors, and recovery

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coaches (Cohn et al. 2011). These applications are designed to make the recovery process more efficient by enhancing what individuals are already doing, such as going to meetings or connecting with those in recovery.

Facilitating Treatment Initiation With DHTs

Although the actual integration of DHTs into alcohol treatment has been limited in comparison with the explosion of direct-to-consumer programs, DHTs specifically designed for implementation within traditional treatment are beginning to emerge (Carroll and Rounsaville 2010) in the research literature and offer significant promise to increase the efficiency and quality of care. In health care, and in other settings such as schools and workplaces, computer and mobile DHT screening and brief intervention programs have enhanced the ability to reach individuals opportunistically in those moments when they are motivated to seek more information about their drinking. For example, programs such as Hazelden, a large inpatient and outpatient treatment organization with centers in 5 states, include digital screeners on their Web sites to assist and engage individuals seeking services. Along similar lines, treatment program Web sites can include appointment schedulers for those who are reluctant to initiate help seeking with a phone call, as well as digital copies of all clinic forms (e.g., consent forms) to make the engagement process both more efficient and transparent. Ideally, these tools could be programmed to take into account a client's insurance, financial, and location constraints as well as his or her treatment preferences (Boudreaux et al. 2009).

Table DHT Examples, Including Some of the Most Common DHT Features, How They Can Be and Have Been Implemented in Alcohol Treatment Settings, and Some Basic Strengths of Each

DHT Feature	Examples of Use	Strengths
Treatment-based Digital Kiosk (Computer, Tablet, etc.)	Intake and follow-up assessments, psychoeducation, virtual reality, digital enhancement, and replacement interventions.	"Captive audience" with provider contact to foster adherence and support. Behind firewall for enhanced security and data processing.
Client Computer/Mobile (General)	See above/below.	Distal assessment and intervention in one's natural environment.
E-mail	Appointment reminders, Web links, group communications, natural-language processing.	Ubiquitous, inexpensive, high acceptability.
Text (including SMS, or short message service)	Appointment reminders, ecological momentary assessment, JITAIs (just-in-time adaptive interventions), Web links, natural-language processing.	Ubiquitous, real-time contact, inexpensive, high acceptability.
Camera/Video	Telehealth, modeling, distal environmental monitoring, journaling, exposure, ambient environmental analysis.	Ubiquitous, contextual, nonverbal, distal.
Sound	Speech analysis, environmental sound.	Ambient passive acoustic sensing, contextual environmental cues.
Geolocation	Trigger alerts, activity scheduling, positive activities, proximal social connections.	Objective location data, passive, social connectivity.
Accelerometer/Gyroscope	Activity assessment, behavioral activation, sleep, movement, side effects, intoxication.	Passive, objective, quantifiable, multiple existing systems.
Proximity Sensors	Proximal social monitoring, alerts.	Specific phones within private networks.
Mobile/Web Data Analytics	Everyday data pattern analysis, increases and decreases in social interaction, app usage.	Passive monitoring of secondary data, low invasiveness and battery drain.
Wireless Physiological Sensors: (e.g., Heart Rate Variability, Add-ons)	Physiological reaction and arousal, ability to predict outcome with objective data, relapse and side effects.	Objective data, physiological reactions outside of awareness, contextualized self-report.

Evidence from the general mental health literature suggests that once individuals agree to start treatment, they often have misconceptions about the treatment experience. Educating clients about what to expect can improve retention and therapeutic outcomes. Technology-based educational orientations (i.e., orientation videos) can be a useful and efficient means to orient someone to the treatment process (Zwick and Attkisson 1985). Video orientations are as effective as in-person orientations for many health and behavior problems and improve overall outcomes compared with no-orientation control groups (Walitzer et al. 1999; Zwick and Attkisson 1985). Just as screening and feedback tools can be added to Web sites, pretreatment video orientations can be added to intakes to demystify the treatment process either before treatment entry or in the waiting room during the first appointment.

DHTs to Improve Client Intake

Digital technologies also can almost certainly improve the burdensome client intake process, which at most treatment centers typically involves hours of paper-and-pencil questionnaires and forms that may or may not be transferred to an electronic health record (EHR). The benefits of digital assessments compared with both paper-and-pencil and face-to-face assessment have been repeatedly supported by a robust literature over the last 40 years (Paperny et al. 1990; Skinner and Allen 1983; Tourangeau and Smith 1996; Turner et al. 1998). Although digital assessments provide numerous benefits within the clinic from an administrative perspective (i.e., reduced staffing costs, improved compliance with reporting, etc.), several advantages stand out from a clinical perspective as well. Digital assessments can collect more relevant information from clients more efficiently using decision-support algorithms. These programs collect broad information through liberal stem questions then target the assessments to the most relevant domains, which can be missed sometimes during traditional assessments (Davenport et al. 1987; Paperny et al. 1990; Quaak et al. 1986).

A related body of research provides significant evidence that computer-assisted interviews can collect more sensitive information than face-to-face interviews (Weisband and Kiesler 1996), including data pertaining to alcohol use (Lucas et al. 1977), sexual behavior, and drug use (Skinner and Allen 1983; Tourangeau and Smith 1996; Turner et al. 1998). Recently, Kang and Gratch (2010) found that individuals seeking treatment for social phobia revealed more information to a virtual avatar than a human counselor, revealing that client–DHT interactions may be beneficial during the intake process. Whereas the mechanisms behind this observation are not entirely clear, it seems that the fear of judgment and negative feedback that comes from revealing sensitive information to a human does not apply when disclosing to a digital system. This suggests that individuals perceive digital systems to be a safer means to disclose potentially stigmatizing information. Such findings imply that by integrating digital assessment into care, treatment providers can collect the most relevant data while also helping clients feel comfortable disclosing personal information that they might not disclose otherwise. Collecting more sensitive and relevant information more efficiently in turn promotes more informed treatment suggestions and diagnoses (Bennett and Hauser 2013).

Similar to medical systems like ISABEL (Ramnarayan et al. 2004), which can identify a symptom cluster as being a strong indicator of a specific diagnosis, computerized feedback systems can help providers develop tailored treatment plans driven by these more precise assessments. As described below, they can also trigger use of standalone DHTs to mimic current therapies or augment treatment by offering interventions in domains outside staff expertise (e.g., HIV risk reduction) (Litvin et al. 2013).

Enhancing Care Using DHTs

The enhancement or partial replacement model of digital interventions, in which a DHT delivers all or a portion of care that would traditionally be delivered by a counselor, is designed to deliver standardized empirically supported therapies electronically to enhance the services offered within a clinic. This model has been shown to be as or more effective than stand-alone in-person care in several studies of polysubstance users (Litvin et al. 2013; Marsch et al. 2014). For example, Carroll and colleagues (2009, 2010) integrated a digital cognitive behavioral therapy (CBT) intervention into outpatient substance abuse treatment and saw a significant reduction in the number of positive urine samples and an increase in participants' use of coping skills when compared with treatment as usual. Similar results have been found in studies of other systems such as the Therapeutic Education System (TES) when tested with polysubstance users (Marsch et al. 2014). These programs offer multiple modules that, like in-person interventions, can be delivered flexibly and tailored to the individual. It is important to note that these studies on enhancement DHTs have been conducted within formal treatment settings where there is significant in-person therapeutic support to encourage use and respond to questions about the DHT. Studies have revealed that without therapist contact, multiple-session Internet-based interventions are rarely used after a few sessions (Cunningham et al. 2011), which should be noted when interpreting results of these studies. Another enhancement to care that typically involves more clinician oversight is using new technologies rarely integrated into traditional care, such as virtual-reality cue exposure for alcohol use (Lee et al. 2007). Virtual-reality programs expose individuals to virtual alcohol-related cues and teach them coping skills through modeling and rehearsal. These technologies are examples of how DHTs expand what currently is possible within a single treatment setting.

Addressing Comorbidities Through DHTs

Individuals with AUDs often present with multiple comorbid problems, and difficulties arise for treatment programs in creating a continuum of care when certain conditions lie outside a clinic's area of expertise. Although clinicians cannot be trained in empirically supported treatments for all disorders, DHTs can augment care for individuals with specific pressing needs that are related, but secondary, to their alcohol use, such as HIV risk reduction and polysubstance abuse (Moore et al. 2013). The proliferation of DHTs across health domains beyond substance abuse treatment (Lal and Adair 2014; Portnoy et al. 2008) could improve the likelihood that comorbid conditions can be addressed in a single treatment setting. In those areas where treatment programs do not have the expertise and budgets to meet the diverse needs of treatment seekers, DHTs can help deliver specialized treatment for a number of conditions such as insomnia and depression without the need for significant staff expertise in the relevant health domains. Those who need more intensive services for comorbid disorders can be referred to specialty care.

Extending Care Beyond the Clinic

Most of the benefits of DHTs described above can be implemented via any digital device—computer, tablet, or phone—but only mobile and wireless devices expand the use of DHTs into a patient's everyday experience. Mobile DHTs are uniquely capable of reaching, assessing, and intervening with individuals in their natural environment over extended periods to provide just-in-time therapeutic support and salience beyond the clinic. These tools can keep individuals engaged in care (Branson et al. 2013) and facilitate long-term continuing-care contact (Gustafson et al. 2014).

Improving Treatment Attendance

In the last 10 years, DHT research outside of alcohol treatment has demonstrated that DHTs, particularly those disseminated via mobile messaging and e-mail, increase appointment adherence in medical settings (Gurol-Urganci et al. 2013). Although the evidence is mixed as to whether a text message or e-mail is any better than a phone call for increasing appointment adherence, digital messaging has advantages over phone calls. It reduces staffing costs and increases efficiency, because multiple messages can be programmed simultaneously and responses can be collected automatically and reviewed in a single sitting (Gurol-Urganci et al. 2013; Perron et al. 2013). From a client perspective, text or e-mail communications allow for increased confidentiality. Individuals do not have to speak out loud on their phones, can use their devices' security settings to safeguard messages (Pal 2003), and can refer back to a message at any point after they have received it. E-mails also do not require the phone to be active when the message is sent, making clients less vulnerable to missed communications (Anhoj and Moldrup 2004).

Therapeutic Salience

Even when clients engage regularly in treatment, they may fail to remain mindful of treatment goals and practices when outside the clinic. DHTs that remind clients of their goals could help them adhere to them in challenging situations. Because mobile messaging has become the most widely available mobile technology of the last 15 years, it has the largest empirical base at this time compared with smartphone applications. Numerous studies have shown that mobile messaging, including interactive voice response for substance users (Moore et al. 2013), can improve outcomes across physical and mental health disorders (Free et al. 2013). Some small mobile-messaging studies have been performed with problem drinkers (Suffoletto et al. 2012; Weitzel et al. 2007). Weitzel and colleagues (2007), for example, found that heavy-drinking college students not seeking treatment who received tailored mobile messages about drinking consequences via a personal digital assistant reported consuming fewer drinks per drinking day than a control group not receiving messages.

Adherence to the use of computer-based DHTs outside of the treatment setting tends to decline over time, even when traditional substance abuse treatment protocols are followed (Klein et al. 2012). Recent reviews suggest that the addition of mobile messaging and other prompts improves the effects of Web-based interventions, because they promote user action and engagement in the intervention (Fry and Neff 2009; Riley et al. 2011; Webb et al. 2010), which could be useful to trigger greater use of DHTs for alcohol and drug use that have low adherence (Brendryen et al. 2013; Cunningham et al 2009).

Using Mobile Assessment Throughout Treatment

Computer-based assessments conducted in clinical settings during intake procedures can assess usual drinking times and trigger assessments and interventions when these moments occur. Following intake, real-time assessments administered via mobile and wireless devices can take the assessment process a step further by generating a record of the everyday experiences of clients in the real world (Hufford et al. 2002; Shiffman 2009). For example, Kuerbis and colleagues (2013) revealed that self-efficacy judgments collected via mobile assessment during the first week of treatment significantly predicted reduced problem drinking compared with static baseline assessments. Although it is beyond the scope of this paper to review the range of mobile assessments, they represent an opportunity to understand clients in their natural environment across subjective states, such as craving to drink and confidence to abstain or moderate (Shiffman 2009), while measuring objective parameters using context and location sensing (Vahabzadeh et al. 2010) and transdermal sensing (Hawthorne and Wojcik 2006). For example, Gustfason and colleagues (2014) used self-report items to measure subjective craving states while simultaneously collecting

geolocation data to better understand craving in the context of the participant's location. Other methods used in general health behavior change, such as qualitative journaling and ecological video journaling (Melton et al. 2013) and a range of data visualization dashboards, also provide new DHT methods to help providers understand their clients' everyday lives.

Just-in-Time Adaptive Interventions

Assessing the everyday experiences of clients can both provide a means to understand how they progress through treatment and also trigger personalized stepped care via just-in-time adaptive interventions (JITAIs) (Riley et al. 2011). Most adjunctive DHTs used at treatment facilities can flexibly adapt and tailor content as the individual progresses through care (Marsch and Gustafson 2013). However, newer mobile interventions are able to assess progress and adapt intervention timing, content, and strength in one's environment based on changes in key outcome variables, a capability akin to that of phone-based stepped care interventions for AUDs (McKay 2009).

The most comprehensive mobile JITAI for substance use disorders is the A-CHESS system developed by Gustafson and colleagues (2011, 2014), which is designed to assess and support individuals continually following alcohol treatment. The program provides extended skills training over time based on a client's current needs and a panic button for high-risk situations. It evaluates individuals for relapse risk based on their assessment results and/or via geolocation if they are entering a high-risk environment. Based on risk, it first sends the client reminders of his or her therapeutic goals, self-modeling audio and image reminders, and tailored educational and therapeutic materials. The application then triggers in-person peer and provider support if the individual is nonresponsive or requests additional assistance. When compared with a treatment-as-usual aftercare condition, the A-CHESS mobile application significantly reduced the number of risky drinking days and increased the number of abstinent days in an AUD sample over the 8 months following inpatient alcohol treatment. Moreover, these results were maintained for 4 months after participants stopped using the application, demonstrating that the A-CHESS system did not engender unhealthy dependence among participants upon the DHT.

Although research is in its nascent stages, soon many programs will work like A-CHESS, using subjective and objective parameters and a range of assessment tools to trigger JITAIs that help individuals either become aware of risky patterns that could lead to relapse or alert support networks in an emergency (Chih et al. 2014). A range of DHTs also offers the opportunity for providers to reach out to clients proactively for check-ins in addition to having client self-assessments drive care. Whereas client self-assessments may be more predictive of relapse and outcomes than those of counselors (Walton et al. 2000), both can reveal valuable information, and combining both types of assessment will help identify the best methods to monitor outcomes.

The Power of Connection

One of the strongest methods for improving outcomes of AUD interventions seems to be the combination of DHTs with human support (Andersson and Cuijpers 2009; Christensen et al. 2009; Spek et al. 2007). As Fox (2013) suggests, the clinical value of technology lies not in its computing power but in its ability to connect providers to their patients. Although some evidence indicates that brief interventions through DHTs for low-severity populations may not require in-person contact (Cunningham et al. 2011), this finding has not been established in the cases of more severely affected populations needing long-term continued-contact interventions. The lack of both research on and evidence of efficacy of standalone DHTs in more severely affected populations underscores both the ethical concerns related to using DHTs in more severely affected populations without provider contact or guidance and the limitations of DHTs in general.

Overall, DHTs such as computer-based interventions without provider accountability or proactive alerts have extremely high attrition rates (Price et al 2012). This has been termed the "law of attrition" for Web-based interventions (Eysenbach 2005). As Postel and colleagues (2011) highlight, completion rates for Web-based alcohol intervention studies range from about 16.5 percent to 92 percent, depending on the study design, but are lower for real-world trials. For example, in the real-world trial of a Web-based computer continuing-care intervention, 90 percent of all individuals did not access the Web site after 6 months (Klein et al. 2012). Similarly, in the author's automated text-messaging study to improve attendance in methadone treatment, clients responded to automated messages for the first couple of weeks even though they were told it was a completely automated system (Muench et al. 2012). When they received no response, they stopped texting. Mohr and colleages (2011) stress the importance of human accountability in technology-based interventions because of the demotivating nature of automated human–computer interaction over the long term and ethical concerns related to automated systems for high-severity populations. Fortunately, newer mobile interventions within and outside the alcohol treatment field, including prompts, JITAIs, and human support, seem to be resulting in more engagement than older, primarily Web-based interventions (Alemi et al. 1996; Fry and Neff 2009; Gustafson et al. 2014), highlighting the power of combining DHTs with provider support.

Even the direct-to-consumer market seems to recognize the value of person-to-person contact. Many consumer-based substance abuse DHTs for individuals in recovery connect users to 12-step groups or peer support rather than being standalone behavior-change support applications. Social media sites and discussion boards offer some social

interaction to combat the loneliness that often is associated with the behavior change process and may be particularly helpful early on. Applications such as In The Rooms provide online 12-step groups, counteracting the justification that meetings are too far away or inconvenient. Alternative self-help programs such as SMART Recovery and Moderation Management offer online support meetings, expanding their reach to those regions in which only 12-step meetings are available in person. These are just a few examples of how DHTs can facilitate support and connect users to peer-based recovery services as adjuncts to care.

Client Acceptability

No matter how sophisticated and responsive, DHTs will only improve treatment if clients accept and use them. Evidence strongly supports the acceptability of alcohol and other substance use DHTs to clients, whether the technologies are delivered in the context of treatment or via a mobile intervention (Moore et al. 2011; Muench et al. 2013). This is even true outside the domain of alcohol use among the most disenfranchised clients with severe mental illness (Ben-Zeev 2012). DHTs also can expand participant treatment options, further increasing client satisfaction and improving client engagement with the treatment of their choice. For example, Hester and colleagues (2013) revealed that a subgroup of participants enrolled in a DHT with an online interactive support group component who only chose to use the noninteractive components of the DHT had drinking outcomes equivalent to those who opted to participate in the group component. DHTs thus offer treatment-seeking populations the flexibility to choose the components of an intervention they find most helpful and relevant to their needs.

Pitfalls of DHTs

Barriers to Integration

The previous sections reviewed the benefits of DHTs and their promise for improving overall outcomes. However, the field still is in the nascent stages of this paradigm shift, and integration of DHTs into care faces significant barriers. The cost of development is one of the most globally pressing concerns, but few feasible resolutions exist. Similarly, no DHTs for alcohol treatment and care are currently reimbursable, despite the costs of development, implementation, and maintenance. Thus, providers have limited incentives to embrace these new models. Some of the most common barriers to integration are reviewed below. These issues fall into six broad categories, including finding/developing and managing DHTs, data security and privacy, consent, usefulness and efficacy concerns, organizational integration, and client concerns.

Integrating DHTs Into Practice and Managing Their Data

At present, no single technology framework securely supports all of the requisite features of DHTs for substance abuse treatment, from intake to charting to continuing care. Using multiple fragmented programs that each lack some necessary features can increase staff burden and result in the needless generation of overlapping data structures (i.e., using multiple platforms or methods to collect the same data in a single treatment setting). Some more comprehensive DHT support systems can be used as adjuncts to a treatment center's existing structure (Brendryen et al. 2013). However, these systems also face barriers, including limitations on data privacy, data sharing, business associates' agreements, and a lack of control over program modifications. However, these systems do represent a promising means to begin integrating DHTs into care at a low level of development burden.

Some individual organizations have created their own internal systems (e.g., Hazelden) that are customizable to their specific needs. However, this requires substantial up-front capital and entails additional maintenance costs. Developing internal or custom systems involves forming an interdisciplinary team that includes user experience and user interface designers; front-end and back-end developers; data managers and analysts; and privacy, content, and health technology experts. As in other instances of technology integration, creating DHTs that meet the needs of providers will probably require a mix of internal and external systems, and most treatment programs will integrate technology in piecemeal, flexible ways. Newer research studies are combining and testing multiple DHT modalities such as Web-based and mobile components (Brendryen et al. 2013), as well as within-treatment and mobile programs (e.g., TES & A-CHESS), to lay the groundwork for more comprehensive care systems.

One of the newer challenges arising from the development of comprehensive programs centers on the massive amounts of big data that are collected by these systems, particularly information collected by ecological momentary assessment (EMA) and passive continuous sensing through mobile and wireless devices. Although these data sources represent some of the most promising components of JITAIs, continuously collecting heart rate, for example, while inquiring about craving to train a smart passive-sensing system requires new methods of data cleaning and analysis (Shiffman 2013). Cleaning the data alone requires significant resources because of the poor data quality collected by sensor-based sources (Kumar et al. 2013) and the increased risk of missing self-report data that accompanies EMA (Shiffman 2013). Analytical methods such as Bayesian modeling (Chih et al. 2014), dynamic systems modeling (Timms et al. 2013), and mathematical modeling (Banks et al. 2014)—which are not traditionally used in data analysis of client progress—can

help clarify the dynamic relationship between real-time data and the temporal unfolding of the behavior-change process. However, collecting and analyzing this type of data requires new expertise and interdisciplinary collaboration that has not yet been integrated into existing systems of care. Moreover, all of these new and promising methods of understanding clients through data are coupled with the greatest barrier to integrating technology into care—ensuring data security and privacy.

Data Security and Privacy

Integrating technology into treatment poses progressively more significant challenges related to data privacy and confidentiality as data collection grows and moves beyond the confines of the clinic. (See also article by Arora in this issue.) The most secure means to integrate technology is to use digital programs such as intake and follow-up assessments within treatment centers, which typically are protected by powerful firewalls like those used in all hospitals. However, as data collection expands beyond the confines of the agency, significant issues arise for maintaining privacy and security (Luxton et al. 2012). New options apply when using any external communication, but given the relative novelty of mobile health technology, these are nebulous at best. For example, a treatment provider can use messaging encryption services, but these services require all clients to have specialized apps or software, and the only guarantees of security at present come from the companies' own claims. Recently, a company designed to evaluate apps on efficacy and security had to suspend its operations because it was certifying apps with security limitations. Because security and privacy essentially are the kryptonite of most external communication applications, agencies should assess their communication needs and goals before deciding to implement a mobile DHT. Simply reminding patients of their appointments, for example, may require a different level of security than providing an actual intervention.

Despite these limitations, technology offers the ability to be creative in developing assessment and intervention protocols depending on treatment or research goals. In the author's current National Institute on Alcohol Abuse and Alcoholism (NIAAA)-sponsored study testing various forms of mobile messaging to reduce problem drinking, participants who are concerned about the privacy or security of their messages can be placed in a condition in which they receive messages that make no explicit reference to alcohol or drinking. In this group, the focus is on general motivation salience to meet personal goals. It is entirely possible that interventions need not mention the disease state to be effective but can instead be tailored based on variables such as time and other processes such as self-efficacy and context. Other options include using generic self-monitoring applications to assess and intervene with participants, or viewing their progress on a shared dashboard or via mobile messaging/e-mails to trigger a Web-based portal that is password protected and secure. Establishing best practices for ensuring data security and privacy when using DHTs is a work in progress. Until secure external communication technologies are invented, clinicians need to be creative in how they work with client populations outside the clinic.

Using Consent Effectively for DHTs

Incorporation of DHTs into care not only requires creativity and data security but also consent forms modified to include all the potential risks of using a digital platform. These additions can increase the length of consent forms by several pages, since they must cover every potential risk of using the technology. The risks associated with digital communications are numerous and vary based on the types of technology employed. DHT consent forms likely will need to include information such as the scope of digital communication, information communicated and method used, inherent privacy risks of communication, security and storage of communication, use of outside vendors who have access to communication, security of external vendor applications, procedures for lost provider devices, training clients on how to secure communication devices, lack of control over timing of digital communication, likelihood of missed communications, inappropriateness of digital communication as an emergency platform, recorded digital communication as part of the client's health record, risk of misinterpretation in text-based communication (e.g., cryptic tone or context), possible charges incurred by the client, protection of agency and agency staff devices, and opt-out and help options. These are just some of the topics that a consent form might need to cover related to digital communication, but all possible scenarios should be explored when an agency plans to employ DHTs.

Evaluating DHT Usefulness and Efficacy

At present, the empirical literature evaluating DHTs lags behind the number of DHTs developed for alcohol use and substance use more generally. The process of validating an assessment or treatment is remarkably slow when compared with the pace of technological development (Price et al. 2013). Although most existing DHTs are modified or enhanced digital versions of existing in-person behavioral interventions or bibliotherapeutic techniques (Marsch and Dallery 2012), adoption of DHTs will only become widespread as reputable studies demonstrate efficacy.

Unfortunately, many evaluations of DHTs to date have been flawed or limited only to certain populations. Recent reviews of computer-based interventions found significant methodological flaws in research designs, evaluations of treatment exposure and adherence, rates of follow-up assessment, and conformity to intention-to-treat principles (Kiluk et al. 2011). Furthermore, the well-designed trials solely assessing alcohol use typically have targeted young binge drinkers—a highly specific sample that under-

represents the heterogeneity of the broader problem-drinking population.

DHTs discussed above that have been integrated into traditional alcohol and drug treatment with success, such as TES and A-CHESS, have used rigorous study designs and have dealt with more severely affected substance-using populations. However, it is important to note that many of the studies on DHT treatment integration have been conducted among polysubstance users, rather than alcohol users specifically, which limits generalizability to the latter population.

In the only review of mobile applications for alcohol use problems to date, Cohen and colleagues (2011) highlighted the dearth of outcomes and quality-control guidelines for alcohol intervention apps that are directly available to consumers. However, credible governmental Web sites, such as the Health Apps Library in the United Kingdom, may assist organizations in evaluating which DHTs are safest and best suited to their needs, even when a controlled trial has not been conducted on an application translated from the empirical literature. Also, in contrast to implementation of in-person, evidence-based treatments, which generally is slow going (Kumar et al. 2013), once a DHT is validated, it can be disseminated rapidly.

Readying Organizations to Adopt DHTs

Once DHTs reach an acceptable level of validation, their successful integration into a treatment practice will depend on the staff's preparedness and willingness to learn new technologies. Organizational and staff norms tend to reinforce the status quo rather than focusing on continuous quality improvement. Agencies should focus on integrating new procedures into existing workflows, creating new staff roles (e.g., project managers who will train staff and deal with resistance to or fear of integration), balancing a DHT's financial costs against its potential rewards, and understanding how technology shifts certain roles and responsibilities. A flexible deployment model that focuses on the best uses of DHTs within an organization and harnesses the strengths of existing resources is a useful first step (Marsch and Gustafson 2013).

Even with organizational support and a technology project manager, there often are staff-related barriers to technology adoption. The most pressing staff concerns usually fall within the realms of time burden and level of comfort with the use of technology (Campbell et al. 2012). Understanding how to use the actual technology is one of the most common barriers to integration across all domains. For example, Kuhn and colleagues (2014) found that although all VA providers expressed fairly high interest in integrating a smartphone app into posttraumatic stress disorder treatment, younger clinicians and those with smartphones found the app more usable than older clinicians and those without smartphones. These variables predicted clinicians' intentions to use the app in treatment. Integration requires an understanding of staff members' degree of comfort with technology and the selection of appropriate training to increase staff confidence in navigating potentially foreign technologies.

Even when providers are trained and confident in the use of DHTs, new continuing-care applications in which providers view dashboards or are constantly on call increase rather than decrease staff burden by expecting staff to exceed their typical job responsibilities. Thus, managers should understand how any new technology will affect staff workload before adopting it. For example, Muench and colleagues (2013) found that although 80 percent of providers want to be alerted if their client is at risk of relapse, only 8 percent would want an immediate mobile alert. Most providers are interested in e-mails or phone messages on their work phones so as not to be on call at all times. Developing rotating staff or peer on-call procedures like those used in hospital settings can help. Another option involves using a graded alert system based on the overall risk of relapse, as is used by the A-CHESS system. Graded alerts can reduce unnecessary staff burden. When taken together, the emerging trend towards minimal long-term continuous contact interventions as a standard of care will not only require a shift in treatment models but also a change in policies, staff, procedures, and payment methods.

The elephant in the room, however, is the question of how these technologies will shift provider roles and responsibilities and alter current treatment models. No evidence exists that DHTs are better than in-person care, and evidence suggests that higher-severity populations do better with in-person care than with standalone DHTs for alcohol use. However, even the suggestion that an automated system may perform some aspect of someone's job as well as or better than that person can be inherently demotivating. This is the case with some diagnostic and follow-up systems that use big data to make diagnoses (Graber and Mathew 2008) or predictive modeling to understand the change process (Chih et al. 2014). Similar to the way Amazon has changed the publishing and bookselling industry, DHTs will change how we provide substance abuse care. Amazon did not reduce the amount that people read, but it did change how they buy books, how books are published, and what the job landscape within the publishing world looks like. DHTs require a rethinking of how to provide care and offer the opportunity to improve service delivery in new and innovative ways. For example, some evidence suggests that Internet-based interventions with human support are equally effective when delivered by a technician versus a clinician. The finding highlights the need to understand how DHTs will affect current models of care (Titov et al. 2010).

Addressing Client Concerns

Despite clients' apparent enthusiasm for DHTs, they have concerns that will need to be addressed, particularly in the context of mobile monitoring systems. First and foremost is the Orwellian nature of real-world monitoring. Clients may

not feel comfortable being continuously monitored outside of the treatment setting, and some will feel that it imposes on their freedom. Assuring clients that DHT communication and monitoring is an optional component of treatment will help to reduce this concern. Second, clients need to be trained in the use of these systems, since evidence shows that comfort with technology is a driver not only of provider use but also of client use (Ranney et al. 2012). Moreover, training needs to cover how to deal with emergencies and service outages beyond what simple consent procedures discuss. For example, training clients that DHTs are not designed to respond to emergencies, that outages in service are to be expected, and that they should not anticipate 24-hour-a-day communication will serve to create realistic expectations about these programs.

Among many low-income clients, another common problem occurs when they have their phone service turned on and off repeatedly for not paying their bills on time. In other cases, individuals may have temporary or disposable phones and therefore change their phone numbers often, creating discontinuity in service provision (McClure et al. 2013). In a methadone treatment text-messaging study (Muench et al. 2013), approximately 20 percent of participants had their phone service turned off at least once over the course of the 5-week study as a result of nonpayment (Muench et al. 2012). When their phones were eventually turned on again, clients received all of the messages they had missed over the stoppage period at once. Several individuals were also using family phones, raising unanticipated questions about confidentiality and privacy. This problem occurs across mobile interventions—whether they be smartphone applications or text-messaging programs. Finally, DHTs that promise regular contact can fail because of programming and communication errors, which can become a source of stress for clients. Whereas an informed consent procedure may warn individuals of these lapses in communication, it may not prepare them for an instance in which they expect communication that never occurs.

Finally, smartphone technology presents challenges of its own. It is unfair and possibly unethical to integrate services into treatment programs that only a subset of clients will have the resources to access. The more expensive smartphones have not yet saturated the mobile-phone market. Even when a client has a smartphone, problems arise with regard to interoperability between operating systems when using native applications (e.g., iOS vs. Android). Newer options that are device agnostic (i.e., that can be used on any mobile operating system), such as HTML5 applications, are becoming more commonplace, but still only account for about 30 percent of mobile development. These nuanced limitations of DHT integration are the rule rather than the exception. It is therefore imperative to any digital integration effort that treatment providers understand their population's needs and constraints.

Conclusions and Future Directions

Innovative DHTs that are now over 15 years old, such as the Drinker's Check-Up, set the stage for the current proliferation of alcohol-related DHTs. Although research clearly emphasizes the benefits of DHTs to assess and intervene with individuals with low-severity alcohol problems, there is little evidence that standalone DHTs are helpful for those with more severe alcohol problems. Moreover, the current research suggests that standalone DHTs have limited long-term impact and high attrition rates, although there is evidence that adding mobile prompts improves the effectiveness of computer-based DHTs. The strongest evidence of efficacy to date supports DHTs that are included as part of in-person treatment as an adjunct or enhancement to current care. However, few treatment programs outside of research settings seem to be integrating assessment and intervention DHTs beyond electronic charting. This is attributed to a combination of tangible barriers, such as privacy and security concerns, organizational norms, unclear financial models, and lack of knowledge about the potential promises of DHTs beyond their pitfalls. Despite these uncertainties, more research now suggests that DHTs can at minimum be a helpful adjunct to various touch points in the treatment process. Treatment professionals can feel secure taking some initial steps into the world of DHTs without moving into the realm of equivocal efficacy. For example, one of the easiest methods to improve outcomes is to include digital client monitoring. This does not require mobile devices and tight security features but rather a weekly check-in at a kiosk behind the treatment center's firewall. This could be a first step in using the power of DHTs to improve client outcomes without significant disruption of current models of care.

In the not-so-distant future, early identification of alcohol problems through predictive algorithms by supercomputers connected to a mobile application will warn individuals and providers of the likelihood of problem use long before problems start. These algorithms will alert individuals and counselors to relapse risk based on behavioral decisions that, although seemingly irrelevant at face value, in fact predict a lapse (Bekiroglu et al. 2013; Chih et al. 2014). For example, a recent simulation study of smokers revealed that machine learning applications can provide personalized JITAIs exclusively at times when support is most needed, which can reduce staff and client burden (Lagoa et al. 2014). Sensors on the mobile phone will be able to measure speech characteristics and gait of clients at risk of problematic alcohol use to trigger in-the-moment interventions that remind them to order a seltzer with lime rather than a beer. These technologies already exist and—once validated—will dramatically improve our ability to help individuals wanting to change their alcohol use. Mobile interventions might be especially powerful for individuals attempting to moderate their drinking. Unlike abstinence-oriented individuals for whom being in a high-risk situation would trigger an alert, individuals with moderation goals are often in high-risk

situations and therefore require flexible adaptive drinking plans and methods to promote healthy drinking beyond stimulus control. This is where the nuances of smart systems will reveal their greatest benefits.

