Alcohol-use disorders
Marc A Schuckit

Alcohol dependence and alcohol abuse or harmful use cause substantial morbidity and mortality. Alcohol-use disorders are associated with depressive episodes, severe anxiety, insomnia, suicide, and abuse of other drugs. Continued heavy alcohol use also shortens the onset of heart disease, stroke, cancers, and liver cirrhosis, by affecting the cardiovascular, gastrointestinal, and immune systems. Heavy drinking can also cause mild anterograde amnesias, temporary cognitive deficits, sleep problems, and peripheral neuropathy; cause gastrointestinal problems; decrease bone density and production of blood cells; and cause fetal alcohol syndrome. Alcohol-use disorders complicate assessment and treatment of other medical and psychiatric problems. Standard criteria for alcohol dependence—the more severe disorder—can be used to reliably identify people for whom drinking causes major physiological consequences and persistent impairment of quality of life and ability to function. Clinicians should routinely screen for alcohol disorders, using clinical interviews, questionnaires, blood tests, or a combination of these methods. Causes include environmental factors and specific genes that affect the risk of alcohol-use disorders, including genes for enzymes that metabolise alcohol, such as alcohol dehydrogenase and aldehyde dehydrogenase; those associated with disinhibition; and those that confer a low sensitivity to alcohol. Treatment can include motivational interviewing to help people to evaluate their situations, brief interventions to facilitate more healthy behaviours, detoxification to address withdrawal symptoms, cognitive-behavioural therapies to avoid relapses, and judicious use of drugs to diminish cravings or discourage relapses.

Introduction
The alcohol-use disorders consist of alcohol dependence, alcohol abuse, and dependence or harmful use. These are common and potentially lethal disorders that mimic and exacerbate a wide range of additional medical and psychiatric conditions, and thereby shorten the lifespans of affected people by more than a decade. However, most people with alcohol-use disorders are hard to identify, since they are likely to have jobs and families, and present with general complaints such as malaise, insomnia, anxiety, sadness, or a range of medical problems.

Both primary-care physicians and specialists can help to screen for these disorders, institute brief interventions, and refer patients for more intensive care if needed. This paper presents a selective update of clinical developments regarding alcohol-use disorders that are relevant to practising physicians, and focus on skills that they already have or can easily acquire.

Epidemiology
Alcohol-use disorders are common in all developed countries, and are more prevalent in men than women, with lower, but still substantial rates in developing countries. Although rates of these disorders are lower in Mediterranean countries (eg, Greece, Italy, and Israel), and higher in northern and eastern Europe (eg, Russia and Scandinavia), they are responsible for a large proportion of the health-care burden in almost all populations.

As many as 80% of men and 60% of women in developed countries drink at some time during their lives. In any year, between half and two-thirds of individuals who ever drank are likely to consume alcohol; recent abstainers are most likely to have stopped because of medical concerns. 30–50% of people who drank in the past year experience at least one adverse alcohol-related problem during their lifetime, such as missing work or school, driving after drinking, or interpersonal problems. The lifetime risk of alcohol-use disorders for men is more than 20%, with a risk of about 15% for alcohol abuse and 10% for alcohol dependence.

The risk of developing an alcohol-use disorder in the previous year is about 10% overall. Only a quarter of people with alcohol-use disorders ever seek help for these conditions, with higher proportions for women than men. Most receive care from their general practitioner, where they represent about a fifth of patients seen; the proportions seen for diabetes and hypertension are similar. The challenge for the clinician is to learn enough about these disorders to identify them, since missing an alcohol-use disorder can complicate the assessment and treatment of other medical and psychiatric issues.

