Alcohol use disorders

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Alcohol use disorders consist of disorders characterised by compulsive heavy alcohol use and loss of control over alcohol intake. Alcohol use disorders are some of the most prevalent mental disorders globally, especially in high-income and upper-middle-income countries; and are associated with high mortality and burden of disease, mainly due to medical consequences, such as liver cirrhosis or injury. Despite their high prevalence, alcohol use disorders are undertreated partly because of the high stigma associated with them, but also because of insufficient systematic screening in primary health care, although effective and cost-effective psychosocial and pharmacological interventions do exist. Primary health care should be responsible for most treatment, with routine screening for alcohol use, and the provision of a staggered treatment response, from brief advice to pharmacological treatment. Clinical interventions for these disorders should be embedded in a supportive environment, which can be bolstered by the creation of alcohol control policies aimed at reducing the overall level of consumption.

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See Online for appendix

Introduction

Alcohol use disorders rank among the most prevalent mental disorders globally, predominantly affecting men.[1,2] Individuals with such disorders have impaired control over their alcohol consumption and chronically exhibit a heavy and often escalating pattern of alcohol use despite serious detrimental costs to their overall health, the lives of their family members and friends, and to society in general (hereafter referred to as compulsive use). Despite their important public health consequences, alcohol use disorders remain some of the most undertreated mental disorders.

In this Seminar, we provide a comprehensive review of the epidemiology, diagnosis, and treatment of alcohol use disorders. We focus on developments from the past 5 years, which were not covered in the previous *Lancet* Seminars on this topic.[3,4] Future research directions are also discussed.

Diagnosis

Alcohol use disorders are characterised by loss of control over alcohol intake, compulsive alcohol use, and a negative emotional state when not drinking, which can follow a chronic, relapsing course. Alcohol use disorders are defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM) and the International Classification of Disease (ICD; appendix pp 4–6) by operational criteria: continued alcohol use despite negative psychological, biological, behavioural, and social consequences, of which a minimum number must be met during the same 12-month period to qualify for the diagnosis (appendix pp 4–6).

If more than one criterion is met, alcohol use disorder is diagnosed under the DSM-5, with severity being measured by the number of criteria met.[5] In the ICD-11, these disorders are either diagnosed as "alcohol dependence" or a "harmful pattern of use of alcohol", where dependence is the more severe manifestation.[6,7] The widening gap between diagnostic systems (ie, between DSM-5 and ICD-11) is problematic, and especially relates to the differences between the diagnoses of a "harmful pattern of use of alcohol" in ICD-11, and any DSM criteria. This widening gap does not help health professionals in designing interventions for alcohol use disorders.[8–10]

Because we share some of the reservations about the various definitions of alcohol use disorders, and in particular about DSM-5,[11–14] we will use the term alcohol use disorder in this Seminar to denote a pattern of compulsive heavy alcohol use and a loss of control over alcohol intake, which can for instance be seen when use is continued despite adverse consequences and despite the availability of other rewarding activities. This definition coincides with a moderate to severe alcohol use disorder in the DSM-5,[14] or with alcohol dependence in the ICD-11. This more informal definition also seems to correspond with clinical practice, where formal diagnosis is the exception, and to the core set of criteria of past definitions since establishing the alcohol dependence syndrome.[15]

The definition and measurement of alcohol use disorders with criteria based on a set of psychological, biological, behavioural, and social consequences of alcohol use, where only some have to be fulfilled, attempts to capture the complexity of this disorder. In 1960, Jellinek[16] reported different manifestations of alcohol use disorders in different cultures, with only two elements in common: heavy alcohol use (either chronic or intermittent) and negative health or social consequences. Definitions and conceptualisations from the past decade have again focused on heavy drinking as the core of the disorders.[17,18]

Search strategy and selection criteria

A systematic literature search (appendix pp 2–3) was done for each of the subject areas (eg, epidemiology), with search terms optimised for each area. The search included publications in the English language, published between Jan 1, 2015, and Dec 31, 2018. The databases Web of Science, Embase, MEDLINE, and PsycINFO were searched by subject headings, wildcards, and truncation. Additionally, the Cochrane Library and reference lists of relevant manuscripts were searched. Highly cited manuscripts were given higher preference for inclusion.

Conceptualising alcohol use disorders as heavy drinking over time would be in line with the biological changes in the brain caused by alcohol use, which are partly reversible after abstinence.[19] This notion would also be in line with a shifting measurement of effectiveness for pharmaceutical interventions for alcohol use disorder, which focuses on drinking status and reductions in drinking levels that have been linked to a decrease in mortality.[20–24] Clinically, reduction of alcohol consumption is a vital goal of any treatment for alcohol use disorders, because it has been shown to reduce subsequent disease and mortality. If such reductions lead to abstinence, the largest effect on mortality is achieved.[24]

Measurement of alcohol use is usually done by self-report, but in the clinical context, biomarkers associated with heavy drinking should be used. Although the latest generation of biomarkers, such as phosphatidylethanol, certainly outperform older ones in terms of specificity, sensitivity, and quantifying consumption over time,[25,26] the question of costs remains, especially in non-specialised settings. Various practical and ethical questions need to be answered to avoid patient perceptions of constant control and monitoring; these questions need to be discussed between clinician and patient before use.[27]

Epidemiology

Alcohol use disorders are among the most prevalent mental disorders globally, affecting 8·6% (95% CI 8·1–9·1) of men and 1·7% (1·6–1·9) of women in 2016 (total point estimate 5·1%; 4·9–5·4).[1,2] Although the prevalence of alcohol use disorder in men is still five times that in women, globally some signs exist of the gender gap narrowing over time.[1] Furthermore, the prevalence of alcohol use disorders was highest in high-income countries (8·4%, 95% CI 8·0–8·9) and upper-middle-income countries (5·4%, 5·0–6·0), for both sexes.[1] We provide an overview of the prevalence of alcohol use disorders among adults (aged 15 years and older) by country (figure 1).[1] Since several of the aforementioned criteria are culturally specific,[12,13] these prevalence figures, which are based on general population surveys, should be considered rough estimates.[28]

Alcohol use disorders are associated with a high burden of disease.[4] They cause considerable disability[29] and are also associated with high mortality through medical conditions such as liver cirrhosis or injury.[30] This excess mortality is not found in burden-of-disease reports, in which alcohol poisoning is the main cause of death listed under alcohol use disorders,[2] but only in special analyses (eg, Charlson and colleagues[31]). Register analyses in Nordic countries have shown that excess mortality associated with these disorders can lead to a reduction in life expectancy of more than 20 years from the population average.[32]

The risk of alcohol use disorders and related mortality follows a socioeconomic gradient, with individuals with low socioeconomic status being at increased risk.[33,34] Moreover, individuals in this group are at least twice as likely to die from their disorders and prolonged heavy alcohol use than their counterparts with high socioeconomic status.[35] The risk ratio between low versus high socioeconomic status for alcohol-attributable causes of death is higher than the risk ratio for all causes, indicating an interaction between alcohol use s and socioeconomic status[35] (for a striking example in a middle-income country, see Probst and colleagues[36]). Overall, alcohol use and alcohol use disorders seem to contribute to socioeconomic health inequities with greater harm per litre of alcohol consumed in individuals with low socioeconomic status than in those with high socioeconomic status.

Genetics and other risk factors

Patients, their families, and society in general should be aware that alcohol use disorders are not a result of any

