HHS Public Access

Author manuscript

Lancet Psychiatry. Author manuscript; available in PMC 2020 February 07.

Published in final edited form as:

Lancet Psychiatry. 2019 December ; 6(12): 1068–1080. doi:10.1016/S2215-0366(19)30222-6.

Psychiatric comorbidities in alcohol use disorder

Alvaro Castillo-Carniglia, **Katherine M Keyes**, **Deborah S Hasin**, **Magdalena Cerdá**

Society and Health Research Center, Facultad de Humanidades, Universidad Mayor, Santiago, Chile (A Castillo-Carniglia PhD); Department of Population Health, New York University School of Medicine, New York, NY, USA (A Castillo-Carniglia, M Cerdá DrPH), and Department of Epidemiology (K M Keyes PhD) and Department of Psychiatry, College of Physicians and Surgeons, Mailman School of Public Health, Columbia University and New York State Psychiatric Institute, New York, NY, USA (Prof D S Hasin PhD)

Abstract

Alcohol use disorder is a major contributor to the morbidity and mortality burden worldwide. It often coexists with other psychiatric disorders; however, the nature of this comorbidity is still a matter of debate. In this Series paper, we examine the main psychiatric disorders associated with alcohol use disorder, including the prevalence of co-occurring disorders, the temporal nature of the relationship, and mechanisms that might explain comorbidity across the lifespan. Overall, this disorder co-occurs with a wide range of other psychiatric disorders, especially those disorders involving substance use and violent or aggressive behaviour. The causal pathways between alcohol use disorder and other psychiatric disorders are heterogeneous. Hypotheses explaining these relationships include reciprocal direct causal associations, shared genetic and environmental causes, and shared psychopathological characteristics of broader diagnostic entities (eg, externalising disorders). Efforts to untangle the associations between alcohol use disorder and other disorders across the lifespan remain a crucial avenue of research.

Introduction

Alcohol use disorder is among the leading causes of morbidity and mortality worldwide;[1–3] an estimated 95 million people live with alcohol dependence globally.[4] Alcohol use disorder refers to impaired control over alcohol use, leading to physiological dependence and tolerance, and detrimental psychological, social, and physical consequences. These disorders are highly disabling, associated with many physical and psychiatric comorbidities,[1,5,6] and are responsible for 10% of the burden of disease related to substance use and mental disorders.[7] In this Series paper, we refer to alcohol use disorder when describing the clinical

Correspondence to: Dr Alvaro Castillo-Carniglia, Society and Health Research Center, Facultad de Humanidades, Universidad Mayor, 7560908 Santiago, Chile, alvacasti@gmail.com.

Contributors

AC led the literature review and drafted the first version of the article. KMK, DSH, and MC drafted sections of the article and contributed to framing the Series paper. All authors were directly involved in writing, editing, and approving the final version of this paper.

Declaration of interests

We declare no competing interests.

This is the second in a **Series** of two papers on alcohol use disorder

diagnoses of DSM-IV alcohol abuse or dependence, as well as DSM-5 alcohol use disorder, which combined DSM-IV alcohol abuse and dependence symptoms.

Psychiatric comorbidity is the presence, simultaneously or in sequence, of more than one disorder within an individual within a certain time period.[8] The prevalence of most mood, anxiety, substance, and thought disorders is higher in people with alcohol use disorder than in the general population,[9–11] although the magnitude of the correlation varies across disorders.[12,13] Alcohol use disorder comorbidity could arise from several potential mechanisms, including a direct or indirect causal effect of the disorder on other psychiatric disorders, or vice versa, shared genetic and environmental causes of the disorder and other psychiatric disorders, or because alcohol use disorder and other psychiatric disorders share psychopathological characteristics and form part of a single diagnostic entity.

Although previous reviews have documented patterns of comorbidity between alcohol use disorder and other psychiatric disorders, they have tended to focus on single psychiatric disorders and on isolated pieces of the pathways linking the disorder to psychiatric disorders. To our knowledge, no previous review has attempted to evaluate the evidence on the relationship between alcohol use disorder and the range of internalising, externalising, and thought disorders, to summarise the evidence on the directionality of these relationships, or to critically examine the types of mechanisms linking these disorders. Understanding how comorbid patterns of alcohol use disorder and other psychiatric disorders arise (ie, which disorder presents first), and how they are connected (ie, a causal link, or shared causes or psychopathological characteristics) is necessary to determine effective interventions to reduce the risk of comorbidity, and to treat existing comorbid psychiatric disorders.

In this Series paper, we address existing research gaps in three ways. First, we discuss evidence on the prevalence of psychiatric disorders in people with alcohol use disorder, and the prevalence of alcohol use disorder in people with psychiatric disorders. We report the available median or pooled prevalence (table), results from individual studies, or the range of prevalence across studies. We have organised the psychiatric disorders into three groups, internalising disorders (eg, depression, anxiety), externalising disorders (eg, other substance use disorders, personality disorders), and thought disorders (eg, psychosis), on the basis of covariation symptoms among these disorders.[39–41] Because borderline personality disorder and bipolar disorder share covariation with disorders from more than one domain,[39,42] we have grouped borderline personality disorder in the externalising domain, and bipolar disorder within the thought disorder domain. Second, we reviewed evidence on the directionality of these relationships—that is, whether alcohol use disorder preceded another psychiatric disorder, or vice versa. To our knowledge, the directionality of these relationships has not been the subject of a broad review to date. Finally, we present evidence on the types of mechanisms used to explain the comorbidity between alcohol use disorder and other psychiatric disorders.

The structure of mental disorders and alcohol use disorder

Contemporary psychiatric epidemiology suggests that developmental pathways for alcohol use disorder are initiated before problematic alcohol use begins,[1,44] and are likely to be

causally related to processes that increase vulnerabilities to externalising and internalising psychiatric disorders.[45,46] The internalising–externalising framework of psychopathology is a statistically derived model that accounts well for the covariation among psychiatric symptoms and disorders in children and adults.[40] This framework has been suggested as a guide for research on common causal pathways underlying lifetime disorder comorbidity, including alcohol use disorder.[45]

Krueger[40] provided the foundational evidence for the factor structure of common mental disorders, suggesting that psychiatric symptoms are dimensional and that comorbidity arises from common, underlying, core psychopathological processes.[1,14] Internalising disorders involve sadness, fear, and rumination, whereas externalising disorders involve rule-breaking and aggression. Since the early 2000s, studies have evaluated the cross-national stability of the internalising–externalising model, replicating and expanding its structure, in which somatoform, psychotic, and thought disorders form a separate domain that is highly correlated with internalising symptoms.[39,47,48]

Alcohol use disorder has been consistently classified within the externalising dimension, although other more extensive psychopathology frameworks have conceptualised the externalising domain as comprising two spectra characterised by identifiable personality counterparts: disinhibited and antagonistic.[49] In this framework, alcohol use disorder fits more purely within the disinhibited spectrum of externalising disorders, conforming to a subfactor characterised by substance use problems.[49]

Alcohol use disorder and disorders within the externalising dimension of psychopathology

Substance use disorders

Compared with other psychiatric disorders, substance use disorders have strong connections to alcohol use disorder. Similar to alcohol use disorder, substance use disorders involve impaired control and negative consequences due to use of an intoxicating or addictive substance. Historically, 40·6% of men and 47·1% of women with alcohol use disorder have also had a lifetime substance use disorder (table).[38]

In US studies published in 2007 and 2015, a DSM-IV alcohol use disorder diagnosed in the past 12 months increased the odds of a substance use disorder by a factor of 5·5,[43] whereas DSM-5 alcohol use disorder increased the odds of substance use disorder by a factor of 3·3.[1] A longitudinal study published in 2016 showed that substance use disorders during early and late adolescence increased the risk for alcohol use disorder in early adulthood by a factor of 3·5 for early adolescence and 4 for late adolescence.[14] The role of alcohol use disorder as a potential cause of substance use disorder is, however, largely unexplored in longitudinal studies.

Two main models have been proposed to explain the relationship between substance use disorders and alcohol use disorder: the gateway hypothesis and the common liability model. The gateway hypothesis describes alcohol use preceding the use of marijuana and other drugs, on the basis of longitudinal studies that show a predictable chronological sequence in

the onset of use. In their foundational study, Kandel and Kandel[50] showed that about 65% of marijuana users started drinking alcohol before they started using marijuana, and about 97% of cocaine users started drinking alcohol before using cocaine. In a study across 17 countries, Degenhardt and colleagues[51] confirmed a common temporal order of drug initiation that is relatively consistent across countries. However, the gateway sequence varies across time and place,[51–53] suggesting that the causal mechanism might be influenced by the social context of which drugs are normative and available. A key mechanism in the gateway hypothesis is the exposure opportunity, in which individuals who are already users of legal substances are more likely to be exposed to illegal drugs within their homes or peer environment.[54] Increasing legal access to marijuana across the world (ie, in the USA, Canada, and Uruguay) could therefore affect the sequence of drug initiation.[53] Although the gateway hypothesis seems to account for drug initiation and non-problematic use, it does not satisfactorily explain the path from alcohol and illicit substance use to alcohol use disorder and substance use disorder. By contrast, the common liability model offers a clearer explanation of this process, by introducing the concept of liability to addiction.[55] In this model, liability denotes a latent characteristic that, when measured, would provide a continuous gradation in which normality is affected.[55] The gradations of normality correspond to variation in the propensity (resulting from genetic and environmental interactions) to develop a psychiatric disorder, in this case alcohol use disorder or substance use disorder.[55,56]

Nicotine use disorder

Upwards of 80% of individuals with DSM-IV alcohol dependence smoke cigarettes, and up to 30% of smokers have DSM-IV alcohol dependence.[57,58] In the USA, individuals with DSM-IV alcohol dependence are three times more likely to smoke than the general population, and people who have tobacco dependence are four times more likely to have alcohol dependence.[16,59] In a German general population study, 18·1% of people who met tobacco dependence criteria had alcohol use disorder (table), by contrast with 3·9% among never-smokers and 7·6% among non-tobacco-dependent ever-smokers.[15]

