ALCOHOL RESEARCH
Current Reviews

Alcohol Use Disorder and Co-Occurring Mental Health Conditions

THE JOURNAL OF THE NATIONAL INSTITUTE ON ALCOHOL ABUSE AND ALCOHOLISM

VOLUME 40 • NUMBER 1 • 2019

National Institute on Alcohol Abuse and Alcoholism

Alcohol Research: Current Reviews is committed to publishing only the most informative, accurate, and impartial information possible from the field of alcohol research. We hold authors accountable for the articles submitted to the journal and require authors to declare any potentially competing financial interests that might be construed as influencing the results or interpretations of a reported study.

Readers should note that disclosure of a competing financial interest does not imply that the information in the article is questionable or that conclusions are biased. Note, too, that *Alcohol Research: Current Reviews* is not in the position to verify the accuracy of disclosure statements made by authors. We rely instead on authors to provide complete and accurate information. This information is provided at the end of each article.

Alcohol Research: Current Reviews (ISSN: 2168-3492) is a peer-reviewed journal produced twice per year under contract to ICF by the National Institute on Alcohol Abuse and Alcoholism (NIAAA). Cara Anjos Breeden, M.L.S., is the project officer. Opinions expressed in contributed articles do not necessarily reflect the views of NIAAA. The U.S. government does not endorse or favor any specific commercial product or commodity. Trade or proprietary names appearing in this publication are used only because they are considered essential in the context of the studies reported herein. Unless otherwise noted in the text, all material appearing in this journal is in the public domain and may be reproduced without permission. Citation of the source is appreciated.

Recent issues of *Alcohol Research: Current Reviews* are available online at https://www.arcr.niaaa.nih.gov. Back issues are archived at https://www.arcr.niaaa.nih.gov/archives.htm.

Issues of *Alcohol Research: Current Reviews* are indexed in PubMed at https://www.ncbi.nlm.nih.gov/pubmed.

About This Issue

Co-occurring alcohol use disorder (AUD) and other mental health conditions present unique challenges for both substance use and mental health professionals. The extent of AUD and type of co-occurring mental health condition can make it difficult for clinicians to distinguish each condition and identify potential treatment strategies. This issue examines the current literature on the etiology, prevalence, diagnosis, and treatment of co-occurring AUD and mental health conditions.

CONTENTS • Volume 40, Number 1 • 2019

Alcohol Use Disorder and Co-Occurring Mental Health Conditions

1 **From the Editors**
Laura E. Kwako, Jenica Patterson, Ihsan M. Salloum, and Ryan S. Trim

3 **Alcohol Use Disorder and Depressive Disorders**
R. Kathryn McHugh and Roger D. Weiss

FOCUS ON 11 **Suicidal Behavior: Links Between Alcohol Use Disorder and Acute Use of Alcohol**
Kenneth R. Conner and Courtney L. Bagge

15 **Co-Occurring Alcohol Use Disorder and Anxiety: Bridging Psychiatric, Psychological, and Neurobiological Perspectives**
Justin J. Anker and Matt G. Kushner

FOCUS ON 27 **Biobehavioral Interactions Between Stress and Alcohol**
Marcus M. Weera and Nicholas W. Gilpin

35 **Alcohol Use Disorder and Antisocial and Borderline Personality Disorders**
Ashley C. Helle, Ashley L. Watts, Timothy J. Trull, and Kenneth J. Sher

51 **Alcohol Use Disorder and Schizophrenia or Schizoaffective Disorder**
Luke Archibald, Mary F. Brunette, Diana J. Wallin, and Alan I. Green

61 **Integrating Treatment for Co-Occurring Mental Health Conditions**
Amy M. Yule and John F. Kelly


Laura E. Kwako


Jenica Patterson


Ihsan M. Salloum


Ryan S. Trim

Alcohol Use Disorder and Co-Occurring Mental Health Conditions

Laura E. Kwako, Jenica Patterson, Ihsan M. Salloum, and Ryan S. Trim

Laura E. Kwako, Ph.D., is a program director in the Division of Treatment and Recovery Research, National Institute on Alcohol Abuse and Alcoholism, Rockville, Maryland.

Jenica Patterson, Ph.D., is a program officer in the Division of Neuroscience and Behavior, National Institute on Alcohol Abuse and Alcoholism, Rockville, Maryland.

Ihsan M. Salloum, M.D., is a professor in the Department of Psychiatry and Behavioral Sciences, chief of the Division of Substance and Alcohol Abuse, and director of the Addiction Psychiatry Fellowship Program, University of Miami Miller School of Medicine, Miami, Florida.

Ryan S. Trim, Ph.D., is an associate professor in the Department of Psychiatry, University of California San Diego School of Medicine, La Jolla, California.

This issue of *Alcohol Research: Current Reviews* (ARCR) delves into studies on co-occurring alcohol use disorder (AUD) and mental health conditions, exploring how this co-occurrence affects symptom severity, prognosis, and outcomes. Increased risk because of co-occurrence, challenges because of disorder heterogeneity, and efficacy of treatment interventions are reviewed.

Among people with AUD, depressive disorders are one of the most common co-occurring psychiatric conditions. In **Alcohol Use Disorder and Depressive Disorders,** McHugh and Weiss discuss the prevalence, course, and treatment of co-occurring AUD and depressive disorders. They also examine disproportionately affected populations, developmental pathways to co-occurrence, and the challenges of diagnosis because of overlapping symptoms.

In the "Focus On" review **Suicidal Behavior: Links Between Alcohol Use Disorder and Acute Use of Alcohol,** Conner and Bagge explore the connection between alcohol use and suicidal behavior. Postmortem investigations on individuals who have died by suicide have found that AUD is prevalent among this group and that acute use of alcohol was often present. In their review, Conner and Bagge discuss the role alcohol plays in increasing risk for suicidal behavior and consider the efficacy of various interventions.

Anker and Kushner consider the association between AUD and anxiety in **Co-Occurring Alcohol Use Disorder and Anxiety: Bridging Psychiatric, Psychological, and Neurobiological Perspectives.** They review the research on the psychiatric classifications of alcohol misuse and negative affect and examine the relationship between negative affect and alcohol use from a neurobiological standpoint.

Weera and Gilpin, in the "Focus On" review **Biobehavioral Interactions Between Stress and Alcohol,** examine how brain stress systems mediate the effects of stress on alcohol drinking. They summarize key findings from animal models and suggest that brain stress systems may be useful targets for medications development.

In **Alcohol Use Disorder and Antisocial and Borderline Personality Disorders,** Helle and colleagues focus on co-occurring AUD and personality disorders. They discuss prevalence rates, potential explanations and causal models of comorbidity, and the status of treatment research. Helle and colleagues also discuss how personality traits, symptoms, and etiology can affect diagnosis and treatment.

In **Alcohol Use Disorder and Schizophrenia or Schizoaffective Disorder,** Archibald and colleagues explore schizophrenia spectrum disorders and their high co-occurrence with AUD. They describe how shared neurobiological mechanisms may explain the co-occurrence of these disorders. These authors suggest that combining pharmacologic interventions with other therapeutic modalities may address both issues more effectively.

Yule and Kelly, in **Integrating Treatment for Co-Occurring Mental Health Conditions,** consider the prevalence and treatment of co-occurring AUD and mental health conditions. They discuss screening tools, assessment, and the development of different treatment approaches. They also review the challenges to effective treatment and emphasize the importance of treating of both conditions.

From the Editor in Chief

After much consideration, NIAAA leadership and journal staff have made the decision that ARCR will transition to an online-only publication format in 2020. An analysis of the readership found that although print subscriptions have declined in recent years, readers regularly access ARCR content online through PubMed, PubMed Central, and the ARCR website. The online-only format will allow for more frequent and timely publications, permit reviews of emerging areas of alcohol research, and reduce ARCR's carbon footprint. As an open-access journal, ARCR will continue to be freely available to the public and the alcohol research community.

—Troy J. Zarcone, Ph.D.

Alcohol Use Disorder and Depressive Disorders

R. Kathryn McHugh and Roger D. Weiss

R. Kathryn McHugh, Ph.D., is an assistant professor in the Department of Psychiatry, Harvard Medical School, Boston, Massachusetts, and an associate psychologist in the Division of Alcohol and Drug Abuse, McLean Hospital, Belmont, Massachusetts.

Roger D. Weiss, M.D., is a professor in the Department of Psychiatry, Harvard Medical School, Boston, Massachusetts, and the chief of the Division of Alcohol and Drug Abuse, McLean Hospital, Belmont, Massachusetts.

Alcohol use disorder (AUD) and depressive disorders are among the most prevalent psychiatric disorders and co-occur more often than expected by chance. The aim of this review is to characterize the prevalence, course, and treatment of co-occurring AUD and depressive disorders. Studies have indicated that the co-occurrence of AUD and depressive disorders is associated with greater severity and worse prognosis for both disorders. Both pharmacologic and behavioral treatments have demonstrated efficacy for this population. However, treatment response is somewhat modest, particularly for drinking outcomes, highlighting the importance of further research on the etiology and treatment of co-occurring AUD and depressive disorders. Key future directions include studies to understand the heterogeneity of both AUD and depressive disorders, research on novel treatment approaches to enhance outcomes, and better understanding of sex and gender differences.

KEY WORDS: alcohol use disorder; co-occurring disorders; depression; dysthymia; sex differences

Introduction

Psychiatric disorders, such as anxiety and mood disorders, commonly co-occur with alcohol use disorder (AUD). Depressive disorders are the most common psychiatric disorders among people with AUD.[1] The co-occurrence of these disorders is associated with greater severity and worse prognosis than either disorder alone,[2,3] including a heightened risk for suicidal behavior.[4] This review provides an overview of the literature on the co-occurrence of AUD and depressive disorders and includes data on prevalence, course, and treatment outcomes. High-priority future research directions are suggested to better understand the co-occurrence of these conditions and to improve treatments.

Much of the published literature on the co-occurrence of AUD and depressive disorders uses the classifications from the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV).[5] Where possible, this review specifies if the cited literature used the DSM-IV classifications for diagnosis (alcohol abuse or alcohol dependence) or the fifth edition (DSM-5) classification for diagnosis (AUD).[6] If a study reported results based on the combined DSM-IV diagnoses

(i.e., included participants with alcohol abuse and participants with alcohol dependence), this review refers to the diagnosis as "DSM-IV AUD." Although DSM-IV and DSM-5 AUD share many symptoms, the diagnoses are defined differently. In the DSM-5, AUD requires at least two symptoms, whereas DSM-IV alcohol abuse required only one symptom. Also, from DSM-IV to DSM-5, modifications were made to the symptoms that were included as diagnostic criteria. For example, the criterion of legal problems related to alcohol was removed, and the criterion of alcohol craving was added. Thus, where possible, this review identifies which version of the DSM was used in a study.

Overview of Depressive Disorders

Depressive disorders are complex and heterogeneous syndromes. These disorders are characterized by disrupted mood (e.g., low, numb, or irritable), along with an array of cognitive (e.g., feelings of worthlessness and difficulty concentrating) and physical (e.g., fatigue and lack of energy) symptoms. The DSM-5 includes seven distinct disorders under the category of depressive disorders, including major depressive disorder, persistent depressive disorder (dysthymia), premenstrual dysphoric disorder, substance/medication-induced depressive disorder, disruptive mood dysregulation disorder, other specified depressive disorder, and unspecified depressive disorder.[6] This review focuses on major depressive disorder, dysthymia, and substance-induced depressive disorder, which are the depressive disorders that have been studied most often in both the general population and among people with AUD.

Major depressive disorder is characterized by the presence of five or more symptoms that are present for at least 2 weeks. One of these symptoms must include depressed mood or anhedonia (significant loss of interest or pleasure in activities). Other symptoms are disturbances in appetite, sleep, psychomotor behaviors, energy, concentration, and decision-making; beliefs about worthlessness or guilt; and thoughts of suicide or suicide attempt. Dysthymia is more chronic than major depressive disorder, yet it is typically a milder disorder, characterized by at least 2 years of depressed mood and at least two additional symptoms, including dysfunction in appetite, sleep, energy, self-esteem, concentration, or decision-making, and feelings of hopelessness. Alcohol-induced depressive disorder refers to a depressive-like syndrome (characterized by depressed mood or anhedonia) that occurs only during and shortly after alcohol intoxication or withdrawal, remits after 3 to 4 weeks of alcohol abstinence, and is associated with significant distress and impairment.

Prevalence of depressive disorders and AUD

Major depressive disorder is the most common psychiatric disorder, affecting an estimated 10% to 15% of people in their lifetime, according to U.S. and international population-based surveys.[7,8] Dysthymia is less common than major depressive disorder, affecting less than 2% of people in their lifetime.[9]

Likewise, major depressive disorder is the most common co-occurring psychiatric disorder among people with DSM-IV AUD.[1] Considering the prevalence of major depressive disorder and AUD in the general population, co-occurrence of these disorders is more frequent than can be expected based on chance, with odds ratios indicating a small effect size. Specifically, people with DSM-IV AUD, relative to those with no AUD, are 2.3 times more likely to also have major depressive disorder in the previous year, and they are 1.7 times more likely to have dysthymia in the previous year.[1] The prevalence of depressive disorders is greater among those with alcohol dependence, as compared to those diagnosed with alcohol abuse, with high prevalence of depression reported among treatment-seekers. People with DSM-IV alcohol dependence are 3.7 times more likely to also have major depressive disorder, and 2.8 times more likely to have dysthymia, in the previous year. Among people in treatment for DSM-IV AUD, almost 33% met criteria for major depressive disorder in the past year, and 11% met criteria for dysthymia. However, major depressive disorder is the most common co-occurring disorder among people who have AUD, partly because it is among the most common disorders in the general population.

Data from large population-based surveys suggest that the prevalence of alcohol-induced depression is small. For example, among people who also had a substance use disorder, less than

1% of their depressive disorders were classified as substance induced.[1] Studies have found a much higher prevalence of substance-induced depressive disorder among patients with AUD who were in treatment settings, when compared with studies of general population samples. One study reported that more than 25% of patients experienced a substance-induced depressive episode in their lifetime.[10] Nonetheless, studies have found that many cases initially diagnosed as substance-induced depression were later reclassified as independent depression (i.e., not substance induced) because the condition persisted after a period of abstinence.[11]

Disproportionately affected populations

Several groups are disproportionately affected by co-occurring AUD and depressive disorders. For example, women are 1.5 to 2 times more likely in their lifetime to experience major depressive disorder than men.[12] Likewise, women with DSM-IV AUD are more likely than men with DSM-IV AUD to meet the criteria for major depressive disorder or dysthymia.[13,14] Sex differences are not limited to prevalence; they also are observed in the course of depressive disorders. A longitudinal study of young adults found that depression predicted alcohol problems in women but not in men.[15] This finding is consistent with reports from retrospective studies that examined relative age of onset for AUD and depressive disorders, in which women were more likely to experience depression before AUD, whereas men were more likely to develop AUD before depression.[16,17]

Although race and ethnicity are clearly factors in the risk for developing AUD or depressive disorders, studies examining racial and ethnic differences in the prevalence of co-occurring AUD and depressive disorders have been hampered by small sample sizes, which make group comparisons difficult.[18] Nonetheless, data strongly support significant disparities in health care for co-occurring AUD and depressive disorders among racial and ethnic minority groups. The likelihood of receiving AUD care is similar across racial and ethnic groups, but people who identify as Black or Latino are significantly less likely than people who identify as White to receive services for mood and anxiety disorders or to receive integrated mental health and substance use disorder care.[19,20]

Pathways to Co-Occurrence

Several potential developmental pathways have been proposed to explain the high rate of co-occurring AUD and depressive disorders, including: (1) depressive disorders increase risk for AUD, (2) AUD increases risk for depressive disorders, and (3) both conditions share pathophysiology or have common risk factors. Although evidence supports all three of these pathways, much research is still needed to understand the development of co-occurrence.

Etiology

Much of the research on the development of co-occurring AUD and depressive disorders has relied on retrospective and longitudinal studies that examine the age of onset of the disorders. These studies have yielded mixed evidence. Some studies indicate that depressive disorders typically precede the onset of AUD,[21] others suggest that AUD generally precedes depressive disorders,[22] and still others report that the order of onset varies by gender (with women more likely to have earlier onset of depression than men).[17]

Literature on the onset of substance use among youth and young adults has indicated that internalizing symptoms (e.g., depression and anxiety) generally protect against the onset of alcohol misuse in adolescents.[23] However, the association between internalizing symptoms and risk for alcohol use and misuse is influenced by key moderating factors, such as the presence of both internalizing and externalizing symptoms (e.g., impulsivity and aggression),[23] motives for substance use,[24] and gender.[25] For example, research has indicated that internalizing symptoms are a risk factor for the development of AUD in women but not in men.[25]

AUD has been associated with risk for the onset of depressive symptoms and disorders. In one review, regular or heavy drinking in adolescents was shown to be associated with the risk for developing depressive symptoms and disorders.[26] In studies of adults, DSM-IV AUD was associated with risk for the onset of major depressive disorder and with dysthymia.[22,27]

Research on the possibility of a common pathophysiology of co-occurring AUD and

depressive disorders is limited, yet it is a growing area of inquiry. Studies of genetic liability have identified some evidence that AUD and depressive disorders share susceptibility.[28-30] Although much remains to be understood about the possible shared pathophysiology for these conditions, a number of candidate systems and processes have been identified, such as dysfunction in the reward and stress systems.[31]

Data from studies of depressive disorders suggest that specific symptom profiles may reflect distinct pathophysiology. For example, different symptom types have been associated with electrical activity (measured by electroencephalogram) in the brain while patients are at rest.[32] A diagnosis of major depressive disorder can involve 227 unique symptom combinations;[6] thus, the combination of symptoms from AUD and depressive disorders can take many forms. Consideration of disorder heterogeneity is essential to better understand the development of the co-occurring disorders.

Course and prognosis

The prognosis of co-occurring AUD and depression is highly variable and depends on several factors, such as age of onset and the severity of the disorders. For example, DSM-IV alcohol dependence (particularly severe dependence) has been associated with persistence of depressive disorders, whereas alcohol abuse has not.[33] Furthermore, the association between depressive disorders and AUD outcomes depends on how depression was measured. A diagnosis of major depressive disorder typically has been associated with worse AUD treatment outcomes,[2,3] whereas more severe depressive symptoms alone have not been associated with worse AUD treatment outcomes, when compared to less severe depressive symptoms.[2] Depressive symptoms have been shown to significantly improve after a period of abstinence from alcohol (typically 3 to 4 weeks),[34] which may explain the lack of association between symptoms and drinking outcomes outside of the context of a depressive disorder.

Evidence from longitudinal data on whether AUD worsens depression outcomes is somewhat mixed, with some studies finding evidence for worse outcomes and others finding no difference.[35] However, large studies have suggested that recovery from both conditions is linked, with remission from one condition strongly related to remission from the other.[36] For example, results from a large (N = 2,876) multisite trial of treatment for depressive disorders found that patients who had co-occurring substance use disorder had a lower likelihood of depressive disorder remission and had a longer time to remission, when compared to patients with no substance use disorder.[37]

Although alcohol-induced depressive disorder is defined by remission of the depression after discontinuation of alcohol, the disorder has been associated with risk for onset of later major depressive disorder.[11] Another study reported that patients with alcohol-induced depressive disorders experienced worse alcohol-related outcomes than patients with alcohol dependence who had other types of depressive disorders.[38]

Treatment of Co-Occurring AUD and Depressive Disorders

Many randomized trials have investigated treatments for co-occurring AUD and depressive disorders. In this section, trials that used medication and psychotherapy treatments are discussed, as are the effects of those treatments on depressive symptoms and AUD symptoms.

Medication trials

Medication trials for co-occurring AUD and depressive disorders have focused mostly on antidepressant medications. Several meta-analyses have integrated these findings.[39-42] In general, the research shows that for people with co-occurring AUD and depressive disorders, antidepressants are more effective than placebo at reducing symptoms of depression. The magnitude of the benefit of medication over placebo is similar to the benefit reported in studies of people diagnosed with depression alone.[40,41] Few medication trials have compared treatments directly; most trials compare a single medication with a placebo. Thus, little is known about the comparative effectiveness of active treatments.[39] However, meta-analyses have suggested that older antidepressant medications, such as tricyclic antidepressants, are more effective at reducing depressive symptoms than newer agents,

such as selective serotonin reuptake inhibitors (SSRIs).[40,42] These results may be attributable—at least in part—to a large placebo response reported in studies of SSRIs.[41]

The effects of antidepressants on drinking outcomes are modest.[40,42] However, the effect of antidepressant medications on drinking outcomes may be dependent on how those medications affect depression. Some evidence indicates that depression mediates the effect of antidepressants on drinking outcomes.[43] Consistent with these findings, a meta-analysis of trials of antidepressant treatment for people with AUD only (i.e., without co-occurring depression) did not demonstrate a significant effect on drinking outcomes when compared to treatment with placebo.[42]

Studies of patients with co-occurring AUD and depressive disorders have demonstrated that treatments using medications (e.g., naltrexone) for AUD are safe and effective for reducing drinking and depression symptoms.[44,45] A meta-analysis of studies that used acamprosate to treat AUD found similar effects among people with and without depression, but these researchers also found a strong effect of alcohol abstinence on remission of depression.[46] Combinations of antidepressants and AUD medications (e.g., sertraline with naltrexone and acamprosate with escitalopram)[47,48] have also shown some promise for the treatment of these co-occurring disorders, with positive outcomes for both AUD and depressive symptoms.

Psychosocial treatments and mutual help

Researchers have examined the effects of behavioral and psychosocial therapies on co-occurring AUD and depressive disorders, although many of these studies have had small sample sizes. A meta-analysis of 12 studies that examined combined motivational interviewing and cognitive behavioral therapy for AUD and depression found significant, but modest, improvements in both depression and drinking outcomes.[49] These results are consistent with an earlier meta-analysis of several psychotherapies (e.g., interpersonal psychotherapy and cognitive behavioral therapy) that also indicated relatively modest, but positive, effects for depression and drinking outcomes.[50]

Several studies have examined a transdiagnostic behavioral approach to treatment, which integrates the treatments for AUD and depressive symptoms. Behavioral activation is a behavioral therapy that specifically targets reward dysfunction to improve mood through better engagement with natural reinforcers. Treatment with behavioral activation therapy has demonstrated efficacy for depressive disorders[51] and for AUD;[52] thus, it may be particularly promising for treating the co-occurring disorders. A therapy called "life enhancement treatment for substance use," or "LETS ACT," is a modification of behavioral activation therapy for people with substance use disorders. This therapy has been shown to reduce substance-related consequences and improve likelihood of abstinence in samples of adults with substance dependence (including alcohol dependence).[52] In another study, an integrated cognitive behavioral therapy treatment for depressive disorders and substance use disorders was associated with greater reduction in alcohol use, but similar reductions in depression, when compared with the control condition, which was a 12-step facilitation therapy.[53]

Some researchers have suggested that the effects of psychotherapy may account for some of the pill placebo response observed in medication studies. Specifically, for medication trials in which all participants also received some form of psychotherapy, pill placebo response rates were higher than they were for studies that did not include psychotherapy in the pill placebo condition.[41] Likewise, in a study of sertraline and naltrexone in which all participants received weekly psychotherapy, sertraline had no additive benefit.[54] These findings suggest that the psychotherapies used in these trials may have provided some antidepressant effect, either directly or through their effects on drinking.

Mutual-help groups also can be effective elements of treatment for co-occurring AUD and depressive disorders. Attendance at Alcoholics Anonymous (AA) meetings has been shown to decrease symptoms of depression.[55] In one study, researchers found that a reduction in depression mediated the effect that AA meeting attendance had on drinking outcomes,[56] indicating that a change in depression symptoms may be a mechanism through which attendance at AA meetings improves drinking outcomes.

Future Research Directions

Research has substantially improved understanding of the etiology, course, and treatment of co-occurring AUD and depressive disorders. However, significant gaps remain in our understanding of these two disorders, and these gaps present important opportunities for future research.

More knowledge about optimal treatments for co-occurring AUD and depressive disorders is needed. Although medication and behavioral therapy have both shown promise, response rates have been somewhat modest. Efforts to enhance treatment outcomes would benefit from investigation into the characteristics of people who do not respond to existing treatments. A better understanding of the heterogeneity within this population will inform more personalized treatment approaches and might ultimately improve treatment response.

The substantial variability in the course of co-occurring AUD and depressive disorders may reflect discrete underlying mechanisms, requiring distinct treatment approaches. For example, AUD that develops after the onset of a depressive disorder and is characterized by coping motives for alcohol use may differ critically from a depressive disorder that develops following chronic alcohol administration. Data from studies of depression indicate that the substantial variability in the symptoms presented reflects a heterogeneous pathophysiology,[32] yet research on heterogeneity in co-occurring AUD and depressive disorders remains limited. Although little is known about the possible shared pathophysiology of AUD and depressive disorders, preclinical research has identified common disruptions in reward and stress processing that are important candidates for further research.[31] Efforts to better characterize the mechanistic processes that may underlie observed clinical presentations will help identify more precise and personalized interventions.

Future research that leverages novel technologies, such as ecological momentary assessment and multimodal neuroimaging, will enhance our understanding of the interactions between mood and alcohol use and how those interactions may influence the nature, course, and treatment of co-occurring AUD and depressive disorders. Assessment of co-occurring AUD and depressive disorders using dimensional measures rather than discrete, categorical measures will be critical to understanding the full spectrum of severity of these conditions, including subclinical presentations.

Finally, the etiology, course, and treatment of both AUD and depression differ substantially by gender. Women have been underrepresented in much of the research on co-occurring AUD and depressive disorders, particularly in the early research on this topic. The research needs more representation of women to increase understanding of the sex differences and to better characterize the mechanisms underlying women's heightened vulnerability for depressive disorders. For example, an important area for future research could be women who have co-occurring AUD and premenstrual dysphoric disorder, which is a depressive disorder characterized by a fluctuation of mood symptoms across the menstrual cycle.[6] Likewise, research is urgently needed to better understand co-occurring AUD and depressive disorders among racial and ethnic minorities. These populations experience disparities in access to care for AUD and depressive disorders but are underrepresented in studies of these disorders.

Conclusion

People with AUD have a heightened risk for depressive disorders, which are the most common co-occurring psychiatric disorders for this population. AUD and depressive disorders appear to share some behavioral, genetic, and environmental risk factors, yet these shared risks remain poorly understood.

