

Alcohol-use disorders

Marc A Schuckit

Lancet 2009; 373: 492–501

Published Online

January 26, 2009

DOI:10.1016/S0140-6736(09)60009-X

See [Editorial](#) page 433

Department of Psychiatry,
University of California,
San Diego, CA, USA

(M A Schuckit MD); and VA

San Diego Healthcare System,
San Diego, CA, USA

(M A Schuckit)

Correspondence to:

Dr Marc A Schuckit, VA San Diego
Healthcare System, 3350 La Jolla
Village Drive, San Diego,
CA 92161-2002, USA
mschuckit@ucsd.edu

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,¹ and dependence or harmful use.² 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.³ 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.^{3–5} 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.^{3–5}

As many as 80% of men and 60% of women in developed countries drink at some time during their lives.⁴ 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.⁵ 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.^{4,6} 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.^{4,7,8} The risk of developing an alcohol-use disorder in the previous year is about 10% overall.^{4,7,8}

Only about a quarter of people with alcohol-use disorders ever seek help for these conditions, with higher proportions for women than men.^{4,7,9} 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.⁸ 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)¹ and the 10th International Classification of

Search strategy and selection criteria

This Seminar was based on a comprehensive survey of PubMed between January, 2000, and March, 2007, excluding papers not published in English. The search terms used was “alcoholism”, in combination with “criteria”, “course” “treatment”, and “etiology”.

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.^{1,10,12} 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.^{3,13} 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.¹³ 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.^{13,15,16} Four of the AUDIT items are used for the shorter fast alcohol screening test (FAST), which has similar accuracy to the full AUDIT test.¹⁷ 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.

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).^{3,17} 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.¹⁸ 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.¹⁹ 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.¹⁷ 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.

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

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.

Table 1: Alcohol use disorders identification test (AUDIT)

available in most chemistry laboratories, is inexpensive, and has sensitivities and specificities that approach 60% in men, although the sensitivity might be closer to 50% in women.²⁰ A second useful test is for carbohydrate-deficient transferrin, which measures a change in the structure of a proportion of transferrin that is likely to occur with heavy drinking over a long period; a result of 20 units per L or more indicates heavy drinking.^{3,21,22} The sensitivities for identification of heavy drinking and alcohol-use disorders range from 30% to 75% across studies (with higher figures for men), and specificities are as high as 90%, although results might be difficult to interpret in the context of iron deficiency.^{20,23,24} Tests of liver function that measure alanine and aspartate aminotransferases can identify heavy drinking and alcohol-use disorders with sensitivities of between 25% and 45% and specificities as high as 90%.²⁰ A ratio of aspartate aminotransferase to alanine aminotransferase of greater than 2, especially if concentrations for each of these enzymes do not exceed 400 units per L, raises the possibility of alcoholic hepatitis.^{3,25} Finally, very high blood alcohol (eg, 35 mmol/L or higher) should raise suspicion of alcohol dependence, especially if encountered in emergency departments and trauma-room settings.¹⁸

Clinical course

The course of an alcohol-use disorder is as predictable as most medical or psychiatric disorders, with differences across subgroups (eg, men vs women) that reflect more general characteristics of each group in society.³ However, most studies of the clinical course and treatment of alcohol-use disorders focus on patients who do not have major comorbid psychiatric disorders. Therefore, these issues are not as well understood in people with severe anxiety, mood, or psychotic disorders. Overall, women who have alcohol-use disorders have a slightly shorter time between onset of problems and seeking help than men do, and are less likely to be violent or arrested.^{3,26} Similarly, compared with younger people, older people with alcohol-use disorders have more medical problems, less violence, and are less likely to be employed.²⁷

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.^{3,30} 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.^{3,30} 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,^{3,32} 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.^{3,33} However, many of these forms of psychopathology are substance-induced, and likely to improve within 2–4 weeks of abstinence.³³ 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).^{3,29} 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.³⁴ These comorbidities can make treatment more difficult.³⁵

As is true of many chronic relapsing disorders (eg, hypertension), the course of alcohol-use disorders

fluctuates over time.³ 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.³⁶ 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.^{3,9,36–38}

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.^{39,40} 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.⁴⁰

Continued alcohol problems increase the rate of early death by three or four times.^{26,41,42} 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.^{43,44} 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.^{43,44}

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.^{43,45} 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.⁴⁶ Second, gene forms associated with impulsivity, disinhibition, and

	Suggested cut value
Gamma glutamyltransferase (GGT)	>35 u/L
Carbohydrate deficient transferin (CDT)	>20 G/L or >2.6%
Alanine aminotransferase (ALT)	>67 u/L
Aspartate aminotransferase (AST)	>65 u/L