The longitudinal association between alcohol use disorder and nicotine use disorder is less clear, mainly because of the infrequent measurement of clinical symptoms of nicotine use disorder in epidemiological studies that often measure quantity and frequency of use. However, early initiation of smoking is clearly a risk factor for the development of alcohol use disorder and related problems, including comorbidity of the disorder and nicotine use disorder.[60–62]

Twin and family studies suggest that as much as half the risk for nicotine use disorder and alcohol use disorder is mediated by genetic factors.[63] Shared environmental factors also link alcohol and nicotine use, which can vary across different developmental stages. In a study of adolescent and young adult twins, Koopmans and colleagues[64] observed that environmental factors have a crucial role in the co-use of alcohol and tobacco in early adolescence, particularly among men, whereas genetic factors account for most of the variance in adulthood. The early onset of both alcohol and nicotine use is, by itself, a risk factor for alcohol use disorder and nicotine use disorder.[65] At the neurobiological level, two main

models explain the comorbidity of alcohol and nicotine dependence: the cross-reinforcement and the cross-tolerance.[59] Cross-reinforcement refers to the ability of alcohol and nicotine to enhance the motivation to consume the other substance by acting on shared neurobiological mechanisms that underlie the reinforcement of drug effects (ie, mesolimbic dopamine pathway). The cross-tolerance model proposes that the repeated use of both alcohol and nicotine can facilitate tolerance to the pharmacological effects of one another;[63] eg, chronic nicotine use decreases the effects of alcohol,[66] causing an escalation of alcohol use and subsequently the progression to alcohol use disorder.[59]

Personality disorders

Although only antisocial personality disorder has been consistently classified within the externalising domain,[67,68] borderline personality disorder also commonly co-occurs with alcohol use disorder.[17] Individuals with antisocial personality disorder engage in aggressive and abusive relationships, lack empathy, engage in risk taking, lie, and manipulate; whereas individuals with borderline personality disorder engage in risk-taking behaviour and have intense relationships, distorted self-image, and suicidal behaviour. A 1995 review indicated a median prevalence of antisocial personality disorder of 18% and borderline personality disorder of 21%, in people with alcohol use disorder (table).[18] In a 2018 meta-analysis, however, the lifetime prevalence of alcohol use disorder was 77% in people with antisocial personality disorder, 52% in people with borderline personality disorder, and 39% in people with other personality disorders (including combined or undifferentiated personality disorder).[17]

In a 2012–13 US epidemiological study, the odds for antisocial personality disorder were 1·7 in individuals with moderate lifetime alcohol use disorder and 2·4 in individuals with severe lifetime alcohol use disorder, and the odds for borderline personality disorder were 1·5 in individuals with moderate lifetime alcohol use disorder and 2·5 in individuals with severe lifetime alcohol use disorder.[1] The excess prevalence of alcohol use disorder in people with personality disorders, and vice versa, is particularly challenging in the context of treatment, mainly because of the lower retention of people with personality disorders in alcohol use disorder treatments.[69,70] Studies exploring the longitudinal association between personality disorders and alcohol use disorder are lacking, although personality traits of antisocial personality disorder and borderline personality disorder generally precede alcohol use disorder.[71,72]

Alcohol use disorder and personality disorder comorbidity, particularly antisocial personality disorder and borderline personality disorder, is hypothesised to operate through behavioural disinhibition.[73] This hypothesis posits that individuals with antisocial and impulsive traits have lower thresholds to deviant behaviours, which added to low constraint, low harm avoidance, and lack of social conformity, favours the engagement in early alcohol use and development of alcohol use disorder.[72,73] In a study of adoptees in Sweden, low harm avoidance and high novelty seeking at age 11 years exponentially increased the risk for alcohol abuse at age 27 years.[71] This study, started more than 50 years ago, has provided valuable insights into how personality traits in childhood predict alcohol misuse in later life. In addition to the plausible direct effect of personality disorders on alcohol use disorder,

indirect path ways have also been proposed. For example, personality traits of people with personality disorders have been linked to known social and environmental risk factors for alcohol use disorder, such as deficient socialisation, school performance, family functioning, and deviant peers.[74–76] Although the role and strength of these mediating factors is not well described in the context of causal analysis, the known predictive power of these factors in personality disorder and alcohol use disorder is indicative for this potential indirect causal pathway.

Alcohol use disorder and disorders within the internalising dimension of psychopathology

Major depressive disorder (MDD)

Lifetime prevalence of alcohol use disorder in those with lifetime MDD ranges from approximately 27% to 40% across epidemiological studies in the USA[77–79] with a median prevalence of 30% across 35 studies.[19] The prevalence of MDD in people with current alcohol use disorder (past 12 months) ranges from 4% to 22%.[20]

The link between these two conditions is complex. A 2008 longitudinal study found that depressive symptoms in childhood doubled the odds of DSM-IV alcohol dependence in young adulthood.[80] A higher severity of depression, measured through the number and frequency of depressive symptoms, is also associated with initiating alcohol use without parental permission (in boys), early onset of first alcohol intoxication episodes, and presence of alcohol dependence criteria.[80,81] The average ages of onset for alcohol use disorder and MDD are similar, although alcohol use disorder tends to precede MDD more often than vice versa.[82,83] In a meta-analysis of longitudinal and cross-sectional studies, Boden and Fergusson[21] reported that the odds of MDD in people with alcohol use disorder was 2 times higher, and for alcohol use disorder in people with MDD it was 2·1 times higher.

There is a long-standing debate about whether alcohol use disorder and depression are independent disorders or overlapping illnesses connected by common causative factors.[84] The use of alcohol to relieve depressive symptoms (ie, the self-medication hypothesis),[85,86] and the development of depressive symptoms as a result of the social and biological consequences of alcohol use disorder, have both been reported.[21,84,87] Several studies have found common genetic links between depression and alcohol use disorder. For example, in 1874 monozygotic male twins, index twins with a lifetime diagnosis of MDD had 2·8 times higher odds of alcohol use disorder than index twins who did not report an episode of MDD.[88] In another study of 3372 pairs of male twins, MDD in one twin was associated with risk of MDD alone and MDD plus DSM-IV alcohol dependence, but not DSM-IV alcohol dependence alone, in the co-twin.[89] These findings suggest a genetic influence on the development of alcohol use disorder, MDD, and the co-occurrence of these psychiatric disorders. Gene–environment interaction (interaction in which the genetic effect is conditional for expression on environmental triggers) has been studied for both depression and alcohol use disorder;[90,91] comorbidity of these disorders may plausibly arise from exposure to common environmental causes, as suggested by a genome-wide association study in which the relationship between a genetic risk variant (ie, SEMA3A) and the

comorbidity of depression and alcohol use disorder was only present among African Americans.[92]

Attention-deficit hyperactivity disorder (ADHD)

ADHD is a condition marked by impaired ability to maintain focus and attention as well as frequent distraction, restlessness, and impulsive behaviour. Alcohol use disorder in people with ADHD is prevalent, ranging from 19% to 26% of young adults in different countries.[23,24] The prevalence of ADHD in people with alcohol use disorder has a similar range in adolescents,[25] and rises to 33% in adults.[25,26]

Early-onset ADHD has been prospectively associated with future alcohol use and alcohol use disorder.[93] In two meta-analyses of longitudinal studies, the pooled odds ratio for alcohol use disorder in people with ADHD in childhood ranged between 1·35 (95% CI 1·11–1·64) and 1·74 (1·38–2·20), relative to youths without ADHD.[27,28] These findings support the hypothesis of a causal connection between these two disorders, and emphasise the importance of early detection of ADHD in childhood and adolescence.

Studies have shown biological and cognitive differences in individuals with and without ADHD that might be related to the increased risk of alcohol use disorder in this population.[94] In a meta-analysis of case-control and family studies, Faraone and colleagues[95] found that the pooled odds ratio of having a D4 dopamine receptor mutation in people with ADHD ranged from 1·4 to 1·9.[95] When the dopamine system is altered, the effect of alcohol on the dopamine system is similar to the use of stimulant medications commonly used to treat ADHD.[94] Studies that use functional neuroimaging have shown hypoactivation of the prefrontal cortex in individuals with ADHD when performing brain activation tasks (eg, go/no go tasks).[96,97] The prefrontal cortex is essential for the development of executive functions, including planning, reasoning, and inhibition control; alterations of these functions have been indicated as a predictor of alcohol initiation and heavy drinking.[98]

Anxiety disorders

The group of disorders classified as anxiety disorders (eg, generalised anxiety disorder, social anxiety, and panic disorder), and alcohol use disorder, are among the five most prevalent psychiatric diagnoses in the USA.[99] Comor bid alcohol use disorder and anxiety disorder is a common dual diagnosis; the estimated prevalence of alcohol use disorder among people with anxiety disorders in epidemiological surveys across countries ranges from 20% to 40%.[20]

The adjusted odds ratio of the 12-month comorbidity between alcohol use disorder and anxiety disorder ranges from 2·1 to 3·3 across epidemiological studies, with generalised anxiety disorder, social anxiety, and panic disorder showing the strongest association with alcohol use disorder.[100] However, in a nationally representative study in the USA, past year DSM-5 alcohol use disorder (moderate and severe) was not associated with any anxiety disorders, whereas lifetime association was mostly weak (from 1·2 to 1·4), and only significant for any anxiety disorder, panic disorder, specific phobia, and generalised anxiety disorder.[1] Although there is support for a longitudinal association in both directions (alcohol use disorder to anxiety disorders and anxiety disorders to alcohol use disorder), consistency

and precision of estimates tends to be weak, and confidence intervals often include the null value (table).[22,29]