Diagnosis and treatment of the commonly co-occurring AUD and depressive disorders have many challenges. Diagnosis is particularly challenging because of overlapping symptoms, such as the depressant effects of alcohol, and because of features that are common to both alcohol withdrawal and depressive disorders, such as insomnia and psychomotor agitation. The DSM-5 distinguishes a substance-induced disorder from a primary depressive disorder based on whether "the substance is judged to be etiologically related to the symptoms."[6(p180)] Accordingly, any diagnosis of depression during active periods of drinking or during acute alcohol withdrawal should be made provisionally. Attempts to diagnose depression should focus on identifying periods of depression outside periods of drinking or withdrawal and

should use collateral information (e.g., reports from family members or significant others) when possible. If depressive symptoms persist after a period of abstinence—4 weeks is the typical recommendation—a diagnosis of an independent (i.e., not substance-induced) depressive disorder can be made with more confidence.[6]

Nonetheless, substance-induced depression is also associated with the risk for independent depressive disorders. Thus, treatment of depression should be considered, along with close monitoring of mood, for people who have substance-induced depression.[11] Treatment studies have supported the effects of both AUD medications (e.g., naltrexone)[44] and antidepressants[47] for the treatment of co-occurring AUD and depressive disorders. However, because of a lack of comparative trials on effectiveness (i.e., studies comparing more than one active treatment), the most effective approach is unknown. Behavioral therapy is understudied in this population despite evidence supporting the therapy as treatment for depressive disorders[51] and AUD[57] separately. Indeed, in placebo-controlled studies of medications for co-occurring AUD and depression, the inclusion of behavioral therapy as part of the standard treatment may explain the small effect sizes often observed. Behavioral activation therapy—a treatment that targets disruption in reward functioning, which is a common dysfunction in both AUD and depressive disorders—may have particular promise for treating the co-occurring disorders.[52]

Despite the availability of several evidence-based medications and behavioral therapy approaches for treating co-occurring AUD and depressive disorders, improvements in treatment for this population are clearly needed. Consideration of disorder heterogeneity and key subgroup differences may help develop more targeted and personalized treatments to improve outcomes for this population.

Acknowledgments

This article was supported by the Charles Engelhard Foundation and National Institute on Drug Abuse grants K23DA035297 and K24DA022288.

Financial Disclosure

Dr. McHugh declares no competing financial interests. Dr. Weiss has been a consultant to Alkermes, Braeburn, Daiichi-Sankyo, GW Pharmaceuticals, Indivior, Janssen, and US WorldMeds.

References

1. Grant BF, Stinson FS, Dawson DA, et al. Prevalence and co-occurrence of substance use disorders and independent mood and anxiety disorders: Results from the National Epidemiologic Survey on Alcohol and Related Conditions. *Arch Gen Psychiatry*. 2004;61(8):807-816. PMID: 15289279.
2. Greenfield SF, Weiss RD, Muenz LR, et al. The effect of depression on return to drinking: A prospective study. *Arch Gen Psychiatry*. 1998;55(3):259-265. PMID: 9510220.
3. Hasin D, Liu X, Nunes E, et al. Effects of major depression on remission and relapse of substance dependence. *Arch Gen Psychiatry*. 2002;59(4):375-380. PMID: 11926938.
4. Conner KR, Gamble SA, Bagge CL, et al. Substance-induced depression and independent depression in proximal risk for suicidal behavior. *J Stud Alcohol Drugs*. 2014;75(4):567-572. PMID: 24988255.
5. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed. Washington, DC: American Psychiatric Association; 1994.
6. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Washington, DC: American Psychiatric Association; 2013.
7. Hasin DS, Goodwin RD, Stinson FS, et al. Epidemiology of major depressive disorder: Results from the National Epidemiologic Survey on Alcoholism and Related Conditions. *Arch Gen Psychiatry*. 2005;62(10):1097-1106. PMID: 16203955.
8. Kessler RC, Ormel J, Petukhova M, et al. Development of lifetime comorbidity in the World Health Organization world mental health surveys. *Arch Gen Psychiatry*. 2011;68(1):90-100. PMID: 21199968.
9. Kessler RC, Chiu WT, Demler O, et al. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry*. 2005;62(6):617-627. PMID: 15939839.
10. Schuckit MA, Tipp JE, Bergman M, et al. Comparison of induced and independent major depressive disorders in 2,945 alcoholics. *Am J Psychiatry*. 1997;154(7):948-957. PMID: 9210745.
11. Nunes EV, Liu X, Samet S, et al. Independent versus substance-induced major depressive disorder in substance-dependent patients: Observational study of course during follow-up. *J Clin Psychiatry*. 2006;67(10):1561-1567. PMID: 17107247.
12. Kessler RC. Epidemiology of women and depression. *J Affect Disord*. 2003;74(1):5-13. PMID: 12646294.
13. Kessler RC, Crum RM, Warner LA, et al. Lifetime co-occurrence of DSM-III-R alcohol abuse and dependence with other psychiatric disorders in the National Comorbidity Survey. *Arch Gen Psychiatry*. 1997;54(4):313-321. PMID: 9107147.
14. Khan S, Okuda M, Hasin DS, et al. Gender differences in lifetime alcohol dependence: Results from the National Epidemiologic Survey on Alcohol and Related Conditions. *Alcohol Clin Exp Res*. 2013;37(10):1696-1705. PMID: 23763329.
15. Moscato BS, Russell M, Zielezny M, et al. Gender differences in the relation between depressive symptoms and alcohol problems: A longitudinal perspective. *Am J Epidemiol*. 1997;146(11):966-974. PMID: 9400339.
16. Hanna EZ, Grant BF. Gender differences in DSM-IV alcohol use disorders and major depression as distributed in the general population: Clinical implications. *Compr Psychiatry*. 1997;38(4):202-212. PMID: 9202877.
17. Prescott CA, Aggen SH, Kendler KS. Sex-specific genetic influences on the comorbidity of alcoholism and major depression in a population-based sample of U.S. twins. *Arch Gen Psychiatry*. 2000;57(8):803-811. PMID: 10920470.
18. Smith SM, Stinson FS, Dawson DA, et al. Race/ethnic differences in the prevalence and co-occurrence of substance use disorders and independent mood and anxiety disorders: Results from the National Epidemiologic Survey on Alcohol and Related Conditions. *Psychol Med*. 2006;36(7):987-998. PMID: 16650344.
19. Hatzenbuehler ML, Keyes KM, Narrow WE, et al. Racial/ethnic disparities in service utilization for individuals with co-occurring mental health and substance use disorders in the general population: Results from the National Epidemiologic Survey on Alcohol and Related Conditions. *J Clin Psychiatry*. 2008;69(7):1112-1121. PMID: 18517286.

20. Nam E, Matejkowski J, Lee S. Racial/ethnic differences in contemporaneous use of mental health and substance use treatment among individuals experiencing both mental illness and substance use disorders. *Psychiatr Q.* 2017;88(1):185-198. PMID: 27271529.
21. Abraham HD, Fava M. Order of onset of substance abuse and depression in a sample of depressed outpatients. *Compr Psychiatry.* 1999;40(1):44-50. PMID: 9924877.
22. Fergusson DM, Boden JM, Horwood LJ. Tests of causal links between alcohol abuse or dependence and major depression. *Arch Gen Psychiatry.* 2009;66(3):260-266. PMID: 19255375.
23. Colder CR, Frndak S, Lengua LJ, et al. Internalizing and externalizing problem behavior: A test of a latent variable interaction predicting a two-part growth model of adolescent substance use. *J Abnorm Child Psychol.* 2018;46(2):319-330. PMID: 28229368.
24. Crum RM, Mojtabai R, Lazareck S, et al. A prospective assessment of reports of drinking to self-medicate mood symptoms with the incidence and persistence of alcohol dependence. *JAMA Psychiatry.* 2013;70(7):718-726. PMID: 23636710.
25. Foster KT, Hicks BM, Iacono WG, et al. Gender differences in the structure of risk for alcohol use disorder in adolescence and young adulthood. *Psychol Med.* 2015;45(14):3047-3058. PMID: 26118496.
26. Pedrelli P, Shapero B, Archibald A, et al. Alcohol use and depression during adolescence and young adulthood: A summary and interpretation of mixed findings. *Curr Addict Rep.* 2016;3(1):91-97. PMID: 27162708.
27. Falk DE, Yi HY, Hilton ME. Age of onset and temporal sequencing of lifetime DSM-IV alcohol use disorders relative to comorbid mood and anxiety disorders. *Drug Alcohol Depend.* 2008;94(1-3):234-245. PMID: 18215474.
28. Andersen AM, Pietrzak RH, Kranzler HR, et al. Polygenic scores for major depressive disorder and risk of alcohol dependence. *JAMA Psychiatry.* 2017;74(11):1153-1160. PMID: 28813562.
29. Kuo PH, Gardner CO, Kendler KS, et al. The temporal relationship of the onsets of alcohol dependence and major depression: Using a genetically informative study design. *Psychol Med.* 2006;36(8):1153-1162. PMID: 16734951.
30. Zhou H, Polimanti R, Yang BZ, et al. Genetic risk variants associated with comorbid alcohol dependence and major depression. *JAMA Psychiatry.* 2017;74(12):1234-1241. PMID: 29071344.
31. Renoir T, Pang TY, Lanfumey L. Drug withdrawal-induced depression: Serotonergic and plasticity changes in animal models. *Neurosci Biobehav Rev.* 2012;36(1):696-726. PMID: 22037449.
32. Webb CA, Dillon DG, Pechtel P, et al. Neural correlates of three promising endophenotypes of depression: Evidence from the EMBARC study. *Neuropsychopharmacology.* 2016;41(2):454-463. PMID: 26068725.
33. Boschloo L, Vogelzangs N, van den Brink W, et al. Alcohol use disorders and the course of depressive and anxiety disorders. *Br J Psychiatry.* 2012;200(6):476-484. PMID: 22322459.
34. Liappas J, Paparrigopoulos T, Tzavellas E, et al. Impact of alcohol detoxification on anxiety and depressive symptoms. *Drug Alcohol Depend.* 2002;68(2):215-220. PMID: 12234651.
35. Sullivan LE, Fiellin DA, O'Connor PG. The prevalence and impact of alcohol problems in major depression: A systematic review. *Am J Med.* 2005;118(4):330-341. PMID: 15808128.
36. Hasin DS, Tsai WY, Endicott J, et al. Five-year course of major depression: Effects of comorbid alcoholism. *J Affect Disord.* 1996;41(1):63-70. PMID: 8938207.
37. Davis LL, Wisniewski SR, Howland RH, et al. Does comorbid substance use disorder impair recovery from major depression with SSRI treatment? An analysis of the STAR*D level one treatment outcomes. *Drug Alcohol Depend.* 2010;107(2-3):161-170. PMID: 19945804.
38. Samet S, Fenton MC, Nunes E, et al. Effects of independent and substance-induced major depressive disorder on remission and relapse of alcohol, cocaine and heroin dependence. *Addiction.* 2013;108(1):115-123. PMID: 22775406.
39. Agabio R, Trogu E, Pani PP. Antidepressants for the treatment of people with co-occurring depression and alcohol dependence. *Cochrane Database Syst Rev.* 2018;4:CD008581. PMID: 29688573.
40. Iovieno N, Tedeschini E, Bentley KH, et al. Antidepressants for major depressive disorder and dysthymic disorder in patients with comorbid alcohol use disorders: A meta-analysis of placebo-controlled randomized trials. *J Clin Psychiatry.* 2011;72(8):1144-1151. PMID: 21536001.
41. Nunes EV, Levin FR. Treatment of depression in patients with alcohol or other drug dependence: A meta-analysis. *JAMA.* 2004;291(15):1887-1896. PMID: 15100209.
42. Torrens M, Fonseca F, Mateu G, et al. Efficacy of antidepressants in substance use disorders with and without comorbid depression. A systematic review and meta-analysis. *Drug Alcohol Depend.* 2005;78(1):1-22. PMID: 15769553.
43. Nunes EV, Quitkin FM, Donovan SJ, et al. Imipramine treatment of opiate-dependent patients with depressive disorders. A placebo-controlled trial. *Arch Gen Psychiatry.* 1998;55(2):153-160. PMID: 9477929.
44. Petrakis I, Ralevski E, Nich C, et al. Naltrexone and disulfiram in patients with alcohol dependence and current depression. *J Clin Psychopharmacol.* 2007;27(2):160-165. PMID: 17414239.
45. Salloum IM, Cornelius JR, Thase ME, et al. Naltrexone utility in depressed alcoholics. *Psychopharmacol Bull.* 1998;34(1):111-115. PMID: 9564207.
46. Lejoyeux M, Lehert P. Alcohol-use disorders and depression: Results from individual patient data meta-analysis of the acamprosate-controlled studies. *Alcohol Alcohol.* 2011;46(1):61-67. PMID: 21118900.
47. Pettinati HM, Oslin DW, Kampman KM, et al. A double-blind, placebo-controlled trial combining sertraline and naltrexone for treating co-occurring depression and alcohol dependence. *Am J Psychiatry.* 2010;167(6):668-675. PMID: 20231324.
48. Witte J, Bentley K, Evins AE, et al. A randomized, controlled, pilot study of acamprosate added to escitalopram in adults with major depressive disorder and alcohol use disorder. *J Clin Psychopharmacol.* 2012;32(6):787-796. PMID: 23131884.
49. Riper H, Andersson G, Hunter SB, et al. Treatment of comorbid alcohol use disorders and depression with cognitive-behavioural therapy and motivational interviewing: A meta-analysis. *Addiction.* 2014;109(3):394-406. PMID: 24304463.
50. Hesse M. Integrated psychological treatment for substance use and co-morbid anxiety or depression vs. treatment for substance use alone. A systematic review of the published literature. *BMC Psychiatry.* 2009;9:6. PMID: 19232121.
51. Dimidjian S, Hollon SD, Dobson KS, et al. Randomized trial of behavioral activation, cognitive therapy, and antidepressant medication in the acute treatment of adults with major depression. *J Consult Clin Psychol.* 2006;74(4):658-670. PMID: 16881773.
52. Daughters SB, Magidson JF, Anand D, et al. The effect of a behavioral activation treatment for substance use on post-treatment abstinence: A randomized controlled trial. *Addiction.* 2018;113(3):535-544. PMID: 28963853.
53. Lydecker KP, Tate SR, Cummins KM, et al. Clinical outcomes of an integrated treatment for depression and substance use disorders. *Psychol Addict Behav.* 2010;24(3):453-465. PMID: 20853931.
54. Farren CK, Scimeca M, Wu R, et al. A double-blind, placebo-controlled study of sertraline with naltrexone for alcohol dependence. *Drug Alcohol Depend.* 2009;99(1-3):317-321. PMID: 18644685.
55. Kelly TM, Daley DC, Douaihy AB. Treatment of substance abusing patients with comorbid psychiatric disorders. *Addict Behav.* 2012;37(1):11-24. PMID: 21981788.
56. Wilcox CE, Tonigan JS. Changes in depression mediate the effects of AA attendance on alcohol use outcomes. *Am J Drug Alcohol Abuse.* 2018;44(1):103-112. PMID: 27892692.
57. National Institute on Alcohol Abuse and Alcoholism. Matching Alcoholism Treatments to Client Heterogeneity: Project MATCH posttreatment drinking outcomes. *J Stud Alcohol.* 1997;58(1):7-29. PMID: 8979210.

Cite this as:
Alcohol Res. 2019;40(1):01. **https://doi.org/10.35946/arcr.v40.1.01.**

Suicidal Behavior

Links Between Alcohol Use Disorder and Acute Use of Alcohol

Kenneth R. Conner and Courtney L. Bagge

Kenneth R. Conner, Psy.D., M.P.H., is a professor in the Departments of Emergency Medicine and Psychiatry, University of Rochester Medical Center, Rochester, New York.

Courtney L. Bagge, Ph.D., is an associate professor in the Department of Psychiatry and Human Behavior, University of Mississippi Medical Center, Jackson, Mississippi.

Research on associations of suicidal behavior, including suicide and suicide attempt, with alcohol use disorder (AUD) and acute use of alcohol (AUA) are discussed, with an emphasis on data from meta-analyses. Based on psychological autopsy investigations, results indicate that AUD is prevalent among individuals who die by suicide. Results also indicate that AUD is a potent risk factor for suicidal behavior. Risk estimates are higher for individuals with AUD in treatment settings, when compared to individuals in the community who have AUD. Also, although rates of suicide and prevalence of AUD remain higher in men, they have increased more among women in recent decades. Based on postmortem blood alcohol concentrations, AUA was commonly present among those who died by suicide. AUA is a potent proximal risk factor for suicidal behavior, and the risk increases with the amount of alcohol consumed, consistent with a dose-response relationship. Research indicates that AUA increases risk for suicidal behavior by lowering inhibition and promoting suicidal thoughts. There is support for policies that serve to reduce alcohol availability in populations with high rates of AUD and suicide, that promote AUD treatment, and that defer suicide risk assessments in intoxicated patients to allow the blood alcohol concentration to decrease.

KEY WORDS: alcohol consumption; alcohol use disorder; intoxication; suicide; suicide attempt

Introduction

Suicide claims more than 800,000 lives each year worldwide and is the second-leading cause of death among people ages 15 to 29.[1] For every suicide, at least 20 nonlethal suicide attempts have occurred, primarily by attempted overdose. These attempts are a leading cause of hospitalizations from injury and a potent risk factor for eventual suicide. Therefore, examination of suicide and suicide attempt is a critical focus for injury research and prevention efforts. Alcohol use may confer risk for these outcomes proximally through the acute use of alcohol (AUA), which has been defined as the use of alcohol within 3 hours or within 6 hours of suicidal behavior, or as any blood alcohol concentration (BAC) in an individual who attempted suicide or died by suicide.[2] Alcohol use may also confer risk for suicidal behavior more distally through chronic effects, including those manifested in alcohol use disorder (AUD).[3] Accordingly, the role of AUA and AUD in suicidal behavior, including suicide and suicide attempt, is discussed.

AUD and Suicidal Behavior

Estimates of risk for suicide associated with the presence of AUD were provided by meta-analyses of postmortem case-control studies (N = 35, OR = 3.68, 95% confidence interval [CI: 1.99, 6.82]),[4] and studies using mixed designs, including case-control and cohort studies (N = 31, OR = 2.59, 95% CI [1.95, 3.23]).[5] The latter study also produced an estimate of risk for suicide attempt associated with AUD (OR = 3.13, 95% CI [2.45, 3.81]). These meta-analyses suggest that the odds of suicidal behavior are about three times higher among individuals with AUD compared to those without AUD. Higher risk estimates were produced in a meta-analysis of suicide based on cohort studies

of treated patients with AUD (N = 17),[6] which is attributable to its examination of clinical populations with more severe symptoms.

AUD is the second-most commonly identified mental disorder among suicide decedents worldwide (the most common is mood disorder),[7] suggesting that AUD is a major contributor to population-level rates of suicide.[8] However, the percentage of suicide decedents who had AUD, as identified in psychological autopsy studies, has ranged widely, from a low of 7% in the National Psychological Autopsy Study in China[9] to a high of 61% in a report from Estonia.[10] Key reasons that AUD is a major risk factor for suicide include its role in contributing to substance-induced depressive episodes, disruptions in interpersonal relationships (e.g., breakups), and repeated exposure to alcohol intoxication.[11]

Although two of the aforementioned meta-analyses did not identify gender differences in the risk for suicide associated with AUD,[4,5] the meta-analysis of cohorts of patients with AUD produced a higher risk estimate for suicide among women with AUD (standardized mortality risk [SMR] = 16.39, 95% CI [10.66, 25.19]) than among men with AUD (SMR = 8.75, 95% CI [6.35, 12.06]).[6] This result suggests that women who receive AUD treatment have about a 16-fold risk for suicide compared with women in the general population, whereas men who have received AUD treatment have approximately a 9-fold risk for suicide compared with men in the general population. The need to examine gender differences in AUD-related risk is underscored by trends in recent decades in the United States, which show substantially greater increases among women than men in rates of suicide[12] and prevalence of AUD.[3]

AUA and Suicidal Behavior

In the United States, approximately 36% of male and 29% of female suicide decedents ages 18 and older have a postmortem BAC of 0.001 g/dL or more, and 24% of males and 17% of females have BAC levels that exceed 0.08 g/dL, the U.S. national legal limit for drinking and driving.[13] To estimate risk for suicidal behavior associated with AUA, controlled studies have compared AUA that occurred before suicidal behavior to AUA that occurred within the same subjects during a lower-risk control period (case-crossover design) and to AUA that occurred during a comparable period of time in a lower-risk control group (case-control design).[2] A meta-analysis of such reports showed that although risk for suicide attempt increases at low levels of AUA (OR = 2.71, 95% CI [1.56, 4.71]), risk increases markedly at high levels of AUA (OR = 37.18, 95% CI [17.38, 79.53]), as defined by a BAC of more than 0.10 g/dL, which is consistent with a dose-response relationship. A rigorous, controlled study of AUA and suicide by firearm also demonstrated a dose-response relationship between the amounts of alcohol consumed and risk.[14] Such data provide a strong empirical rationale for the common clinical practice of holding intoxicated, suicidal patients in emergency settings to allow for a drop in BAC before assessing suicidal risk and considering discharge.

A seminal review posited several mechanisms by which AUA may increase risk for suicidal behavior, including alcohol-related increases in psychological distress, depressed mood, aggressiveness, and impulsivity.[15] The role of alcohol in cognitive constriction, a narrowing of attention to one's present emotional state and circumstances, is another likely mechanism.[16] Recent research has shown that during the 24-hour period preceding a suicide attempt, AUA in a given hour is associated with increased intensity of suicidal ideation in the next hour.[17] Research has also shown that AUA is associated with a rapid transition from acute suicidal impulse to action,[18] suggesting that the role of AUA in promoting suicidal ideation and disinhibition is a mechanism of risk for suicidal behavior. A link between AUA and the use of firearms, the most lethal form of self-injury and the most common method of suicide in the United States, is also critical to consider.[19] Data show that alcohol intoxication is most commonly present in suicide by firearm among young adult and middle-aged men.[20] This research indicates the importance of focusing suicide by firearm prevention efforts on this segment of the U.S. population.

There is heterogeneity in the motives for AUA preceding suicidal behavior, with approximately a quarter to a third of individuals who drank acutely before a suicide attempt reporting they did so in an effort to facilitate the act of suicide by seeking to build courage, numb fears, or anesthetize the pain of dying.[21,22] Also, for suicide risk, AUA may act synergistically with other substances, as demonstrated by a report showing that co-ingestion of AUA and

acute use of other central nervous system depressants (sedatives, anxiolytics, or opioids) increased risk for a suicide attempt, with an *OR* of 8.76 (95% CI [1.02, 75.44]), when compared with AUA only (*OR* = 4.07, 95% CI [2.06, 8.02]) or when compared with acute use of other central nervous system depressants only (*OR* = 3.01, 95% CI [1.09, 8.31]).[23]

Implications and Future Directions

Interventions that serve to decrease alcohol use and AUD in general populations through policies such as alcohol taxes or restrictions on alcohol availability[24] may be expected to have the greatest effect on suicide rates in countries with high rates of AUD and alcohol consumption per capita. Illustrating this idea, a national campaign in Russia to reduce alcohol availability led to reduced rates of suicide, which increased to preintervention levels following cessation of the campaign.[25] Moreover, the temporary decline in suicide rates appeared to be attributed to the decrease in suicides associated with BAC levels of more than 0.15 g/dL.[25] See the report by Xuan and colleagues for a comprehensive review of the literature on alcohol policies and suicide.[24]

Clinical policy interventions targeting AUD also have the potential to affect suicide rates in health systems that have high rates of AUD and suicide. AUD is a potent risk factor for suicide and the second-most common mental disorder (the most common is depression) among U.S. veterans receiving treatment in the Veterans Health Administration (VHA) who eventually die by suicide.[26] Moreover, initiation of AUD treatment has been shown to lower prospective risk for suicide attempt among veterans in VHA treatment,[27] suggesting the importance of AUD screening and suicide prevention efforts during treatment for AUD.

Assessments of the role of AUA in suicide attempts should begin with establishing if AUA occurred and estimating the amount of alcohol consumed. Assessments may include determining a patient's motivation for drinking before the attempt and a collaborative chain analysis with the patient.[28] Chain analysis is a retrospective method for determining the sequence of events, thoughts (e.g., suicide premeditation and drinking motivations), and behaviors (e.g., drinking) that led up to a suicidal act. The information learned from a chain analysis can be used to develop a personalized distress safety plan that highlights high-risk periods and warning signs, and to devise strategies for avoiding alcohol.[17] Overall, the goal of the plan is to prevent escalation of suicidal risk in the context of AUA.

Future research directions include the study of real-time interventions via mobile applications, which could potentially coach individuals on adaptive strategies for suicidal thoughts, urges to drink, or distressing experiences. Another future direction is to accelerate research on pharmacological interventions that target individuals at risk for alcohol-related suicidal behavior.

Acknowledgments

The authors have no funding sources to disclose.

Financial Disclosure

The authors declare that they have no competing financial interests.

References

1. World Health Organization. *National Suicide Prevention Strategies: Progress, Examples and Indicators*. Geneva, Switzerland: World Health Organization; 2018.
2. Borges G, Cherpitel CJ, Orozco R, et al. A dose-response estimate for acute alcohol use and risk of suicide attempt. *Addict Biol*. 2017;22(6):1554-1561. PMID: 27507572.
3. Grant BF, Chou SP, Saha TD, et al. Prevalence of 12-month alcohol use, high-risk drinking, and DSM-IV alcohol use disorder in the United States, 2001–2002 to 2012–2013: Results from the National Epidemiologic Survey on Alcohol and Related Conditions. *JAMA Psychiatry*. 2017;74(9):911-923. PMID: 28793133.
4. Conner KR, Bridge JA, Davidson DJ, et al. Metaanalysis of mood and substance use disorders in proximal risk for suicide deaths. *Suicide Life Threat Behav*. 2019;49(1):278-292. PMID: 29193261.
5. Darvishi N, Farhadi M, Haghtalab T, et al. Alcohol-related risk of suicidal ideation, suicide attempt, and completed suicide: A meta-analysis. *PLoS One*. 2015;10(5):e0126870. PMID: 25993344.
6. Roerecke M, Rehm J. Cause-specific mortality risk in alcohol use disorder treatment patients: A systematic review and meta-analysis. *Int J Epidemiol*. 2014;43(3):906-919. PMID: 24513684.
7. Cavanagh JT, Carson AJ, Sharpe M, et al. Psychological autopsy studies of suicide: A systematic review. *Psychol Med*. 2003;33(3):395-405. PMID: 12701661.
8. Li Z, Page A, Martin G, et al. Attributable risk of psychiatric and socio-economic factors for suicide from individual-level, population-based studies: A systematic review. *Soc Sci Med*. 2011;72(4):608-616. PMID: 21211874.
9. Phillips MR, Yang G, Zhang Y, et al. Risk factors for suicide in China: A national case-control psychological autopsy study. *Lancet*. 2002;360(9347):1728-1736. PMID: 12480425.
10. Kõlves K, Värnik A, Tooding LM, et al. The role of alcohol in suicide: A case-control psychological autopsy study. *Psychol Med*. 2006;36(7):923-930. PMID: 16650347.
11. Conner KR, Ilgen MA. Substance use disorders and suicidal behavior: A conceptual model. In: O'Connor RC, Pirkis J, eds. *The International Handbook of Suicide Prevention*. 2nd ed. Hoboken, NJ: Wiley; 2016:110-123.
12. Hedegaard H, Curtin SC, Warner M. *Suicide Rates in the United States Continue to Increase*. Hyattsville, MD: National Center for Health Statistics, Centers for Disease Control and Prevention; June 2018.