Diagnosis

Criteria for screening and diagnosis
Clinicians should screen for unhealthy drinking (eg, more than three or four standard drinks per day), just as they counsel their patients for other risky behaviours such as being 10% overweight. A standard drink is defined as 8 g of ethanol in the UK and about 10 g in the USA. Both the US-based 4th Diagnostic and Statistical Manual (DSM-IV) and the 10th International Classification of Diseases
Diseases (ICD10)\(^{2}\) describe alcohol dependence as the more severe condition, associated with major physiological consequences and life impairment. Dependence can be identified as repetitive problems, affecting three or more areas of life, and about 80% of people who are diagnosed with dependence at any point still have alcohol-related problems when assessed a year or more later.\(^{3,9}\) Dependence criteria are reliable across different ages, sexes, and most cultural groups.\(^{3}\) The concordance between ICD and DSM approaches to diagnosis is about 80% (panel).\(^{10}\) Alcohol abuse and harmful use, however, have different definitions from dependence. The DSM-IV defines alcohol abuse as one or more problems with functioning in a 12-month period in a person without dependence: failure in obligations; alcohol use in hazardous situations; recurrent legal problems; or continued use despite social or interpersonal problems. The ICD10 defines harmful use as either a physical or mental problem associated with alcohol in a 12-month period, or both. The ICD10 label of harmful use is not as reliable as that for abuse, and the two diagnostic systems have low agreement.\(^{10,11}\) People who abuse alcohol drink smaller quantities than those with dependence do, but the abuse label predicts a risk of about 50% for continued problems.\(^{10,12}\) Only 10% of those with alcohol abuse go on to dependence.\(^{10,12}\)

Questionnaires

Although they are not a substitute for a careful clinical interview, a range of self-administered questionnaires can be used to screen for heavy drinking and alcohol-use disorders in clinical settings.\(^{13}\) The shortest of the most widely-used instruments is the CAGE questionnaire, which is an acronym for whether a patient has ever felt the need to Cut down on drinking; felt Annoyed when criticised about alcohol use; felt Guilty about drinking, or ever needed an Eye-opener on awakening. Results vary across different subgroups (with highest accuracy in men and white people). The cut-off score of two of a possible four positive responses has a sensitivity of between 53% (in heavy drinkers) and 77% in patients who have alcohol dependence, with specificities of 80% or higher.\(^{14}\) The sensitivity measures the proportion of actual positives who are correctly identified as such; and the specificity measures the proportion of negatives who are correctly identified. This short test might operate best in medical and surgical settings, especially when combined with blood tests for heavy drinking. Another questionnaire is the ten-item version of the Michigan Alcohol Screening Test, in which five to six affirmative answers indicate a possible alcohol-use disorder (with sensitivity and specificity of about 80%), and seven indicates a probable alcohol-use disorder.\(^{15}\) Table 1 shows questions for the ten-item alcohol-use identification test (AUDIT),\(^{15}\) in which a score of eight or above identifies both heavy drinkers and those with alcohol-use disorders with a sensitivity of 50–90%, and a specificity of about 80%, although a lower sensitivity has been reported in women and elderly people.\(^{16,17}\) Four of the AUDIT items are used for the shorter fast alcohol screening test (FAST), which has similar accuracy to the full AUDIT test.\(^{18}\) Another short instrument is the TWEAK questionnaire, which asks about Tolerance, Worry about drinking by friends, Eye-opener drinks in the morning, Amnesia about drinking, and feeling the need to Cut down down.

Blood tests

Although not as sensitive as questionnaires, blood tests for markers that are likely to change in the context of heavy drinking can also help to identify patients who consume hazardous amounts of alcohol (table 2).\(^{19,20}\) These tests can be especially useful if the veracity of the history is in doubt, and can also be used to help the patient recognise that alcohol has adversely affected their health.\(^{21}\) These markers of heavy drinking indicate relatively high amounts of intake of alcohol (eg, five or more standard drinks per day) consumed on a regular basis (eg, for 5 days or more). High values are likely to return to normal within several weeks of abstinence, an evanescence that can be useful in monitoring adherence to treatment.\(^{20}\) Values are likely to be highest in the heaviest drinkers, and might have the greatest sensitivities and specificities for men and for patients who are not grossly overweight, diabetic, or smokers.\(^{20}\)

One such marker is the serum activity of γ glutamyl transferase, an enzyme important in aminoacid transport. Results of at least 35 units per L γ glutamyl transferase indicate the probability of heavy drinking.\(^{22}\) This test is

Panel: Criteria for diagnosis of alcohol dependence, according to Diagnostic and Statistical Manual (DSM-IV)\(^{1}\) and International Classification of Diseases (ICD10)\(^{2}\)

**Diagnostic and Statistical Manual (DSM-IV)**

- Tolerance to alcohol
- Withdrawal syndrome
- Greater alcohol use than intended\(^*\)
- Desire to use alcohol and inability to control use
- Devotion of large proportion of time to getting and using alcohol, and recovering from alcohol use
- Neglect of social, work, or recreational activities
- Continued alcohol use despite physical or psychological problems

**International Classification of Diseases (ICD10)**

- Strong desire or compulsion to use alcohol
- Inability to control use
- Withdrawal syndrome
- Tolerance to alcohol
- Neglect of pleasures or interests
- Continued alcohol use despite physical or psychological problems

Alcohol dependence is defined as three or more of these criteria in a 12-month period.