Family and twin studies have shown that genetic and environmental factors are both important contributors to alcohol use disorder and anxiety disorder comorbidity.[101] For example, Maier and colleagues[102] have found a significantly increased risk of comorbidity among family members of individuals with anxiety disorder alone or alcohol use disorder alone, and Hodgson and colleagues have reported shared genetic underpinnings of alcohol use disorder and anxiety disorder.[103] A 2017 systematic review identified six studies on risk factors for comorbid social anxiety disorder and alcohol use disorder in adolescents. The identified risk factors included female sex, peer acceptance, and affective problems, as well as other co-occurring disorders, such as depression, generalised anxiety disorder, agoraphobia, separation anxiety, and obsessive-compulsive disorder.[104] The hypothesis that anxiety disorder causes alcohol use disorder has also been considered as a plausible mechanism for the comorbidity between these two conditions.[101] Some anxiety disorders, such as social anxiety disorder, precede alcohol use disorder in up to 80% of cases.[105] Alcohol might be used to cope with anxiety symptoms, thus increasing the likelihood of developing alcohol use disorder.[85] A prospective study of young adults between 19 and 21 years old at baseline found that social anxiety disorder increased the risk of alcohol use disorder onset, particularly among women, but not the other way around.[106] Additionally, the odds of developing alcohol use disorder in people with anxiety (including panic disorder, social and specific phobia, and generalised anxiety disorder) who self-medicate with alcohol was 2·5 (95% CI 1·26–4·97).[107] Yet, the strength of the evidence for the causal connection between anxiety disorder and alcohol use disorder is still debated. For example, in a birth cohort of 1265 children in New Zealand followed up for 21 years, the odds for developing alcohol use disorder among people with anxiety disorder were 1·99 times higher than for people without anxiety disorder; however, after adjusting for other childhood factors (eg, depression and peer affiliations) the strength of the association was attenuated and became statistically non-significant.[29]

Post-traumatic stress disorder (PTSD)

PTSD is characterised by intrusive thoughts and anxiety following exposure to trauma. Prevalence of comorbid alcohol use disorder in individuals in the general population meeting criteria for PTSD ranges between 34% (Brazil) and 55% (USA).[30,31] Among German patients receiving alcohol use disorder treatment, the prevalence of PTSD was 22·9%,[32] whereas in the US general population with alcohol use disorder the prevalence of PTSD was 26·2% in women, which was 2·5 times higher than in men (table).[38]

Although studies addressing the longitudinal association between PTSD and alcohol use disorder are lacking, the general consensus is that PTSD tends to precede the onset of alcohol use disorder.[108,109] For example, in a longitudinal study of US troops screened before and after deployment to Iraq, predeployment alcohol use was unrelated to the onset of PTSD; however, PTSD symptoms substantially increased the risk of screening positive for new-onset alcohol use disorder.[33] Research also suggests that although alcohol consumption generally increases after exposure to a traumatic event (a necessary although not sufficient

condition for PTSD),[110] such increases are relatively acute, and development of alcohol use disorder after exposure to a traumatic event is almost entirely restricted to those with problem alcohol use preceding trauma.[111]

As with other psychiatric disorders, the relationship between PTSD and alcohol use disorder could have other causal pathways. For example, alcohol use is a risk factor for being victimised, including sexual victimisation (particularly of women[112]) and aggravated assaults, and thus drinking alcohol or alcohol use disorder might indirectly increase the risk of PTSD.[112,113] Alcohol use disorder can also affect the psychological mechanisms used to cope with traumatic events, increasing individual vulnerability to anxiety symptoms, including PTSD.[101] Furthermore, common risk factors of both PTSD and alcohol use disorder have been examined, including previous history of depression and other psychiatric disorders,[114,115] and early life stressors, such as inter personal violence, emotional abuse in childhood, and socio-economic deprivation.[108] However, the evidence for a causal direct or indirect connection between PTSD and alcohol use disorder remains inconclusive.

Alcohol use disorder and thought disorder

Schizophrenia and psychotic disorders

Alcohol use disorder is the second most frequent form of comorbidity in patients diagnosed with schizophrenia, after nicotine dependence.[116] In a 2009 systematic review and meta-analysis, the median lifetime prevalence of alcohol use disorder in patients diagnosed with schizophrenia was 21% and current prevalence in this group was 11%.[34] In the WHO's World Mental Health Survey,[35] which includes nationally representative samples of 18 countries, the prevalence of lifetime alcohol use disorder in people with psychotic experiences was 17·1%, in contrast to 7·2% in people without a previous history of psychotic experiences.[35]

In the World Mental Health Survey, the adjusted odds ratio of psychotic experiences given previous history of alcohol use disorder was 1·6 (95% CI 1·2–2·0), whereas the odds ratio of alcohol use disorder given previous history of psychotic experiences was 1·5 (1·2–2·0).[35] These results support the hypothesis of a bidirectional relationship between alcohol use disorder and psychotic experiences, even after adjusting for antecedent mental disorders.[35]

Family and twin studies show that individuals diagnosed with schizophrenia who have first-degree relatives who meet diagnostic criteria for alcohol use disorder have a greater risk of this disorder than other individuals with schizophrenia.[117] The incidence of schizophrenia, however, is not increased in the children of parents with alcohol use disorder, and the incidence of this disorder in family members is also not increased in individuals with schizophrenia but not with comorbid alcohol use disorder.[118,119] Common exposures and life experiences are also distinctive in these groups. Patients diagnosed with schizophrenia with alcohol use disorder are often exposed to conditions that increase their risk for excessive alcohol use (thus increasing their risk for developing the disorder), such as lower educational attainment, homelessness, and childhood conduct problems.[120] Overall, the extent of the neurobiological understanding of the comorbidity of alcohol use disorder and schizophrenia is still limited. Evidence suggests that alcohol-induced psychotic disorder is a

separate entity that can be clinically distinguished from Wernicke's encephalopathy, Korsakoff's psychosis, alcohol-induced dementia, alcohol-withdrawal delirium, and schizophrenia.[121] Patients with alcohol-induced psychotic disorder represent about a third of patients experiencing psychotic symptoms associated with alcohol dependence[121,122] and lifetime prevalence of this disorder in people with alcohol dependence is 4% in the European population.[123] Various hypotheses about alcohol-induced psychotic disorder development have been proposed. It can occur secondary to schizophrenia (ie, the self-medication hypothesis), as an underlying form of schizophrenia triggered by excessive alcohol use, as a direct toxic effect of alcohol, and as a coincidental occurrence of schizophrenia in someone with alcohol use disorder.[121,124] Although evidence for all these four causal hypotheses exists, the overall conclusion is that more evidence is needed to draw definitive answers.[121]

Bipolar disorder

Epidemiological and clinical studies have found high prevalence of comorbid alcohol use disorder in patients with bipolar disorder. In a systematic review in treatment-seeking patients (both inpatients and outpatients) with bipolar disorder, the prevalence of alcohol use disorder across the reviewed studies (reflecting data from 65 785 patients) was 42%, higher than that of any other substance.[125] In the general population, the prevalence ranges between 24% and 44% in people with any bipolar disorder or type I bipolar disorder (characterised by depressive symptoms and manic episodes), and between 24% and 39% for patients with type II bipolar disorder (characterised by depressive symptoms and hypomanic episodes).[36]

Overall, evidence suggests that patients with bipolar disorder with current or past history of comorbid alcohol use disorder show more severe or more widespread neurocognitive deficits than patients without bipolar disorder, although information on the long-term health effects of this comorbidity is still scarce.[126,127]

Bipolar disorder is highly heritable, with a family history in about 80% of patients.[127] The hypothesis of alcohol use disorder causing bipolar disorder could then be framed as alcohol use disorder triggering a predisposition towards bipolar disorder. This hypothesis has little empirical evidence,[127,128] although studies suggest that alcohol use disorder destabilises the longitudinal course of illness for patients with bipolar disorder.[129] The self-medication hypothesis has also been analysed; however, no consensus exists for mechanisms that would explain the full spectrum of alcohol use disorder and bipolar disorder comorbidity.[127]

Gaps in knowledge and recommendations for future research

As we have shown in this Series paper, alcohol use disorder co-occurs with a wide range of other psychiatric disorders. This disorder is most commonly comorbid with disorders on the externalising spectrum, including substance use disorders, nicotine dependence, antisocial personality disorder, and other disorders characterised by unconstrained and socially unadjusted behaviour. Mechanisms that explain comorbidity remain under investigation, but generally involve both common liability (eg, genetic and environmental underpinnings), and reinforcing and reciprocal direct causal relationships.

Comorbidity research: the next decade

The structure of comorbidity itself remains an active area of research.[49] Classification systems categorise disorders as either present or absent, on the basis of a set of diagnostic criteria, and assume that boundaries are stable across diagnoses. However, the dimensional nature of these disorders suggests that dichotomies and separation across disorders are not accurate representations of the way that psychiatric and substance use symptoms are organised in populations.[46] Within the diagnosis of alcohol use disorder, evidence is substantial for dimensionality rather than presence or absence of alcoholism.[130,131] However, a broader debate remains about the nature of the correlation between alcohol use disorder symptoms and other psychopathological disorders.

Many classification systems have been proposed to replace or augment a dichotomous classification system. These include the transdiagnostic risk factor model that incorporates dimensions of psychopathology,[41] ranging from a basic two-factor model to broader structures.[39] These structures have been formalised through several different research programmes. The Hierarchical Taxonomy of Psychopathology initiative,[49] for example, aims to provide both researchers and clinicians with a new measurement and diagnostic system for mental disorders. Dimensional representations of comorbidity have also been formalised as a p-factor,[132] conceptualised similarly to a general dimension of intelligence from which several different subfactors can emerge. Caspi and colleagues[132] propose that this general psychopathological factor emerges in different stages across the lifespan, and should be reconceptualised more broadly than typical co-occurrence of thought or behaviour symptoms to include cognitive ability and a range of other traits, which then unfold across the life course in specific ways (such as alcohol use disorder), depending largely on environmental factors (eg, alcohol availability). Still more broadly, the US National Institute of Mental Health[133] has launched an agenda to redefine classification symptoms. Although diagnostic indicators of pathology across these domains have yet to be identified for many disorders, the framework in place for the use of new scientific information to better understand comorbidity across psychopathological symptoms remains an important future direction for research. Science is changing to represent the causal direction of comorbid symptoms of psychopathology as a network,[134] rather than straightforward correlations or associations. Because symptoms arise from a common source of dysfunction, this model assumes that symptoms are directionally caused, which implies that intervening on one or several symptoms that are key to the network can prevent the broader cascade of psychopathology (see panel for additional information on integrated treatment for alcohol use disorder and other psychiatric comorbidities).