13. Kaplan MS, McFarland BH, Huguet N, et al. Acute alcohol intoxication and suicide: A gender-stratified analysis of the National Violent Death Reporting System. *Inj Prev.* 2013;19(1):38-43. PMID: 22627777.
14. Branas CC, Richmond TS, Ten Have TR, et al. Acute alcohol consumption, alcohol outlets, and gun suicide. *Subst Use Misuse.* 2011;46(13):1592-1603. PMID: 21929327.
15. Hufford MR. Alcohol and suicidal behavior. *Clin Psychol Rev.* 2001;21(5):797-811. PMID: 11434231.
16. Steele CM, Josephs RA. Alcohol myopia: Its prized and dangerous effects. *Am Psychol.* 1990;45(8):921-933. PMID: 2221564.
17. Bagge CL, Littlefield AK, Conner KR, et al. Near-term predictors of the intensity of suicidal ideation: An examination of the 24h prior to a recent suicide attempt. *J Affect Disord.* 2014;165:53-58. PMID: 24882177.
18. Bryan CJ, Garland EL, Rudd DM. From impulse to action among military personnel hospitalized for suicide risk: Alcohol consumption and the reported transition from suicidal thought to behavior. *Gen Hosp Psychiatry.* 2016;41:13-19. PMID: 27302719.
19. Branas CC, Han S, Wiebe DJ. Alcohol use and firearm violence. *Epidemiol Rev.* 2016;38(1):32-45. PMID: 26811427.
20. Conner KR, Huguet N, Caetano R, et al. Acute use of alcohol and methods of suicide in a U.S. national sample. *Am J Public Health.* 2014;104(1):171-178. PMID: 23678938.
21. Bagge CL, Conner KR, Reed L, et al. Alcohol use to facilitate a suicide attempt: An event-based examination. *J Stud Alcohol Drugs.* 2015;76(3):474-481. PMID: 25978835.
22. Spokas M, Wenzel A, Brown GK, et al. Characteristics of individuals who make impulsive suicide attempts. *J Affect Disord.* 2012;136(3):1121-1125. PMID: 22119087.
23. Bagge CL, Borges G. Acute substance use as a warning sign for suicide attempts: A case-crossover examination of the 48 hours prior to a recent suicide attempt. *J Clin Psychiatry.* 2017;78(6):691-696. PMID: 28682530.
24. Xuan Z, Naimi TS, Kaplan MS, et al. Alcohol policies and suicide: A review of the literature. *Alcohol Clin Exp Res.* 2016;40(10):2043-2055. PMID: 27618526.
25. Värnik A, Kõlves K, Väli M, et al. Do alcohol restrictions reduce suicide mortality? *Addiction.* 2007;102(2):251-256. PMID: 17222279.
26. Ilgen MA, Bohnert AS, Ignacio RV, et al. Psychiatric diagnoses and risk of suicide in veterans. *Arch Gen Psychiatry.* 2010;67(11):1152-1158. PMID: 21041616.
27. Ilgen MA, Jain A, Lucas E, et al. Substance use-disorder treatment and a decline in attempted suicide during and after treatment. *J Stud Alcohol Drugs.* 2007;68(4):503-509. PMID: 17568953.
28. Linehan MM. *Cognitive-Behavioral Treatment of Borderline Personality Disorder.* New York, NY: Guilford Press; 1993.

Cite this as:
Alcohol Res. 2019;40(1):02. **https://doi.org/10.35946/arcr.v40.1.02.**

Co-Occurring Alcohol Use Disorder and Anxiety

Bridging Psychiatric, Psychological, and Neurobiological Perspectives

Justin J. Anker and Matt G. Kushner

Justin J. Anker, Ph.D., is an assistant professor in the Department of Psychiatry, University of Minnesota, Minneapolis, Minnesota.

Matt G. Kushner, Ph.D., is a professor in the Department of Psychiatry, University of Minnesota, Minneapolis, Minnesota.

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

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

Introduction

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

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

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

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

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

Psychiatric Disorder Classifications and Diagnoses

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

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

Comorbidity paradigm

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

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

Epidemiology of co-occurring disorders

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

Alcohol-related diagnoses

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

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

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

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

Anxiety disorder diagnoses

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

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

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

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

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

Temporal and causal priority

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

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

Prospective relative risk

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

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

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

Effects of co-occurrence on alcohol treatment outcomes

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

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

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

Psychological Theories

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

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

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

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

Neurobiological Theories

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

Psychophysiological and neurobiological correlates

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

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

Opponent process model

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

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

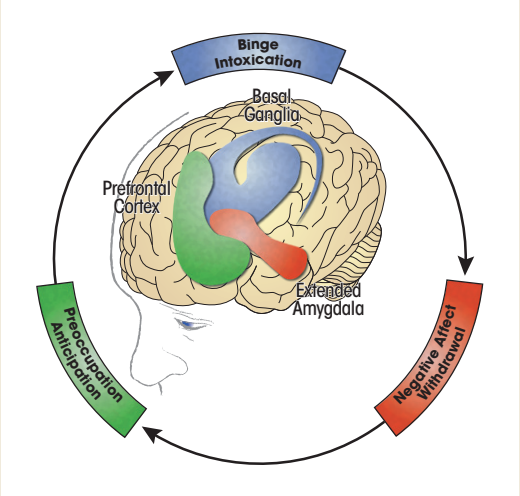

Figure 1 Addiction cycle stages and associated brain regions. *Source:* Adapted from U.S. Department of Health and Human Services, Office of the Surgeon General. *Facing Addiction in America: The Surgeon General's Report on Alcohol, Drugs, and Health*. Washington, DC: U.S. Department of Health and Human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

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

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

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

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

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

Discussion and Future Directions

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

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

Unidirectional causation theories

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

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

Shared neurobiology

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

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

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

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

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

Anxiety problems in the absence of alcohol misuse

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

Alcohol misuse in the absence of anxiety

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

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

Stress reactivity and regulation

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

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

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

Limitations

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

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

Conclusion

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

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

Acknowledgments

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

Correspondence may be sent to Matt G. Kushner, University of Minnesota, 2450 Riverside Avenue, 282-2A West, Minneapolis, Minnesota 55454, kushn001@umn.edu.

Financial Disclosure

The authors declare that they have no competing financial interests.

References

1. Kushner MG, Abrams K, Thuras P, et al. Follow-up study of anxiety disorder and alcohol dependence in comorbid alcoholism treatment patients. *Alcohol Clin Exp Res.* 2005;29(8):1432-1443. PMID: 16131851.
2. Chan YF, Dennis ML, Funk RR. Prevalence and comorbidity of major internalizing and externalizing problems among adolescents and adults presenting to substance abuse treatment. *J Subst Abuse Treat.* 2008;34(1):14-24. PMID: 17574804.
3. Byers AL, Yaffe K, Covinsky KE, et al. High occurrence of mood and anxiety disorders among older adults: The National Comorbidity Survey Replication. *Arch Gen Psychiatry.* 2010;67(5):489-496. PMID: 20439830.
4. Grant BF, Stinson FS, Dawson DA, et al. Prevalence and co-occurrence of substance use disorders and independent mood and anxiety disorders: Results from the National Epidemiologic Survey on Alcohol and Related Conditions. *Arch Gen Psychiatry.* 2004;61(8):807-816. PMID: 15289279.
5. Babor TF. The classification of alcoholics: Typology theories from the 19th century to the present. *Alcohol Health Res World.* 1996;20(1):6-14.

6. Cloninger CR, Sigvardsson S, Gilligan SB, et al. Genetic heterogeneity and the classification of alcoholism. *Adv Alcohol Subst Abuse*. 1988;7(3-4):3-16. PMID: 3066194.
7. Cloninger CR, Sigvardsson S, Bohman M. Type I and type II alcoholism: An update. *Alcohol Health Res World*. 1996;20(1):18-24.
8. Lewis ND. Psychiatric resultants of alcoholism: Alcoholism and mental disease. *Q J Stud Alcohol*. 1941;2:293-311.
9. Feinstein AR. The pre-therapeutic classification of co-morbidity in chronic disease. *J Chronic Dis*. 1970;23(7):455-468. PMID: 26309916.
10. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 3rd ed. Washington, DC: American Psychiatric Association; 1980.
11. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Washington, DC: American Psychiatric Association; 2013.
12. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed. Washington, DC: American Psychiatric Association; 1994.
13. Kushner MG, Krueger R, Frye B, et al. Epidemiological perspectives on co-occurring anxiety disorder and substance use disorder. In: Stewart SH, Conrod PJ, eds. *Anxiety and Substance Use Disorders: The Vicious Cycle of Comorbidity*. Boston, MA: Springer; 2008:3-17.
14. Kushner MG, Sher KJ, Beitman BD. The relation between alcohol problems and the anxiety disorders. *Am J Psychiatry*. 1990;147(6):685-695. PMID: 2188513.
15. Goodwin RD, Lieb R, Hoefler M, et al. Panic attack as a risk factor for severe psychopathology. *Am J Psychiatry*. 2004;161(12):2207-2214. PMID: 15569891.
16. Himle JA, Hill EM. Alcohol abuse and the anxiety disorders: Evidence from the Epidemiologic Catchment Area Survey. *J Anxiety Disord*. 1991;5(3):237-245.
17. Krueger RF. The structure of common mental disorders. *Arch Gen Psychiatry*. 1999;56(10):921-926. PMID: 10530634.
18. Kushner MG, Wall MM, Krueger RF, et al. Alcohol dependence is related to overall internalizing psychopathology load rather than to particular internalizing disorders: Evidence from a national sample. *Alcohol Clin Exp Res*. 2012;36(2):325-331. PMID: 21895708.
19. Crum RM, Mojtabai R, Lazareck S, et al. A prospective assessment of reports of drinking to self-medicate mood symptoms with the incidence and persistence of alcohol dependence. *JAMA Psychiatry*. 2013;70(7):718-726. PMID: 23636710.
20. Buckner JD, Heimberg RG, Ecker AH, et al. A biopsychosocial model of social anxiety and substance use. *Depress Anxiety*. 2013;30(3):276-284. PMID: 23239365.
21. Kushner MG, Sher KJ, Erickson DJ. Prospective analysis of the relation between DSM-III anxiety disorders and alcohol use disorders. *Am J Psychiatry*. 1999;156(5):723-732. PMID: 10327905.
22. Schuckit MA. Alcohol-use disorders. *Lancet*. 2009;373(9662):492-501. PMID: 19168210.
23. Farris SG, Epstein EE, McCrady BS, et al. Do co-morbid anxiety disorders predict drinking outcomes in women with alcohol use disorders? *Alcohol Alcohol*. 2012;47(2):143-148. PMID: 22215000.
24. Schellekens AF, de Jong CA, Buitelaar JK, et al. Co-morbid anxiety disorders predict early relapse after inpatient alcohol treatment. *Eur Psychiatry*. 2015;30(1):128-136. PMID: 24630346.
25. Book SW, Thomas SE, Randall PK, et al. Paroxetine reduces social anxiety in individuals with a co-occurring alcohol use disorder. *J Anxiety Disord*. 2008;22(2):310-318. PMID: 17448631.
26. Hobbs JD, Kushner MG, Lee SS, et al. Meta-analysis of supplemental treatment for depressive and anxiety disorders in patients being treated for alcohol dependence. *Am J Addict*. 2011;20(4):319-329. PMID: 21679263.
27. Conger JJ. Alcoholism: Theory, problem and challenge. II. Reinforcement theory and the dynamics of alcoholism. *Q J Stud Alcohol*. 1956;17(2):296-305. PMID: 13336262.
28. Cappell HD, Herman CP. Alcohol and tension reduction: A review. *Q J Stud Alcohol*. 1972;33(1):33-64. PMID: 4551021.
29. Donovan DM, Marlatt GA. Assessment of expectancies and behaviors associated with alcohol consumption: A cognitive-behavioral approach. *J Stud Alcohol*. 1980;41(11):1153-1185. PMID: 7278260.
30. Cooper ML. Motivations for alcohol use among adolescents: Development and validation of a four-factor model. *Psychol Assess*. 1994;6(2):117.
31. Cooper ML, Frone MR, Russell M, et al. Drinking to regulate positive and negative emotions: A motivational model of alcohol use. *J Pers Soc Psychol*. 1995;69(5):990-1005. PMID: 7473043.
32. Menary KR, Kushner MG, Maurer E, et al. The prevalence and clinical implications of self-medication among individuals with anxiety disorders. *J Anxiety Disord*. 2011;25(3):335-339. PMID: 21094020.
33. Campbell J, Ehlert U. Acute psychosocial stress: Does the emotional stress response correspond with physiological responses? *Psychoneuroendocrinology*. 2012;37:1111-1134. PMID: 22260938.
34. Sher KJ. Stress response dampening. In: Blane HT, Leonard KE, eds. *Psychological Theories of Drinking and Alcoholism*. 1st ed. New York, NY: Guilford Press; 1987:227-271.
35. Brady KT, Back SE. Childhood trauma, posttraumatic stress disorder, and alcohol dependence. *Alcohol Res*. 2012;34(4):408-413. PMID: 23584107.
36. Thomas S, Bacon AK, Sinha R, et al. Clinical laboratory stressors used to study alcohol-stress relationships. *Alcohol Res*. 2012;34(4):459-467. PMID: 23584112.
37. Clarke TK, Nymberg C, Schumann G. Genetic and environmental determinants of stress responding. *Alcohol Res*. 2012;34(4):484-494. PMID: 23584114.
38. Sinha R. How does stress lead to risk of alcohol relapse? *Alcohol Res*. 2012;34(4):432-440. PMID: 23584109.
39. Herman JP. Neural pathways of stress integration: Relevance to alcohol abuse. *Alcohol Res*. 2012;34(4):441-447. PMID: 23584110.
40. Becker HC. Effects of alcohol dependence and withdrawal on stress responsiveness and alcohol consumption. *Alcohol Res*. 2012;34(4):448-458. PMID: 23584111.
41. Koob GF, Buck CL, Cohen A, et al. Addiction as a stress surfeit disorder. *Neuropharmacology*. 2014;76:370-382. PMID: 23747571.
42. Kenny PJ, Hoyer D, Koob GF. Animal models of addiction and neuropsychiatric disorders and their role in drug discovery: Honoring the legacy of Athina Markou. *Biol Psychiatry*. 2018;83(11):940-946. PMID: 29602521.
43. Kwako LE, Momenan R, Litten RZ, et al. Addictions Neuroclinical Assessment: A neuroscience-based framework for addictive disorders. *Biol Psychiatry*. 2016;80(3):179-189. PMID: 26772405.
44. Schwandt ML, Cortes CR, Kwako LE, et al. The CRF1 antagonist verucerfont in anxious alcohol-dependent women: Translation of neuroendocrine, but not of anti-craving effects. *Neuropsychopharmacology*. 2016;41(12):2818-2829. PMID: 27109623.
45. Agoglia AE, Herman MA. The center of the emotional universe: Alcohol, stress and CRF1 amygdala circuitry. *Alcohol*. 2018;72:61-73. PMID: 30220589.
46. Haass-Koffler CL, Swift RM, Leggio L. Noradrenergic targets for the treatment of alcohol use disorder. *Psychopharmacology (Berl)*. 2018;235(6):1625-1634. PMID: 29460163.
47. Simpson TL, Saxon AJ, Meredith CW, et al. A pilot trial of the alpha-1 adrenergic antagonist, prazosin, for alcohol dependence. *Alcohol Clin Exp Res*. 2009;33(2):255-263. PMID: 18945226.
48. Petrakis IL, Desai N, Gueorguieva R, et al. Prazosin for veterans with posttraumatic stress disorder and comorbid alcohol dependence: A clinical trial. *Alcohol Clin Exp Res*. 2016;40(1):178-186. PMID: 26683790.
49. Anker JJ, Kushner MG, Thuras P, et al. Drinking to cope with negative emotions moderates alcohol use disorder treatment response in patients with co-occurring anxiety disorder. *Drug Alcohol Depend*. 2016;159:93-100. PMID: 26718394.
50. Gilpin NW, Herman MA, Roberto M. The central amygdala as an integrative hub for anxiety and alcohol use disorders. *Biol Psychiatry*. 2015;77(10):859-869. PMID: 25433901.
51. Noronha A, Cui C, Harris RA, et al, eds. *Neurobiology of Alcohol Dependence*. 1st ed. Waltham, MA: Academic Press; 2014.
52. Roberto M, Gilpin NW. Central amygdala neuroplasticity in alcohol dependence. In: Noronha A, Cui C, Harris RA, et al, eds. *Neurobiology of Alcohol Dependence*. 1st ed. Waltham, MA: Academic Press; 2014:207-226.
53. Breese GR, Sinha R, Heilig M. Chronic alcohol neuroadaptation and stress contribute to susceptibility for alcohol craving and relapse. *Pharmacol Ther*. 2011;129(2):149-171. PMID: 20951730.
54. Markou A, Kosten TR, Koob GF. Neurobiological similarities in depression and drug dependence: A self-medication hypothesis. *Neuropsychopharmacology*. 1998;18(3):135-174. PMID: 9471114.

55. Kushner MG, Maurer E, Menary K, et al. Vulnerability to the rapid ("telescoped") development of alcohol dependence in individuals with anxiety disorder. *J Stud Alcohol Drugs.* 2011;72(6):1019-1027. PMID: 22051216.
56. Kushner MG, Menary KR, Maurer EW, et al. Greater elevation in risk for nicotine dependence per pack of cigarettes smoked among those with an anxiety disorder. *J Stud Alcohol Drugs.* 2012;73(6):920-924. PMID: 23036209.
57. Menary KR, Corbin WR, Chassin L. Associations between early internalizing symptoms and speed of transition through stages of alcohol involvement. *Dev Psychopathol.* 2017;29(4):1455-1467. PMID: 28397620.
58. Adinoff B, Martin PR, Bone GH, et al. Hypothalamic-pituitary-adrenal axis functioning and cerebrospinal fluid corticotropin releasing hormone and corticotropin levels in alcoholics after recent and long-term abstinence. *Arch Gen Psychiatry.* 1990;47(4):325-330. PMID: 2157379.
59. Dieleman GC, Huizink AC, Tulen JH, et al. Alterations in HPA-axis and autonomic nervous system functioning in childhood anxiety disorders point to a chronic stress hypothesis. *Psychoneuroendocrinology.* 2015;51:135-150. PMID: 25305548.
60. Insel T, Cuthbert B, Garvey M, et al. Research domain criteria (RDoC): Toward a new classification framework for research on mental disorders. *Am J Psychiatry.* 2010;167(7):748-751. PMID: 20595427.

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

Biobehavioral Interactions Between Stress and Alcohol

Marcus M. Weera, Ph.D., is a postdoctoral fellow in the Department of Physiology, Louisiana State University Health Sciences Center, New Orleans, Louisiana.

Nicholas W. Gilpin, Ph.D., is a professor in the Department of Physiology, Louisiana State University Health Sciences Center, New Orleans, Louisiana.

Marcus M. Weera and Nicholas W. Gilpin

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

KEY WORDS: alcohol; animal models; stress

Behavioral Interactions Between Stress and Alcohol

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

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

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

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

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

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

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

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

Neurobiological Interactions Between Stress and Alcohol

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

Hypothalamic pituitary adrenal axis

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

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

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

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

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

CRF system

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

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

Dynorphin system

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

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

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

Neuropeptide Y system

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

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

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

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

Norepinephrine system

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

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

(a subdivision of the autonomic nervous system, which mediates the flight-or-fight response) and thereby affect the function of many organ systems, in part through increased noradrenergic signaling. For example, psychosocial stress in mice has been shown to increase blood pressure via an $alpha_1$-adrenergic receptor–dependent mechanism.[70]

During withdrawal from chronic, high-dose alcohol exposure, increases in sympathetic activity contribute to aversive physiological symptoms, such as increased blood pressure, heart rate, and sweating, which are thought to contribute to relapse in abstinent individuals.[71] In studies of rats, blockade of $alpha_1$- and beta-adrenergic receptors[72,73] and activation of $alpha_2$-adrenergic autoreceptors[73] reduced alcohol withdrawal symptoms such as convulsions, tremors, and locomotor hyperactivity. In another study of rats, blockade of norepinephrine signaling during withdrawal attenuated alcohol drinking.[68] See the review by Vazey and colleagues[74] for further discussion of this topic.

Conclusion and Future Directions

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

Acknowledgments

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

Financial Disclosure

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

References

1. Keyes KM, Hatzenbuehler ML, Grant BF, et al. Stress and alcohol: Epidemiologic evidence. *Alcohol Res.* 2012;34(4):391-400. PMID: 23584105.
2. Lê AD, Quan B, Juzytch W, et al. Reinstatement of alcohol-seeking by priming injections of alcohol and exposure to stress in rats. *Psychopharmacology (Berl).* 1998;135(2):169-174. PMID: 9497022.
3. Mantsch JR, Baker DA, Funk D, et al. Stress-induced reinstatement of drug seeking: 20 years of progress. *Neuropsychopharmacology.* 2016;41(1):335-356. PMID: 25976297.
4. Noori HR, Helinski S, Spanagel R. Cluster and meta-analyses on factors influencing stress-induced alcohol drinking and relapse in rodents. *Addict Biol.* 2014;19(2):225-232. PMID: 24589296.
5. Meyer EM, Long V, Fanselow MS, et al. Stress increases voluntary alcohol intake, but does not alter established drinking habits in a rat model of posttraumatic stress disorder. *Alcohol Clin Exp Res.* 2013;37(4):566-574. PMID: 23126586.
6. McCool BA, Chappell AM. Early social isolation in male Long-Evans rats alters both appetitive and consummatory behaviors expressed during operant ethanol self-administration. *Alcohol Clin Exp Res.* 2009;33(2):273-282. PMID: 19032581.
7. Norman KJ, Seiden JA, Klickstein JA, et al. Social stress and escalated drug self-administration in mice I. Alcohol and corticosterone. *Psychopharmacology (Berl).* 2015;232(6):991-1001. PMID: 25242256.
8. Advani T, Hensler JG, Koek W. Effect of early rearing conditions on alcohol drinking and $5\text{-}HT_{1a}$ receptor function in C57BL/6J mice. *Int J Neuropsychopharmacol.* 2007;10(5):595-607. PMID: 17134528.
9. Manjoch H, Vainer E, Matar M, et al. Predator-scent stress, ethanol consumption and the opioid system in an animal model of PTSD. *Behav Brain Res.* 2016;306:91-105. PMID: 26965572.
10. Edwards S, Baynes BB, Carmichael CY, et al. Traumatic stress reactivity promotes excessive alcohol drinking and alters the balance of prefrontal cortex-amygdala activity. *Transl Psychiatry.* 2013;3:e296. PMID: 23982628.
11. Molander A, Vengeliene V, Heilig M, et al. Brain-specific inactivation of the *Crhr1* gene inhibits post-dependent and stress-induced alcohol intake, but does not affect relapse-like drinking. *Neuropsychopharmacology.* 2012;37(4):1047-1056. PMID: 22113086.
12. Anderson RI, Lopez MF, Becker HC. Forced swim stress increases ethanol consumption in C57BL/6J mice with a history of chronic intermittent ethanol exposure. *Psychopharmacology (Berl).* 2016;233(11):2035-2043. PMID: 26935824.
13. Spanagel R, Noori HR, Heilig M. Stress and alcohol interactions: Animal studies and clinical significance. *Trends Neurosci.* 2014;37(4):219-227. PMID: 24636458.