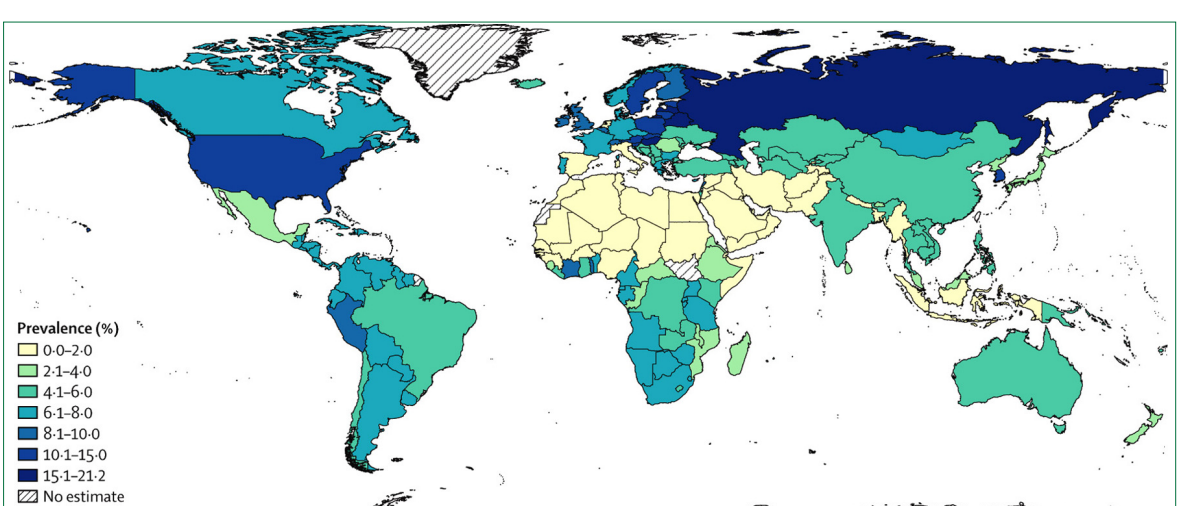

Figure 1: **Prevalence of alcohol use disorders in 2016**

individual weakness or moral failing, but arise from a complex interaction of individual, social, cultural, and biological factors. Family and twin studies were the first to show the role of genetics in these disorders.[37] An Australian twin study found a heritability estimate of 64%.[38] Twin and adoption studies from the past 35 years have reported that heritability estimates range from 40% to 70%, with no sex difference; a meta-analysis provided evidence that about 50% of alcohol use disorders are heritable,[39] which might be an underestimate resulting from measurement bias and other methodological issues. Even though genetic factors have a major role in the development of alcohol use disorders, concordance rates of less than 50% indicate that environmental risk factors and gene-environment interactions must also contribute to the emergence and persistence of these illnesses.

Individual alleles that mediate risk have been difficult to identify. Alcohol dehydrogenase (*ADH*) and the mitochondrial form of aldehyde dehydrogenase (*ALDH2*) are liver enzymes involved in alcohol metabolism. The *ALDH2* gene has two primary alleles known as *ALDH2*1* and *ALDH2*2*. Carriers of the *ALDH2*2* allele, and homozygotes in particular, have impaired alcohol metabolism. If they drink alcohol, acetaldehyde accumulates, leading to the emergence of flushing, headache, sweating, tachycardia, nausea, and vomiting, all of which serve to protect against the development of an alcohol use disorders.[40] This polymorphism is carried by about 40% of East Asian individuals but is rare in European people. Additionally, polymorphisms in the *ADH* group of genes (eg, *ADH1B*2*) also protect against alcohol use disorders.[41] In 2019, the largest genome-wide association meta-analysis of the Alcohol Use Disorders Identification Test (AUDIT) found ten risk loci associated with the AUDIT total score.[42] This effort replicated previous findings of loci related to both pharmacokinetic (eg, *ADH1B* and *ADH1C*) and pharmacodynamic (eg, *KLB* encoding beta-klotho and *GCKR* encoding glucokinase regulatory protein)[43–45] factors that determine alcohol consumption.

The first gene-by-environment genome-wide interaction study showed that the rs1729578 polymorphism in the *PRKG1* gene, which encodes cGMP-dependent protein kinase 1, moderated the influence of traumatic life experiences on alcohol misuse in two independent cohorts.[46,47] Additionally, epigenetic mechanisms, including histone modifications and DNA methylation, have been increasingly implicated in the pathophysiology of alcohol use disorders and might mediate the effect of known environmental risk factors for it, such as stress, on the emergence and persistence of such disorders.[48,49]

Known personality risk factors for might be, at least in part, genetically sensitive. For example, a 2018 twin study[50] showed that impulsivity is a genetic risk factor for alcohol use disorders. Further, polygenic risk scores in genome-wide association results DSM-IV alcohol dependence scores predicted problematic alcohol use during adolescence, and this effect was partly mediated by the personality trait of sensation seeking.[51]

Several environmental risk factors might contribute to the emergence and perpetuation of alcohol use disorders. For example, the prevalence tends to be higher in cultural groups that adopt a more permissive attitude towards heavy drinking and alcohol intoxication. In such cultures, alcohol is usually readily available at low cost and alcohol intoxication is socially approved of and encouraged through advertisements.[52–54] Also, expectations of alcohol effects might also have a role in the patterns of alcohol use. For instance, expectations of the positive effects of excessive drinking on social interactions, the alleviation of anxiety, and improved sexual performance seem associated with heavier drinking.[55] Other risk factors include poor family support, conduct and mood disorders, and low self-control.[50,55–57] The perceived pattern of drinking among peers might also have a role in the development of alcohol use disorders, especially during adolescence.[58]

Parental factors such as low parental monitoring, parental drinking, and favourable parental attitudes towards alcohol use are risk factors for the disorders.[50,55,56] A 2018 prospective cohort study showed that parental alcohol supply was associated with adolescent drinking, alcohol-related harms, and symptoms of alcohol use disorder.[59] Other factors that might affect the likelihood of developing such a disorder include the availability of financial resources to buy alcohol, level of education, and religious beliefs and practices.[53,54]

Alcohol has prominent effects on γ-aminobutyric acid (GABA)-ergic and glutamatergic transmission, mainly through facilitation of GABA-A receptor signalling and inhibition of N-methyl-D-aspartate (NMDA) receptor signalling. These mechanisms underlie a global suppression of nervous system excitability that acutely results from alcohol intake, and rebounds during withdrawal. Additional important alcohol effects are produced through interactions with dopamine, opioid, and cannabinoid transmission.[60,61] Extensive individual, age-dependent, and sex-dependent, variation in the effects of alcohol exists.[62] At a systems level, alcohol's effects on the brain result in a biphasic effect profile that encompasses an initial psychomotor component, and a subsequent sedative-ataxic component. The contribution of the respective component varies between individuals and over time; a higher than normal stimulation and lower than normal sedation are predictors of progression to alcohol use disorder.[63]

A framework encompassing the various stages of alcohol use disorders from a neurobiological perspective proposes that specific neurocircuitry is altered by the effects of alcohol and stress on the brain.[60,64,65] According to this model, which synthesises preclinical and clinical findings, three distinct phases encompass the alcohol addiction cycle: (1) binge or intoxication; (2) withdrawal

or negative affect; and (3) preoccupation or craving. Each of these phases entails neuroadaptive changes in specific brain networks, which might progress over the course of the disorder.[65]

The rewarding effects of alcohol, the development of incentive salience, and the seeking habits in the binge or intoxication phase entail changes in the amounts of dopamine and opioid peptides in the basal ganglia. The emergence of dysphoric and stressful states that characterise the withdrawal or negative affect stage (also referred to as the dark side of alcohol use disorders[49]) might mean a decrease in dopaminergic function in the reward system and a recruitment of brain stress neurotransmitters in the extended amygdala. The cravings and deficits that affect executive function might promote a reduction in self-control, and in the preoccupation or craving phase might lead to a progressive dysregulation of descending projections from the medial prefrontal cortex and insula to the basal ganglia and extended amygdala.

Glutamate might have a major role in the preoccupation or craving phase.[60,65] Other neurotransmitters and brain circuits might also be implicated in the pathophysiology of alcohol use disorders as discussed in greater detail elsewhere.[60,66] An important aspect of clinical disease with important therapeutic implications is that as the condition develops, a shift from positively to negatively reinforced alcohol use occurs.[67] This model has provided clinically important insights into the neurobiology of alcohol use disorders, but some caveats deserve consideration. First, it does not take into account the recovery phase. Additionally, evidence indicates that structural and functional brain changes might reverse after abstinence, and that a substantial proportion of people recover with no or minimal treatment. Therefore, alternative models have been proposed.[68]

Biological mechanisms could also help to explain differences in both the prevalence and presentation of alcohol use disorders in men and women.[69] For example, a PET study[62] of social drinkers showed that the magnitude of ventrostriatal dopamine release after oral alcohol administration was higher in men than in women, and that dopamine release correlated with measures of subjective activation in men but not in women. This mechanism could contribute to sex-related differences in vulnerability for alcohol use disorders.

Clinical presentation and treatment use

Alcohol use disorders are among the disorders with the lowest treatment prevalence. In a large study of representative samples of more than 13 000 patients and 358 general practitioners in regions of six European countries, only 22·3% of patients identified with alcohol dependence received interventions.[70] The low treatment prevalence seen in these European countries is not common in other regions.[71] In fact, the global treatment prevalence in the most recent overview was almost the same, at 21·9%,[72] and treatment prevalence in some countries such as the USA was even lower.[73,74] These numbers suggest that the treatment gap for alcohol use disorders is higher than for any other mental disorder,[72] even though effective and cost-effective treatments exist,[75] with similar effect sizes as for other common diseases.[76] Factors related to (1) the patient, (2) the clinician, and (3) the health system have roles in the low treatment prevalence.