Clients and consumers are already embracing DHTs and creating a patient-centered health movement—a phenomenon that echoes the initial rise of 12-step treatments outside of medical institutions. This patient-centered movement empowers people to take control of their health. As evidenced throughout this paper, consumers will be the greatest beneficiaries of the digital revolution. In time, however, agencies and providers will experience significant benefits as well. Like all continuous quality-improvement systems, the integration of DHTs into treatment will be an iterative process that focuses on simultaneously maximizing outcomes and system harmony, which means that there will be many bumps in the road along the way. One question that requires an answer is how provider roles and responsibilities change as we integrate more DHTs into AUD treatment. However, as the research has repeatedly revealed, DHTs are most effective when combined with human support, reinforcing how providers will remain the foundation of care for those seeking help for their alcohol use for the foreseeable future.

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Computerized Cognitive–Behavioral Therapy

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With an estimated 90 percent or more of alcohol use disorders going untreated (Substance Abuse and Mental Health Services Administration 2012), the search for interventions that easily, effectively, and economically reach more people has become a priority. The landmark 1990 report, *Broadening the Base of Treatment for Alcohol Problems* (Institute of Medicine 1990), refocused alcohol treatment research toward an emphasis on developing, standardizing, and disseminating new behavioral therapies to expand the reach of alcohol treatment. A particularly exciting development on this front has been the creation of computerized versions of interventions shown to be effective in clinical settings.

Computerized treatments have multiple potential advantages for expanding the base of treatment for alcohol use disorders, including broad availability 24 hours a day, lower cost, standardization, greater ability to reach rural and underserved populations, and greater confidentiality, leading to fewer concerns about stigma (Carroll and Rounsaville 2010; Cunningham and Van Mierlo 2009). In effect, computer-based interventions can serve as "clinician extenders," offering a means of delivering high-quality, standardized versions of screening, evaluation, and brief treatments, at relatively low cost. That said, these interventions are relatively new, and, therefore, both their quality and the level of rigor of the studies supporting them varies widely (Carey et al. 2009; Kiluk et al. 2011; Rooke et al. 2010). Here, we will highlight only approaches with at least preliminary validation in clinical trials.

Electronic Screenings and Brief Interventions (eSBIs)

Many Web sites exist that allow people to assess their alcohol use from their personal computers or other devices using Web-based versions of more traditional, clinician-delivered SBIs (Babor et al. 2007). These sites connect people with SBI services immediately, when their motivation may be highest, rather than asking them to wait several days or weeks for an appointment with a clinician. Called electronic SBI (eSBI), these sites typically are based on principles of clinician-delivered SBIs, using a validated instrument such as the Alcohol Use Disorders Identification Test (AUDIT) to assess alcohol use and risk (Allen et al. 1997; Bohn et al. 1995), provide feedback about the user's level of risk, and offer some suggestions or additional resources for reducing drinking.

Many eSBIs exist; however, only a few have been evaluated in randomized clinical trials, and the majority of those studies have been conducted on college populations and may not generalize to broader society (Bewick et al. 2008; Rooke et al. 2010; White et al. 2010). In fact, one recent meta-analysis found only 17 randomized controlled trials of eSBIs that provided enough data for comparison, and 13 of those studied student populations (Donoghue et al. 2014). Despite this limitation, Donoghue and colleagues reported that the eSBIs studied had a significant effect on participants' drinking behavior for up to 12 months postintervention. Overall, studies of eSBIs find a small but significant effect size for eSBIs and conclude that some users can benefit from these computer-based interventions, particularly

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people unlikely to seek out more traditional services (Bewick et al. 2008; Donoghue et al. 2014; Rooke et al. 2010; White et al. 2010).

To date, the English-language eSBIs designed for the general public that have the strongest evidence supporting their efficacy based on randomized controlled trials are The Drinker's Checkup (www.drinkerscheckup.com) (Hester et al. 2005) and Check Your Drinking (www.checkyourdrinking.net) (Cunningham et al. 2009).

Web-Based Multisession Interventions

Compared with eSBIs, fewer computer-based intensive, multiple-session interventions for alcohol use disorders exist, and even fewer have been tested with randomized controlled clinical trials. Those have shown some promise.

One study, for example, examined whether study participants who utilized the Check Your Drinking SBI would get an added benefit if also offered an extended Internet intervention called the Alcohol Help Center (AHC). AHC provides cognitive–behavioral, motivational, and relapse prevention components that previous research has shown helps problem drinkers (Cunningham 2012). People using the AHC can complete whichever exercises they choose in whatever order they like over an unspecified, extended period of time. The study recruited 170 problem drinkers from the general population and randomly assigned them access to Check Your Drinking alone or Check Your Drinking along with AHC. Ninety percent of participants returned a 6-month follow-up questionnaire that assessed their drinking behavior. Both groups significantly reduced their drinking, but participants who accessed AHC showed an added benefit of the extended intervention. The study did not assess how often study participants engaged with AHC.

Another study of nondependent problem drinkers showed that online training in moderation management using the "Moderate Drinking" application (www.moderatedrinking.com) combined with online moderation management through the Moderation Management Web site (www.moderation.org) is effective in reducing drinking days (Hester et al. 2011). The study randomly assigned 78 participants to either use the two interventions in tandem or to just use Moderation Management. Although both groups significantly decreased the amount they drank, even after a full year, participants that used both Web sites had a higher percentage of days abstinent and fewer alcohol-related problems than the group utilizing Moderation Management only. This study did not report participants' level of engagement with the interventions.

A more structured, 6-week online cognitive–behavioral self-help intervention for adult problem drinkers also showed promise in a randomized controlled trial conducted in the Netherlands (Riper et al. 2008). Participants who utilized the interactive self-help intervention reduced their drinking significantly more than participants who received an online psychoeducational brochure about alcohol use. Specifically, 17 percent of those receiving the intervention reduced their drinking to levels considered low risk in the Netherlands (no more than two units or 20 g of alcohol per day) compared with 5.4 percent of those receiving the brochure. Overall, the intervention group decreased their weekly alcohol consumption significantly more than the control group.

Although those findings are promising, another study of adult problem drinkers in the Netherlands suggests that it might be more effective to combine online self-help interventions with Internet-based one-on-one therapy (Blankers and Koeter 2011). The randomized controlled trial assigned 205 problem drinkers to one of three interventions:

- A waitlist for treatment (the no treatment control);
- Self-Help Alcohol Online (SAO), a fully automated, Internet based, self-guided treatment program based on a cognitive–behavioral treatment (CBT)/motivational interviewing (MI) treatment protocol; or
- Therapy Alcohol Online (TAO), which provides the same CBT/MI treatment protocol as SAO but also includes up to seven synchronous text-based chat-therapy sessions with a trained therapist.

Three months after starting the program, study participants in both treatment groups had reduced their alcohol consumption and their level of alcohol-related problems significantly more than those on the waitlist, but there was no significant difference between the treatment groups. That changed after 6 months when participants receiving TAO showed larger reductions in alcohol consumption than those receiving SAO. The researchers concluded that both TAO and SAO effectively reduced drinking and drinking-related problems but that TAO

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seemed to lead to better results after 6 months.

A recent meta-analysis comparing nine randomized controlled clinical trials of guided and unguided low-intensity Internet interventions for adults (the authors excluded studies of college students) found that Internet interventions had a small but significant effect on drinking behavior (Riper et al. 2014). Participants in the Internet interventions drank an average of 22 grams per week less than participants in control groups and were more likely to adhere to low-risk drinking guidelines postintervention. Riper and colleagues note that, although the effect sizes of these interventions are small ($g = 0.20$), because they have the potential to reach so many people, they could have a large influence on public health.

A higher-intensity computer-based intervention that shows promise is computer-based training for CBT (CBT4CBT). This eight-session computer-based version of CBT focuses on teaching basic coping skills, presenting video examples of effective coping skills used in a number of realistic situations and providing opportunities for patients to practice and review new skills. Two completed trials indicate that CBT4CBT improves outcomes over standard treatment alone. One study (Carroll 2008) tested CBT4CBT in an outpatient setting with a mixed group of 77 substance users, including a large number of alcohol-dependent individuals. The other study tested the intervention among 101 cocaine-dependent methadone-maintained patients (Carroll et al. 2014). Both studies found CBT4CBT had a durable effect on substance use, with improvement in substance use increasing over time, suggesting that CBT's "sleeper effect" is retained in its Web-based version (Carroll et al. 2009). These studies also found that CBT4CBT effectively taught the targeted skills and that skill acquisition in turn mediated the effects on substance use (Kiluk et al. 2010). Researchers recently have developed a version of CBT4CBT specifically for individuals with alcohol use disorders and have begun randomized clinical trials evaluating its efficacy, including one evaluating CBT4CBT as a standalone intervention. More information can be found at the Web site: www.cbt4cbt.com.

Conclusion

Computer and Web-based interventions hold great promise for reaching the large number of individuals who may benefit from alcohol treatment but do not access it. Thus far, the meta-analytic work in this area points to a modest but significant effect of these interventions and hence their potential to improve public health by extending the reach of interventions beyond the clinic.

At the same time, enthusiasm regarding the potential of these interventions should be tempered with some caution. It is critical to carefully evaluate these interventions before they are broadly disseminated. Relatively few of the many available Web-based interventions have been carefully evaluated in well-controlled clinical trials (Kiluk et al. 2011), and the conclusions that can be drawn from many studies are constrained by high levels of dropout, high attrition, and weak control conditions (e.g., waitlists). Indeed, recent meta-analyses have included only one-tenth of available published reports (Riper et al. 2014) because of methodological limitations. The field, while not still in its infancy, remains young, and basic questions regarding which individuals are best served by and most responsive to online versus face-to-face interventions have not been addressed (Carey et al. 2012). That said, if research demonstrates computer-based interventions to be safe and even moderately effective, they may have tremendous impact for individuals with alcohol use disorders and their families, potentially reaching people who would not access more traditional treatment options.

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Computerized Working-Memory Training as a Candidate Adjunctive Treatment for Addiction

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Alcohol and other drug dependencies are, in part, characterized by deficits in executive functioning, including working memory. Working-memory training is a candidate computerized adjunctive intervention for the treatment of alcoholism and other drug dependencies. This article reviews emerging evidence for computerized working memory training as an efficacious adjunctive treatment for drug dependence and highlights future challenges and opportunities in the field of working-memory training, including duration of training needed, persistence of improvements and utility of booster sessions, and selection of patients based on degree of deficits.

Key words: Alcohol and other drug use, abuse, and dependence; alcoholism; addiction; treatment; brain function; working memory; computerized working-memory training; computer technology; electronic health technology

Computerized adjuncts for the treatment of alcohol dependence and other drug dependencies have taken many forms (Bickel et al. 2011). Some have focused on computerizing various forms of cognitive–behavior therapy (CBT) (Bickel et al. 2008; Budney et al. 2007; Carroll et al. 2004). Other approaches have focused on rehabilitating aspects of executive dysfunction (Bates et al. 2013), or as it has been called in other literatures, impulsivity (Bickel et al. 2012). The importance of the latter foci is supported by evidence that between 50 and 80 percent of people with alcohol disorders or other drug dependencies experience mild to severe executive function impairments (Aharonovich et al. 2006; Bates et al. 2006; Goldman 1990; Gonzalez et al. 2004). Among people in substance abuse treatment, these neuropsychological impairments are related to greater attrition, violations of clinic rules, and poor treatment outcomes (Aharonovich et al. 2003, 2006; Bates et al. 2006; Teichner et al. 2002).

Rehabilitative efforts focused on improving executive function have been increasing in the last 10 years, partly as a result of advances in computerized training, particularly "adaptive-training" programs (Klingberg 2010). Adaptive-training programs rely on computerized algorithms that adjust intervention content to a patient's skill level in real-time in order to tax participants at the limit of their capacity and maintain engagement during training (Morrison and Chein 2011). Other advantages of computerized training include standardized delivery of intervention content and the ability to automatically track a patient's progress in relation to the dose, duration, and content of the training received (Bickel et al. 2011*a*). The increasing reach of computer technology and the Internet, which can provide patients with greater access to adjunctive interventions at times and places that fit their schedule, also contributes to interest in computerized training programs (Bickel et al. 2011*a*).

Computerized training to address executive function has focused on broad-based training or training of specific executive functions (Bates et al. 2013). One such computerized approach has trained a form of response inhibition to certain alcohol- or drug-related stimuli (e.g., attention bias modification [Wiers et al. 2013]) as a means to prevent the automaticity often observed in addiction. This article will focus on another computerized approach that trains a specific executive function, namely, working memory.

Working memory refers to "the ability to retain some information active for further use, and to do so in a flexible way allowing information to be prioritized, added, or removed" (Bledowski et al. 2010, p. 172). Some investigators have suggested that working-memory is a foundational executive function that undergirds many others (Baddeley 2012). In addition, Hofmann and colleagues (2012) have suggested that working-memory operations undergird successful self-regulation. More specifically, they state that working memory is important for (1) adequate representation of self-regulatory goals, (2) the control of attention, and (3) protecting goals from interferences such as desires and craving. Thus, working-memory capacity may be related to delay discounting, which refers to the discounting of the value of a reward as a function of longer delays to receipt of the reward (Bickel et al. 2011*a*). Specifically, people with

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lower working-memory capacity may show greater delay discounting, a form of impulsivity, by preferring sooner, smaller rewards relative to later, larger rewards (Bickel et al. 2011).

Not surprisingly, working-memory deficits and excessive delay discounting have been observed in substance-dependent groups, including alcohol- (e.g., Beatty et al. 1995), cocaine- (e.g., Berry et al. 1993), methamphetamine- (e.g., McKetin and Mattick 1997; Bickel et al. 2011*a*) and opioid-dependent individuals (e.g., Ersche et al. 2006). Of course, these groups typically show other executive dysfunctions. However, if working memory is central to the other executive functions, theoretically related to self-regulation and delay discounting, and diminished or dysfunctional among those with alcohol or other drug dependencies, then examining the effects of working-memory training in addiction is worthwhile.

This article will review the current research on the use of computerized working-memory training as a target for intervention in addiction. Specifically, it will (1) review the status of working-memory training as a relevant tool in addiction treatment, and (2) address potential challenges and opportunities related to the use of working-memory training as an adjunctive treatment.

Computerized Working-Memory Training

Working-memory training has been identified as a possible means to enhance executive function in various populations (for a review, see Shipstead et al. 2012). Typically, computerized working-memory training occurs several times a week, over multiple weeks (e.g., 4 to 6 weeks), during which four to eight blocks of working-memory tasks are completed (Klingberg 2010). Computerized training programs have been developed to address different aspects of working memory, have been administered according to various schedules and durations in different populations, and have demonstrated mixed findings with regard to generalizability and sustainability of training effects (Klingberg 2010; Shipstead et al. 2012).

Within healthy populations, evidence of working-memory improvement has been limited and often conflicting. For example, in young adults, two studies (Jaeggi et al. 2008, 2010) found that computerized working-memory training was not associated with increases in fluid intelligence, although a third study using the same working-memory training exercise (i.e., dual N-back[1]) did find this improvement in older adults (Seidler et al. 2010). One possible explanation for these contradictory results throughout the healthy population literature (for a review, see Shipstead et al. 2012) is that improvements are harder to achieve or less consistent in those with adequate abilities. Thus, improvements may have only been seen in people with significant deficits, such as elderly people, people with schizophrenia, and those with alcohol or drug dependencies (Lett et al. 2014).

Studies of working memory and other executive-function training within impaired populations have proved more promising. Bickel and colleagues (2011*b*) examined effects pre– and post–working-memory training in an experimental and control group of stimulant-dependent individuals in treatment. In the experimental condition, participants completed a series of computerized working-memory tasks, whereas those in the control group received a similar task battery where the answers were provided so that working-memory ability was not taxed. After receiving between 4 and 15 training sessions, the excessive-delay discounting of the experimental group decreased significantly more than in the control group, suggesting increased self-control and valuation of delayed rewards in the experimental group. Changes in delay discounting were not accompanied by changes in other measures that were concurrently assessed, including a response inhibition task. One possible explanation is that the neural areas associated with working memory and future valuation (i.e., delay discounting) overlap in the posterior dorsolateral prefrontal cortices, which would support concurrent change in working memory and future valuation but not change in behaviors subserved by brain regions/circuits with less overlap (Wesley and Bickel 2014).

Another study of working-memory training conducted via the Internet in problem drinkers found reduced alcohol consumption, particularly in more impulsive individuals (Houben et al. 2011). Houben and colleagues (2011) provided problem drinkers with 25 sessions of either active or control working-memory training. At the conclusion of computerized training, working-memory improvements and decreased alcohol intake were demonstrated in the experimental group and persisted 1 month after training cessation. Moreover, they found that people with stronger automatic (implicit) preferences for alcohol benefited the most from working-memory training. The reduction in discounting of future rewards in stimulant users (Bickel et al. 2011*b*) and the finding of reduced alcohol consumption in problem drinkers (Houben et al. 2011) provide converging evidence that suggests computerized working-memory training can improve working memory, aspects of self-regulation (e.g., delay discounting), and excessive alcohol consumption in certain subgroups (see Verbeken et al. 2013 for interesting complementary findings in obesity treatment).

The exact mechanism or mechanisms of these effects are unknown. One mechanism may be related to a conceptual model of addiction that stipulates an imbalance between two neurobehavioral decision systems that should ideally be in regulatory balance (Bechara and Damasio 2002; Bickel et al. 2014; Jentsch and Taylor 1999). This model is a specialized variant of the numerous dual models developed to address nonpathological behavior (Kahneman and Tversky 1979). In the addiction-related dual model, referred to as the competing neurobehavioral decision systems hypothesis, individuals with addiction often show greater control by the impulsive decision system and less by the executive decision

[1] Games based on N-back tests require players to remember the location of a symbol or the sound of a particular letter presented just before (1-back), the time before last (2-back), the time before that (3-back), and so on.

system. The impulsive decision system is embodied in the limbic and paralimbic brain regions and often functions in the short term to obtain biologically relevant reinforcers. The executive decision system is embodied in aspects of the prefrontal cortices and functions to obtain longer-term outcomes and reinforcers. Working-memory training, by strengthening an aspect of the executive decision system, may reestablish some degree of regulatory balance in addicted individuals.

Conclusions: The Challenges and Opportunities of Working-Memory Training

Working-memory training is not a panacea, but for some individuals receiving treatment for alcohol or other drug dependencies it may be a useful adjunct. Some of the challenges and opportunities related to working-memory training are reviewed below.

Challenges of computerized working-memory training are at least sixfold. First, the number and breadth of working-memory training sessions necessary to produce an improvement on working memory or other outcomes like delay discounting (a measure of impulsivity or self-control) are unknown. Second, it is not known whether the extent of training would vary by the type of drug dependence or the degree of dependence. A recent study (Bickel et al. 2014) suggests that the largest effect of working-memory training will occur among those who discounted delayed rewards the most at the start of treatment. Third, the duration of the improvements in working memory once trained also is unknown. However, two studies with clinical populations have shown sustained effects of working-memory training from 1 month (Houben et al. 2011) to 2 months (Verbeken et al. 2013). Fourth, if the effect dissipates, research is needed to determine whether booster sessions of working-memory training could facilitate retention of the clinical improvements. Fifth, working-memory training can be long and laborious for the participant, raising questions about motivation techniques that would ensure compliance with the training regimen. Sixth and finally, the extent to which working-memory training will generalize to behaviors beyond alcohol consumption and delay discounting remains to be determined.

The opportunities associated with computerized working-memory training lie in its potential to improve the efficacy of existing treatments as an adjunctive intervention. If patients at the beginning of treatment could complete an assessment that would discern their working-memory ability or perhaps their delay discounting, then those individuals showing the greatest impairment could receive adjunctive treatment with computerized working-memory training (Bickel et al. 2014; McCrady and Smith 1986). Whether this training should occur concurrently with other aspects of treatment or start before the other treatment components is an important issue to address. That is, those patients with executive dysfunction may not be able to benefit from important aspects of treatment until some of their dysfunction has been repaired. Nonetheless, the prevalence of working-memory dysfunction in alcohol and other drug dependencies, its relationship to poor clinical outcomes, and the theoretical relationship between working memory ability and self-regulation collectively suggest the importance of exploring the full therapeutic implications of computerized working-memory training as an adjunctive intervention in addictions treatment.

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Mobile Delivery of Treatment for Alcohol Use Disorders

A Review of the Literature

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Several systems for treating alcohol-use disorders (AUDs) exist that operate on mobile phones. These systems are categorized into four groups: text-messaging monitoring and reminder systems, text-messaging intervention systems, comprehensive recovery management systems, and game-based systems. Text-messaging monitoring and reminder systems deliver reminders and prompt reporting of alcohol consumption, enabling continuous monitoring of alcohol use. Text-messaging intervention systems additionally deliver text messages designed to promote abstinence and recovery. Comprehensive recovery management systems use the capabilities of smartphones to provide a variety of tools and services that can be tailored to individuals, including in-the-moment assessments and access to peer discussion groups. Game-based systems engage the user using video games. Although many commercial applications for treatment of AUDs exist, few (if any) have empirical evidence of effectiveness. The available evidence suggests that although texting-based applications may have beneficial effects, they are probably insufficient as interventions for AUDs. Comprehensive recovery management systems have the strongest theoretical base and have yielded the strongest and longest-lasting effects, but challenges remain, including cost, understanding which features account for effects, and keeping up with technological advances.

Key words: Alcohol consumption; alcohol use disorders; intervention; treatment; continuing care; electronic health technology; mobile health technology; mobile phone; smartphone; Internet; telecommunication; literature review

The advent of mobile-phone technology has been one of the most influential technological advances in world history. In 2014, the International Telecommunications Union (ITU) estimated that the number of mobile-phone subscriptions worldwide (including both personal and business subscriptions) would reach about 7.0 billion at the end of 2014 and thus approach the number of people on Earth (corresponding to a global penetration rate of 96 percent) (ITU 2014). Furthermore, Google's "Our Mobile Planet"—a marketing survey commissioned by Google to assess worldwide use of mobile technology—indicated that the use of smartphones (i.e., mobile phones with computer-like capabilities) has increased significantly in recent years (Google, Inc. 2013). According to the survey, more than 50 percent of the population in most developed countries used smartphones in 2013, and rates of smartphone ownership have been increasing steadily year after year. In addition to their many other uses, mobile phones offer an opportunity to monitor various behaviors of their users, such as alcohol consumption, and to deliver interventions to users in near–real time and in the individual's natural environment. Several review and commentary articles about the use of mobile health (mHealth) and Internet technology in health care, and specifically in the treatment of alcohol use disorders (AUDs), have been published in recent years (Bewick et al. 2008; Carey et al. 2009; Gustafson et al. 2011, 2014; Hester and Miller 2006; Kypri et al. 2005; Savic et al. 2013).

A plethora of research supports the conceptualization of addiction as a chronic, relapsing disease (Bradizza et al. 2006; Brownell et al. 1986; Dennis et al. 2003; Donovan 1996; Lowman et al. 1996; McKay and Weiss 2001; McLellan 2002; Mueller et al. 2007; Witkiewitz and Marlatt 2004). As with other chronic diseases, patient self-management and continuing care are fundamental to effective treatment (Wagner et al. 1996). Although research supports the effectiveness of continuing care in addiction treatment (McKay 2005; McLellan et al. 2005; Simpson 2004), the field historically has offered little ongoing support to patients, whether during treatment when the patient is outside of the clinic walls or after the patient has completed treatment (McLellan et al. 2000; White et al. 2002). Mobile technology may make it possible to provide both self-management help and continuing care more widely.

This article explores the following questions about mobile applications intended for patients dealing with AUDs:

- What mHealth applications to treat AUDs exist that have been evaluated in the peer-reviewed literature and how can they be categorized?

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- What are common features of these applications?
- How effective are currently commercially available mHealth applications for AUDs?
- What are the characteristics, benefits, and limitations of mHealth applications for AUDs?
- What is the theoretical grounding underlying these applications?
- What are the challenges and opportunities facing mHealth approaches for AUDs?

By design, this discussion is limited to systems that (1) use mobile technology (i.e., do not rely solely on Web-based approaches); (2) focus on AUDs and not on tobacco or other drugs; and (3) have been evaluated in the peer-reviewed literature.

Identifying mHealth Applications to Treat AUDs

To identify mobile applications for AUDs, the authors of this article searched electronic databases of the peer-reviewed research literature.[1] To further identify relevant studies, they also examined the reference lists of the initially retrieved studies. Because the field is changing so rapidly and the discussion should focus on the current state, the initial search only included studies and reports published since 2009. A subsequent expansion of the search to studies published in earlier years (i.e., between 2002 and 2009) yielded no additional results. Based on the abstracts of the identified studies, a final list of studies was created for in-depth analysis. Despite this broad search approach, however, it is possible that some mHealth systems were missed, especially more recent ones derived from currently funded research endeavors that have not yet published their results or descriptions of their systems.

The initial literature search yielded a total of 486 articles, the vast majority of which upon closer inspection were not germane to the issue of mobile treatment for AUDs. Other articles were excluded because they were reviews rather than original studies, did not report results of specific applications, or had not been published in peer-reviewed journals. (More detailed information on the selection process of the articles chosen for further analysis is available from the authors of this article.) Ultimately, the following description and review of mHealth applications for AUDs was based on a set of 20 published studies that describe 14 unique mobile systems, including their originators, names (if applicable), key features, how they were tested, theories on which they are based, target populations, and results (see table). If possible, special attention was paid to the theories on which the systems were based because theory-based development of mHealth interventions may yield more durable and relevant results (Baker et al. 2014).

Of the 14 identified systems, 11 delivered interventions that relied primarily on text-messaging technology. Two systems were designed for smartphones and offered a more comprehensive approach. One system had users play games on mobile devices. For the following discussion, the 14 systems were divided (somewhat arbitrarily) into four categories:[2]

- Text-messaging monitoring and reminder systems that primarily use the mobile phones' text-messaging capabilities to monitor alcohol use or remind the user to report their alcohol consumption;
- Text-messaging intervention systems that, in addition to monitoring alcohol use, deliver text messages intended to promote abstinence and recovery;
- Comprehensive recovery management systems that use the internal sensors (e.g., monitoring of GPS coordinates) and other computer-like capabilities of modern smartphones to deliver multifaceted messages and interventions; and
- Game-based systems that attempt to engage the user through game playing.

Text-Messaging Monitoring and Reminder Systems

Several mobile systems have been studied that rely upon texting to deliver reminders and to prompt reporting of alcohol consumption. Keeping track of alcohol use and associated symptoms via text messages or Web-based formats seems to be widely accepted among patients, with high response rates. Thus, an application that used text messages to collect data from patients about their drinking had a response rate of 84.4 percent (Kuntsche and Robert 2009), similar to the response rate of 88 percent reported for an application that used texting as a means of delivering a brief alcohol intervention (Irvine et al. 2012).

Self-assessments using mHealth approaches can provide patients and their counselors with a way to continually monitor patient recovery. One such text-based assessment system is called ICAT; it can be used to collect patient self-assessment data on drinking (Kuntsche and Labhart

[1] The search of electronic literature databases used a combination of two keyword sets: (1) "App" OR "Apps" OR "mobile application*" OR "mobile health" OR "mhealth" OR "text" OR "texting" OR "text message*" OR "messaging" OR "smartphone*" OR "iphone*" OR "Android" OR "mobile device*" and (2) "alcohol addiction" OR "alcohol abuse" OR "alcohol dependen*" OR "alcoholic" OR "alcoholism" OR "alcohol* recovery" OR "sobriety" OR "sober" OR "addiction recovery." (An asterisk is used in a search term to include any string of letters that follows it; for example, searching on "alcohol dependen*" would produce search results that include both "alcohol dependent" and "alcohol dependence".) Articles were retrieved from several databases, including EBSCO HOST (including PsychInfo and Academic Search Premier), Web of Knowledge, and Engineering Village.

[2] It should be noted that the categorization is somewhat subjective and may not have categorized all systems appropriately.

2012) as well as their motives for drinking (Kuntsche and Labhart 2013). Bernhardt and colleagues (2005, 2007, 2009) developed another system that uses automatic texting and phone messages as reminders to encourage college students to submit a daily electronic alcohol use assessment via mobile phones; their research focuses on the validation of texting as an electronic assessment method, not on possible interventions. Such mHealth monitoring and assessment tools can be used for various practical applications. For example, Tiplady and colleagues (2009) have used texting in alcohol research to send reminders and assessments to study participants that were related to performing cognitive tasks. Moore and colleagues (2013) used texting primarily as a surveillance tool, although in this case the mHealth application also offered a limited intervention by providing users with feedback on how much money they likely were spending on alcohol given their self-reported consumption.

In general, reminder systems that focus primarily on monitoring consumption do not seem to be effective in reducing alcohol use. Although these systems are not specifically intended to reduce consumption, it could be argued that the process of monitoring alcohol use itself could lead to a reduction in drinking. However, this issue is not likely to receive much more research attention, because basic

Table Summary of Peer-Reviewed Mobile Application Systems to Treat Alcohol Use Disorders

Originator & Lead-Author Affiliation	Name	Features	Design	Theoretical/ Empirical Basis	Target Population	Results	Reference(s)
Text-Messaging Monitoring and Reminder Systems							
Kuntsche and colleagues, Switzerland Research Institute on Addiction, Lausanne, Switzerland	Internet-based, cell phone–optimized assessment technique (ICAT)	Frequent text messages with hyperlinks to questionnaires on weekend alcohol consumption	Survey (n = 183)	None noted	College students	High retention rate; alcohol consumption similar to Internet-based assessment. Data collected via ICAT helped clarify the relationship between motive at pretest and alcohol consumption.	Kuntsche and Robert 2009; Kuntsche and Labhart 2012, 2013
Bernhardt and colleagues, Centers for Disease Control and Prevention, Atlanta, Georgia	Handheld-assisted network diary (HAND)	Self-reported alcohol consumption using a daily diary administered via mobile phone	Randomized controlled trial (RCT) (n = 168) Intervention: HAND Control: paper-and-pencil daily social diary	None noted	College students	HAND assessment reported similar level of total drinks, drinking days, and drinks per drinking days as paper-based daily social diary over a 30-day period and timeline followback at the 30-day followup, supporting validity of mobile technology for assessment of alcohol use.	Bernhardt et al. 2005, 2007, 2009
Tiplady and colleagues, University of Edinburgh, Edinburgh, United Kingdom	N/A	Text messages remind participants to complete cognitive assessments and inquire about alcohol use	Twice-daily cognitive assessments, followed by a two-period crossover lab study (n = 38)	None noted	Moderate drinkers	Mobile phones allowed practical research on cognitive performance in everyday setting.	Tiplady et al. 2009
Moore and colleagues, Cardiff University, Cardiff, United Kingdom	N/A	Text messages collect daily alcohol consumption and deliver feedback intervention on estimated alcohol expenditures	Feasibility study (n = 82) and exploratory RCT (n = 86); Intervention: text-message drinking survey plus drinking expenditure feedback; Control: text-message drinking survey	Cites prior empirical evidence on text-messaging monitoring studies	College students	Self-reported alcohol consumption data was significantly associated with severity scores obtained using formal screening instruments. Attrition was not associated with greater alcohol use. Text messaging was acceptable to participants and preferred over email and Web-based methods. The exploratory RCT results showed that the reduction of drinking in the intervention group warrants a future large-scale RCT study.	Moore et al. 2013

Table Summary of Peer-Reviewed Mobile Application Systems to Treat Alcohol Use Disorders *(continued)*

Originator & Lead-Author Affiliation	Name	Features	Design	Theoretical/ Empirical Basis	Target Population	Results	Reference(s)
Text-Messaging Intervention Systems							
Agyapong and colleagues, University of Alberta, Alberta, Canada	N/A	Supportive text messaging; messages designed to improve mood and offer support for alcohol abstinence	RCT (n = 54); Intervention: daily support text messages Control: fortnightly thank-you text message	Cites prior empirical evidence on text-messaging interventions	Patients with alcohol use disorders and comorbid depression	High retention and perceived usefulness among intervention-group participants; significantly lower depression reported in intervention group compared with the control group; no effect on cumulative abstinence or depression score at 3-month postintervention.	Agyapong et al. 2012, 2013
Irvine and colleagues, University of Dundee, Scotland, United Kingdom	N/A	36 text messages; 9 of these messages asked questions	Feasibility study (n = 67)	Communication theory; social cognition model; motivational interviewing; transtheoretical model of behavior change	Socially disadvantaged men	88% of participants responded to text messages; little attenuation in followup; participants engaged with text messages and provided personal responses.	Irvine et al. 2012
Stoner and Hendershot, Talaria, Inc., Seattle, Washington	Adaptive goal-directed adherence tracking and enhancement (AGATE) system	Text messages sent based on self-reported adherence patterns	RCT (sample size not reported); Intervention: AGATE Control: structured alcohol and side effects diary	Medication-adherence literature and empirical evidence from the literature on assessment methods	Treatment-seeking heavy drinkers who take naltrexone	N/A (currently in trial phase)	Stoner and Hendershot 2012
Alessi and Petry, University of Connecticut, Storrs, Connecticut	N/A	Video recording using breath analyzer; contingency management (increased rewards for not drinking)	RCT (n = 30) Intervention: increased compensation if nondrinking; Control: same compensation for any drinking status	Contingency management using tangible incentives	Regular drinkers (non–alcohol dependent)	Increased percentage of patients who provided a negative drinking sample and reduced self-reported number of drinking days	Alessi and Petry 2013
Weitzel and colleagues, Emory University, Atlanta, Georgia	N/A	Tailored messages based on self-reported drinking status and consequences	RCT (n = 40); Intervention: daily survey via a handheld computer plus tailored messages; Control: daily survey via a handheld computer only	Cites prior empirical evidence on text messaging interventions	College students	Fewer drinks per drinking day and lower expectancies to get into trouble as a result of alcohol consumption among intervention group participants compared with those in the control group.	Weitzel et al. 2007

Table Summary of Peer-Reviewed Mobile Application Systems to Treat Alcohol Use Disorders *(continued)*

Originator & Lead-Author Affiliation	Name	Features	Design	Theoretical/ Empirical Basis	Target Population	Results	Reference(s)
Text-Messaging Intervention Systems (continued)							
Mason and colleagues, Virginia Commonwealth University, Richmond, Virginia	N/A	Tailored messages based on baseline survey response	RCT (n = 18) Intervention: text messages; Control: no messages	Motivational interviewing	College students	Increased readiness to change drinking behavior among intervention-group participants compared with those in the control group.	Mason et al. 2014
Suffoletto and colleagues, University of Pittsburgh, Pittsburgh, Pennsylvania	N/A	Weekly text message–based feedback with goal setting (intervention)	Three-arm RCT (n = 45); Control: uniform message reminding of the final survey; Assessment: text message–based drinking survey; Intervention: same as assessment plus tailored text-message response	NIAAA recommendations for alcohol brief interventions, customized based on individual responses	Young adults (ages 18–25 years) presenting to the emergency department	Compared with baseline, intervention group had 3.4 fewer heavy drinking days (HDDs) and 2.1 fewer drinks per drinking day (DPDDs) in the last month, whereas the assessment group had 1.8 more HDDs and 1.1 more DPDDs and the control group had 1.1 fewer HDDs and 0.6 fewer DPDDs.	Suffoletto et al. 2014
Comprehensive Recovery Management Systems							
Dulin and colleagues, University of Alaska, Anchorage, Alaska	LBMI-A (Buddy System)	Assessment and feedback; high-risk locations; supportive people; craving-coping strategies; communication skills training; pleasurable activities	Pilot study (n = 52): Intervention: LBMI-A; Control: publicly available Web-based intervention plus bibliotherapy	Motivational enhancement; community reinforcement	Adults (ages 18–45 years) with alcohol use disorders not in other types of treatment	Both interventions resulted in significant and large decreases in HDDs and DPDDs (LBMI-A group evidenced a 60 percent drop in HDDs over 6 weeks). LBMI-A group evidenced more rapid change in first month of use and had better retention than the Web-based intervention.	Dulin et al. 2013, 2014*a,b;* Gonzalez and Dulin 2014
Gustafson and colleagues, University of Wisconsin, Madison, Wisconsin	A-CHESS	Weekly check-in; panic button; My Team; team feed; news; recovery information; AA/NA meeting locator; My Messages; easing distress	RCT (n = 349) Intervention: A-CHESS plus usual care; Control: usual care	Self-determination theory; Marlatt's relapse model	Alcohol-dependent patients exiting residential treatment	Intervention-group patients reported reduced risky drinking days by 57 percent compared with the control group.	Chih et al. 2014; Gustafson et al. 2014
Gaming systems							
Gamito and colleagues, Lusophone University of Humanities and Technologies, Lisbon, Portugal	N/A	Cognitive games on mobile phone systems	RCT (n = 54); Intervention: games plus usual care; Control: usual care	Cognitive rehabilitation	Alcohol-dependent patients	Patients in the intervention group showed improved frontal lobe functions compared with those in the control group.	Gamito et al. 2014

texting systems are increasingly being supplanted by approaches that focus on the more sophisticated capabilities of smartphone-based applications. Any text-based reminder systems that are being implemented, however, should also include a confirmation step to increase efficacy. Thus, reminders alone are unlikely to be highly effective unless the recipient of the message confirms that the recommended actions have taken place.