\(^*\)For example, exceeding set limits.
Table 1: Alcohol use disorders identification test (AUDIT)

<table>
<thead>
<tr>
<th>Question</th>
<th>Score (0–4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. How often do you have a drink containing alcohol?</td>
<td>Never (0) to more than four per week (4)</td>
</tr>
<tr>
<td>2. How many drinks containing alcohol do you have on a typical day?</td>
<td>One or two (0) to more than ten (4)</td>
</tr>
<tr>
<td>3. How often do you have six or more drinks on one occasion?</td>
<td>Never (0) to daily or almost daily (4)</td>
</tr>
<tr>
<td>4. How often during the last year have you found that you were not able to stop drinking once you had started?</td>
<td>Never (0) to daily or almost daily (4)</td>
</tr>
<tr>
<td>5. How often during the last year have you failed to do what was normally expected from you because of drinking?</td>
<td>Never (0) to daily or almost daily (4)</td>
</tr>
<tr>
<td>6. How often during the last year have you needed a first drink in the morning to get yourself going after a heavy drinking session?</td>
<td>Never (0) to Daily or almost daily (4)</td>
</tr>
<tr>
<td>7. How often during the last year have you had a feeling of guilt or remorse after drinking?</td>
<td>Never (0) to daily or almost daily (4)</td>
</tr>
<tr>
<td>8. How often during the last year have you been unable to remember what happened the night before because you had been drinking?</td>
<td>Never (0) to Daily or almost daily (4)</td>
</tr>
<tr>
<td>9. Have you or someone else been injured as a result of your drinking?</td>
<td>No (0) to yes, during the last year (4)</td>
</tr>
<tr>
<td>10. Has a relative, friend, doctor or other health worker been concerned about your drinking or suggested that you should cut down?</td>
<td>No (0) to yes, during the last year (4)</td>
</tr>
</tbody>
</table>

The AUDIT score is the sum of the response values. A score of 8 or more identifies heavy drinkers and those with alcohol-use disorders. Adapted from reference 15.

Moreover, although children who have persistent conduct disorders and adults who have antisocial personalities have similar alcohol problems to others with alcohol-use disorders, they exhibit more drug dependence and criminality, and the combination of problems is sometimes referred to as type 2 or type B alcoholism.28,29

The usual age of first drinking, independently of the family, is about 15 years (although this varies across cultural groups), and has not changed much in decades. This age does not differ much for those who go on to develop alcohol-use disorders and those who do not, although an earlier onset of regular drinking is associated with a greater likelihood of later problems.1,9 The period of heaviest drinking is usually between 18 and 22 years of age, and also does not differ much between those with future alcohol-use disorders and the general population.1,30

More than 60% of teenagers, even those without alcohol-use disorders, have experienced drunkenness by the age of 18 years, and about 30% have either given up events such as school or work to drink, or have driven while intoxicated.6,31 Alcohol abuse and dependence often begin in the early to mid-20s,5,12 at a time when most people begin to moderate their drinking as their responsibilities increase.

Repeated heavy drinking in alcohol-use disorders is associated with a 40% risk of temporary depressive episodes, associated suicidal ideas and attempts, and severe anxiety and insomnia.15 However, many of these forms of psychopathology are substance-induced, and likely to improve within 2–4 weeks of abstinence.11 Additional comorbidities include use, abuse, and dependence on illicit drugs, especially for patients who have very early-onset alcohol-use disorders and antisocial personalities (ie, type 2 or type B subtypes of dependence).19 As many as 80% of alcohol-dependent people are regular smokers, a co-occurrence that could reflect either use of the second drug to deal with effects of the first or overlapping genetic predispositions.17 These comorbidities can make treatment more difficult.15