As treatment is sought very late in the disease process, compared with patients who do not receive treatment, individuals who do receive treatment can be characterised by higher levels of social disintegration, alcohol use, comorbidity, and functional losses.[77,70] Additionally, fear of stigmatisation has been associated with decreased treatment access.[78] The stigma attached to alcohol use disorders consists of aspects such as dangerousness, which might be associated with observed behaviour such as higher levels of aggression under the influence of alcohol and harm inflicted to others. However, the stigma also encompasses aspects that are not supported by empirical evidence such as perceiving people with the disorder as weak willed and responsible for their illness. Comparative studies over time have shown that whereas the stigmatisation of mental disorders has generally improved, this has not been the case for alcohol use disorders.[79] Stigmatisation is not just a barrier to seek treatment for the patient; it also affects if and how clinicians treat patients.

High levels of stigmatisation towards patients with an alcohol use disorder have been recorded among health professionals.[80] Furthermore, inadequate education, training, and support structures exist for clinicians dealing with patients with an alcohol use disorder. These factors connect to more structural treatment barriers related to the health system.

The first contact with the health-care system for most people with alcohol use disorders is usually with the primary health-care (PHC) system. However, no systematic screening for alcohol problems or disorders exists in PHC in most countries,[3] even though valid screening instruments are available (eg, AUDIT or AUDIT-C, the short form of the AUDIT comprising only the three consumption items).[81] Even in countries with guidelines for such screening,[82] only a few patients are screened. In a study in five European jurisdictions, including two with the highest screening rates (Catalonia and England), the proportion of eligible adult patients who were screened for potential problem drinking was 5·9% (95% CI 3·4–8·4) during the 4-week baseline measurement period.[83] This proportion could be increased even if screening is applied only on the basis of comorbidities such as hypertension, insomnia, or injury.[84–86]

The aforementioned large study in six European countries showed that PHC providers rely on the level of alcohol use and other tell-tale indicators, such as the smell of alcohol on a patient's breath, the presence of red eyes, and findings of raised liver enzymes or other

comorbidities, rather than on official criteria.[70] On one hand, this approach led to a situation in the European study in which only 30·3% (95% CI 27·1–33·7) of patients with an alcohol use disorder identified by standardised instruments were also identified as such by their general practitioners.[70] On the other hand, standardised instruments identified only 39·9% (95% CI 36·0–43·9) of patients with alcohol dependence identified by their general practitioners (own calculations based on Rehm and colleagues[70]).

Thus, patients with alcohol use disorders are fairly prevalent in PHC settings and, although almost no formal screening for alcohol use is done, general practitioners recognise a substantial proportion of them, yet only a few receive treatment. Reasons for this treatment gap seem to be threefold. First, a series of individual-level factors, including fear of stigma, preclude those affected from seeking treatment; second, clinicians are not well trained to identify alcohol use disorder and can hold stigmatising views towards patients with this problem; and third, without a formal screening process, many patients in PHC are not recognised and treated or connected to specialised care even though effective treatments exist.

Interventions

Before we consider the treatment system and acute and long-term management, we present currently available psychosocial and pharmacological interventions. In their seminal work on the comparative effectiveness of treatments, Miller and Wilbourne[87] showed that psychosocial treatments such as brief counselling, motivational enhancement therapy, the community reinforcement approach, guided self-change, behaviour contracting, and social skills training were among the top ten most effective interventions for alcohol use disorders, together with some pharmacological interventions. Not much has changed since their overview, and the evidence clearly shows that specific, well defined psychosocial therapies are more effective than others, including unstructured therapist-patient interactions. However, to date the successful therapies have not been fully broken down to identify the key effective elements.[88,89] A comprehensive overview of psychological and psychosocial interventions can be found elsewhere.[82]

Here we discuss novel approaches, such as internet-based and internet-supported interventions.[90,91] These approaches strive to incorporate knowledge about neurocognitive and pathophysiological processes into treatments for alcohol use disorders.[92,93] One such mechanism is the enhanced emotional and behavioural reactivity to alcohol cues inpatients that might contribute to enhanced craving and relapse. Evidence is emerging that cognitive bias modification training can change the biased cognitive processing of alcohol cues by pairing alcohol cues with an avoidance reaction. The most comprehensive review to date showed that cognitive bias modification interventions seemed to have a small effect on cognitive bias (0·23, 95% credible interval 0·06 to 0·41) and relapse rate (–0·27, –0·68 to 0·22), but not on the reduction of substance use.[94] However, although this area seems promising for providing new methods to be integrated into the treatment of alcohol use disorders, when added to other psychosocial or pharmaceutical interventions,[95] current evidence is not conclusive and needs to be strengthened with more rigorous randomised trials.[94,96,97]

	Mechanism of action	Dosage	Adverse effects	Observations
Acamprosate	Glutamate system modulator but mechanism unclear	FDA-approved dosage: 1998 mg/day orally; dosage used in clinical trials: 1000–3000 mg/day	Diarrhoea, pruritus, rash, and altered libido	Does not undergo first-pass metabolism; can be used in patients with liver disease
Disulfiram	Aldehyde dehydrogenase inhibitor	FDA-approved dosage: 250–500 mg/day orally; dosage used in clinical trials: 125–500 mg/day	Drowsiness, metallic taste, hepatotoxicity, neuropathy, psychosis, confusional states, optic neuritis, psychosis, and mood changes	Disulfiram–ethanol interaction might constitute an emergency, hence, disulfiram can be used to sustain abstinence but not to reduce drinking
Nalmefene	Antagonistic at μ-opioid and δ-opioid receptors and partly agonistic at κ-opioid receptors	Not approved by FDA but approved by EMA; to be used on an as-needed basis: 18 mg/day orally on days of increased risk of drinking, preferably before consumption	Dizziness, headache, insomnia, nausea, and vomiting	Nalmefene can block the effects of opioid analgesics and can precipitate opioid withdrawal
Naltrexone (intramuscular injection)	μ-preferring opioid antagonist that reduces opioid-mediated reward to alcohol	Monthly 380 mg intragluteal injections	Serious adverse effects are rare; common adverse events include rash, headache, restlessness, insomnia, nausea, vomiting, abdominal pain, and joint or muscle pain; potential injection site reactions and other adverse events due to injections	Naltrexone can block the effects of opioid analgesics and can precipitate opioid withdrawal
Naltrexone (oral)	μ-preferring opioid antagonist that reduces opioid-mediated reward to alcohol	FDA-approved dosage: 50 mg/day; dosage used in clinical trials: 50–100 mg/day	Serious adverse effects are rare; common adverse events include rash, headache, restlessness, insomnia, nausea, vomiting, abdominal pain, and joint or muscle pain	Naltrexone can block the effects of opioid analgesics and can precipitate opioid withdrawal

FDA=Food and Drug Administration. EMA=European Medicines Agency.

Table 1: **FDA-approved or EMA-approved pharmacological treatments**

	Original indication	Mechanism of action	Clinical implications
Baclofen	Spasticity	Agonist of GABA-B receptors	Particularly used for high severity dependence; meta-analyses based mostly on small studies have shown divergent results, but efficacy was robustly replicated in an adequately powered multicentre randomized controlled trial; because it is a direct (orthosteric) agonist at GABA-B receptors, baclofen results in tolerance and a need for dose escalation, in turn associated with a potential for serious adverse events
Gabapentin	Epilepsy or neuropathic pain	Complex molecular mechanisms of action; one major effect is inhibition of α2δ-subunit-containing voltage-dependent calcium channels	Gabapentin promoted abstinence and decreased relapse to heavy drinking; it also decreased alcohol-related insomnia, dysphoria, and craving; effects were dose-dependent and most pronounced at the dose of 1800 mg/day
Ondansetron	Nausea and vomiting	$5HT_3$ receptor antagonism	Potential for use in early-onset alcohol use disorder; prescriber should consider pharmacogenetics markers in serotonergic genes
Sodium oxybate	Narcolepsy	Unknown mechanism; a metabolite of GABA; interacts with GABA-B receptors, but unknown whether this mediates therapeutic actions in alcohol use disorder	Sodium oxybate was safe and effective in severe alcohol dependence; it has a high abuse liability, and use should be reserved for specialist treatment settings under a Risk Evaluation and Mitigation Strategy
Topiramate	Epilepsy	Complex molecular mechanisms of action; glutamatergic actions are likely to be key in alcohol use disorder treatment; Effectiveness is moderated by a polymorphism at the locus encoding the glutamatergic kainate receptor subunit GRIK1 (also known as GluK1).	Limited to specialist treatment because it needs to be carefully titrated over an extended period of time, and is initially associated with cognitive side-effects, including impairments of working memory
Varenicline	Smoking cessation	Partial agonist of the α4β2 isoform of the nicotinic acetyl choline receptor	Highest effectiveness seen with phosphatidylethanol as outcome, which is a biomarker for short and intermediate heavy alcohol intake; medication should start immediately after detoxification

See the appendix (pp 8–9) for reference details. GABA=γ-aminobutyric acid.

