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

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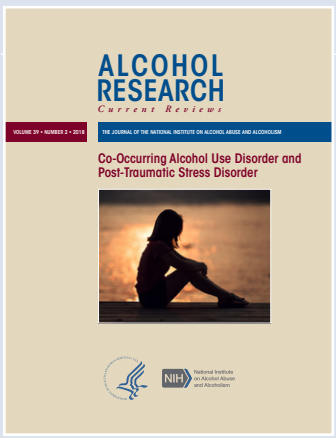

About This Issue

Alcohol use disorder (AUD) and post-traumatic stress disorder (PTSD) commonly co-occur in active military service members, veterans, and victims of violence and sexual assault. The co-occurrence of these conditions is a public health concern because it worsens adverse health outcomes and complicates treatment for both. This issue of *Alcohol Research: Current Reviews* examines the current literature on the prevalence, diagnosis, causes, risk factors, and treatment for co-occurring AUD and PTSD.

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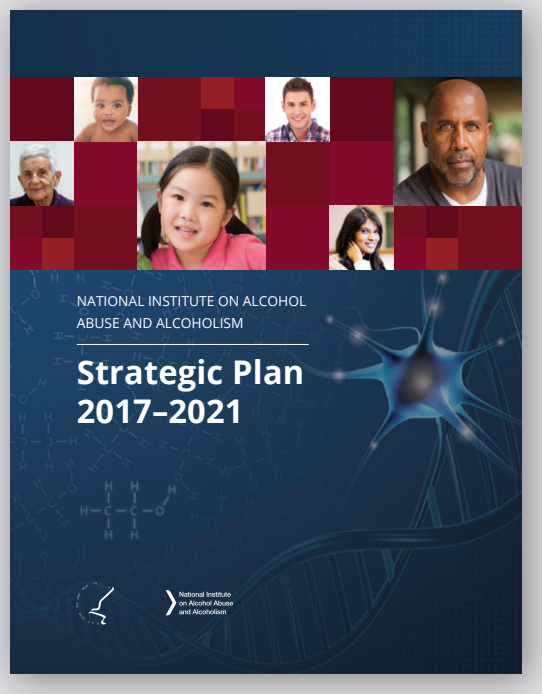

As scientific advances continue to expand our understanding of how alcohol affects human health and point to ways to address alcohol-related harm, NIAAA has released its 2017–2021 strategic plan for research. The new plan serves as a road map for optimizing the allocation of NIAAA's resources to areas of alcohol research most likely to benefit from additional support, translating scientific discoveries for the benefit of the public, and continuing to build on NIAAA's position as the nation's key source of evidence-based information on alcohol and health.

Download your free copy today at https://www.niaaa.nih.gov/strategic-plan.


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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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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.

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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.

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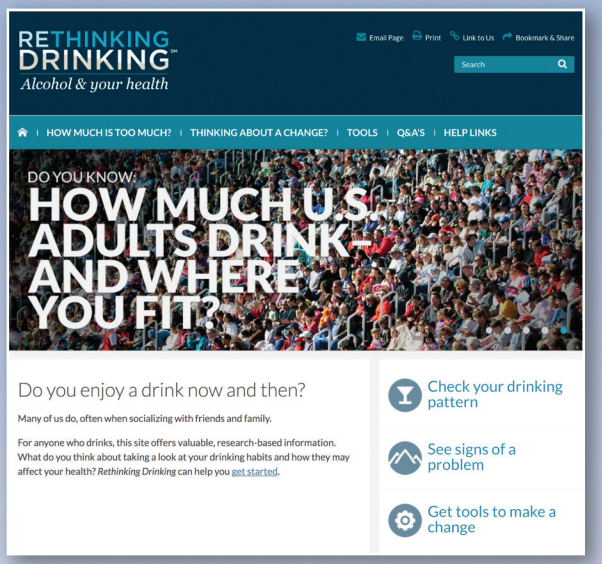

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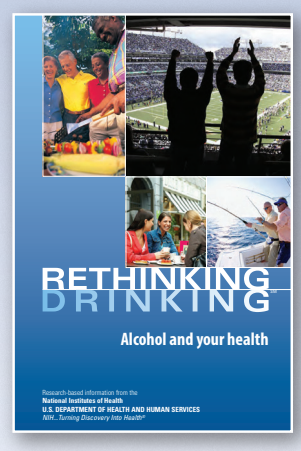

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Common Biological Mechanisms of Alcohol Use Disorder and Post-Traumatic Stress Disorder

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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).

