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Alcohol Res. 2022;42(1):12 | https://doi.org/10.35946/arcr.v42.1.12 Published: 27 October 2022

NIAAA 50th ANNIVERSARY FESTSCHRIFT

Alcohol's Negative Emotional Side: The Role of Stress Neurobiology in Alcohol Use Disorder

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Acknowledgments
This article is a summary of the presentation delivered at the NIAAA 50th Anniversary Science Symposium on December 1, 2020. It serves as a tribute to NIAAA in commemoration of their persistent commitment to developing the science of alcohol effects and associated harm, and to developing novel cutting-edge strategies in support of prevention and treatment of, and recovery from, alcohol use disorder. I was honored to present at this symposium that captured some of the innovative research supported by NIAAA over the years. It is especially personally meaningful as the discoveries presented here would not have been possible without the financial and intellectual support provided by NIAAA and its dedicated staff to my work and lab over the past 25 years. It has been a real privilege to receive this support from NIAAA to conduct this work and to have this opportunity to share the research findings at this important symposium.

Disclosures
The author declares no competing financial or nonfinancial interests.

Publisher's Note
This article was based on a presentation at the NIAAA 50th Anniversary Science Symposium, "Alcohol Across the Lifespan: 50 Years of Evidence-Based Diagnosis, Prevention, and Treatment Research," held on November 30–December 1, 2020. Links to the videocast are available on the NIAAA 50th Anniversary Science Symposium agenda webpage. Opinions expressed in contributed articles do not necessarily reflect the views of NIAAA, National Institutes of Health. The U.S. government does not endorse or favor any specific commercial product or commodity. Any trade or proprietary names appearing in *Alcohol Research: Current Reviews* are used only because they are considered essential in the context of the studies reported herein.

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. Sinha's presentation at the event. NIAAA Director George F. Koob, Ph.D., serves as editor of the Festschrift.

KEYWORDS: alcohol; distress; craving; relapse; negative emotions; neural activity; glucocorticoids

The word "alcohol" often conjures up positive feelings and associations with fun, socializing, relaxing, and partying. Yet there is another side to drinking alcohol, especially with risky, hazardous levels of consumption. This side is associated with distress and may include anxiety, loneliness, pain, and depressive symptoms.[1] This has been labeled the "dark side," or "negative emotional, stress side," of alcohol intake.[2] These two paradoxical, dialectically opposing alcohol experiences map onto the biphasic drug effects of alcohol, with alcohol being both a stimulant and a depressant drug. They also represent a shift from positive to negative situations that may drive alcohol intake, especially as alcohol intake increases from low or moderate "social" levels of drinking to binge, heavy, and chronic consumption. The National Institute on Alcohol Abuse and Alcoholism (NIAAA) defines drinking in moderation as an intake of two drinks or less per day for men and one drink or less per day for women. Binge drinking is generally defined as five or more drinks per occasion for men and four or more drinks per occasion for women. Heavy drinking is generally defined as more than four drinks per day or more than 14 drinks per week for men and as more than three drinks per day or more than seven drinks per week for women.[3]

One aspect of the research the author has conducted with the support of NIAAA, and which is the topic of this article, has focused on identifying the physiological and neural effects, as well as the subjective and cognitive effects, of binge and chronic alcohol use. This research also has explored the factors that influence these effects and investigated whether these effects can be reversed or normalized to allow for recovery from any of the long-term changes that occur with binge and chronic alcohol misuse.

The worldwide coronavirus (COVID-19) pandemic is a chronic, ongoing stressor. Research has shown that alcohol consumption has increased significantly during this period, especially among individuals who regularly binge drink or drink heavily.[4,5] While onsite alcohol sales were down as businesses closed, e-commerce profits increased more than 30% during the COVID-19 pandemic.[4,5] Who is most susceptible to increased drinking episodes during COVID-19–related stress? This question highlights the need to understand the well-known bidirectional relationship between stress or trauma and alcohol intake, and why those with binge and chronic alcohol use are most vulnerable to increased alcohol use under high levels of stress and with traumatic exposure.

This article reviews human research investigating neurobiological and psychological changes related to alcohol misuse that are associated with greater distress and stress-related alcohol craving and their role in predicting risk of binge drinking, relapse, and impact on treatment outcomes. The author presents the effects of stress and trauma on brain stress responses and their associations with resilient coping and describes the impact of binge and chronic alcohol use on brain and peripheral stress responses and their role in promoting alcohol craving and relapse risk. Specific clinical and biobehavioral markers of both risk of developing alcohol use disorder (AUD) and relapse are also reviewed. Finally, the article discusses recent findings on treatments that focus on reversing stress and craving disruptions related to chronic alcohol misuse to improve treatment outcomes.

Alcohol and Stress—Shift From Positive to Negative Effects

It is well known that one or two standard alcoholic drinks have a stimulating and physiologically arousing effect; for example, heart rate increases acutely, and blood pressure changes have been documented. These responses are part of the autonomic nervous system readouts that occur with alcohol intake, but also are observed in challenging situations such as when faced with acute stressful life events.[6,7] The arousing response to alcohol is associated with a sense of feeling energized and stimulated as well as increases in sociability.[6] With increasing levels of alcohol intake in one sitting, however, alcohol also stimulates the hypothalamic-pituitary-adrenal (HPA) axis, and increases in cortisol are observed.[8,9] Alcohol also activates brain emotion and stress pathways, including the amygdala, under emotional arousing and stressful states.[10,11] In addition, acute alcohol use stimulates the brain cortico-striatal pathways involved in reward, motivation, and goal-directed behaviors. These include the ventral and dorsal striatum, the orbitofrontal cortex (OFC), and the ventromedial prefrontal cortex (VmPFC).[10-13] The emotion/stress pathway and the reward/motivation pathways closely interact, and such interactions are involved in emotional cue-related drinking motivation.[11,12]

Binge and hazardous alcohol drinking patterns are associated with well-documented changes both in the brain stress and emotion regions, such as the amygdala,[8,12] and in associated brain networks, including the ventral and dorsal striatum as well as the OFC, VmPFC, and dorsolateral prefrontal cortex.[9,12,14,15] These brain changes are associated with blunted autonomic and cortisol responses to stress and to acute alcohol intake,[6,8] as well as with increases in negative emotional and stress responses and greater alcohol craving.[6,9,14-17] Together, these changes are part of the psychobiological adaptations in humans that occur with increasing patterns of binge and hazardous alcohol intake.

Stress, Alcohol Craving, and Binge Alcohol Intake

Acute stress exposure stimulates the autonomic, endocrine, and brain emotion and motivation regions that process and regulate negative emotion and distress responses, and it also activates

stress coping.[6,12,18] Additionally, acute stress exposure increases physiological arousal, including cortisol responses, and activates brain stress pathways involved in emotional arousal, emotional learning, and memory. This activation occurs via circuits involving the hypothalamus, amygdala, hippocampus, insula, and prefrontal regions, including the OFC, VmPFC, and inferior frontal cortices. Also activated is the premotor supplementary motor area, which is involved in behavioral intent, response selection, and action.[6,18,19] Previous studies reported that there are dynamic time-dependent changes in the cortico-striatal regions involving the ventral and dorsal striatum and the VmPFC during stress versus non–stress conditions; these changes were associated with active, goal-directed stress coping.[18] Additionally, greater dynamic responses in these brain stress-reward pathways were associated with lower daily numbers of alcoholic drinks consumed, lower reports of emotional conflicts, and lower emotional eating, whereas blunted ventral striatum and VmPFC responses during stress were associated with greater reports of binge drinking, emotion dysregulation, and emotional eating.[18] Based on these findings, the dynamic neural responses in the striatum and VmPFC are thought to document neurophysiological flexibility during stress, and their associations with behavioral coping suggest that this circuit is part of the resilient stress-coping pathway involved in behavioral control and self-regulation of stress, emotions, and reward impulses.[6,18]

These adaptations to alcohol also vary by sex, as fundamental differences between men and women exist in brain organization, structure, and functional networks[20] as well as in the responses of brain stress, emotion, and reward regions[21] and in patients with cocaine use disorder.[22] Moreover, sex differences in the responses to stress and to alcohol-related stimuli have been documented in people who drink moderately. Unlike in animal studies, males in human studies show greater adrenocorticotropic hormone (ACTH) and cortisol responses to stress,[23] whereas females show higher autonomic physiologic arousal to stress; a greater response to stress cues in the amygdala, insula, OFC, and VmPFC; and greater VmPFC response to alcohol cues.[24-28] This suggests that the psychological and biological responses to alcohol and to stress vary by sex and that although men and women report similar levels of alcohol motivation when matched for recent drinking history, the psychological and neurobiological pathways that facilitate alcohol use are different for men and women who drink moderately.

Regardless of sex, repeated escalated alcohol use induces changes in both peripheral and brain stress systems.[2,12,16] Higher binge levels of alcohol use increase basal cortisol levels and blunt the peripheral stress responses; these changes also predict greater craving and behavioral motivation for alcohol use in people who binge drink or drink heavily (see Figure 1).[8,9] Additionally, changes in the amygdala responses to emotional cues and ventral striatal responses to alcohol have been reported with higher binge levels of alcohol use.[14,29] Along with these neural changes, increased salience of alcohol and greater alcohol craving levels have been observed in response to stress as well as in response to alcohol and to alcohol cues, which then promote increased alcohol intake and escalation to risky drinking.[8,15,17] These brain stress system, physiologic, and behavioral effects of binge drinking history need to be further examined by sex to better understand the recent data on greater escalation of binge drinking in women compared to men.[30]

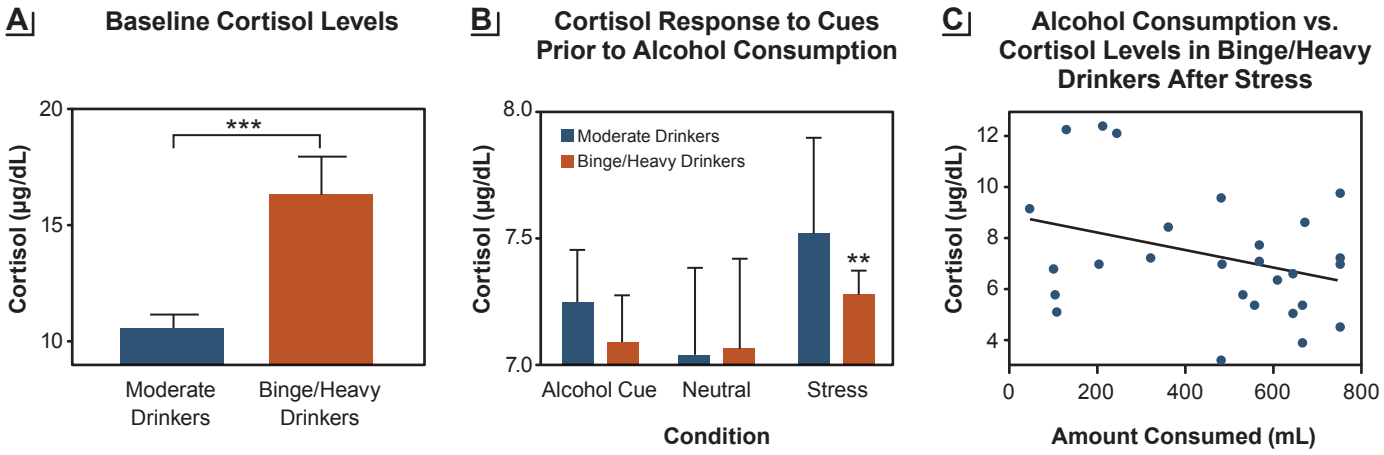

Figure 1. Baseline cortisol levels and responses to stress differ between moderate drinkers and binge/heavy drinkers. (A) Fasting morning plasma levels of cortisol (µg/dL) were higher in binge/heavy drinkers (orange bars) compared to moderate drinkers (blue bars) (***$p < .001$). (B) Cortisol responses to stress and alcohol cues, but not to neutral cues, were blunted in binge/heavy drinkers compared with moderate drinkers (**$p < .01$). (C) In binge/heavy drinkers, the behavioral motivation for alcohol use as reflected in the amount of alcohol consumed post stress in an ad lib drinking task was greater in individuals with a more blunted cortisol response to stress ($r^2 = .11$, $p = .0022$). *Source:* Adapted with permission from Blaine et al. (2019).[8]

Effects of Stress and Trauma on Brain Pathways and AUD Risk

Stress and trauma are associated with greater levels of risky alcohol intake as well as greater severity of AUD.[19] Numerous different types of traumatic stress and life events as well some temperament and individual-level variables relate to risk of binge drinking and developing AUD (see Table 1). Exposure to repeated stress and trauma also contributes to changes in the brain and body's responses to stress and emotions as well as to changes in alcohol motivation and adaptive coping responses.

Greater levels of cumulative adversity, stressful life events, and trauma are associated with lower brain volume and greater negative emotion and subjective stress responses. They also are associated with dysregulated neural and peripheral physiological responses to stress and to alcohol cues in the brain regions involved in stress, emotion, reward regulation, and self-control, including the OFC, VmPFC, supplementary motor area, amygdala, insula, and striatum.[31-33] Furthermore, altered or blunted ACTH and cortisol and autonomic responses to stress and to alcohol and drug cues are observed with greater trauma or stress.[19,33] These stress- and trauma-related brain and peripheral alterations co-occur alongside emotional and behavioral dysregulation and higher alcohol motivation. As a result, people with more risky drinking exposed to stress or trauma are at greater risk of emotion dysregulation as evidenced by more arguments, fights, emotional eating, and higher maximum drinks consumed per occasion (see Figure 2).[18,34]

Several interacting brain networks are activated during stress, including those involved in emotion experiences (e.g., amygdala, insula), emotional memory (e.g., amygdala, hippocampus), reward and motivation regions (e.g., ventral and dorsal striatum), and goal-directed behavior (e.g., OFC, VmPFC).[13,18,19,21,29] These regions form networks and patterns of activation that enable emotional and motivational coping, and both stress and alcohol directly act on these networks to influence active coping, motivation, and flexible control of behavior, such as exercising self-control with drinking. The accumulating evidence shows that stress and trauma exposure alter these emotional and motivational responses involved in adaptive stress coping, such that people become more vulnerable to craving and consuming higher levels of alcohol, which increases risk of hazardous and risky drinking.

The research described above resulted in the development of a model explaining the role of glucocorticoids in drinking behavior on the basis of changes in peripheral cortisol levels and responses across the full spectrum of alcohol consumption levels.[8] At baseline, people who binge drink or drink heavily have higher cortisol levels than those who drink moderately (see Figure 1A), indicating a shift in HPA axis functioning. This also suggests possible changes in brain glucocorticoid pathways in

Table 1. Types of Adverse Life Events, Trauma, Chronic Stressors, and Individual-Level Variables Predictive of Addiction Risk

Adverse Life Events	Childhood and Life Trauma	Chronic Stressors	Stressful Internal States
• Loss of parent • Parental divorce and conflict • Isolation and abandonment • Single-parent family structure • Forced to live apart from parents • Loss of child by death or removal • Unfaithfulness of significant other • Loss of home to natural disaster • Death of significant other or close family member	• Physical neglect • Physical abuse by parent, caretaker, family member, spouse, or significant other • Emotional abuse and neglect • Sexual abuse • Rape • Victim of gun shooting or other violent acts • Observing violent victimization	• Being overwhelmed • Unable to manage life problems • Difficulties with job, living situation • Financial problems • Interpersonal conflicts, loneliness • Unfulfilled desires • Problems with children • Illness of loved ones • Negative emotionality • Poor behavioral control • Poor emotional control	• Hunger or food deprivation • Food insecurity • Extreme thirst • Sleep deprivation or insomnia • Extreme hypothermia or hyperthermia • Excessive drug use • Drug withdrawal states • Chronic illness

Source: Included with permission from Milivojevic & Sinha (2018).[37]

humans that may increase risk of hazardous drinking. As stated earlier, alcohol consumption stimulates cortisol release; however, in response to either stress or alcohol exposure, the increase in cortisol is lower in people who binge drink or drink heavily than in those who drink moderately. Thus, when given one standard alcoholic drink, those drinking at binge levels do not feel its effects as robustly as do people who drink moderately.[8,9] As cortisol is critical for survival, humans have well-preserved neurobehavioral signals with the brain stress system pathways[12] that seek to enhance cortisol release in response to stress. In people with blunted cortisol responses due to heavy drinking, this mechanism may signal greater motivation for alcohol to increase alcohol-related cortisol responses.[9] Thus, there is a neurophysiologic drive to enhance wanting alcohol in order to increase cortisol and HPA axis functioning in people who drink heavily. This disruption in alcohol-related cortisol signaling and the need to drive the homeostatic HPA axis rhythm back to functional levels may be one component of the enhanced motivation for alcohol in those who drink alcohol at binge and heavy levels. This conceptual model suggests that normalizing the brain and body's stress and motivational coping responses may reduce risk of hazardous drinking. Researchers are seeking to develop and evaluate novel strategies to achieve this normalization and to reduce the risk of heavy drinking.

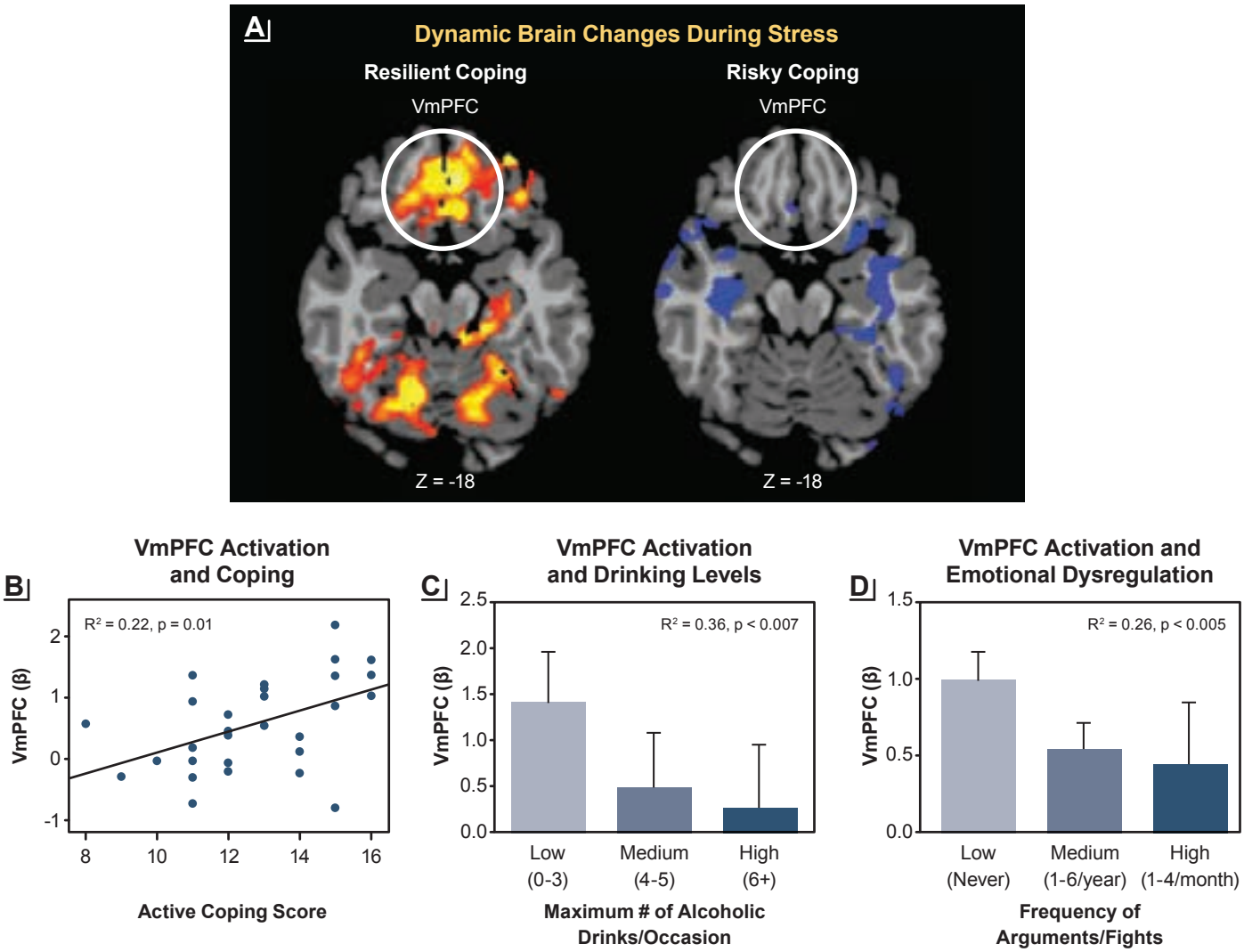

Figure 2. Associations between brain stress responses and resilient coping. (A) Dynamic activation in the ventromedial prefrontal cortex (VmPFC) during stress challenge (represented by red and yellow) was a sign of resilient coping, whereas a lack of dynamic changes in the VmPFC during stress, suggesting inability to mobilize during stress, was a sign of risky coping. (B) Greater dynamic activation of the VmPFC was associated with greater self-reported active coping. (C) Lack of dynamic activation of the VmPFC was more pronounced in binge drinkers. (D) Greater emotional dysregulation (measured by greater frequency of arguments or fights) also was associated with less dynamic activation of the VmPFC. *Source:* Adapted with permission from Sinha et al. (2016).[18]

Effects of Stress and Alcohol Cues in AUD

Researchers also have investigated the role of stress biology and stress responses in people with AUD. Chronic heavy drinking or binge drinking increases the risk of disrupted alcohol-related autonomic and HPA axis responses as described in previous sections. These disruptions contribute to clinical symptoms associated with the negative emotional side of AUD,[15] such as increased levels of anxiety, negative mood, sleep difficulties, emotional reactivity, and impulsivity, along with high levels of craving for alcohol.[1,35] Furthermore, these disruptions increase the risk of relapse and heavy drinking during treatment and posttreatment, thereby jeopardizing long-term recovery.[6,36,37] Alcohol relapse refers to return to heavy drinking (at binge levels) after any period of abstinence, whereas treatment failure refers to maintaining or returning to binge and hazardous drinking levels during or after treatment.[3] These observations have led researchers to investigate which factors contribute to early risk of dropout and recovery failure during treatment.

A series of studies assessed brain and body responses as well as cognitive, emotional, and motivational responses to both stress and alcohol cues in a laboratory study of human participants with AUD who were entering treatment and control participants without AUD. The analyses also included structural and functional magnetic resonance imaging as well as real-world daily assessment of stress and motivational responses using smartphones. These analyses using multiple approaches across different samples of individuals with AUD found that stress exposure increased alcohol craving. This response was accompanied by higher emotional, mood, and anxiety symptoms and lower ability to regulate emotions and control alcohol cravings.[36,37] Furthermore, the biological stress response was significantly disrupted during the early recovery period. Thus, individuals in early recovery exhibited a higher basal heart rate and higher free cortisol levels, but lower levels of endogenous bound cortisol. Additionally, these individuals did not show a significant normal response to stress or alcohol challenge.[6,37] Thus, the biological responses that support emotion and mood regulation are disrupted during this early recovery phase, and the greater these levels of dysfunction, the higher the risk of relapse or heavy drinking. Notably, sex differences in these biological responses have been reported, where women with AUD showed a more blunted ACTH and cortisol level than men with AUD; however, women had much higher basal norepinephrine levels, which in turn affected their response to stress and to alcohol cues.[26,38]

Another series of experiments examined brain correlates of later alcohol relapse and treatment failure. These analyses found that the volume of gray matter cells in the medial prefrontal brain regions—which are involved in regulating emotions, reward, and actions—was lower among individuals entering treatment compared with healthy control participants.[39] Also, individuals with the lowest gray matter volume in the medial prefrontal brain region tended to be most likely to relapse and not do well in treatment.[39] Analyses assessing the function of these brain regions during experimental exposure to stress and to alcohol cues (compared to neutral cues) detected disrupted, hyperactive VmPFC responses to neutral relaxing cues, but blunted, hypoactive VmPFC responses to stress and cue exposure. These observations suggest that the brain pathways that help regulate emotions and desires showed dysfunction and that the greater the VmPFC disruption, the higher the risk of alcohol relapse and heavy drinking.[40,41]

The studies described above have led to the characterization of a risk profile to identify individuals who are most vulnerable for alcohol relapse and heavy drinking during treatment. Thus, risk was determined by specific clinical measures—such as alcohol craving and withdrawal,[42,43] mood, anxiety, and sleep difficulties—and biological markers[37] as well as by additional moderating factors, including childhood maltreatment (see Table 2).[44] Furthermore, this research supported the conceptualization that the effects of binge drinking and chronic alcohol use on stress biology occur along a continuum, with higher levels of alcohol intake associated with more significant chronic stress pathophysiology, which in turn contributes to greater risk of alcohol relapse and treatment failure.[35]

AUD Treatments Targeting Stress, Craving, and Loss of Control of Alcohol Intake

Critical basic science and translational work by Koob and colleagues[45] had focused on stress pathophysiology to develop novel therapeutics for AUD. Similarly, the findings described above motivated additional research to evaluate whether reversal of the chronic alcohol-related disruptions in stress psychobiology that are associated with increased alcohol craving and relapse risk could improve treatment and treatment outcomes for individuals most vulnerable to alcohol-related stress pathophysiology. Previous research by Arnsten had shown that noradrenergic agents such as guanfacine and prazosin could rescue the prefrontal cortex from the toxic effects of high uncontrollable stress.[46] Because the effects of chronic alcohol exposure are similar to those of high chronic stress, it seemed plausible that pharmacologic targets that reduce prefrontal norepinephrine and the toxic effects of stress-related damage also could be of benefit in improving the stress and craving-related pathology associated with AUD. Studies to test these hypotheses have shown positive results. Guanfacine, an alpha-2 adrenergic agonist that reduces brain norepinephrine in the prefrontal cortex, improved prefrontal functioning and reduced alcohol and drug craving.[47,48]

Table 2. Markers and Moderators Associated With Relapse to Alcohol Use and Treatment Failure in Alcohol Use Disorder (AUD)

Clinical and Biological Markers	Moderating Factors
• Increased levels of alcohol craving • High early physical, sexual, emotional abuse and trauma history • High basal beat-by-beat heart rate and blunted autonomic response to stress and cues • Altered bound and free fasting morning cortisol levels, and adrenal sensitivity • Blunted and hypoactive cortisol response to stress • Lower medial prefrontal gray matter volumes in magnetic resonance imaging • Blunted medial prefrontal cortex response to stress and alcohol cues • Hyperactive striatal responses to alcohol cues	• AUD severity, including life span factors of early or late AUD; acute withdrawal symptoms, including anxiety, sleep, and negative mood; alcohol abstinence days • Early physical, sexual, and emotional abuse and lifetime traumas; chronic stress; and trauma-related pathophysiology • Sex differences and gender-related comorbid psychopathology and medical conditions • Genetic and pharmacogenomic effects

Furthermore, guanfacine had some sex-specific effects, with greater benefits in women than in men.[49,50]

Similarly, prazosin—an alpha-1-adrenergic antagonist that had been shown to improve working memory and prefrontal functioning during stress[46] as well as withdrawal-related drinking in laboratory animals[51]—reduced stress-related craving and stress dysfunction in AUD.[52,53] Based on these findings, an NIAAA-supported, 12-week proof-of-concept, double-blind, placebo-controlled, randomized trial of prazosin versus placebo (16 mg/day, three times a day dosing, titrated over 2 weeks) was conducted with 100 individuals with AUD. The study found that alcohol withdrawal symptoms were a moderating factor impacting prazosin efficacy in improving drinking outcomes over 12 weeks; that is, prazosin treatment benefit was determined by the presence of alcohol withdrawal symptoms at treatment entry. Thus, individuals with more severe alcohol withdrawal symptoms at treatment initiation experienced greater reductions in heavy drinking days and drinks per occasion during the 12-week treatment period.[54] In addition, prazosin reduced alcohol craving, anxiety, and negative mood compared with placebo in participants with high alcohol withdrawal symptoms, but had no impact in those with no or low levels of alcohol withdrawal symptoms. Finally, prazosin appeared to reverse VmPFC and dorsal striatal dysfunction, improving medial prefrontal response to stress and reducing dorsal striatal response to alcohol cues in participants treated with prazosin compared with those receiving placebo.[55] These findings support further development of prazosin in the treatment of severe AUD. However, they also underscore the need to pursue further research to identify behavioral and pharmacologic strategies to prevent and treat chronic alcohol effects on stress pathophysiology in AUD.

Conclusions

This article summarizes research by the author's group demonstrating that binge, heavy, and chronic drinking leads to adaptations in brain, biological, and psychological stress responses. These adaptations are associated with alcohol's negative emotional aspects, as evidenced by greater alcohol craving, higher alcohol withdrawal, greater negative mood and anxiety symptoms, as well as sleep difficulties that are commonly reported by individuals with AUD entering treatment. These changes occur in brain stress, reward, and motivation pathways that represent the stress pathophysiology of AUD. This stress pathophysiology directly targets brain circuits that underlie people's ability to cope with stress and day-to-day challenges and are involved in jeopardizing recovery from AUD.

This research also has identified various clinical and biobehavioral markers that are associated with relapse and treatment failure and has allowed for identification of individuals who may be at greatest risk of treatment failure. Additionally, identification of these markers has led to research seeking to develop new strategies to target and reverse the stress pathophysiology of AUD to optimize interventions for AUD. Current and future work is focused on developing and testing specific treatments that can target this particular stress pathophysiology and help individuals who are most vulnerable to jeopardizing their recovery in the early phase of AUD treatment.

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ALCOHOL RESEARCH
Current Reviews

Alcohol Res. 2020;40(2):05 • https://doi.org/10.35946/arcr.v40.2.05

Published: 20 August 2020

The Role of Stress, Trauma, and Negative Affect in Alcohol Misuse and Alcohol Use Disorder in Women

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Recent evidence indicates that the United States is facing a public health crisis of alcohol misuse and alcohol use disorder (AUD), which has been fueled in part by dramatic rises in binge and heavy drinking and prevalence of AUD in women. Historically, alcohol misuse and AUD have been more prevalent in men than in women. However, recent evidence on data from the past decade shows increases in AUD prevalence rates that are associated with substantially higher binge and heavy drinking and AUD prevalence in women compared to men. This paper first addresses the key roles of stress, trauma, childhood maltreatment, negative affect, and mood and anxiety disorders; sex differences in the presentation of these psychosocial and psychological factors; and their contributions to alcohol misuse, escalation to binge and heavy drinking, and transition to AUD in women. Also examined are potential central and peripheral biological mechanisms by which stressors and traumatic experiences, as well as chronic stress states—including depression and anxiety—may facilitate differential pathways to alcohol misuse, escalation, and transition to AUD in women. Finally, this paper discusses major gaps in the literature on sex differences in these areas as well as the need for greater research on sex-specific pathways to alcohol misuse and transition to AUD, so as to support a more comprehensive understanding of AUD etiology and for the development of new strategies for prevention and treatment of alcohol misuse and AUD in women.

KEY WORDS: girls and women; sex differences; early trauma; child maltreatment; alcohol craving

INTRODUCTION

There has been a global increase in alcohol misuse and rates of alcohol use disorder (AUD) over the last two decades.[1] Recent substantial increases in the United States come from dramatic rises in the prevalence of alcohol misuse and AUD in women relative to men (women, 84% increase; men, 35% increase).[2] This dramatic rise stems from increases in hazardous and binge drinking in girls during adolescence as well as in women.[3] Even though alcohol misuse and AUD are more prevalent in men than in women, there are no sex differences in prevalence of alcohol use during adolescence.[4] These increases are especially alarming given the fact that women tend to experience greater alcohol-related health problems than do men.[5] This article focuses on the roles of stress, trauma, childhood maltreatment, negative affect, and mood and anxiety disorders and their contributions to the increases in alcohol misuse, escalation of binge and heavy drinking, and transition to AUD in women. Although there are likely additional genetic and social factors and related mechanisms that may contribute to specific risks of binge drinking and AUD in women, a review of this literature is beyond the scope of this review. Rather, this article focuses on the psychosocial and biological processes by which stress, trauma, negative affect, and mood and anxiety disorders increase the risk of binge and heavy drinking, AUD, and relapse.

PSYCHOSOCIAL FACTORS INVOLVED IN THE ONSET AND PREVALENCE OF AUD IN WOMEN

Women in the United States are largely overrepresented in stress-related psychopathology rates,[6] and stress along with drug-related environmental cues are among the most important risk factors driving alcohol seeking, maintenance, and relapse.[7] Studies suggest that men and women differ in risk trajectories for the development of AUD and in AUD-related health consequences.[8] For example, women are more likely than men to experience certain types of stressors, such as sexual trauma,[9] and higher levels of stress have been shown to increase alcohol misuse and AUD vulnerability.[10] Also, women demonstrate a significantly "more rapid and risk-oriented path to compulsive drug seeking,"[11] pointing to a significant need to understand sex differences in risk for AUD development and maintenance in order to develop novel prevention and treatment approaches for AUD in women.

Psychosocial Factors of Early Trauma, Maltreatment, and Adversity

Early trauma, maltreatment, and cumulative adversity are psychosocial stress factors that have long been associated with alcohol misuse, development of AUD, AUD maintenance, and relapse.[10] Both boys and girls face physical and emotional abuse and neglect, sexual abuse, and cumulative adversity stemming from specific adverse childhood experiences such as substance use and mental health problems in the home, parental discord, and divorce, which are each associated with greater alcohol initiation in childhood.[12] However, girls and women face significantly higher rates of childhood sexual abuse and violent victimization.[13] Notably, higher rates of sexual abuse and violent victimization, especially in girls and women, are factors that produce the highest odds ratios for association with heavy drinking, drinking to cope with negative affect, and development of AUD.[10,12,14]

Sex Differences in Stress Factors, Early Onset Alcohol Misuse, and AUD

An extensive number of studies point to a positive association between negative affect, trauma, adversity, and chronic stress and vulnerability in developing AUD. Recent studies have shown that girls who report a history of abuse before adulthood are more vulnerable to developing AUD.[15] Other studies have found that adolescents who face a number of negative life events show increased levels of drug use (and misuse)

compared to those who do not face these adverse events.[7,10] Exposure to early life stress may be especially harmful for women, who are exposed to more high-impact trauma (e.g., sexual abuse) than men are, and at a younger age.[16] Thus, early trauma and chronic adversity both may increase vulnerability to alcohol use initiation, as well as maintenance, especially in girls. However, it is important to consider estimation biases, as women may be more likely to endorse stressful life events; thus, the contribution of these factors to binge drinking and AUD risk among women may be influenced by such estimation biases.

A study by Cheng and Anthony conducted between 2006 and 2014 assessed the dates of first full drink and first heavy drinking episode in around 33,000 females and males (ages 12 to 21) in the United States who had their first heavy drinking episode within the past 24 months.[15] Their findings revealed that, among adolescents who started to drink between ages 11 and 14, females progressed to a heavy drinking episode more quickly than males. This suggests that when drinking starts before age 15, females are at greater risk than males of progressing to a heavy drinking episode. When considered with the information that girls are more likely than boys to suffer sexual abuse before age 18, these findings raise the possibility that sexual abuse and other trauma, and victimization-related increases may contribute to increased risk of alcohol misuse and development of AUD in women.[17] However, the specific contribution of these factors to the development of AUD in women needs to be further explored.

PSYCHOLOGICAL ASPECTS OF STRESS AND TRAUMA EFFECTS ON AUD IN WOMEN

Experiencing stress, trauma, and adversity activates psychological processes of cognitive, affective, and behavioral emotion regulation and self-control to cope with and adapt to such negative life circumstances. During adolescence and young adulthood, emotion regulation becomes particularly relevant because of the rapid brain changes in regions associated with regulating emotion, stress, reward, and higher-order cognitive functioning; such changes underlie the significant biological and psychological changes that boys and girls undergo throughout adolescent development.[18] Alcohol experimentation occurs frequently during adolescence and young adulthood, and there is a higher risk for the development of AUD or substance use disorder during this time.[19] Findings indicate that exposure to early trauma and life stressors is associated with greater difficulties in emotional experiences, behavioral control, executive function, and decision-making, which contribute to behavioral control of alcohol intake, and thus could be one pathway that contributes to early onset of alcohol intake and risk of alcohol and substance use disorders.[12,19] Discussed below are the sex differences and impact of negative affect, mood and anxiety symptoms, and post-traumatic stress disorder (PTSD) and their contribution to development of binge and heavy drinking and AUD in women.

Negative Affect and Alcohol Intake

Negative affect is broadly defined as a state of emotional distress, and is associated with unpleasant feelings, such as anxiety, fear, anger, irritability, and sadness. Repeated and cumulative exposure to stress, trauma, adversity, and maltreatment is associated with greater levels of negative affect, anxiety, and depressed mood. Past literature suggests that women report more negative affect compared to men,[20] and higher negative affect has been linked to greater emotion dysregulation and associated with affective, anxiety, and substance use disorders.[10,21] A previous experimental study exposed healthy social drinkers to emotional stress, alcohol cues, and a control neutral relaxing cue using a personalized guided imagery method that individually calibrates stress imagery so as to

remove any provocation-related bias between men and women.[22] Results indicated that men and women were similar in cue-induced craving ratings. However, women reported greater stress-provoked sadness, anxiety, and body sensations compared to men (see Figure 1). These data indicate sex differences in stress and negative affect responses in women versus men, separate from alcohol motivation.

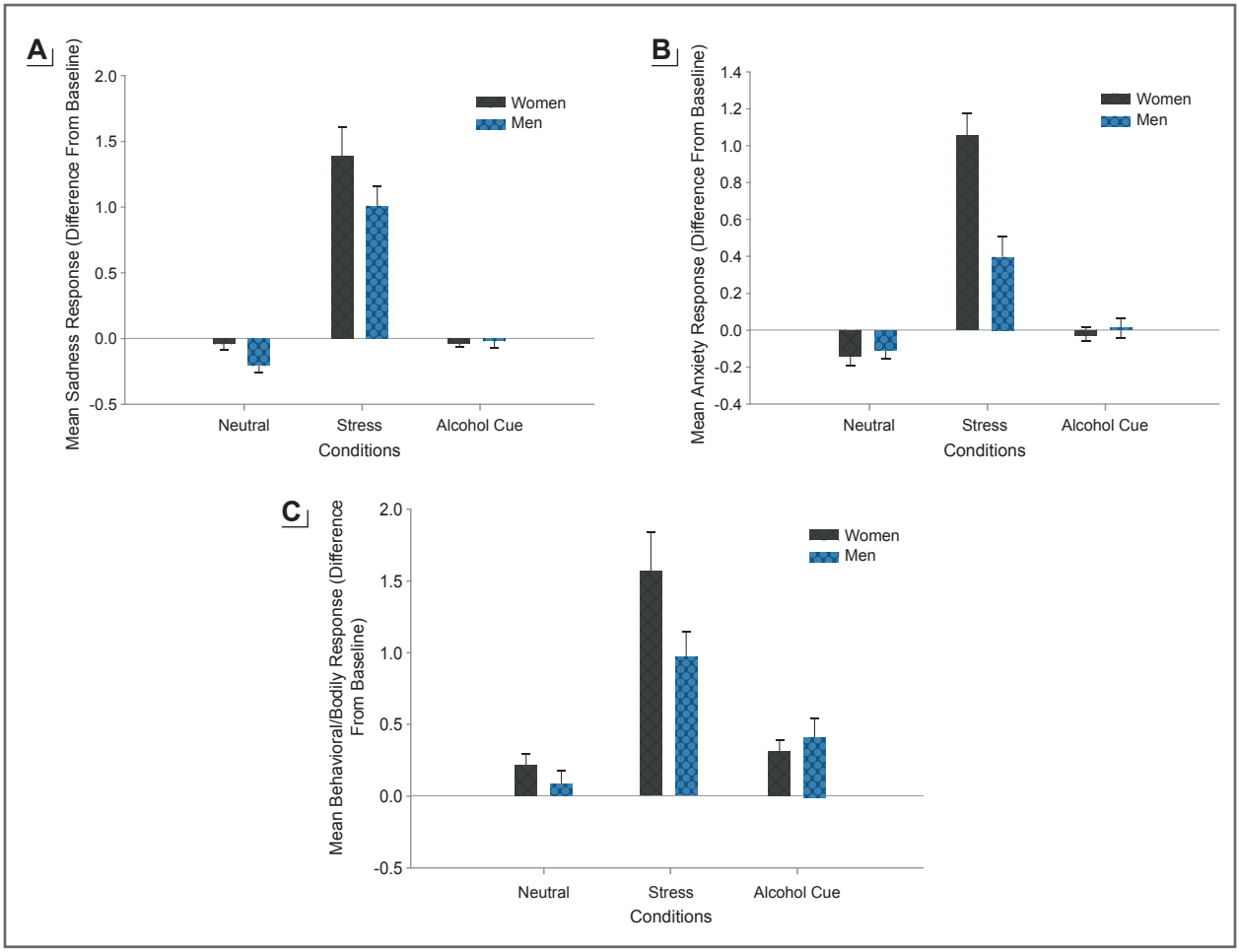

Figure 1 Gender differences in socially drinking volunteers' average subjective responses to individually calibrated exposure to stress, alcohol cue, and neutral-relaxing control provocation conditions, assessed repeatedly over time in an experimental study. *Figure 1a:* Average subjective sadness response over time to neutral, stress, and alcohol cue conditions by gender (in stress: women > men, $p = .01$). *Figure 1b:* Average subjective anxiety response over time to neutral, stress, and alcohol cue conditions by gender (in stress: women > men, $p < .0001$). *Figure 1c:* Average observed nonverbal behavioral and body responses to neutral, stress, and alcohol cue conditions by gender (in stress: women > men, $p = .04$). *Source:* Reproduced with permission from Chaplin et al. 2008.[22] Copyright © 2008 Research Society on Alcoholism and the International Society for Biomedical Research on Alcoholism. Published by Wiley-Blackwell. All rights reserved.

Higher levels of negative affect have specifically been linked to initiation and relapse in alcohol and other substance use disorders.[23] In adolescents, negative affect is strongly associated with the onset of drinking and alcohol misuse, and higher levels of negative affect are also associated with greater child maltreatment, victimization, and adversity.[23] Girls show greater negative affect such as sadness in response to early life stress than boys,[19] similar to findings for adults (and as shown in Figure 1). A number of studies have shown that emotional stress and negative

affect also elicit significant alcohol craving,[10] and negative affect and anxiety are key symptoms of alcohol withdrawal that are further exacerbated by exposure to alcohol cues.[7] Such a link between stress and negative affect and alcohol motivation highlights the need to assess sex differences and women-specific vulnerability in processes underlying the association between stress and negative affect and alcohol intake, alcohol misuse, and risk of AUD.

Negative affect becomes an important component in the development of AUD in women because past literature has documented that, while men tend to consume alcohol to enhance positive feelings,[24] women more frequently consume alcohol in response to negative emotions.[11,25] Much like the association between early trauma and substance use, negative affect, such as temperamental negative mood, has also been associated with the development and maintenance of substance use disorders.[11] Negative emotions, drinking to regulate negative affect, and stress are among the factors associated with increasing rates of AUD in women.[11] Furthermore, studies have also shown that, in addition to trauma, abuse, and chronic stress, negative affect is predictive of alcohol misuse and addiction vulnerability.[10] Thus, temperamental negative emotionality, which is often documented as higher in women and is linked to substance use vulnerability, may place women at a higher risk of subsequent alcohol and substance misuse, but its specific role in women's substance misuse needs further investigation.

Sex Differences in Anxiety and Depression

Gender gaps in rates of mental illnesses tend to emerge and/or widen during puberty and have been associated with the rise of different sex steroid hormones in boys and girls that occurs during this period. Before puberty, boys and girls have similar rates of depression; however, soon after puberty, depression becomes twice as prevalent in girls than in boys until late adulthood.[26] This is also true of other mental conditions such as anxiety disorders.[18] Adult women report more mental health problems than men,[21] with women with AUD reporting greater mental health problems than women without AUD. In fact, affective disorders have been shown to be the most commonly comorbid psychiatric disorders in individuals with substance use disorder, including AUD.[10] Even though there exists a representation and estimation bias of women in epidemiological mental health studies, a better understanding of sex-based differences in mental health is crucial to understanding specific risk factors in the development of AUD in women.

Stress is significantly associated with affective and anxiety disorders, raising the issue of whether these disorders contribute to the association between stress and AUD.[11] Research has shown that individuals with anxiety disorders who reported drinking to cope with their anxiety symptoms drank more alcohol and had a higher rate of DSM-IV alcohol dependence than those who did not report drinking to lessen their symptoms.[27] There are higher rates of AUD in those with PTSD than in those without PTSD,[28] and PTSD precedes AUD more often in women than in men.[29] Both stress and trauma exposure experimentally increase alcohol craving,[30] and women with both PTSD and AUD report higher levels of trauma, anxiety, and mood symptoms than men.[31] Furthermore, studies have found that co-occurring AUD, mood and anxiety disorders, and PTSD are associated with higher relapse rates than AUD without such comorbidity.[32,33] Women present different biological, psychological, and physiological effects of alcohol misuse that are crucial to the maintenance of their alcohol use.[5,11] For this reason, sex differences in mental health not only are relevant in the development of AUD, but also need further consideration, especially with regard to prognosis and treatment outcome. Due to the differential physiological and subjective effects of alcohol use in women,[5] AUD symptoms and progression of disease are accelerated in women, including progression to comorbidities of AUD with other psychopathology such as depression, phobias, and other anxiety and affective illnesses.[11,21]

BIOLOGICAL FACTORS INVOLVED IN THE ONSET AND PREVALENCE OF AUD IN WOMEN

Exposure to stressful and traumatic events as well as chronic adverse environments trigger a biological stress response characterized by neural, physiological (autonomic), hormonal (hypothalamic-pituitary-adrenal [HPA] axis), and immune response changes to support resilient, adaptive coping.[10] However, uncontrollable events, repeated or chronic stress, and trauma disrupt these responses, thereby breaking down the adaptive nature of stress responses.[10] This results in allostasis and maladaptive psychological and behavioral responses that put an individual at risk for neuropsychiatric illnesses, including AUD.[10] Well-documented sex differences start in childhood and continue throughout the life span in these physiological, hormonal, and immune responses, and in the disruption and adaptations that occur as a result of childhood trauma, chronic adversity, and repeated stress experiences.[10,11,21] Findings from the authors of this paper and other studies have shown that repeated stress and childhood trauma result in sex-specific adaptations in the autonomic, HPA axis, and immune responses, which have not been well addressed in the literature on risk of AUD.[10,11] For example, girls and women with childhood maltreatment show a blunted HPA axis stress response,[10] but those without trauma histories and with high negative affect and mood disorders have a hyperreactive HPA axis response to stress.[10] Changes such as a hyporeactive HPA axis response to acute stress are associated with greater risk of alcohol misuse and AUD, as documented in large longitudinal studies tracking adolescents through young adulthood.[14] Thus, these youth may seek out substances to normalize their lower basal level of arousal.

Other studies document the highly sexually dimorphic stress response, represented by girls and women showing a higher autonomic, catecholaminergic, and immune response to stress, whereas boys and men show greater glucocorticoid and HPA axis responses to acute stress.[11] Recent findings also document that increased exposure to childhood victimization results in higher C-reactive protein levels in girls but not boys,[34] suggesting more stress-related immune compromise and susceptibility in girls relative to boys. In addition, the HPA axis and the autonomic pathways—including the sympathetic and parasympathetic components that coordinate the peripheral biological stress response—show significant dysregulation associated with early life trauma as well as childhood maltreatment, with sex differences in the extent and nature of dysregulation.[10,35] However, specific data on sex differences are not entirely clear. Chronic stress and comorbid mood and anxiety disorders are also associated with altered stress responses,[21] with higher stress responses in women with mood disorders and without childhood maltreatment, but also blunted stress responses in women who misuse alcohol or who have AUD.[11,36] These findings highlight that a critical aspect of the biological stress response is the associated plasticity in peripheral and central stress biology associated with repeated stress, trauma, and adversity. The sex-specific nature of the stress response also results in sex-specific adaptations and allostatic responses to repeated or chronic stress, adversity, and early life trauma and maltreatment.[35] The effects on alcohol motivation and intake of such changes in the stress response are discussed below.

Alcohol Effects on Stress, Negative Affect, and Motivation for Drinking

Alcohol consumption dramatically affects human physiology, and repeated high-intensity use and misuse is associated with significant neuroadaptations and breakdown of the brain and peripheral systems that coordinate stress, emotion, and reward regulation.[36] Growing evidence suggests that these adaptations promote a feedforward development of compulsive motivation for alcohol use and misuse.[10,21,33] Not only does alcohol stimulate striatal dopaminergic pathways, but it also directly stimulates the HPA axis and affects glucocorticoid receptors in extrahypothalamic, limbic, forebrain, and medial

prefrontal cortex (mPFC) circuits associated with the development and progression of AUD.[36] Alcohol-associated neuroadaptations in HPA axis responses to stress and alcohol cues may serve as psychobiological markers of the cycle of recurring alcohol consumption.[36] Sex differences in individuals with AUD in the phasic response to stress and in basal tonic levels of HPA axis and the peripheral catecholamines have also been documented.[11] For example, women with AUD show lower tonic adrenocorticotropic hormone (ACTH) levels but higher norepinephrine (NE) levels relative to men, but also higher relative stress-induced ACTH response and more blunted stress-induced NE response relative to men[11] (see Figure 2). Thus, neuroadaptations resulting from alcohol consumption (acute and chronic) may facilitate the risk for AUD susceptibility and maintenance in a sex-specific manner.

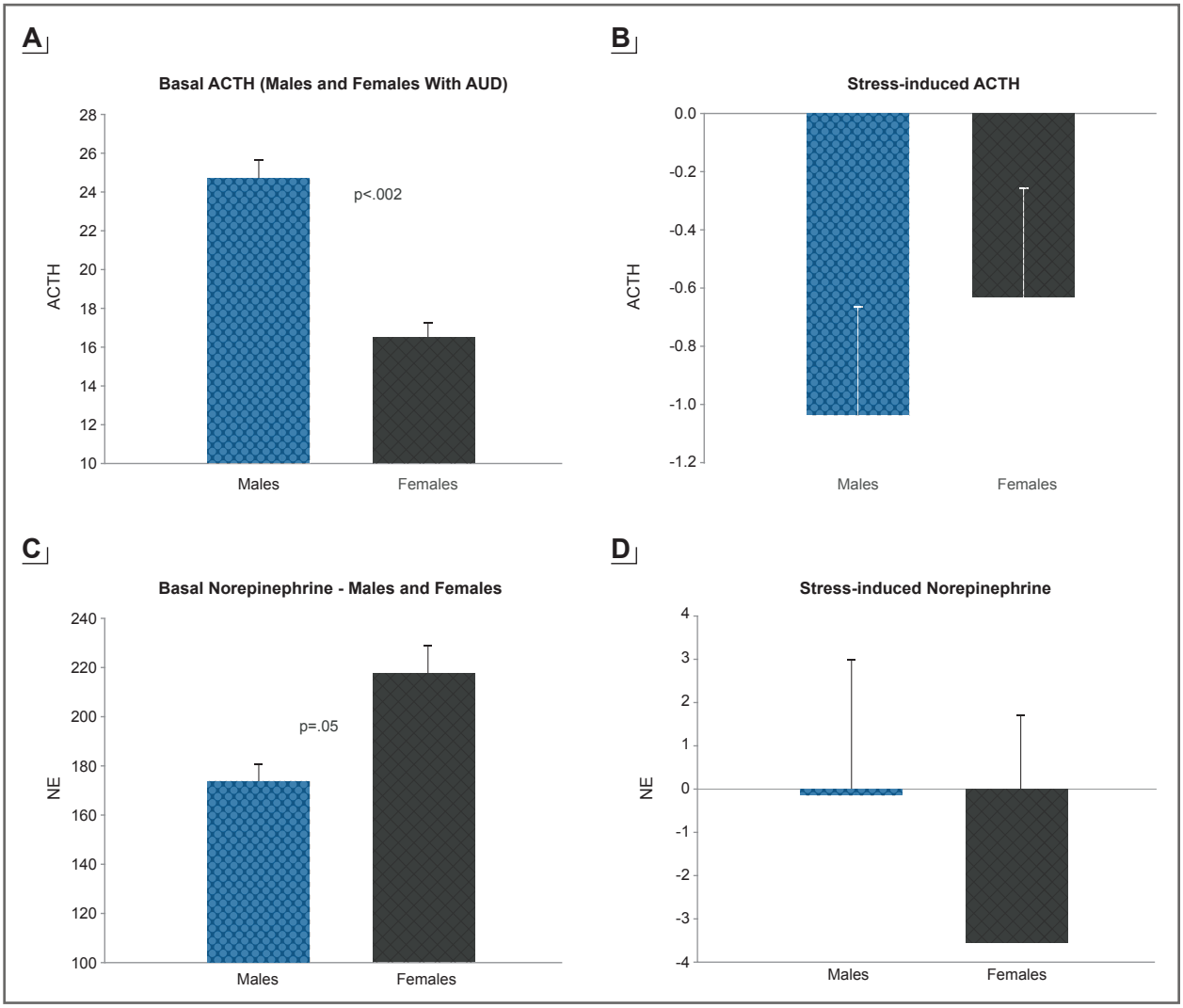

Figure 2 Gender differences in ACTH and NE in men and women with alcohol use disorder (AUD) participating in a laboratory experiment with exposure to individually calibrated stress, alcohol cue, and neutral relaxing imagery on 3 separate days, one condition per day. *Figure 2a and Figure 2b:* ACTH differences between males and females with AUD at baseline (a) and following stress exposure (b) relative to their neutral response. Attenuation of the diurnal drop is shown in females (Stress > Neutral, $p = .0009$) but not in males. *Figure 2c and Figure 2d:* NE differences between males and females with AUD at baseline (a) and following stress exposure (b) relative to their neutral response. Attenuation of the diurnal drop is shown in males, but not in females (Neutral > Stress, $p < .0001$). *Note:* ACTH, adrenocorticotropic hormone; NE, norepinephrine.

Following acute, moderate exposure to alcohol or stress, dopaminergic, hypothalamic autonomic, and catecholaminergic pathways have the opportunity to return to their basal states after activation. With alcohol misuse, binge or heavy drinking, and chronic alcohol use, large-scale adaptations and allostatic overload to neuroendocrine regulation circuits occur. These physiological changes have been associated with the transition from controlled to compulsive alcohol seeking in humans.[36] In fact, in binge and heavy drinkers, a neuroendocrine tolerance to stress and alcohol consumption is observed. For example, a blunted cortisol response to alcohol is observed among individuals with a history of binge or heavy drinking relative to moderate drinkers.[37] This blunted response to alcohol in those with a history of binge or heavy drinking is identified as neuroendocrine tolerance. Recent findings indicate that, in binge or heavy drinkers, blunted cortisol responses and higher subjective craving are each associated with greater amounts of alcohol intake in the laboratory.[37] It is important to note that the sample had a majority of men, and sex differences in these effects have yet to be explored. Thus, although binge and heavy alcohol use and associated adaptations in stress biology appear to be involved in the development of neuroendocrine tolerance and in the resulting increases in compulsive motivation,[36,37] neither sex differences in the alcohol-related neuroendocrine tolerance nor the possible sex differences on its effects on alcohol motivation and intake have been explored thus far.

Alcohol and Stress Interactions on Peripheral and Central Nervous System Responses and Sex Differences

Sex differences have been found in pharmacokinetics and pharmacodynamics of alcohol[38] as well as in neuroanatomy and chemistry.[24] Blood alcohol levels rise faster and stay elevated for longer in women than in men. Sex hormones affect the neural pathways and influence neurotransmitter activity, which affects an individual's physiological and behavioral responses to drugs.[24] For example, even though men show stronger activation of the brain reward system in response to alcohol than do women,[24] the female brain suffers more damage and inflammation from alcohol withdrawal.[39] Important to the current discussion, alcohol stimulates the biological stress pathways in similar ways to psychological stress and trauma.[36] Similarly, significant adaptations and changes occur as a function of repeated and binge alcohol use in these biological stress pathways, and stress and alcohol misuse may act synergistically to modify HPA as well as autonomic and neural responses to stress and alcohol, which may in turn drive greater craving and compulsive seeking for alcohol.[10,36]

A number of studies have linked greater stress reactivity in plasma/salivary cortisol responses as a risk factor for comorbidity of mood disorders and AUD.[40] Research has also shown that blunted salivary cortisol response to stress is a risk factor for AUD development in at-risk children with a family history of substance misuse or substance use disorder.[41] There also may be significant variation in these responses as assessed by concentrations in plasma/serum for ACTH, plasma/serum and saliva for cortisol, salivary alpha-amylase (a measure of autonomic adrenergic arousal), and physiological assessments of heart rate and heart rate variability, as a function of extent of chronic stress or trauma exposure.[10,42] Specifically, one study evaluated at-risk prepubertal boys (ages 10 to 12) with fathers with substance use disorder and found that high-risk boys secreted significantly less salivary cortisol in response to an anticipated stressor compared to controls.[41] These findings were corroborated by another study using a stress task in adolescents, which documented that blunted physiological and emotional responses to stress in adolescents were related to greater risk of alcohol and substance use.[43] In a larger cohort that also evaluated sex differences in adolescents ages 14 to 17 who were prenatally exposed to cocaine relative to nonexposed youth, elevated basal salivary concentrations of cortisol were found in the at-risk group relative to nonexposed youth.[44] In contrast, at-risk youth exhibited a blunted salivary cortisol response to a social stressor compared to controls.[44] Furthermore, sex differences were

found in prediction of future substance use: for girls, self-reported sadness in response to the social stressor predicted future drug use, whereas for boys, blunted salivary alpha-amylase (an autonomic nervous system measure) in response to the same social stressor predicted future drug use.[44] These results suggest that distinct physiological and emotional stress responses among boys and girls are associated with different risk profiles for future drug use.

In another series of studies, impaired neuroendocrine responses to alcohol and to stress have also been associated with an increased motivation for binge or heavy drinking, thereby serving as a potential risk marker for the progression from heavy drinking to DSM-IV alcohol dependence.[45] In a large population-based study where children were followed longitudinally between ages 14 and 20, the age at which the first alcoholic drink was consumed varied as a function of cortisol levels, and blunted cortisol responses to stress were associated with greater risk of alcohol misuse.[46] Furthermore, among heavy- and light-drinking adults who were exposed to an oral alcohol challenge and followed for 6 years, heavy drinkers showed greater sensitivity to stimulating effects and lower sensitivity to the sedative effects of alcohol compared to light drinkers.[45] Moreover, heavy drinkers demonstrated lower salivary cortisol release in response to the alcohol challenge and, 6 years later, presented with a greater number of AUD symptoms than did light drinkers.[45] These findings suggest that alcohol and stress significantly impact the psychological and biological stress responses—altering affect, mood, and anxiety as well as biological stress responses. However, a significant gap remains in understanding sex differences in these effects given that differences by gender have not been well studied in the literature.

One of the effects of acute administration of alcohol is the activation of both reward and stress pathways in the brain. The mesocorticolimbic dopaminergic system, involved in reward processing, is activated alongside the corticotropin-releasing factor (CRF)-HPA axis and the autonomic nervous system pathways involved in stress responses. Activation of these central pathways results in increased levels of ACTH and cortisol, as well as changes in heart rate, blood pressure, and skin conductance responses.[10] Withdrawal and abstinence following chronic alcohol use also are associated with dysfunctional sympathetic and parasympathetic responses, highlighting the effect of alcohol misuse on these peripheral stress pathways; as shown in Figure 2, there are sex differences in these alcohol-related adaptations of the stress pathways.

Even though acute administration of drugs, such as alcohol, may increase mesolimbic dopamine levels, sustained alcohol misuse downregulates the mesolimbic dopamine pathways and thus decreases basal dopamine levels.[10] Using brain imaging, research has shown that there are fewer dopamine D2 receptors and less dopamine transmission in frontal regions and in the ventral striatum area of individuals with AUD during withdrawal.[10] Furthermore, dopamine response to drugs is sex-specific, with men showing greater dopamine release than women.[47] Prolonged exposure to drugs, such as alcohol, results in altered and blunted neurochemical responses to drugs as well as to stress. Behavioral sensitization to drugs and stress can also be observed and is associated with CRF and noradrenergic effects on dopaminergic (and non-dopaminergic) pathways and with synaptic alterations in the ventral tegmental area, amygdala, nucleus accumbens, and mPFC.[10] More importantly, sex differences in both stress and reward circuitry have been reported using functional magnetic resonance imaging (fMRI) research, where responses to stress and to alcohol cues relative to neutral cues show a differential profile in men who drink socially versus women who drink socially[48] (see Figure 3). Furthermore, although striatal activation during alcohol cue exposure was associated with alcohol craving, this effect was seen in men only and not in women, and different prefrontal regions were associated with stress-induced anxiety in men and women (see Figure 4). These data suggest that central brain pathways differentially modulate stress and alcohol motivation responses in men and women who drink socially and point to a significant need to

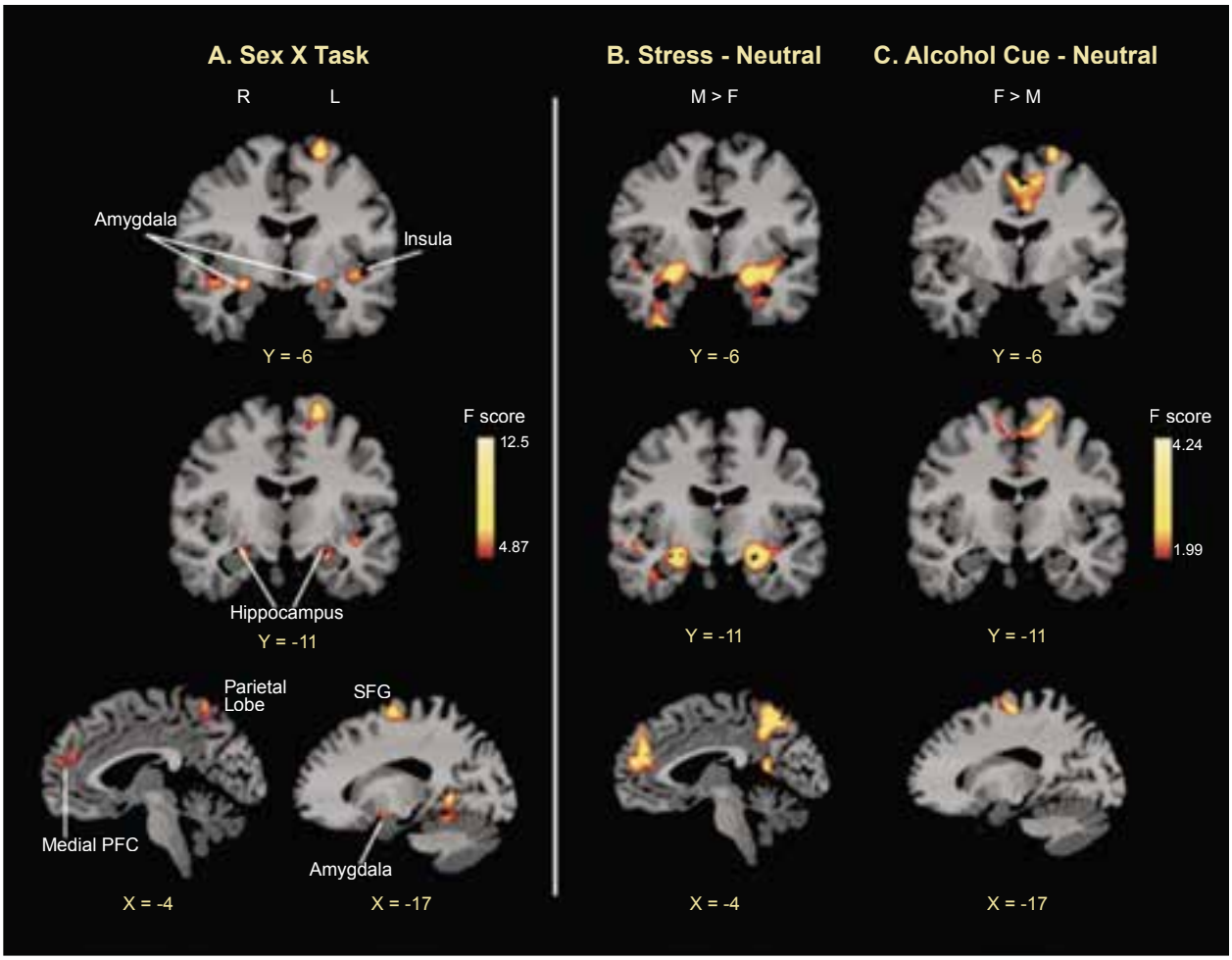

Figure 3 Whole-brain voxel-based functional magnetic resonance imaging (fMRI) showing a sex × condition interaction and corresponding activations in the stress-neutral and alcohol cue-neutral contrasts for males (M) and females (F) who drink socially. **A**: The sex × condition interaction effect was significant in regions of the superior and middle frontal gyrus (SFG/MFG), medial prefrontal cortex (mPFC, dorsomedial and ventromedial), rostral anterior cingulate cortex, emotion limbic regions (posterior insula, putamen, amygdala, hippocampus, and parahippocampal gyrus), temporal lobe, and visuomotor perception areas (parietal lobe, occipital lobe, and cerebellum) ($p < 0.01$ whole-brain familywise error [FWE] rate corrected). To elucidate the source of the interaction, male versus female contrasts were conducted for (**B**) stress relative to neutral, and (**C**) alcohol cue relative to neutral brain responses at the $p < .05$ whole-brain FWE corrected. Significantly, greater M > F stress-induced activity in the mPFC and limbic regions was observed. Alcohol cue-induced activity in the SFG/MFG was significantly higher in women than in men. No differences in F > M for the stress-neutral and in M > F contrast for the alcohol cue-neutral survived whole-brain correction. Coordinates are given in Montreal Neurological Institute space. *Note:* F, female; L, left; M, male; mPFC, medial prefrontal cortex; R, right. *Source:* Reproduced with permission from Seo et al., 2011.[49] Copyright © 2010 Wiley-Liss, Inc. All rights reserved.

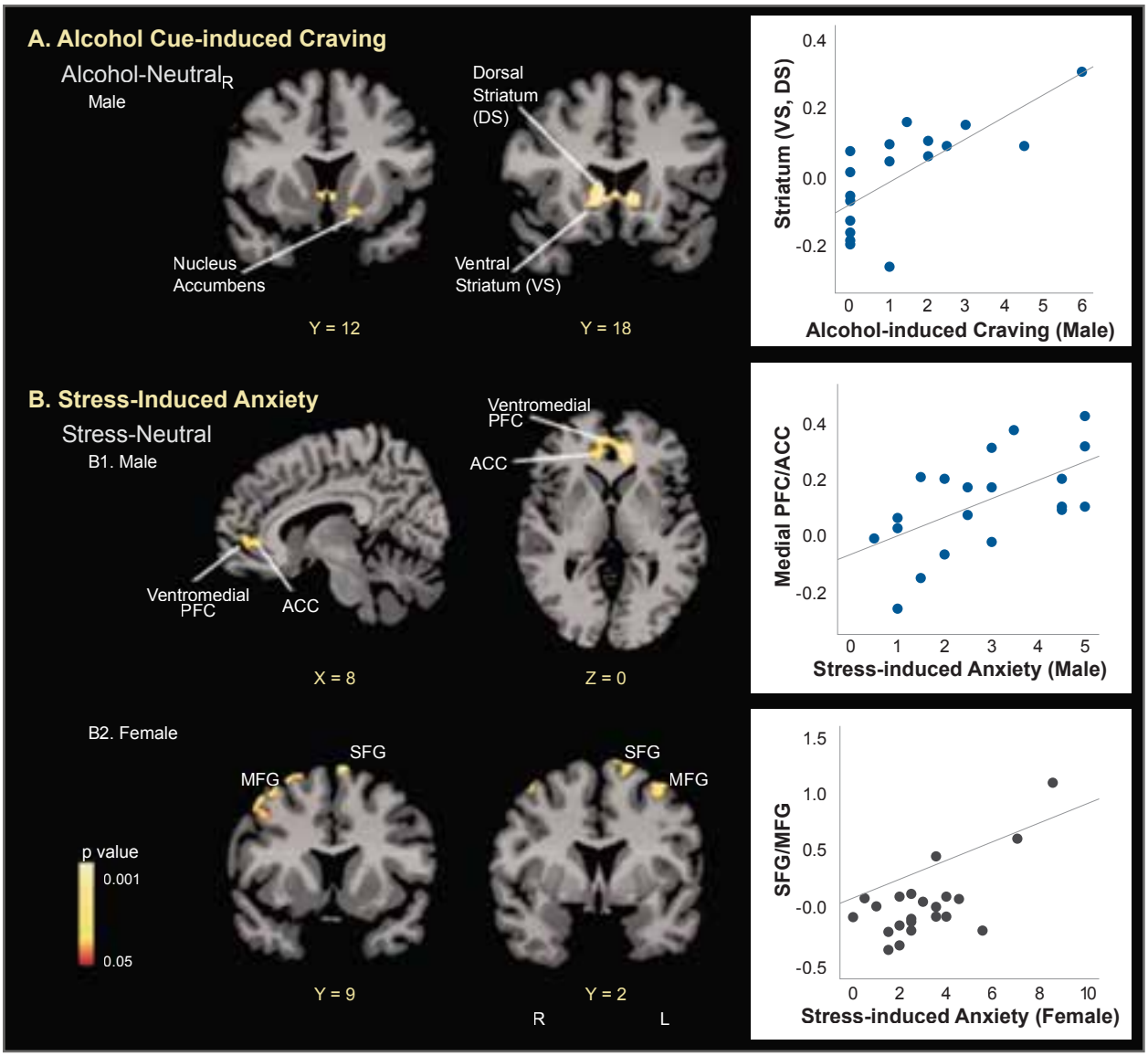

Figure 4 In men and women who drink socially, whole brain voxel-based correlation and corresponding scatter plots for (A) alcohol cue-induced craving ratings with neural responses during alcohol cue versus neutral cue exposure in males as well as (B) stress-induced anxiety ratings with neural response during stress versus neutral cue exposure in males and females ($p < .05$, whole-brain familywise error rate [FWE] corrected). **A**: In males, elevated alcohol craving ratings were associated with increased activity in the striatum cluster ($r = .74$) that encompassed ventral and dorsal striatum, including the left nucleus accumbens (X = −13, Y = 12, Z = −12). **B1**: In males, enhanced stress-induced anxiety ratings were associated with increased brain activity in a medial prefrontal cortex cluster that included the ACC, ventromedial PFC, and medial PFC ($r = .59$). **B2**: In females, stress-induced anxiety ratings were positively correlated with bilateral brain activity in superior/middle frontal gyrus (winsorized $r = 0.62$). Coordinates are given in Montreal Neurological Institute space. *Note:* ACC, anterior cingulated cortex; L, left; MFG, middle frontal gyrus; PFC, prefrontal cortex; R, right; SFG, superior frontal gyrus. *Source:* Reproduced with permission from Seo et al., 2011.[49] Copyright © 2010 Wiley-Liss, Inc. All rights reserved.

understand the neurobiology of binge drinking and chronic alcohol misuse in women.

STRESS NEUROCIRCUITRY, EMOTION REGULATION, AND ALCOHOL CRAVING

Previous human research indicates that trauma, adversity, and chronic stress alter the activity and structure of the prefrontal cortical, limbic, and striatal brain networks involved in regulating stress and emotions as well as reward and higher cognitive or executive control functions.[10] These brain circuits also show significant sexual dimorphism, suggesting a need to explore the role of sex differences in their structure and function in critical regulation and coping functions for stress, trauma, and self-control over alcohol intake. These functions can include the regulation of distress and emotions, such as controlling and inhibiting impulses, refocusing and shifting attention, employing working memory, monitoring conflict and behavior, linking behaviors to possible future consequences, and demonstrating flexible consideration of alternatives for response selection and decision-making.[10]

Recent evidence from human brain structural and magnetic resonance imaging shows that recent life stressors (e.g., death in family, divorce, relationships ending, being assaulted, financial crises, robberies), trauma (physical, emotional, or sexual abuse), and chronic stress (subjective experience of continual stressors or ongoing life problems) are associated with lower gray matter volume in medial prefrontal, amygdala, hippocampus, and insula regions of the brain.[50,51] Similarly, recent life stress and acute stress exposure (such as those listed above) may decrease responses in the prefrontal regions (such as the dorsolateral prefrontal cortex and ventromedial prefrontal cortex) associated with working memory, reward processing, and resilient coping.[52] Such changes in the neural circuits underlying emotion and reward dysregulation may promote risky alcohol use (e.g., binge drinking), emotional eating, and frequency of arguments and fights.[52] Furthermore, these circuits are sexually dimorphic in their responses to stress and anxiety, where differential brain regions are associated with stress-induced anxiety in men versus women[52] (see Figure 5). As anxiety and stress responses are associated with alcohol motivation and increased alcohol use, sex differences in the neurocircuits that respond to and regulate stress and anxiety suggest that there are also sex differences in the brain regions that drive stress-induced alcohol craving and intake. However, there is a need for examining this association in a sex-specific manner in future research.

Across at-risk children and adults with exposure to stress, trauma, or in utero substance use, sex-specific brain changes in emotion and reward regions are associated with risk of alcohol misuse and AUD.[53] A study of prenatally cocaine-exposed and non-exposed adolescents (ages 14 to 17) found lower gray matter volume in limbic and frontal regions of the brain as assessed by MRI and whole-brain voxel-based morphometry in the at-risk prenatally exposed relative to non–cocaine-exposed adolescent controls.[53] In addition, lower gray matter volume in these brain regions was associated with initiation of tobacco, alcohol, and cannabis use.[53] Furthermore, sex-specific effects were found in adults who misuse cocaine and alcohol, with women showing lower gray matter volume in emotional-limbic regions of the insula, amygdala, and hippocampus, and men showing lower gray matter volume in the midcingulate and frontal regions.[54] These data suggest that changes in brain volume may serve as biological risk markers for alcohol misuse, AUD, and substance use. Indeed, low behavioral and cognitive control are linked to lower prefrontal and insular cortex volume, and high activation of limbic-emotional and striatal-motivation brain regions under stress suggest one specific pattern underlying risk of addictive behaviors where there is a decreased ability to control rewarding behaviors.[10] Thus, cortico-striatal reward and motivational brain pathways appear to be key targets of disrupted

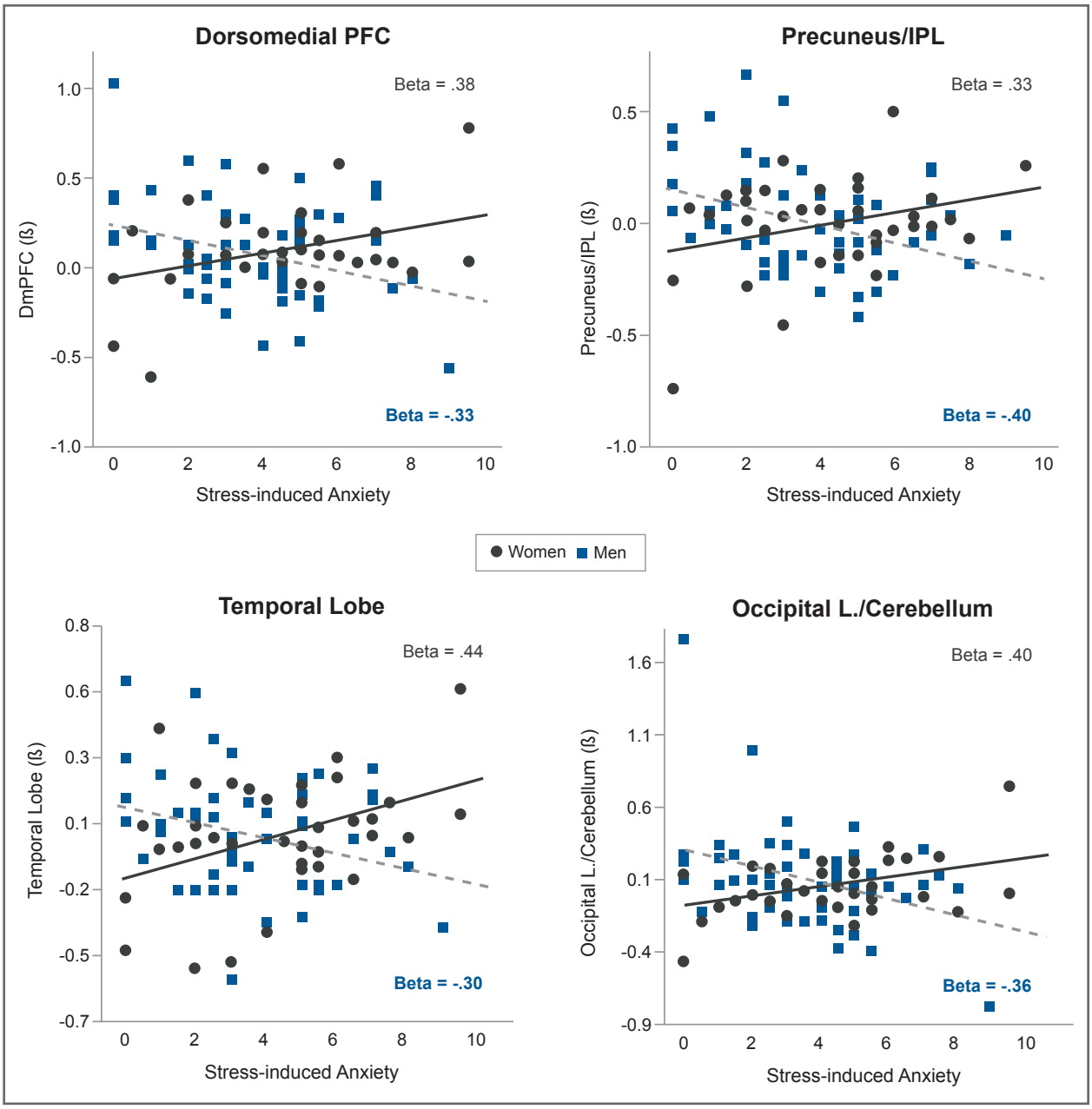

Figure 5 Scatter plots and regression lines for stress-induced anxiety ratings with neural responses during stress relative to neutral-relaxing exposure for specific regions of interest (ROIs). Simple effects in ROIs from whole-brain regression of significant regions from the gender-by-anxiety interaction effects analyses are shown separately in men and women. Stress-induced anxiety predicted brain responses to stress differentially by gender. The plots show (A) positive (women [W]) and negative (men [M]) associations between stress-induced anxiety ratings and activity in the dorsomedial prefrontal cortex (PFC) (W: β = .38; M: β = −.33), precuneus and inferior parietal lobe (W: β = .33; M: β = −.40), middle/inferior temporal gyrus (W: β = .44; M: β = −.30), and occipital lobe and cerebellum (W: β = .40; M: β = −.36). Beta (β) indicates the standardized coefficient. There were no outliers in any of these brain regions for both men and women. *Note:* DmPFC, dorsomedial prefrontal cortex; IPL, inferior parietal lobe; Occipital L., occipital lobe. *Source:* Reproduced with permission from Seo et al., 2017.[48] Copyright © 1999-2020 Wiley-Liss, Inc. All rights reserved.

central stress and emotional responses, suggesting a potentially important sex-specific mechanism by which stress may affect susceptibility to alcohol misuse and AUD vulnerability. As these pathways are sex-specific, the stress- and alcohol-related adaptations also occur in a sex-specific manner, resulting in sex differences in the biological pathways of risk for AUD. However, there is a desperate need for research to elucidate these sex-specific changes and risk factors for AUD.

TRANSITION TO ADDICTION

Women report different motives for alcohol use than men,[10,11] and are more likely to self-medicate their emotional distress, negative affect stemming from high stress, and mood and anxiety disorders.[10,11] As outlined above, sex differences in addiction vulnerabilities set women at a disadvantage related to exposure to and risk of alcohol misuse, maintenance, and relapse.[11] As described in the previous sections, some research has documented sex-based differences in neuroendocrine stress and reward pathways with chronic alcohol use.[11]

The cross-sensitization process of stress and alcohol effects suggests that sex-specific adaptations occur with alcohol misuse and chronic use, which may contribute to alcohol craving, continued use, and relapse. The progression from alcohol misuse to AUD often includes overpowering cravings seen as a physiological need rather than a hedonic desire.[10] This craving is associated with compulsive seeking of alcohol, which becomes stronger in the context of alcohol cues or stress exposure, increasing the chances of relapse. Sex differences in stress assessment and cue reactivity in social drinkers and in patients with AUD have been reported. For example, findings in social drinkers indicate that the incentive value of alcohol may be less sensitized by negative mood and stress in female social drinkers compared with male social drinkers.[55,56] However, findings show that, compared to men with AUD, women with AUD demonstrate greater alcohol cue reactivity following negative mood induction.[57] Furthermore, HPA-axis hyporeactivity to social stress, alcohol cue exposure, and alcohol intake, as well as a blunted cortisol response to stress in women with AUD have been reported concurrently with enhanced emotional distress and greater craving, which, in turn, have been shown to increase the risk of relapse and return to alcohol use in early treatment.[11] Although conducted using separate stress- and cue-reactivity paradigms, this research consistently reflects robust sex-specific dissociations between participants with and without AUD in relation to stress system function and alcohol cue reactivity, supporting the notion that there are sex differences in the mechanisms that drive the transition to AUD, its maintenance, and the relapse to alcohol use. However, the specific link between the robust sex-specific stress and cue reactivity responses and actual binge and heavy alcohol intake in women are not clear and needs greater study in future research.

IMPLICATIONS FOR ONSET AND MAINTENANCE OF AUD IN WOMEN AND FUTURE DIRECTIONS

Sex differences in the onset of alcohol misuse and the development of AUD have been reported. The effects of greater exposure to and experience of stress, trauma, victimization, negative affect, and mood and anxiety disorders in women represent a specific risk pathway for the onset and development of AUD in women. However, estimation bias in occurrence of mood and anxiety disorders needs specific consideration in assessing these associations to alcohol misuse and AUD. Also, although this paper has not focused on genetic mechanisms and epidemiological and sociocultural factors that may explain sex differences, these areas also need further attention. Nonetheless, sex differences in the psychological and biological response to both stress and alcohol intake are well known. Animal studies have revealed that sex steroid hormones interact with

the HPA axis to influence stress regulation, and these sex hormones also modulate brain limbic, striatal, and frontal circuits to influence alcohol seeking in sex-specific ways.[11] However, research in humans assessing interactions between stress, reward, and sex steroid hormones has lagged behind. For example, fluctuations in sex hormones across the menstrual cycle may impact neuroadaptations in stress response and alcohol craving[11] as described below, and, in doing so, may point to specific prevention and treatment efforts.

Although not specifically examined in risk of AUD or in women with AUD, some evidence in other substance use disorders indicates that during the follicular phase of the menstrual cycle, positive rewarding drug effects may be potentiated in women to the same levels as men.[11] Similarly, increased levels of progesterone and decreased estrogen/progesterone ratio have been shown in women who misuse substances relative to healthy controls.[11] Such changes across the menstrual cycle may then alter brain responses to stress and cues as well as affect intensity of emotional responses and craving states in women with AUD relative to men with AUD.[11] As the hypothalamic-pituitary gonadal (HPG) axis modulates sex steroid levels during the menstrual cycle and influences stress responses in women, adaptations in the HPG and HPA axes with the transition to AUD may lead to altered levels of estrogen, progesterone, and their related neuroactive steroids. This could further predispose women to increased anxiety, negative emotion, and lowered tolerance to stress, which in turn may increase vulnerability to craving and compulsive alcohol use in women.

At a time when alcohol misuse is on the rise among girls, and binge drinking and AUD rates have substantially increased in women, there is a major gap in understanding the mechanisms and processes that specifically increase risks for the onset and development of AUD in girls and women and for the maintenance of AUD in women. Greater specific, targeted future research on risk pathways for girls and women can address the need for focused development of targeted prevention and early treatment efforts in females. Prevention and early treatment may reduce the prevalence rates of AUD—as well as the much higher rates of alcohol-related health problems and morbidity in women compared to men—and such efforts may increase alcohol recovery rates among women.

Acknowledgments

This work was supported in part by the National Institutes of Health/National Institute on Alcohol Abuse and Alcoholism grants R01-AA013892 and R01-AA026514.

Financial Disclosure

The authors declare that they have no competing financial interests.

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Co-Occurring Alcohol Use Disorder and Anxiety

Bridging Psychiatric, Psychological, and Neurobiological Perspectives

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A substantial number of people who have problems with alcohol also experience strong anxiety and mood problems. This article provides an overview of the evolving perspectives of this association in the context of three related disciplines—psychiatry, psychology, and neuroscience. Psychiatric and epidemiological studies show that having either an anxiety- or alcohol-related diagnosis elevates the prospective risk for developing the other disorder. From the psychological perspective, behavioral research demonstrates that drinking to cope with negative affect is a potent marker for current and future problems with alcohol. Neuroscientific research implicates overlapping neurobiological systems and psychological processes in promoting the rise of negative affect and alcohol misuse. The psychiatric perspective that alcohol misuse and co-occurring anxiety represent neurobiologically distinct diagnostic conditions has dominated the field for many decades. However, recent research provides increasing support for the neuroscientific perspective that these conditions share underlying, mutually exacerbating, neurobiological processes.

KEY WORDS: alcohol; anxiety; comorbidity; negative affect; stress

Introduction

"Those who cannot remember the past are condemned to repeat it."
—*George Santayana*

Few observations in psychiatry have been documented as long and as consistently as the association between anxiety (and general negative affect) and the chronic misuse of alcohol. Research has shown that up to 50% of individuals receiving treatment for problematic alcohol use also met diagnostic criteria for one or more anxiety disorders.[1,2] This percentage can be compared with the prevalence of current (within the past 12 months) anxiety disorders in the U.S. community, which is estimated to be 11%.[3,4]

The psychiatric, psychological, and neuroscientific disciplines have developed theories to explain the association between alcohol and anxiety disorders. Each discipline has independently contributed to the understanding of how to best describe and treat alcohol use disorder (AUD) in the context of negative affectivity. However, very little cross-communication has occurred among these disciplines. This insularity and particularism continue to impose significant opportunity costs in this field.

A key challenge to applying a comparative perspective across disciplines and time is the use of unique and evolving terminology and definitions for similar phenomena. Terms such as anxiety, anxiety disorder, depression, mood disorder, tension, stress, stress disorder, and negative affect are used differently across disciplines and time. The relationships among these constructs can be conceptualized as a Venn diagram, with the shared spaces representing overlapping constructs. In these overlapping spaces, the greatest opportunities for integration across disciplines can be found. In this review, the term "negative affect" (i.e., negative hedonic tone and the biology that underpins it) describes the shared psychological and biological space for related constructs of anxiety, tension, stress-responding, and anxiety disorder.

First, historical trends and research related to the psychiatric classifications of alcohol misuse, negative affect, and their co-occurrence are reviewed, including typologies and diagnoses. Next, a history of behavioral examinations of negative affect and alcohol misuse is presented from the psychological perspective, along with a discussion of research on the use of alcohol to cope with negative affect. Finally, neurobiological research on the relationship between negative affect and alcohol use is reviewed, and the opponent process model is explained. The concluding section synthesizes the discipline-specific research to identify conclusions and unanswered questions about the connections between alcohol use and negative affect.

Psychiatric Disorder Classifications and Diagnoses

Typologies are the oldest formal approach to categorizing alcohol misuse accompanied by strong negative affect. Summarizing dozens of such typologies from the past 200 years, Babor observed that virtually all identified an anxious-depressed subtype (Apollonian) and a revelry-oriented, rule-breaking subtype (Dionysian).[5] The promulgation of these typologies occurred primarily in the "prescientific" era (before the 1940s), but their legacy remains evident today.

For example, Cloninger described a model in which heritable personality traits set the stage for the development of Type I or Type II "alcoholism."[6,7] Type I included people whose problems with alcohol use began later in adult life, often contemporaneous with increasing negative affect or stressful life experiences. These individuals were characterized as shy, anxious, and pessimistic (Apollonian), and their alcohol use was believed to be motivated by an effort to cope with the unpleasant subjective experiences associated with these traits. Type II included people whose problems with alcohol use began early in adult life, without reference to environmental conditions or fluctuations in internal emotional states. These individuals were characterized as having relatively less fear and guilt while engaging in relatively more rule-breaking and antisocial behavior (Dionysian), often including drinking alcohol and other drug use. Past and present typology approaches share the view that negative affect is not a separate, co-occurring condition but rather an inherent trait of a significant subtype of people who have problems with alcohol.

Comorbidity paradigm

By the middle of the 20th century, medically oriented researchers increasingly attempted to categorize and quantify psychopathological and medical conditions observed among people being treated for the chronic misuse of alcohol.[8] Unlike earlier typologies in which strong negative affect was considered an inherent trait of a subtype of people who had problems with alcohol, this descriptive, medical approach viewed strong anxiety and other psychiatric problems as distinct, diagnosable conditions that often co-occur with alcohol-related conditions. This conceptualization led to co-opting the medical term "comorbidity" to indicate the presence of two or more distinct psychiatric disorders.[9] The psychiatric paradigm of comorbidity was first fully realized and codified nearly 40 years ago in the third edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM).[10] In

the more recent DSM-5, the paradigm remains the standard psychiatric model for describing, characterizing, and treating co-occurring negative affect and AUD.[11]

Epidemiology of co-occurring disorders

Within the co-occurring psychiatric disorder (comorbidity) paradigm, and armed with the DSM's observable and reliable diagnostic criteria, several large, epidemiological surveys have quantified the relative risk for an alcohol-related diagnosis in the presence versus absence of a diagnosed anxiety disorder. The largest and most comprehensive community-based surveys in the United States include the Epidemiologic Catchment Area study ($N \sim 20{,}000$), the National Comorbidity Survey ($N \sim 8{,}000$), and the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC, $N \sim 43{,}000$).

Alcohol-related diagnoses

An important issue in interpreting epidemiological findings is the diagnostic definition of AUD. The DSM-IV included two separate alcohol-related diagnoses: alcohol abuse and alcohol dependence.[12] A DSM-IV diagnosis of alcohol abuse required a maladaptive pattern of ongoing drinking resulting in multiple impairments. Some impairments that met the criteria were: not fulfilling major obligations at work, school, or home; using alcohol while driving or in other physically dangerous situations; having recurrent legal problems from driving under the influence, fighting, or other actions related to alcohol use; and experiencing exacerbation of interpersonal problems because of continued alcohol use.

A DSM-IV diagnosis of alcohol dependence required meeting at least three of seven criteria.[12] The first two criteria were physical—development of tolerance to alcohol and development of withdrawal symptoms. The remaining five criteria were behavioral signs of dependence, such as spending a great deal of time obtaining, drinking, or recovering from the effects of alcohol and drinking more alcohol, or for longer, than intended.

In the DSM-5, however, alcohol abuse and dependence have been integrated into a single diagnosis of AUD with mild, moderate, or severe subclassifications.[11] The separate classifications of alcohol abuse and alcohol dependence were removed.

Most available epidemiological studies used diagnostic criteria from DSM-IV or earlier, and they uniformly showed a positive association between anxiety or mood disorders and alcohol dependence but not alcohol abuse. A synthesis of the major epidemiological studies showed the risk (odds) for meeting diagnostic criteria for alcohol dependence more than doubled ($OR = 2.3$) among individuals with an anxiety disorder compared to those with no anxiety disorder.[13] However, the odds of receiving a diagnosis of alcohol abuse alone were about the same for individuals with or without an anxiety disorder ($OR \sim 1$). These results suggest that the association between anxiety disorders and AUD will diminish in forthcoming epidemiological findings (e.g., in results from the NESARC III) that use the DSM-5 diagnosis criteria.

Anxiety disorder diagnoses

Parallel to the question of how the definitions for alcohol-related diagnoses affect the magnitude of the association with anxiety disorders is the question of how the definitions for anxiety disorders affect that association. An early analysis[14] of research on co-occurring disorders in the 10 years following the introduction of DSM-III criteria reached the provisional conclusion that each major subtype of anxiety disorder (i.e., social phobia disorder, panic disorder, and generalized anxiety disorder)[10] had a unique relationship to alcohol misuse, presumably because of distinct neurobiology and symptom manifestations (e.g., discrete symptom triggers, omnipresent symptoms, or random symptom episodes). This conclusion fit neatly within the zeitgeist of that era, which presumed important clinical and biological distinctions for all psychiatric diagnoses.[10,13]

However, restricting attention to a single diagnosis and its relationship to alcohol misuse does not align with more recent research. For example, it is now better understood that various anxiety disorder subtypes are commonly present in the same individual.[15,16] Therefore, conclusions based on epidemiological findings that focused exclusively on one anxiety disorder diagnosis without accounting for the likely presence of additional anxiety subtypes have become suspect. Also, the conclusion that each

anxiety disorder subtype has a unique association with alcohol misuse is inconsistent with research showing that all the subtypes individually confer a similar increase in risk for alcohol misuse,[13] and that the risk increases substantially for each additional anxiety disorder subtype.

Recent "big data" modeling approaches have advanced the understanding of epidemiological data related to the association between anxiety disorder subtypes and risk for alcohol misuse. Seminal work using this approach comes from Krueger, who applied structural equation modeling of latent variables related to anxiety and depression diagnoses.[17] This research showed that a large proportion of the covariation in anxiety or mood disorder diagnoses could be characterized along a single continuum called "negative emotionality." However, some of the variance of specific anxiety disorders was distinct from the negative emotionality continuum; that is, some variance was unique to a specific anxiety disorder subtype.

Kushner and colleagues applied this analytic approach to NESARC data to assess the relationship between risk for alcohol misuse and the shared versus unique components of several anxiety and depressive disorders.[18] This analysis showed a strong positive relationship between risk for DSM-IV alcohol dependence and the shared components of the anxiety and depression diagnoses. However, the analysis also showed virtually no relationship between risk for alcohol dependence and the unique components of those diagnoses. These findings are inconsistent with the idea that each anxiety disorder has a unique association with the risk for alcohol misuse. Instead, the results suggest that all anxiety and mood disorders contribute to general negative emotionality, which, in turn, correlates with the risk for alcohol dependence.