Text-Messaging Intervention Systems

Several mHealth systems exist that provide targeted interventions to their users. Agyapong and colleagues (2012) developed a message-based intervention that twice a day delivered personalized supportive text messages to patients with AUDs and comorbid depression. This intervention, which was provided for 3 months, led to reduced depression and better cumulative abstinence at 3 months. However, these effects were not observed at the 6-month followup, 3 months after the end of the intervention (Agyapong et al. 2013).

Irvine and colleagues (2012) evaluated a brief alcohol intervention delivered via text messages but focused on the users' engagement with the intervention (e.g., they assessed whether and how participants used the intervention-related text messages) rather than on the intervention per se. The analysis demonstrated that text messaging can be used not only to deliver an intervention but also to evaluate specific aspects of the treatment process, such as participant engagement with and reaction to intervention components when treatment is delivered via a mobile delivery platform.

Another mHealth intervention, the AGATE system (Stoner and Hendershot 2012), uses tailored texting frequency to promote adherence to pharmacotherapy for addiction treatment by reminding participants to take their medication and confirming that medications are taken. The frequency of these reminders can be adjusted based on adherence rates. For example, if a patient achieves a predetermined goal of medication adherence (e.g., 90 percent of scheduled doses over 2 weeks), the frequency of the texted reminders can be reduced. Although results of a clinical trial testing the effectiveness of this system have not yet been published, the intervention's design should help clarify whether both reminders and confirmation of reminder receipt are important for promoting medication adherence.

Another innovative mobile-phone-based intervention application involved a contingency management component to reinforce alcohol abstinence (Alessi and Petry 2013). In this study, texting was used to remind patients to take a breath alcohol concentration (BrAC) test, which the patients video recorded using their mobile phones. The video and BrAC data were electronically submitted in real time to the study organizers. The contingency-management portion of the intervention involved a reward that also was delivered via text messaging if the BrAC results were submitted on time and negative. The study found that those patients who received the reminder messages had a higher percentage of negative breathalyzer tests than those who did not. The study demonstrated the feasibility of using mobile phones to support a contingency-management intervention, based on real-time behavioral assessment in the natural environment and timely provision of reinforcement.

Several studies have examined the effects of tailored text messaging on alcohol use. The feasibility of delivering a text-based goal-setting and feedback system to reduce heavy drinking was demonstrated in a study of young adults presenting to the emergency department (Suffoletto et al. 2012). This trial showed promising results in reducing heavy-drinking days and drinks per drinking day, with a larger trial indicating small reductions in self-reported binge drinking and the number of drinks consumed per drinking day over 12-week intervention (Suffoletto et al. 2014). Weitzel and colleagues (2007) were the first to determine the efficacy of tailored text messaging. Their pilot trial found that drinkers who received tailored messages after filling out daily surveys about their drinking behavior had fewer drinks and were less likely to expect getting into trouble because of their drinking than were drinkers who filled out the same surveys but received no feedback messages. A more recent intervention using tailored text messages was based on motivational interviewing principles along with social-networking counseling (Mason et al. 2014). The investigators found that their tailored message intervention may increase the readiness of drinkers to change drinking behavior.

Overall, the text-based intervention systems described here have shown mixed results regarding effectiveness. Although some studies reported positive results (e.g., Suffoletto et al. 2012), most of these studies have been of short duration and only involved relatively small numbers of participants. Conversely, the arguably best designed study by Agyapong and colleagues (2012, 2013) showed little long-term effect.

Comprehensive Recovery Management Systems

The literature search identified two comprehensive mHealth recovery systems, LBMI-A (Dulin et al. 2013) and A-CHESS (Gustafson et al. 2014). Both systems operate on smartphones and comprise a variety of tools and services that utilize the capabilities characteristic of such mobile devices, including broadband Internet connection, interactive multimedia applications, text messages, GPS location awareness, and social networking, which have been shown to improve recovery outcomes (Gustafson et al. 2014). For example, both systems include user self-assessment and feedback, a GPS-based tool to warn users when they approach high-risk locations (e.g., a bar they used to frequent), various strategies for coping with cravings, lists of healthy activities, and methods of communicating with supportive others. Many of these resources can be tailored to the specific needs and preferences of the individual user. However, the two systems were developed based on different assumptions about the relationship between mHealth technology and the addiction treatment system.

LBMI-A

Dulin and colleagues (2013) were influenced by two findings from previous research when developing the LBMI-A. First, the vast majority of people with diagnosable alcohol dependence do not receive treatment, in large part because of the stigma associated with attending traditional alcohol treatment and other barriers that keep individuals from accessing services (Cohen et al. 2007; Grant et al. 2007). Second, even individuals who are not willing to enter formal treatment may be receptive to using interactive Web sites related to alcohol reduction, and using the technology can increase their motivation to change (Lieberman and Huang 2008). Based on these observations, Dulin and colleagues (2013) created a self-administered, portable alternative to traditional treatment. The LBMI-A design was oriented toward motivating a change in drinking through enhanced awareness of drinking and drinking-related problems and providing intervention options for the user to choose from (Dulin et al. 2013). The system includes modules designed to enhance awareness of a drinking problem through assessment and feedback as well as daily interviews about alcohol use. In the daily interviews, users report triggers they experienced and if they drank in response to them. These responses are summarized in a weekly feedback report. Users also receive suggestions and tools for managing their triggers, as well as other issues that could lead to resumed drinking, such as cravings and psychological distress. Additionally, the system focuses on developing social support through an intervention module that encourages users to identify individuals in their social network who they can turn to for support. If users choose, they can share their initial feedback reports with their support team (which could include a health-care provider). A pilot study that included 28 individuals who met DSM–5 criteria for an AUD, were drinking heavily, and were not engaged in another form of treatment produced encouraging early results regarding the system's effectiveness (Dulin et al. 2014). Thus, participants who utilized the LBMI-A system reduced the number of days spent drinking hazardously by approximately 60 percent over the course of 6 weeks, and the number of drinks per day dropped from a mean of 5.6 at baseline to 2.9 while using the system, producing a large effect size (Cohen's d =1.1). This study also contained a qualitative component in which participants were queried about aspects of the system they found helpful and not helpful. The results of this component have driven the creation of a new app called Step Away that currently is running on an iPhone platform (Dulin et al. 2014). LBMI-A is currently being tested in a clinical trial.

A-CHESS

In contrast to LBMI-A, A-CHESS is designed to be integrated into the traditional treatment system. The A-CHESS design process was informed by a series of patient/user assessments, the results of which were organized around Marlatt's relapse prevention model (Brownell et al. 1986; Lowman et al. 1996; Witkiewitz and Marlatt 2004). Training in its use begins before the patient is discharged from residential treatment, so that the patient is familiar with the program's various features and can use relevant content once back in the community. The patient's counselor sets up the device so that the information and settings are tailored to the patient and his or her specific situation and interests. For example, set-up information includes the patient's therapeutic goals and care plan, his or her triggers and high-risk situations for drinking, healthy activities the patient is interested in, or benefits the patient expects from sobriety. Services provided by the A-CHESS system include contacts for emergency (i.e., when the patient is at immediate risk of relapse) and nonemergency situations (e.g., weekly check-ins), triage and feedback through various resources (e.g., coping skills, diversionary activities), social support (e.g., discussion groups, contacts with experts), and information services. Through these services, A-CHESS can help patients meet the challenges they often face in life, such as loneliness and isolation, transportation problems, difficulties managing the treatment regimen, and lack of informal support. A-CHESS also addresses such issues as craving and insufficient coping skills in high-risk situations. Additionally, A-CHESS includes a service that—with patient permission—reports patient responses to a weekly Brief Alcohol Monitor that warns clinic staff of imminent relapse and signals a need for clinical intervention (Chih et al. 2014). This clinician-reporting function was included because previous work had shown that a clinician report could facilitate earlier interventions (Dubenske et al. 2008) and that patients whose caregivers could communicate patient symptoms to clinicians had less symptom distress than patients without access to a clinician report (Dubenske et al. 2010). A-CHESS currently is being extended to include a cognitive behavioral therapy–based treatment component (Marsch et al. 2014) for implementation in primary care settings (Quanbeck et al. 2014).

The efficacy of A-CHESS was evaluated in a randomized clinical trial comparing patients using A-CHESS with a control group receiving treatment as usual. The trial found that patients assigned to A-CHESS had 57 percent fewer heavy drinking days compared with the control group (Gustafson et al. 2014). Analyses of the possible mechanisms that may underlie A-CHESS effects indicated that the mobile intervention, delivered in the natural environment as part of continuing care, seems to reduce risky drinking by enhancing the patient's perceived competence (Gustafson et al. 2014), a construct similar to self-efficacy.

Other analyses of A-CHESS have explored how the data generated by such a mobile intervention (e.g., the data obtained from the weekly "check-in" function that tracks the recovery process) can be used to predict relapse risk and tailor the intervention accordingly to the needs of the patient (Chih et al. 2014). Using more than 2,900 weekly responses from 152 patients, the model was shown to have good ability to predict relapse. Although challenges still

exist in analyzing large, complex, time-intensive datasets such as the ones generated by A-CHESS, the predictive model is a step toward "just-in-time" and adaptive interventions that provide support when and where patients need it most.

Game-Based Systems

Modern mobile devices such as smartphones have various capabilities not found in traditional mobile phones, including the capacity to provide multimedia applications, such as streaming videos and gaming. In a recent randomized controlled trial, Gamito and colleagues (2014) compared a mobile-delivered, gaming-based, neuropsychological intervention plus treatment as usual with treatment as usual only in a sample of alcohol-dependent patients. The results indicated that the addition of cognitive games delivered via a mobile device (i.e., an Android tablet) to treatment as usual helped to improve certain cognitive functions, specifically those associated with frontal lobe–related impairment. Although the intervention effects were somewhat limited, the results suggest that mobile delivery of a game-based neuropsychological intervention, which can help engage patients and provide intervention "on demand," may help improve certain aspects of cognitive functioning among alcohol-dependent patients. However, current development in this area is still in its infancy (Gamito et al. 2014).

Other mobile applications and capacities, such as sensors, have not been widely studied. Sensors on wireless-connected mobile devices generally hold the potential to enhance continuous monitoring and instant support to addiction patients. However, further development and research are needed in order to provide evidence for clinical applications.

Commercial Applications

In addition to the applications discussed here, a plethora of other commercial applications are available for smartphone users via Apple's app store and the Google Play store that have not been evaluated in the peer-reviewed literature. Two recent reviews of alcohol treatment applications found in these online marketplaces have summarized the functions and features as well as the underlying evidence base of these commercial systems. Cohn and colleagues (2011) reviewed 222 apps available in the Apple app store that intervene on alcohol use. The review focused on codifying the principles and evidence base underlying the applications. Subsequently, Savic and colleagues (2013) evaluated 87 apps available in the Google Play store that were aimed at recovery from both AUDs and addiction to other drugs, focusing on the applications' features and functions. Taken together, the two analyses allowed for the following conclusions:

- The most common features of apps were information on recovery, motivational content, social support tools, and tools for monitoring alcohol use.
- Few of the recovery apps found in both market places were reported to have been created by clinical experts.
- Apps that claim to function as interventions provided little or no empirical evidence of effectiveness.
- Quality control seems to be a concern and an important barrier to use; in the review section of the Google Play store, the most common criticisms concerned technical glitches (22.1 percent) and improvements needed (21.0 percent).

Although some apps include features that reflect empirically based treatment (including motivational enhancement, coping/self-control training, social skills training, and/or cognitive therapy components), very few report that they have been designed according to evidence-based practices. However, citing evidence-based practice may not be an effective marketing strategy in such a direct-to-consumer model. In these marketplaces, users may be more likely to purchase an app based on factors such as the number of downloads and user ratings.

In sum, the evidence base used to develop most commercial systems, as well as empirical tests of their efficacy, are insufficient, despite the popularity and availability of these systems. This commercialization of health products or applications with unproven efficacy is of concern from a public health perspective. To address this concern, researchers might consider conducting comparative studies of some of these applications, particularly those that seem to be more promising based on their underlying theoretical grounding. As mHealth technologies are evolving, reviews of the available commercial systems and their efficacy, such as those conducted by Savic and colleagues (2013) and Cohn and colleagues (2011), should be updated regularly.

Characteristics, Advantages, and Limitations of mHealth Systems

Technology, Complexity, and Integration

The mHealth systems described in this article cover a broad spectrum of complexity, ranging from relatively simple text-based monitoring and reminder systems to comprehensive recovery management support systems. In general, the less complex text-based systems were designed with minimal theoretical grounding. With the addition of more diverse intervention functions to create more comprehensive systems, however, communication, behavioral, and social support theories increasingly were used to inform the design of these functions. In general, both simple and complex systems have their advantages and disadvantages.

Systems that rely primarily on texting for monitoring and intervention have the advantage of being inexpensive and widely available, given the nearly universal penetration of

basic mobile phones. Moreover, they are easy to operate for both senders and receivers of text messages. These characteristics make it relatively easy to incorporate text-based approaches into existing treatment. For example, text-based reminders are relatively common in addiction treatment and in daily life. Treatment providers can easily avail themselves of free, Web-based systems that automatically generate text-messaging reminders for appointments, medications, or other tasks a provider deems important for a patient to self-manage (see www.ohdontforget.com for an example of such texting software). An example of a text-based reminder system used in a health-care setting (although not in the realm of mobile treatment for AUDs) is a system called text4baby (see www.text4baby.org) that was developed to promote the health of pregnant women and their unborn children. The system has been widely used and evaluated. Studies of the system have suggested that text messages need to be timely and relevant to be valuable to users, a requirement that may lend itself more readily to relatively predictable health episodes, like pregnancy, than to chronic and relapsing conditions such as AUDs.

The main disadvantage of texting-based systems to date is that evidence of their effectiveness is rather limited. The studies reviewed for the preparation of this article showed only limited effectiveness of the text-based interventions for AUDs and only involved relatively small trials of short duration. For instance, the studies by Agyapong and colleagues (2012, 2013) evaluated a 3-month intervention and 3-month followup among 54 patients. Statistically significant effects on depression scores were observed at 3 months, as well as a trend toward increased abstinence, but these effects had dissipated by the 6-month mark (after the intervention was removed). Beyond alcohol treatment, recent evidence has suggested that text4baby has had little success in changing health behaviors (Evans et al. 2014). The available evidence thus suggests that texting-based applications alone probably are insufficient as interventions for AUDs, although it is possible that longer interventions could produce longer-lasting effects. Nevertheless, text-messaging could serve important functions as a component of more comprehensive systems.

Of the various mobile systems tested thus far, the comprehensive A-CHESS system has had the strongest and longest lasting effects, including a reduction in heavy-drinking days of 57 percent, compared with a control group, over an 8-month intervention and 4-month follow-up period (Gustafson et al. 2014). Compared with simple text-messaging interventions, more complex applications that combine various comprehensive training and support tools may produce more substantial and lasting effects. One potential explanation for this greater effectiveness is that a comprehensive application can provide more modes of treatment and tools, such as appropriate contact information for people who can support the user in different risk situations, GPS-data–based warnings of potential high-risk locations, suggestions for alternative activities, or different coping tools. This wide variety of options and tools allows the system to better address the individual user's preferences in terms of coping styles and interests, leading to better learning and longer-lasting recovery.

However, the enhanced features and effectiveness of comprehensive systems also are associated with increased costs. Although smartphone use is proliferating, owning and operating a smartphone still is considerably more expensive compared with standard cellular phones. Moreover, designing these comprehensive systems requires skilled computer programmers, who must be retained to maintain and improve the system over time, also contributing to the systems' overall costs. To date, no studies have compared the costs and effects of texting interventions vs. comprehensive mHealth systems.

Theoretical Grounding

The level of theoretical support for the various applications analyzed in this literature review varied greatly. Particularly for those applications that could be characterized as text-message monitoring and reminder systems, the reviewed studies provided minimal theoretical grounding. The studies that assessed text messages as an intervention approach (rather than just for reminders and monitoring of alcohol use) were more likely to be based on a theoretical framework. For example, several of these studies designed text messages based on theories in communication and behavioral sciences, such as the social-cognition model and motivational-interviewing methods, to improve participants' mood and offer support for abstinence or reducing alcohol use. Studies that collected feedback from patients (e.g., via texting, Web forms, or e-mail) often employed empirically validated methods, such as contingency management, medication adherence, or guidelines for brief intervention recommended by the National Institute on Alcohol Abuse and Alcoholism, to generate customized messages based on patient responses. Both LBMI-A and A-CHESS were designed as comprehensive recovery-management support systems and are supported by well-established theories about addiction recovery. Thus, in addition to theories based in communication and behavioral sciences, both of these comprehensive systems incorporate social–support-based theories, such as community reinforcement (Dulin et al. 2013) and self-determination theory (Ryan and Deci 2000).

One should note, however, that the concept of theory-based developments may be a double-edged sword. On one hand, established theories can provide a structure that can guide the development mHealth systems. For example, during the development of the A-CHESS system, the developers based their approach on self-determination theory (Ryan and Deci 2000), which states that quality of life is determined by three domains—social relatedness, coping competence, and intrinsic motivation. An understanding of the concepts of this theory can provide a structure for the design of such a system and can suggest ways of achieving goals in each domain. Thus, acknowledgement of the

theory might suggest ways in which technology could help develop coping competence so that the user gains the confidence that he or she can cope with stressors that arise. On the other hand, overly strict adherence to theory can be restrictive and may lead to a disregard of the real-life needs, experiences, and struggles of both the patients and the treatment providers involved in their care. In some cases, the involvement of experts from outside disciplines with innovative approaches can add new dimensions to such programs that address the actual needs of the patients and their care providers. Thus, to design effective mHealth applications, it is necessary to strike a balance between adhering to theory and incorporating innovative outreach approaches that can help ensure that the system is appealing to patients and treatment providers in the real world.

Challenges and Opportunities

Developing and executing mHealth applications, whether they are research driven or commercial, are extraordinarily challenging processes. Users increasingly expect applications to be intuitively designed (so that they require little or no instruction), to provide feedback confirming data transfers, to provide notifications about new actions to take, and so on. Applications that fall short of these expectations are unlikely to be used regularly and, consequently, to be effective. Building a well-designed, adaptable, seamless application requires extensive technical resources, including hardware, software, and programming support. As a result, it is difficult to develop and maintain effective, yet inexpensive, mHealth systems for small populations or short-term goals. Additionally, cost is a concern not only in terms of development but also in terms of availability to patients. Although cellular phones have become commonplace, smartphones that allow the most comprehensive applications may be less available to low-income patients.

Another challenge is that although many features are available in mHealth applications, it is not known which of these are responsible for any observed effects (i.e., are the "active ingredients") or which features might be most important for different types of patients. Research will need to address these questions.

Finally, technological advances proceed so swiftly that research can hardly keep pace; by the time results from a randomized clinical trial are available and published, the application studied may already be outdated (and, possibly, its results as well) (Baker et al. 2014). Nevertheless, this rapid progress also offers opportunities. For example, continuously evolving technology will make it possible to include new tools and services in mHealth applications, such as wirelessly connecting an application to BrAC testing (Alessi and Petry 2013). Other potential features and applications may include the use of data from mHealth systems to create models that predict relapse (Chih et al. 2014) and initiate measures to prevent its occurrence; multimedia delivery of interventions (Gustafson et al. 2014); and tailored delivery of intervention components to make the applications optimally effective (Gustafson et al. 2014; Mason et al. 2014; Suffoletto et al. 2012; Weitzel et al. 2007). The gold standard of scientific evidence—the randomized trial—may be an unrealistically high bar in this fast-changing field that already is saturated with commercial applications that lack evidence (Baker et al. 2014; Cohn et al. 2011). Instead, researchers could use statistically efficient designs (such as fractional-factorial and quasi-experimental designs) as well as surrogate endpoints to evaluate interventions and delivery systems already in use. Thus, the pace of technological advances offers both a challenge to researchers and great promise for the development of new and effective mHealth approaches.

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Ecological Momentary Assessment and Alcohol Use Disorder Treatment

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The ability to capture real-time data on human behavior inexpensively, efficiently, and accurately holds promise to transform and broaden our understanding of many areas of health science. One approach to acquiring this type of real-time data is ecological momentary assessment (EMA). This method has been used to collect data in many domains of addiction research, including research on the treatment of alcohol use disorders (AUDs). Empirical evidence supports the hypothesis that use of EMA can improve the quality of AUD treatment research when compared with standard assessment methods because it provides more accurate reporting, allows investigators to examine the dynamic unfolding of the behavior change process at an individual level, and can be used to augment and improve clinical assessment and treatment. Overall, the existing literature provides strong support for the advantages of EMA when combined with standard assessment of addictive behaviors in general. Nevertheless, use of EMA in AUD treatment research thus far has been limited, especially in the area of research on mechanisms of behavior change. Existing research indicates, however, that EMA can be used to deliver tailored feedback as a novel and potentially transformative approach to improving AUD treatment. This research area clearly warrants additional future efforts.

Key words: Alcohol use, abuse, and dependence; alcohol use disorders (AUDs); assessment; assessment methods; ecological momentary assessment (EMA); real-time assessment; feedback; mobile technologies; mHealth; literature review

Ecological momentary assessment (EMA) involves repeated sampling of individuals' behaviors and experiences in real-time, in the individuals' natural environment (see article by Arora in this issue). Whereas early EMA studies used paper diaries, recent developments in mobile technologies now enable EMA-based studies to use smartphones equipped with increasingly sophisticated sensors that can passively measure such variables as geolocation, physical activity, and heart rate. The ability to capture real-time data on human behavior inexpensively, efficiently, and accurately is poised to transform and broaden our understanding of many areas of health science. As a result, there has been a dramatic increase in the use of EMA as a research tool over the last decade (Mehl and Conner 2012; Stone et al. 2007). The primary aim of this article is to examine EMA in the context of alcohol treatment research. Specific topics addressed include what types of research questions or treatments have been studied using EMA, whether these studies have yielded new knowledge regarding critical treatment constructs or improved treatment outcomes, and what lessons can be drawn from EMA research that can inform future studies.

The article addresses these questions by focusing on three areas where EMA is thought to confer an advantage over standard assessment methods, including (1) more accurate or unbiased reporting of behavior and experience; (2) the ability to examine the dynamic unfolding of behavior change processes within individuals; and (3) the ability to extend observation or intervention from the clinic to the natural environment, thereby augmenting clinical assessment or treatment. For each of these areas, the article briefly will describe the potential advantage of EMA, present studies that illustrate how the issue has been evaluated, and summarize findings to date with a focus on clarifying how EMA has advanced our understanding of AUD treatment. This review is not designed to provide an exhaustive overview of all available studies but seeks to illustrate the types of studies that have been conducted and the knowledge gained. Although the focus here is on treatment for alcohol use disorders (AUDs), EMA research on other addictive behaviors, notably nicotine addiction, has on occasion advanced further than it has in the AUD arena. Thus, when appropriate, the article will describe EMA studies of other addictive behaviors and discuss how they might be applied to AUD treatment. Finally, the article will summarize the current status of EMA research in AUD treatment and offer several recommendations for future work.

EMA and Reporting Accuracy

EMA is thought to substantially improve accuracy of reporting compared with global, lab-based self-report measures. With

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certain research questions (e.g., in studies of relapse), standard self-report sometimes requires participants to recall events over lengthy periods. Such recall may introduce a systematic bias that distorts accurate reporting. In addition, standard assessments often ask individuals to aggregate or summarize their experiences. Aggregation of subjective states (e.g., cravings) or cognitive processes (e.g., self-efficacy), especially when in a laboratory setting, is likely to introduce some level of error. The accuracy of EMA has been compared with standard self-report measures using three types of approaches:

- EMA analyses of drinking have been compared to calendar methods, such as timeline follow-back (TLFB) interviews (Sobell et al. 1996) to assess drinking outcomes.
- EMA of cognitive, affective, or motivational processes have been compared with standard measures of similar constructs.
- Retrospective recall of relapse has been compared with real-time EMA of these events.

All three types of studies have found discrepancies between standard measurement and EMA, but the degree of divergence varied depending of the phenomena being examined.

EMA vs. Calendar Methods in Drinking Outcomes

A handful of alcohol treatment studies (Kranzler et al. 2004, 2014; Lincoln et al. 2011) have compared real-time and calendar methods to assess drinking outcomes. Kranzler and colleagues (2004) assessed nine participants seeking AUD treatment using TLFB and daily interactive voice recording (IVR) during a 12-week treatment trial. Results indicated poor correspondence between the two approaches on measures comparing the amounts participants drank on specific days, even when comparing a 2-week TLFB recall period to IVR. An aggregate measure of drinking showed better correspondence, but IVR yielded a significantly higher level of drinking on average than did the 12-week TLFB recall. Similarly, Searles and colleagues (1995, 2002) found that respondents significantly underestimated their alcohol consumption using timeline methods compared with daily IVR in 1- and 3-month outcomes. This discrepancy was significantly more pronounced among people with higher alcohol consumption (Searles et al. 2000). In a similar study, Lincoln and colleagues (2011) compared IVR and a 6-week TLFB of drinking outcomes for 28 participants in AUD treatment. The results showed poor agreement in recall of daily drinking patterns; however, unlike the studies by Kranzler and colleagues (2004) and Searles and colleagues (1995, 2002), the research of Lincoln and colleagues (2011) yielded no significant differences between the two approaches with respect to aggregate drinking measures. Finally, Kranzler and colleagues (2014) conducted a set of outcome analyses using both TLFB and IVR drinking outcomes and found no differences in clinical trial results. These findings generally are consistent with the larger literature comparing real-time and calendar methods in community and college-student samples (Shiffman 2009).

Taken together, these findings suggest that although calendar methods appear to be less accurate in capturing day-to-day variations in drinking patterns and may underestimate consumption, especially in cases of longer recall periods, they seem to be adequate for capturing aggregate measures of drinking outcome. In addition, it is important to note that reliance on IVR alone to assess drinking outcomes puts investigators at risk of missing data if there is any inconsistency in IVR compliance; TFLB data, in contrast, are relatively complete. Thus, even AUD treatment studies that use IVR to assess outcome tend to augment their analyses with TLFB (Morgenstern et al. 2012).

Combining multiple data collection methods such as baseline laboratory measurements and EMA has several advantages. It may improve our understanding of how trait measurements interact with dynamic process variables collected through EMA, leading to better understanding of certain mechanisms of change (Shiffman et al. 2008). It can also help create more reliable methods of data collection for different populations. For example, in an analysis by Patrick and Lee (2010), three different methods of data collection resulted in different measurements of consumption that were further influenced by moderator variables, such as gender. The combination of data collection methods using multiple mediums also will become more commonplace as mobile and wireless alcohol sensors become more reliable and less invasive (Leffingwell et al. 2013). Methods such as transdermal alcohol sensors and mobile phone–based blood alcohol concentration (BAC) calculators, breath-based alcohol measurements, speech analysis, and infrared spectroscopy (Marques and McKnight 2007) are being developed and tested. Such methods hold promise to significantly improve investigators' ability to accurately assess alcohol consumption, understand the determinants of risky drinking, and trigger real-time interventions. As these methods of data collection become more reliable, the ability to capture real-time information-process determinants will help build more accurate models of change. Although an in-depth discussion of these methods is beyond the scope of this article, it is important to note that these newer methods also require significantly greater data-management and analysis expertise than do self-report methods. Similarly, factors such as technology outages, user burden, and poor understanding of proper assessment schedules (e.g., fixed vs. variable) represent new challenges to the integration of mobile methods into alcohol research.

Testing Putative Process Theories

Until recently, virtually all empirical tests of putative links between process determinants, mediators or moderators, and alcohol treatment outcomes have been examined using standard aggregate measures. For example, the hypothesized link between self-efficacy and outcome has generally been assessed using standard self-report measures that ask

participants to recall their self-efficacy during a period of several weeks and then aggregate these ratings to arrive at a composite index. A handful of alcohol studies have compared EMA and questionnaire methods to assess putative process variables, but only one of those was conducted in an AUD treatment-seeking population. The study compared standard measures of self-efficacy and readiness to change with daily IVR measures of these constructs in a sample of 89 participants seeking AUD treatment (Kuerbis et al. 2013). The investigators aggregated the daily scores of the IVR variables into a single index for the week prior to randomization and compared that index with the standard pretreatment measures of readiness and self-efficacy to assess their agreement and ability to predict drinking outcomes during an 8-week treatment period. The results indicated only modest agreement across methods. Moreover, IVR measures of readiness and self-efficacy significantly predicted drinking outcomes, whereas standard measures did not.

Several studies have used EMA methods to probe the hypothesized relationship between drinking-to-cope (DTC) motives and real-time relationships between negative mood and drinking in community samples. DTC theories (Cooper et al. 1992) posit that relief of stress and negative affect is a powerful determinant of drinking and that the potency of this motive differs across individuals. Studies have used EMA methods generating real-time reports of drinking and affects to examine whether people scoring high on a DTC questionnaire show stronger relationships between stress or negative affect and drinking (Armeli et al. 2008, 2010; Piasecki et al. 2014; Todd et al. 2005). These studies have yielded substantially weaker support for the DTC hypothesis than prior cross-sectional studies. Generally, the results suggested that although DTC questionnaires tap some individual differences in drinking motives, the relationship between dispositional motives, proximal mood or stress, and drinking is much more complex than anticipated, suggesting the need for substantial revision of drinking-motive theory (Shiffman 2009).

EMA approaches also can be used to investigate relapse processes. Relapse theories have had a pivotal influence on the treatment of addictive disorders, including AUDs (Marlatt and Gordon 1986; Witkiewitz and Marlatt 2007). Until the mid-1990s, research on relapse was based on retrospective recall of relapse events, many of which took place weeks or even months prior to data collection. Shiffman and colleagues (1996, 1997) conducted several seminal studies examining the influence of recall bias on the reports of putative relapse processes in smoking. These studies compared retrospective recall of smoking lapse and relapse with real-time monitoring of similar processes using electronic diaries among smokers seeking to quit smoking. Results indicated that agreement between recall and real-time report of lapses was quite poor. In addition, contrary to existing relapse-theory hypotheses, neither negative affective reactions to lapse and feelings of guilt nor decreases in self-efficacy predicted progression from a lapse to a relapse. Surprisingly, no similar studies of relapse have yet been conducted for AUD treatment.