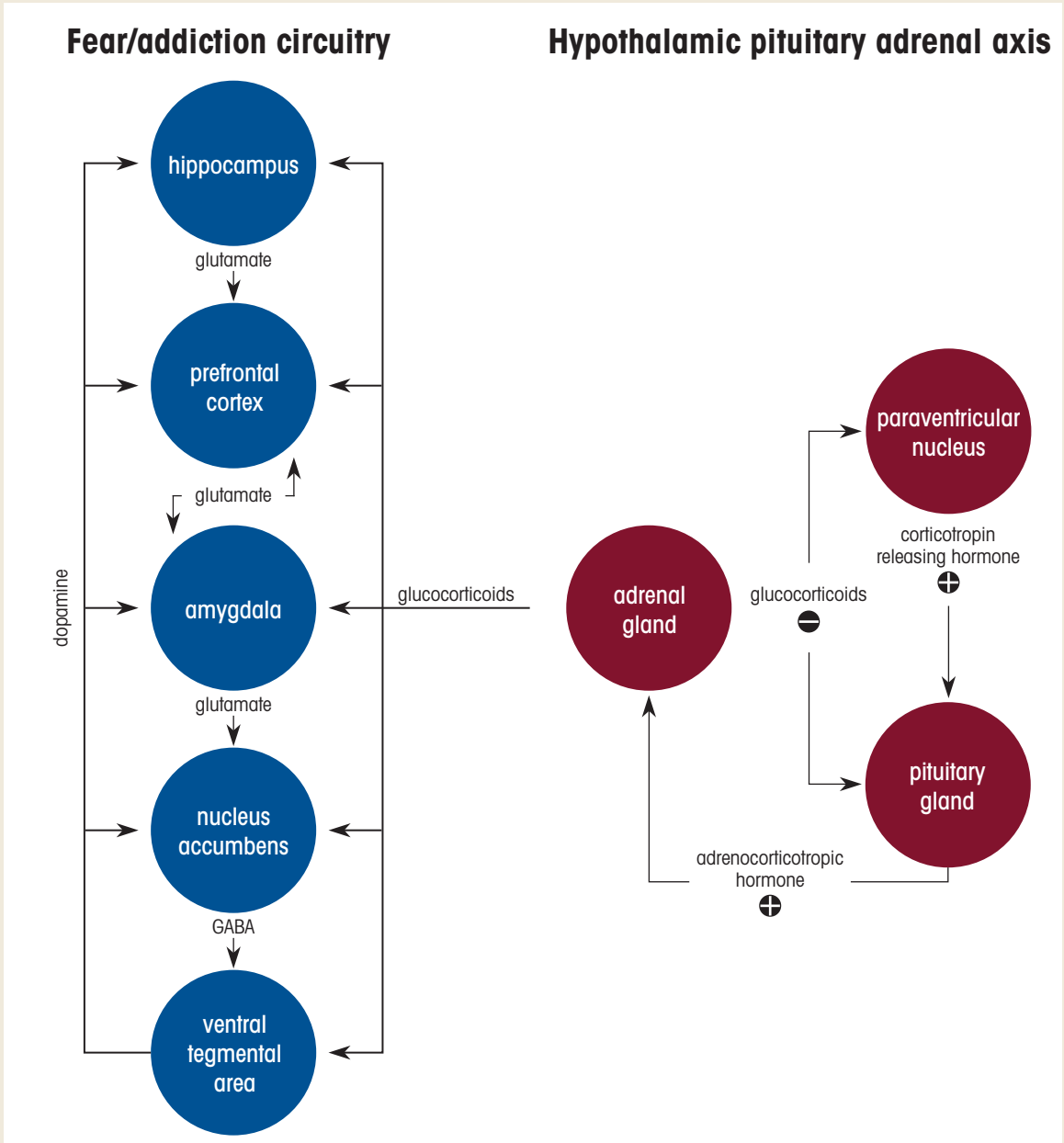

Figure 1 Interactions between the fear/addiction neural circuitry and the hypothalamic pituitary adrenal (HPA) axis. The fear/addiction circuitry includes the hippocampus, prefrontal cortex, amygdala, nucleus accumbens, and ventral tegmental area. The prefrontal cortex mutually connects with the amygdala, 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.

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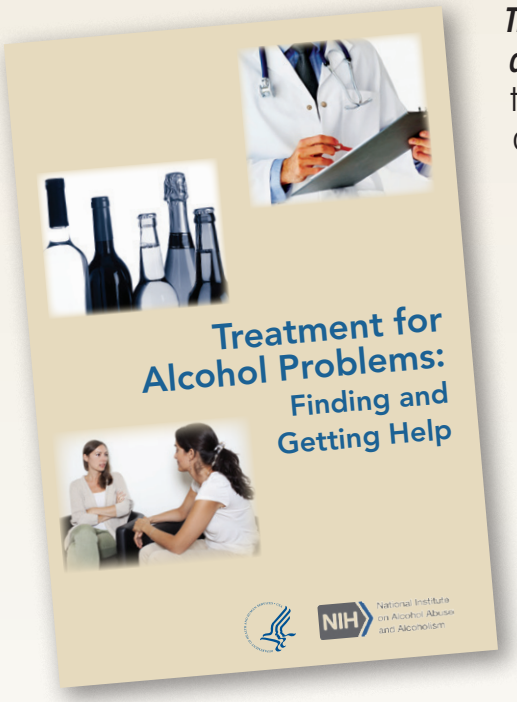
Treatment for Alcohol Problems: Finding and Getting Help



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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.

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

Emily R. Dworkin, Hannah E. Bergman, Thomas O. Walton, Denise D. Walker, and Debra L. Kaysen

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.

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Alcohol Use Disorder and Traumatic Brain Injury

