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Primer

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Hazardous drinking and alcohol use disorders

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Abstract

Alcohol is one of the most widely consumed psychoactive drugs globally. Hazardous drinking, defined by quantity and frequency of consumption, is associated with acute and chronic morbidity. Alcohol use disorders (AUDs) are psychiatric syndromes characterized by impaired control over drinking and other symptoms. Contemporary aetiological perspectives on AUDs apply a biopsychosocial framework that emphasizes the interplay of genetics, neurobiology, psychology, and an individual's social and societal context. There is strong evidence that AUDs are genetically influenced, but with a complex polygenic architecture. Likewise, there is robust evidence for environmental influences, such as adverse childhood exposures and maladaptive developmental trajectories. Well-established biological and psychological determinants of AUDs include neuroadaptive changes following persistent use, differences in brain structure and function, and motivational determinants including overvaluation of alcohol reinforcement, acute effects of environmental triggers and stress, elevations in multiple facets of impulsivity, and lack of alternative reinforcers. Social factors include bidirectional roles of social networks and sociocultural influences, such as public health control strategies and social determinants of health. An array of evidence-based approaches for reducing alcohol harms are available, including screening, pharmacotherapies, psychological interventions and policy strategies, but are substantially underused. Priorities for the field include translating advances in basic biobehavioural research into novel clinical applications and, in turn, promoting widespread implementation of evidence-based clinical approaches in practice and health-care systems.

Sections

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Introduction

Human consumption of alcohol (ethanol) predates recorded history and is theorized to have adaptive evolutionary significance[1,2]. In modern life, alcohol is one of the most widely consumed psychoactive drugs globally. More than 80% of adults report lifetime alcohol use in most high-income countries, with more variable rates in low-income and middle-income countries, and at least annual alcohol use is reported by the majority of adults in Europe (59.9%), the Americas (54.1%) and the Western Pacific (53.8%)[3]. Around 2.3 billion adults drink alcohol at least annually globally[3]. Alcohol has strong symbolic and cultural meaning and is used to enhance social events, improve gustation, signify accomplishments and celebrate special occasions. However, alcohol use is also associated with many harms. Acutely, alcohol consumption can lead to injury from accidents, aggression and violence, and, at high doses, can cause death. Chronic regular alcohol use contributes to alcohol use disorders (AUDs) and other psychiatric disorders, increases the risk of other medical conditions, including cancers, and is a teratogen during pregnancy. These harms constitute a major public health problem, a massive economic burden, and a vast human toll.

Understanding the harmful effects of alcohol is complicated by differences in definitions and medical classification (Box 1). The definitions of a standard unit of alcohol and hazardous drinking differ between countries[4]. Moreover, the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) and the 11th revision of the International Classification of Diseases (ICD-11) have substantively different categories for defining clinically meaningful alcohol involvement. The DSM-5 has one diagnosis (that is, AUD) with three levels of severity, whereas the ICD-11 has two diagnoses with escalating severity (that is, harmful pattern of use of alcohol followed by alcohol dependence) and also a subclinical designation of hazardous alcohol use that denotes a risk factor that has not reached the point of having caused harms to the person or others. Fundamentally, however, these clinical diagnoses reflect an inability to regulate alcohol consumption, and, although not formally designated as such, the more severe manifestations (severe AUD in DSM-5, alcohol dependence in ICD-11) are often considered the clinical equivalent of the colloquial term 'alcoholism'[5–8].

Given these definitional differences, this Primer primarily uses two terms for clarity. First, the term hazardous drinking is used to refer to drinking behaviour (such as per episode, daily or weekly) that reflect meaningful increases in risk of negative alcohol-related outcomes (acute or chronic), but not necessarily the presence of those outcomes (an individual may routinely engage in hazardous drinking but not experience the outcome for which there are elevated risks). Second,

Box 1

Definitions of standard units of alcohol, hazardous drinking and alcohol use disorders

Standard units of alcohol (that is, a 'standard drink')

- North America: ~14 g (USA 14 g and Canada 13.5 g), approximately 5 oz wine, 12 oz beer or 1.5 oz liquor, depending on concentration
- Europe: 8–20 g (for example, UK 8 g; France, Ireland, Netherlands and Spain 10 g; Germany and Portugal 11 g; Denmark, Finland, Italy, Sweden and Switzerland 12 g; Hungary 17 g; Austria 20 g)
- Asia: 10–20 g (Hong Kong 10 g; Japan 19.75 g)
- Oceania: 10 g (Australia and New Zealand 10 g)

Definitions of hazardous drinking

World Health Organization risk levels

- Males: medium 41–60 g/day; high 61–100 g/day; very high ≥101 g/day
- Females: medium 21–40 g/day; high 41–60 g/day; very high ≥61 g/day
- Heavy episodic drinking: 60 g of ethanol on at least one occasion at least once per month

National Institute on Alcohol Abuse and Alcoholism (USA)

- Males: >14 drinks (196 g) per week or >4 drinks (56 g) per occasion
- Females: >7 drinks (98 g) per week or >3 drinks (42 g) per occasion
- Binge drinking: ≥5 standard drinks (70 g) in males and ≥4 standard drinks (56 g) in females

National Health Service (UK)

Both sexes: >14 units weekly (112 g) distributed over ≥3 days

Canadian Low-risk Drinking Guidelines

- Males: >14 drinks/week, >3 drinks per occasion (>4 drinks per special occasion)
- Females: >10 drinks/week, >2 drinks per occasion (>3 drinks per special occasion)

Definitions of alcohol use disorders

Diagnostic and Statistical Manual 5th Edition (DSM-5)[a]

- Substance-related and addictive disorders (parent category)
  - Alcohol use disorder; modifiers of mild, moderate and severe

International Classification of Diseases 11th Revision (ICD-11)[a]

- Health risk factors (parent category)
  - Hazardous alcohol use
- Disorders due to substance use (parent category)
  - Harmful pattern of use of alcohol (lower severity; single episode or a pattern)
  - Alcohol dependence (higher severity)

[a]Additional clinical diagnoses: alcohol intoxication (DSM-5 and ICD-11); alcohol withdrawal (DSM-5 and ICD-11); alcohol-induced delirium, psychotic disorder, mood disorder, anxiety (ICD-11).

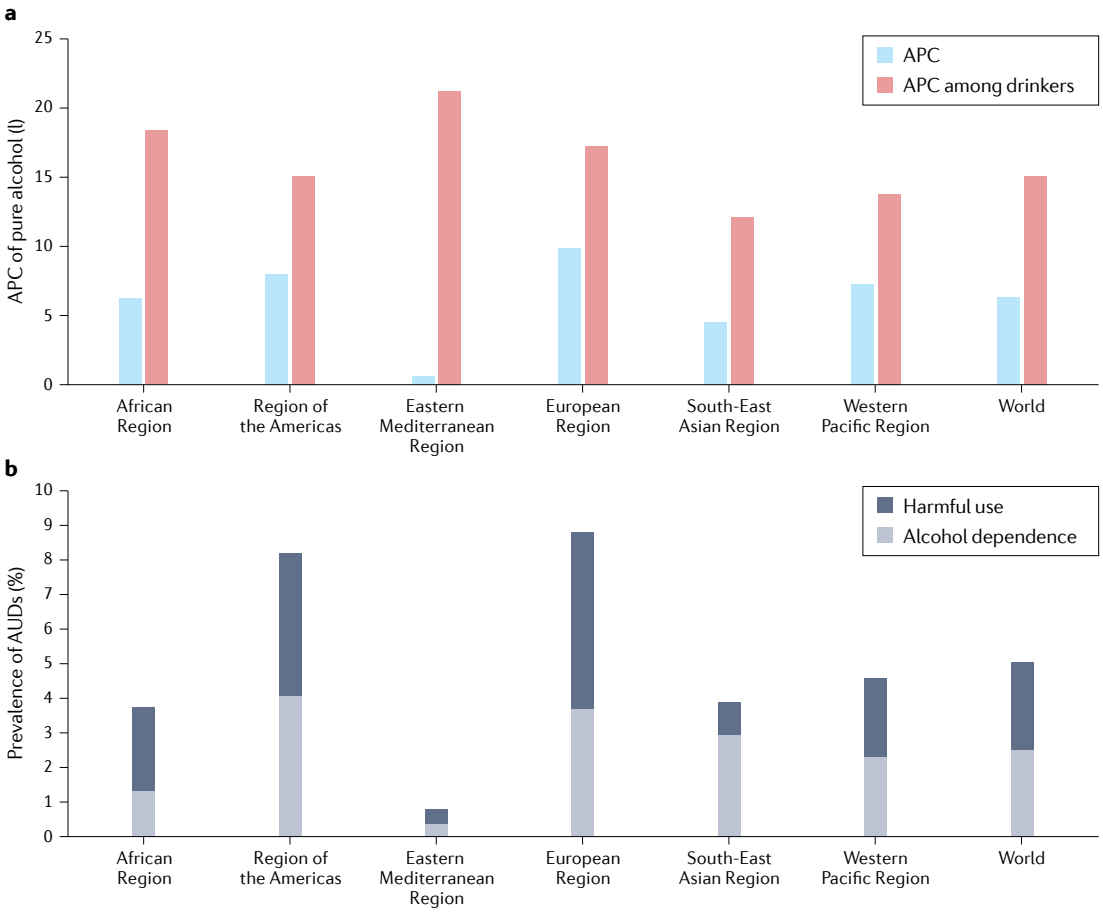


Fig. 1 | Alcohol consumption and prevalence of alcohol use disorders. Key indicators of global alcohol consumption (panel **a**) and AUDs (panel **b**) in WHO regions in 2016. Drinkers are defined as individuals reporting alcohol use in the past 12 months. APC, adult (15 years and older) alcohol consumption per capita of pure alcohol (in litres); AUDs, alcohol use disorders. Adapted with permission from ref.[3].

the term AUDs is used to refer to clusters of clinically important signs and symptoms that produce harm or distress from alcohol involvement that is currently present in individuals, including the diagnoses in both nosological systems. Finer terminological gradations can be made[9], but would be unwieldy for a Primer and these distinctions based on consumption patterns and clinical diagnosis are the most widely used in the field. Finally, AUDs have historically been highly stigmatizing conditions[5,6] and this Primer follows recent terminology recommendations[7,8], particularly emphasizing person-first language (for example, individuals with an AUD).

In terms of foci, this Primer provides a concise overview of the global epidemiology, a contemporary biopsychosocial aetiological perspective, and evidence-based practices in screening, assessment and clinical management of AUDs. In addition, the Primer discusses quality of life (QOL), outlook and future priorities.

Epidemiology

Global and regional prevalence

Alcohol consumption at the population level varies substantially globally, with the lowest reported consumption in the Middle East and the highest in Europe (Fig. 1). Hazardous drinking, defined using the WHO criteria for heavy episodic drinking (Box 1), is relatively prevalent among those who consume alcohol in all regions, with an overall prevalence of 39.5% (range 10.4–50.2%)[3].

In 2018, around 1 in 20 adults (≥15 years of age) were reported to have an AUD, globally, with a slightly higher prevalence of ICD-11 harmful use over alcohol dependence[3] (Fig. 1). The highest prevalence of AUDs (both harmful use and alcohol dependence) was in the WHO European Region, followed by the Americas[3]. Notable sex differences were present, with alcohol per capita consumption being 2.8 times larger for males than females and hazardous drinking being 2.5 time higher globally. Indeed, females exhibit lower alcohol involvement on all indicators[3]. For clinical diagnoses, AUDs are more common in males than in females in all parts of the world (with an overall prevalence about four to five times higher in men[3]), but with evidence of a closing of the male–female gap over time[10,11].