Overall, evidence supports the advantages of EMA in terms of reporting accuracy over standard laboratory assessment methods, which have been the mainstay of AUD clinical research. The limitations of standard assessment methods are especially notable in assessing cognitive, affective, or motivational processes. When taken together with studies conducted on other addictive behaviors (Shiffman 2014), the studies that have assessed EMA approaches in AUDs suggest that the real-time assessment of process variables can counterbalance a number of the existing limitations to global report methods and lead to substantial revisions in theories of predictors, mediators, and moderators of AUD treatment (Riley et al. 2011).

EMA and Temporal Unfolding of Within-Individual Change Processes

Because EMA allows for collection of frequent, repeated measures of individuals' thoughts and behaviors over time, it provides a powerful tool for examining within-person change processes. In addition, EMA is able to capture contextual events and, thus, can facilitate the exploration of person-by-context interactions. As a result, EMA enables researchers to describe and analyze the unfolding of sequences of experiences and events as they play out over time. Shiffman and colleagues (2009) have described this feature of EMA research as analogous to a "movie" that shows dynamic relationships as they unfold, whereas global or recall methods can be likened to still photography that provides a static single-shot representation of what is essentially a dynamic phenomenon.

In a series of seminal studies, Shiffman and colleagues (2005) used EMA to test the dynamic role of negative affect and self-efficacy in smoking relapse. The study design included two novel features enabled by EMA. First, relapse was represented as a sequence of conditional events that began with a triggering event or high-risk situation, which in turn led to either a highly tempting situation (experience of craving but no smoking) or a lapse. The lapse then led to either a relapse or a return to abstinence. Second, factors influencing relapse were ordered based on their dynamic properties. Thus, they were classified as either stable (e.g., gender), tonic or slow moving (e.g., stress build-up), or momentary (e.g., rapid change in negative affect). Contrary to relapse theory, tonic relapse factors, such as higher levels of stress or negative affect in the days immediately prior to the lapse/relapse episode did not significantly predict a lapse. By contrast, momentary factors, such as rapid increases in negative affect in the minutes or hours before the episode did predict a lapse. In addition, the link between negative affect and a lapse seemed to be moderated by a person-level factor: nicotine dependence severity. Thus, people with more severe dependence were more likely to lapse in the

context of negative affect, whereas people with less severe dependence were more likely to lapse in the context of drinking alcohol. Analyses of self-efficacy and lapse revealed a similar set of complex interrelations among person-level factors, slow-moving background factors, momentary influences, and contextual events as predictors of a return to smoking.

Only a handful of studies have examined dynamic features of relapse as predictors in AUD treatment using EMA (Chih et al. 2014; Collins et al. 1998; Cooney et al. 2007; Holt et al. 2011). These studies all examined the momentary influence of predictors on lapse by assessing these factors in the period immediately prior to the lapse event, while controlling for baseline levels of the same factors. For example, Holt and colleagues (2012) examined dynamic changes in affective states, urge, and self-efficacy in the hours before a first lapse to drinking among participants in concurrent alcohol and smoking cessation treatment. Constructs were assessed at baseline and then repeatedly during treatment using random and event-based prompts to assess dynamic change in a prospective design. Contrary to study hypotheses, only the urge to smoke among those who had smoked already significantly predicted lapse to drinking. Although results differed across the studies, none of the analyses supported negative affect and urge as momentary predictors of lapse in alcohol treatment. A few other studies have used daily IVR to examine the role of affective states, urge, and self-efficacy in alcohol treatment (Armeli et al. 2006; Kranzler et al. 2004). However, these studies are limited in their ability to fully assess the temporal relationships between precipitants of consumption and drinking, in part because they measured same-day rather than lagged relationships.

Overall, a large and comparatively sophisticated literature on smoking cessation (see Shiffman 2014) illustrates the novel ability of EMA both to capture and analyze the temporal unfolding of hypothesized sequences of experiences and events within individuals and to probe complex person level-by-context interactions. In addition, studies have begun to examine the relationship between momentary influences and relapse in illicit drug users in treatment (Epstein and Preston 2010; Epstein et al. 2009). In contrast, EMA approaches and their features to date have received little attention in the AUD treatment literature. The lack of EMA studies in AUD treatment relative to smoking cessation likely reflects early concerns among researchers that AUD clinical populations may not be able to manage relatively expensive electronic diary devices and provide reports when intoxicated. Recent feasibility studies among illicit drug users indicate, however, that these problems are surmountable, especially given the growing use of smartphones (Epstein et al. 2009).

Another important factor in the slow uptake of EMA methods to study change process in AUD treatment research may be a failure to fully appreciate the value of well-conducted EMA studies in improving AUD treatment. Programmatic research by Shiffman and colleagues (2005, 2008) on the dynamic interaction of processes in smoking cessation has revealed two central findings, both of which have far reaching implications for addiction treatment research. These findings relate to substantive advances in understanding relapse as a dynamic and complex phenomenon with individuals struggling to regain and maintain self-control over addictive behaviors and to the match between theory and method in behavior change research (Riley et al. 2011; Sterba and Bauer 2010; Tan et al. 2012).

Relapse As a Dynamic and Complex Phenomenon

As mentioned previously, EMA research on smoking cessation has identified the heightened importance of proximal or momentary influences in the relapse process (Shiffman 2005). For example, affective processes may be highly variable, exhibiting changes in the span of minutes or even seconds. Such sudden changes in mood or rapid depletion of self-control resources have been shown to predict relapse (Brandon et al. 2007). Similarly, rapidly changing contextual factors (e.g., being offered a cigarette by a friend) also play an important role in relapse. Although prior conceptualizations identified cognitions, affects, and situations as relapse predictors, these factors were largely seen as slow moving or tonic. Current conceptualizations, in contrast, view relapse as a process occurring over time, where stable traits and slow-moving background factors (e.g., stress) create a vulnerability to relapse. These factors then interact with momentary influences to trigger relapse (McKay et al. 2006; Shiffman et al. 2009).

This revised perspective suggests the importance of research on momentary influences on the behavior change process as a strategy to improve AUD treatment. By definition, momentary influences can be difficult to predict. In addition, they often occur outside of the individual's awareness. EMA studies—including those that assess factors such as implicit cognitions—are needed to fully understand the unfolding of behavior change processes (Marhe et al. 2013) and identify critical junctures as temporal targets for interventions. Smartphones include numerous features that can aid in the assessment of explicit and implicit influences on behavior. The assessment of objective parameters, such as context and location sensing, physiology, speech, sleep, and activity among others, have tremendous potential to help researchers understand the mechanisms of behavior change (Bacon 2013; Dulin et al. 2013, 2014; Gustafson et al. 2014; Scharnweber et al. 2013; Vahabzadeh et al. 2010). Other methods used in general health behavior change, such as qualitative journaling and ecological video journaling (Melton and Bigham 2013) also provide real-time methods to improve understanding of clients in their everyday lives.

Research on momentary influences and relapse suggest that helping people monitor implicit and explicit processes in real time and using this information to deliver interventions at critical moments in the natural environment might improve AUD treatment outcomes (Ebner-Premier and

Trull 2009; Shiffman et al. 2008). Accordingly, EMA-enabled research on the dynamics of change processes in AUD treatment will help improve our understanding of the mechanisms of behavior change and thus allow us to improve treatment.

Treatment Theory–Method Match

Recent discussions of behavior change research methods have demonstrated the importance of using methods that adequately capture the dynamic and complex nature of most behavior change processes (Collins 2006; Sterba and Bauer 2010; Tan et al. 2012). AUD treatment theories posit that interrelationships among stable patient characteristics, internal states, and environmental contexts predict drinking and that these interrelationships change as a result of treatment and time. Moreover, the temporal dynamics of critical constructs likely vary substantially. For example, the impact of stressful events on drinking likely is cumulative and occurs over days or weeks and may account for fewer than expected findings on the relationship between momentary stress and drinking. By contrast, the impact of craving on drinking likely occurs within seconds or minutes. From a methods perspective, real-time, intensive longitudinal assessment that matches the temporal resolution of the hypothesized relationships is necessary to adequately test AUD behavior change theories. Appropriately selected EMA methods allow for the collection of information with sufficient detail to provide discriminating tests of AUD treatment theories.

Shiffman and colleagues (2008) have referred to research that examines the interplay of motivational, cognitive, affective, and behavioral processes as they unfold over time as the study of "microprocesses." These investigators note that insight into microprocesses potentially will have a major impact on improving behavioral interventions because such insight helps identify leverage points in treatment. In fact, EMA's ability to enable this type of research may be its most important contribution to clinical psychology. Nevertheless, several relatively challenging methodological issues associated with using EMA remain as researchers strive to understand intra-individual change and translate this knowledge into timely and context-sensitive interventions.

Using EMA to Augment AUD Clinical Assessment and Treatment

EMA tools are increasingly being incorporated into behavioral intervention, an approach that has been called ecological momentary intervention (EMI) (Heron and Smyth 2010). EMIs are characterized by the delivery of interventions to people during the course of their everyday lives (i.e., real time) and in their normal settings (i.e., real world). EMIs can take many forms, from a patient receiving a text message as part of an alcohol intervention (Muench et al. 2014; Suffoletto et al. 2012, 2014) to the delivery of long-term care management for AUDs using a smartphone application that is linked to clinical support (Gustafson et al. 2014). The development of EMIs or mHealth interventions is a rapidly evolving area, and a comprehensive review is beyond the scope of this article (for more information, see the article by Beckjord and Shiffman in this issue). Instead, this section will focus on the role of real-time or ambulatory assessment in the delivery of EMIs and, more specifically, their utility in tailoring treatments.

EMA and EMIs have several features that could improve AUD treatment. Given problems associated with recall bias, real-time assessment could improve the accuracy of clinical assessment and treatment planning. EMA also could be used to reduce burden and increase compliance with self-monitoring of symptoms—an important component of most behavioral interventions—even over lengthy periods. In addition, self-monitoring across behavior-change interventions is associated with improved outcomes (Heron and Smyth 2011), including improved alcohol use outcomes. For example, Dulin and colleagues (2014) found that participants rated the alcohol-tracking feature in a smartphone application for problem drinking as the most helpful feature. Moreover, these authors found that more intensive use of the smartphone application was associated with improved outcomes, results that correspond to Web-based alcohol research literature (Cunningham et al. 2011).

In addition to self-monitoring, many AUD treatments involve some skills training with the expectation that patients will practice and master those skills in their natural environments. EMI could be used to provide such in vivo skills training (Dulin et al. 2014; Gustafson et al. 2014). EMI could further be used to personalize or tailor treatment in two ways. First, information collected during real-time assessments could be used to provide tailored feedback to patients either at a single point in time or repeatedly over the course of treatment (Riley et al. 2011). Second, feedback could be individually timed to match a predetermined context, such as a high-risk situation or subjective state (e.g., craving) (Gustafson et al. 2014). Given the dynamic and momentary nature of relapse precipitants, the ability to intervene in the moment would add an important component to AUD treatment that could dramatically improve outcomes.

The ability to tailor interventions in a just-in-time setting can be seen as a natural extension of adaptive treatments—that is, treatments that are successively modified based on response to a prior stage of the intervention (McKay et al. 2009). This type of EMI has been called a just-in-time-adaptive intervention (JITAI). The widespread use and multiple technological features of today's smartphones provide a resource-rich platform for delivering JITAIs. As noted above, smartphones are equipped with passive data collection capabilities that can substantially diminish the burden of data collection, provide virtually continuous monitoring and increase the amount and type of information available to generate feedback. Although a number of technological obstacles remain, a critical scientific challenge in developing

JITAIs is how to translate the wealth of real-time information available into effective personalized, timely, and context-sensitive feedback.

Examples of EMA-Augmented AUD Treatments

Litt and colleagues (2009) used EMA to assess high-risk situations and coping response in a study of the effectiveness of coping skills training. The investigators hypothesized that one reason for the apparent lack of evidence for a specific therapeutic effect of a commonly used treatment approach—cognitive behavioral therapy (CBT)—may have been the failure of manual-driven CBT to accurately assess and intervene with a patient's specific coping-skills deficit. Participants were asked to use cellphones in the 2 weeks prior to treatment to record their urges, coping responses, and drinking behavior as they occurred. This idiographic information on drinking antecedents was summarized and then provided to therapists who used the feedback to tailor their skills training. Participants were randomly assigned to the individualized assessment and treatment program (IATP)–CBT condition or to standard, manualized CBT (SCBT). IATP–CBT yielded a higher proportion of abstinent days, more momentary coping, and less drinking in high-risk situations than SCBT. These findings provided one of the earliest examples of how EMA can be used to tailor treatments and improve their efficacy.

In a recent study, Gustafson and colleagues (2014) reported on the efficacy of a continuing-care EMI intervention for AUD patients transitioning from residential care. The EMI was a multi-feature smartphone application based on self-determination theory called Addiction-Comprehensive Health Enhancement Support System (A-CHESS). It was designed to provide continuous real-time monitoring and support during early recovery and included internet data access to deliver static educational content as well as interactive features, such as a GPS-activated alert that automatically warned patients when they entered a high-risk situation. In addition, patients completed a Web-based weekly survey (Weekly Check-In) on A-CHESS that assessed drinking over the prior week, as well as a set of items designed to assess relapse risk (e.g., relationship problems) and protective factors (e.g., AA meeting attendance). A randomized clinical trial comparing A-CHESS to standard continuing care found that A-CHESS yielded significantly lower rates of drinking over a 12-month period (Gustafson et al. 2014). (For more information on the A-CHESS application and its evaluation, see the article by Quanbeck et al. in this issue.)

These two examples demonstrate how EMA has been used to tailor AUD interventions. In IAPT, EMA data was collected prior to treatment, summarized, and provided to the clinician who then used this information to develop a personalized treatment plan. In A-CHESS, EMA data was collected repeatedly over the extended treatment period, and a predictive model iteratively determined the probability of weekly relapse risk based on a cumulative record of patient lapse history and current functioning. The A-CHESS feedback could be adjusted weekly based on current risk categorization and delivered to the patient in his natural setting. Several other technology-based EMI systems currently are being developed, such as the Location-Based Monitoring and Intervention System for Alcohol Use Disorders (LBMI-A) (Dulin et al. 2014) and the Scandinavian combined Web- and mobile-based alcohol intervention (Brendryen et al. 2014). Researchers also are testing an adaptive text-messaging intervention for problem drinking that adapts weekly to the user's self-reported goal achievement using EMA (Muench et al. 2014), highlighting that even simple technologies available on every phone can be used to develop adaptive interventions.

Challenges to the Development of Personalized, Timely, and Context-Sensitive AUD Interventions

One obstacle to the future development of JITAIs is that the behavior-change theories that underlie AUD treatment have provided limited guidance in prior efforts to tailor treatments (Morgenstern and McKay 2007). The development of any JITAI requires an understanding of how stable patient characteristics interact with momentary subjective states and contextual factors to predict intra-individual change. As noted above, studies on the temporal unfolding of behavior change processes indicate that current theories are either inaccurate or inadequately specified to provide a framework for such predictions (Riley et al. 2011; Shiffman et al. 2005).

A related challenge is the use of standard statistical approaches to analyzing the temporal unfolding of multiple factors within individuals, which can be assessed using intensive longitudinal data. Standard methods have significant limitations in testing theories about complex and time-varying interactions that occur within individuals. For example, standard methods such as multilevel modeling aggregate individuals under the assumption that groups share a similar set of change processes (Sterba and Bauer 2010). However, this assumption may be erroneous because examining interactions at a group level (i.e., determining average change) may have little to do with what happens for an individual (Bolger et al. 2013; Molenaar 2004). Similarly, standard methods are limited in their ability to model nonlinear and time-varying interactions among variables (Tan et al. 2012; Walls and Shafer 2006). Overall, researchers are recognizing that new efforts to revise behavior-change theory, coupled with the novel analytic approaches, will be needed to inform the development of JITAI (Mohr et al. 2013; Riley et al. 2011; Tan et al. 2012; Timms et al. 2014). (See also the article by Beckjord and Shiffman in this issue.)

One novel and promising direction towards meeting these goals is to conceptualize behavior-change processes as a complex, dynamic system (Resnicow and Vaughn 2008; Witkiewitz and Marlatt 2007) and to use analytic approaches such as mathematical modeling and control engineering to develop JITAIs for behavioral problems, including AUDs (Banks et al. 2014; Riley et al. 2011; Rivera 2007). This approach has been used successfully to develop adaptive

interventions in people with HIV (Rosenberg et al. 2007). With this approach, complex dynamic systems are characterized as possessing multiple factors that interact dynamically and change over time. The components of such systems are highly interconnected, such that each influences the others, often in nonlinear ways. Moreover, relationships between elements of the system can be short-lived and characterized by positive- and negative-feedback loops. Finally, the system's functioning is influenced both by its cumulative history (i.e., prior characteristics) and by current context (Marewski and Olsson 2009).

Several empirical studies (Hufford et. 2003; Witkiewitz et al. 2007) have supported the hypothesis that relapse is a highly complex process characterized by nonlinear dynamics. A recent study by Banks and colleagues (2014) used mathematical modeling of dynamic systems to examine behavior change processes among 89 problem drinkers in AUD treatment, using daily EMA. These analyses provided strong support for the conceptualization of behavior change as a dynamic nonlinear process and illustrated the limitations of using standard approaches to examine intra-individual change using EMA data. Although the results were promising, however, the investigators noted that research in this area still is in its early stages.

Summary and Future Directions

EMA is widely considered to represent a major advance in assessment methodology because of its ability to increase the accuracy of reporting, enable the examination of the dynamic unfolding of behavior change processes within individuals, and augment clinical assessment and treatment (Mehl and Connor 2013). The studies reviewed in this article support these advantages for addictive behaviors in general. Given these advantages, it is surprising that EMA has not been used more widely in AUD treatment research. Only a handful of studies have compared the accuracy of global self-report with that of EMA for drinking outcomes. These studies suggest that global measures like the TLFB yield similar findings to EMA for aggregate measures of drinking outcome, but are less effective at capturing day-to-day variation in drinking patterns.

Reporting bias seems to be even more problematic for global measures assessing cognitive, motivational, affective processes than for measures of behavior (Shiffman 2009). The few AUD treatment studies reviewed above suggest similar limitations for constructs representing global measures of change processes, such as drinking motives, motivation to change, and self-efficacy. The overwhelming majority of AUD treatment studies to date have used global measures rather than EMA to assess change processes. These studies have addressed critical aspects of AUD treatment, including hypothesized treatment moderators and mediators. Findings reviewed above suggest that the true limitations of standard methods to assess change processes may be underappreciated. More research is needed that allows for comparison of EMA and global self-report measures to determine whether better measurement of change processes might lead to substantive modifications in understanding the change process, especially regarding moderators and mediators of AUD treatment. In addition, the combination of multiple methods and media of data collection has significant advantages over single methods, and more research should be conducted with a variety of assessment types when feasible.

The use of EMA to study the temporal unfolding of behavior change represents a major methodological advance in efforts to understand mechanisms underlying behavior change. EMA allows investigators to capture events and experiences with a high degree of temporal resolution and to probe the interrelationship of multiple factors within an individual over time. As noted above, current treatment theories implicitly postulate that behavior change represents the cumulative influence of multiple, time-varying influences that occur within an individual. However, standard research methods have limited our ability to represent and test dynamic, complex interactions. Surprisingly few studies have used temporal unfolding designs to examined AUD treatment, and even these studies were limited to testing the relationship between a single dynamic factor and relapse.

The development of EMI or mHealth interventions represents a promising and rapidly evolving area. EMI offers new features compared with standard interventions, including the ability to deliver tailored feedback based on ambulatory assessment. Several AUD treatment studies have incorporated novel EMA approaches to deliver tailored feedback, and the results demonstrate the potential for this approach to improve AUD treatment. The technological sophistication of smartphones with multimodal assessment capabilities suggests that this may be a feasible platform for a new and previously difficult-to-imagine form of personalized treatment through the provision of automated tailored feedback. Development of JITAIs for AUDs will require a substantially stronger empirical knowledge base regarding the mechanism of behavior change. The research on the temporal unfolding of behavior change in smoking cessation represents an important step in that direction, but further novel advances in theory building and methods are needed to adequately capture the complex and dynamic nature of behavior change processes and translate this process into actionable feedback.

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Dr. Muench consults with mobile health companies and is the co-owner of a text messaging company focused on behavioral change.

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Putting the Screen in Screening

Technology-Based Alcohol Screening and Brief Interventions in Medical Settings

Sion Kim Harris, Ph.D., and John R. Knight, M.D.

Alcohol is strongly linked to the leading causes of adolescent and adult mortality and health problems, making medical settings such as primary care and emergency departments important venues for addressing alcohol use. Extensive research evidence supports the effectiveness of alcohol screening and brief interventions (SBIs) in medical settings, but this valuable strategy remains underused, with medical staff citing lack of time and training as major implementation barriers. Technology-based tools may offer a way to improve efficiency and quality of SBI delivery in such settings. This review describes the latest research examining the feasibility and efficacy of computer- or other technology-based alcohol SBI tools in medical settings, as they relate to the following three patient populations: adults (18 years or older); pregnant women; and adolescents (17 years or younger). The small but growing evidence base generally shows strong feasibility and acceptability of technology-based SBI in medical settings. However, evidence for effectiveness in changing alcohol use is limited in this young field.

Key words: Alcohol use, abuse, and dependence; screening and brief intervention; medical setting; primary care; emergency room; adult; adolescent; pregnant women; technology; computer-based screening and brief intervention; literature review

Alcohol-related screening and brief interventions (SBIs) in medical settings have the potential to transform the treatment of alcohol misuse and prevent considerable alcohol-related harm (Babor and Higgins-Biddle 2001). Rapid screening and assessment tools allow health care providers to quickly assess the extent of patients' alcohol use, identify those with problematic use, provide them with an immediate brief intervention, and refer patients with more severe alcohol use disorders to a substance abuse specialist when available. SBIs have proven effective for detecting potential alcohol problems and reducing the severity of problems in a wide range of populations and settings (Kaner et al. 2009; O'Donnell et al. 2014)—so much so that agencies focused on preventing and treating alcohol use, including the U.S. Preventive Services Task Force (USPSTF), the National Institute on Alcohol Abuse and Alcoholism (NIAAA), and the Substance Abuse and Mental Health Services Administration (SAMHSA), recommend that primary care and other medical settings expand their SBI use for patients ages 18 years and older (Moyer 2013; NIAAA 1995; SAMHSA 2011). Although the USPSTF cited insufficient evidence to recommend SBIs for adolescents (Moyer 2013), recognition of and evidence for the potential utility of SBIs for adolescents have been building in recent years (Harris et al. 2012; Mitchell and Gryczynski 2012; Pilowsky and Wu 2013), leading the American Academy of Pediatrics to recommend that all pediatricians use SBIs in their practices as part of routine care (American Academy of Pediatrics 2011).

Despite the push for using SBIs in medical settings, they remain underused. In a recent national survey of U.S. adults, only one in six (15.7 percent) respondents reported discussing alcohol use with a health professional in the past year, with State-specific estimates ranging from 8.7 percent to 25.5 percent (McKnight-Eily et al. 2014). The percentage was higher (34.9 percent), but still inadequate, among those with 10 or more binge-drinking episodes in the past month. An often-cited barrier to SBI implementation is lack of time (Van Hook et al. 2007; Wilson et al. 2011). Computer-facilitated SBI delivery may offer a solution for busy medical settings, allowing more widespread implementation. This article focuses on current- and emerging-technology–facilitated SBI tools that have been evaluated in primary care, pediatric, and emergency department (ED) settings. We review studies of technology-based SBI as they relate to adults (18 years or older), pregnant women, and adolescents (17 years or younger), the primary patient populations in which alcohol SBIs have been implemented.

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The studies reviewed here come from a systematic electronic literature search conducted between February 2014 and December 2014 using PubMed and PsycINFO, as well as the reference lists of published studies and review articles. We summarize the characteristics of the studies, including population, design, and results, in the table.

Value Added With Electronic SBIs

Technology-based SBIs could help increase the frequency and quality of SBI use in medical settings by enhancing efficiency and standardizing implementation. In terms of screening, touchscreen devices or standalone computers with Internet connections can allow patients to enter information in the waiting room prior to an appointment. Programs automatically score the screening results that staff can print or electronically transmit to practitioners. This reduces clinician time needed for administering and scoring a questionnaire during the visit. In addition, programs can be loaded with validated measures that improve the quality of screening and can automatically select appropriate questions according to the patient's age and previous responses. Patients also may be more willing to disclose sensitive information to a computer than to a person (Butler et al. 2009; Turner et al. 1998), and integration of computerized screening results with electronic health records may boost screening and documentation rates (Anand et al. 2012).

Similarly, computer-facilitated brief intervention delivery has the potential advantages of greater standardization, lower cost, and greater ease of implementation compared with face-to-face delivery. As with screening, programs can automatically tailor intervention content to individual patients. Interventions vary based on the program, but, as with face-to-face SBIs, computer-based SBI tools often follow screening with personalized feedback that includes a summary of patients' consumption patterns and risk status, a comparison of their consumption with recommended limits, estimated blood alcohol concentrations for their heaviest drinking occasion in the reported time frame, and a comparison between their consumption and consumption reported by others in their peer group. More extensive programs may incorporate intervention strategies based on principles of evidence-based face-to-face treatments, such as motivational interviewing (Miller and Rollnick 2012) and cognitive–behavioral therapy (Kadden et al. 1995).

Using technology for SBIs in medical settings may be especially valuable for reaching young people who are highly engaged with technology and nearly universal access to computers, cell phones, and the Internet (Madden et al. 2013; Marsch et al. 2007; Pew Research Center's Internet and American Life Project 2014). Indeed, using technology-facilitated alcohol SBIs in medical settings to reach adolescents may be a powerful mechanism to reduce medical costs and gain productive years of life, since alcohol use disorders are strongly linked to the leading causes of adolescent and adult mortality, including motor-vehicle crashes and suicide.

This high level of online engagement has fueled a surge of interest in the potential of standalone Web-based SBI programs to address problematic alcohol use, particularly among college students. These programs provide a means to inexpensively reach people less likely to access traditional health services. Detailed reviews of research on these standalone online alcohol SBIs are provided in articles by Carroll and Cronce in this issue and suggest that, at least among college students and adults, these programs tend to yield small to moderate effects, which are greatest at followups less than 3 months, gradually declining to little or no effect by 12 months (Donoghue et al. 2014). The lack of interpersonal contact with these programs may contribute to lower participation rates and adherence over time (Murray et al. 2013; Naimi and Cole 2014; Postel et al. 2011). In addition, alcohol use is strongly linked to many physical and mental health problems, such as cancer, cirrhosis, and depression (National Center on Addiction and Substance Abuse 2011). Therefore, standalone programs are unlikely to obviate the need for SBIs in medical settings, which is the focus of this review.

Medical Setting SBI for Adults

Twelve studies of varying design and stages of research (reported in 13 published papers) have examined computerized SBIs for adults in medical settings that include four studies in primary care (Bendtsen et al. 2011; Butler et al. 2003; Cucciare et al. 2013; Kypri et al. 2008), seven in EDs (Blow et al. 2006; Karlsson and Bendtsen 2005; Murphy et al. 2013; Neumann et al. 2006; Nilsen et al. 2009; Suffoletto et al. 2012; Trinks et al. 2010; Vaca et al. 2011), and one in a hospital outpatient department (Johnson et al. 2013) (see the table for study details). Half of the studies used a randomized design (Blow et al. 2006; Cucciare et al. 2013; Kypri et al. 2008; Neumann et al. 2006; Suffoletto et al. 2012; Trinks et al. 2010); one used a before-and-after design, with each clinic serving as its own control (Butler et al. 2003); and five are earlier-stage observational studies with small sample sizes (Bendtsen et al. 2011; Johnson et al. 2013; Karlsson and Bendtsen 2005; Murphy et al. 2013; Vaca et al. 2011). Generally, followup, where it existed, was short, with two studies following participants for 3 months, four for 6 months, and three for 12 months. The studies shared some common components.

SBI Delivery Method

All but one study by Suffoletto and colleagues (2012), tested screening and/or brief intervention delivery on a tablet or desktop computer located in the medical setting. Suffoletto and colleagues (2012) delivered their intervention through weekly mobile text messages following patient discharge from the ED.

Table 1 Characteristics of Computer-Assisted Alcohol Screening and Brief Intervention (SBI) Studies Conducted in Health Care Settings

Authors (Year)	Study Population	Setting	Screening and Other Measures	Study Design/ Treatment Conditions	Follow-up Period (% Completed)	Results
Adults (Age 18 or Older): Primary Care						
Butler et al. (2003)	English- or Spanish-speaking primary care patients (ages 18–99, *N* = 2,053 screened, 128 screened positive and completed followup, 68% female)	Primary care practices in Massachusetts, New York, and Florida	1) Alcohol Use Disorders Identification Test (AUDIT) 2) Stage-of-change measure	Before-and-after, each site own control: 1) Control phase (*N* = 66): Standard care with AUDIT after visit 2) Treatment phase (*N* = 62): 20-minute computerized SBI completed in medical office before visit, with tailored feedback and information to reduce risky drinking; clinician can be given printed report with suggested brief interventions	6 months (85%)	• Spanish version had lower AUDIT+ detection rates than English version; no such difference found with traditional AUDIT. • AUDIT-C scores declined for both groups during followup; no intervention effect; no difference between language groups.
Kypri et al. (2008)	University health service patients screening positive for at-risk drinking (ages 17–29; *N* = 975 screened, 429 screened positive, 52% female)	University health service in New Zealand	1) AUDIT 2) Past-2-weeks alcohol consumption 3) Alcohol Problems Scale	Randomized controlled trial (RCT) three groups: 1) Single-dose 10-minute Web-based SBI (*N* = 138): Assessment, personalized normative feedback, risk status, comparison of consumption with recommended limits 2) Multi-dose Web-based SBI (*N* = 145): same as above repeated at 1 and 6 months 3) Control (*N* = 146): Information pamphlet only	6 months (84%) 12 months (84%)	• Both intervention groups had lower alcohol consumption, AUDIT scores, and alcohol problems at 6 and 12 months compared with the control group. • Single-dose and multi-dose effects similar; provision of up to two additional sessions did not increase efficacy.
Bendtsen et al. (2011)	Primary care patients with risky drinking (ages 18 or older; *N* = 7,863 screened, 3,169 screened positive, 578 received e-SBI, 347 completed followup, 41% female)	Primary care clinics in one Swedish county	1) Average weekly use 2) Heavy episodic drinking (HED) occasions per month	Observational study of two cohorts: 1) "Self-referred" (*N* = 139): computerized SBI in clinic completed on own initiative 2) "Staff-referred": (*N* = 208) invited by clinician to complete computerized SBI after visit Behavioral intervention (BI) for both was printout of personalized written feedback	3 months (60%)	• No significant between-group differences at baseline and 3 months. • "Staff-referred" had reduction in weekly alcohol use but "self-referred" did not. • Significant reduction in HED for both. • Follow-up responders more likely to be older, have lower weekly alcohol use at baseline than non-responders; no difference in HED.

Table 1 Characteristics of Computer-Assisted Alcohol Screening and Brief Intervention (SBI) Studies Conducted in Health Care Settings *(continued)*

Authors (Year)	Study Population	Setting	Screening and Other Measures	Study Design/ Treatment Conditions	Follow-up Period (% Completed)	Results
Cucciare et al. (2013)	Military veterans screening positive for alcohol misuse (*N* = 167, 12% female)	Veterans Affairs primary care clinics in California	1) AUDIT-C 2) Timeline Follow-Back 3) Alcohol-related consequences	RCT two groups: 1) Intervention (*N* = 89): Standard care plus Web-based 10-minute SBI with assessment, personalized normative feedback, education, summary of alcohol-related consequences and risk factors, and self-reported motivation to change 2) Control (*N* = 78): Standard care only (brief counseling by PCP)	3 months (86%) 6 months (84%)	• Alcohol consumption and severity of alcohol-related problems declined for both groups. • No differences between groups.
Adults (Age 18 or Older): Emergency Department (ED)						
Karlsson and Bendtsen (2005)	ED patients (ages 18–70, *N* = 44, % female not available)	ED of university hospital in Sweden	1) Modified AUDIT-C 2) Patients' ratings of computerized screening and personalized feedback	Single-group acceptability study: Computerized screening and printout of personalized feedback and advice given to patient	N/A	• 95% rated computer easy to use. • 67% rated being screened positively. • 76% rated feedback and advice printout positively. • 74% preferred printout over nurse or doctor delivery. • 93% would read advice.
Blow et al. (2006)	Sub-critically injured ED patients screening positive for at-risk drinking (ages 19 or older, *N* = 4,476 screened, 577 screened positive and received BI, 29% female)	Midwestern level 1 trauma center in university hospital	1) Frequency of alcohol consumption and HED in past 3 months 2) Drinker Inventory of Consequence—Short Inventory of Problems	RCT four groups: Computerized screening plus computer generated: 1) Tailored message booklet with clinician-delivered brief advice (*N* = 129) 2) Tailored message booklet only (*N* = 121) 3) Generic message booklet with advice (*N* = 124) 4) Generic message booklet only (*N* = 120)	3 months (86%) 12 months (86%)	• All groups reduced mean drinks per week, HED, and alcohol-related consequences by 12 months. • No difference in outcomes between tailored vs. generic message conditions. • Brief advice had greater reductions than no advice, particularly among females and those aged 22 and older.