Temporal and causal priority

The elevated risk for alcohol misuse in the presence of anxiety represents a positive correlation between these conditions. One of the co-occurring conditions could be causing the other, but a third, unmeasured factor could be causing an increased risk for both conditions. When medical conditions correlate, the search for causality commonly starts by evaluating which condition preceded the other. This approach is based on the logical truism that an effect cannot precede its cause. However, preceding conditions do not necessarily cause later outcomes—the logical fallacy called "post hoc, ergo propter hoc." Still, studies have sought to illuminate the causal associations between the co-occurring disorders by determining which began first.[19] This research has shown that the onset of anxiety disorders preceded alcohol misuse in up to three-quarters of the people who had both conditions,[14] especially for those who had social anxiety disorder.[20]

Failing to clearly distinguish between temporal priority and causal priority is common in interpretation of order-of-onset studies.[20,21] Since its third edition, the DSM's hierarchical diagnostic scheme designates anxiety disorders in the presence of alcohol disorders as an alcohol-induced condition unless the anxiety symptoms presented first or persisted during a period of protracted abstinence.[11,12] This approach not only risks the logical error already discussed but also risks conflating initiating factors with maintaining factors. That is, this approach ignores the possibility that alcohol misuse played some role in the initiation of anxiety symptoms that over time evolved into independent anxiety disorders. However, these logical concerns may be moot empirically, because NESARC data show that the prevalence of substance-induced anxiety and mood disorders among individuals with a diagnosed alcohol disorder is vanishingly small.[4] Unfortunately, clinical guidelines designed to avoid mistaking substance-induced anxiety or mood problems for other anxiety or depressive disorders discourage clinicians from providing effective treatments for these conditions in people who are actively drinking or recently abstinent.[22]

Prospective relative risk

Compared to retrospective assessments of the order of onset for co-occurring disorders, assessments of prospective relative risk (i.e., the risk for developing a condition given the presence or absence of another condition) provide more information about conferred risk. For example, people typically experience onset of social anxiety disorder before they are old enough to legally purchase alcohol, so the anxiety disorder typically precedes problems with alcohol. Therefore, retrospective assessments showing that social anxiety disorder commonly

precedes problems with alcohol superficially suggest that the former causes the latter. However, this type of examination provides no information about the effects of alcohol misuse on later development of social anxiety disorder.

Prospective relative risk avoids problems related to retrospectively examining the order of onset. In a study by Kushner and colleagues, the prospective relative risk of alcohol dependence and several common anxiety diagnoses was examined among approximately 500 college students during their first year, senior year, and third postgraduation year.[21] Although anxiety disorders were more common than alcohol dependence at all assessment years, the prospective risk for new onset of either condition in a later assessment was two to five times greater if the other condition was present at an earlier assessment. Both conditions substantially increased the prospective relative risk for developing the other.

Effects of co-occurrence on alcohol treatment outcomes

Data show that individuals who have co-occurring anxiety or depressive disorders and alcohol-related disorders have a poor response to treatment for alcohol misuse.[23,24] For example, Kushner and colleagues reported that more than twice as many participants who had alcohol-related disorders and co-occurring anxiety or mood disorders, versus participants with no anxiety or mood disorder, returned to any drinking within 4 months following intensive residential treatment for alcohol misuse (52% vs. 21%).[1]

Efforts to mitigate the deleterious effects of co-occurring anxiety disorders on alcohol treatment outcomes, as well as to illuminate causal influences between these conditions, have inspired investigations into how treatment for one co-occurring condition affects symptoms of the other condition. For example, if an anxiety disorder maintains alcohol misuse, effectively treating the anxiety should reduce alcohol use and reduce the likelihood of relapse after treatment. In one study, researchers administered paroxetine or placebo in a double-blind fashion to participants who had AUD and social anxiety disorder.[25] They found that although the medication was clinically effective in reducing social anxiety symptoms, alcohol use severity was unchanged.

Several clinical trials have examined the effect of supplementing standard AUD treatment with a validated treatment for anxiety or mood disorders among individuals with both conditions. A meta-analysis of 15 randomized controlled trials, in which medication or cognitive behavioral therapy for co-occurring anxiety or depressive disorder was added to standard treatment for AUD, showed results similar to the paroxetine study.[25,26] That is, the meta-analysis showed that conventional treatments were effective at reducing co-occurring symptoms of anxiety and depression, but they did not meaningfully improve alcohol-related treatment outcomes.

Psychological Theories

In parallel to the evolution of the descriptive psychiatric paradigm for co-occurring disorders, early psychological researchers began studying alcohol's tension-reducing properties in laboratory (typically animal) models.[27] It is often forgotten (or at least ignored) that this early experimental work began as a test of Freud's theory that alcohol misuse served as an externalized ego defense mechanism. However, the research soon developed into operant-behavioral examination of what was called the "tension-reduction hypothesis." The hypothesis maintained that alcohol's pharmacological properties reduced tension, and this effect resulted in escalated drinking through negative reinforcement (i.e., reward generated by diminution of a noxious stimulus). In this research, the tension was any noxious state (e.g., frustration, approach-avoidance conflicts, or pain) that elicited a subjective or physiological stress response. Many dozens of laboratory studies through the latter half of the 20th century tested the tension-reduction hypothesis. Ultimately, however, the cumulative results were deemed to be "negative, equivocal, and contradictory."[28]

In reaction to the early experimental failures and ambiguities of the operant-behavioral tension-reduction hypothesis, psychological researchers increasingly deemphasized alcohol's putative pharmacological effects on tension. They began to emphasize the subjective expectancies, beliefs, and motivations presumed to affect a person's decision to drink when experiencing negative affect.[29] Drinking to cope with negative affect was viewed

as a primary drinking motive.[30] Keeping with the tension-reduction hypothesis, these researchers did not focus on formal diagnostic categories for negative affect or alcohol misuse.[31] However, other research has linked drinking-to-cope motives with individuals who met diagnostic criteria for co-occurring AUD and anxiety disorder.[19]

An analysis of NESARC data has demonstrated that individuals who reported using alcohol to cope with the symptoms of anxiety disorder are at increased risk for persistent alcohol dependence.[19,32] In addition, people with anxiety disorders who reported drinking to cope had a fivefold increased risk for developing alcohol dependence within 3 years.[32] People with anxiety disorders who did *not* drink to cope had virtually the same prospective risk for developing alcohol dependence as people with no anxiety disorders. Further, people with anxiety disorders who did not report any drinking to cope drank less daily than people with no anxiety disorder.

Neurobiological Theories

Starting in the 1970s, the increasing availability of biological measures offered researchers an opportunity to study the effects of alcohol on stress-responding (and vice versa) in more refined and controlled ways. This allowed for distinctions between subjective (e.g., self-reported) and objective (e.g., serum cortisol) responses to stress, as well as between immediate stress reactivity and subsequent stress regulation. Surprisingly, distinguishing subjective and objective stress-response measures revealed little connection between the two, with the former relating more directly to predictions from the tension-reduction hypothesis.[33] Early research on stress and alcohol used these technological advancements to test the operant tension-reduction hypothesis, albeit with mixed results.[34]

Psychophysiological and neurobiological correlates

Beginning in the 1990s, stress-related alcohol research evolved from its roots in tension-reduction research to become a multifaceted subspecialty focused primarily on the psychophysiological and neurobiological correlates of the stress response, stress regulation, and alcohol misuse. Increasingly, this research includes examination of the long-term genetic and environmental influences on stress reactivity and regulation and their connections to the development of AUD vulnerability.

For example, Brady and Back reviewed research linking early trauma and exposure to chronic stressors with permanent dysregulation in the brain systems implicated in the pathophysiology of depression, anxiety, and addiction.[35] Other investigators reviewed research that reported associations between alcohol dependence or genetic risk for alcohol dependence and dysregulated patterns of laboratory stress-responding.[36,37] Several studies have implicated chronic alcohol misuse in the dysregulation of the stress response, which contributed to further alcohol craving and increased likelihood of relapse.[38-40] These and related studies demonstrate that heritable traits associated with risk for alcohol-related disorders; as well as environmental insults such as acute trauma, chronic stress, and chronic alcohol misuse; can produce durable neurobiological and subjective stress-response changes that have been associated with the development or persistence of both AUD and anxiety disorders.

Opponent process model

Koob and colleagues have placed both the neurobiological and subjective experiences of stress-responding and negative affect at the very center of addiction pathology (Figure 1).[41] More specifically, they conceptualized addiction as a three-stage, pathodevelopmental cycle that engages executive function, incentive salience, and negative emotionality at different degrees during specific stages of addiction. In this opponent process model, the term "addiction" refers to the neurobiological and motivational changes that occur as a consequence of chronic substance use.

The first stage—binge/intoxication—involves activating reward circuits (e.g., the release of dopamine and opioid peptides in the ventral striatum) in response to alcohol or other drug use, which also engages incentive salience circuits.[41] In this early stage of addiction, positive reinforcement from direct activation of the brain's positive valence systems, as well as from formerly neutral stimuli that have become classically conditioned to evoke a pleasurable response, motivates ongoing and

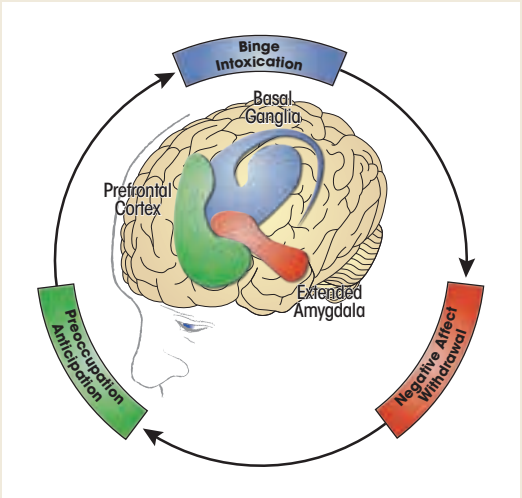

Figure 1 Addiction cycle stages and associated brain regions. *Source:* Adapted from U.S. Department of Health and Human Services, Office of the Surgeon General. *Facing Addiction in America: The Surgeon General's Report on Alcohol, Drugs, and Health*. Washington, DC: U.S. Department of Health and Human Services; November 2016.

increased substance use. This is characterized as the impulsive stage of addiction because the goal of increasing pleasure, rather than avoiding or escaping discomfort, motivates seeking alcohol or other drugs.

In response to chronic alcohol or other drug use, both within-system and between-system brain processes seek homeostasis through dynamic, neuroregulatory, countervailing effects.[41] However, as chronic use continues, homeostasis gives way to neuroadaptations that reset the baseline operation (allostasis) in these systems. These allostatic adaptations in the brain lead to the second stage of addiction—withdrawal/negative affect. In this stage, reward circuits become blunted because of within-system neuroadaptations. The brain's stress systems, including corticotropin releasing factor and norepinephrine in the central amygdala and bed nucleus of the stria terminalis, become increasingly dysregulated because of between-system compensatory neuroadaptations. At this point in the addiction process, subjective negative affect predominates, especially during periods of sobriety and withdrawal. This later stage of addiction marks a shift from impulsive use driven by positive reinforcement to compulsive use driven by negative reinforcement. In this stage, compulsive substance use is aimed, in part, at decreasing the negative affect caused or aggravated by the allostatic reset in the brain's stress and mood systems.

Finally, after these neuroadaptations have been established, the third stage of addiction—preoccupation/anticipation—undermines attempts at abstinence from drinking.[41] At this point, chronic alcohol or other drug use becomes an integral, exogenous input for maintaining equilibrium in the brain's mood and stress regulation systems.

Preclinical research supports the tenets of the neurobiological opponent process model.[42] Although the model has not yet been translated to validated clinical applications, it informed the development of the Addictions Neuroclinical Assessment, a framework that uses neuropsychological data that correspond to the three stages of the neurobiological opponent process model to classify the individual differences in AUD to improve diagnosis and treatment.[43] The model does imply specific treatment targets, such as corticotropin releasing factor[44,45] and alpha$_1$-noradrenergic systems.[46] Simpson and colleagues found clinical benefit from prazosin, an alpha$_1$ antagonist, in participants with an alcohol dependence diagnosis.[47] However, the only study to examine prazosin in a sample of people with co-occurring disorders (alcohol dependence and post-traumatic stress disorder) reported that the medication had no effect on stress-responding or alcohol treatment outcomes.[48]

The opponent process model also implies that psychosocial treatments could usefully target the motive of using alcohol to cope with negative affect. Epidemiological data and the opponent process model both support the concept that this motive is a primary link between the neurobiological and subjective manifestations of negative affect and drinking behavior.[49]

Discussion and Future Directions

The term "comorbidity" has become a fairly generic reference for co-occurring alcohol and anxiety or depressive disorders. Yet ontologically, the presence of two or more distinct, clinical diagnoses remains firmly fixed in an increasingly strained medical-diagnostic paradigm of psychopathology

classification. Central to this strain is the assumption that specific diagnostic dyads are the appropriate unit of analysis for studying co-occurring negative affect and alcohol misuse. However, negative affect is common to many anxiety and depressive disorders and can increase the risk for alcohol misuse, particularly when drinking to cope with negative affect is the motive.

Unidirectional causation theories

The notion of a simple, unidirectional, causal link between co-occurring disorders is not supported by the findings reviewed in this article. A prospective study has shown that either experiencing clinical-level anxiety or engaging in chronic alcohol misuse increases the risk of developing the other.[21] In addition, clinical research shows that effectively treating one co-occurring condition does not substantively affect the other. Viable explanations for the relationship between co-occurring conditions include the possibility of a common cause for both conditions or bidirectional causation between the conditions. For example, dysregulated stress response or regulation may be a common risk factor for the development of both alcohol and anxiety disorders.

Also, the concept of causation among co-occurring conditions may be based on an incorrect assumption. Rather than two distinct conditions, each requiring a cause, negative affect and alcohol misuse may be parts of a single, neurobiological-behavioral syndrome. This view aligns mostly with recent neurobiological theories of addiction, but it also shares similarities with early typologies, in which negative affect was considered a fundamental trait among a large subgroup of people who had problems with alcohol.

Shared neurobiology

The research reviewed in this article shows that trauma and chronic stress, as well as a familial risk for problems with alcohol, are associated with the dysregulated stress-response systems implicated in the development of both alcohol and anxiety disorders. In addition, chronic alcohol use is associated with dysregulated stress-responding, which, in turn, is associated with relapse following treatment for alcohol problems. Collectively, these and related findings point to overlapping neurobiological vulnerabilities.

The overlapping neurobiology of negative affect and AUD is supported by several lines of research that implicate specific brain circuits related to both conditions. The central amygdala regulates negative affect states,[45,50] and research suggests the central amygdala plays a role in physiological and behavioral responses to stress, anxiety, and alcohol- or drug-related stimuli. Similarly, human imaging and animal research demonstrate abnormal central amygdala function in individuals with alcohol or anxiety disorders.[50] A consensus is building that the central amygdala serves as a central hub for anxiety and alcohol circuits owing to its strong connection and influence on brain areas involved in executive function (medial prefrontal cortex), emotion regulation, stress responsivity (paraventricular hypothalamus and locus coeruleus), and reward processing (nucleus accumbens shell and ventral tegmental area).[45,50-53] Crucial to the overlapping neurobiology conjecture, research shows that chronic alcohol use results in neuroadaptations to the central amygdala that are similar to the neuroadaptations that occur after chronic stress.[53] If the neurodysregulations underlying anxiety or mood conditions and alcohol misuse overlap, it becomes reasonable to hypothesize that the common co-occurrence of these conditions may be an outgrowth of this shared neurobiology.[54]

The shared neurobiology thesis implies several unique and nonobvious hypotheses. For example, having either condition should be a risk marker for developing the other. This is consistent with prospective, observational studies showing that having either an anxiety disorder or AUD at any time increases the relative risk for future development of the other disorder. The shared neurobiology view also implies that the transition from nonproblematic alcohol use to AUD (roughly corresponding to the withdrawal/negative affect stage of addiction in the opponent process model)[41] should require less overall alcohol exposure for people with anxiety and depressive disorders.

This hypothesis, called "telescoping," theorizes that having either condition indicates perturbed neurobiology that is also relevant to developing the other condition. Examinations of transitions from nonproblematic or no use to problematic use of alcohol or nicotine support the telescoping hypothesis.[55,56] People with anxiety disorders transitioned significantly faster than those with

no anxiety disorder from initial use milestones to substance dependence. This effect was more pronounced for people who had multiple anxiety or mood disorders, even after controlling for lifetime drug exposure.[57,58]

Anxiety problems in the absence of alcohol misuse

As already discussed, an analysis of epidemiological data shows that people who report drinking to cope with anxiety symptoms have increased prospective risk for developing alcohol dependence.[19,32] People with anxiety disorders who do not drink to cope with their symptoms do not have an increased risk for AUD. This is good news, because most people with anxiety disorders do not report drinking to cope with their symptoms, but it also raises questions. For example, why do some people with anxiety problems drink to cope and others do not? Also, if this population has no increased risk for AUD, how is that consistent with the shared neurobiology thesis? Perhaps currently unknown factors—cultural, psychological, or biological—protect these biologically vulnerable individuals by discouraging drinking to cope.

Alcohol misuse in the absence of anxiety

Not all people struggling with alcohol problems meet diagnostic criteria for anxiety disorders. As already discussed, an analysis of epidemiological data suggests that a DSM-IV diagnosis of alcohol abuse (i.e., negative consequences from alcohol use) without alcohol dependence does not correlate with anxiety disorder diagnoses.[13] The opponent process model suggests that all advanced cases of substance use disorder ultimately involve negative affect (although they may not necessarily manifest as diagnosable anxiety disorders), whereas the typology and medical/diagnostic models suggest that only a particular subgroup of people who have problems with alcohol will have the key feature of negative affect.

These different models are not necessarily irreconcilable when considering the patho-developmental trajectory of addiction. During the early binge/intoxication (impulsive) stage of addiction, the opponent process model would anticipate low levels of negative affect, but during the later stage of negative affect/withdrawal, the model specifies the presence of significant negative affect and drinking to cope. Cross-sectional snapshots of people who have significant alcohol problems might reveal groups with anxiety (Apollonian) and groups without anxiety (Dionysian), but, ultimately, all may become Apollonian types as addiction advances. People who manifest anxiety problems before alcohol problems may transition very rapidly (telescope) from binge/intoxication (Dionysian) to negative affect/withdrawal (Apollonian), whereas others may make this transition more slowly or, perhaps, never.

Stress reactivity and regulation

Stress responses in terms of both reactivity and regulation include frequently disjunctive, subjective and objective indicators. Curiously, subjective indicators of acute stress response commonly are elevated in individuals who have anxiety or alcohol problems, whereas the objective indicators tend to be acutely blunted, with diminished regulation.[58,59] Also, research has well-established that perturbations in the neurobiological systems that govern biological responses to stress are associated with poorer alcohol and other substance use disorder treatment outcomes.[38,53]

For investigators seeking to bridge the multiple disciplines included in this review, the findings concerning stress responses pose challenges and opportunities for future research. For example, can individuals with AUD be distinguished meaningfully based on objective stress reactivity and regulation indicators, and do subjective anxiety symptoms mark or moderate this distinction? For augmenting treatment for AUD, would targeting biological stress reactivity (e.g., hypothalamic pituitary adrenal activation) be more promising than targeting anxiety disorders? Among people who have problems with alcohol, do those with versus those without co-occurring anxiety disorder react differently to protracted abstinence and withdrawal in terms of severity and persistence of dysregulation of the stress response? Prospective studies across the distinct stages of treatment and recovery for alcohol-related disorders may shed needed light on the relationships between alcohol, anxiety, and stress reactivity and regulation. Such studies have the potential to reveal the trajectory of re-regulation of the stress response during abstinence and how

it relates to anxiety symptoms and relapse risk. Understanding these parameters could make a valuable contribution toward using the stress system as a recovery biomarker.

Limitations

This review of literature from multiple disciplines required sacrificing depth for breadth. The material cited is largely limited to seminal studies and other reviews. In addition, complex research on stress and neurobiology is discussed in ways sufficient to make particular points but without providing a comprehensive or in-depth description of the underlying work. Doing so is beyond the scope of this article, but the approach presented in this article runs the risk of oversimplifying complex topics and obscuring relevant details. Also, this review does not address potentially important individual differences, such as sex.

Finally, the assumption that common areas of construct space exist across the disciplines of psychiatry, psychology, and neuroscience is open to debate. For example, medically oriented researchers might view subclinical negative affect as qualitatively rather than quantitatively distinct from diagnosed anxiety disorders. Similarly, it could be argued that dysregulated biological stress responses share little construct space with subjective negative affect and drinking to cope. However, as already noted, a dysregulated stress response is a known biological marker for the development of anxiety disorders and AUD, as well as for relapse.

Conclusion

This review broadens the psychiatric perspective on the association between diagnosable alcohol and anxiety disorders to include the psychological/learning and neuroscientific disciplines. Cross-referencing and reconciling (if not integrating) discipline-specific approaches may reveal opportunities for synergy.

The opponent process model offers a uniquely suitable framework for transdisciplinary cross-referencing and integration. This neurobiological model aligns with the Research Domain Criteria[60] framework's approach to characterizing psychopathology and, thereby, avoids being trapped by the diagnostic specificity that has failed to survive empirical scrutiny. In this model, the roles of motivation and reinforcement in fundamental learning processes, which were first explored in the operant-behavioral tension-reduction hypothesis, are integrated within a pathodevelopmental framework for substance misuse. The model also accommodates individual differences in neurosusceptibility to AUD within brain systems known to be affected by stress, anxiety, and depression. To better evaluate how negative affect is associated with alcohol misuse, the opponent process model expands the scope from a narrowly defined subset of individuals with co-occurring alcohol and anxiety disorder diagnoses to include the wider range of individuals who have advanced to the negative affect/withdrawal stage of addiction. Finally, the model provides promising and specific neurobiological (e.g., corticotropin releasing factor) and psychological (e.g., drinking to cope) targets for novel interventions.

Acknowledgments

This article was supported by National Institute on Alcohol Abuse and Alcoholism grants K01AA024805 and R01AA015069. The authors thank Amanda Unruh, Nikki Degeneffe, and Kelly Ochocki for their editorial assistance.

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Financial Disclosure

The authors declare that they have no competing financial interests.

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Cite this as:
Alcohol Res. 2019;40(1):03. **https://doi.org/10.35946/arcr.v40.1.03.**

Biobehavioral Interactions Between Stress and Alcohol

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In this review, the effects of stress on alcohol drinking are discussed. The interactions between biological stress systems and alcohol drinking are examined, with a focus on the hypothalamic pituitary adrenal axis, corticotropin releasing factor, dynorphin, neuropeptide Y, and norepinephrine systems. Findings from animal models suggest that these biological stress systems may be useful targets for medications development for alcohol use disorder and co-occurring stress-related disorders in humans.

KEY WORDS: alcohol; animal models; stress

Behavioral Interactions Between Stress and Alcohol

Epidemiological studies of humans suggest that stress increases alcohol drinking. For example, findings from the 2001–2002 National Epidemiologic Survey on Alcohol and Related Conditions show that the number of past-year stressors is positively associated with prevalence of current drinking, current binge drinking, and alcohol use disorder (AUD) diagnosis.[1] However, as with most epidemiological human studies, the temporal and causal relationships between stress exposure and alcohol drinking are difficult to determine. Therefore, studies using animal models represent a useful complement for examining relationships between stress and alcohol drinking. Keyes and colleagues reviewed key epidemiological findings that show that stress exposure is associated with increased risk for AUD.[1]

Historically, studies using animal models to test the relationship between stress and alcohol drinking have focused on stress-induced reinstatement of alcohol-seeking as a model of stress-induced alcohol relapse in humans. In this procedure, animals are trained to self-administer alcohol in an operant task, that behavior is then extinguished (by omitting alcohol as reinforcement for lever pressing), after which exposure to a stressor (e.g., footshock) reinstates lever pressing for alcohol (i.e., alcohol-seeking).[2] In fact, stress has consistently been shown to reinstate seeking of a variety of drugs, including heroin, cocaine, and nicotine.[3]

A more limited body of literature shows that stress may increase alcohol consumption, but this effect depends heavily on a number of factors, including the stressor and the alcohol-drinking model used, as well as the species, sex, and age of the experimental animals.[4] Studies that show stress-induced escalation of alcohol drinking in rodents, with or without prior experience of alcohol drinking, are summarized in Table 1.[5-11] Stress also can synergize with exposure to high doses of alcohol to produce faster and more robust escalation of alcohol drinking in mice.[12] However, it is noteworthy that many stress procedures do not produce escalated alcohol drinking in rodents, and there is a paucity of animal models for studying stress-induced escalation of alcohol drinking and related behaviors (e.g., anxiety).[13,14]

On the other hand, chronic exposure to high doses of alcohol (which is an animal model of alcohol dependence) increases stress reactivity during withdrawal. For example, rats[15] and mice[16] exposed to chronic high-dose alcohol, followed by restraint stress during withdrawal, show higher levels of stress-induced anxiety-like behavior (in the elevated plus maze test) and suppression of social interaction, respectively, compared to their alcohol-naïve counterparts.

Table 1 Studies of Stress-Induced Escalation of Alcohol Drinking in Rodents

Procedure	Developmental Stage at Exposure	Stressor	Alcohol-Drinking Procedure
Stress → Alcohol Drinking			
In Rats	Adult	Repeated footshocks[5]	Two-bottle choice drinking
	Adolescent	Postweaning social isolation[6*]	Two-bottle choice drinking and operant self-administration
In Mice	Adult	Repeated social defeat[7]	Two-bottle choice drinking
	Adolescent	Postweaning social isolation[8]	Two-bottle choice drinking
Alcohol Drinking → Stress → Alcohol Drinking			
In Rats	Adult	Single exposure to soiled cat litter[9†]	Two-bottle choice drinking
	Adult	Single exposure to bobcat urine[10†‡]	Operant self-administration
In Mice	Adult	Repeated social defeat or forced swim[11]	Two-bottle choice drinking

*Stress increased alcohol drinking only in male rats.
†Stress increased alcohol drinking only in rats that were highly stress reactive.
‡Stress increased responding for quinine-adulterated alcohol (aversion-resistant responding) in rats that were highly stress reactive.

Data from animal models suggest that stress may not only trigger relapse to alcohol drinking but also increase subsequent alcohol drinking. Animal studies also show that exposure to high doses of alcohol increases stress reactivity. These studies suggest that stress exposure may facilitate development of AUD in humans, which may increase the likelihood of developing a stress-related disorder, further exacerbating AUD. The precise mechanisms through which this occurs are unclear, but dysregulation of brain stress signaling systems is likely to play a central role. Stress and chronic alcohol exposure alter the activity of brain stress systems, and dysregulation of these systems has demonstrable effects on alcohol drinking. The next section summarizes key findings from animal studies regarding the interaction between alcohol and brain stress systems.

Neurobiological Interactions Between Stress and Alcohol

Although alcohol often is consumed to alleviate stress,[1] alcohol may activate some brain stress systems and may be considered a stressor itself.[17] A body of literature shows that dysregulation of brain stress systems induced by stress or chronic high-dose alcohol exposure contributes to escalation of alcohol drinking or to alcohol-seeking relapse. This section summarizes key findings from research on several brain stress systems that likely mediate stress-alcohol interactions.

Hypothalamic pituitary adrenal axis

One of the main physiological responses to stress is activation of the hypothalamic pituitary adrenal (HPA) axis. This process begins with release of corticotropin releasing factor (CRF) from cells in the paraventricular nucleus of the hypothalamus, which leads to increased release of adrenocorticotropic hormone in the pituitary, which stimulates glucocorticoid (cortisol in humans and corticosterone in rodents) release in the adrenal gland. Therefore, HPA activation is generally considered to be "pro-stress," but the effects of HPA activity and corticosterone level on stress-related outcomes (e.g., anxiety-related behaviors) may depend on several factors. In animals, administration of corticosterone systemically or into the brain increases alcohol drinking,[18] and systemic glucocorticoid receptor blockade with mifepristone reduces alcohol drinking,[19] suggesting that glucocorticoid signaling modulates alcohol drinking. In addition, research has shown that infusion of mifepristone into the central amygdala attenuated stress-induced reinstatement of alcohol-seeking,[20] suggesting that glucocorticoids act on specific brain regions to modulate alcohol relapse-like behavior.

Interestingly, in a study that used a predator odor stress model, a blunted plasma corticosterone response in rats following predator odor exposure predicted high stress reactivity (avoidance of a stress-paired context).[21] Also, systemic corticosterone treatment before the stress exposure reduced the percentage of animals that were highly stress reactive (Avoiders) and reduced the magnitude of their stress reactivity (avoidance).[22] After stress, the Avoiders exhibited increased alcohol drinking, as compared to the Non-Avoiders,[10] which suggests that failure to mount a proper HPA response to traumatic stress predicts later escalation of alcohol drinking, which is similar to the notion that failure to mount a proper HPA response to traumatic stress predicts later post-traumatic stress disorder pathology[23] and poor treatment response[24,25] in humans.

Studies of rodents have demonstrated that acute alcohol exposure (experimenter-administered or self-administered) stimulates corticosterone release, mimicking a stressor.[26,27] In one study that used a model of chronic, high-dose alcohol exposure, alcohol-dependent rats, when compared with control rats, showed lower basal corticosterone levels during withdrawal and smaller increases in corticosterone following experimenter-administered or self-administered alcohol.[27] However, this effect may depend on factors such as the rodent species[28] and whether total or free amounts of glucocorticoids were measured.[29] This response is akin to the blunted corticosterone response shown in Avoider rats following exposure to traumatic stress.

In addition, a high basal corticosterone level in rats has been shown to protect against stress-induced and corticosterone injection–induced exacerbation of anxiety-like behavior.[30] Therefore, a blunted corticosterone response to alcohol or stress may be a common mechanism through which chronic, high-dose alcohol or traumatic stress increases alcohol drinking and stress-related disorders. However, Perusini and colleagues found that inhibition of corticosterone synthesis before stress blocked stress-enhanced fear conditioning.[31]

Studies of rats also have shown that glucocorticoid receptor levels in the brain were elevated following chronic alcohol exposure, and that mifepristone blockade of glucocorticoid receptors in these rats, systemically or within the central amygdala, reduced escalation of alcohol drinking.[32] Collectively, these findings suggest that HPA function and glucocorticoid receptor signaling in the brain, perhaps in specific brain regions, are important targets for medications development for AUD and co-occurring stress-related disorders.

CRF system

Aside from being a critical component of the neuroendocrine stress response, CRF signaling in extrahypothalamic brain regions is also a critical mediator of stress-alcohol interactions. For example, intraventricular infusions of a CRF receptor antagonist have been shown to attenuate stress-induced reinstatement of alcohol-seeking in rats,[33] and systemic blockade of CRF_1 receptors has produced similar effects.[34] Systemic CRF_1 receptor blockade also has been shown to reduce escalated alcohol drinking after exposure to stress induced by predator odor (in rats)[35] or by social defeat (in mice).[36] In studies of alcohol-dependent animals, intraventricular infusions of the CRF receptor antagonist D-Phe-CRF(12-41) reduced escalated alcohol drinking for both rats[37] and mice[38] during withdrawal. This effect is mediated, at least in part, by the central amygdala, as infusion of D-Phe-CRF(12-41) into the central amygdala also has been shown to reduce escalated alcohol drinking in alcohol-dependent rats during withdrawal.[39] CRF effects on escalated alcohol drinking appear to be mediated largely by the CRF_1 receptor. For example, researchers have reported that systemic CRF_1 receptor blockade reduced escalated alcohol drinking in mice[40] and rats[41] after chronic exposure to high doses of alcohol.

Collectively, these findings suggest that neural processes mediated by CRF–CRF_1 receptor signaling play an important role in escalation of alcohol drinking, and in alcohol-seeking relapse, induced by stress or by chronic, high-dose alcohol exposure. For more detailed discussions of this topic, please refer to reviews by Phillips and colleagues,[42] Spierling and Zorrilla,[43] and Pomrenze and colleagues.[44]

Dynorphin system

Stress generally increases brain dynorphin levels,[45] and dynorphin signaling via kappa-opioid receptors (KORs) mediates stress effects on behavior. For example, chronic stress (repeated forced-swim or repeated footshock stress) has been shown to

produce dysphoria-like behaviors in mice that can be attenuated by systemic KOR blockade or by gene deletion.[46] In one study, systemic administration of KOR antagonists reduced stress-induced escalation of alcohol drinking and alcohol-induced place preference in mice.[47] In another study, systemic KOR blockade attenuated reinstatement of alcohol-seeking in rats, which had been induced by yohimbine (an alpha$_2$-adrenergic receptor antagonist often used as a pharmacological stressor).[48]

These results are complemented by findings that dynorphin-KOR signaling in the brain is enhanced by chronic, high-dose alcohol exposure. For example, alcohol-dependent rats, relative to nondependent controls, have been shown to exhibit higher dynorphin levels and increased KOR function in the amygdala during withdrawal.[49] In the same study, KOR blockers, administered systemically or directly into the central amygdala, reduced escalated drinking in alcohol-dependent rats during withdrawal. Reviews by Anderson and Becker[50] and Karkhanis and colleagues[51] provide further discussion on the role of this system in stress-alcohol interactions.

Neuropeptide Y system

In contrast to the CRF and dynorphin systems, the neuropeptide Y system is generally thought to produce anti-stress effects. For example, following predator odor exposure, rats that exhibited high stress reactivity had lower neuropeptide Y levels in the brain, relative to rats that had lower stress reactivity.[52] In the same study, an infusion of neuropeptide Y into the brain an hour after stress exposure reduced the number of rats that subsequently exhibited high stress reactivity. In another study, neuropeptide Y infusion into the brain, followed by yohimbine-induced stress, attenuated reinstatement of alcohol-seeking.[53]

Compared to alcohol-naïve controls, alcohol-dependent rats have been shown to exhibit lower neuropeptide Y expression in several brain areas associated with negative affect and motivation, including amygdalar, cortical, and hypothalamic subregions.[54] These results suggest that chronic, alcohol-induced neuropeptide Y deficits in the brain may contribute to escalation of alcohol drinking and to negative affect during withdrawal. In other studies, an intracerebroventricular infusion of neuropeptide Y into the whole brain[55] or specifically into the central amygdala[56] reduced escalation of alcohol drinking in alcohol-dependent rats, suggesting that modulation of neuropeptide Y signaling in the brain may have therapeutic value in the treatment of AUD.

Both neuropeptide Y receptor subtypes (Y_1 and Y_2) have demonstrated roles in regulating alcohol drinking in rodents. For instance, intraventricular infusion of a Y_1 receptor agonist or a Y_2 receptor antagonist has been shown to reduce alcohol drinking in mice.[57] In a study of rats, the ability of a Y_2 receptor antagonist (via intracerebroventricular administration) to reduce alcohol drinking may have been potentiated in animals that were chronically exposed to high-dose alcohol.[58] However, Kallupi and colleagues found that a Y_2 receptor antagonist (administered systemically or into the central amygdala) attenuated only anxiety-like behavior, but not alcohol drinking, in rats chronically exposed to high-dose alcohol.[59]

Researchers have reported that Y_1 and Y_2 receptors regulate alcohol drinking in a brain region–specific manner. For example, research has demonstrated that Y_1 receptor activation or Y_2 receptor blockade in the medial prefrontal cortex reduced alcohol drinking in mice,[60] whereas Y_1 receptor activation in the paraventricular nucleus increased alcohol drinking in rats.[61] Further discussions of this topic can be found in reviews by Robinson and Thiele[62] and Thorsell and Mathé.[63]

Norepinephrine system

The locus coeruleus is densely packed with noradrenergic neurons that project to specific brain nuclei in the amygdala, prefrontal cortex, and hippocampus and that are important in the regulation of emotion and motivation.[64] Stress engages some of these projections. For example, in a study of rats, immobilization stress increased norepinephrine release in the central amygdala.[65] In a different study of the central amygdala, alpha$_1$-adrenergic receptor blockade with prazosin reduced stress-induced augmentation of anxiety-like behavior.[66] Research has also demonstrated that prazosin blocked stress-induced reinstatement of alcohol-seeking in rats.[67] In a study of rats chronically exposed to high-dose alcohol, administration of prazosin[68] or the beta-adrenergic receptor blocker propranolol[69] blocked escalation of alcohol drinking during alcohol withdrawal.

Stress and chronic alcohol exposure also increase the activity of the sympathetic nervous system

(a subdivision of the autonomic nervous system, which mediates the flight-or-fight response) and thereby affect the function of many organ systems, in part through increased noradrenergic signaling. For example, psychosocial stress in mice has been shown to increase blood pressure via an alpha$_1$-adrenergic receptor–dependent mechanism.[70]

During withdrawal from chronic, high-dose alcohol exposure, increases in sympathetic activity contribute to aversive physiological symptoms, such as increased blood pressure, heart rate, and sweating, which are thought to contribute to relapse in abstinent individuals.[71] In studies of rats, blockade of alpha$_1$- and beta-adrenergic receptors[72,73] and activation of alpha$_2$-adrenergic autoreceptors[73] reduced alcohol withdrawal symptoms such as convulsions, tremors, and locomotor hyperactivity. In another study of rats, blockade of norepinephrine signaling during withdrawal attenuated alcohol drinking.[68] See the review by Vazey and colleagues[74] for further discussion of this topic.

Conclusion and Future Directions

Brain stress systems mediate the effects of stress on alcohol drinking and the effects of chronic alcohol exposure on subsequent alcohol drinking and stress reactivity. Therefore, brain stress systems are useful targets for the development of medications for AUD and for co-occurring stress-related disorders. More specifically, glucocorticoid, CRF, dynorphin, neuropeptide Y, and norepinephrine systems may be useful targets for modulating stress-alcohol interactions. Several pharmacological agents that target these systems are promising candidates for the treatment of AUD and co-occurring mental health conditions in humans.[75] In addition, emerging evidence has shown that several other brain stress signaling systems, such as oxytocin,[76] nociceptin,[77,78] and neuropeptide S,[79] also contribute to stress-alcohol interactions, suggesting they also may be promising therapeutic targets. To guide medications development for AUD and co-occurring stress-related disorders, future studies should elucidate the mechanisms through which stress-related neuropeptide and neurotransmitter systems affect alcohol- and stress-related behaviors, including how these systems interact or modulate glutamate and gamma-aminobutyric acid (GABA) neurotransmission in specific circuits.[80,81]

Acknowledgments

This article was supported by National Institutes of Health grants R01AA023305, R01AA026531, R01AA025792, T32AA007577, R21AA026022, and F32AA027145; by U.S. Department of Veterans Affairs grant I01BX003451; and by Cohen Veterans Bioscience.

Financial Disclosure

Dr. Gilpin owns shares in Glauser Life Sciences, a company with interest in developing therapeutics for mental health disorders. There is no direct link between those interests and the work contained herein.

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Cite this as:
Alcohol Res. 2019;40(1):04. https://doi.org/10.35946/arcr.v40.1.04.

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.

Acknowledgments

This research was supported by the National Institutes of Health Ruth L. Kirschstein National Research Service Award Institutional Research Training Grant T32DA007238 and the National Institutes of Health Alcohol Use Disorders: Treatment, Services Research, and Recovery grant R01AA022285.

Financial Disclosure

Ismene L. Petrakis has consulted to Alkermes. Sherry A. McKee has consulted to Cerecor and Embera NeuroTherapeutics; has received research support for investigator-initiated studies from Pfizer, Cerecor, and Janssen; and has ownership in Lumme. Terril L. Verplaetse declares that she has no competing financial interest.

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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.

Acknowledgments

This article was supported by National Institute on Alcohol Abuse and Alcoholism grants K23AA023845 and T32AA007474 and the National Institute on Drug Abuse grant T32DA007288.

Financial Disclosure

Dr. Back receives royalties from sales of *Concurrent Treatment of PTSD and Substance Use Disorders Using Prolonged Exposure (COPE)*, published by Oxford University Press.

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Alcohol Use Disorder and Traumatic Brain Injury

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Alcohol use and traumatic brain injury (TBI) are inextricably and bidirectionally linked. Alcohol intoxication is one of the strongest predictors of TBI, and a substantial proportion of TBIs occur in intoxicated individuals. An inverse relationship is also emerging, such that TBI can serve as a risk factor for, or modulate the course of, alcohol use disorder (AUD). Critically, alcohol use after TBI is a key predictor of rehabilitation outcomes, prognosis, and additional head injuries. This review provides a general overview of the bidirectional relationship between TBI and AUD and a discussion of potential neuropsychological and neurobiological mechanisms that might underlie the relationship.

KEY WORDS: alcohol and other drug use (AODU) development; AODU initiation; brain; injury; trauma

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Overview of Traumatic Brain Injury

Traumatic brain injury (TBI) is characterized by neurological dysfunction caused by a bump, blow, or penetrating injury to the brain. The duration and severity of dysfunction may range from "mild" TBI (concussion), which may involve a brief period of loss of consciousness and a transient neurological impairment with rapid recovery, to "severe" TBI, involving an extended period of loss of consciousness and permanent brain damage.[1] The extent of neurological damage is determined by an evolving pathophysiology over the hours and days following the injury, during which time brain swelling, increased intracranial pressure, and reduced cerebral blood flow contribute to the development of cognitive and functional deficits.[2] Further, the injuries can be divided into those that cause focal or penetrating damage to local brain regions versus those that result in more diffuse damage.[3] Consequently, TBI is a highly heterogeneous injury state resulting in a patient population with markedly different injuries, comorbidities, and predicted outcomes.

Public understanding of TBI is currently undergoing a shift due, in part, to recent events that have focused public and media attention on the issue.[4,5] Although these recent events, which include the emerging understanding of the role of TBI in later neurodegeneration and the

recognition of the high incidence of TBI among amateur and public athletes, as well as military personnel, represent tragedies with real human cost, they have also helped focus public attention on an ongoing public health crisis.

Annually, about 2.8 million civilians in the United States receive medical treatment for TBI, but the true incidence of TBI is actually far higher, as many TBI patients are never seen by health care providers[6,7] (although rates of emergency department visits are rising, likely due to increasing public awareness of the seriousness of TBI).[8] Even among those patients seen by medical personnel, the lack of definitive diagnostic tools, or even consensus on a definition, means that a substantial proportion of TBIs go undiagnosed.[9] Additionally, TBI was declared the signature injury among military personnel involved in the protracted conflicts in Iraq and Afghanistan (Operations Enduring Freedom, Iraqi Freedom, and New Dawn).[10] During the first 12 years of these conflicts, nearly 250,000 service members were diagnosed with TBI,[11] although the difficulties associated with reporting, identifying, and diagnosing head injuries indicate that this number likely is underestimated.

What is becoming clear, is that even relatively mild TBI can have far-reaching consequences that last well beyond the initial symptoms.[12] The long-term sequelae of TBI can include psychiatric and neurological dysfunction, as well as a whole host of nonneurological diseases. Additionally, survivors of TBI can suffer from cognitive issues and are more likely to be unemployed, socially isolated, and incarcerated.[13,14] Thus, the total cost, comprising health care dollars, loss of productivity, and quality of life, associated with TBI in the United States is substantial, with estimates of lifetime cost (in 2009 dollars) ranging from more than $75 billion to more than $200 billion.[15]

Alcohol Use Disorder Before TBI

TBI has long been closely associated with acute alcohol intoxication. Most studies estimate that between 30% and 50% of patients treated for TBI were intoxicated at the time of injury, with even greater intoxication estimates for patients injured in motor vehicle accidents and assaults.[16] Binge drinking is a major risk factor for trauma, particularly brain trauma.[17] Individuals who consume more than five drinks in a sitting are more than three times as likely to suffer a trauma.[18] One illustrative example involves cyclists. Individuals who cycle while intoxicated are more likely to fall, and, among cyclists who fall, being intoxicated greatly increases the probability of TBI.[19] The lifetime incidence of TBI is approximately four times higher among individuals who drink, relative to those who do not.[20]

Not surprisingly, given the powerful relationship between alcohol intoxication and brain injuries, the overall rate of alcohol use disorder (AUD) is very high among patients who incur TBI, with estimates ranging from one-third to half of all patients meeting diagnostic criteria for AUD.[21] More than half the patients admitted for rehabilitation following TBI meet the diagnostic criteria for AUD[22] or are considered at risk for problem drinking because of self-reported binge drinking or Short Michigan Alcoholism Screening Test (SMAST) scores.[21] Thus, the population of persons with TBI disproportionately consists of individuals who drink alcohol and those who meet AUD diagnostic criteria or are at risk for developing AUD.

Given that alcohol intoxication is a major risk factor for the incidence of TBI, a substantial population exists from which researchers can study the effects of blood alcohol concentration at time of injury on survival and on functional outcomes. There is controversial literature (beyond the scope of the current review) suggesting that better long-term outcomes are associated with patients who had low to moderate levels of alcohol in their blood at the time of their injuries, when compared with patients who had no alcohol in their blood,[23,24] although not all studies have reached that conclusion.[25] What is much clearer, however, is that drinking *after* TBI represents a major impediment to successful outcomes in several critical domains.[16,26]

Patterns of Drinking After TBI

Alcohol use falls off immediately after TBI, and this reduction appears to be due to three factors.[21] First, many patients are advised to abstain from alcohol in the early postinjury period to reduce the likelihood of post-traumatic seizures.[27] Second, many patients with TBI have limited access to alcohol because

they are hospitalized, living with family, or admitted to an inpatient rehabilitation facility, or because they have impairments in cognition or mobility.[21] Finally, many patients, especially those whose injuries occurred secondary to intoxication, choose to use this early period to stop drinking. Indeed, involvement in car crashes increases the likelihood that patients will enter AUD treatment.[28] Some patients stop drinking permanently, but a large subset (25%, by some estimates) resumes drinking after injury, and consumption levels can rise to (or above) preinjury levels by 1 to 2 years after injury.[29] The strongest predictor of postinjury AUD is drinking before injury. Patients who scored high on the SMAST before TBI were more than 10 times likely to exhibit problem drinking after injury.[22]

There exists some controversy in the literature as to whether TBI can act as an independent risk factor for the development of AUD in adult patients who did not previously meet the diagnostic criteria for AUD.[30,31] Epidemiological studies have generally concluded that TBI does not induce new cases of AUD, but some patients return to drinking after TBI (approximately 25%, by some estimates),[21,30] and this has significant negative consequences (see **Consequences of Drinking After TBI** in this article). Still, there is reason to suspect that TBI can increase the likelihood of AUD. For instance, in one study, approximately 20% of patients who were abstainers or "light" drinkers before injury exhibited high-volume drinking after injury.[32] Similarly, among military personnel, several studies have reported that service men and women who experienced combat-related TBI were more likely than uninjured individuals to binge drink.[33] Additionally, among patients with a primary diagnosis of substance use disorder (defined as misuse of alcohol or drugs), a lifetime history of TBI is remarkably common. In one study of individuals seeking treatment for substance abuse in New York, more than 50% had a history of TBI, and nearly half had experienced more than one TBI.[34]

Still, any potential causal relationship between adult TBI and AUD has been difficult to establish for several reasons (although causality may exist). First, the TBI population disproportionately consists of people who exhibit AUD, potentially masking any relationship. Second, patients who have AUD after TBI appear more likely to be lost to follow-up in epidemiological and outcome studies.[35] Third, patients who have the most severe injuries, the subset of people with TBI who, theoretically, are most likely to develop AUD, are also the group most likely to have no access to alcohol because of disability or institutionalization.[36] Fourth, it is becoming increasingly clear that a large subset of patients treated for TBI also had previous TBI, and, as described in this article, injury during early development is a powerful risk factor for AUD.[37] Fifth, the populations most at risk for TBI, including adolescent and young adult males, risk-takers, and enlisted military personnel, are also at elevated risk for AUD.[38]

The relationship between TBI and AUD is much clearer in individuals who were injured as children. Incurring TBI during childhood increases the likelihood of later development of AUD. This relationship is easier to discern because the effects of injury on the developing nervous system can be profound,[39] and because this population is less affected by many of the confounders already discussed. Younger patients, presumably, are less likely to be experienced with alcohol or meet the diagnostic criteria for AUD.

For instance, results from the Christchurch birth cohort studies indicated that children who experienced mild TBI with hospitalization before age 5 were 3.6 times more likely to meet the *Diagnostic and Statistical Manual of Mental Disorders (Third Edition–Revised)* criteria for alcohol dependence during adolescence, when compared with those who had no similar injury.[40] A 10-year, nationwide, longitudinal cohort study in Taiwan indicated that there was a more than sixfold increase in the rate of alcohol abuse (as defined by the *International Classification of Diseases, Ninth Revision: Clinical Modification*) among patients with a history of TBI, when compared with uninjured control patients.[41] Among Canadian high school students, the odds ratio for binge drinking in the previous year (at the time of the study) was between two- and fourfold higher in students who had a history of TBI (defined as loss of consciousness or an overnight hospitalization), when compared with uninjured students.[42] Moreover, in a study of patients admitted for inpatient rehabilitation following TBI, approximately 20% of the population had experienced previous TBI, many sustained before age 16.[37] Among the patients in this study, those with a history of childhood brain injury had twice the rate

of problem alcohol use as those without previous TBI. (Problem alcohol use was defined as more than 14 drinks per week for males and 7 for females, or any incidence of binge drinking that included 5 or more drinks in a night.)

Also, TBI appears to act indirectly by limiting protective factors and increasing risk factors for incurring a subsequent TBI.[43] For instance, individuals with a history of TBI early in life are less likely to participate in extracurricular activities, finish school, marry, and be employed, and they are more likely to engage in risky behavior and experience long-term alienation from family and peer groups, all of which serve as risk modifiers for alcohol misuse.[37,44,45] TBI, particularly when it occurs in young patients, can modify the risks for development of AUD, and, among individuals who have AUD, there is a high incidence of prior TBI.

Comorbidity Among TBI, PTSD, and AUD

TBI is closely linked to post-traumatic stress disorder (PTSD), but not only because both conditions have trauma as a precipitating factor (see Figure 1). Among combat veterans who had physical trauma excluding the brain, 16% developed PTSD symptoms, whereas 44% of combat veterans with a history of TBI developed symptoms of PTSD.[46] Similar patterns have been observed among civilians.[47] Remarkably, this relationship exists even among individuals who experienced post-traumatic amnesia that prevented them from remembering the trauma.[48] The potential physiological links between the two conditions remain under investigation, but they may involve dysregulation of the hypothalamic

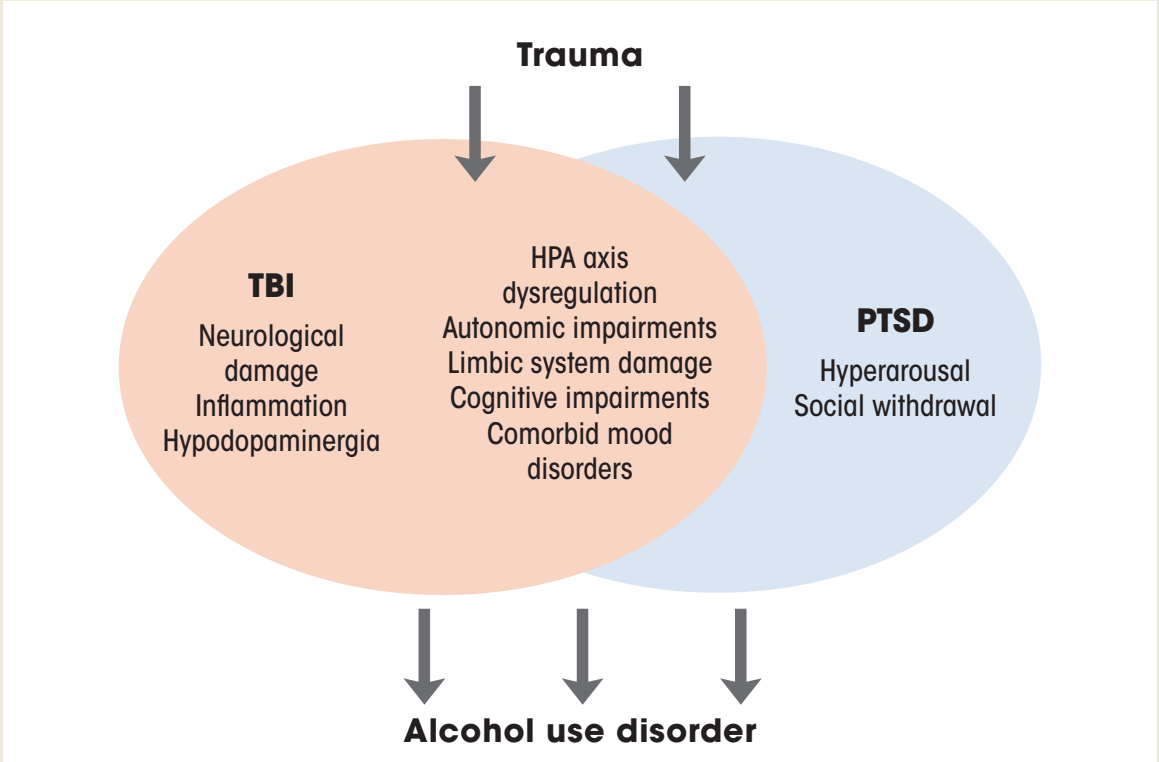

Figure 1 Overlapping neurobehavioral links among TBI, PTSD, and alcohol use disorder. TBI and PTSD share trauma as a precipitating event. They are also linked by dysregulation of stress response systems, cognitive impairments, and affective symptoms, which, together, can increase the likelihood of alcohol misuse. *Note:* HPA, hypothalamic pituitary adrenal; PTSD, post-traumatic stress disorder; TBI, traumatic brain injury.

pituitary adrenal axis, impairments in autonomic physiology, and damage to frontal and limbic structures that impair physiological regulation and the ability to manage traumatic memories.[49,50]

Critically, TBI, PTSD, and AUD are commonly comorbid, which is unsurprising given that intoxication elevates risk of TBI, and that generally high rates of alcohol misuse occur among patients who have TBI.[21] The relationships among these conditions are an area of active investigation. Numerous studies have investigated relationships between two of the conditions, and far fewer have investigated all three.[51] There are clearly relationships between and among all these conditions, but there are a number of overlapping characteristics of individuals with PTSD and TBI that can make drinking more likely.[52] For instance, the hyperarousal to stressful events that is central to PTSD pathology is unpleasant and can increase social withdrawal, thus exacerbating ongoing negative affect.[52] TBI can make it more difficult for patients to manage these symptoms, increasing the likelihood that they will drink alcohol. Moreover, the cognitive impairments combined with decreased frustration tolerance that are central to both TBI and PTSD can increase the likelihood that daily difficulties will lead to drinking. Because some of the relationship between TBI and AUD is likely mediated by PTSD, it has been difficult to disentangle the contribution of TBI and PTSD to the development of AUD, given their similar etiology and symptomatology. Further work is required to uncover the physiological substrates that link these conditions.

Consequences of Drinking After TBI

Multiple epidemiological studies have reported that a subset of people with TBI eventually drinks at or above preinjury levels.[20,22,31,32] This propensity to resume consuming alcohol at preinjury levels is of critical importance, because alcohol use after injury is deleterious in a number of different domains and is predictive of negative outcomes over the long term.[16]

A distinction has to be drawn between AUD and alcohol use in the absence of problem drinking. People who have brain injuries likely suffer negative consequences from patterns of drinking that would not produce significant harm in uninjured individuals. For instance, drinking can promote development of post-traumatic seizures directly and by interfering with the efficacy of prescribed antiseizure medications.[53] Critically, alcohol affects peripheral tissues, including in the liver and kidneys, and impairs wound healing, which can have outsized effects on patients recovering from trauma. Also, cognitive consequences of drinking appear to be magnified by prior TBI. For instance, patients with TBI who drank at "heavy social" levels (with a mean Alcohol Use Disorders Identification Test score of 16.9) exhibited impaired event-related potentials and greater cognitive deficits, when compared with patients who abstained.[54]

Finally, both drinking and a history of TBI are powerful risk factors for suffering subsequent head injuries.[55] Moreover, suffering TBI while intoxicated more than triples the likelihood of suffering a future TBI.[56] Repeated TBIs produce more severe long-term damage and permanent disability than a single injury.[55] Patients with TBI often report reduced tolerance to alcohol,[57] and they can also have balance problems associated with their injuries, meaning that intoxication, even at relatively low blood ethanol concentrations, can increase the risk of injury.

Patients with AUD who continue (or restart) drinking after TBI have significantly poorer long-term outcomes than patients who do not.[58] A chronic high level of drinking can be proinflammatory and deleterious to brain health and thus has the potential to impair functional recovery and further damage vulnerable and already impaired neural structures.[59] Many of the brain regions commonly injured in TBI, including the frontal and medial temporal regions, are also key sites of inflammatory reactions in people who have been drinking alcohol for a long time. Patients with TBI who were previously diagnosed with AUD and relapsed had smaller frontal gray matter volumes within the first year after injury than patients who did not relapse.[60] Finally, in a retrospective study of patients who had TBI, individuals who met the criteria for substance use disorder (including alcohol) at the time of their injuries were four times more likely to die from suicide than patients who did not meet the criteria.[61]

Some of the negative consequences of drinking after TBI may be related to treatment compliance. Patients with AUD are less compliant with TBI rehabilitation and have poorer rehabilitation outcomes than patients who do not have AUD.[16]

Patients with AUD are also more likely to have lower levels of life satisfaction.[62] Alcohol misuse also impairs reintegration into the workforce after injury. Among people who have TBI, alcohol misuse is the most commonly cited reason for termination from a vocational placement program.[63] Also, patients with TBI and AUD are more likely than patients with TBI who do not have AUD to meet the diagnostic criteria for mood disorders and less likely to return to work.[60]

Because of the many deleterious consequences associated with drinking alcohol after TBI, treating AUD in people with TBI has the potential to markedly improve outcomes and reduce the likelihood of devastating repeated injuries.

Treatment of Co-Occurring TBI and AUD

There are special considerations for treating co-occurring AUD and TBI. As already mentioned, people who have TBI may be disproportionately vulnerable to negative consequences of alcohol misuse. However, there are unique challenges and opportunities for treatment of AUD among people with TBI. After their injuries, many patients with TBI significantly reduce the amount of alcohol they drink.[21,30] Although a substantial subset (approximately 25%) of these individuals eventually returns to (or surpasses) preinjury drinking levels, this initial period of abstinence has been characterized as a "window of opportunity" for screening and intervention. There is limited, but generally positive, evidence that brief interventional strategies and cognitive-behavioral therapies can be effective in this population.[52]

Although screening and monitoring for AUD are key steps in the management of TBI, many patients, particularly those who do not receive specialized or follow-up care, are not assessed for AUD risk. Moreover, patients with TBI represent a special challenge for treatment of AUD. TBI is a heterogeneous condition, but there are certain brain regions that are more likely to be damaged because of their anatomical location. These regions include the key areas for cognitive control and executive function in the frontal and anterior temporal regions. Thus, it is extremely common after moderate to severe TBI to suffer from cognitive deficits, impaired emotional regulation, and difficulty focusing attention. Therefore, AUD treatment protocols must be tailored to address the specific challenges of this population.

Additionally, people with TBI have high rates of neuropsychiatric comorbidities, including depression, anxiety, and PTSD, all of which can promote alcohol misuse and complicate AUD treatment.[60] Treatment for comorbid psychiatric disorders, particularly addiction, is more challenging in patients with a history of TBI, but the existing evidence indicates that treatments targeting both PTSD and comorbid alcohol dependence produced greater reductions in symptoms for both disorders than treatments for either condition alone.[64]

Moreover, the efficacy of drugs (e.g., disulfiram and naltrexone) approved specifically for treatment of AUD has been minimally investigated in the TBI population.[65] These drugs are not contraindicated for people who have TBI, but medication for this population tends to require careful titration and close monitoring of responses. Also, the elevated risks of substance misuse should be considered when using medication to manage TBI symptoms in this patient population.

The pharmacological treatments for management of TBI fall into two general classifications.[66] In the acute phase after injury, a small number of compounds are administered to manage symptoms and to (attempt to) reduce damage from the initial injury. In the later phases, several psychoactive compounds (e.g., cholinesterase inhibitors, stimulants, and amantadine) are prescribed to modulate cognitive symptoms, fatigue, and insomnia.[66-68] Although little direct evidence indicates that these compounds can increase the likelihood of developing AUD, it is imperative to consider how their potential and efficacy are influenced by alcohol if they are to have appropriate clinical effects.

Mechanisms Linking AUD to TBI

There are a number of potential mechanisms that link TBI to AUD across both cognitive and psychosocial domains. Further, there is mounting evidence that central inflammatory signaling can interact with deficits in neural reward systems,

which may indicate that people with TBI are more vulnerable to developing AUD.

Cognitive and psychosocial links

The incentive motivation theory of drinking predicts that individuals drink alcohol to either enhance positive affect (i.e., directly improve mood or facilitate socialization) or reduce negative affect (i.e., alleviate depression or anxiety).[69] The decision to drink or not drink alcohol, as predicted by this theory, is based on weighing the perceived benefits against the potential costs, which may include legal and occupational issues, hangovers, monetary costs, and social pressures. However, people with TBI often have difficulty weighing the future costs of their actions. For instance, laboratory-based neuropsychological tests demonstrate that people who have frontal lobe injuries consistently have deficits in decision-making, as assessed by their performance in delay discounting and gambling tasks that require judgment about future consequences of immediate actions.[70,71] This pattern of cognitive deficits is superficially similar to what occurs in patients with AUD, and these cognitive deficits are worse in patients with TBI who meet the diagnostic criteria for AUD.[72] Thus, despite future negative consequences, people with TBI may be less likely than those without TBI to decide to not drink.

Neurobiological substrates

Neurobiological links between TBI and AUD remain unspecified, although a potential link has received increased attention in recent years, and new animal models have been developed.[73,74] Injury to the brain often results in affective, cognitive, and psychosocial impairments that can promote alcohol misuse. Moreover, the underlying neurobiological roots of these impairments may also render the brain more vulnerable to developing alcohol dependence.

To investigate the potential relationship between TBI during development and future alcohol use, we developed an animal model in which we administered a mild TBI to mice during juvenile development and allowed the animals to grow into adults.[75] Animals that experienced TBI as juveniles exhibited markedly greater alcohol self-administration as adults, when compared to noninjured animals. The difference in alcohol self-administration between the two groups of animals was independent of changes in sensory function. Also, for the mice that had TBI, the difference was associated with enhanced reward responses to intraperitoneal alcohol. Thus, the injury during juvenile development altered the rewarding properties of alcohol. Moreover, we could block the enhanced drinking behavior that followed TBI by housing the animals in enriched environments, which served as a proxy for sustained cognitive and physical rehabilitation. We have begun to use this model to investigate the neurobiological substrates of alterations in alcohol-related circuitry.

For instance, as already discussed in this article, TBIs are remarkably heterogeneous in etiology, location, and severity, but they do possess some common features.[3] Specifically, virtually all TBI produces acute neuroinflammatory response and persistent alterations in neuroimmune physiology.[76] This is important because alcohol and central inflammatory responses are bidirectionally linked. High doses of alcohol produce a characteristic inflammatory response in the brain, including activation of microglia and upregulation of proinflammatory signaling molecules.[59] Further, this inflammatory response to alcohol is exacerbated in animals with a history of TBI. We recently showed that mice that experienced TBI during juvenile development exhibited exaggerated inflammatory responses, cognitive deficits, and neural degeneration following binge-like alcohol administration in adulthood.[77] Moreover, inflammatory responses in the brain drive alcohol-drinking behavior in animals, and blocking or reducing neuroinflammatory signaling can attenuate alcohol self-administration.[78-80] Thus, we postulate that TBI establishes a state of constant escalation in which it directly induces an inflammatory response and also enhances the neuroinflammatory response to subsequent exposure to alcohol.[73] Future studies need to address whether inhibiting TBI-induced inflammatory responses can also prevent increases in drinking alcohol.

TBI also may produce a state of hypodopaminergia. In clinical populations, imaging data and the widespread use of dopaminergic agents (e.g., methylphenidate and amantadine) for the treatment of TBI-related cognitive issues provide indirect evidence of the hypodopaminergia.[14] Whether the effectiveness of dopaminergic agents in patients with TBI reflects

a true dysregulation of mesocorticolimbic dopamine, or if higher dopaminergic tone is beneficial for cognitive function in survivors of TBI, remains unspecified. However, in animals, TBI produces a biphasic alteration in dopamine signaling characterized by an initial upregulation of dopaminergic synthesis pathways and dopamine release, followed by prolonged suppression.

Neuroinflammatory responses have significant antidopaminergic effects,[81] and blunted dopaminergic release is a major risk factor for the development of AUD.[82] In our juvenile TBI model, injured mice exhibited markedly attenuated dopaminergic signaling in adulthood and altered patterns of neuronal activation in dopaminergic cells.[83] There are many unanswered questions, but injury during periadolescent development in mice seems to persistently alter the development of the dopaminergic system and the response to alcohol in this key reward system. Clearly, there are many other mechanisms beyond neuroinflammation and hypodopaminergia that could underlie greater vulnerability to AUD in people with TBI, and this review is limited in scope.

Future Research Needs

There are many unanswered questions regarding the relationship between TBI and AUD. Most pertinently, we need to determine if TBI exacerbates AUD or increases vulnerability to the development of AUD. We also need to ascertain how underlying neural mechanisms affect TBI and AUD. In particular, what are the roles of chronic neuroinflammatory signaling, impairments in reward processing, and cognitive issues in mediating susceptibility to AUD? We know that many people with TBI meet the diagnostic criteria for AUD and continue to drink alcohol after their injuries. Further, we know this pattern of behavior is associated with varied, but serious, negative consequences. Thus, future research needs to address the best ways to screen and treat people with TBI to minimize the harm associated with drinking alcohol after injury.

Acknowledgments

This article was supported by an Ohio State University Neurological Institute Pilot Award. Additional support was provided by the National Institute of Neurological Diseases and Stroke Institutional Center Core Grant P30 NS104177.

Financial Disclosure

The authors declare that they have no competing financial interests.

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Co-Occurring Post-Traumatic Stress Disorder and Alcohol Use Disorder in U.S. Military and Veteran Populations

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Co-occurring post-traumatic stress disorder (PTSD) and alcohol use disorder (AUD) are costly and consequential public health problems that negatively affect the health and well-being of U.S. military service members and veterans. The disproportionate burden of comorbid PTSD and AUD among U.S. military service members and veterans may be due to unique factors associated with military service, such as aspects of military culture, deployment, and trauma exposure. This review addresses the prevalence of co-occurring PTSD and AUD in military and veteran populations, population-specific factors that contribute to development of the comorbid conditions, and evidence-based treatments that have promise for addressing these conditions in military and veteran populations. Future directions for research and practice relevant to military and veteran populations are discussed.

KEY WORDS: addiction; alcohol use disorder; post-traumatic stress disorder; military; veteran

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Post-traumatic stress disorder (PTSD) and alcohol use disorder (AUD) are costly and consequential public health concerns that have disproportionately affected U.S. military service members and veterans.[1,2] Understanding the co-occurrence of PTSD and AUD is especially important because of the negative implications for the health and well-being of veterans and active-duty service members.

Prevalence of PTSD and AUD in Military and Veteran Populations

Examined separately, prevalences of PTSD and AUD are high in military and veteran populations when compared with the civilian population. Reports estimate current PTSD prevalence at 6% of predeployed and 13% of postdeployed service members, and from 5% to 13% among

veterans, compared to 5% of civilians.[2-8] Lifetime prevalence of PTSD ranges from 7% to 8% among veterans, compared with 6% of civilians.[2,8,9] With regard to high-risk drinking, a 2011 U.S. Department of Defense (DOD) survey found that 33% of service members, compared with 27% of civilians, endorsed past-month binge drinking.[10] Among Operation Enduring Freedom (OEF) and Operation Iraqi Freedom (OIF) veterans, 10% had an AUD diagnosis in their U.S. Department of Veterans Affairs (VA) electronic medical records.[11]

PTSD and AUD often co-occur in military and veteran populations,[2] as they do in the general population,[12] and having PTSD or AUD increases the likelihood of experiencing the other.[1] In national studies, 55% to 68% of veterans with probable PTSD, compared with 40% to 55% of veterans without PTSD, showed evidence of having AUD as well.[2,9] Similarly, among service members and veterans who misuse alcohol, prevalence of PTSD is high. A review of VA electronic medical records indicated that 63% of veterans with AUD and 76% of veterans with comorbid AUD and drug use disorder also had a PTSD diagnosis.[11]

In the general civilian population[13] and in military and veteran populations, there is evidence that PTSD and AUD are functionally related. For example, in a sample of Vietnam veterans, increases in alcohol use corresponded to increases in PTSD symptom severity,[14] and veterans with PTSD and substance use disorder (SUD) reported that they perceived that the conditions were interrelated.[15] Longitudinal studies of veterans have supported the self-medication hypothesis,[16] which may explain why veterans with unresolved PTSD are more likely to relapse after treatment for substance misuse.[17]

Factors That Contribute to PTSD and AUD

Among military and veteran populations, the risk for both PTSD and alcohol misuse may vary because of differences in demographic factors, aspects of military culture, and trauma or stress exposure. Relatively little research has addressed risk factors for co-occurring PTSD and AUD. Therefore, we do not know the extent that risk factors may increase the risk for one disorder or both, or whether these risk factors may have additive or interactive effects.

Demographics

Gender is associated with differential risks for PTSD and AUD. Consistent with the literature on civilians, studies of veteran populations show that lifetime prevalence of PTSD is higher among female veterans (13% to 19%) than male veterans (6% to 7%).[2,9] Civilian men have a higher risk for alcohol misuse than women,[18] and men are overrepresented in military and veteran populations. Also, male service members report more past-month binge drinking than female service members.[7,10] Despite these gender differences, research on the experiences of women veterans and active-duty service members is limited, and more work is needed in this area.

Racial differences in the prevalence of PTSD have been identified, with higher prevalence occurring among non-White veterans and service members.[2] In a nationally representative sample of veterans, the lifetime prevalence of PTSD was significantly higher for Black (11%) and Native American veterans (24%), compared with the prevalence for White veterans (6%).[9] Across military branches, the percentage of service members who reported past-year heavy drinking was similar across Hispanic (9%), White (9%), and African American (8%) groups.[10]

Younger age is associated with higher prevalence of PTSD[9] and with alcohol misuse.[10,16] For example, a 2011 DOD survey found that among service members ages 18 to 25, 20% endorsed past-year heavy drinking, and 67% endorsed past-month binge drinking.[10] During a 12-month period, more than 20% of junior enlisted service members experienced serious consequences from alcohol use, including military punishment and arrest.[19] In a national sample, veterans ages 18 to 29 had the highest odds of a PTSD diagnosis in their lifetimes, and veterans age 65 or older had the lowest odds.[9] Therefore, the high prevalence of comorbid PTSD and AUD in the military may be due, in part, to the overrepresentation of younger adults in this population.

Military culture

The military as a whole and each of the military branches have their own distinct cultures, which may influence alcohol-related behaviors and ways to cope with post-traumatic stress. Drinking alcohol is part of military culture as a means for group bonding, recreation, and stress relief.[19] The drinking behavior of service members and veterans may be influenced by their perception of alcohol consumption norms. For example, in a study among service members who had SUD, the participants tended to overestimate both the average number of drinks consumed by service members and the percentage of service members who were heavy drinkers.[20]

Military trauma and stress exposure

Researchers have found that military service members and veterans are more likely than civilians to have been exposed to childhood traumatic events, such as physical and sexual abuse and sexual assault, which leads to the suggestion that some individuals enter the military to escape dangerous family environments.[21,22] In particular, one study reported that men with a history of military service had a higher prevalence of exposure to adverse childhood events, especially sexual abuse, than men who had not served in the military.[22] Childhood stressors also have been associated with high-risk drinking in military recruits,[23] which may increase vulnerability to stressors encountered during military service.

Veterans and service members report a higher prevalence of trauma exposure than the general population, and they may have a higher likelihood of exposure to specific traumas.[24] In cross-sectional[25] and longitudinal studies,[6] exposure to combat, specifically, has been associated with psychological distress and hazardous drinking. Military sexual assault is also associated with higher PTSD risk than other forms of military and civilian trauma.[26] According to VA data, about 22% of women and 1% of men report experiencing military sexual trauma, which, in part, may explain the gender differences in the prevalence of PTSD described earlier.[27]

In addition, deployment may expose service members to interpersonal stressors (e.g., separation from social supports and working in close proximity with other service members), mission-related hardship, and prolonged exposure to perceived threats.[25] Among demobilizing soldiers, 15% reported at least one alcohol-related consequence, and the soldiers' levels of perceived stress predicted these consequences,[28] illustrating possible relationships between deployment-related stressors and alcohol misuse.

Interventions for Prevention of PTSD and AUD

To our knowledge, no study has examined strategies that aim to prevent the development of comorbid PTSD and AUD in military and veteran populations. However, some research has examined the prevention of PTSD or AUD separately in this population, which could inform the prevention of comorbid PTSD and AUD.

Universal prevention strategies

Universal prevention strategies target all members of a population to prevent the onset of a condition.[29] According to the *VA/DOD Clinical Practice Guideline for the Management of Posttraumatic Stress Disorder and Acute Stress Disorder*,[30] no universal prevention strategies for PTSD are currently recommended. Indeed, we know of no research that has tested primary prevention efforts targeting PTSD, AUD, or the comorbid conditions in any population.

Selective prevention strategies

Selective prevention strategies target members of a population at high risk for developing a condition.[29] Selective prevention strategies for PTSD involving the use of psychotherapy or pharmacotherapy in the early aftermath of trauma exposure have received some empirical attention, with mixed results.[31] In general, psychological debriefing interventions have failed to demonstrate beneficial effects in civilian or military samples,[31,32] and in some cases these interventions have been associated with increased PTSD symptom severity.[33,34] In a review of pharmacological selective interventions for PTSD, researchers reported some evidence that hydrocortisone may be effective.[35] Overall, the VA/DOD practice guideline for PTSD indicates there is insufficient evidence to recommend psychotherapy or pharmacotherapy for selective

prevention.[30] We found no research that has tested selective prevention efforts targeting AUD or comorbid PTSD and AUD in trauma-exposed military populations.

Indicated prevention strategies

Indicated prevention strategies aim to prevent disorder onset or chronic expression among people already exhibiting symptoms.[29] Meta-analytic results indicate that trauma-focused psychotherapies involving exposure and/or cognitive restructuring may prevent PTSD among individuals who have acute stress disorder.[31] However, results are insufficient and mixed regarding the use of pharmacotherapy for the indicated prevention of PTSD.[30,36] For individuals who screen positive for risky alcohol use, providing a single, initial brief intervention about alcohol-related risks and a recommendation to abstain from or moderate drinking may reduce alcohol misuse.[37,38]

Treatment Interventions for PTSD and AUD

Evidence indicates that concurrent treatment of PTSD and AUD can be safe and effective.[30,39] Before reporting on concurrent treatment approaches, we describe evidence-based treatments targeting either PTSD or AUD. We also discuss the efficacy of these treatments for military and veteran populations.

Treatments for AUD

The *VA/DOD Clinical Practice Guideline for the Management of Substance Use Disorders* recommends using psychotherapy and pharmacotherapy treatments for AUD.[38] Recommended psychotherapies include cognitive behavioral therapy, behavioral couples therapy, community reinforcement, motivational enhancement therapy, and 12-step facilitation. Recommended pharmacotherapies include acamprosate, disulfiram, naltrexone, and topiramate. Treatment availability and patient preferences are considerations when selecting a treatment.

Treatments for PTSD

The VA/DOD practice guidelines for treating PTSD recommend using individual, trauma-focused psychotherapy.[30] Pharmacotherapy (i.e., sertraline, paroxetine, fluoxetine, and venlafaxine) and individual psychotherapy that is not trauma-focused are recommended only if trauma-focused psychotherapy is not available or if a patient has a preference. Recommended psychotherapies include prolonged exposure therapy, cognitive processing therapy, and eye movement desensitization and reprocessing. In a recent systematic review of randomized controlled trials, researchers examined the effectiveness of psychotherapy among individuals who had military-related PTSD.[40] The researchers reported that cognitive processing and prolonged exposure therapies produced large within-group effect sizes, and patients achieved meaningful symptom change, although dropout rates were a problem.

Concurrent treatments

Veterans with comorbid PTSD and SUD report a preference for integrated treatments that address both conditions simultaneously, and several protocols have been developed to accomplish this.[15] We found no randomized controlled trials of concurrent treatments for PTSD and AUD conducted in military and veteran populations, but several case studies and small, open or uncontrolled trials provide some preliminary information regarding concurrent treatment in these populations.

Psychotherapy

"Seeking safety," a cognitive behavioral psychotherapy, targets co-occurring PTSD and SUD but is not trauma-focused. Trials of this intervention have had small sample sizes, but the participants, including service members and male veterans, have demonstrated reductions in PTSD symptoms and alcohol misuse.[41,42] One test of this treatment was conducted with female veterans who were homeless.[43] The participants were not randomly assigned to study conditions, which makes it difficult to determine whether the results were attributable to participant characteristics or treatment effect. When compared

with women in the treatment-as-usual condition, women who received the treatment had a greater reduction in PTSD symptoms, but there were no group differences in alcohol use. However, a randomized controlled trial indicated no added benefit of this treatment among male veterans with comorbid PTSD and AUD.[44] Given that few tests of this treatment have used randomized controlled trials, and findings from other types of studies are mixed, the seeking safety method is not currently recommended for treatment of comorbid PTSD and AUD.[1,30]

In one case study of an OEF/OIF veteran, researchers examined the effectiveness of concurrent treatment of PTSD and SUD using prolonged exposure (COPE) therapy.[45] COPE involves 12, 90-minute sessions that integrate relapse prevention with prolonged exposure therapy. The veteran who received the therapy reported reduced alcohol use throughout treatment, scored in the nonclinical range for PTSD at the end of treatment, and maintained treatment gains at a 3-month follow-up.

Cognitive processing therapy has begun to be examined as a potential treatment for co-occurring PTSD and AUD. This therapy is a 12-session, predominantly cognitive, intervention developed for treatment of PTSD. In a case study, a veteran diagnosed with both PTSD and AUD received cognitive processing therapy that was enhanced to address alcohol use.[46] The veteran demonstrated clinically significant improvements in PTSD symptoms and alcohol-related problems at the end of treatment and maintained the improvements 12 weeks after treatment. In addition, a review of VA medical records of individuals who received cognitive processing therapy showed no differences for veterans with or without AUD diagnoses in the likelihood of dropping out of treatment, self-reported depression symptoms, or clinician-rated PTSD symptom severity.[47]

Interventions for couples show promise for treating co-occurring PTSD and AUD. Couple treatment for AUD and PTSD (CTAP) is a 15-session manual-guided (also known as "manualized") therapy that integrates behavioral couples therapy for AUD with cognitive behavioral conjoint therapy for PTSD.[48] In an uncontrolled trial, 13 male veterans and their female partners enrolled, and 9 couples completed the CTAP program. Eight of the veterans showed clinically reliable reductions in PTSD outcomes after treatment. Most of the veterans showed clinically reliable reductions in their percentage of days of heavy drinking.

A couples therapy called "project VALOR," which stands for "veterans and loved ones readjusting," involves 25 sessions of cognitive behavioral therapy for PTSD and alcohol misuse, enhanced for significant others. Two OEF/OIF veterans received VALOR therapy in two separate case studies.[49] These veterans greatly reduced their alcohol use at the start of treatment or shortly before beginning the treatment, and their PTSD symptoms substantially decreased over the course of treatment.

Pharmacotherapy

Overall, research on the use of pharmacotherapies for comorbid PTSD and AUD in military and veteran populations is insufficient, and the results are mixed.[30] For example, in a randomized controlled trial of 30 veterans with comorbid PTSD and AUD, treatment with topiramate, when compared with placebo, was not effective at reducing PTSD symptoms, but the treatment was associated with reduced drinking days.[50] Also, results from this study indicated that topiramate, when compared with placebo, had a trend-level effect for a reduction in hyperarousal symptoms.

In a double-blind, randomized controlled pilot trial of 9 veterans and 21 civilians, all with comorbid PTSD and AUD, prazosin (which is often used to treat PTSD-related sleep disturbances) did not effectively improve PTSD symptoms.[51] However, it did reduce the percentage of drinking days. In another double-blind, randomized clinical trial, 96 veterans with comorbid PTSD and AUD received either prazosin or placebo.[52] In this study, prazosin was not effective in treating PTSD symptoms or reducing alcohol consumption. Overall, prazosin was not effective in treating PTSD symptoms, and its effectiveness regarding alcohol use is unclear. It is possible that alcohol's effect on sleep interferes with prazosin's benefits.[51,52]

In a double-blind, randomized trial, 88 male veterans with comorbid PTSD and AUD received either paroxetine and naltrexone, paroxetine and a placebo, desipramine and naltrexone, or desipramine and a placebo.[53] Desipramine outperformed paroxetine in reducing drinking days, and both medications showed some benefit in reducing

drinking and core PTSD symptoms, but the addition of naltrexone had no effect on outcomes.

A recent pilot study of *N*-acetylcysteine among veterans with co-occurring PTSD and SUD indicated that *N*-acetylcysteine was associated with significant reductions in both PTSD symptoms and substance craving.[54] Veterans in this trial received concurrent cognitive behavioral therapy, providing initial evidence for the potential benefit of *N*-acetylcysteine as an adjunct to psychotherapy.

Combined psychotherapy and pharmacotherapy

A combination of psychotherapy and pharmacotherapy may be an effective treatment strategy for service members and veterans with comorbid PTSD and AUD. In a single-blind, randomized clinical trial of civilians and veterans with comorbid PTSD and AUD, participants were randomly assigned to receive prolonged exposure therapy and naltrexone, prolonged exposure and a placebo, supportive counseling and naltrexone, or supportive counseling and a placebo.[55] Participants in all conditions reported reductions in drinking days and PTSD symptoms, and those who received naltrexone had a lower percentage of drinking days than those who received a placebo. There was no statistically significant main effect for prolonged exposure therapy on PTSD symptoms and no observed differences in the number of dropouts across conditions. In the same sample, prolonged exposure was more beneficial for those with non–combat-related traumas and higher baseline PTSD severity.[39] Also, naltrexone was most beneficial for those with the longest duration of AUD.

Future Directions for Research and Practice

In research and practice, several notable gaps exist in addressing co-occurring PTSD and AUD in military and veteran populations. First, although military service appears to increase risk for the comorbid conditions, more research is needed to identify factors that contribute to the increased risk for the development of these disorders within the specific military context. In addition, military-specific barriers to accessing care need to be identified. For example, policies that have potential career consequences, such as requiring that treatment participation be recorded in a service member's military record, may inhibit voluntary participation in treatment. Also, there may be opportunities for prevention during predeployment and postdeployment periods, but research on such programs is scarce. More information about military-specific factors and barriers will help guide prevention and intervention efforts.

Second, although treatments for PTSD and SUD have been disseminated systemwide within the VA, there is a dearth of literature about the effectiveness of these treatments for those in this population who have both conditions. (See Table 1 for brief summaries of treatments that have preliminary reports.) Addressing whether cognitive processing therapy and prolonged exposure therapy can be used for those who have co-occurring PTSD and AUD is a high priority, as existing implementation efforts could be leveraged to address the needs of those with comorbidity.

Comparative efficacy studies also are lacking. Future research should explore which treatments work best for whom, and if matching treatment to patient characteristics improves outcomes. Research on personalized treatment could lead to the development of a menu of evidence-based treatments from which practitioners and patients could jointly tailor a treatment plan for the patient. This menu of treatments could be based on biomarkers, demographics, and other patient characteristics, and it could identify promising alternatives if first-line treatments fail.

Third, it is unclear whether SUD treatments help those who have PTSD. Implementing SUD treatments for individuals with co-occurring PTSD and AUD could be a way for providers to address clinical needs without learning another manual-guided treatment. Motivational enhancement therapy could be used for this purpose, as it has been used successfully to reduce drinking among soldiers with untreated AUD, most of whom also had severe symptoms of PTSD.[56] This therapy may be useful as an intervention for increasing treatment engagement and preventing treatment dropout. Motivational enhancement therapy also shows promise as a way to increase treatment initiation among veterans and military personnel who are reluctant to enter treatment or address their substance misuse during treatment for PTSD,

Table 1 Review of Literature on Treatments for Co-Occurring PTSD and AUD in U.S. Military and Veteran Populations

Treatment	Research Findings
Pharmacotherapies	
Desipramine	Reduced drinking and PTSD symptoms in randomized controlled trials.[53]
N-acetylcysteine	Observed PTSD symptom reductions in pilot study, as adjunct to psychotherapy.[54]
Paroxetine	Reduced drinking and PTSD symptoms in randomized controlled trials.[53]
Prazosin	Reduced drinking but not PTSD symptoms in pilot randomized controlled trial.[51] No effects in large randomized controlled trial.[52]
Topiramate	Reduced drinking but not PTSD symptoms in randomized controlled trial.[50]
Psychotherapies	
Cognitive Processing Therapy Enhanced for Alcohol Use	Reported symptom reductions in case study.[46]
Concurrent Treatment of PTSD and Substance Use Disorders Using Prolonged Exposure (COPE)	Reported symptom reductions in case study.[47]
Couple Treatment for AUD and PTSD (CTAP)	Observed symptom reductions in uncontrolled trial.[48]
Project Veterans and Loved Ones Readjusting (VALOR)	Observed symptom reductions in case studies.[49]
Seeking Safety	Observed symptom reductions in small trials[41,42] and pre-post trial.[43] No added benefit in randomized controlled trial.[44]

particularly if they perceive that substance use eases their PTSD symptoms.

Finally, more clinical trials are needed on the treatment and prevention of comorbid PTSD and AUD within military and veteran populations.[57] Several barriers interfere with the progress of this literature, including the exclusion of people with dual diagnoses, and difficulties recruiting and retaining participants.[50] Dropout rates for trials testing combined PTSD and AUD treatments tend to be higher than dropout rates for treatment of either disorder alone. Research on the factors leading to participant dropout and on ways of increasing treatment engagement and retention is critical.

Conclusion

Military and veteran populations have a critical need for interventions that aim to reduce the burden of co-occurring PTSD and AUD. Treating these conditions simultaneously has been challenging and complex in the general population, and military service adds additional risk factors for the likelihood of their onset and maintenance. Although promising interventions exist, more research is needed to assess the degree to which current interventions are effective for service members and veterans. Also, new interventions that target this population should be developed and tested.

Acknowledgments

This article was supported by National Institute on Alcohol Abuse and Alcoholism (NIAAA) grants T32AA007455, K99AA026317, and R01AA020252, and by U.S. Department of Defense grant W81XWH-17-1-0002.

Financial Disclosure

The authors declare that they have no competing financial interests.

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Early Life Stress as a Predictor of Co-Occurring Alcohol Use Disorder and Post-Traumatic Stress Disorder

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During the critical developmental periods of childhood when neural plasticity is high, exposure to early life stress (ELS) or trauma may lead to enduring changes in physiological stress systems and enhanced vulnerability for psychopathological conditions such as post-traumatic stress disorder (PTSD) and alcohol use disorder (AUD) in adulthood. Clinical and preclinical studies have sought to understand the possible mechanisms linking ELS, PTSD, and AUD. Preclinical studies have employed animal models of stress to recapitulate PTSD-like behavioral deficits and alcohol dependence, providing a basic framework for identifying common physiological mechanisms that may underlie these disorders. Clinical studies have documented ELS-related endocrine dysregulation and genetic variations associated with PTSD and AUD, as well as disruption in crucial neural circuitry throughout the corticomesolimbic region. Despite limitations and challenges, both types of studies have implicated three interrelated mechanisms: hypothalamic pituitary adrenal (HPA) axis and glucocorticoid signaling dysregulation, genetics, and epigenetics. ELS exposure leads to disruption of HPA axis function and glucocorticoid signaling, both of which affect homeostatic cortisol levels. However, individual response to ELS depends on genetic variations at specific genes that moderate HPA axis and brain function, thus influencing susceptibility or resilience to psychopathologies. Epigenetic-influenced pathways also are emerging as a powerful force in helping to create the PTSD and AUD phenotypes. Dysregulation of the HPA axis has an epigenetic effect on genes that regulate the HPA axis itself, as well as on brain-specific processes such as neurodevelopment and neurotransmitter regulation. These studies are only beginning to elucidate the underpinnings of ELS, PTSD, and AUD. Larger human cohorts, identification of additional genetic determinants, and better animal models capable of recapitulating the symptoms of PTSD and AUD are needed.

KEY WORDS: **addiction; alcohol use disorder; animal models; genotype; post-traumatic stress disorder; psychological stress**

Overview

Although various forms of stress experienced during adulthood can be antecedents for the onset of alcohol use disorder (AUD) and post-traumatic stress disorder (PTSD), stressful events suffered during childhood may produce mechanistically distinct changes in the developing nervous system that increase lifelong risks for the co-occurrence of both disorders.[1] Early life stress (ELS) has been characterized as any form of severe trauma experienced before age 18 that could lead to pathological consequences in adulthood.[2] The trauma may have resulted from maltreatment, such as sexual, physical, or emotional abuse; or stressful life events, such as loss of a parent, economic adversity, or family violence.

Unfortunately, childhood maltreatment is all too common. In 2014, child protective service agencies received an estimated 3.6 million referrals involving approximately 6.6 million children.[3] Roughly, 702,000 of these referrals, 9.4 out of 1,000 children nationally, were considered victims of maltreatment (abuse or neglect). Percentages were similar for boys (48.9%) and girls (50.7%). However, for children younger than age 6, percentages for boys were consistently larger than they were for girls, whereas for older age groups, percentages for girls were larger than they were for boys. Although these numbers are appalling, they likely represent only the tip of the iceberg, as they do not include cases that go unreported or unverified and do not include other forms of ELS.

There has been growing awareness that the consequences of ELS extend beyond immediate effects, such as fear, injury, or isolation, to include lifelong ramifications on risks for an array of physical (e.g., cardiovascular disease, cancer, diabetes, fractures, and autoimmune disorders) and mental health (e.g., depression, anxiety, PTSD, and substance use disorder) problems, as well as on symptom severity and response to treatment. The idea that such effects could be a result of ELS-induced, long-term alterations in the central nervous system and other biological systems was initially met with some resistance in the scientific community.[4] However, a robust body of evidence now supports the validity of such hypotheses. Findings from a growing number of studies, beginning with the landmark Adverse Childhood Experiences study, suggest that there is a "dose-response" relationship between ELS and adult pathology, such that greater trauma is associated with greater risks for negative sequelae.[5] Moreover, studies of ELS report significant gender-specific prevalence, not only in the types and durations of trauma exposure, but also in rates of psychiatric outcomes such as depression, dissociation, and PTSD.[6] Studies also report physiological consequences, such as reduced hippocampal volume.[7] In general, findings of clinical studies suggest that ELS-induced sequelae are more severe in females than in males, and preclinical studies support this notion.[8]

ELS increases the risk for a variety of adulthood psychiatric and metabolic disorders, but it has a particularly powerful influence on the emergence of AUD and PTSD. Not only are individuals who lived through significant ELS at high risk for developing AUD, but they also have increased risk of a more severe form of the disorder characterized by early age of onset.[9] The increased risk for AUD associated with early childhood maltreatment remains sustained into middle life,[10] implicating long-term changes in key neural circuitry regulating the stress response and the reward systems. Studies have also shown that the risk for developing AUD in adulthood correlates with the number of adverse childhood experiences endured.[11] This dose-dependent effect (severity and frequency) of stress can result from an acute and toxic exposure but is often the consequence of chronic maltreatment.[12] Typically, these individuals have been exposed to multiple and varied types of abuse.[13] Although all forms of significant trauma and abuse (physical, sexual, and emotional) during childhood can precede the development of AUD, sexual abuse appears to be one of the more potent risk factors.[14]

The fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* reclassified PTSD as a trauma-related disorder rather than an anxiety disorder. This new grouping recognizes that the array of symptoms associated with PTSD emerges only after exposure to a significant traumatic event. In addition to increasing the risk for AUD, the types of trauma falling under the definition of ELS can increase vulnerability for the development of PTSD.[15] Therefore, it is not surprising that a number of studies have found high co-occurrence of AUD and PTSD.[16,17] A review by Shorter and colleagues identified that alcohol is the most commonly

misused drug among individuals with PTSD.[18] Other researchers have noted that the severity and number of childhood abusive episodes are associated with the prevalence of AUD and the gravity of PTSD symptoms, once again indicating a dose effect of stress.[19] A large epidemiological study showed that the risk of AUD was increased in women with a history of ELS, when compared with women who had no such history, but a history of trauma resulting in PTSD increased the risk for AUD almost twofold, indicating an additive effect on risk.[20] It is assumed that PTSD precedes the development of AUD in most individuals with comorbid disorders.[15] This hypothesis makes sense, given that many of the symptoms of PTSD (e.g., hypervigilance, insomnia, flashbacks, and lability of mood) are mitigated by the sedative effects of alcohol.

In this review, we examine some of the relevant preclinical models that address the effect of ELS on PTSD-like behavioral deficits and on alcohol consumption. We then integrate existing findings from preclinical and clinical literature to offer several potential mechanisms that may play a central role in the transition from ELS to later development of PTSD and AUD. These emerging findings provide evidence that genetic variation, epigenetic modulation of certain "stress" genes, and sustained alterations in hypothalamic pituitary adrenal (HPA) axis dynamics contribute to risks for PTSD and AUD in people who have a history of ELS.

Preclinical Models

Preclinical animal models have been indispensable in terms of providing access to brain tissues and circuits, minimizing confounding factors, and enabling the examination of behavioral phenotypes associated with ELS, PTSD, and AUD. In particular, to identify molecular substrates that directly contribute to disease symptoms, researchers can examine the brain in close detail for candidate genes and for epigenetic and other mechanisms within specialized neural circuits. However, animal models may lack validity for modeling the human condition.

A vast number of studies have examined animal facsimiles of human stress or alcohol administration, but the types of stressors, trauma, and alcohol exposure differ (see Gilpin and Weiner for a review).[15] The ideal model would be a paradigm of ELS that can manifest symptoms consistent with human PTSD, and the animals engage in increased alcohol consumption. However, creating models in which alcohol-naïve animals increase consumption following acute or chronic stress exposure is challenging. Researchers have been more successful using models in which animals resume alcohol consumption following a period of alcohol dependence, brief abstinence, and then stress exposure. Also, most researchers have used stress paradigms in adult rodents rather than in pups.