Although the overall rate of drinking is not notably different between young people and adults, hazardous drinking is particularly prevalent in Europe, in certain high-income countries, such as the USA, Canada, Australia, and New Zealand, and in certain South American countries such as Argentina and Chile[3]. Age patterns vary considerably by region. In North America, the highest prevalence of AUDs is in young adults[12] (18–29 years of age), sometimes referred to as emerging adults[12]. By contrast, the highest prevalence of AUDs

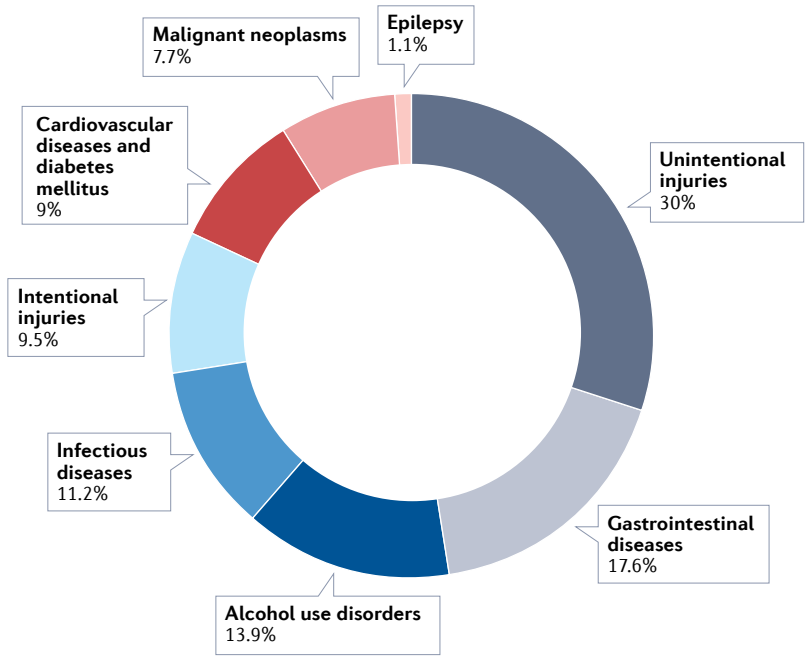


Fig. 2 | Harms associated with alcohol use. Distribution of the alcohol-attributable burden of disease as a percentage of all alcohol-attributable disability-adjusted life years by broad disease categories in 2016. Adapted with permission from ref.[3].

is in older age groups in other parts of the world. For example, in Thailand, the highest prevalence of AUDs is among individuals aged 30–39 years[13], in Finland, the highest prevalence is among individuals aged 30–44 years[14], and in Russia, the highest prevalence is among individuals aged 45–59 years[15,16].

Medical consequences of AUDs

Alcohol is implicated in a wide variety of adverse medical outcomes (Fig. 2). In 2016, alcohol use was implicated in eight major disease categories[3] encompassing both acute and chronic effects, and reflecting a loss 133 million disability-adjusted life-years (Fig. 2).

Psychiatric disorders. Alcohol use may contribute to a number of psychiatric disorders, indicated by the inclusion of alcohol-induced psychotic, mood and anxiety disorders in ICD-11 (ref.[16]). In addition to disorders defined as alcohol-induced, AUDs are often comorbid with other substance use disorders and may be comorbid with mood disorders, anxiety disorders, borderline personality disorder and antisocial personality disorder[12,17]. For psychiatric disorders with marked associations with AUDs, causality is generally thought to be bi-directional or may be based on shared vulnerabilities[18]. However, developmental investigations indicate that hazardous drinking and AUDs are preceded by externalizing disorders, such as conduct disorder and attention deficit hyperactivity disorder, in childhood[19]. Furthermore, there is evidence that these precursors are an expression of an individual's genetic liability for alcohol outcomes[20–23].

Acute medical consequences. Unintentional and intentional injuries, such as car accidents and falls, to both alcohol users and other individuals are among the major consequences of alcohol use. The relationship between all types of injury and alcohol use is dose-dependent[24] owing to the dose-dependent effect of blood-alcohol concentration on psychomotor coordination and reaction time, an effect that starts at low levels of alcohol consumption[25].

Infectious diseases. Alcohol use, particularly heavy use, is also linked to the incidence and course of various infectious diseases, including lower respiratory infections, HIV/AIDS and other sexually transmitted infections and tuberculosis[20]. The main underlying mechanisms of these associations includes weakening of the innate and acquired immune systems and maladaptive decision-making during intoxication[26].

Chronic diseases and cancer. The chronic medical risks of alcohol use include gastrointestinal disease, cardiovascular disease and cancer[27]. Alcohol-attributable gastrointestinal disease includes liver disease (mainly cirrhosis) and pancreatitis, and is mainly linked to heavy drinking over time[28]. Of note, moderate drinking can also aggravate existing liver disease with severe consequences[28]. Alcohol is implicated in approximately half of liver cirrhosis cases[3] and it is the alcohol-attributable disease category associated with the highest number of premature deaths[5]. For cardiovascular disease, heavy drinking, both intermittent and chronic, has also been linked to hypertension, stroke and heart disease (including alcoholic cardiomyopathy)[7]. Regarding cancer, alcohol is a well-established group 1 carcinogen, the highest level of causality (that is, carcinogenic to humans), and increases risk of cancers of the liver, mouth, throat (pharynx and larynx), oesophagus, bowel and female breast in a dose-dependent manner without a lower threshold of no risk[29,30]. Indeed, all disease risk curves are dose-dependent, albeit with different dose–response relationships[24,31].

Neurological diseases and brain damage. Among individuals with an AUD, malnutrition can lead to thiamine (vitamin B_1) deficiency leading to neurological conditions of Wernicke encephalopathy and Korsakoff syndrome[32]. The former refers to a time-limited syndrome comprising mental confusion, gait disturbance and abnormal eye movements, although all domains may not be present concurrently, whereas the latter refers to a long-term syndrome characterized by anterograde amnesia (that is, inability to encode new memories). Untreated with thiamine supplementation, in ~80% of individuals

Wernicke encephalopathy progresses to Korsakoff syndrome. Other neurological sequelae of AUDs include Marchiafava–Bignami disease and central pontine myelinolysis[32], both of which reflect damage to neural myelination. More generally, it is well established that AUDs accelerate brain ageing, including ventricular enlargement and global cortical shrinkage[33,34] and heavy drinking is also an important risk factor for dementia[35] but these findings are relatively recent so are not included in Fig. 2. Alcohol has high teratogenicity and can cause fetal alcohol spectrum disorders, which are a group of neurodevelopmental disorders with one of the highest prevalences[36].

Other medical consequences. Other negative consequences[35] include interactions of alcohol with commonly used medications, which can limit the therapeutic effects or increase the risk of potentially serious adverse effects[36,37].

Harm to others and economic burden

Drinking alcohol can also cause harm to other individuals, such as partners, families, the community and society in general. A survey of harm in nine high-income countries and low-income and middle-income countries found the prevalence of any harm or tangible harm from others' drinking varied across countries, ranging between 19.4% and 61.3%[38]. Women were more likely to experience harms from family members who drink alcohol compared to others (such as friends, co-workers or strangers), whereas men were more likely to experience harm from friends and co-workers than from family members. Younger people were more likely to report experiencing harm than older persons. Respondents who themselves reported hazardous drinking tended to experience more harm from others' drinking than those who did not report hazardous drinking[39]. Of note, using multicriteria decision analysis, an expert panel has identified alcohol as the most harmful psychoactive drug, partly due to its substantial adverse effects on both the drinker and those in the drinker's orbit[40].

In terms of economic burden, one systematic review and modelling study estimated the annual alcohol-attributable costs per adult added up to, on average, 2.6% of a country's gross domestic product, primarily in lost productivity costs (61.2%)[41]. In practical terms, this reflected an average of International $1,306 per person[41].

Mechanisms/pathophysiology

Susceptibility to AUDs is highly multifactorial, including distal influences that start at conception and proximal biological, psychological and social environmental influences. Indeed, a contemporary aetiological perspective emphasizes an integrative biopsychosocial framework for understanding the risk of and protection from AUDs.

Distal factors

Genetic factors. Differences in the risk of developing an AUDs are partially due to genetic differences among individuals. Early adoption studies found a higher risk of developing an AUD among adoptees with a positive biological family history of AUDs[42,43] and twin studies found a higher concordance for AUDs in monozygotic (identical) twins than in dizygotic (fraternal) twins[44,45]. Across studies, the heritability in developing an AUD has been estimated to be in the range 40–60%[45]. Genetic factors have also been implicated in the pathophysiology of other substance use and psychiatric disorders, and these disorders have varying degrees of shared genetic risk with AUDs[46–49]. Importantly, it is increasingly clear that the genetic susceptibility to AUDs overlaps with the susceptibility to substance use disorders more generally and externalizing psychopathology[20–23]. In other words, genetic contributions to drinking phenotypes are commonly understood to comprise both alcohol-specific components that pertain to the drug itself and components not specific to alcohol that pertain to features that are common across conditions associated with over-consumption and under-control.

More recent studies have aimed to identify specific genetic variants that confer risk of developing an AUD and the underlying mechanisms[50]. One example is that of alcohol flushing syndrome, in which alcohol produces an unpleasant reddening of the face and chest, dizziness, nausea and rapid heart rate. Flushing syndrome is inherited in a semi-dominant manner and is caused by a guanine (G) to adenine (A) substitution (SNP rs671) in *ALDH2* (encoding aldehyde dehydrogenase, a critical enzyme for alcohol metabolism). This variant decreases enzymatic activity and leads to acetaldehyde accumulation[51] (Fig. 3) and flushing syndrome. The prevalence of individuals carrying at least one A allele is 28–45% in people of East Asian ancestry[52] but it is rare in other ancestry groups. Individuals susceptible to flushing syndrome often avoid consuming alcohol and are therefore strongly protected from developing an AUD[51]; however, social pressure to consume alcohol can at least partially overcome this protective effect[53]. Individuals who are susceptible to flushing syndrome should be counselled to avoid alcohol because they have an increased risk for alcohol-induced oesophageal cancer, putatively due to excess acetaldehyde accumulation, although a causal relationship has not been demonstrated[54].

A polymorphism (rs1229984) of *ADH1B* can also influence drinking and risk of developing an AUD. In this case, the A allele causes faster metabolism of ethanol into acetaldehyde (Fig. 3) and is associated with decreased drinking and protection from AUDs[51]. Similar to rs671 of *ALDH2*, the protective allele of *ADH1B* is most prevalent in individuals of Asian ancestry, but is found in other groups at lower frequencies[51]. Of note, *ADH1B* variants do not cause alcohol flushing syndrome, putatively because the acetaldehyde build-up is less substantial than in those with the protective allele of *ALDH2*. Of note, although these are the most robustly associated, other *ADH* and *ALDH* variants have been implicated in hazardous drinking and risk of developing an AUD[55]. Genetically influenced differences in alcohol pharmacodynamics may also contribute to AUD susceptibility[56–59]. The functional mechanisms remain incompletely understood but are speculated to involve lower sensitivity to the unpleasant sedative and ataxic effects of alcohol and greater sensitivity to the pleasurable stimulant effects of alcohol[58,60–62].