Table 1 Characteristics of Computer-Assisted Alcohol Screening and Brief Intervention (SBI) Studies Conducted in Health Care Settings *(continued)*

Authors (Year)	Study Population	Setting	Screening and Other Measures	Study Design/ Treatment Conditions	Follow-up Period (% Completed)	Results
Neumann et al. (2006)	Sub-critically injured ED patients screening positive for at-risk drinking (ages 18 or older, *N* = 1,139, 79% female)	ED in Germany	1) AUDIT 2) Readiness-to-Change questionnaire 3) Percent of patients with at-risk drinking (more than 30 g/d men; more than 20 g/d women)	RCT two groups: 1) Intervention: Standard care plus computerized SBI (*N* = 561): with customized normative feedback, advice, change strategies, and summary letter printed for patient before ED discharge 2) Control (*N* = 575): Standard care only	6 months (63%) 12 months (58%)	• Significant intervention effects at 6 and 12 months: intervention group had lower percent of patients reporting at-risk drinking, and greater decrease in alcohol intake, compared with control subjects.
Nilsen et al. (2009) Trinks et al. (2010)	ED patients screening positive for risky drinking (ages 18–69, *N* = 1,570 screened, 560 screened positive and received BI, 93 completed followup, 39% female)	County hospital ED in Sweden	1) AUDIT-C	RCT two groups: Computerized screening with printout given to patient of: 1) "Long-feedback" (*N* = 52): Traffic light graphic with risk level (hazardous, elevated, or no risk) and other tailored feedback about drinking pattern, and information to enhance motivation to change behavior 2) "Short-feedback" (*N* = 41): Traffic light graphic only	6 months (17%)	• 41% of those requested to do computer SBI did. • Both groups had reduced weekly alcohol consumption and HED frequency at 6 months. • No differences in change over time between groups. • 6-month respondents had lower HED frequency at baseline than non-respondents.
Vaca et al. (2011)	English- or Spanish-speaking ED patients (ages 18–65 or older, *N* = 4,375 screened, 742 screened positive and received BI, 385 consented to follow-up, 35% female)	University hospital ED in California	1) AUDIT 2) Drinks per week	Single-cohort observational study: Intervention: Computerized SBI involving brief negotiated interview, and personal alcohol reduction plans	6 months (57%)	• 47% of at-risk drinkers reduced drinking to below NIAAA-recommended limits. • Decreased frequency of driving while impaired. • Reductions greater among those with AUDIT scores higher than 8.

Table 1 Characteristics of Computer-Assisted Alcohol Screening and Brief Intervention (SBI) Studies Conducted in Health Care Settings *(continued)*

Authors (Year)	Study Population	Setting	Screening and Other Measures	Study Design/ Treatment Conditions	Follow-up Period (% Completed)	Results
Suffoletto et al. (2012)	ED patients (ages 18–24; *N* = 109, 52 screened positive, 45 consented to participate, 64% female)	Urban EDs in Pennsylvania	1) AUDIT 2) Timeline Follow-Back	RCT three groups: 1) Intervention (*N* = 15): Weekly text message (TM) feedback with goal setting 2) Assessment only (*N* = 15): Weekly TM-based assessments, no feedback 3) Control (*N* = 15): Weekly TM notifying number of weeks until 3-month followup	3 months (86%)	• 93% of intervention and assessment groups replied *one or more times* to weekly TM queries about drinking; 80% of intervention group replied to all 12 weeks of queries. • Intervention reduced heavy-drinking days and drinks per drinking day more than assessment-only.
Murphy et al. (2013)	ED patients (ages 21–85 years, *N* = 517, 63% female)	ED of urban academic medical center in New York	1) AUDIT 2) Patient acceptance and comprehension questionnaire 3) Research staff questionnaire	Single-group feasibility study: 15-minute Web-based SBI with assessment, tailored risk-level education, customized normative feedback, list of local alcohol treatment agencies	N/A	• 98% completed CASI program. • 89% liked program. • 93% found it easy to use. • 90% accurately reported alcohol risk level after program completion.
Adults (Age 18 or Older): Hospital Outpatient Clinics						
Johnson et al. (2013)	Hospital outpatients (ages 18 or older, *N* = 99 completed SBI, 69 invited for followup, 46% female)	Hospital ambulatory care center in Australia	1) AUDIT 2) Peak blood alcohol concentration (BAC) 3) Leeds Dependence Questionnaire 4) History of Trauma scale	Single-group feasibility study: Computerized SBI with normative feedback on screening results and peak BAC, comparison to recommended limits (not shown for low-risk drinkers), information about health and behavioral risks of different BACs, estimate of spending on alcohol per month, tips for reducing risk and local treatment options	Within few days of visit (75%)	• 93% of eligible consenting patients completed SBI. • 94% found it easy to complete. • 95% reported responding honestly. • 80% found feedback useful. • 96% had no concern about privacy.

Table 1 Characteristics of Computer-Assisted Alcohol Screening and Brief Intervention (SBI) Studies Conducted in Health Care Settings *(continued)*

Authors (Year)	Study Population	Setting	Screening and Other Measures	Study Design/ Treatment Conditions	Follow-up Period (% Completed)	Results
Pregnant Women						
Tzilos et al. (2011)	Pregnant women screening positive for problem alcohol use (ages 18–45, *N* = 50)	Urban prenatal care clinic in Michigan	1) T-ACE 2) Timeline Follow-Back 3) Readiness to Change 4) Acceptability of software 5) Birth outcome variables	RCT two groups: 1) Intervention (*N* = 27): 15- to 20-minute computerized SBI with educational content tailored to pregnant women, and to their current drinking status and motivation to change 2) Control (*N* = 23): Questionnaire on television show preferences and shown videos of popular shows	1 month (96%)	• High acceptability of computerized screening and BI. • Both groups showed significant decline in reported alcohol consumption during followup; no differences between groups. • Babies born to BI group had significantly higher birth weight compared with control subjects.
Pollick et al. (2013)	Pregnant African-American women who screened positive for problem drinking but quit during pregnancy (ages 18–29, *N* = 18)	Urban prenatal care clinic in Michigan	1) T-ACE 2) Alcohol use 3) Acceptability of software 4) Semistructured interview about user experience	Single-group pretesting study Computerized SBI: 20-minute interactive tailored program with content based on MI techniques with normed feedback, decisional balance exercise, menu of change (or relapse prevention) options, referral to local treatment options	N/A	• High ratings for software approval, ease of use, and perceived helpfulness. • Videos and graphs/ charts rated most useful components.
Adolescents (Age 17 or Younger)						
Gregor et al. (2003) Maio et al. (2005)	ED patients with minor injuries (ages 14–18 years, *N* = 655, 33% female)	ED of academic medical centers in Michigan	1) Alcohol Misuse Index of negative consequences of alcohol use 2) Binge-drinking episodes in past 3 months 3) Driving after drinking or riding with a driver that had been drinking	RCT two groups: 1) Intervention (*N* = 329): Computerized screening and single-session BI interactive educational program (virtual house party) to increase knowledge about risks, enhance refusal skills, decrease intention to use 2) Control (*N* = 326): Baseline survey with standard care only	3 months (93%) 12 months (89%)	Overall sample • 94% liked program, 74% reported it made them rethink their alcohol use, 5% needed assistance to use it. • No differences in alcohol outcomes between intervention and control: both decreased from baseline to 3 months, but returned to baseline levels by 12 months. Subgroup with baseline drinking and driving • Alcohol misuse and binge drinking lower at 12 months in intervention group.

Table 1 Characteristics of Computer-Assisted Alcohol Screening and Brief Intervention (SBI) Studies Conducted in Health Care Settings *(continued)*

Authors (Year)	Study Population	Setting	Screening and Other Measures	Study Design/ Treatment Conditions	Follow-up Period (% Completed)	Results
Cunningham et al. (2009, 2012) Walton et al. (2010)	ED patients with past-year violence and alcohol use (ages 14–18, *N* = 3,338 screened, 726 screened positive and consented to study, 56% females)	Urban ED in Michigan	1) AUDIT-C 2) POSIT 3) Conflict Tactic scale 4) Violence consequences	RCT three groups: 1) Computerized BI (*N* = 237) 2) Therapist-delivered BI (*N* = 254) • Both 35 minutes and based on motivational interviewing, with normative feedback and skills training 3) Control (*N* = 235): standard care with community resource brochure (also given to BI groups)	3 months (86%) 6 months (86%) 12 months (84%)	• 3 months: computer and therapist BI groups showed similar significant reductions in positive alcohol and violence attitudes, increases in refusal self-efficacy. • 6 months: Both BI groups less likely to report alcohol-related consequences than control group, but no effect on drinking frequency. • 12 months: significant therapist-BI effect on peer aggression and victimization; no BI effect (computer or therapist) on any alcohol variables.
Harris et al. (2012) Louis-Jacques et al. (2014)	Primary care patients (ages 12–18, *N* = 2,092 in United States [USA], 589 in Czech Republic [CZR]; USA/CZR 57%/47% females)	Primary care clinics in New England, and Prague, Czech Republic	1) CRAFFT screener 2) Timeline Follow-Back 3) Postvisit questionnaire 4) Personal Consequences Scale	Before-and-after, each site own control: 1) Control phase (USA/CZR *N* = 1,068/297): Treatment as usual (TAU) 2) Intervention phase (USA/CZR *N* = 1,028/292): 10-minute computer-assisted screening and provider brief advice (cSBA) with screening, risk-level feedback, educational pages, and provider report with screen results and prompts for 2 to 3 minutes of counseling	3 months (73%/88%) 12 months (73%/90%)	• 3 months: cSBA significantly reduced alcohol use rates compared with TAU in USA sample but not in CZR sample. Larger cSBA cessation effect found among drinking youth with peer risk (having friends who drank). • 12 months: cSBA effect attenuated but still significant among New England youth.

Table 1 Characteristics of Computer-Assisted Alcohol Screening and Brief Intervention (SBI) Studies Conducted in Health Care Settings *(continued)*

Authors (Year)	Study Population	Setting	Screening and Other Measures	Study Design/ Treatment Conditions	Follow-up Period (% Completed)	Results
Walton et al. (2014)	ED patients screening positive for risky drinking (ages 14–20, *N* = 4,389 screened, 1,053 screened positive, 836 consented to study, 48% female)	Urban ED in Michigan	1) AUDIT-C 2) Alcohol-related consequences (RAPI) 3) Psychological constructs related to behavior change: – Importance of cutting back – Likelihood to cut down in next 30 days – Readiness to stop – Desire for help to cut down	RCT three groups: 1) Computerized BI (*N* = 252): Offline "Facebook"-styled program 2) Therapist-delivered BI (*N* = 256) – Both BI had tailored normative feedback, based on motivational interviewing and cognitive–behavioral strategies 3) Control (*N* = 281): Standard care with community resource brochure (also given to BI groups)	Immediate posttest (99%)	• Increased importance of change in both BI groups compared with control groups. • Increased readiness to stop in Therapist BI group. • BI components positively related to changes in psychological constructs: *Computer BI* – Benefits of change – Alternate activities – Choosing goal to reduce or stop *Both* – Tools for reducing or stopping use – Personal strengths review

NOTES: Abbreviations:

AUDIT-C: Alcohol Use Disorders Identification Test—Consumption items (items 1–3)
CASI: Computerized alcohol screening and intervention
CRAFFT: Car, Relax, Alone, Forget, Family/Friends, Trouble
PCP: Primary care provider
POSIT: Problem Oriented Screening Instrument for Teenagers
RAPI: Rutgers Alcohol Problem Index
T-ACE: Mnemonic for 4-item screener for problem alcohol use (Tolerance, Annoyed, Cut down, Eye-opener)

Screening

All 12 studies used a self-administered computerized screener that assessed quantity and frequency of alcohol consumption and heavy episodic drinking (HED) episodes. Ten of the 12 studies (Butler et al. 2003; Cucciare et al. 2013; Johnson et al. 2013; Karlsson and Bendtsen 2005; Kypri et al. 2008; Murphy et al. 2013; Neumann et al. 2006; Suffoletto et al. 2012; Trinks et al. 2010; Vaca et al. 2011) used the Alcohol Use Disorders Identification Test (AUDIT) screening tool (Reinert and Allen 2002) or its shortened form, the AUDIT-C (Bush et al. 1998).

Brief Intervention Delivery

Seven of the studies (Blow et al. 2006; Cucciare et al. 2013; Kypri et al. 2008; Neumann et al. 2006; Suffoletto et al. 2012; Trinks et al. 2010; Vaca et al. 2011) only provided the brief intervention portion of the SBI to patients who screened positive for risky drinking, typically defined as AUDIT-C scores of 4 or higher for men and 3 or higher for women, or AUDIT scores of 8 or higher. The other five studies (Bendtsen et al. 2011; Butler et al. 2003; Karlsson and Bendtsen 2005; Murphy et al. 2013; Johnson et al. 2013) provided a brief intervention regardless of alcohol use level.

Brief Intervention Format

The brief interventions in 4 of the 12 studies (Bendtsen et al. 2011; Blow et al. 2006; Karlsson and Bendtsen 2005; Nilsen et al. 2009) were provided to patients using computer-generated printouts, whereas the rest were offline or Web-based computer programs. All but one computerized brief intervention consisted of a single session that lasted 10 to 20 minutes. The outlier examined both a single-dose Web-based brief intervention and a multi-dose version, where patients repeated the brief intervention at the 1- and 6-month followups (Kypri et al. 2008).

Brief Intervention Content

Nearly all of the brief interventions tested in these studies used at least some components of the FRAMES (Feedback, Responsibility, Advice, Menu of options, Empathy, Self-efficacy) model of brief intervention (Hester and Miller 1995). All the brief interventions in these studies provided feedback about the patient's risk level, drinking pattern relative to recommended limits, advice and information to enhance motivation to avoid use, and suggestions for behavior change strategies, if applicable. Capitalizing on a key feature of computerization, most of the brief interventions automatically tailored feedback and information to patients' screening results and other characteristics. That said, one of the randomized studies specifically examined the effect of tailored messages, compared with generic messages, either with or without clinician brief advice and found no significant effect of tailoring on alcohol consumption or related consequences after 12 months (Blow et al. 2006). Instead, patients who received brief advice from clinicians showed greater reductions in drinking than those who only received feedback from the computer SBI. Only one other study (Butler et al. 2003) included a printed report for the clinician with screening results and suggested brief intervention options. All other studies used technology-based self-guided brief intervention, with no explicit clinician involvement.

Findings

Among the seven experimental or quasi-experimental trials (Blow et al. 2006; Butler et al. 2003; Cucciare et al. 2013; Kypri et al. 2008; Neumann et al. 2006; Suffoletto et al. 2012; Trinks et al. 2010), findings were mixed, with several reporting differences between the intervention and comparison conditions in follow-up outcomes and others not. Overall, the 12 studies suggested that using technology-based SBIs in medical settings is feasible and acceptable to patients but were not able to clarify whether they are effective.

Primary Care

One controlled trial in a primary care setting (Kypri et al. 2008) found significant reductions in alcohol consumption scores and alcohol-related problems at both the 6- and 12-month followups among university health service patients in New Zealand who screened positive for alcohol problems and received a Web-based brief intervention, compared with patients who received a brochure. Two other trials (Butler et al. 2003; Cucciare et al. 2013) found reductions in alcohol consumption and related consequences out to 6 months, but the reductions were similar for both the standard care control and the computerized SBI groups. A fourth nonexperimental implementation study (Bendtsen et al. 2011) found that patients given access to a computerized SBI kiosk in a primary care clinic showed declines in heavy episodic drinking frequency at a 3-month followup. Patients referred to the SBI by a clinician, as opposed to those who self-initiated SBI use, showed a decline in weekly alcohol consumption. Without a control group, it is impossible to determine how much the decline is attributable to the SBI or some other confounder. That said, this study is unique in its examination of a computerized SBI system that routinely was offered at a primary care clinic, independent of a research study, showing that patients and clinicians are willing to use the system.

EDs

Only two of the ED studies used a nonintervention control group. One study (Neumann et al. 2006), a large German trial of 1,139 sub-critically injured ED patients with at-risk drinking, found significantly reduced prevalence of at-risk drinking and alcohol consumption at both the 6- and 12-month followups for patients receiving computerized

SBIs compared with those receiving standard care alone. Another, much smaller study (Suffoletto et al. 2012) conducted in three Pennsylvania EDs sent weekly text messages (TMs) to young-adult risky drinkers discharged from the EDs. The intervention group received TMs asking them to evaluate their drinking and providing them with information about setting alcohol consumption goals. Another group received TMs asking them to assess their drinking. A third group simply received TM notifications about the study's 3-month followup. Participants in the goal-setting intervention significantly reduced hazardous drinking behavior, compared with participants in the control groups (Suffoletto et al. 2012). However, this study found the greatest change among those with the highest baseline drinking levels, suggesting potential regression to the mean, which is a statistical phenomenon where more extreme values in data tend to move spontaneously towards the mean over time as a result of a certain amount of natural variation (Barnett et al. 2005). The other two ED studies did not use nonintervention control groups. Instead, they compared different active interventions. Both found that all the interventions tested reduced weekly alcohol consumption and HED frequency (Blow et al. 2006; Trinks et al. 2010), as well as alcohol-related consequences (Blow et al. 2006). All ED studies excluded patients that were intoxicated, had a high blood alcohol concentration at time of recruitment, were suicidal, or were otherwise being referred to psychiatry, which may have excluded patients with the most severe alcohol problems.

SBIs for Pregnant Women

Previous studies have shown the benefits of SBIs for addressing alcohol and drug use in pregnant women (Chang 2002; Ondersma et al. 2011). However, only one published randomized-controlled trial (Tzilos et al. 2011) has examined a computerized SBI for alcohol use during pregnancy. This early-stage randomized controlled trial in an urban prenatal care clinic included a convenience sample of 50 pregnant women that either screened positive on the T-ACE alcohol screening tool (Elliot and Hickam 1990; Sokol et al. 1989) or had drinking patterns before pregnancy that exceeded NIAAA drinking limits for women (NIAAA 2010). Participants randomly completed either the computerized SBI or an unrelated questionnaire. Those receiving the intervention gave it high marks for ease of use, likability, and respectfulness. Both intervention and control groups showed significant and equivalent reductions in drinking at the 1-month followup, although babies born to women in the intervention group had higher newborn birth weights.

More recently, Pollick and colleagues (2013) found high acceptability of, and user satisfaction with, a computerized brief intervention for alcohol use in pregnancy (C-BIAP) in a qualitative pilot study among 18 pregnant African-American women. Given the paucity of studies in this population, and that alcohol use in pregnant and parenting women additionally can cause secondary lifelong harm to the fetus or infant, more studies are critically needed to elucidate the utility of computerized strategies to enhance the efficient and effective implementation of alcohol SBIs in prenatal and antenatal clinics.

Targeting Adolescents

Numerous studies suggest that computerized screening of adolescent patients for alcohol use problems is acceptable, feasible, and effective in medical settings (Chisolm et al. 2008; Harris et al. 2012; Olson et al. 2009; Ozer et al. 2005; Stevens et al. 2008). Using computerized alcohol screening can increase adolescent satisfaction with the medical encounter (Gadomski et al. 2014; Harris et al. 2012) and efficiently boost physician recognition of substance use issues and patient–physician dialogue around substance-use topics (Harris et al. 2012; Olson et al. 2009; Stevens et al. 2008). These findings may help to bolster the case for increased adolescent screening for alcohol in medical settings, where screening rates remain suboptimal (Hingson et al. 2013).

Few studies have tested integrated computerized alcohol SBIs in adolescents. In fact, only four trials, yielding eight published papers (Cunningham et al. 2009, 2012; Gregor et al. 2003; Harris et al. 2012; Louis-Jacques et al. 2014; Maio et al. 2005; Walton et al. 2010, 2014), support computerized alcohol SBIs as feasible, acceptable, and, in some cases, effective for reducing drinking or alcohol-related problems among adolescents seen in medical settings.

Three of the four studies (Cunningham et al. 2012; Maio et al. 2005; Walton et al. 2014) were randomized controlled trials conducted among adolescent ED patients in the United States. These studies compared adolescents receiving standard care with adolescents receiving an integrated computerized SBI that screened patients and then delivered an approximately 30-minute single-session, highly interactive, tailored brief intervention that reflected principles of motivational interviewing (MI) and the social cognitive theory of behavior change (Bandura 1977). One trial (Maio et al. 2005) implemented a universal brief intervention aimed at both preventing and reducing use in adolescents with minor injuries. The other two only provided the brief intervention for adolescents who reported drinking in the past 12 months (Cunningham et al. 2012) or that screened positive for risky drinking on the AUDIT-C (Walton et al. 2014). The latter two trials additionally compared a single-session, computer-delivered brief intervention with a therapist-delivered version that was similar in content (Cunningham et al. 2012; Walton et al. 2014).

Overall, these ED-based studies found no significant differences in alcohol consumption outcomes between the intervention and standard-care control groups during followup, but some did find that the computer-based SBIs

influence other alcohol-related behaviors in certain populations:

- Maio and colleagues (2005) found in post hoc subgroup analysis a significant intervention effect on frequency of alcohol misuse and HED behaviors among adolescents admitting to having driven while impaired before entering the study. It may be that computerized brief interventions based on motivational enhancement approaches, like their face-to-face counterparts, tend to be more effective for individuals that have at least a certain level of substance use, or experience of negative consequences (Blow et al. 2009; Palfai et al. 2011; Spirito et al. 2004). Alternatively, those with greater use may be more subject to regression to the mean (Finney 2008).

- At a 6-month followup, Cunningham and colleagues (2009, 2012) found that their computerized and therapist-delivered brief interventions, which addressed peer violence and alcohol use (Walton et al. 2010) were associated with greater reductions in alcohol-related consequences, such as missing school because of alcohol use, compared with patients receiving the standard-care control. By the 12-month followup, patients receiving the therapist-delivered brief intervention maintained reductions in peer violence, but neither intervention continued to influence alcohol-related outcomes. The authors postulate that it may be difficult to address effectively more than one risk area with a brief intervention.

- Walton and colleagues (2014) examined the intermediate effects of a single-session, computerized or therapist-delivered brief intervention on psychological constructs hypothesized to be key moderators of behavior change. They were looking for the "active ingredients" that bring about change in adolescent risky drinkers. They found that, among 836 urban adolescent ED patients with risky drinking, those receiving either brief intervention significantly increased their perception that it was important to stop drinking, compared with adolescents receiving standard care. In addition, those receiving the therapist-delivered intervention increased their readiness to stop drinking. The analysis teased out two brief intervention components that had the strongest effect on these psychological outcomes, regardless of delivery mode: a review of personal strengths and suggested tools patients could use to reduce or stop drinking. Within the computer-delivered brief intervention, the components that most influenced outcomes were those that helped patients identify more benefits of behavior change, imagine sports activities that could be alternatives to alcohol use, and choose a goal to reduce or stop drinking. In contrast, the component of the therapist-delivered brief intervention that provided normative statistics/personalized feedback about current level of use was associated with negative effects on these cognitive outcomes. This study is ongoing and has yet to determine how these intermediate changes and brief intervention components connect to actual alcohol use and related consequences. However, it represents an important direction for future research into computerized SBI systems, such as the determination of the most effective ingredients, thus promoting the development of the most efficient and effective interventions possible.

The one adolescent trial of a computer-facilitated SBI conducted in a primary care setting involved several primary care clinics in the United States and the Czech Republic (Harris et al. 2012). The study utilized a before-and-after comparison design. Each clinic enrolled participants while providing standard care; then the clinic enrolled a comparison group of participants after implementing a computer-facilitated SBI system. The system consisted of three components:

- A pre-visit computerized screening using the CRAFFT behavioral health screening tool designed for children under age 21 (Knight et al. 2002);

- Immediate computer-delivered feedback to patients about their risk level, followed by several interactive pages of science-based and true-life information about substance-related health-risks and other harms; and

- Brief advice from a clinician during the primary care visit based on a printed provider report that suggested discussion points about substance use and related driving/riding risks tailored to each patient according to the screening results.

This multisite study found that U.S. adolescents, but not Czechs, had significantly reduced their alcohol use at the 3- and 6-month followups, although reductions at 12 months were less robust. In addition, the computer-facilitated SBI reduced both drinking initiation and cessation in the U.S. sample (Harris et al. 2012), and the short-term cessation effect actually was largest among drinking youth with friends who drink or approve of drinking (Louis-Jacques et al. 2014). This study also found a significant intervention effect in both countries at the 3-month followup on prevalence of driving after drinking or riding with a driver who had been drinking (Harris et al. 2011).

Because the computer system used in this study was designed to be integrated into a face-to-face primary care visit, these findings cannot disentangle the relative effects of the computerized versus the face-to-face components of the brief intervention. To this end, studies in adolescents are needed that use a factorial design (such as the study by Blow et al. 2006) to test the relative efficacy of clinician advice versus the computerized component.

With only four trials (Cunningham et al. 2009, 2012; Gregor et al. 2003; Harris et al. 2012; Louis-Jacques et al. 2014; Maio et al. 2005; Walton et al. 2010, 2014), the evidence currently is insufficient to recommend computerized

alcohol SBIs among adolescents in either EDs or primary care settings. More high-quality studies with randomized controlled designs and large sample sizes are needed, particularly in the primary care setting, which represents a key touch point with the health care system for adolescents where alcohol use can be detected early and where brief interventions are most likely to be effective. Alcohol and drug dependence are chronic, relapsing disorders with high treatment costs that most often begin during childhood. Given the relatively low risks and costs, and potential for benefit, of computerized prevention and early intervention, clinicians may wish to implement them as they become available.

Discussion and Future Directions

Research on technology-facilitated SBIs in medical settings is in its infancy. As such, there remain many questions and methodological issues that researchers should address when evaluating these interventions.

Special Populations

Although there is some evidence that the effectiveness of alcohol SBIs may be greater for people who have already experienced problems or negative consequences of drinking, it is unclear whether such programs are useful for patients with alcohol dependence (Saitz 2010). In addition, more studies should be conducted among pregnant women and adolescents, as well as in diverse racial and ethnic groups. Finally, studies should evaluate the effectiveness of Web-based alcohol SBI in high-risk, underserved, and remote populations, such as military personnel, American Indians, and Eskimo/Inuit, as such systems are particularly suited to access such hard-to-reach groups.

Screening Validity

Evidence to date suggests that responses to computerized screening are reliable and comparable to other screening modes (McNeely et al. 2014; Thomas and McCambridge 2008; Williams et al. 2000). However, other studies suggest differences between the two modalities that researchers may want to consider as they design their programs. For example, some studies find that people are more likely to report more sensitive or stigmatized behaviors, such as illicit drug use or higher levels of alcohol consumption, on computer self-administered questionnaires compared with face-to-face interview (e.g., Beck et al. 2014; Butler et al. 2009; Perlis et al. 2004) or even self-administered paper-and-pencil questionnaires (Wright et al. 1998). Additionally, adolescents seem to be particularly sensitive to mode and context effects when reporting sensitive behaviors (Gfroerer et al. 1997; Turner et al. 1998; Wright et al. 1998). In fact, a study of adolescent primary care patients found that their reactions to computerized screening was highly associated with their level of trust in the data being kept secure and private and used only for health care (Chisolm et al. 2008). Other studies suggest that factors such as language (Butler et al. 2003) and gender (Neumann et al. 2004) also may affect computerized screening performance.

Intervention Intensity

There is little evidence to date that the length of the intervention influences its effectiveness. No study in this review directly compared the effects of low-intensity to longer interventions, but there seemed to be no consistent pattern across trials indicating greater efficacy of longer interventions over shorter. A recent meta-analysis (Carey et al. 2012) of a computerized brief intervention targeting college students found that the effectiveness of the intervention was not affected by duration.

As for single-session versus multi-session interventions, the primary care study by Kypri and colleagues (2008) was the only trial reviewed here to compare the two directly. It found no increased benefit of additional brief intervention doses given at 1 and 6 months. This finding corroborates the conclusions of other reviews (Rooke et al. 2010; Donoghue et al. 2014; Kaner et al. 2007) that found no significant effect of the number of treatment sessions on the average effect size of computer-delivered and face-to-face SBIs (Kaner et al. 2007). A more recent 2012 review of face-to-face SBI studies did find larger effect sizes for brief (less than 15 minutes each) multi-contact interventions, compared with very brief (up to 5 minutes) or brief (5 to 15 minutes) single-contact interventions (Jonas et al. 2012). Compared with face-to-face delivery, technology-based delivery modes, including via the Internet or cell phones, offer the advantage of relative ease and low cost of delivering multiple doses. Therefore, further exploration of the question of optimal number of doses is clearly warranted.

Face-to-Face vs. Computerized Delivery

Another important question is whether self-guided computerized SBIs are as effective as face-to-face SBIs. Only four of the reviewed trials compared the two modalities. Two trials (Cunningham et al. 2012; Walton et al. 2014) directly compared a 35-minute therapist-delivered SBI and a self-guided computerized SBI provided to adolescent ED patients. Both modalities showed similar reductions in alcohol-related consequences and positive changes in psychological precursors to behavior change compared with a standard-care control (Cunningham et al. 2012; Walton et al. 2014). Other studies and reviews comparing face-to-face and technology-facilitated SBIs outside medical settings find an edge for face-to-face (Carey et al. 2012; Donoghue et al. 2014). It may be that combining face-to-face and technology-based SBI will be the most effective. Such a combination is easily accomplished in a medical setting where patients could complete a computerized portion of the alcohol SBI before a face-to-face encounter. This would

screen and "prime" the patient to discuss the topic when meeting with the clinician and could increase clinician fidelity of brief intervention implementation by using "prompts" to guide the clinician. Although computers have certain logistical advantages, they cannot convey empathy, regard, and complex reflections, which represent some of the most important ingredients of brief motivational interventions (Miller and Rollnick 2012). Also, patients may put less attention, thought, and effort into completing a computerized brief intervention compared with a face-to-face intervention (Walters and Neighbors 2011). Future research will benefit from examining a combination of face-to-face and computerized SBI delivery, as it may help to achieve larger and more enduring effects than self-guided computerized SBIs alone (White et al. 2010).

Outcome Measures

In terms of what intervention studies measure, more need to consider alcohol-related outcomes other than consumption, including negative consequences and problems related to alcohol use such as school problems for adolescents, driving while impaired, traffic violations, and crashes and injuries. Among the studies reviewed here, not all examined these outcomes, yet, in the face-to-face alcohol SBI literature, intervention effects on alcohol-related consequences or risks often have been larger than on alcohol consumption (Newton et al. 2013; Wachtel and Staniford 2010; Yuma-Guerrero et al. 2012). Therefore, failure to measure such outcomes, which have great public health import, may be a missed opportunity to identify some key intervention benefits.

Mediators and Moderators

There is a dearth of studies on mediators and moderators of the effects of computerized SBI in any setting and, in particular, within the small subset of studies examining these interventions within medical settings. Only one study (Walton et al. 2014) reviewed here attempted to elucidate the potential mechanisms and "active ingredients" underlying the effects of the computerized SBIs delivered to adolescents in an ED. Within the broader literature, the meta-analysis by Carey and colleagues (2012) found reduced computerized SBI effectiveness when the intervention included a decisional-balance or values-clarification exercise, identified high-risk situations, or included moderation strategies.

A few studies have found that certain patient characteristics, such as baseline stage-of-change or severity of alcohol involvement also may moderate the effectiveness of computerized SBIs. Among the studies reviewed here, Neumann and colleagues (2006) found greater intervention impact among patients who were contemplating changes in their drinking habits when they entered the study, and Vaca and colleagues (2011) found their SBIs to be more effective among patients reporting recent drinking and driving. The finding that an intervention may be more effective among individuals with more risky drinking behavior matches findings from a recent review of face-to-face alcohol/drug SBIs for adolescents seen in medical settings (Mitchell et al. 2013) and a study of a computerized SBI for college students (Carey et al. 2012).

Assessment Reactivity

One of the major methodological issues facing SBI research in general is the degree to which simply being part of a study that assesses alcohol use may affect study results (Elbourne 2014; Finney 2008; McCambridge and Kypri 2011; McCambridge et al. 2014). Indeed, studies find that simply evaluating people's drinking—as would happen in the screening part of an SBI—has a robust effect on drinking behavior over time (Dearing et al. 2013; Epstein et al. 2005). This "assessment reactivity" may underlie the similar changes in both the intervention and control groups seen among many of the studies reviewed here. To reduce the potential for assessment reactivity, future randomized controlled studies could include an additional minimal-assessment control arm that only measures outcomes at the final followup.

Summary

There is robust evidence that in-person alcohol SBIs are effective when delivered to patients by staff in medical settings (Moyer 2013; Newton et al. 2013; O'Donnell et al. 2014). However, the implementation rates of these face-to-face SBIs remain suboptimal (Hingson et al. 2013; McKnight-Eily et al. 2014). Technology-based solutions, such as computerized SBI systems, may help to address this problem, but evidence for their effectiveness is less clear. This review found a burgeoning, but still small, research field with only 23 published papers representing 18 different trials evaluating the use of technology-based alcohol SBIs among adults, pregnant women, and adolescents in medical settings. The studies all found that technology-based alcohol SBIs are feasible for delivery in the medical setting and acceptable among patients, but most had methodological limitations. Only 13 of the 18 were controlled trials, and the majority were conducted in adult populations, with just four conducted among adolescents and only two among pregnant women. More than half of the studies took place in EDs, which offers a prime "teachable" moment, particularly for injured patients. However, more studies are needed in primary care and other ambulatory medical care settings, where patients may have periodic and ongoing contact with their health care providers. Such longitudinal patient–clinician relationships would allow for continued support and followup regarding recommended behavior changes. New studies also will benefit from bigger sample sizes to increase the power of their findings, more comprehensive participant recruitment, higher retention rates, and longer follow-up periods.

Finally, a promising new direction for the field would be to evaluate the potential of mobile technologies that can be used in medical settings. Suffoletto and colleagues (2012) demonstrated that mobile devices offer the potential to act as "clinician-extenders," allowing clinicians to support and interact with patients after a visit and potentially boost the effect of a computerized brief intervention delivered in the medical setting. A review by Heron and Smyth (2010) of studies examining the use of ecological momentary interventions delivered through mobile technology, such as cell phones and tablet computers, found them to be feasible and acceptable and show efficacy for addressing a variety of psychosocial and other health behaviors, including alcohol use. Research also may begin to emerge on the use of smartphone apps and social-networking sites like Facebook for underage drinking prevention and intervention.