Alcohol consumption and disorders over time: implications for comorbidity research

Comorbidity between alcohol use disorder and other disorders is often assumed to be immutable, given that what underlies the association between alcohol use disorder and other psychopathology is rooted in causal associations with common causes and outcomes. The next decade of research, however, will need to contend with rapidly shifting patterns of psychopathology in populations, and the implications of these shifts for the strength and nature of comorbidity. Indeed, per capita consumption of alcohol in the USA,[145] and several other countries, has been increasing gradually for approximately 10 years. Although not all

data sources agree,[146] several existing data sources indicate that alcohol use disorder and alcohol-related hospitalisations have also increased.[147–149] At the same time, non-medical opioid use, opioid use disorder, and opioid overdoses have increased exponentially in the US population,[150] as well as cannabis use, cannabis use disorder, depression, suicidal behaviour, and suicide.[151–156] The extent to which these increases affect comorbidity depends on changes in the prevalence of factors that are causally related to increases across these dimensions. For example, if alcohol use is a causal factor in some cases of depression and suicide, then increases in the population prevalence of alcohol use and alcohol use disorder would lead to an increase in mental health problems, and the strength of comorbidity would be expected to remain relatively constant. If, however, a different array of causal factors underlies each of these dimensions, then the strength of the association with alcohol use disorder might shift and change over time. For example, alcohol use and alcohol use disorder might increase because of de creases in price (eg, as inflation-adjusted value of taxation decreases),[157] whereas depression might increase because of rising unemployment.

Conclusion: causal inference remains crucial

In this Series paper we have summarised a large body of literature and discussed the strength of comorbidity between alcohol use disorder and other psychopathology. Throughout, we have discussed evidence for what causal relationships underlie these associations—ie, is alcohol use disorder associated with other disorders because it causes other psychopathology, because psychopathology causes alcohol use disorder, or because they both share common causes? Should the answer be “all of the above”, what would the implications be for how we design and implement interventions? Answering these questions is difficult from a causal inference standpoint, given that we cannot randomly assign individuals to alcohol use or psychiatric disorders. Creative study designs and novel tests of causal hypotheses are crucial to advancing this research agenda, understanding the causes of comorbidity, and ultimately in determining the best way to intervene to improve health and wellness in the population. Alcohol use disorder remains among the most common mental health problems in the population. Points of intervention that include concomitant identification of comorbid substance use and other psychiatric disorders are needed. Epidemiological and experimental research designed to untangle the associations between alcohol use disorder and other disorders across time will continue to be an exciting and necessary avenue of research.

Acknowledgments

ACC was supported by the Comisión Nacional de Investigación Científica y Tecnológica of Chile (FONDECYT Regular 1191282). KMK was supported by the National Institute on Alcohol Abuse and Alcoholism (K01AA021511) and the National Institute on Drug Abuse (R21DA041154). DSH was supported by the National Institute on Drug Abuse (R01DA018652), the National Institute on Alcohol Abuse and Alcoholism (R01AA025309), and the New York State Psychiatric Institute. MC was supported by the National Institute on Drug Abuse (R21DA041154). The views expressed in this publication are those of the authors and do not necessarily represent the views or policies of the US National Institutes of Health.

References

1. 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: 757–66. [PubMed: 26039070]
2. GBD 2016 Alcohol Collaborators. Alcohol use and burden for 195 countries and territories, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet 2018; 392: 1015–35. [PubMed: 30146330]
3. GBD 2017 DALYs and HALE Collaborators. Global, regional, and national disability-adjusted life-years (DALYs) for 359 diseases and injuries and healthy life expectancy (HALE) for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet 2018; 392: 1859–22. [PubMed: 30415748]
4. GBD 2013 Risk Factors Collaborators. Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet 2015; 386: 2287–323. [PubMed: 26364544]
5. Cargiulo T. Understanding the health impact of alcohol dependence. Am J Health Syst Pharm 2007; 64 (suppl 3): S5–11.
6. Rehm J. The risks associated with alcohol use and alcoholism. Alcohol Res Health 2011; 34: 135–43. [PubMed: 22330211]
7. Whiteford HA, Degenhardt L, Rehm J, et al. Global burden of disease attributable to mental and substance use disorders: findings from the Global Burden of Disease Study 2010. Lancet 2013; 382: 1575–86. [PubMed: 23993280]
8. de Graaf R, Bijl RV, Smit F, Vollebergh WA, Spijker J. Risk factors for 12-month comorbidity of mood, anxiety, and substance use disorders: findings from the Netherlands Mental Health Survey and Incidence Study. Am J Psychiatry 2002; 159: 620–29. [PubMed: 11925301]
9. 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: 807–16. [PubMed: 15289279]
10. Melchior M, Prokofyeva E, Younes N, Surkan PJ, Martins SS. Treatment for illegal drug use disorders: the role of comorbid mood and anxiety disorders. BMC Psychiatry 2014; 14: 89. [PubMed: 24670230]
11. Sorensen T, Jespersen HSR, Vinberg M, Becker U, Ekholm O, Fink-Jensen A. Substance use among Danish psychiatric patients: a cross-sectional study. Nord J Psychiatry 2018; 72: 130–16. [PubMed: 29117747]
12. Preuss UW, Gouzoulis-Mayfrank E, Havemann-Reinecke U, et al. Psychiatric comorbidity in alcohol use disorders: results from the German S3 guidelines. Eur Arch Psychiatry Clin Neurosci 2018; 268: 219–29. [PubMed: 28439723]
13. Jane-Llopis E, Matytsina I. Mental health and alcohol, drugs and tobacco: a review of the comorbidity between mental disorders and the use of alcohol, tobacco and illicit drugs. Drug Alcohol Rev 2006; 25: 515–36. [PubMed: 17132571]
14. Farmer RF, Gau JM, Seeley JR, Kosty DB, Sher KJ, Lewinsohn PM. Internalizing and externalizing disorders as predictors of alcohol use disorder onset during three developmental periods. Drug Alcohol Depend 2016; 164: 38–46. [PubMed: 27141839]
15. Schumann A, Hapke U, Meyer C, Rumpf HJ, John U. Prevalence, characteristics, associated mental disorders and predictors of DSM-IV nicotine dependence. Eur Addict Res 2004; 10: 29–34. [PubMed: 14665803]
16. Grant BF, Hasin DS, Chou SP, Stinson FS, Dawson DA. Nicotine dependence and psychiatric disorders in the United States: results from the national epidemiologic survey on alcohol and related conditions. Arch Gen Psychiatry 2004; 61: 1107–15. [PubMed: 15520358]
17. Guy N, Newton-Howes G, Ford H, Williman J, Foulds J. The prevalence of comorbid alcohol use disorder in the presence of personality disorder: systematic review and explanatory modelling. Personal Ment Health 2018; 12: 216–28. [PubMed: 29611335]

18. Verheul R, van den Brink W, Hartgers C. Prevalence of personality disorders among alcoholics and drug addicts: an overview. Eur Addict Res 1995; 1: 166–77.
19. 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: 330–41. [PubMed: 15808128]
20. Lai HM, Cleary M, Sitharthan T, Hunt GE. Prevalence of comorbid substance use, anxiety and mood disorders in epidemiological surveys, 1990–2014: a systematic review and meta-analysis. Drug Alcohol Depend 2015; 154: 1–13. [PubMed: 26072219]
21. Boden JM, Fergusson DM. Alcohol and depression. Addiction 2011; 106: 906–14. [PubMed: 21382111]
22. Bellos S, Skapinakis P, Rai D, et al. Longitudinal association between different levels of alcohol consumption and a new onset of depression and generalized anxiety disorder: results from an international study in primary care. Psychiatry Res 2016; 243: 30–34. [PubMed: 27344590]
23. Romo L, Ladner J, Kotbagi G, et al. Attention-deficit hyperactivity disorder and addictions (substance and behavioral): prevalence and characteristics in a multicenter study in France. J Behav Addict 2018; 7: 743–51. [PubMed: 30010409]
24. Riegler A, Volkl-Kernstock S, Lesch O, Walter H, Skala K. Attention deficit hyperactivity disorder and substance abuse: an investigation in young Austrian males. J Affect Disord 2017; 217: 60–65. [PubMed: 28391109]
25. van Emmerik-van Oortmerssen K, van de Glind G, van den Brink W, et al. Prevalence of attention-deficit hyperactivity disorder in substance use disorder patients: a meta-analysis and meta-regression analysis. Drug Alcohol Depend 2012; 122: 11–19. [PubMed: 22209385]
26. Ohlmeier MD, Peters K, Te Wildt BT, et al. Comorbidity of alcohol and substance dependence with attention-deficit/hyperactivity disorder (ADHD). Alcohol Alcohol 2008; 43: 300–14. [PubMed: 18326548]
27. Charach A, Yeung E, Climans T, Lillie E. Childhood attention-deficit/hyperactivity disorder and future substance use disorders: comparative meta-analyses. J Am Acad Child Adolesc Psychiatry 2011; 50: 9–21. [PubMed: 21156266]
28. Lee SS, Humphreys KL, Flory K, Liu R, Glass K. Prospective association of childhood attention-deficit/hyperactivity disorder (ADHD) and substance use and abuse/dependence: a meta-analytic review. Clin Psychol Rev 2011; 31: 328–41. [PubMed: 21382538]
29. Goodwin RD, Fergusson DM, Horwood LJ. Association between anxiety disorders and substance use disorders among young persons: results of a 21-year longitudinal study. J Psychiatr Res 2004; 38: 295–304. [PubMed: 15003435]
30. de Matos MB, de Mola CL, Trettim JP, et al. Psychoactive substance abuse and dependence and its association with anxiety disorders: a population-based study of young adults in Brazil. Rev Bras Psiquiatr 2018; 40: 349–53. [PubMed: 29451585]
31. Smith SM, Goldstein RB, Grant BF. The association between post-traumatic stress disorder and lifetime DSM-5 psychiatric disorders among veterans: data from the National Epidemiologic Survey on Alcohol and Related Conditions-III (NESARC-III). J Psychiatr Res 2016; 82: 16–22. [PubMed: 27455424]
32. Driessen M, Schulte S, Luedecke C, et al. Trauma and PTSD in patients with alcohol, drug, or dual dependence: a multi-center study. Alcohol Clin Exp Res 2008; 32: 481–88. [PubMed: 18215214]
33. Kline A, Weiner MD, Ciccone DS, Interian A, St Hill L, Losonczy M. Increased risk of alcohol dependency in a cohort of national guard troops with PTSD: a longitudinal study. J Psychiatr Res 2014; 50: 18–25. [PubMed: 24332924]
34. Koskinen J, Lohonen J, Koponen H, Isohanni M, Miettunen J. Prevalence of alcohol use disorders in schizophrenia—a systematic review and meta-analysis. Acta Psychiatr Scand 2009; 120: 85–96. [PubMed: 19374633]
35. Degenhardt L, Saha S, Lim CCW, et al. The associations between psychotic experiences and substance use and substance use disorders: findings from the World Health Organization World Mental Health Surveys. Addiction 2018; 113: 924–34. [PubMed: 29284197]
36. Hunt GE, Malhi GS, Cleary M, Lai HM, Sitharthan T. Comorbidity of bipolar and substance use disorders in national surveys of general populations, 1990–2015: systematic review and meta-analysis. J Affect Disord 2016; 206: 321–30. [PubMed: 27426694]