Genome-wide association studies (GWAS) investigating susceptibility to AUDs[63] have identified large numbers of variants that individually have small effects but collectively have a substantial effect on the risk of developing an AUD. These studies varied in terms of the type of alcohol phenotype examined (such as self-reported consumption or clinical diagnosis of AUD) and the screening instruments used (such as the Alcohol Use Disorder Identification Test (AUDIT) or clinical diagnoses of AUD). The largest alcohol-related GWAS evaluated drinks per week in 941,280 individuals and identified 99 independent loci[54]. With regard to AUDs, a trans-ancestral GWAS in 14,904 individuals with an AUD and 37,944 controls found only the previously mentioned rs1229984 SNP in *ADH1B*[64]. Another large GWAS in 274,424 mostly male individuals from the Million Veterans Project identified associations between five loci and AUD in addition to 13 loci and a measure of alcohol consumption[65]. A meta-analysis integrated hazardous drinking and AUDs to reach a sample size of 435,563, leading to the identification of 29 loci[49]. However, not all these studies replicated the associations between rs1229984 and alcohol consumption. Although the

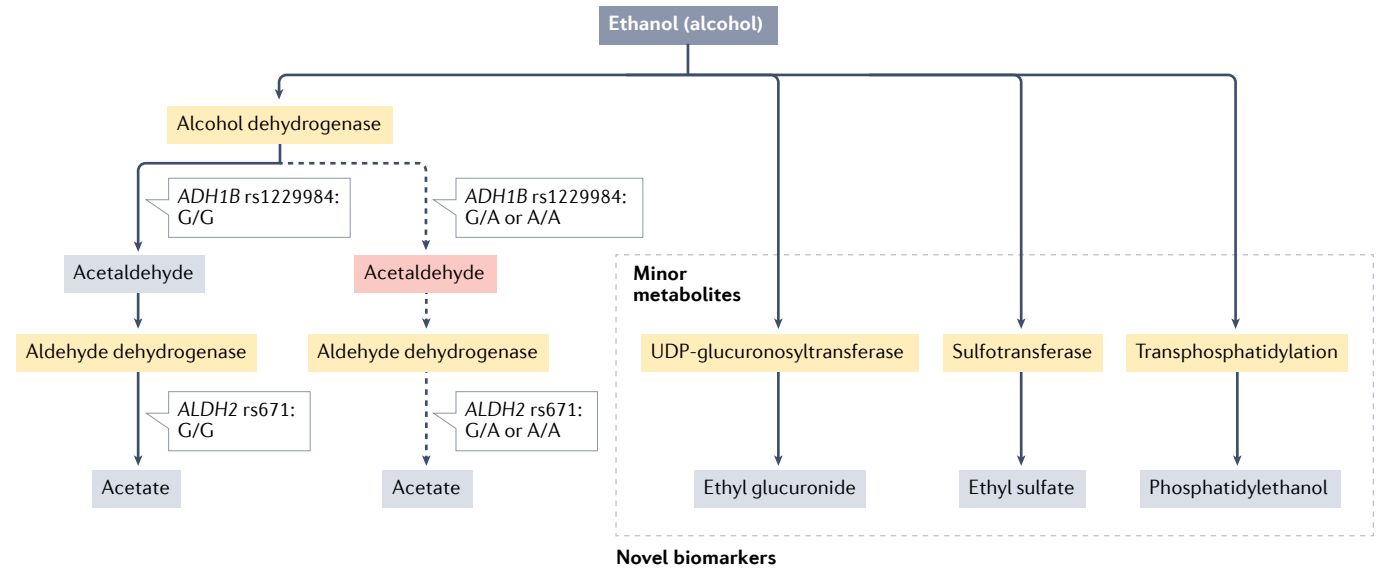


Fig. 3 | Major pathways in alcohol metabolism. Polymorphisms associated with clinically relevant pharmacokinetic differences are indicated. The broken line for A allele carriers of rs1229984 in *ADH1B* reflects more rapid metabolism of alcohol into acetaldehyde and the broken line for A allele carriers of rs671 reflects slower metabolism of acetaldehyde into acetate.

aetiological significance of most other implicated variants is unclear, some results suggest that genetic risk factors for high alcohol consumption are at least partially different from those that mediate the risk of developing an AUD[66–68]. In other words, consistent with the heterogeneity of human alcohol phenotypes, meaningful variation is present in the genetic correlates of different alcohol indicators[63].

Limitations of contemporary alcohol-related GWASs were sample size (even though their sample sizes were much larger than in early studies), the use of low-resolution cross-sectional phenotypes, and that the identified loci accounted for very small amounts of phenotypic variability. Another limitation of these studies was the over-reliance on individuals of European ancestry, and future studies are needed to better explore other ancestry groups, which are expected to harbour different risk variants. Finally, it is notable that independent variant influences are only one piece of the puzzle when it comes to genetic influences on alcohol consumption outcomes. There is evidence that gene–environment correlations and interactions are also implicated[69], albeit without definitive relationships ascertained at this point.

Environmental risk factors. Environmental and developmental risk factors also confer a risk of hazardous drinking and AUDs, although the potential for confounding with genetic risk or gene–environment interactions should be noted. Environmental risk starts *in utero*, whereby prenatal alcohol exposure is a substantial risk factor for future hazardous drinking and other behavioural problems[70]. During childhood, several environmental exposures and pre-morbid conditions similarly increase the risk. For example, exposure to childhood adversity (such as abuse, neglect or family dysfunction) is a significant risk factor for AUDs[71–74]. Furthermore, exposure to adverse childhood events is associated with prenatal alcohol exposure, with potentially synergistic effects[75]. Teasing out familial confounding is challenging in understanding the link between childhood adversity and substance use disorders in general, but one study that incorporated numerous confounders found that maltreatment conferred a threefold increase in the risk of substance use disorders[73]. Importantly, genetic and environmental risk factors for AUDs may interact. For example, there is evidence of genetic influences on fetal vulnerability to prenatal alcohol exposure[76], highlighting the complex interplay between nature and nurture.

Other parental behaviours, such as more frequent drinking or providing alcohol to children are also well-established risk factors[77,78]. However, parenting can also have a protective role. Specifically, an authoritative parenting style is protective[79,80], but hostile or harsh parenting styles are risk factors for drinking[81–83]. Other protective factors include parent–child connectedness and parental support[79,80]. These findings generally pertain to drinking outcomes rather than risk of developing an AUD per se and causality is unclear due methodological challenges and possible confounding. Some premorbid psychiatric conditions can increase the risk of hazardous drinking, namely externalizing symptoms[84] (such as disinhibition, inattention and antisociality) and internalizing symptoms[85] (such as depression, anxiety and fearfulness). However, these symptoms may be related to adverse exposures during childhood; for example, prenatal alcohol exposure is also linked to the subsequent development of psychiatric symptoms[86].

Several features of drinking during the teenage years and emerging adulthood (typically defined as the age range 18–25 years) predict future risk of hazardous drinking and developing an AUD. During this wide but critical alcohol-related developmental period, most individuals have their first drink[87], and the lifetime prevalence of hazardous drinking and AUDs peak[12]. Furthermore, by the end of emerging adulthood, hazardous drinkers and individuals with an AUD typically substantially reduce drinking, reflecting an 'ageing out' trajectory[88]. Although an earlier age of drinking initiation was initially considered a risk factor for hazardous drinking and AUDs, supporting evidence is inconsistent[89] and earlier onset drinking may be better understood as a behavioural marker of increased genetic risk[90]. The severity of hazardous drinking during young adulthood is a predictor of future

AUDs and other long-term drinking outcomes, and can interfere with attaining important psychosocial end points, such as educational, vocational and interpersonal outcomes[91–93]. Reciprocally, ageing out of hazardous drinking is predicted by psychosocial role transitions in work, marriage and parenthood[94–96]. Thus, the extent to which young adult drinking disrupts salutary psychosocial development in terms of adult roles is a risk factor for long-standing challenges with alcohol.

Proximal factors

Biological determinants. Alcohol differs from other addictive substances because it does not have a unique high-affinity molecular target in the nervous system. As such, doses of ethanol for humans are typically measured in grams, unlike most other drugs which are measured in milligrams or micrograms.

At intoxicating levels, alcohol affects several biological pathways, with effects that vary between individuals and across the lifespan. The initial mechanisms of action of alcohol are not fully understood but proteins are believed to be the primary targets. Among ligand-gated ion channels, glutamatergic and γ-aminobutyric acid (GABA)ergic receptors directly mediate alcohol effects that, collectively, result in central nervous system (CNS) depression. Specifically, alcohol acutely dampens glutamatergic transmission by reducing calcium ion movement through *N*-methyl-D-aspartate (NMDA) receptors[97,98]. Alcohol also directly potentiates GABAergic transmission by increasing chloride movement through GABA-A receptors, and probably also by increasing pre-synaptic GABA release[97], actions that are putatively responsible for the subjective anxiolytic effects of alcohol. With chronic alcohol use, both glutamatergic and GABAergic effects are associated with the development of marked tolerance[97,98]. Once tolerance develops, cessation of alcohol intake results in a rebound of both glutamatergic and GABAergic effects, causing a global CNS hyperexcitability that underlies acute clinical alcohol withdrawal manifestations and contributes to long-term changes in brain function[99]. Over time, cycles of a hyperglutamatergic state promote wide-ranging and persistent long-term adaptations of neuronal function, through mechanisms that are not fully understood but include both neurotoxic insult and epigenetic dysregulation of key brain circuits[99,100]. For instance, meta-analysis of structural MRI data has shown grey matter losses in the prefrontal cortex (PFC), dorsal striatum and insula[101], that are believed to contribute to impairments of top-down cognitive control over motivation and salience attribution.

As glutamatergic and GABAergic systems are fundamental for brain function, the effects of alcohol on these targets results in wide-ranging downstream actions. Key consequences are actions on G protein-coupled (GPCR) neurotransmitter receptors that have an important role in drug reward, such as dopamine, endorphin and endocannabinoid systems[97]. Indeed, endogenous opioid peptides (endorphins) are released by alcohol in several brain structures, including the ventral tegmental area (VTA) and nucleus accumbens (NAcc), which are part of the classic dopaminergic reward pathway[102]. Alcohol-mediated endorphin release in the VTA is believed to remove inhibitory tone from dopaminergic neurons, leading to their increased firing and dopamine release in their terminal areas such as the NAcc[103,104]. Endogenous opioids also have direct, dopamine-independent effects on the function of the NAcc[105]. Overall, this second wave of alcohol effects results in psychostimulant-like actions.

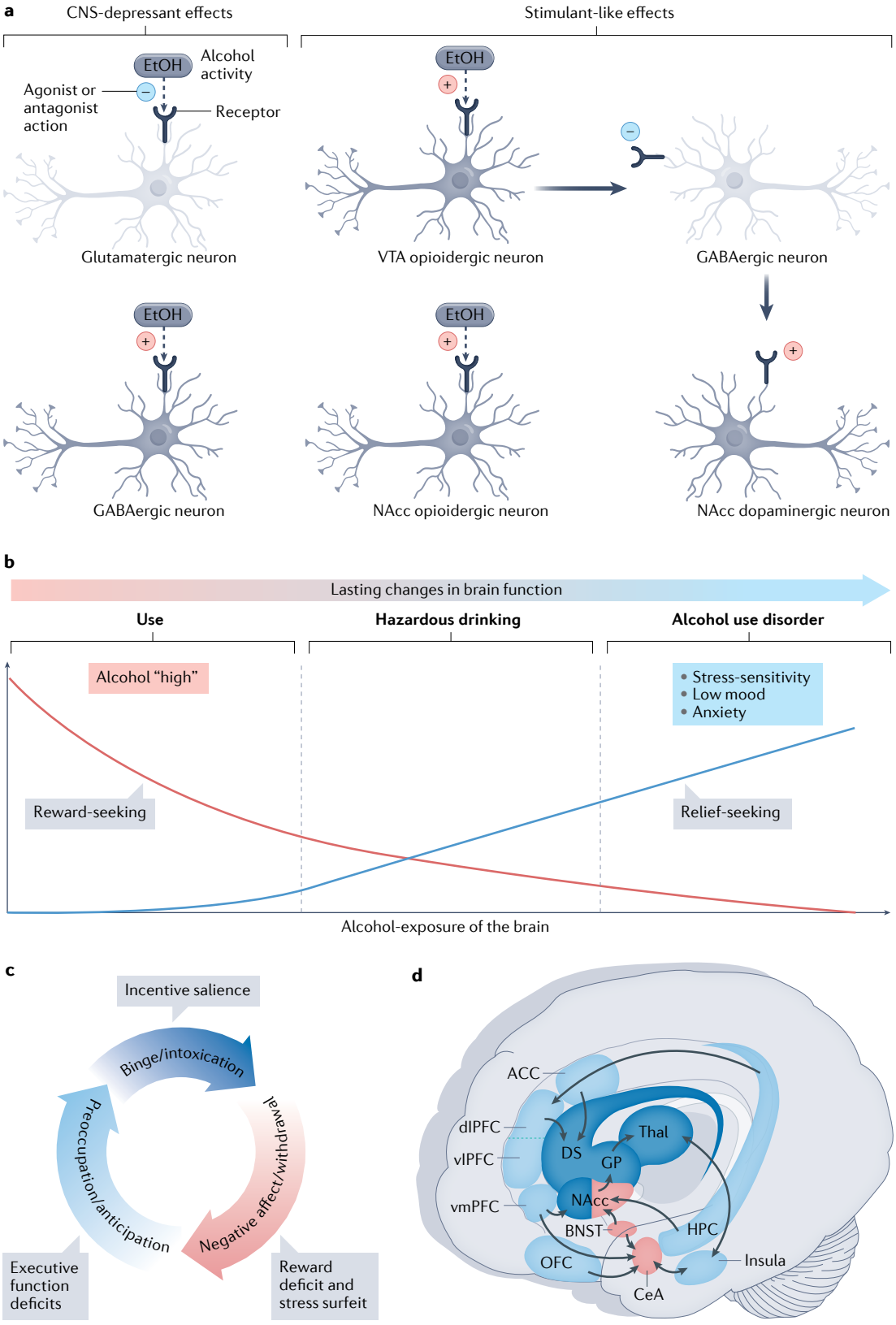
Thus, collectively and somewhat paradoxically, the acute effects of alcohol are both CNS depressant (sedative and anxiolytic), primarily mediated via ionotropic receptor actions, and psychostimulant-like, primarily mediated via GPCRs. The psychoactive effects of alcohol are generally described as being biphasic, with the ascending limb of the blood alcohol curve associated with stimulant effects and the descending limb associated with sedative effects[106,107]. As noted above, individual differences in the balance between sedative and stimulant-like alcohol actions are in part genetically determined and related to the risk of developing an AUD.