Currently, few promising paradigms exist. Because of the onus of documenting the relevant behavioral, biochemical, and neuroendocrine factors associated with ELS, PTSD, and AUD, no single study has successfully identified all facets of the interrelationships and causality among the three conditions. Instead, investigators have used animal models to examine different features of the three phenotypes. For example, in two studies of adult animals, exposure to predatory odors produced highly stress-reactive rats that increased their alcohol consumption.[21,22] In another study, experiments using mice showed that a repetitive forced swim test coupled with chronic, intermittent, alcohol vapor exposure escalated alcohol consumption.[23]

Social isolation studies imposed on adolescent rats are very relevant to a link between ELS and AUD. Socially isolated adolescent rats have exhibited a wide range of behavioral changes, such as anxietylike behavior,[24] sensory gating impairment,[25] hyperactivity in a novel environment,[26] and deficits in fear extinction,[27] all of which are component behaviors associated with PTSD. These behavioral impairments can persist from adolescence into adulthood, as was demonstrated in a study in which rats that were socially isolated as adolescents increased their alcohol intake as adults, when compared with group-housed counterparts.[27] In other studies, alcohol intake,[28] alcohol preference,[29] and PTSD-associated symptoms[30,31] such as anxiety, sensory impairments, and fear extinction deficits were observed in socially isolated adolescent mice.

Only a few studies have focused on an earlier developmental period. One study induced stress in rats through maternal separation and then examined alcohol intake during adolescence.[32] In this study, adolescent alcohol intake was exacerbated by additional stress exposure. However, it is unclear whether these maternally separated

animals developed other PTSD-related behavioral deficits, such as those exhibited by rats in the social isolation studies.

A common theme that emerges from these animal stress models is that exposure to stress, especially during early development, leads to a number of anxiety- and PTSD-like behavioral deficits that persist for some time throughout development. Further, in some of the studies, the animals either escalated or resumed alcohol intake, serving as promising models for examining the physiological processes and other underlying mechanisms that link stress exposure to alcohol consumption.

Potential Mechanisms

The disruption of substantially overlapping circuitries is central to preclinical and clinical research on the mechanisms through which ELS contributes to PTSD and AUD. In this section, we examine HPA axis and glucocorticoid signaling, genetic variations, and epigenetic mechanisms. These interrelated mechanisms may underlie the comorbid symptomatology that characterizes PTSD and AUD. Although it is possible that the relationships among ELS, PTSD, and AUD can be mediated by glucocorticoid-independent mechanisms, we consider the mechanisms in the context of glucocorticoid signaling.

The HPA axis and glucocorticoid signaling

The HPA axis is the key neuroendocrine component of the stress response. Release of corticotropin-releasing hormone (CRH) and adrenocorticotropic hormone (ACTH) neuropeptides from the hypothalamus and the pituitary, respectively, culminates in the release of the stress hormone cortisol (or corticosterone in rodents) from the adrenal cortex. Cortisol is a glucocorticoid that, in addition to its primary role in the release of stored glucose during the fight-or-flight response, targets a number of cellular processes by binding to the glucocorticoid receptor encoded by the nuclear receptor subfamily 3 group C member 1 gene, *NR3C1*. Negative feedback mechanisms in brain regions such as the hippocampus and the prefrontal cortex (PFC), and positive feedback mechanisms in the amygdala, dampen or amplify the HPA axis, respectively. There has been substantial focus on the HPA axis and glucocorticoid signaling, because normal function is dysregulated in individuals exposed to ELS and in those with AUD and PTSD.[33] Glucocorticoids have also attracted attention in the pathophysiology of ELS, PTSD, and AUD, because glucocorticoid signaling is involved in some forms of learning consolidation and memory formation, as well as in emotion regulation and reward reinforcement.

The consequences of glucocorticoid signaling follow an inverted U-shaped function in which extremely high and extremely low levels can be detrimental.[34] Both extremes are observed in people who have experienced ELS and in those with PTSD and AUD. The high concentrations of glucocorticoids achieved during the early phase of ELS lead to profound and durable changes in HPA axis function and in hypothalamic and extrahypothalamic CRH expression. For example, in studies that used maternal deprivation models in which rats were separated from their mothers for up to 24 hours, or macaques were raised without their mothers after age 6 months, the animals showed increased concentrations of the stress peptide CRH that persisted into adulthood within the mesolimbic system (e.g., in the amygdala) and cerebrospinal fluid.[35-37] These allostatic modifications were associated with marked increases in anxietylike behavior. Given that amygdala CRH neurons are known targets of glucocorticoid signaling, it is not surprising that altered *NR3C1* gene expression has been observed in this region.

Findings of several studies now indicate that ELS-related behavioral changes in rodents can be prevented or normalized with glucocorticoid receptor or CRH type 1 receptor antagonists.[38-40] A glucocorticoid receptor antagonist has also been shown to decrease amygdala activation in rats undergoing a forced swim test, a result consistent with inhibition of central stress activation.[41] In addition, elevated CRH in cerebrospinal fluid has been observed in people who have experienced ELS. For participants in one study, CRH levels were correlated with scores on the Childhood Trauma Questionnaire, particularly with emotional neglect.[42]

Dysregulation of cortisol levels is often associated with ELS. However, whether ELS exposure leads to high or low cortisol levels remains inconclusive. Low levels may occur more frequently in individuals

who experienced ELS episodes more often or with more severity. However, enhanced sensitivity to glucocorticoid negative feedback and blunted cortisol responses to acute stress have been reported.[43]

Similar to what has been demonstrated in rodent models, human behavioral manifestations of ELS often mimic mood and anxiety states, including hyperresponsiveness of limbic regions, hyporesponsiveness of prefrontal regions that regulate limbic responses, and decreased engagement of striatal regions involved in reward processing. Both the amygdala and medial PFC (mPFC) are particularly affected by ELS. Most neuroimaging studies of people who have experienced ELS show an increased amygdala volume and hyperresponsivity, both of which have been associated with increased trait anxiety and diminished reward sensitivity.[44] Other research has demonstrated that adults who experienced ELS have reduced mPFC volume[45] and reduced mPFC activation during cognitive tasks.[46]

PTSD and AUD are also associated with persistent alterations in HPA axis dynamics. The HPA axis dysfunction observed in individuals with PTSD is characterized by a state of low basal glucocorticoid levels and increased sensitivity to glucocorticoids.[47] This pattern mirrors findings observed in those who have experienced multiple episodes of ELS.[48] These modifications in stress pathways may be mechanistically related to the symptoms of PTSD. However, in a recent clinical trial, the glucocorticoid receptor antagonist mifepristone was not demonstrated to be an effective treatment for Gulf War veterans.[49] The treatment consisted of a 6-week phase both before and after a 1-month washout period. The researchers determined that the mifepristone treatment did not affect neurocognitive functioning or self-reported physical health, depression, PTSD symptoms, or fatigue. Therefore, it remains uncertain whether alterations in glucocorticoid signaling are fundamentally related to the PTSD phenotype.

HPA axis dynamics in AUD are modified as a function of alcohol consumption, withdrawal, and abstinence. In individuals who have AUD, glucocorticoid levels are high during episodes of drinking and acute withdrawal from alcohol.[33] During prolonged periods of abstinence from alcohol, glucocorticoid levels may be low in the unstressed state and following stressful stimulation.[50,51] In contrast, individuals with a history of ELS or PTSD exhibit low glucocorticoid levels and enhanced sensitivity to glucocorticoid negative feedback.[52]

The magnitude of alcohol activation of dopamine reward circuitry is considered an early mechanism for accelerating alcohol consumption. However, in more severe forms of AUD, the emergence of stress peptide expression may become the dominant mechanism for provoking alcohol cravings and alcohol-seeking behavior. In rodent models of AUD, there is an allostatic shift in CRH expression in the central amygdala. The advent of increased CRH expression is associated with anxietylike behavior, which has been called the "dark side" of AUD pathogenesis.[53]

A similar mechanism is at work in people with AUD, causing dysphoria and craving rather than dopamine-induced pleasure and reward. Alcohol's modulation of the HPA axis coupled with its sedative properties are possibly causally related to and compensatory for both ELS-related trauma and PTSD. Although this theory may be premature, it is supported by the candidate gene studies discussed in the next section.

Genetic variations

In addition to dysregulated HPA axis function and glucocorticoid signaling, genetics are a mechanism that could link ELS to PTSD and AUD. Specifically, DNA sequence variations are believed to contribute to an individual's response to ELS and serve as risk or resilience factors for the development of PTSD or AUD symptoms. At the molecular level, these variations alter protein activity through changes in the encoded peptide sequence. The variations can also affect gene expression levels by altering gene activation mediated by transcription factor binding. In general, variations relevant to ELS, PTSD, or AUD are found in genes with encoded proteins that regulate glucocorticoid signaling, neurotransmitter regulation, or alcohol metabolism. It is believed that disease is precipitated by alterations in protein function or gene activation, which are moderated by these genetic variations. Glucocorticoid-related and epigenetic mechanisms associated with trauma exposure can also result in changes in gene function.

Genetic risk factors are innate and inherited. Transgenerational inheritance of epigenetic modifications related to ELS, PTSD, or AUD is an active area of research. The heritability for PTSD

following exposure to trauma ranges from 24% to 72%, and the heritability percentage for women is larger than the percentage for men.[54] A 2002 meta-analysis of 50 family, twin, and adoption studies indicated an upper limit of 30% to 36% for AUD heritability.[55] A more recent meta-analysis that examined twin and adoption studies showed the heritability of AUD to be an estimated 50%, with a modest proportion (10%) attributed to shared environmental factors.[56]

Genetic research examining the molecular underpinnings of PTSD and AUD includes both hypothesis-driven, candidate gene association studies and unbiased, genome-wide approaches. Researchers have used both of these methods to identify variations at specific genomic loci associated with PTSD or AUD.

Candidate gene association studies

In candidate gene association studies, genes related to neurotransmitter regulation, alcohol metabolism, and the stress response (HPA axis) have been examined. Small candidate gene association studies of trauma survivors with and without PTSD have implicated the tandem repeat sequence of the dopamine transporter gene, *SLC6A3*,[57] and a functional insertion/deletion within the serotonin transporter gene, *SLC6A4*.[58] In addition, a single nucleotide polymorphism (SNP) within the putative estrogen receptor binding site in the stress response gene encoding the pituitary adenylate cyclase activating polypeptide (*ADCYAP1*) has been shown to be associated with PTSD diagnosis and symptoms in women.[59] In other studies, although statistically significant associations with PTSD were lacking, SNPs associated with *NR3C1*[60] and FK506 binding protein 5 (*FKBP5*)[61] have been shown to interact with trauma exposure to predict the severity of PTSD symptoms.

Several notable AUD studies have examined catechol-O-methyltransferase (*COMT*),[62] gamma-aminobutyric acid type A receptor alpha2 subunit (*GABRA2*),[63] cholinergic receptor muscarinic 2 (*CHRM2*),[64] and several genes involved in alcohol metabolism.[65] Other studies have attempted to assess whether candidate SNPs can moderate the effect of stress or trauma exposure on AUD. Blomeyer and colleagues found that an interaction between an intronic SNP in the corticotropin releasing hormone receptor 1 (*CRHR1*) gene and stressful life events predicted heavy alcohol use.[66] Another study of the interaction between *CRHR1* SNPs and adult traumatic stress exposure showed a significant effect on the likelihood of developing AUD.[67] Similarly, in other research, women who experienced childhood sexual abuse and who carried the low-activity allele of the monoamine oxidase A (*MAOA*) gene had significantly higher rates of AUD, when compared to control subjects.[68]

Some researchers have employed gene knock-in or knockout strategies in mice to assess the functional consequences of genetic variations identified in humans. A mouse knock-in study of the Val68Met SNP in the human brain derived neurotrophic factor (*BDNF*) gene, which is regulated by glucocorticoids, showed that introduction of the Met68BDNF allele dramatically increased alcohol consumption.[69] In a functional study of the *FKBP5* gene, researchers examined the effect of SNPs that are significantly associated with severity of alcohol withdrawal symptoms by knocking out the gene in mice.[70] In an analysis of human subjects, researchers determined that one of the same SNPs influenced allele-specific epigenetic modifications following exposure to ELS.[71] A study of healthy individuals showed that several of these SNPs were associated with differential cortisol responses to stress, strongly supporting their role in glucocorticoid signaling and HPA axis function.[72] Together, these studies demonstrate that genetic variations that potentially affect gene function can moderate the effect of stress or trauma on AUD.

Genome-wide association studies

Over the past 10 years, genome-wide association studies with large cohort sizes have gained traction because they can provide statistical power and an unbiased approach to uncovering novel genomic loci associated with a disease. However, in a 2017 genome-wide association study (N = 20,070), the Psychiatric Genomics Consortium for PTSD found no transethnic SNPs of genome-wide significance, although the researchers did find genetic overlap with schizophrenia.[54] In fact, several studies have shown that psychiatric disorders and PTSD share genetic risk. Another recent genome-wide association study uncovered several loci associated with alcohol consumption, including several genes

associated with alcohol metabolism.[73] In addition, a 2017 analysis that used a polygenic score approach reported that AUD shared genetic susceptibility with depression.[74]

Currently, there are no genome-wide association studies of genetic variants that interact with ELS to precipitate PTSD and AUD. However, both genetic and genome-wide studies of PTSD and AUD have identified loci associated with neurotransmitter regulation, alcohol metabolism, and the HPA axis. Further, studies that examined genomic loci across different disorders found evidence for overlap of genetic risk factors for PTSD, AUD, and other psychiatric disorders. This genetic overlap becomes especially relevant in understanding the epigenetic mechanisms associated with PTSD and AUD and helps us understand ELS-induced comorbidities in the larger context of psychiatric and substance use disorders.

Epigenetic mechanisms

In general, epigenetics refers to DNA, DNA-associated histone protein, or noncoding RNA modifications that can coordinate sustained gene regulation without changing the underlying DNA sequence. The detrimental effect of ELS on the human brain cannot be fully captured by the permanent information encoded by DNA. Physiological consequences of ELS may be mediated by epigenetic mechanisms, since ELS can lead to prolonged changes in gene function without changing the DNA sequence. The early-life exposure event in conjunction with genetic susceptibility is believed to lead to long-lasting changes in gene function to precipitate symptoms of PTSD and AUD in adulthood.

A number of epigenetic studies have examined the molecular consequences of exposure to stress or glucocorticoids, with potential implications for PTSD and AUD. Glucocorticoid signaling, which can directly alter epigenetic marks via glucocorticoid receptors, is one of the central mechanisms that enables stress-related events to alter brain function. Studies have demonstrated that chronic glucocorticoid exposure or isolation stress can lead to long-lasting loss of DNA methylation at *Fkbp5*[75] and tyrosine hydroxylase (*Th*) in vivo,[76] respectively, as well as at hundreds of loci across the genome.[77]

Exposure to ELS or glucocorticoids has also been shown to lead to epigenetic alterations of genes such as *CRH*, *NR3C1*, and *FKBP5*. Epigenetic regulation of these glucocorticoid target genes is noteworthy and has long-term implications, given their prominent role in HPA axis function. For instance, it has been well-established that genetic and epigenetic variations in the *NR3C1* and *FKBP5* genes contribute to hypercortisolemia and glucocorticoid resistance, because changes in *NR3C1* and *FKBP5* gene expression directly affect extracellular glucocorticoid levels and intracellular glucocorticoid signaling.[78]

Another group of glucocorticoid targets consists of genes that control tissue-specific processes. Genes that are expressed in the brain and are involved in neurodevelopment and neurotransmission are relevant to ELS, PTSD, and AUD. ELS-induced, long-term disruption of HPA axis function and epigenetic regulation of genes such as *NR3C1* and *FKBP5*, in turn, can affect epigenetic regulation of the *BDNF*, *TH*, and *MAOA* genes. These glucocorticoid target genes are critical for neurodevelopment and neurotransmitter function and, along with the glucocorticoid signaling genes *NR3C1* and *FKBP5*, can serve as molecular substrates that link ELS exposure and behavioral disorders such as PTSD, AUD, and substance use disorder. A causal relationship between glucocorticoid exposure and risk for psychiatric disorders is strongly supported by findings from large epidemiological studies.[79]

In the overall framework proposed, ELS disrupts homeostatic glucocorticoid levels in the system via epigenetic changes at specific genes that regulate glucocorticoid signaling. This disruption of homeostasis, in turn, leads to alterations of genes that precipitate psychiatric symptoms. Many of the genes that are epigenetically modified by ELS also play prominent roles in AUD and PTSD.

Epigenetics research on candidate genes that mediate the effect of ELS on PTSD and AUD is scarce. In this section we discuss the research on several genes in the context of stress, PTSD, or AUD, including studies that used human cohorts and those that used animal models of stress and alcohol intake. We briefly discuss six genes, *CRH*, *NR3C1*, *FKBP5*, *BDNF*, *MAOA*, and *TH,* to exemplify how ELS can epigenetically alter gene function, which then potentially

can affect behavioral symptoms, such as those observed in PTSD and AUD. For individuals who have experienced ELS and PTSD, alcohol use may induce gene expression and epigenetic changes to compensate for gene expression and epigenetic deficits.

CRH gene

CRH is a gene that has been implicated in ELS, PTSD, and AUD. It acts as one of the primary determinants of the brain's stress response and alcohol dependence. In adult mice, social defeat stress has been associated with a decrease in methylation at the *Crh* promoter in the paraventricular nucleus.[80] This finding is supported by studies that reported increased CRH levels in the cerebrospinal fluid and plasma of individuals with PTSD.[81-83] In other studies, adult rodents and nonhuman primates that were deprived of their mothers during youth have shown increased CRH concentrations within and outside the hypothalamus and in the cerebrospinal fluid.[35-37] These animals may exhibit hyperactive HPA axis and behavioral stress responses throughout life. As mentioned previously, elevated CRH in cerebrospinal fluid has also been observed in humans who have a history of ELS.[42]

CRH plays a critical role in AUD. Administration of CRH type 1 receptor antagonists in mice has been shown to attenuate alcohol-seeking behavior and withdrawal-induced drinking,[84,85] although such observations have not been strongly supported in human studies. As with stress exposure, alcohol administration activates the HPA axis, inducing release of CRH, ACTH, and cortisol. CRH production in the amygdala increases with chronic alcohol administration, resulting in long-term upregulation of *CRHR1* gene expression in specific regions of the brain. One of the mechanisms that potentiates alcohol-seeking behavior following exposure to ELS may be transactivation of the *CRH* gene resulting from a loss of methylation at its promoter.

NR3C1 gene

The *NR3C1* gene encodes the primary receptor for binding cortisol, and this receptor is believed to be responsible for the detrimental effects of HPA axis dysregulation. Recent evidence has implicated glucocorticoid signaling as a prominent factor in AUD and in many aspects of other substance use disorders.[86,87] In research relevant to ELS, poor maternal nursing behavior in rats has been shown to alter adulthood HPA axis function, as indicated by an increase in DNA methylation at one of the *Nr3c1* promoters.[88] In a study that examined human cord blood, researchers suggested that a similar mechanism developed in infants exposed in utero to maternal depression.[89]

In contrast, one study has documented different epigenetic patterns in individuals with PTSD, with those participants exhibiting a reduction in overall methylation and an increase in *NR3C1* expression, which enhances glucocorticoid trafficking.[90] In another study that compared individuals with PTSD to healthy controls, those with PTSD had consistently lower baseline cortisol levels, and they had a greater ability to suppress cortisol levels following a dexamethasone suppression test.[47] Although the molecular transition in glucocorticoid receptor sensitivity from ELS to PTSD is unclear, it is likely dependent on the type and duration of ELS. Further, the elevated cortisol levels achieved during alcohol intoxication may be compensating for hyperreactive glucocorticoid signaling and lower cortisol levels.

FKBP5 gene

FKBP5 is another gene that plays a crucial role in regulating systemic and intracellular glucocorticoid signaling. It encodes a chaperone protein that tethers the glucocorticoid receptor and prevents downstream glucocorticoid signaling, thereby attenuating glucocorticoid sensitivity. A study of primates implicated *FKBP5* as one of the main determinants of glucocorticoid resistance.[78] A study in humans examined gene-environment interaction between a risk allele associated with enhanced gene expression and ELS exposure.[71] The researchers reported that ELS-exposed, risk-allele carriers showed loss of intronic methylation near a glucocorticoid response element that affected glucocorticoid-induced activation of *FKBP5*. Another study reported that *FKBP5* alleles interacted with ELS to increase the risk for PTSD.[91]

ELS-induced modulation of *FKBP5* expression also has important implications for AUD. In preclinical studies, *Fkbp5* expression levels modulated alcohol intake and withdrawal severity, with *Fkbp5* knockout mice increasing alcohol intake and exhibiting sensitivity to alcohol withdrawal.[70,92]

In humans, a study has linked a SNP genotype of *FKBP5* and the presence of poor child-parent relationships to problematic drinking behavior.[93] Collectively, ELS exposure leads to epigenetic changes at genes that alter HPA axis function, and those changes, along with genetic variations, may increase the risk for the development of PTSD. Although the molecular transition that takes place from ELS exposure to PTSD is still unclear, the effect of ELS exposure on glucocorticoid signaling is associated with increased alcohol intake and withdrawal severity.

BDNF gene

In addition to genes that regulate the HPA axis and glucocorticoid signaling, downstream glucocorticoid receptor target genes that regulate brain-specific processes also have a significant effect on ELS-induced behavior. As a member of the neurotrophin family of growth factors, the BDNF protein promotes neuronal survival, protection, and growth, as well as synaptic plasticity and neurotransmission.

A well-studied SNP, the Val66Met polymorphism, has been shown to interact with ELS to predict symptoms consistent with depression, anxiety, and cognitive decline.[94] In rodent models, stress exposure in many forms and during several developmental periods leads to a decrease in *Bdnf* expression via epigenetic mechanisms. For example, maternal separation or early weaning has been shown to lead to decreased expression by promoting histone deacetylation at exon IV,[95] social isolation has been associated with an increase in intronic glucocorticoid response element DNA methylation during adolescence,[96] and social defeat has been linked to histone deacetylation during adulthood.[97]

Similar findings have been observed in individuals with PTSD. In one study, a meta-analysis implicated the Val66Met polymorphism in trauma-exposed individuals with PTSD.[98] Researchers have reported that in veterans with PTSD, when compared to veterans without PTSD, peripheral BDNF protein levels were lower, and DNA methylation in the gene promoter was higher.[99] For the *BDNF* gene, alcohol appears to compensate for ELS- or PTSD-induced deficiencies, as demonstrated by a study in which acute alcohol administration led to histone acetylation-associated increases in the central and medial amygdala of alcohol-preferring rats.[100]

MAOA and *TH* genes

The *MAOA* gene encodes an enzyme that oxidizes and breaks down monoamine neurotransmitters such as dopamine, serotonin, and adrenaline. Of these monoamine neurotransmitters, dopamine has garnered the most interest regarding alcohol and substance misuse because of its involvement in stress and reward pathways. The *TH* gene encodes the rate-limiting enzyme involved in the synthesis of dopamine, tyrosine hydroxylase. Both the *MAOA* and *TH* genes are regulated by glucocorticoids.[96,101,102] Through glucocorticoid-mediated, epigenetic dysregulation of dopamine function, these genes provide the means for ELS exposure to increase risk for the development of PTSD and AUD.

In a study using an animal model, exposure to peripubertal stress increased *Maoa* gene expression in the prefrontal cortex of rats, supported by an increase in histone H3 acetylation at the gene promoter.[103] In another study, socially defeated mice showed a similar increase in the raphe nuclei.[104] No studies have examined MAOA protein levels in relation to PTSD, but in one study of ELS-exposed rodents, alcohol exposure decreased MAOA activity and led to increased dopamine levels.[105] In a study analyzing macaques, alcohol intake reduced expression levels of the *MAOA* gene in a dose-dependent manner.[106]

TH is another glucocorticoid target gene, and its expression levels are diminished in animals exposed to ELS.[96] Although this gene has not been examined in the context of PTSD, *TH* expression levels have been increased by exposure to alcohol, providing yet another example of how alcohol use may be compensatory behavior to normalize gene function.[107] A small study of pharmacological dopamine stimulation in humans showed enhanced reward-induced performance accuracy in participants who had poor parental care, further supporting the animal findings.[108]

Future Research Needs

A brief review of the above candidate genes reflects the relative scarcity of data on the effects of ELS on comorbid PTSD and AUD, which necessitates additional investigations. First, an ELS model capable of recapitulating the component symptoms of both PTSD and AUD is needed. Animal model studies underscore the difficulty

of modeling stress and alcohol exposure. Factors such as intensity, duration, and types of stress superimposed on different brain regions, circuits, and neurotransmitters have all contributed to different outcomes and further confounded conclusions. Development of robust animal models that can produce predicted phenotypical outcomes under standardized conditions is needed. Once established, these models can be implemented to examine the molecular underpinnings of PTSD and AUD. Use of genome-wide approaches can provide a bigger picture of relevant neuroadaptations, such as ELS-induced changes in specific pathways and gene sets. Specifically, genome-wide "omics" approaches, consisting of transcriptomics (RNA sequencing), epigenomics (methylation sequencing), and proteomics (mass spectrometry), can facilitate discovery and characterization of targets.

Similarly, human studies are lacking, except for a few clinical and candidate gene association studies. First and foremost, there is an urgent need for recruiting individuals who have comorbid AUD and PTSD rather than those who have AUD or PTSD alone, as underlying molecular mechanisms governing the comorbid condition may be unique and distinct. In addition, these cohorts need to be large enough to identify genetic variants that interact with ELS and are associated with PTSD and AUD. Once susceptibility genes and their variants have been identified, preclinical studies manipulating these genes can establish how the genes interact with ELS to precipitate PTSD and AUD symptoms. In addition, assays can be developed to identify individuals who may be predisposed genetically or epigenetically to PTSD and AUD.

Also, functional studies are needed to verify whether AUD is compensatory behavior to offset the molecular consequences of stress. Preclinical and clinical studies are needed to examine at the molecular level whether alcohol consumption can reverse many of the deficits caused by ELS exposure. Identification of such substrates of AUD can lead to development of medications that do not have the detrimental and addictive properties of alcohol.

Key questions that need to be addressed include:

- What mechanisms underlie the increased risks of developing AUD and PTSD following exposure to ELS?
- How do the allostatic changes that result from ELS remain durable over the lifetime of the individual?
- Why are only a subset of individuals at risk for AUD or PTSD following ELS?
- Are the allostatic changes that result from ELS both necessary and sufficient to produce the symptom complex associated with AUD and PTSD?
- Can these altered systems be targeted for therapeutic intervention?

Conclusion

In this review, we sought to understand the mechanisms that underlie the link between ELS exposure and comorbid PTSD and AUD. Physiologically, the observed relationships are the result of ELS-induced, long-lasting, maladaptive changes in the stress and reward systems in the brain. Changes to these overlapping neural circuits have significant implications for PTSD and AUD. At the molecular level, a brief overview of several candidate genes suggests that ELS-induced epigenetic and transcriptional changes function as risk factors for AUD by promoting alcohol consumption.

Studies of genes such as *CRH* and *FKBP5* demonstrate that ELS-induced alterations in gene expression mimic the expression levels observed during alcohol intoxication, which may potentiate alcohol-seeking behaviors. Alternatively, studies of genes such as *NR3C1*, *BDNF*, *MAOA*, and *TH* suggest that alcohol consumption has an effect on gene expression and epigenetic regulation that may counteract the expression and epigenetic deficits caused by ELS. Therefore, alcohol consumption may be a coping behavior in an attempt to compensate for the molecular consequences of ELS.

The study of comorbid PTSD and AUD arising from ELS exposure is fertile ground for further investigation, as relatively few studies have been conducted. Additional animal model development; human studies; transcriptomic, epigenomic, and proteomic approaches; and specific therapeutic approaches are needed to understand and treat these debilitating psychiatric disorders.

Financial Disclosure

The authors declare that they have no competing financial interests.

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Common Biological Mechanisms of Alcohol Use Disorder and Post-Traumatic Stress Disorder

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Post-traumatic stress disorder (PTSD) and alcohol use disorder (AUD) are highly comorbid. Although recent clinical studies provide some understanding of biological and subsequent behavioral changes that define each of these disorders, the neurobiological basis of interactions between PTSD and AUD has not been well-understood. In this review, we summarize the relevant animal models that parallel the human conditions, as well as the clinical findings in these disorders, to delineate key gaps in our knowledge and to provide potential clinical strategies for alleviating the comorbid conditions.

KEY WORDS: **addiction; animal models; depression; neural circuitry; post-traumatic stress disorder (PTSD); stress; trauma**

Alcohol use disorder (AUD) is one of the most common co-occurring disorders among individuals diagnosed with post-traumatic stress disorder (PTSD).[1] Many people who have PTSD use alcohol in an attempt to ameliorate debilitating symptoms such as anxiety and hyperarousal. Clinical and epidemiological studies have consistently reported that PTSD is associated with a threefold higher risk for developing AUD, and for individuals who have PTSD, the lifetime prevalence of AUD has been estimated at 40%.[2] The severity of PTSD symptoms is positively related to the level of alcohol use, and it also predicts alcohol craving in response to trauma- and alcohol-related cues. Despite the high rates of comorbidity, there is a substantial gap in understanding how traumatic experience leads to transition from initially controlled alcohol consumption (reward phase) to the development of alcohol-seeking and dependence (negative reinforcement phase). This review summarizes clinical observations and highlights findings from preclinical animal models, and focuses particularly on the alterations and dysfunctions in neural circuitry and stress hormone systems that may underlie enhanced vulnerability to AUD in context of PTSD (Figure 1).

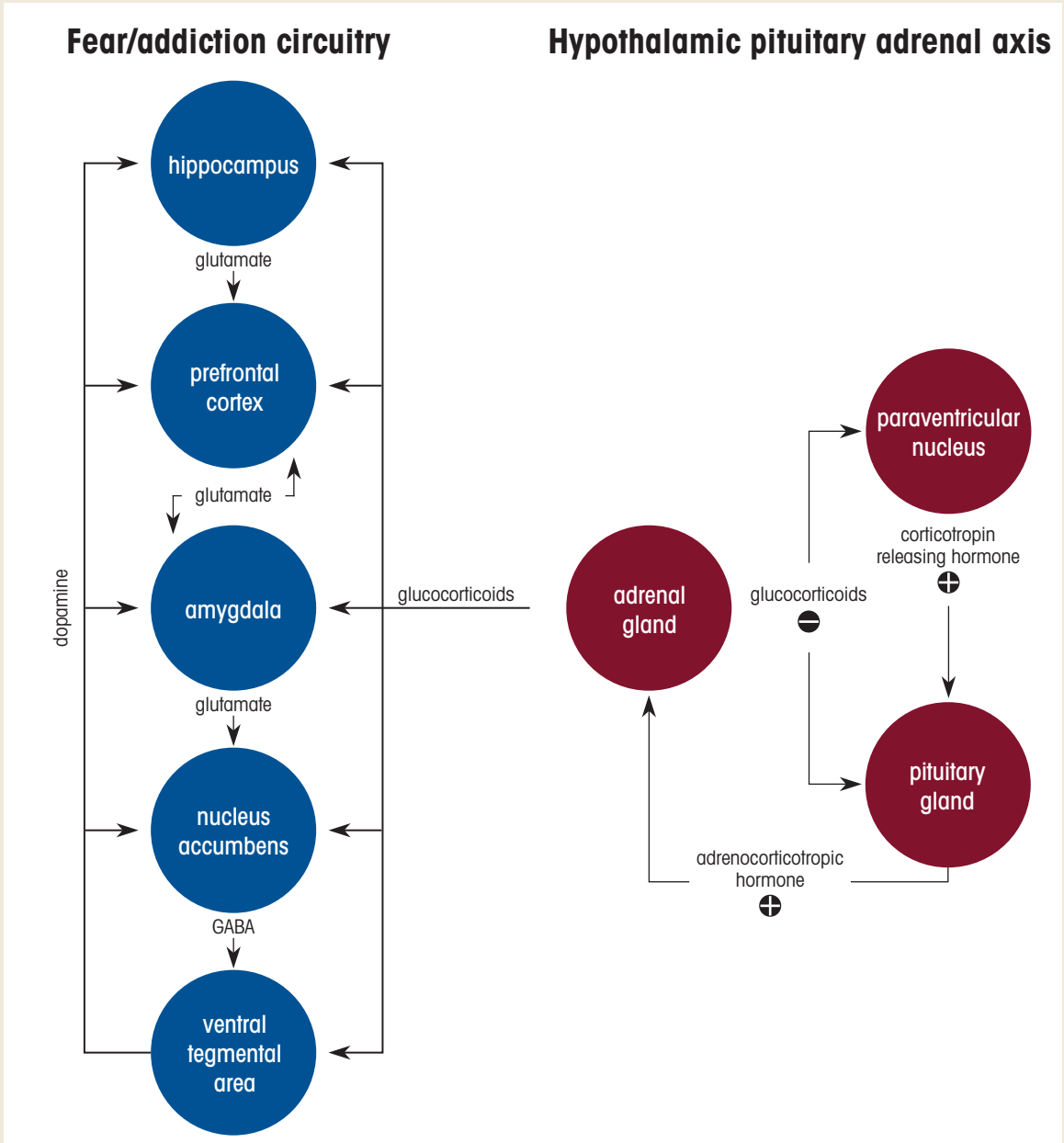

Figure 1 Interactions between the fear/addiction neural circuitry and the hypothalamic pituitary adrenal (HPA) axis. The fear/addiction circuitry includes the hippocampus, prefrontal cortex, amygdala, nucleus accumbens, and ventral tegmental area. The prefrontal cortex mutually connects with the amygdala, and the amygdala projects to the nucleus accumbens via its glutamatergic innervations. All these areas receive projections from dopamine neurons in the ventral tegmental area. The major components of the HPA axis include the paraventricular nucleus of the hypothalamus and the pituitary and adrenal glands. Corticotropin releasing hormone from the paraventricular nucleus stimulates adrenocorticotropic hormone (ACTH) release from the anterior pituitary into the bloodstream, then ACTH induces glucocorticoid release from the adrenal gland. Glucocorticoids mediate negative feedback in the HPA axis to reduce the stress response. Glucocorticoids also affect the fear/addiction circuitry via the glucocorticoid receptors, which triggers molecular, cellular, and physiological changes, including epigenetic alterations. *Note:* GABA, gamma-aminobutyric acid.

Preclinical Models of PTSD and AUD

Animal model approaches

There are several procedures commonly used to create animal models of stress or PTSD and to employ stress components that are known to lead to enhanced risk for AUD.[3] Many procedures are simple, easy to implement, and effective at inducing a broad departure from endocrinological, physiological, and neurobiological homeostasis.[4] Also, both acute and chronic stressors can lead to physical and psychiatric pathology. First, we briefly describe a range of stress-related approaches to modeling the phenotypes of PTSD and AUD. Then, we review supporting studies in more detail, examining common biological components of both disorders.

Widely used physical stressors include exposure to immobilization, restraint, cold-water swimming, electric footshocks, and noxious stimuli.[4] Immobilization or restraint stress commonly is produced by confining a naïve animal inside a bag or tube. Also, relevant naturalistic or ethological stressors have been used to trigger stress states.[4] Models of psychological stress include exposure to predator odor; an elevated platform; or a bright, open area; whereas models of social stress include social isolation, maternal deprivation, and social defeat. In some studies, more than one stressor is applied concomitantly to test the generality of a hypothesized mechanism or to enhance the intensity of desired responses.

Alcohol behaviors include various responses and changes elicited by alcohol exposure and withdrawal. Examples of these behaviors are alcohol craving, compulsive alcohol-seeking, excessive alcohol intake, alcohol dependence, and relapse. In this review, we survey the recent progress in animal modeling for two main aspects of AUD-related alcohol behaviors—alcohol consumption and alcohol-seeking. In general, experiments designed to investigate the effects of stress and alcohol behaviors can be divided into three categories. In the first category, alcohol-naïve animals experience stress, then alcohol is introduced concurrently or after an incubation period.[5-7] In the second category, animals are familiarized to alcohol or to drinking alcohol before stress is introduced.[8] In the third category, animals develop alcohol behaviors, subsequently extinguish those behaviors, and then stress is introduced during a development, extinction, or reinstatement period.[9] In these experimental designs, alcohol behaviors are generally monitored through preference ratios and by measuring intake. Typically, animals have free access to water or an alcohol solution, and alcohol preference and intake are determined by the amount of liquid consumed and the number of approaches.

A considerable body of evidence suggests that stress triggers negative affective states and subsequent adaptive changes that lead to the development of AUD, so many animal models for AUD have focused on creating a condition in which a stress procedure precedes alcohol exposure (or re-exposure).[3] Notably, however, it also has been suggested that excessive drinking is a risk factor for developing anxiety disorders such as PTSD. There are several reasons this may be the case. One possibility is that in cortical regulatory areas such as the medial prefrontal cortex (mPFC), impairments from excessive drinking are similar to impairments from repeated stress. For example, in a 2012 study of mice, Holmes and colleagues examined the effects of chronic alcohol exposure on the prefrontal cortex (PFC) and its capacity to mediate fear extinction.[8] Fear extinction is a reduction in the frequency or intensity of a conditioned fear response (e.g., freezing) after repeated presentation of a conditioned stimulus (e.g., a sound) in the absence of the unconditioned aversive stimulus (e.g., a footshock). Holmes and colleagues found that mice intermittently exposed to continuous vaporized alcohol had significant remodeling of mPFC neurons and demonstrated impaired fear extinction.[8]

Using a combination of these preclinical models and molecular, genetic, and pharmacologic manipulation approaches, recent investigations have made great strides in delineating the neurobiological processes underlying stress-induced escalated alcohol intake or alcohol-seeking behavior. Next, we summarize some details of these models and their relevance to both disorders, as well as to comorbid PTSD and AUD.

Restraint or immobilization stress

Restraining rodents in small tubes or on a platform in an acute or chronic manner leads to increased

manifestations of anxiety and changes in neuronal morphology within brain regions that mediate fear and anxiety.[10,11] In previous studies, acute immobilization stress in mice significantly elevated hypothalamic pituitary adrenal (HPA) axis activity, resulting in impaired fear extinction and extinction retention following Pavlovian fear conditioning.[12,13] Furthermore, exposure to this stressor led to impaired long-term declarative memory and enhanced anxietylike behavior.[14]

Because of the practical simplicity of restraint-related procedures, numerous studies have employed them to elucidate the relationship between stress and alcohol consumption. However, the results are not conclusive. In some cases the stressor significantly increased alcohol intake, whereas in others alcohol consumption decreased or did not change.[15,16] Therefore, although researchers have speculated about many factors, such as time, individual differences, and stress-induced long-term sensitization or desensitization of the HPA axis,[17] there appears to be no clear primary determinant on the outcome in those studies.

Social stress

Social isolation, such as maternal deprivation, is a demonstrated risk factor for alcohol consumption during adolescence and adulthood, particularly in male rats.[18] In one study, when rat pups were separated from their mothers for 6 hours per day for 20 days, they exhibited increased ethanol consumption during their adolescence, compared with rat pups that had only 15 minutes of deprivation per day. In a similar study, rats (male and female) that experienced a single, 24-hour maternal deprivation on postnatal day 9 and subsequent exposure to restraint stress showed higher ethanol intake than animals that experienced only a single maternal deprivation.[19] Furthermore, isolation stress during adolescence seemed to similarly increase alcohol consumption. For example, rats housed individually during adolescence exhibited increased ethanol intake and ethanol preference during adulthood.[20] Moreover, when an intermittent procedure was used to offer these rats alcohol, they drank significantly more ethanol solution and obtained higher blood ethanol levels than rats that received a continuous procedure. In addition, when induced by chronic early life stress, the increase in ethanol consumption lasted for at least 8 weeks.[21] Notably, the stressed rats displayed a significant deficit in fear extinction but not in fear memory acquisition.

Also, several studies have shown through self-administration and place-conditioning paradigms that exposure to social defeat stress induced escalation of alcohol consumption as well as reinstatement of alcohol-seeking behavior after extinction.[22] Procedures for invoking social stress can be divided into acute versus repeated, or agonistic encounters in a neutral environment versus resident or intruder settings. In these stress paradigms, the observation of escalated alcohol intake is related to when the stress experience occurred. The animals showed no significant change in alcohol consumption immediately after stress, but they showed an increase 2 hours after stress.[22]

More recent studies with mice demonstrated that a 10-day social defeat stress experience increased ethanol drinking and preference for at least 20 days after the defeat.[6,7] Elevated alcohol consumption was correlated with plasma corticosterone levels and was modulated by the signaling pathway of corticotropin releasing hormone receptor 1 (*CRHR1*) in the ventral tegmental area (VTA) and by dopamine within the nucleus accumbens. Chronic social defeat in rats and mice is well-known for inducing some core PTSD symptoms, such as increased social avoidance[23] and anxiety,[22] as well as enhanced fear memory acquisition.[23]

Predator-based stress

In rodents, exposure to a natural predator has been shown to provoke high levels of intense fear and stress, followed by long-lasting endocrine and behavioral responses. Typically, the rodents are exposed very briefly (5 to 10 minutes) to a predator or to predator odorants, such as predator urine, which leads to elevation of long-lasting anxietylike behavior.[24] Specifically, rats exposed to chronic social instability in conjunction with cat odor showed reduced basal glucocorticoid levels, increased glucocorticoid suppression following dexamethasone administration, heightened anxiety, and enhanced fear memory.[25] These results mimic common endocrine and behavioral measures found in humans with PTSD. Another study demonstrated that rats with higher stress reactivity

to predator urine exhibited more alcohol drinking than rats with lower stress reactivity.[5]

Genetic differences

It has been well-reported that background strain differences can confound stressor reactivity measures and alcohol-related behaviors in the same manner demonstrated for other behavioral measurements, including learning and memory performance, aggression, and emotionality. For example, a phenotypic survey study comparing fear extinction in a panel of inbred mouse strains revealed fear extinction impairment in the 129/SvImJ strain due to a failure in the engagement of corticolimbic extinction circuitry, despite the strain's normal fear conditioning and nociception.[26] A similar study showed that chronic exposure to swim stress resulted in a significant decrease in ethanol consumption in mouse strains DBA/2J and BALB/cByJ but not in strain C57Bl/6J, although stress increased sensitivity to the sedative/hypnotic effects of ethanol in all three strains.[27]

Neurobiological Circuits

Neuroimaging studies have suggested that stress-induced alcohol behaviors may relate to convergent or divergent changes in multiple brain areas. However, to provide a framework for identifying alterations in neural circuitry, we will focus on a few brain areas well-associated with processing fear, anxiety, stress, and rewards. These areas include the amygdala, PFC, hippocampus, and VTA.

Amygdala

The amygdala is well-known for its role in physiological and behavioral responses to fear, stress, and substance misuse.[5,28,29] During fear learning, the amygdala receives multisensory information from the cerebral cortex and thalamus and projects to brain regions that produce behavioral and physiological fear responses.[28] During fear extinction and fear extinction recall, the mPFC and hippocampus regulate the amygdala from the top down through rich, mutual connections between these areas to modulate previously conditioned fear. Furthermore, severe stress facilitates fear and anxietylike behavior via amygdala-dependent anatomical and physiological changes at synaptic, cellular, and network levels.[4,28,29] Neuroimaging studies of healthy humans have shown that increased amygdala activity was evoked by fearful cues and during fear conditioning.[30] In other studies, combat veterans with PTSD who were exposed to fearful faces exhibited higher levels of amygdala activation than healthy individuals, and they also exhibited hyperreactivity in the presence of trauma-related stimuli.[31,32]

In a 2014 study, Garfinkel and colleagues examined amygdala activity in individuals with PTSD.[33] The researchers used conditioning to generate a fear response to a conditioned stimulus of a colored light (the dangerous context). Later, in a different (safe) context, participants were conditioned to extinguish that fear response. The individuals with PTSD exhibited an increase in amygdala activity when reintroduced to the conditioned stimulus in the safe context, indicating impaired fear extinction. However, in the same study, individuals with PTSD demonstrated low amygdala activity when the extinct conditioned stimulus was reintroduced in the original dangerous context to elicit a fear response (i.e., fear renewal). The low amygdala activity could indicate that these individuals have impaired fear renewal. These findings suggest that individuals with PTSD have a globally diminished capacity to use contextual information to modulate fear expression.

In addition to functional changes, structural changes in the amygdala have been reported in individuals who have PTSD and a history of early life stress. Notably, smaller amygdala and hippocampus volumes have been found in children exposed to different forms of early life stress and have been associated with greater cumulative stress exposure and behavioral problems.[34] Interestingly, in men who had alcohol dependence, amygdala volume reduction was associated with increased alcohol craving and intake.[35] Furthermore, it has also been demonstrated that alcohol cues triggered amygdala reactivation in men with alcohol dependence alone,[35] as well as in individuals who had PTSD and AUD.[31] However, the neuroimaging data generated by functional magnetic resonance imaging and positron emission tomography do not yet provide the resolution to reliably differentiate amygdala nuclei.

Studies with animal models greatly help extend understanding of the structures and functions

of the amygdala in anxiety and fear memory, because the gross anatomy, connectivity, and cellular composition of amygdala nuclei are well-conserved across species.[28] The amygdala comprises multiple interconnected nuclei that can be classified largely into two groups: cortexlike and striatumlike structures. The cortexlike structure includes the basolateral complex, consisting of the lateral, basolateral, and basomedial amygdala. The striatumlike structure consists of the central nucleus of the amygdala (CeA), which has lateral and medial subdivisions and intercalated cell clusters. During fear conditioning, output activity in the medial division of the CeA is enhanced by excitatory signals originating directly from the lateral amygdala and indirectly through the basolateral amygdala. The output also is modulated by reciprocal connections between the basolateral amygdala and the prelimbic area of the PFC. In contrast, during fear extinction, neural activity in the lateral and basolateral amygdala is reduced, and the infralimbic area of the PFC participates in suppression of fear through the basolateral amygdala and the intercalated cells.

Recent studies suggest functional and molecular heterogeneity for the cell types and projections within some of the amygdala subnuclei. For example, in one of our studies, we found that tachykinin receptor 2 (*TACR2*)-expressing neurons in the medial division of the CeA were involved in fear consolidation.[36] In another study, researchers found that protein kinase C delta (*PRKCD*) expression in the lateral division of the CeA provided inhibitory regulation in the medial division of the CeA, reducing fear expression.[37] Similarly, through optogenetic manipulations, we demonstrated that Thy-1 cell surface antigen (*THY1*)-expressing neurons in the basolateral amygdala were involved in fear extinction and fear extinction recall.[38,39]

Because a generalized fear response is considered a hallmark of anxiety, researchers have examined intra-amygdala circuits and long-range projections and demonstrated that microcircuits in the amygdala play a role in anxiety. In one study, increased tonic firing of output neurons in the medial division of the CeA activated by neurons in the lateral division of the CeA was required for fear responses to the conditioned stimulus and to an unconditioned stimulus.[40] These findings suggest that tonic activity within CeA fear circuits may be an underlying neuronal substrate for anxiety. Similarly, in the lateral amygdala, activity in distinct neuronal populations also seems to be necessary for fear generalization. One study reported that in rats that exhibited generalized fear, cells in the lateral amygdala responded to a conditioned stimulus that was not paired with an unconditioned stimulus.[41]

Because alcohol-seeking in humans has long been considered to be motivated by the desire to reduce stress and anxiety, the amygdala has been linked to behavior associated with alcohol misuse. In particular, the gamma-aminobutyric acid (GABA) neurotransmitter system in the CeA has been implicated in mediating behavior associated with acute and chronic alcohol consumption. In one study, rat brain slices exposed to an acute superfusion of ethanol increased presynaptic GABA release and enhanced postsynaptic GABA receptor function in CeA neurons.[42] The same researchers also demonstrated that chronic ethanol exposure promoted increased basal GABA release without presynaptic effects.[43] Furthermore, stereotactic injection of gabapentin, an anticonvulsant GABA analog, attenuated elevated operant ethanol responses in ethanol-dependent rats.[43] Studies with transgenic mice showed that ethanol enhanced the activity of CRHR1 receptors in the CeA, implicating potential cell type–specific interactions between the stress corticotropin releasing hormone (CRH) signaling pathway and alcohol consumption and dependence.[44] Consistent with this idea, studies have shown that rats that displayed persistent avoidance of a predator odor–paired context consumed more alcohol and exhibited compulsivelike responding for alcohol,[5] and they expressed hyperalgesia via the CRH signaling pathway in the CeA.[45]

PFC

The PFC, a large and complex brain region that is greatly expanded in nonhuman primates and humans, is topographically organized and has anatomically distinct subfields, roughly divided into dorsolateral, ventromedial, and orbital regions. These subfields are believed to be involved in various cognitive and emotional functions. For example, the dorsolateral regions of the PFC provide top-down regulation of attention, thought, and action and have extensive connections with sensory and motor cortices.[46] In contrast, the ventromedial regions of the PFC regulate emotional responses

and have vast connections with various subcortical structures, such as the amygdala, nucleus accumbens, and hypothalamus.[47] The PFC also has direct and indirect interactions with the monoamine system, including noradrenergic projections from the locus coeruleus and dopaminergic inputs from the substantia nigra and VTA. The PFC is sensitive to the detrimental effects of stress exposure, as even mild uncontrolled acute stress can cause a rapid and dramatic loss of cognitive abilities, and more prolonged stress exposure causes anatomical changes in the PFC. All of these PFC pathways are critically involved in appetitive behavior, as occurs with AUD, and in emotion regulation, which is disrupted during fear processing, as occurs with PTSD.

Given the mutual connectivity between the PFC and amygdala, it has been suggested that the fortified emotional memory traces in individuals with PTSD may be a product of imbalanced interactions between the two brain areas. The PFC seems to exert an inhibitory response on the amygdala, which is a central node for emotional reactivity. In neuroimaging studies, participants with PTSD showed decreased prefrontal blood flow,[48,49] and a study that used trauma reminders to provoke symptoms in patients with PTSD reported reduced activation in the ventromedial PFC.[50] This decreased PFC activity is often accompanied by increased amygdala activity,[49,51] suggesting there may be a failure of top-down cortical inhibition on the reactivation of memory traces associated with trauma-related thoughts and feelings.

The failure of top-down cortical inhibition may also relate to functional mechanisms associated with stress-related alcohol craving and relapse. Alcohol-related dysfunction in the PFC affects higher order executive function, including response inhibition and decision-making. Alcohol-related neuroadaptations in the prefrontal networks, including in the corticostriatal motivation pathways,[52] could also promote increased relapse risk and craving for alcohol consumption. In support of these ideas, researchers have used individually calibrated, script-driven, guided-imagery procedures and neuroimaging to identify neural responses to stress and alcohol context cues.[53,54] These studies demonstrated that, in healthy individuals, stress and alcohol cue exposure induced overlapping neural responses, with increased activation of the corticolimbic striatal circuit, encompassing the mPFC, orbitofrontal cortex, and anterior cingulate cortex. Healthy men displayed greater stress-induced activations throughout the prefrontal areas than healthy women, whereas women showed greater alcohol cue–related activity in the superior and middle frontal gyrus than men.[53] These findings suggest that differential neural responses in these cortical areas may contribute to the sex differences found in stress-related coping and in vulnerabilities to stress-induced alcohol consumption and alcohol-seeking.

A follow-up study with a similar approach showed that individuals with AUD, when compared with control subjects, had less neural activity in the ventromedial PFC and anterior cingulate cortex when exposed to an alcohol-enticing or stressful stimulus.[54] These same participants showed increased activity in the ventromedial PFC and anterior cingulate cortex during exposure to relaxing cues. These neuroimaging studies indicate that disrupted functions in the PFC, as well as in motivation-reward brain regions, may be neural mechanisms underlying alcohol craving and relapse.

Although it has been difficult to determine exactly analogous rodent and human brain regions, it is generally accepted that rodents have a PFC equivalent.[55] Based on examination of rodent cellular structure, lamination, and projection patterns, findings suggest there are clear distinctions between the dorsal (precentral and anterior cingulate) and ventral (prelimbic, infralimbic, and medial orbital) subdivisions of the mPFC.[47] The rodent dorsal PFC, similar to the primate PFC, is implicated in memory for motor responses, including the temporal processing of information and response selection.[56] The ventral PFC is involved in emotional responses, such as anxiety, and in the expression and extinction of conditioned fear memory.[57,58]

Hippocampus

The hippocampus is defined by its characteristic trisynaptic circuit and is well-known for its crucial roles in spatial navigation and episodic memory (i.e., recall of events within the spatial and temporal context in which they occurred).[59] Dysfunctions of the hippocampus lead to not only memory deficits, but also anxiety, depression, epilepsy, and schizophrenia, suggesting that the hippocampus contributes to attention, arousal, and emotional

states, including stress.[60] Stress produces intense and long-lasting memories that can be a source of serious distress, but prolonged stress seems to impair performance on hippocampus-dependent memory tasks. For example, individuals diagnosed with PTSD and healthy individuals injected with cortisol (a human glucocorticoid) have been shown to be impaired in various verbal recall tests.[61] In addition, clinical and preclinical studies have shown that stress changes synaptic plasticity and firing properties of hippocampus neurons, induces morphological atrophy, suppresses neuronal proliferation, and reduces hippocampal volume.[61] These wide-ranging changes appear to be mediated by stress hormones. Glucocorticoids act, in part, via negative feedback of the HPA axis through the hippocampus, which is densely concentrated with glucocorticoid receptors. Similarly, rodent studies have shown that exposure to stress or high doses of corticosterone (a rodent glucocorticoid) produces deficits in hippocampus-dependent spatial memory tasks.[60]

Neuroimaging studies have demonstrated that acute alcohol exposure affects the hippocampal function of contextual or episodic memory encoding.[62] In addition, chronic alcohol misuse seems to cause a reduction in hippocampal volume and activity.[63,64] In animal studies, alcohol exposure during fetal or adolescent development has been shown to induce reductions in hippocampal neurogenesis.[65,66] In addition, chronic alcohol exposure has been shown to disrupt adult hippocampal neurogenesis, alter connectivity of new neurons, and result in behavioral deficits, as demonstrated through the hippocampus-dependent novel-object recognition task and Y-maze test.[67]

VTA and dopamine regulation

The VTA is in the midbrain, situated adjacent to the substantia nigra, and it is primarily characterized by its dopaminergic neurons, which project to limbic and cortical areas via the mesolimbic and mesocortical pathways, respectively. Electrophysiological studies in monkeys demonstrated that rewards and reward-predicting cues elicited strong phasic firing of midbrain dopamine neurons.[68] Functional magnetic resonance imaging studies in humans have reported that increased midbrain activation occurred during anticipation of pleasant tastes[69] and monetary gains,[70] as well as for reward-predicting cues.[71] Because VTA dopamine neurons project densely to the nucleus accumbens in the ventral striatum via the mesolimbic pathway, these brain areas have been implicated as major areas for processing natural rewards, reinforcement, and drugs of abuse.[72]

Studies using pharmacological perturbation and biochemical measurements have provided strong evidence for the reinforcement role of alcohol via the mesolimbic dopamine system. In a study with rats, systemic injection of dopamine receptor antagonists decreased responding for alcohol in a free-choice task, but the injection did not affect responses for water.[73] Furthermore, in a study of nondependent rats, alcohol self-administration increased extracellular levels of dopamine in the nucleus accumbens.[74] Such increases occurred during and also before the self-administration, indicating the motivational properties of cues associated with alcohol. Similar results have been shown in dopamine neurons of monkeys responding to reward cues.[68]

Acute exposure to different forms of stress reportedly increases dopamine release in the nucleus accumbens,[75] whereas long-term, repeated exposure to different stressors decreases basal dopamine output in the nucleus accumbens.[76] If the base level of dopamine has been reduced by stress, the phasic dopamine release induced by alcohol may have an amplified effect. This amplified dopamine effect may further enhance the reward-learning process, consequently leading to increases in alcohol consumption and preference.

Stress-induced alcohol preference and alcohol consumption seem to be due to alterations in both excitatory and inhibitory circuits within the VTA. A 2013 study in rats demonstrated that social isolation stress enhanced the acquisition of memories for alcohol-associated environmental cues.[77] The learning processes were facilitated by long-term potentiation of *N*-methyl-D-aspartate (NMDA) receptor–mediated excitatory transmission in the VTA, and the facilitation could not be reversed by resocialization. In contrast, Ostroumov and colleagues showed that stress promoted alcohol use through actions on inhibitory GABA signaling in the VTA.[78] Rats that underwent acute restraint stress 15 hours before introduction to ethanol self-administered considerably more ethanol than controls, and this increase in alcohol consumption

lasted for more than 7 days. Electrophysiological recordings in the same study revealed that stress blunted the ethanol-induced increase in the firing rate of VTA dopamine neurons, which was restored by application of a $GABA_A$ receptor antagonist. The stress also increased the concentration of intracellular chloride ions in VTA GABA neurons and seemed to alter the chloride gradient of GABA neurons such that, paradoxically, GABA excited these cells.

VTA dysfunction is clearly relevant to AUD. However, in PTSD, both the anhedonic component and the dopamine regulation of fear extinction may represent neuroanatomical VTA dysfunction, which may contribute to AUD and PTSD comorbidity.

Stress Axis Function

HPA axis

The HPA axis is the main neuroendocrine response system to stress.[61] The activation of this system is characterized by adrenal gland synthesis and release of steroids known as glucocorticoids, such as cortisol in humans and corticosterone in rodents, triggered by the release of adrenocorticotropic hormone (ACTH) from the pituitary gland. ACTH release into the general circulation is controlled by the secretion of CRH from the paraventricular nucleus of the hypothalamus to the anterior pituitary gland via the portal blood vessels.

Glucocorticoids act on the brain through two main receptors: type I, the mineralocorticoid receptor (MR), and type II, the glucocorticoid receptor (GR). These are nuclear receptors working as transcription factors. They modulate targeted gene expression by binding to DNA or by interfering with the activity of other transcription factors.[61] Notably, the MR has a 10-fold higher binding affinity for glucocorticoids than the GR. This differential binding affinity is assumed to create a two-tier system with negative feedback.[79] Due to their high affinity, MRs are bounded by glucocorticoids and appear to be in a constant activated state under any physiological condition. In contrast, GRs with low binding affinity are occupied only after a significant rise of glucocorticoids. These GRs play a role in exerting negative feedback on enhanced HPA axis activity and in stress-related adaptation.[79]

As part of homeostatic processes, the actions of the HPA axis are tightly regulated to ensure that the body can optimally face stress challenges, adapt to environmental stimuli, and return to a normal state. Dysfunctions in the HPA axis frequently have been found in humans diagnosed with PTSD or AUD, so comorbidity may stem from an overlapping neurobiological mechanism. However, the details of this mechanism as a possible link between these disorders are not yet well-understood. In this section we describe recent findings on PTSD or AUD in humans and animals and how these conditions relate to the role of the HPA axis in comorbid high-stress reactivity and enhanced alcohol intake.

Stress hormones and PTSD

Neuroendocrine studies have shown profound alterations in the HPA axis in individuals with PTSD. In particular, it has been well-documented that reduced baseline cortisol levels, in addition to enhanced cortisol suppression to a low-dose dexamethasone challenge, are present in some individuals with PTSD.[80] These individuals also displayed augmented cortisol feedback inhibition of ACTH secretion at the level of the pituitary and a blunted ACTH response to CRH. Furthermore, because studies have consistently shown that individuals with PTSD have glucocorticoid receptor hypersensitivity, lower cortisol levels in plasma could be due to homeostatic feedback.

Glucocorticoids readily cross the blood-brain barrier, exert negative feedback at the HPA axis, and consequently reduce CRH and ACTH secretion (Figure 1). They also bind to MRs and GRs throughout the brain, including in the amygdala, hippocampus, PFC, nucleus accumbens, and septum, where they influence signaling pathways and synaptic plasticity. It has been hypothesized that different anatomical populations of GRs in the brain have unique functions in modulating plasma glucocorticoid levels. For example, in one study, application of corticosterone to the hippocampus inhibited HPA axis activation in male rats.[81] However, in a different study, hormonal stimulation to the amygdala in rats increased plasma corticosterone and increased CRH expression in the CeA.[82] Recent studies that used conditional knockout mouse models demonstrated that the ablation of GRs in glutamatergic, but not in

GABAergic, neurons induced hyperreactivity in the HPA axis and reduced fear- and anxiety-related behavior.[83] Furthermore, viral-mediated deletion of GRs indicated that within the basolateral amygdala glutamatergic circuits, GRs played a role in fear expression but not in anxiety. The findings suggest that fear-related behavior is modulated by GR-signaling pathways in the basolateral amygdala, whereas pathological anxiety may result from altered GR signaling in excitatory circuits in several brain areas, including the bed nucleus of the stria terminalis—which is also potentially involved in AUD and PTSD.

CRH and its receptors are expressed not only in stress-responsive areas, but also in areas of the fear- and threat-processing circuits, including in the basolateral amygdala and CeA. It has been shown that infusion of CRH or CRH binding protein into the basolateral amygdala prior to fear extinction impairs extinction recall without affecting extinction acquisition.[84] In contrast, a CRH receptor antagonist improved extinction recall. A study that used a conditional knockout mouse model demonstrated similar results.[85] Deletion of the $alpha_1$ subunit of the $GABA_A$ receptor in CRH-expressing amygdala neurons resulted in increased CRH expression in the amygdala. Consequently, anxiety behavior increased, and extinction of conditioned fear was impaired, which coincided with increased corticosterone levels in plasma.

Stress hormones and alcohol intake

Many individuals with AUD show altered HPA axis function, raising the strong possibility that HPA axis dysfunction contributes to the development of AUD. Several studies with animal models also demonstrated that the HPA axis plays a direct role in the control of alcohol drinking. For instance, administration of corticosterone into the body or brain of rats increased their voluntary alcohol drinking, whereas administration of a corticosterone synthesis inhibitor or the removal of the adrenal glands caused decreased alcohol intake.[86,87] Furthermore, a recent study demonstrated that attenuation of GR signaling reduced compulsivelike alcohol intake in alcohol-dependent rats and reduced both excessive drinking and alcohol craving in recently abstinent individuals with AUD.[88]

Given that alcohol increases dopamine release in the nucleus accumbens in animals[89] and humans,[90] glucocorticoids may be involved in voluntary alcohol consumption via direct action on mesocorticolimbic reward systems where GRs are abundantly expressed. A study that used a mouse model demonstrated that selective ablation of GRs in dopaminergic neurons in the brain, or of dopamine receptor D1-expressing medium spiny neurons in the striatum, highly reduced the firing rate of dopamine neurons.[91] In the same study, mice with GR ablation in D1-expressing neurons, not in dopaminergic neurons, displayed decreased self-administration of cocaine. These findings suggest that GRs act on the postsynaptic neurons of the dopaminergic system via negative feedback from the nucleus accumbens to the VTA to increase the propensity to self-administer drugs.

In addition to the role of MRs in glucocorticoid regulation, aldosterone and MRs are the principal modulators of blood pressure and extracellular volume homeostasis via renal sodium reabsorption and potassium excretion. Although MRs are expressed in various brain areas, including in the amygdala and hippocampus, their role in stress modulation and alcohol consumption historically has received less attention. Nevertheless, recent studies with rodents, nonhuman primates, and humans have implicated the importance of the aldosterone and MR pathway in alcohol drinking and in alcohol-seeking behavior.[92] Since MRs are also abundantly expressed in the dopaminergic system, future studies using conditional knockout mouse models are needed to determine whether these receptors contribute to alcohol intake and dependence in a manner specific to cell types or brain areas.

CRH and its receptors are also involved in alcohol behavior. In a free-choice paradigm with water and increasing concentrations of alcohol, mice lacking functional CRHR1 receptors increased alcohol intake after repeated episodes of social defeat stress.[93] Notably, these mutant mice did not increase alcohol intake during or immediately after stress, but they did significantly increase intake 3 weeks later. Furthermore, this increased alcohol intake persisted at 6 months after the stress exposure. These findings suggest that the stress response in the HPA axis may require some time for adaptation to concurrent alcohol and stress exposure.

Alcohol-induced stress hormone response

A large body of data suggests that alcohol is a robust activator of the HPA axis. As an example, in one study, plasma glucocorticoids in humans increased during acute and chronic alcohol consumption and during the initial phase of the alcohol withdrawal period.[94] In another study, peripheral injection of alcohol into rats stimulated HPA axis activity, including activating the hypothalamic paraventricular nucleus, CRH release, and ACTH release.[95]

Other neuropeptide systems associated with stress and alcohol

In addition to CRH, numerous neuropeptides have been shown in various animal models to be affected by stress or to be involved in the stress response. Studies on postmortem brain samples showed that other neuropeptides and their receptors could be suitable targets for PTSD and AUD treatments. These neuropeptides include substance P, neuropeptide Y, vasopressin, and pituitary adenylate cyclase–activating polypeptide. Progress in identifying their roles in stress and alcohol consumption has been facilitated by recent preclinical investigations, but we summarize the findings related to only two of those neuropeptides.

Substance P, with its preferred neurokinin 1 (NK1) receptor, is highly expressed in the amygdala and nucleus accumbens. Stressors induce substance P release in the amygdala, and pharmacologic blockade of NK1 receptors inhibits amygdala-associated behavioral responses in rodents.[96] Mice genetically deficient in NK1 receptors have displayed decreased voluntary alcohol consumption and a loss of conditioned place preference for opiates.[97,98] Furthermore, in a study of recently detoxified patients with AUD, treatment with an NK1 receptor antagonist suppressed spontaneous alcohol cravings and blunted cravings induced by a challenge procedure.[97]

Neuropeptide Y is well-known for opposing effects of CRH, reducing stress and anxiety, and decreasing alcohol intake in rodents. Both neuropeptides and their receptors are abundant in the amygdala and extended amygdala, including in the bed nucleus of the stria terminalis. A recent study showed that neuropeptide Y suppressed binge drinking in mice by inhibiting the activity of CRH neurons through a neuropeptide Y_1 receptor–mediated G_i signaling pathway that enhances the ability of GABA to generate inhibitory currents postsynaptically.[99] Chemogenetic activation of CRH neurons in the bed nucleus of the stria terminalis blocked the inhibitory effects of Y_1 receptor activation on binge drinking. The same study demonstrated that chronic alcohol drinking led to persistent alterations in neuropeptide Y_1 receptor function and suggested that shifts in the balance between neuropeptide Y and CRH might change an individual's vulnerability to binge drinking cycles. Moreover, medications that alter this balance could be a good approach for treating binge drinking.

Sex-Dependent Differences

Awareness is increasing regarding the crucial roles that neuronal circuits and hormones play in fear and reward processing differences between men and women. For example, researchers have reported that women suffer from anxiety and PTSD more than men,[100] and that women use alcohol and opioids more frequently than men to handle anxiety.[53] Although research on sex-related differences in comorbid PTSD and AUD is still in its infancy, recent clinical and preclinical studies have started disentangling the neurobiological mechanisms that may place men and women at different risk for the development of each disorder. For example, upon stress cue exposure, men display greater activation in the PFC, amygdala, and hippocampus than women, whereas women showed greater alcohol cue–related activity in brain regions associated with high-level cognitive processing.[53] Furthermore, several studies in rodents have shown sex-related differences in neuronal morphology and in sex-hormone receptor expression in fear circuits, including in the PFC.[101] These sex-related anatomical and molecular differences contribute to disparate functionality in the fear circuits. For example, in a rat study, researchers found that PFC function was important for fear extinction recall in males, but it was critical to fear extinction in females.[102] Similarly, sex-related differences have been detected in the VTA dopaminergic system, and sex hormones have been implicated in differential responsiveness to drugs of abuse.[103]

Conclusions and Future Research Needs

Epidemiological studies suggest that the diagnosis of PTSD represents a major risk factor for the development of AUD, as PTSD symptoms drive excessive alcohol consumption, and AUD worsens PTSD symptoms. Findings from the studies discussed in this article show that a vast array of neurobiological and neuroendocrine changes occur in fear/anxiety and reward/addiction circuitry, as well as in the HPA axis. Analogous changes that occur in overlapping brain areas and high rates of AUD and PTSD comorbidity suggest that these disorders share a common neurobiological etiology.

It has been extremely difficult to systematically delineate the neural basis of comorbidity. Comorbidity may be due to a conjunction of independent risk factors, shared risk factors from two disorders, or a multiform expression of one of the disorders. In this review, we focused on the comorbidity in a context in which one disorder causes the other through dysfunctions in shared neural circuitry. Since the activity of a brain area interacts with and affects other brain areas via mutually connected pathways, investigating comorbid AUD and PTSD in human and animal studies is challenging. However, the development of advanced neuroimaging has enabled an assessment of structural and functional brain network architecture at an unprecedented level of detail. New theoretical frameworks combined with network approaches are needed to focus more on the dimensional and complex nature of brain disorders.[104]

Modeling the comorbid condition in nonhuman animals is crucial, because circuit manipulations and monitoring single-neuronal activity in specific pathways and cell types will provide a better snapshot of causal relationships between PTSD and AUD. Although several studies have used rodent models to examine comorbid PTSD and AUD,[105] preclinical studies have been challenging because of the wide array of stress procedures, different time courses of pathological behavior development, and individual differences within a model. However, technological progress in the next generation of optical, molecular, and observational tools offers a productive direction for future research using preclinical models. System-level interrogation with greater specificity may lead to identifying pathophysiological abnormalities and formulating coherent principles that explain the interactions between these disorders. Ultimately, the promise is that this knowledge may translate to hypothesis-driven, individual clinical interventions and therapeutic strategies for treating comorbid PTSD and AUD.

Acknowledgments

This article was supported by National Institutes of Health grants R01MH108665, R01MH094757, and R21MH112956 and the Frazier Foundation Grant for Mood and Anxiety Research.

Financial Disclosure

Dr. Ressler is on the scientific advisory boards for Resilience Therapeutics, Sheppard Pratt-Lieber Research Institute, Laureate Institute for Brain Research, the Army Study to Assess Risk and Resilience in Servicemembers, VA San Diego Healthcare System Center of Excellence for Stress and Mental Health, and the Anxiety and Depression Association of America. He provides fee-for-service consultation for Biogen and Resilience Therapeutics. He receives or has received research funding from the National Institute of Mental Health, the Howard Hughes Medical Institute, the Brain and Behavior Research Foundation, and the Burroughs Wellcome Fund.

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Functional and Psychiatric Correlates of Comorbid Post-Traumatic Stress Disorder and Alcohol Use Disorder

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Post-traumatic stress disorder (PTSD) and alcohol use disorder (AUD) are common comorbid conditions that affect large segments of the population. Individuals with comorbid PTSD/AUD face greater clinical and functional stressors than those with diagnoses of either PTSD or AUD alone. The purpose of this article is to review the phenomenology and functional associations of PTSD/AUD and address the common social, occupational, and psychological concerns associated with both disorders. Given the increased problems associated with comorbid PTSD/AUD, clinical and research efforts should focus on targeting functional and psychosocial problems in conjunction with psychiatric symptoms.

KEY WORDS: **alcohol use disorder; comorbidity; diagnostic criteria; post-traumatic stress disorder; psychosocial environment**

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Introduction

Post-traumatic stress disorder (PTSD) and alcohol use disorder (AUD) frequently co-occur. In the general population, approximately one-third of individuals with lifetime PTSD also meet criteria for lifetime AUD.[1] In substance use treatment samples, up to two-thirds of those with AUD meet criteria for PTSD.[2,3] Comorbid PTSD/AUD is associated with a more complex and severe profile than either disorder alone, including greater rates of having experienced childhood maltreatment, increased psychiatric comorbidities and reported symptom distress, decreased psychosocial functioning, and poorer prognosis.[1,4]

Despite the psychosocial impairment associated with PTSD/AUD, reviews on the comorbidity have largely focused on the clinical and neurobiological correlates associated with both disorders. Reviewing the psychosocial and functional burden of comorbid PTSD/AUD may

improve understanding regarding the disorders and advance standards of care for a largely underserved population. The purpose of this review is to examine the clinical phenomenology, functional associations, and psychosocial factors associated with comorbid PTSD/AUD. Suggestions for future research and clinical practice are provided.

Diagnostic Classifications of PTSD and AUD

According to the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders,* PTSD develops as a result of trauma exposure that included actual or threatened death, serious injury, or sexual violence (Criterion A).[5] Common forms of trauma exposure include natural disasters, car accidents, combat, and physical or sexual abuse. Exposure must be either directly experienced, witnessed, learned about in the case of a close family or friend, or indirectly experienced in the course of one's professional duties.

PTSD is characterized by four symptom clusters, which must be present for at least 1 month.[5] The re-experiencing cluster (Criterion B) includes symptoms that are intrusive in nature and cause emotional or physiological reactivity (e.g., intrusive memories and psychological or physiological distress related to trauma reminders). Avoidance of internal or external trauma-related reminders (Criterion C; e.g., avoidance of memories, thoughts, people, or places associated with the traumatic event) is a prominent symptom cluster that contributes to the development and maintenance of PTSD. Negative alterations in cognition and mood (Criterion D) and alterations in arousal and reactivity (Criterion E) include exaggerated cognitive (e.g., negative beliefs about oneself, others, or the world), emotional (e.g., persistent negative emotional states and feelings of detachment or estrangement), and physiological responses (e.g., hypervigilance and problems with concentration) that appear or worsen after the traumatic event. In addition, the diagnosis requires that the symptoms cause either significant distress or functional impairment in social or occupational domains.

Symptoms of AUD fall within four domains:[5]

1. Impaired control (e.g., have had times when you ended up drinking more, or longer, than you intended)
2. Social impairment (e.g., continued to drink even though it was causing trouble with your family or friends)
3. Risky use (e.g., more than once have gotten into situations while or after drinking that increased your chances of getting hurt, such as driving, swimming, using machinery, walking in a dangerous area, or having unsafe sex)
4. Physical dependence (e.g., having to drink much more often than you once did to get the effect you want)

The diagnosis requires that at least 2 out of the 11 symptoms are met within the same 12-month period. The severity of impairment is based on the number of present symptoms (mild = 2 to 3, moderate = 4 to 5, or severe = 6 or more). Although diagnostically distinct, AUD and PTSD diagnoses share common psychosocial risk factors, and both result in impairments across multiple domains.

Functional Associations Between PTSD and AUD

The high rates of comorbidity between PTSD and AUD necessitate the question of why these disorders frequently co-occur. Several causal mechanisms may link PTSD and AUD. (See the box **Functional Association Models** for a summary of these models.) First, the self-medication hypothesis posits that individuals use alcohol to cope with PTSD symptoms, such that PTSD causally influences risk for AUD. For instance, individuals with PTSD may use alcohol to improve sleep, irritability, or hypervigilance. Second, the high-risk hypothesis suggests that alcohol use may enhance the risk for PTSD by increasing the likelihood of trauma exposure or by impairing the detection of danger cues in the environment. Third, the susceptibility hypothesis theorizes that alcohol use may make individuals who have been exposed to trauma more vulnerable to its deleterious effects, thereby increasing risk for PTSD. AUD may increase

Functional Association Models

Self-Medication

PTSD increases risk for AUD.

- Alcohol use is an attempt to reduce PTSD symptoms.

High Risk

AUD increases risk for PTSD.

- Alcohol use impairs detection of danger cues in the environment.
- Alcohol use increases the risk of trauma exposure.

Susceptibility

AUD increases risk for PTSD.

- Alcohol use interferes with emotional processing after exposure to trauma.
- Alcohol withdrawal symptoms increase anxiety and hyperarousal.

Shared Vulnerability

PTSD and AUD have similar risk factors and the association is noncausal. Risk factors can be:

- Genetic
- Environmental
- Individual (e.g., personality)

susceptibility to PTSD by interfering with emotional processing following trauma exposure or by increasing anxiety or hyperarousal due to withdrawal symptoms.[6] Finally, the shared vulnerability hypothesis posits that shared risk factors account for both PTSD and AUD, and their association is noncausal.

The self-medication hypothesis posits that having PTSD increases the risk for developing AUD, as individuals with PTSD may attempt to alleviate PTSD symptoms through the use of alcohol. A large body of evidence supports this hypothesis.[4,7-10] For instance, data from a large, nationally representative sample demonstrated that using alcohol with the intent of reducing PTSD symptom distress was significantly associated with a lifetime history of AUD.[4] Further, using longitudinal data from a community sample, Haller and Chassin found that PTSD symptoms predicted higher levels of later alcohol and drug problems, even when controlling for the effects of trauma exposure itself, pretrauma substance use, and pretrauma family risk factors that increase risk for both PTSD and AUD.[7]

Treatment studies also provide support for the self-medication hypothesis. For example, in a sample of women seeking treatment, improvement in PTSD symptom severity was associated with reduced substance use; however, substance use improvement was not related to decreased PTSD symptoms.[11] These findings suggest that changes in PTSD symptoms may drive patterns of substance use, as posited by the self-medication hypothesis.

Stewart and Conrod summarized the research on the association between both disorders by concluding that "PTSD has been shown to develop before the SUD [substance use disorder] in the large majority of comorbid cases in retrospective studies, and PTSD has been shown to increase risk for SUDs in prospective studies."[12(p37)]

While several studies find support for a self-medication mechanism that may lead individuals with PTSD to develop drug and alcohol disorders,[13,14] other studies specifically examining alcohol outcomes have failed to support a self-medication pathway causally linking PTSD to AUD.[15] In a prospective longitudinal study of Persian Gulf War veterans, PTSD symptom clusters did not predict subsequent alcohol use concerns, although they did predict illicit drug use.[14] Similarly, PTSD was not found to directly influence later problem drinking in a longitudinal study of women survivors of sexual assault.[15] These studies reflect the complex relationship between PTSD and AUD and highlight the need to consider moderating factors and other mechanisms of risk. For instance, it may be that the functional association between PTSD and AUD varies based on both the form of trauma exposure and the type of substance use disorder.

Both the high-risk and susceptibility hypotheses suggest that AUD causally increases the risk for PTSD. Studies examining these hypotheses have generated mixed findings, with certain studies supporting only the high-risk hypothesis,[16,17] others supporting only the susceptibility hypothesis,[18] and

some, when controlling for other risk factors, failing to support either hypothesis.[19] Age and type of trauma may play a role in these mixed findings. At least two studies indicated that binge drinking[7] and other high-risk behaviors (i.e., delinquent behavior, alcohol use, and drug use)[20] during adolescence increased the likelihood of later exposure to assaultive violence (e.g., rape and physical assault), which carries an especially high risk for developing PTSD compared to other trauma types.[21] Haller and Chassin found that although adolescent substance misuse conferred risk of exposure to assaultive violence, it did not increase the overall risk for trauma exposure.[7] These findings suggest that alcohol use during adolescence may lead to PTSD as a result of the type of associated trauma exposure.

Shared environmental, genetic, and individual (e.g., personality) factors may also contribute to the overlap between PTSD and AUD in a noncausal manner. Behavioral genetic research indicates that heritable influences common to alcohol and drug use disorders account for 15.3% of PTSD variance,[22] and genetic factors that contribute to trauma exposure and PTSD among women correlate (r = .54) with factors that contribute to AUD.[23] Parental psychopathology and associated familial risk factors, such as family conflict/stress and exposure to childhood adversity, may also be shared risk factors for PTSD and AUD.[24,25] Moreover, adverse childhood environments are associated with individual vulnerabilities and personality factors that may further increase risk for PTSD and AUD.

Relatedly, a variant of the shared vulnerability model—the trait vulnerability model—hypothesizes that PTSD symptoms may augment preexisting traits that confer risk for problems with alcohol. Multiple studies support this hypothesis.[26,27] In particular, externalizing behavior (e.g., anger and aggression) appears to indirectly confer risk of both PTSD and AUD. In a community sample, PTSD was associated with an increase in early adulthood externalizing behavior that, in turn, was associated with alcohol misuse later in adulthood.[26] Similarly, in a large sample of college students, PTSD was associated with increased disconstraint (i.e., the tendency to engage in risky or impulsive behavior), which was then associated with alcohol use problems.[27]

It is important to note that shared risk factors for PTSD and AUD may differ based on gender. For instance, in a study using a college sample, different facets of emotion regulation (e.g., problems controlling impulses and engaging in goal-directed behavior) for men and women were associated with PTSD and the alcohol-related consequences.[28] In men, PTSD symptoms were related to increased impulse control difficulties, which, in turn, were associated with alcohol-related consequences. In women, PTSD was associated with difficulties engaging in goal-directed behavior, which, in turn, were associated with an increase in alcohol-related consequences. However, this study used a cross-sectional design, so it is not possible to infer a temporal association between the variables. Nonetheless, these findings underscore the need for models to account for the contribution of shared factors common to both PTSD and AUD, while also considering how such factors may vary based on gender.

Regardless of the causal mechanisms or shared factors responsible for the emergence of PTSD/AUD, once both disorders exist, it is possible that they mutually maintain and exacerbate one another (mutual maintenance model). For instance, alcohol may be used to attempt to suppress PTSD symptoms, but repeated use may interfere with natural recovery from trauma and also lead to physiological effects that heighten anxiety. As a result, PTSD symptoms and alcohol misuse may exert bidirectional influences on each other over time. A number of findings provide evidence of a bidirectional relationship between the disorders. For instance, in a sample of individuals seeking treatment for substance use disorder, avoidance symptoms (e.g., evading trauma-related reminders) were significantly elevated in patients with AUD, when compared to patients without AUD.[29] The authors suggested that individuals with PTSD/AUD initially may have used alcohol in an attempt to alleviate avoidance symptoms, however, alcohol use could have subsequently exacerbated their avoidance. Further, in a sample of adults, PTSD symptoms predicted risk of AUD symptoms and vice versa, although the bidirectional relationship was stronger for women.[30] Such findings are bolstered by the observations of individuals diagnosed with PTSD/AUD. Brown and colleagues found that patients with PTSD/AUD perceived the two disorders to be functionally related.[31] These patients reported that when one disorder worsened, the other disorder was also more likely to worsen.

Although patient perceptions support the mutual maintenance model, empirical evidence regarding this model is mixed. In a recent longitudinal study, results indicated that PTSD symptoms led to alcohol misuse, but alcohol misuse did not appear to worsen the severity of PTSD over time.[32] Prospective daily monitoring designs (measuring day-to-day symptom changes) provide a more nuanced method of examining comorbid disorders and the mutual maintenance model, but results from these studies are inconsistent. While some studies have shown partial support for both the mutual maintenance and self-medication models,[9,33] another study supported only the self-medication hypothesis.[34] Taking these mixed findings into account, Simpson and colleagues concluded that PTSD and AUD symptoms do influence one another (mutual maintenance model), but that PTSD appears to exert a greater influence on AUD symptoms (self-medication hypothesis), rather than the reverse.[9]

In summary, research suggests that there are multiple nonmutually exclusive pathways that underlie comorbid PTSD/AUD. Although the greatest body of evidence exists for the self-medication hypothesis, it is clear that common etiological risk factors also contribute to the comorbidity. Further, PTSD and AUD may have bidirectional influences on one another that serve to mutually maintain and exacerbate the symptoms of both disorders.

Psychosocial Risk Factors

A substantial body of literature has demonstrated the association between having experienced childhood maltreatment (e.g., neglect or physical, sexual, or emotional abuse) and PTSD/AUD. Convergent findings suggest that biological and environmental determinants play a role in the comorbidity. For instance, neurobiological data suggest that childhood environmental stressors interact with genetic factors to contribute to the development of both disorders (see Brady and Back for a review).[35] Moreover, individuals with co-occurring PTSD/AUD are more likely than those with PTSD or AUD alone to have experienced childhood maltreatment and other childhood environmental stressors.[1]

The heightened rate of childhood stressors in PTSD/AUD samples holds across diverse groups. In a nationally representative sample in the United States, individuals with comorbid PTSD/AUD had greater odds of having experienced childhood maltreatment (i.e., neglect or verbal, physical, or sexual abuse) and environmental stressors (i.e., vulnerable family environment, parental divorce, parental behavioral problems, or parental alcohol/drug problems) than individuals with either disorder alone.[1] Similarly, in a small Austrian community sample, individuals with co-occurring PTSD/AUD were more likely to have experienced childhood sexual abuse (younger than age 16) or other adverse childhood stressors (e.g., growing up in the foster care system) than those who had PTSD only.[36] Moreover, on average, those with PTSD/AUD were exposed to trauma a decade earlier than individuals with PTSD only. These findings suggest that childhood maltreatment and environmental stressors may lead to an increased risk of developing comorbid PTSD/AUD.

To add further support to this claim, a number of studies indicate that childhood maltreatment is associated with more severe and complex PTSD and AUD symptom profiles. Compared with trauma exposure during adolescence or adulthood, childhood maltreatment is associated with a longer course of PTSD,[37] earlier onset of alcohol use and heaviest drinking periods,[38] greater alcohol cravings in response to trauma cues,[39] and increases in trauma-related symptom complexity (defined as the number of symptoms over a specified cutoff).[40] The nature of childhood maltreatment also appears to uniquely affect psychiatric outcomes. In a sample of primary care patients in an urban community, greater childhood trauma exposure predicted higher PTSD total symptom severity scores, when controlling for level of adulthood trauma exposure.[41] Furthermore, increases in childhood maltreatment exposure predicted greater alcohol use symptom severity, even when PTSD symptoms were held constant. Such findings may be explained, in part, by the characteristics of childhood maltreatment (e.g., chronic exposure perpetrated by attachment or authority figures) and the effects on the developing brain.[42] Overall, the findings from these studies highlight the heightened rate and impact of childhood maltreatment for individuals who have PTSD/AUD.

Psychosocial Outcomes

Comorbid PTSD/AUD is also associated with a range of deleterious mental health problems. A number of studies have demonstrated that in comparison to either disorder alone, co-occurring PTSD/AUD is associated with increased depression and anxiety, more severe PTSD and AUD symptoms,[1,43,44] a greater likelihood of additional psychiatric comorbidities,[45] and higher rates of suicide attempts.[1,4] Given the severity of the mental health problems associated with co-occurring PTSD/AUD, it is not surprising that individuals with both diagnoses also experience psychosocial impairments across social, financial, and occupational domains.

Although the construct of social support is multidimensional and its association to trauma outcomes is varied,[46] greater perceived social support likely serves as a protective factor against trauma-related disorders[47] and is inversely associated with PTSD symptom severity[48] and problematic alcohol use.[49] The presence of PTSD and AUD, however, is associated with poorer social functioning. Although the existing literature has primarily focused on the relationship between social support variables and PTSD or AUD alone, a small body of work has investigated the social functioning deficits associated with comorbid PTSD/AUD.

In a study conducted by Riggs and colleagues, treatment-seeking individuals with comorbid PTSD/AUD were less likely to report living with a significant other (14%) than individuals with a single diagnosis of PTSD (42%) or AUD (56%).[50] The specific pattern of social network problems was explored using a nationally representative sample in which individuals with comorbid PTSD/AUD were compared with those who had no psychopathology or who had either disorder alone.[51] Individuals with comorbid PTSD/AUD experienced more problems with family support and apprehension (e.g., distress, discomfort, and anxiety) about engaging in close interpersonal relationships than individuals with either no diagnosis or a single diagnosis of PTSD or AUD.

The limited research on comorbid PTSD/AUD and functional impairments prompted Drapkin and colleagues to evaluate additional psychosocial factors (employment status, education level, income, and relationship status) across three samples of individuals seeking treatment.[52] The samples consisted of individuals with comorbid PTSD/AUD, PTSD only, and AUD only. Interestingly, while comorbid PTSD/AUD was not associated with greater PTSD and AUD symptom severity (excluding alcohol craving), it was related to increased psychosocial impairment across multiple domains. Fewer individuals with co-occurring PTSD/AUD were employed or had a college education, when compared to those with either disorder alone. Furthermore, individuals with co-occurring PTSD/AUD were less likely than those with only PTSD or AUD to be living with a romantic partner. However, the authors noted that racial and gender differences across the groups could limit the validity of their results. While preliminary, these results suggest that both mental health and psychosocial deficits frequently affect individuals with comorbid PTSD/AUD.

Clinical and Research Implications

Despite the many mental health and psychosocial problems associated with PTSD/AUD, a significant portion of individuals do not seek treatment for either disorder.[1] Epidemiological studies reveal that only approximately one-quarter of individuals with AUD or PTSD diagnoses engage in disorder-specific treatment.[53-55] Furthermore, when individuals with comorbid PTSD/AUD do initiate treatment, attrition rates are high and treatment effect sizes are small.

The literature discussed in this review highlights the many reasons why treatment retention and outcomes may be poor in this population. In particular, psychosocial concerns, including functional problems in social, educational, and occupational domains, disproportionately affect those with comorbid PTSD/AUD. Treatment studies with individuals who have comorbid PTSD/AUD have focused primarily on developing new treatments or modifying existing treatments to improve symptom outcomes. The findings of this review suggest that targeting functional problems and psychosocial stressors may help people with comorbid PTSD/AUD engage in treatments and achieve better outcomes. Multiple researchers[50,56] have posited that the psychosocial factors associated

with comorbid PTSD/AUD could partially account for the high attrition rates in randomized controlled trials, and that modifications to decrease psychosocial barriers to treatment may be critical. For instance, in a small study of veterans with comorbid PTSD and substance use disorder, all nine participants initiated and successfully completed prolonged exposure therapy while in a residential treatment program.[57] Although the sample size was small, these preliminary findings highlight the potential of higher levels of care (e.g., intensive outpatient or residential treatment) to directly target psychosocial risk factors, such as decreased social support and housing issues, and, by doing so, improve PTSD treatment engagement. Further research is needed to examine the effectiveness of providing treatment for PTSD/AUD within higher levels of care.

Future research is also needed to continue to assess the relationship between key areas of psychosocial concerns and treatment outcomes in individuals with comorbid PTSD/AUD. Given the literature[55] and current clinical practice guidelines put forth by the U.S. Department of Veterans Affairs and the American Psychological Association,[58,59] which support the provision of trauma-focused treatments in comorbid populations, it will be important to continue to work toward improving initiation and completion of gold-standard treatments for PTSD among individuals with PTSD/AUD. The effectiveness of supplemental interventions designed to target nonclinical stressors (e.g., financial problems, occupational difficulties, and reduced social support) that might interfere with treatment engagement and completion should also be evaluated.

Such supplemental interventions may be designed and implemented at the program level (e.g., through higher levels of care, multidisciplinary models of care, or case management services) or at the individual level (e.g., through psychosocial assessments, gender-specific interventions, or developmental and patient-centered approaches to case conceptualization). Also, the delivery method for interventions may target the clinical and functional difficulties associated with comorbid PTSD/AUD. For instance, implementing interventions within a group context may bolster social support. Peer support programming, which emphasizes recovery-oriented and person-centered services, may facilitate positive social interaction and enhance individual self-efficacy within the treatment setting. Lastly, future research should examine whether preventive interventions designed to increase psychosocial resources are effective in reducing the likelihood of developing comorbid PTSD/AUD. For instance, enhancing engagement and functioning in social and occupational domains may protect against the development of PTSD/AUD.

Conclusion

PTSD and AUD commonly co-occur and are associated with more complex and severe clinical presentations than either disorder alone. There are multiple etiological pathways that may influence the onset of comorbid PTSD/AUD and subsequently maintain and aggravate both disorders. Furthermore, comorbid PTSD/AUD is associated with more environmental risk factors, including a history of childhood maltreatment and functional problems (e.g., social and occupational concerns), than either disorder alone. Given the functional problems and low rates of treatment engagement and retention associated with PTSD/AUD, future research should evaluate the effect of psychosocial problems on treatment outcomes. Ultimately, an integrated model of care that focuses on both reducing symptoms and improving functional capacity across psychosocial domains may help improve treatment outcomes for this challenging clinical population.

Acknowledgments

This article was supported by the U.S. Department of Veterans Affairs (VA), Office of Academic Affiliations, Advanced Fellowship Program in Women's Health; the VA Rehabilitation Research and Development Merit Award 347328; the U.S. Department of Defense Congressionally Directed Medical Research Program Award W81XWH-15-1-0330; the VA Office of Clinical Science Research and Development Merit Award 120469; the VA Clinical Science Research and Development Merit Grant 1I01CX000756; and the National Institute on Alcohol Abuse and Alcoholism Institutional Ruth L. Kirschstein National Research Service Award T32 AA013525.

Financial Disclosure

The authors declare that they have no competing financial interests.

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The Epidemiology of Post-Traumatic Stress Disorder and Alcohol Use Disorder

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For more than 40 years, research has shown that individuals with post-traumatic stress disorder (PTSD) use alcohol and experience alcohol use disorder (AUD) to a greater degree than those with no PTSD. AUD and PTSD have shown a durable comorbidity that has extended through decades and through changes in disorder definitions. Some research shows that veterans who have experienced PTSD have a high likelihood of developing AUD, perhaps reflecting the self-medication hypothesis. Other research shows that people with substance use disorder are likely to be exposed to traumatic situations and develop PTSD. These two areas of research could represent two separate relationships between PTSD and AUD. Finally, there is still no clear determination of which cluster of PTSD symptoms is most closely associated with AUD.

KEY WORDS: alcohol use disorder; epidemiology; NESARC; post-traumatic stress disorder; veterans

Introduction

The harmful use of alcohol has been of interest to doctors for centuries, and minimizing the harm caused by alcohol use disorder (AUD) has been a priority of psychiatrists in the United States since at least 1917.[1] However, although traumatic experiences are ubiquitous throughout human history, it was only after the Vietnam War that psychiatrists codified the harms caused by traumatic stress into a distinct diagnosis.[2] For more than 40 years, it has been known that individuals with post-traumatic stress disorder (PTSD) use alcohol and experience AUD more than those with no PTSD. This link between PTSD and AUD subsequently has been broadened beyond Vietnam veterans to include veterans of other wars and anyone exposed to trauma. The considerable psychological distress caused by AUD and PTSD, both separately and together, affects the lives of millions of men and women, including

underrepresented populations, such as people with other mental health conditions.

Disorder Definitions

This section provides an overview of commonly used definitions and how they have changed over time.

AUD

In 1952, the first edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) included "alcoholism" as one of two disorders under the category of "addiction."[3] The pithy, two-sentence definition instructed that an alcoholism diagnosis be used in cases of "well-established addiction to alcohol." Since then, the definition of what is now called AUD has been significantly expanded and refined for each edition of the DSM.[2,4-7]

The third edition of the DSM (DSM-III) was published in 1980. In this edition, the disorders were called "alcohol abuse" and "alcohol dependence."[2] A diagnosis of alcohol abuse required:

- A "pattern of pathological alcohol use," which was defined by features such as the need for daily alcohol consumption to function, the inability to reduce or stop drinking, remaining intoxicated for at least 2 days, or blackouts
- "Impairment in social or occupational functioning due to alcohol use," which could include violent behavior, absences from work, or losing a job
- "Duration of disturbance of at least 1 month"

A diagnosis of alcohol dependence required the first two criteria of alcohol abuse, along with indications of tolerance (the need to increase the amount of alcohol to achieve the desired effect) or withdrawal (the development of physical symptoms after reducing or discontinuing alcohol consumption).