Zachary M. Weil, John D. Corrigan, and Kate Karelina

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

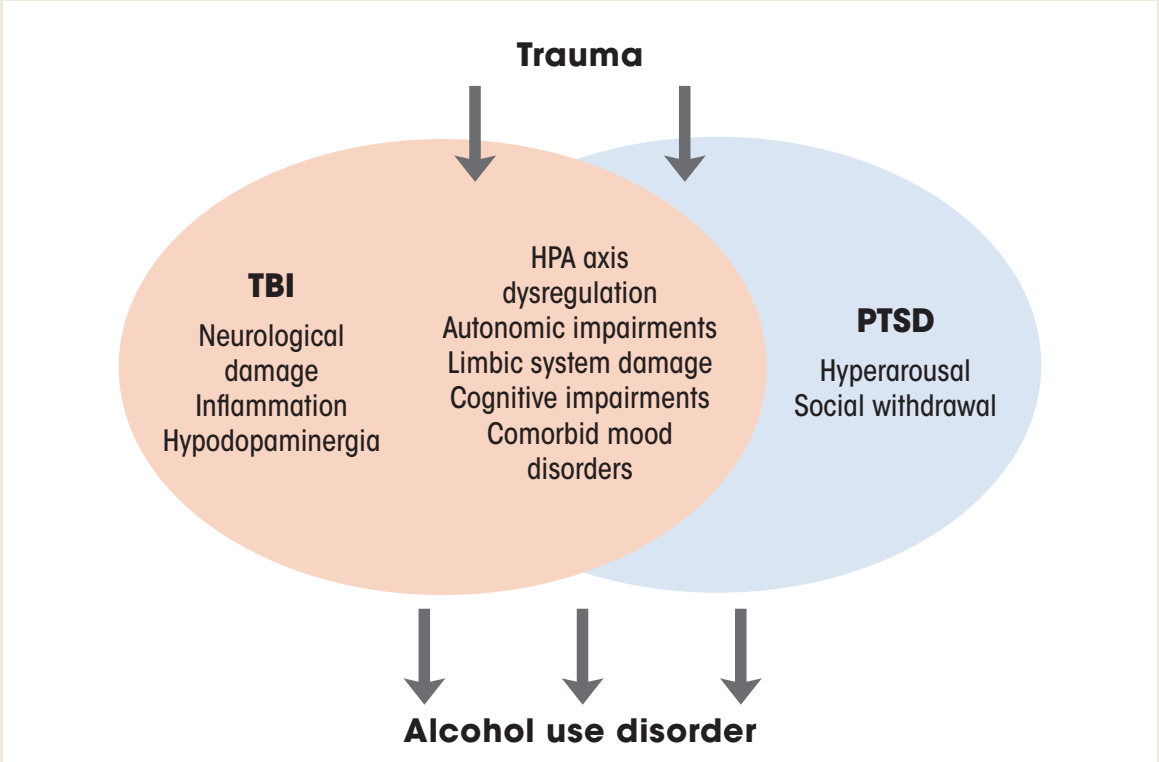

Figure 1 Overlapping neurobehavioral links among TBI, PTSD, and alcohol use disorder. TBI and PTSD share trauma as a precipitating event. They are also linked by dysregulation of stress response systems, cognitive impairments, and affective symptoms, which, together, can increase the likelihood of alcohol 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.

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

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

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

Overview

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

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

Behavioral Treatments for AUD

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

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

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

Relapse prevention

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

Contingency management

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

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

Motivational enhancement

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

Couples therapy

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

Twelve-step facilitation

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

Community reinforcement

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

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

Mindfulness

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

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

Behavioral Treatments for PTSD

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

Prolonged exposure

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

Cognitive processing

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

Eye movement desensitization and reprocessing

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

Narrative exposure

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

Present-centered therapy

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

Cognitive behavioral conjoint therapy

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

Other interventions

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

Behavioral Treatments for Comorbid AUD and PTSD

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

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

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

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

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

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

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

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

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

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

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

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

Integrated Behavioral Treatments

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

Seeking safety

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

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

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

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

Other treatments

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

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

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

Future Research

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

Table 1 Empirically Supported Integrated Treatments for AUD and PTSD

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