With prolonged alcohol use, distress systems that involve the amygdala and its outputs are also recruited, and promote a shift of alcohol taking driven by distress-relieving (negatively reinforcing) rather than rewarding (positively reinforcing) actions[99,108,109]. The exact mechanisms underlying this transition is not known, but repeated activation of distress systems during cycles of withdrawal that follows intoxication has been conceptualized to result in a shift of affective homeostasis, driven by progressively upregulated activity of stress-mediating neurotransmitter systems including corticotropin-releasing factor, dynorphin and noradrenaline[110,111] (Fig. 4). Animal studies have suggested that these amygdala systems are involved in a shift of choice between natural rewards and alcohol[112], as well as continued use of alcohol despite negative consequences (compulsivity)[113]. Compulsivity also seems to involve the insular[114] and orbitofrontal[115] cortices, and probably converges with amygdala inputs at the brainstem. The involvement of the amygdala in addiction-related behaviours points to additional putative treatment targets, and to a likely need to tailor the choice of pharmacotherapies to the individual and the stage of AUD[116].

In humans, MRI and PET have been instrumental in helping understand susceptibility to and the effects of AUDs on brain structure and function. Structural studies using MRI have shown that moderate to severe AUD is associated with grey matter loss, particularly of the PFC[33,101,117]. These changes putatively underpin alcohol-related cognitive impairments (such as poor inhibitory control or decision making) that may contribute to continued alcohol misuse. There is also evidence to support the theory that chronic heavy alcohol consumption accelerates brain ageing[118]. However, of note, abstinence from alcohol results in recovery of brain volume and cognitive improvement, although to a lesser extent in older individuals[118,119]. Heavy alcohol consumption in adolescence is associated with lower grey matter volume, particularly in the frontal and temporal lobes, and reduced white matter integrity[120]. Whether these differences are a consequence of alcohol exposure or pre-existing differences that increase the risk of developing an AUD is unclear but is being evaluated in large cohort studies[121–123].

Given the important role of environmental cues in motivating drinking, many functional MRI (fMRI) studies have aimed to characterize brain responses to alcohol-related cues. Greater responses to salient cues (such as pictures or tiny amounts of alcohol) are observed in the mesolimbic reward system including the anterior cingulate, orbitofrontal, dorsolateral PFCs, amygdala and ventral striatum[124]. Such responses are associated with higher risk of relapse[125] and pharmacotherapy-induced attenuation of responses to cues in the ventral striatum[124,126,127]. By contrast, anticipation of monetary reward is associated with blunted responses in the striatum in people with an AUD, providing a potential neural substrate for the increased choice of alcohol over natural rewards in people with an AUD[128]. Of note, treatment with a dopamine D3 antagonist normalizes this blunting[129].

Resting state fMRI (rsfMRI), or examination of connectivity among large-scale brain networks while an individual is not performing any specific task, is increasingly used to define dysregulated networks in addiction[130]. Although only a modest number of studies have been conducted on alcohol[130], consistent with preclinical studies that have found amygdala dysregulation with chronic alcohol exposure, persistently elevated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CNS-depressant effects
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GABAergic neuron
GABAergic neuron
NAcc opioidergic neuron
NAcc dopaminergic neuron
b
Lasting changes in brain function
Use
Hazardous drinking
Alcohol use disorder
Alcohol "high"
Stress-sensitivity
Low mood
Anxiety
Reward-seeking
Relief-seeking
Alcohol-exposure of the brain
c
Incentive salience
Binge/intoxication
Withdrawal/negative affect
Preoccupation/anticipation
Executive function deficits
Reward deficit and stress surfeit
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Fig. 4 | A contemporary overview of the neurobiology of alcohol use disorders. **a**, Acute direct and indirect neuropharmacological effects of alcohol (EtOH), including antagonism of glutamatergic neurons and agonism of both GABAergic neurons and opioidergic neurons. Of note, in addition to agonism of opioidergic neurons in the nucleus accumbens (NAcc), endogenous opioid release in the ventral tegmental area (VTA) leads to an inhibitory effect on GABAergic neurons that in turn increases dopamine release in the NAcc. **b**, Progressive transition from positively reinforcing (rewarding) effects to negatively reinforcing (relieving) effects. **c**, A theorized sequence and associated deficits in the progression to alcohol use disorders. **d**, The putative neurocircuitry associated with each feature of the cycle. ACC, anterior cingulate cortex (preoccupation/anticipation); BNST, bed nucleus of the striatum (negative affect/withdrawal); CeA, central nucleus of the amgygdala (negative affect/withdrawal); dlPFC, dorsolateral prefrontal cortex (preoccupation/anticipation); DS, dorsal striatum (binge/intoxication); GP, globus pallidus (binge/intoxication); HPC, hippocampus (preoccupation/anticipation); OFC, orbitofrontal cortex (preoccupation/anticipation); Thal, thalamus (binge/intoxication); vlPFC, ventrolateral prefrontal cortex (preoccupation/anticipation); vmPFC, ventromedial prefrontal cortex (preoccupation/anticipation); VS, ventral striatum (binge/intoxication). Source Volkow et al. OUD NRDP. Parts **c** and **d** adapted with permission from refs.[373,374]. Q22

rsfMRI connectivity between the amygdala and substantia nigra and VTA has also been found in abstinent individuals with an AUD[131].

PET directly assesses variation in molecular substrates in humans, and PET studies using [^{11}C]raclopride, a dopamine D2 receptor tracer, have demonstrated an increase in dopamine release following alcohol consumption in all subregions of the striatum, particularly the ventral striatum[132]. Notably, this effect is significantly larger in males than in females[132]. Moreover, fewer dopamine D2 receptors and blunted amphetamine-related dopamine release in the striatum in individuals with a moderate to severe AUD have been found in some studies[133]. One study using a selective dopamine D3 receptor PET tracer, ^{11}C-PHNO, found no differences in the striatum and higher levels in the hypothalamus in abstinent individuals with a moderate to severe AUD compared with controls[134]. Thus, the contribution of different dopamine receptor systems seems to vary in those with an AUD. Although earlier studies found that individuals with a moderate to severe AUD have a higher level of mu opioid receptors throughout the brain, which were positively associated with craving[135], more recent studies have found no differences[136,137], although these studies had notable methodological differences. Nevertheless, blunted amphetamine-induced endogenous opioid release has been reported in abstinent individuals with a moderate to severe AUD, suggesting enduring opioid dysregulation[137].

Q23 Important considerations in the neuroimaging literature include a limited understanding of sex differences in AUDs, as females tend to be under-represented in neuroimaging studies and sex differences are not a common focus[138]. However, the ENIGMA Addiction working group has combined datasets and demonstrated smaller, dose-dependent amygdala volumes only in males with an AUD[139]. In addition, AUDs are commonly comorbid with other psychiatric disorders and the specificity of neuroimaging findings for AUD is often unclear. For example, alterations in reward-related system (PFC, striatum, amygdala and hippocampus) in adolescents are associated with a higher risk of any drinking, and higher risks of major depressive disorder, schizophrenia and attention deficit hyperactivity disorder[140].

Q24 **Psychological determinants.** Contemporary theories for the psychological causes of AUDs are extensions of basic behavioural science, including learning theory, cognitive psychology, human psychopharmacology and personality psychology.

From the perspective of learning theory, alcohol use is motivated behaviour reflecting instrumental (operant) learning, or learning based on direct outcomes to the individual. From this viewpoint, the primary determinants of drinking behaviour are its reinforcing consequences (including both positive reinforcement reflecting hedonic effects and negative reinforcement reflecting alleviation of distress), the rapid onset of its reinforcing effects, and the availability of alternative reinforcers (motivationally appealing non-drinking options)[141–143]. Foundational evidence supporting this theoretical approach came from studies using residential laboratory paradigms and experimental decision-making tasks[144–147]. Based on these findings, alcohol consumption in daily life is an operant choice behaviour among competing reinforcers, effectively constituting a microeconomy in which individuals over-allocate resources (such as time, effort and money) to drinking behaviour. With increasing integration of concepts from microeconomics, the operant learning approach has evolved into what is referred to as the contemporary behavioural economic perspective[148]. Specifically, this approach emphasizes three core factors: elevated alcohol reinforcing value, over-valuation of immediate rewards and limited availability of alternative non-alcohol reinforcers, each of which is robustly linked with AUDs[149–152]. Moreover, the reinforcement-based perspective is the foundation for treatments of AUDs and hazardous drinking, such as the community reinforcement approach (CRA), contingency management (CM) and substance-free activity interventions, which incentivize treatment-related outcomes or focus on developing alternative non-alcohol reinforcers, and are discussed below in this Primer.

Associative (pavlovian) learning is also theorized to be an important determinant of drinking behaviour, with extensive evidence that environmental conditional stimuli elicit dynamic changes in craving, reinforcing value, affect and psychophysiology[153,154] that have important roles in motivating drinking behaviour. This is critical owing to extensive preclinical evidence of both the persistence of associative learning[155] and its role in the transition of putatively volitional goal-based behaviour to more automatic habit-based behaviour[156]. However, the extent to which addiction motivation reflects goal-directed drug choice versus habitual (compulsive) behaviour is debated, and one appraisal of the evidence concluded that studies in humans generally provide more evidence in support of goal-directed drug choice, particularly in the context of negative affect[157]. Regardless, the role of operant and associative learning processes are widely agreed upon to be foundational factors in alcohol and other drug addiction.

Perspectives from cognitive psychology emphasize key roles of information processing mechanisms in hazardous drinking and AUDs. Alcohol expectancies, or mental templates based on direct experience and social learning, include a person's beliefs about the effects of alcohol on social facilitation, assertiveness, sexual enhancement and stress relief[158], and predict alcohol use[159–161]. Motives for drinking are conceptually similar and multifaceted, and include social, enhancement and coping dimensions[162–165], of which coping is particularly linked to alcohol problems[164,166]. Complementing these processes that are measured by a person's self-perception, implicit cognition measures the attentional bias a person has towards alcohol-related

stimuli. These measures putatively assess how saliently and robustly alcohol as a stimulus is instantiated in a person's cognitive network and have been linked to severity of alcohol involvement[167] and treatment response[168,169]. Another element of a cognitive perspective on AUDs is recognition of deficits in executive function among individuals with an AUD. Executive function comprises higher order cognitive processes, including attention, deliberation, set shifting, working memory and inhibition, and there is evidence of impairment in these domains in people with an AUD[170]. Although temporal causality is not definitively established, these relationships are putatively bidirectional, reflecting both vulnerability to initiate and progress in drinking, and the neurotoxic effects of alcohol itself. From this perspective, AUDs are understood as a disorder of excessive motivation for alcohol and reflecting innate and acquired deficits in executive functioning.

Moreover, individual differences in the pharmacological effects of alcohol and personality traits are also implicated in AUDs. As previously mentioned, alcohol has both stimulant and sedative effects[106,171]. A family history of AUDs is associated with a reduced sedative–ataxic response to alcohol[172] and early studies of alcohol response similarly identified low response as a longitudinal risk factor[173,174]. More recent investigations have also found that stimulant effects are prospectively predictive[60,175]. In terms of personality, although an 'addictive personality' is a popular lay notion, there is limited evidence for any singular personality profile conferring a risk of developing an AUD[176]. Instead, certain personality traits are significantly associated with AUDs, namely neuroticism (positively associated) and conscientiousness (negatively associated)[177–180]. The most robust associations between personality and drinking are arguably with impulsivity-related traits[165], measured using the Barrett Impulsiveness Scales[181] or the UPPS-P Impulsive Behaviour Scales[182,183], particularly facets reflecting emotional regulation (negative urgency and positive urgency) and lack of premeditation or planning[184]. Of note, these measures of impulsive personality traits are moderately-to-highly intercorrelated, but not substantially correlated with behavioural measures of impulsivity[185], such as revealed preferences for smaller immediate rewards over larger delayed rewards (that is, delay discounting) or ability to inhibit a prepotent motor response (that is, behavioural inhibition). Indeed, the contemporary perspective is that impulsivity is a multidimensional construct, reflecting conceptually related but often quantitatively distinct indicators[185,186]. The extent to which different forms of impulsivity are causes versus consequences of AUDs is an area of active investigation, but longitudinal and genetic studies are increasingly suggesting deficits in these processes at least partially pre-date AUDs[187,188].