The 1987 revision of the third edition, the DSM-III-R, introduced major diagnostic changes for alcohol-related disorders. In the DSM-III-R, an "alcohol dependence" diagnosis required three out of nine possible criteria, and an "alcohol abuse" diagnosis required only two.[5] The diagnosis of alcohol abuse was to be used only for individuals who had alcohol-related problems but did not meet the requirements for alcohol dependence. The DSM-IV diagnoses were substantially similar to those in the DSM-III-R.[6]

In the DSM-5, the terms "alcohol dependence" and "alcohol abuse" were removed, and the two separate diagnoses were replaced with one diagnosis—AUD.[7] The DSM-5 lists 11 symptoms for the disorder, and an AUD diagnosis now has levels of severity based on the number of symptoms presented. The presence of two to three symptoms indicates mild AUD, four to five symptoms indicate moderate AUD, and six or more symptoms indicate severe AUD.

PTSD

Unlike AUD, PTSD has only been included in the DSM since the third edition. In one of the first published articles on the occurrence of PTSD in the general population, Helzer and colleagues described the inclusion of PTSD in the DSM-III as a "compromise" for veterans' groups and mental health personnel advocating for recognition of what was commonly called "post-Vietnam syndrome."[8] Adding PTSD as a possible diagnosis for anyone who had experienced a trauma was a middle ground between those who hypothesized that the disorder was unique to Vietnam veterans and those who believed it might not exist at all.

In the DSM-III-R and DSM-IV, a PTSD diagnosis was defined by experiencing a qualifying traumatic event (Criterion A) and three other clusters of symptoms: re-experiencing the event (Criterion B), emotional numbing and avoidance of cues and reminders of the event (Criterion C), and hyperarousal (Criterion D).[5,6] King and colleagues conducted a factor analysis on the Clinician-Administered PTSD Scale, a measurement tool based on the DSM-IV diagnostic criteria, and found that these four clusters of symptoms best defined the disorder.[9] This four-cluster model subsequently has been used in many examinations of the connections between PTSD symptoms and alcohol use.

The definition of PTSD was updated significantly for the DSM-5.[7] The major changes included:

- Reclassification of PTSD as a trauma- and stressor-related disorder instead of an anxiety disorder
- Elimination of the criterion that the person's response to the traumatic event must involve intense fear, helplessness, or horror

- Addition of the requirement that the symptoms cannot be attributed to the physiological effects of substance misuse, a medication, or another medical condition

Conditional disorders

Both PTSD and AUD are conditional disorders; that is, both disorders can be diagnosed only if certain prerequisite conditions are met—specifically, a traumatic event or alcohol use. In the DSM-III, the prerequisite condition for PTSD was "existence of a recognizable stressor that would evoke significant symptoms of distress in almost everyone."[2] In the same edition, the section on substance use disorder (SUD) referred to "the maladaptive behavior associated with more or less regular use of the substances."

Importantly, analyses can be conducted on the risk for the exposure to an event among the entire population, and then among those who experienced an event. Social determinants of health for the diagnoses may vary considerably based on likelihood of being exposed to an event or exposure to a substance. Conversely, risk for who later develops a diagnosis, given exposure, may be different as well. For this reason, it is important to evaluate both risk for exposure as well as risk for a disorder among those exposed.

Prevalence Surveys in the United States

Since the late 1970s, several U.S. surveys have collected information on mental health conditions, including AUD, SUD, and PTSD. These surveys include the Epidemiological Catchment Area (ECA) program, the National Comorbidity Survey (NCS), and the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC).

ECA

In 1978, the President's Commission on Mental Health concluded that the existing body of research could not answer these fundamental questions: What is the prevalence of mental health conditions in the United States, and are people with mental health conditions receiving adequate treatment?[10] The ECA was designed to answer these questions.[11] Although the ECA study did not include a nationwide sample, sites were chosen to be representative of the U.S. population and included Baltimore, Maryland; Durham, North Carolina; Los Angeles, California; New Haven, Connecticut; and St. Louis, Missouri. The ECA program used the National Institute of Mental Health (NIMH) Diagnostic Interview Schedule (DIS) to conduct face-to-face interviews with more than 20,000 people.[12,13] The NIMH DIS questions were based on DSM-III diagnostic criteria. At all five sites, information on alcohol use was collected, and the St. Louis location also assessed traumatic event experiences and PTSD.[8]

The ECA program reported that the lifetime prevalence of DSM-III alcohol abuse and dependence was almost 14%.[14] Prevalence varied by location, from about 11% in New Haven and Durham to about 16% in St. Louis. Individuals who had problems with alcohol were almost three times as likely to have a co-occurring mental disorder as those with no alcohol problem. Antisocial personality disorder and SUD were the most common co-occurring disorders.

The information collected at the St. Louis location provided one of the first estimates of the prevalence of PTSD in the general population. Of the 2,493 participants, about 16% were exposed to at least one qualifying traumatic event.[8] Of this group, about 8.4% developed PTSD.[15] Also, individuals who met criteria for PTSD were more likely to report alcohol-related problems than those who did not meet PTSD criteria.

NCS

The Survey Research Center at the University of Michigan's Institute for Social Research conducted a national study of comorbidity between 1990 and 1992.[16] Trained interviewers administered a modified version of the World Health Organization's Composite International Diagnostic Interview (CIDI), which was based on the DIS, to 8,098 individuals representing the contiguous 48 states. The NCS used the DSM-III-R definitions to assess alcohol dependence, alcohol abuse, and PTSD.

In the NCS sample, qualifying PTSD traumatic events were reported by 61% of men and 51% of women.[16] Although more men reported experiencing traumatic events than women, women who

experienced trauma were more than twice as likely than men to develop PTSD (20% vs. 8%). About 14% of the sample met criteria for lifetime alcohol dependence.[17] Also, respondents who met criteria for PTSD were more than twice as likely to report co-occurring alcohol abuse or dependence, and they were almost three times as likely to report drug abuse or dependence.[16]

NESARC Waves 1 and 2

The NESARC studies conducted in 2001 to 2002 (Wave 1) and 2004 to 2005 (Wave 2) collected nationally representative data on AUD and other mental disorders using the Alcohol Use Disorder and Associated Disabilities Interview Schedule (AUDADIS), which was designed by the National Institute on Alcohol Abuse and Alcoholism (NIAAA). The AUDADIS interview questions, heavily based on the CIDI, used DSM-IV criteria. NESARC Wave 2 consisted of 34,653 face-to-face interviews with individuals previously interviewed in Wave 1.[18] According to data from Wave 2, the lifetime prevalence of alcohol abuse was found to be about 27% for men and 13% for women, and the lifetime prevalence of alcohol dependence was about 21% for men and 10% for women.[19]

The survey data showed that 77% of the respondents had experienced a qualifying traumatic event, as defined by the DSM-IV.[18] The most commonly reported stressful life events were indirect experience of 9/11, serious illness or injury to someone close, and unexpected death of someone close. Of those who had experienced a trauma, about 8% developed PTSD. Individuals with PTSD were more likely to report mood disorders, anxiety disorders, SUD, and suicidal behavior than respondents without PTSD. Also, respondents with PTSD were more likely than those without PTSD to have co-occurring AUD, after controlling for sociodemographic factors such as age and race. However, this association was no longer significant when the analysis controlled for other co-occurring mental health conditions in addition to the sociodemographic characteristics.

NESARC-III

The most recent NESARC interviews, conducted between 2012 and 2013, included a representative sample of 36,309 adults in the United States, and DSM-5 criteria were used.[20] According to data from the NESARC-III, lifetime prevalence of AUD was 29%, and past 12-month prevalence was about 14%.[21] Prevalences were higher among men, Whites, Native Americans, younger adults, and those who were previously married or never married. The lifetime prevalence of severe AUD was about 14%, and the past 12-month prevalence was more than 3%. Less than 20% of respondents who experienced AUD in their lifetime ever sought treatment for the condition.

In the NESARC-III sample, about 69% of respondents had experienced a qualifying traumatic event.[22] Of this group, almost 9% met lifetime criteria for PTSD, and almost 7% met the criteria in the previous 12 months. Rates were higher among younger adults, Whites, Native Americans, and those with less education and lower incomes. PTSD was significantly associated with other psychiatric conditions, such as SUD, mood disorders, anxiety disorders, and personality disorders. Specifically, respondents who had PTSD, versus those who did not, were 1.5 times as likely to meet criteria for SUD and 1.2 times as likely to meet criteria for AUD in their lifetime, even after adjusting for other psychiatric disorders.

Prevalence Surveys Outside the United States

Through many decades, despite numerous definition changes for each, AUD and PTSD consistently co-occur. This durable comorbidity has been found in large, small, representative, and targeted samples. U.S. surveys, such as the St. Louis sample of the ECA,[8] the NCS,[16] and the NESARC,[23] have consistently found relationships between alcohol problems and PTSD.

Co-occurrence of AUD and PTSD has also been found in Europe, where rates of trauma exposure and PTSD vary greatly from country to country.[24] In a 2004 analysis of a survey of the general population of six European countries, the European Study of the Epidemiology of Mental Disorders, which used the DSM-IV criteria for disorders, researchers reported that individuals with PTSD were twice as likely than those without PTSD to have co-occurring

alcohol abuse and were three times as likely to have co-occurring alcohol dependence.[25] An examination of the 1997 National Survey of Mental Health and Wellbeing, an Australian survey of more than 10,000 individuals, reported that about 1 in 4 individuals with PTSD also had AUD.[26]

Co-Occurring Disorders

Some populations, such as military veterans and people with SUD, are at high risk for comorbidities, including co-occurring AUD and PTSD. For example, in one study of a sample of individuals seeking treatment for SUD, alcohol misuse was associated with meeting the criteria for a PTSD diagnosis.[27] In another notable case, 141 Australian firefighters who had been exposed to a trauma and screened positively for potential PTSD were followed for several years.[28,29] After 42 months, 42% of the participants had AUD, and 54% had experienced PTSD.

PTSD before AUD

The consistent association between PTSD and AUD has led to debate about which condition develops first. One theory is that individuals with PTSD use alcohol and other substances to numb their symptoms and later develop AUD or SUD. This self-medication hypothesis was proposed by Khantzian to explain behavior exhibited by individuals with AUD and SUD who were being treated in a clinical setting.[30] This theory has been supported by the demonstration of a mechanism that may encourage alcohol cravings. In laboratory settings, individuals with both AUD and PTSD reported increased cravings for alcohol after being presented with a trauma stimulus, as compared to a neutral stimulus.[31] Other epidemiologic research has shown that a diagnosis of PTSD using the DSM-III-R criteria was predictive of later development of SUD.[32,33] Trauma exposure alone, in the absence of a PTSD diagnosis, did not predict SUD.

Alternatively, some evidence shows that people exposed to trauma might be less likely to develop AUD after a traumatic experience. In a study of survivors of the Oklahoma City bombing in 1995, North and colleagues found that no new cases of AUD were reported after the bombing.[34] This finding mirrors a previous study of individuals who experienced a mass shooting in 1991.[35] In that study, three new cases of AUD were reported, but overall incidence of alcohol misuse significantly decreased in both men and women. These findings may indicate that some traumatic experiences bestow a type of survivor resilience that is protective against later development of AUD. Further research is needed to understand this phenomenon.

AUD before PTSD

An alternative to the self-medication hypothesis was proposed in 1992. Using the St. Louis ECA, Cottler and colleagues hypothesized that individuals who had SUD may have been exposed to more circumstances that cause traumatic events.[15] This heightened exposure may lead to experiencing more traumatic events and, ultimately, increase the likelihood of developing PTSD; although other explanations, such as AUD increasing sensitivity for developing PTSD, may also contribute. In the St. Louis ECA example, Cottler and colleagues confirmed their hypothesis, and they suggested that the use of substances such as opiates or cocaine led to even greater risk of exposure to traumatic events and an increased likelihood of developing PTSD.[15]

Several years later, this hypothesis was tested again in a sample of 464 drug users.[36] In this study, the onset of drug use preceded exposure to traumatic events for men, but for women there was no difference in the timing of the events. A similar pattern of substance misuse leading to dangerous and traumatic experiences was found among African American women at risk for HIV.[37] In a study that examined African Americans with SUD who were not receiving treatment, alcohol and substance misuse, with the exception of crack cocaine use, preceded the traumatic events.[38] Finally, a longitudinal study of adults in Michigan found that PTSD predicted increased likelihood of SUD at a 5-year follow-up, but preexisting SUD did not predict later exposure to trauma or PTSD.[33]

Prevalence in veterans

Drinking alcohol has been associated with the military for centuries. Military personnel use alcohol to cope with fear and other strong emotions

experienced during and after combat.[39] Combat is the traumatic event most strongly associated with PTSD, and the ECA found that about 20% of veterans who were wounded in the Vietnam War developed PTSD.[8] More recently, veterans of the Iraq and Afghanistan wars who had PTSD were twice as likely to report alcohol misuse as those with no PTSD.[40] More than 28% of veterans screened positive for alcohol misuse, and 37% screened positive for PTSD. Of those who met criteria for PTSD, 76% had co-occurring depression, which was more than twice the rate of depression among veterans who did not have PTSD. Similarly, a prospective study of service members in the United Kingdom found that those who had experienced combat increased their drinking more than those who had not been deployed.[41] This finding was particularly strong for respondents who thought they might be killed or for those who experienced hostility from civilians while deployed.

Soldiers with PTSD who experienced at least one symptom of AUD may be disinhibited in a way that leads them to make risky decisions, including the potential for aggression or violence. One study conducted with veterans of the wars in Iraq and Afghanistan demonstrated a link between PTSD and AUD symptoms and nonphysical aggression.[42] Veterans with milder PTSD symptoms who misused alcohol were more likely to perpetrate nonphysical aggression than veterans who did not misuse alcohol. However, this relationship was not demonstrated with significance among veterans who had more severe PTSD symptoms.

Prevalence in women

Researchers continue to find more traumatic events and PTSD in women than in men. For example, in the NESARC Wave 2, lifetime prevalence of PTSD among women who experienced trauma was twice as high as the prevalence among similar men.[18] A review of community samples reported that the prevalence of co-occurring SUD and PTSD among women is higher than the prevalence among men,[43] and women who experienced abuse or neglect were significantly more likely to have AUD than controls.[44] Higher prevalence in women compared to men has also been found in women who use illicit substances.[36]

Women who have experienced sexual assault or childhood sexual abuse appear to have particularly high rates of psychiatric disorders, including PTSD and AUD. In one notable study, women who self-reported childhood sexual abuse had an increased likelihood of having psychiatric disorders or SUD.[45]

AUD and PTSD Symptom Clusters

Several studies have examined how the four clusters of PTSD symptoms (re-experiencing, effortful avoidance, emotional numbing, and hyperarousal) may affect how individuals develop and recover from PTSD and AUD. If some symptom clusters are closely associated with AUD, that information may be useful when screening people with PTSD for potential AUD. In an early study, hyperarousal symptoms were associated with AUD, whereas other clusters were not.[46] However, later research found mixed results, with one study finding no relationship between any symptom cluster and AUD,[47] and another study finding that the re-experiencing cluster was most strongly associated with alcohol problems.[48] A study of veterans of the Iraq and Afghanistan wars found that the emotional numbing cluster, compared to the other symptom clusters, was significantly associated with alcohol misuse, even when controlling for other variables associated with AUD, such as depression and direct combat exposure.[40] Finally, in a different study, a reduction of PTSD symptoms in each cluster was associated with less severe drinking overall, and a reduction in hyperarousal symptoms preceded positive changes in alcohol use.[49]

Conclusion

The association between AUD and PTSD has been elucidated due to the development of standardized assessments for the ECA using the DSM-III DIS. Assessments that followed have used the foundational structure and question format of the DIS to interview participants. They include the CIDI, AUDADIS, and, recently, the Psychiatric Research Interview for Substance and Mental Disorders. In fact, the DIS has continued to be revised based on the DSM and the International

Classification of Diseases, making it one of the most durable standardized diagnostic assessments in the field.

AUD and PTSD have shown a consistent comorbidity over many decades and in diverse populations. The strong relationship is present in representative surveys of the United States, throughout Europe, and in Australia. The relationship persists in studies of population subgroups at risk, such as veterans of the wars in Vietnam, Iraq, and Afghanistan; firefighters; women; and people with SUD. Although men have a higher prevalence of AUD than women, and women have a higher prevalence of PTSD than men, any individual with either disorder is more likely to have the other.

The evidence suggests that there is no distinct pattern of development for the two disorders. Some evidence shows that veterans who have experienced PTSD tend to develop AUD, perhaps reflecting the self-medication hypothesis. However, other research shows that people with AUD or SUD have an increased likelihood of being exposed to traumatic situations, and they have an increased likelihood of developing PTSD. It is possible that these two bodies of evidence represent two separate relationships between PTSD and AUD. Additionally, the conditional nature of the disorders, based on the exposure to an event or a substance, makes this a complex relationship for analysis, interpretation, and intervention for treatment.

Currently, there are several questions that remain unanswered. How different are the outcomes of the disorders when one or the other develops first? Are any of the PTSD symptom clusters more likely to lead to AUD? Are there particular traumatic experiences that provide some resilience against developing AUD? Are there significant differences in the occurrence and trajectory of PTSD and AUD among racial and ethnic minorities? These questions, and others, should be addressed by further research to ultimately minimize the harm experienced by the millions of individuals who experience AUD and PTSD.

Acknowledgments

This article was supported by the National Institute on Drug Abuse grant DA035167, University of Florida Substance Abuse Training Center in Public Health and National Center for Research Resources grant 5KL2RR029888, and the University of Florida Clinical and Translational Science Award.

Financial Disclosure

The authors declare that they have no competing financial interests.

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

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Alcohol use disorder (AUD) is a chronic, relapsing brain disease characterized by a reduced ability to stop or control alcohol use despite negative social, work, or health consequences. Often, it co-occurs and interacts with post-traumatic stress disorder (PTSD), which may develop after experiencing or witnessing a life-threatening event, such as combat, a natural disaster, a car accident, or sexual assault, and can result in shock, confusion, anger, and anxiety.

Co-occurring AUD and PTSD is a public health concern, especially among active military service members and veterans, as well as victims of violence and sexual assault. Approximately one in three people who have experienced PTSD have also experienced AUD at some point in their lives.[1,2] In addition, 30% to 60% of patients seeking treatment for AUD also meet diagnostic criteria for PTSD.[3,4] The co-occurrence of AUD and PTSD worsens adverse health outcomes and complicates treatment for both conditions.

This issue of *Alcohol Research: Current Reviews* examines the current literature on the prevalence, diagnoses, causes, and risk factors of AUD and PTSD, their co-occurrence, and treatment for individuals facing both conditions.

Smith and Cottler, in **The Epidemiology of Post-Traumatic Stress Disorder and Alcohol Use Disorder**, describe the changes in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) definitions of AUD and PTSD. They review key surveys that have measured these disorders, the possible relationships between the two disorders, the risk factors, and which populations are at risk.

In **Functional and Psychiatric Correlates of Comorbid Post-Traumatic Stress Disorder and Alcohol Use Disorder**, Straus and colleagues present the DSM-5 definitions for PTSD and AUD and discuss models for functional relationships between the disorders. They also examine risk factors and their associations with co-occurring disorders.

Suh and Ressler, in **Common Biological Mechanisms of Alcohol Use Disorder and Post-Traumatic Stress Disorder**, review animal models

for and clinical studies of AUD and PTSD. They discuss the relevant neurobiological circuits and examine the role of stress in these disorders.

Lee and colleagues investigate childhood stress as a predictor for PTSD and AUD in **Early Life Stress as a Predictor of Co-Occurring Alcohol Use Disorder and Post-Traumatic Stress Disorder**. They review both human and preclinical models of these disorders and examine potential biologic, genetic, and epigenetic mechanisms.

In **Co-Occurring Post-Traumatic Stress Disorder and Alcohol Use Disorder in U.S. Military and Veteran Populations**, Dworkin and colleagues report on the frequency of co-occurring PTSD and AUD in military personnel and veterans, and they examine population-specific factors contributing to the development of PTSD and AUD. They also describe evidence-based psychological and pharmacological treatments for these populations and suggest future directions for research on treatment effectiveness.

Weil and colleagues provide an overview of the bidirectional relationships between traumatic brain injury and AUD in **Alcohol Use Disorder and Traumatic Brain Injury**. The potential neuropsychological and neurobiological mechanisms underlying those relationships are discussed.

In **Behavioral Treatments for Alcohol Use Disorder and Post-Traumatic Stress Disorder**, Flanagan and colleagues describe evidence-supported behavioral interventions for treating AUD, PTSD, and co-occurring AUD and PTSD. They also examine the debate regarding sequential versus integrated treatment models.

In **Pharmacotherapy for Co-Occurring Alcohol Use Disorder and Post-Traumatic Stress Disorder: Targeting the Opioidergic, Noradrenergic, Serotonergic, and GABAergic/Glutamatergic Systems**, Verplaetse and colleagues report on pharmacotherapies for co-occurring AUD and PTSD. They discuss current clinical trials for medications and highlight future directions for neurobiological targets that have potential for treating individuals with this dual diagnosis.

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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

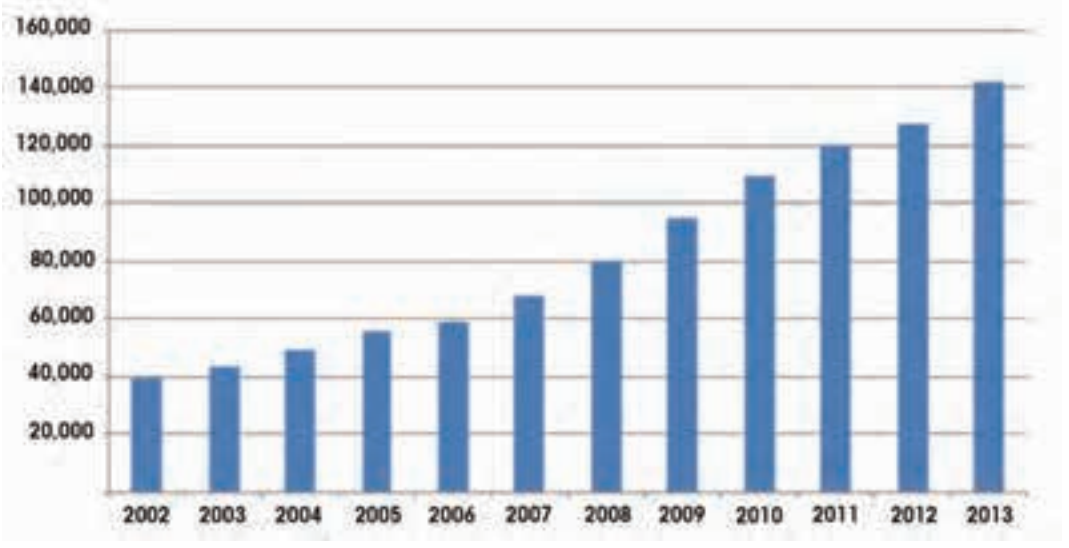

Figure Veterans receiving care in the Veterans Health Care Administration for comorbid PTSD and substance use disorder by year.

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.

Acknowledgments

The authors particularly thank Dr. Daniel Kivlahan, National Mental Health Program Director, Addictive Disorders, Veterans Health Administration, for his expertise and generosity in critiquing this article and for his extremely helpful comments on it.

Financial Disclosure

The authors declare that they have no competing financial interests.

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Alcohol's Burden on Immunity Following Burn, Hemorrhagic Shock, or Traumatic Brain Injury

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Alcohol consumption contributes to increased incidence and severity of traumatic injury. Compared with patients who do not consume alcohol, alcohol-consuming patients have higher rates of long-term morbidity and mortality during recovery from injury. This can be attributed in part to an impaired immune response in individuals who consume alcohol. Acute and chronic alcohol use can affect both the innate and adaptive immune defense responses within multiple organ systems; the combination of alcohol use and injury results in increased susceptibility to bacterial and viral pathogens. This review examines the major deleterious effects of alcohol on immunity following tissue damage or traumatic injury, with a focus on alcohol's influence on the ability of the immune and major organ systems to fight disease and to repair damaged tissues following injury.

Key words: Alcohol consumption; alcohol use, abuse, and dependence; chronic alcohol use; acute alcohol use; injury; traumatic injury; morbidity; mortality; immune response; impaired immune response; bacterial pathogens; viral pathogens; tissue; organs; disease

The incidence of traumatic injury in alcohol-intoxicated individuals continues to escalate. According to the Centers for Disease Control and Prevention (2012*a*), more than 38 million American alcohol users consume 5 or more drinks on the same occasion (i.e., binge drink) and do so about 4 times per month. This behavior is highly conducive to unintentional or accidental traumatic injury, which according to the National Vital Statistics Reports is the leading cause of years of potential life lost (YPLL) before age 45. Unintentional injury causes more YPLL than that attributed to cancer, intentional injuries, heart disease, and HIV individually (Centers for Disease Control and Prevention 2009). Data from the National Center for Injury Prevention and Control, as well as data derived from prospective and retrospective studies, show that up to 40 percent of victims of traumatic injury have positive blood alcohol concentrations (BAC), with 35 percent presenting with blood alcohol levels above the legal limit of intoxication (Beech and Mercadel 1998).

The severity of trauma, reduced blood flow and oxygen delivery (i.e., hemorrhagic shock, referred to as shock in this article), and tissue injury is greater in intoxicated victims than in sober victims, resulting in higher mortality rates in the alcohol-consuming patient population (Pories et al. 1992). Although immediate mortality from traumatic injury has improved significantly as a result of aggressive resuscitation, long-term morbidity and mortality continue to be unacceptably high during the recovery period. The prevalence of morbidity and mortality is particularly attributable to the altered immune response among impaired patients to subsequent challenges, such as surgery or infection, leading to multiple organ failure (Roumen et al. 1993; Sauaia et al. 1994). Acute alcohol intoxication complicates the initial management of trauma victims and is associated with greater incidences of pneumonia and respiratory distress, requiring ventilator assistance during hospitalization (Gurney et al. 1992; Jurkovich et al. 1992). In addition, major complications including tracheobronchitis, pneumonia, pancreatitis, and sepsis are significantly

increased in patients with high levels of carbohydrate-deficient transferrin (CDT), a marker for alcoholism (Spies et al. 1998). European studies show that, compared with nonalcoholics, alcoholics more frequently develop major complications and require a significantly prolonged stay in the intensive care unit (ICU) following trauma (Spies et al. 1996*a*).

Excessive acute and chronic alcohol consumption has significant effects at multiple cellular levels, affecting both innate and adaptive immune mechanisms (Molina et al. 2010). Both chronic and acute patterns of alcohol abuse lead to impaired immune responses, resulting in increased susceptibility to infectious diseases caused by bacterial and viral pathogens (Brown et al. 2006). Clinical and preclinical studies show that the combined effects of alcohol and injury result in greater immune disruption than either insult alone (Messingham et al. 2002). This article reviews the current understanding of the burden of alcohol on the immune response to three specific traumatic events: burn, shock, and traumatic brain injury (TBI). The major pathophysiological consequences of these injuries on other major organ systems—including the cardiovascular system, pulmonary system, and gastrointestinal tract—are highlighted with emphasis on the contribution of alcohol-induced immunomodulation to postinjury morbidity.

Reestablishment of homeostasis after a traumatic insult involves activation of host defense mechanisms for self-protection against toxic inflammatory processes and tissue repair. Trauma victims frequently are subjected to necessary invasive procedures, such as surgery and anesthesia. In addition, trauma victims frequently are exposed to subsequent challenges, particularly infection. These additional stresses to an already compromised inflammatory and neuroendocrine milieu further contribute to morbidity and mortality in this patient population. Traumatic injury and hemorrhagic shock produce a temporal pattern with early upregulation of pro-inflammatory cytokine[1] gene product expression and with later suppression of stimulated pro-inflammatory cytokine release (Hierholzer et al. 1998; Molina et al. 2001). Together, these alterations lead to generalized immunosuppression, ultimately resulting in an increased susceptibility to infection (Abraham 1993; Ertel et al. 1993).

Alcohol has been shown to affect multiple aspects of the host immune response, contributing to pathological processes (Szabo 1998). For example, alcohol alters the expression and processing of cytokines and a type of cytokine known as chemokines (D'Souza et al. 1989; Standiford and Danforth 1997), the expression of adhesion molecules (Zhang et al. 1999), inflammatory cell recruitment (Patel et al. 1996; Shellito and Olariu 1998) and accumulation, and oxidative capacity of macrophages (Nilsson and Palmblad 1988). The monocyte/macrophage production of cytokines and chemokines, in particular interleukin (IL)-8 and tumor necrosis factor-α (TNF-α), is critical in the regulation of the acute inflammatory host response to infectious challenge. The combined inhibition of pro-inflammatory cytokine production and neutrophil activation and migration to a site of infection has been suggested to contribute to the enhanced susceptibility to infection in alcoholic individuals (Nelson et al. 1991) and to the increased risk of trauma- and burn-related infections associated with alcohol intoxication (Arbabi et al. 1999). Several lines of evidence show that these alcohol-mediated alterations in host defense following injury lead to increased morbidity and mortality from infections during the recovery period (Faunce et al. 2003; Messingham et al. 2002; Zambell et al. 2004). In addition, considerable evidence suggests that the severity of disease processes is greater in intoxicated trauma victims than in nonintoxicated counterparts (Spies et al. 1996*a,b,* 1998). In particular, immunoparalysis characterized by inhibition of stimulated pro-inflammatory cytokine release (Angele et al. 1999) and alterations of both cellular and humoral immunity (Napolitano et al. 1995; Wichmann et al. 1998) have been identified as risk factors for infection and progression to organ injury during the post-traumatic injury period (Abraham 1993; Ertel et al. 1993).

The systemic response to injury is associated with marked activation of neuroendocrine pathways that contribute to cardiovascular adaptation to blood loss, injury, and pain but also exert immunomodulatory effects (Molina 2005). Catecholamines (e.g., dopamine, norepinephrine, and epinephrine), and drugs that mimic their effects (i.e., adrenergic agonists), are especially known to exert important regulatory functions on macrophages as well as on B- and T-lymphocyte cytokine production, proliferation, and antibody secretion; dendritic cell function; cytokine and chemokine release; and nitric oxide (NO) production (Madden et al. 1995). The relevance of these control mechanisms and the implications of their dysregulation have been demonstrated by the high incidence of infection in patients who experience elevated temperature, increased heart rate, and perspiration (i.e., "sympathetic storm") following acute brain trauma and myocardial infarction (Woiciechowsky et al. 1998). Alcohol intoxication produces marked disruption of several neuroendocrine pathways. Disruption of the homeostatic neuroendocrine counterregulatory response to shock impairs hemodynamic stability and recovery, contributing to compromised blood flow and increased end-organ injury (Molina et al. 2013). Specifically, binge alcohol use blunts central neuroendocrine and autonomic activation, and this seems to result from alcohol-accentuated NO production in the periventricular nucleus (PVN) of the hypothalamus (Whitaker et al. 2010). Alcohol-mediated impairment of neuroendocrine counterregulatory responses to traumatic injury not only

[1] Cytokines are proteins involved in cell signaling. They are produced by a variety of cells including immune cells and regulate the immune response.

exacerbates low blood pressure (i.e., hypotension) during hemorrhage but also attenuates blood pressure recovery during fluid resuscitation, leading to significant alterations in blood flow redistribution and notably affecting circulation in the gastrointestinal tract (Wang et al. 1993). Studies have shown that alcohol-intoxicated animals have greater reduction of blood flow to the liver, kidney, and small and large intestines than nonintoxicated animals, following shock and fluid resuscitation (Sulzer et al. 2013). These macro- and microcirculatory changes during trauma and hemorrhage have been implicated in the subsequent development of sepsis and multiple organ failure (Peitzman et al. 1995) and contribute to an increased host susceptibility to infection and tissue injury during recovery (Mathis et al. 2006; Xu et al. 2002). People who abuse alcohol, including both binge and chronic drinkers, have a higher incidence of traumatic injury such as burn, shock, and TBI. The host response to these diverse insults is markedly affected by both patterns of alcohol abuse and some systems—including gastrointestinal, cardiovascular, and pulmonary—are more affected than others according to the specific injury.

Alcohol and Burn Injury

Burn injury is a common type of traumatic injury that affects thousands of people in the United States every year (Bessey et al. 2014). Approximately 50 percent of burn-injured patients have detectable blood alcohol levels at the time of hospital admission (Haum et al. 1995; McGwin et al. 2000), and these patients have more complications, require longer hospital stays, and have greater mortality rates than those with a similar degree of injury who are not intoxicated at the time of injury (McGill et al. 1995). Most morbidity and mortality among patients who survive initial injury is attributed to complications stemming from infection (Baker et al. 1980). Therefore, the pre-burn immunological condition of injured patients affects susceptibility to infection and survival. Several mechanisms contribute to infection in burn patients, including loss of barrier function, changes in normal flora, wound ischemia, and cellular immunosuppression resulting from pro-inflammatory processes. Neutrophil, helper T-cell, and macrophage dysfunction; increased pro-inflammatory cytokine production; and enhanced production of immunosuppressive factors have all been shown to contribute to the pathophysiological response to burn injury (Faunce et al. 1998; Messingham et al. 2000). The mechanisms that contribute to infection in burn patients are influenced by acute and chronic alcohol intoxication and will be discussed below (see figure 1).

Research by Kovacs and colleagues (2008) has offered insight into the combined effects of burn injury and alcohol intoxication on immunity (Bird and Kovacs 2008). Chronic alcohol abuse alone increases the risk for lung infection (Baker and Jerrells 1993), impairs the phagocytic activity of alveolar macrophages and clearance of infectious particles from the airways, and impairs oxidant radicals, chemokine, and cytokine release that are required for microbial killing (Brown et al. 2007; Mehta and Guidot 2012; Molina et al. 2010). Acute alcohol intoxication prior to burn injury significantly suppresses the immune response relative to the insult alone (Faunce et al. 1997) and causes greater suppression of T-cell proliferation and response, reduced IL-2 production, and increased IL-6 production and circulating levels (Choudhry et al. 2000; Faunce et al. 1998). The T-cell and cytokine impairment caused by the combined effect of alcohol and burn injury may further suppress cell-mediated immunity, resulting in even greater susceptibility to infection than burn alone. Alcohol-mediated immunomodulation contributes to tissue injury in target organs as described below.

Gastrointestinal Tract

A multitude of studies have demonstrated that the gut is a reservoir for pathogenic bacteria, which may contribute to increased susceptibility to infections following traumatic injury (Deitch 1990). The intestinal mucosal barrier serves a major role in the local defense against bacterial entry and the translocation of endotoxin to the systemic circulation (Xu et al. 1997). Increased permeability and immune dysfunction indicate the compromised state of the intestinal mucosal barrier to bacterial translocation following trauma (Deitch et al. 1990; Willoughby et al. 1996). Increased intestinal permeability enhances bacterial and endotoxin translocation from the intestinal tract to the systemic circulation, triggering a systemic inflammatory response (Xu et al. 1997). Activated macrophages and lymphocytes release pro-inflammatory cytokines including TNF-α, IL-1β, and IL-6, thereby contributing to tissue injury (Fink 1991). Studies have determined that chronic alcohol consumption disrupts intestinal barrier function and induces gut leak (Li et al. 2008; Tang et al. 2009). In addition, reports have shown a loss of intestinal barrier function followed by an increase in endotoxin and bacterial translocation to the systemic circulation following burn injury alone (Carter et al. 1990; Deitch and Berg 1987; Horton 1994), alcohol intoxication alone (Keshavarzian et al. 1994; Tabata et al. 2002), and burn injury with alcohol intoxication (Choudhry et al. 2002; Kavanaugh et al. 2005; Napolitano et al. 1995). Acute alcohol intoxication at the time of burn injury enhances bacterial growth in the intestine and is reflected in a proportional increase in mesenteric lymph node bacterial count (Kavanaugh et al. 2005). Acute alcohol intoxication also modulates intestinal immune defense by suppressing T-cell proliferation and increasing bacterial accumulation in mesenteric lymph nodes, spleen, and blood, which suggests that T-cell suppression may play a role

in bacterial translocation from the lumen of the gut (Choudhry et al. 2002). Moreover, studies have shown that following shock, trauma, or burn injury, the gut leaks bacteria and pro-inflammatory factors that are carried by the mesenteric lymphatic system, which contributes to acute lung injury (ALI) (Magnotti et al. 1999). The possibility that alcohol exacerbates toxin delivery to the systemic circulation through the lymphatics is supported by studies demonstrating that alcohol regulates the contractile cycle of mesenteric lymphatic vessels modulating the driving force of lymph flow (Keshavarzian et al. 1994; Souza-Smith et al. 2010). Thus, the contribution of gut–lymph to end-organ damage following burn injury and alcohol intoxication may be significant.

Collectively, studies indicate that alcohol consumption preceding burn injury (1) increases gut permeability; (2) enhances intestinal bacterial growth, translocation, and systemic accumulation; and (3) suppresses T-cell proliferation. Further, research supports the concept that the intestine is not only a source of infection but also the site of the initial immune perturbation leading to the development of multiple organ dysfunction or organ failure.

Cardiovascular System

Immediately following a burn injury, the cardiovascular system responds with a decrease in cardiac output (Cuthbertson et al. 2001) as a result of low blood volume and reduced venous return (Kramer et al. 2007). This phase is associated with decreased cardiac contractility, mediated by the release of vasoactive and pro-inflammatory mediators (Williams et al. 2011). Subsequently, there is a surge in counterregulatory neuroendocrine mediators (catecholamines, glucagon, and cortisol) that contribute to the development of a hyperdynamic cardiovascular state—characterized by increased heart rate and cardiac output—and is associated with increased myocardial oxygen consumption and myocardial hypoxia (Williams et al. 2011). These pathophysiological processes enhance oxidative metabolism and increase the risk for free-radical generation, further

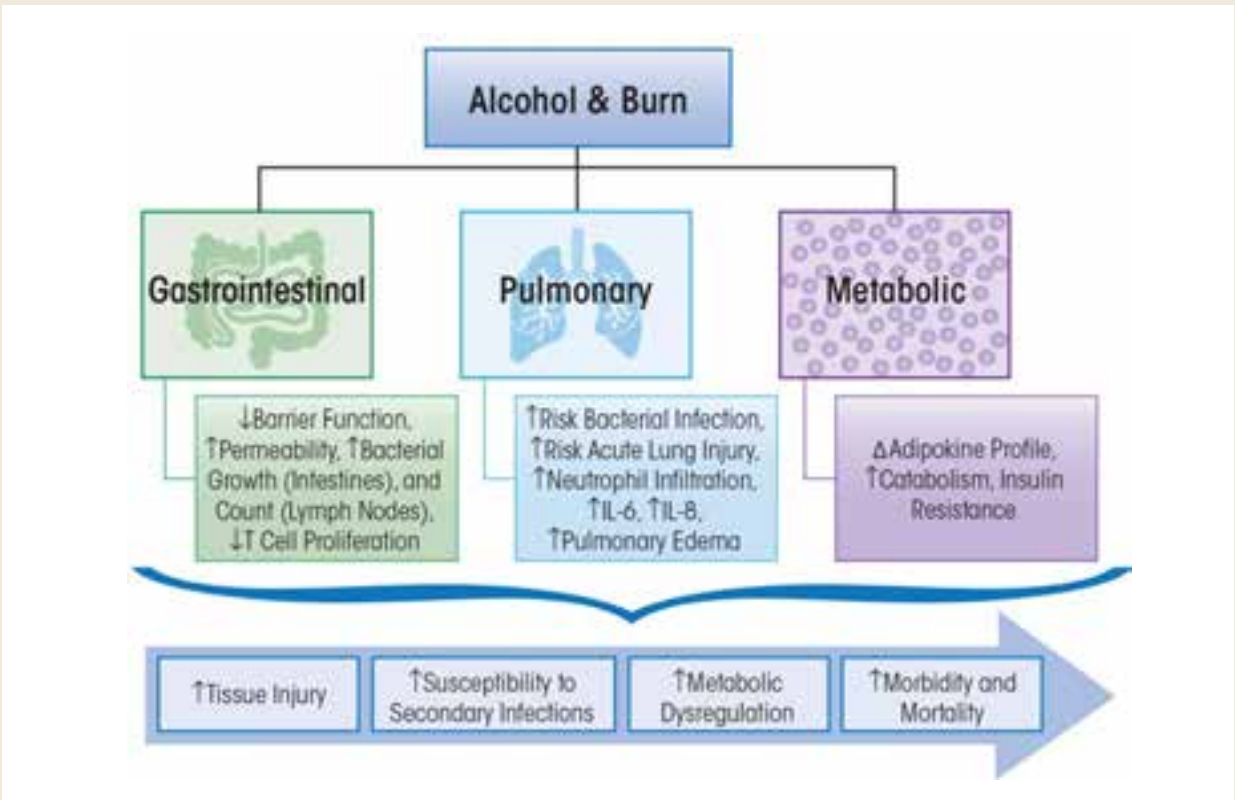

Figure 1 Salient gastrointestinal, pulmonary, and metabolic pathophysiological consequences of alcohol abuse prior to, or at the time of, burn injury. The decrease in gut barrier function leads to increased permeability and bacterial translocation that enhances the risk for bacterial infections and lung injury. Marked alterations in metabolic responses, characterized by altered adipokine profile consistent with increased insulin resistance, collectively contribute to greater morbidity and mortality post–burn injury.

exacerbating the pro-oxidative environment that has been proposed to contribute to impaired wound healing in burn patients (Herndon and Tompkins 2004). Chronic binge alcohol consumption also has been shown to promote a pro-oxidative and pro-inflammatory milieu (Rashbastep et al. 1993), and these factors may further impede wound healing in patients consuming alcohol prior to experiencing burn injury. Additional research is needed to better understand immunomodulation effects following the combined insults of alcohol and burn injury and the mechanisms underlying the more severe outcome of burn injury with alcohol abuse.

Pulmonary System

Adult respiratory distress syndrome (ARDS) is a frequent cause of death in burn patients. The lungs are one of the first organs to fail following traumatic injury (Turnage et al. 2002). Chronic and acute alcohol abuse impair pulmonary host defense to infection, thus increasing the risk of bacterial infection and acute lung injury (Boe et al. 2009; Happel and Nelson 2005). Lung injury as a result of the combination of alcohol intoxication and burn injury may be attributed to the delicate architecture of the lungs combined with other alcohol-related factors, such as bacterial and endotoxin leakage from the gut and a higher risk of contact with pathogens from the circulation and airways (Bird and Kovacs 2008; Li et al. 2007). Previous studies show that the combined insult of acute alcohol consumption and burn injury in mice leads to increased infiltration of the lungs by white blood cells, called neutrophils, and pro-inflammatory cytokine expression of IL-6 (Chen et al. 2013). Systemic and pulmonary IL-6 reflect the inflammatory state of the host and have been shown to be decreased in the absence of Toll-like receptor-4 (TLR-4) and intercellular adhesion molecule-1 (ICAM-1) (Bird et al. 2010). The role of IL-6 in lung injury has been demonstrated in studies in IL-6 knockout mice or following neutralization of IL-6, both of which result in significantly reduced lung inflammation (Chen et al. 2013). Studies also have shown that acute alcohol intoxication at the time of burn injury induces an upregulation of IL-18 production and neutrophil infiltration within the lung compartment, all leading to pulmonary edema (Li et al. 2007).

Metabolism

The post-burn period is characterized by a hypermetabolic state (Pereira and Herndon 2005) consisting of increased oxygen consumption; increased breakdown of glycogen, fats, and proteins; elevated resting energy expenditure and glucose synthesis; and reduced insulin-stimulated glucose uptake into skeletal muscle and adipose tissue (Gauglitz et al. 2009). Previous studies suggest that development of this hypermetabolic state during the post-burn period occurs as a consequence of (1) increased plasma catecholamine and corticosteroid concentrations (Jeschke et al. 2008; Williams et al. 2009; Wilmore and Aulick 1978), (2) increased systemic pro-inflammatory mediator expression, favoring processes that release energy (i.e., catabolic) over those that store energy (i.e., anabolic) (Jeschke et al. 2004), and (3) increased adipose tissue mRNA (Zhang et al. 2008) and protein (Yo et al. 2013) expression of uncoupling protein-1 (UCP-1), enhancing heat production and metabolism. Further, circulating levels of TNF-α, a known anti-insulin cytokine, are increased (Keogh et al. 1990), and the post-burn period can be described as a state of marked insulin resistance (IR) (Gauglitz et al. 2009). Insulin sensitivity has been reported to be decreased by more than 50 percent at 1-week post–burn injury in pediatric patients (Cree et al. 2007) as well as in rodent models of burn injury (Carter et al. 2004). The relevance of insulin levels to overall outcome from burn injury is supported by results from clinical studies showing that exogenous insulin therapy in pediatric burn patients decreased pro-inflammatory cytokines, increased anti-inflammatory cytokines, and increased serum concentrations of insulin-like growth factor-1 (IGF-1) and insulin-like growth factor binding protein-3 (IGFBP-3). Together, these changes could help to preserve organ function and better promote anabolic processes during the post-burn hypermetabolic state (Jeschke et al. 2004). Chronic alcohol consumption decreases insulin responsiveness and can alter insulin signaling through various mechanisms, including increased hepatic protein expression of the gene phosphatase and tensin homologue (PTEN), which directly inhibits insulin signaling through the phosphatidylinositol-5,5-bisphosphate 3-kinase (PI3K)/protein kinase B (Akt) pathway (de la Monte et al. 2012). In addition to the negative regulation of the pathway by PTEN proteins, the enzyme protein tyrosine phosphatase dephosphorylates and decreases activity of important molecules involved in the insulin signaling cascade, potentially contributing to impaired insulin action (Gao et al. 2010; Koren and Fantus 2007). In addition, Lang and colleagues (2014) demonstrated that chronic alcohol consumption reduces Akt and AS160 phosphorylation, reduces membrane localization of glucose transporter type 4 (GLUT-4) protein, and increases serine phosphorylation at serine-307 of insulin receptor substrate-1 (IRS-1), all of which will attenuate insulin-stimulated skeletal muscle glucose uptake and other insulin-mediated anabolic effects (Lang et al. 2014). These negative effects on insulin signaling occurred in conjunction with sustained increases in pro-inflammatory cytokines TNF-α and IL-6 following chronic alcohol exposure (Lang et al. 2014). Thus, both burn injury and chronic alcohol exposure alter metabolic pathways—favoring catabolic and opposing anabolic pathways—possibly resulting in long-lasting alterations in metabolic processes. The metabolic dysregulation

following burn injury is likely to produce more severe consequences in chronic alcohol burn victims. Previous studies assessing nutritional status of alcoholic patients have been discordant, with some studies suggesting that increased alcohol consumption increases the prevalence of malnutrition in alcoholic patients (Hillers and Massey 1985), whereas other studies do not show a role for excessive, or chronic, alcohol consumption in malnutrition (Nicolas et al. 1993; Urbano-Marquez et al. 1989). A study assessing the influences of aging and chronic alcohol feeding in mice on protein synthesis demonstrated that chronic alcohol feeding decreases gastrocnemius muscle protein synthesis, which provides a mechanism for loss of lean body mass (Korzick et al. 2013; Lang et al. 2014). Decreased anabolism during the post-burn period, which itself is a state of heightened catabolic processes, could significantly impair recovery for these alcoholic patients experiencing burn injury. Further, the hypermetabolic state of the post-burn period is thought to contribute to delayed or impaired wound healing, increased susceptibility to infections, and erosion of lean body mass (Pereira and Herndon 2005). Moreover, both binge alcohol consumption (Pravdova and Fickova 2006; You and Rogers 2009) and burn injury (Venkatesh et al. 2009; Wade et al. 2013) can contribute to dysregulation of cytokines secreted by adipose tissue (i.e., adipokines). Recent studies show that mice exposed to a single alcohol binge prior to burn injury have a dramatic increase in pro-inflammatory response and a decrease in anti-inflammatory response in adipose tissue (Qin et al. 2014). The heightened pro-inflammatory response during the post-burn period would be predicted to modulate leptin levels. Thus, recovery from burn injury is likely to be severely impaired in alcoholic individuals as a result of a greater disruption in metabolic processes as well as impairment of host defense mechanisms, leading to greater morbidity and health care costs associated with the management of these patients. Therefore, further investigation is warranted to understand the modulation of the immune system by the combined effect of alcohol and burn that might result in dysregulation of adipose tissue and altered metabolism.

Alcohol and Hemorrhagic Shock

Studies from several investigators have provided evidence that traumatic injury and hemorrhagic shock produce an immediate upregulation of pro-inflammatory cytokine gene product expression (Ayala et al. 1991; Hierholzer et al. 1998). The early pro-inflammatory response is later followed by suppression of stimulated pro-inflammatory cytokine release (Angele et al. 1999; Xu et al. 1998) and alterations of both cellular and humoral immunity (Napolitano et al. 1995; Wichmann et al. 1998), leading to generalized immunosuppression, which ultimately results in an increased susceptibility to infection (Abraham 1993; Ertel et al. 1993). Along with marked alterations in hemodynamic homeostasis and neuroendocrine regulation, immunological derangements and subsequent infections are also a major cause of increased morbidity and mortality following hemorrhagic shock (Livingston and Malangoni 1988; Phelan et al. 2002).

Studies focused on the immune modulatory effects of alcohol exposure following hemorrhagic shock have demonstrated that even 24 hours after the post-hemorrhagic shock, alcohol-intoxicated animals had a marked suppression in cytokine release to an inflammatory challenge (Greiffenstein et al. 2007), affecting the ability to fight secondary infectious challenges. Conversely, findings observed at the tissue level determined that alcohol intoxication enhanced the pro-inflammatory milieu following hemorrhagic shock, priming tissues for injury. The burden of alcohol and hemorrhagic shock on specific target organ systems is discussed below and summarized in figure 2.

Gastrointestinal Tract

Hemorrhagic shock produces similar alterations in gut barrier function to those resulting from burn injury. Alcohol intoxication at the time of hemorrhagic shock further exacerbates hemorrhagic injury-induced gut permeability and leakage (Sulzer et al. 2013). Chronic alcohol consumption has been shown to disrupt intestinal barrier function and induce gut leak (Li et al. 2008; Tang et al. 2009). The combination of greater hypotension and inadequate tissue blood flow (i.e., hypoperfusion) observed in alcohol-intoxicated animals and the increased gut leak observed in alcohol-intoxicated hemorrhaged animals are speculated to contribute to increased host susceptibility to infection and tissue injury during recovery (Molina et al. 2013). Alcohol-intoxicated, hemorrhaged animals have been shown to have greater reduction in hepatic, renal, and intestinal blood flow than that observed in nonintoxicated animals (Sulzer et al. 2013). This reduction in critical organ blood flow was associated with enhanced tissue damage. An additional mechanism that could contribute to tissue injury in the alcohol-intoxicated, hemorrhaged host is the disruption of gut-associated lymphoid tissue function, which has been shown to play a role in other disease states.

Cardiovascular System

Studies using a rodent model of binge-like alcohol consumption prior to hemorrhagic shock have shown that acute alcohol intoxication decreases basal mean arterial blood pressure (MABP), exacerbates hypotension, and attenuates blood pressure recovery during fluid resuscitation (Mathis et al. 2006; Phelan et al. 2002). Following fixed-volume hemorrhage, alcohol-intoxicated animals were significantly more hypotensive throughout the

hemorrhage and resuscitation periods (Mathis et al. 2006). In response to a fixed-pressure (40 mmHg) hemorrhage, a significantly lesser amount of blood was removed from the alcohol-intoxicated animals than controls (Phelan et al. 2002). Similarly, McDonough and colleagues, using a guinea pig model of ethanol exposure prior to hemorrhagic shock (loss of 60% blood volume) and resuscitation, demonstrated that a low dose of ethanol (1 g/kg) decreases MABP and heart rate and exacerbates the metabolic effects of hemorrhagic shock, as shown by increased glucose and lactate concentrations (McDonough et al. 2002). Despite the plethora of previous studies that have examined functional cardiovascular consequence of hemorrhagic shock and hemorrhage with alcohol intoxication, few studies have examined the combined effects of alcohol, hemorrhagic shock, and immune dysfunction on the cardiovascular system. However, exacerbation of pre-existing cardiovascular disease and prolonged recovery are anticipated outcomes of the combined effects of alcohol and hemorrhagic shock, all leading to an impaired immune response.

Pulmonary System

As mentioned previously, alcohol intoxication produces significant dysregulation of the host defense mechanism during the post-injury period. Lung IL-6 and TNF-α are suppressed, while granulocyte-colony stimulating factor (GCSF) mRNA is increased in alcohol-intoxicated, hemorrhaged animals (Mathis et al. 2006; Ono et al. 2004). Moreover, isolated pleural cells and peripheral blood mononuclear cells (PBMCs) from alcohol-intoxicated, hemorrhaged animals display suppressed TNF-α, IL-1β, and IL-6 release following lipopolysaccharide stimulation (Greiffenstein et al. 2007), suggesting greater impairment of humoral immune response than that resulting from hemorrhagic shock alone. The importance of these alterations in host defense mechanisms was demonstrated in animals inoculated with *Klebsiella pneumonia* following hemorrhagic shock. These studies showed suppressed neutrophil response,

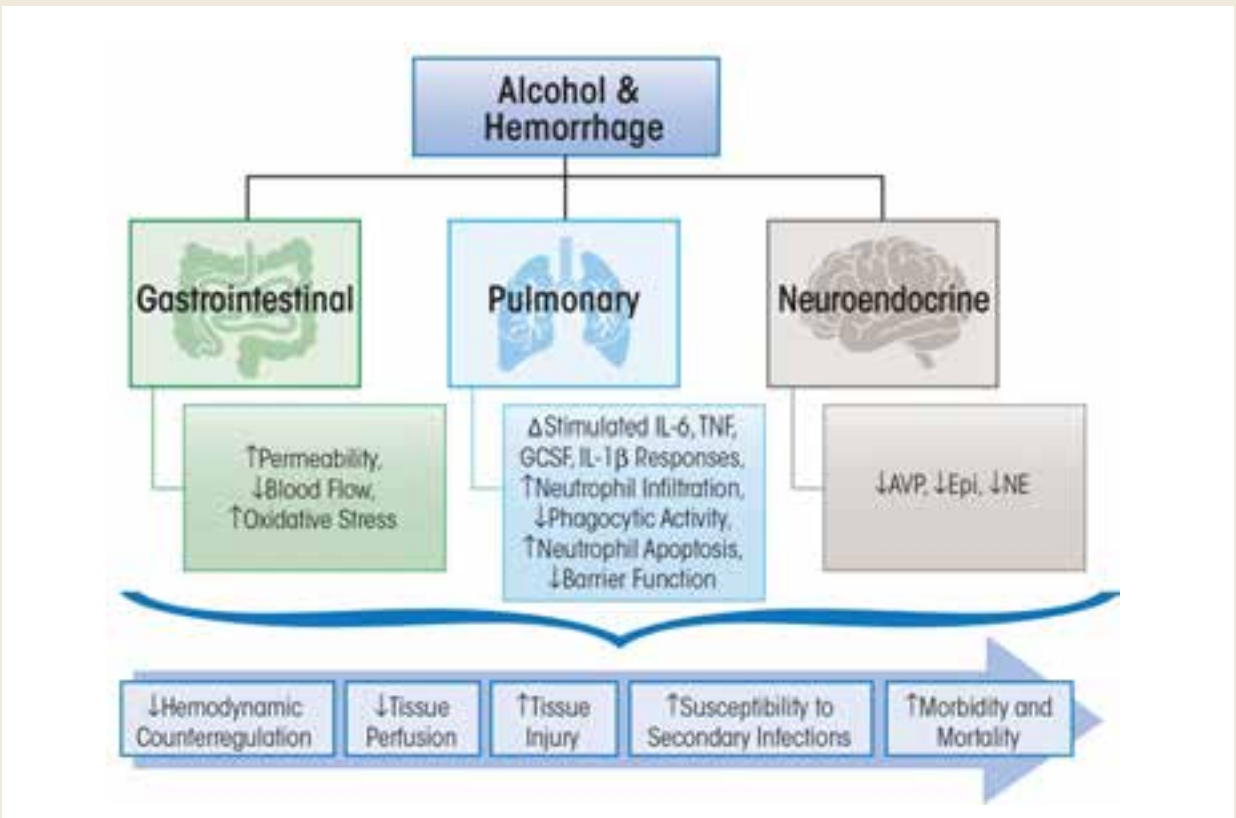

Figure 2 Salient gastrointestinal, pulmonary, and neuroendocrine pathophysiological consequences of alcohol abuse prior to, or at the time of, hemorrhagic shock. The decreased hemodynamic counterregulatory response leads to decreased tissue perfusion, accentuated oxidative stress, and enhanced tissue injury. In addition, the alcohol/hemorrhaged host shows greater susceptibility to secondary infections leading to increased morbidity and mortality during the post-injury period.

decreased phagocytic activity, and increased neutrophil apoptosis in hemorrhaged animals that were alcohol intoxicated at the time of injury (Zambell et al. 2004). This was associated with greater lung bacterial counts and prolonged elevation in TNF-α and IL-6 levels (18 h) post-infection. Furthermore, only 30 percent of alcohol-intoxicated, hemorrhaged animals survived compared with 70 percent survival of dextrose/hemorrhage animals (Zambell et al. 2004). In addition to cytokine dysregulation, alcohol impairs innate barrier functions of the lung by increasing epithelial cell permeability and altering the function of the ciliated epithelium (Elliott et al. 2007; Molina et al. 2010).

Neuroendocrine System

The pathophysiology of traumatic-hemorrhagic injury involves decreased blood volume (i.e., hypovolemia) and hypoperfusion, which results in signaling to central cardiovascular centers aimed at restoring hemodynamic stability through activation of descending autonomic neuroendocrine pathways (Molina 2005). Several mechanisms have been proposed to account for the increased hypotension and impaired hemodynamic stability observed with alcohol intoxication, with one proposed mechanism being blunted neuroendocrine activation. Studies demonstrated that acute alcohol intoxication at the time of injury results in significant attenuated release of counterregulatory hormones and potent vasoconstrictors such as arginine vasopressin (AVP), epinephrine, and norepinephrine in response to fixed-pressure hemorrhage (Phelan et al. 2002). A disruption in the neuroendocrine response with alcohol intoxication at the time of injury is associated with enhanced expression of lung and spleen TNF-α as well as suppression of circulating neutrophil function, which would be expected to enhance the risk for tissue injury (Whitaker et al. 2010). Conversely, Sato and colleagues (2013) demonstrated that alcohol aggravates hemorrhagic shock in a dose-dependent manner not by triggering an immune response but by suppressing hormonal and neurohumoral responses, thereby inhibiting hemodynamic auto-regulation and shortening the survival interval. Thus, both alcohol and hemorrhagic shock have detrimental effects on neuroendocrine responses that are likely to modulate the host immune system in addition to impacting on hemodynamic stability and recovery and accentuating tissue hypoperfusion and end-organ injury.

Alcohol and Traumatic Brain Injury

Traumatic brain injury (TBI) accounts for approximately 50 percent of all trauma-related mortality (Centers for Disease Control and Prevention 2012*b*). TBI affects multiple sectors of the population, and young males have the highest rates of hospital visits and death (Faul et al. 2010). Falls are the first leading cause of TBI, followed by motor vehicle accidents and unintentional trauma sustained during sports activities such as football or boxing. TBI can be categorized as mild, moderate, or severe, and the majority of TBIs sustained in the United States are in the mild category (Centers for Disease Control and Prevention 2012*b*). In addition to the physical dysfunction caused by injury, TBI patients frequently experience lingering psychological symptoms, such as heightened anxiety, depression, sleep disturbances, and pain hypersensitivity (Whyte et al. 1996). These symptoms have been implicated in increased alcohol intake following TBI in humans (Adams et al. 2012). Furthermore, it is well accepted that alcohol consumption increases the risks of sustaining a TBI (Corrigan 1995; Hurst et al. 1994). Nevertheless, a comprehensive understanding of the influences of alcohol on TBI-induced inflammation, recovery from injury, and long-term damage currently is limited and is summarized in the following section (see figure 3).

Neuroinflammation

The pathophysiology of TBI involves a primary mechanical injury followed by a secondary tissue injury resulting from neuroinflammation (Werner and Engelhard 2007). A large percentage of TBI victims show signs of further deterioration following the event (Sauaia et al. 1995). This suggests the induction of a secondary brain injury and immune activation as the key cascades contributing to the pathophysiological processes of the secondary damage (Cederberg and Siesjo 2010). After TBI, a series of events occurs, including the activation of resident immune cells such as astrocytes and microglia, release of pro-inflammatory cytokines and chemokines, upregulation of endothelial adhesion molecules, and recruitment and activation of blood-derived leukocytes across the disrupted blood brain barrier (Feuerstein et al. 1998; Morganti-Kossmann et al. 2001; Ransohoff 2002). An increase in the levels of TNF-α in the serum or cerebrospinal fluid in victims of TBI also has been detected in rodents following closed head injury (Goodman et al. 1990; Ross et al. 1994; Shohami et al. 1994). IL-1β is released after TBI (Fan et al. 1995) and induces nuclear factor-kappa B (NF-κ B), a key transcription factor that regulates the expression of genes encoding cytokines, as well as inducible NO synthase (iNOS), and cyclooxygenase-2 (COX-2) (Blanco and Guerri 2007; Woodroofe et al. 1991; Ziebell and Morganti-Kossmann 2010). Following the rise of early cytokines, the release of IL-6 is associated with increased acute-phase proteins, as well as blood–brain barrier disruption (Kossmann et al. 1995; Shohami et al. 1994; Woodcock and Morganti-Kossmann 2013) and sustained elevation of chemokines such as chemokine (C-C motif) ligand-2 (CCL-2) in the cerebrospinal fluid for as long as 10 days post-injury (Semple et al. 2010). Although early

cytokine release is essential in mediating the reparative processes after injury (Ziebell and Morganti-Kossmann 2010), sustained elevation of pro-inflammatory mediators has been increasingly recognized to play a role in neuropathological changes associated with long-term degenerative diseases (Fan et al. 1995; Lyman et al. 2014). Accordingly, the additional risks of alcohol as a factor contributing to the alterations of TBI-induced neuroinflammatory processes may affect the overall recovery.

Alcohol exerts a profound impact on neuroinflammation. Although there are some conflicting reports in the literature about the role of alcohol on recovery, the major findings are summarized here. Some animal studies suggest that acute alcohol administration prior to TBI leads to an early reduction in the levels of pro-inflammatory cytokines and chemokines in the injured cortex, hippocampus, and hypothalamus, as well as in the serum shortly after TBI (Goodman et al. 2013; Gottesfeld et al. 2002). Recent studies also have confirmed that acute alcohol intoxication at the time of TBI does not exacerbate the expression of pro-inflammatory cytokines and chemokines at 6 hours post-injury. However, results obtained at a later time point (24 hours) show a sustained mRNA expression of IL-1β, TNF-α, IL-6, and CCL-2 following a lateral fluid percussion injury in rodents that were alcohol-intoxicated at the time of TBI (Teng and Molina 2014). Overall, some preclinical studies suggest that acute alcohol treatment prior to TBI may lead to a suppressed release of pro-inflammatory mediators during the early phase post-injury. Thus, the temporal pattern of neuroinflammatory responses and the impact of alcohol intoxication on neuroinflammatory responses are factors to consider when drawing conclusions on the role of alcohol in modulating the outcome from TBIs.

Because the literature surrounding the relationship between acute alcohol intoxication and response to trauma is conflicting, it is important to consider the pattern of alcohol abuse and the

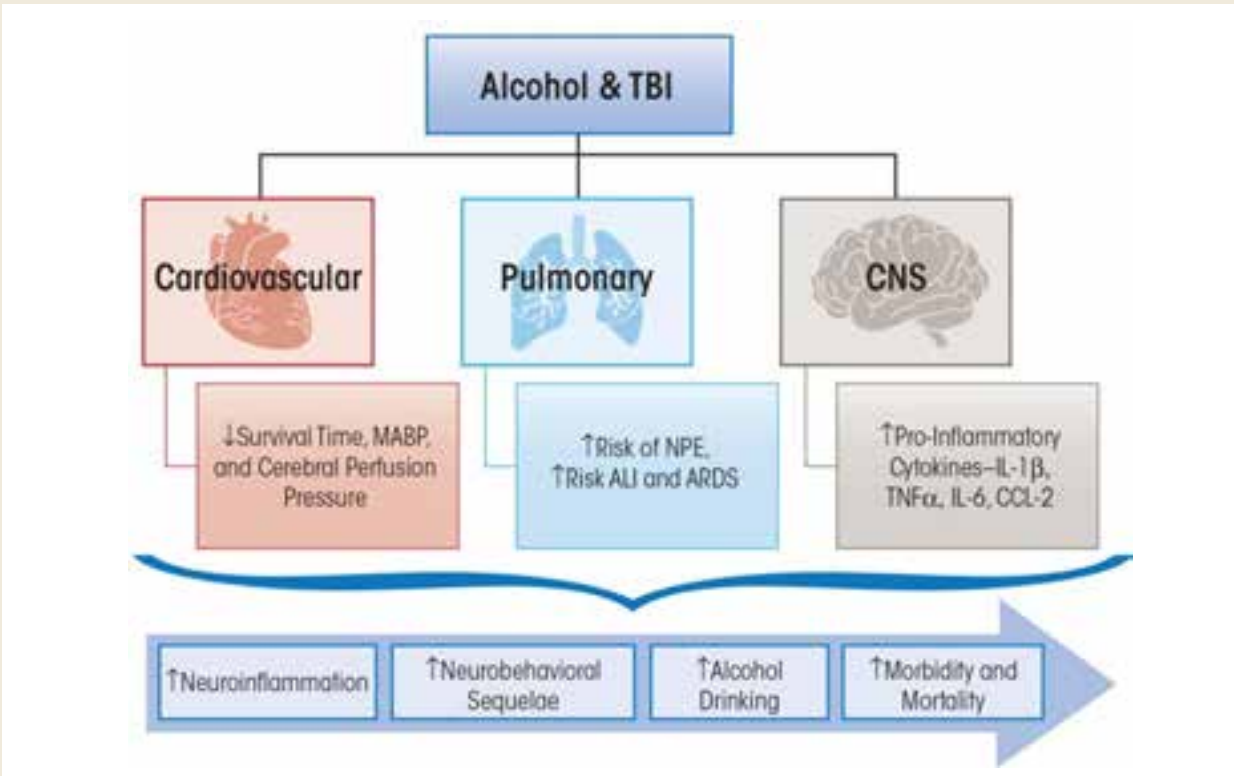

Figure 3 Salient cardiovascular, pulmonary, and central nervous system pathophysiological consequences of alcohol abuse prior to, or at the time of, traumatic brain injury (TBI). The disruption in hemodynamic homeostasis resulting from TBI contributes to decreased cerebral perfusion pressure. The lung is affected through neurogenic mechanisms leading to neuropulmonary edema (NPE) and associated risk for acute lung injury (ALI) and adult respiratory distress syndrome (ARDS). In the brain (CNS), alcohol accentuates neuroinflammation, which is associated with neurobehavioral dysfunction that can potentially promote alcohol drinking. Together, these pathophysiological consequences increase morbidity and mortality from TBI.

model used in different studies. In general, reports in the literature indicate that chronic alcohol exposure produces immune activation in the brain, inducing an enhanced pro-inflammatory state, as evidenced by the presence of CCL-2 and microglial activation in postmortem brains of human alcoholics (He and Crews 2008). Animal studies show that chronic, intermittent binge alcohol administration to rodents results in increased microglial activation and inflammatory cytokine expression in the cortex and hippocampus (Zhao et al. 2013). In addition, Crews and colleagues (2004) have found that chronic alcohol treatment induces expression of inflammatory cytokines such as TNF-α, which further activates resident glial cells to secrete additional pro-inflammatory cytokines and chemokines, resulting in an increased immune activation in the brain. The overall pro-inflammatory effects of alcohol also have been shown by Guerri and colleagues (2007) who reported alcohol-mediated stimulation of TLR-4 and IL-1 receptor signaling pathways, including extracellular regulated-kinase 1/2 (ERK1/2), stress-activated protein kinase/c-Jun N-terminal kinases (JNK), and p38 mitogen-activated protein kinase (MAPK), as well as the expression of NF-kB, activator protein-1 (AP-1), iNOS, and COX-2 in cultured glial cells (Alfonso-Loeches et al. 2010; Fernandez-Lizarbe et al. 2009). The role of TLR4 has been identified in studies where 5 months of chronic alcohol administration increased glial activation and levels of caspase-3, iNOS, COX-2, and cytokines (IL-1β, TNF-α, and IL-6) in the cerebral cortex of wild-type mice but not in the TLR-4–deficient mice (Alfonso-Loeches et al. 2010). Another mediator of alcohol-mediated neuroinflammation is high-mobility group protein B1 (HMGB1), which has been reported to be increased along with TLR-2, TLR-3, and TLR-4 in postmortem brains of human alcoholics (Alfonso-Loeches et al. 2010). Despite a substantial amount of evidence showing increased neuroinflammatory responses to chronic alcohol exposure, there have not been sufficient preclinical studies performed to determine the combined effect of chronic alcohol consumption and TBI on neuroimmune activation. Because both TBI and alcohol can induce inflammation in the brain, we speculate that the combination of the two events would further accentuate neuroinflammation.

Alcohol combined with traumatic injury can significantly affect morbidity and mortality through disruption in host immune responses.

Retrospective studies have revealed that outside of the central nervous system, peripheral organ damage can contribute to the increased mortality rate among TBI patients as a result of cardiovascular, pulmonary, and endocrine dysfunction (Gennarelli et al. 1989; Shavelle et al. 2001). More specifically, TBI patients have an increased incidence of ALI, pulmonary infection, neuroendocrine alterations, and cardiovascular dysfunction during the post-injury period (Vermeij et al. 2013). Although the combined effects of alcohol and TBI and the role of local or systemic immune responses in peripheral organs are understudied, the current knowledge is summarized below (figure 3).

Pulmonary System

ALI, one of the most common nonneurologic complications following TBI, results from acute pulmonary edema and inflammation and can lead to ARDS (Holland et al. 2003; Johnson and Matthay 2010). ALI is characterized by hypoxemia, loss of lung compliance, and bilateral chest infiltrates (Dushianthan et al. 2011). Development of ALI post-TBI has been associated with increased inpatient mortality following injury and worse long-term neurologic outcome in survivors of TBI (Bratton and Davis 1997; Holland et al. 2003). Post-TBI medical interventions including induced systemic hypertension and mechanical ventilation can result in nonneurogenic ALI (Contant et al. 2001; Lou et al. 2013). Development of neurogenic pulmonary edema (NPE) occurs minutes to hours following TBI and typically resolves within days (Bratton and Davis 1997). The possible underlying factors in NPE are the severity of injury leading to increased intracranial pressure and the subsequent increased circulating catecholamines (Demling and Riessen 1990). TBI also is associated with greater incidence of pulmonary infections than that seen following major surgeries, burn injury, and polytrauma (Dziedzic et al. 2004). Clinical reports indicate that over 40 percent of TBI patients with artificial ventilation develop pneumonia and are four times more likely to die from pneumonia (Harrison-Felix et al. 2006). The increased risk of developing pneumonia post-TBI is potentially attributed in part to a systemic immune response syndrome (SIRS) characterized by increased circulating pro-inflammatory cytokines (TNF-α and IL-6) (Keel and Trentz 2005; Kossmann et al. 1995).

The combined impact of alcohol and TBI on pulmonary infections has been minimally investigated. Although, epidemiological studies have shown that in trauma patients, chronic alcohol abuse can independently increase the risk of ALI and ARDS two- to four-fold (Guidot and Hart 2005). In a prospective study of traumatic injury patients with evidence of acute alcohol intoxication or chronic alcohol abuse, chronic alcohol was associated with increased incidence of pneumonia or respiratory failure as a result of its immunosuppressive effects. However, no significant increase in incidence of pneumonia or respiratory failure and

mortality was observed in patients with acute alcohol intoxication with BAC above 100mg/dL (De Guise et al. 2009; Jurkovich et al. 1993). The importance of length and amount of pre-existing alcohol intake and TBI severity may be the key factors in determining a patient's risk for pneumonia. Taken together, the potential effects of chronic alcohol abuse and TBI could potentiate and further increase immunosuppression or immune dysfunction, thus leading to greater susceptibility for pneumonia, ARDS, and ultimately death.

Neuroendocrine System

TBI can lead to a variety of neuroendocrine abnormalities, such as gonadotropin deficiency, growth hormone deficiency, corticotrophin deficiency, and vasopressin alterations (Behan and Agha 2007; Powner and Boccalandro 2008). As a result of the mechanical compression to the pituitary gland or disruption of the pituitary stalk, hypopituitarism can occur and corticotrophin insufficiency is commonly observed after TBI (Agha et al. 2004; Cohan et al. 2005). Excessive alcohol use also has been reported to be associated with neuroendocrine dysfunction, notably in the form of altered regulation of hypothalamic–pituitary–adrenal axis (HPA), resulting in a decreased corticotrophin release (Behan and Agha 2007; Helms et al. 2014). Therefore, it is possible that the combination of alcohol and TBI-induced HPA dysfunction can lead to a dampened cortisol release, which may have an impact on the immune system. Interestingly, a hyperadrenergic state marked by elevated levels of catecholamines can occur after TBI, and alcohol intoxication at the time of TBI has been shown to blunt the sympatho-adrenal activation in a dose-dependent manner (Woolf et al. 1990). Vasopressin has been suggested to play a role in blood brain barrier disruption, edema formation, and the production of pro-inflammatory mediators after TBI (Szmydynger-Chodobska et al. 2010). Vasopressin abnormalities leading to diabetes insipidus or the syndrome of inappropriate anti-diuretic hormone (SIADH) frequently are observed after TBI (Behan and Agha 2007), and acute alcohol intoxication is known to alter AVP release (Taivainen et al. 1995). Whether alcohol intoxication at the time of TBI or during the recovery period from TBI further dysregulates these neuroendocrine mechanisms remains to be examined.

Cardiovascular System

Cardiovascular complications including slow heart rate (i.e., bradycardia), hypotension, electrocardiographic changes, arrhythmias, and increased circulating cardiac enzymes have been reported following TBI (Bourdages et al. 2010; Wittebole et al. 2005). Chronic alcohol abuse alone can lead to alcoholic cardiomyopathy and potentially heart failure (Skotzko et al. 2009), and the underlying etiology has been reviewed (Lang et al. 2005). Several studies by Zink and colleagues (1998*a*,*b*, 2006) focused on the combined effects of acute alcohol intoxication on hemorrhagic shock and TBI in swine, showing decreased survival time, lowered MABP, and reduced cerebral perfusion pressure, which may worsen secondary brain injury. These studies did not investigate alterations in immune function or expression and levels of immune modulators or their actions on cardiovascular function. Overall, the post-TBI cardiovascular complications, including vascular function, have been understudied in both clinical and experimental models of TBI. More specifically, the combined impact of alcohol, TBI, and immune alterations on cardiovascular dysfunction and disease progression has not been examined. A possible prediction is that chronic alcohol-induced immunosuppression would worsen post-TBI cardiovascular complications; and in chronic alcoholics, dilated cardiomyopathy may compound TBI-related cardiovascular complications increasing morbidity and mortality.

Summary

The deleterious effects of alcohol on the immune system in three traumatic injuries are discussed in this review and are summarized in figures 1, 2, and 3. It is evident that, independently, acute or chronic alcohol consumption and traumatic injury negatively modulate the immune system, and the end result is an uncontrolled release of inflammatory mediators. The most important message of this review is the accumulation of evidence that alcohol combined with traumatic injury can significantly affect morbidity and mortality through disruption in host immune responses. Following burn injury, for instance, the risk for infection is greatly increased because of increased gut permeability and increased pro-inflammatory cytokine expression in the lungs (figure 1). Alcohol use following hemorrhage can increase inflammation and oxidative stress in the gut while decreasing lung barrier function and subsequently increasing susceptibility to infection (figure 2). In the central nervous system, alcohol use following TBI can increase neuroinflammation and prolong the recovery period (figure 3). Overall this information is important, because it provides a wealth of evidence that alcohol combined with trauma is a dramatic and preventable cause of increased morbidity and mortality following injury. Mechanistically, two common pro-inflammatory cytokines that are consistently upregulated in all burn injury, hemorrhagic shock, and TBI are TNF-α and IL-6. A fuller understanding of their temporal pattern of expression and downstream effects requires further investigation. Although the studies described in this review have generated important information on the impact of alcohol combined with different types of traumatic injury, and the resultant adverse effects on the immune system, further preclinical

and clinical studies to dissect the complex cascade of immunomodulation following injury are necessary. Specifically, further investigation is warranted to determine the underlying mechanisms involved in immune modulation by acute or chronic alcohol intake and the effects on (1) metabolism and the cardiovascular system following burn, (2) the neuroendocrine system following hemorrhagic shock, and (3) neuroinflammation and the neuroendocrine system following traumatic injury. The responses of the immune system to these inflammatory stimuli are variable and appear to be dependent on the severity of the injury, comorbidities, and the level of alcohol intoxication. Thus, it is necessary to systemically address these variables for translational research to identify potential therapeutic strategies. Furthermore, therapeutic targets for immunomodulation and attenuation of tissue injury in intoxicated and injured patients are likely to reduce morbidity and mortality and improve post-injury quality of life among these patients.

Acknowledgments

We thank Dr. Liz Simon for her intellectual contribution to this review and Rebecca Gonzales for her editorial support.

Financial Disclosure

The authors declare that they have no competing financial interests.

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Focus on: The Burden of Alcohol Use—Trauma and Emergency Outcomes

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Hospital emergency departments (EDs) see many patients with alcohol-related injuries and therefore frequently are used to assess the relationship between alcohol consumption and injury risk. These studies typically use either case–control or case–crossover designs. Case–control studies, which compare injured ED patients with either medical ED patients or the general population, found an increased risk of injury after alcohol consumption, but differences between the case and control subjects partly may account for this effect. Case–crossover designs, which avoid this potential confounding factor by using the injured patients as their own control subjects, also found elevated rates of injury risk after alcohol consumption. However, the degree to which risk is increased can vary depending on the study design used. Other factors influencing injury risk include concurrent use of other drugs and drinking patterns. Additional studies have evaluated cross-country variation in injury risk as well as the risk by type (i.e., intentional vs. unintentional) and cause of the injury. Finally, ED studies have helped determine the alcohol-attributable fraction of injuries, the causal attribution of injuries to drinking, and the impact of others' drinking. Although these studies have some limitations, they have provided valuable insight into the association between drinking and injury risk. **KEY WORDS: Alcohol consumption; alcohol-related injury; alcohol and drug related–injury; alcohol-attributable fractions; risk factors; alcohol and other drug–induced risk; hospital; emergency department; emergency room; emergency care; trauma; injury; intentional injury; unintentional injury; patients; case–control studies; case–crossover studies**

Alcohol consumption is a leading risk factor for morbidity and mortality related to both intentional (i.e., violence-related) and unintentional injury. In 2000, 16.2 percent of deaths and 13.2 percent of disability-adjusted life years (DALYs) from injuries, worldwide, were estimated to be attributable to alcohol (Rehm et al. 2009). Alcohol affects psychomotor skills, including reaction time, as well as cognitive skills, such as judgment; as a result, people drinking alcohol often place themselves in high-risk situations for injury.

Much of the data linking alcohol with nonfatal injuries have come from studies conducted in hospital emergency departments (EDs). As described in this article, in these settings the prevalence of alcohol involvement in the patients' injuries, as measured by a positive blood alcohol concentration (BAC) at the time of arrival in the ED or self-reported drinking prior to the injury event, is substantial. To accurately assess the relationship between alcohol use and injury risk, ED studies generally have used probability sampling designs, in which all times of day and days of the week are represented equally. This approach circumvents biases associated with sampling that might occur, for example, if samples were identified only on weekend evenings, when a higher prevalence of drinking and, possibly, of injury might be expected. Although the high prevalence rates mentioned above suggest that alcohol is an important risk factor for injury, they do not provide the information necessary to evaluate the actual level of risk for injury at which drinking places the individual.

Data to establish drinking-related risk of both intentional and unintentional injury in ED samples generally have come from two types of study design: case–control studies and case–crossover studies. This article summarizes the findings of these studies and explores specific aspects of the relationship between alcohol use and injury risk.

Risk of Injury in ED Studies

Case–Control Studies

Two types of case–control studies have been used to estimate the risk of injury from drinking for patients treated in the ED. The most commonly used type of case–control study uses noninjured (i.e., medical) patients attending the same ED during the same period of time as quasi-control subjects. These patients presumably come from the same geographic area as the injured patients and likely share other characteristics (e.g., socioeconomic status). Researchers conducted a meta-analysis of 15 ED studies conducted in 7 countries that participated in the Emergency Room Collaborative Alcohol Analysis Project (ERCAAP) (Cherpitel et al. 2003*a*) and which all used the same methodology and instrumentation. The studies only included those patients who arrived at the ED within 6 hours of the injury event and excluded those medical patients who primarily were admitted to the ED for alcohol intoxication or withdrawal symptoms. The meta-analysis found a pooled odds ratio (OR) of injury associated with a positive BAC (≥0.01 percent) of 2.4 (95% CI = 1.9–3.0);[1] moreover, the OR was higher (OR = 2.9) for patients with higher BAC levels (≥0.10 percent) (Ye and Cherpitel

[1] The OR is the ratio between the risk that a person with a certain characteristic (e.g., positive BAC) experiences a certain outcome (e.g., an injury) and the risk that a person without that characteristic experiences the same outcome. In other words, an OR of 2.4 indicates that people who have a positive BAC are 2.4 times as likely to be injured as people without a positive BAC.

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2009). A similar likelihood of injury (OR = 2.1) was found for patients who reported drinking within 6 hours prior to the injury event, regardless of time of arrival in the ED.

One concern with this approach of using medical patients as control subjects for injured patients is the possibility of underestimating the true risk of drinking associated with injury. Noninjured patients have been found to be heavier drinkers than people in the general population from which they come who do not seek emergency care (Cherpitel 1993). Thus, these patients may be attending the ED for conditions related to their drinking (in addition to those associated with alcohol intoxication or withdrawal).

In the second type of case–control study used to estimate risk of injury from drinking in ED patient samples, people in the general population of the community from which the ED patients come are used as control subjects. These individuals presumably are free of conditions that may be related to their drinking. Only four such studies have been reported to date, including two from Australia (Mcleod et al. 1999; Watt et al. 2004) and one each from the United States (Vinson et al. 2003) and Mexico (Borges et al. 1998). In these studies, the ORs ranged from 6.7 in the Mexican study to 3.1 in the U.S. study and around 2.0 in the Australian studies. Moreover, both the U.S. and the Australian studies demonstrated a dose-response relationship.

Case–Crossover Studies

The second study design used to estimate the risk of injury from alcohol consumption is the case–crossover study (Maclure 1991). This approach is thought to circumvent at least some of the problems raised with the case–control design, such as demographic and others differences between case and control subjects that may be related to both alcohol consumption and likelihood of injury. There are two approaches to the case–crossover design, both of which use injured patients as their own control subjects, thereby theoretically reducing confounding of the alcohol–injury relationship from stable risk factors, such as age and gender.

- *The matched-interval approach.* Studies using the matched-interval approach compare drinking within 6 hours prior to the injury event with drinking during a predetermined control period, such as the same 6-hour period during the previous day or previous week. Such studies have reported ORs ranging from 3.2 (based on any drinking at the same time the previous day) (Vinson et al. 2003) to 5.7 in a 10-country study (based on any drinking at the same time the previous week) (Borges et al. 2006*b*). Both studies demonstrated a dose-response relationship. Thus, the analysis of Vinson and colleagues (2003) determined ORs ranging from 1.8 with consumption of 1 to 2 drinks prior to injury to 17 with consumption of 7 or more drinks. Likewise, Borges and colleagues (2006*b*) found ORs ranging from 3.3 with consumption of one to two drinks to 10.1 with consumption of six or more drinks prior to injury.
- *The usual-frequency approach.* This approach compares the patients' drinking in the 6 hours preceding the injury to their expected drinking during that time, based on their usual frequency of drinking. In a study using this approach that included 28 EDs across 16 countries, the estimated ORs ranged from 1.05 (Canada) to 35.0 (South Africa), with a pooled estimate of 5.69 (95% CI = 4.04–8.00) (Borges et al. 2006*a*).

Comparison of Methods to Estimate Risk

The results described above indicate that the estimates of risk of injury in samples from the same country can vary depending on the method used. For example, in analyses across eight countries participating in ERCAAP, analyses using the case–control method found that the pooled OR of injury for self-reported drinking prior to the event was 2.1, compared with an OR of 5.2 when the usual-frequency method of case–crossover analysis was used (Ye and Cherpitel 2009). Furthermore, the World Health Organization (WHO) Collaborative Study on Alcohol and Injury, which used the case–crossover method across 12 countries, found a pooled OR of injury of 6.8 using the usual-frequency approach, compared with 5.7 using the matched-interval approach (Borges et al. 2006*b*). Case–control designs may underestimate the risk of injury if noninjured control subjects are presenting to the ED with other conditions related to their drinking, whereas both the matched-interval and usual-frequency approaches to the case–crossover design are subject to recall bias of drinking in the past.

Effects of Other Factors on Risk of Injury

Effects of Other Drug Use

None of these estimates of risk of injury related to drinking have taken into consideration other drug use at the time of injury, although multiple substances commonly are used together in ED populations (Buchfuhrer and Radecki 1996). Other drug use might be expected to elevate the risk of injury, either alone or in combination with alcohol; however, this may not be the case. One study found an OR of 3.3 for drinking within 6 hours prior to injury and an OR of 3.0 for drinking in combination with other drug use during the same time; in contrast, drug use alone had no significant effect on risk (Cherpitel et al. 2012*b*). It is important to consider that in this study the majority of drug users reported using marijuana. However, given their different pharmacological properties, all drugs would not be expected to act in a similar manner, either alone or in combination with alcohol. Consequently, in other populations with different drug use patterns the findings might be different.

Effects of Usual Drinking Patterns

The risk of injury from drinking prior to the event (i.e., acute consumption) also is influenced by the drinker's usual drinking patterns (i.e., chronic consumption). Cherpitel and colleagues (2004) found that the risk of injury from drinking prior to the event was lower among frequent heavy drinkers than among infrequent heavy drinkers, suggesting that heavier drinkers may have developed tolerance against some adverse effects of alcohol that lead to injury. Likewise, in an analysis by Gmel and colleagues (2006), the risk of injury was greater among usual light drinkers who occasionally drink heavily (i.e., report episodic heavy drinking) than among people who usually drink heavily but report no episodic heavy drinking or among people who usually drink heavily as well as report episodic heavy drinking.

Risk of Alcohol-Related Injury

Although acute alcohol consumption, modified by drinking pattern, has been found to be associated with risk of injury, drinking pattern also has been found to be associated with risk of an alcohol-related injury[2] (defined as drinking within 6 hours prior to injury), with frequency of drinking among non–heavy drinkers (Cherpitel et al. 2003*b*) and both episodic and frequent heavy drinking predictive of alcohol-related injury (Cherpitel et al. 2012*c*). An analysis of combined data from ERCAAP and from the WHO Collaborative Study on Alcohol and Injury across 16 countries found the pooled risk of alcohol-related injury was increased with heavy episodic drinking (OR = 2.7) as well as with chronic high-volume drinking (OR = 3.5); moreover, the risk was highest for people reporting both patterns of drinking (OR = 6.1) (Ye and Cherpitel 2009).

Cross-country Variation in Risk of Injury

A great deal of variation has been found across countries in risk of injury and risk of alcohol-related injury, and this heterogeneity seems to be associated with a country's level of detrimental drinking pattern (DDP). The DDP score, which is based on aggregate survey data and key informant surveys, is a measure developed for comparative risk assessment in the WHO's Global Burden of Disease study (Rehm et al. 2004). It includes such indicators of drinking patterns as heavy drinking occasions, drinking with meals, and drinking in public places. The DDP has been assessed in a large number of countries around the world as a measure of the "detrimental impact" on health, and other drinking-related harms, at a given level of alcohol consumption (Rehm et al. 2001, 2003). Countries with a higher level of DDP have been found to have a higher risk of injury related to alcohol than those with lower DDP scores (Cherpitel et al. 2005*b*).

Risk by Type and Cause of Injury

Risk of injury from alcohol also varies by type (i.e., intentional vs. unintentional) and cause of injury. For example, Macdonald and colleagues (2006) found that the risk was highest for violence-related (i.e., intentional) injuries. A case–crossover analysis using the usual-frequency approach that included data from 15 countries in the ERCAAP and WHO projects found that greater variations across countries existed in risk of an intentional injury than in risk of unintentional injury; this difference was at least in part explained by the level of DDP in a country (Cherpitel and Ye 2010). Overall, the pooled OR for intentional injury related to drinking in these countries was 21.5, compared with 3.37 for unintentional injury (Borges et al. 2009). Furthermore, the risk of intentional injury showed a greater dose–response association than the risk of unintentional injury (Borges et al. 2009). Thus, the ORs for intentional injuries ranged from 11.14 for one to two drinks prior to injury to 35.57 for five or more drinks during this time, whereas the ORs for unintentional injuries ranged from 3.86 to 6.4, respectively. Among the unintentional injuries, the risk also varied depending on the cause of the injury. For example, the OR was 5.24 for traffic-related injuries, compared with 3.39 for injuries related to falls.

Alcohol-Attributable Fraction

Another variable that has been studied in the context of assessing the risk of injuries after drinking is the alcohol-attributable fraction (AAF). This variable represents the proportional reduction in injury that would be expected if the risk factor (i.e., drinking prior to injury) was absent; it reflects the burden of injury in a given society that results from alcohol use. The AAF also varies across countries in ED studies, because it is related to both the risk of injury and the prevalence of alcohol-related injury. In a case–control study of 14 EDs from six countries in ERCAAP, the AAF based on self-reported drinking within 6 hours prior to the injury event varied from 0.5 percent to 18.5 percent for all types of injury, and from 19.1 percent to 83.3 percent for intentional injury (Cherpitel et al. 2005*a*). The pooled estimate from all EDs for the AAF was 5.8 percent for all types of injury and 42.5 percent for intentional injury. In other words, more than 40 percent of all intentional injuries would not have occurred if the people involved had not been drinking. Moreover, the investigators determined higher AAF estimates for male than female subjects for both unintentional injuries (5.5 percent vs. 1.7 percent) and intentional injuries (50.0 percent vs. 7.7 percent).

[2] As used here, the term "alcohol-related injury" refers to injuries where the patient reported using alcohol in the 6-hour period immediately preceding the injury; in contrast, the term "injury" is used here to refer to any injury, regardless of whether it was preceded by alcohol use or not.

Causal Attribution

The ED studies in the ERCAAP and WHO projects also assessed the patients' causal attribution of their injuries to their drinking—that is, patients were asked whether they believed the injury would have occurred if they had not been drinking. In an evaluation that included 15 countries, one-half of the patients who reported drinking prior to injury also reported a causal attribution (Cherpitel et al. 2006). This information was used to establish a subjective AAF—an AAF derived from the patient's own causal attribution of their injury to drinking. This subjective AAF then was compared to the AAF obtained using the standard formula based on the relative risk of injury from alcohol and prevalence of drinking in the 6-hour period (i.e., the objective AAF) from the six ERCAAP countries, as described above. This comparison found that for unintentional injuries, the subjective AAF generally was somewhat higher than the objective AAF. For intentional injuries, however, the subjective AAF was substantially lower (i.e., 5.9 percent to 46.7 percent) than the objective AAF (i.e., 24.9 percent to 83.3 percent) (Bond and Macdonald 2009).

Others' Drinking

Researchers also increasingly are interested in studying the harm, including injury, resulting from other people's drinking. Evaluating these so-called externalities is important for a fuller understanding of the burden of alcohol-related injury in society. To assess such externalities, investigators for the ED studies in the WHO project also obtained data on whether the patient being treated for a violence-related injury believed the other person had been drinking. Across the 14 countries, from 14 percent to 73 percent of the victims believed that others definitely had been drinking. Based on these data, the pooled estimate for the AAF was 38.8 percent when both victim and perpetrator were considered, compared with an AAF of 23.9 percent when only the patient was considered (Cherpitel et al. 2012*a*).

Considerations and Limitations in Estimating Risk of Injury

The data reported here on the risk of injury primarily were derived from patients' self-reports of drinking prior to injury. Although the ED studies all estimated the patient's BAC at the time of ED admission based on breath alcohol levels, self-reports seem to be a better measure of drinking, because in many cases a substantial period of time may have lapsed between the patient's last drink, the injury event, and arrival at the ED. As a result, the BAC may be negative even though the patient reports drinking prior to injury. Indeed, this discrepancy has been found in an analysis of the concordance between self-reported drinking and BAC measurements in the ERCAAP and WHO studies across 16 countries (Cherpitel et al. 2007).

The studies reported here all have been conducted in EDs, rather than in trauma centers that generally treat the most serious injury cases and, consequently, are less conducive to the detailed data collection effort required in studies of alcohol and injury, unless the patient is admitted to the hospital. It is unknown how this may affect the resulting conclusions regarding the rates of the risk of injury from drinking, because the literature has been mixed regarding alcohol's association with injury severity.

As noted earlier, some limitations also apply to the methods that have been used to estimate the risk of injury related to alcohol consumption. Case–control studies may underestimate this risk because the medical patient controls also may have drinking-related conditions. The matched-interval approach to case–crossover analyses eliminates the heaviest drinkers (i.e., those who report drinking both during the period preceding the injury and during the control period), which may lead to underestimates of the risk of injury for these drinkers. Likewise, the usual-frequency approach may underestimate the risk of injury for heavy drinkers because of the increase in expected drinking occasions for the heaviest drinkers.