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Gaps in Clinical Prevention and Treatment for Alcohol Use Disorders

Costs, Consequences, and Strategies

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Heavy drinking causes significant morbidity, premature mortality, and other social and economic burdens on society, prompting numerous prevention and treatment efforts to avoid or ameliorate the prevalence of heavy drinking and its consequences. However, the impact on public health of current selective (i.e., clinical) prevention and treatment strategies is unclear. Screening and brief counseling for at-risk drinkers in ambulatory primary care has the strongest evidence for efficacy, and some evidence indicates this approach is cost-effective and reduces excess morbidity and dysfunction. Widespread implementation of screening and brief counseling of nondependent heavy drinkers outside of the medical context has the potential to have a large public health impact. For people with functional dependence, no appropriate treatment and prevention approaches currently exist, although such strategies might be able to prevent or reduce the morbidity and other harmful consequences associated with the condition before its eventual natural resolution. For people with alcohol use disorders, particularly severe and recurrent dependence, treatment studies have shown improvement in the short term. However, there is no compelling evidence that treatment of alcohol use disorders has resulted in reductions in overall disease burden. More research is needed on ways to address functional alcohol dependence as well as severe and recurrent alcohol dependence. **KEY WORDS: Alcohol use, abuse, and dependence; heavy drinking; alcohol use disorders (AUDs); alcohol-related problems; alcohol burden; burden of disease; morbidity; mortality; prevention; treatment; prevention strategy; treatment strategy; screening and brief intervention; primary care; cost-effectiveness of AOD health services**

Heavy drinking takes a high toll on society. Other articles in this issue summarize the disease burden and economic cost to society attributable to alcohol use, which provide a powerful incentive to develop and implement ways to reduce them. The focus of this article is on the role of selective (i.e., clinical) prevention and treatment approaches for heavy drinkers and people with alcohol use disorders (AUDs) in reducing the burden associated with excessive alcohol use. As used here, selective, or clinical, prevention refers to strategies targeted at individuals at higher risk of experiencing adverse alcohol effects, such as screening and brief counseling of heavy drinkers in health care settings or internet-based screening and advice provided to college students. The term "treatment" refers to services for alcohol dependence provided by a professional, such as a counselor, social worker, nurse, psychologist, or physician. Community peer-led support groups such as Alcoholics Anonymous are considered to be distinct from professional treatment services, much like a diabetes support group would be distinguished from endocrinology services. The article focuses on the following three questions: (1) Can selective prevention and treatment reduce the disease burden attributable to heavy drinking? (2) Are some treatment approaches more cost-effective than others? (3) Do gaps exist in the current continuum of care? After addressing these issues, the review suggests research priorities to help close existing gaps and reduce the burden of disease.

Selective Prevention and Treatment: Effectiveness, Cost-Effectiveness, and Disease Burden

Screening and brief advice for at-risk (i.e., nondependent) drinkers, commonly known as screening and brief intervention (SBI), is effective at reducing drinking for a year or more and in many studies also has been shown to reduce alcohol-related harms, such as motor-vehicle crashes and driving violations. Its efficacy is supported by numerous randomized controlled trials and multiple meta-analyses; as a result, the U.S. Prevention Task Force has listed it as a Type B recommendation for medical prevention services (Babor et al. 2007; Whitlock et al. 2004). The evidence is strongest for nondependent heavy drinkers who present for primary care services in ambulatory settings. Unfortunately, a recent meta-analysis of studies of SBI in primary care settings failed to show significant reductions in subsequent health care utilization (Bray et al. 2011). The efficacy of SBI in other settings, such as emergency departments (EDs) or hospitals, has not been established, although several randomized controlled trials have been conducted (Field et al. 2010). One explanation for the observed differences may be the patient populations analyzed. Thus, in most of the outpatient primary care studies, participants with alcohol dependence were excluded from the analysis, whereas that generally was not

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the case for studies conducted in EDs or hospital settings. Moreover, patients with alcohol dependence are much more commonly encountered in ED and hospital settings than in primary ambulatory care. In summary, at this time, SBI in primary care ambulatory settings for adults can be strongly recommended as highly efficacious, whereas SBI in EDs or hospitals cannot.

SBI also seems to be effective among select groups when delivered through internet-based or computerized applications. In particular, there is strong evidence that digital SBI can effectively reduce drinking and associated consequences among college students (Moreira et al. 2009). It is not clear whether or to what extent this finding might generalize to other population subgroups, but it is certainly plausible that it could, provided the target population has easy access to computers and is computer literate. The same holds true for other methods, such as telephone-based SBI or use of the relatively new publication and Web site called Rethinking Drinking, which is published by the National Institute on Alcohol Abuse and Alcoholism (NIAAA).

Despite the evidence supporting its effectiveness, SBI is not yet being implemented widely (Hingson et al. 2012). Widespread dissemination of information about recommended drinking limits and easy access to screening and brief counseling has the potential to make a significant public health impact. Because at-risk drinkers are much more numerous than alcohol-dependent people, at-risk drinking contributes a much greater disease burden than alcohol dependence. Accordingly, widespread implementation of SBI has the potential to reduce a greater proportion of disease burden than even very effective treatment, a concept known as the prevention paradox (Rose 1981). Therefore, more research is needed to expand the implementation of SBI in the at-risk population and further increase its effectiveness.

Estimating the effectiveness and cost-effectiveness of treatment is more complex. Most reviews conclude that treatment is effective at reducing drinking and associated consequences. Multiple behavioral treatment approaches—such as cognitive– behavioral therapy, motivational enhancement therapy, 12-step facilitation, behavioral marital therapy, and community reinforcement—have similar and relatively high levels of short-term success in reducing drinking and associated consequences, at least when treatment is provided by the highly trained, motivated, and closely supervised clinicians participating in clinical efficacy trials (Project MATCH Research Group 1998). Why these technically diverse counseling techniques produce almost identical drinking outcomes is unclear. Three alternative explanations have been offered:

- The specific technique is less important than other, mostly unidentified, factors associated with psychotherapy.
- Each approach works via different mechanisms but produces similar results on average, much like different antidepressants acting through different mechanisms produce similar outcomes in the treatment of depression.
- Professional treatment only has a small effect in determining outcome compared with other, nontreatment factors, such as social control (e.g., driving-while-intoxicated laws, family pressure, or employer mandate), natural history of alcohol dependence, and the tendency to revert to usual levels of drinking following resolution of a crisis where drinking had peaked (i.e., regression to the mean).

This last explanation is supported by recent research demonstrating that changes in drinking habits begin weeks before treatment entry (Penberthy et al. 2007). Likewise, in another study of treatment of alcohol dependence that examined events leading to treatment seeking (Orford et al. 2006), the findings suggested that the change point occurred prior to treatment entry. Thus, it is unclear how much of the positive change can be attributed to the treatment processes themselves as opposed to other factors leading to and following treatment seeking.

What is clear, however, is that researchers and clinicians do not yet understand how or why some people change in response to treatment and others do not. To address this issue, NIAAA led the way at the National Institutes of Health (NIH) in shifting the focus of behavioral treatment research to identifying the mechanisms of behavior change rather than encouraging more comparisons of different psychotherapy approaches (Willenbring 2007). The NIH subsequently developed a major initiative on basic behavioral research (Li 2009). This research initiative provides an opportunity to investigate many obvious questions. For example, what are the social forces that either support or impede positive health behavior change? What determines their impact, in terms of the response of the individual? Why and how do people begin to change, and what determines the resilience of that change? What is the basic science underlying behavior change, at all levels from genetic and genomic to cellular, organic, individual, and social interactions? Research elucidating the basic science of behavior change is an exciting and promising area that has the potential to substantially change the types of interventions that are available, making them more powerful, available, and cost-effective.

The lack of clarity about what causes change in drinking behavior also results in uncertainty as to whether treatment of alcohol dependence reduces disease burden. The community prevalence of alcohol dependence, which is about 4 percent in any year, has not changed substantially in recent years (Substance Abuse and Mental Health Services Administration 2011). Earlier studies found a cost offset of treatment—that is, lower health care costs after treatment than before treatment (Holder 1998). More recent studies, however, have found that heavy drinkers who are not in crisis underutilize health care, at least in an employed population, suggesting that the observed cost reduction is more a reflection of the natural history of drinking behavior and of a regression to the mean (Finney 2008; Zarkin et al. 2004). In other words, people suffering from any disease tend to seek treatment when their condition is most severe. In the case of alcohol dependence, treatment seeking therefore would be preceded by an escala-

tion of drinking, complications, and utilization of medical services and, consequently, high costs before treatment entry. Because chronic conditions such as alcohol dependence wax and wane, most people will tend to improve after a period of greater severity, even without effective treatment, so that subsequent reduced costs may not necessarily be associated with treatment. Also, every patient's disease trajectory is different, so that when drinkers are assessed before and after treatment, some of them will be well at followup, whereas for others their condition will be more severe. The average severity, however, will be less following treatment, because for all patients studied, their disease severity at treatment entry will have been high. The most rigorous study of cost-effectiveness of alcoholism treatment, the COMBINE trial, found that treatment was cost-effective, especially pharmacotherapy with medical management (Zarkin et al. 2008, 2010). The interpretation of these findings is limited, however, by the study's highly rigorous trial design, intensive follow up, and exclusion criteria (Anton et al. 2006), and it is unknown to what extent these findings generalize to community treatment programs and participants.

Another limitation when estimating the effects of treatment on public health is that relatively few affected people seek treatment. For example, among people who develop alcohol dependence at some point in their lives only 12 percent seek treatment in a specialty treatment program (Hasin et al. 2007). Among people who have AUDs and who perceive a need for treatment, almost two-thirds (i.e., 65 percent) fail to obtain it because they are not ready to stop drinking or feel they can handle it on their own. Other common reasons for the failure to seek treatment include practical barriers, such as lack of health insurance, the cost of treatment, and lack of transportation or access to treatment, which are reported by 59 percent of respondents, and stigma, which is reported by 31 percent (Center for Behavioral Health Statistics and Quality 2012).[1] Thus, more people might seek treatment if it was less expensive, stigmatizing, and disruptive than most treatment approaches. Efforts to improve access, affordability, and attractiveness of treatment, especially for individuals with less severe AUDs should be encouraged.

Despite these limitations, some tentative conclusions can be drawn as to which approaches to treating alcohol dependence are more cost effective. Studies found no significant difference in outcomes between residential and outpatient treatment and no clear relationship between intensity of treatment and outcome (Fink et al. 1985; Longabaugh et al. 1983; McCrady 1986). For example, medical management plus pharmacotherapy with naltrexone generated similar outcomes to more expensive counseling approaches, even when counseling was performed once weekly and on an outpatient basis (Anton et al. 2006; O'Malley et al. 2003). These studies suggest that a more individualized, outpatient, and medically based approach may provide a cost-effective alternative to approaches favoring intensive psycho-education, which often are provided in residential settings. Treatment provided in residential rather than outpatient settings may add considerable expense without a commensurate improvement in outcomes. In addition, confidential treatment by their usual primary care physician involving only routine clinic visits may attract more people, thus expanding access to effective treatments.

Gaps in the Continuum of Care

There are several gaps in the continuum of care that deserve attention, affecting drinkers across the spectrum of alcohol involvement. Recent epidemiological research has demonstrated that alcohol involvement varies along a continuum ranging from asymptomatic heavy drinking (i.e., at-risk drinking), through functional alcohol dependence, and to severe and recurrent alcohol dependence (Willenbring et al. 2009). The continuum of care ideally should correspond to this epidemiology but does not at this time. Most studies and treatment approaches have focused on the more severe end of the spectrum—that is, people with severe, recurrent dependence. However, the vast majority of heavy drinkers either does not have alcohol dependence or has a relatively milder, self-limiting form (Moss et al. 2007). This spectrum of severity is similar to that for other chronic diseases, such as asthma. Likewise, examining treatment seekers in the current system of care yields similar results to studying hospitalized asthmatics: thus, heavy drinkers in treatment exhibit more severe dependence, more comorbidity, less response to treatment, and a less supportive social network compared with people who do not seek intensive treatment (Bischof et al. 2003; Dawson et al. 2005; Sobell et al. 2000). In contrast, people with functional alcohol dependence[2] predominantly exhibit "internal" symptoms, such as impaired control; a persistent desire to cut down on their drinking but finding it hard to do; and alcohol use despite internal symptoms such as insomnia, nausea, or hangover. These individuals generally drink much less than more seriously affected people (Moss et al. 2007). Functional alcohol dependence typically resolves after a few years, mostly without requiring specialty treatment (Hasin et al. 2007). Large gaps in services exist for people at both ends of the spectrum of dependence severity—that is, both for people at the milder end of the spectrum (i.e., at-risk drinkers and people with functional alcohol dependence) and for those at the most severe end (i.e., with recurrent, treatment-refractory dependence).

There currently are few services for at-risk drinkers and people with functional alcohol dependence. In primary medical care, very few patients are screened and positive screening results addressed (McGlynn et al. 2003). Furthermore, functional alcohol dependence largely is ignored because although these individuals meet diagnostic criteria for dependence, they rarely seek treatment in the current system (Moss et al. 2007). These gaps are significant from a public health perspective because the prevalence of at-risk drinking

[1] The numbers add up to more than 100 percent because respondents could endorse multiple reasons.

[2] People with functional alcohol dependence are those who meet the criteria for a medical diagnosis of alcohol dependence but remain functional in society (i.e., in their jobs, families, and social lives).

and functional dependence is much higher than that of more severe disorders and these conditions therefore account for the majority of excess morbidity, mortality, and associated costs attributable to alcohol consumption (Centers for Disease Control and Prevention 2012). Whether wider implementation of SBI would result in a reduction in disease burden is not known at this time. However, enhancement of these approaches, especially among young people and community-dwelling heavy drinkers not seeking medical care, might reduce disease burden, although the two populations require somewhat distinct approaches. More studies of secondary prevention efforts outside of medical settings therefore are needed.

SBI in primary care settings to identify people with AUDs at the milder end of the severity spectrum is effective and may be cost-effective (Solberg et al. 2008), but many questions remain. For example, is it more cost-effective to target higher-risk groups (e.g., young people) for routine screening or is universal screening better overall? And when should screening occur (e.g., only during annual prevention visits or at every new patient visit) and how often should it be repeated? However, the biggest problem remains that effective selective prevention interventions such as SBI are not widely implemented. Although implementation has worked well in situations where additional grant funds were available, it still is unknown whether physicians will engage in this widely or how to best facilitate implementation. The Veterans Affairs health services system has been the most effective at implementing annual screening, but this system is unique in its structure and hierarchical nature. Implementation of such approaches in private health care organizations is much more complex and difficult. Therefore, more research is needed on low-cost ways to encourage wider adoption of SBI in primary care settings. Additional research should focus on SBI in other medical settings, especially mental health settings and medical specialties particularly affected by heavy drinking, such as gastroenterology (with patients with alcohol-related liver disease, gastritis, and pancreatitis) and otolaryngology (with patients with alcohol-related head and neck cancers).

Because so many hospitalized heavy drinkers have dependence, SBI is much less effective in this group (Saitz et al. 2007) and its effectiveness with patients in EDs or trauma centers also is unknown. Although some early studies showed positive results, subsequent research has yielded as many negative as positive findings (Field et al. 2010). Current efforts to implement SBI in these more acute-care settings therefore are premature, and more research is needed to determine if heavy drinkers encountered in such settings require more intensive services, linkage to ambulatory care services, or both.

People with functional alcohol dependence likely require more than brief counseling, but there is a major gap in research concerning optimal treatment strategies. Currently, few, if any, services are available for this group because they fall between at-risk drinkers and those with severe recurrent alcohol dependence (who are most likely to enter the current specialty treatment system). Pharmacotherapy (e.g., antirelapse medications) combined with medical management offers an attractive possible approach for this group, and evidence suggests that this combination yields comparable results to state-of-the-art counseling (Anton et al. 2006; O'Malley et al. 2003). Such an approach would allow most people with functional dependence to be treated in primary care and mental health care settings, similar to people with mild to moderate depression. More research, especially regarding effectiveness and implementation, is needed on this approach. Although most people with functional alcohol dependence eventually recover without any treatment (Hasin et al. 2007; Moss et al. 2007), their period of illness is associated with less severe but still significant dysfunction, such as absenteeism, attending work or school while sick (i.e., presenteeism), and reduced productivity. Early identification and treatment could reduce or hopefully eliminate these costs to the affected individuals and society.

Gaps in treatment also exist for people with severe recurrent alcohol dependence—the group that most people tend to think of when they think of "alcoholism." A recent exhaustive report examining the current treatment system concluded that "Most of those who are providing addiction treatment are not medical professionals and are not equipped with the knowledge, skills or credentials necessary to provide the full range of evidence-based services to address addiction effectively," (p. 3) and that "Addiction treatment facilities and programs are not adequately regulated or held accountable for providing treatment consistent with medical standards and proven treatment practices." (National Center on Addiction and Substance Abuse at Columbia University 2012, pp. 3–4). The current addiction treatment system first was conceptualized in the middle of the last century, as documented by White (2002), and has changed little since. No other chronic disease is treated with brief stints in a program with limited follow up care. Instead, for other chronic conditions patients are followed closely by physicians and other professionals over long periods of time, with the goal of minimizing symptoms and relapses, treating complications, and maximizing function. In these cases, care is provided indefinitely, often for life. Such a longitudinal-care approach also offers considerable promise in treating people with severe recurrent alcohol dependence. Several studies have found a highly significant positive effect for longitudinal care in people who have one or more medical complications of alcohol dependence (Kristenson et al. 1984; Lieber et al. 2003), including two studies that found significant reduction in 2-year mortality (Willenbring and Olsen 1999; Willenbring et al. 1995). Some findings also indicate that integrating treatment for substance use disorders into that for severe and persistent mental illness may be effective at reducing substance use, although no high-quality randomized controlled trials of this approach have been published (Drake et al. 2006). Pharmacotherapy for AUDs also may be effective in people with severe mental illnesses (Petrakis et al. 2004, 2005, 2006; Salloum et al. 2005). Finally, the ongoing need for recovery support and maintenance should be addressed.

Thus, more research is needed on the best long-term management strategies for recurrent alcohol dependence.

Conclusion

At this time no solid conclusions can be drawn as to whether current approaches to prevention of and treatment for AUDs reduce the disease burden attributable to heavy drinking, although these strategies have shown positive outcomes in the short term. SBI for at-risk drinkers in ambulatory primary care settings has the strongest evidence for efficacy, and some evidence supports its cost-effectiveness and associated reduction in excess morbidity and dysfunction. However, these benefits do not necessarily indicate that health care costs for these patients are reduced. Widespread implementation of SBI for nondependent heavy drinkers outside of the medical context has the potential to have a large public health impact. For heavy drinkers with more severe conditions (i.e., recurrent alcohol dependence), time-limited counseling may improve short-term recovery rates, but its long-term impact is less clear. Moreover, recent research findings have not been widely implemented. Scientifically based, medically anchored treatment approaches may provide a more attractive and cost-effective approach than the current intensive but time-limited treatment. More research is needed on ways to address functional alcohol dependence as well as severe and recurrent alcohol dependence. ■

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Treatment of Alcohol Dependence With Drug Antagonists of the Stress Response

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Alcohol dependence is a chronic relapsing disorder characterized by neuroadaptations that may result in the emergence of negative affective states and stress responses upon discontinuation of alcohol use. Clinical studies have demonstrated that alcohol-dependent people are more sensitive to relapse provoking cues such as alcohol, negative affect, and stress. Moreover, stress relief during protracted abstinence is thought to be a major motivation for excessive alcohol consumption. The relationship between chronic alcohol use, stress, and relapse has implications for the treatment of alcohol dependence. Recent research suggests that neural systems mediating stress responses may offer useful targets for pharmacotherapy of alcoholism. **KEY WORDS: Alcohol dependence; alcoholism; alcohol use disorder; stress; stress response; relapse; relapse prevention; antagonists; negative affective states; treatment; neuroadaptation; pharmacotherapy; brain; neurochemistry**

Although alcohol dependence affects 4 percent of the adult population and is the third leading cause of preventable death in the United States (Substance Abuse and Mental Health Services Administration 2009), fewer than 15 percent of people with alcoholism receive treatment (Hasin et al. 2007). The *Diagnostic and Statistical Manual of Mental Disorders–Fourth Edition Text Revision (DSM–IV–TR)* (American Psychiatric Association 2000) characterizes alcohol dependence as a maladaptive pattern of drinking leading to clinically significant impairment, as manifested by a compulsion to drink, a lack of control over the amount of alcohol consumed, and continued drinking despite realization of the associated problems. Despite significant progress in the development of efficacious behavioral and pharmacologic treatments for alcohol dependence, relapse rates remain very high. Relapse is one of the principle characteristics of alcohol dependence. Given that one of the most challenging aspects of recovering from alcohol dependence is maintaining abstinence, understanding the factors underlying relapse susceptibility is especially important. Research indicates that alcohol-associated cues, negative-affective states, and stress are common relapse triggers (Higley et al. 2011; Mason et al. 2008; Sinha et al. 2009).

Several neurochemical systems and brain regions are involved in the development of alcohol dependence (for review, see Koob and Le Moal 1997). Such neuroadaptations may result in the emergence of negative-affective states and stress responses upon discontinuation of alcohol use, thus motivating dependent people to resume drinking. Alcohol is a powerful activator of the stress response. Chronic alcohol use is associated with several atypical stress responses, which could have important implications for understanding the neurobiology of dependence and relapse. Specifically, alcohol-dependent individuals show decreased release of the stress hormones cortisol and adrenocorticotropic hormone (ACTH) in response to acute intervening stressors (Berman et al. 1990; Wand and Dobs 1991), an effect that remains for up to 12 weeks after cessation of drinking (Bernardy et al. 1996; Ehrenreich et al. 1997; Errico et al. 1993; Lovallo et al. 2000). These attenuated reactions of the hypothalamic–pituitary–adrenal (HPA) axis, which controls the body's major hormonal stress response, have been associated with alcohol relapse (Junghanns et al. 2003) and suggest that neural systems mediating stress responses may offer useful targets for pharmacotherapy of alcoholism.

Stress relief during protracted abstinence is thought to be a major motivation for excessive alcohol consumption. The signaling molecule corticotropin-releasing factor (CRF), a 41–amino acid neuropeptide[1] with wide distribution throughout the brain and high concentrations in cell bodies in part of the hypothalamus (i.e., the paraventricular

[1] For definitions of this term and other technical terms used in this article, see the Glossary on page 522–524.

nucleus), the group of structures located near the bottom of the front of the brain (i.e., the basal forebrain), and notably the extended amygdala[2] and brainstem, has been shown to play an integral role in mediating behavioral stress responses (Funk et al. 2006; Merlo Pich et al. 1995; Olive et al. 2002). CRF produced in and released from the hypothalamus activates the HPA axis. The physiologic mechanism of stress relief following alcohol consumption is thought to occur mainly in the extended amygdala outside the HPA system (for review, see Heinrichs and Koob 2004). However, the HPA axis may contribute to the dysregulation of the extended amygdala stress system. Acute alcohol administration has been shown to enhance levels of HPA axis hormones in humans and animal models (for review, see Koob and Le Moal 1997; Koob 2003). As dependence on alcohol develops, the extended amygdala stress system becomes sensitized and HPA axis activity appears to become dysregulated, and over time, chronic exposure to alcohol may actually decrease the responsiveness of the HPA axis to external stimuli, potentially impairing a person's ability to cope with relapse-inducing stressors (Junghanns et al. 2003; Le et al. 2000; Zorrilla et al. 2001; see above).

Such alcohol-induced neurobiological changes represent possible molecular targets for pharmacotherapies of alcoholism, which help to facilitate abstinence or greatly reduce alcohol consumption by stabilizing neurobiological systems dysregulated by chronic alcohol use. Medications that normalize the dysregulation or balance of the reward and stress systems may protect against relapse. In fact, evidence shows that pharmacological treatments can support abstinence or decrease the number of heavy drinking days. Three medications are approved for the treatment of alcohol dependence in the United States—disulfiram, naltrexone, and acamprosate. Recent efforts to develop new medications have focused on specific neural responses to factors (e.g., stress) that increase risk of relapse to heavy drinking during protracted abstinence. The following sections will describe a series of neuropharmacological agents that alter the stress response and have potential for or have been used in the treatment of alcohol dependence.

CRF Antagonists

Recent research has led to the hypothesis that the transition to alcohol dependence involves the dysregulation not only of neural circuits involved in reward but also of circuits that mediate behavioral responses to stressors. Alcohol-induced dysregulation of the brain's stress and anti-stress systems is hypothesized to contribute to the negative emotional state characteristic of alcohol withdrawal. More specifically, several observations indicate that CRF contributes to the development of alcohol dependence. For example, alcohol is a powerful activator of stress systems involving both the HPA axis and extrahypothalamic CRF systems in the extended amygdala; the latter also become hyperactive during withdrawal, leading to increased CRF levels in certain brain regions (i.e., the central nucleus of the amygdala [CeA] and the BNST) (Funk et al. 2006; Merlo Pich et al. 1995; Olive et al. 2002). In animal models, acute withdrawal and protracted abstinence from alcohol and all other major drugs of abuse produce anxiety-like responses that are mediated by CRF and can be reversed by agents that block or reverse the actions of CRF (i.e., CRF receptor antagonists) (for review, see Heilig and Koob 2007). Preclinical studies show that CRF antagonists block alcohol withdrawal–induced anxiety (Baldwin et al. 1991), and CRF may be involved in increased alcohol self-administration during withdrawal (Valdez et al. 2002). Likewise, injections of small molecule antagonists of the CRF-1 receptor blocked increased alcohol intake during acute withdrawal and protracted abstinence in alcohol-dependent rats (Funk and Koob 2007). Moreover, CRF antagonists reduce stress-induced reinstatement to alcohol seeking (Le et al. 2000; Liu and Weiss 2002).

Dysregulation of the brain CRF system (innate or resulting as a maladaptive response to drugs of abuse or stress) seems to be one of the major elements common to depression, anxiety, and addiction. Genetic studies indicate an association between polymorphisms of the *CRHR1* gene and drinking behavior. Treutlein and colleagues (2006) found a significant correlation between *CRHR1* gene polymorphisms and both binge drinking and lifetime prevalence of alcohol intake in an adolescent sample from the Mannheim Study of Children at Risk[3] as well as years of heavy drinking in a sample of adult alcoholics (Treutlein et al. 2006). Polymorphisms in the *CRHR1* gene also were found to moderate the relationship between the number of negative life events and rates of lifetime alcohol use and excessive alcohol use per occasion in the same study sample (Blomeyer et al. 2008), suggesting a clinical relevance for the CRF system in the treatment of alcoholism.

The above evidence suggests that the CRF system may be implicated in stress-induced relapse to alcohol drinking and that CRF antagonists may have therapeutic potential in alcohol dependence, particularly for people with genetic variants in the *CRHR1* gene that exacerbate a stress-induced susceptibility to alcohol dependence and relapse (Clinicaltrials.gov NCT01187511, 2010, Clinicaltrials.gov NCT01227980, 2011).

α1-Noradrenergic System

Advances in the understanding of the neurobiology of alcohol dependence and relapse offer preclinical evidence that the noradrenergic systems (i.e., those related to the stress hormone and

[2] The amygdala is an almond-shaped group of neurons located deep within the medial temporal lobe of the brain. They encompass several nuclei, or structures in the central nervous system, including the central, lateral, and basal nuclei. The extended amygdala is hypothesized to be a group of structures that includes the central nucleus of the amygdala, bed nucleus of the stria terminalis (BNST), and a transition zone in the shell of the nucleus accumbens.

[3] The Mannheim Study of Children at Risk is a longitudinal study that followed children over a period of more than 20 years from infancy to adulthood.

neurotransmitter norepinephrine) have intimate involvement in brain processes relevant to alcohol dependence and contribute to the brain stress activation associated with withdrawal. A study of recently abstinent alcohol-dependent patients revealed elevated plasma levels of norepinephrine and the related neurotransmitter epinephrine (Ehrenreich et al. 1997), suggesting central noradrenergic overdrive may play an important role in alcohol dependence. Moreover, the use of pharmacological ligands targeting both pre- and postsynaptic noradrenergic receptor subtypes attenuates certain symptoms of alcohol withdrawal (Riihioja et al. 1997).

Prazosin, an α1-noradrenergic receptor antagonist, has kindled interest as an effective drug in reducing alcohol use. Pfizer Pharmaceuticals introduced Prazosin in 1973 as an antihypertensive drug. An inexpensive generic drug for many years, prazosin has been used chronically by millions of people for hypertension. It is the most lipid soluble α1-noradrenergic antagonist and the only clinically available α1-noradrenergic antagonist demonstrated to be active at central nervous system sites when administered peripherally (Menkes et al. 1981). Prazosin blocks the α1-noradrenergic receptor implicated in stress responsivity and possibly in driving forebrain CRF release. Prazosin reduced self-administration of alcohol in both dependent and nondependent rats during acute withdrawal. However, prazosin was more potent in dependent animals, suggesting an increase in the sensitivity to Prazosin in dependent animals due to alterations in the norepinephrine system during chronic exposure to alcohol (Walker et al. 2008). Rasmussen and colleagues (2009) demonstrated the efficacy of acute and chronic Prazosin treatment in suppressing alcohol drinking in rats selectively bred for alcohol preference.

A 6-week, double-blind, placebo-controlled pilot study of Prazosin for the treatment of alcohol dependence reported a significant reduction in drinking behavior in actively drinking alcohol dependent patients (Simpson et al. 2009). Large controlled studies currently are in progress to further investigate the role of Prazosin in alcohol dependence (e.g. NCT00762710, 2010).

Neurokinin 1 (NK1) Receptor and Substance P Antagonists

Targeting the receptor system for Substance P, which modulates emotional states, has been suggested as a viable therapeutic target for the treatment of alcohol dependence (Ebner et al., 2009). Substance P, a neurotransmitter from the tachykinin family, is released in response to stress, and preferentially binds to the NK1 receptors, which are highly expressed in brain regions critical for the regulation of emotional behavior and neurochemical responses to stress (for review see Commons 2010). Substance P also facilitates stress-induced HPA axis activation as reflected in ACTH and cortisol levels (for review see Ebner and Singewald 2006). Noxious or aversive stimuli activate Substance P pathways. In addition, Substance P administration into the brain produces anxiety-inducing and aversive effects (Aguiar and Brandao 1996, Elliott 1988, Teixeira et al.1996). Furthermore, mice that lack the NK1 receptor have been found to consume lower quantities of alcohol compared with control animals (for review see George et al. 2008).

A double-blind clinical trial of alcohol dependence found treatment with an NK1 antagonist significantly decreased craving, blunted cortisol responses, and decreased functional magnetic resonance imaging responses to affective stimuli in recently detoxified alcohol-dependent study participants (for review, see George et al. 2008). Together, these results suggest that Substance P-NK1 systems may play a role in drug reward, dependence, and reinstatement.

Neuropeptide Y

Neuropeptide Y (NPY), a 36–amino acid peptide, also is involved in regulating the body's stress response but with a neural and behavioral profile that in almost every aspect is opposite to that of CRF. For example, NPY has powerful anxiety-reducing effects in animals. It is one of the most abundant neuropeptides in the central nervous system (CNS) and is considered an important regulating factor in emotional behavior. Administration of NPY from an external source (i.e., exogenous NPY) has antianxiety and sedative effects that rely, at least partially, on activation of Y_1, a G-protein–coupled receptor located in the amygdala (Britton et al. 1997; Broqua et al. 1995; Heilig et al. 1993; Heilig and Thorsell 2002).

Several findings point to a role for NPY produced in the body (i.e., endogenous NPY) in the control of stress- and anxiety-related behaviors, supporting the antistress effects observed following central administration of NPY. In animal models, acute physical restraint, which promotes experimental anxiety, suppresses NPY expression within the amygdala and cortex, an effect that parallels the anxiety-inducing effects of stress. In contrast, repeated exposure to a siren stressor leads to complete behavioral and endocrine habituation, accompanied by an upregulation of amygdalar NPY expression (Thorsell et al. 1999, 2010). These findings suggest that NPY expression seems to be involved in the behavioral adaptation to stressors.

NPY levels are lower in the CeA of alcohol-preferring (P) rats compared to non-P (NP) rats, and NPY infusion in the CeA attenuates the anxiety-like and alcohol drinking behaviors of P rats. Thus, a deficiency in NPY signaling in the CeA may be involved in regulating both anxiety and alcohol-drinking behaviors (Zhang et al. 2010) and NPY system modifications can influence alcohol intake (Ehlers et al. 1998; Hwang et al. 2004; Hwang et al. 1999). Furthermore, stimulation of NPY activity in this brain structure suppresses anxiety-like behavior (for review, see Thorsell 2007) and dependence-induced increases in alcohol drinking (Gilpin et al. 2008). Administration of NPY into the cerebral ventricles of the

brain (i.e., intracerebroventricular infusion) in rats dose-dependently blocks the reinstatement of alcohol-seeking induced by a pharmacological stressor (Cippitelli et al. 2010). Moreover, alcohol-dependent rats exhibit decreased NPY content in the CeA during withdrawal (Roy and Pandey 2002), whereas, as stated above, CRF levels in this brain region are increased in alcohol-dependent animals. Together, these preclinical studies suggest that the NPY receptor may represent a novel pharmacological target for alcoholism.