Table 2: **Wave 2 medications for the treatment of alcohol use disorders**

Medications are available for the treatment of alcohol use disorders in both primary and specialised care. The most common drugs (referred to here as Wave 1; table 1) were discussed extensively in the previous *Lancet* seminar on alcohol use disorders[3] and in guidelines elsewhere.[74,82,98] In brief, these drugs include disulfiram, a dehydrogenase inhibitor, the opioid antagonist naltrexone (either in the form of tablets or as a depot formulation), nalmefene, and the homo-taurine analogue acamprosate. All these treatments have meta-analytic support for effectiveness, and have different indications. Disulfiram should be used only under supervision, for instance when sobriety must be ensured for a short time to diagnose psychiatric comorbidity in a valid manner. Naltrexone and nalmefene mainly prevent relapse to heavy drinking, and thus could also be used in therapy with the goal of controlling drinking. Acamprosate promotes abstinence in people with severe alcohol use disorders. Although hoping for novel therapeutics to improve on effectiveness of these approved treatments, we note that their effect sizes are similar to those of many common medical interventions[76]—for instance, the number needed to treat for naltrexone to prevent return to heavy drinking has been estimated at 12.[99] Accordingly, sizable clinical benefits could be achieved by improving on the low prescription rates of existing drugs for alcohol use disorder.

Meta-analytic support for efficacy has also been reported for several medications that do not have marketing approval for the treatment of alcohol use disorders, but are approved for other indications and can therefore be prescribed off-label—ie, Wave 2 (table 2). When doing so, prescribers need to be aware of the potential for side-effects that might be specific to patients with alcohol use disorder, and monitor for those.

In this group, perhaps the strongest support is available for topiramate. Although its effectiveness is robust, topiramate is likely to remain a specialist treatment, because of the complexity involved in managing its delivery and side-effects (table 2).[100]

Mechanisms explored in experimental settings in both animal and human laboratory studies might bring additional aids to the treatment kit in the future (Wave 3). Blockade of neurokinin 1 (NK-1) receptors has consistently proved to reduce alcohol self-administration and relapse to alcohol-seeking behaviour in rodents, and suppressed stress-induced alcohol craving in patients with alcohol-dependency.[101,102] Because of variable results with NK-1 antagonists in depression trials, these programmes have been discontinued by the pharmaceutical industry, but analyses have shown that effectiveness is consistently achieved if near-complete receptor occupancy is reached.[103]

The combined progesterone and glucocorticoid receptor antagonist mifepristone has shown an ability to reduce alcohol intake in alcohol-dependent rats but not in non-dependent animals. In a small laboratory study in men, individuals with alcohol dependence who received short-term (1-week) treatment with mifepristone reported reduced craving triggered by alcohol-associated cues, and reduced their alcohol consumption during treatment and at 1-week follow-up.[104]

The stomach-derived, appetite-regulating hormone ghrelin appears to be involved in promoting alcohol craving. A ghrelin antagonist is being assessed in heavy-drinking and alcohol-dependent volunteers, and

has so far proved safe and well tolerated.[105,106] Finally, κ-opioid receptors appear to mediate dysphoric states in addiction,[107] and preclinical studies suggest that their blockade could be beneficial in alcohol dependence.[108] Assessment of medications in this class has been initiated (in 2019; NCT03852628). Clinical development always faces challenging odds, but bringing forward mechanistically innovative therapeutics is an important part of addressing the unmet needs of patients with alcohol use disorder.

Whether approved for the indication of alcohol use disorders or available for off-label use, several medications reviewed here have solid support for modest, but clearly clinically useful effectiveness. Nevertheless, these drugs are prescribed only to a small fraction of patients with alcohol use disorders, estimated to be 0·07% overall and 5·8% for those seeking specialty treatment.[109] Although research into novel medications remains a high priority, implementing currently available treatments offers the greatest opportunity to improve outcomes in the short term.

Acute and long-term management

We provide an overview of the worst possible course of alcohol use disorders (figure 2) to illustrate the various options of interventions and where they are situated in the health-care system. Despite the importance of the health-care system, it should not be forgotten that an important proportion of alcohol use disorders improve without formal intervention.[110]

PHC is not only the entry point for most people with alcohol use disorders into the health-care system, but it is also the place where secondary prevention and most clinical interventions should take place.[84,111] This practice requires regular checks for alcohol use, similar to routine blood pressure checks,[112] which could be accomplished by any PHC staff member, via biomarkers, or self-administered tests.[90] On the basis of the level of alcohol use and of the presence of comorbidities, interventions should start with brief advice to reduce hazardous drinking, which could be done by non-medical health-care professionals, or via the internet.[90,91] At higher levels of drinking, treatment interventions should begin with lifestyle interventions aimed at stopping or reducing the patient's drinking. If this approach proves to be unsuccessful, specific psychological and pharmacological interventions[84] should be considered.

Several pharmacological treatment options are suitable for PHC.[99] These options might include detoxification (see guidelines from the National Institute for Health and Clinical Excellence[82] and Rolland and colleagues[113]). Non-pharmacological treatment options, such as psychological treatment, are effective,[87,114] but implementing them in PHC remains difficult, since in many countries not enough trained personnel are available and most general practitioners are not familiar with administering structured psychological interventions. This option, of

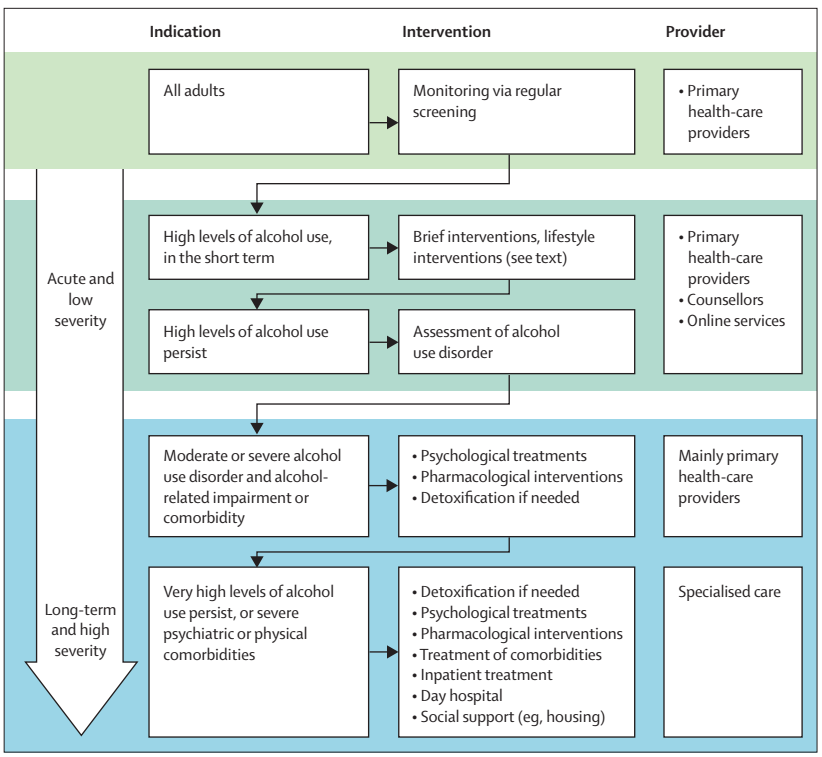

Figure 2: **Indications for monitoring and interventions in the health-care system**

providing these interventions in PHC settings, could therefore be restricted to selected high-income countries with the necessary infrastructure. Use of the internet might be an option even outside of high-income countries, in addition to other measures taken by the general practitioner.[90,91] Although attempting to achieve synergistic effects of psychological and pharmacological interventions is ideal, inability to provide the psychological support should not be taken as an excuse to neglect the provision of pharmacological intervention.

The key to the success of secondary prevention and treatment will be regular monitoring of a patient's level of alcohol use. As indicated previously, this monitoring can be achieved with a high level of specificity with the use of modern biomarkers such as phosphatidylethanol.[25,26] If the level of alcohol use continues to be high or if there are comorbidities that cannot be handled at the PHC level, referral to specialists should be considered.