As is true of many chronic relapsing disorders (eg, hypertension), the course of alcohol-use disorders...
fluctuates over time. Abstinence often develops after a crisis, and the subsequent days to months of sobriety are often followed by temporary controlled drinking, which carries a subsequent enhanced likelihood of increasing intake and problems. This fluctuating course relates to the controversy about whether a person with an alcohol-use disorder can return to long-term controlled non-problematic drinking. Abstinence is the usual goal for treatment of dependence in the USA, although efforts to control drinking, or reduce harm, are more often deemed appropriate goals in the UK and other parts of Europe. Some studies have reported that about 20% of those with alcohol dependence were able to drink moderately without problems in the previous year, but this is often temporary, and other studies indicate that fewer than 10% ever develop long periods of non-problematic drinking.

Another element in the course of alcohol-use disorders is the 20–30% rate of long-term remission of alcohol-related problems in the absence of formal treatment or self-help programmes. Remission is usually associated with deteriorating health, new life-partners, parenthood, a new job, or maturation over time, and, once achieved, is likely to remain stable.

Continued alcohol problems increase the rate of early death by three or four times. The most common causes are early onset of heart disease, stroke, and cancers; and a high risk of accidents, suicide, and liver cirrhosis (although about 80% of people with alcohol-use disorders do not have this disorder). Alcohol-related mortality contributes to 2–4% of all deaths in adults, with the highest rate in the first decade after treatment.

**Pathophysiology**

**Causes and origins**

About 40–60% of the risk of alcohol-use disorders is explained by genes and the rest through gene–environment associations. The environment includes the availability of alcohol, attitudes towards drinking and drunkenness, peer pressures, levels of stress and related coping strategies, models of drinking, and laws and regulatory frameworks.

Recent advances in our understanding of genes that operate through intermediate characteristics (or phenotypes) to affect the risk of alcohol-use disorders can help parents with alcohol-use disorders to identify children who might be at high risk of alcohol-use disorders. These could contribute to preventive approaches in the future through early intervention in those at highest risk, even before problems develop. First, variations (polymorphisms) in genes for enzymes that metabolise alcohol are generally associated with a lower risk of alcohol-use disorders, since they increase sensitivity to alcohol. At least one variant of aldehyde dehydrogenase (the ALDH2*2 allele), produces an aversive response to alcohol. Second, gene forms associated with impulsivity, disinhibition, and sensation-seeking contribute to vulnerability to both drug-use and alcohol-use disorders in people with type 2 and type B disorders, perhaps through impaired judgment and difficulty learning from mistakes that could reduce control of alcohol intake. Relevant polymorphisms include variations in receptors for γ-aminobutyric acid (eg, GABRA2), acetylcholine (eg, CHRM2), and dopamine (eg, DRD2). Third, people who have low responsiveness (or low sensitivity) to alcohol are more likely to drink more on each occasion to get the desired effect, which increases their risk of alcohol-use disorders, but not other drug-related disorders. Relevant genes include those that encode an allele of the serotonin transporter (SLC6A4), some potassium channels (eg, KCNMA1), variations in γ-aminobutyric acid receptors (eg, GABRA6), second messenger systems (eg, AC9), and genes that affect glutamate receptors (GRM3). Additional genetic mechanisms might operate via genes that regulate dopamine-reward systems.

**Alcohol metabolism**

Although 2–10% of alcohol is excreted through the lungs, urine, and sweat, the remainder is metabolised to acetaldehyde, mainly by alcohol dehydrogenase (ADH). This metabolite is then quickly converted to carbon dioxide and water, primarily through the actions of aldehyde dehydrogenase (ALDH). The wildtype forms of ADH decrease the concentration of alcohol in blood by about 4–5 mmol/L ethanol per h (this is the equivalent of about one drink per h).

At least two variations of ADH genes (ADH1B*2 and ADHIC*1) produce a slightly more rapid breakdown of alcohol, and therefore potentially faster production of acetaldehyde. ALDH*2, the form most relevant for acetaldehyde metabolism, then rapidly destroys this product. However, about 40% of Asian people (Japanese, Chinese, and Koreans) have an inactive ALDH*2 mutation that results in much more acetaldehyde after drinking than normal. About 10% of people who are homozygous for this gene form cannot drink alcohol without becoming sick, and have almost no risk of alcohol-use disorders, whereas those who are heterozygous have a relatively low rate of alcohol-use disorders.