Social and societal determinants. Direct social and higher-order societal factors are involved in drinking behaviour. For example, drinking for social enhancement features prominently in measures of expectancies and motives[158,162–165] and estimates of drinking in an individual's proximal social network are highly correlated with personal alcohol use[189,190]. Studies using social network analysis, which quantitatively characterizes the structure of relationships among people[191–193], have revealed that drinkers cluster together in networks and social network characteristics predict changes in drinking over time[194–196], with parallel findings for other addictive disorders[190,197–199]. Clinically, changes in an individual's social circle to include fewer people who drink alcohol predict recovery[200,201], and salutary changes in social networks is a mechanism recognized in the treatment programmes of Alcoholics Anonymous (AA)[202]. Furthermore, an intervention developed to create social networks that are less supportive of drinking and more supportive of abstinence has been shown to significantly decrease drinking consequences and increase the number of days abstinent[203,204]. In social networks, not all members are of equal importance and influence varies across the lifespan. During adolescence and young adulthood, parental influences and peer influences are particularly powerful, but during adulthood dyadic influences become increasingly prominent. This form of assortative mating reflects the fact that substance-using individuals are more likely to be romantically involved with individuals who are also substance users[205,206]. Thus, hazardous drinking in both members of a dyad represents a particularly deep embedding within a social network, one that is particularly pernicious insofar as it is also associated with parenting deficits and intimate partner violence[207].

These social dynamics are nested within broader influences of culture and society. Religion substantially influences drinking levels, with certain religions, such as Islam, proscribing the consumption of alcohol, resulting in much lower rates of drinking in regions where these religions are dominant[3], and religiosity as a trait is associated with lower drinking[208–211]. Policy strategies, such as licensed sales outlets, government monopolies and price and tax levels have significant impacts on alcohol consumption (see Prevention, below)[212–215]. Equally, the availability and costs of evidence-based treatment across health-care systems affect the population level alcohol burden[216–218]. More broadly, social determinants of health, or the non-medical factors that affect health outcomes, such as income, housing, early childhood development, social inclusion and non-discrimination, and access to quality health services, are well established as increasing the risk of hazardous drinking and AUDs[219–221]. In each case, sociocultural factors create an environmental niche that is variably potentiating for or protective against a person developing hazardous drinking or an AUD.

Diagnosis, screening and prevention

Diagnosis

AUDs are typically diagnosed on the basis of a clinical interview by a trained mental health-care worker to evaluate symptoms and supplemental assessments, such as the presence of withdrawal symptoms (Box 2). In some jurisdictions, a formal diagnosis can only be made by a physician or psychologist. As noted, DSM-5 uses a single dimensional diagnosis of AUD, whereas ICD-11 has two diagnoses: Harmful Pattern of Alcohol Use and Alcohol Dependence (Box 2). Definitive assessments can be made using a structured or semi-structured clinical interview, such as the Structured Clinical Interview for DSM-5 (ref.[222]) or the Diagnostic Assessment for Research and Treatment tool[223]. Clinical interviews are resource-intensive and can impose a burden on the patient, and self-reported symptom checklists have been validated in primary care[224], mental health settings[225] and AUD treatment settings[226].

Screening

Routine alcohol screening (Box 3) is recommended across adult medical settings because it is often unrecognized by drinkers[227] and because of how commonly individuals with an AUD interact with the health-care system. For example, in one study of the UK hospital system, one in five patients used alcohol harmfully and one in ten patients had alcohol dependence[228]. Universal screening is particularly warranted in primary care[229] because of its role in routine care and in mental health settings because of the high comorbidity of hazardous drinking and AUDs with other common psychiatric disorders[12].

Box 2

Medical diagnoses of alcohol-related harms in the 5th edition of the Diagnostic and Statistical Manual (DSM-5) and 11th edition of the International Classification for Diseases (ICD-11)

DSM-5 (2013) *Alcohol Use Disorder*[375]

The presence of two or more symptoms within the past 12 months. The presence of two or three symptoms denotes mild AUD, four or five symptoms denotes moderate AUD; and six or more symptoms denotes severe AUD.

1. Alcohol often consumed in larger amounts or over a longer period than intended.
2. A desire or unsuccessful efforts to cut down or control alcohol use.
3. A substantial amount of time spent in activities needed to obtain alcohol, use alcohol, or recover from the effects of alcohol.
4. Craving, or a strong desire or urge to use alcohol.
5. Recurrent alcohol associated with failure to fulfil responsibilities at work, school or home.
6. Continued alcohol use despite related social or interpersonal problems.
7. Stopping or reducing social, occupational or recreational activities due to alcohol use.
8. Recurrent alcohol use in physically hazardous situations.
9. Continued alcohol use despite knowledge of a physical or psychological problem likely to be caused or exacerbated by alcohol.
10. Tolerance, defined by either: a need for markedly increased amounts of alcohol to achieve intoxication or desired effect, or a markedly reduced effect with continued use of the same amount of alcohol.
11. Withdrawal, manifesting as either: alcohol withdrawal syndrome, or alcohol or a closely related drug is taken to relieve or avoid withdrawal symptoms.

ICD-11 *Harmful pattern of alcohol use*[16]

The presence of one or more symptoms over at least 12 months with episodic substance use or at least 1 month with continuous use.

1. Harm to health of the individual occurs due to one or more of the following: behaviour related to intoxication, toxic effects on body organs and systems, and harmful route of administration.
2. Harm to health of others (that is, physical harm, including trauma, or mental disorder that is directly related to the behaviour of the individual with a harmful pattern of alcohol use).

ICD-11 *Alcohol Dependence*[16]

The patient exhibits the characteristic feature of a strong internal drive to use alcohol (manifested by impaired ability to control use, increasing priority given to use over other activities and persistence of use despite harm or negative consequences). These experiences are often accompanied by a subjective sensation of urge or craving to use alcohol. Physiological features of dependence may also be present, including tolerance to the effects of alcohol, withdrawal symptoms following cessation or reduction in use of alcohol, or repeated use of alcohol or pharmacologically similar substances to prevent or alleviate withdrawal symptoms. The features of dependence are usually evident over a period of at least 12 months but the diagnosis may be made if alcohol use is continuous (daily or almost daily) for at least 3 months.

Implementation of screening varies widely[230], influenced by lack of training, availability of integrated care, or capacity to transition positively screened individuals to specialist services (due to, for example, availability of inpatient, partial-care, and/or outpatient alcohol treatment services)[231]. Another obstacle is that many health-care providers do not feel sufficiently trained to follow-up with positively screened patients in specific subpopulations, such as women of childbearing age, pregnant women and those with a medical illness[232,233]. This issue is unfortunate as there is evidence that clinical initiatives to address high-risk subpopulations can substantially improve detection of hazardous drinking[234].

Effective screening approaches incorporate validated questions and brief counselling[230,235,236]. Strategies to improve implementation of screening procedures include training of clinical staff and the use of specialty clinicians who can oversee screening and referral to alcohol prevention and intervention programmes. There is substantial evidence that efforts to increase the frequency of alcohol screening within primary care settings are effective[230,237,238]. Screening is more common in settings with stronger facilitation of clinical practices and facilitative electronic health records[230]. A promising approach to promoting integration of evidence-based practices is the Consolidated Framework for Implementation Research, and its application to increasing alcohol screening has been informative[239,240].

Screening itself is now well-established as clinically beneficial. Specifically, the benefits of screening and brief intervention (SBI)[241] in primary care settings and other numerous time-limited settings are well-supported[241,242]. In general, SBI is carried out by trained staff who begin with a brief screening tool in combination with a discussion using a FRAMES (feedback, responsibility, advice, menu, empathy and self-efficacy) approach. The clinical style in SBI largely involves the empathic and non-judgemental approach used in motivational interviewing (MI)[243] and culminates with a brief discussion of clinical options that are tailored to the individual's level of risk[244]. The level of evidence is such that the US Public Service Task Force recommends SBI for all adults in primary care[229]. While SBI also historically included a referral to treatment component, the evidence does not support its efficacy for transitioning individuals into formal treatment[245–247].

Biomarkers of alcohol use

Several biomarkers can be used in conjunction with clinical assessments to assess the level and recency of alcohol involvement (Box 4), although not AUDs per se. The most widely used alcohol detection instrument is the breathalyser, which is available in numerous device formats. Given the hepatic metabolism of alcohol, blood tests that measure liver enzymes (aspartate and alanine aminotransferases (AST and ALT) and γ-glutamyl transferase (GGT)) are used to indirectly ascertain drinking heaviness, although the precision of these indicators is suboptimal[248]. Other serum-based biomarkers include the percentage of disialocarbohydrate-deficient transferrin, mean corpuscular volume and phosphatidyl ethanol (PEth) levels. Recent alcohol use can be ascertained using several biomarkers, including transdermal alcohol[249] (such as via ankle monitoring devices) and metabolic byproducts (such as urinary ethyl glucuronide)[250]. A novel epigenetic biomarker is the Alcohol T Score (ATS), which measures average methylation at four sites selectively sensitive to alcohol consumption[251] and has accurately differentiated heavy drinkers from controls[252]. Of these biomarkers, PEth is in increasingly widespread use to detect recent drinking and, given its sensitivity to drinking at low levels for up to several weeks and quantitative scaling across a wide range of levels, it could render other biomarkers increasingly obsolete.

Box 3

Alcohol assessment measures for screening and diagnosis in clinical practice

Screening

Alcohol Use Disorders Identification Test (AUDIT)[9]

This is a ten-item questionnaire developed by the WHO that has been validated globally. The AUDIT is one of the most widely used measures for detecting hazardous drinking, including across elevated risk groups (such as individuals with unstable housing or individuals with co-occurring medical and/or psychiatric conditions). Scores of 7 and 8 represent hazardous drinking for women and men, respectively. The first three items measuring consumption can be used as a stand-alone screen, referred to as the AUDIT-C.

Alcohol, Smoking and Substance Involvement Screening Test (ASSIST)[376]

This is an eight-item (per substance) questionnaire also developed by the WHO as a culturally neutral measure for health-care workers in medical settings worldwide. Scores reflect low-risk, moderate-risk and high-risk categories, and map to no treatment, brief intervention and referral to specialist assessment and treatment.

CAGE/CRAFFT/TWEAK[377–379]

These mnemonic acronym-based brief screens are used across a number of settings and populations. Patients endorse the presence or absence of a feature of drinking for each letter in the acronym. CAGE stands for: cut down (C), annoyed by drinking (A), guilty (G), and eye opener (E). CRAFFT is for use in adolescents, and stands for: car (C), relax (R), alone (A), forget (F), family (F), and trouble (T). TWEAK is for use in pregnant women, and stands for: tolerance (T), worried (W), eye-opener (E), amnesia (blackouts) (A), and cut down (K).

Diagnosis and treatment planning

Symptom-based assessments

Symptom-based assessments for diagnosis include structured and semi-structured interviews, such as the Structured Clinical Interview for DSM-5 (ref.[380]), Mini-International Neuropsychiatric Interview[381] and the Diagnostic Assessment for Research and Treatment tool[223]. Recent evidence indicates high correspondence between self-report symptom checklists and interview-based diagnosis[226].

Timeline followback

Timeline followback[382] (TLFB) has support for being one of the most widely used tools to measure quantity and frequency of alcohol use, although it should be noted that drinking patterns are not used to diagnose AUDs. It uses a calendar-based approach to quantify the number of drinking days and drinks per drinking day for the past 1–3 months. This interview can also be used to assess quantity and frequency of the co-occurring use of other substances (for example, cannabis, e-cigarettes or vaping, or prescription drugs).