14. Gilpin NW, Weiner JL. Neurobiology of comorbid post-traumatic stress disorder and alcohol-use disorder. *Genes Brain Behav.* 2017;16(1):15-43. PMID: 27749004.
15. Valdez GR, Zorrilla EP, Roberts AJ, et al. Antagonism of corticotropin-releasing factor attenuates the enhanced responsiveness to stress observed during protracted ethanol abstinence. *Alcohol.* 2003;29(2):55-60. PMID: 12782246.
16. Breese GR, Overstreet DH, Knapp DJ, et al. Prior multiple ethanol withdrawals enhance stress-induced anxiety-like behavior: Inhibition by CRF_1- and benzodiazepine-receptor antagonists and a $5\text{-}HT_{1a}$-receptor agonist. *Neuropsychopharmacology.* 2005;30(9):1662-1669. PMID: 15726114.
17. Becker HC. Influence of stress associated with chronic alcohol exposure on drinking. *Neuropharmacology.* 2017;122:115-126. PMID: 28431971.
18. Fahlke C, Hård E, Hansen S. Facilitation of ethanol consumption by intracerebroventricular infusions of corticosterone. *Psychopharmacology (Berl).* 1996;127(2):133-139. PMID: 8888379.
19. Koenig HN, Olive MF. The glucocorticoid receptor antagonist mifepristone reduces ethanol intake in rats under limited access conditions. *Psychoneuroendocrinology.* 2004;29(8):999-1003. PMID: 15219650.
20. Simms JA, Haass-Koffler CL, Bito-Onon J, et al. Mifepristone in the central nucleus of the amygdala reduces yohimbine stress-induced reinstatement of ethanol-seeking. *Neuropsychopharmacology.* 2012;37(4):906-918. PMID: 22048462.
21. Whitaker AM, Gilpin NW. Blunted hypothalamo-pituitary adrenal axis response to predator odor predicts high stress reactivity. *Physiol Behav.* 2015;147:16-22. PMID: 25824191.
22. Whitaker AM, Farooq MA, Edwards S, et al. Post-traumatic stress avoidance is attenuated by corticosterone and associated with brain levels of steroid receptor co-activator-1 in rats. *Stress.* 2016;19(1):69-77. PMID: 26482332.
23. Yehuda R, Southwick SM, Nussbaum G, et al. Low urinary cortisol excretion in patients with posttraumatic stress disorder. *J Nerv Ment Dis.* 1990;178(6):366-369. PMID: 2348190.
24. Yehuda R, Bierer LM, Sarapas C, et al. Cortisol metabolic predictors of response to psychotherapy for symptoms of PTSD in survivors of the World Trade Center attacks on September 11, 2001. *Psychoneuroendocrinology.* 2009;34(9):1304-1313. PMID: 19411143.
25. Norrholm SD, Jovanovic T, Gerardi M, et al. Baseline psychophysiological and cortisol reactivity as a predictor of PTSD treatment outcome in virtual reality exposure therapy. *Behav Res Ther.* 2016;82:28-37. PMID: 27183343.
26. Lee S, Smith GW, Vale W, et al. Mice that lack corticotropin-releasing factor (CRF) receptors type 1 show a blunted ACTH response to acute alcohol despite up-regulated constitutive hypothalamic CRF gene expression. *Alcohol Clin Exp Res.* 2001;25(3):427-433. PMID: 11290855.
27. Richardson HN, Lee SY, O'Dell LE, et al. Alcohol self-administration acutely stimulates the hypothalamic-pituitary-adrenal axis, but alcohol dependence leads to a dampened neuroendocrine state. *Eur J Neurosci.* 2008;28(8):1641-1653. PMID: 18979677.
28. Tabakoff B, Jafee RC, Ritzmann RF. Corticosterone concentrations in mice during ethanol drinking and withdrawal. *J Pharm Pharmacol.* 1978;30(6):371-374. PMID: 26769.
29. Keedwell PA, Poon L, Papadopoulos AS, et al. Salivary cortisol measurements during a medically assisted alcohol withdrawal. *Addict Biol.* 2001;6(3):247-256. PMID: 11900603.
30. Rao RP, Anilkumar S, McEwen BS, et al. Glucocorticoids protect against the delayed behavioral and cellular effects of acute stress on the amygdala. *Biol Psychiatry.* 2012;72(6):466-475. PMID: 22572034.
31. Perusini JN, Meyer EM, Long VA, et al. Induction and expression of fear sensitization caused by acute traumatic stress. *Neuropsychopharmacology.* 2016;41(1):45-57. PMID: 26329286.
32. Vendruscolo LF, Estey D, Goodell V, et al. Glucocorticoid receptor antagonism decreases alcohol seeking in alcohol-dependent individuals. *J Clin Invest.* 2015;125(8):3193-3197. PMID: 26121746.
33. Lê AD, Harding S, Juzytsch W, et al. The role of corticotrophin-releasing factor in stress-induced relapse to alcohol-seeking behavior in rats. *Psychopharmacology (Berl).* 2000;150(3):317-324. PMID: 10923760.
34. Gehlert DR, Cippitelli A, Thorsell A, et al. 3-(4-chloro-2-morpholin-4-yl-thiazol-5-yl)-8-(1-ethylpropyl)-2,6-dimethyl-imidazo[1,2-b]pyridazine: A novel brain-penetrant, orally available corticotropin-releasing factor receptor 1 antagonist with efficacy in animal models of alcoholism. *J Neurosci.* 2007;27(10):2718-2726. PMID: 17344409.
35. Roltsch EA, Baynes BB, Mayeux JP, et al. Predator odor stress alters corticotropin-releasing factor-1 receptor (CRF1R)-dependent behaviors in rats. *Neuropharmacology.* 2014;79:83-89. PMID: 24269607.
36. Newman EL, Albrechet-Souza L, Andrew PM, et al. Persistent escalation of alcohol consumption by mice exposed to brief episodes of social defeat stress: Suppression by CRF-R1 antagonism. *Psychopharmacology (Berl).* 2018;235(6):1807-1820. PMID: 29696309.
37. Valdez GR, Roberts AJ, Chan K, et al. Increased ethanol self-administration and anxiety-like behavior during acute ethanol withdrawal and protracted abstinence: Regulation by corticotropin-releasing factor. *Alcohol Clin Exp Res.* 2002;26(10):1494-1501. PMID: 12394282.
38. Finn DA, Snelling C, Fretwell AM, et al. Increased drinking during withdrawal from intermittent ethanol exposure is blocked by the CRF receptor antagonist D-Phe-CRF(12-41). *Alcohol Clin Exp Res.* 2007;31(6):939-949. PMID: 17403068.
39. Funk CK, O'Dell LE, Crawford EF, et al. Corticotropin-releasing factor within the central nucleus of the amygdala mediates enhanced ethanol self-administration in withdrawn, ethanol-dependent rats. *J Neurosci.* 2006;26(44):11324-11332. PMID: 17079660.
40. Chu K, Koob GF, Cole M, et al. Dependence-induced increases in ethanol self-administration in mice are blocked by the CRF_1 receptor antagonist antalarmin and by CRF_1 receptor knockout. *Pharmacol Biochem Behav.* 2007;86(4):813-821. PMID: 17482248.
41. Gilpin NW, Richardson HN, Koob GF. Effects of CRF_1-receptor and opioid-receptor antagonists on dependence-induced increases in alcohol drinking by alcohol-preferring (P) rats. *Alcohol Clin Exp Res.* 2008;32(9):1535-1542. PMID: 18631323.
42. Phillips TJ, Reed C, Pastor R. Preclinical evidence implicating corticotropin-releasing factor signaling in ethanol consumption and neuroadaptation. *Genes Brain Behav.* 2015;14(1):98-135. PMID: 25565358.
43. Spierling SR, Zorrilla EP. Don't stress about CRF: Assessing the translational failures of CRF_1 antagonists. *Psychopharmacology (Berl).* 2017;234(9-10):1467-1481. PMID: 28265716.
44. Pomrenze MB, Fetterly TL, Winder DG, et al. The corticotropin releasing factor receptor 1 in alcohol use disorder: Still a valid drug target? *Alcohol Clin Exp Res.* 2017;41(12):1986-1999. PMID: 28940382.
45. Shirayama Y, Ishida H, Iwata M, et al. Stress increases dynorphin immunoreactivity in limbic brain regions and dynorphin antagonism produces antidepressant-like effects. *J Neurochem.* 2004;90(5):1258-1268. PMID: 15312181.
46. Land BB, Bruchas MR, Lemos JC, et al. The dysphoric component of stress is encoded by activation of the dynorphin kappa-opioid system. *J Neurosci.* 2008;28(2):407-414. PMID: 18184783.
47. Sperling RE, Gomes SM, Sypek EI, et al. Endogenous kappa-opioid mediation of stress-induced potentiation of ethanol-conditioned place preference and self-administration. *Psychopharmacology (Berl).* 2010;210(2):199-209. PMID: 20401606.
48. Funk D, Coen K, Lê AD. The role of kappa opioid receptors in stress-induced reinstatement of alcohol seeking in rats. *Brain Behav.* 2014;4(3):356-367. PMID: 24944865.
49. Kissler JL, Sirohi S, Reis DJ, et al. The one-two punch of alcoholism: Role of central amygdala dynorphins/kappa-opioid receptors. *Biol Psychiatry.* 2014;75(10):774-782. PMID: 23611261.
50. Anderson RI, Becker HC. Role of the dynorphin/kappa opioid receptor system in the motivational effects of ethanol. *Alcohol Clin Exp Res.* 2017;41(8):1402-1418. PMID: 28425121.
51. Karkhanis A, Holleran KM, Jones SR. Dynorphin/kappa opioid receptor signaling in preclinical models of alcohol, drug, and food addiction. *Int Rev Neurobiol.* 2017;136:53-88. PMID: 29056156.
52. Cohen H, Liu T, Kozlovsky N, et al. The neuropeptide Y (NPY)-ergic system is associated with behavioral resilience to stress exposure in an animal model of post-traumatic stress disorder. *Neuropsychopharmacology.* 2012;37(2):350-363. PMID: 21976046.
53. Cippitelli A, Damadzic R, Hansson AC, et al. Neuropeptide Y (NPY) suppresses yohimbine-induced reinstatement of alcohol seeking. *Psychopharmacology (Berl).* 2010;208(3):417-426. PMID: 20012021.

54. Roy A, Pandey SC. The decreased cellular expression of neuropeptide Y protein in rat brain structures during ethanol withdrawal after chronic ethanol exposure. *Alcohol Clin Exp Res.* 2002;26(6):796-803. PMID: 12068247.
55. Thorsell A, Slawecki CJ, Ehlers CL. Effects of neuropeptide Y and corticotropin-releasing factor on ethanol intake in Wistar rats: Interaction with chronic ethanol exposure. *Behav Brain Res.* 2005;161(1):133-140. PMID: 15904720.
56. Gilpin NW, Misra K, Koob GF. Neuropeptide Y in the central nucleus of the amygdala suppresses dependence-induced increases in alcohol drinking. *Pharmacol Biochem Behav.* 2008;90(3):475-480. PMID: 18501411.
57. Sparrow AM, Lowery-Gionta EG, Pleil KE, et al. Central neuropeptide Y modulates binge-like ethanol drinking in C57BL/6J mice via Y_1 and Y_2 receptors. *Neuropsychopharmacology.* 2012;37(6):1409-1421. PMID: 22218088.
58. Rimondini R, Thorsell A, Heilig M. Suppression of ethanol self-administration by the neuropeptide Y (NPY) Y_2 receptor antagonist BIIE0246: Evidence for sensitization in rats with a history of dependence. *Neurosci Lett.* 2005;375(2):129-133. PMID: 15670655.
59. Kallupi M, Vendruscolo LF, Carmichael CY, et al. Neuropeptide YY_2R blockade in the central amygdala reduces anxiety-like behavior but not alcohol drinking in alcohol-dependent rats. *Addict Biol.* 2014;19(5):755-757. PMID: 23639035.
60. Robinson SL, Marrero IM, Perez-Heydrich CA, et al. Medial prefrontal cortex neuropeptide Y modulates binge-like ethanol consumption in C57BL/6J mice. *Neuropsychopharmacology.* 2019;44(6):1132-1140. PMID: 30647448.
61. Kelley SP, Nannini MA, Bratt AM, et al. Neuropeptide-Y in the paraventricular nucleus increases ethanol self-administration. *Peptides.* 2001;22(3):515-522. PMID: 11287109.
62. Robinson SL, Thiele TE. The role of neuropeptide Y (NPY) in alcohol and drug abuse disorders. *Int Rev Neurobiol.* 2017;136:177-197. PMID: 29056151.
63. Thorsell A, Mathé AA. Neuropeptide Y in alcohol addiction and affective disorders. *Front Endocrinol (Lausanne).* 2017;8:178. PMID: 28824541.
64. Samuels ER, Szabadi E. Functional neuroanatomy of the noradrenergic locus coeruleus: Its roles in the regulation of arousal and autonomic function part I: Principles of functional organisation. *Curr Neuropharmacol.* 2008;6(3):235-253. PMID: 19506723.
65. Pacák K, Palkovits M, Kvetnanský R, et al. Effects of single or repeated immobilization on release of norepinephrine and its metabolites in the central nucleus of the amygdala in conscious rats. *Neuroendocrinology.* 1993;57(4):626-633. PMID: 8367029.
66. Cecchi M, Khoshbouei H, Morilak DA. Modulatory effects of norepinephrine, acting on alpha$_1$ receptors in the central nucleus of the amygdala, on behavioral and neuroendocrine responses to acute immobilization stress. *Neuropharmacology.* 2002;43(7):1139-1147. PMID: 12504920.
67. Lê AD, Funk D, Juzytsch W, et al. Effect of prazosin and guanfacine on stress-induced reinstatement of alcohol and food seeking in rats. *Psychopharmacology (Berl).* 2011;218(1):89-99. PMID: 21318567.
68. Walker BM, Rasmussen DD, Raskind MA, et al. Alpha$_1$-noradrenergic receptor antagonism blocks dependence-induced increases in responding for ethanol. *Alcohol.* 2008;42(2):91-97. PMID: 18358987.
69. Gilpin NW, Koob GF. Effects of beta-adrenoceptor antagonists on alcohol drinking by alcohol-dependent rats. *Psychopharmacology (Berl).* 2010;212(3):431-439. PMID: 20676608.
70. Lee DL, Webb RC, Brands MW. Sympathetic and angiotensin-dependent hypertension during cage-switch stress in mice. *Am J Physiol Regul Integr Comp Physiol.* 2004;287(6):R1394-R1398. PMID: 15308486.
71. Heilig M, Egli M, Crabbe JC, et al. Acute withdrawal, protracted abstinence and negative affect in alcoholism: Are they linked? *Addict Biol.* 2010;15(2):169-184. PMID: 20148778.
72. Trzaskowska E, Puciłowski O, Dyr W, et al. Suppression of ethanol tolerance and dependence in rats treated with DSP-4, a noradrenergic neurotoxin. *Drug Alcohol Depend.* 1986;18(4):349-353. PMID: 3816531.
73. Riihioja P, Jaatinen P, Oksanen H, et al. Dexmedetomidine, diazepam, and propranolol in the treatment of ethanol withdrawal symptoms in the rat. *Alcohol Clin Exp Res.* 1997;21(5):804-808. PMID: 9267529.
74. Vazey EM, den Hartog CR, Moorman DE. Central noradrenergic interactions with alcohol and regulation of alcohol-related behaviors. *Handb Exp Pharmacol.* 2018;248:239-260. PMID: 29687164.
75. Akbar M, Egli M, Cho Y-E, et al. Medications for alcohol use disorders: An overview. *Pharmacol Ther.* 2018;185:64-85. PMID: 29191394.
76. Lee MR, Weerts EM. Oxytocin for the treatment of drug and alcohol use disorders. *Behav Pharmacol.* 2016;27(8):640-648. PMID: 27603752.
77. Witkin JM, Statnick MA, Rorick-Kehn LM, et al. The biology of nociceptin/orphanin FQ (N/OFQ) related to obesity, stress, anxiety, mood, and drug dependence. *Pharmacol Ther.* 2014;141(3):283-299. PMID: 24189487.
78. Murphy NP. The nociceptin/orphanin FQ system as a target for treating alcoholism. *CNS Neurol Disord Drug Targets.* 2010;9(1):87-93. PMID: 20201819.
79. Rodriguez FD, Coveñas R. Targeting NPY, CRF/UCNs and NPS neuropeptide systems to treat alcohol use disorder (AUD). *Curr Med Chem.* 2017;24(23):2528-2558. PMID: 28302012.
80. Wise RA, Morales M. A ventral tegmental CRF-glutamate-dopamine interaction in addiction. *Brain Res.* 2010;1314:38-43. PMID: 19800323.
81. Martin-Fardon R, Zorrilla EP, Ciccocioppo R, et al. Role of innate and drug-induced dysregulation of brain stress and arousal systems in addiction: Focus on corticotropin-releasing factor, nociceptin/orphanin FQ, and orexin/hypocretin. *Brain Res.* 2010;1314:145-161. PMID: 20026088.

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

Alcohol Use Disorder and Antisocial and Borderline Personality Disorders

Ashley C. Helle, Ashley L. Watts, Timothy J. Trull, and Kenneth J. Sher

Ashley C. Helle, Ph.D., is a postdoctoral fellow in the Department of Psychological Sciences, University of Missouri-Columbia, Columbia, Missouri.

Ashley L. Watts, Ph.D., is a postdoctoral fellow in the Department of Psychological Sciences, University of Missouri-Columbia, Columbia, Missouri.

Timothy J. Trull, Ph.D., is a Curators' Distinguished Professor and a Byler Distinguished Professor in the Department of Psychological Sciences, University of Missouri-Columbia, Columbia, Missouri.

Kenneth J. Sher, Ph.D., is a Curators' Distinguished Professor in the Department of Psychological Sciences, University of Missouri-Columbia, Columbia, Missouri.

Alcohol use disorder (AUD) frequently co-occurs with other psychiatric disorders, including personality disorders, which are pervasive, persistent, and impairing. Personality disorders are associated with myriad serious outcomes, have a high degree of co-occurrence with substance use disorders, including AUD, and incur significant health care costs. This literature review focuses on co-occurring AUD and personality disorders characterized by impulsivity and affective dysregulation, specifically antisocial personality disorders and borderline personality disorders. Prevalence rates, potential explanations and causal models of co-occurrence, prognoses, and the status of existing treatment research are summarized. Several important future research considerations are relevant to these complex, co-occurring conditions. Research assessing mechanisms responsible for co-occurring AUD and antisocial personality disorder or borderline personality disorder will further delineate the underlying developmental processes and improve understanding of onset and courses. In addition, increased focus on the efficacy and effectiveness of treatments targeting underlying traits or common factors in these disorders will inform future prevention and treatment efforts, as interventions targeting these co-occurring conditions have relatively little empirical support.

KEY WORDS: **alcohol use disorder; antisocial personality disorder; borderline personality disorder; comorbidity**

Introduction

The quest to understand the etiology, course, and treatment of alcohol use disorder (AUD) has given rise to an extensive body of work on identifying factors that contribute to these phenomena. Many of these factors, such as temperament and personality traits, are common to multiple psychiatric conditions, and some, such as variants of alcohol metabolizing genes, are specific to AUD. This review describes the co-occurrence of AUD with antisocial personality disorder (ASPD) and borderline personality disorder (BPD). The prevalence and effects of

these personality disorders, their co-occurrence with AUD through the lens of several current models, and the treatment and overall implications of these complex co-occurrences are discussed.

The conceptualization and diagnostic criteria for AUD has evolved over the years and through editions of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM). For example, in the text revision of the fourth edition of the DSM (DSM-IV-TR) the conceptualization included alcohol abuse and dependence, which were categories that comprised two different symptom sets and required a number of criteria for diagnosis.[1] More recent conceptualizations of AUD are seen in the fifth edition of the DSM (DSM-5), which describes AUD as a single disorder with 11 criteria and includes a severity gradient designated by the number of criteria met (e.g., two to three symptoms constitute mild AUD).[2] Although this conceptualization inherently is still categorical, the changes are consistent with a transition toward dimensional approaches (e.g., severity can be graded across one set of symptoms).[3] Additional work needs to be done to capture a fully dimensional diagnosis for AUD.

Other diagnostic systems, such as the 11th revision of the *International Classification of Diseases* (ICD-11), have implemented new conceptualizations of AUD that differ from the alcohol abuse and dependence categories and that attempt to capture potential features of severity (e.g., harmful use diagnosis and recurrent problems).[4] Note that many of the studies reported in this review focus on previous DSM conceptualizations of AUD, such as the categories of alcohol abuse and dependence from the DSM-IV-TR. In addition, much of the work described here conceptualizes AUD as a categorical diagnosis, either present or absent, although support for a categorical AUD taxonomy is declining.[1] Differing AUD conceptualizations may affect the general consensus of research findings.

Personality disorder diagnoses and, more generally, psychopathology are migrating toward a dimensional classification system. For example, the ICD-11 includes a dimensional approach to personality disorder diagnosis.[4] For classifying personality disorders, there has been a call for and transition to dimensional approaches, and a number of the proposed models largely align with robust and well-validated models of personality.[5-8] The DSM-IV-TR personality disorder categories were retained in the DSM-5, but the DSM-5 (Section III: Emerging Measures and Models) proposes a new model that integrates dimensional aspects (e.g., dimensional personality traits) into a more traditional categorical classification model.[2] This hybrid categorical-dimensional model, the alternative DSM-5 model for personality disorders, is described in more detail in the following section.

Personality Disorders

Although the long-standing research aimed at identifying an "alcoholic personality"[9] has not been particularly fruitful, these efforts have nevertheless identified some personality traits, or constellations thereof, that are associated with increased risk for alcohol use and misuse. ASPD and BPD, both characterized by impulsivity, negative emotionality, and antagonism, are two such constellations. This review focuses on ASPD and BPD; however, personality disorders in general are the focus of some research presented and are noted throughout.

ASPD is characterized by behavior patterns that show a lack of regard for and violation of the rights of others, deceit, manipulation, and impulsivity that have occurred since age 15, in addition to evidence of conduct disorder before age 15.[2] BPD is conceptualized as a disorder of emotion dysregulation, impulsivity, suicidality, identity disturbance, and difficulties in interpersonal relationships. Although the DSM-5 classifies personality disorders categorically, the DSM-5 alternative, hybrid dimensional-categorical model of personality disorder describes these disorders in terms of broad personality domains (negative affectivity, detachment, antagonism, disinhibition, and psychoticism) and facets that are largely consistent with popular models of general personality, namely the five-factor model (see the section Trait Explanations for a detailed explanation of this model).[5] Individual personality disorders such as BPD are then characterized by specific traits, resulting in a hybrid model that describes the disorders in terms of both dimensional trait features (e.g., disinhibition) and categories (e.g., BPD).

Within the alternative DSM-5 model for personality disorders, ASPD and BPD are characterized by high levels of disinhibition,

with BPD additionally associated with high levels of negative affectivity, and ASPD additionally associated with high levels of antagonism. The ICD-11 conceptualizes personality disorders in a manner similar to the DSM-5 alternative model, such that dimensional traits (e.g., negative affectivity and disinhibition) are included in the diagnosis.[4] Further, in the ICD-11, these traits accompany a general diagnosis for mild, moderate, or severe personality disorder.

Prevalence

Epidemiological, community, and clinical psychiatric samples across all 10 categorical personality disorders have yielded prevalences ranging from 9% to 21% in community (nonclinical) samples[10] to approximately 31% in psychiatric outpatient samples,[11] with many individuals receiving diagnoses of more than one personality disorder. Across epidemiological studies, community prevalences for ASPD and BPD, individually, range from 1% to 4% and 1% to 6%, respectively.[10]

ASPD and BPD manifest in a broad array of maladaptive behaviors, including suicide, self-harm, aggression, criminal behavior, and substance misuse. Moreover, ASPD and BPD are associated with profound economic costs.[12-15] ASPD is associated with criminal offenses, with ASPD prevalence as large as 60% in prison populations,[12] and BPD is associated with higher suicide rates than those among the general population.[13] Both conditions are associated with higher rates of chronic illness, sleep disturbances, and health care utilization when compared to rates among individuals with no diagnosis of personality disorder.[14,15] Evidence shows that ASPD and BPD are related, and that they are serious psychiatric disorders associated with significant consequences, including consequences undergirded by poor emotional and behavioral control (e.g., excessive alcohol use), making the disorders likely to co-occur with AUD.

Diagnosis limitations and considerations

Because the literature on co-occurrence is largely based on categorical diagnoses, the limitations and biases of the current diagnosis classification system for personality disorders should be considered. A few well-documented limitations include lack of coverage of an individual's presenting concerns within the existing personality disorders, an arbitrary number of symptoms required for a diagnosis, large variation of presentation and symptoms within each personality disorder, and high co-occurrence of personality disorder categories.[7] Although substantial evidence supports dimensional as opposed to categorical conceptualizations of personality disorders, such as the five-factor model and the DSM-5 alternative model for personality disorders,[6] the current exploration of co-occurrence inherently relies on categorical diagnoses.[16]

Consequently, some apparent co-occurrence may be misleading because of overlapping features and aspects of diagnostic bias. Moreover, subthreshold levels of alcohol or personality pathology, such as binge drinking and impulsivity, which are not diagnostic categories, may co-occur before co-occurring alcohol and personality disorders can be detected. Thus, an association between personality disorders and AUD may manifest before formal diagnoses of either condition and may occur at varying levels of pathology. These factors should be considered when examining the conceptualization and diagnosis of co-occurring AUD and personality disorders.

Epidemiology of Co-Occurring AUD and Personality Disorders

Data from large epidemiological studies of psychopathology highlight the intertwined nature of AUD and personality disorders. In the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), which was a large, population-based study, 42% of participants who met the diagnostic criteria for any personality disorder also met the criteria for DSM-IV alcohol dependence.[10] Diagnostic co-occurrence tended to be most pronounced for Cluster B personality disorders, particularly ASPD and BPD, which are characterized by disinhibited and antagonistic forms of externalizing traits and behaviors. Recent reviews have indicated that of those individuals who met diagnostic criteria for BPD, 46% to 49%

also met diagnostic criteria for current AUD, and 59% met diagnostic criteria for lifetime AUD.[17] The prevalence of AUD among those diagnosed with ASPD was about 68%.[18] Among the general population or clinical samples of individuals with a current diagnosis of AUD or alcohol dependence, the prevalence of a BPD diagnosis was approximately 12% to 17%.[17] Among individuals with an AUD diagnosis, especially clinical samples, ASPD diagnoses were slightly more prevalent than BPD diagnoses, ranging from 19% to 22%.[18] Overall, AUD and ASPD and BPD overlap to a high degree.

Nevertheless, it is important to consider co-occurrence estimates in the context of their sampling limitations and interpretive challenges. For instance, many studies that establish populationwide estimates are cross-sectional, which precludes investigating the temporal relations among onset of AUD and personality disorders. Moreover, epidemiological data tend to rely on retrospective self-reports and lifetime diagnoses, which may be influenced by an individual's current emotional state (e.g., momentary affect) and general personality traits (e.g., level of negative emotionality).

In addition, when assessing for AUD, interviewers ask about the various consequences of alcohol use. In practice, establishing alcohol as a cause or contributor to a criterion (e.g., hazardous use) can be extremely challenging, but the assumption that alcohol played a causal or consequential role is often the default.[19] For example, if an individual routinely drinks while driving, is this behavior best understood as caused by AUD or by a more general pattern of rule-breaking and risky behavior? Therefore, some ostensible co-occurrence could be due to imprecision in the diagnostic criteria and how those criteria are assessed.

Explanations and Models of Co-Occurrence

Relevant to developing effective treatment and prevention are the mechanisms responsible for co-occurring AUD and personality disorders, that is, how or why personality disorders relate to AUDs. Explanations or models of co-occurring AUD and ASPD or BPD include common third-variable (e.g., trait) explanations and causal (e.g., AUD leads to personality disorder or personality disorder leads to AUD) explanations.

Trait explanations

Meta-analytic research suggests that personality disorders can be conceptualized as combinations, or even configurations, of extreme variants of general personality traits, which often are based on or correspond with the five-factor model.[8] The five-factor model encompasses the broad personality domains of neuroticism, extraversion, openness to experience, agreeableness, and conscientiousness, each of which includes narrower traits, termed "facets." Five-factor model domains and facets are dimensional, such that variability in personality lies on a continuum, with each pole reflecting an extreme of a basic trait. For simplicity, the two poles are described as high and low. For example, social cooperativeness and affiliation reflect high agreeableness, which is the opposite pole of antagonism. ASPD and BPD reflect low levels of agreeableness and conscientiousness and high levels of antagonism and impulsivity, respectively. ASPD and BPD have key associations with neuroticism and extraversion, although the personality trait associations are different for each disorder. BPD is characterized by high levels of neuroticism, whereas ASPD is not robustly associated with neuroticism but is characterized by high levels of two of neuroticism's facets: anger and impulsiveness. ASPD is characterized by high levels of the excitement-seeking facet of extraversion, whereas BPD is characterized by low levels of the warmth and positive emotionality facets of extraversion.

From a trait perspective, BPD and ASPD tend to relate similarly to AUD. This similarity can be explained by their overlapping profiles of general personality traits, particularly antagonism and impulsivity (disinhibition).[8] Although AUD often is conceptualized as an episodic condition rather than a chronic (trait-like) condition, it is increasingly apparent that AUD is related to several personality traits, and that these traits are similar to the traits that undergird ASPD, BPD, and other psychopathology in general. Trull

and Sher first established that alcohol abuse and dependence were characterized by high levels of neuroticism and low levels of agreeableness and conscientiousness.[20] Even with no diagnosis of AUD, features or patterns of alcohol use (e.g., ever using alcohol, quantity of alcohol use, and problematic use of alcohol) have been characterized by the same general personality traits (e.g., low conscientiousness).[21]

Of note, typologies for AUD have shown similar patterns of personality dimensions. Cloninger conceptualized two subtypes of AUD.[22] Type I had later onset (after age 25) and was associated with more anxious rather than impulsive features. Type II was more common in men and represented individuals who had early onset of alcohol use and frequent aggressive behaviors or arrests. Cloninger examined Type II AUD[22] and ASPD[23] separately and posited that they both had high novelty-seeking, low harm avoidance, and low reward dependence. This literature converges evidence that AUD on one hand and BPD and ASPD on the other have comparable relationships with general personality traits. Personality traits associated with aggressive, impulsive, and neurotic tendencies coalesce into the trait complexes of ASPD and BPD. These same trait complexes may contribute to a broad swath of externalizing forms of psychopathology, including alcohol and other substance misuse, risky sex, and other antisocial behavior.[24,25]

Developmental explanations

Adolescence and emerging adulthood are crucial developmental periods for understanding the sources and trajectory of AUD. In addition to being a period of heightened alcohol use,[26] adolescence tends to be associated with increased independence and acquisition of adult roles, exploration, and reward-seeking, as well as heightened levels of impulsivity, sensation-seeking, and, to a lesser extent, neuroticism.[27] Declines in alcohol use and reductions in personality trait levels across development have been called "maturing out"[28] and the "maturity principle,"[29] respectively. For example, late adolescence and emerging adulthood are associated with heightened prevalence of alcohol use and associated problems, the risk for which tends to decline with age. Although personality traits are believed to reflect a person's stable, internal disposition,[30] the transition from emerging to young adulthood is associated with normative changes in personality that reflect development toward psychological maturity, such as increases in emotional stability, self-control, and affiliation, and a shift to adult roles, such as committed relationships and parenthood.[27]

Researchers have empirically linked these developmental changes in personality and alcohol use.[31-33] Specifically, changes in impulsivity, neuroticism, and problematic alcohol use tend to correlate. Across adolescence and early adulthood, individuals with steeper declines in impulsivity and neuroticism demonstrated steeper declines in problematic alcohol use.[33] Individuals with a less substantial decline (or even an increase) in impulsivity and neuroticism had either increases, or smaller decreases, in problematic alcohol use. In the same vein, increases in risk-taking behavior across development are associated with increases in alcohol use among adolescents.[34,35] Still, there are individual differences in these general developmental trends, and some research suggests that personality may moderate AUD trajectories such that individuals who exhibit more impulsivity and neuroticism are more likely to experience more severe or chronic problems with alcohol. Relatedly, other research suggests variability in the developmental course of personality and alcohol use. Some individuals do not exhibit the maturity principle or mature out of alcohol use and instead exhibit chronic and stable alcohol, emotional, and behavioral control issues.[36,37]

Causal models

At least four major co-occurrence models, each of which contains different assumptions, explain how AUD relates to ASPD and BPD: the predisposition (or vulnerability) model, the complication (or scar) model, the exacerbation model, and the spectrum model.[38] The predisposition model purports that existing personality disorder elicits environmental responses, such as interpersonal or occupational problems, that provoke the onset of AUD. The temporal relationship between AUD and ASPD or BPD is reversed in the complication model, whereby AUD "scars" an individual's personality. For instance, neuroadaptation due to excessive

alcohol consumption across time might result in increased impulsivity or negative emotionality. The exacerbation model purports that ASPD and BPD add to or modify the manifestation, course, or expression of AUD, resulting in a distinctive AUD symptom profile. For instance, the presence of ASPD or BPD might increase the longevity of AUD or the extent of impairment. The spectrum model posits that the two disorders share common etiology.