**Effects on the brain**

Even low doses of alcohol enhance activity in the inhibitory γ-aminobutyric acid systems throughout the
Cancer is the second leading cause of early death in people with alcohol-use disorders, even after controlling for the effect of smoking. Almost 75% of patients who have head and neck cancers have alcohol-use disorders, and alcohol-use disorders also double the risk of cancers of the oesophagus, rectum, and breast. These findings could reflect alcohol-induced impairment of the immune system.

Other disorders related to heavy drinking include acute haemorrhagic gastritis, pancreatitis, and liver changes ranging from fatty infiltration to alcoholic hepatitis and cirrhosis. Alcohol-induced immune dysfunction can exacerbate the course of hepatitis C and complicate the treatment of AIDS. Furthermore, heavy drinking is associated with a decrease in bone density, an enhanced vulnerability to hip fractures, and alterations in blood-producing systems that decrease white blood cells, platelets, and granulocyte mobility.

Additional problems include heavy drinking associated with fatal accidents. Furthermore, a pregnant woman who drinks heavily can cause adverse effects on her developing fetus, including low birthweight, spontaneous abortions, premature deliveries, fetal-alcohol syndrome, and fetal alcohol spectrum disorders. Fetal-alcohol spectrum disorders include abnormalities in facial features, such as an absent philtrum, a flattened nose, and shortened palpebral fissures; ventricular septal heart defects; syndactyly; and mental retardation.

### Treatment

Despite perceptions to the contrary, efforts to help patients decrease heavy drinking commonly result in changes in behaviours, and most patients with alcohol-use disorders do well after treatment. About 50–60% of men and women with alcohol dependence abstain or show substantial improvements in functioning the year after treatment, and such outcomes are excellent predictors of their status at 3–5 years. Although anyone in treatment might do well, better outcomes are associated with more intense treatment, less severe alcohol problems, less cognitive impairment, higher self-confidence about outcome, and fewer comorbid psychiatric disorders. The figure sets out the process of treatment, in which clinicians first identify alcohol-use disorders and share their concerns with patients, and then follow through with brief interventions, treatment, and referral to a specialist if problems are severe. For most clinicians, the goal of treatment for severe alcohol dependence is abstinence, and only a few favour teaching control of drinking. At the same time, individuals who drink unhealthy amounts (eg, more than 35 g absolute ethanol per day) and those with alcohol abuse who refuse to abstain might benefit from approaches that emphasise moderation of drinking.

Treatment centres on clinicians’ interactions with patients to help them to recognise their problems, and to
enhance motivation for change and implementation of changes.

**Intervention**

The intervention step effectively starts the process of recovery and can be delivered by the general physician. The process incorporates the principles of motivational interviewing, brief interventions, or both, to help a patient recognise their problem and take steps to minimise future difficulties. Interventions can be offered both to those who seek help and to patients with excessive drinking or alcohol-use disorders who are opportunistically identified.

In motivational interviewing, clinicians explore the assets and liabilities of the drinking pattern, offer feedback on risk, encourage patients to take responsibility for change, offer advice, give a menu of options, interact in an empathetic way, and enhance self-efficacy or the ability to take responsibility for change; this combination is summarised by the acronym FRAMES. Brief interventions are broader in scope, and use a range of tools to educate the patient about the norms of consumption, emphasise the dangers of heavy drinking, suggest ways to reduce (or cease) alcohol consumption, and help to identify and avoid situations in which heavy drinking is most likely to occur.

Both approaches aim to increase patients’ motivations for change, elicit their perceptions of the situation and what needs to be done, and offer suggestions. Reluctance to change should be explored through discussions, to gauge when the patient is ready to implement the necessary steps. One approach for the more directive brief interventions offers information about the patient’s risk of problems, education about the dangers of continued heavy drinking, and a discussion of the benefits of change. Steps include the suggestion that a patient keeps a diary of behaviours, provision of reading materials, and a follow-up several weeks later by nursing or counselling staff.