Dynorphin/κ Opioid System

Dynorphins are opioid peptides that derive from the prodynorphin precursor and are the presumed endogenous ligands for the κ opioid receptor (Chavkin et al., 1982). Dynorphins have widespread distribution in the CNS and play a role in a wide variety of physiological systems, including neuroendocrine regulation, pain regulation, motor activity, cardiovascular function, respiration, temperature regulation, feeding behavior, and stress responsivity (Koob 2008). Products of prodynorphin processing include dynorphin A(1-17), dynorphin A(1-8), and dynorphin B(1-29). Immunocytochemical distribution of dynorphin A and B shows significant cell bodies and terminals in addiction-relevant brain areas, such as the nucleus accumbens, CeA, BNST, and hypothalamus (Koob 2008).

Activation of the dynorphin/κ receptor system can produce analgesic actions similar to other opioids but also actions that are opposite to those of μ opioid receptors in the motivational domain, where dynorphins produce aversive, dysphoric-like effects in animals and humans (Shippenberg et al. 2007). Dynorphin has long been hypothesized to mediate negative emotional states. κ receptor agonists produce place aversions in rodents (Mucha and Herz 1985) and depression and dysphoria in humans (Pfeiffer et al. 1986). κ agonists also increase brain stimulation reward thresholds (Todtenkopf et al. 2004). Dynorphin inhibits dopamine release, both via the origins and terminals of the mesolimbic dopamine system, and this effect has been hypothesized to contribute to the aversive effects of dynorphin (Spanagel et al. 1992).

The evidence for a role of the dynorphin/κ opioid system in the neuroadaptive actions of ethanol (i.e., alcohol) is based both on biochemical studies and antagonist studies. Chronic self-administration of ethanol in C57BL/6J mice produced increases in dynorphin B in the amygdala and substantia nigra 21 days after cessation of drinking (Ploj et al. 2000). Chronic ethanol produced a decrease in κ opioid receptors in the nucleus accumbens (Rosin et al. 1999) and an increase in dynorphin B expression in the nucleus accumbens (Lindholm et al. 2000), providing further evidence of upregulation of dynorphin systems with ethanol dependence. Direct support for the hypothesis that dynorphin is part of the negative emotional systems recruited in dependence is the observation that a κ antagonist, norbinaltorphimine (nor-BNI), when injected intracerebroventricularly or systemically, blocked ethanol self-administration in dependent, but not in nondependent, animals (Doyon et al. 2006; Walker and Koob 2008; Walker et al. 2010). κ knockout mice also drank less ethanol in a two-bottle choice test using escalating doses of ethanol (Kovacs et al., 2005).

Alcohol has a complex neuropharmacology and can affect many different neurotransmitter systems.

Stress also increases dynorphin activity (Shirayama et al. 2004), suggesting a potential interaction with CRF systems. Forced swim stress and inescapable footshock produced place aversions in mice that were blocked by a κ antagonist and dynorphin knockout. In other studies, CRF was hypothesized to produce its aversive effect via dynorphin activation (Land et al. 2008). Evidence also exists showing that reinstatement of drug-seeking behavior via activation of κ opioid receptors is mediated by CRF (Valdez et al. 2007). Thus, the dynorphin/κ system mimics stressor administration in animals in producing aversive effects and inducing drug-seeking behavior, and this aversive response may involve reciprocal interactions with nucleus accumbens dopamine and the brain extrahypothalamic CRF system. Thus, the dynorphin/kappa peptide system may be a parallel extrahypothalamic brain stress system that interfaces between the loss of reward function and gain in brain stress function associated with the transition to alcohol dependence (Koob et al. 2008).

Summary

Alcohol has a complex neuropharmacology and can affect many different neurotransmitter systems. Several pharmacological agents that interact with specific neurotransmitter systems affected by alcohol already have shown efficacy in the treatment of alcohol dependence and many exciting experimental agents are on the horizon. Stress relief during protracted abstinence is thought to be a major motivation for excessive alcohol consumption and the present overview outlines several new targets for medications development based on interactions with the brain stress systems. The development of these agents has been based on translational approaches ranging from the use of molecular techniques to understand alcohol neurobiology and identify candidate molecules, to the use of numerous animal models of alcohol-related behaviors to test the effects and mechanisms of action underlying these agents, and finally the use of human clinical trials and laboratory paradigms to evaluate the clinical efficacy of these

agents. Future research needs to focus on realizing the therapeutic potential of agents acting on the brain stress systems and examining genetic and patient-specific predictors of treatment response. A better understanding of the mechanisms underlying treatment response could lead to appropriate treatment matching and efficient utilization of such novel medications. ■

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Anxiety and Alcohol Use Disorders

Comorbidity and Treatment Considerations

Joshua P. Smith, Ph.D., and Carrie L. Randall, Ph.D.

The co-occurrence of anxiety disorders and alcohol use disorders (AUDs) is relatively common and is associated with a complex clinical presentation. Sound diagnosis and treatment planning requires that clinicians have an integrated understanding of the developmental pathways and course of this comorbidity. Moreover, standard interventions for anxiety disorders or AUDs may need to be modified and combined in targeted ways to accommodate the unique needs of people who have both disorders. Optimal combination of evidence-based treatments should be based on a comparative balance that considers the advantages and disadvantages of sequential, parallel, and integrated approaches. **KEY WORDS: Alcohol use disorders; stress; anxiety disorders; comorbidity; developmental pathway; treatment; treatment method; sequential approach; parallel approach; integrated approach**

Co-occurring anxiety disorders and alcohol use disorders (AUDs) are of great interest to researchers and clinicians. Cumulative evidence from epidemiological and clinical studies over the past few decades has highlighted both the frequency and clinical impact of this comorbidity. Investigations into the unique connections between specific anxiety disorders and AUDs have shown that this association is multifaceted and complex, underscoring the importance of careful diagnostic scrutiny. Of clinical relevance, treatment for people with comorbid anxiety and AUDs can be complicated, and both the methods used and the timing of the interventions are relevant factors in treatment planning and delivery. This article explores the relationship between anxiety disorders and AUDs, focusing on the prevalence, clinical impact, developmental and maintenance characteristics, and treatment considerations associated with this fairly common comorbidity. The distinctive nature of the relationship between posttraumatic stress disorder (PTSD) and AUDs is discussed separately, in the article by Brady and Back, p. 408 in this journal issue.

Prevalence and Clinical Impact of Comorbid Anxiety and AUDs

Accuracy in prevalence estimates of comorbid anxiety and AUDs is essential for gauging the magnitude of the clinical and social impact of this comorbidity; therefore, data should be carefully selected with attention to sampling methods. Information derived from clinical samples, although enlightening in its own right, produces inflated approximations of the prevalence of comorbidity (Kushner et al. 2008; Regier et al. 1990; Ross 1995). The most frequently offered explanation for the biased estimates from clinic-based samples suggests that individuals with multiple disorders are more likely to be referred for treatment than individuals with a single disorder (Galbaud Du Fort et al. 1993; Kushner et al. 2008). To avoid this bias, epidemiological data drawn from large-scale community samples can provide the most informative figures.

Over the past three decades, multiple population-based studies have surveyed the prevalence of addictive and mental disorders in the United States and abroad, including the following:

- The Epidemiological Catchment Area (ECA) survey (Regier et al. 1990) was based on diagnostic information using the *Diagnostic and Statistical Manual of Mental Disorders, Third Edition* (DSM–III) (American Psychiatric Association [APA] 1980); it was conducted between 1980 and 1984 and collected information from nearly 20,000 respondents ages 18 and older in the United States.

- The National Comorbidity Survey (NCS) (Kessler et al. 1994, 1997), also conducted in the United States, used the DSM–III–R criteria (APA 1987) while sampling 8,098 individuals ages 15 to 54 years.

- Burns and Teesson (2002) published findings on the comorbidity between AUDs and anxiety, depression, and other drug use disorders from the Australian National Survey of Mental Health and Well-Being (NSMH&WB) project. This project was a cross-sectional analysis of 10,461 Australian adults ages 18 and older, with data collected in 1997 using diagnostic criteria from the DSM–IV (APA 1994).

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- The most recent epidemiological study to date, and the largest reviewed here, was the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) (Grant et al. 2004; Hasin et al. 2007). This survey, which was conducted by the National Institute on Alcohol Abuse and Alcoholism in 2001–2002, also applied DSM–IV diagnostic algorithms in a sample of 43,093 adults ages 18 and older.

The respective prevalences of comorbid anxiety disorders and AUDs from each of these epidemiological studies are summarized in table 1. These data show that, across different large-scale studies, at different times, and both in the United States and abroad, anxiety and AUDs co-occur at rates greater than would be expected by chance alone. The odds ratios (ORs) characterizing the comorbidity between an AUD and any anxiety disorder in these studies ranged between 2.1 and 3.3—in other words, the two conditions co-occurred about two to three times as often as would be expected by chance alone.

Three additional trends emerging from community-based samples are noteworthy. First, anxiety disorders are more strongly associated with alcohol dependence than with alcohol abuse (e.g., Hasin et al. 2007; Kessler et al. 1996; Kushner et al. 2008). Analysis of the NESARC data demonstrated that this finding generally was consistent across racial/ethnic groups (Smith et al. 2006). Alternative explanations for these results suggest that either people with anxiety disorders are more likely to become psychologically dependent on alcohol because they use it to self-medicate (e.g., Tran and Smith 2008) or anxiety disorders in these individuals largely are an artifact of alcohol withdrawal (e.g., Schuckit and Hesselbrock 1994).

Second, the magnitude of the relationship between specific anxiety disorders and AUDs varies across the specific combinations. For example, panic disorder typically has a relatively large association with AUDs (odds ratio [OR] = 1.7–4.1 in table 1), whereas obsessive-compulsive disorder has the least consistent and typically weakest relationship with alcohol problems (e.g., Gentil et al. 2009; Kessler et al. 1997; Schuckit et al. 1997; Torres et al. 2006). A classic review in this field (Kushner et al. 1990) indicated even more pronounced differences in the comorbidity rates of specific anxiety disorders among clinic-based samples of patients with alcohol problems. These ranged from rates near community-based rate estimates (e.g., for simple phobia) to rates nine times greater than community estimates (e.g., for social phobia). It is important to note, however, that the influence of treatment seeking and related variables confounds interpretation of these clinic-based estimates.

Third, different comorbidity patterns exist among patient subgroups with different demographic characteristics such as race/ethnicity and gender. For example, in the NESARC, Native Americans had elevated rates both of anxiety disorders and of AUDs over the past 12 months but lower rates of co-occurrence between these disorders compared with other ethnic groups (Smith et al. 2006). Gender differences in anxiety–alcohol comorbidity have been reported across a variety of samples (e.g., Hesselbrock et al. 1985; Kessler et al. 1997; Mangrum et al. 2006; Merikangas et al. 1998), and research in this area also has identified notable clinical differences between men and women. These gender differences are discussed in more detail in the sidebar.

The importance of these prevalence data is underscored by the clinical impact of comorbid anxiety and AUDs. Both types of disorder are associated with substantial societal costs that have been estimated in monetary terms at $184.6 billion per year for AUDs (Harwood 2000) and between $42 and $47 billion for anxiety disorders (DuPont et al. 1996; Greenberg et al. 1999). Kessler and Greenberg (2002) suggested that the costs for anxiety disorders were grossly underestimated and actually exceeded $100 billion per year in the total U.S. population. Furthermore, clinical studies have shown that both anxiety and AUDs can negatively impact the course and treatment outcome for the other condition. For example, anxiety problems have been associated with increased severity and persistence of AUDs, increased risk for relapse following treatment, and increased lifetime service utilization in the context of substance use disorders more generally (Driessen et al. 2001; Falk et al. 2008; Kushner et al. 2005; Johnston et al. 1991; Perkonigg et al. 2006; Sannibale and Hall 2001). Conversely, concurrent AUDs have been associated with greater severity and chronicity of anxiety disorders, and substance use problems can decrease the likelihood of recovery from anxiety disorders (Bruce et al. 2005; Hornig and McNally 1995; Schade et al. 2004). Studies also have demonstrated that alcohol use can increase anxiety (see Kushner et al. 2000), which can result in a positive feedback loop leading to exacerbation of both disorders.

Table 1 Adjusted Odds Ratios of the 12-Month Comorbidity Between Certain Anxiety Disorders and Alcohol Use Disorders Across Epidemiological Samples

	ECA	NCS	NSMH & WB	NESARC
Agoraphobia	2.7	2.6	2.3	3.6
Generalized anxiety disorder	—	4.6	3.3	3.0
Obsessive–compulsive disorder	—	—	2.7	—
Panic disorder	4.1	1.7	3.9	3.5
Simple phobia	2.0	2.2	—	2.3
Social phobia	1.8	2.8	3.2	2.3
Any	**2.1**	**2.6**	**3.3**	**2.7**

NOTES: ECA = Epidemiologic Catchment Area Survey; NCS = National Comorbidity Survey; NSMH & WB = National Survey of Mental Health & Well-being; NESARC = National Epidemiologic Survey on Alcohol and Related Conditions.

Taken together, the epidemiological and clinical literature describing the relationship between anxiety and AUDs shows that this comorbidity is both prevalent and clinically relevant. Therefore, it is important to enhance understanding of this comorbidity. The following sections will review fundamental concepts related to how these disorders co-occur and describe approaches to diagnosing and treating comorbid anxiety and AUDs.

Development of Comorbid Anxiety and AUDs

The question of how anxiety and AUDs coalesce has intrigued investigators and clinicians for decades and still is a subject of debate. Three primary pathways have been proposed:

- The common-factor model that uses a third variable to explain the co-occurrence of anxiety and AUDs;
- The self-medication pathway, which posits that people consume alcohol to cope with anxiety disorders, leading to co-occurring AUDs; and
- The substance-induced pathway, wherein AUDs lead to increased anxiety and vulnerability for co-occurring anxiety disorders.

The Common-Factor Model

The common-factor model of comorbid anxiety and AUDs presumes that no direct causal relationship exists between the two disorders. Instead, so-called third variables are posited to account for their joint presence. The potential relevance of such factors was demonstrated in a 21-year longitudinal study of young people (Goodwin et al. 2004), in which early presence of anxiety disorders seemed to predict the later development of alcohol dependence. However, when the investigators controlled for other variables, such as prior other drug dependence and depression, the presence of anxiety disorders no longer was a significant predictor. The results of this study suggest that the link between anxiety and AUDs was not direct but instead may have been a consequence of those other variables studied. The potential range of common factors can be difficult to estimate, but a review of the literature shows that the most consistently proposed third variables are genetic factors and personality traits such as anxiety sensitivity. Support for the role of genetic factors as a cause for the co-presence of these disorders indirectly has been provided by family and twin studies (e.g., Merikangas et al. 1994, 1996; Tambs et al. 1997). Anxiety sensitivity also has been linked to the incidence of both anxiety and substance use disorders (DeHaas et al. 2001; DeMartini and Carey 2011; Schmidt et al. 2007). Based on findings demonstrating a genetic contribution to anxiety sensitivity (Stein et al. 1999), Stewart and Conrod (2008) proposed a causal sequence wherein genetic factors and anxiety sensitivity operate together to create a genetically based personality that is vulnerable to comorbid anxiety and alcohol use problems. To date, rigorous empirical evaluation of the common-factor model has been limited, and publications directly addressing this topic are sparse. Additional research and exploration of additional third variables therefore is necessary to more clearly appraise their unique and interactive influence on the relationship between these disorders.

The Self-Medication Model

The self-medication explanation for the comorbidity of anxiety and AUDs has received the most attention in the clinical and research literature. This model proposes that people with anxiety disorders attempt to alleviate negative consequences of these conditions (i.e., are negatively reinforced) by drinking alcohol to cope with their symptoms, eventually leading to the later onset of AUDs. This concept, in fact, is shared by several models of alcoholism, including the self-medication (Khantzian 1985; Quitkin et al. 1972), tension reduction (Conger et al. 1999), and stress-response dampening models (Sher 1987; Sher and Levenson 1982). Several lines of evidence provide support for this pathway. When people with comorbid anxiety and AUDs are queried about their drinking, they typically endorse purposeful and targeted drinking to cope with their anxiety. The reported rates of self-medication in clinical samples of people with both types of disorders have ranged from 50 to 97 percent, with the highest rates among people with phobias (Bibb and Chambless 1986; Smail et al. 1984; Thomas et al. 2003; Turner et al. 1986).

It is interesting to note that participants with anxiety disorders in community samples show significantly less robust rates of self-medication than typically found in clinical samples, highlighting the potential selection bias in treatment settings (e.g., Bolton et al. 2006; Menary et al. 2011; Robinson et al. 2009). For example, in the NCS (Bolton et al. 2006) only 21.9 percent of individuals with anxiety disorders in the community endorsed self-medicating with either alcohol or drugs, with the highest rates found among those with generalized anxiety disorder (35.6 percent), panic disorder (23 percent), or social phobia–complex subtype (21.2 percent). In the NESARC, Robinson and colleagues (2009) separately analyzed rates of self-medication with alcohol, drugs, or both among respondents with anxiety disorders. The investigators found that these individuals were most likely to endorse self-medication with alcohol alone and that the highest rates of alcohol-based self-medication were found among respondents with generalized anxiety disorder (18.3 percent), social phobia (16.9 percent), and panic disorder with agoraphobia (15.0 percent). More recently published longitudinal analyses of alcohol-using NESARC participants showed nearly identical rates of self-medication with alcohol among those with anxiety disorders at both Wave 1 (20.3 percent) and Wave 2 (20.8 percent) (Menary et al. 2011). Interestingly, this report also showed that although only 1 in 5 individuals with anxiety disorders reported using alcohol to cope with anxiety, the rate of alcohol dependence in this

subgroup (34.5 percent) was almost four times higher than the comparison rates found among respondents with anxiety who did not report self-medication (9.3 percent) and almost seven times higher than among respondents with no anxiety diagnosis (5.1 percent). Moreover, endorsement of alcohol-based self-medication at Wave 1 increased the risk of developing new alcohol dependence at Wave 2 nearly four-fold (OR = 3.77). These epidemiological findings reveal that although only a minority of people with anxiety disorders uses alcohol to self-medicate, the risk for co-occurring alcohol dependence is concentrated among this subgroup.

Additional epidemiological support for this causal pathway comes from analyses of order of onset as well as from analyses of whether the anxiety disorders are considered independent or substance induced. Data showing that anxiety disorders predate AUDs and that anxiety disorders are independent (i.e., not merely a consequence) of AUDs are essential prerequisites for the self-medication model. Consistent with this causal explanation of comorbidity, timelines gathered in community surveys show that anxiety disorders often predate the development of alcohol dependence. For example, Kushner and colleagues (2008) reviewed findings from several large-scale studies and calculated that three of four individuals with comorbid disorders developed the anxiety disorders first. The classification of anxiety disorders as independent versus substance-induced requires that one of two conditions is met: (1) the anxiety disorder must precede the AUD and (2) the anxiety disorder persists outside the direct influence of alcohol use. Because alcohol withdrawal can mimic and/or exacerbate anxiety problems, an extended period of abstinence (e.g., 4 weeks) from alcohol is necessary for a disorder to be considered a stand-alone, independent diagnosis. Using these criteria with the NESARC sample, which strictly followed DSM–IV rules for differential diagnosis, only 0.2 percent of anxiety disorders were not classified as independent (Grant et al. 2004). Likewise, low rates of substance-induced anxiety disorders (0.3 percent) were found in a community sample of 1,095 Australian women (Williams et al. 2010), based on DSM–IV–TR criteria (APA 2000).

Taken together, all of these findings provide compelling support for the self-medication explanation for co-occurring anxiety and AUDs. However, these lines of evidence are associated with several limitations. For example, the analyses often rely on retrospective self-reported data. Findings derived from clinical samples also can inflate prevalence estimates of self-medication, especially if alcohol-dependent individuals are evaluated during acute alcohol withdrawal. Finally, it is notable that laboratory studies examining alcohol's anxiety-reducing (i.e., anxiolytic) effects have produced mixed findings (see Tran and Smith 2008). One possible explanation for the incongruence between laboratory and self-report survey data is that a person's expectations about alcohol's effects can motivate drinking independent of alcohol's actual physiological effects (e.g., Abrams and Kushner 2004). Nevertheless, laboratory-based investigations of whether (and how) alcohol actually reduces anxiety are essential to critically evaluate the self-medication hypothesis. The current state of the science on this point is inconclusive, and additional research is necessary before any firm conclusions regarding this pathway can be drawn.

The Substance-Induced Anxiety Model

The third causal explanation for comorbid anxiety and AUDs asserts that anxiety largely is a consequence of heavy, prolonged alcohol consumption. Alcoholism leads to a range of biopsychosocial problems, and anxiety can result from alcohol-related disturbances in each of these domains. The course of alcohol dependence is fraught with repeated intermittent episodes of excessive and frequent consumption and withdrawal, which can result in changes in the nervous systems that produce and/or worsen anxiety. For example, whereas acute alcohol intake has anxiolytic effect by increasing the activity of the brain chemical (i.e., neurotransmitter) γ-aminobutyric acid (GABA), chronic alcohol dependence results in an overall GABA deficiency that offsets the effects of acute consumption and may induce anxiety. Withdrawal periods also can induce changes in the brain, which can include excessive activity (i.e., hyperexcitability) of certain brain systems (i.e., the limbic system and the norepinephrine system) (Kushner et al. 2000; Marshall 1997), both of which are involved in the production of panic attacks (Graeff and Del-Ben 2008; Marshall 1997). Across time, repeated withdrawal episodes can result in a progressive neural adaptation (i.e., a process known as kindling) that makes the drinker more susceptible to anxiety and exacerbates stress-induced negative affect when alcohol intake stops (Breese et al. 2005). Not surprisingly, clinical studies show that people with alcoholism who are recently abstinent characteristically report increased feelings of anxiety, panic, and phobic-like behaviors in the short term, and symptoms of autonomic activity (i.e., sympathetic activation, such as increased heart rate and faster/shallower breathing) and persistent anxiety across protracted withdrawal (see Schuckit and Hesselbrock 1994).

The psychosocial impact of alcoholism also has been implicated in the genesis of anxiety. Social consequences of habitual excessive drinking are common and include pervasive and cumulative problems in vital areas of life, such as employment, interpersonal relationships, and finances (Klingemann 2001; Klingemann and Gmel 2001). In fact, such difficulties in everyday living are so intertwined with heavy use that they are reflected in the DSM–IV criteria for AUDs (APA 2000). The interaction between pathologic alcohol use and enhanced life stress can lead to anxiety in at least two ways. First, the consistent presence of social disturbances may activate and intensify anxiety symptoms among these already vulnerable individuals. Second, alcohol use in the presence of stress stimuli may interfere with extinction-based learning necessary for normal adaptation to stressors. Thus, hazardous drinking can lead to anxiety through a noxious combination of greater levels of life stress coupled with relatively poor coping skills.

Gender Differences in Comorbid Anxiety and Alcohol Use Disorders

Numerous studies have attempted to evaluate possible gender differences in the frequency of comorbid anxiety disorders and alcohol use disorders (AUDs). Population surveys consistently show that anxiety disorders are more common among women, whereas AUDs are more common among men (e.g., Hasin et al. 2007; Kessler et al. 1997; Lewis et al. 1996). To account for these base-rate differences when estimating gender-specific comorbidity rates for anxiety disorders and AUDs in the National Comorbidity Survey, Kessler and colleagues (1997) used adjusted odds ratios (ORs). These analyses found that among alcohol-dependent men in the sample, 35.8 percent (OR = 2.22) had a co-occurring anxiety disorder, compared with 60.7 percent (OR = 3.08) among alcohol-dependent women. Moreover, not only did women in the study have an increased likelihood of independent anxiety disorders compared with men, but prior anxiety disorders also were more strongly predictive of later alcohol dependence among the women. Furthermore, a multisite trial in Germany demonstrated that anxiety disorders had a substantial influence on the course and severity of alcoholism in women (Schneider et al. 2001). Thus, in this treatment-seeking sample women who had an anxiety disorder reported an accelerated temporal sequence of alcoholism, including earlier onset of first drink, regular drinking, and incidence of alcohol withdrawal than women with no anxiety disorder.

One potential explanation for these findings is that the reasons for using alcohol may differ by gender. For example, women may be more prone than men to self-medicate for mood problems with substances such as alcohol (Brady and Randall 1999). Furthermore, empirical inspection of gender differences in stress-related drinking has shown that women report higher levels of stress and have a stronger link between stress and drinking (Rice and Van Arsdale 2010; Timko et al. 2005). Together, these results suggest that women may be more likely to rely on alcohol to manage anxiety.

Anxiety disorders also may have a particularly detrimental impact on alcohol-focused treatment for women. This has been demonstrated in a series of studies evaluating the intersection of gender, social anxiety disorder, and treatment modality. Early work in this area from the Project MATCH sample revealed an intriguing interaction (Thevos et al. 2000). Specifically, whereas socially phobic men benefitted equally well from either cognitive–behavioral therapy (CBT) or 12-step facilitation (TSF), women with social phobia fared less well if they were assigned to TSF. To shed light on the potential role of social anxiety in addiction treatment, Book and colleagues (2009) compared participants in an intensive outpatient program with high and low social anxiety on attitudes toward treatment activities. Members of the group with high social anxiety, who predominantly were female (71 percent), overall showed less treatment participation than did members of the comparison group. For example, they were less likely to speak up in group therapy, attend a 12-step meeting, or seek sponsorship within a 12-step group. A recent secondary analysis of alcoholics who were assigned to TSF in Project MATCH yielded findings consistent with and complementary to these observations, demonstrating that women with comorbid social phobia were 1.5 times more likely to relapse than noncomorbid women (Tonigan et al. 2010). In contrast, no differences in relapse rates were found among the men with or without social phobia in the study. Interestingly, socially phobic women were less likely than women without social phobia to obtain an Alcoholics Anonymous sponsor, which may help explain the poor outcomes for TSF among this subgroup.

Taken together, the findings reviewed here provide some instructive information on gender differences in the comorbidity of anxiety and AUDs. Thus, women are more likely than men to have both disorders, and the presence of anxiety disorders may exacerbate the course and severity of alcohol problems in women. Furthermore, treatment for women with this comorbidity may be especially complex, both because they are likely to use alcohol to self-medicate for stress and because women with social phobia may be reluctant to participate in treatment (e.g., Alcoholics Anonymous) that could otherwise be effective. These factors spotlight the importance of probing for anxiety disorders in women entering alcohol treatment and reinforce the need to remain sensitive to the different ways that gender can influence the process and outcomes of therapy. ■

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Evidence for the substance-induced hypothesis comes from multiple sources. A central prediction of this causal model is that abstinence from alcohol should be followed closely by a conspicuous decrement in anxiety symptoms. Data from a study of 53 patients who participated in alcohol treatment at a residential substance abuse program were consistent with this prediction (Kushner et al. 2005). Thus, among those 23 patients who had an anxiety disorder at baseline and remained abstinent after approximately 120 days, 61 percent no longer met criteria for an anxiety disorder at follow-up. Another study with 171 male veterans demonstrated that self-reported measures of temporary anxiety (i.e., state anxiety) decreased rapidly during inpatient alcohol treatment (Brown et al. 1991). It was furthermore noteworthy that scores on a measure of the participants' overall anxiety levels (i.e., trait anxiety) also changed significantly at 3-month follow-up. This latter finding suggests that state anxiety that occurs during early abstinence can lead respondents to consider their increased anxiety levels as more chronic than they actually are. Therefore, retrospective self-reports collected at baseline should be interpreted with caution.

Additional evidence for the substance-induced pathway comes from prospective studies demonstrating that the presence of alcohol dependence predicts the later development of anxiety disorders. For example, in a sample of college students followed for 7 years, anxiety disorders increased fourfold among those diagnosed as alcohol dependent at either year 1 or year 4 of the study period (Kushner et al. 1999). A final line of support is found in differential comorbidity rates among samples of anxiety and alcohol patients. In a seminal review, Schuckit and Hesselbrock (1994) noted that the frequency of alcoholism among anxiety patients was not markedly higher than in the general population, contrary to what would be predicted by the self-medication hypothesis. In contrast, some studies have found greatly elevated rates of anxiety disorders in samples of individuals with alcohol problems (e.g., Kushner et al. 1990).

Similar to the common-factor and self-medication hypotheses, the literature underpinning the substance-induced pathway to comorbid anxiety and AUDs is convincing but cannot account for the findings consistent with the other causal models. It also is important to note that reliance on timeframes, although useful, could mask an independent course of anxiety symptoms among individuals who also have an AUD. For example, it is possible that an anxiety disorder which appears at a time when the person is experiencing alcohol-related problems may have an etiology separate from alcohol use. Likewise, a reduction in anxiety symptoms following alcohol treatment, which often is interpreted as an indication that the anxiety symptoms were a consequence of alcohol use, could also be explained by anxiolytic therapy and/or the natural course of anxiety independent of any effects related to abstinence.

Compared side by side, these proposed causal models provide competing explanations for the joint development of anxiety disorders and AUDs. It is apparent that the collective findings in this area do not unequivocally point to one pathway or exclude another. It is unclear whether this is a result of a failure of the aforementioned theoretical models or of the methods used to test the pathways or if it simply reflects the complexity inherent within this comorbidity. In fact, the support for multiple causal models may reflect that etiological differences exist among individuals who share this comorbidity, based on which disorder or predisposing variable was initially present. The continued viability of all these competing hypotheses suggests that further and more advanced research attention is essential to disentangle the predisposing factors, primary variables, sequencing, and early course involved with these co-occurring disorders.

Mutual Maintenance of Anxiety and AUDs

Once comorbidity between anxiety disorders and AUDs has been established, the two disorders may influence and maintain each other in ways that are independent of the developmental pathway. In other words, the processes involved in the initiation and the maintenance of comorbidity may differ in meaningful ways. One hypothesis emerging from the comorbidity literature is that anxiety and AUDs become intertwined in a reciprocal, perpetuating cycle. This positive feedback loop often is characterized as a feed-forward or mutual-maintenance pattern. Stewart and Conrod (2008) dubbed this progressive sequence the "vicious cycle of comorbidity" in which biopsychosocial outcomes of one disorder (e.g., anxiety) serve to maintain or even worsen the other disorder (e.g., alcoholism), whose respective outcomes, in turn, further maintain or exacerbate the first disorder, and so on. For example, a person who copes with anxiety by self-medicating with increasing amounts of alcohol likely will experience greater alcohol-related consequences (e.g., poor job performance, interpersonal problems, and anxiety induction from alcohol withdrawal), thus exacerbating the initial anxiety and leading to further drinking, which in turn sustains and/or amplifies the cycle.

Empirical support for this mutual-maintenance model comes from various sources, which in many ways reflects a synthesis of data supporting the three developmental pathways. Taken together, the sets of supportive findings suggest that (1) anxiety disorders can increase the severity, persistence, and poor treatment response of comorbid AUDs and (2) AUDs can increase the severity, persistence, and poor treatment response of comorbid anxiety disorders. Evidence that comorbid anxiety disorders can worsen and perpetuate AUDs and impair alcohol treatment response includes the following findings:

- People with social anxiety disorder endorsed greater alcohol dependence severity and had more dependence symptoms than alcoholics without social phobia (Thomas et al. 1999).

- The presence of social anxiety disorder and generalized anxiety disorder predicted increased long-term mental distress among treatment-seeking, substance-dependent patients (Bakken et al. 2007).

- Alcoholic inpatients with anxiety disorders had increased severity of alcohol withdrawal (Johnston et al. 1991).

- Comorbid panic disorder with agoraphobia and generalized anxiety disorder were related to increased risk of persistent alcohol dependence (Falk et al. 2008).

- Symptoms of generalized anxiety disorder and social anxiety disorder can interfere with substance use treatment (Book et al. 2009, Smith and Book 2010).

- Anxiety disorders are associated with elevated risk for relapse following alcohol treatment (e.g., Driessen et al. 2001; Kushner et al. 2005).

Similarly, other studies reported a negative impact of comorbid AUDs on the course of anxiety disorders, consistent with the mutual maintenance hypothesis, as follows:

- AUDs were related to increased psychiatric severity among individuals who were diagnosed with phobic disorders (Schade et al. 2004).

- People with panic disorder who also had a substance use disorder were significantly more likely to report attempted suicide (Hornig and McNally 1995).

- Repeated withdrawals from alcohol can produce neurobiological changes that sensitize anxiety (Breese et al. 2005).

- Substance use disorders were associated with chronicity of generalized anxiety disorder (Bruce et al. 2005).

- Substance use disorders predicted worse outcomes following treatment for patients with panic disorder with agoraphobia, generalized anxiety disorder, and social anxiety disorder (Bruce et al. 2005).

Collectively, these independent findings are consistent with the mutual-maintenance model of comorbid anxiety and AUDs. However, although it may be reasonable to infer that the pattern of results demonstrates the heuristic utility of this model as a way to synthesize outcomes from various studies in this research area, the conclusion that a discontinuity between developmental and maintenance phases of this comorbidity exists remains speculative. Furthermore, to date no studies have empirically tested these dynamic and interactive factors in a longitudinal model. Thus, the status of the science underpinning the mutual maintenance hypothesis at this time only yields indirect agreement.