In addition, when estimating risk of injury using the case–crossover approach, it is important to consider the activity in which the patient was engaged at the time of injury. For example, for a patient injured in a motor vehicle accident who had been drinking, the comparison with the control time interval only would be valid if the patient also had been in a motor vehicle during the control interval. Otherwise, the patient would not have been exposed to the risk of incurring a motor vehicle–related injury, regardless of whether he or she had been drinking. This is an important consideration in future studies that seek to examine risk of injury related to alcohol.

Lastly, the risk of injury related to drinking likely is affected by a number of individual-level characteristics such as age, gender, and risk-taking disposition, as well as by societal-level characteristics such as detrimental drinking pattern, as discussed above. Estimates of AAFs for injury, which are required for determining the global burden of disease for injury related to alcohol, generally have not taken these variables into consideration, and this is a necessary direction for future research on the burden alcohol-related injury puts on society. ■

Acknowledgements

Work on this article was supported by National Institute on Alcohol Abuse and Alcoholism grant 2–RO1–AA–013750–04.

Financial Disclosure

The author declares that she has no competing financial interests.

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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. ■

Financial Disclosure

The authors declare that they have no competing financial interests.

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Resilience to Meet the Challenge of Addiction

Psychobiology and Clinical Considerations

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Acute and chronic stress–related mechanisms play an important role in the development of addiction and its chronic, relapsing nature. Multisystem adaptations in brain, body, behavioral, and social function may contribute to a dysregulated physiological state that is maintained beyond the homeostatic range. In addition, chronic abuse of substances leads to an altered set point across multiple systems. Resilience can be defined as the absence of psychopathology despite exposure to high stress and reflects a person's ability to cope successfully in the face of adversity, demonstrating adaptive psychological and physiological stress responses. The study of resilience can be approached by examining interindividual stress responsibility at multiple phenotypic levels, ranging from psychological differences in the way people cope with stress to differences in neurochemical or neural circuitry function. The ultimate goal of such research is the development of strategies and interventions to enhance resilience and coping in the face of stress and prevent the onset of addiction problems or relapse. **KEY WORDS: Addiction; substance abuse; stress; acute stress reaction; chronic stress reaction; biological adaptation to stress; psychological response to stress; physiological response to stress; resilience; relapse; coping skills; psychobiology**

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Evidence from different disciplines suggests that acute and chronic stress–related mechanisms play an important role in both the development and the chronic, relapsing nature of addiction (Baumeister 2003; Baumeister et al. 1994; Brady and Sinha 2005). Stress is defined as the physiological and psychological process resulting from a challenge to homeostasis by any real or perceived demand on the body (Lazarus and Fokman 1984; McEwen 2000; Selye 1976). Stress often induces multisystem adaptations that occur in the brain and body and affect behavioral and social function. The resulting dynamic condition is a dysregulated physiological state maintained beyond the homeostatic range. This definition and conceptualization of stress was further developed to explain the chronic abuse of substances and comfort foods and has been studied in the context of behavioral addiction (i.e., pathological gambling) (Dallman et al. 2005; Koob and Le Moal 1997; Koob 2003).

Persistent challenges to an organism through chronic substance use may ultimately lead to an altered set point across multiple systems. This hypothesis is consistent with evidence that suggests adaptations in brain reward and stress circuits, and local physiology (e.g., energy balance) can contribute to addictive processes. Cravings or urges, decreases in self-control, and a compulsive engagement in unhealthy behaviors each characterize patients with addiction (Dallman et al. 2005; Kalivas and

Volkow 2005; Koob et al. 2004; Sinha 2001). Alternatively, a person's ability to successfully cope with high stress is reflected in adaptive physiological and psychological responses (Charney 2004; MacQueen et al. 2003).

Resilience, defined as the absence of psychopathology despite exposure to high stress, can be studied by examining interindividual differences in stress responsivity across an organism's various types (i.e., at multiple phenotypic levels). Responsivity ranges from psychological differences in the way individuals cope with stress to differences in neurochemical or neural circuitry function (Cicchetti and Blender 2006). Variability within the genetic makeup and quality of early-life experience, as well as interactions between the two, are known to contribute to differences in stress resilience (Enoch 2010; Heim and Nemeroff 2001). Genetic influences can stem from gene–environment interactions, changes in gene expression influenced by the environment (i.e., epigenetic changes), or variation within the actual genetic code. Some examples of genetic influences on resilience include variability in the genes involved in the body's stress response (i.e., those controlling the hypothalamic–pituitary–adrenal [HPA] axis). These include those coding for the corticotropin-releasing factor (CRF) type 1 receptor or the glucocorticoid receptor (GR) (which cortisol can activate) as well as the serotonin transporter cathecol-O-methyltransferase (COMT), neuropeptide Y (NPY), and brain-derived neurotrophic factor (BDNF) genes (Feder et al. 2009) Genetic variation in the gene encoding the CRH1 receptor was found to moderate the impact of stress, for example, among adolescents engaging in heavy drinking (Blomeyer et al. 2008; Schmid et al. 2010). This gene-by-environment interaction predicted the initiation of drinking in adolescence as well as progression to heavy drinking by young adulthood (Schmid et al. 2010). The following sections highlight resilient responses to stress in studies in which stress was identified as an important factor contributing to the neurobiology of alcohol dependence.

Psychosocial Factors Associated With Resilience

Early studies of children exposed to adversity (Masten 2001; Masten and Coatsworth 1998; Rutter 1985) as well as more recent studies in resilient adults (Ahmad et al. 2010; Alim et al. 2008; Bonanno 2004) have identified a range of psychosocial factors associated with successful adaptation to stressful or traumatic events. For example, the ability to simultaneously experience both positive and negative emotions when confronted with a high-stress situation increases flexibility of thinking and problem solving and can buffer individuals from developing stress-induced adverse consequences (Fredrickson 2001; Ong et al. 2006). Likewise, optimism has been associated with resilience to stress-related disorders, including alcohol use disorders (Ahmad et al. 2010; Alim et al. 2008).

The ability to focus attention on performing and completing tasks was identified as a protective factor against substance use.

Unlike personality characteristics associated with increased risk for substance use disorders (e.g., impulsivity, novelty seeking, and negative emotionality), positive emotionality, the tendency to experience positive mood frequently, was found to be associated with resilience to substance use in a large longitudinal study of public school students followed from late childhood through midadolescence (Wills et al. 2001). In this study, positive emotionality was found to buffer the effects of parent–child conflict and of parental and peer substance use on adolescent substance use. The ability to focus attention on performing and completing tasks was identified as a protective factor against substance use (Wills et al. 2001). The ability to focus attention might relate to the capacity to cope by planning and problem solving in times of stress, both types of coping styles characteristic of resilient individuals (Southwick et al. 2005).

Veenstra and colleagues (2007) examined the impact of coping style on alcohol use in response to stressful life events in a sample of 1,608 men and 1,645 women drawn randomly from the Dutch Lifestyle and Health Study (Veenstra et al 2007). Individuals who scored high on emotion coping, a coping style focused on feelings and emotional content to cope with stress, used more alcohol when experiencing a negative life event, compared with those who scored low on emotion coping. Alcohol use in times of stress did not vary by cognitive or by action coping, but the study found that cognitive coping and having more social contacts was linked to lower alcohol use in general. Another study of more than 1,300 adult drinkers in the general population from a New York county found stress-induced drinking in a subset of men (but not women) who scored high on avoidance coping and on positive expectancy from alcohol (Cooper et al. 1992). Men with low-avoidance coping and low expectancy from alcohol, on the other hand, actually showed a negative relationship between stressful life events and alcohol use. Of note, low avoidance coping has been linked to stress resilience in general, in several other studies (Alim et al. 2008; Carver et al. 1997).

Neurochemistry of Resilience

"Allostasis" refers to the dynamic process through which the body adapts to daily stressors and maintains homeostasis (Sterling and Eyer 1988). Sudden

stressful events trigger the release of the "flight-or-fight" hormones (i.e., catecholamines) and other stress hormones in the brain, preparing the organism to cope with stress and avert harm. This process is mediated by a stress circuit (see figure 1), which is consistently implicated in stress-related disorders such as mood and anxiety disorders and addictive disorders. Interindividual variability in stress resilience results from differences in the coordinated stress response. This response comprises the function and interactions of numerous hormones, neurotransmitters, and neuropeptides, some of which are discussed below.

HPA Axis

The HPA axis is a system regulated by a complex negative-feedback system. CRF, released by the hypothalamus in response to stress, triggers the release of adrenocorticotrophic hormone (ACTH) from the anterior pituitary gland. This process leads to the synthesis and release of cortisol by the adrenal cortex. Cortisol secretion acutely facilitates cognitive, metabolic, immunologic, and behavioral adaptations to stress. It also results, however, in "allostatic overload" when stress becomes chronic or overwhelming (McEwen 2003). Resilience is maintained when the stress response is both activated and terminated efficiently. The adaptive responses of the HPA axis are thought to involve an optimal balance of the cortisol-binding receptors GR and mineralocorticoid receptor (de Kloet et al. 2005, 2007).

Studies showing lower plasma levels of ACTH but not cortisol in men with a family history of alcoholism (Dai et al. 2007; Gianoulakis et al. 2005) suggest that HPA axis dysfunction might predate the onset of alcoholism. Long-term alcohol abuse is associated with increased extrahypothalamic CRF signaling and dampened HPA axis responsivity (Richardson et al. 2008). Increases in extrahypothalamic CRF contribute to negative emotional states during abstinence, increasing risk for relapse (Koob and Le Moal 2008). In a recent study, researchers asked alcoholics who had been abstinent for 1 month to imagine a relaxing situation of their choice while listening to a previously recorded audiotape of this situation. A greater cortisol-to-corticotropin ratio (i.e., higher adrenal sensitivity) during this relaxed state was found to predict a shorter time to alcohol relapse, thus suggesting that new treatments aimed a decreasing adrenal sensitivity could reduce relapse rates (Sinha et al. 2011).

Norepinephrine

During the acute stress response, the hormone norepinephrine (NE) is released through direct projections from the brain site where NE is synthesized (i.e., locus coeruleus) and other brain stem nuclei (i.e., structures that act as transit points for brain signals) into the amygdala, hippocampus, nucleus accumbens, prefrontal cortex (PFC), and other brain areas mediating emotional responses. Several studies have linked abnormal regulation of brain NE systems to stress disorders (Krystal and Neumeister 2009; O'Donnell et al. 2004). As drug dependence develops, levels of the neurotransmitter dopamine decrease and the NE stress system in the brain is activated, contributing to "stress-like states" and increased vulnerability to stressors during periods of abstinence (Koob and Le Moal 2008). In combi-

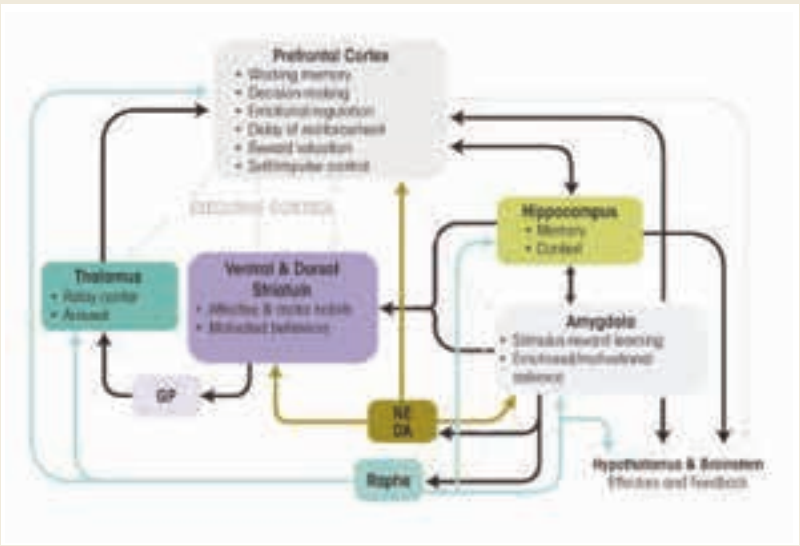

Figure 1 Norepinephrine (NE) and dopamine (DA) are the principle chemical messengers employed in central and peripheral sympathetic synapses, and the human NE transporter rapidly clears NE and DA from the synaptic cleft via efficient transport system-attenuating signaling, recycling 90 percent of these synaptic monoamines. NE neurons innervate nearly all parts of the neuroaxis, with the locus coeruleus (LC) being responsible for most of the NE in the brain. NE exerts neuromodulatory effects on the cellular activity of post-synaptic target neurons in many brain circuits, thereby moderating synaptic transmission in target circuits including the thalamus, prefrontal-cortex (PFC), ventral striatum (via PFC), and amygdala, which have been implicated in substance use disorders. The widespread and divergent anatomical organization positions the NE system to be involved in widely varying functions including responses to stress, which alters both the electrophysiological activity of NE neurons in the LC and the release of NE in the terminal regions of these cells, as well as crucial cognitive functions, including attention and arousal. NE mediates many of the adaptive and maladaptive consequences of stress exposure, implicating this system in a variety of abnormal behaviors including alcohol dependence.

nation with CRF, NE also might contribute to the consolidation of emotional memories associated with drug use in the amygdala (Koob et al. 2009).

Stress resilience may be enhanced through the regulation of NE system responsiveness, which is mediated through effects on the NE transporter on catecholamine receptors (i.e., α2 adrenoreceptors), as well as interactions between the NE and other neurobiologic systems, such as the dopamine and serotonin systems (Krystal and Neumeister 2009). For example, animal studies have shown that PFC NE nerve cell projections (i.e., axons) have a latent capacity to enhance synthesis and recovery of transmitter, which might underlie the capacity to adapt to stress (Miner et al. 2006). This mechanism deserves further study in humans with positron emission tomography (PET), which uses positron-emitting radiotracers to show where and how compounds act in the brain (Ding et al. 2005). Other targets include the α2a and α2c receptors, which have complementary roles in the regulation of stress responses (Small et al. 2000). Yohimbine, a drug that blocks the α2 receptors (i.e., a receptor antagonist), increases alcohol self-administration and induces reinstatement of alcohol seeking (Le et al. 2005; Marinelli et al. 2007). The recent finding that an α2c receptor polymorphism (Del322-325) reduces feedback inhibition of sympathetic NE release (Neumeister et al. 2005) as well as evidence from studies in mice bred to have an inactivated α2c receptor (i.e., knockout mice) (Sallinen et al. 1999), suggest that interventions targeting this receptor might modulate stress and anxiety responses.

Serotonin

The serotonin (5-HT) system, which consists primarily of neurons from the dorsal raphe nuclei that project widely throughout the brain (including the amygdala, ventral striatum, and PFC), is involved in the regulation of stress and anxiety. Serotonin has an important role in promoting neuroplasticity in the central nervous system, both during development and in adulthood. Serotonin also regulates the neurochemical effects of drugs of abuse, including alcohol, and is involved in modulating impulsivity, known to increase risk for alcohol and drug abuse (Kirby et al. 2011). The 5-HT system is itself modulated by drugs of abuse. For example, alcohol administration elevates 5-HT levels in the nucleus accumbens, ventral tegmental area (VTA), amygdala, and hippocampus, an effect that is more pronounced in alcohol-preferring rats. Reduced activity of the 5-HT system might contribute to depression during withdrawal and increase vulnerability to relapse (Kirby et al. 2011). In studies of macaques, differential function of the 5-HT system in interaction with early life stress was found to affect alcohol consumption: peer-reared female macaques with a specific variant (i.e., the l/s genotype) of the serotonin transporter polymorphism showed higher levels of ethanol preference and increased consumption over time (Barr et al. 2004).

The 5-HT system is extremely complex, including at least 14 receptor subtypes. Of these receptors, the 5-$HT1_A$, 5-$HT1_B$, 5-$HT2_A$, and 5-$HT2_C$ receptors are well understood through research on anxiety regulation in both animals and humans (Krystal and Neumeister 2009). The 5-$HT1_A$ receptor is thought to counteract the deleterious effects of 5-$HT2_A$ receptor activation (i.e., the disruption of brain cell creation), mediated by increased release of the neurotransmitter glutamate and direct glucocorticoid effects (Hoebel et al 2007). Restrained function of another 5-HT receptor, $5HT1_B$, might be central to resilient stress responses by enhancing synaptic availability of 5-HT in the amygdala and other cortical regions as well as promoting dopamine release in the ventral striatum (Clark and Neumaier 2001; Krystal and Neumeister 2009; Sari 2004) (see figure 2).

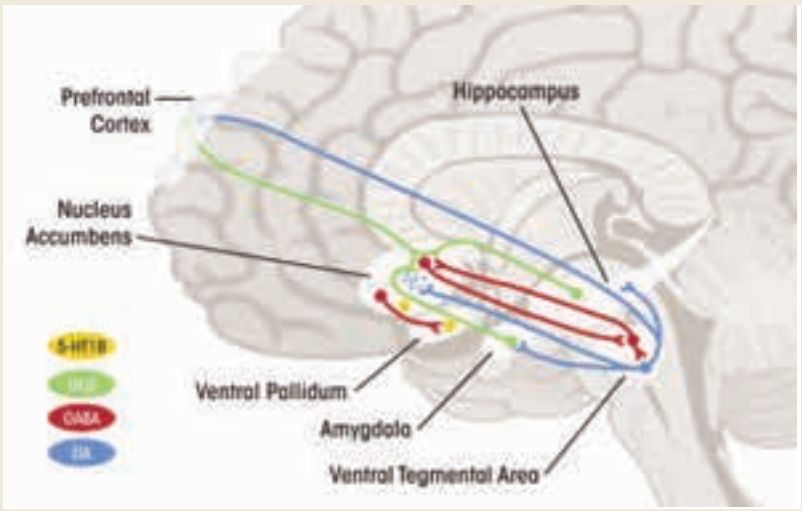

Figure 2 Alterations in serotonin 1B receptor ($5HT_{1B}R$) function might contribute to alcohol dependence by influencing not only serotonin (5HT) input to the ventral striatum via the receptors' role as 5HT terminal autoreceptors,[1] but also dopaminergic input to the striatum via the role of these receptors as heteroreceptors[2] on GABA terminals within the ventral tegmental area, and glutamatergic activity within the ventral striatum via heteroreceptors on corticofugal projections.

[1] Autoreceptor: A site on a neuron that binds the neurotransmitter released by that neuron, which then regulates the neuron's activity.
[2] Heteroreceptor: A site on a neuron that binds a modulatory neuroregulator other than that released by the neuron.

The role of this receptor subtype in addiction disorders recently was studied in humans. The report demonstrated that alcohol dependence in humans, like in rodent models, is associated with increased levels of ventral striatal 5-HT_{1B} receptors (Hu et al. 2010). Additional research is necessary to understand the complex function of the 5-HT system. However, these findings suggest possible novel targets for the treatment of stress-related disorders and, most important, addiction disorders.

Dopamine

Dopaminergic neurons in the ventral tegmental area (VTA) of the midbrain project to the nucleus accumbens and other limbic areas to form the mesolimbic dopamine system, the most studied reward circuit. Dopamine neurons are activated in response to reward or the expectation of reward, and generally are inhibited by aversive stimuli. Dopamine signaling is central to the onset of addiction, as well as to the transition to dependence in interaction with other neurotransmitter systems (Ross and Peselow 2009). Drugs of addiction trigger large but brief increases in extracellular dopamine in the nucleus accumbens. Over time, chronic drug use downregulates dopamine receptors and dopamine release, leading to decreased sensitivity to natural rewards, such as food and sex, and leading also to further drug use (Volkow et al 2010).

Although findings from animal studies suggest that early-life stress can lead to long-lasting changes in gene expression in the mesolimbic dopamine pathway, ultimately increasing vulnerability to addictive disorders, not all individuals with a history of childhood abuse develop addictive or other disorders, thereby stressing the role of protective factors such as genetic variants conferring resilience (Enoch 2010).

Findings from several studies suggest that higher dopamine D2 receptor availability in the striatum might promote resilience to alcohol use disorders. In a study of unaffected members of alcoholic families, higher striatal dopamine D2 receptor availability was associated with higher positive emotionality, discussed above as a protective factor against alcohol use disorders (Volkow et al 2006). Other studies found that higher striatal dopamine D2 receptor availability was associated with resistance to the reinforcing effects of stimulants in healthy volunteers (Volkow et al. 1999, 2002) and in rats (Thanos et al. 2008).

NPY

NPY, a 36–amino acid peptide, is widely distributed in the brain. NPY has anxiety-reducing properties in rodents and is thought to enhance resilience to stress in humans (Feder et al. 2009; Morgan et al. 2000). Evidence from animal and human studies suggests that NPY has a key role in regulating alcohol intake, dependence, and withdrawal. Mice genetically modified to overexpress NPY consume less alcohol (Thiele et al. 1998), and administration of NPY into the cerebral ventricles of the brain (i.e., intracerebroventricular infusion) reduces alcohol consumption in alcohol-preferring rats (Thorsell 2007). Infusion of NPY into the central nucleus of the amygdala has been shown to normalize both anxiety behaviors and alcohol intake, suggesting that NPY might work by modulating anxiety responses (Zhang et al. 2010). In rhesus macaques exposed to early life stress, and in human studies, certain NPY gene polymorphisms are associated with differential susceptibility to alcohol or cocaine dependence (Koehnke et al. 2002; Lindell et al. 2010; Mottagui-Tabar et al. 2005; Wetherill et al. 2008).

Endocannabinoids

An emerging body of evidence suggests an important role for the endogenous cannabinoid (eCB) system and specifically the CB_1 receptor in alcohol-related behaviors (for review, see Basavarajappa 2007). To date, however, only peripheral measures of eCB function have been collected in living humans with alcohol dependence (AD) (Mangieri et al. 2009), and no human in vivo data on the potentially critical role of the brain CB_1 receptor in AD have been collected yet. At a neurobiological level, studies show impairments in decision making in alcohol-dependent patients (Dom et al. 2006), which is associated with altered functions in a cortico-limbic-striatal circuit, including the amygdala, hippocampus, anterior cingulate cortex, insula, and the ventral striatum. Three sets of factors are thought to be responsible for high alcohol relapse rates. First, individual differences in the positive, reinforcing properties of alcohol are known to increase risk of alcoholism and possibly alcohol relapse (Schuckit and Smith 1996). Second, stimuli previously associated with alcohol use and its physiological and subjective effects become paired with alcohol and are thought to serve as "conditioned cues" that can increase alcohol craving and subsequent alcohol use (O'Brien et al. 1998). Finally, stress has been found to increase the risk of alcohol relapse (Brown et al. 1990; Miller et al. 1996; Sinha 2001). All three factors can be linked to the eCB system and its attending CB_1 receptor and increasing evidence derived from animal studies suggests a role of the eCB system in alcohol-related behaviors (Vinod and Hungund 2006).

Such research suggests that upregulation of CB_1 receptor–mediated G-protein signaling in a brain circuit that mediates AD susceptibility (involving the amygdala, hippocampus, ventromedial prefrontal cortex, insula, and ventral striatum) (Sullivan and Pfefferbaum 2005) might contribute to the increased alcohol consumption in patients with chronic AD. For example, CB_1 inactivation (Hungund et al. 2003; Naassila et al. 2004; Poncelet et al. 2003; Thanos et al. 2005) and pharmacological manipulation of CB_1 receptor function (Femenia et al. 2010; Maccioni et al.; Maccioni et al. 2008; Malinen and Hyytia 2008) result in reduced voluntary alcohol intake. In addition, administration of an agent that binds to the CB_1 receptor (i.e., a CB_1 receptor agonist) (Colombo et al. 2002; Gallate et al. 1999; Vinod et al. 2008*b*) enhances alcohol consumption.

In contrast, acute, short-term alcohol intoxication is associated with elevated eCB levels (Basavarajappa et al. 2006; Blednov et al. 2007; Vinod et al. 2008*a*), reduced activity of the enzyme fatty acid amide hydrolase (FAAH), and reduced CB_1 receptor–mediated G-protein signaling (Vinod et al. 2011). This mediates the activation of the mesolimbic dopaminergic system (Cheer et al. 2007; Hungund et al. 2003), which has been extensively studied in alcohol dependence. Evidence suggests a functional interaction between these systems, which might be associated with the reinforcing effects of alcohol and therefore may be an important mechanism in the etiology of alcohol dependence. Findings in animal studies recently have stimulated interest in the therapeutic potential of enhancing eCB signaling, with research in humans having just begun (Hill et al. 2009). However, an accumulating body of evidence suggests that the eCB system, and in particular its attending CB_1 receptor, provides novel leads for treatment development in alcohol dependence (Bailey and Neumeister 2011).

Behavioral Interventions to Enhance Resilience

To date, most studies on resilience have been conducted in clinical populations with people exposed to traumatic life events as a prototype of stress-related disorders. However, these studies also can inform the development and implementation of behavioral interventions to address alcohol dependence. This is a critical application because the ultimate goal of research attempting to delineate a range of psychological, neurochemical, and brain circuitry mechanisms underlying resilience is the development of strategies and interventions aimed at enhancing resilience in the face of stress, which is of particular relevance for people struggling with alcohol dependence. As related to alcohol dependence, improving resilience would influence cognitive and emotional control in the face of stress, resulting in the ability to weather cravings without using alcohol, mindfulness to be aware of impulsive behavior and potentially avoid impulsive behaviors associated with alcohol use, and the development of prosocial behavior and interpersonal relations that could serve to support the individual in the face of stress and prevent alcohol use. Several cognitive and behavioral interventions have been developed in an effort to develop these capacities. These interventions, which include various forms of cognitive and behavioral psychotherapies (Butler et al. 2006; Marlatt 2001), mindfulness-based stress reduction (e.g., Astin 1997; Shapiro et al. 1998; Teasdale et al. 2000) and other therapeutic approaches, aim to help prevent the onset or minimize the extent of alcohol use behaviors. In addition, therapeutic approaches based on positive psychology might also help promote psychological resilience (e.g., Seligman and Csikszentmihalyi 2000) and are currently being evaluated for their effectiveness in addressing alcohol dependence.

Researchers have hypothesized that the chronic nature of addiction disorders is rooted in the neurotoxic effects of stress on the brain.

Taken together, interventions aimed at enhancing resilience to stress that focus on developing cognitive reappraisal skills, fostering mindfulness, and facilitating social interaction that results in enhanced social support could be particularly effective in helping people cope with stress and preventing the onset of alcohol use problems or relapse. Indeed, cognitive–behavioral models of addiction and relapse treatment such as those provided by Marlatt and colleagues (e.g., Marlatt 2001) highlight the role of experiencing negative affect as a primary trigger for using alcohol and relapsing. Mindfulness skills can be particularly useful in helping an individual cope with negative affect in the moment without resorting to the use of substances. Moreover, the attributions that individuals make upon relapsing (whether the attribution for use is internal and stable: "I just can't handle stress and I'm bound to keep using"—versus external and unstable: "This was really stressful and difficult to deal with, and I decided to take the easy route this time") can influence whether the relapse develops into a full-blown relapse or remains an isolated event. Cognitive reappraisal of these situations and the attributions that individuals make of their alcohol use can thus be of great importance in developing resilience in the treatment of alcohol use disorders.

Conclusions and Future Directions

Despite extensive research and knowledge regarding their serious adverse consequences, addiction disorders continue to contribute to the top preventable causes of death and morbidity in the United States (Centers for Disease Control and Prevention 2003). The mechanisms underlying the persistent and compulsive engagement in these behaviors remain poorly understood. Based on previous evidence, researchers have hypothesized that the chronic nature of addiction disorders is rooted in the neurotoxic effects of stress on the brain. These effects undermine the neuroplasticity within networks required for the recovery process to take place. As a result, mechanisms of resilience are crucial to the understanding of neuroadaptive potential and its behavioral consequences. This is an important topic of current research, which stands at a unique crossroad in the study of addiction disorders. The explosion in the field of molecular and cellular neuroscience calls for interdisciplinary,

collaborative team-based approaches. A greater understanding of the neurobiology of stress and resilience, as well as its implications on the neurobiology of addictions, is crucial to the prevention of such disorders and to the development of evidence-based treatment strategies. ■

Financial Disclosures

This paper was supported by the National Institute on Alcohol Abuse and Alcoholism (NIAAA) through the following awards: R21 AA–018329, RL1 AA–017540, and RL1 AA–017540–S1.

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Stress, Epigenetics, and Alcoholism

Sachin Moonat, M.S., and Subhash C. Pandey, Ph.D.

Acute and chronic stressors have been associated with alterations in mood and increased anxiety that may eventually result in the development of stress-related psychiatric disorders. Stress and associated disorders, including anxiety, are key factors in the development of alcoholism because alcohol consumption can temporarily reduce the drinker's dysphoria. One molecule that may help mediate the relationship between stress and alcohol consumption is brain-derived neurotrophic factor (BDNF), a protein that regulates the structure and function of the sites where two nerve cells interact and exchange nerve signals (i.e., synapses) and which is involved in numerous physiological processes. Aberrant regulation of BDNF signaling and alterations in synapse activity (i.e., synaptic plasticity) have been associated with the pathophysiology of stress-related disorders and alcoholism. Mechanisms that contribute to the regulation of genetic information without modification of the DNA sequence (i.e., epigenetic mechanisms) may play a role in the complex control of BDNF signaling and synaptic plasticity—for example, by modifying the structure of the DNA–protein complexes (i.e., chromatin) that make up the chromosomes and thereby modulating the expression of certain genes. Studies regarding the epigenetic control of BDNF signaling and synaptic plasticity provide a promising direction to understand the mechanisms mediating the interaction between stress and alcoholism. **KEY WORDS: Alcoholism; alcohol consumption; genetic factors; epigenetics; acute stressors; anxiety disorders; stress-related psychiatric disorders; physiological response to stress; dysphoria; brain; brain-derived neurotrophic factor (BDNF); synaptic plasticity**

Alcoholism is a complex disorder characterized by compulsive alcohol seeking and consumption that also is impacted by related psychiatric states, such as anxiety (Koob 2003; Pandey 2003). Both environmental and genetic factors influence alcohol drinking patterns and may increase susceptibility to the development of alcohol addiction (Cloninger 1987; Crabbe 2002). The presence or development of comorbid stress-related psychiatric disorders, which typically are characterized by features such as altered mood and anxiety, often has been associated with an increased propensity for alcoholism (Bolton et al. 2009; Grant et al. 2004; Schuckit and Hesselbrock 1994). More specifically, alcohol consumption is thought to reduce negative symptoms such as depressed mood and anxiety (i.e., dysphoria) linked with stress-related disorders, which ultimately results in self-medication (Bolton et al. 2009; Robinson et al. 2009).

Acute and chronic stressors also may be important factors in regulating alcohol craving and may play a significant role in the relapse to alcohol and drug dependence (Breese et al. 2011; Self and Nestler 1998; Sinha 2007; Uhart and Wand 2009). Various forms of stress, including early-life stress; severe acute stress, such as that experienced in posttraumatic stress disorder (PTSD); and chronic stress, likely can be associated with an increased risk of alcohol and drug dependence (Gordon 2002; Sinha 2008; Uhart and Wand 2009). At the same time, early alcohol exposure and acute alcohol withdrawal may increase vulnerability to stress that may result in the development of negative affective states, such as anxiety or depression (Guerri and Pascual 2010; Hellemans et al. 2010; Koob 2003; Pandey 2003). Taken together, these findings delineate an intricate and complex relationship between stress and alcohol exposure and have stimulated various lines of research that attempt to identify the molecular mechanisms involved in the development of dysphoric symptoms related to the pathophysiology of alcoholism (Koob 2003; Moonat et al. 2010; Pandey 2003).

One focus of this research is the hypothalamus, a key brain region involved in the body's two main stress response systems: (1) the hormonal system known as the hypothalamic–pituitary–adrenal axis that culminates in the release of stress hormones from the adrenal glands to elicit responses throughout the body and (2) the brain's central stress response system that includes clusters of brain cells (i.e., nuclei) in the limbic system and autonomic centers of the brain stem (Koob 2008; Smith and Vale 2006). The neurocircuitry related to the central stress response comprises connections between various hypothalamic nuclei, the hippocampus, brain stem nuclei, and a system of interconnected nuclei in the basal forebrain, the extended amygdala (Koob 2008, 2009). These include the central nucleus of amygdala (CeA), medial nucleus of amygdala (MeA), bed nucleus of the stria terminalis, and the shell of the nucleus accumbens (NAc) (Alheid 2003; Koob 2003). Some regions of the extended amygdala, such as the CeA, also have been associated with the development of alcoholism and stress-related disorders such as anxiety,

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suggesting that the extended amygdala is a neuroanatomical substrate for the interaction between stress and alcoholism (Koob and Volkow 2010; Pandey 2003, 2004).

One mechanism that may provide a link between stress-related psychiatric disorders and alcoholism is modification of synaptic plasticity via neuroadaptation (figure 1) (Moonat et al. 2010; Pandey et al. 2008*b*; Pittenger and Duman 2008). Studies found that ethanol exposure and related withdrawal symptoms can result in structural and functional modifications at the sites where two nerve cells (i.e., neurons) interact and transmit nerve signals (i.e., at the synapse). These modifications at the synaptic level have been observed in various brain regions as well as in neuronal cultures (Carpenter-Hyland and Chandler 2006; Pandey et al. 2008*b*; Roberto et al. 2002; Zhou et al. 2007). Chronic stress also is associated with changes in structural and functional plasticity in various brain regions, including the hippocampus, amygdala, and prefrontal cortex (Goldwater et al. 2009; Pavlides et al. 2002; Roozendaal et al. 2009). Neuroadaptation associated with ethanol exposure or stress plays a role in the onset of dysphoric symptoms that may manifest as stress-related psychiatric disorders or withdrawal-induced anxiety (Pandey et al. 2008*b*; Pittenger and Duman 2008; Roozendaal et al. 2009).

One molecule that has been implicated in synaptic plasticity and long-term memory formation is a protein, cAMP-responsive element binding (CREB) (Abel and Kandel 1998; Alberini 2009; Waltereit and Weller 2003). It also has been recognized as a critical modulator of neuroadaptation associated with alcoholism (Misra et al. 2001; Pandey 2004; Pandey et al. 2003, 2005) and the effects of stress (Barrot et al. 2002; Bilang-Bleuel et al. 2002; Carlezon et al. 2005). CREB is a transcription factor—that is, it helps regulate the first step in the conversion of the genetic information encoded in the DNA into finished protein products (i.e., transcription) by binding to specific DNA sequences in its target genes. To exert its effects, CREB must be activated by the addition of a phosphate group to (i.e., phosphorylation of) the amino acid serine at position 133 of the CREB protein. This phosphorylation is performed by enzymes, protein kinases, that are associated with various signaling cascades, including the mitogen-activated protein kinase (MAPK) pathway (Impey et al. 1999; Shaywitz and Greenberg 1999; Waltereit and Weller 2003). One target gene of CREB encodes a molecule, brain-derived neurotrophic factor (BDNF), which plays an important role in the regulation of synaptic plasticity and dendritic spine structure (Minichiello 2009; Poo 2001; Tao et al. 1998; Soule et al. 2006). (For more information on dendritic spines, see the textbox "Histone Acetylation and Dendritic Spines.") BDNF also may mediate changes in synaptic plasticity that accompany both alcohol exposure (Moonat et al. 2010, 2011; Pandey et al. 2008*b*) and stress (Briand and Blendy 2010; Duman and Monteggia 2006). Accordingly, researchers have begun to investigate how BDNF activity is controlled. These studies have determined that mechanisms contributing to the regulation of gene transcription that do not involve alterations of the DNA sequence (i.e., epigenetic mechanisms) seem to play a role in the regulation of BDNF activity as well as in synaptic plasticity (Guan et al. 2009; Lubin et al. 2008; Tsankova et al. 2006). Accordingly, this topic has become a focus of research in stress and alcoholism (Elliott et al. 2010; Hunter et al. 2009; Moonat et al. 2010; Pandey et al. 2008*a*; Qiang et al. 2010).

This article reviews research that attempts to describe the role of epigenetic mechanisms in the regulation of BDNF function in alcoholism and stress. After providing an overview of epigenetic mechanisms and their role in the control of gene transcription, the article will summarize research regarding the regulation of BDNF signaling, focusing on epigenetic mechanisms involved in the regulation of BDNF expression. Finally, the article will outline the potential role of the epigenetic control of BDNF signaling and synaptic plasticity in alcoholism and stress.

Epigenetic Regulation of Gene Transcription

The term epigenetics refers to chemical modifications occurring within a genome that may modulate gene expression without changing the DNA sequence (Holliday 2006; Murrell et al. 2005; Waddington 1942). Common epigenetic alterations include the chemical modification (e.g., addition or removal of acetyl groups) of the proteins around which the DNA is wrapped (i.e., histone proteins) to form the chromosomes and the direct addition of methyl groups (i.e., methylation) to DNA. These modifications are performed by enzymes,

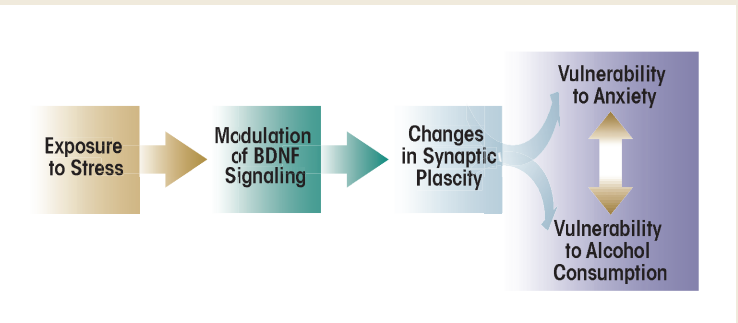

Figure 1 A psychiatric model for the relationship between stress, anxiety, and alcohol consumption and its modulation by brain-derived neurotrophic factor (BDNF) and synaptic plasticity. Exposure to stress is thought to result in the modulation of BDNF and synaptic plasticity in various brain regions. These changes may result in increased vulnerability to the development of stress-related disorders such as anxiety. Vulnerability to alcohol consumption also may be increased, either directly due to stress exposure or in response to the development of anxiety.

such as histone deacetylases (HDACs) and DNA methyltransferases (DNMTs). Both of these mechanisms work in concert to remodel the structure of the protein–DNA complex (i.e., the chromatin), thereby regulating the access of the transcriptional machinery to the DNA and, consequently, gene expression in the cell (Borrelli et al. 2008; Jenuwein and Allis 2001; Levenson and Sweatt 2005; for more information, also see Starkman et al. 2012).

Histone Acetylation

The basic unit of chromatin, a nucleosome, consists of four histone protein subtypes that form an octamer around which the DNA is wrapped (Jenuwein and Allis 2001; Smith 1991). Histone modification occurs at lysine amino acids near one end of the histone proteins and, as mentioned earlier, involves the addition and removal of acetyl groups. The level of acetylation of the histones determines how tightly the DNA is wound around the histones and how tightly the nucleosomes are stacked together. In the presence of many acetyl groups (i.e., hyperacetylation) at specific lysine residue of histones H3 and H4, the chromatin is relaxed and accessible to the transcriptional proteins, resulting in increased gene transcription; conversely, in the presence of only few acetyl groups (i.e., hypoacetylation), the chromatin is condensed, preventing access of transcriptional proteins and resulting in gene silencing (Smith 1991; Strahl and Allis 2000).

HDACs are enzymes that can remove acetyl groups from histone proteins; they seem to be key elements in the regulation of chromatin structure and function (figure 2) (Jenuwein and Allis 2001). Inhibition of HDAC enzymes by pharmacological intervention is effective in the treatment of some cancers, and numerous HDAC inhibitors have been approved or are in clinical trials for this purpose (Dokmanovic et al. 2007; Lane and Chabner 2009). Recently, HDAC inhibitors also have been explored as potential therapeutic agents in the treatment of psychiatric disorders, including stress-related disorders and addiction, and have become an important focus of research in the neuroscience field (Covington et al. 2009; Kumar et al. 2005; Pandey et al. 2008*a*; Renthal and Nestler 2008; Tsankova et al. 2007). Several HDAC isoforms have been identified and grouped into four classes based upon their regulation and cellular localization (de Ruijter et al. 2003; Dokmanovic et al. 2007). Specific HDAC variants (i.e., isoforms) recently have been identified as regulators of neuronal processes such as synaptic plasticity (Guan et al. 2009; Renthal and Nestler 2008). This suggests that use of isoform-specific HDAC inhibitors may increase the specificity and efficacy of these drugs in the treatment of psychiatric disorders.

HDAC-Induced Histone Deacetylation and Dendritic Spines

Dendritic spines are protuberances that make up the sites where incoming signals from other nerve cells are received (i.e., the postsynaptic terminals) along dendritic processes. The overall number of dendritic spines, their shape, and their distribution on the dendritic processes can change rapidly. This compartmentalization of dendritic spines may allow for the regulation of synaptic plasticity at an individual synapse (Yuste 2011; Higley and Sabatini 2008). For example, various intracellular signaling mechanisms, including brain-derived neurotrophic factor (BDNF) signaling via activity-regulated cytoskeleton-associated (Arc) protein, can regulate the structural and functional components of dendritic spines associated with long-term potentiation (LTP) and synaptic plasticity (Bramham et al. 2008; Minichiello 2009; Soule et al. 2006).

Epigenetic mechanisms also may play a role in the regulation of dendritic spines. Specifically, a recent study (Guan et al. 2009) noted that one histone deacetylase (HDAC) subtype, HDAC2, is involved in the regulation of dendritic spines. When studying mice that produced excessive levels of HDAC2, the investigators found that increased HDAC2 levels were associated with reduced memory formation in a fear-conditioning paradigm and that this impairment was associated with a reduction in dendritic spine density in the hippocampus. Treatment of HDAC2-overexpressing mice with HDAC inhibitors reversed these deficits. On the other hand, animals in which the gene encoding HDAC2 was inactivated (i.e., HDAC2 knockout animals) showed improved learning and increased dendritic spine density (Guan et al. 2009). These findings suggest that HDAC2 plays a role in the regulation of synaptic plasticity; however, future studies may be necessary to identify the specific genes that are regulated by HDAC2 in the control of neuronal function and structure. Given the involvement of brain-derived neurotrophic factor (BDNF) in synaptic plasticity, it may be useful to evaluate the potential regulation of BDNF signaling by HDAC2 in learning at the neuronal and behavioral levels.

DNA Methylation

The chromatin structure also can be modified by adding methyl groups to certain DNA building blocks (i.e., cytosine nucleotides) in a particular gene, resulting in transcriptional silencing (see figure 2). The level of DNA methylation is controlled by three DNMT subtypes that seem to be differentially regulated and preferentially methylate at specific DNA sequences (Antequera 2003; Bestor 2000; Okano et al. 1999). DNA methylation can inhibit transcription either directly, by blocking the binding of transcriptional machinery to DNA, or indirectly, via methyl-CpG binding domain proteins (MBDs) (Fan and Hutnick 2005; Wade 2001).

These proteins, including MeCP2, seem to directly regulate the condensation of chromatin structure and recruit HDACs and DNMTs, which may further enzymatically modify chromatin components (see figure 2) (Fuks et al. 2000; Kimura and Shiota 2003; Nan et al. 1998). Mutations in the *MeCP2* gene and, consequently, the resulting protein that alter transcription of the gene encoding BDNF and affect synaptic plasticity are thought to underlie a neurodevelopmental disorder, Rett syndrome (Chahrour and Zoghbi 2007; Chang et al. 2006; Monteggia and Kavalali 2009; Zhou et al. 2006). Thus, the coordinated actions of HDACs, DNMTs, and MBDs form a complex regulatory network that modulates neuronal function, and dysregulation of these proteins has been implicated in a variety of psychiatric disorders.

Researchers are beginning to identify the role of epigenetic mechanisms in the regulation of gene transcription related to alcohol exposure and the development of alcoholism (Kim and Shukla 2006; Moonat et al. 2010; Pandey et al. 2008*a*; Qiang et al. 2010). Moreover, histone modifications and DNA methylation are involved in the dysphoric states induced by acute and chronic stress (Elliott et al. 2010; Fuchikami et al. 2009; Hunter et al. 2009; Tsankova et al. 2006). Specifically, various studies have demonstrated that epigenetic mechanisms are involved in the regulation of *BDNF* gene transcription, which in turn plays a role in the modulation of synaptic structure and function (He et al. 2010; Lubin et al. 2008; Tsankova et al. 2006). This will be discussed in the following section.

The Regulation of BDNF Expression and Signaling

BDNF signaling seems to be an important factor in the intracellular processes which occur following neuronal activation (i.e., activity-dependent processes) that play a role in synaptic plasticity and the regulation of dendritic morphology (Messaoudi et al. 2007; Poo 2001; Soule et al. 2006; Ying et al. 2002). BDNF acts by binding to a receptor molecule,

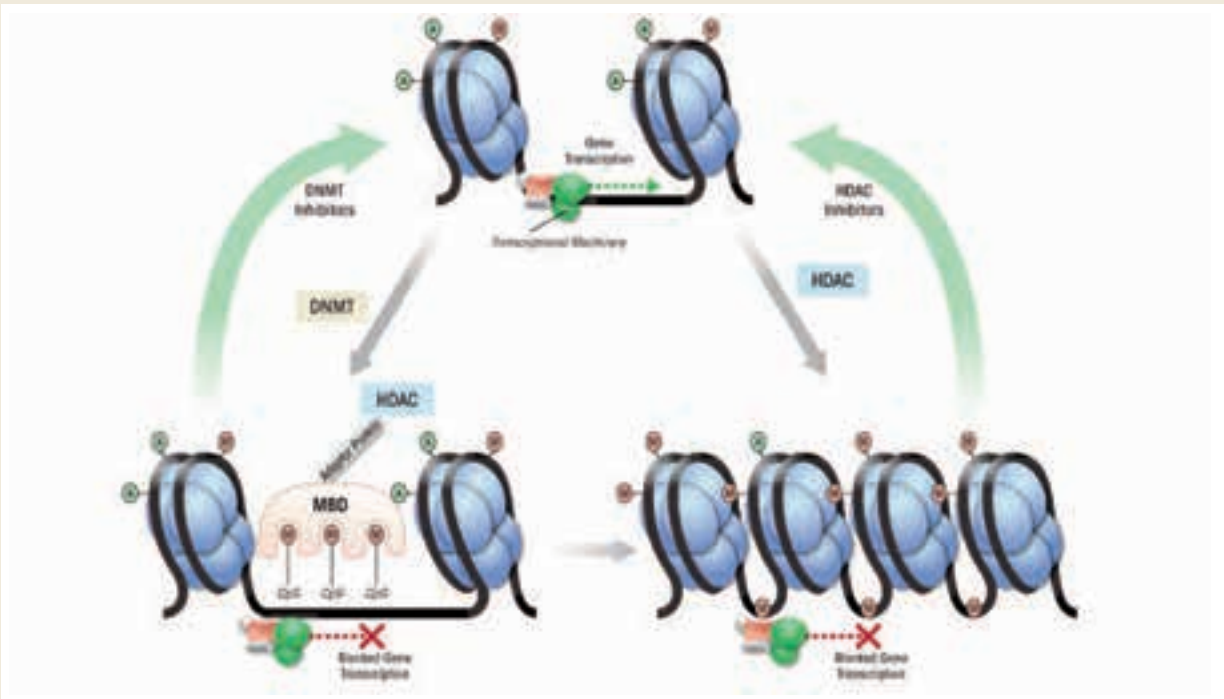

Figure 2 The coordinated actions of proteins involved in epigenetic modifications that regulate gene transcriptional processes. During the first step in the conversion of genetic information encoded in the DNA into gene products (i.e., during gene transcription), the DNA to be transcribed is associated with histone proteins (light blue) that are modified by the addition of acetyl groups (green). This modification results in a relaxed chromatin configuration that allows the transcriptional machinery access to the DNA. Enzymes, DNA methyltransferases (DNMTs), can add methyl groups (red) to the DNA at certain sequences of DNA building blocks (i.e., CpG islands). This methylation causes recruitment of methyl binding domain (MBD) protein complexes that also include repressor proteins, such as histone deacetylases (HDAC). The HDACs remove acetyl groups from histone proteins, resulting in a condensed chromatin that limits the binding of the transcriptional machinery, thereby decreasing gene transcription. Thus, activation of both DNMT and HDAC causes a reduction in gene transcription. Treatment with DNMT inhibitors and HDAC inhibitors may block these enzymatic processes and return the chromatin to a relaxed state, allowing gene transcription.

tyrosine kinase B (TrkB), which can phosphorylate other proteins as well as itself. The interaction of TrkB with BDNF results in dimerization and autophosphorylation of the receptor (Minichiello 2009; Reichardt 2006). When the TrkB receptor becomes phosphorylated, it can bind to "adaptor molecules" that then can initiate three primary intracellular signaling cascades (Impey et al. 1999; Minichiello 2009; Reichardt 2006):

- The MAPK pathway;
- The phospatidylinositol 3-kinase (PI3K) pathway; and
- The phospholipase Cγ (PLCγ) pathway.

The activation of these cascades, particularly the MAPK pathway, ultimately results in the recruitment and phosphorylation of two transcription factors, CREB and Elk-1, which in turn enhance the expression of a gene, *activity-regulated cytoskeleton-associated* (*Arc*) immediate-early gene,[1] (see figure 3) (Bramham et al. 2008; Pandey et al. 2008*b*; Ramanan et al. 2005; Ying et al. 2002). Arc protein plays a role in the induction of a process, long-term potentiation, and is believed to result in the proliferation of dendritic spines (Huang et al. 2007; Messaoudi et al. 2007; Pandey et al. 2008*b*; Ying et al. 2002). Thus, BDNF plays an important role in the regulation of synaptic plasticity by activating TrkB-coupled signaling and causing induction of *Arc* immediate-early gene.

BDNF is a member of the neurotrophin family whose activity is governed by complex regulatory mechanisms at the transcriptional, translational, and posttranslational levels of gene expression.[2] The gene encoding BDNF has a complex structure that allows for dynamic control over the expression of the gene region that encodes the actual BDNF protein by allowing for differential regulation of transcription via a wide variety of signaling and epigenetic mechanisms (Aid et al. 2007; Tao et al. 1998; Tsankova et al. 2004). For example, several regulatory elements (i.e., promoters) control *BDNF* transcription, with certain promoters active only in certain cells. As a result, several distinct *BDNF* transcripts (i.e., messenger RNAs [mRNAs]) can be generated that differ in the tissues and cells where they are produced; for example, certain *BDNF* mRNAs specifically are targeted to the neuronal dendrites (Aid et al. 2007; An et al. 2008; Greenberg et al. 2009; Timmusk et al. 1993). Specific *BDNF* transcripts also seem to be differentially regulated by activity-dependent processes. For example, some *BDNF* transcripts are regulated by the CREB transcription factor, and transcription of the same *BDNF* mRNAs is increased after consolidation of fear learning (Lubin et al. 2008; Ou and Gean 2007; Tao et al. 1998). In this manner, BDNF expression is regulated by CREB and, in turn, BDNF signaling also helps modulate CREB activity (Pandey et al. 2008*b*; Pizzorusso et al. 2000; Ying et al. 2002).

Role of Epigenetic Mechanisms

Epigenetic mechanisms, specifically histone modifications and DNA methylation, regulate BDNF expression via specific promoter regions for the *BDNF* gene. Huang and colleagues (2002) demonstrated that histone acetylation resulted in enhanced BDNF expression. Specifically, the level of histone acetylation associated with *BDNF* promoter II was increased in the hippocampus, suggesting a role for chromatin remodeling in the regulation of *BDNF*. Tsankova and colleagues (2004) also showed that histone acetylation influenced hippocampal BDNF expression in a model of electroconvulsive shock therapy, demonstrating that time- and promoter-dependent changes in histone acetylation levels were associated with similar changes in BDNF expression. Other investigators subsequently found that histone modifications were involved in the regulation of BDNF expression in the striatum during chronic cocaine exposure and in the hippocampus in a model of depression induced by chronic social-defeat stress (Kumar et al. 2005; Tsankova et al. 2006). Importantly, these studies determined that specific HDAC isoforms participated in the complex process of chromatin remodeling, suggesting a therapeutic role for isoform-specific HDAC inhibitors in alcohol and drugs of abuse as well as in depression (Kumar et al. 2005; Tsankova et al. 2006; Renthal and Nestler 2008). (Another role for HDAC activity—namely, in the regulation of dendritic spines—is discussed in the textbox "Histone Deacetylation and Dendritic Spines.")

As mentioned earlier, DNA methylation can inhibit transcription indirectly, via MBDs that seem to regulate the condensation of chromatin structure and recruit HDACs and DNMTs. One of these MBDs is MeCP2, which represses gene transcription via coordinated binding of methylated DNA, HDACs, and DNMT1 (Ballestar and Wolffe 2001). MeCP2 plays a role in the activity-dependent regulation of BDNF expression in neurons. Specifically, enhanced expression of one of the BDNF variants (i.e., BDNF exon IV) following arrival of a nerve impulse in the neurons (i.e., following depolarization) was associated with increased histone acetylation, reduced DNA methylation, and reduced MeCP2 binding at the promoter for that BDNF variant. This suggests that BDNF expression is regulated dynamically by chromatin remodeling (Martinowich et al. 2003). MeCP2-dependent regulation of this BDNF variant also is involved in regulating the formation of dendritic spines (Zhou et al. 2006).

The association between MeCP2 and BDNF exon IV levels is mediated at least in part by a protein, RACK1. This protein associates with histones H3 and H4 at the *BDNF* exon IV promoter and causes MeCP2 to dissociate from the *BDNF* gene (He et al. 2010). RACK1-mediated dissociation of MeCP2 from the *BDNF* gene leads to increased histone

[1] This gene also is known as activity-regulated gene 3.1 (Arg3.1).

[2] Transcription is the first step of gene expression, in which the genetic information encoded in the DNA is copied into an intermediate molecule, mRNA. In the second step of gene expression, translation, the mRNA then serves as a template for the synthesis of the proteins that are the gene products. After translation (i.e., posttranslationally) these proteins can be modified further by the addition of certain chemical groups.

acetylation at the *BDNF* exon IV promoter and, in turn, increases BDNF expression (He et al. 2010). Other studies found that reduction of DNA methylation levels in the *BDNF* exon IV promoter region increased BDNF expression during a fear conditioning experiment (Lubin et al. 2008). Of interest, in that study BDNF exon IV expression specifically was associated with the consolidation of fear memory, whereas increases in other BDNF variants (i.e., BDNF exons I and VI) occurred with the presentation of context alone (Lubin et al. 2008).

Taken together, these findings provide evidence for the overlap between histone modifications and DNA methylation in the regulation of *BDNF* gene expression, which may be associated with activity-dependent changes in synaptic plasticity.

BDNF and Epigenetic Mechanisms in Stress and Alcoholism

BDNF and Stress

Chronic stress has been linked with shrinkage of brain tissue (i.e., neuronal atrophy) and modulation of dendritic structure in the hippocampus (McEwen 2008; Watanabe et al. 1992) and was associated with reduced BDNF levels in that brain structure (Smith et al. 1995). In addition, both acute and chronic stress may modulate BDNF levels and structural plasticity in a variety of brain areas, including the hippocampus, prefrontal cortex, and amygdala (Calabrese et al. 2009;

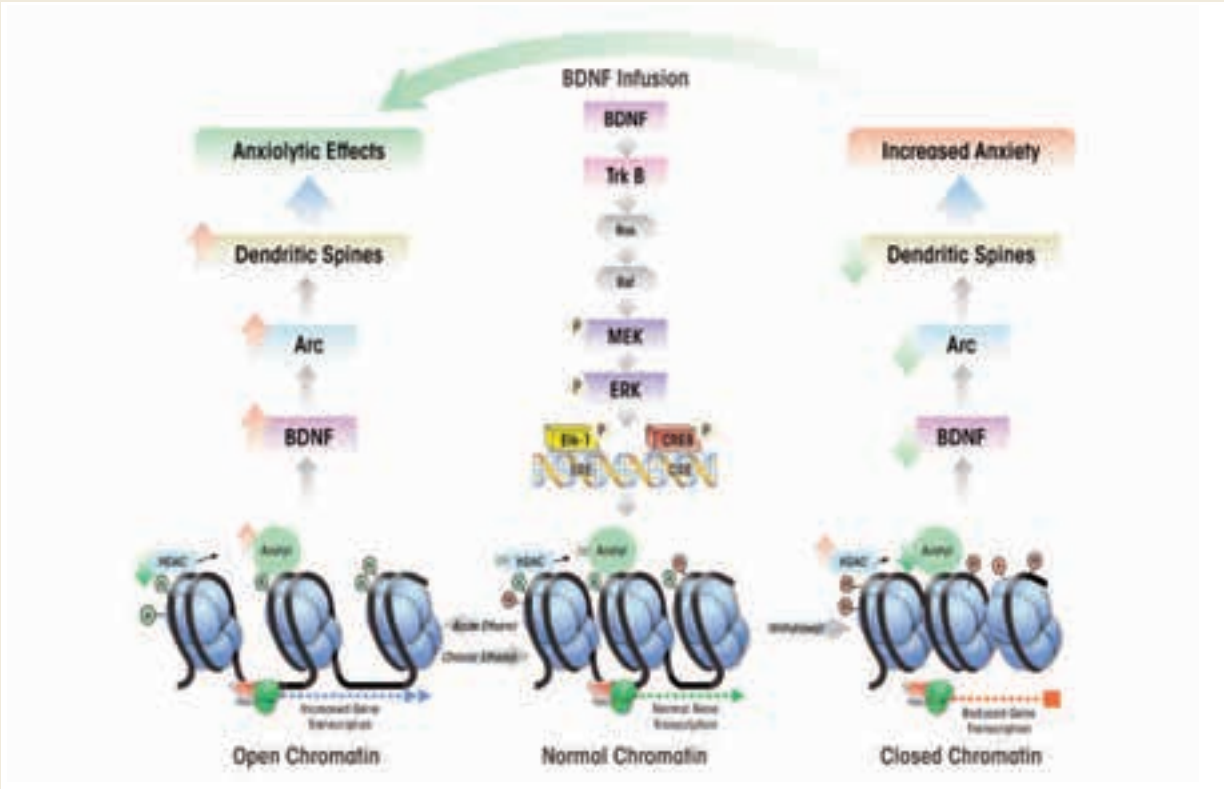

Figure 3 A hypothetical model for the role of brain-derived neurotrophic factor (BDNF) signaling and chromatin remodeling in central amygdaloid brain regions in the regulation of anxiety induced by acute ethanol and ethanol withdrawal. BDNF binding to tyrosine receptor kinase B (TrkB) triggers several signaling cascades that culminate in the activation of transcription factors, Elk-1 and cAMP-responsive element binding protein (CREB). Under normal conditions, histone deacetylase (HDAC) levels and histone acetylation are adequate to allow for normally regulated chromatin structure and gene transcription. Acute ethanol exposure inhibits HDAC, resulting in increased histone acetylation and an open chromatin conformation. This may lead to increased transcription of BDNF as well as higher levels of a protein, activity-regulated cytoskeleton associated protein (Arc), thereby increasing dendritic spine density. The modulation of these synaptic factors results in anxiety-reducing (i.e., anxiolytic) behavioral effects. In contrast during withdrawal from chronic ethanol exposure HDAC activity increases, resulting in a reduction of histone acetylation that in turn closes the chromatin conformation and reduces gene transcription. The resulting low BDNF levels decrease Arc and dendritic spine density, all of which are associated with anxiety-like behaviors. This model is further supported by the fact that exogenous infusion of BDNF into the CeA reduces anxiety-like behaviors in ethanol withdrawn rats and is associated with increased BDNF and Arc levels (Moonat et al. 2010; Pandey et al. 2008*a*, 2008*b*).

McEwen 2008; Pizarro et al. 2004). In the hippocampus, acute stress caused by immobilization as well as swim stress increased the levels of *BDNF* mRNA. This increase was associated with increased MeCP2 phosphorylation, suggesting that epigenetic mechanisms help mediate the effects of acute stress (Marmigere et al. 2003; Molteni et al. 2009). Increased BDNF expression may represent a protective mechanism in response to stress; conversely, reduced BDNF levels after exposure to repetitive and chronic stress appear to represent a dysregulation of this mechanism (Calabrese et al. 2009; McEwen 2008). This assumption is supported by findings that the antidepressant effects of medications used in chronic-stress models of depression are mediated by an increase in BDNF levels in the hippocampus (Nibuya et al. 1995; Shirayama et al. 2002; Tsankova et al. 2006). It also is interesting to note that low BDNF levels in the CeA and MeA mediate anxiety-like behaviors, and the anxiety-reducing (i.e., anxiolytic) effects of alcohol may be associated with an increase in BDNF signaling (Moonat et al. 2011; Pandey et al. 2006, 2008*b*). These observations clearly suggest that aberrations of BDNF signaling contribute to the development of stress-related dysphoric behaviors, and the BDNF signaling pathway therefore may be a promising potential therapeutic target for treatment of these disorders.

Role of Chromatin Remodeling. Researchers recently also have begun to investigate the role of chromatin remodeling in BDNF signaling associated with stress-related dysphoria. Using a model of depression induced by chronic stress, Tsankova and colleagues (2006) found that the levels of the *BDNF* exon IV and exon VI were reduced in the hippocampus and that this effect could be blocked by chronic antidepressant treatment (Tsankova et al. 2006). Further analyses found that this effect likely was associated with changes in histone methylation because chronic stress increased the levels of methylated histone H3 protein near the *BDNF* exons IV and VI promoters, which interferes with *BDNF* transcription. Conversely, treatment with antidepressants reduced the levels of histone methylation and increased the levels of acetylated H3 associated with these *BDNF* promoters, thereby increasing BDNF expression. Simultaneously, antidepressant treatment reduced the expression of HDAC5, but when the levels of HDAC5 were elevated through genetic engineering, the effects of antidepressant treatment were reduced (Tsankova et al. 2006).

The levels of several HDACs in the NAc also may influence the development of stress-related dysphoria. In contrast to the hippocampus, HDAC2 and HDAC5 levels in the NAc were reduced by chronic stress, suggesting opposing roles for histone modifications in the hippocampus and NAc in stress-related dysphoria (Renthal et al. 2007). Interestingly, systemic treatment with HDAC inhibitors or infusion of HDAC inhibitors into the NAc reduced stress-related dysphoria (Covington et al. 2009; Tsankova et al. 2006). Taken together, all these results suggest that histone modifications may be involved in the regulation of BDNF in stress-related dysphoria and the therapeutic effects of antidepressants.

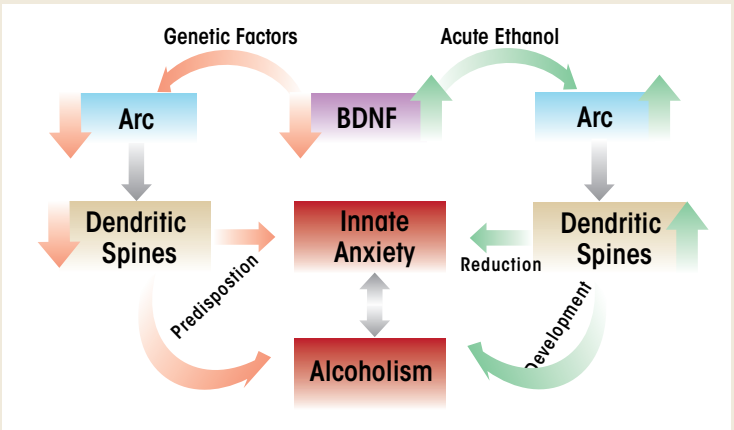

Figure 4 A hypothetical model for the role of amygdaloid brain-derived neurotrophic factor (BDNF) in the regulation of activity-regulated cytoskeleton-associated protein (Arc) and dendritic spine density in the comorbidity between innate anxiety and alcohol preference. Genetic factors may lead to innately low levels of amygdaloid BDNF that result in reduced Arc and dendritic spine density and which are associated with a predisposition to innate anxiety-like behaviors. Acute ethanol exposure increases BDNF signaling and associated synaptic factors, Arc, and dendritic spine density and results in a reduction of innate anxiety. Taken together, innate anxiety and a reduction of this anxiety by acute ethanol may be responsible for the development of alcoholism (Moonat et al. 2011).

Role of DNA Methylation. DNA methylation also plays a role in the development of stress-related dysphoria as well as synaptic plasticity in the NAc. Specifically, chronic stress increased expression of one DNA methyltransferase, DNMT3a, in the NAc, which was associated with an increase in depressive-like behavior (LaPlant et al. 2010). Infusion of a DNMT inhibitor into the NAc of chronically stressed animals reduced these observed behaviors. Conversely, overexpression of DNMT3a in the NAc precipitated a depression-like phenotype in animals that had not been exposed to stress. DNMT3a overexpression also resulted in the proliferation of dendritic spines (LaPlant et al. 2010). These results indicate that DNMT3a may contribute to stress-related dysphoria and control of dendritic spine structure. It would be interesting to expand upon these results and determine if a link exists between stress-associated changes in DNMT3a and methylation of the *BDNF* gene and alcoholism.

BDNF, Stress, and Alcoholism

Various researchers have explored the association of BDNF with ethanol preference, the effects of ethanol exposure, and dysphoric states associated with withdrawal from chronic ethanol exposure. BDNF deficits may lead to an increased preference for ethanol, because transgenic animals with reduced BDNF expression have a higher ethanol preference and conditioned place preference for ethanol compared with wild-type control animals (Hensler et al. 2003; McGough et al. 2004). Furthermore, ethanol exposure results in increased BDNF expression in the dorsal striatum. This increase involved a regulatory mechanism mediated by RACK1 because exogenous increases in RACK1 led to increased BDNF expression, resulting in reduced ethanol consumption (McGough et al. 2004). These findings suggest that BDNF in the dorsal striatum helps regulate neuronal homeostasis and prevent alcohol addiction (McGough et al. 2004). In addition, endogenous BDNF signaling in the dorsolateral striatum participates in the regulation of ethanol intake (Jeanblanc et al. 2009). Because, as mentioned earlier, MeCP2 is involved in the RACK1-mediated regulation of BDNF (He et al. 2010), future studies should determine whether chromatin remodeling affects BDNF expression in the dorsal striatum and, ultimately, ethanol's effects and ethanol preference.

Various studies have examined how BDNF impacts the interaction between alcohol preference and anxiety. For example, Pandey and colleagues (2006) reduced BDNF levels in the extended amygdala by introducing small molecules that can inhibit BDNF expression (i.e., antisense oligodeoxynucleotides) into the CeA or MeA. This caused increased voluntary ethanol intake and anxiety-like behaviors. The low BDNF levels resulted in reduced BDNF signaling, as evidenced by decreased levels of the phosphorylated forms of CREB and another regulatory molecule (Pandey et al. 2006). Both the effects on behavior and protein phosphorylation were reversed when BDNF was introduced together with the antisense oligonucleotides (Pandey et al. 2006). Additional studies identified a subsequent step in the signaling cascade induced by BDNF involving the Arc protein mentioned earlier. The findings suggested that the effects of reduced amygdaloid BDNF expression on ethanol preference and anxiety-like behaviors may be mediated by the downstream regulation of Arc (Pandey et al. 2008*b*). These behavioral changes were accompanied by a reduction in dendritic spine density in the CeA.

In an extension of these findings, investigators used an animal model of genetic predisposition to alcoholism and anxiety (i.e., selectively-bred alcohol-preferring [P] and nonpreferring [NP] rats) to study the role of BDNF in the extended amygdala. The studies found that compared with NP rats, P rats expressed lower levels of BDNF and Arc and had lower dendritic spine density in the CeA and MeA and that these characteristics were associated with high innate anxiety-like behaviors (Moonat et al. 2011; Prakash et al. 2008). Furthermore, acute ethanol exposure had anxiolytic effects that were associated with increased BDNF and Arc levels as well as increased dendritic spine density in the CeA and MeA in P rats, but not in NP rats (Moonat et al. 2011). These findings were consistent with earlier findings in Sprague-Dawley rats, which showed that increases in BDNF–Arc signaling and dendritic spine density in the extended amygdala were associated with the anxiolytic effects of acute ethanol (Pandey et al. 2008*b*). Withdrawal from chronic ethanol exposure provoked anxiety-like behaviors, which resulted in reduced BDNF signaling in the CeA and MeA, whereas BDNF infusion into the CeA normalized Arc levels and prevented anxiety-like behaviors (Pandey et al. 2008*b*). Taken together, these studies suggest that reduced BDNF–Arc signaling and synaptic plasticity contribute to both dysphoria associated with a genetic vulnerability for anxiety and to anxiety induced by environmental stressors, such as alcohol withdrawal (see figures 3 and 4).

Recent findings further suggest that the anxiolytic effects of acute ethanol exposure are associated with reduced HDAC activity and increased histone acetylation in the CeA and MeA (Pandey et al. 2008*a*). Conversely, withdrawal-induced anxiety following chronic ethanol treatment was linked with increased HDAC activity levels and reduced histone acetylation in these amygdaloid brain regions (see figure 3). Systemic administration of an agent that inhibits HDAC activity (i.e., trichostatin A) reduced the effects of withdrawal on histone acetylation and anxiety-like behaviors (Pandey et al. 2008*a*). Thus, treatment with HDAC inhibitors appears to have similar effects on withdrawal-induced anxiety as BDNF, and acute ethanol exposure may have similar effects on histone acetylation and BDNF levels (Pandey et al. 2008*a*, 2008*b*). Therefore, it may be important to study the potential regulation of amygdaloid BDNF by chromatin remodeling and its role in dysphoria associated with the development of alcoholism. Similarly, it may be interesting to explore the possibility that innate abnormalities in chromatin structure may affect BDNF levels, resulting in innate anxiety-like behaviors, such as those demonstrated by P rats, that may be critical to the development of alcoholism.

Conclusions

The studies reviewed here suggest that the reduction of BDNF levels may play a role in the neuroadaptation to repetitive or chronic exposure to alcohol or stress and the development of dysphoric states. Moreover, it appears that abnormalities in BDNF signaling serve as predisposing factors to innate dysphoric states that may associated with alcohol-drinking behaviors, such as anxiety (see figure 4). It also is possible that the environmental effects and genetic factors involved in an increased vulnerability to stress and alcoholism may be related to a common epigenetic mechanism that results in the dysregulation of BDNF signaling in various brain regions. Future studies are necessary to further evaluate the role of specific HDAC and DNMT variants that are involved in the epigenetic regulation of BDNF or other genes associated with synaptic plasticity during the development of pathological

behaviors associated with stress and alcohol addiction. Finally, the development and assessment of specific pharmacological agents that act via epigenetic mechanisms, such as HDAC and DNMT inhibitors, could have a significant psychotherapeutic impact on the development of stress-related disorders and the comorbidity with alcoholism. ■

Acknowledgements

The work described here from the laboratory of Dr. Subhash Pandey was supported by National Institute on Alcohol Abuse and Alcoholism grants AA-016690, AA-019971, AA-010005, and AA-013341 and by the Department of Veterans Affairs (Merit Review Grant; Research Career Scientist award).

Financial Disclosure

The authors declare that they have no competing financial interests.

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Genetic and Environmental Determinants of Stress Responding

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The risk for alcohol dependence throughout development is determined by both genetic and environmental factors. Genetic factors that are thought to modulate this risk act on neurobiological pathways regulating reward, impulsivity, and stress responses. For example, genetic variations in pathways using the brain signaling molecule (i.e., neurotransmitter) dopamine, which likely mediate alcohol's rewarding effects, and in two hormonal systems involved in the stress response (i.e., the hypothalamic–pituitary–adrenal axis and the corticotropin-releasing factor system) affect alcoholism risk. This liability is modified further by exposure to environmental risk factors, such as environmental stress and alcohol use itself, and the effects of these factors may be enhanced in genetically vulnerable individuals. The transition from alcohol use to dependence is the result of complex interactions of genes, environment, and neurobiology, which fluctuate throughout development. Therefore, the relevant genetic and environmental risk factors may differ during the different stages of alcohol initiation, abuse, and dependence. The complex interaction of these factors is yet to be fully elucidated, and translational studies, ranging from animal studies to research in humans, and well-characterized longitudinal studies are necessary to further understand the development of alcohol dependence. **KEY WORDS: Alcohol dependence; alcoholism; alcohol use and abuse; alcohol and other drug use initiation; risk factors; genetic factors; environmental factors; stress; stress response; neurobiology; biological development; brain; hypothalamic–pituitary–adrenal axis; corticotropin-releasing factor system; animal studies; human studies; literature review**

The development of alcohol dependence is a complex process influenced by both genetic and environmental risk factors (Prescott and Kendler 1999). The relative contributions of genetic and environmental influences fluctuate across development. During adolescence the initiation of alcohol use is strongly influenced by environmental factors (Dick et al. 2007; Heath et al. 1997; Karvonen 1995; Latendresse et al. 2008; McGue et al. 2000), whereas the genetic contribution to alcohol use at this stage is nonspecific and increases the risk for general externalizing behavior (Moffitt 1993; Moffitt et al. 2002). Specific genetic factors increasingly become relevant, however, as patterns of alcohol use are established (Hopfer et al. 2003; Pagan et al. 2006), particularly in mid-adulthood when dependence tends to emerge (Kendler et al. 2010; Schuckit et al. 1995). Gene–environment interactions also play a role because the influence of certain genetic factors seems to increase when a person is exposed to relevant environmental risk factors (Uhart and Wand 2009). Therefore, the development of dependence can be conceptualized within a temporal framework of genes, environment, and behavior.

The purpose of this review is to explore, within this framework, the contribution of some of the neurobiological systems that are important for the development of alcohol dependence. One of these is the mesolimbic dopaminergic system, which is involved in inducing the rewarding effects of alcohol and plays a central role in early alcohol use. Another pathway that also has been implicated in alcohol abuse, and particularly in the transition to alcohol dependence, involves two stress-response systems, the hypothalamic–pituitary–adrenal (HPA) axis and the extrahypothalamic corticotropin-releasing factor (CRF) stress response system, which mediate the interaction of psychosocial stress and early alcohol use. Both of these systems exemplify how the effects of genes and environment may be augmented during critical periods of alcohol use and dependence across the lifespan. For example, the dopaminergic system undergoes developmental transformations during adolescence that are associated with increased reward sensitivity and risk taking (Spear 2000), which presents a window of vulnerability for exposure to alcohol and stress. Then, as alcohol use continues through life, chronic exposure to alcohol can enhance the activity of (i.e., upregulate) the HPA and CRF systems. This dysregulation of the stress response systems

becomes a pathological feature of alcohol dependence, perpetuating chronic alcohol drinking based on an allostatic shift[1] of the CRF system (Koob 2010). Moreover, the HPA, CRF, and dopaminergic systems can influence early alcohol drinking as a result of gene–environment interactions. This article will summarize the literature that has explored how genetic variation within the dopaminergic and stress response systems can influence the risk of alcohol dependence and how the exposure to relevant environmental risk factors and their interaction with genetic variants may influence alcoholism pathology. The effects of genes and environment on alcohol dependence will be discussed in a developmental framework from early childhood to adolescence as well as in the context of the development of dependence, when drinking behavior shifts from recreational use to dependence.

Role of Dopaminergic and Stress Response Systems in Alcohol Initiation and Early Alcohol Use

Environmental Factors and the Dopaminergic System

Several environmental factors have been shown to influence the initiation of alcohol consumption and its use during adolescence, including the level and quality of parental monitoring, peer-group influences, alcohol availability, and socioregional effects (Dick et al. 2007; Heath et al. 1997; Karvonen 1995; Latendresse et al. 2008; McGue et al. 2000). Thus, maternal and paternal alcohol use has been positively correlated with adolescent alcohol use at ages 14 and 17 (Latendresse et al. 2008). Moreover, the level of urbanization was found to correlate with alcohol use in Finnish adolescents at ages 16 and 18 (Karvonen 1995), and peer-group drinking behavior was one of the strongest predictors of problematic drinking in a cohort of Spanish adolescents (Ariza Cardenal and Nebot Adell 2000).

Once alcohol use has been initiated, neuronal networks are activated that engage the brain circuits mediating the rewarding effects of alcohol use (i.e., the reward neurocircuitry). This activation attributes salience to alcohol and serves as an incentive for alcohol use to continue (Robinson and Berridge 1993). Neuronal networks that are known to mediate these effects include those using the signaling molecules (i.e., neurotransmitters) glutamate and γ-aminobutyric acid (GABA) as well as the endogenous opioids (Gass and Olive 2008; Malcolm 2003; Oswald and Wand 2004). In addition, signal transmission involving the neurotransmitter dopamine in the mesolimbic system (Di Chiara and Imperato 1988) is particularly important for the establishment of regular alcohol consumption because alcohol-induced dopamine release is believed to contribute to the rewarding effects of alcohol (for reviews see, Soderpalm et al. 2009; Tupala and Tiihonen 2004). The mesolimbic system is a set of interconnected brain structures including the ventral tegmental area (VTA), nucleus accumbens (NAc), and components of the limbic system (e.g., the amygdala). Studies in rats found that alcohol consumption can increase dopamine signaling in the NAc (Weiss et al. 1996). Conversely, dopaminergic neurotransmission is decreased during withdrawal in the NAc and VTA of rats treated chronically with ethanol (Diana et al. 1993).

Environmental risk factors during early life and adolescence may interact with the dopaminergic system to influence alcohol intake. Two such factors are exposure to environmental stress and alcohol consumption itself. The developing adolescent brain undergoes substantial changes in the strength with which signals are transmitted between neurons (i.e., in synaptic plasticity) (Bava and Tapert 2010; Giedd 2003). These changes include increased dopaminergic inputs to the prefrontal cortex that peak during adolescence and decrease later in life (Kalsbeek et al. 1988; Rosenberg and Lewis 1994). Furthermore, dopamine levels in the NAc also peak during adolescence, before decreasing during subsequent brain maturation (Philpot and Kirstein 2004). These neuronal alterations are believed to promote sensation-seeking and risk-taking behavior during adolescence, which in turn increase the propensity for alcohol initiation and alcohol use (Spear 2000). Exposure to alcohol and/or stress during early life (i.e., from the prenatal period through adolescence) has been shown to have lasting consequences on the dopamine system that have a significant impact on the risk for alcohol abuse.

The Effects of Early Alcohol Use on the Dopaminergic System

Studies in rats found that exposure to alcohol during the prenatal period decreases the levels of two important enzymes involved in regulating dopamine activity—the dopamine transporter and the dopamine hydroxylase enzyme—in the VTA (Szot et al. 1999). Moreover, rats chronically treated with ethanol during adolescence displayed persistently elevated baseline dopamine levels in the NAc during adulthood, even after a period of 15 days abstinence (Badanich et al. 2007). Finally, repeated ethanol injections in preadolescent and adolescent rats increased subsequent dopamine activity in the NAc, with the largest increases observed in preadolescence. Early ethanol exposure in these rats decreased the ability of subsequent ethanol injections to elicit dopamine release from the NAc (Philpot and Kirstein 2004). These findings suggest that ethanol exposure in early life may influence the response to alcohol in later life. Indeed, additional studies have confirmed that both pre- and postnatal exposure to alcohol increase the sensitivity of rats to the locomotor effects of alcohol and to an agent that mimics dopamine's effects (i.e., a dopamine agonist), apomorphine

[1] The term allostasis refers to the process through which various biological processes attempt to restore the body's internal balance (i.e., homeostasis) when an organism is threatened by various types of stress in the internal or external environment. Allostatic responses can involve alterations in HPA axis function, the nervous system, various signaling molecules in the body, or other systems.

(Barbier et al. 2009). Therefore, at least in rodents, early alcohol exposure seems to confer lasting effects on neuronal dopamine activity that can alter behavioral responses to subsequent alcohol exposure. Indeed, rats chronically treated with ethanol both prenatally and during adolescence also show an increased preference for alcohol and increased alcohol intake as adults (Barbier et al. 2009; Pascual et al. 2009). Furthermore, stress-induced alcohol consumption was associated with an earlier age of drinking onset in Wistar rats (Fullgrabe et al. 2007; Siegmund et al. 2005).

Studies in humans have confirmed the potential long-lasting impact of early alcohol exposure, demonstrating that an early initiation of alcohol use is associated with an increased risk of later problems with alcohol. For example, Hawkins and colleagues (1997) noted that the earlier drinking is initi-

The Extrahypothalamic Corticotropin-Releasing Factor System and the Transition to Alcohol Dependence

As described in the main article, corticotropin-releasing factor (CRF) is a key component of one of the body's main stress response systems, the hypothalamic–pituitary–adrenal (HPA) axis. Moreover, activation of the HPA axis in response to stressful situations as well as alcohol ingestion plays an important role in the development of alcohol dependence. However, studies in rodents and macaques have shown that enhanced activity (i.e., upregulation) of the CRF system in response to chronic alcohol exposure in several brain regions not immediately related to the HPA system (e.g., the amygdala) also is a key characteristic of alcohol dependence. CRF is an anxiety-inducing peptide, and rodent models of motivation have demonstrated that CRF, administered either directly into the brain or under the skin, induces conditioned place aversion (Cador et al. 1992). In addition, studies in mice found that transient elevation of CRF levels in the forebrain during early development increased anxiety in later life compared with control animals (Kolber et al. 2010).

Studies of a rat strain bred for high alcohol preference (i.e., the mSP rats) found that the animals display an increased behavioral sensitivity to stress and a lowered threshold for stress-induced reinstatement of alcohol-seeking behavior (Hansson et al. 2006). Gene expression analyses across different brain regions of the mSP strain revealed a significantly enhanced expression of a gene, *CRF1,* which encodes one of the CRF receptors. Additional gene sequence analyses of the mSP rats identified a DNA variation (i.e., polymorphism) in a regulatory region (i.e., the promoter) of the *CRF1* gene that is unique to the mSP rats, suggesting that segregation of this polymorphism may have occurred during selection for the alcohol preference trait. However, alcohol consumption reduced CRF1 levels in the amygdala and the nucleus accumbens (NAc) in mSP rats, indicating that the animals may consume alcohol to reduce CRF activity in these regions (Hansson et al. 2007).

Studies in *Rhesus* macaques also have confirmed the link between the CRF system, stress, and alcohol because a polymorphism (–248C/T) in the promoter of the CRF gene was associated with differential behavioral and hormonal responses to stress. Animals that carried the T allele DNA variant at this site displayed greater HPA axis responses to separation stress and increased alcohol intake if they were exposed to early-life adversity in the form of peer rearing (Barr et al. 2009). These findings demonstrate that genetic variation in the CRF system associated with increased sensitivity to stressors also is correlated with increased alcohol consumption in both rats and primates. Because alcohol consumption is known to reduce the activity of the HPA axis, hyperactivity of this system in animals carrying risk variants of the CRF gene likely is a motivating factor for alcohol consumption in these animals, and this effect is enhanced when the animals are exposed to stressors.

Animal studies also have demonstrated that agents that block the activity of the CRF1 receptor (i.e., CRF1 antagonists) may be suitable for treatment of alcohol dependence (Gehlert et al. 2007). Although animals do not exhibit all aspects of alcohol dependence found in humans, certain components of the disorder can be modeled in rodents. Thus, researchers induced a "postdependent state" in rats by first subjecting the animals to involuntary intermittent exposure to alcohol vapor and then allowing them 3 weeks of recovery from the exposure (Sommer et al. 2008). After this recovery period, the animals displayed increased CRF1 levels in the amygdala, comparable to those observed in mSP rats at baseline. In addition, the postdependent animals exhibited increased fear suppression of behavior that persisted for 3 months after cessation of alcohol exposure, as well as increased voluntary alcohol consumption. This postdependent phenotype could be reversed by a CRF1 antagonist, 3-(4-chloro-2-morpholin-4-yl-thiazol-5-yl)-8-(1-ethylpropyl)-2,6-dimethyl-

ated in adolescence, the greater the levels of alcohol misuse at ages 17 to 18. Furthermore, people who begin drinking at age 14 or younger are more likely to become alcohol dependent later in life (Grant and Dawson 1997). Few studies have been conducted to determine the precise mechanism by which early alcohol exposure affects the risk for subsequent alcohol abuse and dependence. However, Pascual and colleagues (2009) demonstrated that in adolescent rats chronically treated with ethanol, two neurotransmitter receptors—dopamine receptor 2 (DRD2) and glutamate receptor (NMDAR2B)—show lower levels of a chemical modification (i.e., phosphorylation) in the prefrontal cortex compared with adults chronically treated with ethanol. This finding suggests that alcohol use during adolescence causes neurobiological changes to the dopamine system that are not observed in adult animals.

imidazo[1,2-b]pyridazine (MTIP) (Funk et al. 2006; Sommer et al. 2008), confirming the role of increased CRF activity during alcohol dependence. Other studies also demonstrated that selective CRF1 antagonists reduced alcohol self-administration in alcohol-dependent animals but had no effect in alcohol-naïve animals (Funk et al. 2006, 2007). The exposure to stress, which often triggers relapse in abstaining alcoholics, also reinstates alcohol-seeking behavior in postdependent animals. CRF1 antagonists can suppress this behavior in animals (Le et al. 2000; Liu and Weiss 2002; Marinelli et al. 2007), further confirming their relevance as a potential pharmacotherapy for alcohol dependence. Finally, CRF1 antagonists can block the anxiety-like responses exhibited during withdrawal from alcohol in animals (Breese et al. 2005).

The potential of CRF1 antagonists in the treatment of alcohol dependence now also is being considered in humans. CRF1 antagonists previously have been assessed in the treatment of depression and anxiety (Zobel et al. 2000) and Phase II/Phase III clinical trials with these agents currently are underway for the treatment of alcohol use disorders (www.clinicaltrials.gov; Zorrilla and Koob 2010). The results of these trials may pave the way for the clinical consideration of CRF1 antagonists for addictive disorders. If such compounds are efficacious in humans, pharmacogenetic studies may identify those patients who are most amenable to CRF1 antagonist treatment, especially among those who are exposed to high levels of lifetime stress.

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The Effects of Environmental Stress on the Dopaminergic System

Environmental stress is one of the most pertinent risk factors for alcohol dependence. The exposure to early-life stress sensitizes animals to drugs of abuse (Fahlke et al. 1994; Piazza et al. 1991; Shaham and Stewart 1994) and also increases alcohol consumption in later life (Fahlke et al. 2000). Alterations in the dopaminergic mesolimbic system that persist into adulthood are believed to explain, at least in part, these behavioral adaptations (for review, see Rodrigues et al. 2011). For example, studies in rats found that chronic exposure to cold stress in adolescence altered both basal and stress-evoked release of dopamine and another neurotransmitter, norepinephrine,[2] in the medial prefrontal cortex, NAc, and striatum compared with stress-naïve rats (Gresch et al. 1994). Other studies in Sprague-Dawley rats demonstrated that stress caused by separation from the mother during the first 2 weeks of life blunted the animals' dopamine response to restraint stress in adulthood (Jahng et al. 2010). Although no human studies analyzing the effect of early-life stress and alcohol sensitization exist, imaging studies using functional magnetic resonance imaging (fMRI) to analyze reward anticipation have found that childhood adversity is associated with blunted subjective responses to reward-predicting cues as well as with impaired reward-related learning and motivation (Dillon et al. 2009). Such findings demonstrate that early environmental experiences can alter the impact of a reward and that similar effects can be observed across species.

Other studies have evaluated the effects of early-life stress on alcohol consumption or alcohol dependence. Such studies found that even exposure to prenatal stress can have an impact on later alcohol-related behaviors because the offspring of mice that repeatedly were restrained during the last 7 days of gestation subsequently demonstrated enhanced alcohol consumption—an effect that has been linked to persistently elevated dopaminergic and glutamatergic neurotransmission in the forebrain (Campbell et al. 2009). In humans, retrospective studies examining early-life experiences and alcohol consumption found that childhood stressors were associated with alcohol dependence during adulthood (Ducci et al. 2009; Pilowsky et al. 2009). In a study of the adult American population (i.e., the National Epidemiologic Survey on Alcohol and Related Conditions [NESARC]), two or more stressful life events in childhood significantly increased the risk for alcohol dependence in adulthood (Pilowsky et al. 2009). Furthermore, early initiation of alcohol use in human adolescents is associated with exposure to traumatic life events and symptoms of posttraumatic stress disorder (Wu et al. 2010).

Thus, exposure to stress and/or alcohol consumption during early life may influence dopaminergic neurotransmission, with lasting adaptations into adulthood and notable consequences for subsequent alcohol use. However, the impact on different individuals varies, and a portion of this variability can be attributed to genetic factors. Indeed, studies of rats have shown that exposure to chronic unpredictable stress increases the levels of a dopamine-metabolizing enzyme, tyrosine hydroxylase (TH), in the VTA but that the extent of this increase differs drastically between different rat strains (Ortiz et al. 1996). Additional research in *Rhesus macaques* identified a variation (i.e., polymorphism) in the gene encoding dopamine receptor 1 (DRD1)[3] that was associated with increased alcohol consumption in animals exposed to peer-rearing conditions compared with maternally reared animals that carried the same polymorphism (Newman et al. 2009).

Studies in humans also have shown that genetic factors mediate the effects of stress and alcohol on the risk for alcohol dependence. Schmid and colleagues (2009) analyzed 291 young adults in the Mannheim Study of Children at Risk for two polymorphisms in the gene encoding the dopamine transporter. The investigators found that the age of first alcohol use and of intensive alcohol consumption mediated the association between these polymorphisms and early alcohol abuse and dependence. Genetic variation in another gene, *KCNJ6*, which is expressed in the brain, mediates the effects of early-life stress on alcohol abuse in adolescence. It induces inhibition of neuronal signaling at the level of the signal-receiving (i.e., postsynaptic) dopaminergic neurons (Kuzhikandathil et al. 1998). Furthermore, the protein encoded by the *KCNJ6* gene, the membrane potasium channel GIRK2, is co-expressed in TH-positive cells of mice (Schein et al. 1998). Individuals who carry a certain *KCNJ6* variant and are exposed to high levels of psychosocial stress in early life display increased risky drinking behavior in adolescence; moreover, the same polymorphism is associated with alcohol dependence in adults (Clarke et al. 2011).

Genes in other neurobiological systems also mediate the effects of early-life stress on alcohol consumption, including genes encoding the serotonin receptor (Laucht et al. 2009) and the GABA receptor subunit α-2 (*GABRA2*) (Enoch et al. 2010). Another important gene is that encoding the μ-opioid receptor (*OPRM1)*. It also moderates the effects of stress and alcohol with implications not only for alcohol use but also for recovery from alcohol dependence. Alcohol activates the μ-opioid receptor in the VTA, which causes inhibition of GABAergic neurons; this in turn results in disinhibition of dopaminergic neurons and, thus, increased dopamine release in the ventral striatum (Spanagel 2009). In macaques, a certain polymorphism in the *OPRM1* gene (i.e., the C77G polymorphism) predicts the degree of distress upon exposure to maternal separation (Barr et al. 2008). In humans, the equivalent polymorphism (i.e., the A118G polymorphism) is associated

[2] Norepinephrine also is known as noradrenaline.

[3] The variation was located at the beginning of the gene, in a DNA region that did not encode a part of the final protein (i.e., in the 5′ untranslated region of the gene).

with the quality of parent–child interactions under conditions of poor parenting (Copeland et al. 2011). Finally, in both macaques and humans the same polymorphisms are associated with subjective/behavioral responses to alcohol (Barr et al. 2007, 2008; Ramchandani et al. 2010). The role of this polymorphism further has been demonstrated in studies using a μ-opioid receptor antagonist, naltrexone, that commonly is used to treat alcohol dependence. In heavy drinkers, the A118G polymorphism mediates the effects of naltrexone on positive mood, craving, and enjoyment from alcohol (Ray and Hutchison 2004). Furthermore, the presence or absence of the A118G polymorphism can help predict which individuals will benefit from naltrexone treatment for alcohol dependence (Oslin et al. 2003).

Taken together, the findings described here indicate that early exposure to alcohol and stress can increase the subsequent risk for alcohol dependence, at least in part because they induce changes in the dopamine system. However, these effects are moderated by genetic factors in the dopamine pathways and other neurobiological systems.

Brain Stress Response Systems and the Development of Alcohol Dependence

As indicated by the observations discussed in the preceding section, the dopamine system is an important neurobiological system mediating early alcohol use. In addition, stress response systems in the brain have been implicated in alcohol initiation and in the escalation of alcohol use from episodic use to abuse and, ultimately, dependence. Stress responses are crucial for survival by allowing the organism to coordinate appropriate behavioral adaptations to adverse stimuli and are essential homeostatic processes. Central components of the stress response include activation of the HPA axis, increases in norepinephrine turnover in a brain region, the locus coeruleus, and activation of CRF systems (Habib et al. 2001). CRF acts through two pathways. First, it acts as a signaling hormone inside the HPA axis, where it is released from the paraventricular nucleus of the

The IMAGEN Study

The IMAGEN study (www.imagen-europe.com) is the first study aimed at identifying the genetic and neurobiological basis of individual variability in impulsivity, reinforcer sensitivity, and emotional reactivity, as well as determining their predictive value for the development of common psychiatric disorders. The data collection of IMAGEN began in 2007. Since then, the study has collected comprehensive behavioral and neuropsychological data, as well as functional/structural neuroimaging data for 2,000 14-year-old adolescents. These data are complemented by genome-wide association (GWA) data on the study participants. These genetic analyses target approximately 600,000 DNA markers distributed across the genome, using the Illumina Quad 660 chip.

Data from the first wave of IMAGEN became available in 2010 in an extensive database (Schumann et al. 2010), and since then several articles have been published on the dataset, contributing toward a greater understanding of the adolescent brain. For example, Peters and colleagues (2010) showed that adolescent smokers display lower activation of the ventral striatum during reward anticipation compared to their nonsmoking peers. Other studies identified gender-dependent amygdala lateralization during face processing and created probabilistic maps of the face network in the adolescent brain (Schneider et al. 2010; Tahmasebi et al. 2010).

The sample will be followed up at age 16 to investigate the predictive value of genetic factors and intermediate phenotypes for the development of mental disorders, such as alcohol dependence. The full dataset from the follow-up will be completed in 2012. A second follow-up is planned to be completed when the participants reach age 18.

In conclusion, IMAGEN integrates technological and methodological advances in the field of cognitive neuroscience as well as in the fields of human and molecular genetics. This comprehensive approach, together with the large sample sizes, will provide new insights into the interplay between genes and environments that results in individual variability in brain structure, function, and psychological traits. The complex phenotypic and genotypic profiling provided by IMAGEN will be vital in identifying biomarkers that aid in earlier diagnosis and in the developments of treatments for psychiatric disorders, including alcohol dependence.