**Detoxification**

About 50% of alcohol-dependent patients develop clinically relevant symptoms of withdrawal. These represent a rebound from the usual effects of alcohol intoxication, begin about 8 h after a pronounced decrease in blood-alcohol concentrations, peak on day 2, and are substantially reduced by day 4 or 5. A syndrome associated with protracted abstinence can persist for several months; it consists of mild anxiety, insomnia, and autonomic dysfunction, including modest elevations in blood pressure, pulse and respiratory rates; and sweating, tremor, anxiety, and insomnia. Fewer than 5% of alcohol-dependent people ever have a grand mal seizure during withdrawal (usually on day 2), or a severe agitated confusion (delirium tremens). Such seizures require care by a specialist, usually in a hospital setting, where the intensity of withdrawal can be closely monitored, including through the clinician-observer-based Clinical Institute Withdrawal Assessment for alcoholism scale.

A physical examination is essential for patients with withdrawal symptoms (since risks of seizures and delirium rise with medical problems), followed by education and reassurance about the temporary nature of the symptoms. Doses of oral multivitamins, including oral thiamine (about 10 mg per day) can be beneficial; intramuscular or intravenous routes and higher doses are needed for the rare Wernicke–Korsakoff syndromes, which are much less likely to be seen in general-practice settings. Withdrawal symptoms are most safely and efficiently diminished by prescribing depressants (e.g., drugs that boost γ-aminobutyric acid); benzodiazepines are the most cost-effective approach. Anticonvulsants confer no additional benefit, are more expensive, and have more side-effects; β blockers or α-adrenergic agonists can mask signs of withdrawal that might highlight impending seizures or delirium.

Detoxification can begin with 25 mg chlordiazepoxide every 4–6 h for 1 day, deleting a dose if the patient is sleeping or resting comfortably, along with a supplementary 25–50 mg if a severe tremor or autonomic dysfunction is seen about 1 h after the scheduled dose. Higher doses of benzodiazepines can be used if needed, depending on the level of autonomic dysfunction. Over the next 5–7 days, the dose used on day 1 should be decreased by 15–20% each day, or maintained at the same dose if symptoms worsen. If a shorter-acting benzodiazepine (e.g., lorazepam, 2–4 mg, four times a day) is used, it must be given on a strict schedule to avoid a higher risk of withdrawal seizures if concentrations of benzodiazepine in blood fluctuate. The average patient with a stable social situation, no severe medical problems, and no previous history or indicators of impending delirium or seizures can usually be treated with similar outcomes but less cost as an outpatient. Alternative
Seminar

Rehabilitation

The goals of rehabilitation for alcohol-use disorders are the same as for any chronic relapsing disorder: to help to keep motivation high, change attitudes toward recovery, and diminish the risk of relapse. Cognitive-behavioural steps can help people to change how they think about alcohol and its role in their lives (the cognitive component); learn new behaviours for development and maintenance of abstinence or diminished drinking; and avoid relapses.

The Alcoholics Anonymous programme offers support, emphasises changes in attitudes and behaviour, helps to rebuild life in the absence of alcohol, and decreases the demand for more expensive care. In fact, incorporation of the key elements of the Alcoholics Anonymous programme through 12-step facilitation has been reported to increase the likelihood of a positive outcome.

Rehabilitation can be offered through groups in which participants are encouraged to talk about their alcohol-related problems, consider how alcohol contributed to the difficulties, develop supportive peers, improve their relationships, deal with stress, make the most of work and free time, and avoid relapse. Such groups encourage patients to use their own and others’ experiences to identify situations that are associated with a risk of relapse, to learn how to avoid them and how to re-establish sobriety if heavy drinking resumes. Although outpatient rehabilitation is often successful, the better outcome with more intensive treatment indicates that some patients might need inpatient or residential-based care.

The role of drugs

Although many clinicians believe that medications are helpful, the core of treatment rests with motivational interviewing, brief interventions, and cognitive-behavioural approaches. Placebo-controlled studies are important for assessment of drugs because alcohol-use disorders have a high rate of spontaneous remission and fluctuating courses that contribute to outcomes, even with placebo. Table 3 lists drugs shown to have probable effectiveness across most placebo-controlled trials.