Table 2: State markers of heavy drinking

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.^{29,47} Relevant polymorphisms include variations in receptors for γ -aminobutyric acid (eg, *GABRA2*), acetylcholine (eg, *CHRM2*), and dopamine (eg, *DRD2*).^{48–50} 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.^{43,51} 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*).^{52,53} Additional genetic mechanisms might operate via genes that regulate dopamine-reward systems.⁵⁴

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).³

At least two variations of ADH genes (*ADH1B*2* and *ADH1C*1*) produce a slightly more rapid breakdown of alcohol, and therefore potentially faster production of acetaldehyde.⁵⁵ *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*2* mutation that results in much more acetaldehyde after drinking than normal.^{55,56} 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

brain.^{3,57} These sedating effects cause muscle relaxation, somnolence, and intoxicated feelings. Adaptations in these systems are prominent in the development of tolerance to alcohol, and diminished activity of γ -aminobutyric acid contributes to anxiety and insomnia during acute and protracted alcohol withdrawal.^{57,58} Having an alcoholic drink also diminishes the activity of the stimulating glutamate N-methyl-D-aspartate receptor system, and withdrawal is associated with enhanced activity of these pathways.⁵⁹

Drinking releases dopamine and increases activity at related synapses.^{54,60} Such brain changes, especially in the nucleus accumbens and the ventral tegmental areas, contribute to the rewarding effects of this drug, and might contribute to both craving and disinhibition during intoxication.^{50,60} Drinking also enhances the release of opioid peptides (eg, β endorphin) that are not only rewarding but also associated with dopamine release, which potentially contributes to sensitisation to alcohol and craving.^{61,62}

Alcohol also stimulates the serotonergic system; low concentrations of serotonin in the synapse are associated with a diminished effect of alcohol and, perhaps, a propensity towards consumption of this drug.⁶³ Additional effects are seen for epinephrine,⁶⁴ cannabinoid receptors,⁶⁵ adenosine systems,⁶⁶ acetylcholine,⁶⁷ and stress-related systems such as corticotropin-releasing hormone.⁶⁸

Alcohol-related organ damage

In the nervous system, the severe anterograde amnesia of Wernicke–Korsikoff syndrome is seen in fewer than 1% of those with alcohol dependence (usually in the context of transketolase deficiency).^{3,69} However, mild anterograde amnesias (alcoholic blackouts) are common,⁷⁰ as are temporary cognitive deficits, including difficulties in problem-solving, abstraction, memory, and learning.⁷¹ Cognitive deficits, such as problems with memory, learning, and problem-solving, usually reverse within weeks to months of abstinence, as do related brain-imaging findings such as sulcal widening and ventricular enlargement.^{26,72} Other common problems with heavy drinking include intensification of sleep apnoea, trouble falling asleep, and frequent awakenings in the second half of the night, complaints that enhance the risk of a return to heavy drinking.^{73,74} Also, 15% of those with alcohol dependence develop peripheral neuropathy (alcoholic polyneuropathy) associated with numbness, paraesthesias, and decreases in vibration and position sense, especially in the legs.⁷⁵

Heavy drinking affects the cardiovascular system. Three or more drinks per day increase both blood pressure and LDL cholesterol, and also enhance the risk of cardiomyopathy.^{76,77} Heavy drinking is associated with temporary arrhythmias (so-called holiday heart), which are usually atrial in origin, but sometimes ventricular and associated with increased dispersion of QT intervals.⁷⁷

Cancer is the second leading cause of early death in people with alcohol-use disorders, even after controlling for the effect of smoking.⁷⁸ 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.^{3,78} 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.^{79,80} Alcohol-induced immune dysfunction can exacerbate the course of hepatitis C and complicate the treatment of AIDS.^{81,82} Furthermore, heavy drinking is associated with a decrease in bone density, an enhanced vulnerability to hip fractures,⁸³ and alterations in blood-producing systems that decrease white blood cells, platelets, and granulocyte mobility.^{25,84}

Additional problems include heavy drinking associated with fatal accidents.³ 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 deficits; syndactyly; and mental retardation.^{85,86}

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.^{87,88} 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.^{26,36,37,39,89} Although anyone in treatment might do well, better outcomes are associated with more intense treatment,^{87,89} less severe alcohol problems, less cognitive impairment, higher self-confidence about outcome, and fewer comorbid psychiatric disorders.^{36,37,90} 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.⁹¹ 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.^{91–93} 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.^{94,95}

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.^{92,93} Motivational interviewing or brief interventions can be used in sessions of 15–30 min, and the time spent generates more savings than costs.⁹⁶ 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.^{97,98} 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.^{3,99} 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 5.³ A syndrome associated with protracted abstinence can persist for several months;³ 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