The specialist care system for alcohol use disorders is usually accessed via referral from PHC, but dependent on the country, direct or other access for patients might be available. Other possible points of access could be acute hospital and emergency room settings. However, systematic screening for alcohol use disorders in such places is also low,[115] despite the fact that people with alcohol problems frequent acute care hospitals[116] and emergency rooms overproportionately.[116,117] In addition to these pathways, in many jurisdictions people with

Panel: **Hazardous alcohol use and alcohol use disorders in Colombia**

Heavy drinking is a public health problem in Colombia, particularly among minors (people younger than 18 years). Even though adult per-head consumption (at around 6 L per year) is less than there than in the USA or many European countries,[1] a high concentration of weekend heavy alcohol users exists, and reports show that Colombia shares, with Argentina, first place for the number of underage heavy alcohol users.[127–130] Prevalence of alcohol use disorders is also higher than the global average, at 7% in 2016.[1]

Before 2012, people with alcohol use disorders in Colombia had only two options: to attend Alcoholic Anonymous groups, or to look for private care (eg, psychiatric, toxicological, or psychological), private care being virtually impossible for people of low socioeconomic status. But in 2012, a new law (Law #1566) was approved, bringing fundamental changes to the treatment of individuals with substance use disorders:

1. Substance use and substance use disorders were dealt with as a matter of public health; this was a major shift from the traditional criminal view applied to these problems before; a similar change has been seen in several Latin American countries in the past decade (such as Argentina, Brazil, Chile, Mexico, Peru, and Uruguay); in Colombia, currently, courts or other legal institutions cannot mandate treatment for alcohol use disorders
2. The law states that any person with problems related to psychoactive substances, legal or illegal, has the right to ask for state-of-the-art and free-of-charge treatment under the public system of health, either in private or public institutions

With almost 500 000 drug users in need of treatment and at least a similar number of individuals with alcohol use disorders,[129] the law was initially received with enthusiasm. However, two drawbacks quickly became apparent with implementation: first, the law took 5 years to put into place since the private treatment institutions refused to accept new patients without a formal guarantee of reimbursement; and second, according to directors of treatment institutions, most people with alcohol use disorders refused to be in treatment together with drug users, since they felt their problem was completely different in nature. The change is happening very slowly, and in the main cities (Bogotá, Medellín, and Cali), facilities for only alcohol use disorders have been opened where people can be treated as inpatients for up to 90 days. However, as of May, 2019, these facilities remained almost empty.

alcohol use disorders might be referred to treatment by the legal or social welfare system or by employers' programmes. Overall, treatment can be characterised by a high degree of formal or informal social pressure.[118]

In most cases, the aim of specialised care interventions is to manage a situation of low consumption or abstinence after detoxification or lifestyle changes, to prevent relapse to a pattern of lasting heavy consumption. Guidelines exist for treatment at the specialist level, with or without pharmacological support.[82,98] The specialist treatment system usually treats more severe patients, often with comorbidities.[77,119] Comorbidities are sometimes treated in parallel in integrated care pathways,[120] even though the systematic evidence for these treatments might not yet be available.[121,122]

Another barrier to the treatment of alcohol use disorders is that universal health-care coverage has not yet been globally implemented despite such a call from the UN,[123] and despite it making economic sense.[124] Treatment for mental disorders in general, and for alcohol use disorders in particular, is often not covered by health insurance, and thus pressure is increasing on governments to improve the current situation.[125,126] *The Lancet* Commission on global mental health and sustainable development[125] proposed, as their first of six key actions, that "mental health services should be scaled up as an essential component of universal health coverage and should be fully integrated into the global response to other health priorities, including non-communicable diseases, maternal and child health, and HIV/AIDS." For the treatment of alcohol use disorders, this recommendation would mean a radical step to close the treatment gap we describe. However, this possibility is still a long way off. Colombia (panel) might provide some useful illustrations of potential difficulties, even in a situation where the legal right for the treatment of alcohol use disorders was established 7 years ago.

The role of the wider environment and alcohol policy

Thus, alcohol use disorders and their associated heavy drinking are clearly major public health problems, which could be reduced by treatment.[131] However, as indicated in the section on risk factors, the wider environment has an important role in the cause and course of alcohol use disorders. For instance, on the basis of experience in the treatment of other mental disorders such as depression, a reduction in the stigma associated with alcohol use disorders would probably result in an increased number of individuals seeking treatment.[78] A supportive environment in the community might also be important, and is currently being explored in a large-scale implementation trial in three countries in the Americas: Colombia, Peru, and Mexico.[132]

Moreover, the overall permissiveness of cultures is important, either via informal control, such as in the classic Mediterranean cultures, where alcohol is restricted to meals and showing signs of intoxication is met with disapproval,[133] or by formal control such as restrictions on availability and a ban on marketing.[18,134] Another effective way to reduce alcohol consumption and alcohol-attributable harm is to increase prices via taxation.[135] All these policy measures are based on the association between overall level of consumption and the prevalence of alcohol use disorders (Spearman correlation at 0·69; 95% CI 0·60–0·76; based on the WHO *Global Status Report on Alcohol and Health 2018*[1] and Manthey and colleagues[136]).

Establishing a minimum unit price for alcoholic beverages is another mechanism to increase price, mainly to reduce binge drinking. This measure has been implemented in several Eastern European countries,[137] in Scotland, and in some provinces of Canada, with promising results.[138] The formal alcohol control policies of restricting availability, banning marketing, and increasing taxation have also proved highly cost-effective compared with other measures to reduce alcohol-attributable

harm,[139] even measures to reduce burden of non-communicable diseases.[140]

Contributors

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AFC, AP, and CP declare no competing interests. MH reports personal fees from BrainsWay Technologies, Indivior, and Aelis Farma, and other income from Pfizer and Adial Pharmaceuticals, outside the submitted work. JR reports grants from Lundbeck and from D&A Pharma, outside the submitted work.