Unfortunately, there is a relative paucity of empirical data for comparing these causal models. Existing data tend to support the predisposition model, in which the personality traits that undergird ASPD or BPD, particularly impulsivity, novelty-seeking, and neuroticism, tend to predict later alcohol problems, including AUD diagnosis[39] and onset.[40] Tracing the prospective, longitudinal relationships between impulsivity, neuroticism, and AUD across adolescence, Elkins and colleagues demonstrated that, after accounting for preexisting AUD, impulsivity and negative emotionality uniquely predicted new onset of AUD at age 20 after a baseline at age 17.[40]

Still other research suggests that personality may contribute to AUD by means of "niche-picking," whereby those with higher levels of certain personality traits select into high-risk environments for AUD. Park and colleagues found that undergraduates who scored highly on extraversion, despite not drinking heavily before college, were more likely to enter into the Greek system and thus were at increased risk for alcohol problems later in college.[41] Novelty-seeking (a facet of extraversion) also has been shown to have a proximal association with alcohol use, such that enhancement motives for drinking (to "get high" or enhance positive affect) were associated with sensation-seeking.[42] Together, these findings suggest that traits associated with ASPD and BPD, namely impulsivity and negative emotionality, appear to reflect broad liability for precocious alcohol use and AUD. Other traits associated with ASPD, namely novelty-seeking, tend to be associated with AUD both directly and indirectly by influencing selection into high-risk environments and motives for drinking.

The exacerbation model has some limited support, in that individuals with higher levels of outgoingness, impulsivity, aggression, and antisociality have been shown to be more likely to experience reinforcing, stress-dampening effects of alcohol.[43] The complication model also has some limited support, as demonstrated by research in which chronic, heavy-drinking adolescents exhibited short-term (1 year) increases in impulsive behavior.[35] Research also has implicated alcohol use as a predictor of aggressive and violent behavior.[24]

Of note, the temporal relatedness of alcohol use to changes in personality is relevant, such that "proximal, but not necessarily distal, alcohol use influences subsequent changes in personality."[44(p363)] Barnes wrote about the directionality of these relationships, noting that neuroticism tended to increase from "prealcoholic" to "clinical alcoholism," suggesting that such a change in personality may be a result of heavy or chronic drinking.[45]

The increase in neuroticism as alcohol use progresses aligns with neurobiological models of addiction, such as the allostatic model. This model posits that as addiction and compulsion for a substance progresses, negative affect increases in the absence of the substance, thereby contributing to substance use as negative reinforcement and becoming a continuing cyclical process.[46] The result is progressive allostatic changes of less positive and more negative mood. The persistence and reversibility of such presumed allostatic effects in the absence of continued heavy drinking is unclear.[45] Together, these findings highlight the intertwined, bidirectional connections between AUD and personality disorders, which likely cannot be described by one causal model.

The predisposition, complication, and exacerbation models presume independent etiology and onset of AUD and personality disorders. The spectrum model, in contrast, contains two major assumptions: Personality disorders and AUD are not distinct and rise, at least in part, from a set of common etiological factors. In addition, each disorder exists on a continuum or comprises multiple components along a continuum, ranging from subclinical traits to full-blown psychopathology. This model has received considerable support and also has historical roots. Cloninger first proposed that personality mediated genetic risk for AUD,[23] a theory that Slutske and colleagues later instantiated empirically.[47] Using a multivariate behavioral genetic twin design, these researchers found that the genetic variance associated with the broad trait of behavioral undercontrol, which included impulsivity, novelty-seeking, and aggression, accounted for 40% of

the genetic variance in alcohol dependence. These findings highlight the notion that the overlap of impulsivity and AUD originates from shared genetic mechanisms. Other work has demonstrated the same for AUD and BPD.[48] This shared genetic mechanism appears to give rise to externalizing behavior and psychopathology generally,[25] including AUD, other substance use disorder (SUD), conduct disorder, and antisocial behavior, rather than to impulsivity and AUD specifically.

These findings align with burgeoning evidence that internalizing and externalizing are two broad, heritable spectra of psychopathology. Internalizing is characterized by elevated negative emotionality, and externalizing is characterized by behavioral undercontrol and novelty-seeking. These two spectra are responsible for well-documented co-occurrence of psychiatric conditions that share phenomenological similarities.[49,50]

Contemporary taxonomies organize psychopathology dimensionally and hierarchically, with signs and symptoms of psychiatric conditions at the bottom of the hierarchy and externalizing and internalizing toward the top.[51] Much research places AUD, ASPD, and BPD squarely within externalizing. Externalizing can be broken down into disinhibited and antagonistic forms. Disinhibited externalizing comprises all substance-related disorders, whereas antagonistic externalizing comprises BPD as well as narcissistic, histrionic, and paranoid personality disorders. Notably, an antisocial behavior subfactor is believed to contribute to both the disinhibited and antagonistic externalizing subspectra and includes ASPD, conduct disorder, oppositional defiant disorder, attention deficit hyperactivity disorder, and intermittent explosive disorder. Some research suggests that BPD contributes to both externalizing and internalizing spectra,[52] although this possibility warrants more research attention.

Tully and Iacono proposed a hierarchical common liabilities model, which suggests that disorders (e.g., SUD and ASPD) that load onto the same psychopathology spectrum (e.g., externalizing) share common etiologic mechanisms.[50] As noted previously, a significant amount of evidence demonstrates that genes influence the covariation among disorders within externalizing and internalizing spectra, likely because of the common neurobiological mechanisms within each spectrum. These researchers offered that neurobiological mechanisms responsible for behavioral control and negative emotionality give rise to externalizing and internalizing, respectively, and likely are responsible for the co-occurrence among AUD, ASPD, and BPD. Specific genetic and other neurobiological mechanisms responsible for the development of AUD, ASPD, and BPD remain elusive. Further research is needed to identify more specific neurobiological mechanisms and biologically based endophenotypes implicated in the covariation among AUD, ASPD, and BPD, as well as those that are unique to each condition.[53]

Closely aligned to the spectrum perspective is the notion that AUD is heterogeneous and has two or more subtypes, each one associated with a different spectrum.[54,55] A number of these subtypes, such as Knight's "essential" type,[54] Babor's Type B,[55] and Cloninger's Type II,[22] are characterized by early onset and antisocial features. Thus, a relevant consideration is the possibility that the apparent co-occurrence between AUD and ASPD, for example, could be viewed as a subtype of AUD associated with the externalizing spectrum. Other subtypes, such as Knight's "reactive alcoholism," Babor's Type A, and Cloninger's Type I, are associated more with the internalizing spectrum. The subtyping literature highlights that the phenomenon of co-occurrence need not be viewed as the overlap of two relatively homogeneous conditions but could represent a single, relatively homogeneous, subtype of a heterogeneous condition.

Prognosis and Course

The course of AUD has much variation, with some cases limited to a specific period of time, others showing a relapsing and remitting pattern, and still others showing a persistent, chronic pattern.[56] Given the chronic nature of personality disorders, it seems likely that the presence of a co-occurring personality disorder would be associated with a more pernicious course of AUD. Relatively little research has used community-based samples to examine the course of AUD and personality disorders. However, existing data suggest co-occurring personality disorders augur poor prognoses. For example, in a general population sample, ASPD and BPD were significantly associated with persistence of alcohol dependence.[57]

Few in-depth investigations focus on the course of co-occurring AUD and ASPD. One study investigated the prevalence and course of SUD, including AUD, in a treatment-seeking sample that included a small number (n = 54) of individuals diagnosed with ASPD and a comparison sample (n = 552) of individuals with no ASPD diagnosis.[58] The investigators found that individuals diagnosed with ASPD started drinking alcohol at younger ages. However, AUD diagnosis and indicators of course (i.e., years of alcohol use, days of alcohol use in the past year, and days of abstinence) were not significantly different between the ASPD and non-ASPD groups.

A prospective, 10-year study focused on the course of BPD in a clinical sample and demonstrated a few major themes relevant to the course of SUD, including alcohol abuse and dependence.[59] The study included two groups of participants: those diagnosed with BPD and those diagnosed with another personality disorder. First, diagnoses of alcohol abuse and dependence were more common among participants who were diagnosed with BPD when compared with participants diagnosed with another personality disorder. Second, the prevalence of alcohol disorders similarly decreased over time for both groups, but it remained more common among those diagnosed with BPD.

The course of alcohol and substance disorders was examined more closely within the BPD group. The findings indicated that a vast majority (about 90%) of participants diagnosed with BPD had a remission of alcohol abuse or dependence by the 10-year follow-up.[59] Further, participants with BPD were more likely to experience remission than recurrences of use, and individuals who had BPD but no alcohol diagnosis at baseline were unlikely to develop an alcohol-related diagnosis during the study. Although this was not a treatment-specific study, the participants were recruited from inpatient samples and were in treatment for most of the study period.

In a review of treatment outcomes for individuals with co-occurring AUD and ASPD, Newton-Howes and colleagues concluded that alcohol outcomes and psychosocial functioning improved for those who stayed in treatment, although attrition was high.[60] The prognosis of co-occurring AUD and BPD is complex and difficult to disentangle given the varied pathways of each disorder. Intensive longitudinal studies are critical to assess variations in course and prognosis and can potentially provide indicators of co-occurrence and severity. Additional research in this area is needed.

Treatment

Clinical approaches to and research on treatment for personality disorders and SUD (including AUD) have often been tackled from a silo approach, such that one condition (e.g., addiction) is addressed separately from other psychological symptoms and disorders. Addressing personality disorders and SUD independently may be necessary in the clinical realm because of active substance use or threats of relapse thwarting treatment progress. Also, this approach may be necessary for research trials to maximize internal validity.

Depending on the severity of AUD, the detoxification period may first be necessary for the most accurate assessment of mood and personality. For example, increased irritability, anxiety, and low mood may be present primarily during heavy use or during withdrawal and may resolve if substance induced.[2,46] Assessment of affective symptoms after withdrawal or detoxification, incorporating known information about premorbid emotional and behavioral functioning when available, may help with diagnosis decisions and may serve to disentangle substance use from symptoms that may be associated with other disorders. However, some individuals do not receive treatment following detoxifications, as it is estimated that approximately 50% of detoxifications are followed by other treatment.[61]

Although co-occurring AUD or SUD and personality disorders understandably can make the assessment and intervention process challenging, it may be unrealistic to require that treatment focus on only one aspect at a time (e.g., target only substance use and then treat the personality disorder). For co-occurring AUD and BPD, a number of complications may arise, such as suicidal thoughts or behavior associated with the personality disorder, potentially undermining the ability to continue with AUD treatment. Thus, it may not always be possible or ideal to treat only the AUD or personality disorder and then proceed to treat the co-occurring disorder. These complexities are evident throughout the research literature, as few studies specifically examine co-occurring conditions.

Although treatments have been developed or adapted for AUD, SUD, BPD, and ASPD, there is limited empirical support for these treatments among samples of individuals diagnosed with AUD and co-occurring ASPD or BPD. Treatment research involving those with AUD and psychiatric disorders other than personality disorders also is limited, highlighting a major gap in empirical and intervention fields.[62] However, studies examining various disorder-specific treatments may be useful for treating the co-occurring disorders. It should be noted that a number of treatments may be effective for AUD and ASPD or BPD, but they have not been established as efficacious because of limited trials, small samples, or a broad focus on SUD or outcomes rather than AUD.[63] Regardless, research in which SUD is the focus may provide a starting point for further treatment research on alcohol use and AUD in the context of BPD and ASPD. (See Table 1 for brief descriptions of the treatments discussed in this article.)

Psychosocial treatments

There is modest support for treatments that show reductions in substance use while primarily treating BPD (i.e., dialectical behavior therapy, dynamic deconstructive psychotherapy, and dual-focused schema therapy) or while treating SUD in the context of BPD.[63,76] For example, one study examined dialectical behavior therapy for SUD and included medication assistance (e.g., replacing opiates with methadone) in the initial phases of treatment, called "transitional maintenance."[64] The investigators reported that at the end of treatment and at a 16-month follow-up, this treatment was more effective at reducing substance use than treatment as usual.

Other studies have found dialectical behavior therapy to be as effective at treating BPD symptoms for those with BPD and SUD as it is for participants with no SUD.[77] However, for the reduction of substance-related symptoms, no difference was found between the dialectical behavior therapy group and the treatment as usual group.[77] Although dialectical behavior therapy is primarily used for BPD, it was found to be acceptable in a clinical trial intended to treat men with both BPD and ASPD, most of whom also reported substance use.[78] Rates of alcohol and substance use did not change substantially in this trial, however. A review examining effective treatments for BPD determined that other treatments, such as mentalization-based therapy, showed promise, although the small number of studies limited the strength of possible recommendations.[79]

Effective treatments for ASPD are limited because few trials with sufficient evidence have been identified.[80] ASPD treatments showing promise, such as treatment with contingency management, often were originally developed for SUDs, further highlighting the possibility of a common thread across interventions for co-occurring AUD and ASPD or BPD.

As noted by Garofalo and Wright, treatment approaches based on transdiagnostic constructs such as neuroticism and disinhibition may target changes in the constructs.[24] Transdiagnostic factors, which have been described as "psychological constructs that are observed across a range of disorders" and "functionally causal mechanisms that inform the development of classes of disorders," align with a dimensional approach to both understanding and treating psychopathology.[81(p135)] Some treatment packages that use a transdiagnostic approach are acceptance and commitment therapy,[71] dialectical behavior therapy,[64] and the unified protocol.[72] Through various treatments and across an array of disorders, including BPD and SUD, research has supported changes related to transdiagnostic constructs, such as increases in emotion regulation.[82] In addition, indirect evidence supporting transdiagnostic approaches comes from research on personality and alcohol, which has revealed that using alcohol to cope with negative emotions mediates the association between personality traits, such as neuroticism and impulsivity, and reported alcohol problems.[83]

The integration of relevant treatment components such as emotion regulation skills, as opposed to stand-alone, single-disorder treatment, is highly compatible with transdiagnostic approaches. For example, contingency management, an effective treatment for AUD that uses behavioral principles to decrease ineffective and increase effective behaviors, has been incorporated into treatment for other disorders, such as dialectical behavior therapy.[70] Integrated treatment for personality disorders proposes using key treatment components from multiple therapies and developing a treatment

Table 1 Treatment Descriptions

Treatment	Key Concepts
Dialectical Behavior Therapy for SUD[64]	• Uses primarily behavioral approaches to target problematic behaviors organized within a predetermined hierarchy: life-threatening behaviors, behaviors that interfere with treatment, and behaviors that interfere with quality of life. • Targets substance use as the top behavior within the quality-of-life level of the hierarchy. • Includes skills training in four domains: mindfulness, emotion regulation, distress tolerance, and interpersonal effectiveness. • Includes 12 months of weekly individual therapy and group skills training, telephone coaching, and therapist consultation. • Emphasizes attachment strategies and dialectical abstinence. • Targets BPD and AUD simultaneously.
Dynamic Deconstructive Psychotherapy[65]	• Includes weekly individual therapy for 12 months. • Emphasizes alliance building, emotion identification, polarization awareness, judgment awareness and modification, and distance from idealizing fantasies. • Targets AUD and BPD simultaneously.
Dual-Focused Schema Therapy[66]	• Includes 6 months of individual and group therapies. • Emphasizes relapse prevention, stimulus control, interpersonal and emotion regulation skills, coping with craving, and identification and obstruction of maladaptive schemas. • Addresses substance use as a coping mechanism for emotions and conflicts related to schemas. • Targets AUD and BPD simultaneously.
Mentalization-Based Therapy[67]	• Uses psychodynamic-oriented treatment in group and individual formats. • Emphasizes improvement of mentalization within a safe, collaborative, and attached therapy relationship and focuses on internal states of self and others, with a goal of improving interpersonal relatedness, emotion regulation, and identity.
Metacognitive Treatment[68,69]	• Emphasizes metacognitive mastery, which is the "ability to use knowledge about mental states of self and others to cope with distress and solve social problems."[6(p22)] • Targets the cognitive attentional syndrome to modify unhelpful thinking patterns.
Contingency Management[70]	• Uses behavioral economics and operant conditioning principles to modify behaviors. • Emphasizes the use of reinforcements and consequences to increase desired (e.g., abstinence) and decrease undesired (e.g., substance use) behaviors.
Acceptance and Commitment Therapy[71]	• Emphasizes acceptance, values, and psychological flexibility through approaches such as mindfulness, identification of values and congruent living, and thought diffusion. • Offers individual and group formats.
Unified Protocol Therapy[72]	• Uses transdiagnostic treatment for emotional disorders. • Emphasizes emotional and physical awareness, appraisal flexibility, exposure, and emotion-driven behaviors.
Emotion-Regulation Therapy[73]	• Uses an acceptance-based approach to emotion regulation and is delivered in group format as an adjunctive treatment. • Includes participation in groups focused on improving skills such as, among others, impulse control and increasing awareness of emotions and their functions.
Integrated Therapy[74]	• Uses a coordinated, goal-oriented approach integrating evidence-based components of other treatments (e.g., dialectical behavior therapy and cognitive behavioral therapy) and follows a sequential process of therapy stages, beginning with establishing safety. • Emphasizes therapeutic relationships, motivation for change, and self-observation.
Mindfulness and Modification Therapy[75]	• Includes individual or group transdiagnostic treatment targeting behavioral dysregulation. • Emphasizes mindfulness and components of other treatments (e.g., acceptance and commitment therapy and dialectical behavior therapy).

Note: This table does not include all the available treatment approaches, and these descriptions are not intended to be comprehensive descriptions of the treatments or their components.

adapted to a patient's needs.[74] This approach inherently integrates key transdiagnostic components such as emotion regulation.

Research specific to co-occurring SUD and personality disorders (not exclusively ASPD and BPD) has concluded that using evidence-based strategies across therapies (e.g., combining contingency management with pharmacotherapy) tends to be most effective.[84] Research on AUD treatment has suggested that targeting specific traits, such as impulsiveness, using a matched treatment approach may effectively reduce alcohol use.[85] Mindfulness and modification therapy, which is another transdiagnostic treatment that targets behavioral dysregulation, has been shown to be related to decreased alcohol use and aggression among voluntary and court-ordered participants.[75] Collectively, the research suggests that identifying transdiagnostic features and treating conditions using evidence-supported treatment components that target those features may be a useful approach for treating co-occurring AUD and personality disorders.

Important to note is attrition during treatment for co-occurring AUD or SUD and personality disorders (e.g., 40% in a sample of SUD and BPD), and some evidence shows higher dropout rates for participants who had AUD and a personality disorder, as compared to those with AUD and no personality disorder.[60,64] This attrition is not surprising given that this population faces many challenges and complexities with the presenting problem and related to the broader environment and context. However, some studies have pointed to factors and existing strategies that may improve retention rates, such as making treatment enrollment contingent on predetermined attendance rules and establishing strong therapeutic relationships.[64] Other research has called for a focus on improving dual-diagnosis treatments and retention strategies for people with AUD.[60]

Pharmacological interventions

Comprehensive treatment for people with co-occurring AUD and ASPD or BPD often adopts a multifaceted approach using psychosocial and pharmacological interventions, including medication-assisted treatment for AUD and for BPD. Treatment for AUD may include acamprosate, naltrexone, disulfiram, or off-label medications such as topiramate,[86] and treatment for BPD may include naltrexone or topiramate.[87,88] This review focuses on studies of personality disorders and AUD outcomes and is organized by class of medication (i.e., alcohol-specific medications, anticonvulsants, and psychoactive drugs).

An investigation of the effectiveness of medications among individuals with alcohol dependence found that treatment with naltrexone, naltrexone plus disulfiram, or disulfiram plus placebo was just as effective for alcohol use outcomes among individuals who had co-occurring BPD or ASPD as it was among those with no ASPD or BPD.[89] In another study, Rohsenow and colleagues identified that the presence of antisocial traits was associated with increased effectiveness of naltrexone when compared to placebo.[90]

Before discussing pharmacotherapy for personality disorders, it should be noted that no medications for ASPD or BPD have been approved by the U.S. Food and Drug Administration. Further, no clinical trials have directly examined the efficacy of medications for people with co-occurring AUD and ASPD or BPD. Most studies have focused on one medication that targets similar mechanisms (e.g., impulsivity) across co-occurring conditions.

Research supporting specific pharmacotherapy for BPD is mixed, largely because the quality and quantity of studies provide insufficient evidence to evaluate efficacy.[91] Although the evidence regarding pharmacotherapy approaches for BPD is equivocal, certain medications, such as mood stabilizers and antipsychotics, matched to specific symptom presentations, such as affective lability, may show improvement for BPD symptoms, whereas selective serotonin reuptake inhibitors (SSRIs) demonstrate little to no efficacy.[87] Similarly, studies have preliminarily supported use of naltrexone for symptoms in the impulsive behavior domain and have reported reductions in self-injurious thoughts and behaviors.[87,88] The general recommendation is to use psychotherapy as the primary treatment with pharmacotherapy as an adjunctive treatment, since the efficacy of specific medications for BPD is not currently robust. Regarding ASPD, little evidence supports pharmacotherapy, and medications are often used to treat symptoms but not as a stand-alone treatment.[92]

Anticonvulsants such as topiramate and lamotrigine and atypical, second-generation

antipsychotics such as olanzapine have been investigated for the treatment of AUD and BPD. Topiramate has been identified as a possible off-label medication for AUD and BPD separately, suggesting a mechanism of action (of increased inhibitory control) applicable to both conditions.[93] A review of the medications for co-occurring AUD and BPD noted that topiramate was associated with fewer drinking days for participants who had AUD and with decreased anger intensity and reactions for those who had BPD.[63] In addition, topiramate and lamotrigine have demonstrated some effectiveness for decreasing craving, and lamotrigine has been associated with a decrease in impulsivity and anger symptoms of BPD.[63]

The atypical antipsychotics aripiprazole and olanzapine have been associated with impulsivity changes in BPD.[94,95] The effect of atypical antipsychotics on alcohol-related outcomes is mixed. An inconsistent effect for outcomes such as craving or abstinence has been reported across studies, and some research has suggested that genetic influences may act as primary moderators.[96,97]

The literature on antidepressants has demonstrated mixed results across studies and conditions. As previously mentioned, SSRIs generally have been ineffective in the treatment of BPD. On the other hand, research investigating AUD and ASPD has found more promising results. For instance, one study concluded that people with AUD and ASPD who also had another mood disorder benefited from antidepressants, whereas those with no additional mood disorder did not.[98] In a review of pharmacotherapy for ASPD, the tricyclic antidepressant nortriptyline was identified as one of the medications that was superior to placebo on at least one alcohol-related outcome (i.e., drinking days).[92] However, only one study reported this result, and several other outcomes, such as patient drinking ratings and craving, did not differ between the nortriptyline and placebo groups.[92] As with the atypical antipsychotics, antidepressants have been associated with different pharmacological outcomes across the traditional alcohol typologies. For individuals in the Type A typology group compared with those in the Type B group, the SSRI sertraline was more effective for the outcomes of fewer drinking days, time to relapse, and continuous abstinence period.[99]

Considerations and future directions for treatment

ASPD and BPD are complex and heterogeneous disorders often accompanied by other disorders, such as anxiety or depression. Therefore, as with psychosocial approaches, pharmacotherapy has focused on transdiagnostic dimensions or assumed neurophysiology rather than diagnosis categories for treatment of these disorders.[100] This focus has led to the investigation of medications specific to affective dysregulation or impulsive behavioral dysregulation instead of medications specific to a diagnosis.

Other treatment complexities include determining level of care based on severity of presentation and addressing barriers to accessible care. For individuals with severe AUD, inpatient or detoxification treatment may be a necessary component of treatment. For individuals with BPD, hospitalization or specific safety measures may be necessary if suicide is a risk. For those with ASPD, incarceration or other related limitations may be barriers to treatment. When any of these disorders occur independently or simultaneously, the risks of addiction, intentional or accidental overdose, and self-harm are heightened and may affect the course of treatment, particularly pharmacotherapy decisions.

Stepped care is an approach that can potentially help navigate the complex and evolving nature of co-occurring AUD and ASPD or BPD. Stepped care, or continuing care, has been associated with positive outcomes and longer treatment engagement for individuals with AUD or SUD.[101] Stepped care is an adaptive approach, evolving as the patient's needs change over time. For example, intensive in-person treatment may be necessary at times, whereas other modes of treatment with varying levels of intensity, such as telephone-based care or medication, may be more appropriate over the period of treatment. A flexible treatment team is necessary for a stepped care approach to work effectively. Time in treatment has been positively associated with better outcomes for people who have been diagnosed with co-occurring AUD and other psychopathology,[84] further highlighting the potential utility of stepped care approaches for these co-occurring conditions.

In conclusion, future research investigating pharmacotherapies specific to co-occurring conditions is needed. The extant research, often limited to a few studies per finding, generally concludes:

- Pharmacotherapies for AUD do not produce different outcomes for individuals with a co-occurring personality disorder.
- Some anticonvulsants and atypical antipsychotics may be useful for the treatment of AUD, BPD, and their co-occurrence.
- Research is mixed on the effectiveness of antidepressants for ASPD alone and for co-occurring AUD and ASPD, and effectiveness often depends on important moderating variables.

Evidence-based treatments for co-occurring AUD and personality disorders, in addition to realistic implementation and dissemination strategies that accommodate the treatments to these multifaceted disorders, need to be explored further.