37. 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: 2511–18. [PubMed: 2232018]
38. Kessler RC, Crum RM, Warner LA, Nelson CB, Schulenberg J, Anthony JC. 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: 313–21. [PubMed: 9107147]
39. Keyes KM, Eaton NR, Krueger RF, et al. Thought disorder in the meta-structure of psychopathology. Psychol Med 2013; 43: 1673–83. [PubMed: 23171498]
40. Krueger RF. The structure of common mental disorders. Arch Gen Psychiatry 1999; 56: 921–16. [PubMed: 10530634]
41. Eaton NR, Rodriguez-Seijas C, Carragher N, Krueger RF. Transdiagnostic factors of psychopathology and substance use disorders: a review. Soc Psychiatry Psychiatr Epidemiol 2015; 50: 171–82. [PubMed: 25563838]
42. 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: 1041–50. [PubMed: 20836905]
43. Hasin DS, Stinson FS, Ogburn E, Grant BF. 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: 830–42. [PubMed: 17606817]
44. Clark DB. The natural history of adolescent alcohol use disorders. Addiction 2004; 99 (suppl 2): 5–22.
45. Hussong AM, Jones DJ, Stein GL, Baucom DH, Boeding S. An internalizing pathway to alcohol use and disorder. Psychol Addict Behav 2011; 25: 390–404. [PubMed: 21823762]
46. Krueger RF, Markon KE. Reinterpreting comorbidity: a model-based approach to understanding and classifying psychopathology. Annu Rev Clin Psychol 2006; 2: 111–33. [PubMed: 17716066]
47. de Jonge P, Wardenaar KJ, Lim CCW, et al. The cross-national structure of mental disorders: results from the World Mental Health surveys. Psychol Med 2018; 48: 2073–84. [PubMed: 29254513]
48. Kotov R, Ruggero CJ, Krueger RF, Watson D, Yuan Q, Zimmerman M. New dimensions in the quantitative classification of mental illness. Arch Gen Psychiatry 2011; 68: 1003–11. [PubMed: 21969458]
49. 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: 454–77. [PubMed: 28333488]
50. Kandel D, Kandel E. The gateway hypothesis of substance abuse: developmental, biological and societal perspectives. Acta Paediatr 2015; 104: 130–17. [PubMed: 25377988]
51. Degenhardt L, Dierker L, Chiu WT, et al. Evaluating the drug use “gateway” theory using cross-national data: consistency and associations of the order of initiation of drug use among participants in the WHO World Mental Health Surveys. Drug Alcohol Depend 2010; 108: 84–97. [PubMed: 20060657]
52. Tarter RE, Vanyukov M, Kirisci L, Reynolds M, Clark DB. Predictors of marijuana use in adolescents before and after licit drug use: examination of the gateway hypothesis. Am J Psychiatry 2006; 163: 2134–40. [PubMed: 17151165]
53. Keyes KM, Rutherford C, Miech RA. Historical trends in the grade of onset and sequence of cigarette, alcohol, and marijuana use among adolescents from 1976–2016: implications for “Gateway” patterns in adolescence. Drug Alcohol Depend 2019; 194: 51–58. [PubMed: 30399500]
54. Wagner FA, Anthony JC. Into the world of illegal drug use: exposure opportunity and other mechanisms linking the use of alcohol, tobacco, marijuana, and cocaine. Am J Epidemiol 2002; 155: 918–25. [PubMed: 11994231]
55. Vanyukov MM, Tarter RE, Kirillova GP, et al. Common liability to addiction and “gateway hypothesis”: theoretical, empirical and evolutionary perspective. Drug Alcohol Depend 2012; 123 (suppl 1): S3–17. [PubMed: 22261179]

56. Kendler KS, Myers J, Prescott CA. Specificity of genetic and environmental risk factors for symptoms of cannabis, cocaine, alcohol, caffeine, and nicotine dependence. Arch Gen Psychiatry 2007; 64: 1313–20. [PubMed: 17984400]
57. Hertling I, Ramskogler K, Dvorak A, et al. Craving and other characteristics of the comorbidity of alcohol and nicotine dependence. Eur Psychiatry 2005; 20: 442–50. [PubMed: 16095883]
58. Miller NS, Gold MS. Comorbid cigarette and alcohol addiction: epidemiology and treatment. J Addict Dis 1998; 17: 55–66. [PubMed: 9549603]
59. Adams S. Psychopharmacology of tobacco and alcohol comorbidity: a review of current evidence. Curr Addict Rep 2017; 4: 25–34. [PubMed: 28357192]
60. Slade EP, Stuart EA, Salkever DS, Karakus M, Green KM, Ialongo N. Impacts of age of onset of substance use disorders on risk of adult incarceration among disadvantaged urban youth: a propensity score matching approach. Drug Alcohol Depend 2008; 95: 1–13. [PubMed: 18242006]
61. Lewinsohn PM, Rohde P, Brown RA. Level of current and past adolescent cigarette smoking as predictors of future substance use disorders in young adulthood. Addiction 1999; 94: 913–21. [PubMed: 10665079]
62. Riala K, Hakko H, Isohanni M, Jarvelin MR, Rasanen P. Teenage smoking and substance use as predictors of severe alcohol problems in late adolescence and in young adulthood. J Adolesc Health 2004; 35: 245–54. [PubMed: 15313508]
63. Schlaepfer IR, Hoft NR, Ehringer MA. The genetic components of alcohol and nicotine co-addiction: from genes to behavior. Curr Drug Abuse Rev 2008; 1: 124–34. [PubMed: 19492010]
64. Koopmans JR, van Doornen LJ, Boomsma DI. Association between alcohol use and smoking in adolescent and young adult twins: a bivariate genetic analysis. Alcohol Clin Exp Res 1997; 21: 537–46.
65. Jackson KM, Sher KJ, Wood PK. Prospective analysis of comorbidity: tobacco and alcohol use disorders. J Abnorm Psychol 2000; 109: 679–94. [PubMed: 11195992]
66. Madden PA, Heath AC, Starmer GA, Whitfield JB, Martin NG. Alcohol sensitivity and smoking history in men and women. Alcohol Clin Exp Res 1995; 1: 1111–20.
67. Krueger RF, Markon KE, Patrick CJ, Iacono WG. Externalizing psychopathology in adulthood: a dimensional-spectrum conceptualization and its implications for DSM-V. J Abnorm Psychol 2005; 114: 537–50. [PubMed: 16351376]
68. Lilienfeld SO. Comorbidity between and within childhood externalizing and internalizing disorders: reflections and directions. J Abnorm Child Psychol 2003; 31: 285–91. [PubMed: 12774861]
69. Newton-Howes G, Foulds J. Personality disorder and treatment outcome in alcohol use disorder. Curr Opin Psychiatry 2018; 31: 50–56. [PubMed: 29059106]
70. Newton-Howes GM, Foulds JA, Guy NH, Boden JM, Mulder RT. Personality disorder and alcohol treatment outcome: systematic review and meta-analysis. Br J Psychiatry 2017; 211: 22–30. [PubMed: 28385703]
71. Cloninger CR, Sigvardsson S, Bohman M. Childhood personality predicts alcohol abuse in young adults. Alcohol Clin Exp Res 1988; 12: 494–505. [PubMed: 3056070]
72. Newton-Howes G, Horwood J, Mulder R. Personality characteristics in childhood and outcomes in adulthood: findings from a 30 year longitudinal study. Aust N Z J Psychiatry 2015; 49: 377–86. [PubMed: 25688124]
73. Verheul R, van den Brink W. The role of personality pathology in the aetiology and treatment of substance use disorders. Curr Opin Psychiatry 2000; 13: 163–69.
74. Fergusson DM, Swain-Campbell NR, Horwood LJ. Deviant peer affiliations, crime and substance use: a fixed effects regression analysis. J Abnorm Child Psychol 2002; 30: 419–30. [PubMed: 12108769]
75. Wills TA, Windle M, Cleary SD. Temperament and novelty seeking in adolescent substance use: convergence of dimensions of temperament with constructs from Cloninger's theory. J Pers Soc Psychol 1998; 74: 387–406. [PubMed: 9491584]
76. Newton-Howes G, Foulds J. Personality disorder and alcohol use disorder: an overview. Psychopathology 2018; 51: 130–16. [PubMed: 29466805]