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References

1 WHO. Global status report on alcohol and health 2018. World Health Organization. 2018. https://www.who.int/substance_abuse/publications/global_alcohol_report/en/ (accessed May 20, 2019).
2 Rehm J, Shield KD. Global Burden of Disease and the Impact of Mental and Addictive Disorders. *Curr Psychiatry Rep* 2019; **21:** 10.
3 Connor JP, Haber PS, Hall WD. Alcohol use disorders. *Lancet* 2016; **387:** 988–98.
4 Schuckit MA. Alcohol-use disorders. *Lancet* 2009; **373:** 492–501.
5 American Psychiatric Association. Diagnostic and statistical manual of mental disorders 5th edition. Philadelphia, USA: American Psychiatric Association, 2013.
6 WHO. ICD-10 Classification of Mental and Behavioural Disorders: Clinical Descriptions and Diagnostic Guidelines. Geneva, Switzerland: World Health Organization, 1992.
7 Saunders JB, Degenhardt L, Reed GM, Poznyak V. Alcohol use disorders in ICD-11: past, present, and future. *Alcohol Clin Exp Res* 2019; **43:** 1617–31.
8 Degenhardt L, Bharat C, Bruno R, et al. Concordance between the diagnostic guidelines for alcohol and cannabis use disorders in the draft ICD-11 and other classification systems: analysis of data from the WHO's World Mental Health Surveys. *Addiction* 2019; **114:** 534–52.
9 Room R, Rehm J. Commentary on Degenhardt et al (2019): harm to others matters in substance use disorders, and so does discordance between the diagnostic systems. *Addiction* 2019; **114:** 553–54.
10 Rehm J, Heilig M, Gual A. ICD-11 for alcohol use disorders: not a convincing answer to the challenges. *Alcohol Clin Exp Res* (in press).
11 Martin CS, Langenbucher JW, Chung T, Sher KJ. Truth or consequences in the diagnosis of substance use disorders. *Addiction* 2014; **109:** 1773–78.
12 Rehm J, Room R. Cultural specificity in alcohol use disorders. *Lancet* 2015; published online Sept 4. http://dx.doi.org/10.1016/S0140-6736(15)00123-3.
13 Rehm J, Room R. The cultural aspect: how to measure and interpret epidemiological data on alcohol use disorders across cultures. *Nordisk Alkohol Nark* 2017; **34:** 330–41.
14 Rehm J, Anderson P, Gual A, et al. The tangible common denominator of substance use disorders: a reply to commentaries to Rehm et al (2013a). *Alcohol Alcohol* 2013; **49:** 118–22.
15 Room R. Alcohol and drug disorders in the International Classification of Diseases: a shifting kaleidoscope. *Drug Alcohol Rev* 1998; **17:** 305–17.
16 Jellinek EM. Alcoholism, a genus and some of its species. *Can Med Assoc J* 1960; **83:** 1341–45.
17 Rehm J, Marmet S, Anderson P, et al. Defining substance use disorders: do we really need more than heavy use? *Alcohol Alcohol* 2013; **48:** 633–40.
18 Anderson P, Braddick F, Conrod P, et al. The new governance of addictive substances and behaviours. Oxford: Oxford University Press, 2017.
19 Schulte MHJ, Cousijn J, den Uyl TE, et al. Recovery of neurocognitive functions following sustained abstinence after substance dependence and implications for treatment. *Clin Psychol Rev* 2014; **34:** 531–50.
20 European Medicines Agency. Guideline on the development of medicinal products for the treatment of alcohol dependence. European Medicines Agency. 2010. https://www.ema.europa.eu/documents/scientific-guideline/guideline-development-medicinal-products-treatment-alcohol-dependence_en.pdf (accessed Feb 16, 2019).
21 American Society of Clinical Psychopharmacology. Alcohol Clinical Trials Initiative (ACTIVE). 2019. https://ascpp.org/resources/alcohol-clinical-trials-initiative-active/ (accessed Feb 16, 2019).
22 Hasin DS, Wall M, Witkiewitz K, et al. Change in non-abstinent WHO drinking risk levels and alcohol dependence: a 3 year follow-up study in the US general population. *Lancet Psychiatry* 2017; **4:** 469–76.
23 Roerecke M, Sørensen P, Laramée P, Rahhali N, Rehm J. Clinical relevance of nalmefene versus placebo in alcohol treatment: reduction in mortality risk. *J Psychopharmacol* 2015; **29:** 1152–58.
24 Roerecke M, Gual A, Rehm J. Reduction of alcohol consumption and subsequent mortality in alcohol use disorders: systematic review and meta-analyses. *J Clin Psychiatry* 2013; **74:** e1181–89.
25 Viel G, Boscolo-Berto R, Cecchetto G, Fais P, Nalesso A, Ferrara SD. Phosphatidylethanol in blood as a marker of chronic alcohol use: a systematic review and meta-analysis. *Int J Mol Sci* 2012; **13:** 14788–812.
26 Wurst FM, Thon N, Yegles M, Schruck A, Preuss UW, Weinmann W. Ethanol metabolites: their role in the assessment of alcohol intake. *Alcohol Clin Exp Res* 2015; **39:** 2060–72.
27 Barrio P, Wurst FM, Gual A. New alcohol biomarkers. New challenges. *Alcohol Alcohol* 2018; **53:** 762–63.
28 Rehm J. How should prevalence of alcohol use disorders be assessed globally? *Int J Methods Psychiatr Res* 2016; **25:** 79–85.
29 Samokhvalov AV, Popova S, Room R, Ramonas M, Rehm J. Disability associated with alcohol abuse and dependence. *Alcohol Clin Exp Res* 2010; **34:** 1871–78.
30 Schwarzinger M, Thiébaut SP, Baillot S, Mallet V, Rehm J. Alcohol use disorders and associated chronic disease—a national retrospective cohort study from France. *BMC Public Health* 2017; **18:** 43.
31 Charlson FJ, Baxter AJ, Dua T, Degenhardt L, Whiteford HA, Vos T. Excess mortality from mental, neurological, and substance use disorders in the Global Burden of Disease Study 2010. In: Patel V, Dua T, Laxminarayan R, Medina-Mora ME, eds. Mental, neurological, and substance use disorders, disease control priorities. Washington, DC: The International Bank for Reconstruction and Development/The World Bank, 2016: 41–65.
32 Westman J, Wahlbeck K, Laursen TM, et al. Mortality and life expectancy of people with alcohol use disorder in Denmark, Finland and Sweden. *Acta Psychiatr Scand* 2015; **131:** 297–306.
33 Collins SE. Associations between socioeconomic factors and alcohol outcomes. *Alcohol Res* 2016; **38:** 83–94.
34 Lewer D, Meier P, Beard E, Boniface S, Kaner E. Unravelling the alcohol harm paradox: a population-based study of social gradients across very heavy drinking thresholds. *BMC Public Health* 2016; **16:** 599.
35 Probst C, Roerecke M, Behrendt S, Rehm J. Gender differences in socioeconomic inequality of alcohol-attributable mortality: a systematic review and meta-analysis. *Drug Alcohol Rev* 2015; **34:** 267–77.
36 Probst C, Parry CDH, Wittchen HU, Rehm J. The socioeconomic profile of alcohol-attributable mortality in South Africa: a modelling study. *BMC Med* 2018; **16:** 97.
37 Cloninger CR, Bohman M, Sigvardsson S. Inheritance of alcohol abuse: cross-fostering analysis of adopted men. *Arch Gen Psychiatry* 1981; **38:** 861–68.
38 Heath AC, Bucholz KK, Madden PA, et al. Genetic and environmental contributions to alcohol dependence risk in a national twin sample: consistency of findings in women and men. *Psychol Med* 1997; **27:** 1381–96.

39 Verhulst B, Neale MC, Kendler KS. The heritability of alcohol use disorders: a meta-analysis of twin and adoption studies. *Psychol Med* 2015; **45:** 1061–72.

40 Li D, Zhao H, Gelernter J. Strong protective effect of the aldehyde dehydrogenase gene (*ALDH2*) 504lys (*2) allele against alcoholism and alcohol-induced medical diseases in Asians. *Hum Genet* 2012; **131:** 725–37.

41 Tawa EA, Hall SD, Lohoff FW. Overview of the genetics of alcohol use disorder. *Alcohol Alcohol* 2016; **51:** 507–14.

42 Sanchez-Roige S, Palmer AA, Fontanillas P, et al. Genome-wide association study meta-analysis of the Alcohol Use Disorders Identification Test (AUDIT) in two population-based cohorts. *Am J Psychiatry* 2019; **176:** 107–18.

43 Clarke TK, Adams MJ, Davies G, et al. Genome-wide association study of alcohol consumption and genetic overlap with other health-related traits in UK Biobank (N=112 117). *Mol Psychiatry* 2017; **22:** 1376–84.

44 Jorgenson E, Thai KK, Hoffmann TJ, et al. Genetic contributors to variation in alcohol consumption vary by race/ethnicity in a large multi-ethnic genome-wide association study. *Mol Psychiatry* 2017; **22:** 1359–67.

45 Schumann G, Liu C, O'Reilly P, et al. KLB is associated with alcohol drinking, and its gene product beta-Klotho is necessary for FGF21 regulation of alcohol preference. *Proc Natl Acad Sci USA* 2016; **113:** 14372–77.

46 Polimanti R, Kaufman J, Zhao H, et al. A genome-wide gene-by-trauma interaction study of alcohol misuse in two independent cohorts identifies *PRKG1* as a risk locus. *Mol Psychiatry* 2018; **23:** 154–60.

47 Heilig M, Barbier E, Johnstone AL, et al. Reprogramming of mPFC transcriptome and function in alcohol dependence. *Genes Brain Behav* 2017; **16:** 86–100.

48 Pucci M, Micioni Di Bonaventura MV, Wille-Bille A, et al. Environmental stressors and alcoholism development: focus on molecular targets and their epigenetic regulation. *Neurosci Biobehav Rev* 2018; published online July 11. DOI:10.1016/j.neubiorev.2018.07.004.

49 Pandey SC, Kyzar EJ, Zhang H. Epigenetic basis of the dark side of alcohol addiction. *Neuropharmacology* 2017; **122:** 74–84.

50 Rosenstrom T, Torvik FA, Ystrom E, et al. Prediction of alcohol use disorder using personality disorder traits: a twin study. *Addiction* 2018; **113:** 15–24.

51 Li JJ, Savage JE, Kendler KS, et al. Polygenic risk, personality dimensions, and adolescent alcohol use problems: a longitudinal study. *J Stud Alcohol Drugs* 2017; **78:** 442–51.

52 Morgenstern M, Sargent JD, Sweeting H, Faggiano F, Mathis F, Hanewinkel R. Favourite alcohol advertisements and binge drinking among adolescents: a cross-cultural cohort study. *Addiction* 2014; **109:** 2005–15.

53 Casswell S, Huckle T, Wall M, et al. Policy-relevant behaviours predict heavier drinking and mediate the relationship with age, gender and education status: analysis from the International Alcohol Control study. *Drug Alcohol Rev* 2018; **37** (suppl 2)**:** S86–95.

54 Castaldelli-Maia JM, Bhugra D. Investigating the interlinkages of alcohol use and misuse, spirituality and culture—insights from a systematic review. *Int Rev Psychiatry* 2014; **26:** 352–67.

55 Chartier KG, Hesselbrock MN, Hesselbrock VM. Development and vulnerability factors in adolescent alcohol use. *Child Adolesc Psychiatr Clin N Am* 2010; **19:** 493–504.

56 Yap MBH, Cheong TWK, Zaravinos-Tsakos F, Lubman DI, Jorm AF. Modifiable parenting factors associated with adolescent alcohol misuse: a systematic review and meta-analysis of longitudinal studies. *Addiction* 2017; **112:** 1142–62.

57 Yang P, Tao R, He C, Liu S, Wang Y, Zhang X. The risk factors of the alcohol use disorders-through review of its comorbidities. *Front Neurosci* 2018; **12:** 303.

58 Leung RK, Toumbourou JW, Hemphill SA. The effect of peer influence and selection processes on adolescent alcohol use: a systematic review of longitudinal studies. *Health Psychol Rev* 2014; **8:** 426–57.

59 Mattick RP, Clare PJ, Aiken A, et al. Association of parental supply of alcohol with adolescent drinking, alcohol-related harms, and alcohol use disorder symptoms: a prospective cohort study. *Lancet Public Health* 2018; **3:** e64–71.