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hypothalamus. It then is transported to the anterior pituitary, where it binds to CRF receptors (CRF1 and CRF2), thereby eliciting the release of adrenocorticotrophic hormone (ACTH). ACTH production ultimately results in the release of stress hormones (i.e., glucocorticoids) from the adrenal glands. The main glucocorticoid in humans is cortisol. Second, CRF acts outside of the hypothalamus (i.e., extrahypothalamically) because immunological tests have detected its presence in the extended amygdala and the brainstem (Swanson et al. 1983).

Studies have demonstrated that exaggerated HPA axis responses to stress can precede the onset of alcoholism. Nondependent sons of alcoholic fathers (who are at increased risk of alcoholism) displayed increased cortisol and ACTH responses to psychosocial stress compared with people with no family history of alcoholism (Uhart et al. 2006; Zimmermann et al. 2004*a*, *b*). Furthermore, alcohol had a greater attenuating effect on ACTH and a related hormone (i.e., arginine vasopressin [AVP]) in people with alcoholic fathers, suggesting that alcohol may be more rewarding for such individuals (Zimmermann et al. 2004*b*). These findings also indicate that interindividual differences in HPA axis activity may underlie some of the variation observed in the vulnerability to alcohol dependence.

As alcohol dependence develops, the stress response systems are upregulated, and this hyperactivity may in fact be a pathological component of dependence (Koob 2008). It has been hypothesized that as dependence develops, the motivation for alcohol use shifts from positive reinforcement, whereby alcohol is consumed for its pleasurable effects, to negative reinforcement—that is, the drinker consumes alcohol to alleviate the negative emotional effects encountered during withdrawal and into protracted abstinence (Koob and Le Moal 2008). The development of negative emotional states has been proposed to include the recruitment and subsequent deregulation of various brain stress system, including the HPA axis, extrahypothalamic CRF, and various others[4] (George et al. 2008; Koob 2008). Genetic variation in genes encoding components of these stress response systems therefore may be relevant for the risk for alcohol dependence.

Genetic Influences on Stress Responding and Their Role in Alcohol Dependence

The variability between individuals in stress responding results at least partially from inherited factors (Armbruster et al. 2009; Linkowski et al. 1993; Meikle et al. 1988) that also may influence the risk of alcohol dependence. For example, polymorphisms that affect only a single DNA building block (i.e., single nucleotide polymorphisms [SNPs]) in the gene encoding CRF1 were associated with alcohol consumption and a lifetime prevalence of drunkenness in two independent samples (Treutlein et al. 2006). One of those polymorphisms, known as rs1876831, was found to moderate the effects of stress on drinking. Thus, adolescents at age 15 who had experienced negative life events in

[4] Additional brain stress response systems involve the signaling molecules norepinephrine, neuropeptide Y, tachykinins, and dynorphins.

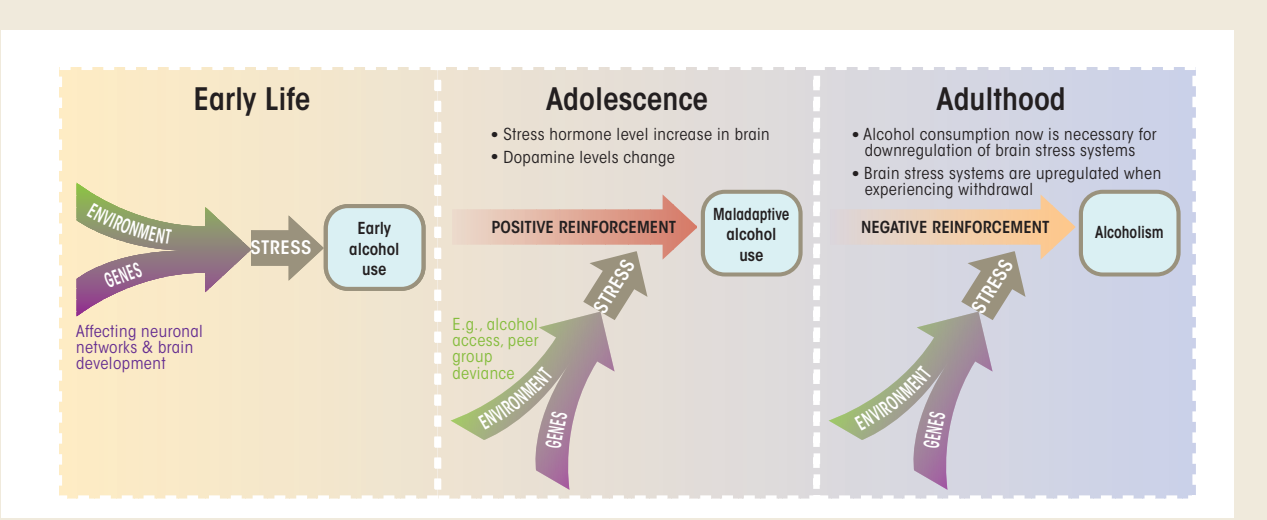

Figure Schematic depiction of the typical progression from alcohol use to alcohol dependence. Both genetic and environmental factors influence each stage of disease progression. Early-life experiences, including prenatal environments and early-life stressors, may affect the onset of alcohol use. In adolescence, heightened sensation seeking, resulting from an increase in cortical dopamine neurons, often results in experimentation with alcohol. In adulthood, alcohol use may occur to downregulate brain stress systems in individuals suffering from alcohol dependence. Thus, early alcohol use is motivated by positive reinforcement, whereas later stages are driven by negative reinforcement, when alcohol is consumed to alleviate negative emotional states.

the past 3 years and who carried the variant (i.e., allele) of rs1876831 that was associated with increased risk of drinking displayed increased alcohol consumption per drinking occasion and greater lifetime rates of heavy drinking (Blomeyer et al. 2008). A similar effect also was observed at age 19, when the risk allele was associated with earlier age of onset of alcohol use and higher alcohol consumption in individuals exposed to stressful life events (Schmid et al. 2010). Furthermore, a gene–environment interaction was detected with a combination of several gene variants (i.e., a haplotype) in the *CRF1* gene (which also contains rs1876831) and childhood sexual abuse in a large cohort of Australians recruited for the Nicotine Genetics Project (Saccone et al. 2007). Individuals who had experienced childhood abuse but carried a protective polymorphism of the *CRF1* gene had lower lifetime alcohol consumption scores and rates of alcohol dependence (Nelson et al. 2009).

Further genetic factors mediating the association between the stress response and alcohol consumption are found in genes encoding the receptors to which cortisol binds after it is released from the adrenal gland when the HPA becomes activated (Bjorntorp 2001). Cortisol binds to glucocorticoid receptors (GRs) that are made up of two identical subunits (i.e., form homodimers). These receptors interact with certain DNA sequences, glucocorticoid response elements (GREs), in the target genes, thereby activating those genes as part of the stress response (Gower 1993; Simons et al. 1992). The GRs are encoded by a family of genes known as nuclear member subfamily 3 (*NR3C*) genes.

Researchers have identified functional polymorphisms in the genes encoding two receptors, NR3C1 and NR3C2, which are associated with differential responses to stress (Wust et al. 2004). For example, a SNP, N363S that results in an altered receptor, protein (i.e., a non-synonymous SNP) in *NR3C1* is associated with increased glucocorticoid sensitivity (Huizenga et al. 1998) as well as elevated levels of cortisol in the saliva of healthy people in response to psychosocial stress (Wust et al. 2004). Moreover, a haplotype that includes three SNPs and is located in a noncoding region of the *NR3C1* gene also is associated with enhanced sensitivity to glucocorticoids (Stevens et al. 2004). Because chronic alcohol consumption can increase HPA axis activity in animals and humans (Rivier 1996; Rivier and Lee 1996; Waltman et al. 1994), polymorphisms in genes encoding components of the HPA axis may increase the risk for alcohol abuse. Indeed, a recent study of 26 SNPs across the *NR3C1* gene in 4,534 adolescents identified several variants that were associated with onset of drinking and drunkenness by age 14, suggesting that genetic variation in *NR3C1* can influence the risk of alcohol abuse in adolescence (Desrivieres 2010). Likewise, variants in the gene encoding the ACTH precursor, promelanocortin *(POMC)*, have been associated with substance abuse, including alcohol abuse (Zhang et al. 2009).

Genes encoding components of the norepinephrine stress response system also have been linked to variability in the response to stress. Thus, polymorphisms in the *ADRA2A* gene, which encodes adrenergic receptors that inhibit norepinephrine release from the neuron, are associated with certain aspects of the stress response as determined by measuring blood pressure and heart rate (Finley et al. 2004). In addition, variants in the *ADRA2A* gene are associated with alcohol abuse phenotypes in humans. For example, in a study analyzing 23 SNPs in *ADRA2A* as well as in a gene *SLC6A2* (which encodes the norepinephrine transporter, NET1) in association with adult alcohol dependence identified two SNPs in *ADRA2A* associated with a positive family history of alcoholism and four SNPs in *SLC6A2* associated with adult alcohol dependence (Clarke et al. 2010).

All of these studies demonstrate that genes that regulate stress responding also influence the risk for alcohol dependence. Thus, people who display increased sensitivity to stress may consume alcohol to dampen the exaggerated stress responses and therefore may find alcohol more rewarding. These people also may more readily experience the negative emotional states associated with withdrawal after chronic alcohol exposure, which may accelerate the transition to dependence. However, the precise relationship between genes, stress, and alcohol use is complex, and gene–environment interactions are notoriously difficult to elucidate (Flint and Munafo 2008). Therefore, translational studies analyzing the effects of genetic factors and stress and their interactions under tightly controlled experimental conditions using animal models are warranted (Barr and Goldman 2006). Indeed, the study of the extrahypothalamic CRF system in animals has helped to clearly delineate the role of brain stress systems in the pathology of alcoholism, and this system is now a plausible target for future alcoholism pharmacotherapies. (For more information on these studies, see the sidebar "The Extrahypothalamic CRF System and the Transition to Alcohol Dependence.")

Another confounding issue for the study of gene–environment interactions is that many studies are conducted retrospectively, and the participants' recall of environmental risk factors may not be accurate. Therefore, prospective longitudinal studies are of great importance to advance the field of gene–environment interactions in alcohol dependence. One study that illustrates how such methodological issues can be addressed is the IMAGEN study, a longitudinal initiative funded by the Framework 6 program of the European Commission and the Medical Research Council that tracks the interplay between genetic polymorphisms and environmental stressors from early adolescence onward. The study collects neuropsychological, behavioral, and functional/structural neuroimaging data and also conducts genetic analyses on a sample of 2,000 adolescents from age 14 onward. (For more information

on this study, see the sidebar "The IMAGEN Study.")

Conclusion and Future Perspectives

Dopaminergic and stress response pathways jointly are engaged upon the commencement of alcohol consumption. Genetic polymorphisms within these pathways may affect the risk of developing alcohol dependence. The effects of exposure to environmental stressors that increase the risk of developing alcohol dependence may be augmented in genetically vulnerable individuals. In some cases, these genetic variants may vary the impact that a particular stressor has within a specific time window (see the figure). To elucidate the role of alcohol usage as a consequence of environmental stressors, and as an environmental stressor in itself, longitudinal studies of the interplay between genes and environments are needed.

The IMAGEN study is an ongoing longitudinal study that attempts to address the role of genes and the environment in alcohol use. The extensive phenotypic database available from this study will allow researchers to test the hypothesis that overactivity of the brain's stress systems, resulting from childhood maltreatment and neglect, may affect brain development and ultimately behaviors such as alcohol use. Alcohol use patterns of the IMAGEN participants are recorded to investigate the long-term effects of early intoxication on cognitive development and behavior. Finally, genetic analyses investigating the association of genetic markers distributed across the genome with specific traits or behaviors (i.e., genomewide association data) are available for each participant and may demonstrate the relationship between genes of the stress response system and intermediate phenotypes (Schumann et al. 2010).

Longitudinal gene–neuroimaging studies, such as the IMAGEN study, aim to clarify the role of the HPA axis and supplementary stress systems in the development and maintenance of alcohol dependence. Such studies will elucidate how alcohol use fluctuates throughout development under the influence of genetic and environmental factors. A better understanding of these factors will promote novel therapies for alcohol dependence as well as approaches to prevent the disorder. ■

Financial Disclosure

The authors declare that they have no competing financial interests.

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Stress and the HPA Axis

Role of Glucocorticoids in Alcohol Dependence

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Stress has long been suggested to be an important correlate of uncontrolled drinking and relapse. An important hormonal response system to stress—the hypothalamic–pituitary–adrenal (HPA) axis—may be involved in this process, particularly stress hormones known as glucocorticoids and primarily cortisol. The actions of this hormone system normally are tightly regulated to ensure that the body can respond quickly to stressful events and return to a normal state just as rapidly. The main determinants of HPA axis activity are genetic background, early-life environment, and current life stress. Alterations in HPA axis regulation are associated with problematic alcohol use and dependence; however, the nature of this dysregulation appears to vary with respect to stage of alcohol dependence. Much of this research has focused specifically on the role of cortisol in the risk for, development of, and relapse to chronic alcohol use. These studies found that cortisol can interact with the brain's reward system, which may contribute to alcohol's reinforcing effects. Cortisol also can influence a person's cognitive processes, promoting habit-based learning, which may contribute to habit formation and risk of relapse. Finally, cortisol levels during abstinence may be useful clinical indicators of relapse vulnerability in alcohol-dependent people. **KEY WORDS: Alcohol dependence; problematic alcohol use; alcohol use disorders; alcohol abstinence; relapse; stress; stress response; stress hormones; hypothalamic–pituitary–adrenal axis; glucocorticoids; cortisol; brain reward pathway**

Stress, generally defined as any stimulus that disrupts the body's internal balance (i.e., physiological homeostasis), has long been suggested to be an important correlate of uncontrolled alcohol consumption or relapse to drinking following a period of abstinence. Large epidemiological studies have reported that a variety of stressors are associated with increased alcohol consumption and binge drinking. These include hazardous and demanding work environments, legal stress, family stress (e.g., unhappy marriage and divorce), and low income (Richman et al. 1996; Rospenda et al. 2000; San Jose et al. 2000; Vasse et al. 1998). Likewise, the Health and Retirement Study found an association between stress from retirement and divorce and increased alcohol intake (Perreira and Sloan 2001). Studies also have shown that people experiencing more severe or highly threatening social stress following alcoholism treatment have higher rates of relapse compared with people not experiencing such stress (Brown et al. 1990; Noone et al. 1999). On the other hand, prospective and human laboratory studies exploring the relationship between stress, alcohol craving, and relapse have found mixed results, with more recent research suggesting that several factors moderate the effects of stress on alcohol consumption (e.g., Breese et al. 2011; Brennan et al. 1999; Fox et al. 2008; Helzer et al. 2006; Sinha 2007; Sinha and Li 2007; Thomas et al. 2011).

It remains uncertain how stress, per se, might influence vulnerability to alcohol use disorders (AUDs). However, production of the stress hormone cortisol, which is triggered by stress-induced activation of a hormonal system known as the hypothalamic–pituitary–adrenal (HPA) axis, is thought to be involved. The HPA axis is one of the main stress response pathways and has been studied extensively in relation to alcohol use (Wand 2008). Over 20 years of research has demonstrated that altered HPA axis regulation is associated with problematic alcohol use and dependence and that the nature of this dysregulation varies with respect to the stages of progression toward alcohol dependence. The finding that HPA axis dysregulation and alcohol misuse tend to co-vary has implied a "guilt-by-association" relationship—that is, that abnormal variations in stress-related cortisol production are a risk factor for developing alcoholism in the first place (Wand et al. 1993). A recent review of studies on youth and adolescents similarly suggests that HPA axis dysfunction and exposure to stress are critical components that interact to convey risk for developing AUDs (Schepis et al. 2011).

As with mood and affective disorders, many researchers consider alterations in HPA axis function crucial for understanding the underlying brain mechanisms of substance use disorders. In contrast to mood and affective disorders, however, alcohol dependence has a biphasic effect on HPA axis dynamics as a person traverses through the various phases of heavy hazardous drinking, including dependent drinking, withdrawal, abstinence, and relapse. Generally speaking, these developmental stages seem to be mirrored by a shift between hyper- and hyporesponsiveness of the HPA axis to stressful events (Rose et al. 2010). For example, hyperresponsiveness has been identified in people with a family history of alcoholism (Uhart et al. 2006; Zimmermann et al. 2004*a*,*b*), a population that is at increased risk for alcohol dependence (Windle 1997). This observation raises the question whether heightened stress responsivity is clinically meaningful to the development of alcoholism. This view is supported by studies showing that cortisol responsivity correlates with the activity of a brain system, the mesolimbic dopaminergic pathway, which is a central neural reward pathway (Oswald et al 2005; Wand et al. 2007). With transition to alcohol dependence, compensatory allostatic mechanisms result in injury to HPA axis function and elevation of stress peptide levels (e.g., corticotropin-releasing factor [CRF]) in brain regions outside the hypothalamus. The term allostasis refers to the process through which various biological processes attempt to restore homeostasis when an organism is threatened by various types of stress in the internal or external environment. Allostatic responses can involve alterations in HPA axis function, the nervous system, various signaling molecules in the body, or other systems. Allostatic alterations in HPA axis function have been posited to, among other things, injure brain reward pathways, contribute to depressed mood (i.e., dysphoria) and craving, and further contribute to the maintenance of problem drinking behavior.

This article provides an overview of the clinical evidence for HPA axis and glucocorticoid dysfunction across the developmental phases of alcoholism and explores whether this dysfunction is causally related to, or a consequence of, alcohol dependence. The article describes behavioral and physiological pathogenesis resulting from dysregulation of basal and reactive HPA axis activity. This discussion primarily focuses on human studies and studies that specifically address the glucocorticoid activation component of the stress response. The article also discusses whether these findings have potential predictive value and whether altered glucocorticoid function, regardless of etiology, may serve as a useful clinical marker for the progression of alcohol dependence and treatment prognosis. The review will not address the important role that extrahypothalamic CRF pathways play in mediating the relationship of stress and reward dysfunction (for a review of this issue, see Koob 2010).

Physiology of the HPA Axis

The body responds to stress with self-regulating, allostatic processes aimed at returning critical systems to a set point within a narrow range of operation that ensures survival. These self-regulating processes include multiple behavioral and physiological components. Perhaps the best-studied component of the stress response in humans and mammals is activation of the HPA axis (see figure 1). Neurons in the paraventricular nucleus (PVN) of the hypothalamus release two neurohormones—CRF and arginine vasopressin (AVP)—into the blood vessels connecting the hypothalamus and the pituitary gland (i.e., hypophysial portal blood). Both hormones stimulate the anterior pituitary gland to produce and secrete adrenocorticotropic hormone (ACTH) into the general circulation. The ACTH, in turn, induces glucocorticoid synthesis and release from the adrenal glands, which are located atop the kidneys. The main glucocorticoid in humans is cortisol; the main glucocorticoid in rodents, which frequently are used as model systems to investigate the relationship between stress and alcohol use, is corticosterone. Hypothalamic activation of the HPA axis is modulated by a variety of brain signaling (i.e., neurotransmitter) systems. Some of these systems have inhibitory effects (e.g., γ-aminobutyric acid [GABA] and opioids), whereas others have excitatory effects (e.g., norepinephrine and serotonin) on the PVN. Thus, the central nervous system (CNS) and the hormone (i.e., endocrine) system are tightly interconnected to coordinate glucocorticoid activity.

To protect against prolonged activity, the HPA system is carefully modulated through negative-feedback loops designed to maintain predetermined hormone levels (i.e., set points) and homeostasis. To this end, secretion of CRF, AVP, and ACTH in part are controlled by sensitive negative feedback exerted by cortisol at the level of the anterior pituitary gland, PVN, and hippocampus. There are two types of receptors for cortisol—mineralocorticoid (type-I) and glucocorticoid (type-II) receptors—both of which participate in the negative-feedback mechanisms. Cortisol binds more strongly (i.e., has higher binding affinity) for the mineralocorticoid receptors (MRs)[1] than the glucocorticoid receptors (GRs). Because of this difference in binding affinity, the MRs help maintain the relatively low cortisol levels circulating in the blood during the normal daily (i.e., circadian) rhythm. Only when the cortisol concentration is high (e.g., during a stressful situation) does it bind to the GRs with lower affinity; the resulting activation of the GRs terminates the stress response. This delicate negative feedback control mechanism maintains the secretion of ACTH and cortisol within a relatively narrow bandwidth. This is an extremely important homeostatic mechanism because too much or too little exposure

[1]Cortisol has similar affinity to the MR as does the mineralocorticoid aldosterone, which helps regulate kidney function.

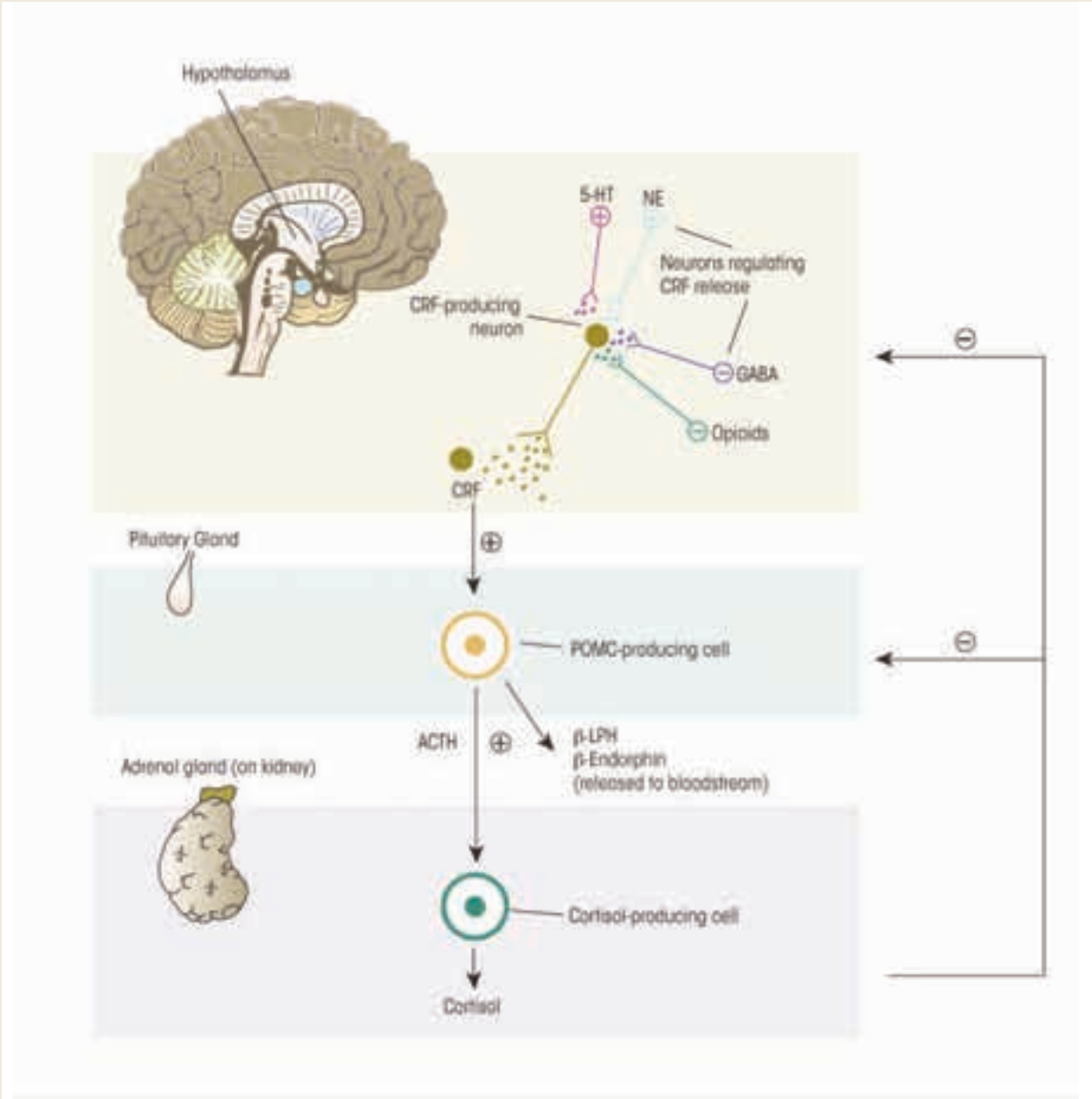

Figure 1 The major components of the stress response mediated by the hypothalamic–pituitary–adrenal (HPA) axis. Both alcohol and stress can induce nerve cells in one brain region (i.e., the hypothalamus) to produce and release corticotropin-releasing factor (CRF). Within the hypothalamus, CRF stimulates the release of a hormone that produces morphine-like effects (i.e., β-endorphin). CRF also is transported to a key endocrine gland, the anterior pituitary gland. There, CRF stimulates production of a protein proopiomelanocortin (POMC). POMC serves as the basis for a number of stress-related hormones, including adrenocorticotropic hormone (ACTH), β-lipotropin (β-LPH), and β-endorphin. ACTH stimulates cells of the adrenal glands to produce and release the stress hormone cortisol. When cortisol levels reach a certain level, CRF and ACTH release diminishes. Other neurons releasing serotonin (5-HT), norepinephrine (NE), γ-aminobutyric acid (GABA), or endogenous opioids also regulate CRH release.

NOTE: ⊕ = excites; ⊖ = inhibits.

to cortisol can have adverse consequences to health and well being.

Growing evidence suggests that a protein, FK506 binding protein 5 (FKBP5), regulates GR sensitivity. Binding of this protein to the GR reduces the receptor's affinity for cortisol and its movement (i.e., translocation) to the nucleus. A genetic variation in FKBP5 is associated with enhanced expression of the protein following GR activation. This leads to more GR resistance, diminished negative feedback, and prolonged stress hormone activation following a stressor (Binder et al. 2004; Wochnik et al. 2005).

Physiological Actions of Glucocorticoids

Glucocorticoids are a class of steroid hormones that are essential for the organism to survive. Cortisol, the main glucocorticoid in humans, has been placed in this class because of its effects on the metabolism of the sugar glucose, where its primary function is to increase blood glucose levels by inducing production of additional glucose molecules (i.e., gluconeogenesis). Cortisol also modifies fat and protein metabolism to support the nutrient requirements of the CNS during stress. However, cortisol also has many other wide-ranging effects when it binds to GRs. For example, it influences cardiovascular function, immunologic status (i.e., inflammatory reactions), arousal, and learning and memory; all of these systems therefore are affected when the HPA axis is activated in response to stress.[2] Thus, cortisol helps maintain or can increase blood pressure by increasing the sensitivity of the blood vessels to signaling molecules, catecholamines. In the absence of cortisol, widening of the blood vessels (i.e., vasodilation) and hypotension occurs. The anti-inflammatory effects of cortisol are brought about by reducing proinflammatory cytokine and histamine secretion and stabilizing the membranes of cell components, lysosomes.

One of the most important actions of cortisol in the context of alcohol use and the stress response is its role in modifying learning and memory. Both stress and exposure to cortisol can transiently block memory retrieval (van Stegeren 2009), with retrieval of emotional memory more strongly affected than that of neutral memory. Of interest, both cortisol and stress also enhance memory consolidation; this process generally favors consolidation of emotionally arousing information, facilitating habit-based learning. Consistent with the multiple-systems theory to memory organization in the mammalian CNS, studies have identified unique roles for various brain regions in learning and memory. For example, "cognitive" learning and memory is associated with activation of brain circuits in the hippocampus, whereas "habit" learning and memory is associated with activation of the dorsal striatum and the basolateral amygdala (BLA). In addition, nerve fibers projecting from the BLA modulate memory processes occurring in other brain structures. The implications of the fact that cortisol selectively affects emotionally charged memory and habit learning are discussed below.

Determinants of HPA Axis Activity and Cortisol Exposure

Correct regulation of cortisol levels is necessary for survival, and too little or too much cortisol exposure can result in serious harm. Therefore, both basal and stress-induced cortisol levels are maintained carefully. A healthy stress response is characterized by a quick rise in cortisol levels, followed by a rapid decline with the termination of the stressful event. When the organism is burdened by cumulative stress, however, the cortisol burden increases. This results in wear and tear on the organism from excessive exposure to the catabolic properties of glucocorticoids, stress peptides, and proinflammatory cytokines. This burden taxes the organism and can influence the development of neuropsychiatric and metabolic disorders. It therefore is essential to understand the systems that regulate cortisol production.

Three main determinants of HPA axis activity control the amount of cortisol a person is exposed to during adulthood: genetic background, early-life environment, and current life stress. In addition, studies found that post-traumatic stress disorder (PTSD) can contribute to HPA axis disturbances.

Genetic Factors. Differences among individuals in cortisol responses to stress result from a complex interplay between genetic and environmental factors. The genetic contribution to the variability in HPA axis reactivity is believed to arise from DNA variations (i.e., polymorphisms) in the genes encoding neurotransmitters involved in HPA axis regulation. Overall, heritable influences account for approximately 62 percent of the etiological variance in basal glucocorticoid levels (Bartels et al. 2003). Recent candidate gene association studies using laboratory-based stress procedures also have implicated multiple gene variants in explaining some of the variance in cortisol responses to stress, including polymorphisms in the following genes:

- *Nr3c1*, which encodes a glucocorticoid receptor protein (Wust et al. 2004);
- *Nr3c2*, which encodes a mineralocorticoid receptor protein (DeRijk et al. 2006);
- *FKBP5* (Ising et al. 2008);
- *CRFR1*, which encodes the CRF receptor 1 protein (Clarke and Schumann 2009);
- *CRF-BP*, which encodes CRF binding protein (Wang et al. 2007);

[2] Certain tissues, however, need to be protected from cortisol, such as the kidneys, colon, and placenta. In these tissues, an enzyme ,11-β hydroxysteroid dehydrogenase type II, mediates the conversion of glucocorticoids to 11-dehydro metabolites, which are inactive.

- *GABRA6*, which encodes the GABA receptor subunit alpha-6 protein (Uhart et al. 2004);
- *OPRM1*, which encodes the mu opioid receptor protein (Chong et al. 2006); and
- *SLC6A4*, which encodes a serotonin transporter protein (Way and Taylor 2010).

It is certain that additional genes and polymorphisms will be identified in the future.

Early-Life Environment. Pre- and postnatal processes contribute to the lifelong responsiveness of the HPA axis to stressors. In animal models, prenatal ethanol exposure is associated with impaired HPA axis responsivity in adulthood (Hellemans et al. 2010; Weinberg et al. 2008), and emerging evidence suggests that these effects also occur in human infants and toddlers (Haley et al. 2006; Ouellet-Morin et al. 2010). Maternal stress during gestation also modifies HPA axis responsivity of infant and adult offspring (see Charil et al. 2010; Harris and Seckl 2010 for reviews). More recently, studies have focused on the consequences of early-childhood events on the stress response. Childhood trauma is a significant problem in the United States and is associated with mental and physical health problems in adulthood as well as with alterations in HPA axis function (Heim et al. 2009, 2010; Dong et al. 2004; Mangold et al. 2010). For example, it has been hypothesized that exposure to sexual and physical abuse in childhood during critical periods of brain development (i.e., during periods of neural plasticity) may permanently alter stress responsivity (Gillespie et al. 2009; Heim and Nemeroff 2001; Heim et al. 2001). Animal models that have studied this phenomenon have shown that certain forms of neonatal stress results in a modification (i.e., epigenetic methylation) of the glucocorticoid gene that has long-lasting effects on glucocorticoid responsivity (Weaver 2009). This alteration in stress responsivity may explain the observation that childhood adversity is a risk factor for the development of alcohol and other drug abuse (Epstein et al. 1998) as well as anxiety and depressive disorders in adulthood (Kessler et al. 1997; Safren et al. 2002).

Glucocorticoids also can alter the methylation patterns of other genes. For example, glucocorticoid administration to adolescent mice reduces methylation of the *FKBP5* gene in the hippocampus, hypothalamus, and blood, which is associated with enhanced expression of *FKBP5* and increased anxiety-like behavior (Lee et al. 2010). The investigators proposed that in addition to altering behaviors, methylation of the gene may be a marker of cortisol burden. Polymorphisms in *FKBP5* also have been associated with psychiatric disorders, such as depression and PTSD, that are characterized by alterations in HPA dynamics (Binder et al. 2004; Yehuda et al. 2009).

An emerging literature also addresses the role of early-childhood adversity on the development of AUDs (for a review, see Enoch 2010). For example, Schmid and colleagues (2010) found an interaction between stressful early-life events and a variant in the *CRFR1* gene that influenced age of drinking initiation and drinking progression in a population of 19-year-olds. Other studies demonstrated that certain variants of the *CRFR1* gene influenced cortisol responses to CRF and the synthetic glucocorticoid dexamethasone (Binder et al. 2010; Tyrka et al. 2009) and were associated with binge drinking in adolescents and total lifetime alcohol consumption in adults (Clarke and Schumann 2009; Hansson et al. 2006; Pastor et al. 2008; Treutlein et al. 2006). Thus, it seems that an interaction between the *CRFR1* gene and early-life events can modify HPA axis dynamics and risk for AUDs. It is certain that other stress gene variants also will be found to interact with environmental factors to increase the risk of AUDs.

Current Stress. Independent of prenatal and childhood stressors, periods of severe, chronic stress in adulthood, such as family- and work-related problems, combat exposure, neighborhood violence, chronic illness, or the development of neuropsychiatric disorders, alter HPA axis dynamics and increase the cortisol burden. Chronic stress triggers an allostatic shift in the normal circadian rhythm of cortisol release as well as in stress-induced cortisol levels. Thus, after chronic stress baseline cortisol levels are elevated, the body's cortisol response to acute stress is blunted, and it takes longer for stress-induced cortisol levels to return to pre-stress levels (e.g., Juster et al. 2010; McEwen 2000; Wingenfeld et al. 2009). This allostatic injury makes the HPA axis more sensitive, resulting in higher cortisol exposure or greater cortisol burden following each stressful episode (McEwen and Gianaros 2010).

PTSD Symptomatology. A fourth potential determinant of HPA axis activity is the presence of PTSD symptoms. The HPA axis has been the main focus of neuroendocrine research in PTSD. In a meta-analysis of 37 studies involving people with PTSD, Meewisse and colleagues (2007) examined cortisol levels in people with PTSD and control subjects. These analyses found no differences in basal cortisol levels between the two groups; however, differences did exist under certain conditions or among certain subgroups of subjects. For example, people with PTSD had lower afternoon levels of cortisol than did control subjects, and women with PTSD had significantly lower cortisol levels than women without PTSD. The specific type of trauma experienced by a person also mattered. Thus, only people who had experienced physical or sexual abuse had significantly lower cortisol levels than control subjects. These findings highlight the complexity of the relationship between HPA axis activity and PTSD pathophysiology.

People with AUDs have a high prevalence of PTSD (Kessler et al. 1997); conversely, women with PTSD were 3.5 times more likely to develop alcoholism than women who did not report past trauma (Sartor et al. 2010). It is difficult to define whether the alterations in the HPA axis seen in people with PTSD by themselves modulate risk for alcoholism because, as discussed above, a history of childhood trauma also increases risk for developing PTSD as well as alcoholism (Binder et al. 2008; Epstein et al. 1998). Therefore, it is possible that exposure to trauma in early childhood may confer the initial insult to HPA axis regulation that later influences the interaction between PTSD and alcohol use (Yehuda et al. 2010). This view is consistent with the finding that people with a flattened cortisol response following trauma had a higher risk of developing PTSD symptoms than did those with normal cortisol levels (e.g., Aardal-Eriksson et al. 2001; Anisman et al. 2001). It remains unclear, however, whether the lower levels of circulating cortisol preceded the traumatic event (Yehuda et al. 2010).

Regardless of whether an underlying HPA axis dysregulation precedes PTSD symptomatology, evidence suggests that dysregulation occurs through increased sensitivity of the negative feedback mechanisms regulating the HPA axis, resulting in lower circulating cortisol levels. Yehuda and coworkers (2009) examined the expression of all genes active in whole-blood samples as well as cortisol levels in people with and without PSTD. This analysis identified 17 genes whose expression differed between people with and without PTSD. Several of the uniquely expressed genes are involved in HPA axis function. For example, the *FKBP5* gene, which serves as a modulator of GR sensitivity, showed reduced expression in people with PTSD, consistent with enhanced GR responsiveness. Moreover, statistical analyses found that *FKBP5* expression was predicted by cortisol levels when PTSD severity also was taken into consideration (Yehuda et al. 2009). Of interest, this profile of HPA axis dysregulation is distinct from that seen with other psychiatric disorders, such as depression (Handwerger 2009). Taken together, it seems likely that dysregulation of the HPA axis associated with PTSD interacts with epigenetic and environmental influences (Yehuda et al. 2010) and that this interaction translates into increased risk for the development of AUDs.

The HPA Axis and Alcoholism

HPA Axis Dynamics in People at Risk for AUDs

Altered HPA axis responsivity may be present before alcohol exerts its toxic effects on the CNS and may contribute to initial vulnerability to alcoholism. This vulnerability risk likely is a result of gene–environment interaction (Clarke et al. 2008; Schepis et al. 2011). The current state of knowledge stems from an early and large body of research suggesting that people who have alcoholic family members (i.e., who are family-history positive [FHP] for alcoholism) may be more likely to develop the disorder than those with no such family history (i.e., who are family-history negative [FHN] for alcoholism) (Windle 1997). This risk seems to be linked to abnormal HPA activity (e.g., Dai et al. 2002; King et al. 2002; Sorocco et al. 2006; Uhart et al. 2006; Wand et al. 1998, 1999*a,b*), although the relationships appear complex. Laboratory findings have been mixed and may depend on several factors, such as which type of stressor is used, whether basal or reactive HPA response is measured, and how cortisol is stimulated. The first studies comparing HPA axis responsivity in FHP and FHN people assessed cortisol levels in response to an agent that can block the opioid receptors (i.e., the opioid receptor antagonist, naloxone). These studies identified stronger cortisol responses to naloxone in FHP subjects than in FHN subjects (Wand et al. 1998, 1999*a,b,* 2001). These findings were replicated using another opioid receptor antagonist, naltrexone (King et al. 2002). These observations are particularly interesting because they implicate the endogenous opioid system in the interaction between HPA axis activity and alcoholism risk. This signaling system not only modulates the HPA axis but also is a pharmacological target for the treatment of alcohol dependence. Other studies using a psychosocial stressor rather than a pharmacologic stimulator such as naloxone also found a stronger HPA response in FHP than in FHN subjects (Uhart et al. 2006; Zimmermann et al. 2004*a,b*). More recent studies among infants and toddlers with prenatal alcohol exposure who also are believed to be at increased risk for alcoholism have corroborated these latter findings in male but not female children (Haley et al. 2006; Ouellet-Morin et al. 2010). Other studies, however, found blunted HPA axis function in FHP individuals (e.g., Dai et al. 2002; Sorocco et al. 2006).

HPA Axis Dynamics During Intoxication and Withdrawal

As with stress, acute alcohol consumption also directly and indirectly activates the HPA axis by resulting in elevated levels of glucocorticoids (Richardson et al. 2008). In fact, alcohol and other drugs of abuse have been described as a physiological stressor because they can activate the HPA axis. In social drinkers, acute doses of alcohol usually increase cortisol levels, particularly if blood alcohol levels exceed 100 mg percent (Waltman et al. 1993). At some point during the transition from social drinking to alcohol dependence and abstinence, however, the HPA axis becomes dysregulated. For example, King and colleagues (2006) found that cortisol reactivity to acute alcohol administration is attenuated in heavy, hazardous drinkers compared with light, social drinkers. This observation may be related to the general process of tolerance that emerges during heavy hazardous drinking. It is important to note that the subjects in this study were binge drinkers—which reflects a pattern of drinking frequently associated with adverse consequences—but

were not alcohol dependent, suggesting that alterations in the HPA axis may begin even before dependence develops.

The onset of alcohol dependence, however, is accompanied by bouts of elevated cortisol levels in the blood (i.e., hypercortisolism) as the drinker cycles though repeated episodes of alcohol intoxication and the stress of withdrawal (Adinoff et al. 1998; Wand and Dobs 1991). This transition to alcohol dependence is accompanied by an allostatic shift in HPA axis functioning, resulting in abnormally low cortisol responsivity (Koob and Le Moal 2001). Under conditions of alcohol dependence, the allostatic load—a hypothetical measure of cumulative stress—increases and burdens the organism with excessive exposure to stress hormones and peptides as well as pro-inflammatory cytokines (McEwen 2007). Increased allostatic load has been implicated not only in AUDs and other drug use disorders but also in the development psychiatric disorders (e.g., depression), metabolic syndrome, and systemic hypertension. In the context of drug use, allostatic load not only impacts the stress response via the HPA axis but also encompasses a state of reward dysregulation. At this point, the organism constantly seeks the initial rewarding effects of the drug while tolerance to those effects develops through repeated drug self-administration. This results in a dysfunctional reward system and a maladaptive response to stress. Specifically, the allostatic alterations in cortisol responsivity may have a detrimental effect on the reward systems (Wand 2008).

HPA Axis Dynamics During Abstinence

Wand and Dobs (1991) studied HPA axis function in alcohol-dependent subjects during the first week of abstinence following supervised alcohol withdrawal on a clinical research unit. Although the participants had modestly to highly significantly elevated cortisol levels in the urine during the withdrawal period, they also demonstrated blunted HPA axis responses to CRF, a medication that blocks cortisol production (i.e., metyrapone), and the ACTH analog cosyntropin immediately following alcohol detoxification. In fact, many of the alcohol-dependent subjects met diagnostic criteria for adrenal insufficiency. Other studies have corroborated these findings of elevated cortisol during the first week of withdrawal and also showed that cortisol levels decreased significantly over time, even plunging below the normal range (Esel et al. 2001; Keedwell et al. 2001; Majumdar et al. 1989).

Later in abstinence (i.e., at 2 to 6 weeks), alcoholics generally regain normal diurnal patterns of cortisol levels (e.g., Leggio et al. 2008). However, they may continue to exhibit a deficient cortisol response to psychosocial and pharmacological HPA axis stimulation for several months (Adinoff et al. 1998, 2005*a*,*b*; Anthenelli et al. 2001; Bernardy et al. 1996). Junghanns and colleagues (2007) compared HPA axis activity in early abstainers (i.e., mean abstinence 22 days) and long-term abstainers (i.e., mean abstinence 117 days). These investigators found that longer-abstaining people showed a stronger cortisol awakening response, another indicator of HPA axis function, implying that diurnal patterns of cortisol may begin to normalize over longer periods of abstinence. Whether regulation of the HPA axis returns completely to normal, and under what conditions, remains unknown.

Several factors may impact and moderate HPA axis recovery, including severity of withdrawal symptoms (Bernardy et al. 1996), severity and duration of dependence, comorbid childhood trauma (Schafer et al. 2010), and genetic factors underlying the individual stress response. The exact role of cortisol in HPA axis recovery is unclear. Coiro and colleagues (2007) examined the effect of exercise as a biobehavioral stressor in control subjects and alcoholics over an 8-week period. Consistent with other studies, ACTH and cortisol levels were significantly lower in alcoholics in the first month of withdrawal; by 8 weeks, however, the hormonal response had returned to normal. Interestingly, exercise itself can induce cortisol release (Beaven et al. 2010; Coiro et al. 2007; Usui et al. 2011) and has been investigated as an adjunct for smoking cessation with somewhat promising findings (Williams et al. 2010). This suggests that manipulation of cortisol levels may have therapeutic potential (see below). Indeed, determining the nature, extent, and time course of the attenuated HPA axis response during abstinence may have significant clinical relevance because low levels of basal cortisol and of the ACTH response may predict relapse to alcohol use during early abstinence (Adinoff et al. 1998; Junghanns et al. 2003, 2005; Kiefer et al. 2002).

No prospective longitudinal studies have examined HPA axis changes over longer periods of abstinence. One study of alcoholics who had been abstinent for a mean of 3.5 years found similar ACTH and cortisol responses compared with healthy controls in response to both psychological and pharmacological (i.e., opioid challenge) stressors (Munro et al. 2005). However, the study did not determine whether the alcoholics had recovered a normal level of HPA response with prolonged abstinence, whether they had had a normal response all along, or whether their lack of psychological comorbidity indicated that they were less affected by secondary characteristics related to a hyporesponsive HPA axis. Another study compared alcoholics who had relapsed with abstainers after one year and found that, contrary to findings during short-term abstinence, 1-year abstainers had significantly lower levels of cortisol (Walter et al. 2006). This suggests that the relationship between HPA axis activity and alcohol recovery is dynamic and changes as abstinence persists over time.

One major limitation of these studies is that most of the work has been conducted with male alcoholics; therefore, less is known regarding the HPA hyporesponsiveness during abstinence in females. Adinoff and colleagues (2010) focused on female alcoholics

and found no differences in HPA axis activity between women who had been abstinent for 4 to 8 weeks and age-matched healthy control women. Thus, HPA axis functioning over the long term and its relationship to alcohol use and recovery remains unclear and warrants further investigation.

Possible Roles of Cortisol in the Risk and Development of AUDs

Cortisol's Interaction with Dopaminergic Reward Systems

Studies in animal models have demonstrated that mesocorticolimbic dopamine pathways are involved in the brain's reward system and that the nucleus accumbens in the ventral striatum is a critical region for mediating the rewarding effects of drugs. Virtually all drugs of abuse, including alcohol, have an impact on dopaminergic activity within this brain region (Pierce and Kumaresan 2006). Imaging studies using positron emission tomography (PET) in humans have corroborated the animal findings that drugs of abuse alter mesolimbic dopaminergic activity and have helped elucidate potential neurobiological underpinnings of drug addiction (for a review, see Martinez and Narendran 2009). These and other studies in humans have shown that mesolimbic dopamine release is correlated with the positive subjective effects of the drug (Drevets et al. 2001; Hamidovic et al. 2010; Oswald et al. 2005; Volkow et al. 2002; Wand et al. 2007). However, whereas acute alcohol administration increases synaptic dopamine activity and accumulation, chronic alcohol consumption can lead to lower-than-normal dopamine levels (i.e., a hypodopaminergic state) that may motivate the drinker to seek alcohol in order to restore the normal levels of the neurotransmitter (Volkow et al. 2007). It has been postulated that elevated levels of glucocorticoids contribute to alcohol's reinforcing effects by enhancing modulation of the dopaminergic and subjective response to alcohol (e.g., Melis et al. 2009).

Glucocorticoids and stress interact with the dopamine reward system in ways that may increase vulnerability for developing addiction (Marinelli and Piazza 2002). For example, glucocorticoids play a critical role in the reinforcing effects of psychostimulants because surgical removal of the adrenal glands (i.e., adrenalectomy), which prevents cortisol production, decreases drug self-administration. Moreover, re-introduction of glucocorticoids at levels similar to those induced by stress reverses this effect (Deroche et al. 1997). In fact, acute stress and drugs of abuse, through different mechanisms, appear to converge upon a common pathway that modifies dopamine neuron output by enhancing long-term potentiation (LTP) of excitatory synapses (Saal et al. 2003) and long-term depression (LTD) of inhibitory synapses (Niehaus et al. 2010). However, these studies did not demonstrate that this effect directly was attributable to cortisol. Another study found that the magnitude of stress-induced cortisol release significantly correlates with mesolimbic dopamine release in the ventral striatum (Pruessner et al. 2004). Taken together, these studies suggest that cortisol may facilitate firing of dopaminergic neurons and, consequently, the reward circuitry and that this process is common with and specific to many drugs of abuse (Saal et al. 2003).

Glucocorticoids themselves also are believed to have reinforcing properties in rats as they seem to modulate self-administration of alcohol and increase brain sensitivity to other addictive drugs (e.g., stimulants and opioids) in the animals. A review by Piazza and Le Moal (1997) concluded that glucocorticoid administration at levels similar to those found in physiological stress responses had positive reinforcing effects. The investigators proposed that under natural conditions (e.g., during conflicts with other animals) the rewarding effects of the glucocorticoids might counteract the aversive effects of external aggressions, thereby allowing the animal to better cope with threatening situations. Such a mechanism may play a key role in fine-tuning an individual's adaptation to stress and in determining reward-related behavioral pathologies. Thus, increased levels of cortisol may have reinforcing effects, acting on the brain to perpetuate behaviors (e.g., alcohol consumption) that maintain high cortisol levels.

The interactions of the stress response and the rewarding effects of drugs also have been investigated in humans. Imaging studies using PET found that higher cortisol levels in response to amphetamine administration (Oswald et al. 2005) or to a psychosocial stressor (Wand et al. 2007) were positively associated with amphetamine-induced dopamine release in the ventral striatum. Furthermore, subjects with a high cortisol response to these stimuli reported more positive subjective drug effects after amphetamine administration than did subjects with a low cortisol response (Hamidovic et al. 2010; Oswald et al. 2005; Wand et al. 2007). These studies provide evidence that cortisol may play a role in drug reinforcement through its interactions with the dopaminergic reward pathway, which may, in turn, influence vulnerability for and maintenance of alcohol and other drug use.

Cortisol's Effect on Cognitive Processes

LTP is a process that ultimately enhances signal transmission at the synapse. This enhanced synaptic transmission, which has been observed in a variety of neural structures, is widely considered one of the leading cellular mechanisms that underlie learning and memory (Goosens and Maren 2002). As mentioned above, LTP is enhanced by stress. Cortisol has been implicated in this phenomenon because a widespread system of glucocorticoid receptors is found above the hypothalamus, for example, in the limbic system, notably the hippocampus and amygdala, and in the prefrontal cortex. This section discusses the impact of glucocorticoids

on some of the basic (e.g., learning, acquisition, and memory) and higher (e.g., decision-making) cognitive processes that may potentially underlie development of addictive behaviors. This discussion focuses on the regulatory actions of glucocorticoids on neural structures critically involved in cognitive processes related to alcoholism but does not cover the equally important reciprocal effects these structures have on regulating HPA axis function (e.g., Dedovic et al. 2009).

Optimal levels of cortisol are needed not only to meet the body's physical needs but also for learning, memory, and cognitive performance. Both too little and too much cortisol may be damaging and disruptive to memory formation, whereas normal levels of glucocorticoids protect the brain against adverse events and are essential for cognitive processes. Several studies partly may explain this paradox by describing the roles of MRs and GRs in the various stages of information processing and the context in which glucocorticoid-receptor activation takes place. The effects of glucocorticoids on brain tissue as well as cognition can turn from adaptive into maladaptive when actions via both receptor types are imbalanced for a prolonged time (Joels et al. 2008; de Kloet et al. 2007).

The secretion of cortisol and norepinephrine in response to acute stress is known to affect learning and memory (Smeets et al. 2011; van Stegeren et al. 2010). The mammalian brain does not house a solitary brain region mediating the acquisition, consolidation, and retrieval of all types of learned information. Instead, memory and learning are organized in multiple brain systems. Certain brain regions (e.g., the prefrontal cortex) govern goal-directed learning, whereas others (e.g., the dorsal striatum) are responsible for habit formation. Stress can induce a bias by promoting habit-based forms of learning and memory in lieu of goal-directed performance. Specifically, studies in rodents have determined that corticosterone and norepinephrine promote habit-based memory formation by acting on the amygdala, hippocampus, dorsal striatum, and prefrontal cortex—all of which also are involved in alcohol dependence. The relationship between cortisol and the vulnerability to alcohol dependence as well as to relapse after abstinence could involve cortisol's effects on habit-based learning. In view of the habit-like nature of addictive behaviors, it is fascinating that recent evidence indicates a role for the habit memory system located in the dorsal striatum in the maintenance and expression of drug-seeking and drug-taking behaviors (Everitt et al. 2008). For example, anxiety-inducing (i.e., anxiogenic) drugs can promote the use of dorsal striatal-dependent habit memory in rats (Packard 2009).

Research in humans also has shown that stress is associated with decreased use of cognitive behavioral strategies, which involve the hippocampus, and increased use of stimulus-response strategies, which involve the caudate nucleus (Kim et al. 2001; Schwabe et al. 2007). It is possible that the heightened cortisol responsivity in people at increased risk for alcohol dependence may promote the transition to heavy, hazardous drinking through cortisol's ability to promote habit-based memory formation and learning during alcohol intoxication, especially during states of heightened arousal (Smeets et al. 2009). Furthermore, the wide fluctuations in cortisol secretion observed in alcohol-dependent people could help maintain these habit-based addictive behaviors. Additionally, the hypercortisolism associated with alcohol dependence may in part promote relapse by favoring the use of habit-based memory to guide the expression of maladaptive behaviors. Finally, persistent hypercortisolism observed during repeated episodes of acute alcohol intoxication and withdrawal may be toxic to neurons in the hippocampus. Hippocampal damage, in turn, may result in alcohol-related symptoms such as personality changes, memory loss, and depression.

Chronic exposure to elevated glucocorticoid levels also can have a detrimental effect on prefrontal cortex function with concomitant neuronal degeneration (Bennett 2008). As mentioned earlier, the prefrontal cortex is involved in complex cognitive operations, including assessing likelihood of reward or punishment during critical decision-making situations as well as assessing internal and external affective cues and responding adaptively, particularly in stressful situations. Psychosocial stress can disrupt prefrontal cortex function in humans (e.g., Liston et al. 2009). However, the specific effects of glucocorticoids in this process remain to be determined (Het et al. 2005) because other physiological changes that occur as part of the overall stress response, such as increased catecholamine levels, also alter prefrontal cortex function (Qin et al. 2009). Animal studies have suggested that glucocorticoids play a role in the cognitive deficits observed after withdrawal from chronic alcohol consumption (Rose et al. 2010). In mice, the glucocorticoid receptor antagonist mifepristone reduced memory deficits during the first and second week after alcohol withdrawal, suggesting that heightened glucocorticoid levels during withdrawal directly contribute to these cognitive deficits (Jacquot et al. 2008). Studies in humans found that cognitive impairment in abstinent alcoholics was related to an attenuated cortisol response to a psychosocial stressor (Errico et al. 2002). Poorer cognitive performance also was related to more withdrawal episodes, heavier alcohol consumption, and higher cortisol levels during withdrawal (Errico et al 2002; Keedwell et al. 2001). Thus, further studies should investigate the mechanism through which altered stress regulation of the HPA axis impairs cognitive function and relates to poor prognosis in recovering alcoholics.

The amygdala is another limbic structure that is affected by cortisol in ways that might contribute to alcohol dependence. The amygdala is a major extrahypothalamic source of CRF-containing neurons that carry large numbers of CRF-1 and CRF-2 receptors; it has a primary role in the processing and memory of emotional reactions.

Thus, the extended amygdala is crucial for the expression of anxiety, and the central amygdala is a major extrahypothalamic site where CRF is produced and plays a role in mediating fear and anxiety (Gray and Bingaman 1996; Heilig et al. 1994). Whereas the hypothalamic CRF system is important for modulating neuroendocrine responses to stress, the extrahypothalamic CRF system manifests the behavioral response to stress via the amygdala and other limbic regions. In rats with high alcohol preference and anxiety levels, CRF gene expression is reduced in the central nucleus of the amygdala (Hwang et al. 2004); moreover, the extracellular levels of CRF in the central amygdala are increased during acute alcohol withdrawal and during exposure to various forms of stress (Merlo-Pich et al. 1995). Chronically elevated corticosterone levels also increase CRF expression in the central amygdala (Shepard et al. 2000; Schulkin et al. 1998). This enhanced CRF production may contribute to anxiety-like behaviors. The heightened or exaggerated emotional and fearful reactivity to perceived stress, in turn, may drive alcohol consumption observed during heavy, hazardous drinking and alcohol dependence. Consistent with this theory, administration of CRF antagonists reverses anxiety-like behaviors and excessive alcohol drinking associated with alcohol withdrawal (Valdez et al. 2003). These observations suggest that heightened cortisol exposure influences alcohol consumption by inducing anxiety and dysphoria via CRF-mediated activation of the amygdala.

Early Abstinence and Relapse

As mentioned earlier, a blunted hormonal response to stress during early abstinence is related to increased risk for relapse (Junghanns et al. 2003, 2005; Kiefer et al. 2002). The mechanism underlying this relationship is not clear. Because cortisol levels in alcohol-dependent people negatively correlate with self-reported alcohol craving (Bohn et al. 1995), it is possible that relapse to alcohol consumption during early abstinence partly is driven by alcohol's ability to induce cortisol elevation (Junghanns et al. 2005). If this is the case, cortisol may influence the motivation to drink and relapse via a potential negative-reinforcement pathway. Several observations support this hypothesis. For example, several studies evaluating pharmacological treatments for relapse prevention during early abstinence have examined the relationships among HPA activity, craving, and alcohol intake during early abstinence, based on the hypothesis that risk for relapse may be attenuated through mechanisms that reduce craving and increase cortisol. For example, O'Malley and colleagues (2002) administered naltrexone or placebo for 6 days to alcohol-dependent, non-treatment seekers who then participated in an alcohol self-administration session. Naltrexone treatment resulted in higher cortisol levels, which were associated with lower levels of craving and less alcohol consumption. Similarly, Kiefer and colleagues (2006) studied the efficacy of naltrexone and/or an agent that can block receptors for the neurotransmitter GABA (i.e., acamprosate), both of which are used in alcoholism treatment to reduce craving. The study found that without an active treatment, both ACTH and cortisol levels decreased during early abstinence; conversely, treatment with naltrexone and acamprosate prevented these declines. Moreover, increased ACTH and cortisol during treatment was associated with reduced risk of relapse. Finally, Sinha and colleagues (2009) found that alcohol-dependent patients who had been abstinent for 28 days showed significantly elevated basal cortisol levels as well as a blunted cortisol response to a psychological stressor and to exposure to an alcohol-related cue. Further, stress and cue exposure resulted in significantly enhanced and persistent craving. Although some studies have not been able to demonstrate correlations between changes in cortisol and craving (e.g., Pratt and Davidson 2009), decreased cortisol levels in general have been accompanied by increased craving during early abstinence, which may underlie risk for relapse to alcohol use. Taken together, these studies suggest that cortisol levels and HPA axis reactivity may be useful clinical indicators in the management of relapse risk and that manipulating HPA axis regulation through either pharmacological or psychosocial intervention is a viable avenue of research for developing new alcoholism treatments.

Summary

The HPA axis, an important physiological stress pathway, may play a significant role in the risk and development of AUDs, and the glucocorticoid cortisol may be useful as a biomarker for HPA axis homeostatic regulation. The hormones of the HPA axis act to maintain homeostasis in the presence of stress through a variety of mechanisms. When the HPA axis becomes dysregulated, regardless of cause, deviations in cortisol reactivity result that have been associated with the progressive stages of alcoholism risk, dependence, and abstinence (see figure 2). Considerable research has been devoted to identifying potential underlying mechanisms of the HPA axis dynamics that contribute to progressive stages of alcohol dependence, and the available evidence support several of these potential mechanisms.

First, non-alcohol–dependent drinkers believed to be at risk for developing an AUD, either because of their family history or because of their hazardous drinking patterns, clearly have altered HPA axis function compared with low-risk individuals. The findings regarding the exact nature of this dysregulation (i.e., whether the HPA axis shows hyper- or hyporesponsivity) are mixed, particularly within the family-history literature. However, the equivocal results most likely are related to differences in experimental strategies used and in the levels of alcohol consumption in these drinkers (e.g., tolerance level). Nevertheless, this body of literature generally has established that

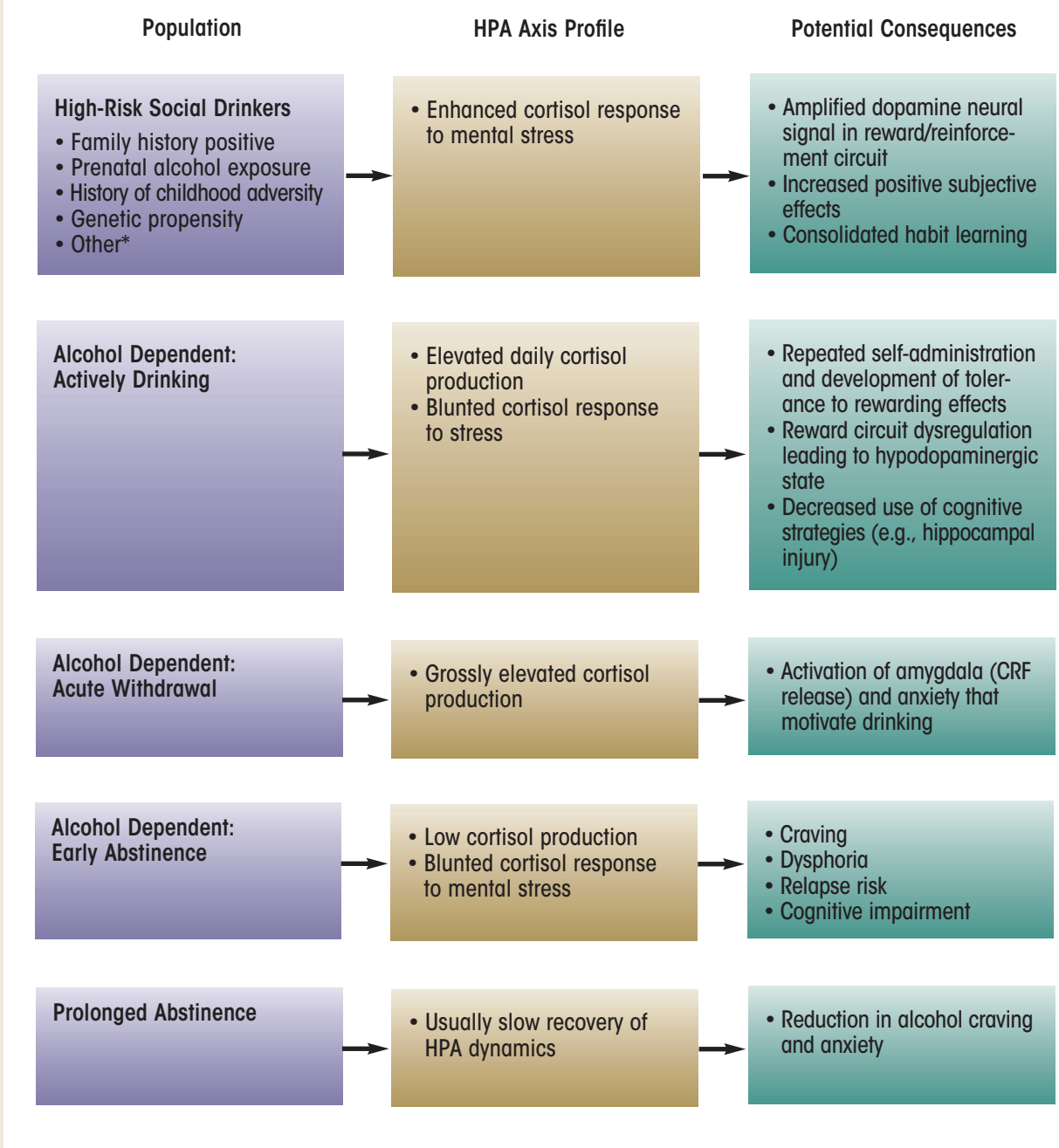

Figure 2 Summary of the activity of the hypothalamic–pituitary–adrenal (HPA) axis during different stages of alcoholism development and their potential consequences.

NOTE: *Low level of response (LR) to alcohol is a phenotype that predicts higher risk for alcohol-related problems (Hu et al. 2005); currently, there are no data characterizing HPA axis response to mental stress in this high-risk group. Posttraumatic stress disorder (PTSD) is a complicated disorder with multiple subtypes and comorbidities; the HPA axis profile of individuals with PTSD symptomatology generally is not thought to react to mental stress with enhanced responsivity and therefore does not fit the model depicted above for other high-risk social drinkers.

cortisol responsivity serves as a risk marker for the propensity for abuse or dependence.

Second, considerable evidence supports the effect of glucocorticoids in facilitating dopamine-mediated signal transmission in the brain, which has been linked to reward pathways involved in almost all drugs of abuse. Moreover, glucocorticoids themselves have positive reinforcing properties. Conversely, reduced glucocorticoid activity seems to suppress acquisition and self-administration of drugs of abuse (Fahlke et al. 1996; Goeders and Guerin 1996). Thus, glucocorticoids appear to play a critical mediating role in the dopamine reward circuit.

Third, cortisol plays a key role in brain regions that are important for cognitive learning and memory retrieval, encoding, and consolidation. These are central processes affected by shifting hyper- and hypocortisolism throughout alcohol dependence as well as by cortisol responses to stress. It is possible that such perturbations in the HPA axis consolidate the type of habit-based learning (rather than goal-directed learning) that sustains maladaptive behaviors related to alcohol use.

Finally, deficiency in cortisol response during early abstinence is predictive of relapse to alcohol and may modulate conditions that often accompany relapse episodes, such as craving, dysphoria, and severe withdrawal symptoms. Thus, cortisol levels during abstinence may be useful clinical indicators of relapse vulnerability, and interventions that increase cortisol and decrease craving might be useful to prevent relapse.

Taken together, HPA axis function may serve as a predictor of risk for alcohol dependence in alcohol-naïve or social drinkers, facilitate initiation and maintenance of alcohol use, or serve as a predictor for risk of relapse in abstinent alcohol-dependent individuals. Using HPA axis reactivity as a predictive marker may help to identify individuals at risk for dependence or relapse prior to development of those conditions, which would allow the individuals and their treatment providers to take action and improve overall prevention and treatment efforts for AUDs. ■

Acknowledgements

Authors' work cited in this article was supported by National Institute on Alcohol Abuse and Alcoholism grants AA–12303 and AA–10158.

Financial Disclosure

The authors declare that they have no competing financial interests.

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Clinical Laboratory Stressors Used to Study Alcohol–Stress Relationships

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Understanding the biologic systems that underlie the relationship between stress and alcohol consumption may lead to better prevention efforts and more effective treatments for alcoholism. Clinical laboratory studies offer a unique opportunity to examine these relationships by using a controlled environment to study how an acute stressor affects alcohol drinking and alcohol craving, how individuals in recovery or those at risk for alcoholism may respond differently to stressors relative to control subjects, and how alcohol differentially affects stress reactivity in these groups. This article reviews some of the most common physical, psychological, and pharmacological stressors used in stress-induction studies designed to reveal details about the relationship between stress reactivity and alcohol use and abuse. **KEY WORDS: Alcohol consumption; alcohol use and abuse; alcoholism; stress; stressor; physiological stressor; psychological stressor; pharmacological stressor; biological adaptation to stress; stress reactivity; stress-induction study; clinical study; laboratory study; controlled study**

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A comprehensive understanding of the relationship between stress and alcohol use is important for understanding the risks of developing alcohol problems and subsequent relapse. Although the relationship is complex, substantial evidence supports that exposure to chronic stress early in life (e.g., Sher et al. 1997), adult trauma (Kessler et al. 1995), and the presence of anxiety disorders (Grant et al. 2004) all are associated with increased prevalence of alcohol use and risk of developing of an alcohol use disorder. Although people with high levels of stress may report that they use alcohol to reduce stress (Thomas et al. 2003), there is inconsistent evidence that stress promotes subsequent drinking (Helzer et al. 2006; Park et al. 2004; Todd et al. 2009). Likewise, inconsistent evidence exists as to whether inducing stress in people with alcohol dependence leads to craving or drinking (Cooney et al. 1997; Fox et al. 2007; Ray 2011; Thomas et al. 2011*a*,*b*) or whether alcohol use actually relieves stress (see Sayette 1999). Even so, stress is a frequently cited reason for relapse by people with alcohol dependence, and most evidence-based treatments for alcohol dependence include stress coping and mood management (Marlatt and Gordon 1985; Vieten et al. 2010).

The complexity of this issue warrants investigation with well-controlled studies. With clinical laboratory studies, researchers can conduct experiments to establish causal relationships between stress and alcohol use. In contrast to studying stress and drinking in the real world, the clinical laboratory setting allows scientists to carefully calibrate and apply a stressor, to administer different types of stressors, and to assess the interaction among multiple preexisting variables (e.g., genotype, temperament, drinking motives, alcohol

expectancies, or comorbid psychiatric conditions) and stress response variables (i.e., subjective, physiological, and neuroendocrine responses). Such studies permit the study of sensitivity or resilience to acute stressors in at-risk or currently dependent individuals, of how alcohol can differentially reduce stress reactivity in different groups of participants, or how and whether a stressor induces alcohol craving or consumption.

A Review of Clinical Laboratory Stressors

This article reviews some of the most common methods used to induce a stress response in participants in a clinical laboratory setting. The stressors are divided into three main categories: physical, psychological, or pharmacologic. As explained throughout this article, the best stressor to use depends on the research question of interest.

Physical Stressors

Physical stressors, such as pain, exercise, or extreme temperatures, are communicated directly to the hypothalamus by way of the nervous system (Herman and Cullinan 1997). These stress responses minimize the subjective interpretation of the stressor, which is useful when subjective interpretation of the stressor is considered noise variability.

In the Cold Pressor Test (CPT), participants submerge their hand in a cold water bath (0° to 6°C) for as long as can be tolerated up to a given maximum duration, typically 1 to 2 minutes (Velasco et al. 1997). The CPT reliably induces cardiovascular activation, subjective distress/discomfort, and may induce brief and modest activation of stress hormones such as adrenocorticotropic hormone (ACTH) and cortisol (McRae et al. 2006). Alcohol-dependent and non–alcohol-dependent people differ in their response to the CPT in that the former show a less robust neuroendocrine response but report more subjective distress (Brady et al. 2006). Generally speaking, the CPT does not increase craving in alcoholics, although individual differences in craving response following the CPT have been shown to predict alcohol use 1 month later (Brady et al. 2006).

Physical exercise evokes activation of the hypothalamic–pituitary–adrenal (HPA) axis, which controls the body's major hormonal stress response, both in nonalcoholic study participants (Coiro et al. 2007; Singh et al. 1999) and alcoholics (Coiro et al. 2007). Coiro and colleagues (2007) examined how length of abstinence (4, 6, and 8 weeks) associated with stress reactivity using a stationary bicycle that measures work performed, with activity workload increasing every 3 minutes until participants reached exhaustion (approximately 15 minutes). Whereas exercise induced a significant rise in plasma ACTH and cortisol in nonalcoholics, 4-week-abstinent alcoholics failed to show an exercise-induced rise in either measure. After 6 weeks of abstinence, the endocrine response was partially normalized, and after 8 weeks of abstinence the ACTH and cortisol response was nearly identical to the nonalcoholic group (Coiro et al. 2007). Physical exercise has not, to the authors' knowledge, been examined in a clinical laboratory setting for its ability to induce craving or drinking in alcoholics or social drinkers or to compare stress reactivity between at-risk individuals and healthy study participants.

The isometric handgrip exercise is a classic physical stressor frequently used in laboratory studies examining cardiovascular response because it reliably produces elevations in blood pressure and heart rate (Ewing et al. 1974). With this task, the participant squeezes a handgrip dynamometer as firmly as possible to determine his or her maximal handgrip strength. Then the participant is instructed to squeeze and maintain pressure at 20 to 40 percent of maximum strength for 2 to 5 minutes. No studies of the handgrip stressor alone have reported how the stressor differentially affects alcoholics versus control subjects, although studies combining the handgrip exercise with additional stressors produced a blunted cortisol response in alcoholics compared with nonalcoholics (Bernardy et al. 1996). To date, the isometric handgrip stressor has not been used as an applied stressor to examine its effect on craving or drinking.

In general, physical stressors are best suited to study specific mechanisms underlying the stress response that may be perturbed as a result of repeated alcohol exposure. In addition, they may be used to characterize individuals as high- and low-stress responders and examine subsequent response to nonphysical stressors (Singh et al. 1999). Physical stressors do not mimic stressful experiences that likely lead to drinking or relapse in the real world, so if the research question is how a stressor affects subsequent alcohol use or urge to use, psychological stressors may be a better choice.

Psychological Stressors

Psychological stressors, by definition, involve cognitive assessment of the stressor and can be classified broadly into three main categories—performance tasks, social interaction tasks, and individualized guided imagery or other mood-inducing stimuli, although a stressor may include more than one type.

Performance Tasks

Performance tasks are designed to induce a stress response by challenging a person to solve a problem that is either difficult in its own right or is made difficult with stringent time constraints. The stress response is typically characterized by subjective measures (e.g., degree of reported distress, frustration, and anger) and objective measures, such as cardiovascular responses and electrical conductance of the skin (i.e., skin conductance, which varies with the amount of sweat produced).

The mirror star-tracing task requires participants to trace a star while being provided misleading visual feedback regarding how to adjust one's course

(e.g., up/down and left/right are reversed). Although there are no known studies examining the effects of this task specifically in alcoholics, a similar procedure has been used in individuals in a general substance abuse treatment facility. The degree of distress/frustration induced by the task (as measured by the participant discontinuing the task) was negatively related to subsequent retention in treatment (Daughters et al. 2005). Correlational in nature, these results do not yet reveal whether the mirror star-tracing task can be used to evaluate an individual's stress reactivity or its effect on alcohol consumption or craving.

In the computerized Paced Auditory Serial Addition Task (PASAT) (Lejuez et al. 2003), numbers are sequentially presented on a computer screen and participants are requested to sum consecutive numbers in sets of two. For example, values 2 and 4 are presented (correct answer = 6) and then followed by 8 (correct answer = 12, because 8 is added to the last number presented and not the sum previously derived). The PASAT has been shown to induce changes in skin conductance, elevations in heart rate, and emotional distress (Lejuez et al. 2003) and small increases in salivary cortisol (Pratt and Davidson 2009). High PASAT-induced distress predicted early dropout from a substance abuse treatment program (Daughters et al. 2005). However, the PASAT did not induce craving or subsequent drinking in a clinical laboratory study with alcoholics (Pratt and Davidson 2009).

Social Interaction Tasks

Performance tasks lack an important element of inducing psychological distress—the threat of social evaluation (see Dickerson and Kemeny 2004 for a review). In healthy men, a performance test increased blood pressure by 5 to 10 mmHg, whereas a social interaction task induced changes of twice that magnitude (Dimsdale et al. 1988). Not surprisingly, social-interaction tests also have been shown to induce greater cardiovascular, neuroendocrine, and subjective responses than physical stressors (Dimsdale et al. 1988; McRae et al. 2006).

A variety of methods are available to induce social interaction stress, including methods to induce feelings of social rejection and self-consciousness about physical appearance (Sayette et al. 2001; Stroud et al. 2000), but the gold standard of social interaction stressors is the Trier Social Stress Test (TSST). The TSST (Kirschbaum et al. 1993) is a widely used standardized social stress procedure in which the participant is sequentially exposed to three unique stress-inducing situations: a preparation phase, an interview phase, and a mental arithmetic phase. In the preparation phase, the participant is instructed to prepare his or her talking points for a subsequent mock job interview. A few minutes later, the participant engages in a mock job interview, presenting to confederates who are trained to remain stoic during the interview process. Finally, the participant performs a serial subtraction task to the audience, and if an incorrect value is given, the participant must begin again with the initial number. Each element of the TSST typically lasts 5 minutes, for a total exposure time of about 15 minutes (Kirschbaum et al. 1993).

The TSST has been shown to evoke a robust and predictable response curve for subjective distress, heart rate, blood pressure, cortisol, and ACTH (Kirschbaum et al. 1993; Singh et al. 1999). Generally speaking, the TSST induces a two- to fourfold increase in cortisol levels (Kirschbaum et al. 1993; Singh et al. 1999). Because the TSST yields such a marked and objectively measurable stress response, it is especially well suited for studies in which stress reactivity outcomes are of particular interest.

The TSST has been widely used to compare the magnitude of stress reactivity and stress-response dampening by alcohol in individuals at risk for alcoholism, as defined by heavy drinking or a family history of alcoholism. These studies generally support that at-risk individuals differ from healthy counterparts on both stress reactivity and stress-response dampening (Croissant and Olbrich 2004; Uhart et al. 2006; Zimmermann et al. 2009). Research also generally suggests that alcoholics and nonalcoholics differ in their response to the TSST (Lovallo et al. 2000; McRae et al. 2006; Munro et al. 2005).

Relatively few studies have examined the effect of the TSST or other social interaction–based stressors on alcohol craving or consumption. The TSST has been shown both to induce craving (Nesic and Duka 2008) and also to have no effect on craving (de Wit et al. 2003; Nesic and Duka 2006) in social drinkers. In studies of stress-induced craving or drinking in problem drinkers, Thomas and colleagues (2011*a*) found that the TSST increased drinking but not alcohol craving or alcohol cue reactivity (Thomas et al. 2011*a*,*b*) in non–treatment-seeking alcoholics.

In general, the TSST is especially well suited for research questions related to stress reactivity—for example, variables that predict stress reactivity, such as family history of alcoholism (Uhart et al. 2006) and the effect of alcohol on the stress response (Zimmermann et al. 2009). The TSST may be valuable for examining stress-induced drinking in a laboratory setting (Thomas et al. 2011*a*), but more studies are needed to replicate this finding. Most clinical laboratory studies conducted to examine whether stress induces drinking or craving have relied on personalized (rather than standardized) stressors, such as individualized guided imagery.

Individualized Guided Imagery

Significant individual differences exist in what is interpreted as stressful. Guided imagery paradigms use stimuli that are individually calibrated for emotionality and stressfulness to induce emotion and stress reactivity while approximating real-life situations (for review, see Sinha 2009). The individualized guided imagery procedure involves developing personalized imagery scripts for both stressful and nonstressful situations.

Scripts are developed based on the participants' own descriptions of each situation. Individualized scripts are then recorded on an audiotape and presented to the participant in the laboratory with instructions to imagine the situation "as if it were happening right now," so that the relevant mood can be induced. Researchers then compare responses to stressful and nonstressful scripts, as well as their respective effects on substance use variables of interest (e.g., craving).

Individualized stress imagery has been shown to increase negative emotions, and to a lesser degree, cardiovascular activity, ACTH, and cortisol (Sinha 2007). The procedure has been used to identify differences in stress responses between social drinkers and people who are alcohol dependent (Sinha et al. 2009) and to show that alcohol and drug craving is elevated following exposure to stressful versus neutral imagery cues in individuals with alcohol dependence (Cooney et al. 1997; Fox et al. 2007; Sinha 2007). It is unknown whether guided imagery stressors increase drinking in alcoholics, although it has been shown that severity of craving following exposure to stressful scripts predicted time to relapse following inpatient treatment (Sinha et al. 2011).

Although guided imagery is the most widely used technique in alcohol and addiction research to induce a specific mood, other mood induction approaches include exposure to somber or otherwise emotionally laden music (Birch et al. 2004; Grant et al. 2007; Jansma et al. 2000; Willner et al. 1998) or to sad or disturbing images (Mason et al. 2008). In general, these techniques are effective in inducing the target mood, although amenable to confirmation only with subjective indices. Only negative mood induction using music has been shown to induce the urge to drink and only in certain subgroups, such as those who report using alcohol as a coping strategy (see Birch et al. 2004; Grant et al. 2007).

Psychological stressors have the advantage of modeling stressors, or at least stress-induced emotions (anxiety, dread, frustration, and embarrassment), that individuals encounter in the real world. If psychological stressors are used and objective confirmation of the stressor is not feasible, investigators are encouraged to use subjective measures that capture a range of emotions, where the participant can report changes in fear, anger, frustration, humiliation, etc., and not simply the level of "stress" experienced. Visual analog scales querying multiple emotions (see de Wit et al. 2003) and standardized instruments (see sidebar) allow the respondent to more fully describe his or her subjective interpretation of the stress experience.

Pharmacologic Stressors

The primary events of the stress response are the release of corticotropin-releasing factor (CRF) and vasopressin from the hypothalamus, resulting in the release of ACTH from the pituitary gland to stimulate the adrenal cortex to release cortisol. Cortisol then inhibits the release of CRF and ACTH in a negative-feedback loop. Pharmacological stressors have been used primarily to identify specific disruptions in this system that occur as a result of alcohol dependence or pre-existing differences between at-risk and low-risk individuals.

CRF, ACTH, and cortisol release can be induced through a number of different agents, including glucose-depriving medications such as insulin (Costa et al. 1996) or 2-deoxyglucose, nicotine (Matta et al. 1998), and alcohol itself. Agents that mimic the actions of serotonin (i.e., serotonergic agonists), such as fenfluramine (Anthenelli et al. 2001), meta-chlorophenylpiperazine (mCPP) (Krystal et al. 1996), and citalopram (Mondelli et al. 2006) also increase hypothalamic CRF, although direct pituitary and adrenal effects also have been posited (Dinan 1996). In addition, agents that block opiate receptors (i.e., antagonists, such as naloxone) block opioid tonic inhibitory modulation of CRF and so result in release of ACTH and cortisol (Inder et al. 1995). Another approach is to apply synthetic or species-specific versions of CRF and ACTH. The administration of ovine CRF (oCRF) mimics the effect of naturally occurring CRF on the pituitary, and a synthetic derivative of ACTH (i.e., cosyntropin) directly stimulates cortisol release from the adrenal cortex. In addition, researchers have used synthetic steroid hormones (i.e., glucocorticoids, such as dexamethasone) to examine the integrity of negative-feedback mechanisms (Khan et al 1984).

Most pharmacological stressors have been used to examine how people with alcohol dependence or risk of developing dependence via positive family history differ from nonaffected study participants or how time in recovery affects the HPA axis. For example, regarding family history, administration of alcohol as a pharmacologic stressor resulted in a blunted cortisol response in young men with an alcohol-dependent biological father but not in a comparison group (Schuckit et al. 1987). On the other hand, opiate receptor antagonists have resulted in higher ACTH and/or cortisol response in people with a positive family history of alcoholism compared with those with a negative family history (King et al. 2003; Wand et al. 2001). Neither oCRF (Waltman et al. 1994) nor cosyntropin (Wand et al. 1999) showed differences between family history positive and negative individuals.

Results from pharmacological challenge studies with people who are alcohol dependent tend to be more consistent. Alcoholics typically exhibit a muted ACTH or cortisol response to these stressors, including insulin (Costa et al. 1996), nicotine (Coiro and Vescovi 1999), naloxone (Inder et al. 1995), and mCPP (Krystal et al. 1996). Some notable exceptions include exaggerated cortisol responses to fenfluramine (Anthenelli et al. 2001) and 2-deoxyglucose (George et al. 1994). Both oCRF and cosyntropin produce

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Quantifying Stress Reactivity

In stress-induction studies, stress response optimally is measured with both subjective and objective indices because together these provide the strongest evidence for the internal validity of the stressor. Data from objective and subjective measures also may provide complementary (not necessarily overlapping) information. For example, a robust stress-induced change in cortisol is not necessarily correlated with a more intense experience of distress (Dickerson and Kemeny 2004). Both objective and subjective outcomes should be assessed prior to, and multiple times following, the stress-induction procedure to reveal the time course of the stress response. The following sections describe the subjective and objective indices most commonly used in stress-induction studies to confirm and quantify stress reactivity in alcohol research (for a more comprehensive review of assessments, see Davis et al. 2007).

Subjective Measures of Stress Reactivity

Subjective measures of stress reactivity quantify the individual's experience of distress or discomfort via his/her self-report. The most commonly used subjective measure of stress reactivity is a 7- (1 to 7) to 11- (0 to 10) point Likert scale or a visual analog scale (VAS) (measured along a 100-mm line) on which the respondent rates his/her severity of distress. For Likert scale items, the low and high values may reflect level of agreement with a statement such as "I feel stressed" or may reflect the degree of a stressed state ("none at all" to "extreme"). For VAS items, the line is labeled "none at all" at the left end and "the most I've ever experienced" at the right end, and the respondent indicates his/her current state by placing a mark along the line. The location of the mark is measured in millimeters from the end with the low-severity anchor. For both the Likert and VAS scale question, the state assessed may be a single concept, such as "distress" or "stress," or several terms may be used with each rated singly, such as fear, nervousness, anger, or anxiety. Likert and VAS scales also have been used to index feelings that are in contrast to the experience of distress, such as neutral, happy, pleasant, relaxed, and calm, with the rationale that such feelings should decrease as aversive states are induced by the stressor. Results from each descriptor typically are analyzed separately rather than summed to compute a total score. In addition to measuring what they intend to measure (i.e., having face validity), these scales have been psychometrically evaluated and have been shown to adequately capture current feelings of anxiety (Davey et al. 2007). They also are simple and inexpensive to administer, and collecting results does not require extensive time. As a result, nearly every stress-induction study includes at least one self-reported Likert scale or VAS item to quantify participants' distress.

Standardized questionnaires also are used to assess distress in stress-induction studies. These instruments include multiple items that are used to compute a total score and/or subscale scores. Standardized instruments also allow comparison of results across studies. Four commonly used instruments in stress induction challenges in alcohol research are the State–Trait Anxiety Inventory (STAI; 20 items) (Spielberger 1983), the Positive and Negative Affect Schedule (PANAS; 20 items) (Watson et al. 1988), the Profile of Mood States (POMS; 65 items) (McNair et al. 1971), and Izard's Differential Emotions Scale (DES; 30 items). Each of these instruments has sound psychometric properties, as reported in their source references (see Boyle 1984 for the DES). Because of the length of these instruments, they may not be suitable for repeated assessment over a short time frame and may induce participant fatigue. To minimize these problems, investigators often use shorter versions such as the 6-item STAI (Marteau and Bekker 1992) or administer selected subscales from the instruments, such as the tension–anxiety subscale (9 items) from the POMS.

Objective Measures of Stress Reactivity

Objective measures of stress reactivity quantify physiological changes that reflect activation of the hypothalamic–pituitary–adrenal (HPA) axis and the sympathetic nervous system. These include neuroendocrine measures, such as levels of the stress hormones adrenocorticotropic hormone (ACTH) and cortisol, and physiologic measures such as heart rate, blood pressure, and, less commonly, skin conductance. Neuroimaging, which recently has been adopted as an additional objective assessment of stress reactivity, can be used to show activation of brain areas associated with regulating emotion (see Sinha and Li 2007). As the latter is restricted in its use to specific stressors amenable to delivery in the scanner, the following section focuses on the objective assessments of stress reactivity that may be collected following any stress induction procedure.

ACTH and cortisol are the two neuroendocrine measures most often used to index stress reactivity and

specifically HPA axis activation. ACTH is produced and secreted by the anterior pituitary gland to promote the adrenal cortex to release cortisol. ACTH must be measured from blood, whereas cortisol may be measured in either blood or saliva. Salivary cortisol reflects the binding protein-free fraction and thus the biologically active form of cortisol and may be less susceptible to interference by oral contraceptives (Vining et al. 1983). Although either serum or salivary cortisol can index HPA axis activity, salivary cortisol provides a more accurate depiction of active circulating cortisol (Gozansky et al. 2005).

If blood is collected in the challenge, care must be taken not to induce "noise" stress by repeatedly sticking the participant to draw the sample. Thus, a peripheral venous catheter is recommended. Timing the collection of samples also is relevant, particularly for cortisol, because there is robust diurnal variation in cortisol levels. Investigators can establish a model of baseline levels of cortisol by collecting samples several times prior to the stress manipulation.

The expense of collecting and measuring ACTH and cortisol may be prohibitive for some studies, and investigators may therefore use cardiovascular activity such as heart rate and blood pressure to objectively assess stress reactivity. These measures can be collected with automated equipment, so no extensive training is needed. Heart rate is assessed by beats per minute; systolic and diastolic blood pressure is measured in millimeters of mercury (mmHg). Mean arterial pressure, which reflects the average arterial pressure over a complete cycle of one heartbeat, is computed using systolic and diastolic pressure values. It is especially well-suited for stress-induction procedures because it indexes the role of the sympathetic and parasympathetic systems in regulating blood pressure. Heart rate variability, specifically respiratory sinus arrhythmia, can be calculated from the heart rate as a noninvasive index of parasympathetic control of cardiac activity (Bernstein et al. 1993).

In summary, confirming the validity of the stress-induction procedure is critical to evaluating the effects of the stressor (or lack thereof) on alcohol-related outcomes such as craving or consumption, or how at-risk and alcohol dependent people differ from others in response to an applied stressor. Depending on the specific research question, the stressor selected, and logistical constraints, investigators may select certain indices over others. Given the host of subjective and objective measures of stress reactivity available, however, investigators should seek to quantify the stress response of participants with both subjective and objective data. ■

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lower ACTH and/or cortisol responses in alcohol-dependent men compared with nonalcoholic men (Adinoff et al. 1990, 2005; Inder et al. 1995; Wand and Dobs 1991).

Although pharmacological stressors have not historically been used to examine the effects of stress on subsequent craving or drinking, these stressors more recently have been applied to study whether they can induce alcohol craving in alcoholics (Umhau et al. 2011). The α-2 adrenergic antagonist, yohimbine, induces anxiety (Holmberg and Gershon 1961) yet has inconsistent evidence of inducing craving (Krystal et al. 1994; Umhau et al. 2011). The stressor mCPP has been more effective at inducing not only robust subjective distress but also enhanced alcohol craving (George et al. 1997; Krystal et al. 1994; Umhau et al. 2011). Because pharmacological stressors have the advantage of being directly applicable to preclinical models, and vice versa, they are especially relevant for translational research efforts.

Summary

The relationship between stress and alcohol use is complex, and clinical laboratory studies in which an acute stressor is applied allow researchers to further clarify links between stress reactivity and alcohol use and abuse through systematic study. Research has identified the architecture of the stress response, and evidence across classes of stressors—physical, psychological, and pharmacologic—generally supports the hypothesis that both people with alcohol dependence and those at risk for alcoholism (e.g., heavy drinkers or those with positive family history of alcoholism) differ from comparison groups in their response to applied stressors. Whether this difference contributes to the development of alcohol problems or is simply a phenotypic marker of pre-existing risk is yet unknown. How stress results in alcohol seeking, craving, and/or relapse in individuals with alcohol dependence also is not well understood, but because it has important treatment implications, it is a fruitful area for future study. For example, clinical laboratory studies in which stressors are applied can result in clinical models in which investigators can study whether promising treatments diminish the ability of stress to enhance motivation to drink and whether such treatments may alter stress reactivity (Kosten 2011).

The stressors described in this article frequently are used in clinical laboratory settings and have empirical support for their ability to induce a measurable stress response. Ideally, the ability of an applied stressor to induce stress (i.e., internal validity) is confirmed by both objective and subjective indices. The optimal stress-induction procedure is determined by the specific research question. For example, guided imagery stressors induce subjective distress as well as alcohol craving but may not induce robust changes in stress reactivity as indexed by objective measures. Conversely, the TSST is considered the gold standard for eliciting neuroendocrine reactivity (Dickerson and Kemeny 2004) but has shown inconsistent effects on inducing the urge to drink. If the research question involves understanding what part of the HPA axis cascade is perturbed, pharmacological stressors may be optimal; they also present an exciting opportunity in translational research studies. If the research question is to examine differences between groups on stress reactivity, a stressor that affords both objective and subjective confirmation is recommended. If the study seeks to determine what type of person is likely to be provoked to craving or alcohol consumption by stress, psychological stressors that approximate real-life situations (such as guided imagery and possibly the TSST) may be the best choice.

The complexity of the relationship between stress and alcohol use has resulted in an empirical base with more questions than answers. Research does show that stress is undoubtedly related to alcohol use and vice versa (Cooney et al. 1997; Sinha 2007). Clinical laboratory studies that examine the effects of acute stressors on alcohol-relevant outcomes are critical to elucidating this complex relationship because they provide the opportunity to determine mechanistic links between stress reactivity and alcohol use and abuse, thus providing direction for optimal treatment and prevention efforts. ■

Acknowledgements

This work was supported by grants P50–AA–10761 and T32–AA–07474 to MUSC, R01–AA–13892 (to Dr. Sinha), K23–AA–017466 (to Dr. Uhart), and U01–AA–016668 and the Department of Veterans Affairs (to Adinoff).

Financial Disclosure

The authors declare that they have no competing financial interests.

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Effects of Alcohol Dependence and Withdrawal on Stress Responsiveness and Alcohol Consumption

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A complex relationship exists between alcohol-drinking behavior and stress. Alcohol has anxiety-reducing properties and can relieve stress, while at the same time acting as a stressor and activating the body's stress response systems. In particular, chronic alcohol exposure and withdrawal can profoundly disturb the function of the body's neuroendocrine stress response system, the hypothalamic–pituitary–adrenocortical (HPA) axis. A hormone, corticotropin-releasing factor (CRF), which is produced and released from the hypothalamus and activates the pituitary in response to stress, plays a central role in the relationship between stress and alcohol dependence and withdrawal. Chronic alcohol exposure and withdrawal lead to changes in CRF activity both within the HPA axis and in extrahypothalamic brain sites. This may mediate the emergence of certain withdrawal symptoms, which in turn influence the susceptibility to relapse. Alcohol-related dysregulation of the HPA axis and altered CRF activity within brain stress–reward circuitry also may play a role in the escalation of alcohol consumption in alcohol-dependent individuals. Numerous mechanisms have been suggested to contribute to the relationship between alcohol dependence, stress, and drinking behavior. These include the stress hormones released by the adrenal glands in response to HPA axis activation (i.e., corticosteroids), neuromodulators known as neuroactive steroids, CRF, the neurotransmitter norepinephrine, and other stress-related molecules. **KEY WORDS: Alcohol consumption; alcohol dependence; chronic alcohol exposure; drinking behavior; withdrawal; relapse; stress; stress response; biological adaptation to stress; brain; brain stress pathway; hypothalamic–pituitary–adrenocortical axis; corticotropin-releasing factor; corticosteroids; norepinephrine; human studies; animal models**

Although stress is known to be an important contributing factor to alcohol abuse and alcoholism, the interaction between stress and alcohol drinking behavior, as well as the mechanisms underlying this interaction in the context of dependence are complex and not well understood. On the one hand, alcohol is an effective anxiety-reducing agent (i.e., anxiolytic). Hence, motivation for drinking may be related to its ability to alleviate stress, including stress associated with periods of abstinence following bouts of heavy drinking (Cappell and Greeley 1987; Sayette 1999). On the other hand, alcohol itself can serve as a stressor, activating the hypothalamic–pituitary–adrenocortical (HPA) axis, which constitutes a major component of the hormonal (i.e., neuroendocrine) stress response (Smith and Vale 2006). Furthermore, chronic alcohol exposure and withdrawal experiences not only produce robust perturbations in the HPA axis but also engage neuroendocrine-independent (i.e., extrahypothalamic) brain stress systems that influence drinking behavior in a dynamic and complex manner (Koob and Kreek 2007).