77. Kessler RC, Berglund P, Demler O, et al. The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). JAMA 2003; 289: 3095–105. [PubMed: 12813115]

78. Grant BF, Harford TC. Comorbidity between DSM-IV alcohol use disorders and major depression: results of a national survey. Drug Alcohol Depend 1995; 39: 197–206. [PubMed: 8556968]

79. Hasin DS, Sarvet AL, Meyers JL, et al. Epidemiology of adult DSM-5 major depressive disorder and its specifiers in the United States. JAMA Psychiatry 2018; 75: 336–46. [PubMed: 29450462]

80. Crum RM, Green KM, Storr CL, et al. Depressed mood in childhood and subsequent alcohol use through adolescence and young adulthood. Arch Gen Psychiatry 2008; 65: 702–12. [PubMed: 18519828]

81. Crum RM, Storr CL, Ialongo N, Anthony JC. Is depressed mood in childhood associated with an increased risk for initiation of alcohol use during early adolescence? Addict Behav 2008; 33: 24–40. [PubMed: 17587505]

82. 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: 234–45. [PubMed: 18215474]

83. Fink DS, Gallaway MS, Tamburrino MB, et al. Onset of alcohol use disorders and comorbid psychiatric disorders in a military cohort: are there critical periods for prevention of alcohol use disorders? Prev Sci 2016; 17: 347–56. [PubMed: 26687202]

84. Davis L, Uezato A, Newell JM, Frazier E. Major depression and comorbid substance use disorders. Curr Opin Psychiatry 2008; 21: 14–18. [PubMed: 18281835]

85. Turner S, Mota N, Bolton J, Sareen J. Self-medication with alcohol or drugs for mood and anxiety disorders: a narrative review of the epidemiological literature. Depress Anxiety 2018; 35: 851–60. [PubMed: 29999576]

86. Khantzian EJ. The self-medication hypothesis of substance use disorders: a reconsideration and recent applications. Harv Rev Psychiatry 1997; 4: 231–44. [PubMed: 9385000]

87. Agosti V, Levin FR. The effects of alcohol and drug dependence on the course of depression. Am J Addict 2006; 15: 71–75. [PubMed: 16449095]

88. Lin N, Eisen SA, Scherrer JF, et al. The influence of familial and non-familial factors on the association between major depression and substance abuse/dependence in 1874 monozygotic male twin pairs. Drug Alcohol Depend 1996; 43: 49–55. [PubMed: 8957142]

89. Lyons MJ, Schultz M, Neale M, et al. Specificity of familial vulnerability for alcoholism versus major depression in men. J Nerv Ment Dis 2006; 194: 809–17. [PubMed: 17102704]

90. Rose RJ, Dick DM. Gene–environment interplay in adolescent drinking behavior. Alcohol Res Health 2004; 28: 222–29.

91. Dick DM. Gene-environment interaction in psychological traits and disorders. Annu Rev Clin Psychol 2011; 7: 383–409. [PubMed: 21219196]

92. Zhou H, Polimanti R, Yang BZ, et al. Genetic risk variants associated with comorbid alcohol dependence and major depression. JAMA Psychiatry 2017; 74: 1234–41. [PubMed: 29071344]

93. Squeglia LM, Brammer WA, Ray LA, Lee SS. Attention deficit/hyperactivity disorder (ADHD) symptoms predict alcohol expectancy development. J Child Adolesc Subst Abuse 2016; 25: 159–79. [PubMed: 27110089]

94. Maxwell A. Are some individuals diagnosed with ADHD prone to alcohol abuse? Consideration of two possible mediating factors for this susceptibility. J Atten Disord 2013; 17: 98–101. [PubMed: 22100688]

95. Faraone SV, Doyle AE, Mick E, Biederman J. Meta-analysis of the association between the 7-repeat allele of the dopamine D(4) receptor gene and attention deficit hyperactivity disorder. Am J Psychiatry 2001; 158: 1052–57. [PubMed: 11431226]

96. Smith AB, Taylor E, Brammer M, Toone B, Rubia K. Task-specific hypoactivation in prefrontal and temporoparietal brain regions during motor inhibition and task switching in medication-naive children and adolescents with attention deficit hyperactivity disorder. Am J Psychiatry 2006; 163: 1044–51. [PubMed: 16741205]

97. Monden Y, Dan I, Nagashima M, et al. Individual classification of ADHD children by right prefrontal hemodynamic responses during a go/no-go task as assessed by fNIRS. Neuroimage Clin 2015; 9: 1–12. [PubMed: 26266096]

98. Day AM, Kahler CW, Ahern DC, Clark US. Executive functioning in alcohol use studies: a brief review of findings and challenges in assessment. Curr Drug Abuse Rev 2015; 8: 26–40. [PubMed: 25877524]

99. Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the national comorbidity survey replication. Arch Gen Psychiatry 2005; 62: 593–602. [PubMed: 15939837]

100. Smith JP, Randall CL. Anxiety and alcohol use disorders: comorbidity and treatment considerations. Alcohol Res 2012; 34: 414–31. [PubMed: 23584108]

101. Kushner MG, Abrams K, Borchardt C. The relationship between anxiety disorders and alcohol use disorders: a review of major perspectives and findings. Clin Psychol Rev 2000; 20: 149–71. [PubMed: 10721495]

102. Maier W, Minges J, Lichtermann D. Alcoholism and panic disorder: co-occurrence and co-transmission in families. Eur Arch Psychiatry Clin Neurosci 1993; 243: 205–11. [PubMed: 8117765]

103. Hodgson K, Almasy L, Knowles EE, et al. Genome-wide significant loci for addiction and anxiety. Eur Psychiatry 2016; 36: 47–54. [PubMed: 27318301]

104. Cruz E, Martins PDC, Diniz PRB. Factors related to the association of social anxiety disorder and alcohol use among adolescents: a systematic review. J Pediatr (Rio J) 2017; 93: 442–51. [PubMed: 28579354]

105. Oliveira LM, Bermudez MB, Macedo MJA, Passos IC. Comorbid social anxiety disorder in patients with alcohol use disorder: a systematic review. J Psychiatr Res 2018; 106: 8–14. [PubMed: 30236640]

106. Buckner JD, Turner RJ. Social anxiety disorder as a risk factor for alcohol use disorders: a prospective examination of parental and peer influences. Drug Alcohol Depend 2009; 100: 128–37. [PubMed: 19022589]

107. Robinson J, Sareen J, Cox BJ, Bolton JM. Role of self-medication in the development of comorbid anxiety and substance use disorders: a longitudinal investigation. Arch Gen Psychiatry 2011; 68: 800–17. [PubMed: 21810645]

108. Gilpin NW, Weiner JL. Neurobiology of comorbid post-traumatic stress disorder and alcohol-use disorder. Genes Brain Behav 2017; 16: 15–43. [PubMed: 27749004]

109. Jacobsen LK, Southwick SM, Kosten TR. Substance use disorders in patients with posttraumatic stress disorder: a review of the literature. Am J Psychiatry 2001; 158: 1184–90. [PubMed: 11481147]

110. Hasin DS, Keyes KM, Hatzenbuehler ML, Aharonovich EA, Alderson D. Alcohol consumption and posttraumatic stress after exposure to terrorism: effects of proximity, loss, and psychiatric history. Am J Public Health 2007; 97: 2268–75. [PubMed: 17971553]

111. North CS, Ringwalt CL, Downs D, Derzon J, Galvin D. Postdisaster course of alcohol use disorders in systematically studied survivors of 10 disasters. Arch Gen Psychiatry 2011; 68: 173–80. [PubMed: 20921113]

112. Strunin L, Diaz-Martinez LR, Diaz-Martinez A, et al. Drinking patterns and victimization among male and female students in Mexico. Alcohol Alcohol 2015; 50: 226–35. [PubMed: 25534933]

113. Castillo-Carniglia A, Pizarro E, Luengo D, Soto-Brandt G. Alcohol use and self-reported violent events in Chile. Adicciones 2014; 26: 46–53 (in Spanish). [PubMed: 24652398]

114. Debell F, Fear NT, Head M, et al. A systematic review of the comorbidity between PTSD and alcohol misuse. Soc Psychiatry Psychiatr Epidemiol 2014; 49: 1401–25. [PubMed: 24643298]

115. McCarthy E, Petrakis I. Epidemiology and management of alcohol dependence in individuals with post-traumatic stress disorder. CNS Drugs 2010; 24: 997–1007. [PubMed: 21090836]

116. Leposavić L, Dimitrijević D, Đorđević S, Leposavić I, Balkoski GN. Comorbidity of harmful use of alcohol in population of schizophrenic patients. Psychiatria Danubina 2015; 27: 84–89. [PubMed: 25751441]