60 Koob GF. Neurocircuitry of alcohol addiction: synthesis from animal models. *Hand Clin Neurol* 2014; **125:** 33–54.

61 Spanagel R. Alcoholism: a systems approach from molecular physiology to addictive behavior. *Physiol Rev* 2009; **89:** 649–705.

62 Urban NB, Kegeles LS, Slifstein M, et al. Sex differences in striatal dopamine release in young adults after oral alcohol challenge: a positron emission tomography imaging study with [^{11}C]raclopride. *Biol Psychiatry* 2010; **68:** 689–96.

63 King AC, Hasin D, O'Connor SJ, McNamara PJ, Cao D. A prospective 5-year re-examination of alcohol response in heavy drinkers progressing in alcohol use disorder. *Biol Psychiatry* 2016; **79:** 489–98.

64 Koob GF. Alcoholism: allostasis and beyond. *Alcohol Clin Exp Res* 2003; **27:** 232–43.

65 Koob GF, Volkow ND. Neurobiology of addiction: a neurocircuitry analysis. *Lancet Psychiatry* 2016; **3:** 760–73.

66 Volkow ND, Koob GF, McLellan AT. Neurobiologic advances from the brain disease model of addiction. *N Engl J Med* 2016; **374:** 363–71.

67 Heilig M, Egli M, Crabbe JC, Becker HC. Acute withdrawal, protracted abstinence and negative affect in alcoholism: are they linked? *Addict Biol* 2010; **15:** 169–84.

68 Lewis M. Brain change in addiction as learning, not disease. *N Engl J Med* 2018; **379:** 1551–60.

69 Erol A, Karpyak VM. Sex and gender-related differences in alcohol use and its consequences: Contemporary knowledge and future research considerations. *Drug Alcohol Depend* 2015; **156:** 1–13.

70 Rehm J, Allamani A, Della Vedova R, et al. General practitioners recognizing alcohol dependence: a large cross-sectional study in 6 European countries. *Ann Family Med* 2015; **13:** 28–32.

71 Rathod SD, Roberts T, Medhin G, et al. Detection and treatment initiation for depression and alcohol use disorders: facility-based cross-sectional studies in five low-income and middle-income country districts. *BMJ Open* 2018; **8:** e023421.

72 Kohn R, Saxena S, Levav I, Saraceno B. The treatment gap in mental health care. *Bull World Health Organ* 2004; **82:** 858–66.

73 Rehm J, Dawson D, Frick U, et al. Burden of disease associated with alcohol use disorders in the United States. *Alcoholism* 2014; **38:** 1068–77.

74 Kranzler HR, Soyka M. Diagnosis and pharmacotherapy of alcohol use disorder: a review. *JAMA* 2018; **320:** 815–24.

75 Rehm J, Barbosa C. The cost-effectiveness of therapies to treat alcohol use disorders. *Expert Rev Pharmacoecon Outcomes Res* 2018; **18:** 43–49.

76 Leucht S, Helfer B, Gartlehner G, Davis JM. How effective are common medications: a perspective based on meta-analyses of major drugs. *BMC Med* 2015; **13:** 253.

77 Rehm J, Manthey J, Struzzo P, Gual A, Wojnar M. Who receives treatment for alcohol use disorders in the European Union? A cross-sectional representative study in primary and specialized health care. *Eur Psychiatry* 2015; **30:** 885–93.

78 Probst C, Manthey J, Martinez A, Rehm J. Alcohol use disorder severity and reported reasons not to seek treatment: a cross-sectional study in European primary care practices. *Subst Abuse Treat Prev Policy* 2015; **10:** 32.

79 Schomerus G, Matschinger H, Angermeyer MC. Attitudes towards alcohol dependence and affected individuals: persistence of negative stereotypes and illness beliefs between 1990 and 2011. *Eur Addict Res* 2014; **20:** 293–99.

80 van Boekel LC, Brouwers EP, van Weeghel J, Garretsen HF. Stigma among health professionals towards patients with substance use disorders and its consequences for healthcare delivery: systematic review. *Drug Alcohol Depend* 2013; **131:** 23–35.

81 National Center for Biotechnology Information. Screening and behavioral counseling interventions to reduce unhealthy alcohol use in adolescents and adults: an updated systematic review for the US Preventive Services Task Force. November, 2018. Agency for Healthcare Research and Quality. https://www.ncbi.nlm.nih.gov/books/NBK534916/ (accessed Feb 27, 2019).

82 National Institute for Health and Clinical Excellence. Alcohol use disorders: diagnosis, assessment and management of harmful drinking and alcohol dependence. 2011. National Institute for Health and Clinical Excellence. https://www.nice.org.uk/guidance/cg115 (accessed Feb 17, 2019).

83 Anderson P, Bendtsen P, Spak F, et al. Improving the delivery of brief interventions for heavy drinking in primary health care: outcome results of the Optimizing Delivery of Health Care Intervention (ODHIN) five-country cluster randomized factorial trial. *Addiction* 2016; **111:** 1935–45.

84 Rehm J, Anderson P, Manthey J, et al. Alcohol use disorders in primary health care: what do we know and where do we go? *Alcohol Alcohol* 2016; **51:** 422–27.

85 Rehm J, Anderson P, Arbesu Prieto JA, et al. Towards new recommendations to reduce the burden of alcohol-induced hypertension in the European Union. *BMC Medicine* 2017; **15:** 173.

86 Lange S, Shield K, Monteiro M, Rehm J. Facilitating screening and brief interventions in primary care: a systematic review and meta-analysis of the AUDIT as an indicator of alcohol use disorders. *Alcohol Clin Exp Res* 2019; published online Aug 6. DOI:10.1111/acer.14171.

87 Miller WR, Wilbourne PL. Mesa Grande: a methodological analysis of clinical trials of treatments for alcohol use disorders. *Addiction* 2002; **97:** 265–77.

88 Miller WR, Moyers TB. The forest and the trees: relational and specific factors in addiction treatment. *Addiction* 2015; **110:** 401–13.

89 Magill M, Kiluk BD, McCrady BS, Tonigan JS, Longabaugh R. Active ingredients of treatment and client mechanisms of change in behavioral treatments for alcohol use disorders: progress 10 years later. *Alcohol Clin Exp Res* 2015; **39:** 1852–62.

90 Riper H, Hoogendoorn A, Cuijpers P, et al. Effectiveness and treatment moderators of internet interventions for adult problem drinking: an individual patient data meta-analysis of 19 randomised controlled trials. *PLoS Med* 2018; **15:** e1002714.

91 Kaner EF, Beyer FR, Garnett C, et al. Personalised digital interventions for reducing hazardous and harmful alcohol consumption in community-dwelling populations. *Cochrane Database Syst Rev* 2017; **9:** CD011479.

92 Naqvi NH, Morgenstern J. Cognitive neuroscience approaches to understanding behavior change in alcohol use disorder treatments. *Alcohol Res* 2015; **37:** 29–38.

93 Wiers RW, Gladwin TE, Hofmann W, Salemink E, Ridderinkhof KR. Cognitive bias modification and cognitive control training in addiction and related psychopathology: mechanisms, clinical perspectives, and ways forward. *Clin Psychol Sci* 2013; **1:** 192–212.

94 Boffo M, Zerhouni O, Gronau QF, et al. Cognitive bias modification for behavior change in alcohol and smoking addiction: Bayesian meta-analysis of individual participant data. *Neuropsychol Rev* 2019; **16:** 52–78.

95 Wiers RW, Boffo M, Field M. What's in a trial? on the importance of distinguishing between experimental lab studies and randomized controlled trials: the case of cognitive bias modification and alcohol use disorders. *J Stud Alcohol Drugs* 2018; **79:** 333–43.

96 Kakoschke N, Kemps E, Tiggemann M. Approach bias modification training and consumption: a review of the literature. *Addict Behav* 2017; **64:** 21–28.

97 Cristea IA, Kok RN, Cuijpers P. The effectiveness of cognitive bias modification interventions for substance addictions: a meta-analysis. *PLoS One* 2016; **11:** e0162226.

98 Soyka M, Kranzler HR, Hesselbrock V, et al. Guidelines for biological treatment of substance use and related disorders, part 1: alcoholism, first revision. *World J Biol Psychiatry* 2017; **18:** 86–119.

99 Jonas DE, Amick HR, Feltner C, et al. Pharmacotherapy for adults with alcohol use disorders in outpatient settings: a systematic review and meta-analysis. *JAMA* 2014; **311:** 1889–900.

100 Kranzler HR, Covault J, Feinn R, et al. Topiramate treatment for heavy drinkers: moderation by a *GRIK1* polymorphism. *Am J Psychiatr* 2014; **171:** 445–52.

101 George DT, Gilman J, Hersh J, et al. Neurokinin 1 receptor antagonism as a possible therapy for alcoholism. *Science* 2008; **319:** 1536–39.