care providers, have additional treatment options available.

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

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

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

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

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

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

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

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

Introduction

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

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

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

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

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

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

Agents Acting on the Opioidergic System

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

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

Other Opioidergic Medications

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

have examined nalmefene for comorbid AUD and PTSD.

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

Agents Acting on the Noradrenergic System

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

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

Other Noradrenergic Medications

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

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

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

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

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

Agents Acting on the Serotonergic System

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

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

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

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

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

Other Serotonergic Medications

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

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

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

Agents Acting on the GABAergic and Glutamatergic Systems

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

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

Other GABAergic and Glutamatergic Medications

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

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

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

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

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

Other Targets

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

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

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

Combination Pharmacotherapies

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

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

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

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

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

Clinical and Research Implications

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

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

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

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

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

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

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

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

Conclusion

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

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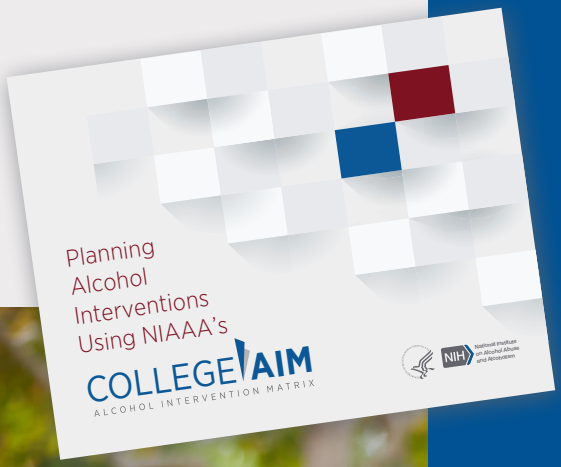

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