Clinical Institute Withdrawal Assessment for Alcohol Revised

The Clinical Institute Withdrawal Assessment for Alcohol–Revised[383] (CIWA-Ar) is a widely used measure for detecting the alcohol withdrawal syndrome and guiding decision-making around the need for intervention.

Drinker Inventory of Consequences

The Drinker Inventory of Consequences[384] (DrInC) assesses alcohol-related consequences in five domains: physical consequences, interpersonal consequences, intrapersonal consequences, impulse control and social responsibility. Subsequent psychometric analysis suggests more valid scoring as mild, moderate and severe consequences[385].

Severity of Alcohol Dependence Questionnaire

The Severity of Alcohol Dependence Questionnaire[386] (SADQ) is a validated 20-item measure assessing AUD severity. It contains five subscales: physical withdrawal, affective withdrawal, withdrawal relief drinking, alcohol consumption and rapidity of reinstatement.

Young Adult Adverse Alcohol Consequences Questionnaire

The Young Adult Adverse Alcohol Consequences Questionnaire[387] (YAACQ) assesses alcohol-related consequences among adolescents and young adults with eight subscales: social/interpersonal, impaired control, self perception, self care, risky behaviours, academic/occupational, physiological dependence and blackout drinking. A brief version is also available.

Prevention

Prevention of harms from alcohol can broadly be divided into policy-level (environmental) and person-level (individual) strategies. In terms of policy, recent recommendations from the WHO include the five SAFER strategies for governments to reduce harms: (1) strengthening restrictions on alcohol availability; (2) advancing and enforcing drinking and driving countermeasures; (3) facilitating access to the screening, brief intervention and referral to treatment approach; (4) enforcing bans or comprehensive restrictions on alcohol advertising, sponsorship and promotion; and (5) raising prices of alcohol through excise taxes and pricing policies[253]. Two additional recommended evidence-based strategies include rigorous alcohol-related law enforcement (such as enforcing laws that prohibit service to intoxicated persons) and imposing minimum drinking age laws[254].

Each of these strategies is at least moderately effective[254], but alcohol pricing has the most robust effect. Pigouvian taxation[255] (that is, increasing taxes on a product to offset adverse outcomes from commodities that are not factored into the price) reduces alcohol consumption and harms[256]. Many economic costs of alcohol use (such as treatment, other alcohol-related health-care costs, law enforcement/criminal justice, and lost productivity) are distal from the product itself, therefore warranting this supplemental taxation strategy and the use of tax revenue to offset these externalities. Another pricing strategy is minimum unit pricing (MUP), which sets a minimum alcohol cost to avoid the accessibility that promotes hazardous drinking. For example, in Scotland in the UK a minimum price of 50 pence per UK unit of alcohol is mandated[257]. Like increased taxation, MUP is effective in reducing alcohol consumption[258] and, in turn, reducing alcohol-related harms.

With regard to non-financial restrictions on alcohol availability, sales outlet restrictions, such as government monopolies and outlet density, can reduce alcohol use and related crime[259,260]. Similarly, despite arguments that underage youths can obtain alcohol from older peers and siblings, age restrictions on alcohol also reduce alcohol consumption[261,262]. This finding is also supported by more frequent and heavier alcohol consumption by youths in regions with limited existing or enforced age restrictions or younger age restrictions[263,264].

Collectively, these policies can substantively reduce alcohol-related harms, particularly when implemented in concert. One notable example is from Russia over the past 15 years, where restrictions on marketing, monitoring of production, elimination of internet sales, substantial increases in taxation, increases in the minimum unit price, and reductions in retail availability of alcohol, have reversed trends of extremely high alcohol-related morbidity and mortality[265]. However, a coordinated approach is rarely implemented in practice owing to lack of public awareness, lack of government regulatory mechanisms for effective implementation (such as state alcohol monopolies), lobbying by the alcohol industry, and ineffective promotion of specific and feasible actions from the public health community[254].

At the individual level, prevention strategies comprise primary prevention (universal, for all individuals in a target population), secondary prevention (for those at-risk of harm) and tertiary prevention (for those exhibiting a clinically significant level of harm). Primary prevention includes programmes that involve intervention before the onset of health effects. Most studies on primary alcohol prevention are on school programmes that primarily provide education about alcohol's harmful effects, although they have very little effect on preventing youth alcohol use[266–268]. A continued challenge in primary prevention in adults is that many individuals are not aware of some of the health risks of alcohol use; for example, fewer than one in five women attending breast screening programmes were aware of the relationship between alcohol use and breast cancer[269]. Arguably the most promising youth approach, the so-called Icelandic strategy[268], focuses less on alcohol per se and more on improving parental engagement and promotion of alternative reinforcers, such as access to alcohol-free recreational activities. Compared with primary prevention, secondary and tertiary prevention have more supporting evidence for reducing alcohol use and harms[270,271]. For example, a personality-oriented secondary prevention programme has demonstrated efficacy in reducing hazardous drinking and other substance use[272]. As noted above, screening can produce substantive benefits[239,240,273] making it an important part of prevention.

Box 4

Alcohol biomarkers

Level or recency of alcohol use

- Blood alcohol content (BAC) reflects circulating alcohol in the bloodstream, which correlates with level of impairment.
- Breath alcohol (BrAC), measured via a breathalyser, is a valid proxy for BAC.
- Transdermal alcohol is another valid proxy for BAC but transdermal alcohol is available over a longer time window than BrAC via continuous monitoring devices.
- Urinary ethyl glucuronide is a minor metabolite of alcohol that is dose-dependently detectable for up to 72 h after drinking has ended.
- Phosphatidyl ethanol is a cellular membrane phospholipid produced from the interaction of alcohol with phospholipase D, and can reliably detect heavy drinking.

Alcohol burden on the liver and other systems

- Aspartate aminotransferase and alanine aminotransferase (AST and ALT) reflect liver burden from alcohol metabolism. Reference ranges are 0–35 IU/l and 0–45 IU/l, respectively. An AST to ALT ratio of 2:1 or higher is an indicator of heavy drinking.
- γ-Glutamyl transferase (GGT) is a liver enzyme that reflects injury to the liver, particularly to the bile ducts and in response to alcohol. Reference ranges are 0–30 IU/l, but GGT is not specific enough be used alone. Elevated GGT in conjunction with elevated AST may be used as an indicator of heavy drinking.
- The percentage disialocarbohydrate-deficient transferrin (%CDT) reflects proportionate levels of deficiency of an iron transport protein in the serum. In general, consumption of 50–60 g of alcohol per day for two or more weeks increases %CDT, which normalizes after three or more weeks of abstinence. The commonly used cut-off is 2.5% and %CDT can be used in conjunction with measurement of the level of GGT.
- Mean corpuscular volume (MCV) indicates red blood cell size, which increases after four or more weeks of heavy drinking. MCV has low sensitivity but high specificity; therefore, it is most useful when used with other tests.

Management

Specialist treatment is generally intended for individuals with a moderate or severe AUD as per DSM-5 criteria or alcohol dependence as per ICD-11 criteria. Pharmacological treatments are intended for use in conjunction with psychological interventions, and participation in a mutual support organization (for example, AA) is often encouraged. Therapeutic end points range from abstinence to reductions in drinking and harms, and are an area of active discussion in the field. Formal inpatient or outpatient treatment typically prioritizes recovery as the outcome. One definition of recovery from the National Institute on Alcohol Abuse and Alcoholism is as "a process through which an individual pursues both remission from alcohol use disorder (AUD) and cessation from heavy drinking"[274], meaning that the individual no longer meets diagnostic criteria and drinks at or below low-risk guidelines. Abstinence is often a priority but harm reduction is commonly part of treatment. Recently, one-level or two-level alcohol consumption reductions using the WHO guidelines (Box 1) have also been proposed as clinically meaningful reductions[275,276]. Of note, most evidence on the effectiveness of AUD treatments is from high-income regions, with research at an early stage in low-income and middle-income countries[277].

Pharmacological interventions

Approved medications for AWS. Individuals with an AUD can develop alcohol withdrawal syndrome (AWS) when they reduce or stop drinking. Symptoms of AWS reflect hyperarousal, including tremulousness, agitation, headache and diaphoresis (extensive sweating), typically commencing 6–36 h following the last alcoholic drink, and, in those who progress, seizures, hallucinations and delirium tremens (DT; global confusion) 48–96 h following the last alcoholic drink. Heavier alcohol consumption are associated with more severe withdrawal symptoms[278]. Benzodiazepines are the medication of choice for AWS because they effectively reduce the severity of withdrawal and prevent life-threatening consequences, such as seizures and DT[279]. Thiamine and magnesium supplementation are also commonly used during withdrawal to address nutritional deficiencies and prevent Wernicke encephalopathy. However, thiamine supplementation is not universally implemented in specialist settings where it may be beneficial (such as the emergency department) mainly because of lack of training and education among health-care providers[280].

Approved medications for AUDs. In addition to the acute management of AWS, increased understanding of the neurobiological mechanisms of AUDs has contributed to the development of medications to help patients reduce harmful alcohol consumption and to achieve and maintain abstinence[279] (Table 1). Of these pharmacotherapies, disulfiram, naltrexone, acamprosate and nalmefene are approved by one or more national or international regulatory agencies; however, large variability between countries exists in the availability of these medications. Of note, the variability in approval of these therapies between regions is not because of regulatory rejections, but is rather because of the extent to which a pharmaceutical manufacturer has sought an approval, that is typically based on marketing considerations.

Disulfiram was the first approved medication for the treatment of AUDs, and deters drinking by inhibiting alcohol metabolism and increasing circulating acetaldehyde, which triggers an unpleasant reaction (that is, nausea, dizziness and tachycardia). This is the same mechanism by which variation in the *ALDH2* gene confers protection against AUDs. Disulfiram is recommended only in patients who want to maintain abstinence and is contraindicated in those actively drinking alcohol and in those who want to only reduce their drinking of alcohol[279]. Moreover, disulfiram is also contraindicated in those with certain medical conditions in which acetaldehyde accumulation might pose a risk (such as coronary heart disease) or in individuals who are unable to understand the risks due to psychosis or cognitive impairment. Notably, evidence of the effectiveness of disulfiram has been strongest in trials using witnessed administration (such as in collaboration with a spouse or partner), with limited benefits in unwitnessed administration[281,282], putatively due to low medication compliance.

Naltrexone, a competitive μ-opioid receptor antagonist, and acamprosate, an NMDA receptor antagonist and positive allosteric modulator of $GABA_A$ receptors, are approved first-line agents that are modestly effective in the treatment of AUDs. The effect size of naltrexone is larger for alcohol reduction, whereas the effect size for acamprosate is larger for relapse prevention[283,284]. Clinically, naltrexone can be more useful in reducing harmful drinking among patients with an AUD who aim to reduce alcohol consumption but not to achieve and maintain abstinence. By contrast, acamprosate can be more useful in helping patients with an AUD who have achieved abstinence in reducing the risk of relapse to any drinking[283]. However, naltrexone may be less effective in women than in men[285]. Acamprosate is also sometimes used clinically during detoxification to reduce the hyperglutamatergic state that results in hyperarousal. Choosing between naltrexone and acamprosate should be based on patient-specific considerations and contraindications, including liver and kidney function[279]. Of note, patients benefit from combining pharmacotherapy with cognitive behavioural therapy (CBT)[286]. Several predictors of a positive response to naltrexone have been proposed (such as positive family history, early onset of drinking, other drug use, smoking and male sex[287–289]), and may inform its selection. Similar to naltrexone, nalmefene is a μ-opioid antagonist and is approved for use in Europe. The effect size and evidence of efficacy of nalmefene are lower than those of naltrexone and acamprosate (Table 1). In general, less is known about the safety and efficacy of these medications in women with an AUD than in men[290]. Of note, using these medications in adolescents and people older than 65 years is off-label (that is, use is not specifically approved by a regulatory body and is based on clinician judgement).

Off-label medications. Other medications have been tested for the treatment of AUDs, often based on research in rodent models and primarily repurposing medications already approved for other indications. These medications are not approved by a regulatory body, making their use off-label. The most promising are listed in Table 2.