102 Schank JR, Heilig M. Substance P and the neurokinin-1 receptor: the new CRF. *Int Rev Neurobiol* 2017; **136:** 151–75.

103 Ratti E, Bettica P, Alexander R, et al. Full central neurokinin-1 receptor blockade is required for efficacy in depression: evidence from orvepitant clinical studies. *J Psychopharmacol* 2013; **27:** 424–34.

104 Vendruscolo LF, Estey D, Goodell V, et al. Glucocorticoid receptor antagonism decreases alcohol seeking in alcohol-dependent individuals. *J Clin Invest* 2015; **125:** 3193–97.

105 Lee MR, Tapocik JD, Ghareeb M, et al. The novel ghrelin receptor inverse agonist PF-5190457 administered with alcohol: preclinical safety experiments and a phase 1b human laboratory study. *Mol Psychiatry* 2018; published online May 4. DOI:10.1038/s41380-018-0064-y.

106 Leggio L, Zywiak WH, Fricchione SR, et al. Intravenous ghrelin administration increases alcohol craving in alcohol-dependent heavy drinkers: a preliminary investigation. *Biol Psychiatry* 2014; **76:** 734–41.

107 Bruchas MR, Land BB, Chavkin C. The dynorphin/kappa opioid system as a modulator of stress-induced and pro-addictive behaviors. *Brain Research* 2010; **1314:** 44–55.

108 Domi E, Barbier E, Augier E, et al. Preclinical evaluation of the kappa-opioid receptor antagonist CERC-501 as a candidate therapeutic for alcohol use disorders. *Neuropsychopharmacology* 2018; **43:** 1805–12.

109 Harris AH, Kivlahan DR, Bowe T, Humphreys KN. Pharmacotherapy of alcohol use disorders in the Veterans Health Administration. *Psychiatr Serv* 2010; **61:** 392–98.

110 Walters GD. Spontaneous remission from alcohol, tobacco, and other drug abuse: seeking quantitative answers to qualitative questions. *Am J Drug Alcohol Abuse* 2000; **26:** 443–60.

111 Anderson P, O'Donnell A, Kaner E. Managing alcohol use disorder in primary health care. *Curr Psychiatry Rep* 2017; **19:** 79.

112 Nutt DJ, Rehm J. Doing it by numbers: a simple approach to reducing the harms of alcohol. *J Psychopharmacol* 2014; **28:** 3–7.

113 Rolland B, Paille F, Gillet C, et al. Pharmacotherapy for alcohol dependence: the 2015 recommendations of the French Alcohol Society, issued in partnership with the European Federation of Addiction Societies. *CNS Neurosci Ther* 2016; **22:** 25–37.

114 Miller WR, Wilbourne PL, Hettema JE. What works? A summary of alcohol treatment outcome research. In: Hester RK, Miller WR, eds. Handbook of alcoholism treatment approaches. Boston, MA: Allyn and Bacon, 2003: 13–63.

115 Browne AL, Newton M, Gope M, Schug SA, Wood F, Allsop S. Screening for harmful alcohol use in Australian trauma settings. *Injury* 2013; **44:** 110–17.

116 Westwood G, Meredith P, Atkins S, Greengross P, Schmidt PE, Aspinall RJ. Universal screening for alcohol misuse in acute medical admissions is feasible and identifies patients at high risk of liver disease. *J Hepatol* 2017; **67:** 559–67.

117 Urbanoski K, Cheng J, Rehm J, Kurdyak P. Frequent use of emergency departments for mental and substance use disorders. *Emerg Med J* 2018; **35:** 220–25.

118 Storbjörk J. The interplay between perceived self-choice and reported informal, formal and legal pressures in treatment entry. *Contemp Drug Probl* 2006; **33:** 611–43.

119 Rehm J, Allamani A, Aubin H-J, et al. People with alcohol use disorders in specialized care in eight different European countries. *Alcohol Alcohol* 2015; **50:** 310–18.

120 Samokhvalov AV, Probst C, Awan S, et al. Outcomes of an integrated care pathway for concurrent major depressive and alcohol use disorders: a multisite prospective cohort study. *BMC Psychiatry* 2018; **18:** 189.

121 Hesse M. Integrated psychological treatment for substance use and co-morbid anxiety or depression vs. treatment for substance use alone. A systematic review of the published literature. *BMC Psychiatry* 2009; **9:** 6.

122 Agabio R, Trogu E, Pani PP. Antidepressants for the treatment of people with co-occurring depression and alcohol dependence. *Cochrane Database Syst Rev* 2018; **4:** CD008581.

123 UN General Assembly. Sixty-seventh session Agenda item 123 Resolution adopted by the General Assembly on 12 December 2012 67/81. Global health and foreign policy. March 2014. United Nations. http://www.un.org/en/ga/search/view_doc.asp?symbol=A/RES/67/81 (accessed Feb 18, 2019).

124 Summers LH, signatories. Economists' declaration on universal health coverage. *Lancet* 2015; **386:** 2112–13.

125 Patel V, Saxena S, Lund C, et al. The Lancet Commission on global mental health and sustainable development. *Lancet* 2018; **392:** 1553–98.

126 Vigo DV, Patel V, Becker A, et al. A partnership for transforming mental health globally. *Lancet Psychiatry* 2019; **6:** 350–56.

127 Inter-American Drug Abuse Control Commission (CICAD), Organization of American States. Observatorio Interamericano de Drogas (2015). Informe sobre el uso de drogas en las Américas. 2015. http://www.oas.org/es/centro_noticias/comunicado_prensa.asp?sCodigo=C-154/15 (accessed Feb 18, 2019).

128 Pérez A, Mejía J, Reyes MF, Cardozo F. Consumo de Estudio alcohol en menores de 18 años en Colombia. Bogotá, Colombia: Corporación Nuevos Rumbos, 2015.

129 Ministerio de Justicia y Ministerio de Salud & Observatorio de Drogas de Columbia. Estudio Nacional de Consumo de Sustancias Psicoativas en Colombia 2013. http://www.odc.gov.co/PUBLICACIONES/ArtMID/4214/ArticleID/5768/Estudio-Nacional-de-consumo-de-sustancias-psicoactivas-en-Colombia-2013 (accessed Aug 8, 2019).

130 Ministerio de Justicia y Ministerio de Salud & Observatorio de Drogas de Colombia. Estudio Nacional de Consumo de Sustancias Psicoativas en población escolar. Colombia 2016. http://www.odc.gov.co/PUBLICACIONES/ArtMID/4214/ArticleID/6067/Estudio-Nacional-de-Consumo-de-Sustancias-Psicoactivas-en-Poblaci243n-Escolar-Colombia-2016 (accessed Aug 8, 2019).

131 Rehm J, Shield K, Gmel G, Rehm M, Frick U. Modeling the impact of alcohol dependence on mortality burden and the effect of available treatment interventions in the European Union. *Eur Neuropsychopharmacol* 2013; **23:** 89–97.

132 Anderson P, O'Donnell A, Kaner E, et al. Scaling-up primary health care-based prevention and management of heavy drinking at the municipal level in middle-income countries in Latin America: background and protocol for a three-country quasi-experimental study. *F1000Res* 2017; **6:** 311.

133 Hemström Ö. Informal alcohol control in six EU countries. *Contemp Drug Probl* 2002; **29:** 577–604.

134 Babor TF, Caetano R, Casswell S, et al. Alcohol: no ordinary commodity. Research and public policy. 2nd edn. Oxford and London: Oxford University Press, 2010.

135 Sornpaisarn B, Shield KD, Österberg E, Rehm J. Resource tool on alcohol taxation and pricing policies. Geneva, Switzerland: World Health Organization and others, 2017.

136 Manthey J, Shield KD, Rylett M, Hasan OSM, Probst C, Rehm J. Global alcohol exposure between 1990 and 2017 and forecasts until 2030: a modelling study. *Lancet* 2019; **393:** 2493–502.

137 WHO European Region. Alcohol consumption, harm and policy responses in 30 European countries in 2016. Copenhagen, Denmark: World Health Organization European Region, 2019.

138 Stockwell T, Zhao J, Giesbrecht N, Macdonald S, Thomas G, Wettlaufer A. The raising of minimum alcohol prices in Saskatchewan, Canada: impacts on consumption and implications for public health. *Am J Public Health* 2012; **102:** e103–10.

139 Chisholm D, Moro D, Bertram M, et al. Are the "best buys" for alcohol control still valid? An update on the comparative cost-effectiveness of alcohol control strategies at the global level. *J Stud Alcohol Drugs* 2018; **79:** 514–22.

140 World Health Organization. Tackling NCDs: "best buys" and other recommended interventions for the prevention and control of noncommunicable diseases. 2017. World Health Organization. https://apps.who.int/iris/handle/10665/259232 (accessed May 16, 2019).