Naltrexone is used in the USA for alcohol rehabilitation, but is not licensed in the UK. This opioid antagonist decreases drinking in animals, and might help alcohol-dependent patients by diminishing craving and feelings of reward or pleasure when drinking. Given at 50–100 mg per day (or 150 mg three times a week), most studies report a longer time before relapse or lower alcohol intake on drinking days, with an outcome that is improved by a modest 20%. Some studies show a possible link between response to this drug and a person’s family history or µ-opioid-receptor genotype. Naltrexone can also be given as an intramuscular dose of 380 mg once a month, which, although more expensive, optimises compliance and has shown some promising results. Naltrexone’s side-effects include increased liver function tests, possible interference with pain control, and a potential blunting of mood.

Acamprosate is structurally similar to γ-aminobutyric acid, but with actions that inhibit the N-methyl-D-aspartic acid–glutamate receptor hyperactivity that occurs during protracted withdrawal. Most trials report that this drug increases the time to relapse, decreases the number of drinks per drinking day, or helps to maintain abstinence, with a rate of improved outcome similar to naltrexone. Side-effects include gastrointestinal upset and diarrhoea, which rarely cause patients to stop use of the drug. Combined naltrexone and acamprosate might be slightly better than either drug alone, although not all studies agree.

Disulfiram and calcium carbimide inhibit ALDH2 so that acetaldehyde increases dramatically after drinking, to produce nausea, vomiting, diarrhoea, rapid heart rate, and changes in blood pressure. Several weeks are needed after discontinuation of disulfiram for ALDH to return to normal; calcium carbimide has a more rapid onset and a shorter action. More than 500 mg per day of disulfiram are needed for maximum inhibition of ALDH, but that dose would produce unacceptable side-effects. This drug is best given under observation, to ensure compliance. The efficacy of ALDH inhibitors is controversial, perhaps because the anticipation of adverse effects after drinking could contribute to the outcome even with placebo. At the same time, disulfiram has both relatively benign side-effects (a bad taste, sedation, a rash, and temporary impotence) and rarer but more severe sequelae (neuropathies, depression, psychotic symptoms, an increase in liver function tests, and severe hepatitis). In one study, the risk of fatal disulfiram-related hepatitis was one in every 25 000 patients per year, with as many as one in 200 patients per year having adverse drug reactions. The potentially severe reaction to alcohol in individuals who take these drugs precludes their prescription to patients with diabetes, heart disease, stroke, psychosis, or those who are pregnant; they should

<table>
<thead>
<tr>
<th>Drug</th>
<th>Usual dose*</th>
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<tbody>
<tr>
<td>Naltrexone</td>
<td></td>
</tr>
<tr>
<td>Oral</td>
<td>50–100 mg per day105,106</td>
</tr>
<tr>
<td>Intramuscular injection</td>
<td>380 mg per month107</td>
</tr>
<tr>
<td>Acamprosate</td>
<td>666 mg three times per day108,109</td>
</tr>
<tr>
<td>Naltrexone+acamprosate</td>
<td>Same doses as above105</td>
</tr>
<tr>
<td>Disulfiram</td>
<td>250 mg per day111,112</td>
</tr>
</tbody>
</table>

*These drugs are usually prescribed for 3–12 months.

Table 3: Drugs for rehabilitation of alcohol-use disorders

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be used with caution for patients who have liver disease.\textsuperscript{118}

No other drugs have yet been shown to be more effective than placebo for alcohol-use disorders in sufficient large and broad-based studies.\textsuperscript{19,20} However, a 14-week placebo-controlled trial of 300 mg per day of the anticonvulsant topiramate reported up to a 16% reduction in heavy drinking days, although the rate of modest side-effects was high.\textsuperscript{21}

Conclusions

The criteria for alcohol dependence are reliable, patients face substantial morbidity and mortality, and resources are available to identify patients with unhealthy drinking or alcohol-use disorders, and to offer treatment. Treatment can include motivational interviewing to help people to evaluate their situations, brief interventions to facilitate more healthy behaviours, cognitive-behavioural therapies, and the judicious use of drugs to improve outcomes for alcohol-use disorders.

Conflict of interest statement

MAS directs the Alcohol Medical Scholars Program, which is funded through a grant to the University of California, San Diego Medical School, from the Anheuser-Busch Corporation, and has served as a temporary adviser to several pharmaceutical companies, including Lipha, Cephalon, and Alkermes, but is no longer on any official advisory boards or speakers panels.

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