In one meta-analysis of randomized controlled trials (RCTs), baclofen was found to be significantly superior to placebo for time to lapse and percentage days abstinent[291], with higher efficacy with lower doses, although a second meta-analysis found less consistent evidence of benefit[292]. These findings are complemented by those of a subsequent positive RCT[293], which also found that males may tolerate and selectively benefit from a higher-dose regimen. Baclofen seems to be particularly effective in patients with a more severe AUD, liver disease and anxiety[294,295]. Another promising medication is varenicline, which seems to be more effective in heavy drinkers who are male and smokers[296–298]. Topiramate has the most robust efficacy data of these medications[279], although it has substantive adverse effects, including paraesthesia, headache, taste abnormalities, fatigue, anorexia, dizziness, and difficulties with memory, attention and concentration[299]. A slow dose titration and close monitoring are important with topiramate, making it most suitable for specialist settings[296–298]. Gabapentin may

Table 1 | Medications approved for the treatment of alcohol use disorders

Drug[a] (route)	Indications	Mechanism of action	Benefits and effect sizes	Adverse effects	Recommendations, contraindications, limitations and other notes
Disulfiram (oral)	Patients aiming to maintain abstinence	Inhibits aldehyde dehydrogenase, and therefore leads to acetaldehyde accumulation upon alcohol consumption; this acetaldehyde accumulation induces distressing signs and symptoms ranging from facial flush, nausea, vomiting and headache to severe and rare bradypnea, shock and death; fear of this reaction acts as a deterrent to alcohol use	Better results with disulfiram than with other medications or placebo (for example, rate of abstinent days, mean days of alcohol use); outcomes are better in patients who are aware of the treatment and with supervised disulfiram administration	The most frequent adverse event is drowsiness; others are rare but include hepatitis, neuropathy, optic neuritis, psychosis and confused states	Contraindicated in patients with active alcohol consumption (including those who use alcohol-based products such as perfume or aftershave), those who do not understand the risks of alcohol consumption when they are under disulfiram and those with severe liver disease, psychosis, seizures and/or cardiovascular disease; the main limitations are low adherence, that patients need to abstain from drinking at least 12 h before starting disulfiram, and that a 7-day washout is required
Naltrexone (oral and intramuscular long-acting injection)	Patients aiming to reduce alcohol consumption and/or achieve abstinence	Non-selective antagonist of μ-opioid, κ-opioid and δ-opioid receptors that acts by blocking the interaction between brain receptors and endogenous opioid peptides involved in the rewarding effects of alcohol; reduces the rewarding effects of alcohol consumption	Prevents relapses into any drinking or heavy drinking, reduces the number of drinking and heavy drinking days, and reduces the number of drinks per drinking days compared with placebo	Dizziness, nausea and vomiting	Contraindicated in patients who require opioids for analgesia, those with active opioid use disorder, and those with severe liver disease; the main limitation (especially for the oral formulation) is low adherence
Nalmefene (oral)	Patients who do not need immediate detoxification and have not been able to reduce their drinking with psychosocial support	A μ-opioid and δ-opioid receptor antagonist and a κ-opioid receptor partial agonist; like naltrexone, nalmefene reduces the rewarding effects perceived after alcohol consumption	Although developed for abstinence, nalmefene reduces the number of monthly heavy drinking days compared with placebo	Dizziness, headache, insomnia, nausea and vomiting	Contraindicated in patients who require opioids for analgesia, patients with active opioid use disorder and patients with psychiatric comorbidity; of note, there is no evidence of hepatotoxicity with nalmefene
Acamprosate (oral)	Patients who are abstinent and aiming to maintain abstinence from alcohol	Although not fully understood, acamprosate may work by modulating the altered glutamatergic neurotransmission state in patients with an AUD	Prevents relapses into any drinking and reduces the number of drinking days compared with placebo	Anxiety, diarrhoea and vomiting	Dose adjustment needed or contraindicated in patients with severe renal impairment

AUD, alcohol use disorder. [a]These medications are generally indicated for use in individuals with DSM-5 moderate or severe AUD or ICD-11 alcohol dependence.

be selectively beneficial in patients with a more substantial history of AWS[296–298] and, together with topiramate, is recommended as a second-line treatment (the first-line medications being acamprosate, disulfiram and naltrexone) by the American Psychiatric Association[279]. A further consideration in using gabapentin is that although it is generally safe, it may have misuse potential in some patients[300]. Additional medications are under investigation (such as prazosin[301], ibudilast[302] and D-cycloserine[303]), but data are preliminary.

Psychological interventions

A number of psychological interventions have exhibited consistent evidence of effectiveness in treating AUDs. Except for MI, these therapies are generally intended for use in individuals with a moderate or severe AUD.

Motivational interviewing. MI[304] and its structured version, motivational enhancement therapy (MET)[305], are client-centred, directive therapeutic approaches to bolster alcohol-related behaviour change (Table 3). The cost-effectiveness, viability across settings and flexibility of MI and MET have resulted in their wide adoption globally, including in settings with individuals not seeking treatment such as urgent/emergency care, primary care and correctional settings[306]. Meta-analyses and systematic reviews support the effectiveness of MI and MET in reducing alcohol use[306], with a similar effectiveness to other active psychosocial interventions, including among heavy users, albeit with slightly lower effect sizes in younger age groups[307]. MI and MET are most frequently used as stand-alone therapies, but can also used as adjunctive treatment, commonly as a lead in for other more structured interventions, with the focus based both on building therapeutic rapport and on the need for patient motivation to engage maximally in other psychological treatments. Moreover, the flexible client-centred style of MI makes it a useful therapeutic approach as a platform for delivering other kinds of psychological or pharmacological interventions.

Cognitive behavioural therapy/relapse prevention. Broadly, CBT for AUDs refers to a set of skills-based approaches that are based on the premises that drinking is motivated by functional outcomes (for example, managing negative emotional states or cravings) and that

Q35 **Table 2 | Off-label medications for the treatment of alcohol use disorders**

Drug[a] (route)	Indications	Mechanism of action	Benefits	Adverse effects	Recommendations, contraindications, limitations and other notes
Baclofen (oral)	Approved only in France for decreasing alcohol consumption in those who do not benefit from approved medications	Selective $GABA_B$ receptor agonist; stimulation of $GABA_B$ receptors in the ventral tegmental area; reduces dopamine activity and rewarding effects of alcohol	Higher likelihood of abstinence compared to placebo and increases the number of abstinent days among anxious patients, but not among non-anxious patients	Vertigo, somnolence, dry mouth, paraesthesia and muscle spasm	Caution required in patients with renal impairment, history of epilepsy, mood disorders, suicidal ideation or a history of suicide attempts and in those receiving other sedative medications (including alcohol); treatment should not be abruptly interrupted to avoid the risk of withdrawal symptoms
Gabapentin (oral)	Patients aiming to reduce alcohol consumption and/or achieve abstinence	Although not fully understood, gabapentin inhibits selectively voltage-gated calcium channels containing the α-2-delta-1 subunit and has effects on both inhibitory and excitatory neurotransmission	Reduces the percentage of heavy drinking days compared with placebo	A higher risk of adverse events (such as fatigue, dizziness and somnolence) compared with placebo	Caution required because of possible misuse or renal impairment
Topiramate (oral)	Because of its association with weight loss, suggested in patients with comorbid obesity	Glutamate receptor (AMPA and kainate receptors) antagonist. Potentiates GABA activity by inducing chloride ion flux into neurons, and inhibits dopamine release	Reduces the number of drinking and heavy drinking days, reduces the number of drinks per drinking days and increases abstinence, compared with placebo	Cognitive dysfunction, paraesthesia and taste abnormalities	Contraindicated in patients with risk factors for and/or history of metabolic acidosis, kidney stones and secondary angle closure glaucoma; suggested to assess baseline cognitive status and renal function before commencing therapy; caution required in older people elderly and people at risk of falls
Varenicline (oral)	Individuals with co-occurring nicotine dependence	Partial agonist of α4β2 nicotinic acetylcholine receptors, implicated in both alcohol and nicotine reward	Reduces alcohol consumption compared with placebo	Nausea, insomnia, abnormal dreams and headache	Patients with tobacco use disorder who receive varenicline are at higher risk of any serious adverse event, with rates about 25% higher than those who do not use this medication

AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; GABA, γ-amino butyric acid. [a]These are generally indicated for individuals with DSM-5 moderate or severe AUD or ICD-11 alcohol dependence.

changing drinking behaviour is hindered by a lack of skills for managing life without alcohol. One common form is relapse prevention[308], which emphasizes managing high-risk situations, but other forms focus on coping or social skills training to address common motives for drinking[309]. Meta-analyses suggest that CBT is superior to no treatment, minimal treatment or non-specific therapy control usual care, and is comparable to other evidence-based psychological modalities[271,310]. Manualized protocols for CBT have been developed that can be delivered by a variety of different mental health disciplines and that can be adapted for group delivery to reduce resource demands. Furthermore, CBT in combination with pharmacotherapy is superior to usual care[286] and studies have suggested that technology-delivered CBT shows promise[311]. Of note, relapse prevention has been adapted to incorporate mindfulness approaches and a small number of RCTs of this intervention for substance use disorders in general have generated positive results[312,313]. Behavioural couple therapy integrates CBT and strategies for improving dyadic functioning in a relationship with a non-drinking partner, and has demonstrated robust efficacy in trials[314–316].

Contingency management. CM incentivizes biologically verified alcohol use reductions and/or abstinence (determined using breathalyser or urine screen)[317]. Incentives in CM include direct financial rewards as well as prize-based lotteries in which patients receive vouchers and consumer goods of variable value. Meta-analyses have found medium effect size benefits for CM during treatment and at short-term follow-up after CM for several substances (including alcohol), although effect sizes drop substantially at long-term (6-month) follow-up after CM[318]. Recent research has suggested that spending the rewards is critical for efficacy[319]. Notably, despite effectively modifying target behaviours such as treatment attendance[306], there are concerns from clinicians that CM does not treat the underlying aetiology of AUDs[320], although a similar criticism can be applied to most pharmacotherapies for AUDs. On balance, the available evidence robustly supports CM as a clinical strategy for maximizing benefit from concurrent evidence-based treatment strategies, although not exclusively as a stand-alone intervention.

Community reinforcement approach. CRA[321] and the version for use in adolescents (ACRA)[322] use a reinforcement-based approach to enhance engagement in naturally occurring non-substance-use positive reinforcers[323], such as employment, education and non-drug-related social and recreational activities. Patients also participate in CBT modules, such as anger management, and family and significant-other sessions. Together, CRA and CM can be considered as macroscale and microscale reinforcement-based treatment of AUD, respectively. In other words, CRA aims to reorganize a person's overall psychosocial environment

to create alternative alcohol-free reinforcers that compete with drinking (such as opportunities for meaningful relationships, work and recreation), whereas CM directly reinforces small discrete features of treatment (such as attendance and negative urine drug screens). As such, these interventions are naturally complementary and have been integrated in clinical protocols[314–316,324,325].

Mutual help organizations

Mutual help organizations (MHOs) provide a peer-run network of recovery-specific support without cost in nearly every community and online[326,327]. The largest and most researched AUD MHO is AA, which has approximately two million members in more than 180 countries[328]. AA is based on a 12-step programme of addiction recovery learned within a social network comprising peers with lived experience of recovery from an AUD. Operationally, AA involves group meetings during which members share their alcohol-related experiences and how they have learned to follow the 12-step principles (such as honesty, perseverance and service) and practices (for example, helping others with an AUD) to cope with daily life, maintain sobriety and enhance QOL and functioning[326]. A notable aspect of AA is the role of more experienced members (known as sponsors) who offer guidance and accountability to new members. MHOs also serve families and children at no cost via Al-Anon and Alateen.

Although many individuals access AA directly from the community[329], others access it via referral and linkage from formal AUD treatment settings. Following a call for more rigorous research into AA and 12-step treatments by the Institute of Medicine[330], several Twelve-Step Facilitation (TSF) treatments intended to test the benefit of linkage of patients with an AUD to AA during and following treatment were tested in RCTs. Reviews of the effectiveness of TSF[331,332] indicate that these interventions are at least as good as and in some cases better than (when continuous abstinence and remission are the outcome metrics) other evidence-based interventions, such as MET and CBT[331], and result in substantially reduced health-care costs than other psychosocial interventions[331,333]. Importantly, AA seems to operate via similar therapeutic mechanisms to formal treatments such as CBT (for example by increasing recovery coping skills and self-efficacy, and reducing craving and impulsivity)[334,335]. An advantage, however, is its availability, long-term accessibility and absence of cost, making it an adaptive and durable recovery management resource. Several other MHOs addressing AUDs[336], that operate in similar ways, have been developed but vary in theoretical orientation and related practices (for example, SMART Recovery uses MI and cognitive-behavioural practices)[326]. Rigorous empirical research on the effectiveness of these alternatives is limited but observational studies suggest similar benefits to AA for those self-selecting into the groups[337].