117. Cantor-Graae E, Nordstrom LG, McNeil TF. Substance abuse in schizophrenia: a review of the literature and a study of correlates in Sweden. Schizophr Res 2001; 48: 69–82. [PubMed: 11278155]
118. Kendler KS, Karkowski-Shuman L, Walsh D. The risk for psychiatric illness in siblings of schizophrenics: the impact of psychotic and non-psychotic affective illness and alcoholism in parents. Acta Psychiatr Scand 1996; 94: 49–55. [PubMed: 8841677]
119. Kendler KS, Gardner CO. The risk for psychiatric disorders in relatives of schizophrenic and control probands: a comparison of three independent studies. Psychol Med 1997; 27: 411–19. [PubMed: 9089833]
120. Krystal JH, D'Souza DC, Gallinat J, et al. The vulnerability to alcohol and substance abuse in individuals diagnosed with schizophrenia. Neurotox Res 2006; 10: 235–52. [PubMed: 17197373]
121. Jordaan GP, Emsley R. Alcohol-induced psychotic disorder: a review. Metab Brain Dis 2014; 29: 231–43. [PubMed: 24307180]
122. Soyka M, Raith L, Steinberg R. Mean age, sex ratio and psychopathology in alcohol psychoses. Psychopathology 1988; 21: 19–25. [PubMed: 3222427]
123. Stankewicz HA, Salen P. Alcohol related psychosis. Treasure Island, FL: StatPearls, 2018.
124. Glass IB. Alcoholic hallucinosis: a psychiatric enigma—1. The development of an idea. Br J Addict 1989; 84: 29–41. [PubMed: 2644996]
125. Hunt GE, Malhi GS, Cleary M, Lai HM, Sitharthan T. Prevalence of comorbid bipolar and substance use disorders in clinical settings, 1990–2015: systematic review and meta-analysis. J Affect Disord 2016; 206: 331–49. [PubMed: 27476137]
126. Balanza-Martinez V, Crespo-Facorro B, Gonzalez-Pinto A, Vieta E. Bipolar disorder comorbid with alcohol use disorder: focus on neurocognitive correlates. Front Physiol 2015; 6: 108. [PubMed: 25904869]
127. Farren CK, Hill KP, Weiss RD. Bipolar disorder and alcohol use disorder: a review. Curr Psychiatry Rep 2012; 14: 659–66. [PubMed: 22983943]
128. Maier W, Merikangas K. Co-occurrence and contransmission of affective disorders and alcoholism in families. Br J Psychiatry Suppl 1996; 168 (suppl 30): 93–100.
129. Rakofsky JJ, Dunlop BW. Do alcohol use disorders destabilize the course of bipolar disorder? J Affect Disord 2013; 145: 1–10. [PubMed: 22858208]
130. Hasin DS, O'Brien CP, Auriacombe M, et al. DSM-5 criteria for substance use disorders: recommendations and rationale. Am J Psychiatry 2013; 170: 834–51. [PubMed: 23903334]
131. Hasin DS, Beseler CL. Dimensionality of lifetime alcohol abuse, dependence and binge drinking. Drug Alcohol Depend 2009; 101: 53–61. [PubMed: 19095379]
132. Caspi A, Houts RM, Belsky DW, et al. The p factor: one general psychopathology factor in the structure of psychiatric disorders? Clin Psychol Sci 2014; 2: 119–37. [PubMed: 25360393]
133. Clark LA, Cuthbert B, Lewis-Fernandez R, Narrow WE, Reed GM. Three approaches to understanding and classifying mental disorder: ICD-11, DSM-5, and the National Institute of Mental Health's Research Domain Criteria (RDoC). Psychol Sci Public Interest 2017; 18: 72–145. [PubMed: 29211974]
134. Borsboom D. A network theory of mental disorders. World Psychiatry 2017; 16: 5–13. [PubMed: 28127906]
135. Drake RE, O'Neal EL, Wallach MA. A systematic review of psychosocial research on psychosocial interventions for people with co-occurring severe mental and substance use disorders. J Subst Abuse Treat 2008; 34: 123–38. [PubMed: 17574803]
136. Drake RE, Mueser KT, Brunette MF, McHugo GJ. A review of treatments for people with severe mental illnesses and co-occurring substance use disorders. Psychiatr Rehabil J 2004; 27: 360–74. [PubMed: 15222148]
137. Horsfall J, Cleary M, Hunt GE, Walter G. Psychosocial treatments for people with co-occurring severe mental illnesses and substance use disorders (dual diagnosis): a review of empirical evidence. Harv Rev Psychiatry 2009; 17: 24–34. [PubMed: 19205964]
138. 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: 471–81. [PubMed: 15763752]

139. Tiet QQ, Mausbach B. Treatments for patients with dual diagnosis: a review. Alcohol Clin Exp Res 2007; 31: 513–36. [PubMed: 17374031]
140. Kelly TM, Daley DC, Douaihy AB. Treatment of substance abusing patients with comorbid psychiatric disorders. Addict Behav 2012; 37: 11–24. [PubMed: 21981788]
141. Moak DH, Anton RF, Latham PK, Voronin KE, Waid RL, Durazo-Arvizu R. Sertraline and cognitive behavioral therapy for depressed alcoholics: results of a placebo-controlled trial. J Clin Psychopharmacol 2003; 23: 553–62. [PubMed: 14624185]
142. Knox J, Hasin DS, Larson FR, Kranzler HR. Prevention, screening and treatment for heavy drinking and alcohol use disorder. Lancet Psychiatry 2019; published online Oct 16 10.1016/S2215-0366(19)30213-5.
143. Kranzler HR, Soyka M. Diagnosis and pharmacotherapy of alcohol use disorder: a review. JAMA 2018; 320: 815–24. [PubMed: 30167705]
144. Ramsey AT, Satterfield JM, Gerke DR, Proctor EK. Technology-based alcohol interventions in primary care: systematic review. J Med Internet Res 2019; 21: e10859. [PubMed: 30958270]
145. Haughwout SP, Slater ME. Apparent per capita alcohol consumption: national, state, and regional trends, 1977–2016. Arlington, VA: National Institute on Alcohol Abuse and Alcoholism, 2018.
146. Cheng HG, Kaakarli H, Breslau J, Anthony JC. Assessing changes in alcohol use and alcohol use disorder prevalence in the United States: evidence from national surveys from 2002 through 2014. JAMA Psychiatry 2018; 75: 211–13. [PubMed: 29282472]
147. 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: 911–23. [PubMed: 28793133]
148. Kraus L, Pabst A, Piontek D, et al. temporal changes in alcohol-related morbidity and mortality in Germany. Eur Addict Res 2015; 21: 262–72. [PubMed: 25967383]
149. National Institute on Alcohol Abuse and Alcoholism. Alcohol-related emergency department visits and hospitalizations and their co-occurring drug-related, mental health, and injury conditions in the United States: findings from the 2006–2010 Nationwide Emergency Department Sample (NEDS) and Nationwide Inpatient Sample (NIS). Bethesda, MD: National Institutes of Health, 2013.
150. Seth P, Scholl L, Rudd RA, Bacon S. Overdose deaths involving opioids, cocaine, and psychostimulants—United States, 2015–2016. MMWR Morb Mortal Wkly Rep 2018; 67: 349–58. [PubMed: 29596405]
151. Case A, Deaton A. Rising morbidity and mortality in midlife among white non-Hispanic Americans in the 21st century. Proc Natl Acad Sci USA 2015; 112: 15078–83. [PubMed: 26575631]
152. Curtin SC, Warner M, Hedegaard H. Increase in suicide in the United States, 1999–2014. NCHS Data Brief 2016; 241: 1–8.
153. Mojtabai R, Olfson M, Han B. National trends in the prevalence and treatment of depression in adolescents and young adults. Pediatrics 2016; 138: e20161878. [PubMed: 27940701]
154. Olfson M, Blanco C, Wall M, et al. National trends in suicide attempts among adults in the United States. JAMA Psychiatry 2017; 74: 1095–103. [PubMed: 28903161]
155. Compton WM, Han B, Jones CM, Blanco C, Hughes A. Marijuana use and use disorders in adults in the USA, 2002–14: analysis of annual cross-sectional surveys. Lancet Psychiatry 2016; 3: 954–64. [PubMed: 27592339]
156. Hasin DS, Saha TD, Kerridge BT, et al. Prevalence of marijuana use disorders in the United States between 2001–2002 and 2012–2013. JAMA Psychiatry 2015; 72: 1235–42. [PubMed: 26502112]
157. Naimi TS, Blanchette JG, Xuan Z, Chaloupka FJ. Erosion of state alcohol excise taxes in the United States. J Stud Alcohol Drugs 2018; 79: 43–48. [PubMed: 29227230]

Panel: Treatment of alcohol use disorders and other psychiatric comorbidities

Integrated treatments for alcohol use disorder and comorbid psychiatric disorders have been extensively studied, and the general conclusion is that they tend to yield better results than non-integrated treatments.[135–137] However, evidence is not conclusive on what types of treatments are better for specific psychiatric disorders. In a review of residential treatments for dual diagnoses, Brunette and colleagues[138] concluded that residential treatments tend to have better results than non-residential integrated treatments, although they noted an urgent need for better study designs and randomised controlled trials. Pharmacological treatments in combination with psychological and behavioural interventions often show better results than either treatment alone.[139] SSRIs are effective in treating mood disorders, but contradictory evidence exists regarding outcomes from drinking alcohol.[140] In a randomised controlled trial evaluating cognitive behavioural therapy with and without sertraline, patients assigned to the sertraline group reported fewer drinks per week but did not show improvement in other drinking outcomes; also, women in the treatment group showed fewer depressive symptoms at follow-up compared with women receiving placebo.[141] In a review of 59 studies, including 36 randomised controlled trials, the authors concluded that there is a lack of integrated treatments showing consistent and clear advantages over comparison conditions for both substance use disorders, including alcohol use disorder, and other psychiatric disorders.[139] They did find studies reporting efficacious pharmacological and/or psychosocial treatments for the management of alcohol use disorder in psychiatric patients (eg, percentages of days abstinent, number of drinking days, Addiction Severity Index score), and psychiatric symptoms in patients with alcohol use disorder (eg, Hamilton Depression scale), but evidence on the superiority of integrated treatments was inconclusive.[139] Overall, the general consensus on integrated treatment is that evidence is still limited; most studies have small sample sizes, short follow-up periods, non-experimental designs, high attrition, and highly heterogeneous and poorly described treatments.