The relationship between stress and alcohol drinking is complicated by a host of alcohol-related factors (e.g., history of use, level and pattern of drinking, or timing of accessibility of alcohol in relation to stress experience) as well as stress-related factors (e.g., type, chronicity, intermittency, predictability, and controllability) that intersect with a number of biological variables (e.g., genetics, age, and sex). For example, clear individual differences exist in sensitivity to, perception of, and responsiveness to stress and alcohol, and both clinical and preclinical evidence indicate that

genetic factors help shape the nature of the relationship between stress and alcohol drinking (Clarke et al. 2008; Uhart and Wand 2009). The dynamic interaction of these biological and environmental variables along with experiential factors plays a critical role in defining subjective aspects of stress (i.e., the perception and appraisal of a stressful event) and alcohol intoxication. These subjective effects, in turn, shape the impact of stress on alcohol drinking and of alcohol consumption on stress responsiveness.

Despite the complex interaction between stress and alcohol consumption, it generally is acknowledged that stressful life events prominently influence alcohol drinking and, in particular, relapse (Brady and Sonne 1999; Sinha 2001, 2008). Several animal models have been developed to study the influence of stress on alcohol consumption. However, reviews of this literature have found equivocal results regarding the circumstances and manner in which stress modulates alcohol drinking (Becker et al. 2011; Pohorecky 1990; Sillaber and Henniger 2004). The discrepancies in results no doubt relate to the aforementioned plethora of variables that influence the reciprocal relationship between stress and alcohol. Nevertheless, researchers continue to focus on stress associated with chronic alcohol exposure and withdrawal experiences and recently have directed attention to stress–alcohol interactions in alcohol-dependent subjects (Becker et al. 2011; Heilig et al. 2010; Pohorecky 1990; Sillaber and Henniger 2004).

This article provides an overview of clinical studies and studies involving animal models of alcohol dependence that demonstrate both prolonged alcohol exposure and repeated periods of abstinence constitute potent stressors to the organism. Studies conducted in rodents, monkeys, and humans are described that highlight the impact of chronic alcohol exposure and withdrawal on neuroendocrine and brain stress pathways, as well as how activation of these brain stress systems, which are closely linked to brain reward systems, alter motivation to drink. Finally, evidence will be presented that stress associated with alcohol dependence not only compromises the ability to mount an appropriate behavioral response to a subsequent stress challenge, but also alters the ability of stress challenges to modulate drinking in the dependent state.

Stress Associated With Chronic Alcohol Exposure and Withdrawal

As previously noted, alcohol activates the HPA axis, with the magnitude and response profile influenced by a host of variables, including the individual's genetic makeup (i.e., genotype) and sex as well as dosing parameters (Rivier 2000; Wand 2000). Alcohol stimulates neuronal activity in the paraventricular nucleus of the hypothalamus, thereby inducing release of corticotropin-releasing factor (CRF) (and vasopressin) from these cells. CRF, in turn, induces the secretion of adrenocorticotrophic hormone (ACTH) from the pituitary, which subsequently acts on the adrenal glands to cause an increase in the circulating levels of glucocorticoids (e.g., cortisol in humans and corticosterone in rodents) (Lee et al. 2001, 2004).

Both clinical and experimental studies have documented profound disturbances in HPA axis function following chronic alcohol exposure and withdrawal. For example, studies in humans (Errico et al. 1993; Wand and Dobs 1991), monkeys (Helms et al. 2012*a*, *b*), and rodents (Kakihana and Moore 1976; Lee et al. 2000; Rasmussen et al. 2000; Tabakoff et al. 1978) have shown that chronic alcohol consumption produces general elevation in blood glucocorticoid levels, flattening of normal circadian fluctuations, and a dampened HPA response to subsequent stress challenge. Periods of abstinence (i.e., withdrawal) also are characterized by elevated glucocorticoid levels that reflect increased HPA axis activity, as well as by increased activity of the sympathetic division of the autonomic nervous system[1] that produces an array of physiological symptoms, including rapid heartbeat (i.e., tachycardia), elevated blood pressure (i.e., arterial hypertension), excessive sweating (i.e., diaphoresis), and body temperature dysregulation (Becker 2000; Heilig et al. 2010). For example, studies in rats have demonstrated increased activity of the adrenal glands and sympathetic nervous system (i.e., sympathoadrenal activity) during alcohol withdrawal, as evidenced by elevated plasma levels of the epinephrine and norepinephrine[2] (Rasmussen et al. 2006). Similarly, increased concentrations of norepinephrine in cerebrospinal fluid were reported during acute alcohol withdrawal in alcoholics (Hawley et al. 1994). Finally, elevated plasma levels of epinephrine (Ehrenreich et al. 1997) and norepinephrine (Patkar et al. 2003, 2004) have been reported in abstinent alcoholics.

As is the case with most physiological features of alcohol withdrawal, autonomic-related symptoms typically wax and wane over the course of acute withdrawal; however, some cardiovascular changes may persist, especially when assessed following a stress challenge (Bernardy et al. 2003; Kahkonen 2004; King et al. 1996). Likewise, studies in humans and animals have shown that whereas heightened HPA axis activation associated with withdrawal usually resolves within a few days (Adinoff et al. 1991; Tabakoff et al. 1978), the blunted HPA axis responsiveness, along with reduced basal levels of circulating corticosteroids, appear to persist for a protracted period of time (Adinoff et al. 1990; Cuzon Carlson et al. 2011; Lovallo et al. 2000; Rasmussen et al. 2000; Zorrilla et al. 2001).

[1] The autonomic nervous system controls involuntary functions of many internal organs. It can be divided into the sympathetic nervous system, which promotes actions requiring quick responses (i.e., the fight-or-flight response), and the parasympathetic nervous system, which promotes responses that do not require immediate action (i.e., the rest-and-digest response).

[2] Epinephrine and norepinephrine (also known as adrenaline and noradrenaline) are two hormones and neurotransmitters that are produced in some nerve cells (i.e., neurons) as well as in the adrenal glands and which have many functions in the body. They are both part of the fight-or-flight response of the sympathetic nervous system.

In addition to these HPA-axis–related effects, alcohol alters the activity of the stress-related neuropeptide CRF outside of the HPA axis (Heilig and Koob 2007; Koob and Zorrilla 2010; Uhart and Wand 2009). Increased CRF activity in several brain structures following chronic alcohol exposure represents an important neuroadaptive change that is thought to be key in the emergence of withdrawal-related anxiety and dysphoria, which likely are intimately tied to alcohol drinking and relapse (Becker 2009; Heilig et al. 2010; Heilig and Koob 2007; Koob and Kreek 2007). Moreover, there is evidence that norepinephrine and CRF systems in the brain not only interact closely to mediate behavioral responses to stress, but also play an important role in negative affective states and relapse vulnerability during alcohol/drug abstinence (Dunn and Swiergiel 2008; Smith and Aston-Jones 2008). Thus, chronic alcohol exposure and withdrawal experiences can be viewed as potent stressors that disrupt the functional integrity of the HPA axis as well as recruit extrahypothalamic CRF and other brain stress systems. This perturbation in brain and neuroendocrine stress systems may have significant implications regarding motivation for alcohol self-administration.

Role of CRF in Stress Associated With Alcohol Dependence and Withdrawal

CRF is a 41 amino-acid neuropeptide that is distributed widely throughout the mammalian brain. It is found in high concentrations in the paraventricular nucleus of the hypothalamus where it acts to regulate HPA axis activity, which is critical for orchestrating behavioral and physiological responses to stress. CRF-containing neurons also are found in many brain regions outside the HPA axis, including an extensive network of interconnected neural structures (e.g., amygdala, bed nucleus of the stria terminals, and prefrontal cortex) that are intimately associated with the brain's reward and stress pathways. The actions of CRF (and of the related peptides urocortin I, II, and III) are modulated by CRF-binding protein and mediated through interaction with two receptors known as excitatory G-protein-coupled receptors (i.e., CRF_1 and CRF_2 receptors) (Bale and Vale 2004). These receptors are distributed in overlapping yet distinct patterns within the brain's reward and stress circuits. This anatomical distribution of CRF and its associated binding sites is congruent with the importance of both hypothalamic and extra-hypothalamic CRF in processing and regulating central, autonomic, and emotional/behavioral responses to stress as well as to rewarding stimuli/events, including alcohol and other drugs of abuse (Bruijnzeel and Gold 2005; Ryabinin et al. 2002).

A large body of evidence indicates that CRF plays a significant role in alcohol (and other drug) addiction (Heilig and Koob 2007; Koob and Zorrilla 2010; Lowery and Thiele 2010). Chronic alcohol exposure can alter CRF neurotransmission as evidenced by withdrawal-related HPA axis activation and long-lasting dysregulation (Adinoff et al. 1990; Rivier 2000). In addition, time-dependent changes in extracellular levels of extra-hypothalamic CRF occur during withdrawal (Merlo Pich et al. 1995; Olive et al. 2002; Zorrilla et al. 2001). Numerous studies have shown that such changes in brain CRF activity have important ramifications regarding alcohol self-administration. For example, CRF infusion into the brain ventricles[3] reduces voluntary alcohol intake in rats (Bell et al. 1998; Thorsell et al. 2005). Likewise, mice genetically engineered to produce higher-than-normal CRF levels (i.e., CRF transgenic mice) exhibited reduced voluntary alcohol intake compared with nontransgenic control animals (Palmer et al. 2004), whereas CRF-deficient mice showed the opposite effect (i.e., increased alcohol drinking) (Olive et al. 2003). Also, there is evidence that basal differences in brain CRF expression may relate to genetically determined differences in the propensity to drink (Ehlers et al. 1992; Hayes et al. 2005).

Indeed, a strong genetic influence on stress–alcohol interactions is related to the role of CRF in mediating stress responsiveness as well as alcohol drinking and risk for dependence. Recent studies in humans, monkeys, and rats have suggested that an association exists between certain gene variants involving only a single DNA building block (i.e., single nucleotide polymorphisms [SNPs]) of the CRF and CRF_1 receptor genes and alcohol drinking (Barr et al. 2008, 2009; Blomeyer et al. 2008; Chen et al. 2010; Schmid et al. 2010). For example, studies in rhesus macaque monkeys have shown that SNPs in various components of the regulatory region (i.e., promoter) for the gene encoding CRF (i.e., the *Crh* gene) affected several stress- and alcohol-related behaviors. Thus, a SNP in the glucocorticoid response element region of the *Crh* promoter (Crh-2232 C→G) predicted bold behavior and high-risk drinking, whereas a SNP in the cAMP response element region of the *Crh* promoter (Crh-248 C→G) conferred augmented stress reactivity and elevated alcohol drinking, but only with a history of early stress/trauma (Barr et al. 2008, 2009). In a longitudinal human study, a history of early childhood stress/trauma events interacted with two SNPs in the gene encoding the CRF_1 receptor (i.e., the *CrhR1* gene) that were associated with earlier age for drinking onset as well as heavier drinking at young adulthood (Blomeyer et al. 2008; Schmid et al. 2010). In another clinical study, several other SNPs in the *CrhR1* gene were associated with the height (i.e., amplitude) of a component P3 of a brainwave known as an event-related potential (ERP)[4] as well as with an alcohol dependence diagnosis (Chen et al. 2010).

Additional evidence for the relationship between genetic variation in the *CrhR1* gene and vulnerability to alcoholism comes from a study in rats (Hansson et

[3] The ventricles are large cavities in the brain filled with cerebrospinal fluid, which bathes the central nervous system and plays a crucial role in maintaining a stable environment for the brain.

al. 2006). These investigators examined the relationship of *CrhR1* expression in brain and stress reactivity as well as the ability of stress to reinstate alcohol-seeking behavior in rats that were selectively bred for high alcohol preference over many generations (i.e., Marchigian-Sardinian Preferring [msP] rats) and in control rats (i.e., outbred Wistar rats). The msP rats showed elevated *CrhR1* expression in several limbic brain regions (e.g., several sub-regions of amygdala and hippocampus) as well as greater behavioral stress reactivity and greater sensitivity to stress-induced reinstatement of alcohol responding. This latter effect was blocked by an agent that can interfere with the activity of the CRF_1 receptor (i.e., the CRF_1 receptor antagonist antalarmin) in msP rats but not Wistar rats. Also, a sequence variation in the promoter region of *CrhR1* was more commonly found in msP rats compared with the control rats. Collectively, these findings indicate that genetic variations in the *Crh* and the *CrhR1* genes interact with stressful life events to influence age of drinking onset, progression of heavy drinking in adulthood, and general vulnerability to alcohol dependence.

Changes in CRF activity resulting from chronic alcohol exposure appear to be key to the emergence of affective-related withdrawal symptoms that may be especially relevant in promoting excessive drinking and enhanced susceptibility to relapse. For example, increased anxiety associated with alcohol withdrawal is reduced by administration of non-selective CRF receptor antagonists into the ventricles (Baldwin et al. 1991; Valdez et al. 2003) or the central nucleus of the amygdala (Rassnick et al. 1993). Selective CRF_1 receptor antagonists administered not directly into the brain (i.e., systemically) produced similar effects, suggesting that withdrawal-related anxiety is mediated by CRF_1 receptors (Breese et al. 2005; Sommer et al. 2008), although a role for CRF_2 receptors cannot be ruled out (Valdez et al. 2004).

Studies using operant reinstatement procedures also have demonstrated an important role for CRF in mediating the ability of stress to trigger relapse-like behavior. For example, CRF antagonists can prevent stress-induced increases in alcohol-seeking behavior (Gehlert et al. 2007; Le et al. 2000; Liu and Weiss 2002; Marinelli et al. 2007). This effect appears to be mediated by extrahypothalamic CRF activity, because removal of the adrenal glands (i.e., adrenalectomy) with or without corticosterone supplementation did not affect reinstatement of alcohol responding induced by foot-shock stress (Le et al. 2000). Direct infusion of a CRF antagonist into a brain structure, the median raphe nucleus, blocked stress-induced alcohol seeking behavior (Le et al. 2002). Taken together, this body of evidence suggests that stress associated with alcohol dependence produces significant changes in CRF function within the brain and neuroendocrine systems that may directly, and/or by mediating withdrawal-related anxiety and stress/dysphoria responses, influence motivation to engage in alcohol self-administration.

Alcohol Dependence, Stress, and Drinking

Alcohol dependence long has been postulated to play a significant role in driving and maintaining excessive drinking. Numerous studies involving rodents have demonstrated that alcohol-dependent animals consume increasing amounts of alcohol if they are given free choice between water and an alcohol solution or if they are rewarded with alcohol after performing a certain task (i.e., in operant conditioning procedures). In most cases, dependence has been induced by delivering alcohol vapor via inhalation chambers. For example, one mouse model of dependence and relapse drinking has demonstrated that repeated cycles of chronic alcohol exposure delivered by inhalation result in an escalation of voluntary alcohol drinking (Becker and Lopez 2004; Lopez and Becker 2005). More detailed analysis of the pattern of alcohol consumption revealed that dependent mice not only consumed greater overall amounts of alcohol compared to non-dependent mice, but also the rate of consumption was faster and progressively increased over successive withdrawal test periods (Griffin et al. 2009*b*). This escalation of alcohol consumption in dependent mice produced significantly higher and more sustained blood and brain alcohol levels compared with that achieved by more modest (stable) intake in nondependent mice (Griffin et al. 2009*b*). Additionally, increased numbers of cycles of chronic intermittent alcohol exposure resulted in greater and longer lasting enhancement of voluntary alcohol drinking (Griffin et al. 2009*a*; Lopez and Becker 2005). Importantly, this effect appeared specific to alcohol because the animals exhibited no changes in water intake or consumption of palatable fluids, including sucrose and saccharin solutions (Becker and Lopez 2004; Lopez et al. 2012). Other investigators have reported similar results using inhalation procedures in mice (Dhaher et al. 2008; Finn et al. 2007) and rats (Rimondini et al. 2002; Sommer et al. 2008). Likewise, studies using operant procedures have demonstrated increased alcohol self-administration in mice (Chu et al. 2007; Lopez et al. 2006) and rats (Gilpin et al. 2009; O'Dell et al. 2004*b*; Roberts et al. 2000) with a history of repeated chronic intermittent alcohol exposure. Additional evidence indicates that repeated alcohol exposure enhances the reinforcing efficacy of alcohol (Brown et al. 1998; Lopez et al. 2008). Studies in mice and rats further have demonstrated that significant escalation of alcohol self-administration is facilitated when chronic alcohol vapor exposure to induce dependence occurs intermittently rather than continuously (Lopez and Becker 2005; O'Dell et al. 2004*b*). These latter findings suggest that stress associated with chronic alcohol exposure and, in par-

[4] ERPs are spikes in brain activity that occur in response to a specific signal, and the P3 wave is one component of such an ERP. The P3 amplitude is considered a marker for sensory processing and cognitive function, and a purported substitute indicator (i.e., endophenotype) for risk of alcoholism and other disinhibitory disorders.

ticular, repeated experience with alcohol withdrawal is crucial for the enhanced motivation to consume alcohol.

Indeed, several studies have demonstrated that dependence models involving chronic intermittent alcohol exposure constitute potent stressors, as evidenced by initial activation and subsequent dysregulation of HPA axis activity (Lopez et al. 2010; Richardson et al. 2008). More specifically, increased cycles of chronic intermittent alcohol exposure appeared to blunt HPA axis activation, as measured by reduced levels of plasma corticosterone (Lopez et al. 2010). This reduced HPA response was observed just prior to withdrawal and at peak withdrawal in a mouse model of alcohol dependence. Recent studies suggest that this dampening of HPA axis activity may relate to enhanced activity of receptors for the neurotransmitter γ-aminobutyric acid (i.e., increased $GABA_A$ receptor function) (Li et al. 2011) and/or reduced number of CRF-releasing neurons (Silva et al. 2009) in the paraventricular nucleus of the hypothalamus. These stress-related adaptations produced by chronic alcohol exposure and withdrawal may underlie the long-lasting dampening of basal and stress-stimulated HPA axis activity that has been observed in abstinent alcoholics (Adinoff et al. 1990; Lovallo et al. 2000; Rasmussen et al. 2000).

In addition to engendering elevated drinking and perturbations in HPA axis function, prolonged alcohol exposure also enhances behavioral responsiveness to stress. For example, rats exhibit increased stress responsiveness following withdrawal from chronic alcohol exposure, as measured by several experimental procedures that provoke behavioral measures of stress/anxiety, such as reduced social interaction in a novel environment, reduced exploration in threatening circumstances (e.g., open, brightly illuminated spaces), and greater electroshock-induced suppression of ongoing behavior (Breese et al. 2005; Gehlert et al. 2007; Sommer et al. 2008). Thus, whereas prolonged alcohol exposure and withdrawal experiences lead to disturbances in homeostatic regulation of HPA axis function, behavioral sensitization to stress may be critical in rendering subjects more vulnerable to relapse and return to uncontrolled, harmful levels of alcohol consumption. Indeed, experimental evidence suggests that stress can provoke relapse-like behavior and increase alcohol drinking more easily in subjects with a history of dependence (Liu and Weiss 2002; Sommer et al. 2008).

Mechanisms Underlying the Alcohol Dependence–Stress–Drinking Relationship

The mechanisms by which stress associated with chronic alcohol exposure and withdrawal influences excessive drinking and increased relapse vulnerability are not fully understood, but several pathways have been suggested.

Role of Corticosteroids. Elevated glucocorticoid levels resulting from dependence-related HPA axis activation may contribute to amplified motivation to drink through an interaction with the brain's reward system, the mesocorticolimbic reward circuitry (Piazza and Le Moal 1997). Central and systemic administration of corticosterone has been shown to increase alcohol consumption, whereas adrenalectomy or administration of a corticosteroid synthesis inhibitor (i.e., metyrapone) decreased alcohol intake in rodents (Fahlke et al. 1995, 1996). Likewise, a glucocorticoid receptor antagonist (i.e., mifepristone) reduced alcohol self-administration behavior (Koenig and Olive 2004). Furthermore, mifepristone administered systemically or into the central nucleus (but not the basolateral nucleus) of the amygdala attenuated stress-induced reinstatement of alcohol seeking behavior (Simms et al. 2012).

Chronic corticosterone exposure in rats also can reduce sensitivity to the subjective (i.e., discriminative stimulus) effects of alcohol (Besheer et al. 2012). A similar outcome also has been reported following chronic alcohol exposure and withdrawal in mice (Becker and Baros 2006). These results suggest that following chronic alcohol exposure and withdrawal, blunted subjective feedback regarding intoxication (possibly related to changes in HPA axis activity) may act as a permissive factor promoting higher levels of drinking. Studies in mice and rats also have shown that withdrawal following prolonged alcohol consumption produced elevated corticosterone levels in certain brain regions (i.e., the prefrontal cortex and hippocampus) that persisted long after plasma corticosterone levels returned to baseline levels (Little et al. 2008). Elevations in brain glucocorticoid concentrations following chronic alcohol exposure and withdrawal not only may have significant implications for motivation to drink, but also may contribute to the cognitive deficits and neurotoxic damage that is commonly associated with alcohol dependence (Rose et al. 2010).

Role of Neuroactive Steroids. HPA axis activity also can influence brain activity through the actions of molecules known as neuroactive steroids. Neuroactive steroids are endogenous neuromodulators that interact with several neurotransmitter systems via rapid membrane action (as opposed to other steroid molecules that act via slower intracellular genomic mechanisms) (Genazzani et al. 1998; Patchev et al. 1994, 1996). Among the neuroactive steroids, compounds 3α,5α-THDOC and 3α,5α-THP, or allopregnanolone, which are the 3α,5α-reduced metabolites of deoxycorticosterone and progesterone, respectively, are the most potent positive modulators of $GABA_A$ receptors. These compounds produce anxiolytic, anticonvulsant, and sedative/hypnotic effects similar to other positive modulators of the $GABA_A$ receptor, including alcohol (Khisti et al. 2002; Morrow et al. 2001; Rupprecht and Holsboer 1999). Additionally, these neuroactive steroids can modulate a variety of alcohol effects, including anticonvulsant, anxiolytic, ataxic/

sedative, and cognitive-impairing effects, as well as the discriminative stimulus and reinforcing effects of alcohol (Khisti et al. 2002; Morrow et al. 2001).

Both alcohol and stress increase plasma and brain concentrations of neuroactive steroids in rodents (Barbaccia et al. 1999, 2001; Finn et al. 2010). This increase appears to be mediated by activation of the HPA axis because the increase in neuroactive steroid levels elicited by these stimuli can be blocked by disruption of the HPA axis via adrenalectomy (O'Dell et al. 2004*a*; Purdy et al. 1991). Alcohol and stress also have been reported to produce elevations in plasma concentrations of neuroactive steroids in humans, but the effects are not entirely consistent (Holdstock et al. 2006; Pierucci-Lagha et al. 2006; Torres and Ortega 2003, 2004). Chronic alcohol exposure also can alter brain and plasma levels of neuroactive steroids in rodents and humans (Cagetti et al. 2004; Janis et al. 1998; Morrow et al. 2009; Romeo et al. 1996). Such neuroadaptive changes in activity of neuroactive steroids may enhance the motivational effects of alcohol, perhaps by modifying the expression and/or function of $GABA_A$ receptors (Biggio et al. 2007; Finn et al. 2010; Morrow et al. 2001; Purdy et al. 2005) and/or through interactions with CRF (Genazzani et al. 1998; Patchev et al. 1994, 1996). In fact, in a mouse model of chronic intermittent alcohol exposure and withdrawal, increased drinking was accompanied by increased expression of allopregnanolone in the brain (Morrow et al. 2009).

Additional evidence suggests that changes in activity of neuroactive steroids play a role in dependence, especially in the expression of withdrawal symptoms as well as alcohol drinking (Finn et al. 2010). For example, allopregnanolone administered systemically (Ford et al. 2005; Sinnott et al. 2002) or directly into the brain or ventricles (Finn et al. 2007; Janak and Gill 2003; Janak et al. 1998) altered alcohol self-administration in male rodents in a dose-dependent manner, with low doses increasing intake and higher doses reducing consumption. In contrast, female animals were relatively insensitive to this biphasic effect of allopregnanlone (Ford et al. 2008), possibly because they have higher basal levels of allopregnanolone (Finn et al. 2010). Finally, allopregnanolone can induce relapse-like behavior in mice (Finn et al. 2008) and rats (Nie and Janak 2003).

Role of CRF. As noted above, numerous studies have demonstrated a significant role for altered CRF activity in dependence-related alcohol drinking. The mouse model of dependence and relapse drinking described earlier has provided evidence for reduced HPA axis activation and compromised behavioral response to a stress challenge. At the same time, additional findings point to an accentuation of changes in the expression and release of CRF in extrahypothalamic brain regions that are implicated in motivational effects of alcohol (Doremus-Fitzwater and Becker 2010; Griffin et al. 2011; Lopez et al. 2010). The role of CRF further is emphasized by observations that a nonselective peptide CRF antagonist (i.e., D-Phe-CRF_{12-41}) reduced excessive drinking in dependent animals when administered into the brain ventricles (Funk et al. 2007; Valdez et al. 2002) or into the central nucleus of the amygdala (Funk et al. 2006*a*, *b*). Further, systemic administration of selective antagonists for the CRF_1 receptor reduced upregulated drinking in dependent mice (Chu et al. 2007) and rats (Funk et al. 2007; Gehlert et al. 2007; Gilpin et al. 2008*a*; Roberto et al. 2010; Sommer et al. 2008).

Role of Norepinephrine. Stress associated with alcohol dependence also includes activation of the locus coeruleus, a nucleus of cells in the brainstem that provides most of the norepinephrine in the brain. This increase in noradrenergic activity plays a role in mediating both somatic and affective aspects of alcohol withdrawal. For example, studies in animal models and clinical investigations have demonstrated that reducing the overall level of noradrenergic activity by stimulating presynaptic autoreceptors with alpha2-adrenergic agonists (e.g., clonidine, dexmedetomidine) is effective in ameliorating various symptoms associated with the excessive activation of the sympathetic nervous system that is characteristic of withdrawal. Therefore, this pharmacological approach may be useful as an adjunct in the management of alcohol detoxification (Muzyk et al. 2011). Additional evidence suggests that alcohol dependence–related changes in brain norepinephrine activity might influence motivation to drink. When investigators reduced norepinephrine activity in the brain by blocking certain norepinephrine receptors (i.e., postsynaptic alpha1-adrenergic receptors) with an antagonist, prazosin, alcohol consumption was reduced in both dependent rats (Walker et al. 2008) and alcohol-dependent humans (Simpson et al. 2009). Likewise, treatment with antagonists (e.g., propranolol) for another type of norepinephrine receptor (i.e., the beta-adrenoceptor) also reduced drinking in dependent rats (Gilpin and Koob 2010).

Roles of Other Stress-Related Molecules. Studies using animal models of dependence and withdrawal also have shown that various other stress-related neuropeptides and modulators within the brain's stress–reward pathways may help drive and/or mediate excessive levels of alcohol drinking. For example, a molecule, neuropeptide Y (NPY), is thought to serve as an anti-stress mediator, in many cases having opposite effects to CRF in the brain (Heilig et al. 1994). Likewise, neuromodulators known as endogenous opioids play a role in mediating and regulating endocrine, autonomic, and behavioral responses to stress (Drolet et al. 2001). Both the NPY system (Gilpin et al. 2011; Thorsell et al. 2005*a*) and the opioid system (Gilpin et al. 2008*a*; Walker et al. 2011) have

been implicated in excessive drinking following chronic intermittent alcohol exposure. A compound, brain-derived neurotrophic factor (BDNF), also has been implicated in stress and addiction processes (Briand and Blendy 2010; Chourbaji et al. 2011; Davis 2008). Thus, regional changes in BDNF expression and/or activity in the brain following chronic alcohol exposure may play a role in mediating withdrawal-related anxiety and regulation of alcohol consumption (Logrip et al. 2009; Pandey et al. 2006). Finally, other stress-responsive systems (e.g., adrenergic, Substance P, and orexin/hypocretin systems) have been shown to influence alcohol consumption (Ciccocioppo et al. 2009; Heilig et al. 2010; Sinha et al. 2011), but their role in mediating excessive drinking associated with dependence has not been specifically examined.

Summary

The bidirectional relationship between alcohol consumption, particularly alcohol dependence and withdrawal, and stress is complex. Clinical and preclinical evidence indicates that chronic alcohol use and withdrawal experience constitute potent stressors, leading to HPA axis activation and long-lasting dysregulation of the neuroendocrine stress response as well as perturbations in sympathetic nervous system activity. In addition, extrahypothalamic CRF activity is altered following chronic alcohol exposure and withdrawal, which in turn influences motivation to drink as well as relapse vulnerability. These observations point to a central role of CRF in the alcohol dependence–stress relationship. This pivotal role further is supported by findings that genetic variations in genes encoding CRF and its receptors can influence susceptibility to alcohol dependence as well as a variety of stress- and alcohol-related behaviors.

In addition, changes in CRF activity, both in the context of the HPA axis and in extrahypothalamic circuitry, have been related to the development of withdrawal symptoms and to the ability of stress to trigger relapse and alcohol-seeking behavior. Indeed, research has demonstrated that a history of dependence not only promotes escalation of alcohol consumption, but prolonged alcohol exposure and withdrawal experience also result in enhanced responsiveness to stress. This enhanced behavioral sensitivity to stress may increase an individual's vulnerability to relapse, particularly in stressful situations, and further exacerbate heavy drinking associated with dependence.

In order to better understand and, ultimately, be able to disrupt the detrimental relationship between alcohol consumption, dependence, and stress, researchers are seeking to elucidate the mechanisms underlying these complex relationships. These investigations have demonstrated that in addition to the impact that CRF has on the alcohol dependence–stress relationship, other factors, such as corticosteroids, neuractive steroids, norepinephrine, and other stress-related molecules all are contributing factors. Clearly, more experimental work focused on identifying neuroadaptive changes within relevant motivational and stress pathways associated with dependence that promote/mediate excessive drinking is key to better understanding the complex reciprocal relationship between stress and alcohol, and conditions in which stress modulates drinking in the context of dependence. ■

Acknowledgements

Supported by National Institutes of Health grants P50 AA010761, U01 AA014095, and R01 AA018036, and Veterans Administration Medical Research.

Financial Disclosure

The author declares that he has no competing financial interests.

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Neural Pathways of Stress Integration

Relevance to Alcohol Abuse

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Stress is a critical component in the development, maintenance, and reinstatement of addictive behaviors, including alcohol use. This article reviews the current state of the literature on the brain's stress response, focusing on the hypothalamic–pituitary–adrenal (HPA) axis. Stress responses can occur as a reaction to physiological (or systemic) challenge or threat; signals from multiple parts of the brain send input to the paraventricular nucleus (PVN) within the hypothalamus. However, responses also occur to stressors that predict potential threats (psychogenic stressors). Psychogenic responses are mediated by a series of nerve cell connections in the limbic–PVN pathway, with amygdalar and infralimbic cortex circuits signaling excitation and prelimbic cortex and hippocampal neurons signaling stress inhibition. Limbic–PVN connections are relayed by predominantly GABAergic neurons in regions such as the bed nucleus of the stria terminalis and preoptic area. Chronic stress affects the structure and function of limbic stress circuitry and results in enhanced PVN excitability, although the exact mechanism is unknown. Of importance, acute and chronic alcohol exposure are known to affect both systemic and psychogenic stress pathways and may be linked to stress dysregulation by precipitating chronic stress–like changes in amygdalar and prefrontal components of the limbic stress control network.

KEY WORDS: Addiction; alcohol and other drug–seeking behavior; alcohol use and abuse; stress; stressor; chronic stress reaction; stress integration; physiological response to stress; psychogenic stress responses; brain; neural pathways; limbic-paraventricular pathway; limbic stress control network; hypothalamic–pituitary–adrenal axis; literature review

Adaptation in the face of physical or psychological adversity is required for the survival, health, and well-being of all organisms. Adverse events, often denoted as "stressors," initiate a diverse physiological response from multiple sources, including activation of the hypothalamic–pituitary–adrenal (HPA) axis.[1] The HPA axis is responsible for the glucocorticoid component of the stress response (i.e., steroid hormone response; cortisol in humans, corticosterone in mice and rats). Glucocorticoid secretion is thought to contribute to stress adaptation by causing long-term changes in gene expression via cognate adrenocorticosteroid receptors (i.e., mineralocorticoid receptor [MR] and glucocorticoid receptor [GR]). The adrenocorticosteroid receptors function as ligand-gated transcription factors (De Kloet et al. 1998) but can also modulate transcription by interfering with other transcriptional regulators, such as nuclear factor-κB (NF-κB) and activator protein-1 (AP-1) (Webster and Cidlowski 1999). Glucocorticoids also can have rapid effects on brain chemistry and behavior via nongenomic membrane signaling mechanisms (De Kloet et al. 2008). Glucocorticoids are thought to contribute to termination of the initial stress response (Keller-Wood and Dallman 1984) and to participate in long-term restoration of homeostasis triggered by the initial response (Munck et al. 1984).

Glucocorticoid stress responses can be initiated by physiological perturbations (representing reflexive responses) or by brain processes linking environmental cues with probable negative outcomes. The latter so-called "psychogenic" response is anticipatory in nature and involves brain pathways responsible for innate defense programs or memory of aversive events (Herman et al. 2003). Thus, the psychogenic response is related to prior experience, and it is designed to energetically prepare the organism to either avoid an adverse outcome or engage in behaviors that can maximize the potential for survival.

[1] For the definition of this and other technical terms, see the Glossary, pp. 522–524.

Considerable evidence indicates that stress systems play a major role in addictive processes, including alcohol dependence. For example, exposure to stress can precipitate relapse or increase alcohol use (Sinha 2007). Actions of stress/glucocorticoids on alcohol intake can be linked to modulation of reward/stress circuitry, including, for example, enhancement of dopamine release in the nucleus accumbens (Sutoo and Akiyama 2002; Yavich and Tiihonen 2000) and activation of central corticotropin-releasing factor (CRF) pathways (Heilig and Koob 2007). Notably, the link between alcohol intake and stress is complicated by the fact that exposure to alcohol, like many drugs of abuse, causes the release of glucocorticoids upon exposure and thus can be classified as an acute "stressor" of sorts (see Allen et al. 2011).

This article reviews the organization of neurocircuits that regulate stress responses, focusing on the HPA axis, which is of particular relevance to addictive processes (see Marinelli and Piazza 2002). It also discusses areas of intersection between stress and reward pathways, as these are likely important in mediating the deleterious effects of stress on substance abuse and addiction.

Circuitry Mediating the Reflexive Stress Response

The HPA axis is controlled by neurons within the paraventricular nucleus (PVN) in the hypothalamus (see figure 1). These neurons secrete CRF and the hormone vasopressin into the portal circulation, which then triggers the release of adrenocorticotropin hormone (ACTH) from the anterior pituitary gland. ACTH travels via the systemic circulation to reach the adrenal cortex, wherein glucocorticoids are synthesized and released (see Herman et al. 2003).

Reflexive stress responses occur during emergencies (e.g., infection, starvation, dehydration, or shock), when the brain must respond to a substantial challenge to homeostasis by mobilizing the HPA axis. Sensory information is communicated to the PVN by first- or second-order neurons, generating a direct activation of CRF release (see Herman et al. 2003). For example, low blood pressure associated with blood loss is relayed via sensory nerves to brainstem neurons in the A2 catecholaminergic cell group (Palkovits and Zaborszky 1977), which then project directly to the PVN (Cunningham and Sawchenko 1988) and rapidly elicit noradrenergic activation of CRF neurons (Plotsky et al. 1989).

In addition to neural pathways, information on changes in physiological state also may be relayed via circulating factors that bind to areas outside the blood–brain barrier. For example, peripheral increases in the hormone angiotensin II (signaling dehydration) are sensed by receptors in the subfornical organ (which is located outside the blood–brain barrier and regulates fluid balance), which sends direct angiotensin II projections to the PVN CRF neurons, facilitating HPA activation (Plotsky et al. 1988). Some peripheral stimuli, such as inflammation, produce factors that can signal by multiple mechanisms; for example, the proinflammatory cytokine interleukin 1-b seems to activate the HPA axis via sensory nerve fibers in the vagus nerve; the area postrema, which is outside the blood–brain barrier; and perivascular cells in the region of the A2 cell group (Ericsson et al.

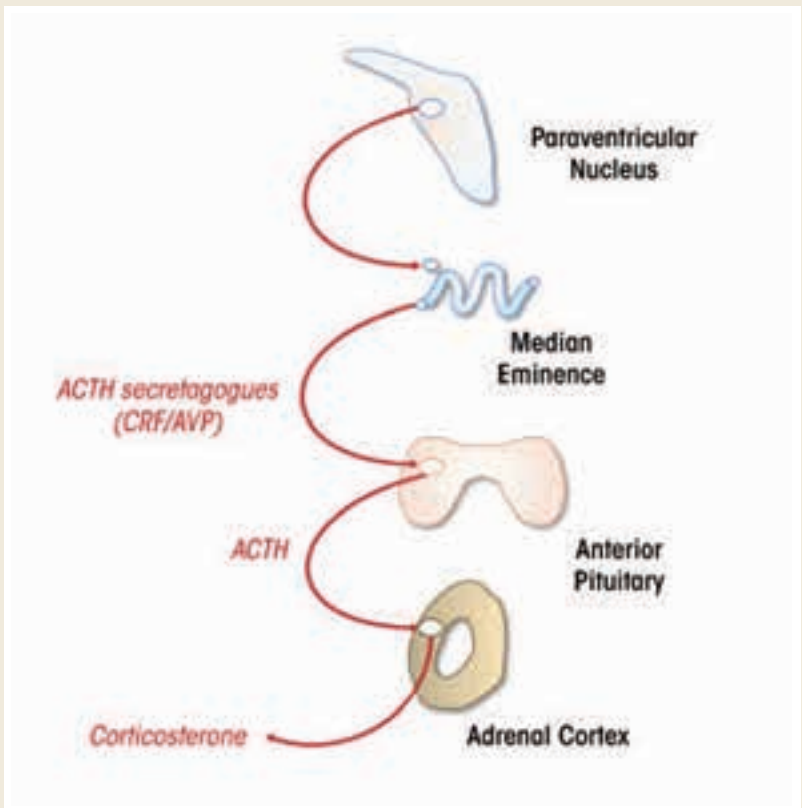

Figure 1 Schematic of the hypothalmic–pituitary–adrenal (HPA) axis of the rat. HPA responses are initiated by neurosecretory neurons of medial parvocellular paraventricular nucleus (mpPVN), which secretes adrenocorticotropin (ACTH) secretagogues such as corticotropin-releasing factor (CRF) and arginine vasopressin (AVP) in the hypophysial portal circulation at the level of the median eminence. These secretagogues promote release of ACTH into the systemic circulation, whereby it promotes synthesis and release of glucocorticoids at the adrenal cortex.

1997; Lee et al. 1998; Wieczorek and Dunn 2006).

Drugs of abuse also may produce an initial corticosterone response via brainstem PVN-projecting pathways. For example, initial exposure to alcohol causes ACTH and corticosterone release, consistent with alcohol acting as an unconditioned stimulus (Allen et al. 2011). Acute HPA axis activation by alcohol is mediated by brainstem noradrenergic systems (Allen et al. 2011). However, chronic exposure to alcohol significantly blunts HPA axis activation to acute alcohol exposure (Rivier 1995), suggesting that, to some degree, direct HPA excitatory effects of alcohol use habituate over time.

Circuitry Subserving Anticipatory Stress Responses: The Limbic Stress-Control Network

Because true physiologic "emergencies" are relatively rare, the vast majority of stress responses are anticipatory in nature, involving interpretation of the threat potential of environmental stimuli with respect to previous experience or innate programs. Anticipatory stress responses are largely controlled by limbic forebrain structures, such as the hippocampus, medial prefrontal cortex (mPFC), and amygdala (see Ulrich-Lai and Herman 2009). These structures all receive processed sensory information and are involved in regulation of emotion, reward, and mood.

Brain lesion and stimulation studies indicate that the hippocampus inhibits the HPA axis. Electrical stimulation of the hippocampus decreases glucocorticoid release in rats and humans. Damage to the hippocampus, or the nerves carrying impulses away from it (i.e., lateral fornix), cause exaggerated responses to psychogenic stressors (e.g., restraint) and manifest as a prolonged return to baseline glucocorticoid levels (for primary references, see Herman et al. 2003; Jacobson and Sapolsky 1991). Some data suggest that the hippocampus also inhibits basal HPA axis activity, but this is not universally observed (Herman et al. 2003; Jacobson and Sapolsky 1991). The effects of hippocampal damage on psychogenic HPA axis stress responses can be localized to the ventral subiculum (vSUB), the main subcortical output of the ventral hippocampus (Herman et al. 2003). Discrete lesions of the vSUB in rats enhance PVN CRF peptide and mRNA expression and increase corticosterone release and PVN activation (as determined by induction of FOS mRNA expression) in response to restraint (Herman et al. 1998).

The effect of the vSUB on stress regulation is stressor specific. Lesions of the vSUB prolong HPA axis responses to novelty but do not affect reflexive responses (e.g., to ether inhalation) (Herman et al. 1998). Some evidence suggests that glucocorticoids play a role in hippocampal inhibition of anticipatory responses, as lesions can block feedback inhibition of the HPA axis by the synthetic steroid dexamethasone (Magarinos et al. 1987). In addition, mice with forebrain GR deletions, including the hippocampus, have exaggerated responses to restraint and novelty (but not hypoxia) and impaired dexamethasone suppression of corticosterone release (Boyle et al. 2005; Furay et al. 2008). Together, the data indicate that the hippocampus is specifically engaged in regulation of responses to psychogenic stressors, in keeping with its role in cognitive processing and emotion.

Unlike the hippocampus, the amygdala is associated with excitation of the HPA axis. Amygdalar stimulation promotes glucocorticoid release, whereas large lesions of the amygdaloid complex reduce HPA axis activity (see Herman et al. 2003). However, there is a marked subregional specialization of stress-integrative functions within the amygdala. The central nucleus of the amygdala (CeA) is highly responsive to homeostatic stressors, such as inflammation and blood loss (Dayas et al. 2001; Sawchenko et al. 2000). Lesions of the CeA attenuate HPA axis responses to these types of stimuli but not to restraint (Dayas et al. 1999; Prewitt and Herman 1997; Xu et al. 1999). In contrast, the medial nucleus of the amygdala (MeA) shows preferential FOS responses to stimuli, such as restraint (Dayas et al. 2001; Sawchenko et al. 2000). Lesions of the MeA reduce HPA axis responses to restraint and light and sound stimuli but not to systemic injection of the protein interleukin 1-b or ether inhalation (Dayas et al. 1999; Feldman et al. 1994). Thus, it seems that reflexive and anticipatory responses may be regulated in part by discrete amygdaloid circuitry.

The mPFC seems to have a complex role in stress regulation. All divisions of the rodent PFC are robustly activated by acute stress. However, the physiological consequences of stress activation seem to vary by region. The prelimbic division of the mPFC (PL) is important in stress inhibition because numerous studies have shown that damage to this region prolongs HPA axis responses to acute psychogenic (but not homeostatic) stressors (Diorio et al. 1993; Figueiredo et al. 2003; Radley et al. 2006), whereas stimulation inhibits stress responses (Jones et al. 2011). The mPFC seems to be a site for glucocorticoid feedback of HPA responses because local glucocorticoid implants inhibit anticipatory (but not reflexive) responses to stressors (Akana et al. 2001; Diorio et al. 1993). In contrast, lesions directed at the more ventral infralimbic PFC (IL) have a markedly different physiological effect. Damage to the IL decreases autonomic responses to psychogenic stressors (Tavares et al. 2009) and also attenuates PVN FOS activation in response to restraint (Radley et al. 2006). Thus, the PL and IL seem to have opposing effects on stress integration.

Running the Relay: Limbic–PVN Networks

Stimulation of the PVN by the hippocampus, prefrontal cortex, and amygdala is quite limited. Therefore, regulation of HPA axis output by these structures requires intermediary

synapses (see figure 2). Studies that trace projections from one part of the brain to another (i.e., tract-tracing studies) reveal the potential for bisynaptic limbic–PVN connections traversing a number of subcortical regions, including the bed nucleus of the stria terminalis (BNST), dorsomedial hypothalamus, medial preoptic area, and peri-PVN region (including the subparaventricular nucleus) (Cullinan et al. 1993; Prewitt and Herman 1998; Vertes 2004). Dual-tracing studies indicate that nerves carrying impulses away from the vSUB, MeA, and CeA (i.e., efferent nerves) directly contact PVN-projecting neurons in these regions, consistent with functional interconnections (Cullinan et al. 1993; Prewitt and Herman 1998).

The differential effects of PL and IL on stress effector systems may reflect their marked divergence in subcortical targets. The PL has substantial projections to reward-relevant pathways, including the nucleus accumbens and basolateral amygdala, as well as the posterior BNST, which is linked to HPA axis inhibition. In contrast, the IL has rich interconnections with regions involved in autonomic regulation, including the CeA, nucleus of the solitary tract (NTS), anteroventral BNST, and dorsomedial hypothalamus (Vertes 2004). Thus, it is probable that the net effect of PFC stress activation requires subcortical integration of PL and IL outflow.

Of note, mPFC, hippocampal, and amygdalar efferents tend to be concentrated in regions sending γ-aminobutyric acid (GABA)-carrying projections to the PVN (see figure 2). Indeed, the vast number of sub-innervated PVN-projecting neurons are GABAergic in phenotype. Projection neurons of the vSUB (as well as the mPFC) are glutamatergic in nature, thus suggesting that these cells engage in transsynaptic inhibition of the PVN following activation by stress. In contrast, the projection neurons of the MeA and CeA are predominantly GABAergic, suggesting that amygdalar excitation of the PVN is mediated by disinhibition, involving sequential GABA synapses (Herman et al. 2003).

The BNST is of particular interest, in that it receives inputs from all of the major limbic stress-integrative structures (CeA, MeA, vSUB, IL, and PL) (Cullinan et al. 1993; Dong et al. 2001; Vertes 2004). Of note, different BNST subregions seem to be responsible for inhibition versus excitation of HPA axis stress responses. For example, lesions of the posterior medial region of the BNST increase the magnitude of ACTH and corticosterone release and PVN FOS activation (Choi et al. 2007), implying a role in central integration of stress

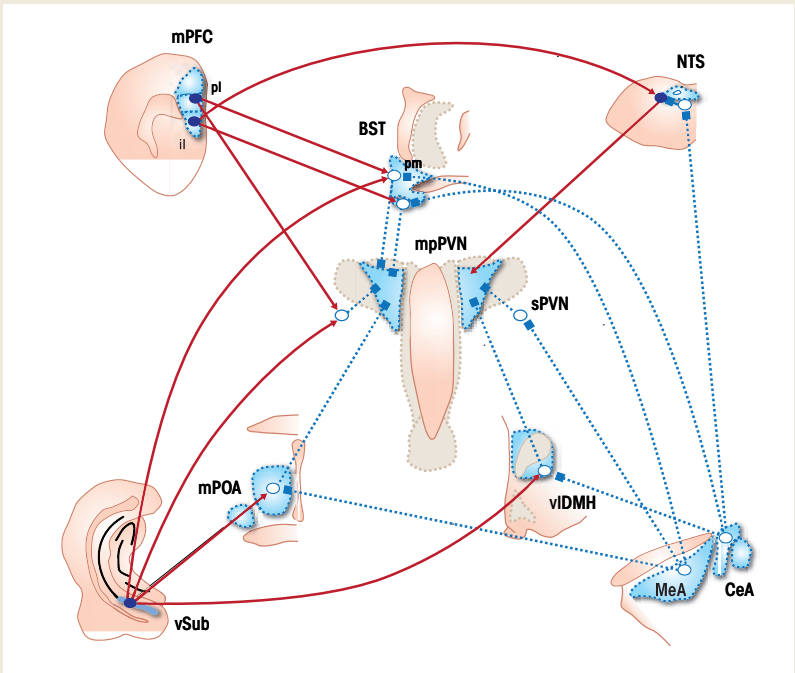

Figure 2 Schematic of limbic stress-integrative pathways from the prefrontal cortex, amygdala and hippocampus. The medial prefrontal cortex (mPFC) subsumes neurons of the prelimbic (pl) and infralimbic cortices (il), which appear to have different actions on the hypothalmic–pituitary–adrenal (HPA) axis stress response. The pl sends excitatory projections (designated as dark circles, filled line with arrows) to regions such as the peri-PVN (peri-paraventricular nucleus) zone and bed nucleus of the stria terminalis (BNST), both of which send direct GABAergic projections to the medial parvocellular PVN (delineated as open circles, dotted lines ending in squares). This two-neuron chain is likely to be inhibitory in nature. In contrast, the infralimbic cortex projects to regions such as the nucleus of the solitary tract (NTS) and the anterior BNST, which sends excitatory projections to the PVN, implying a means of PVN excitation from this cortical region. The ventral subiculum (vSUB) sends excitatory projections to numerous subcortical regions, including the posterior BNST, peri-PVN region (including the subparaventricular zone [sPVN], medial preoptic area [POA] and ventrolateral region of the dorsomedial hypothalamic nucleus [vlDMH]), all of which send GABAergic projections to the PVN and are likely to communicate transsynaptic inhibition. The medial amygdaloid nucleus (MeA) sends inhibitory projections to GABAergic PVN-projecting populations, such as the BNST, POA and sPVN, eliciting a transsynaptic disinhibition. A similar arrangement likely exists for the central amygdaloid nucleus (CeA), which sends GABAergic outflow to the ventrolateral BST and to a lesser extent, the vlDMH. The CeA also projects to GABAergic neurons in the NTS, which may disinhibit ascending projections to the PVN.

inhibition. Lesions of the anteroventral component of the BNST also enhance stress responses (Radley et al. 2009). In contrast, larger lesions of the anterior BNST reduce HPA axis stress responses (Choi et al. 2007), consistent with a role for this region in stress excitation. Thus, the role of the BNST in stress inhibition versus activation is compartmentalized and may be associated with differences in limbic targeting of individual subregions of the BNST. For example, the posterior medial BNST receives heavy innervation from the vSUB and MeA, whereas the anteroventral region receives input from the CeA and most of the IL efferents (Canteras and Swanson 1992; Cullinan et al. 1993; Dong et al. 2001; Vertes 2004).

The medial preoptic area and peri-PVN regions are heavily populated with GABAergic neurons and seem to primarily modulate stress inhibition (Herman et al. 2003). Neurons in these regions are believed to provide tonic inhibition to the PVN, which can be adjusted in accordance with glutamate inputs from the vSUB (enhanced inhibition) or GABAergic inputs primarily from the MeA (disinhibition). Lesions of the medial preoptic nucleus increase HPA axis stress responses and block HPA axis responses elicited by medial amygdalar stimulation, suggesting a primary role in stress inhibition (for primary references, see Herman et al. 2003). Local inhibition of glutamate signaling in the peri-PVN region also enhances HPA axis stress responses (Ziegler and Herman 2000), suggesting that limbic axons terminating in this region may modulate PVN activation.

It is more difficult to pinpoint the role of other hypothalamic regions linking limbic efferents to the PVN, such as the dorsomedial nucleus (Herman et al. 2003). For example, conflicting results are observed following lesion, activation, or inactivation of this dorsomedial hypothalamus, possibly because of heavy mixing of glutamate and GABA neuronal populations (Herman et al. 2003).

Additional potential relays remain to be fully explored. For example, the raphe nuclei and NTS innervate the PVN, are targeted by limbic structures (such as the PL) (see Vertes 2004) and are involved in stress excitation by serotonin and norepinephrine (Herman et al. 2003), respectively. However, as yet, there are no anatomical studies describing bisynaptic limbic–PVN relays through these regions.

Circuitry Subserving Chronic Stress Responses

Prolonged or extended exposure to stress causes long-term upregulation of the HPA axis, characterized by reduced thymus weight (attributed to cumulative elevations in GCs); increased adrenal size (attributed to increased ACTH release); increased adrenal sensitivity to ACTH; facilitated HPA axis responses to novel stressors; and in some (but not all) paradigms/conditions, elevated basal GC secretion (see Herman et al. 1995; Ulrich-Lai et al. 2006). Changes in peripheral hormone release are accompanied by increased PVN CRF and vasopressin mRNA (Herman et al. 1995), suggesting that HPA upregulation is centrally mediated. In addition, chronic stress increases glutamatergic and noradrenergic terminal abutting PVN CRF neuronal somata and dendrites, consistent with enhanced excitatory synaptic drive (Flak et al. 2009).

Central mechanisms of chronic HPA axis activation have yet to be determined. The role of the limbic forebrain in stress control suggests that differential involvement of the PFC, hippocampus, and amygdala may be responsible for prolonged drive. Of note, all regions show significant chronic stress–induced neuroplastic changes: Dendritic retraction is evident in hippocampal and mPFC pyramidal neurons, whereas dendritic extension is observed in the amygdala (for primary references, see Ulrich-Lai and Herman 2009). These studies are consistent with redistribution of limbic input to HPA excitatory circuits, favoring excitation over inhibition.

Enhanced amygdalar drive is proposed to play a major role in chronic stress pathology. For example, chronic stress activates the CeA CRF system, which has been proposed as a chronic stress–recruited pathway (Dallman et al. 2003). However, the CeA does not seem to be required for the development or maintenance of chronic stress symptoms (Solomon et al. 2010). In addition, lesions of the MeA also fail to prevent chronic stress drive of the HPA axis (Solomon et al. 2010). Thus, the overall link between amygdalar hyperactivity and chronic stress–induced HPA axis dysfunction has yet to be firmly established.

The paraventricular nucleus of the hypothalamus (PVT) seems to comprise a component of the chronic-stress pathway. Lesions of the PVT block chronic stress sensitization of HPA axis responses to novel stressors (Bhatnagar and Dallman 1998), suggesting a primary role in the facilitation process. In addition, PVT lesions disrupt the process of HPA axis habituation to repeated stressors (Bhatnagar et al. 2002). Taken together, the data suggest the PVT plays a major role in gating HPA axis drive in the context of prolonged stress exposure. Of note, the PVT and limbic forebrain sites that control acute stress responses are interconnected (see Vertes and Hoover 2008), allowing for possible coordination of corticolimbic stress outputs in this region. The PVT also is positioned to process information regarding ongoing physiological status, receiving inputs from orexinergic neurons (which regulate the release of acetylcholine, serotonin, and noradrenaline) of the dorsolateral hypothalamus (which plays an integral role in control of arousal processes) and ascending brainstem systems involved in autonomic control.

The BNST also is positioned to integrate information on chronic stress. Lesions of the anteroventral BNST attenuate responses to acute stress, but potentiate facilitation of the HPA axis by chronic stress (Choi et al. 2008). These data suggest that this region has chronicity-dependent roles in HPA axis control, with presumably different

neural populations recruited in an attempt to respond to prolonged stress exposure. Given intimate interconnectivity between the anterior BNST and mPFC, hippocampus, and amygdala, it is possible that BNST neurons may be "reprogrammed" by chronic stress–induced changes in limbic activity or innervation patterns.

Stress Circuitry and Alcohol

Readers familiar with the alcohol literature will no doubt find considerable overlap between the stress circuitry described above and brain circuitry linked to alcohol intake. For example, considerable data support a role for the CeA, BNST, and noradrenergic systems in the maintenance of alcohol dependence (see Koob 2009), suggesting that the process of addiction is linked to activation of stress (and HPA axis) excitatory pathways. Indeed, enhanced CeA/BNST CRF expression resembles what would be expected after chronic stress, leading to the hypothesis that negative addictive states (e.g., avoidance of withdrawal) are linked to alcohol-induced recruitment of chronic stress circuits (Koob 2009). Conversely, activation of reward pathways is known to significantly buffer stress reactivity via the amygdaloid complex, suggesting a mechanism whereby the rewarding effects of alcohol may reduce perceived stress (Ulrich-Lai et al. 2010).

Alcohol also has profound effects on medial prefrontal cortical neural activity, and chronic use is associated with prefrontal hypofunction (poor impulse control) in humans (see Abernathy et al. 2010). The mPFC projects to both the CeA and BNST and, at least in the case of the prelimbic region, plays a prominent role in HPA inhibition. In combination with the gain of function seen in amygdalar–BNST circuits, these observations suggest that chronic alcohol use causes marked changes across the limbic stress control network, biasing the organism for stress hyperreactivity.

Overall, adequate control of the HPA axis is a requirement for both short- and long-term survival. Given that key control nodes of HPA axis activity are targeted by alcohol, and that alcohol itself constitutes a threat, it is not surprising that corticosteroids, the "business end" of the axis, have profound interactions with both behavioral and physiological regulation of intake. The overlap between HPA regulatory and addiction circuits identifies key points that may be targets for both the long-term detrimental effects of alcohol abuse as well as dependence itself. The importance of circuit overlap is further underscored by the powerful reciprocal relationship between life stress and drinking, which complicates efforts to establish and maintain abstinence. ■

Acknowledgements

This work was supported by grants MH–049698, MH–069680, and MH–069725.

Financial Disclosure

The author declares that he has no competing financial interests.

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How Does Stress Lead to Risk of Alcohol Relapse?

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Empirical findings from human laboratory and brain-imaging studies are consistent with clinical observations and indicate that chronic alcohol-related dysfunction in emotional and stress responses plays a role in motivation to consume alcohol in people with alcohol use disorders. Recent findings on differences in stress responsivity in alcohol-dependent versus nondependent social drinkers demonstrate alterations in stress pathways that partially may explain the significant contribution of stress-related mechanisms on craving and relapse susceptibility. These findings have significant implications for clinical practice, including (1) the development of novel brain and stress biology–related measures of relapse risk that could serve as biomarkers to identify those most at risk of alcohol relapse during early recovery from alcoholism; and (2) the development of novel interventions that target stress-related effects on the motivation to drink alcohol and on relapse outcomese **KEY WORDS: Alcoholism; alcohol dependence; alcohol and other drug (AOD)-seeking behavior; AOD craving; alcohol cue; relapse; relapse prevention; recovery; motivation; risk factors; stress; stress response; brain; brain imaging; biomarker; intervention; human studies**

It has long been known that stress increases the risk of alcohol relapse (Sinha 2001). Clinical observations, surveys, and epidemiological studies document an association between self-reports of stressors and subsequent return to drinking. Studies assessing alcohol relapse after treatment completion and discharge also indicate the contribution of highly stressful events independent of alcohol use history that increase the risk of subsequent relapse (Brown et al. 1990). Furthermore, negative mood and stress are associated with increased craving, and high levels of urges to use alcohol predict relapse (Cooney et al. 2007). However, the mechanisms by which stress exposure increases alcohol relapse risk have been elusive, until recently. The last two decades have seen a dramatic increase in preclinical and clinical research to understand psychobiological and neural evidence linking stress and alcohol consumption. Evidence suggests that the neural circuits involved in stress and emotions overlap substantially with the brain systems involved in drug reward. Chronic alcohol use can result in neuroadaptive changes in stress and reward pathways. Such changes may alter an alcohol-dependent person's response to stress, particularly with respect to stress and emotion regulation and motivation for alcohol, which in turn may increase the risk of relapse (Sinha 2001, 2005).

To put the stress and alcohol relapse linkage in the clinical context, the sidebar presents sample descriptions of an acute stressful life event and an acute alcohol-related situation that led to subsequent alcohol use in a person with alcohol dependence. The patient vignettes are descriptions provided by patients currently in treatment and refer to previous experiences and episodes of alcohol use and relapse.

Chronic Alcohol-Related Changes in Emotion, Stress, and Motivational Systems

Converging lines of evidence indicate that regular and chronic alcohol use is associated with changes in emotion, stress, and motivational pathways. These changes may in turn influence alcohol craving and relapse risk. Chronic alcohol use increases stress-related symptoms and is associated with increased anxiety and negative emotions; changes in sleep and appetite; aggressive behaviors; changes in attention, concentration, and memory; and desire/craving for alcohol (Sinha 2001, 2007, 2009). Stress-related symptoms are most prominent during early abstinence from chronic alcohol use, but some of these changes also have been documented during active use of specific drugs. Chronic alcohol abuse and acute alcohol withdrawal states are associated

with heightened activity in the brain stress systems, such as increased secretion of the stress hormones corticotropin-releasing factor (CRF), norepinephrine, and cortisol in a number of the brain's stress and emotion centers, such as the hypothalamus[1], amygdala, hippocampus, and prefrontal regions (Koob and Kreek 2007). Chronic alcohol abuse also alters dopaminergic signaling in the ventral striatum (VS) and the ventral tegmental area (VTA). And such changes are associated with increased alcohol seeking (craving) and alcohol self-administration in laboratory animals (Cleck and Blendy 2008; Koob and Kreek 2007; Koob et al. 2004; Rasmussen et al. 2006). Further corroboration from human neuroimaging studies indicates that chronic alcohol abuse reduces dopamine receptors (i.e., D2 receptors) in striatal regions and dopamine transmission in the frontal lobe in alcoholics during acute withdrawal and protracted withdrawal (up to 3–4 months) (see Volkow 2004 for review). Functional imaging studies indicate increased VS activity in response to alcohol cues and altered brain response in the amygdala to emotional stimuli with chronic alcohol use (Gilman and Hommer 2008; Heinz et al. 2004, 2005; Martinez et al. 2007).

The biological stress response is most commonly detected in humans by activation of the hypothalamic–pituitary–adrenal (HPA) axis involving CRF-stimulated release of adrenocorticotropin (ACTH) from the anterior pituitary, which in turn stimulates the adrenal glands to release the stress hormone cortisol, which is involved in mobilizing and regulating the body's stress response. The second pathway involved in the biological stress response is the autonomic nervous system, comprising the sympathetic and the parasympathetic components. The sympathetic component mobilizes arousal by increasing heart rate and blood pressure; the parasympathetic component enforces the "brakes" for sympathetic arousal and functions to decrease and regulate autonomic function. Alcohol use stimulates the HPA axis and initially stimulates the autonomic systems by provoking sympathetic arousal, followed by depressing such activation (Ehrenreich et al. 1997; Lee and Rivier 1997). Reductions in this alcohol-related HPA axis response (similar to tolerance) has been demonstrated with regular and chronic alcohol abuse in animals (Lee and Rivier 1997; Richardson et al. 2008; Zhou et al. 2000) and in humans (Adinoff et al. 1998, 2005; Wand and Dobs 1991).

Likewise, chronic alcohol abuse increases physiological arousal as measured by heart rate but also decreases heart rate variability, which serves as a measure of parasympathetic function (Ingjaldsson et al. 2003; Rechlin et al. 1996; Shively et al. 2007; Thayer and Sternberg 2006). These data represent alcohol-induced changes in peripheral stress pathways, which parallel basic science findings of alcohol-related adaptations in central stress systems, namely the extrahypothalamic CRF and the noradrenergic pathways that are indicative of hyperresponsive brain stress pathways noted in the previous paragraph (Cleck and Blendy 2008; Koob and Kreek 2007; Koob 2009; Rasmussen et al. 2006). These neurochemical changes indicate specific dysregulation in the neurochemical systems that play a role in emotion, stress, and motivation functions in alcoholics. Such changes raise the question of whether these measures contribute to the high levels of emotional distress, alcohol craving, and compulsive alcohol seeking that may lead to increased relapse susceptibility.

Effects of Stress on Alcohol Craving and Arousal

Drug craving or "wanting" for drug is a hallmark feature of addiction. It is an important component in maintaining addictive behaviors (Dackis and Gold 1985; O'Brien et al. 1998; Robinson and Berridge 1993, 2000; Tiffany 1990). Chronic alcohol use leads to changes in the brain reward and motivation pathways that can increase alcohol craving in the context of alcohol and alcohol-related stimuli, but also in the context of stress. In support of these ideas, a growing literature indicates that people with alcohol abuse show greater alcohol craving than social drinkers (Glautier et al. 1992; Greeley et al. 1993; Kaplan et al. 1985; Pomerleau et al. 1983; Willner et al. 1998). Furthermore, severity of alcohol use has been shown to affect the magnitude of cue-related physiological arousal, compulsive alcohol seeking, and stress-related changes, including alcohol-related morbidity (Fox et al. 2005; Grusser et al. 2006, 2007; Rosenberg and Mazzola 2007; Sinha 2008; Yoon et al. 2006). These data are consistent with large population-based studies indicating that the risk of alcohol-related problems, addiction, and chronic diseases increases with greater weekly or daily alcohol and drug use (Dawson et al. 2005; Rehm et al. 2009; Room et al. 2005). Given these responses, the author's research examined whether increases in craving are associated with altered stress responses that occur with chronic alcohol use.

In the clinical context, alcoholic patients entering outpatient substance abuse treatment report high levels of stress and an inability to manage distress adaptively, thereby increasing the risk of succumbing to high levels of drug craving and relapse to drug use (Sinha 2007). Although patients often are successful in learning cognitive–behavioral strategies in treatment, relapse rates remain high (Brandon et al. 2007; Sinha 2011). These data suggest possible difficulties in applying and accessing cognitive–behavioral strategies in real-world relapse situations. Thus, to understand the biobehavioral mechanisms underlying the high stress and craving state during early recovery, the author began to study this phenomenon in the laboratory, using an ecologically relevant method that models such relapse risk. This research used two of the most

[1] For definitions of this term and other technical terms used in this article, see the Glossary on pp. 522–524.

common relapse situations—emotionally stressful situations and alcohol-/drug-related situations—in order to develop a comparable method of provoking stress and the drug-related craving state, and these are compared to a relaxing situation that serves as an experimental control condition to account for the nonspecific aspects of the experimental procedures (Sinha 2009).

Provoking Relapse Situations and Inducing Alcohol and Drug Craving in the Laboratory

To assess relapse risk in laboratory studies, Sinha and O'Malley (1999) targeted alcohol and drug craving as a primary outcome measure that is both a common feature of alcoholism and substance abuse and also is known to relate to the disease state (i.e., high amounts of alcohol use and abuse). The researchers initially compared a commonly used standard social stress task (i.e., giving a speech in front of a video camera with the potential for a monetary reward) with 5-minute individualized guided imagery exposure of each participants' own recent stressful scenarios. In addicted individuals, stress imagery elicited multiple emotions of fear, sadness, and anger when compared with the stress of public speaking, which elicited increased fear, but no anger and sadness. In addition, individualized stress imagery resulted in significant increases in drug craving, whereas public speaking did not (Sinha and O'Malley 1999).

Another study examined stress-induced and drug-related craving and physiological responses using individualized scripts of comparable length and style for stress, drug- related, and neutral-related situations. Among cocaine-dependent individuals, the imagery exposure to stress and nonstress drug cues resulted in significant increases in heart rate, salivary cortisol levels, drug craving, and subjective anxiety, compared with neutral-relaxing cues (Sinha et al. 2000). Using these methods, researchers have been able to reliably induce alcohol and drug craving in multiple groups of treatment-engaged cocaine-, alcohol-, and opiate-dependent individuals and also increase the desire for the drug in healthy social drinkers (Chaplin et al. 2008; Fox et

Patient Vignettes

These patient descriptions illustrate several points about stress and motivation for alcohol use that are relevant from a clinical perspective. The first vignette is an example of an interpersonal stress situation that is a typical precipitant of relapse. Although patients are less likely to divulge specific details of craving situations in a clinical context, the second vignette illustrates that alcohol cues and increased craving states also promote anxiety and stress-related arousal in people who are alcohol dependent. These clinical situations raise many questions about the role of stress in drug seeking and relapse susceptibility. One such question is whether stress and alcohol cues provoke similar drug craving states that may be targeted in treatment. Additional research questions are whether the response to stress and alcohol-related stimuli differs for alcohol-dependent and non–alcohol-dependent people and whether stress responses and managing stress is altered as a function of chronic alcohol use. These vignettes provide anecdotal evidence; research is needed to address the question of whether craving and stress-related arousal are predictive of relapse outcomes and whether stress causes relapse. Finally, if stress plays an important role in both stress- and cue-related relapse, research is needed to identify the most beneficial types of interventions and how clinicians might use the stress and craving responses to better address the treatment needs of alcohol-dependent individuals in early recovery. The main article addresses each of these questions to elucidate how stress increases the risk of alcohol relapse.

Stressful Situation

This situation was rated as a 10 on a 10-point scale of "0 = not at all stressful," to "10 = highly stressful—most you've felt recently" and was narrated by an alcohol-dependent male patient who had been in recovery for 5 weeks. The patient is describing a stressful event that previously led to a relapse episode and an alcohol-related context that led to alcohol use.

"I remember it was about 4:00 pm in the afternoon when Kay woke me up. Her face was red—she looked really upset. She was holding the phone in her hand. She was screaming that I have to call home. I felt tight all over. My heart was pounding. I rolled out of bed. My heart was beating faster. She wants me to call my Dad and tell him about the accident. I did not want to call him yet. She kept following me around the apartment. I tensed up the muscles all over my body. She is badgering me to call. Wherever I go, she was behind me with the phone. I clenched my jaw. I don't want to face this now, I was thinking. Just call them now and get it over with, she kept saying. My heart was racing. Suddenly, she dialed the number and throws the phone at me while it is ringing. I am

al. 2007; Hyman et al. 2007; Sinha et al., 2003; see Sinha 2009 for review). In addition, mild to moderate levels of physiological arousal and subjective levels of distress were found to accompany the alcohol/drug craving state (Sinha 2009).

Stress Dysregulation and Enhanced Drug Craving in Addicted Individuals

As discussed in the previous section, alcohol-dependent individuals in early recovery show increased stress and alcohol cue–induced craving responses. In a study comparing 4-week abstinent alcoholics with matched social drinkers (drinking less than 25 drinks per month), Sinha and colleagues (2009) found that the recovering alcoholics showed greater levels of basal heart rate and salivary cortisol levels compared with the control drinkers. Upon stress and alcohol cue exposure, they showed greater subjective distress, alcohol craving, and blood pressure responses but blunted stress-induced heart rate and cortisol responses compared with control subjects (Sinha et al. 2009). Furthermore, after exposure to stress imagery, alcoholic patients showed a persistent increase in alcohol craving, subjective distress, and blood pressure responses across multiple time points compared with social drinkers, suggesting an inability to regulate this high alcohol craving and emotional stress state. These data indicate greater allostatic load in abstinent alcoholics, which is accompanied by dysregulated stress responses and high levels of craving or compulsive seeking for the preferred drug.

Together, these data indicate altered stress responses in alcoholics, and these alterations also include an enhanced susceptibility to stress and cue-induced alcohol seeking, which is not seen in healthy nonaddicted individuals. In addition, there are basal alterations in peripheral markers of stress (i.e., stress hormones, such as ACTH and cortisol and in heart rate), indicative of stress-related dysregulation in the CRF–HPA axis and in autonomic responses as measured by basal salivary cortisol and heart rate responses. These high basal responses are associated with lower or

gritting my teeth. I put the phone to my ear. My dad answers the phone. I hear his voice. My stomach is in a knot. I start to have a normal conversation. My fists are clenched. I am thinking, "How am I going to tell him about the car accident last night?" I feel jittery and panicky all over. I am pacing back and forth. Casually I say I had a car accident last night. I feel hot all over. He starts screaming, "That's it! Pack your bags! You're coming home!" There are butterflies in my stomach. I see Kay burst into tears. I am breathing faster, gasping for air. She is listening to everything he is saying. "What the hell will I tell your mother? I told her you'd be safe. Now I put myself on the line" he is shouting. My head is pounding. Kay is crying, and I can't do anything about it. I feel stuck. My heart is pounding. My father says he can't talk anymore now and hangs up the phone. I was so mad, I wanted to smash something. I slam down the phone. I did not want to call him. I knew he would be upset. There is a sinking feeling in my chest. If I could fix it, make it all better, I would. I see Kay crying. I get choked up. I had promised her this would not happen. I feel so mad at myself I want to scream. Now I've betrayed her and my Dad."

Alcohol-Related Situation

"It was a bright and sunny summer morning in June. M was gone for the day, and I had the whole day off. I am out working in the yard. It was a warm day and I start to feel hot. I sit down for a break. I've done my chores. I've paid the bills and vacuumed out the pool. I breathe in deeply. My eyes glance around the yard. I've got all the yard work done as well. It looks nice. Now I have half a day left. My heart quickens. I am thinking, 'is there anything else left to do'. I can't think of anything else. I feel warm all over. I sit back and try to relax. Now I start feeling very hot. I feel very thirsty. It would be great to have a nice cold beer, I think. I tighten the muscles of my face and forehead. I've worked hard, I deserve one, you think. I feel a rush of excitement inside you. I walk inside and head toward the refrigerator. My heart is beating faster. I promised M I won't drink. My jaws are tight. The thoughts start racing through my head– "She doesn't need to know." "She won't be home for another four hours." "She won't be able to smell it on my breath by then." My hands feel clammy. I open the fridge and grab an ice cold can of beer. My mouth starts to water. Holding that cold can of beer starts to cool down my whole body. I feel a tingling sensation inside me. I start to think—I shouldn't be drinking this. My stomach is in a knot. I look down at it—it's right here in my hand, and I deserve it. I wet my lips. Before I know it, I have cracked it open. I see the condensation vapor fly into the air. I can almost taste it now. I am holding on to the can tightly. I raise the can to my lips. I let the beer flow into my mouth and down my throat. It is so cold that it makes my teeth ache. It goes down quickly. I feel a sense of being more alive. Now I have a taste for it. I can't wait to have another one."

blunted stress-related arousal (Sinha et al. 2009). It is important to note that these alterations cannot be accounted for by smoking status or lifetime history of anxiety or mood disorders and therefore seem to be related to history of chronic alcohol abuse. The persistence of emotional distress and alcohol craving induced by stress and alcohol cue exposure suggests a dysfunction in emotion regulatory mechanisms. As HPA axis responses and autonomic–parasympathetic responses contribute to regulating and normalizing stress responses and regaining homeostasis, dysfunction in these pathways and their related central mechanisms may be involved in perpetuating alcohol craving and relapse susceptibility.

Laboratory Response to Relapse Situations and Subsequent Alcohol Relapse

An important aspect of modeling hallmark addictive symptoms, such as alcohol craving, in the laboratory is to understand the related mechanisms. Furthermore, researchers should test the predictive validity of the laboratory model by examining whether laboratory responses predict future drug-use behaviors and/or real-world clinical outcomes. Because the laboratory studies described earlier were conducted with treatment-engaged alcoholics who were inpatients at a treatment research unit, it was possible to assess relapse rates after discharge. Then researchers could examine specific markers of the stress and craving states that are predictive of relapse outcomes. They followed the alcohol-dependent individuals (who had been in inpatient treatment for 5 weeks) after discharge for 90 days to assess relapse outcomes. Face-to-face follow-up assessments were conducted at 14, 30, 90, and 180 days after discharge from the inpatient unit. The follow-up rates for these assessments were 96, 89, 92, and 86 percent, respectively.

Initial evidence suggested that laboratory responses to stress- and alcohol-related stimuli exposure were predictive of alcohol treatment outcomes. Stress-induced alcohol craving in the laboratory during inpatient treatment was predictive of number of days of alcohol used and total number of drinks consumed during the 90-day follow-up period (Breese et al. 2005). These data corroborate findings in cocaine abusers, showing that stress-induced cocaine craving and HPA arousal are associated with earlier relapse and more cocaine use at follow-up (Sinha et al. 2006). In a more comprehensive analysis of stress dysregulation, anxiety, alcohol craving, and subsequent return to drinking, researchers found clear evidence of stress dysregulation and alcohol craving relating to relapse risk (Sinha et al. 2011*a*). Alcohol-dependent patients, compared with the control group, were more likely to have significant HPA axis dysregulation, marked by higher basal ACTH and higher basal salivary cortisol, lack of stress- and cue-induced ACTH and cortisol responses, higher anxiety after exposure to neutral relaxed and to alcohol cues, and greater stress- and cue-induced alcohol craving (Sinha et al. 2009, 2011*a*). Stress- and cue-induced anxiety and stress-induced alcohol craving were associated with fewer days in aftercare alcohol treatment. High alcohol craving to both stress and to alcohol cue provocation and greater neutral-relaxed state cortisol/ACTH ratio (adrenal sensitivity) were each predictive of shorter time to alcohol relapse. Although a greater cortisol-to-ACTH ratio in the stress and alcohol cue conditions also predicted relapse, the strongest predictor of relapse was the neutral relaxed state adrenal sensitivity (Sinha et al. 2011*a*). These results identify a significant effect of high adrenal sensitivity, anxiety, and increased stress- and cue-induced alcohol craving on subsequent alcohol relapse and treatment outcomes. They also are consistent with earlier reports of stress system involvement in relapse outcomes in alcoholics. Negative mood and stress-induced alcohol craving and blunted stress and cue-induced cortisol responses have been associated with alcohol relapse outcomes (Breese et al. 2005; Cooney et al. 1997; Junghanns et al. 2003). In summary, these findings support the involvement of stress-related pathophysiology in the alcohol relapse process. Among alcoholics in early recovery, the alcohol-craving state is marked by anxiety and compulsive motivation for drugs, along with poor stress regulatory responses (i.e., high basal HPA axis responses but blunted stress HPA responses), resulting in an enhanced susceptibility to addiction relapse.

Brain-Imaging Studies of Alcoholics' Responses to Alcohol Cues and Stress and Implications for Relapse Risk

Several studies have used brain-imaging techniques to assess chronic alcohol-related brain changes and whether such changes are associated with alcohol craving and alcohol use. Neuroanatomically, the cortico–striatal–limbic brain regions have been most studied in the context of stress, emotion, and motivation for alcohol reward. These regions include the frontal and insular cortices, the ventral and dorsal striatum, the amygdala, hippocampus, and thalamic nuclei, and midbrain regions, such as the VTA and the substantia nigra. An early study to measure blood flow with single-photon emission computed tomography found a change in the caudate nucleus during induction of craving in alcoholics (Modell and Mountz 1995). Subsequently, George and colleagues (2001) found a greater increase in brain response to alcohol cues in alcoholics compared with controls in the anterior thalamus and left dorsal lateral prefrontal cortex using functional magnetic resonance imaging (fMRI). Using a memory task during fMRI, Tapert and colleagues (2001) found dysfunctional cortical responses in alcoholics distinct from those of control subjects. Subsequently, other imaging studies with alcoholic patients have shown an increased association between dorsal striatum regions and

alcohol craving in response to the presentation of alcohol-related stimuli (Grusser et al. 2004; Wrase et al. 2002). Myrick and colleagues (2004) reported that alcohol cues produced changes in the left orbital frontal cortex, anterior cingulate cortex, and nucleus accumbens in alcoholics but not in other study participants (Myrick et al. 2004).

Using fMRI, Sinha and colleagues (2007) compared alcohol-dependent individuals abstinent from alcohol for 4 weeks with social drinkers to assess brain structural changes and also functional responses to stress, alcohol cues, and neutral relaxing guided imagery. Alcoholic patients showed greater activity in the ventromedial prefrontal cortex, the ventral striatum, insula, and specific regions of the thalamus and cerebellum during the neutral-relaxing condition (Sinha 2007; Sinha and Li 2007). These findings indicate that abstinent alcoholics show overall hyperresponsivity of the medial prefrontal and striatal-limbic regions, with no differences in brain responses to the neutral relaxed and stressful cues (Sinha and Li 2007; Sinha et al. 2007*a*). Hyperresponsivity of prefrontal and striatal-limbic regions is consistent with an overall kindling[2] process, which blunts the neural informational processing responses to stressful stimuli, resulting in a dysregulated response to stress in alcoholics (see also review by Breese et al. 2011).

Using positron emission tomography (PET) techniques, researchers have documented reduced glucose metabolism, especially in frontal regions during both acute and protracted alcohol withdrawal (up to 3 to 4 months) (see Volkow and Fowler 2000 for review). Alcoholics also show significant reductions in dopamine D_2 receptors compared with nonalcoholics, particularly in frontal-striatal regions (Volkow and Fowler 2000). Researchers have reported significant associations between dopamine D_2 receptor binding in the ventral striatum and alcohol craving (Heinz et al. 2004, 2005) as well as motivation for alcohol self-administration in alcoholics (Martinez et al. 2005, 2007). To emphasize the importance of this approach, recent PET studies have shown significant positive correlations between selected dorsal striatum brain regions and drug cue–induced cocaine craving (Volkow et al. 2006; Wong et al. 2006). These data point to alterations in frontal and striatal regions of the dopaminergic and noradrenergic pathways that exist past acute withdrawal and may be associated with difficulties in regulating emotions, stress, and problems selecting goal-directed adaptive responses as opposed to the selection of habitual maladaptive responses such as alcohol consumption.

In addition, the research literature has documented chronic alcohol-related structural brain changes, particularly in frontal, parietal, and temporal cortical regions associated with stress, emotion, and cognitive functioning (Cardenas et al. 2007; Fein et al. 2002; Pfefferbaum et al. 1995, 1998). More severe gray matter deficits have been reported in alcohol relapsers than those who maintained abstinence (Pfefferbaum et al. 1998). In a whole-brain analysis, Rando and colleagues (2011) found significantly smaller gray-matter volume in recently abstinent alcohol-dependent patients relative to healthy study participants in three regions: the medial frontal cortex, right lateral prefrontal cortex, and a posterior region surrounding the parietal-occipital sulcus. Smaller medial frontal and parietal-occipital gray-matter volume were each predictive of shorter time to subsequent any alcohol use (first lapse) and to heavy-drinking relapse (Rando et al. 2011). These data suggest that smaller gray-matter volume in specific medial frontal and posterior parietal-occipital brain regions are predictive of an earlier return to alcohol drinking and relapse risk, suggesting a significant role for gray matter atrophy in poor clinical outcomes in alcoholism. Thus, the extent of gray-matter volume deficits in these regions involved in impulse control, emotion regulation, and abstraction abilities could serve as useful neural markers of relapse risk and alcoholism treatment outcome.

[2] Kindling is a phenomenon in which a weak electrical or chemical stimulus, which initially causes no overt behavioral responses, results in the appearance of behavioral effects, such as seizures, when it is administered repeatedly.

Clinical Implications and Conclusion

The previous sections cite evidence from clinical, laboratory, and neuroimaging studies to examine whether stress increases the risk of relapse. Psychobiological and neuroimaging research points to alcohol-related changes in brain volume and function and in biological stress responses. These alterations were found to contribute to higher craving and increased alcohol relapse risk. For example, early abstinence from alcohol is associated with higher levels of anxiety when relaxed and when exposed to alcohol cues, greater emotional distress, and increased stress- and alcohol cue-induced craving. These states are accompanied by disruption in normal functioning of the peripheral stress pathways, including the HPA axis and the autonomic components, which are involved in mobilizing the body for action during stress but also in physiological regulation of the stress response. A lack of normal stress regulation during this early abstinence period leaves the recovering alcoholic highly vulnerable to high craving, anxiety, and risk of relapse, particularly under stressful conditions and when faced with alcohol-related stimuli in the environment. The findings discussed indicate that stress- and cue-induced alcohol craving increase the risk of subsequent relapse. High levels of stress- and cue-induced anxiety are associated with less follow-up in aftercare during the recovery period. Furthermore, disrupted functioning of the HPA axis, particularly in people who have hyperresponsive cortisol release from the adrenal cortex in response to the ACTH signal (cortisol-to-ACTH ratio as a measure of adrenal sensitivity) in the neutral relaxed state, increased the risk of alcohol relapse 2.5 times more than those with lower cortisol

release from the adrenal cortex. Finally, changes in volume and function of the brain regions involved in impulse control and emotion regulation also are predictive of alcohol relapse outcomes. Each of these measures could be further developed as biomarkers of alcohol relapse risk (see Sinha 2011). If validated in future studies, they may be used clinically to identify people at high risk of relapse. In addition, the findings reviewed also indicate that stress-related pathophysiology is important in the alcohol relapse process. Thus, individuals who show chronic alcohol-related effects on neural, biological, and psychological aspects of stress and craving could benefit from treatments that target stress effects on craving and alcohol seeking. Several novel medications that target the stress pathways, such as agents that block CRF, as well as noradrenergic and GABAergic agents, are being tested to assess their efficacy in stress-related relapse (Breese et al. 2011; Sinha et al. 2011*b*). Development of such treatment strategies may be of tremendous help in normalizing stress responses and decreasing alcohol craving so as to improve relapse outcomes in alcoholism. ■

Acknowledgements

Preparation of this review was supported by grants R01–AA–13892, UL1–DE019856, and PL1–DA024859 from the National Institutes of Health. Dr. Sinha also is on the scientific advisory board for Embera NeuroTherapeutics.

Financial Disclosure

The author declares that he has no competing financial interests.

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Anxiety and Alcohol Use Disorders

Comorbidity and Treatment Considerations

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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. ■

Financial Disclosure

The authors declare that they have no competing financial interests.

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Childhood Trauma, Posttraumatic Stress Disorder, and Alcohol Dependence

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Early-childhood trauma is strongly associated with developing mental health problems, including alcohol dependence, later in life. People with early-life trauma may use alcohol to help cope with trauma-related symptoms. This article reviews the prevalence of early-childhood trauma and its robust association with the development of alcohol use disorders and posttraumatic stress disorder. It also examines the potential biological mechanisms by which early adverse experiences can result in long-lasting changes in neurobiology underlying this vulnerability, as well as pharmacological and behavioral interventions. Recent investigations highlight the importance of assessing trauma among patients with alcohol use disorders and the positive benefits associated with the application of integrative psychosocial interventions that target both trauma-related symptoms and alcohol dependence. **KEY WORDS: Alcohol dependence; alcohol use disorders; childhood; childhood trauma; trauma-related symptoms; posttraumatic stress disorder; coping with stress or anxiety; neurobiology; biological mechanisms; treatment; pharmacological intervention; behavioral intervention; integrative psychosocial intervention; adverse child-rearing environment**

Children exposed to severe adversity early in life are at increased risk of subsequently developing mental health problems, including alcohol dependence. In general, the onset of trauma precedes the onset of alcohol dependence. Although it is impossible to establish a direct causal relationship, this temporal relationship suggests a robust and positive relationship between exposure to early-life trauma and alcohol-related problems later in life. People with trauma-related symptoms and other negative consequences of early-life trauma may use alcohol to help mitigate such symptoms. People with both a positive history of early childhood trauma and co-occurring alcohol dependence have a more severe clinical profile, as well as worse treatment outcomes when compared with those with either early trauma or alcohol dependence alone. Recent investigations highlight the importance of assessing trauma among patients with alcohol use disorders and the positive benefits associated with the application of integrative psychosocial interventions that target both trauma-related symptoms and alcohol dependence. This article reviews the prevalence of early-childhood trauma and its robust association with the development of alcohol use disorders and posttraumatic stress disorder (PTSD). It also examines the potential biological mechanisms by which early adverse experiences can result in long-lasting changes in neurobiology underlying this vulnerability, as well as pharmacologic and behavioral interventions.

Prevalence

There is little doubt that severe childhood adversity may place an individual at life-long risk for a variety of problems, including those related to mental health, physical health, employment, and legal difficulties (Putnam 2006). In a study conducted by the Centers for Disease Control and Prevention and Kaiser Permanente (Adverse Childhood Experiences [ACE] study; Felitti et al. 1998), a sample of 17,337 adults recruited from a large health maintenance organization were surveyed concerning a range of adverse events that might occur during childhood (e.g., physical or sexual abuse, incarcerated household member, emotional neglect) and adult risk behaviors, health status, and disease. The investigators found a graded relationship between the number of adverse childhood experiences (i.e., ACE score), risk behaviors during adulthood, and leading causes of morbidity and mortality in the United States, including heart disease, diabetes, liver disease, and emphysema. It is possible that these increased rates of medical conditions are not a direct result of

childhood adversity but rather the result of dysfunctional and unhealthy behaviors in which many victims of childhood abuse engage.

A number of studies also report that victims of child maltreatment are more likely to have emotional difficulties and psychiatric disorders. One of the most consistent results across these studies is the finding that childhood maltreatment is associated with an increased risk for alcohol and drug use disorders (Enoch 2011). In a population-based sample of 1,411 female adult twins, self-reported childhood sexual abuse was positively associated with a number of psychiatric disorders, but the strongest associations were with alcohol and drug dependence (Kendler et al. 2000). In the ACE study, the risk of alcohol dependence increased 7.2-fold, and illicit drug use increased 4.5-fold for people with four or more ACEs (Anda et al. 2006). People with a history of childhood abuse or neglect are vulnerable to using alcohol in order to cope with stressful situations, which in turn may lead to excessive alcohol use (Schuck and Widom 2001). An investigation by Widom and colleagues (2007) demonstrates that the increased risk of excessive alcohol use among victims of childhood abuse or neglect is consistent and stable into middle adulthood (e.g., age 40). Furthermore, research has shown that alcohol-dependent patients with a history of sexual abuse are more likely than nonabused patients to relapse to alcohol use (87.5 vs. 63.3 percent) and to relapse more quickly (median time to first drink = 60 vs. 115 days) in the first year following inpatient treatment for alcohol dependence (Greenfield et al. 2002).

In addition to alcohol use disorders, childhood adversity is associated with an increased risk of PTSD (Widom 1999). Data from a number of studies over the last 20 years have emphasized the high co-occurrence of PTSD and alcohol disorders. For example, among 3,768 female twins participating in the longitudinal Missouri Adolescent Female Twin Study (MOAFTS), Sartor and colleagues (2010) found that women exposed to trauma were nearly twice as likely to develop alcohol dependence (hazard ratio 1.85), and women exposed to trauma who also had PTSD were even more likely to develop alcohol dependence (hazard ratio 3.54; significantly higher than women with trauma exposure alone) when compared with women who had not experienced trauma. Studies of samples of individuals seeking treatment for alcohol use disorders also find a high prevalence of reported childhood adversity and PTSD. In a study of men and women in treatment for addictions, 62 percent reported having been victims of childhood physical or sexual abuse (Grice et al. 1995). A review of studies of individuals seeking treatment for addictions reveals rates of PTSD as high as 50 percent or greater (Dansky et al. 1994). In the majority of cases, the development of PTSD precedes the development of the substance use disorder.

These high rates of childhood victimization in individuals with PTSD and alcohol and other substance-related problems suggests that there is a link between childhood adversity and the development of these disorders, although it is impossible to establish a direct causal relationship. However, even when studies control for demographic differences, family discord, and parental pathology, the specific relationship between childhood abuse and the development of substance use disorders holds true. Several theoretical connections have been postulated (Miller et al. 1993). Childhood victimization may lead to low self-esteem and the subsequent use of alcohol to deal with negative cognitions. It also is possible that victims of childhood abuse feel that their experiences make them "different" from other children and lead them to withdraw from healthier social circles toward fringe groups, where alcohol use is more accepted. In any case, given that victims of child abuse are more likely to develop alcohol use disorders as adults, early intervention, prevention, and training for parents are all important in interrupting this cycle of violence and alcohol problems.

Neurobiology

Recognizing the pervasive and detrimental effects of adverse childhood experiences on quality of life and health outcomes has led to the exploration of potential biological mechanisms by which early experiences can produce long-lasting changes. Evidence from both animal and human research suggests that early stressors can lead to neurobiological changes in systems known to be involved in the pathophysiology of depression, anxiety, and substance use disorders (De Bellis et al. 1999; Heim and Nemeroff 2001). The hypothalamic–pituitary–adrenal (HPA) axis plays a critical role in the stress response and is involved in the pathophysiology of addictive disorders. Early stressors cause long-term increases in the stress response of the hormone cortisol (Plotsky and Meaney 1993) as well as decreased genetic expression of cortisol receptors and increased expression of corticotropin-releasing factor in the hypothalamus, both of which may contribute to dysregulation of the HPA axis (Ladd et al. 1996). The noradrenergic system also plays a key role in stress (Bremner 2003), and early stressors can lead to long-term decreases in α-2 noradrenergic receptors in the locus coeruleus, which may lead to loss of feedback inhibition of noradrenergic activity with associated increases in the noradrenergic stress responses (Caldji et al. 1998; Sanchez et al. 2001).

In addition to the long-lasting effects of early trauma on the stress response, a number of studies indicate that early trauma has specific effects on the neurotransmitter systems involved in the positive reinforcing effects of alcohol and drugs, particularly the brain pathway for dopamine (i.e., the mesocorticolimbic dopamine system) (Meaney et al. 2002). Higley and colleagues (1991) found that adult rhesus monkeys raised in peer groups without maternal care showed increased HPA response to stress and increased alcohol consumption during periods of stress (Higley et al. 1991). In a series of studies, Meaney

and colleagues (2002) demonstrated that repeated periods of maternal separation in the early life of rats decreased dopamine transporter expression and increased dopamine responses to stress and behavioral responses to stress, cocaine, and amphetamine. These findings suggest that early-life experiences can affect the development of the mesocorticolimbic dopamine system and lead to a vulnerability to addiction in later life. Thus, in addition to effects on stress reactivity, early-life events might predispose individuals to the development of alcohol use disorders by directly influencing the reinforcing effects of alcohol. Other neurotransmitter systems involved in the pathophysiology of alcohol dependence, such as brain-derived neurotrophic factor (BDNF), serotonin, and γ-aminobutyric acid (GABA) systems also are affected by early-life trauma in ways that may influence vulnerability to the development of alcohol dependence, but the mechanistic connections in these systems are under active investigation and are not as well understood (Enoch 2011).

Not all children exposed to early-life trauma develop alcohol dependence or other significant pathology, clearly suggesting that resilience and mediating factors play a role (Enoch 2011). The genetic risk for alcohol and drug dependence involves multiple genes. Emerging evidence suggests that variation in some stress-related genes may determine the risk for psychopathology or resilience in people exposed to early-life trauma. In particular, it seems that there are important variations in the genes encoding the CRF system that can influence the development of alcohol dependence following an early-life trauma in a gene-by-environment interaction. One study of at-risk children found an interaction between a particular genetic variant coding for the CRF receptor (i.e., CRHR1) and sexual trauma in adolescents that predicted an earlier age of onset of drinking and heavy alcohol consumption (Blomeyer et al. 2008). This finding is supported by animal studies demonstrating that the CRHR1 genotype and expression interact with environmental stress to reinstate alcohol-seeking in rodents (Hansson et al. 2006), and a functional CRF promoter variant in monkeys conferred increased stress reactivity and was associated with increased alcohol consumption in animals reared under stressful conditions (Barr et al. 2009). These findings suggest that the interaction of genetic susceptibility and environmental exposure can lead to a pathologically activated CRF system, which increases the risk for the development of alcohol dependence in some people.

Treatment

Both behavioral and pharmacological interventions are important to consider in the treatment of alcohol dependence and trauma/PTSD (Davis et al. 2006; Weiss and Kueppenbender 2006). To date, most empirical studies of behavioral or pharmacological agents have investigated the treatment of either alcohol dependence or PTSD alone.