Combining intervention strategies

Combining clinical strategies is recommended to give individuals with an AUD the highest chance of benefit. Although the COMBINE study found only limited formal evidence supporting combined pharmacological and psychological treatments[338], one meta-analysis demonstrated that pharmacotherapy plus CBT is superior to pharmacotherapy plus usual care in those with an alcohol or a substance use disorder[286]. Consistent with the clinical heterogeneity of AUDs, treatment response is highly variable between patients, and multiple strategies maximize the likelihood of a positive outcome. The other consideration from the perspective of combined treatment is that, given the high rates of comorbidity, concurrently treating both the AUD and other co-occurring disorders is recommended[339], although challenges exist in doing so (for example, mental health programmes not permitting individuals with substance use disorders to enrol).

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Table 3 | Evidence-based psychological interventions for the treatment of alcohol use disorders

Intervention	Overview	Typical Duration	Modality
Motivational interviewing (MI)/ motivational enhancement therapy (MET)	MI and MET use a collaborative approach to enhance an individual's existing skills, self-efficacy and autonomy; these typically short-term interventions are characterized by 'meeting people where they are' and engaging non-judgemental, open, empathic and strength-based approaches to match the individual's self-selected behavioural goals; these approaches do not depend on the individual's identification of their alcohol use as problematic and can be helpful as a harm reduction approach in settings that do not require abstinence; one of the key strengths is an emphasis on therapeutic alliance, and it therefore offers an excellent way to reach wary individuals not seeking treatment, including youths	MI is often one or two sessions but can be extended or ongoing; MET is one to four sessions delivered over 1–4 weeks	Face to face and tele-health
Cognitive behavioural therapy (CBT)	This skills-based approach involves a collaborative partnership between therapist and client to characterize and remediate maladaptive cognitions and develop adaptive coping strategies; CBT targets learning and skill development in implementing strategies to reduce alcohol use; individuals are believed to maintain long-term alcohol abstinence by learning and practising skills needed to cope with high-risk situations; a dyadic format is available to address drinking for one member of a couple; some interventions have incorporated mindfulness-based perspectives and techniques	1–14 sessions over 12–18 weeks	Face to face and e-modalities (CBT4CBT)
Contingency management (CM)	CM systematically positively reinforces target behaviours (such as therapy attendance, therapy participation, alcohol abstinence and medication adherence) with tangible rewards (for example, vouchers, prizes or money) to promote reductions in alcohol use; CM approaches have better outcomes in protocols that reinforce the target behaviour immediately, at larger magnitudes, with greater frequency and with schedules that increase throughout the course of the intervention	9–12 sessions over 9–12 weeks	Face to face
Community reinforcement approach (CRA)	CRA and the version for use in adolescents (ACRA) use an operant reinforcement approach to enhance engagement in naturally occurring non-substance-use positive and negative reinforcers to decrease drinking; the adolescent version includes individual and family sessions dedicated to skill building, relapse prevention, increasing positive communication and effective parenting	12–20 sessions	Face to face

Another evolution in the treatment of AUDs is the use of digital platforms, which potentially increase accessibility to interventions and reduce costs. Although at a relatively early stage, evidence suggests small decreases in drinking in those using personalized digital interventions compared to no intervention or control manipulations, particularly digital CBT[311], although outcomes are highly heterogeneous[340].

Quality of life

AUDs are consistently associated with substantive reductions across domains of QOL, including: general and social functioning; physical and mental health; activities of daily living; and sleep[341]. There is evidence that these reductions are causal and specific for AUD[342,343], but QOL is also further reduced in those with comorbid psychiatric conditions, particularly major depressive disorder[341]. In individuals with an AUD, increases and decreases in alcohol consumption over time are commensurately associated with decreases and increases in QOL[344]. This relationship between drinking and QOL may credibly differ among groups experiencing health disparities (for example, racial and ethnic minorities) to the extent that systemic challenges adversely affect QOL, although this has not been systematically evaluated.

Critically, evidence-based pharmacotherapies and psychosocial interventions produce significant increases in QOL[345–348]. Furthermore, alcohol harm reduction, not just abstinence, is associated with increased QOL[349]. In terms of specific levels of reduction, one study found that both one-level and two-level reductions in the WHO drinking levels (Box 1) are associated with significant increases in QOL[350]. However, despite these findings, a gap in the field is the emphasis on drinking outcomes in clinical research without parallel investigation of patient-centred outcomes, such as QOL or psychosocial functioning. Accordingly, there remains a high need for systematic evaluation of the effects of treatments on patient-centred outcomes via comparative effectiveness trials.

Outlook

The biological and clinical understanding of AUDs has increased dramatically over the past few decades but substantial gaps in knowledge remain.

Biobehavioural and aetiological research

Although genetic research has progressed[49], the functional significance of identified genetic variants and polygenic risk scores for AUDs in terms of basic systems biology and alcohol motivation, is largely unclear. Similarly, although researchers have attempted to assemble large enough samples to maximize statistical power, the total amount of variance in AUD is relatively small and substantially below the levels estimated from twin designs, a form of the 'missing heritability problem'[351]. The promise of pharmacogenetic approaches to AUDs (tailoring medication strategies based on individual variants[352]) has not been fulfilled and the clinical relevance of genetic research is increasingly less clear. Converting robust genomic findings into meaningful information for diagnosis and treatment planning remains a priority.

Although numerous preclinical animal models of AUD are available, the extent to which they map to human AUD is debated[353,354]. This is mitigated slightly with the development of novel assays of clinical features[112,113] but remains an issue. Similarly, the translational validity of human laboratory paradigms is also imperfect[354,355]. Moreover, although there is an extensive neuroimaging knowledge base on AUDs and the brain, most studies are cross-sectional, precluding inferences about whether the observed differences are causes and/or consequences of AUD. This issue is being partially addressed with longitudinal initiatives investigating the development of AUD[122,123] and can be addressed using genetic approaches, but with constraints on definitive insights. Moreover, few investigations have been carried out on how the brain regains function after periods of prolonged reduction in drinking, so the neuroscience of AUD recovery fundamentally remains nascent.

Although substantial progress has been made in behavioural and social–environmental research, the translation of concepts and indicators into clinically actionable tools has largely not occurred. A commonly cited statistic is that new drug development takes an average of 20 years, and it is assumed that behavioural measures would take a shorter amount of time to migrate into practice; however, most assessments or experimental assays are not part of a pipeline to develop clinically actionable tools. Moreover, neuroimaging research has not yet generated clinically informative indicators for improving diagnosis, prognosis or treatment planning. A new generation of clinically relevant biological and behavioural markers is needed for AUDs. Such translational efforts are consistent with proposed frameworks for integrating the prepotent processes in AUD, namely the Addictions Neuroclinical Assessment[356] and the Addictions NeuroImaging Assessment[357]. Both of these frameworks prioritize validation of indicators in three integral aetiologically informed domains — incentive salience, negative emotionality and executive function — to improve the nosology and treatment of AUDs.

Treatments

Although evidence-based treatments for AUDs are available, there are several priorities for improving their clinical management. Moreover, although AUDs have more approved pharmacotherapies than most substance use disorders, empirical studies and studies evaluating medication use in patients with other physical and/or mental disorders (such as those with severe liver disease, or mood and/or anxiety disorders), adolescents, older people and pregnant or breastfeeding women is limited. Furthermore, many individuals do not respond to the existing pharmacological therapies, and research is needed to develop new effective medications and more personalized treatment approaches[296,297]. Neuromodulatory interventions, such as repetitive transcranial magnetic stimulation are at an early stage but have promise for the treatment of AUDs[358].

For psychological interventions, novel sequencing strategies, such as adaptive models, sometimes called stepped-care (clinical protocols of escalating intensity over time) and measurement-based care[359] (systematic assessment to inform treatment) have substantial promise but have received comparatively little investigation[360,361]. More generally, patient-centred clinical research, which focuses on helping real-world clinical populations and clinicians navigate a complex treatment landscape, has been scarce. Examples of patient-oriented research include comparative effectiveness trials of multiple active interventions, decision analyses to understand patient values and preferences, and innovations in clinical methods or infrastructure[362].

Another problem for the treatment of AUDs is service underutilization, as only a minority of individuals with an AUD receive specialist treatment. For example, two waves of the National Epidemiological Survey of Alcohol and Related Conditions (a nationally representative population survey in the USA) found that 20–24% of individuals with an AUD received treatment, and this proportion was declining over time[12,363]. Even with strategies such as SBI, increasing access and engagement in treatment remains a priority.

Even within treatment settings, evidence-based practices, such as approved first-line pharmacotherapies, are not widely implemented. For example, a national survey conducted in the USA found that only 1.6% of people with an AUD in the previous year had received approved medications to reduce or stop alcohol use[364]. In Canada, one study found that the prescription rate of an approved AUD medication for individuals diagnosed with an AUD was 3.56 per 1,000 patients[365] (<0.4%). In Australia, the proportion is higher but is still <3%[366] and in the UK the rate is 11.7%[367], although only a single month's supply is typically available. Even in specialist care settings for people with an AUD, physicians prescribe these medications to ~20% of their patients[368] and one US study found that only 16.3% of addiction programmes offered at least one AUD medication[369]. Evidence-based behavioural treatments are similarly under-used[370], as are evidence-based policy implementations[254]. There is a particularly stark contrast in the USA, where high-cost residential treatment is widely available but evidence-based treatments are typically not used[371]. Given this, it is unsurprising that the availability of evidence-based practices is even lower outside high-income countries. Fundamentally, there is a substantial gap between the research and development of effective AUD interventions and their widespread implementation in health-care systems. A final consideration is that health-care system funding substantially affects access to quality care. For example, in the UK, reductions in local funding for the treatment of AUDs may have contributed to increases in hospital admissions for alcohol-related conditions[372].

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Author contributions

Introduction (J.M., A.P., M.H.); Epidemiology (J.M., C.P., J.R.); Mechanisms/pathophysiology (J.M., A.L.-H., A.P., M.H.); Diagnosis, screening and prevention (J.M., A.L.-H., L.L., R.A., S.F.-E., J.R., M.H.); Management (J.M., A.L.-H., L.L., R.A., S.F.-E., L.R., J.F.K., M.H.); Quality of life (J.M., A.P., M.H.); Outlook (J.M., A.P., M.H.); Overview of Primer (J.M.).

Competing interests

J.M. is a Principal in BEAM Diagnostics and a consultant to Clairvoyant Therapeutics; no associated products or services are discussed in the article. Outside his federal employment, L.L. receives an honorarium from the UK Medical Council on Alcoholism (Editor-in-Chief for *Alcohol and Alcoholism*) and royalties from Routledge for a textbook. A.P. is on the Scientific Advisory Board of Vivid Genomics and is listed as an inventor on US patent US20160038559A1. M.H. is a member of the scientific advisory council of the Swedish Medical Products Agency, and Scientific Advisor to the Board of Health and Social Welfare; his views expressed here do not represent those of these agencies; M.H. has received consulting fees, research support or other compensation from Indivior, Camurus, Molteni, BrainsWay, Aelis Farma, Lundbeck and Janssen Pharmaceuticals. A.L.-H. has received honoraria paid into her Institutional funds for speaking and chairing engagements from Lundbeck, Lundbeck Institute UK, Janssen-Cilag, Pfizer and Servier; has received honoraria to deliver training and education for the British Association for Psychopharmacology; has received research grants or support from Lundbeck and GSK, and unrestricted funding from Alcarelle for a PhD; has been consulted by but received no monies from Dobrin; and is a member of a group producing UK Alcohol Clinical Guidelines, UK Government (Office for Health Improvement and Disparities, Department of Health and Social Care). R.A., S.F.-E., J.F.K.., C.P. and L.A.R. report no competing interests.

Additional information

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