Conclusion and Future Research

Existing research on ASPD and BPD has important implications for AUD, likely because the conditions have overlapping symptoms, personality correlates, course, and etiology. Research examining shared mechanisms can contribute to both prevention and targeted intervention efforts. In addition, using new and advanced methodological approaches to assess risk factors and precursors to misuse or relapse can advance understanding of mechanisms that contribute to initial and continued use along the developmental course.[26]

Key aspects of these disorders, such as affect disturbance, reflect volatility. Momentary changes in affect may be challenging to recall or assess using traditional methodological approaches such as asking individuals to rate their mood from a week ago. For example, craving and affect are episodic and may be assessed more accurately when they occur with natural cues. Precise assessment of such symptoms or constructs is relevant to diagnosis, because a comprehensive assessment of important criteria across relevant contexts can provide a full and more accurate picture of the individual's presenting concerns and symptoms. Research incorporating methodological approaches, such as ambulatory assessment and ecological momentary assessment, to assess mood and craving in the moment can resolve critical within-person patterns of response to evocative cues, allowing for a more nuanced and individual evaluation of associations between the behaviors (e.g., drinking) and traits (e.g., impulsivity) commonly related to personality disorders. These methods can facilitate the assessment of an individual's experience (e.g., mood and behaviors) in the moment.

Future research should also continue to focus on assessing and implementing the best methods, times, and places for providing treatment to individuals with co-occurring AUD and ASPD or BPD. For example, individuals with both AUD and a personality disorder tend to seek substance-specific treatment later than those with only AUD, although, on average, they use substances earlier, have greater impairment, and have shorter time to relapse.[102] Research must also address:

- Screening (where and when people get referred to treatment)
- Barriers to treatment entry (factors that influence failure to enter treatment)
- Identification of treatment approaches for co-occurring conditions
- Dissemination and implementation of effective treatment approaches

All three disorders have many similarities, including impulsivity and negative affect, externalizing correlates, and a likely potential for serious consequences and negative outcomes. Nevertheless, the ability to reach people diagnosed with these conditions and to treat them successfully is lacking in many ways. Individuals diagnosed with co-occurring AUD and ASPD, BPD, or another personality disorder clearly have an influential presence across health and legal systems.[12,15] However, people diagnosed with AUD alone have a surprisingly low treatment-seeking rate.[62] In the National Comorbidity Survey, results specific to treatment-seeking behaviors among individuals with co-occurring AUD and a psychiatric condition indicated that this population was more likely to receive specialty mental health treatment not focused on substance use (41%) than substance-specific interventions (16%).[62]

The contrast between patterns of treatment-seeking behaviors is stark for people diagnosed with AUD

alone versus those diagnosed with co-occurring conditions. Further understanding of the barriers to treatment for those with co-occurring conditions may provide points of change that positively influence the consumer's ability to access care that targets relevant transdiagnostic factors. Hopefully, as more investigators focus on the common factors underlying these conditions, newer assessment and treatment approaches can be developed, evaluated, and ultimately disseminated to settings and clinicians that serve these individuals.

Acknowledgments

This article was supported by National Institutes of Health grant T32AA013526.

Financial Disclosure

Timothy J. Trull is a scientific adviser for Boehringer Ingelheim.

References

1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed. Text rev. Washington, DC: American Psychiatric Association; 2000.
2. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Washington, DC: American Psychiatric Association; 2013.
3. Saha TD, Chou S, Grant, BF. Toward an alcohol use disorder continuum using item response theory: Results from the National Epidemiologic Survey on Alcohol and Related Conditions. *Psychol Med*. 2006;36:931-941. PMID: 16563205.
4. World Health Organization. *International Statistical Classification of Diseases and Related Health Problems*. 11th rev. Geneva, Switzerland: World Health Organization; 2018.
5. Costa PT, McCrae RR. Normal personality assessment in clinical practice: The NEO Personality Inventory. *Psychol Assess*. 1992;4:5-13.
6. Hopwood CJ, Kotov R, Krueger RF, et al. The time has come for dimensional personality disorder diagnosis. *Personal Ment Health*. 2018;12:82-86. PMID: 29226598.
7. Trull TJ, Durrett CA. Categorical and dimensional models of personality disorder. *Annu Rev Clin Psychol*. 2005;1:355-380. PMID: 17716092.
8. Samuel DB, Widiger TA. A meta-analytic review of the relationships between the five-factor model and DSM-IV-TR personality disorders: A facet level analysis. *Clin Psychol Rev*. 2008;28:1326-1342. PMID: 18708274.
9. Armstrong JD. The search for the alcoholic personality. *Ann Am Acad Polit Soc Sci*. 1958;315:40-47.
10. Trull TJ, Jahng S, Tomko RL, et al. Revised NESARC personality disorder diagnoses: Gender, prevalence, and comorbidity with substance dependence disorders. *J Pers Disord*. 2010;24:412-426. PMID: 20695803.
11. Zimmerman M, Rothschild L, Chelminski I. The prevalence of DSM-IV personality disorders in psychiatric outpatients. *Am J Psychiatry*. 2005;162:1911-1918. PMID: 16199838.
12. Moran P. The epidemiology of antisocial personality disorder. *Soc Psychiatry Psychiatr Epidemiol*. 1999;34:231-242. PMID: 10396164.
13. McCloskey MS, Ammerman BA. Suicidal behavior and aggression-related disorders. *Curr Opin Psychol*. 2018;22:54-58. PMID: 28829989.
14. Dixon-Gordon KL, Conkey LC, Whalen DJ. Recent advances in understanding physical health problems in personality disorders. *Curr Opin Psychol*. 2018;21:1-5. PMID: 28915400.
15. Quirk SE, Berk M, Chanen AM, et al. Population prevalence of personality disorder and associations with physical health comorbidities and health care service utilization: A review. *Personal Disord*. 2016;7:136-146. PMID: 26461047.
16. Lilienfeld SO, Waldman ID, Israel AC. A critical examination of the use of the term and concept of comorbidity in psychopathology research. *Clin Psych*. 1994;1:71-83.
17. Trull TJ, Freeman LK, Vebares TJ, et al. Borderline personality disorder and substance use disorders: An updated review. *Borderline Personal Disord Emot Dysregul*. 2018;5:15-27. PMID: 30250740.
18. Trull TJ, Solhan MB, Brown WC, et al. Substance use disorders and personality disorders. In: Sher KJ, ed. *The Oxford Handbook of Substance Use and Substance Use Disorders*. Vol 2. New York, NY: Oxford University Press; 2016:116-148.
19. Martin CS, Langenbucher JW, Chung T, et al. Truth or consequences in the diagnosis of substance use disorders. *Addiction*. 2014;109:1773-1778. PMID: 24913314.
20. Trull TJ, Sher KJ. Relationship between the five-factor model of personality and Axis I disorders in a nonclinical sample. *J Abnorm Psychol*. 1994;103:350-360. PMID: 8040504.
21. Lejuez CW, Magidson JF, Mitchell SH, et al. Behavioral and biological indicators of impulsivity in the development of alcohol use, problems, and disorders. *Alcohol Clin Exp Res*. 2010;34:1334-1345. PMID: 20491733.
22. Cloninger CR. Neurogenetic adaptive mechanisms in alcoholism. *Science*. 1987;236:410-416. PMID: 2882604.
23. Cloninger CR. A systematic method for clinical description and classification of personality variants: A proposal. *Arch Gen Psychiatry*. 1987;44:573-588. PMID: 3579504.
24. Garofalo C, Wright, AGC. Alcohol abuse, personality disorders, and aggression: The quest for a common underlying mechanism. *Aggress Violent Behav*. 2017;34:1-8.
25. Krueger RF, Markon KE, Patrick CJ, et al. Externalizing psychopathology in adulthood: A dimensional-spectrum conceptualization and its implications for DSM-V. *J Abnorm Psychol*. 2005;114:537-550. PMID: 16351376.
26. Chassin L, Sher KJ, Hussong A, et al. The developmental psychopathology of alcohol use and alcohol disorders: Research achievements and future directions. *Dev Psychopathol*. 2013;25:1567-1584. PMID: 24342856.
27. Roberts BW, Walton KE, Viechtbauer W. Patterns of mean-level change in personality traits across the life course: A meta-analysis of longitudinal studies. *Psychol Bull*. 2006;132:1-25. PMID: 16435954.
28. Littlefield AK, Winograd RP. Maturing out. In: Miller P, ed. *Principles of Addiction: Comprehensive Addictive Behaviors and Disorders*. San Diego, CA: Academic Press; 2013:363-370.
29. Caspi A, Roberts BW, Shiner RL. Personality development: Stability and change. *Annu Rev Psychol*. 2005;56:453-484. PMID: 15709943.
30. McCrae RR, Costa PT, Ostendorf F, et al. Nature over nurture: Temperament, personality, and life span development. *J Pers Soc Psychol*. 2000;78:173-186. PMID: 10653513.
31. Hicks BM, Durbin CE, Blonigen DM, et al. Relationship between personality change and the onset and course of alcohol dependence in young adulthood. *Addiction*. 2012;107:540-548. PMID: 21851441.
32. Iacono WG, Malone SM, McGue M. Behavioral disinhibition and the development of early-onset addiction: Common and specific influences. *Annu Rev Clin Psychol*. 2008;4:325-348. PMID: 18370620.
33. Littlefield AK, Sher KJ, Wood PK. Is "maturing out" of problematic alcohol involvement related to personality change? *J Abnorm Psychol*. 2009;118:360-374. PMID: 19413410.
34. MacPherson L, Magidson JF, Reynolds EK, et al. Changes in sensation seeking and risk-taking propensity predict increases in alcohol use among early adolescents. *Alcohol Clin Exp Res*. 2010;34:1400-1408. PMID: 20491737.
35. White HR, Marmorstein NR, Crews FT, et al. Associations between heavy drinking and changes in impulsive behavior among adolescent boys. *Alcohol Clin Exp Res*. 2011;35:295-303. PMID: 21073485.
36. Johnson W, Hicks BM, McGue M, et al. Most of the girls are alright, but some aren't: Personality trajectory groups from ages 14 to 24 and some associations with outcomes. *J Pers Soc Psychol*. 2007;93:266-284. PMID: 17645399.

37. Robins RW, Fraley RC, Roberts BW, et al. A longitudinal study of personality change in young adulthood. *J Pers.* 2001;69:617-640. PMID: 11497032.
38. Krueger RF, Tackett JL. Personality and psychopathology: Working toward the bigger picture. *J Pers Disord.* 2003;17:109-128. PMID: 12755325.
39. Sher KJ, Trull TJ, Bartholow B, et al. Personality and alcoholism: Issues, methods, and etiological processes. In: Blane H, Leonard K, eds. *Psychological Theories of Drinking and Alcoholism.* 2nd ed. New York, NY: Plenum; 1999:55-105.
40. Elkins IJ, King SM, McGue M, et al. Personality traits and the development of nicotine, alcohol, and illicit drug disorders: Prospective links from adolescence to young adulthood. *J Abnorm Psychol.* 2006;115:26-39. PMID: 16492093.
41. Park A, Sher KJ, Wood PK, et al. Dual mechanisms underlying accentuation of risky drinking via fraternity/sorority affiliation: The role of personality, peer norms, and alcohol availability. *J Abnorm Psychol.* 2009;118:241-255. PMID: 19413401.
42. Cooper ML, Frone MR, Russell M, et al. Drinking to regulate positive and negative emotions: A motivational model of alcohol use. *J Pers Soc Psychol.* 1995;69:990-1005. PMID: 7473043.
43. Sher KJ, Levenson RW. Risk for alcoholism and individual differences in the stress-response-dampening effect of alcohol. *J Abnorm Psychol.* 1982;91:350-367. PMID: 7142573.
44. Littlefield AK, Sher KJ. Personality and substance use disorders. In: Sher KJ, ed. *The Oxford Handbook of Substance Use and Substance Use Disorders.* Vol 1. New York, NY: Oxford University Press; 2016:351-374.
45. Barnes GE. The alcoholic personality: A reanalysis of the literature. *J Stud Alcohol.* 1979;40:571-634. PMID: 385996.
46. Koob GF, Le Moal M. Drug addiction, dysregulation of reward, and allostasis. *Neuropsychopharmacology.* 2001;24:97-129. PMID: 11120394.
47. Slutske WS, Heath AC, Madden PA, et al. Personality and the genetic risk for alcohol dependence. *J Abnorm Psychol.* 2002;111:124-133. PMID: 11871377.
48. Bornovalova MA, Hicks BM, Iacono WG, et al. Longitudinal twin study of borderline personality disorder traits and substance use in adolescence: Developmental change, reciprocal effects, and genetic and environmental influences. *Personal Disord.* 2013;4:23-32. PMID: 22642461.
49. Krueger RF, Markon KE. Reinterpreting comorbidity: A model-based approach to understanding and classifying psychopathology. *Annu Rev Clin Psychol.* 2006;2:111-133. PMID: 17716066.
50. Tully EC, Iacono WG. An integrative common liabilities model for the comorbidity of substance use disorders with externalizing and internalizing disorders. In: Sher KJ, ed. *The Oxford Handbook of Substance Use and Substance Use Disorders.* Vol 2. New York, NY: Oxford University Press; 2016:187-214.
51. Kotov R, Krueger RF, Watson D, et al. The Hierarchical Taxonomy of Psychopathology (HiTOP): A dimensional alternative to traditional nosologies. *J Abnorm Psychol.* 2017;126:454-477. PMID: 28333488.
52. Eaton NR, Krueger RF, Keyes KM, et al. Borderline personality disorder co-morbidity: Relationship to the internalizing-externalizing structure of common mental disorders. *Psychol Med.* 2011;41:1041-1050. PMID: 20836905.
53. Kwako LE, Momenan R, Litten RZ, et al. Addictions Neuroclinical Assessment: A neuroscience-based framework for addictive disorders. *Biol Psychiatry.* 2016;80:179-189. PMID: 26772405.
54. Knight RP. The dynamics and treatment of chronic alcohol addiction. *Bull Menninger Clin.* 1937;1:233-250.
55. Babor TF, Hofmann M, DelBoca FK, et al. Types of alcoholics, I: Evidence for an empirically derived typology based on indicators of vulnerability and severity. *Arch Gen Psychiatry.* 1992;49:599-608. PMID: 1637250.
56. Jacob T, Bucholz KK, Sartor CE, et al. Drinking trajectories from adolescence to the mid-forties among alcohol dependent males. *J Stud Alcohol.* 2005;66:745-755. PMID: 16459936.
57. Hasin DS, Fenton MC, Skodol A, et al. Personality disorders and the 3-year course of alcohol, drug, and nicotine use disorders. *Arch Gen Psychiatry.* 2011;68(11):1158-1167. PMID: 22065531.
58. Westermeyer J, Thuras P. Association of antisocial personality disorder and substance disorder morbidity in a clinical sample. *Am J Drug Alcohol Abuse.* 2005;31:93-110. PMID: 15768573.
59. Zanarini MC, Frankenbur FR, Weingeroff JL, et al. The course of substance use disorders in patients with borderline personality disorder and Axis II comparison subjects: A 10-year follow-up study. *Addiction.* 2011;106:342-348. PMID: 21083831.
60. Newton-Howes GM, Foulds JA, Guy NH, et al. Personality disorder and alcohol treatment outcome: Systematic review and meta-analysis. *Br J Psychiatry.* 2017;211:22-30. PMID: 28385703.
61. Mark TL, Dilonardo JD, Chalk M, et al. Factors associated with the receipt of treatment following detoxification. *J Subst Abuse Treat.* 2003;24:299-304. PMID: 12867203.
62. Petrakis IL, Gonzalez G, Rosenheck R, et al. Comorbidity of alcoholism and psychiatric disorders: An overview. *Alcohol Res Health.* 2002;26:81-89.
63. Gianoli MO, Jane JS, O'Brien E, et al. Treatment for comorbid borderline personality disorder and alcohol use disorders: A review of the evidence and future recommendations. *Exp Clin Psychopharmacol.* 2012;20:333-344. PMID: 22686496.
64. Linehan MM, Schmidt H III, Dimeff LA, et al. Dialectical behavior therapy for patients with borderline personality disorder and drug-dependence. *Am J Addict.* 1999;8:279-292. PMID: 10598211.
65. Gregory RJ, Remen AL. A manual-based psychodynamic therapy for treatment-resistant borderline personality disorder. *Psychotherapy.* 2008;45:15-27. PMID: 22122362.
66. Ball SA. Manualized treatment for substance abusers with personality disorders: Dual focus schema therapy. *Addict Behav.* 1998;23:883-891. PMID: 9801723.
67. Bateman AW, Fonagy P. Mentalization-based treatment of BPD. *J Pers Disord.* 2004;18:36-51. PMID: 15061343.
68. Dimaggio G, Montano A, Popolo R, et al. *Metacognitive Interpersonal Therapy for Personality Disorders: A Treatment Manual.* London, UK: Routledge; 2015.
69. Outcalt J, Dimaggio G, Popolo R, et al. Metacognition moderates the relationship of disturbances in attachment with severity of borderline personality disorder among persons in treatment of substance use disorders. *Compr Psychiatry.* 2016;64:22-28. PMID: 26541558.
70. Prendergast M, Podus D, Finney J, et al. Contingency management for treatment of substance use disorders: A meta-analysis. *Addiction.* 2006;101:1546-1560. PMID: 17034434.
71. Hayes SC, Luoma JB, Bond FW, et al. Acceptance and commitment therapy: Model, processes and outcomes. *Behav Res Ther.* 2006;44:1-25. PMID: 16300724.
72. Barlow DH, Farchione TJ, Sauer-Zavala S, et al. *Unified Protocol for Transdiagnostic Treatment of Emotional Disorders: Therapist Guide.* 2nd ed. New York, NY: Oxford University Press; 2017.
73. Gratz KL, Gunderson JG. Preliminary data on an acceptance-based emotion regulation group intervention for deliberate self-harm among women with borderline personality disorder. *Behav Ther.* 2006;37:25-35. PMID: 16942958.
74. Livesley WJ. Integrated treatment: A conceptual framework for an evidence-based approach to the treatment of personality disorder. *J Pers Disord.* 2012;26:17-42. PMID: 22369165.
75. Wupperman P, Cohen MG, Haller DL, et al. Mindfulness and modification therapy for behavioral dysregulation: A comparison trial focused on substance use and aggression. *J Clin Psychol.* 2015;71:964-978. PMID: 26287444.
76. Lee NK, Cameron J, Jenner L. A systematic review of interventions for co-occurring substance use and borderline personality disorders. *Drug Alcohol Rev.* 2015;34:663-672. PMID: 25919396.
77. van den Bosch LM, Verheul R, Schippers GM, et al. Dialectical behavior therapy of borderline patients with and without substance use problems: Implementation and long-term effects. *Addict Behav.* 2002;27:911-923. PMID: 12369475.
78. Wetterborg D, Dehlbom P, Långström N, et al. Dialectical behavior therapy for men with borderline personality disorder and antisocial behavior: A clinical trial. *J Pers Disord.* 2018;32:1-18. PMID: 30355023.

79. Stoffers-Winterling JM, Völlm BA, Rücker G, et al. Psychological therapies for people with borderline personality disorder. *Cochrane Database Syst Rev.* 2012;8:CD005652. PMID: 22895952.
80. Gibbon S, Duggan C, Stoffers J, et al. Psychological interventions for antisocial personality disorder. *Cochrane Database Syst Rev.* 2010;6:CD007668. PMID: 20556783.
81. Sauer-Zavala S, Gutner CA, Farchione TJ, et al. Current definitions of "transdiagnostic" in treatment development: A search for consensus. *Behav Ther.* 2017;48:128-138. PMID: 28077216.
82. Sloan E, Hall K, Moulding R, et al. Emotion regulation as a transdiagnostic treatment construct across anxiety, depression, substance, eating and borderline personality disorders: A systematic review. *Clin Psychol Rev.* 2017;57:141-163. PMID: 28941927.
83. Littlefield AK, Sher KJ, Wood PK. Do changes in drinking motives mediate the relation between personality change and "maturing out" of problem drinking? *J Abnorm Psychol.* 2010;119:93-105. PMID: 20141246.
84. Kelly TM, Daley DC, Douaihy AB. Treatment of substance abusing patients with comorbid psychiatric disorders. *Addict Behav.* 2012;37:11-24. PMID: 21981788.
85. Conrod PJ. Personality-targeted interventions for substance use and misuse. *Curr Addict Rep.* 2016;3:426-436. PMID: 27909645.
86. Jonas DE, Amick HR, Feltner C, et al. Pharmacotherapy for adults with alcohol use disorders in outpatient settings: A systematic review and meta-analysis. *JAMA.* 2014;311:1889-1900. PMID: 24825644.
87. Lieb K, Völlm B, Rücker G, et al. Pharmacotherapy for borderline personality disorder: Cochrane systematic review of randomised trials. *Br J Psychiatry.* 2010;196:4-12. PMID: 20044651.
88. Sonne S, Rubey R, Brady K, et al. Naltrexone treatment of self-injurious thoughts and behaviors. *J Nerv Ment Dis.* 1996;184:192-195. PMID: 8600226.
89. Ralevski E, Ball S, Nich C, et al. The impact of personality disorders on alcohol-use outcomes in a pharmacotherapy trial for alcohol dependence and comorbid Axis I disorders. *Am J Addict.* 2007;16:443-449. PMID: 18058408.
90. Rohsenow DJ, Miranda R Jr, McGeary JE, et al. Family history and antisocial traits moderate naltrexone's effects on heavy drinking in alcoholics. *Exp Clin Psychopharmacol.* 2007;15:272-281. PMID: 17563214.
91. Stoffers J, Völlm BA, Rücker G, et al. Pharmacological interventions for borderline personality disorder. *Cochrane Database Syst Rev.* 2010;6:CD005653. PMID: 20556762.
92. Khalifa N, Duggan C, Stoffers J, et al. Pharmacological interventions for antisocial personality disorder. *Cochrane Database Syst Rev.* 2010;8:CD007667. PMID: 20687091.
93. Rubio G, Ponce G, Jiménez-Arriero MA, et al. Effects of topiramate in the treatment of alcohol dependence. *Pharmacopsychiatry.* 2004;38:37-40. PMID: 14750047.
94. Soler J, Pascual JC, Campins J, et al. Double-blind, placebo-controlled study of dialectical behavior therapy plus olanzapine for borderline personality disorder. *Am J Psychiatry.* 2005;162:1221-1224. PMID: 15930077.
95. Zanarini MC, Frankenburg FR. Olanzapine treatment of female borderline personality disorder patients: A double-blind, placebo-controlled pilot study. *J Clin Psychiatry.* 2001;62:849-854. PMID: 11775043.
96. Hutchison KE, Wooden A, Swift RM, et al. Olanzapine reduces craving for alcohol: A DRD4 VNTR polymorphism by pharmacotherapy interaction. *Neuropsychopharmacology.* 2003;28:1882-1888. PMID: 12888781.
97. Martinotti G, DiNicola M, Di Giannantonio M, et al. Aripiprazole in the treatment of patients with alcohol dependence: A double-blind comparison trial vs. naltrexone. *J Psychopharmacol.* 2009;23;123-129. PMID: 18515460.
98. Penick EC, Powell BJ, Campbell J, et al. Pharmacological treatment for antisocial personality disorder alcoholics: A preliminary study. *Alcohol Clin Exp Res.* 1996;20:477-484. PMID: 8727240.
99. Pettinati HM, Volpicelli JR, Kranzler HR, et al. Sertraline treatment for alcohol dependence: Interactive effects of medication and alcoholic subtype. *Alcohol Clin Exp Res.* 2000;24:1041-1049. PMID: 10924008.
100. Soloff PH. Algorithms for pharmacological treatment of personality dimensions: Symptom-specific treatments for cognitive-perceptual, affective, and impulsive-behavioral dysregulation. *Bull Menninger Clin.* 1998;62:195-214. PMID: 9604516.
101. McKay JR. Continuing care in the treatment of addictive disorders. *Curr Psychiatry Rep.* 2006;8:355-362. PMID: 16968615.
102. Zikos E, Gill KJ, Charney DA. Personality disorders among alcoholic outpatients: Prevalence and course in treatment. *Can J Psychiatry.* 2010;55:65-73. PMID: 20181301.

Cite this as:
Alcohol Res. 2019;40(1):05. **https://doi.org/10.35946/arcr.v40.1.05.**

Alcohol Use Disorder and Schizophrenia or Schizoaffective Disorder

Luke Archibald, Mary F. Brunette, Diana J. Wallin, and Alan I. Green

Schizophrenia and schizoaffective disorder are schizophrenia spectrum disorders that cause significant disability. Among individuals who have schizophrenia or schizoaffective disorder, alcohol use disorder (AUD) is common, and it contributes to worse outcomes than for those who do not have co-occurring substance use disorder. Common neurobiological mechanisms, including dysfunction in brain reward circuitry, may explain the high rates of co-occurrence of schizophrenia and AUD or other substance use disorders. Optimal treatment combines pharmacologic intervention and other therapeutic modalities to address both the psychotic disorder and AUD. Further research on the etiology of these co-occurring disorders and on treatment of affected individuals is needed.

KEY WORDS: **addiction; alcohol; pharmacotherapy; schizoaffective disorder; schizophrenia**

Luke Archibald, M.D., is an assistant professor in the Department of Psychiatry, Geisel School of Medicine at Dartmouth, Hanover, New Hampshire.

Mary F. Brunette, M.D., is an associate professor in the Department of Psychiatry, Geisel School of Medicine at Dartmouth, Hanover, New Hampshire.

Diana J. Wallin, Ph.D., is a postdoctoral fellow in the Department of Psychiatry, Geisel School of Medicine at Dartmouth, Hanover, New Hampshire.

Alan I. Green, M.D., is the Raymond Sobel Professor of Psychiatry, a professor in the Department of Molecular and Systems Biology, and the chair of the Department of Psychiatry, Geisel School of Medicine at Dartmouth, as well as the director, Dartmouth Clinical and Translational Science Institute, Dartmouth College, Hanover, New Hampshire.

Introduction

Schizophrenia and schizoaffective disorder are heterogeneous psychotic disorders that often cause significant disability, with symptoms that include delusions, hallucinations, disorganization, and cognitive impairment.[1] In schizoaffective disorder, the psychotic symptoms are present, along with mood episodes of depression or mania.[2] People with these schizophrenia spectrum disorders have high rates of co-occurring substance use disorder, including alcohol use disorder (AUD). This article provides an updated review of the epidemiology, neurobiologic basis of co-occurrence, assessment, and treatment of people with co-occurring AUD and schizophrenia or schizoaffective disorder.

Epidemiology

The lifetime prevalence of schizophrenia is estimated to be about 1%.[1] The lifetime prevalence of schizoaffective disorder is unknown,

given changes in diagnostic criteria and challenges in differentiating this disorder from other diagnoses, but it is believed to be less common than schizophrenia, with regional estimates between 0.3% and 1.1%.[2,3]

Individuals with these psychotic disorders have three times the risk of heavy alcohol use relative to the general population.[4,5] One meta-analysis of individuals with schizophrenia found a lifetime prevalence of AUD of 24.3%.[6] One American study reported that 36.4% of 404 participants had experienced AUD before their first episode of psychosis.[7] In both the general U.S. population and among people with schizophrenia, AUD is associated with male gender and Caucasian race.[7] For individuals who have schizophrenia, AUD is associated with depression, suicidality, medication nonadherence, chronic physical problems, homelessness, aggression, violence, incarceration, and high rates of hospitalization.[7-10]

Basis of Co-Occurrence

The genetic risk for schizophrenia has been fairly well-established. Heritability is estimated to be 80% to 85% for schizophrenia.[11] Studies of twins have been a way to isolate genetic risk from environmental risk. The concordance rate, the likelihood that a second twin will receive a diagnosis of schizophrenia after the first twin, has been estimated at 41% to 65% for monozygotic and 0% to 28% for dizygotic twins.[11] In addition, multiple genetic determinants of risk for schizophrenia (especially within neural systems) may contribute to the risk for both psychosis and addiction. For disorders such as schizophrenia that stem from variation at multiple genetic loci, the various risk alleles can be summed together to determine a polygenic risk score. Strong associations between substance use disorder, including AUD, and the polygenic risk score for schizophrenia indicate that shared genetic liability may contribute to the co-occurrence of these disorders.[12]

Several polymorphisms (genetic variations) of the brain-derived neurotrophic factor (BDNF) protein correlate with co-occurring schizophrenia and alcohol dependence but not with alcohol dependence alone, suggesting that these polymorphisms may contribute to a specific vulnerability to these co-occurring disorders.[13] Recently, a large genome-wide association study of individuals with alcohol dependence (diagnosed using the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders*) revealed 17 traits, including schizophrenia, that had significant genetic correlations to alcohol dependence.[14] These studies support the notion that certain genetic factors can lead to an increased risk for developing co-occurring schizophrenia and AUD.