Psychosocial Interventions

With regard to psychosocial interventions, cognitive–behavioral therapies (CBTs) are the most widely studied and empirically valid treatments for both PTSD and alcohol use disorders. The CBTs used to treat PTSD fall into three main categories: (1) exposure-based therapies, (2) cognition-focused therapy, and (3) anxiety/stress-management therapy. Exposure-based therapies are considered the gold standard treatment for PTSD (Institute of Medicine 2008) and involve having patients confront safe, but anxiety-provoking situations (i.e., physical location where childhood abuse occurred), known as in vivo exposure; and the memory of the traumatic experience, known as imaginal exposure (Foa et al. 2006). With prolonged, repeated in vivo and imaginal exposure, the trauma-related anxiety is extinguished. Cognition-focused therapy includes cognitive therapy, which addresses the meaning that people assign to early-life trauma; and cognitive-processing therapy, which combines a narrative element of exposure therapy with efforts to identify and modify unhelpful cognitions related to the themes of safety, trust, power, esteem, and intimacy (Resick and Schnicke 1992). Finally, stress inoculation training (Meichenbaum and Novaco 1985), one of the most widely used and empirically investigated forms of anxiety management therapies, aims to provide a sense of mastery over PTSD symptoms by teaching patients a variety of coping skills. Stress inoculation training also has been incorporated into CBTs for substance use disorders and includes relaxation training, breathing retraining, thought stopping, self-instruction training, assertiveness training, cognitive restructuring, anger management, and problem solving.

Recently, integrative psychosocial interventions have been developed to address both trauma/PTSD and substance use disorders simultaneously (Back 2010). Clinicians previously believed that trauma interventions were inappropriate until after a patient had been abstinent from alcohol or drugs for a sustained period of time (e.g., 3 months). This model, known as the "sequential" model, posits that continued alcohol use impedes therapeutic efforts to address and process the trauma, and that trauma interventions commenced before sustained abstinence would result in increased risk of relapse. Contrary to these beliefs, however, recent data reported by several different investigators in the United States and Australia show that treatment outcomes of substance dependent patients who engage in integrative CBT interventions typically experience significant improvements in both conditions and that rates of relapse are not increased by the introduction of therapy for trauma (Brady et al. 2001; Hien et al. 2004; McGovern et al. 2009; Najavits 2002; Triffleman et al. 1999). Proponents of integrative treatments posit that unprocessed trauma-related memories and PTSD symptoms may, at least in part, drive alcohol use. Thus, attending to and treating the trauma-related

symptoms early in the process of therapy may improve the chances of long-term recovery from alcohol (Back et al. 2006; Hien et al. 2010). Although more randomized controlled trials of integrative treatments are needed, the studies to date clearly demonstrate that for the majority of alcohol-dependent patients with trauma/PTSD, the inclusion of trauma interventions confers substantial therapeutic benefits.

Pharmacological Interventions

There are several general issues to consider when treating co-occurring alcohol dependence and trauma/PTSD. When pharmacological agents are used, treatment should generally follow routine clinical practice for the treatment of PTSD. Regardless, relapse is common, and it is critical to consider the potential toxic interactions that may occur between the prescribed medication and alcohol. Given the high co-occurrence of alcohol and illicit drug use, potential toxic interactions between the prescribed medication and other substances of abuse must also be addressed. The pharmacological agent with the least abuse liability potential should be chosen for this population. Although benzodiazepines are effective in providing immediate relief of anxiety symptoms, they are generally not considered a first-line treatment for patients with alcohol dependence given the abuse potential of benzodiazepines. During the initial phase of treatment, when latency of onset of antidepressants is an issue, benzodiazepines may be considered as adjunctive medication. The amount of benzodiazepines prescribed to the patient should be limited, and the patient should be closely monitored for relapse or nonmedical use of benzodiazepines or other medications.

The use of pharmacological agents to specifically target alcohol dependence and PTSD is underexplored. Most studies to date, however, show promise and suggest that patients with co-occurring alcohol dependence and trauma/PTSD respond well to standard PTSD pharmacotherapies. Sertraline, a serotonin-specific reuptake inhibitor, has been investigated in patients with comorbid alcohol dependence and PTSD. The first study was a small (n = 9) open-label, 12-week trial, which demonstrated significant pre–post decreases in alcohol use severity (e.g., number of drinking days, number of drinks per day), as well as PTSD symptoms of re-experiencing the trauma, avoidance, and hyperarousal (Brady et al. 1995). A second study examined the efficacy of 12 weeks of sertraline compared with placebo in 94 patients with alcohol dependence and PTSD (Brady et al. 2005). The primary outcome analysis indicated no significant effect of sertraline on alcohol-related outcomes and only trend-level findings for the PTSD outcomes. The sertraline-treated group showed statistical trends for greater improvement in the experience of sudden flashbacks of the traumatic event and hyperarousal symptoms (e.g., insomnia, inability to concentrate). Follow-up cluster analyses suggested that individuals with primary PTSD, compared with primary alcohol dependence, derived more benefit from sertraline treatment as evidenced by significantly less severe alcohol use. The results suggested that patients with early-onset alcohol dependence actually had worse alcohol-related outcomes with sertraline treatment compared with placebo (Brady et al. 2005).

In another study of 254 veterans with alcohol dependence and a variety of co-occurring mood and anxiety disorders (Petrakis et al. 2005), naltrexone, disulfiram, or a combination of both was added to treatment as usual. A high percentage (42.9 percent) of the study participants had PTSD, although data analysis for specific disorders was not conducted. Alcohol-related outcomes improved significantly in patients treated with either medication alone or with combination therapy, compared with placebo, but there was no added improvement with combination therapy when compared with monotherapy. This study strongly suggests that alcohol-dependent patients with co-occurring PTSD should receive medications targeting alcohol consumption.

There is good rationale for the exploration of a number of other compounds in the treatment of co-occurring PTSD and alcohol dependence. Prazosin blocks a specific α_1-adrenergic receptor and has shown promise in several well-controlled trials for the treatment of PTSD, particularly in decreasing PTSD-related sleep disturbance and nightmares (Raskin et al. 2007). In a preliminary study, prazosin decreased alcohol consumption in an alcohol-dependent population (Simpson et al. 2009). This inexpensive and relatively safe drug warrants investigation in the treatment of co-occurring PTSD and alcohol dependence. In addition, several anticonvulsant agents, such as topirimate, have shown promise in the treatment of alcohol dependence (Johnson et al. 2003). It is hypothesized that actions on the glutamatergic systems might be responsible for these agents' therapeutic actions. PTSD also has been associated with glutamatergic dysregulation, and anticonvulsant agents have shown promise in small-number, open-label studies in the treatment of PTSD. This is another area in which additional investigation is warranted. More research clearly is needed to help advance the behavioral and pharmacological treatment of co-occurring trauma/PTSD and substance use disorders.

Conclusions

Epidemiologic studies as well as studies in treatment-seeking populations converge to support the finding that early-life trauma is common in people with alcohol dependence. There are a number of potential mechanistic explanations for the connection between early-life trauma and the development of alcohol dependence. These include psychological and developmental issues that are affected by trauma, as well as neurobiological effects of early trauma that can lead to increased vulnerability to the development of alcohol and other substance use disorders. These explanatory

hypotheses are not mutually exclusive. There is a growing literature on efficacious psychotherapeutic and pharmacotherapeutic treatments for individuals with co-occurring PTSD and alcohol dependence. Integrative psychosocial interventions combining efficacious interventions from the alcohol and PTSD fields have shown promise. Evidence suggests that agents targeting alcohol consumption (i.e., disulfiram, naltrexone) can be useful in patients with co-occurring PTSD and alcohol dependence, but additional investigation clearly is needed. ■

Acknowledgments

This work was supported in part by grants K24 DA–00435 (to Kathleen T. Brady) and K23 DA–021228 (to Sudie E. Back) from the National Institute on Drug Abuse.

Financial Disclosures

The authors declare that they have no competing financial interests.

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Alcohol and Stress in the Military

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Although research has independently linked stress experienced by military personnel to both alcohol use and posttraumatic stress disorder, more recently researchers have noted that there also is a significant overlap between stress reactions and alcohol use in veterans and active-duty service members. This overlap seems to be most understood in individuals who have experienced combat or military sexual trauma. This article will provide a brief review of some potential causal mechanisms underlying this relationship, including self-medication and genetic vulnerability models. It also addresses the possible implications for assessment and treatment of military personnel with co-occurring disorders. **KEY WORDS: Alcohol consumption; alcohol use and abuse; problematic alcohol use; stress; stress reaction; posttraumatic stress disorder; military personnel; active military; veteran; combat; military sexual trauma; causal pathways; self-medication; genetic vulnerability; co-occurring disorders**

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Problematic alcohol use within the United States military has been linked to substantial financial and productivity losses. Data from 2006 revealed that excessive alcohol consumption cost the U.S. military $1.12 billion per year (Harwood et al. 2009). Regarding medical expenditures, studies have found that excessive alcohol use by military members results in an annual cost of $425 million. Excessive drinking within the military is estimated to result in a loss of 320,000 work days and 34,400 arrests per year, half of which are for driving under the influence. Finally, these data indicate that each year excessive alcohol use results in 10,400 active-duty military being unable to deploy and 2,200 being separated from service duty. Given the substantial cost of alcohol misuse, it is imperative to examine factors that may contribute to problematic drinking so that interventions can be employed to address this issue within the military.

This article will examine the links between military traumatic stress and mental health problems, such as posttraumatic stress disorder (PTSD) and between military traumatic stress and problematic alcohol use. Furthermore, it will summarize the pathways that may explain these links and describe possible implications for assessment and interventions with veterans.

Prevalence of Problematic Alcohol Use in the U.S. Military

Frequent heavy drinking, defined as consuming five or more drinks on one or more occasions per week, occurs among a substantial proportion of U.S. military personnel and varies as a function of military demographic characteristics. In a large-scale survey, Bray and Hourani (2005) found that the prevalence of frequent heavy drinking in the military from 1980 through 2005 ranged from 15 to 20 percent. Consistent with findings from civilian samples that show gender differences in rates of heavy drinking, military men were nearly 3.5 times more likely to report frequent heavy drinking compared with women in the military. Frequent heavy drinking also varied as a function of ethnicity, with Hispanic and non-Hispanic Whites exhibiting higher rates of problematic drinking than non-Hispanic Blacks. In addition, military rank significantly correlated with frequent heavy drinking; rates were six times greater among enlisted personnel with the lowest rankings compared with officers. Rates of heavy drinking also varied as a function of military service branch, with those in the Army, Navy, and Marines being more likely to report frequent heavy drinking than

those in the Air Force. Other population-based studies of the U.S. military have found that heavy drinking is more likely to occur among younger military members (Stahre et al. 2009). Together, these results suggest that certain military demographic groups (e.g., younger, low-ranking, non–Air Force, White or Hispanic men) may be especially prone to engage in frequent heavy drinking.

Young adults in the military are more likely than their civilian counterparts to engage in heavy drinking. For example, Ames and Cunradi (2004) found that rates of heavy drinking were significantly higher among male military personnel aged 18 to 25 years (32.2 percent) compared with male civilians in a similar age range (17.8 percent). The researchers also found significantly elevated rates of heavy drinking among women in the military compared with similarly aged female civilians (5.5 percent). In addition to demographic factors, military-related stressful events also may contribute to the high rates of problem drinking observed.

Alcohol misuse also frequently occurs among a substantial proportion of combat veterans. In one population-based study of 88,235 veterans returning from Operation Iraqi Freedom (OIF), Milliken and colleagues (2007) found that 12 to 15 percent of veterans endorsed problematic alcohol use in the 3 to 6 months following their return from combat. These data suggest that alcohol misuse occurs among a substantial number of veterans who are exposed to combat-related traumatic stress and highlight the importance of understanding the relationships between stressful military experiences (e.g., combat and military sexual trauma) and alcohol misuse.

Military Trauma and Stress-Related Disorders

Stress-related disorders in response to military service have been noted throughout history. Whether labeled "combat fatigue" or "shell shock" or PTSD, there have been consistent reports in the literature documenting that exposure to combat experiences can lead to an impairment of psychological functioning in military personnel (Foa et al. 2009). Beginning with the Vietnam War, and more recently with the wars in Iraq and Afghanistan (Department of Defense [DOD], 2007, p. ES-1), PTSD has been the most commonly diagnosed mental health disorder for veterans returning from combat. Epidemiological studies of Operation Enduring Freedom (OEF)/OIF veterans treated in the Department of Veterans Affairs (VA) health care system have found that 14 to 22 percent of returning veterans were diagnosed with PTSD (Seal et al. 2009; Tanelian and Jaycox 2008), making it the signature psychological wound of these two wars (DOD 2007). People are diagnosed with PTSD after exposure to a trauma if they experience a strong emotional response to the event that is followed by persistent difficulty in three key areas, including reexperiencing (e.g., nightmares, flashbacks), arousal (e.g., startle response, sleep disturbance), and avoidance (e.g., withdrawal from people, places, and other reminders of the trauma). These disruptions often lead to an impaired ability to function in social, educational, and work environments, making PTSD a very debilitating condition. More recently, research has found that PTSD and related disorders, such as depression, can develop in military personnel not only as a result of combat exposure but also as a result of childhood traumas, military sexual trauma (MST), mortuary affairs duty, and training accidents (Foa et. al. 2009).

Young adults in the military are more likely than their civilian counter-parts to engage in heavy drinking.

Military Trauma and Alcohol Misuse

Not only does military trauma increase the likelihood of developing stress-related mental health disorders such as PTSD or depression, but, as alluded to earlier, there is also evidence that traumatic experiences are related to problematic alcohol use among military members. One form of military traumatic stress that has been surprisingly under-researched is the psychological impact of exposure to killing within a combat setting. In a series of studies, Maguen and colleagues (2010*a*, *b*) examined the relationships among experiences with killing within combat and psychological adjustment of combat veterans, including problematic alcohol use. As predicted, engaging in killing during combat was related to PTSD symptoms but also was independently linked to problematic alcohol use as well as the overall quantity and frequency of alcohol use among these soldiers. These results suggest that killing within the context of combat may be a distinctive risk factor for heavy drinking and problematic alcohol use following combat among members of the military.

In addition to combat-related traumatic experiences elevating the risk for alcohol misuse, there is also evidence that MST is associated with alcohol misuse among military personnel. In a review of the literature on MST, Suris and Lind (2008) examined the relationship between MST experiences and mental and physical health outcomes. They concluded that MST was related to a variety of negative mental and physical health outcomes, including elevated rates of alcohol misuse among those who experienced MST compared with nontraumatized individuals. Taken together, these results suggest that various forms of military trauma, including exposures to killing in combat and MST, elevate the risk for problematic alcohol use among members of the military. These findings also suggest that alcohol misuse is likely to co-occur with other posttraumatic mental health disorders, such as PTSD and depression, among military

personnel. Therefore, it is important to examine the co-occurrence of alcohol misuse within the context of these posttraumatic mental health disorders and to develop models that might explain these comorbidities.

Is Alcohol Used to Self-Medicate Symptoms of Military Posttraumatic Psychiatric Disorders?

The self-medication hypothesis has been proposed to explain the relationship between military traumatic stress and alcohol use disorders. According to this model, the relationship between traumatic events and the heightened risk for an alcohol use disorders is mediated by the occurrence of PTSD or other posttraumatic psychiatric disorders (Jacobsen et al. 2001; Khantzian 1999). Specifically, traumatic events are proposed to lead to psychiatric disorders such as PTSD or depression, and individuals manifesting these conditions may turn to alcohol use as a means of "self-medicating" their symptoms. From a learning-theory paradigm, alcohol use is hypothesized to be negatively reinforcing in that it provides immediate and short-term relief from posttraumatic psychiatric symptoms. For example, military veterans with PTSD reported using alcohol to specifically cope with re-experiencing and hyperarousal symptoms (Bremner et al. 1996), and given the powerful, short-term negative reinforcement effects of alcohol, the theory postulates that people may begin to use alcohol frequently and excessively, resulting in the development of an alcohol use disorder.

Although the self-medication hypothesis proposes that the initial development of an alcohol use disorder is reactionary to PTSD or other posttraumatic psychiatric disorders, an important corollary is that alcohol abuse impedes recovery and even worsens symptoms of posttraumatic mental health disorders. Within a cognitive–behavioral paradigm that attempts to understand the necessary conditions to recover from PTSD, it is hypothesized that the individual must be able to eliminate avoidance of stressful situations—i.e., they must put themselves into contact with people, places, or things that are objectively safe but that continue to cause distress, such as being in crowds, thinking about the trauma, or experiencing emotions related to the trauma (Foa and Kozak 1986). Alcohol misuse can interfere with this necessary precondition for recovery by leading individuals to continue to engage in unhelpful avoidance behaviors. In fact, within the self-medication framework, alcohol use can in itself be conceptualized as an avoidance behavior (e.g., using alcohol to avoid thinking about the traumas). In addition, alcohol withdrawal symptoms can mirror or exacerbate the symptoms of PTSD (Jacobson et al. 2001). For example, people experiencing post–acute withdrawal may have increased irritability, sleep problems, difficulty concentrating, and anxious and depressed mood, all of which overlap with symptoms of PTSD or depression. Thus, alcohol misuse feeds back into the posttraumatic mental health symptoms, in a bidirectional manner (see the figure).

Not only do alcohol use disorders complicate recovery from posttraumatic mental health disorders, such as PTSD, but these stress-related conditions have been found to impede recovery from alcoholism. Ouimette and colleagues (1999) found that substance-dependent veterans with PTSD had poorer substance abuse treatment outcomes after 2 years compared with those without PTSD. Consistent with these results, Brown and colleagues (1999) found that substance-dependent individuals with co-occurring PTSD relapsed more quickly than those without PTSD. Taken together, these results suggest that the co-occurrence of an alcohol use disorder with PTSD provides a substantial barrier to recovery from both of these disorders.

Although large-scale research from civilian populations have found support for the self-medication hypothesis (e.g., Breslau et al. 1991), there has been less research on this theory in post–Vietnam War era samples. In a study of OEF/OIF veterans, Jakupcak and colleagues (2010) found that although combat exposure per se did not increase the risk for alcohol misuse, screening positive for PTSD or depression doubled this risk. The authors concluded that the findings may be

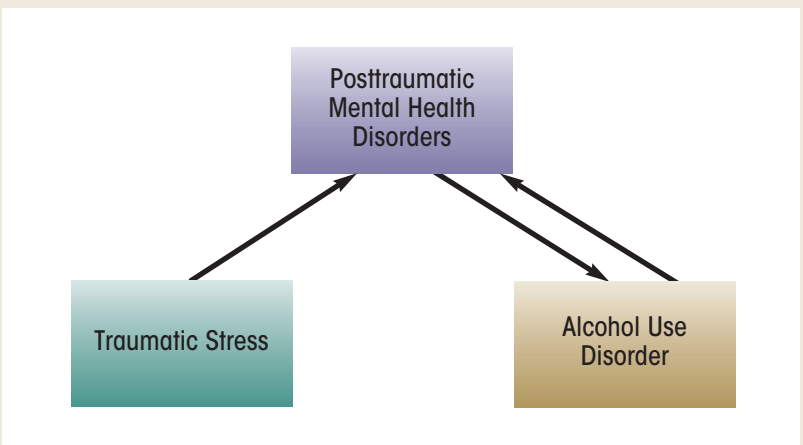

Figure Self-medication model explaining the link between traumatic stress and alcohol use disorder.

consistent with the hypothesis that these veterans were misusing alcohol as a means of coping with symptoms of PTSD and depression. In addition, the authors found that alcohol misuse was particularly associated with emotional numbing symptoms of PTSD, suggesting that veterans may have been drinking alcohol in an effort to improve their mood or to increase emotional connectivity with others. However, because these data were collected cross sectionally, it was not possible to clearly examine the causal and temporal relationship between the development of the psychiatric symptomatology and the onset of alcohol use disorders, raising questions regarding the directionality of these relationships.

Evidence shows that PTSD is not the only stress-related condition that might mediate the relationship between stress and alcohol misuse in military personnel. In a stratified, large-scale sample of military reservists, Gradus and colleagues (2008) examined whether symptoms of depression explained the relationship between military sexual harassment experiences and alcohol misuse, and they found that more severe sexual harassment was related to greater depression symptoms among female reservists. In addition, experiencing greater amounts of sexual harassment was related to higher alcohol misuse. However, when depression symptoms were entered into the equation, the relationship between women's experience of sexual harassment and alcohol misuse was no longer significant. These data suggest that female military reservists may be prone to abuse alcohol as a way of coping with depression symptoms that are secondary to experiencing military sexual harassment.

Does Heritability Play a Role in Military Members' Alcohol Misuse and Posttraumatic Psychiatric Disorders?

Research on veterans suggests that common genetic underpinnings may partially explain the relationship between combat exposure, posttraumatic psychiatric disorders, and alcohol misuse. Much of this evidence comes from studies that are derived from the Vietnam Era Twin Registry (McLeod et al. 2001; Scherrer et al. 2008; Xian et al. 2000). This registry involves a large-scale sample of monozygotic and dizygotic twin pairs who served in the military during the Vietnam era. By examining the relationships between degree of combat exposure, posttraumatic psychiatric disorders, and alcohol misuse among twin pairs that share identical (i.e., monozygotic) or nonidentical (i.e., dizygotic) genetics, researchers derived estimates as to the relative degree of genetic and environmental contributions in explaining experiences in these domains.

Several conclusions were reached by studies of the Vietnam Era Twin Registry data. PTSD and alcohol use problems were both found to be influenced by genetics, although environmental factors explained about one-half of the variance in alcohol misuse and over one-half of the variance in PTSD symptoms (McLeod et al. 2001; Xian et al. 2000). These findings suggest that although genetic factors are notable in explaining these disorders, environmental factors are equal to, if not more substantive, than genetics. Of interest, Xian and colleagues (2000) found that shared family environment did not add to the model in predicting these disorders. This suggests that environmental factors other than the family environment may be responsible for much of the variation in PTSD and alcohol misuse. In addition, these studies concluded that a common genetic element partially accounts for the co-occurrence of combat exposure, posttraumatic psychiatric disorders, and alcohol misuse. In other words, genetic factors may predispose individuals to end up in combat situations and to develop symptoms of PTSD, depression, and alcohol use disorders. Building on this finding, Scherrer and colleagues (2008) found that the genetic and environmental contributions to PTSD, in particular, explained the link between combat and alcohol misuse as well as combat and depression. This suggests that a combination of genetic and environmental vulnerability for the development of PTSD may entirely explain linkages between combat exposure and later alcohol misuse and development of depression. Such a conclusion is important because it suggests that improving understanding of the etiology of and treatment for PTSD may be a key to addressing alcohol misuse and depression following combat exposure.

Is Alcohol Misuse a Pre-existing Risk Factor for Traumatic Stress Recovery?

Although it is possible that military members may engage in alcohol misuse as a way of trying to cope with posttraumatic psychiatric symptoms, there also is evidence to suggest that pre-existing alcohol misuse contributes to posttraumatic psychiatric maladjustment. A longitudinal study by Dickstein and colleagues (2010) found several trajectories of recovery from PTSD symptoms among U.S. soldiers who were deployed to Kosovo on a peacekeeping mission. Although most soldiers (84 percent) exhibited a resilient recovery following their deployment (i.e., low initial PTSD symptoms that decreased over time), a minority exhibited problematic levels of PTSD during the follow-up period. After controlling for other possible risk factors, higher predeployment alcohol misuse distinguished soldiers who experienced PTSD symptoms over the postdeployment follow-up period. These results suggest that problematic drinking prior to the traumatic combat experience may be a risk factor for some soldiers to exhibit PTSD symptoms following combat exposure.

Although these findings suggest that problematic alcohol use may be a risk factor that precedes the development of PTSD, they are not necessarily inconsistent with the self-medication model. Predeployment alcohol misuse may be a behavioral signal for soldiers' pre-existing maladaptive coping strategies. For example, soldiers who misuse

alcohol prior to deployment may be especially prone to abuse alcohol following deployment as a way of trying to self-medicate PTSD re-experiencing symptoms and to avoid difficult and painful emotions. This type of avoidance-based coping strategy is considered an underlying factor in the exacerbation of PTSD symptoms (Foa and Kozak 1986). Hence, these soldiers may be especially prone to attempt to self-medicate posttraumatic psychiatric symptoms, thereby worsening the course of the posttraumatic psychiatric condition.

Findings from Dickstein and colleagues (2010) that alcohol misuse is a risk factor for PTSD can also be considered from the perspective of genetics research on combat, PTSD, and alcohol misuse. As previously described, the common genetic and environmental elements that connect alcohol misuse with combat exposure seem to be those shared through PTSD (Scherrer et al. 2008). Hence, the evidence reported by Dickstein and colleagues (2010) may be attributed to the common genetic and environmental vulnerabilities that alcohol misuse shares with PTSD. In this way, predeployment alcohol misuse may be an observed indicator of an underlying latent environmental and genetic vulnerability for the development of PTSD. Clearly, additional longitudinal research is required to tease out how environmental and genetic risk factors influence the course of developing PTSD and alcohol use disorders.

Traumatic Brain Injury, Alcohol Misuse, and Stress-Related Disorders

The causal links between alcohol misuse and posttraumatic mental health problems are further complicated by the role of traumatic brain injury (TBI) among military members. The rates of traumatic brain injury resulting from combat have increased dramatically with veterans from OEF and OIF versus veterans from prior conflicts. This increase in rates of TBI may be at least partially explained by improvements in body armor and the medical response to combat injuries. With these modern technologies, OEF and OIF veterans are now able to survive injuries that would have resulted in death in prior combat eras. However, many of these OEF and OIF veterans who now survive combat trauma are left with the repercussions of TBI. These TBI events often result from blast exposure during combat, which also can lead to posttraumatic mental health disorders (Corrigan and Cole 2008). Some studies have found that up to 44 percent of veterans who reported loss of consciousness and 27 percent of veterans who reported altered mental status also met criteria for PTSD (Hoge et al. 2008). Given this co-occurrence, defining the etiology of these presenting complaints can be difficult. Furthermore, the relationship between alcohol misuse and TBI often is complex because heavy drinking may predate and predispose individuals to experiencing a TBI (i.e., TBI can result from accidents that occur when people are under the influence of alcohol). In addition, alcohol misuse can exacerbate the complications of TBI by worsening TBI symptom severity (e.g., persistent memory problems) and by further increasing an individual's risk for experiencing additional alcohol-related TBI events. In summary, there are likely to be multiple interrelated factors explaining the relationship between experiencing traumatic events and alcohol misuse among members of the military.

Implications for Assessment and Intervention

Research on the self-medication hypothesis and genetic studies suggests that alcohol misuse following military trauma is likely to be highly related to the co-occurrence of PTSD and other posttraumatic psychiatric problems. Thus, early screening and identification of those who are exhibiting posttraumatic mental health problems is an important first step in intervention. In addition, given the demonstrated vulnerability for those with posttraumatic psychiatric disorders to also exhibit alcohol misuse, screening and intervention efforts should be comprehensive in addressing this common comorbidity.

Although posttraumatic psychiatric problems may be an important mediating factor between military trauma and alcohol misuse, alcohol misuse within the military is a complex phenomenon and one that is likely to have causal factors. As alluded to above, military personnel who misuse alcohol prior to experiencing military-related trauma may be prone to abuse alcohol following trauma, even in the absence of developing posttraumatic mental health problems. Thus, efforts by the military and Veterans Affairs (VA) to screen for early signs of alcohol misuse are important to identify at-risk individuals before they are exposed to combat-related trauma. As shown by Dickstein and colleagues (2010), military members who exhibit a pretrauma history of alcohol misuse may be prone to exhibit poorer recovery from PTSD symptoms following trauma exposure. Therefore, interventions to screen for a history of alcohol misuse also may help to target individuals who are at risk for developing increasingly severe PTSD symptoms following military trauma exposure.

In response to this need, the VA Healthcare System has taken extensive measures to address the issue of co-occurring substance use disorders and PTSD. For example, funding has been provided to establish substance use disorder–PTSD specialists who augment specialized PTSD treatment programs. The role of these specialists is to facilitate the assessment and diagnosis of these disorders in returning veterans and serve as a primary provider of mental health services for veterans with these comorbid conditions. Of note, a VA consensus panel (Department of Veterans Affairs 2009) recommended that specialists in these positions provide first-line evidence-based treatments such as Seeking Safety (Najavits 2002) or motivational interviewing (Miller

and Rollnick 2002). The panel also recommended that substance use disorder treatment programs should continue to use empirically supported treatments focused on treating the substance use disorder. Likewise, the panel recommended that PTSD treatment programs should continue to provide evidence-based treatments targeting PTSD. Finally, the panel concluded that the superiority of any one given treatment approach above another is not supported by the literature to date and that no "gold standard" treatment exists at this time. This serves as a reminder that ample opportunities exist within the VA and military settings to further study these existing treatments and to develop alternative approaches to treating these comorbid conditions.

Summary

Alcohol misuse is a problem among a significant minority of the U.S. military. Military-related traumatic stress seems to elevate risk for individuals to misuse alcohol. The co-occurrence of posttraumatic psychiatric disorders seems to play a major explanatory role in the association between military stress and alcohol misuse. Screening and intervention for alcohol misuse, particularly following exposure to military-related trauma, is clearly needed, as are integrated treatments that address conjoined alcohol and PTSD problems. ■

Acknowledgements

Preparation of this manuscript was supported by the Department of Veterans Affairs, including grant CDA–2–019–09S awarded to the first author. The content of this manuscript does not reflect the opinions of the United States Government or Department of Veterans Affairs.

Financial Disclosure

The authors declare that they have no competing financial interests.

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Stress and Alcohol

Epidemiologic Evidence

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Exposure to stress often is psychologically distressing. The impact of stress on alcohol use and the risk of alcohol use disorders (AUDs) depends on the type, timing during the life course, duration, and severity of the stress experienced. Four important categories of stressors that can influence alcohol consumption are general life stress, catastrophic/fateful stress, childhood maltreatment, and minority stress. General life stressors, including divorce and job loss, increase the risk for AUDs. Exposure to terrorism or other disasters causes population-level increases in overall alcohol consumption but little increase in the incidence of AUDs. However, individuals with a history of AUDs are more likely to drink to cope with the traumatic event. Early onset of drinking in adolescence, as well as adult AUDs, are more common among people who experience childhood maltreatment. Finally, both perceptions and objective indicators of discrimination are associated with alcohol use and AUDs among racial/ethnic and sexual minorities. These observations demonstrate that exposure to stress in many forms is related to subsequent alcohol consumption and AUDs. However, many areas of this research remain to be studied, including greater attention to the role of various stressors in the course of AUDs and potential risk moderators when individuals are exposed to stressors. **Key words: Alcohol use and abuse; alcohol use disorders; stress; stress as a cause of alcohol and other drug use; risk factors; psychological stress; stress response; coping; stressors; general life stress; catastrophe; child abuse; minority group; epidemiological indicators**

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Exposure to varying forms of stress is an integral life experience that can provoke a variety of reactions. In research on alcohol, drug, and psychiatric disorders, the term "stress" often is understood to indicate any experience denoting adversity (Dohrenwend 2000). Stress exposures consist of external stimuli that are threatening or harmful; elicit fear, anxiety, anger, excitement, and/or sadness; and are negative in impact and outcome (Sinha 2001, 2008). Mild to moderate levels of stress can present challenges that are within a person's capability to overcome, producing a sense of mastery and accomplishment that eventually result in a positive outcome. However, adverse experiences that exceed the coping abilities of the individual increase the risk for psychopathology (Lazarus 1999; Levine 2005; McEwen 2007; Selye 1976; Sinha 2008).

Just as people vary in their capabilities, stress exposures can be viewed as varying across several dimensions (see figure 1). One dimension is severity, which can range from mild (e.g., the daily hassles of family and job among healthy individuals whose basic needs are met) to severe (e.g., extreme adversity that threatens the life, physical integrity, health and home of oneself and one's loved ones). Other dimensions, not necessarily orthogonal to each other, include whether the stressor occurred during childhood or maturity, the degree to which the stressor is acute or chronic and expected or unexpected, whether the threat is emotional or physical, and the difficulty of discerning whether the stressor was the cause or consequence of the health outcome under consideration.

This article presents evidence for the effect of four categories of stressors,

including general life stress, catastrophic/fateful stress, childhood maltreatment, and minority stress, each of which encompasses a range of specific kinds of stressors (see figure 2). Each category of stressors is evaluated according to the dimensions shown in figure 1, and the extant epidemiologic evidence for the effect of each on both alcohol use and alcohol use disorders (AUDs) is reviewed.

General Life Stressors and AUDs—Evidence From National Surveys

National surveys often include some measure of general life stress that may range from common experiences, such as moving or changing jobs, to uncommon experiences, such as severe threats to personal integrity and arrest. The severity of the events often is variable; for example, a divorce that may be stressful for some individuals can be a relief for others, and the death of a relative may refer to a parent or spouse or to a distant relative with little connection to the respondent's day-to-day life. Nevertheless, the overall number of these experiences is related to alcohol outcomes (see table 1). In the 2001–2002 National Epidemiologic Survey on Alcohol and Related Conditions, respondents reported on 12 general life stressors, ranging from items such as changing jobs or moving, to trouble with a boss or coworker, trouble with a neighbor, and a family member in poor health, to being the victim of a crime, being unemployed or fired from a job, and divorce or breakup of a steady relationship. The data show that the number of past-year stressors experienced was related to any current drinking, current binge drinking (i.e., consuming five or more drinks for men or four or more drinks for women at least once in the past year), and current AUDs. Among men, the relationship with each alcohol outcome steadily increased from 0 to approximately 6 stressors, after which the relationship tapered off and tended to decrease at 10 or more stressors. Among women, the relationship with each outcome generally was more linear, with increases in prevalence at each increase in past-year stressors (see table 1).

Various studies in smaller adult community samples also have found that the number of general life stressors is associated with alcohol consumption and problem alcohol use (which may not necessarily meet the criteria of an AUD) (Cole et al. 1990; King et al. 2003). However, one population-based longitudinal study of older adults (mean age 61 years) did not demonstrate long-term effects (i.e., at 1 year or more after the event) of acute stressful life events on patterns of alcohol consumption (Skaff et al. 1999). A national prospective study of 3,006 women found an increased risk of alcohol abuse after being an assault victim, with no evidence of reverse causation (i.e., that alcohol consumption alone contributed to the risk for assault) (Kilpatrick et al. 1997). However, other studies have indicated that excessive alcohol use also increases the risk for sexual assault (Abbey et al. 1994; Corbin et al. 2001); therefore, the relationship between assault and alcohol use likely is bidirectional. Finally, several general population studies have found an increase in the incidence of AUDs following job loss, particularly among men (Catalano et al. 1993; Crawford et al. 1987). It is noteworthy, however, that the context of a job loss likely is important for its impact on the risk of AUDs. For example, the meaning of the lost job may be different for a worker whose plant is shut down after he or she has worked for 30 years in the same position compared with an artist or a musician accustomed to temporary work. Nevertheless, these studies indicate that any type of job loss is associated with increased risk of AUDs.

Genetic factors may influence the relationship between exposure to general stressors and alcohol and other drug use. In a longitudinal study of 295 college students who for 2 years

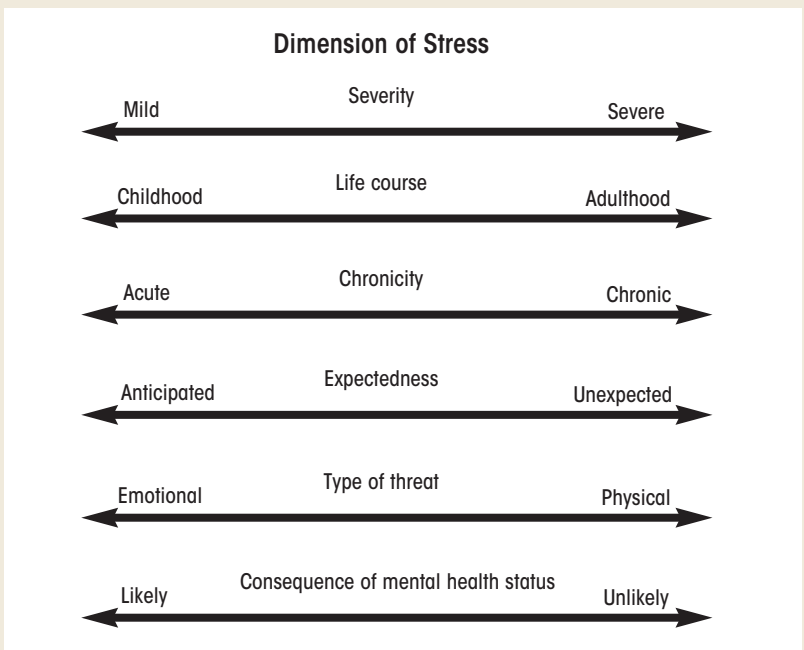

Figure 1 Dimensions of stressful experiences.

provided daily reports of stressful events as well as alcohol and drug use via the internet, those who carried two copies of a specific variant in regulatory region of the gene encoding a protein involved in the actions of the brain signaling molecule serotonin (i.e., who were homozygous for the *s* allele of 5-HTTLPR serotonin transporter promoter) were at substantially increased risk for heavy drinking and drug use if they experienced a high level of stressful life events compared with students carrying only one or no copy of this allele (Covault et al. 2007).

It also is important to note that daily exposure to interpersonal stress, such as problems at work, trouble with the police, or breakup of romantic relationships also may be influenced by having an AUD. Although these exposures likely are stressful for anyone experiencing them, they can be as much a consequence as a cause of an AUD. Therefore, teasing apart the temporal and causal directions of relationships between these adult stressors and alcohol use is a difficult task in general-population epidemiologic samples.

Substantial research on mental health in general and alcohol consumption specifically has been conducted after the terrorist attacks on the World Trade Center.

Fateful/Catastrophic Events and AUDs

With respect to the various correlated dimensions of stress in human populations described earlier, fateful/catastrophic events, such as direct exposure to a disaster or terrorism attack, typically lie on the more extreme end of the severity continuum. These stressors usually are acute and unexpected, and exposure is very unlikely to result from an individual's alcohol consumption. However, the "fatefulness" of the event may depend on the specific circumstances of the event. For example, studies of people exposed to nightclub disasters (e.g., from fires and terrorist attacks) (Kennedy et al. 2005; Mahoney et al. 2005) involve individuals who are younger and more likely to consume alcohol than the general population. The study of such events still may provide important information, but the type of individuals involved and the appropriate control group must be considered carefully. Fateful/catastrophic events can involve both physical threat to one's life and emotional threat (e.g., knowing someone lost or killed in the fateful/catastrophic incident, fear of additional exposures) and generally can occur at any point in the life course.

Both in the United States and internationally, many studies have addressed the relationship between different types of natural and man-made disasters and alcohol consumption, including studies of exposure to natural disasters, such as flooding (North et al. 2004), volcano eruptions (Adams and Adams 1984), earthquakes (Shimizu et al. 2000), and hurricanes (Cerda et al. 2011; Kohn et al. 2005). Studies also have investigated the consequences of exposure to man-made disasters, such as mass shootings (North et al. 1994; Smith et al. 1999), fire or grotesque death (Green et al. 1985; Reijneveld et al. 2003; Sims and Sims 1998), ferry disasters (Joseph et al. 1993), and nuclear accidents (Kasl et al. 1981). Studies covering a timeframe of a year or less after the disaster consistently have indicated postdisaster increases in alcohol consumption (Joseph et al. 1993; Kasl et al. 1981; Kohn et al. 2005; Reijneveld et al. 2003; Sims and Sims 1998; Smith et al. 1999). Studies with multiple and/or longer followups generally have found attenuation of this relationship over time (Joseph et al. 1993).

Several studies also have addressed alcohol consumption in response to

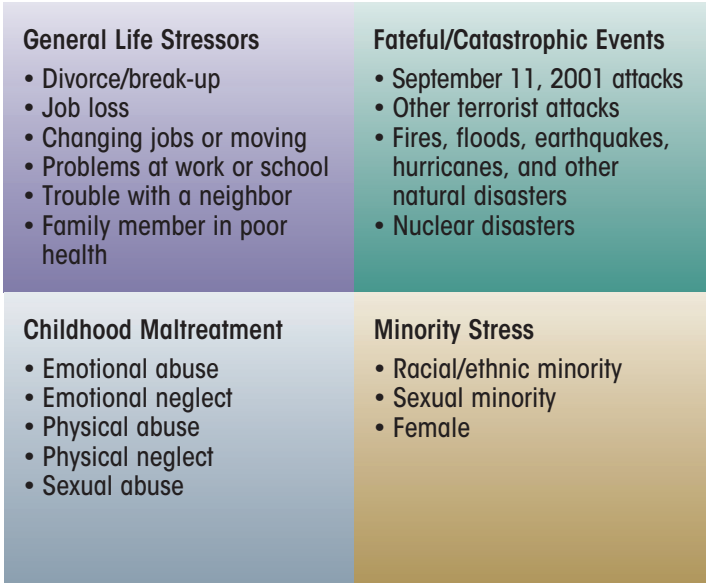

Figure 2 Four categories of stressors and examples of exposures within each stress category.

exposure to terrorism. Substantial research on mental health in general and alcohol consumption specifically has been conducted after the terrorist attacks on the World Trade Center in New York City and the Pentagon in Washington, DC, on September 11, 2001 (9/11). These studies have indicated that alcohol consumption generally increased in both New York City and elsewhere in the short term following the attacks. Thus, increased alcohol use was found among the following groups:

- Survivors of the attack on the Pentagon (Grieger et al. 2003);
- Residents of Manhattan in the one month and/or six months following the attack (Ho et al. 2002; Vlahov et al. 2002, 2004);
- Residents in the tri-State area of Connecticut, New York, and New Jersey (Melnik et al. 2002); and
- Adults from a nationally representative sample (Stein et al. 2004).

Longer-term studies showed increased alcohol consumption 1 and 2 years later among New Yorkers at greater exposure levels to the attack (Boscarino et al. 2006).

Few studies have examined alcohol use and terrorism exposure outside the United States, but two studies of adolescents in different cities in Israel found that geographic proximity to terrorist attacks was associated with greater quantity and frequency of drinking as well as with binge drinking (Schiff et al. 2006, 2007).

Several studies have been able to control for predisaster drinking levels, the lack of which had been a limitation of most of the aforementioned epidemiologic research. These studies have documented an increase in alcohol consumption following exposure to disaster independent of the consumption levels measured prior to the exposure (Cerda et al. 2011; Hasin et al. 2007*a*; Richman et al. 2004). A recent meta-analysis of 27 studies assessing substance use in response to terrorism that included studies with follow-up times ranging from 1 week to more than 2 years found a pooled effect indicating that the population level of alcohol consumption is increased following a terrorist attack (DiMaggio et al. 2009).

The research described above focuses on any alcohol consumption after disaster. Studies of AUDs and problem drinking following major disasters have been less consistent. Following the Oklahoma City bombings in 1995, North and colleagues reported no increase in incident AUDs, either in survivors of the attack (North et al. 1999) or in rescue workers (North et al. 2002). Survivors of other disasters, such as Hurricane Andrew (David et al. 1996), flooding (Green et al. 1992; North et al. 2004), and jet crashes

Table 1 Relationship Between Number of Past-Year Stressors and Prevalence of Current Drinking, Current Binge Drinking, and Current Alcohol Use Disorders Among Men and Women in the 2001–2002 National Epidemiologic Survey on Alcohol and Related Conditions (*N* = 43,093).

	Men			Women		
	Current Drinking (% respondents)	Current Binge Drinking (% respondents)	Current Alcohol Use Disorders (% respondents)	Current Drinking (% respondents)	Current Binge Drinking (% respondents)	Current Alcohol Use Disorders (% respondents)
Number of past-year stressors						
0	65.9	32.0	6.1	49.0	11.9	1.8
1	70.7	41.2	9.8	58.5	13.8	3.3
2	72.8	42.7	12.0	61.6	17.7	4.7
3	77.8	52.3	18.3	68.7	24.5	7.0
4	79.0	60.8	24.6	73.8	28.8	11.5
5	84.1	61.5	30.3	74.6	33.5	11.9
6	87.7	66.1	35.0	77.6	39.2	13.7
7	87.3	69.5	35.8	76.9	36.5	21.2
8	85.6	70.7	35.1	84.0	47.7	23.9
9	96.8	66.9	56.3	86.9	46.1	33.2
10+	66.0	65.2	36.4	89.2	50.9	40.8

SOURCE: National Epidemiologic Survey on Alcohol and Related Conditions

(Smith et al. 1990), as well as a combined sample of survivors from the Oklahoma City terrorist bombing and the bombing of the U.S. embassy in Nairobi, Kenya (North et al. 2005) also showed no evidence of increases in incident AUDs. Studies assessing the impact of 9/11 found that neither living near the attack site nor knowing someone lost or killed was associated with incident alcohol problems 6 months following the attack (Vlahov et al. 2006); moreover, exposure to 9/11 was not associated with the trajectory of alcohol use and binge drinking in the 3 years following the attack (Cerda et al. 2008). In a recent pooled analysis of data from 10 different disasters, including exposure to flooding, shootings, and plane crashes, North and colleagues (2010) again reported no evidence of increased risk for incident AUDs after these events, although people with pre-existing AUDs were more likely to report increased drinking after these events.

Several studies contradict the above evidence, however, as follows:

- Evidence from survivors of Hurricane Katrina indicates elevated rates of alcohol problems compared with national and local predisaster averages (Flory et al. 2009). Furthermore, increases in binge drinking were found among those most exposed to the hurricane, controlling for prehurricane alcohol use (Cerda et al. 2011).

- Among New Yorkers interviewed at 1 and 2 years after 9/11, greater exposure levels predicted binge drinking at 1 year but not 2 years and an increase in alcohol dependence at both time points (Boscarino et al. 2006).

- Seven months after the Mount St. Helens volcano eruption, alcohol-center referrals and liquor-law violations had increased compared with the pre-eruption period (Adams and Adams 1984).

- Survivors of the Beverly Hills Supper Club fire seemed to have an increase in alcohol abuse more than 2 years after the fire (Green et al. 1985).

Thus, the literature is inconsistent on the role of fateful traumatic events in the development of AUDs. It is noteworthy, however, that studies of incident AUDs after major disasters were conducted in adult populations in which the incidence of such disorders generally is low (Hasin et al. 2007*b*). Studies of incident AUD risk following exposure to disaster in adolescent and young adult populations are necessary to comprehensively understand the relation between disaster and incident AUDs.

A substantial literature also has documented increased alcohol consumption and risk for AUDs among war veterans, especially those exposed to active combat (Hoge et al. 2006; Jacobson et al. 2008; Milliken et al. 2007; Shipherd et al. 2005). Causal inference from this literature is complicated, however, because people who perform military duty most often are young men at high baseline risk for AUDs. In addition, exposure to combat is not randomly assigned, and people who have sensation-seeking personality characteristics are more likely to both be assigned to combat and, independently, develop AUDs.

Child Maltreatment and AUDs

Childhood maltreatment includes many adverse exposures (e.g., sexual, emotional, and/or physical abuse and emotional and/or physical neglect) during the first 18 years of life. With respect to the various correlated dimensions of stress in human populations described earlier, childhood maltreatment experiences range from mild (e.g., occasionally saying hurtful things) to severe (e.g., chronic physical and/or sexual abuse). Although these stressors can be acute, they often are chronic throughout childhood; furthermore, they are very unlikely to be a consequence of alcohol consumption as they typically occur before drinking initiation. Childhood maltreatment can involve both physical threat (e.g., physical and sexual abuse or physical neglect of needs) and emotional threat (e.g., emotional abuse and neglect). These experiences are common and may account for a significant proportion of all adult psychopathology (Afifi et al. 2008; Green et al. 2010). Further, events frequently co-occur (Dong et al. 2004; Dube et al. 2002; Edwards et al. 2003; Finkelhor et al. 2007)—in other words, exposure to one type of childhood maltreatment increases the risk of exposure to others.

Epidemiologic studies addressing the impact of adverse childhood events on alcohol consumption and AUDs have employed several types of designs, including cross-sectional studies of adults with retrospective assessment of adverse childhood events, prospective cohort studies, and studies of twin and other genetically informative samples. Studies generally have shown that most forms of child maltreatment are related to higher risk of adolescent alcohol consumption (Bensley et al. 1999; Hussey et al. 2006; Sartor et al. 2007; Thornberry et al. 2001) and adult alcohol consumption and AUDs (Anda et al. 2002; MacMillan et al. 2001; Molnar et al. 2001; Nelson et al. 2006). One review documented that childhood maltreatment and other childhood stressors were associated with earlier onset of adolescent alcohol consumption and with AUDs in adulthood (Enoch 2010).

Childhood maltreatment is more likely to occur among children of alcoholics (Gilbert et al. 2009); in these cases, the parents may not only engage in harmful parenting practices (Kettinger et al. 2000; Stanger et al. 2004; Suchman et al. 2007, 2008) but also may pass along genes increasing the risk of AUDs to their offspring. Thus, the specificity of the relationship between maltreatment and alcohol use in the context of these other risk factors remains an open debate. Furthermore, psychiatric comorbidity also may confound the relationship between early maltreatment and AUDs because mal-

treatment affects the risk for multiple psychiatric disorders (Green et al. 2010; Kendler et al. 2000; Kessler et al. 1997; Widom et al. 2007*a*), and AUDs are highly comorbid with other forms of psychopathology (Hasin et al. 2007*b*). Studies using animal models, which can control for environmental factors and comorbidity, have suggested that extended stress in early life leads to later self-administration of alcohol (Cruz et al. 2008; Miczek et al. 2008). However, some epidemiologic studies suggest that the relationship between maltreatment and AUDs may be at least partially confounded by family history of alcohol problems. For example, a prospective cohort study that compared court-recorded cases of abuse and neglect with matched community controls in the Midwest found no remaining association between early abuse and adult AUDs[1] after controlling for family history of alcohol problems among men (Widom et al. 1995, 2007*b*); only among women physical neglect remained associated with AUDs.

However, several studies that controlled for family history of alcoholism have indicated a persistent relationship between childhood adverse events, including parental divorce (Pilowsky et al. 2009; Thompson et al. 2008) and death of a parent or foster home placement (Kendler et al. 1996; Pilowsky et al. 2009), and adult risk for AUDs. Another study documented strong and significantly increased odds of AUDs based on retrospective assessment of childhood sexual abuse among same-sex twins in Australia (Nelson et al. 2002), even after controlling for family background variables such as parental alcohol problems. Finally, recent data from a population-based study of twins in Virginia reported that participants who reported any maltreatment were 1.74 times as likely to experience an AUD in adulthood as were people who did not report maltreatment, and although controlling for family-level risk factors substantially attenuated the observed association, a direct effect remained after control (Young-Wolff et al. 2011).

Research now is examining specific genetic variations (i.e., polymorphisms) as moderators of the relationship between child maltreatment and AUDs. The finding that functional polymorphisms in the gene encoding the monoamine oxidase A enzyme (MAOA) (Caspi et al. 2002) interact with childhood maltreatment to predict antisocial behavior in adulthood stimulated research on whether this effect generalizes to substance use disorders; however, thus far, the findings could not be replicated (Young et al. 2006). Other studies have focused on the previously mentioned serotonin transporter promoter variant, 5-HTTLPR, and its interaction with stressful experiences in a wide variety of psychiatric outcomes after researchers detected such an interaction for major depression (Caspi et al. 2003). This DNA sequences exists in two alleles, *l* and *s* alleles; thus, a person can carry either two *l* or two *s* alleles (i.e., be homozygous for *l* or *s*) or one *l* and one *s* allele (i.e., be heterozygous). One study found that youth with court-documented maltreatment were at higher risk for early-onset alcohol use if they had the heterozygous (*s/l*) genotype compared with the *l/l* genotype (Kaufman et al. 2007). In another youth study, the effect of the same heterozygous genotype on increased risk for substance use was attenuated in families providing involved-supportive parenting (Brody et al. 2009*a*). In an innovative approach involving random assignment of the environment, the investigators then randomized at-risk families to an intervention designed to increase involved-supportive parenting or a control condition (Brody et al. 2009*b*). Among those with the heterozygous 5-HTTLPR genotype, children in treated families had less substance use at followup compared with children of the control families (Brody et al. 2009*b*). Taken together, these studies suggest that the risk for later alcohol outcomes is affected by an interaction of stressful early home environments and genetic vulnerability.

Minority Stress and AUDs

Minority stress is defined as exposure to specific stressors that result from a person's minority status, especially prejudice and discrimination events (Meyer 2003*b*; Williams et al. 2003). These events range from mild (e.g., daily hassles, such as being followed in a store) to more severe (e.g., being a victim of a violent crime) and include both emotional (e.g., workplace harassment [Waldo 1999]) and physical (e.g., hate crimes [Herek 2009]) threats to self. Minority status cannot be attributed to having an AUD, making one aspect of interpretation straightforward in studies in this area. Although minority stress can involve acute events, it most frequently is viewed as a chronic exposure that occurs across the entire life course (Williams et al. 2003). Finally, minority stressors vary with respect to whether they are expected. Research has indicated that although many stressors that members of minority groups confront are unanticipated, one consequence of repeated exposure to discrimination is that people begin to expect rejection based on their stigmatized identity (Mendoza-Denton et al. 2002).

Racial/Ethnic Minorities

According to minority stress models, the stress resulting from prejudice and discrimination should lead to elevations in alcohol use among minority group members. Patterns of alcohol use among racial/ethnic minorities, however, fail to correspond to these predictions. Although Native Americans have higher rates of alcohol consumption and AUDs compared with non-Hispanic Whites (Hasin et al. 2007*b*), several large surveys have indicated lower rates of alcohol consumption and AUDs among non-Hispanic Blacks, Asians, and Hispanics compared with Whites (Breslau et al. 2006; Hasin et al. 2007*b*; Kessler et al. 1994). These

[1] AUDs in this study were defined according to the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised* (DSM–III–R).

minority groups also have lower rates of other psychiatric disorders (e.g., major depression), leading to what has been called the "minority paradox" (Williams 2001) in mental health research—that is, minority groups such as Blacks and Hispanics have lower rates of psychiatric and substance disorders despite greater exposure to institutional and interpersonal discrimination that has been shown to engender substantial stress via biological (Lewis et al. 2006) and psychological (Hatzenbuehler 2009) mechanisms. In contrast to these findings from between-group studies, within-group studies consistently show that perceived discrimination is associated with alcohol outcomes. This association has been found in Blacks (McLaughlin et al. 2010*b*; Taylor and Jackson 1990; Yen et al. 1999), Filipino Americans (Gee et al. 2007) and Asian-American adolescents (Yoo et al. 2010).

Sexual Minorities

In contrast to racial/ethnic minorities, lesbian, gay, and bisexual (LGB) individuals have higher rates of substance use and substance use disorders than their heterosexual peers (Garofalo et al. 1998; Russell et al. 2002; Ziyadeh et al. 2007); this difference applies to both adolescents (Eisenberg and Wechsler 2003; Hatzenbuehler et al. 2008) and adults (Burgard et al. 2005; Cochran et al. 2000; Drabble et al. 2005). Although research has tended to primarily examine perceived discrimination as a risk factor for internalizing psychopathology, such as depression and anxiety, recent studies also have shown higher levels of alcohol use (Hatzenbuehler et al. 2011) and AUDs (McCabe et al. 2010) among LGBs who perceive that they have experienced higher levels of discrimination.

Because of their design, these studies cannot rule out reverse causality—that is, that individuals with alcohol problems may perceive and report greater discrimination. In order to address some of these methodological limitations of subjective measures of discrimination, recent studies have developed novel measures for operationalizing objective stressors that LGB individuals confront, including institutional forms of discrimination (e.g., anti-marriage laws or employment discrimination policies). Because these institutional stressors occur outside the control of LGB individuals, they are not confounded with mental health status and therefore provide a stronger test of the effect of discrimination on mental health than measures of subjective stress. Studies are beginning to document the relationship between these objective stressors and LGB health, including alcohol use. For example, a recent study examined the impact of State-level ballot initiatives banning gay marriage on the prevalence of psychiatric and substance use disorders in LGB populations (Hatzenbuehler et al. 2010). The results indicated that LGB respondents living in States that passed such bans in 2004 had significantly greater increases in psychiatric disorders and AUDs than did LGB respondents in States that did not pass such bans (Hatzenbuehler et al. 2010). This research demonstrates the potential importance of incorporating more objectively-defined indices of social stress into research on alcohol use among minority populations. Indeed, an examination of how and why such social stressors contribute to the development and maintenance of AUDs within LGB populations represents a crucial avenue for future inquiry.

Conclusion

The psychological and psychiatric effects of stress remain an important mechanism for individual differences in all areas of mental health. Substantial evidence exists that fateful/catastrophic events, such as exposure to disaster and terrorism; childhood adversities, such as maltreatment; interpersonal stressors, such as divorce and job loss; and chronic minority stress affect alcohol consumption and AUDs. Although these data demonstrate the importance of stress in the development of alcohol problems in human populations, substantial work remains to be done in these areas. Refined measures of stress exposures; careful assessment of confounding and reverse causation; an examination of AUD course, including relapse; and the potentiating of stress effects by genetic vulnerability, personality factors, macrosocial factors, and other important biological and social domains remain important topic areas in need of more epidemiologic study. Exploring the epidemiology of stress in human populations can help integrate and translate work in experimental human and animal models in order to demonstrate the real-world effects of these common yet often devastating exposures on alcohol use and misuse. ■

Acknowledgements

This research was supported in part by National Institute on Alcoholism and Alcohol Abuse grants K05–AA–014223 and U01–AA–018111 (to Dr. Hasin), National Institute of Drug Abuse fellowship F31–DA–026689 (to Dr. Keyes), the Robert Wood Johnson Health and Society Scholars program (to Dr. Hatzenbuehler), and New York State Psychiatric Institute (to Dr. Hasin). We would like to thank Philip Bender for assistance in manuscript preparation.

Financial Disclosure

The authors declare that they have no competing financial interests.

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Overview: Stress and Alcohol Use Disorders Revisited

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Nearly 13 years have passed since *Alcohol Research & Health* (now titled *Alcohol Research: Current Reviews*) first visited the topic of "Alcohol and Stress." Since that time, the field has advanced considerably. New terms have been developed to describe the complex physiological interactions that occur when an individual is faced with stressful events and more is known about how the brain and body work to offset the changes induced through stress-response mechanisms. An individual's reactions to stress vary according to a number of factors, such as his or her genetic makeup, environment, life events, gender, age, and type and duration of stress. Drinking alcohol has the unique ability to both relieve stress and to be the cause of it, creating in a sense a double-edged sword. Understanding the link between alcohol drinking, stress, and alcohol use disorders (AUDs) is a critical area for ongoing investigation. Discoveries emanating from this field not only add to the burgeoning literature on stress and the risk for disease but also may provide answers to help prevent and intervene in the development of AUDs. **KEY WORDS: Alcohol consumption; alcohol use disorders; stress as a cause of alcohol and other drug use; stress; stressors; stress response; stress reactivity; physiological response to stress; brain; genetic factors; environmental factors; allostasis; allostatic load; allostatic state; homeostasis**

In the 13 years since *Alcohol Research & Health* (now titled *Alcohol Research: Current Reviews*) first visited the topic of "Alcohol and Stress" (see Vol. 23, No. 4, 1999), there has been a sustained flow of new information in the field prompting us to publish this updated edition. Indeed, one could argue that this second look at the topic is long overdue. An entirely new lexicon of terms[1] has been developed to capture our evolving conceptualization of stress and its effects on health and disease risk. Many of these terms (e.g., allostasis and allostatic load), which were becoming popular around the turn of the 21st century, were hardly mentioned in that previous edition, so there is a fair amount of catching up to do. Unthinkable events (e.g., the 9/11 terrorist attack and its aftermath—Operation Enduring Freedom and Operation Iraqi Freedom) have occurred, spurring renewed interest in the role of uncontrollable acute and chronic stressors on drinking behaviors in civilians and military personnel alike. New fields have emerged (e.g., epigenetics), and their findings demonstrate that early-life trauma can leave an indelible stamp on an individual's genetic makeup (i.e., genome) and stress circuitry. Gene–environment interactions have been discovered that partly quell the artificial argument as to whether nature or nurture most influences disease risk. Finally, new integrated treatments have emerged (e.g., Najavits' Seeking Safety), and mechanisms of action partly defined (e.g., naltrexone's effects on stress axis function), that demonstrate how understanding the links between stress and alcohol drinking promotes improved treatment options for patients with alcohol use disorders (AUDs).

In their opening article to the 1999 *Alcohol Health & Research* edition on "Alcohol and Stress," Anisman and Merali (1999) summarized the literature to develop a working definition of stress and stressors (i.e., stressful situations) that we attempt to update in the present treatise. We also will embellish upon several themes that these authors chose to highlight, including the importance of sex differences and stressor specificity. By introducing these themes, we hope to set the stage for the articles that follow, which delve into several of these topics more deeply.

What Is Stress?

Webster's *Third New International Dictionary* (1981, p. 2260) defined stress as "a physical, chemical, or emotional factor (as trauma, histamine, or fear) to which an individual fails to make a satisfactory adaptation, and

[1] For terms and their definitions, see the Glossary beginning on p. 522.

which causes physiologic tensions that may be a contributing cause of disease." Although this term now is widely used in the common vernacular, it is interesting to note that the scientific conceptualization of this phenomenon dates back only about 150 years.

Most stress research historians agree that the French physiologist, Claude Bernard (1865), was the first to recognize a key element in the stress response—the phenomenon now known as feedback regulation. Bernard noticed that the internal environment of cells ("milieu intérieur") is tightly regulated and largely dependent on feedback it receives from the periphery or "external environment" (Goldstein and Kopin 2007). Some 65 years later, Sir Walter Cannon coined the term "homeostasis" to capture the "coordinated physiological processes that maintain most of the steady states of the organism" (Cannon 1929 as cited by Goldstein and McEwen 2002, p. 55). From Cannon's perspective, which derived from his study of the sympathetic nervous system (he also coined the phrase "fight-or-flight responses"), all organisms adjusted to challenges to their internal environments by making compensatory responses intended to restore homeostasis. By accomplishing such, the organism's chances for survival improved because the homeostatic or steady state was viewed as optimal and fixed at some preordained, stable level (Goldstein and Kopin 2007; Neylan 1998).

The Hungarian scientist, Hans Selye, who was influenced by Cannon's work, developed the concept of the General Adaptation Syndrome in 1936. Selye's theories, which dominated thinking on the nature of the stress response for more than 50 years, hypothesized that a classical syndrome developed in all organisms "the symptoms of which are independent of the damaging agent or the pharmacological type of the drug employed" (Selye 1936, p. 32). He further hypothesized that this stress response had three stages: an initial alarm reaction (akin to Cannon's fight-or-flight response) that involved the release of anterior pituitary hormones; a second, adaptation phase, wherein an attempt is made to resist the stressor; and a third, exhaustion phase, which, at its extreme, could lead to death of the organism (Goldstein and Kopin 2007; Selye 1936).

Over time, scientists began challenging two key concepts in this definition of stress as any real or imagined threat to homeostasis (McEwen and Stellar 1993). First, Selye's assertion that stress responses were uniform and generalized regardless of stressor type was modified in recognition that certain types of stressors (e.g., physical versus emotional, see below) evoked activation of specific effector systems. For example, exposure to extreme cold produces a marked activation of the sympathetic noradrenergic system in an effort to regulate core body temperature, yet it has minimal effects on the endocrine or hormonal stress response (Goldstein and Kopin 2007). Thus, Selye's doctrine of a unitary, nonspecific stress response gave way to a more refined view that individuals activate stress systems more selectively depending on the characteristics of the stressor.

Second, scientists began recognizing that physiological regulatory systems spanned multiple domains, were dynamic and not static, and fluctuated constantly based on the animal's biological rhythms and physiological demands. Moreover, the notion that there existed some static, ideal, homeostatic set point gave way to thinking that, instead, these set points vary across a dynamic operating range which change over time. Thus, Sterling and Eyer ([1988] as cited in McEwen and Stellar 1993) coined the term allostasis to describe this operating range and the organism's ability to increase or decrease body functions to a new steady state when challenged.

McEwen and Stellar (1993) embellished on the principle of allostasis by defining a new concept that these authors labeled allostatic load. This term connotes the toll placed on individuals when they have to constantly or repeatedly adjust the operating range to maintain fluctuating set points. This "wear and tear" can predispose the individual to disease, especially in the context of chronic stress.

It is interesting to note that in this seminal paper, the authors cite "the reciprocal relationship between stress and alcohol consumption" as an example of allostatic load:

In short, whereas drinking may help the person cope with stress in the short-term, there is a longer-term cost. As the person tries to balance the reciprocal effects of stress and alcohol consumption in this manner, the upward spiral of both stress and drinking increases this overall cost (allostatic load) both behaviorally and biologically (McEwen and Stellar 1993, p. 2096).

In summary, although the use of the term stress has become commonplace, the scientific conceptualization of this state is a relatively recent phenomenon and is still evolving. Stress has been broadly defined "as a threat, real or implied, to the psychological or physical integrity of an individual" (McEwen 2000, p. 108). Other terms, however, such as allostasis ("maintaining stability, or homeostasis, through change" [Sterling and Eyer 1988 as cited in McEwen 2000, p. 108]) and allostatic load ("the price the body pays for being forced to adapt to adverse psychosocial or physical situations" [McEwen 2000, p. 110]) are newly emerged and are helping to better define the relationships between stress and disease risk, including the risk for AUDs, as described below.

Stress and Addiction to Alcohol and Other Drugs

Koob and Le Moal (1997, 2001) began formally linking the brain's stress and reward systems in an allostatic model of alcohol and other drug addiction that still holds sway over the field today. As described in detail elsewhere (Koob and Le Moal 1997, 2001) and alluded to in Koob and colleagues' contribution in this edition (see pp. 516–521), these scientists hypothesized that alcohol and other drug

addiction represents an allostatic state whereby an individual's hedonic set point has drifted downward and been recalibrated at a new point below the normal, homeostatic range. The fluctuating hysteresis of this proposed downward sloping "mood" curve reflects the operating range of the brain's reward and stress systems, which engage in a struggle to adjust and readjust in the setting of repetitive alcohol (or other drug) use. Thus, in this allostatic model, alcohol drinking can be viewed as both a reward and a stressor—an interpretation which is consistent with observations that acute doses of alcohol simultaneously increase brain concentrations of mesolimbic dopamine and other reinforcing neurotransmitters as well as brain levels of corticotropin-releasing factor (CRF) and blood levels of adrenocorticotropin hormone (ACTH) and cortisol, the major stress hormones in the brain and body (Rivier and Lee 1996).

At first glance, this notion of alcohol and other drugs of abuse working as stressors (i.e., taxing to the individual) flies in the face of the more commonly held belief that ethanol has stress-response–dampening effects. However, several characteristics of the drug may explain this paradox. First, alcohol's rewarding properties may counterbalance or mask its stress-provoking effects. This happens on a number of different levels: (1) the drug produces brain depressant effects by acutely enhancing GABAergic tone, while inhibiting excitatory glutamatergic signaling; (2) ethanol acutely enhances the release of reinforcing neurotransmitters (e.g., dopamine and endogenous opiates) and neuromodulators (e.g., endocannabinoids); and (3) alcohol's effects on the release of the stress hormone, cortisol, in the periphery triggers further rewarding properties in the brain (see the article by Stephens and Wand, pp. 468–483).

Second, consistent with the second phase in Selye's general adaptation syndrome, and the opponent-process model (Solomon and Corbit 1973) evoked in Koob and Le Moal's allostatic model of addiction, the brain resists or adapts to repeated, alcohol-induced stress hormone elevations. This neuroadaptation underlies the allostatic change associated with chronic heavy drinking and manifests as a blunted stress response in recently abstinent alcoholics (see Stephens and Wand, pp. 468–483).

In summary, although low doses of alcohol in non–alcohol-dependent individuals produce rewarding effects that are perceived to attenuate stress, in actuality, the drug stimulates the release of CRF and stress hormones. Chronic, heavy use of ethanol produces an allostatic state wherein reinforcing and stress-provoking effects of the drug battle and oppose each other but generally contribute to an altered set point below that associated with normal mood states. When repeated over many months to years, this struggle exerts its toll (i.e., produces allostatic load) on the brain and body, as there is a cost associated with the chronic efforts to adapt to these stressors. Thus, drinking to relieve stress proves to be a double-edged sword.

Factors Influencing Stress Reactivity

Casual readers of the alcohol and stress literature can become frustrated by the apparent lack of uniformity of findings. For example, when analyzing studies attempting to determine whether stress leads to relapse to alcoholism (see the article by Thomas and colleagues in this edition, pp. 459–467), readers will observe that sometimes blunted hormonal responses are associated with increased relapse risk; whereas, in other instances, exaggerated hormonal responses predict the return to drinking. However, when one considers that stress responsivity is governed by a host of factors related to (1) the characteristics of the stressor and (2) the characteristics of the individual, some of this heterogeneity in findings can be explained.

Stressor–Specificity

Painstakingly detailed neuroanatomical studies in experimental animals were among the first to demonstrate that organisms have evolved different stress circuits to adapt to life's variety of stressors (Goldstein and Kopin 2007; Pacak et al. 1998). This stressor-specific strategy certainly makes sense from an evolutionary standpoint: it would be extremely inefficient to mobilize the same effector systems to keep an animal's core temperature up when exposed to cold weather as it would to respond to hemorrhagic hypotension. However, there also is an advantage to having some redundancy across these effector systems. For example, the hypothalamic–pituitary–adrenal (HPA) axis, which mediates the endocrine or hormonal response to certain stressors, interconnects with the adrenomedullary hormonal system and the sympathetic noradrenergic system (SNS). This does not mean, however, that specific stressors activate all three effector systems to the same extent. Thus, when researchers measure the outputs of these effector systems (i.e., ACTH and cortisol in the bloodstream of humans to monitor HPA axis reactivity versus heart rate and blood pressure which reflect SNS activity) in response to various stress paradigms they may not necessarily find unanimity of responses.

Scientists have conceptualized different categories of stressors to better capture this phenomenon. Thus, distinctions such as "psychogenic versus neurogenic," "processive versus systemic" (see the article by Herman, pp. 441–447), and "physical versus psychological versus pharmacologic" stress have been used to describe the various stress induction paradigms used in experimental animals and humans (for a partial list, see table 1). The stress-response patterns generated by these different types of stressors are not uniform, however, which is a point frequently lost among casual observers.

Other Stressor Characteristics

In addition to the types of stressors influencing stress reactivity, there are other features associated with the

stressful experience that affect an individual's responsiveness (see table 1). For example, the degree of controllability of the stressor influences response, with uncontrollable stress creating a greater level of response compared with events considered to be under an individual's control (Anisman and Matheson 2005). It is interesting to note that even this seemingly behavioral, subjective phenomenon seems to be governed by stressor-specific neural circuits. For instance, experiments in rodents have demonstrated that the brain's serotonin system seems to be of primary importance in modulating uncontrollable versus controllable stress (Hammack 2002). Whether a stressor is predictable or unpredictable influences the magnitude of the stress response, as does its duration (i.e., chronicity) (Anisman and Matheson 2005).

Table 1 Factors Influencing the Stress Response

Stressor type
Processive (neurogenic or psychogenic)
Systemic (immune insults)
Stressor characteristics
Controllability
Predictability
Ambiguity/uncertainty
Chronicity
Intermittence
Organismic variables
Genetics
Age
Sex
Experiential variables
Previous stressor experiences (sensitization)
Early life events (maternal factors, trauma)
Resource characteristics
Personal characteristics
Coping skills
Self-esteem
Self-efficacy
Personality (hardiness, optimism, neuroticism)
And others
Social characteristics
Social support (perceptions)
Attachment (bonding)

SOURCE: Adapted from Anisman and Matheson 2005.

Individual-Level Variables Affecting Stress Responsivity

Just as the type, predictability, and controllability of the stressor influence its response, an individual's characteristics also affect stress reactivity. Of particular relevance to human-stress researchers is the individual's gender, and a better understanding of this could help explain why women seem to develop AUDs following a stress-related condition, whereas the opposite temporal pattern applies for men (Kessler et al. 1997). Accumulating evidence indicates that women and men have evolved different stress-response activation patterns during the reproductive years (Kajantie and Phillips 2006) and that women respond more robustly to certain stressors than men and vice versa. For example, using one of the most popular psychological stress induction paradigms, the Trier Social Stress Test,[2] several investigators have found that men react more robustly to this type of stressor than do women (Uhart et al. 2006). Additional evidence for this gender X stressor subtype interaction effect was found by Stroud et al. (2002), who reported that women mounted a greater stress response to a social evaluative stressor task (e.g., the participant feeling shunned by two confederate research associates feigning a spontaneous social interaction) than did men. Similarly, research has found gender- and stressor-specific effects to various pharmacological stress tests; women react more robustly to agents directly stimulating the pituitary gland or artificially lowering morning cortisol levels than do men, whereas men exhibit comparatively blunted responses to these manipulations (Anthenelli et al. 2009). Therefore, gender is an important variable to consider when evaluating how individuals react to certain stressors.

As described in other articles in this edition, an individual's genetic makeup (see Schumann and colleagues, pp. 484–491), early-life experiences (see Brady and Back, pp. 408–413), environmental exposures to stress (see Keyes and colleagues, pp. 391–400), and predilection to anxiety and other psychiatric disorders (see Smith and Randall, pp. 414–431 and Schumm and Chard, pp. 401–407) can conspire to influence how adolescents and adults respond to stress and alcohol.

Heavy drinking and repeated withdrawal from alcohol may result in neuroendocrine changes that not only alter the body's ability to respond to stressful challenges but also may undermine efforts to stop or reduce harmful drinking behavior (see articles by Alim and colleagues, pp. 506–515 and Becker, pp. 448–458).

Moreover, environmental insults can affect a person's genetic architecture, and these epigenetic phenomena appear to influence the individual's response to stressful life experiences and alcohol intake (see the article by Pandey and Moonat, pp. 459–467). When one considers that other personal characteristics such as an individual's coping skills and social environment can modify how he or she reacts to stress, it should come as no surprise that laboratory paradigms in humans sometimes produce discrepant results (e.g., see Thomas and colleagues, pp. 459–467) in the literature.

Conclusions

This brief overview sets the stage for the articles and sidebars that follow. In this issue, an esteemed group of alcohol and stress researchers tackle compelling questions such as "How Does Stress Lead to Risk of Alcohol Relapse?" (see the article by Sinha, pp. 432–440). Although the answers to important questions such as this are not fully known, what should shine through is how far the field has come since *Alcohol Research & Health* last tackled this topic. Understanding the

[2] Using the Trier Social Stress Test, the subject is asked to give a speech and perform a simple math task in front of an audience. This test measures both social and cognitive stressors.

relationships among alcohol drinking, stress, and alcohol use disorders is a critical area for ongoing investigation. Discoveries emanating from this field not only add to the burgeoning literature on stress and disease risk but also hold the promise to provide answers on how to prevent and intervene in this disorder. Here we offer a foundation for the next decade of discovery! ■

Acknowledgements

Development of this manuscript was supported, in part, by National Institute on Alcohol Abuse and Alcoholism (NIAAA) grant no. AA–019720, VA Merit Review grant no. NEUA–003–08S, and by the Department of Veterans Affairs Research Service.

The author thanks Reene Cantwell and Marta La Belle for their technical support preparing this manuscript.

Financial Disclosure

The author provides consulting and/or advisory services to Pfizer. The Pacific Treatment and Research Center receives grant support from Pfizer.

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Effects of Stress on Alcohol Consumption

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This issue of *Alcohol Research: Current Reviews* focuses on the impact of stress on alcohol consumption. The significance of stress on alcohol abuse recently has been reemphasized by the alcohol use problems following post-traumatic stress disorder, such as those seen with some combat veterans. Behavior is described as an interaction between genetic constitution and environmental influences. Of the environmental factors affecting an individual, one of the most potent is external stress. Although it generally is held that stress increases drinking, the articles in this issue clearly demonstrate the complexities of this simple construct. It now is appreciated that the notion of stress itself is multidimensional. Early-life stressors such as child abuse can cause delayed and long-term consequences. The stress resulting from a traumatic event, either personal or public, such as an earthquake, can produce changes in drinking behavior. The effect of cumulative stressors throughout life can impact drinking as well. In addition to the dynamics of when stress is experienced, the type of stressor and the genetic constitution of the individual, as well as the stage of alcohol exposure can influence the response to stress. To a social drinker stress can have a different impact than stress for an abstinent alcoholic struggling with relapse. These factors now are better appreciated in the interaction between stress and alcohol use disorders and may help to decipher the often conflicting and contradicting observations found in the literature on this subject.

The connection between stress and alcohol consumption was made early on in alcohol research (Horton 1943). In the tension-reduction hypothesis, stress was seen to increase anxiety, and in response alcohol was consumed to reduce the anxiety. This connection between stress and alcohol was further linked by observations showing that in alcoholics the physiological responses to stress were perturbed. These stress actions involved the hypothalamic–pituitary–adrenal axis. Chronic alcohol consumption is associated with elevated basal glucocorticoid secretion, whereas the hormonal response to a stressor was blunted. In addition, a high dose of alcohol increases the adrenal hormone glucocorticoid. Following these observations, a body of evidence was generated in rodents to suggest that the increase in glucocorticoid would increase drinking. Subsequent findings have implicated other/additional circuits for connecting stress with alcohol use. Stress response also is mediated by the amygdala. Chronic alcohol exposure alters amygdala function, leading to increased corticotropin-releasing factor expression in the amygdala. This neuroadaptation is proposed to produce an altered affective state. Alcohol initially is able to ameliorate this effect and thereby provides a motivation for continued alcohol consumption. Furthermore, stress also affects the prefrontal cortex, reducing its capacity for executive function and resulting in augmented impulsivity.

At present epidemiological data support a link between stress and alcohol use disorders. However, the connection is not predictably causal. Stress under all circumstances does not necessarily lead to alcohol consumption. Genetic factors and past history of life experiences can influence this interaction. These complexities are abundantly exemplified in the experimental animal literature. Perhaps the greatest limitation in investigating the link between stress and alcohol use is the absence of a simple animal model in which a stressor results in a substantial increase in consumption over a sustained period of time. Of similar difficulty is establishing models of stress with full relevance to alcoholics. Financial issues, job loss, divorce, and other events are the day-to-day relevant stressors for human populations in developed countries. How these experiences are modeled in animal studies that are necessary for examining the neurobiological mechanisms involved currently is unresolved.

Future studies taking advantage of better genetic models, neuroimaging in human and animal studies, and findings on epigenetic modifications promise to clarify the linkage between stress and alcohol abuse disorders and help to show where and when stress will affect drinking behavior. Such information should provide targets for effective medication development.

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Circadian Genes, the Stress Axis, and Alcoholism

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The body's internal system to control the daily rhythm of the body's functions (i.e., the circadian system), the body's stress response, and the body's neurobiology are highly interconnected. Thus, the rhythm of the circadian system impacts alcohol use patterns; at the same time, alcohol drinking also can alter circadian functions. The sensitivity of the circadian system to alcohol may result from alcohol's effects on the expression of several of the clock genes that regulate circadian function. The stress response system involves the hypothalamus and pituitary gland in the brain and the adrenal glands, as well as the hormones they secrete, including corticotrophin-releasing hormone, adrenocorticotrophic hormone, and glucocorticoids. It is controlled by brain-signaling molecules, including endogenous opioids such as β-endorphin. Alcohol consumption influences the activity of this system and vice versa. Finally, interactions exist between the circadian system, the hypothalamic–pituitary–adrenal axis, and alcohol consumption. Thus, it seems that certain clock genes may control functions of the stress response system and that these interactions are affected by alcohol. **KEY WORDS: Alcohol consumption; alcohol use, abuse and dependence; alcohol and other drug use pattern; genetics; genetic factors; circadian system; clock genes; stress; stress response; biological adaptation to stress; neurobiology; hypothalamic– pituitary–adrenal axis**

Alcohol abuse and dependence are estimated to affect 1 in 8 adults in the United States and several hundred million people worldwide (Grant et al. 2004). To define at-risk populations and develop better treatments, it is important to further identify the genetic and environmental factors that contribute to alcohol addiction. Recent evidence suggests that the body's internal system that helps control the daily rhythm of the body's activities (i.e., the circadian system), the body's stress response system, and the body's neurobiology of alcohol are extensively intertwined. This article explores some of these interactions.

The Circadian System and Alcohol's Effects on It

The circadian system—or the body's internal clock—is a naturally present regulatory system that helps the body maintain an approximately 24-hour cycle in biochemical, physiological, or behavioral processes, thereby allowing the organism to anticipate and prepare for regular environmental changes (i.e., the day–night cycle). For example, circadian rhythms maintain not only sleeping and feeding patterns but also physiological processes such as body temperature, brainwave activity, hormone production, and cell regeneration. The circadian clockwork results from the interaction of specific clock genes, including genes known as *Period* (*Per1, Per2,* and *Per3*), *Clock*, *Bmal1*, and *Cryptochrome* (*Cry1* and *Cry2*), and others.[1] The activity of these genes is controlled by two tightly coupled transcriptional and translational feedback loops that sustain a near 24-hour periodicity of cellular activity. Expression of these clock genes, in turn, regulates the expression of other clock-controlled genes (Ko and Takahashi 2006).

In both humans and animal models, complex bidirectional relationships seem to exist between alcohol intake or exposure and circadian clock systems. The impact of the circadian system on alcohol use is shown by the fact that both preference for and consumption of alcohol are modulated by time of day, and studies found that genetic interactions link core circadian clock genes with alcohol drinking (Spanagel et al. 2005*a, b*). In addition, disruption of the normal circadian rhythm (i.e., circadian desynchronization) seems to increase the use of alcohol, as seen in frequent travelers and rotating-shift workers, possibly because it frequently activates the body's stress response (i.e., increases the allostatic load[2]) (Rosenwasser et al. 2010; Trinkoff and Storr 1998). At the same time, a strong relationship seems to exist between alcohol drinking and altered circadian functions. For example, alcohol intake can alter the following circadian responses:

- Circadian rhythms in blood pressure, core body temperature, and hormone release in humans (Danel et al. 2009; Devaney et al. 2003; Nakashita et al. 2009);
- Shifts in the normal circadian rhythm (i.e., circadian phase shifting) and in the free-running period[3] in mice (Prosser et al. 2008; Seggio et al. 2009);
- Return to a normal circadian rhythm after a disruption (i.e., circadian phase resetting) and nocturnal activity patterns in hamsters (Ruby et al. 2009; Seggio et al. 2007); and

[1] By convention, gene names in animals are written in uppercase and lowercase and italicized. Gene names in humans are written in all caps and are italicized, whereas the acronyms for the encoded proteins are all caps but not italicized.

[2] The term allostatic load refers to the physiological consequences of chronic exposure to fluctuating or heightened hormonal responses resulting from repeated or chronic stress.

[3] Free-running period is a period that is not adjusted or entrained to the 24-hour cycle in nature or to any artificial cycle.

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- Rhythmicity in the activity of certain brain cells (i.e., proopiomelanocortin [POMC][4]-producing neurons) in a brain region called the hypothalamus (which is involved in the body's stress system) in rats (Chen et al. 2004).

Even alcohol exposure before birth can interfere with circadian systems. Thus, prenatal ethanol exposure in rats can alter core body temperature and phase-shifting ability (Sakata-Haga et al. 2006); rhythmic activity of the pituitary gland and the adrenal gland, both of which are part of the body's stress response system (Taylor et al. 1982); the rhythmic release of the main stress hormone (i.e., corticosterone) (Handa et al. 2006); immune cell rhythms (Arjona et al. 2006); and circadian expression of POMC in the hypothalamus (Chen et al. 2006).

Why Is the Body's Circadian System So Vulnerable to Alcohol Toxicity?

One logical explanation for the sensitivity of the circadian system to alcohol suggests that alcohol specifically targets one or more of the genes that regulate circadian functions. Using different experimental designs, researchers have demonstrated that alcohol exposure significantly alters the expression of several core clock genes. For example, in chronic alcohol-drinking rats, circadian expression of *Per1* and *Per2* is significantly disrupted in the hypothalamus (Chen et al. 2006). Likewise, prenatal alcohol exposure alters circadian expression of *Per1* and *Per2* genes in the hypothalamus and in tissues in other parts of the body in rats and mice (Arjona et al. 2006; Chen et al. 2004; Ko and Takahashi 2006). In addition, neonatal alcohol exposure reduces *Cry1* expression in a brain region called the suprachiasmatic nucleus and advances the phase of the *Per2* rhythm in the cerebellum and liver (Farnell et al. 2008). In human studies, the expression of clock genes (*PER*, *CRY,* and *BMAL1*) is reduced in white blood cells of male alcoholic patients (i.e., after chronic alcohol exposure) (Huang et al. 2010), whereas alcohol drinking in healthy males (i.e., acute exposure) increases *BMAL1* expression in these cells (Ando et al. 2010). Finally, variations of the *PER2* gene in which individual DNA building blocks are altered (i.e., single nucleotide polymorphisms [SNPs]) are associated with increased alcohol consumptions in male patients (Spanagel 2005*a*) and adolescent boys (Comasco et al. 2010). These observations suggest that clock genes are targets through which alcohol may alter circadian functions. However, in-depth molecular studies are necessary to elucidate the potential mechanisms by which alcohol directly or indirectly affects clock gene expression and cellular functions.

[4] POMC is a precursor molecule primarily produced in and secreted by the pituitary gland but also in the hypothalamus. POMC subsequently can be processed in other tissues into numerous different products, which in turn exert specific effects on the organism and play a role in a wide range of physiological processes. One of these products is adrenocorticotropic hormone (ACTH), which is produced in the pituitary gland and is part of the body's stress response system, the hypothalamic–pituitary–adrenal (HPA) axis.

Circadian Systems, the Stress Response, and Alcohol Consumption

The Stress Response System

The circadian system also may be involved in regulating alcohol-drinking behavior by interacting with a hormone system called the hypothalamic–pituitary–adrenal (HPA) axis, which plays a central role in the body's stress response as well as in reward mechanisms. Stress increases the production of a hormone called corticotrophin-releasing hormone (CRH) in certain cells in a region known as the paraventricular nucleus (PVN) in the hypothalamus. The CRH then is secreted into the blood vessels leading to the pituitary gland, where it interacts with a specific molecule, the CRH receptor1 (CRHR1), on specific cells in the anterior pituitary. In response, these cells begin the synthesis and release of adrenocorticotropic hormone (ACTH) into the circulation. ACTH, in turn, stimulates the release of glucocorticoids (i.e., corticosterone in rats and cortisol in humans) from the outer layer (i.e., cortex) of the adrenal glands that are located on top of the kidneys. The glucocorticoids then act on numerous tissues throughout the organism to coordinate the body's stress response. However, the CRH/CRHR1 system is found not only in the hypothalamus but also in other areas of the brain and helps mediate the actions of the brain's central stress response systems.

The CRH–HPA system is controlled by many brain-signaling molecules (i.e., neurotransmitters) and their receptors, including opioid peptides[5] (e.g., β-endorphin [β-EP]) and their receptors. For example, in rats, the bodies of CRF-producing cells are found in the same locations of the PNV as the fibers of β-EP–releasing cells. In another area of the hypothalamus called the median eminence, a certain type of opioid receptors (i.e., μ-opioid receptors [MOP-r]) is located on the ends of CRH-releasing cells. Agents that stimulate the activity of this receptor (i.e., MOP-r agonists) can inhibit neurotransmitter-stimulated CRF release from the hypothalamus in vitro. Likewise, studies in living organisms found that β-EP infusion decreased CRH release in the blood vessels linking the hypothalamus and the pituitary (Plotsky 1991), and morphine pretreatment prevented stress-induced HPA activation (Zhou et al. 1999). Finally, transplantation of β-EP–producing cells into the PVN suppressed HPA activation under different conditions and normalized stress hyperresponse in fetal alcohol-exposed rats (Boyadjieva et al. 2009). All of these data suggest that endogenous opioids (and, by extension, opiate drugs) have a counterregulatory effect on the stress response.

Alcohol and the Stress Response

In the central nervous system, β-EP long has been suspected of contributing to the positive reinforcement and motivational

[5] Opioid peptides are short sequences of amino acids (i.e., peptides) that are naturally produced by the body and have effects resembling those of opiate drugs. The three main classes of endogenous opioids are endorphins, enkephalins, and dynorphins. Endorphins also are derived from POMC, which also is the precursor for ACTH.

properties of several addictive substances. For example, microinjection of this peptide to several regions of the brain's reward system that involves the neurotransmitter dopamine (i.e., the mesolimbic dopamine system), such as the nucleus accumbens, produced place preference (Bals-Kubik et al. 1993). In addition, several studies have demonstrated that repeated administration of alcohol, cocaine, or heroin significantly attenuated β-EP expression in various limbic areas (Jarjour et al. 2009; Rasmussen et al. 2002; Sweep et al. 1988), supporting the notion that β-EP may contribute significantly in the development of alcohol abuse and dependence.

The stress response system also interacts with these reward pathways. For example, the CRH/CRHR1 system can activate mesolimbic dopaminergic pathways and increase dopamine-mediated signal transmission in various parts of the mesolimbic system, including the nucleus accumbens, amygdala, and medial prefrontal cortex. Furthermore, elevation of plasma corticosterone has been associated with increases in alcohol self-administration (Fahlke et al. 1995). Finally, evidence indicates that corticosterone directly stimulates activity of the mesolimbic dopamine system, subsequently increasing drug-seeking behavior (Piazza et al. 1996). Thus, stress, via activation of the CRH–HPA circuits and/or extrahypothalamic CRH circuits, increases mesolimbic dopamine that, in turn, increases drug seeking in drug-treated animals. The relationship between the stress response and the mesolimbic dopamine system is further supported by findings that an abnormality in POMC-mediated regulation of the HPA axis may lead to excess alcohol drinking under stressful conditions. Finally, consistent with animal studies demonstrating acute and chronic effects of alcohol on the HPA axis (Koob and Bloos 1998), studies in humans have documented HPA axis alterations in both actively drinking and recently abstinent alcoholics (Sinha 2007; Uhart and Wand 2009).

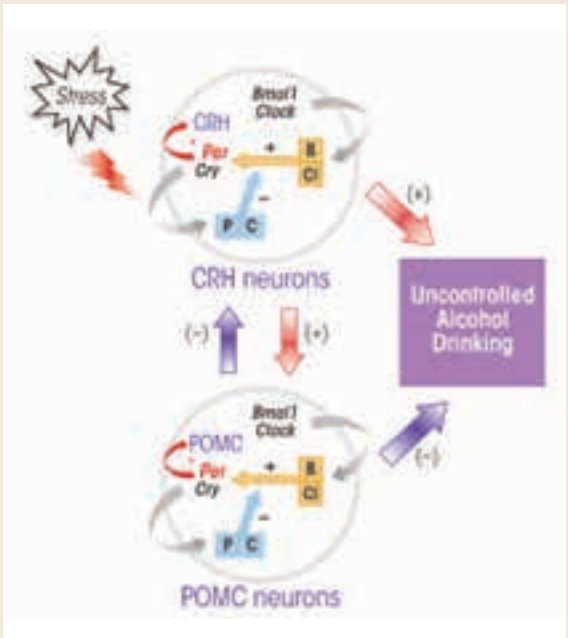

Figure Conceptual framework of how the circadian genes regulating stress-induced excess alcohol drinking. Clock genes (*Per* = P, *Cry* = C, *Bmal1* = B, and *Clock* = Cl) are key components of the circadian mechanism controlling the functions of nerve cells in the hypothalamus and pituitary that produce two molecules important in the body's stress response—corticotrophin-releasing hormone (CRH) and proopiomelanocortin (POMC). Of these clock genes, *Per* might be a potential target of alcohol (indicated by a * symbol) in CRH and POMC neurons and may control the stress-induced propensity to consume alcohol.

NOTE: (+) = stimulatory effect; (–) = inhibitory effect.

Circadian Genes, the Stress Response, and Alcohol

Several findings have suggested that interactions exist between the circadian system, the HPA axis, and alcohol-drinking behavior (see the figure). For example, in animal studies, forced-swimming and immobilization stress elevated expression of the murine *Per1* gene in CRH-positive cells of the PVN (Takahashi et al. 2001). On the other hand, stress-related (i.e., cortisol-induced) transcriptional activation of human *PER1* was reduced in a type of human blood cells (i.e., B-lymphoblastoid cells) that carried an altered form of the *PER1* gene (i.e., the rs3027172 genotype), which has been associated with an increased risk of alcoholism (Dong et al. 2011). Moreover, alcohol consumption can decrease *Per2* expression in POMC-producing neurons in the hypothalamus (Chen et al. 2004), and certain mutations in the murine *Per2* gene interfere with alcohol's stimulatory effect on POMC neurons (Agapito et al. 2010) and alter the rhythmic changes in corticosterone levels in the blood (Yang et al. 2009). Thus, it seems that the *Per1* and *Per2* genes may control functions of CRH- and POMC-producing neurons and that these interactions are affected by alcohol.

It is possible that alcohol-mediated modulation of *Per* genes may play a significant role in modulating HPA axis function, which in turn may lead to an increased propensity to drink alcohol following a stressful event. This view is supported by the recent findings by Dong and colleagues (2011) that the presence of certain *Per1* mutations increased psychosocial stress-induced alcohol drinking in mice, increased alcohol-drinking behavior in human adolescents following psychosocial adversity, and reduced cortisol-induced transcriptional activation of *Per1* in human B-lymphoblastoid cells. Other recent findings, although preliminary, showed that a certain *Per2* mutation increased basal levels of plasma corticosterone and alcohol drinking while preventing stress-induced increases in corticosterone levels and alcohol drinking in mice (Logan et al. 2011). In this context, it is interesting to note that mice carrying mutations in *Per2*, but not *Per1*, display ethanol reinforcement and alcohol-seeking behavior (Spanagel et al. 2005*a*; Zghoul et al. 2007).

Conclusions

The studies reviewed here suggest an intricate interaction between circadian genes, the body's stress response, and alcohol consumption. Thus, it seems that particularly the *Per1* and *Per2* genes, which have a distinct influence on the HPA axis, may control stress-induced propensity to alcohol drinking behavior. However, additional research is needed to address this novel concept involving clock genes, stress, and alcohol drinking. ■

Financial Disclosure

The author declares that he has no competing financial interests.

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