Implications for developing the intervention evidence base

The co-occurrence of alcohol use disorder with other disorders has implications for treatment effectiveness, and the next generation of alcohol use disorder treatment research will continue to expand on the knowledge base regarding how to address comorbidity when treating individuals with alcohol problems. Alcohol use disorder treatments have greatly expanded in the past decade, with well documented evidence for efficacy across both pharmacological and non-pharmacological domains.[142,143] Interventions delivered through smartphone and other new technologies are feasible and acceptable among patients.[144] To that end, however, integrated treatments for simultaneously addressing alcohol use disorder and other externalising disorders (and internalising disorders) are limited in scope and number, in part because of the complexity of treating two or more concurrent disorders, but also because of our limited understanding of the underlying mechanisms linking alcohol use disorder to other psychiatric disorders. Furthermore, developing the evidence base regarding variation by

co-occurring disorders in the effectiveness of treatment of alcohol use disorder is also a necessary area of research, to which the growing databases of electronic and other high-volume data sources will undoubtedly contribute. Identifying and intervening on key common features of alcohol use disorder comorbidity should be a priority for future research in this field.

Search strategy and selection criteria

We searched without restricting publication date for studies published in English and Spanish. For each psychiatric disorder, we searched for information on: (1) its prevalence in people with alcohol use disorder, and the prevalence of alcohol use disorder in people with other psychiatric disorders; (2) the longitudinal association between alcohol use disorder and the other psychiatric disorders; and (3) potential mechanisms that could explain the link between alcohol use disorder and other psychiatric disorders. Whenever available, we report pooled prevalence estimates from meta-analyses (eg, bipolar disorder, major depressive disorder, post-traumatic stress disorder), otherwise we present results for two or more studies for two or more countries (eg, the USA, Australia, Germany, Brazil). To describe the longitudinal relationships between alcohol use disorder and other psychiatric disorders, we prioritised systematic reviews or meta-analyses of longitudinal studies (eg, attention-deficit hyperactivity disorder), otherwise we considered longitudinal cohort studies (eg, anxiety disorders). In terms of the mechanisms connecting alcohol use disorder with other psychiatric disorders, we describe some of the biological pathways, including genome-wide association studies or twin studies when available. Our search scheme typically included PubMed, using standardised search terms. For example, our initial review for alcohol use disorder and major depressive disorder considered the search terms: “alcohol dependence” or “alcohol abuse” or “alcohol use disorder” or “alcoholism” or “alcohol addiction” and “depression” or “depressive” or “unipolar depression” or “major depressive disorder” or “mood disorder”. We then selected studies on the basis of how well they matched our search questions (eg, longitudinal association between alcohol use disorder and other psychiatric comorbidity), the type of study (eg, meta-analysis), and its reach (eg, nationally representative sample, multicentre study).

Table:

Summarised results for alcohol use disorder and psychiatric comorbidities

	Prevalence of alcohol use disorder in people with comorbid diagnosis	Prevalence of comorbid diagnosis in people with alcohol use disorder	Longitudinal association between alcohol use disorder and psychiatric comorbidity
Externalising disorders			
Substance use disorders	ECA survey: 47·3% (in people with substance use disorder)	NCS survey: 40·6% lifetime substance use disorder in men; 47·1% in women	Substance use disorder to alcohol use disorder onset in early adulthood: HR 3·50 (95%CI 2·03–6·03) for early-to-middle adolescent substance use disorder;[14] HR 3 96 (2·22–7·07) for late adolescent substance use disorder[14]
Nicotine use disorders	Lifetime alcohol use disorder in people dependent on tobacco in the general population of Germany 18·1%;[15] NESARC: current (12-month) alcohol use disorder of 22·8% in people currently dependent on nicotine[16]	NESARC: current (12-month) nicotine dependence of 34·5% among people with current alcohol use disorder[16]	Nicotine use disorders to alcohol use disorder: adjusted OR 1·92 (95%CI 1·35–2·74) for any use (past non-daily use up to present daily use)
Personality disorders	Lifetime alcohol use disorder in people with ASPD (pooled estimate from 6 studies): 77% (95%CI 66–86%); [17] alcohol use disorder in people with BLPD (pooled estimate from 5 studies) 52% (42–63%)[17]	ASPD in people with alcohol use disorder: median (across 16 studies) 18%, range 1–52%;[18] BLPD in people with alcohol use disorder: median (across 7 studies) 21%, range 6–66%[18]	Not found *
Internalising disorders			
MDD	Median (across 35 studies) lifetime alcohol use disorder † in people with MDD: 30%, range 10–60%;[19] ECA survey 16·5% MDD (lifetime)	MDD † in people with lifetime alcohol use disorder 37%;[20] MDD † in people with 12-months alcohol use disorder 4–22%[20]	Alcohol use disorder to MDD: pooled OR ‡ 2·00 (95%CI 1·19–3·3);[21] OR § 3·2 (1·4–7·1) primary care attenders from 14 countries;[22] MDD to alcohol use disorder: pooled OR ¶ 2·09 (1·29–3·38)[21]
Attention-deficit hyperactivity disorder	Alcohol use disorder ‖ in French students with ADHD 25·9%;[23] alcohol use disorder ** in young men enlisting to the Military Service in Australia with ADHD 19·3%[24]	ADHD in adolescents with alcohol use disorder †† : 19·9–23·6%;[25] ADHD in adults with alcohol use disorder: 33% (current)[25,26]	ADHD to alcohol use disorder: pooled OR ‡‡ 1·35 (95%CI 1·11–1·64);[27] pooled OR ‡‡ 1·74 (1·38–2·20)[28]
Anxiety disorder	Alcohol use disorder in people with any anxiety disorder 20–40%;[20] ECA survey: 17·9% in people with any anxiety disorder, 28·7% in people with panic disorder	ECA survey: 19·4% any lifetime anxiety disorder; NCS survey: 8'6% lifetime GAD in men, 15·7% in women; NCS survey: 3·6% lifetime panic disorder in men, 12·9% in women; NCS survey: 19·3% lifetime social phobia in men, 30·3% in women	Alcohol use disorder to GAD: OR § 1·5 (95%CI 0·5–4·7) primary care attenders from 14 countries;[22] anxiety to alcohol use disorder: OR 1·61 (0·91–2·83) in adolescents and young adults of New Zealand followed up for 21 years[29]
PTSD	Alcohol use disorder in young adults with PTSD in the general population of Brazil 34·4%;[30] NESARC-III: 54·5% lifetime alcohol use disorder in people with lifetime PTSD[31]	NCS survey: 10·3% lifetime PTSD in men, 26 ·2% in women; current PTSD in German patients with substance use disorder with alcohol dependence 22·9%[32]	Alcohol use disorder to PTSD §§ : OR 1·35 (95%CI 0·40–4·56) in unadjusted model; OR 0·70 (0·17–2·86) in fully adjusted model;[33] PTSD to alcohol use disorder §§ : OR 4·10 (1·41–11·89) in unadjusted model and OR 5·43 (1·56–18·93) in fully adjusted model[33]
Thought and other psychiatric disorders			
Schizophrenia and psychotic disorders	Median lifetime alcohol use disorder ¶¶ 20·6% (IQR 13·5%, 35·9; range 1·3–57·0%)[34]	ECA survey: 3·8% schizophrenia	Alcohol use disorder to psychotic experiences ‖‖ : OR 1·6 (95% CI 1·2–2·0);[35] psychotic experiences to alcohol use disorder ‖‖ : 1·5 (1·2–2·0)[35]

Lancet Psychiatry. Author manuscript; available in PMC 2020 February 07.

	Prevalence of alcohol use disorder in people with comorbid diagnosis	Prevalence of comorbid diagnosis in people with alcohol use disorder	Longitudinal association between alcohol use disorder and psychiatric comorbidity
Bipolar disorders	Lifetime alcohol use disorder*** 24–44% in bipolar disorder or bipolar disorder I;[36] lifetime alcohol use disorder*** 24–39% in bipolar disorder II[36]	Bipolar disorder or bipolar disorder I*** 3·5–5% in people with lifetime alcohol use disorder[36]	Not found*

Results come from meta-analyses or nationally representative studies, whenever possible. Otherwise we present results from for comorbidity prevalence, and longitudinal studies for the association between alcohol use disorder and psychiatric comorbidities. ECA=Epidemiologic Catchment Area study (historical data [early 80s] on prevalence of psychiatric disorders in people with lifetime alcohol use disorder)[37] NCS=National Comorbidity Survey (disorder prevalences are for people with lifetime alcohol dependence).[38] HR=hazard ratio. NESARC=National Epidemiologic Survey on Alcohol and Related Conditions. OR=odds ratios. ASPD=antisocial personality disorder. BLPD=borderline personality disorder. MDD=major depressive disorder. ADHD=attention-deficit hyperactivity disorder. GAD=generalized anxiety disorder. PTSD=post-traumatic stress disorder.

*No longitudinal studies on alcohol use disorder and psychiatric comorbidity were found.

†Estimates from epidemiological studies in the general population; prevalence was extracted from figure 2 in Lai and colleagues,[20] thus might not be exact.

‡Pooled OR from longitudinal and cross-sectional studies.

§AUDIT score of 13 points or more.

¶The meta-analysis includes studies with heavy drinking in their alcohol use disorder category.

//AUDIT score of 12 or more for man or 11 or more for woman indicates risk of addiction.

**CAGE score of 2 or more for alcohol problems.

††Results come from individual studies extracted from van Emmerik-van Oortmerssen and colleagues.[25]

‡‡Meta-analysis of longitudinal studies of childhood ADHD and later alcohol use disorder.

§§Study of 922 National Guard soldiers with pre-Iraq and post-Iraq deployment. Alcohol use disorder screened at baseline considered 12 months alcohol dependence and, at follow-up, 3 months dependence.

¶¶From a systematic review including inpatients and outpatients with schizophrenia and schizophrenia spectrum diagnoses.[34]

////Results based on cross-sectional studies across 18 countries with retrospective reports about age at onset of psychotic experiences and alcohol use disorder.

***Estimates from epidemiological studies in the general population; prevalence was extracted from figures 1 and 2 in Hunt and colleagues,[36] thus might not be exact.