Several theories have emerged to explain the high prevalence of co-occurring schizophrenia and substance use disorder.[8,15] Rosenthal first proposed the diathesis-stress model in 1970 to describe the combined interaction of a neurobiological vulnerability with an environmental vulnerability that leads to the development of schizophrenia.[16] This theory is also called the "two-hit" model. For the development of schizophrenia and AUD, for example, the two hits could be a genetic risk for schizophrenia combined with alcohol drinking during adolescence. Although alcohol use in adolescence predicts future co-occurring mental health disorders and substance use disorder, adolescent exposure to alcohol was not found to be associated with the age of onset of psychosis.[17] A variant of the two-hit model is the cumulative risk factor hypothesis, which posits that among people with schizophrenia, the increased risk for developing substance use disorder stems from the added risks of poor cognitive development, poor social functioning, effects of poverty, and poor social environments.[1]

Another theory explaining the high rate of substance use disorder among individuals who have schizophrenia is the self-medication hypothesis, which suggests that people use substances to find relief from symptoms or in an effort to decrease side effects that arise from antipsychotic treatments.[18] Although clinically plausible, this theory has not been supported by research. Studies indicate that negative symptoms are not necessarily elevated in individuals with schizophrenia and substance use disorder, and that among young people who experienced first-episode psychosis, substance use disorder often developed before the use of medications.[7,19]

In 2018, Khokhar and colleagues reviewed the unifying hypothesis that the co-occurrence of schizophrenia and substance use disorder may

relate to a dysregulation of the mesocorticolimbic reward system in the brain.[15] Sometimes called the primary addiction hypothesis[20] or reward deficiency syndrome,[21] this circuit-level dysregulation has been studied using functional magnetic resonance imaging (fMRI). People with co-occurring schizophrenia and nicotine dependence have been shown to have reductions in resting-state connectivity between the insula and the anterior cingulate cortex, and people with co-occurring schizophrenia and cannabis use disorder have been shown to have a hypoconnectivity between the nucleus accumbens and frontal cortical regions.[22,23] Moreover, studies using task-based fMRI have reported dysfunction in the ventral striatum.[24]

The neurodevelopmental theory of schizophrenia suggests that an early insult in brain development may lead to onset of symptoms of schizophrenia in late adolescence or early adulthood.[25] This theory led to the development of a putative animal model of schizophrenia—the neonatal ventral hippocampal lesion (NVHL) model. In this model, rats receive small, bilateral, hippocampal lesions at the end of the first week of life, and in adulthood they display many of the memory and social deficits associated with schizophrenia.[26] This line of research is also promising for co-occurring substance use disorder, since NVHL rats consume more substances than their control group counterparts, and, after access to alcohol during adolescence, they drink more alcohol as adults.[27] Thus, the NVHL rat may be a promising model for studying changes in the reward circuits of the brain among individuals who have schizophrenia and AUD, and for identifying potential therapeutic targets for those who have schizophrenia and co-occurring substance use disorder.

Although models of co-occurring AUD or substance use disorder and schizophrenia or schizoaffective disorder continue to evolve, understanding the basis of the co-occurrence may inform treatment approaches, especially pharmacologic treatment for the co-occurring disorders. Moreover, regardless of the model, it appears that AUD or substance use disorder and schizophrenia or schizoaffective disorder are linked. Thus, treatment for such co-occurring disorders must address both the psychotic symptoms and the alcohol or other substance misuse.

Assessment, Treatment, and Prognosis

Given the high rates of co-occurring AUD among individuals with schizophrenia or schizoaffective disorder, as well as the clear evidence that such use can worsen the course of the psychotic disorder, diagnostic assessment for any individual presenting with symptoms of psychosis should include screening for alcohol and other substance use. In emergency departments, consideration of possible substance-induced psychosis is important. In one study, 18.9% of those with a diagnosis of substance-induced psychosis had alcohol as the primary substance.[28] In 39.6% of cases, alcohol was used with cocaine or cannabis.

Because alcohol can precipitate psychotic symptoms during acute intoxication, withdrawal, or chronic use, obtaining a detailed history and creating a timeline of periods of psychotic symptoms and substance use can help clinicians differentiate between substance-induced psychosis and a primary psychotic disorder. Individuals with psychotic disorders may not be able or willing to provide these details of their history, particularly during periods of symptom exacerbation. Therefore, collecting information from collateral sources, such as family members, is often necessary. For initial evaluations and assessments of treatment response, laboratory examinations, such as testing for ethyl glucuronide, can provide useful evidence of recent alcohol use.[29]

Treatment for substance-induced psychosis focuses on acute management, often with reduced stimulation, in a supportive, abstinent environment, and sometimes with short-term antipsychotic treatment. Once an individual becomes abstinent and withdrawal has resolved, psychotic symptoms also usually resolve, but 25% of cases may persist, resulting in diagnoses of schizophrenia spectrum disorders.[30] By contrast, treatment for individuals who have primary psychotic disorders with co-occurring AUD usually requires long-term antipsychotic medication and psychosocial interventions, in addition to other interventions for AUD noted in this section. Moreover, for individuals with co-occurring AUD and psychotic disorders, both disorders should be treated simultaneously. Thus, comprehensive

treatment—combining medication with behavioral and psychosocial interventions—is appropriate.

Pharmacologic treatment

This section reviews the evidence for the efficacy of medications used to treat AUD in individuals who have co-occurring schizophrenia or schizoaffective disorder. In addition, this section includes a review of the effects of antipsychotic medications on alcohol intake among individuals who have these co-occurring disorders.

AUD medication implications for schizophrenia or schizoaffective disorder

Several studies have examined the safety and efficacy of medications (i.e., naltrexone, disulfiram, and acamprosate) used to treat AUD in individuals with co-occurring schizophrenia and AUD.[31] In a small, randomized controlled trial of patients with schizophrenia and AUD, those treated with naltrexone reported significantly fewer drinking days, fewer heavy-drinking days, and less craving, as compared to those receiving placebo.[32] In a small, open-label study of naltrexone administered to individuals with schizophrenia spectrum disorders, investigators found improvements in various measures of alcohol intake, as well as in psychotic symptoms.[33]

Another study of patients with serious mental illnesses, including schizophrenia, compared naltrexone and disulfiram individually and in combination with placebo.[34] In this study, participants who received active medication had better alcohol use outcomes than those who received placebo. However, the majority of participants with a psychotic spectrum disorder had a diagnosis of bipolar disorder, limiting the potential applicability for individuals who have schizophrenia or schizoaffective disorder.

No known studies have assessed extended-release naltrexone for AUD in a population that includes individuals with psychotic disorders. However, given the cognitive and executive dysfunction associated with schizophrenia, this formulation (injectable with slow release and gradual absorption over 4 weeks) of naltrexone may have potential benefits for increasing medication adherence.

A small, randomized controlled trial examined the use of acamprosate for individuals with psychotic disorders.[35] In that study, all participants reduced drinking, and there was no difference between acamprosate and placebo in increasing the number of consecutive days of abstinence.

Theoretically, disulfiram has a risk of worsening psychosis in predisposed individuals because of its action of inhibiting dopamine beta-hydroxylase, but this phenomenon appears to be rare in clinical practice.[36] Other than the study that compared naltrexone, disulfiram, or a combination of naltrexone and disulfiram, no known randomized controlled trials have examined disulfiram among individuals with psychotic disorders. However, in a chart review of 33 patients treated with disulfiram who had a diagnosis of alcoholism and also had severe mental illness, 64% experienced remission of the alcoholism for at least 1 year during a 3-year follow-up period.[37]

Few studies have examined use of other medications for off-label treatment of AUD in individuals with schizophrenia spectrum disorders. For example, the effects of topiramate on alcohol outcomes have not been studied in this population, although it has been used to potentially control weight in people with schizophrenia.[38] There is some evidence that the mood stabilizer valproic acid may reduce alcohol consumption in a population that has dual diagnoses, which may have relevance for treating individuals with schizoaffective disorder. Specifically, in a randomized controlled trial of valproic acid versus placebo, in addition to treatment as usual, individuals with bipolar I disorder and alcohol dependence demonstrated a significantly smaller proportion of heavy-drinking days and a trend toward fewer drinks per heavy-drinking day.[39] However, no known trials have examined valproic acid in a population of individuals with schizophrenia and AUD.

Varenicline, which has been approved by the U.S. Food and Drug Administration for the treatment of nicotine use disorder, has been shown to decrease alcohol consumption among participants with AUD.[40] However, the only study of this medication in patients with schizophrenia and AUD reported poor tolerability.[41] Benzodiazepines, although useful for treating alcohol withdrawal and as adjunctive agents for acute manic episodes, are not effective for treatment of AUD and are associated with worse outcomes, including risk of overdose when combined with alcohol.

In summary, although few studies have examined the effects of medications (i.e., naltrexone, disulfiram, and acamprosate) that treat AUD among individuals with psychotic disorders, evidence of the safety and potential benefit is sufficient to encourage increased use in this population (see Table 1).

Schizophrenia or schizoaffective disorder medication implications for AUD

The choice of medication for treating psychotic or affective symptoms in people with psychotic disorders may have implications for alcohol consumption. First-generation antipsychotic medications do not appear to decrease alcohol use and actually may increase substance use and craving in people with schizophrenia and co-occurring substance use disorder.[42] Long-acting injectable formulations of second-generation antipsychotics, as well as clozapine, a novel second-generation antipsychotic, may be preferred.

A hypothetical framework has been delineated that supports the use of clozapine to ameliorate the brain circuit dysfunction experienced by people with schizophrenia and substance use disorder and is related to clozapine's weak dopamine D_2 receptor blockade coupled with its noradrenergic effects.[21,43] Some evidence supports the superiority of clozapine for people who have schizophrenia and AUD.[43] In a naturalistic, prospective study that followed patients with schizophrenia or schizoaffective disorder and co-occurring substance use disorder, a larger proportion of individuals receiving clozapine, versus those taking another atypical antipsychotic, achieved remission from AUD.[44] During the following year, the participants who were in remission and were being treated with clozapine had lower rates of relapse to substance use than participants who were treated with other antipsychotics.[45] Additional evidence from chart reviews and retrospective studies (see Table 2) favors the use of clozapine over other atypical antipsychotics.[46]

Table 1 Studies of Pharmacologic Interventions for AUD Among Individuals Who Have Schizophrenia Spectrum Disorders

Medication	Participants and Design	Results
Naltrexone[32]	Individuals (N = 31) with schizophrenia and co-occurring alcohol abuse or dependence* were treated with naltrexone (50 mg) or placebo, in addition to neuroleptic medication, for a 12-week, randomized controlled trial.	Participants treated with naltrexone, compared to those who received placebo, had significantly fewer drinking days and fewer heavy-drinking days (defined as more than five drinks), and they reported less craving.
Naltrexone and Disulfiram[34]	Individuals (N = 254) with alcohol dependence* and heterogeneous psychiatric disorders were treated with disulfiram and naltrexone alone and in combination. They also received intensive psychosocial treatment during the 12-week, randomized controlled trial.	Individuals with a psychotic spectrum disorder who received an active medication had better alcohol use outcomes when compared with those who received placebo. Neither disulfiram nor naltrexone nor the combination had a clear advantage.
Disulfiram[37]	In this retrospective review, individuals (N = 33) with alcohol abuse or dependence* and severe mental illness had been treated with disulfiram.	At a 3-year follow-up, 64% of individuals experienced remission of alcohol abuse or dependence* for at least 1 year.
Acamprosate[35]	Individuals (N = 23) with a diagnosis of alcohol dependence* and co-occurring schizophrenia, schizoaffective disorder, or nonspecified psychosis received acamprosate or placebo in a randomized controlled trial.	All participants reduced drinking. Acamprosate was not superior to placebo in increasing consecutive days of abstinence. Participants who received acamprosate reported significantly fewer obsessive thoughts of drinking than those who received placebo.
Valproic Acid[39]	Individuals (N = 59) with bipolar I disorder and alcohol dependence* received either valproate or placebo in a randomized controlled trial. All participants received treatment as usual (which included lithium).	The group that received valproate had a significantly smaller proportion of heavy-drinking days and a trend toward fewer drinks per heavy-drinking day when compared to the group that received placebo.
Varenicline[41]	Individuals (N = 55) with schizophrenia or schizoaffective disorder and concurrent alcohol and nicotine dependence* received varenicline or placebo in a pilot, 8-week, randomized controlled trial.	Because of safety concerns or loss to follow-up, only 10 participants started the study. Five received varenicline and five received placebo. Adverse gastrointestinal effects such as severe abdominal pain limited study completion to four participants.

*Study used the classifications of alcohol abuse and alcohol dependence as defined in the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders.*

Long-acting injectable formulations of antipsychotics may help improve adherence or clarify when nonadherence is present, which may be particularly relevant in a dual-diagnosis population. In a randomized controlled trial comparing oral and long-acting injectable risperidone treatment for individuals with schizophrenia and AUD, heavy drinking worsened over time for those in the oral risperidone group compared to those treated with the long-acting injectable formulation.[47] However, another study comparing long-acting injectable versus oral risperidone did not find differences in alcohol use outcomes between the two groups.[48]

Lastly, a randomized, open-label, review board–blinded study comparing once-monthly paliperidone palmitate to daily oral antipsychotics examined real-world outcomes for participants, a majority of whom had a diagnosis of co-occurring substance use disorder.[49] This trial demonstrated the superiority of long-acting injectable paliperidone, including for the primary outcome of time to first treatment failure.

Other second-generation antipsychotics that do not have potent dopamine D_2 blockade may have theoretical benefit over typical antipsychotic medications, although evidence in prospective controlled trials is limited. It has been postulated that the unique mechanism of action of aripiprazole (a partial agonist at dopamine D_2 and 5-HT_{1A} receptors and an antagonist at 5-HT_{2A} receptors) may have beneficial effects for alcohol use.[50] Uncontrolled trials provide support for use of aripiprazole among people who have co-occurring schizophrenia and cocaine or tobacco use disorder but not co-occurring schizophrenia and AUD.[51] Quetiapine, which weakly blocks dopamine D_2 receptors, has support from small, open-label trials that showed reductions in alcohol use.[52] However, no randomized controlled trials of these medications

Table 2 Studies of Antipsychotic Medications Among Individuals With Substance Use Disorder

Medication	Participants and Design	Results
Clozapine[44,45]	Patients (N = 151) with schizophrenia or schizoaffective disorder and co-occurring substance use disorder, of whom 36 were prescribed clozapine, were followed in a prospective study. The same patients were followed over the next year.	A larger proportion of participants who received clozapine, versus those taking a different atypical antipsychotic, achieved remission from AUD (79% vs. 34%). Participants in remission who had been treated with clozapine had lower rates of relapse to substance use (8%) than those treated with other antipsychotics (40%).
Clozapine and Risperidone[46]	In this retrospective review, patients with schizophrenia or schizoaffective disorder and co-occurring alcohol or cannabis use had been treated with clozapine or risperidone.	Abstinence rates were significantly higher for participants treated with clozapine than for those treated with risperidone (54% vs. 13%, p = .05).
Long-Acting Injectable Risperidone[47]	Individuals (N = 95) with schizophrenia and AUD received 6 months of risperidone either by long-acting injection or by mouth in a randomized controlled trial.	In the group that received risperidone by mouth, heavy drinking significantly worsened over time (p = .024). A slight difference between groups was shown for change in the number of heavy-drinking days per week, with the long-acting injection group showing a small decrease (p = .054). The long-acting injection group had significantly fewer drinking days per week than the by-mouth group (p = .035).
Long-Acting Injectable Risperidone[48]	Patients with schizophrenia who were unstable were treated with long-acting injectable or by-mouth risperidone in a randomized controlled trial. The length of time to psychiatric rehospitalization, as well as other clinical outcomes such as substance misuse, were examined.	Patients treated with long-acting injectable risperidone and those treated with by-mouth risperidone had no difference in alcohol use outcomes.
Long-Acting Injectable Paliperidone Palmitate[49]	Participants (N = 450) received either once-monthly paliperidone palmitate or daily oral antipsychotics in a 15-month, open-label, review board–blinded study. A majority of participants had a diagnosis of schizophrenia with co-occurring substance use disorder. Real-world outcomes were examined.	Results demonstrated superiority of long-acting injectable paliperidone, including for the outcome of time to first treatment failure.

examine alcohol outcomes in people with co-occurring schizophrenia and AUD.

Psychotherapeutic and psychosocial interventions

Chronic psychotic illness is often accompanied by cognitive deficits and diminished executive functioning, which may be worsened by the effects of alcohol in those who have co-occurring AUD. Therefore, integrated and tailored care for both the psychotic disorder and AUD can improve access to care, deliver consistent messages about treatment and recovery, provide interventions that support attempts to reduce substance use, and manage behavioral health conditions.[53]

Group therapy using cognitive behavioral therapy, motivational enhancement therapy, or contingency management has a role in treating AUD and co-occurring schizophrenia.[54,55] Considerations for this particular population include using active and ongoing motivation enhancement approaches and modifying cognitive behavioral therapy to account for cognitive, interpersonal, and motivational deficits that commonly occur among people with schizophrenia.[29]

Contingency management involves agreed on, immediate, tangible rewards to reinforce positive behaviors, such as treatment attendance or abstinence that has been verified by biologic measures. Such a management strategy for alcohol abstinence has been shown to be effective for people who have schizophrenia or other serious mental illness and who also have AUD. For example, one study demonstrated that participants who received contingency management intervention were 3.1 times more likely than participants from the control group to have a negative result on a urine test for the alcohol biomarker ethyl glucuronide.[56] Also, these participants were more likely to attain 1.5 weeks of additional alcohol abstinence during a 12-week trial as compared to participants in the control group.

More intensive interventions, including assertive community treatment (ACT) and residential programs, may benefit individuals with co-occurring schizophrenia and AUD. ACT is the most widely tested model of community care for people with severe mental illness. ACT consists of an interdisciplinary team (i.e., the psychiatrist, social workers, nurses, occupational therapists, and peer support) with a low participant-to-staff ratio. This team provides a range of comprehensive services, including community outreach, 24-hour availability for emergency communication, and integrated pharmacotherapy and behavioral treatments for substance use disorder. For people with dual disorders, faithful implementation of and adherence to the ACT model is associated with superior outcomes in substance use, including significantly fewer days of alcohol and drug use.[57] Residential programs that integrate treatment for mental health and substance use disorders can be effective and may be especially indicated for individuals who are homeless or have had suboptimal response to other interventions.[53]

Alcoholics Anonymous is underused among individuals with co-occurring AUD and psychotic disorders, although this population has unique considerations. People who have psychotic disorders benefit from the education and support they receive by attending and processing 12-step meetings, but people who have acute psychosis may not be able to tolerate these meetings.[58] Dual Recovery Anonymous (Double Trouble or Double Trouble in Recovery) is a 12-step program tailored for individuals with co-occurring mental illness and substance use disorder. Evidence shows higher rates of abstinence, better adherence to psychiatric medication, and improved personal functioning for people who attended dual-focused groups as compared to those who attended Alcoholics Anonymous.[59]

Future Research Directions

Additional research related to co-occurring AUD and schizophrenia or schizoaffective disorder is needed. Environmental factors, including substance use, that contribute to the risk of developing schizophrenia continue to be investigated. Prospective longitudinal markers of neurobiological function in adolescence before onset of psychotic symptoms and alcohol consumption could further elucidate the etiology of these disorders. Moreover, further development of evidence-based interventions to address alcohol and other substance use in adolescents before and during first-episode psychosis is required. Lastly, additional investigations into the efficacy of various treatment modalities are necessary, particularly because

individuals with co-occurring disorders often are excluded from clinical trials.

Acknowledgments

This article was supported by National Institute on Drug Abuse grants R21DA044501 and R01DA034699, by National Institute on Alcohol Abuse and Alcoholism grants R01AA018151 and R21AA019534, and by National Center for Advancing Translational Sciences grant UL1TR001086.

Financial Disclosure

Dr. Green has received research funding from Janssen, Novartis, and Alkermes, has served on a data monitoring board for Eli Lilly, and has served as an unpaid consultant to Otsuka and Alkermes. He is the inventor of U.S. patent 9044471, which is related to AUD treatment. Dr. Brunette has received research funding from Alkermes.

References

1. Mueser KT, McGurk SR. Schizophrenia. *Lancet*. 2004;363(9426):2063-2072. PMID: 15207959.
2. Perälä J, Suvisaari J, Saarni SI, et al. Lifetime prevalence of psychotic and bipolar I disorders in a general population. *Arch Gen Psychiatry*. 2007;64(1):19-28. PMID: 17199051.
3. Scully PJ, Owens JM, Kinsella A, et al. Schizophrenia, schizoaffective and bipolar disorder within an epidemiologically complete, homogeneous population in rural Ireland: Small area variation in rate. *Schizophr Res*. 2004;67(2-3):143-155. PMID: 14984873.
4. Regier DA, Farmer ME, Rae DS, et al. Comorbidity of mental disorders with alcohol and other drug abuse. Results from the Epidemiologic Catchment Area (ECA) study. *JAMA*. 1990;264(19):2511-2518. PMID: 2232018.
5. Hartz SM, Pato CN, Medeiros H, et al. Comorbidity of severe psychotic disorders with measures of substance use. *JAMA Psychiatry*. 2014;71(3):248-254. PMID: 24382686.
6. Hunt GE, Large MM, Cleary M, et al. Prevalence of comorbid substance use in schizophrenia spectrum disorders in community and clinical settings, 1990–2017: Systematic review and meta-analysis. *Drug Alcohol Depend*. 2018;191:234-258. PMID: 30153606.
7. Brunette MF, Mueser KT, Babbin S, et al. Demographic and clinical correlates of substance use disorders in first episode psychosis. *Schizophr Res*. 2018;194:4-12. PMID: 28697856.
8. Green AI, Drake RE, Brunette MF, et al. Schizophrenia and co-occurring substance use disorder. *Am J Psychiatry*. 2007;164(3):402-408. PMID: 17329463.
9. Hunt GE, Bergen J, Bashir M. Medication compliance and comorbid substance abuse in schizophrenia: Impact on community survival 4 years after a relapse. *Schizophr Res*. 2002;54(3):253-264. PMID: 11950550.
10. Jones RM, Lichtenstein P, Grann M, et al. Alcohol use disorders in schizophrenia: A national cohort study of 12,653 patients. *J Clin Psychiatry*. 2011;72(6):775-779. PMID: 21733478.
11. Cardno AG, Gottesman II. Twin studies of schizophrenia: From bow-and-arrow concordances to Star Wars Mx and functional genomics. *Am J Med Genet*. 2000;97(1):12-17. PMID: 10813800.
12. Hartz SM, Horton AC, Oehlert M, et al. Association between substance use disorder and polygenic liability to schizophrenia. *Biol Psychiatry*. 2017;82(10):709-715. PMID: 28739213.
13. Cheah SY, Lawford BR, Young RM, et al. BDNF SNPs are implicated in comorbid alcohol dependence in schizophrenia but not in alcohol-dependent patients without schizophrenia. *Alcohol Alcohol*. 2014;49(5):491-497. PMID: 24993285.
14. Walters RK, Polimanti R, Johnson EC, et al. Transancestral GWAS of alcohol dependence reveals common genetic underpinnings with psychiatric disorders. *Nat Neurosci*. 2018;21(12):1656-1669. PMID: 30482948.
15. Khokhar JY, Dwiel LL, Henricks AM, et al. The link between schizophrenia and substance use disorder: A unifying hypothesis. *Schizophr Res*. 2018;194:78-85. PMID: 28416205.
16. Rosenthal D. *Genetic Theory and Abnormal Behavior*. New York, NY: McGraw-Hill; 1970.
17. Large M, Sharma S, Compton MT, et al. Cannabis use and earlier onset of psychosis: A systematic meta-analysis. *Arch Gen Psychiatry*. 2011;68(6):555-561. PMID: 21300939.
18. Khantzian EJ. The self-medication hypothesis of substance use disorders: A reconsideration and recent applications. *Harv Rev Psychiatry*. 1997;4(5):231-244. PMID: 9385000.
19. Brunette MF, Mueser KT, Xie H, et al. Relationships between symptoms of schizophrenia and substance abuse. *J Nerv Ment Dis*. 1997;185(1):13-20. PMID: 9040528.
20. Chambers RA, Krystal JH, Self DW. A neurobiological basis for substance abuse comorbidity in schizophrenia. *Biol Psychiatry*. 2001;50(2):71-83. PMID: 11526998.
21. Green AI, Zimmet SV, Strous RD, et al. Clozapine for comorbid substance use disorder and schizophrenia: Do patients with schizophrenia have a reward-deficiency syndrome that can be ameliorated by clozapine? *Harv Rev Psychiatry*. 1999;6(6):287-296. PMID: 10370435.
22. Moran LV, Sampath H, Stein EA, et al. Insular and anterior cingulate circuits in smokers with schizophrenia. *Schizophr Res*. 2012;142(1-3):223-229. PMID: 23021898.
23. Fischer AS, Whitfield-Gabrieli S, Roth RM, et al. Impaired functional connectivity of brain reward circuitry in patients with schizophrenia and cannabis use disorder: Effects of cannabis and THC. *Schizophr Res*. 2014;158(1-3):176-182. PMID: 25037524.
24. Juckel G, Schlagenhauf F, Koslowski M, et al. Dysfunction of ventral striatal reward prediction in schizophrenia. *Neuroimage*. 2006;29(2):409-416. PMID: 16139525.
25. Weinberger DR. Implications of normal brain development for the pathogenesis of schizophrenia. *Arch Gen Psychiatry*. 1987;44(7):660-669. PMID: 3606332.
26. Tseng KY, Chambers RA, Lipska BK. The neonatal ventral hippocampal lesion as a heuristic neurodevelopmental model of schizophrenia. *Behav Brain Res*. 2009;204(2):295-305. PMID: 19100784.
27. Jeanblanc J, Balguerie K, Coune F, et al. Light alcohol intake during adolescence induces alcohol addiction in a neurodevelopmental model of schizophrenia. *Addict Biol*. 2015;20(3):490-499. PMID: 24725220.
28. Caton CL, Drake RE, Hasin DS, et al. Differences between early-phase primary psychotic disorders with concurrent substance use and substance-induced psychoses. *Arch Gen Psychiatry*. 2005;62(2):137-145. PMID: 15699290.
29. Han BH, Avery JD. Psychotic disorders. In: Avery JD, Barnhill JW, eds. *Co-Occurring Mental Illness and Substance Use Disorders: A Guide to Diagnosis and Treatment*. Washington, DC: American Psychiatric Association; 2018:69-81.
30. Caton CL, Hasin DS, Shrout PE, et al. Stability of early-phase primary psychotic disorders with concurrent substance use and substance-induced psychosis. *Br J Psychiatry*. 2007;190:105-111. PMID: 17267925.
31. Lev-Ran S, Balchand K, Lefebvre L, et al. Pharmacotherapy of alcohol use disorders and concurrent psychiatric disorders: A review. *Can J Psychiatry*. 2012;57(6):342-349. PMID: 22682571.
32. Petrakis IL, O'Malley S, Rounsaville B, et al. Naltrexone augmentation of neuroleptic treatment in alcohol abusing patients with schizophrenia. *Psychopharmacology (Berl)*. 2004;172(3):291-297. PMID: 14634716.
33. Batki SL, Dimmock JA, Wade M. Monitored naltrexone without counseling for alcohol abuse/dependence in schizophrenia-spectrum disorders. *Am J Addict*. 2007;16(4):253-259. PMID: 17661192.