Diagnostic and Treatment Considerations for Comorbid Anxiety and AUDs

The developmental and maintenance factors associated with comorbid anxiety and AUDs show that the pairing of these two types of disorders is heterogeneous, interactive, and potentially progressive. Treatment approaches for comorbid patients correspondingly require comprehensive assessment and thoughtful planning. One paramount concern is the establishment of the correct diagnosis and exclusion of other diagnoses, especially because of the inherent difficulty in discerning whether anxiety present at the initial assessment is substance-induced or the sign of an independent anxiety disorder. As indicated earlier, reliance on self-report data can impair the accuracy of diagnoses, especially in the presence of recall bias that can be expected when a person is acutely anxious (e.g., Brown et al. 1991). Careful assessment therefore entails gathering a thorough and detailed retrospective timeline, interviewing collateral informants, reviewing the patient's medical record and any available laboratory data, and observing symptoms over a sustained period of abstinence (Anthenelli 1997; Watkins et al. 2005). The exact duration of abstinence necessary to establish an independent anxiety disorder varies across disorders. For example, anxiety disorders whose cardinal symptoms are consistent with anxiety induced by alcohol withdrawal (e.g., panic disorder and generalized anxiety disorder) require longer periods of abstinence for a diagnosis than anxiety disorders with less symptom overlap (e.g., obsessive-compulsive disorder). Thus, a prudent diagnostician will wait several weeks to determine the likely source of symptoms that also frequently occur during withdrawal, such as panic or free-floating worry. Conversely, certain types of anxiety (e.g., social anxiety) typically predate alcohol use problems, and the presence of these symptoms therefore is less likely to be an artifact of alcohol withdrawal. A more comprehensive diagnostic algorithm for differential diagnosis is provided by Anthenelli (1997). A realistic limitation of the diagnostic process is that some individuals may not be able to sustain abstinence for a period long enough to clarify whether the constellation of anxiety symptoms represents a substance-induced syndrome or an independent anxiety disorder. In such cases, a prospective functional analysis may be used to identify the antecedents and consequences of both anxiety and alcohol use (Wyman and Castle 2006).

Perhaps most importantly, once the complete assessment data have been gathered through all the available strategies, the full spectrum of information should be integrated and considered as a whole to yield the most accurate diagnosis. To select an appropriate treatment approach using these differential diagnosis methods it also is crucial to consider that substance-induced mood and anxiety disorders can negatively impact treatment and increase overall clinical severity (Grant et al. 2004). Consequently, when it has been determined that an anxiety disorder likely is substance induced it may not be the best approach to simply treat the AUD

alone and wait for the subsequent remission of the anxiety disorder.

When a diagnosis has been established, the treatment provider also needs to take into consideration the unique factors associated with this comorbidity when selecting the appropriate treatment protocol. As discussed below, a variety of pharmacotherapy and psychotherapy approaches are available to address anxiety and AUDs. Each modality has proven to be efficacious for these problems in isolation, and several evidence-based treatment alternatives for each disorder are available (see table 2). However, it sometimes may be necessary to modify these treatment approaches for comorbid individuals because even strategies considered the gold standard for one disorder potentially can have a negative impact on individuals with the other disorder (e.g., Jenson et al. 1990; Larson et al. 1992; Randall et al. 2001; Thevos et al. 2000; Tonigan et al. 2010).

Pharmacotherapy for Anxiety Disorders

Medication-based treatments for anxiety include an assortment of agents from several classes of medication, including benzodiazepines, tricyclic antidepressant drugs (TCAs), monoamine oxidase inhibitors (MAO-Is), and serotonergic-based medications (e.g., selective serotonin reuptake inhibitors [SSRIs], serotonin-norepinephrine reuptake inhibitors [SNRIs], and the 5-HT_{1a} partial agonist buspirone). The efficacy of these drugs for anxiety treatment has been established firmly in well-controlled, randomized clinical trials. However, it is important to note that these studies typically exclude people with AUDs—a requisite standard practice to enhance the internal validity of efficacy studies. This exclusion means, however, that treatment providers must use clinical judgment when prescribing these medications to comorbid patients.

Benzodiazepines. Benzodiazepines can be very safe and effective agents for the short-term management of anxiety disorders. These medications are well-tolerated and have few medical scenarios in which they must not be used (i.e., few contraindications), although patients with pulmonary disorders may be sensitive to the depressant effects of these agents on the central nervous system. Because these medications are absorbed into the body fairly rapidly, patients can experience relatively fast-acting anxiolytic effects from a single oral dose. When multiple doses of benzodiazepines are used to manage anxiety, the duration of action will vary based on the medication's accumulation in the body, which is determined by pharmacokinetic characteristics such as elimination half-life and clearance. According to their elimination half-life, benzodiazepines can be classified into three groups (Greenblatt et al. 1981):

- Ultra–short-acting agents with a half-life of less than 5 hours (e.g., triazolam, midazolam);
- Intermediate/short-acting agents with a half-life of 5 to 24 hours (e.g., alprazolam, lorazepam); and

Table 2 U.S. Food and Drug Administration (FDA)-Approved and Evidence-Based Treatments for Anxiety and Alcohol Use Disorders[a,b,c]

	Generalized Anxiety Disorder	Obsessive–Compulsive Disorder	Panic Disorder	Social Anxiety Disorder	Alcohol Use Disorders
Pharmacotherapy	Buspirone Duloxetine Escitalopram Paroxetine Venlafaxine	Clomipramine Fluoxetine Fluvoxamine Paroxetine Sertraline	Alprazolam Clonazepam Fluoxetine Paroxetine Sertraline Venlafaxine	Fluvoxamine Paroxetine Sertraline Venlafaxine	Acamprosate Disulfiram Naltrexone Topiramate
Psychotherapy	Cognitive and behavioral therapies	Cognitive therapy; exposure and response prevention	Applied relaxation; cognitive and behavioral therapies; psychoanalytic therapy	Cognitive and behavioral therapies	Behavioral couples therapy; brief intervention; cognitive and behavioral therapies; community reinforcement approach; motivational interviewing; relapse prevention therapy; social skills training; 12-step facilitation

NOTES: [a]Pharmacotherapies listed are current FDA-approved indications, with the exception of topiramate, which was added based on results of a critical review of published literature (Shinn and Greenfield 2010).

[b]Psychotherapies for anxiety disorders are those with moderate or strong research support, as listed by the American Psychological Association, Division 12 (Society of Clinical Psychology). Note that psychoanalytic therapy also was listed as "controversial."

[c]Psychotherapies for alcohol use disorders are those with support in a majority of reviews, as identified via the systematic analysis of Miller and colleagues (2005). Twelve-step facilitation was added based on published empirical support (e.g., Project MATCH Research Group 1997, 1998; McKellar et al. 2003; Tonigan 2009).

- Long-acting agents with a half-life of more than 24 hours (e.g., clonazepam, diazepam).

Because benzodiazepines are effective in managing anxiety in the short-term by producing a relatively fast-acting anxiolytic effect, their use as a front-line choice for individuals with comorbid anxiety and AUDs has been controversial (e.g., Brady and Verduin 2005; Ciraulo and Nace 2000; Posternak and Mueller 2001; Sattar and Bhatia 2003). For example, when discussing the relative benefits and risks associated with these medications, Longo and Johnson (2000) elegantly stated that, "Their greatest asset is also their greatest liability: drugs that work immediately tend to be addictive." (p. 2127). Perhaps not surprisingly, the addiction potential of benzodiazepines is highest for the shorter-acting compounds as well as for those agents (e.g., alprazolam) that quickly cross the blood–brain barrier (Longo 1998; Martinez-Cano et al. 1996; Roache and Meisch 1995). People who have a history of AUDs seem to be more sensitive to the rewarding properties of these agents, and benzodiazepines have a positive effect on mood in alcoholics that is not seen in nonalcoholics (Ciraulo et al. 1988, 1997). Additional findings from clinical samples alternately have shown that abuse of sedatives (mostly benzodiazepines) among patients with anxiety was associated with concurrent alcoholism (Van Valkenberg 1999) and that alcohol-dependent patients (who also engaged in other drug abuse) were more likely to abuse benzodiazepines if they also reported panic attacks (Jenson et al. 1990). These factors together suggest an enhanced risk of benzodiazepine misuse among people with co-occurring anxiety and AUDs. Because effective and safe alternatives to manage anxiety are available (e.g., SSRIs and buspirone), it has been suggested that because of these risks, benzodiazepines generally should be avoided when treating patients with alcoholism, especially those with severe alcohol dependence or polydrug abuse (e.g., Longo and Bohn 2001; Sellers et al. 1993).

Some clinical scholars have questioned this viewpoint, however, and proposed that withholding access to potentially beneficial medications is unethical, especially when some studies suggest that a history of substance abuse is not a major risk factor for benzodiazepine abuse (e.g., Posternak and Mueller 2001; Sattar and Bhatia 2003). For example, in prospective studies Mueller and colleagues (1996, 2005) found little evidence that these anxiolytics were associated with poor outcomes among those with both anxiety and AUDs.[1] Specifically, they found that (1) a history of AUDs was not a strong predictor of benzodiazepine use among participants with anxiety disorders, (2) use of these anxiolytics did not increase across time among comorbid participants, and (3) benzodiazepine use was not associated with the later occurrence of any new AUDs. These findings suggest that although the risk for benzodiazepine abuse should be an important consideration when prescribing within this patient subpopulation, these agents safely may be used in cases where they are clinically indicated (e.g., when other treatments are ineffective or potentially harmful). When benzodiazepines are used, patients should be monitored closely and only limited amounts of the agents should be prescribed. A useful algorithm to guide treatment decisions for people with co-occurring anxiety and AUDs was provided by Sattar and Bhatia (2003).

MAO-Is and TCAs. Caution also is suggested with the use of MAO-Is and TCAs for comorbid individuals. Although MAO-Is are quite effective in reducing anxiety, patients taking these agents may suffer a sudden severe increase in blood pressure (i.e., hypertensive crisis) after consuming certain foods and beverages that contain the amino acid tyramine (McCabe-Sellers et al. 2006), resulting in dietary restrictions for MAO-I users. These beverages include certain beers (e.g., imported beers, beer on tap, and nonalcoholic or reduced-alcohol beers), red wines, sherry, liqueurs, and vermouth, which is critical to know when treating people who also have alcohol problems. TCAs also should be used with caution among people with co-occurring AUDs and be prescribed only after other treatments have been ruled out because these medications can have an enhanced adverse-effect profile in this population. Moreover, the impaired judgment and impulsivity among persons with co-occurring alcohol use problems may increase the risks of taking an overdose of the medications that can result in toxicity and, potentially, suicidality. Finally, TCAs may react with alcohol in the brain to cause respiratory depression (Bakker et al. 2002).

Serotonergic-Based Medications. Medications that target a brain signaling system which uses the neurotransmitter serotonin and its receptors perhaps are the safest and most widely used agents to treat anxiety disorders. These agents include the SSRIs, SNRIs, and the serotonin partial agonist buspirone. At present, SSRIs (e.g., fluoxetine, paroxetine, and sertraline) and SNRIs (e.g., venlafaxine and duloxetine) generally are used as first-line treatment in this area because they consistently demonstrate anxiolytic efficacy, including in patients with comorbid AUDs. For example, a direct examination of the efficacy of paroxetine in this population showed that it reduced social anxiety relative to placebo (Book et al. 2008), providing an empirical foundation for its use in these patients. Moreover, serotonergic agents have favorable properties, such as being well-tolerated and having virtually no abuse potential. Another welcome characteristic of SSRIs in patients with comorbid AUDs is that, in contrast to TCAs, they do not interact with alcohol to increase the risk of respiratory depression (Bakker et al. 2002). With both SSRIs and SNRIs it is advisable to inform patients that it may take about 1 to 2 weeks before these medications show full effectiveness. In addition, there is a risk of an electrolyte imbalance involving decreased sodium concentrations in the blood (i.e., hyponatremia), which can reduce the seizure threshold. This may be especially relevant during alcohol withdrawal, and clinicians

[1] For these analyses, anxiolytic use was standardized by converting all reported benzodiazepine use into chlordiazepoxide equivalents.

therefore should monitor fluid intake and sodium levels during these periods.

Buspirone specifically is approved by the U.S. Food and Drug Adminstration (FDA) for the management of generalized anxiety disorder. Similar to other serotonergic-based medications, buspirone has a desirable safety profile but a relatively delayed onset of anxiolytic effects. Previous trials have evaluated buspirone among patients with comorbid generalized anxiety disorder (or anxiety symptoms) and AUDs. The majority of these studies have found reductions in both anxiety and alcohol outcome measures, including cravings (Bruno 1989; Tollefson et al. 1991) and drinking measures (Kranzler et al. 1994). However, one study found no effect of buspirone on either anxiety or alcohol use (Malcolm et al. 1992).

Psychotherapy for Anxiety Disorders

The psychosocial treatment of choice for anxiety disorders is established more clearly, with a family of strategies known collectively as cognitive–behavioral therapies (CBTs) considered the practice standard for people with anxiety problems. Meta-analyses of CBTs for anxiety disorders have shown strong evidence for their efficacy (Hofmann and Smits 2008; Olatunji et al. 2010). The CBT approaches to anxiety consist of two overarching strategies (Gerardi et al. 2009):

- Exposure to feared stimuli; and
- Anxiety management techniques, such as cognitive restructuring, applied relaxation, and coping skills training.

Exposure to feared stimuli is a powerful and active treatment ingredient that is recommended across the spectrum of anxiety disorders. Although the specific cues differ, application of exposure for each disorder generally involves repeated presentation of feared stimuli until the patient has become used to them (i.e., habituation is reached), resulting in extinction of the fear response. The technique largely is effective because when clients who typically avoid and/or escape from situations that lead to anxiety are exposed to these situations for prolonged periods, they encounter corrective information that previously was unavailable.

It nevertheless is appropriate to recognize that anxious clients who also have comorbid AUDs may be vulnerable to negative outcomes from this treatment method. For many of these individuals, drinking itself is a means of limiting exposure to feared situations and thus can be conceptualized as an avoidance strategy that has prevented the development of alternative ways of coping. To borrow terminology from the respective CBT approaches for anxiety and AUDs, the link between anxiety and drinking for comorbid clients may mean that in effect an exposure exercise also becomes a high-risk situation for alcohol relapse. Relapse to avoidance strategies (e.g., reliance on checking behaviors in obsessive-compulsive disorder or avoidance of social gatherings in social anxiety disorder) in the process of exposure is undesirable even for people suffering only from an anxiety disorder. For people who use alcohol as an avoidance strategy, however, a relapse can be especially costly. Moreover, use of alcohol to avoid anxiety during an exposure exercise also can interfere with the corrective learning process required for extinction of the anxiety response. Indeed, research findings suggest that exposure-based methods can lead to worse alcohol outcomes for comorbid individuals and that alcohol use during exposure may hinder extinction (e.g., Randall et al. 2001). Therefore, as a matter of course clinicians carefully should appraise this risk when weighing the potential costs and benefits of this CBT component for people with comorbid anxiety and AUDs. To address this issue, treatment providers may try to enhance the clients' preparedness by focusing on relapse prevention skills prior to engaging in exposure exercises, especially those activities requiring the direct confrontation of feared stimuli (e.g., during prolonged in vivo exposure therapy). Also, therapists can manage the intensity of exposure therapy by introducing clients to feared stimuli using intermediate or purposefully protracted techniques, such as imaginal exposure (e.g., retelling traumatic memories or imagining feared situations or objects) and graded exposure (e.g., step-by-step exposure to stimuli based on a fear hierarchy). Such alterations can allow therapists to calibrate the dose of exposure that optimizes efficacy for extinction of the target fear response while minimizing the risk for relapse to drinking.

Pharmacotherapy for AUDs

There currently are three medications that have received FDA approval for the maintenance treatment of alcoholism:

- Disulfiram, an agent that interferes with ethanol metabolism and induces an adverse reaction (e.g., flushing, nausea, and rapid heartbeat) when a person consumes alcohol;
- Naltrexone, an antagonist acting at receptors for signaling molecules, endogenous opioids, that can interfere with the rewarding properties of alcohol and reduce craving; it is available in both short- and long-acting formulations; and
- Acamprosate, an agent that acts on the GABA system, counteracting alcohol's effects on this system.

Another drug receiving strong empirical support for the treatment of alcohol dependence is the anticonvulsant topiramate (Shinn and Greenfield 2010), although its use has not yet been approved by the FDA. Topiramate reduces the release of the neurotransmitter dopamine in the midbrain, which may reduce the rewarding experiences associated with alcohol intake. However, it is unclear at this time whether adverse effects may hinder its utility as an adjunctive alcoholism treatment, because a recent review of 26 published studies found that its use was associated with high rates of numbness of tingling on the skin (i.e., paresthesia) and cog-

nitive symptoms (Shinn and Greenfield 2010). Additional research in randomized trials evaluating topiramate alongside more established medications, such as disulfiram and naltrexone, may shed light on its relative efficacy and tolerability.

Administration of medications for AUDs may require some adjustment for individuals who also have anxiety disorders compared with the regimen for alcoholics without this comorbidity. As with other conditions, randomized, controlled trials of pharmacotherapies to determine efficacy for alcoholism treatment often exclude individuals with comorbid conditions. Therefore, the impact of these agents on co-occurring psychiatric symptoms has not been explored fully. Some early clinical reports have suggested that disulfiram may precipitate psychiatric problems such as anxiety (e.g., Larson et al. 1992; Snyder and Keeler 1981). However, more thorough analyses suggest that these reports may not reflect current conceptualizations of psychiatric symptoms and dosing schedules (see Petrakis et al. 2002). Another concern is that people with a comorbid anxiety disorder may be taking additional medications to treat their concurrent condition and clinicians therefore must remain vigilant of potential interactions and dosage scheduling associated with multiple drugs. In one study in this underexamined area, data from 254 individuals treated for alcohol dependence on an outpatient basis and with other comorbid psychiatric disorders (including generalized anxiety disorder and panic disorder) showed that both naltrexone and disulfiram were effective and well-tolerated in this population (Petrakis et al. 2005). And in a secondary analysis of a randomized, double-blind trial Krystal and colleagues (2008) reported that among patients receiving antidepressants for mood/anxiety disorders, those receiving naltrexone showed greater reductions in drinking than did those receiving a placebo. Nevertheless, at least in the case of disulfiram, the combination of some historical clinical reports of anxiety induction and overall limited data suggests that clinicians administering this medication should closely monitor comorbid patients for any signs of increased anxiety.

Psychotherapy for AUDs

Psychosocial approaches to treating AUDs have evolved markedly over the past few decades. The historical roots of this treatment modality largely can be traced back to the development of Alcoholics Anonymous (AA) in Akron, Ohio, in the 1930s and 1940s. It has been estimated that nearly 1 in every 10 Americans has attended at least one AA meeting, and it is "the most frequently consulted source of help for drinking problems" (McCrady and Miller 1993, p. 3). Anecdotal and research evidence suggests that AA participation can promote positive alcohol-related outcomes (e.g., Project MATCH Research Group 1997, 1998; McKellar et al. 2003; Tonigan 2009), lending some credence to the oft-quoted adage, "It works if you work it." Several alternative treatments have been developed since and have received favorable empirical support. In a systematic analysis of 10 published reviews of evidence-based psychosocial therapies for AUDs, a majority of the reviews found support for CBTs, the community reinforcement approach (CRA), motivational interviewing (MI), relapse prevention therapy (RPT), social skills training (SST), behavioral marital (couples) therapy (BCT), and brief intervention (BI) (Miller et al. 2005).

Similar to the other modalities described here, administration of these psychosocial treatment strategies for alcohol problems can be less straightforward with individuals who have comorbid anxiety and AUDs. Clients with social anxiety disorder, for example, may have difficulties with several elements of standard psychosocial approaches for alcoholism. Many treatment programs, as well as AA, heavily rely on the mutual help in group settings. Individuals with social anxiety, however, may be reluctant to attend group therapy or AA meetings or may avoid meaningful participation should they make the effort to attend. Other activities that are integral to participation in AA, such as sharing one's story (i.e., public speaking), obtaining a sponsor, and becoming a sponsor (i.e., initiating social contact) also can be impaired among socially anxious alcoholics. Consistent with these hypotheses, research has shown that at least among women with social phobia, participation in AA may be less appealing and less effective than other approaches (Thevos et al. 2000; Tonigan et al. 2010). Two critical elements of CBT skills training also may be especially difficult for patients with comorbid social anxiety disorder, including drink-refusal skills and enhancing one's social support network. In essence, clients need to show assertiveness to engage in the parallel process of ending relationships and habits that are high risk for relapse while also proactively initiating contacts and improving relationships with others who will support recovery efforts. Therefore, clients in CBT who also have social anxiety may particularly benefit from additional practice with assertiveness, perhaps including adjunctive social-skills training.

Standard delivery of RPT also may require a pivotal adaptation when applied to clients with comorbid anxiety disorders. RPT emphasizes the importance of identifying an individual's unique risk factors (e.g., high-risk situations) for relapse and incorporates skill-development techniques to help reduce the likelihood of lapses and to manage them should they occur. It is widely understood in the RPT literature that negative emotional states are particularly perilous to recovery efforts. A classic analysis of over 300 relapse episodes implicated negative emotional states, conflict with others, and social pressure to use in nearly 75 percent of the relapses studied (Cummings et al. 1980). To prevent relapse resulting from negative emotional states such as anxiety, RPT recommends stimulus control (i.e., avoidance of high-risk situations, with escape as the next best option) as a first-order strategy (Parks et al. 2004). Relaxation training also is recommended because it "can help clients reduce their anxiety and tension when facing stressful situations and minimize their typical levels of motor and psychological tension" (Parks et al. 2004, p. 78). For clients with both alcohol use and anxiety disorders, however, a potential limitation of RPT is that avoidance of anxiety-inducing situations can preclude any potential anxiety reduction via exposure therapy, which in contrast requires clients to directly confront such situations. In short,

for comorbid individuals, the avoidance and escape-oriented coping strategies taught within RPT could perpetuate anxiety problems. Skillful use of RPT with this subgroup of alcoholics therefore may require adjustments to complement the goals of exposure therapy for anxiety (e.g., allowing prolonged in vivo exposure within carefully planned high-risk situations designed to elicit anxiety) while also reducing the chances of drinking as much as feasible. This can be achieved, for example, by using abstinence-focused social support during in vivo exposure to situations eliciting anxiety or by conducting in vivo exposure only in environments without access to alcohol. A structured plan using imaginal and/or graded exposure to cues that elicit anxiety also may offer a practical balance of therapeutic risk and reward.

It also is notable that comorbid individuals seem to be especially ambivalent about changing their alcohol use (e.g., Grothues et al. 2005; Velasquez et al. 1999). For example, Grothues and colleagues (2005) found that people with problematic drinking and a comorbid anxiety disorder were more likely to be in the contemplation stage of change compared with problematic drinkers with or without depression, that comorbid participants rated both the positive and negative aspects of drinking higher than comparison groups, and that they had lower self-efficacy to quit drinking. Also, both Grothues and colleagues (2005) and Velasquez and colleagues (1999) found that comorbid individuals reported greater temptation to drink than did individuals without comorbidity. People who are highly ambivalent regarding their desire to stop drinking characteristically experience two opposing alcohol-related motivations—the desire to experience the pleasure associated with drinking (i.e., an appetitive-approach motivation) and the desire to avoid alcohol and its negative consequences (i.e., negative-avoidance motivation). This ambivalence can be a negative prognostic indicator. For example, profiles of approach–avoidance drinkers have discriminated between "high lapsers" and abstainers among alcohol-dependent patients (Stritzke et al. 2007). These findings jointly suggest that ambivalence about changing alcohol use may be particularly salient among people with comorbid anxiety and AUDs, such that decisional balance likely is a principal treatment target.

The resolution of such ambivalence is a key concept of MI and is considered essential for a meaningful change to occur (Miller and Rollnick 1991, 2002). Accordingly, this counseling style seeks to help clients resolve their ambivalence by eliciting a specific class of verbal expressions (i.e., change talk) within sessions that most strongly are associated with actual behavior changes, especially phrases that signify a desire, ability, reasons, need, commitment, or steps taken to reach specified goals (Rollnick et al. 2007). An MI approach therefore may be particularly well-suited for clients with high ambivalence. In fact, meta-analyses have provided support for MI as a BI for problem drinking (Vasilaki et al. 2006). However, brief MI may not be optimal for drinkers with comorbid anxiety disorders because previous studies reported no additive benefit of BIs on either drinking outcomes or further help-seeking in this dually diagnosed population (Grothues et al. 2008*a, b*).

Application of Treatment Methods

In addition to adjusting standard pharmacotherapy and psychotherapy protocols for anxiety and AUDs when treating comorbid clients, it also is crucial to apply these methods in a way that produces the best outcomes for both disorders. Case conceptualizations that implicate one disorder as primary (e.g., because the patient histories are consistent with either the self-medication or the substance-induced models of comorbidity development) may tempt clinicians to focus treatment solely on that primary disorder. However, it generally is accepted in the comorbidity literature that this approach is not advisable (e.g., Kushner et al. 2007; Lingford-Hughes et al. 2002; Stewart and Conrod 2008). As reviewed earlier, one implication of the mutual-maintenance model of comorbidity is that neglecting to treat the second disorder would place individuals at high risk of relapse to the disorder that was treated, and published studies have supported this notion (e.g., Bruce et al. 2005; Driessen et al. 2001; Kushner et al. 2005). Recommendations to treat both anxiety and AUDs therefore appear warranted on both theoretical and empirical grounds. The literature for treating dual problem specifies three primary approaches, including the sequential, parallel, and integrated models (for a comparison, see table 3).

The Sequential Approach. In the sequential approach to treating comorbid anxiety and AUDs one disorder is treated prior to addressing the other disorder. Advocates of this approach point out that it may be prudent to begin, for example, by treating a client's alcohol problem and waiting to see whether abstinence leads to remission of the psychiatric problem (e.g., Allan et al. 2002; Schuckit and Monteiro 1988). This model also allows clinicians to engage clients who may be more ready to address one disorder than the other, and this may be a pragmatic early treatment strategy for comorbid clients who may only have interest in changing one of their problems (Stewart and Conrod 2008). This hypothesis is supported by recent findings from a double-blind, randomized controlled trial of paroxetine for comorbid social anxiety and AUDs, which demonstrated that although this medication did not modify drinking overall, it did reduce drinking prior to social situations and appeared to uncouple social anxiety and alcohol use (Thomas et al. 2008). The results of this study suggest that paroxetine may be useful in this subgroup of alcoholics by alleviating social anxiety as a reason for drinking, and that once social anxiety symptoms are reduced, the stage may be set for the introduction of an alcohol intervention. Examination of this sequential treatment strategy is underway.

The Parallel Approach. The parallel-treatment approach requires that specific treatments for both disorders are

delivered simultaneously, although not necessarily by the same provider or even in the same facility. However, coordination among providers and between facilities becomes a critical issue with parallel treatments when they are not colocated. There are noteworthy advantages of this approach relative to sequenced treatment, such as, at least theoretically, reducing the chances of relapse by attending to both disorders. In light of the mutual-maintenance patterns mentioned earlier this may be a quite significant benefit. Also, parallel treatment may be sensible from a practical standpoint, given that in the current treatment culture addiction and mental health settings generally are separated and efforts to unify and integrate treatment services for comorbid clients have lagged well beyond expert recommendations (Substance Abuse and Mental Health Administration [SAMHSA] 2002). However, several limitations of the parallel approach also exist beyond inherent difficulties with case coordination (Stewart and Conrod 2008). For example, clients may become overburdened with the time and effort involved with participation in two treatments with potentially two providers in separate locations. Thus, previous research has suggested that parallel psychosocial treatments for anxiety and AUDs may be too demanding for clients, which can negatively influence treatment outcomes (Randall et al. 2001). In addition, the parallel approach may convey an implicit (and erroneous) suggestion that the two disorders are separate, and the approach generally may be inefficient.

Table 3 Comparative Balance of Comorbidity Treatment Models

Model	Description	Advantages	Disadvantages
Sequential	Treatment of one disorder followed by treatment of the second comorbid disorder	• Can accommodate differential treatment interests among anxiety versus alcohol treatment seekers • Allows for hypothesis testing of causal relationships among presenting symptoms • If treatment of first disorder (e.g. alcohol use disorders (AUD) leads to reduction in symptoms of second disorder (e.g. anxiety reduction), unnecessary treatment of second disorder may be avoided	• Case coordination can be complicated if different providers or treatment settings are involved • Mutual maintenance pattern may compromise treatment gains for first disorder treated, leading to greater risk for relapse • Implicit communication to clients that one disorder is more important than the other
Parallel/simultaneous	Specific treatment of both comorbid disorders at the same time but not necessarily by the same provider or in the same treatment facility	• Roughly equivalent attention given to both disorders • Both disorders are treated by experts in their respective areas • Recognition that each comorbid disorder needs treatment attention, to reduce risk for relapse to each disorder being treated based on mutual maintenance pattern	• Case coordination can be complicated if different providers or treatment settings are involved • Clients may become overwhelmed by excessive demands of simultaneous treatment of two (or more) disorders • Can ignore functional interrelationship among comorbid disorders
Integrated	Both disorders are treated, or at least monitored simultaneously, by a single qualified provider	• Treatment addresses the functional interrelationship of comorbid disorders • Both disorders are treated by the same provider at the same time, which eliminates case coordination difficulties associated with other treatment models • Treatment efficiency is potentially maximized	• Lack of professionals qualified to treat both disorders, especially considering the wide range of potential unique anxiety–AUD combinations • Clients seeking treatment for one problem may have no interest in addressing the other comorbid disorder, which can compromise therapeutic alliance • Assumption of functional interrelationship between comorbid disorders may not fit all cases

The Integrated Approach. Integrated treatment strategies are akin to parallel methods of combining treatments, but with two additional features: both disorders are treated by a single provider and treatment explicitly addresses the functional interrelationship of the comorbid disorders. This intuitively appealing approach theoretically is matched to the mutual maintenance model, is efficient, and communicates to clients that their dual problems are in fact intertwined and equally require management. Based on the range of potential advantages associated with integrated therapy, expert opinion strongly suggests adopting this approach to treating anxiety and AUDs (e.g., Castle 2008; Stewart and Conrod 2008; Watkins et al. 2005). Research has provided some support for such an integrated approach in the case of co-occurring panic disorder and AUDs (Kushner et al. 2006, 2009). To date, however, unfortunately only few data exist on integrated treatment, and the incongruence between the strength of expert opinion and paucity of supportive data has been noted in several reviews (Baillie et al. 2010; Hesse 2009; Smith and Book 2008; Stewart and Conrod 2008; Watkins et al. 2005). In addition, the practical obstacles to achieving integrated treatments also are considerable, including the need for specialty training in an underdeveloped area, conceptual incongruence between elements of standard anxiety and AUD treatments, and relative lack of funding opportunities from granting agencies for these niche treatments.

Because of the overall lack of empirical data to guide clinical decisions on how to best sequence and combine therapies for anxiety disorders and AUDs, it is recommended that clinicians consider and weigh the relative advantages and disadvantages of each approach when planning treatment for their patients. The sequential, parallel, and integrated models each are beneficial in certain respects, and each method should be considered a valuable option in the practitioner's toolkit.

Summary and Conclusions

The comorbidity of anxiety disorders and AUDs is fairly prevalent and clinically relevant. A growing body of literature has illuminated the developmental pathways through which these disorders merge, including the common factor, self-medication, and substance-induced routes. Although epidemiological evidence most strongly supports the self-medication pathway, empirical support exists for each of these competing models, suggesting that this comorbidity is heterogeneous in its origin. Regardless of the method of onset, however, once anxiety and AUDs co-occur, the mutual maintenance model suggests that these comorbid disorders can become engaged in a feed-forward cycle that could be progressive if left untreated. It is important to be mindful of the unique developmental and maintenance characteristics associated with this comorbidity, because these elements have a considerable influence on both diagnosis and treatment planning.

Fortunately, several evidence-based strategies are available for treating anxiety and AUDs, including both pharmacotherapy and psychotherapy approaches. Administration of these methods for comorbid individuals is complex and may require modification of standard procedures to yield the greatest efficacy. It also is notable that the optimal sequence and timing of treatments remain undetermined even after decades of scientific inquiry. Although it generally has been accepted that both the anxiety disorders and the AUDs should be treated and that integrated approaches should produce the best outcomes, data on the efficacy of combined treatment approaches are limited in scope and mixed overall (e.g., Baillie et al. 2010; Schade et al. 2003; Watkins et al. 2005). In light of the current evidence, the most practical approach to combining treatments is to weigh the benefits and drawbacks of each method and apply them judiciously.

Additional advances and expansion of the empirical evidence are necessary to further move this area of research and clinical practice forward. The significant impact of empirical evidence already is evident when reflecting on the evolution of expert opinion regarding the development and treatment of comorbid anxiety and AUDs. Although these issues likely will not be settled unequivocally, recent epidemiological studies have shown that anxiety disorders among alcoholics often are independent (e.g., Grant et al. 2004; Williams et al. 2010) and clinical studies have demonstrated that efficacious treatment of one disorder does not necessarily yield improvements in the untreated comorbid disorder (e.g., Thomas et al. 2008). Together, these lines of research support putative recommendations that both disorders should be treated (see Castle 2008; Smith and Book 2008; Stewart and Conrod 2008; Watkins et al. 2005). This understanding and standard of care is a significant departure from earlier views that anxiety in this population mainly was a residual effect of heavy alcohol use and would subside with abstinence. Despite the significant contributions that have led to this paradigm shift, the anxiety–alcohol literature has reached a plateau that is defined by frequent reviews but relatively limited original research, especially in the area of randomized clinical trials with comorbid participants as the defined population of study. A practical limitation for such studies is that many potential anxiety disorder–AUD combinations exist, and developing evidence-based protocols for each combination would require a significant investment of resources. Future work may circumvent this difficulty if the recent emergence of transdiagnostic approaches to treating anxiety disorders (Norton and Philipp 2008) generates interventions that are effective across the anxiety spectrum. Transdiagnostic approaches to anxiety treatment focus on common clinical features and maintaining processes among the anxiety disorders, and are designed to synthesize evidence-based components of anxiety disorder treatments into a unified program. This innovative development would open the door to new lines of research primed to produce significant advances in the field. For example, such research could examine which shared features of anxiety disorders are

associated with alcohol-related problems and whether a universal evidence-based transdiagnostic anxiety–AUD treatment protocol focused on these factors could be achieved rather than requiring separate evidence-based treatments for each anxiety disorder–AUD combination. As these and other lines of research in comorbid anxiety and AUDs continue to mature, future studies should provide further insights into the special considerations, treatment needs, and ideal therapeutic strategies for individuals with these dual problems. ■

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