34. Petrakis IL, Nich C, Ralevski E. Psychotic spectrum disorders and alcohol abuse: A review of pharmacotherapeutic strategies and a report on the effectiveness of naltrexone and disulfiram. *Schizophr Bull.* 2006;32(4):644-654. PMID: 16887890.
35. Ralevski E, O'Brien E, Jane JS, et al. Treatment with acamprosate in patients with schizophrenia spectrum disorders and comorbid alcohol dependence. *J Dual Diagn.* 2011;7(1-2):64-73. PMID: 26954912.
36. Das N, Mahapatra A, Sarkar S. Disulfiram induced psychosis: Revisiting an age-old entity. *Asian J Psychiatry.* 2017;30:94-95. PMID: 28843144.
37. Mueser KT, Noordsy DL, Fox L, et al. Disulfiram treatment for alcoholism in severe mental illness. *Am J Addict.* 2003;12(3):242-252. PMID: 12851020.
38. Okuyama Y, Oya K, Matsunaga S, et al. Efficacy and tolerability of topiramate-augmentation therapy for schizophrenia: A systematic review and meta-analysis of randomized controlled trials. *Neuropsychiatr Dis Treat.* 2016;12:3221-3236. PMID: 28008259.
39. Salloum IM, Cornelius JR, Daley DC, et al. Efficacy of valproate maintenance in patients with bipolar disorder and alcoholism: A double-blind placebo-controlled study. *Arch Gen Psychiatry.* 2005;62(1):37-45. PMID: 15630071.
40. Litten RZ, Ryan ML, Fertig JB, et al. A double-blind, placebo-controlled trial assessing the efficacy of varenicline tartrate for alcohol dependence. *J Addict Med.* 2013;7(4):277-286. PMID: 23728065.
41. Meszaros ZS, Abdul-Malak Y, Dimmock JA, et al. Varenicline treatment of concurrent alcohol and nicotine dependence in schizophrenia: A randomized, placebo-controlled pilot trial. *J Clin Psychopharmacol.* 2013;33(2):243-247. PMID: 23422399.
42. Akerman SC, Brunette MF, Noordsy DL, et al. Pharmacotherapy of co-occurring schizophrenia and substance use disorders. *Curr Addict Rep.* 2014;1(4):251-260. PMID: 27226947.
43. Khokhar JY, Henricks AM, Sullivan EDK, et al. Unique effects of clozapine: A pharmacological perspective. *Adv Pharmacol.* 2018;82:137-162. PMID: 29413518.
44. Drake RE, Xie H, McHugo GJ, et al. The effects of clozapine on alcohol and drug use disorders among patients with schizophrenia. *Schizophr Bull.* 2000;26(2):441-449. PMID: 10885642.
45. Brunette MF, Drake RE, Xie H, et al. Clozapine use and relapses of substance use disorder among patients with co-occurring schizophrenia and substance use disorders. *Schizophr Bull.* 2006;32(4):637-643. PMID: 16782758.
46. Green AI, Burgess ES, Dawson R, et al. Alcohol and cannabis use in schizophrenia: Effects of clozapine vs. risperidone. *Schizophr Res.* 2003;60(1):81-85. PMID: 12505141.
47. Green AI, Brunette MF, Dawson R, et al. Long-acting injectable vs. oral risperidone for schizophrenia and co-occurring alcohol use disorder: A randomized trial. *J Clin Psychiatry.* 2015;76(10):1359-1365. PMID: 26302441.
48. Leatherman SM, Liang MH, Krystal JH, et al. Differences in treatment effect among clinical subgroups in a randomized clinical trial of long-acting injectable risperidone and oral antipsychotics in unstable chronic schizophrenia. *J Nerv Ment Dis.* 2014;202(1):13-17. PMID: 24375206.
49. Alphs L, Benson C, Cheshire-Kinney K. Real-world outcomes of paliperidone palmitate compared to daily oral antipsychotic therapy in schizophrenia: A randomized, open-label, review board–blinded 15 month study. *J Clin Psychiatry.* 2015;76(5):554-561. PMID: 25938474.
50. Vergne DE, Anton RF. Aripiprazole: A drug with a novel mechanism of action and possible efficacy for alcohol dependence. *CNS Neurol Disord Drug Targets.* 2010;9(1):50-54. PMID: 20201815.
51. Brown ES, Jeffress J, Liggin JD, et al. Switching outpatients with bipolar or schizoaffective disorders and substance abuse from their current antipsychotic to aripiprazole. *J Clin Psychiatry.* 2005;66(6):756-760. PMID: 15960570.
52. Brunette MF, Dawson R, O'Keefe C, et al. An open label study of quetiapine in patients with schizophrenia and alcohol disorders. *Ment Health Subst Use.* 2009;2(3):203-211.
53. Brunette MF, Mueser KT, Drake RE. A review of research on residential programs for people with severe mental illness and co-occurring substance use disorders. *Drug Alcohol Rev.* 2004;23(4):471-481. PMID: 15763752.
54. Ziedonis DM, Fan X, Bizamcer AN, et al. Co-occurring addiction and psychotic disorders. In: Ries RK, Fiellin DA, Miller SC, et al, eds. *The ASAM Principles of Addiction Medicine.* 5th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2014:1346-1364.
55. Baker AL, Hiles SA, Thornton LK, et al. A systematic review of psychological interventions for excessive alcohol consumption among people with psychotic disorders. *Acta Psychiatr Scand.* 2012;126(4):243-255. PMID: 22632145.
56. McDonell MG, Leickly E, McPherson S, et al. A randomized controlled trial of ethyl glucuronide-based contingency management for outpatients with co-occurring alcohol use disorders and serious mental illness. *Am J Psychiatry.* 2017;174(4):370-377. PMID: 28135843.
57. McHugo GJ, Drake RE, Teague GB, et al. Fidelity to assertive community treatment and client outcomes in the New Hampshire dual disorders study. *Psychiatr Serv.* 1999;50(6):818-824. PMID: 10375153.
58. Bogenschutz MP, Geppert CM, George J. The role of twelve-step approaches in dual diagnosis treatment and recovery. *Am J Addict.* 2006;15(1):50-60. PMID: 16449093.
59. Magura S, Laudet AB, Mahmood D, et al. Role of self-help processes in achieving abstinence among dually diagnosed persons. *Addict Behav.* 2003;28(3):399-413. PMID: 12628615.

Cite this as:
Alcohol Res. 2019;40(1):06. https://doi.org/10.35946/arcr.v40.1.06.

Integrating Treatment for Co-Occurring Mental Health Conditions

Amy M. Yule and John F. Kelly

Amy M. Yule, M.D., is a psychiatrist at Massachusetts General Hospital and an assistant professor of psychiatry at Harvard Medical School, Boston, Massachusetts.

John F. Kelly, Ph.D., is a psychologist at Massachusetts General Hospital and a professor of psychiatry at Harvard Medical School, Boston, Massachusetts.

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

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

Introduction

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

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

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

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

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

Background

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

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

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

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

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

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

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

Screening and Assessment

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

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

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

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

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

Table 3 MHC Screening Tools

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

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

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

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

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

Types of Integrated Treatment

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

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

Behavioral therapy

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

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

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

Pharmacotherapy

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

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

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

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

Recovery support in the community

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

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

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

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

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

Comprehensive integrated treatment for serious mental illness and AUD

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

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

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

Challenges in Implementing Integrated Treatment

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

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

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

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

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

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

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

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

Innovative Models

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

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

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

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

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

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

Future Directions

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

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

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

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

Acknowledgments

This article was supported by the American Academy of Child and Adolescent Psychiatry, by the National Institute on Drug Abuse award K12DA000357, and by the National Institute on Alcohol Abuse and Alcoholism grant K24AA022136.

Financial Disclosure

Dr. Yule was a consultant to the Phoenix House from 2015 to 2017 and currently is a clinical services consultant to the Gavin House.

References

1. Bose J, Hedden SL, Lipari RN, et al. *Key Substance Use and Mental Health Indicators in the United States: Results From the 2017 National Survey on Drug Use and Health*. Rockville, MD: Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration; September 2018.
2. Urbanoski K, Cheng J, Rehm J, et al. Frequent use of emergency departments for mental and substance use disorders. *Emerg Med J*. 2018;35(4):220-225. PMID: 29311114.
3. Granfield R, Cloud W. Social context and "natural recovery": The role of social capital in the resolution of drug-associated problems. *Subst Use Misuse*. 2001;36(11):1543-1570. PMID: 11693955.
4. Conway KP, Swendsen J, Husky MM, et al. Association of lifetime mental disorders and subsequent alcohol and illicit drug use: Results from the National Comorbidity Survey–Adolescent Supplement. *J Am Acad Child Adolesc Psychiatry*. 2016;55(4):280-288. PMID: 27015718.
5. Grant BF, Goldstein RB, Saha TD, et al. Epidemiology of DSM-5 alcohol use disorder: Results from the National Epidemiologic Survey on Alcohol and Related Conditions III. *JAMA Psychiatry*. 2015;72(8):757-766. PMID: 26039070.
6. Groenman AP, Janssen TWP, Oosterlaan J. Childhood psychiatric disorders as risk factor for subsequent substance abuse: A meta-analysis. *J Am Acad Child Adolesc Psychiatry*. 2017;56(7):556-569. PMID: 28647007.
7. Hasin DS, Stinson FS, Ogburn E, et al. Prevalence, correlates, disability, and comorbidity of DSM-IV alcohol abuse and dependence in the United States: Results from the National Epidemiologic Survey on Alcohol and Related Conditions. *Arch Gen Psychiatry*. 2007;64(7):830-842. PMID: 17606817.
8. Hunt GE, Large MM, Cleary M, et al. Prevalence of comorbid substance use in schizophrenia spectrum disorders in community and clinical settings, 1990–2017: Systematic review and meta-analysis. *Drug Alcohol Depend*. 2018;191:234-258. PMID: 30153606.
9. Suter M, Strik W, Moggi F. Depressive symptoms as a predictor of alcohol relapse after residential treatment programs for alcohol use disorder. *J Subst Abuse Treat*. 2011;41(3):225-232. PMID: 21546204.
10. McLellan AT, Luborsky L, Woody GE, et al. Predicting response to alcohol and drug abuse treatments. Role of psychiatric severity. *Arch Gen Psychiatry*. 1983;40(6):620-625. PMID: 6847331.
11. Rounsaville BJ, Dolinsky ZS, Babor TF, et al. Psychopathology as a predictor of treatment outcome in alcoholics. *Arch Gen Psychiatry*. 1987;44(6):505-513. PMID: 3579499.
12. Tómasson K, Vaglum P. Psychopathology and alcohol consumption among treatment-seeking alcoholics: A prospective study. *Addiction*. 1996;91(7):1019-1030. PMID: 8688816.
13. Greenfield SF, Weiss RD, Muenz LR, et al. The effect of depression on return to drinking: A prospective study. *Arch Gen Psychiatry*. 1998;55(3):259-265. PMID: 9510220.
14. Heath B, Wise Romero P, Reynolds K. *A Review and Proposed Standard Framework for Levels of Integrated Healthcare*. Washington, DC: Center for Integrated Health Solutions, Substance Abuse and Mental Health Services Administration and Health Resources and Services Administration; 2013.
15. Drake RE, Mueser KT, Brunette MF, et al. A review of treatments for people with severe mental illnesses and co-occurring substance use disorders. *Psychiatr Rehabil J*. 2004;27(4):360-374. PMID: 15222148.
16. Center for Mental Health Services, Substance Abuse and Mental Health Services Administration. *Integrated Treatment for Co-Occurring Disorders: Getting Started With Evidence-Based Practices*. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2009.
17. Priester MA, Browne T, Iachini A, et al. Treatment access barriers and disparities among individuals with co-occurring mental health and substance use disorders: An integrative literature review. *J Subst Abuse Treat*. 2016;61:47-59. PMID: 26531892.
18. Del Boca FK, McRee B, Vendetti J, et al. The SBIRT program matrix: A conceptual framework for program implementation and evaluation. *Addiction*. 2017;112(suppl 2):12-22. PMID: 28074572.
19. Singh M, Gmyrek A, Hernandez A, et al. Sustaining screening, brief intervention and referral to treatment (SBIRT) services in health-care settings. *Addiction*. 2017;112(suppl 2):92-100. PMID: 28074565.
20. National Institute on Alcohol Abuse and Alcoholism. *Alcohol Screening and Brief Intervention for Youth: A Practitioner's Guide*. Rockville, MD: National Institute on Alcohol Abuse and Alcoholism; 2011.
21. Saunders JB, Aasland OG, Babor TF, et al. Development of the Alcohol Use Disorders Identification Test (AUDIT): WHO collaborative project on early detection of persons with harmful alcohol consumption—II. *Addiction*. 1993;88(6):791-804. PMID: 8329970.
22. Levy S, Weiss R, Sherritt L, et al. An electronic screen for triaging adolescent substance use by risk levels. *JAMA Pediatr*. 2014;168(9):822-828. PMID: 25070067.
23. Kelly SM, Gryczynski J, Mitchell SG, et al. Validity of brief screening instrument for adolescent tobacco, alcohol, and drug use. *Pediatrics*. 2014;133(5):819-826. PMID: 24753528.
24. McNeely J, Wu LT, Subramaniam G, et al. Performance of the tobacco, alcohol, prescription medication, and other substance use (TAPS) tool for substance use screening in primary care patients. *Ann Intern Med*. 2016;165(10):690-699. PMID: 27595276.
25. National Institute on Drug Abuse. *Screening for Drug Use in General Medical Settings: Resource Guide*. Rockville, MD: National Institute on Drug Abuse; March 2012.
26. WHO ASSIST Working Group. The Alcohol, Smoking and Substance Involvement Screening Test (ASSIST): Development, reliability and feasibility. *Addiction*. 2002;97(9):1183-1194. PMID: 12199834.
27. Jellinek MS, Murphy JM, Robinson J, et al. Pediatric Symptom Checklist: Screening school-age children for psychosocial dysfunction. *J Pediatr*. 1988;112(2):201-209. PMID: 3339501.
28. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: Validity of a brief depression severity measure. *J Gen Intern Med*. 2001;16(9):606-613. PMID: 11556941.
29. Spitzer RL, Kroenke K, Williams JB, et al. A brief measure for assessing generalized anxiety disorder: The GAD-7. *Arch Intern Med*. 2006;166(10):1092-1097. PMID: 16717171.
30. Carroll JFX, McGinley JJ. A screening form for identifying mental health problems in alcohol/other drug dependent persons. *Alcohol Treat Q*. 2001;19(4):33-47.
31. McLellan AT, Luborsky L, Woody GE, et al. An improved diagnostic evaluation instrument for substance abuse patients. The Addiction Severity Index. *J Nerv Ment Dis*. 1980;168:26-33. PMID: 7351540.
32. Dennis M, Titus J, White M, et al. *Global Appraisal of Individual Needs: Administration Guide for the GAIN and Related Measures*. Bloomington, IL: Chestnut Health Systems; 2003.
33. Mee-Lee D, ed. *The ASAM Criteria: Treatment Criteria for Addictive, Substance-Related, and Co-Occurring Conditions*. 3rd ed. Rockville, MD: American Society of Addiction Medicine; 2013.

34. Cacciola JS, Pecoraro A, Alterman AI. Development of ASI psychiatric severity cut-off scores to identify co-occurring psychiatric disorders. *Int J Ment Health Addict.* 2008;6:77-92.
35. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders.* 5th ed. Washington, DC: American Psychiatric Association; 2013.
36. Ries R. Clinical treatment matching models for dually diagnosed patients. *Psychiatr Clin North Am.* 1993;16(1):167-175. PMID: 8456042.
37. Center for Substance Abuse Treatment, Substance Abuse and Mental Health Services Administration. *Substance Abuse Treatment for Persons With Co-Occurring Disorders: A Treatment Improvement Protocol Tip 42.* Rockville, MD: Substance Abuse and Mental Health Services Administration; 2005.
38. McDonell MG, Kerbrat AH, Comtois KA, et al. Validation of the co-occurring disorder quadrant model. *J Psychoactive Drugs.* 2012;44(3):266-273. PMID: 23061327.
39. Groshkova T, Best D, White W. The Assessment of Recovery Capital: Properties and psychometrics of a measure of addiction recovery strengths. *Drug Alcohol Rev.* 2013;32(2):187-194. PMID: 22882622.
40. Vilsaint CL, Kelly JF, Bergman BG, et al. Development and validation of a Brief Assessment of Recovery Capital (BARC-10) for alcohol and drug use disorder. *Drug Alcohol Depend.* 2017;177:71-76. PMID: 28578224.
41. Carroll KM. Behavioral therapies for co-occurring substance use and mood disorders. *Biol Psychiatry.* 2004;56(10):778-784. PMID: 15556123.
42. Levin FR, Evans SM, Brooks DJ, et al. Treatment of methadone-maintained patients with adult ADHD: Double-blind comparison of methylphenidate, bupropion and placebo. *Drug Alcohol Depend.* 2006;81(2):137-148. PMID: 16102908.
43. Weiss RD, Griffin ML, Kolodziej ME, et al. A randomized trial of integrated group therapy versus group drug counseling for patients with bipolar disorder and substance dependence. *Am J Psychiatry.* 2007;164(1):100-107. PMID: 17202550.
44. Lydecker KP, Tate SR, Cummins KM, et al. Clinical outcomes of an integrated treatment for depression and substance use disorders. *Psychol Addict Behav.* 2010;24(3):453-465. PMID: 20853931.
45. McGovern MP, Lambert-Harris C, Xie H, et al. A randomized controlled trial of treatments for co-occurring substance use disorders and post-traumatic stress disorder. *Addiction.* 2015;110(7):1194-1204. PMID: 25846251.
46. Najavits LM, Weiss RD, Shaw SR, et al. "Seeking safety": Outcome of a new cognitive-behavioral psychotherapy for women with posttraumatic stress disorder and substance dependence. *J Trauma Stress.* 1998;11(3):437-456. PMID: 9690186.
47. Riper H, Andersson G, Hunter SB, et al. Treatment of comorbid alcohol use disorders and depression with cognitive-behavioural therapy and motivational interviewing: A meta-analysis. *Addiction.* 2014;109(3):394-406. PMID: 24304463.
48. Torchalla I, Nosen L, Rostam H, et al. Integrated treatment programs for individuals with concurrent substance use disorders and trauma experiences: A systematic review and meta-analysis. *J Subst Abuse Treat.* 2012;42(1):65-77. PMID: 22035700.
49. Iovieno N, Tedeschini E, Ameral VE, et al. Antidepressants for major depressive disorder in patients with a co-morbid axis-III disorder: A meta-analysis of patient characteristics and placebo response rates in randomized controlled trials. *Int Clinical Psychopharmacol.* 2011;26(2):69-74. PMID: 20962663.
50. Naglich A, Adinoff B, Brown ES. Pharmacological treatment of bipolar disorder with comorbid alcohol use disorder. *CNS Drugs.* 2017;31(8):665-674. PMID: 28669022.
51. Gimeno C, Dorado ML, Roncero C, et al. Treatment of comorbid alcohol dependence and anxiety disorder: Review of the scientific evidence and recommendations for treatment. *Front Psychiatry.* 2017;8:173. PMID: 29018367.
52. Ipser JC, Wilson D, Akindipe TO, et al. Pharmacotherapy for anxiety and comorbid alcohol use disorders. *Cochrane Database Syst Rev.* 2015;1:CD007505. PMID: 25601826.
53. Agabio R, Trogu E, Pani PP. Antidepressants for the treatment of people with co-occurring depression and alcohol dependence. *Cochrane Database Syst Rev.* 2018;4:CD008581. PMID: 29688573.
54. Petrakis IL, Poling J, Levinson C, et al. Naltrexone and disulfiram in patients with alcohol dependence and comorbid psychiatric disorders. *Biol Psychiatry.* 2005;57(10):1128-1137. PMID: 15866552.
55. Tolliver BK, Desantis SM, Brown DG, et al. A randomized, double-blind, placebo-controlled clinical trial of acamprosate in alcohol-dependent individuals with bipolar disorder: A preliminary report. *Bipolar Disord.* 2012;14(1):54-63. PMID: 22329472.
56. Robertson AG, Easter MM, Lin H, et al. Medication-assisted treatment for alcohol-dependent adults with serious mental illness and criminal justice involvement: Effects on treatment utilization and outcomes. *Am J Psychiatry.* 2018;175(7):665-673. PMID: 29961358.
57. Green AI, Brunette MF, Dawson R, et al. Long-acting injectable vs. oral risperidone for schizophrenia and co-occurring alcohol use disorder: A randomized trial. *J Clin Psychiatry.* 2015;76(10):1359-1365. PMID: 26302441.
58. Gelenberg AJ, Freeman MP, Markowitz JC, et al, eds. *Practice Guideline for the Treatment of Patients With Major Depressive Disorder.* 3rd ed. Washington, DC: American Psychiatric Association; October 2010.
59. Stein MB, Goin MK, Pollack MH, et al, eds. *Practice Guideline for the Treatment of Patients With Panic Disorder.* 2nd ed. Washington, DC: American Psychiatric Association; January 2009.
60. Reus VI, Fochtmann LJ, Bukstein O, et al, eds. *The American Psychiatric Association Practice Guideline for the Pharmacological Treatment of Patients With Alcohol Use Disorder.* Washington, DC: American Psychiatric Association; January 2018.
61. Kelly JF, Yeterian JD. Mutual-help groups for dually diagnosed individuals: Rationale, description, and review of the evidence. *J Groups Addict Recover.* 2008;3(3-4):217-242.
62. Magura S. Effectiveness of dual focus mutual aid for co-occurring substance use and mental health disorders: A review and synthesis of the "double trouble" in recovery evaluation. *Subst Use Misuse.* 2008;43(12-13):1904-1926. PMID: 19016171.
63. General Service Office of Alcoholics Anonymous. *A.A. Fact File.* New York, NY: Alcoholics Anonymous World Services; 2018.
64. Tonigan JS, Pearson MR, Magill M, et al. AA attendance and abstinence for dually diagnosed patients: A meta-analytic review. *Addiction.* 2018;113(11):1970-1981. PMID: 29845709.
65. Lloyd-Evans B, Mayo-Wilson E, Harrison B, et al. A systematic review and meta-analysis of randomised controlled trials of peer support for people with severe mental illness. *BMC Psychiatry.* 2014;14:39. PMID: 24528545.
66. Griffiths KM. Mental health internet support groups: Just a lot of talk or a valuable intervention? *World Psychiatry.* 2017;16(3):247-248. PMID: 28941105.
67. Ashford RD, Bergman BG, Kelly JF, et al. Systematic review: Digital recovery support services used to support substance use disorder recovery. *Hum Behav Emerg Tech.* April 2019.
68. Drake RE, Essock SM, Shaner A, et al. Implementing dual diagnosis services for clients with severe mental illness. *Psychiatr Serv.* 2001;52(4):469-476. PMID: 11274491.
69. Delos Reyes CM, Kubek PM, Kruszynski R, et al, eds. *Clinical Guide for Integrated Dual Disorder Treatment (IDDT).* Cleveland, OH: Center for Evidence Based Practices, Case Western Reserve University; 2012.
70. Hunt GE, Siegfried N, Morley K, et al. Psychosocial interventions for people with both severe mental illness and substance misuse. *Cochrane Database Syst Rev.* October 2013:CD001088. PMID: 24092525.
71. Council for Accreditation of Counseling and Related Educational Programs (CACREP). *2009 Standards.* Alexandria, VA: CACREP; 2009:1-69.
72. Russett JL, Williams A. An exploration of substance abuse course offerings for students in counseling and social work programs. *Subst Abus.* 2015;36(1):51-58. PMID: 25010520.

73. Massella J, Simons L, Young J, et al. A pilot study of addiction professionals' views of certification. *Addict Disord Treat.* 2013;12(4):201-212.
74. Schwartz AC, Frank A, Welsh JW, et al. Addictions training in general psychiatry training programs: Current gaps and barriers. *Acad Psychiatry.* 2018;42(5):642-647. PMID: 30073538.
75. Clark HW, Power AK, Le Fauve CE, et al. Policy and practice implications of epidemiological surveys on co-occurring mental and substance use disorders. *J Subst Abuse Treat.* 2008;34(1):3-13. PMID: 17574794.
76. Padwa H, Guerrero EG, Braslow JT, et al. Barriers to serving clients with co-occurring disorders in a transformed mental health system. *Psychiatr Serv.* 2015;66(5):547-550. PMID: 25686812.
77. Komaromy M, Duhigg D, Metcalf A, et al. Project ECHO (Extension for Community Healthcare Outcomes): A new model for educating primary care providers about treatment of substance use disorders. *Subst Abus.* 2016;37(1):20-24. PMID: 26848803.
78. Ciraulo DA, Barlow DH, Gulliver SB, et al. The effects of venlafaxine and cognitive behavioral therapy alone and combined in the treatment of co-morbid alcohol use–anxiety disorders. *Behav Res Ther.* 2013;51(11):729-735. PMID: 24055681.
79. Meyer EC, Walser R, Hermann B, et al. Acceptance and commitment therapy for co-occurring posttraumatic stress disorder and alcohol use disorders in veterans: Pilot treatment outcomes. *J Trauma Stress.* 2018;31(5):781-789. PMID: 30338561.
80. Wolitzky-Taylor K, Krull J, Rawson R, et al. Randomized clinical trial evaluating the preliminary effectiveness of an integrated anxiety disorder treatment in substance use disorder specialty clinics. *J Consult Clin Psychol.* 2018;86(1):81-88. PMID: 29300100.
81. Kelly JF, Mee-Lee D. Quality, accountability, and effectiveness in addiction treatment: The Measurement-Based Practice Model. In: Danovitch I, Mooney L, eds. *The Assessment and Treatment of Addiction: Best Practices and New Frontiers.* St. Louis, MO: Elsevier; 2019:207-217.

Cite this as:
Alcohol Res. 2019;40(1):07. **https://doi.org/10.35946/arcr.v40.1.07.**

U.S. Department of Health and Human Services

Superintendent of Documents
732 N. Capitol Street, N.W.
Washington, DC 20402-0003

Prsrt Std
Postage & Fees Paid
GPO
Permit No. G–26

Official Business
Penalty for private use—$300

For sale by the Superintendent of Documents,
U.S. Government Publishing Office
Washington, DC 20402