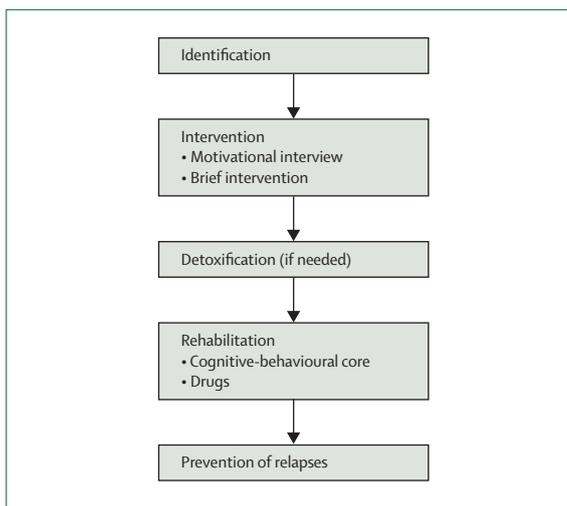


Figure: Stages of treatment

intensity of withdrawal can be closely monitored, including through the clinician-observer-based Clinical Institute Withdrawal Assessment for alcoholism scale.^{3,100}

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.¹⁰¹ Withdrawal symptoms are most safely and efficiently diminished by prescribing depressants (eg, drugs that boost γ -aminobutyric acid); benzodiazepines are the most cost-effective approach.^{17,101} 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.³

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.³ 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 (eg, 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.^{3,99} Alternative

Usual dose*	
Naltrexone	
Oral	50–100 mg per day ^{105,106}
Intramuscular injection	380 mg per month ¹⁰⁷
Acamprosate	666 mg three times per day ^{105,108,109}
Naltrexone+acamprosate	Same doses as above ¹¹⁰
Disulfiram	250 mg per day ^{3,111,112}
*These drugs are usually prescribed for 3–12 months.	
Table 3: Drugs for rehabilitation of alcohol-use disorders	

approaches include higher doses on day 1 and more rapid decreases, and a more fluid sliding scale with doses triggered by direct scoring of symptoms,¹⁰¹ but these are more complex and might be better reserved for specialists.

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.³ 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.^{37,102} 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.³ 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.¹⁰³ Although outpatient rehabilitation is often successful, the better outcome with more intensive treatment¹⁰⁴ 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.³ 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.^{105,108} 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%.^{3,105,106} Some studies show a possible link between response to this drug and a person's family history or μ -opioid-receptor genotype.^{113,114} 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.¹⁰⁷ 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.^{105,109} 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.^{108,115} 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.^{108,110}

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.^{111,112} 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.^{3,112} This drug is best given under observation, to ensure compliance.^{3,112,116} 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).^{3,112,117} 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.¹¹² 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

be used with caution for patients who have liver disease.^{3,118}

No other drugs have yet been shown to be more effective than placebo for alcohol-use disorders in sufficient large and broad-based studies.^{119,120} 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.¹²¹

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.

Acknowledgments

This work was supported by the Veterans Affairs Research Service (NIAAA grants 2R01 AA05526, U10 AA08401, and 5R01AA15760), and by funds provided by the State of California for medical research on alcohol and substance abuse through the University of California, San Francisco.

References

- American Psychiatric Association. Diagnostic and statistical manual of mental disorders—text revision (DSM-IV). 4th edn. Washington, DC, USA: American Psychiatric Association, 2000.
- WHO. ICD-10 classification of mental and behavioural disorders: clinical descriptions and diagnostic guidelines. Geneva, Switzerland: World Health Organization, 1992.
- Schuckit MA. Drug and alcohol abuse: a clinical guide to diagnosis and treatment, 6th edn. New York, USA: Springer, 2006.
- Teesson M, Baillie A, Lynskey A, Manor B, Degenhardt L. Substance use, dependence and treatment seeking in the United States and Australia: a cross-national comparison. *Drug Alcohol Depend* 2006; **81**: 149–55.
- Saxena S. Alcohol, Europe, and developing countries. *Addiction* 1997; **92** (suppl 1): 43–48.
- Johnston LD, O'Malley PM, Bachman JG, Schulenberg JE. Monitoring the future national survey results on drug use, 1975–2006: Vol 1, Secondary school students (NIH Publication No. 06-5727). Bethesda, MD, USA: National Institute on Drug Abuse, 2007.
- Hasin DS, Stinson FS, Ogburn E, et al. Prevalence, correlates, disability, and comorbidity of DSM-IV alcohol abuse and dependence in the United States. *Arch Gen Psychiatry* 2007; **64**: 830–42.
- Mertens J, Weisner C, Ray G, Fireman B, Walsh K. Hazardous drinkers and drug users in HMO primary care: prevalence, medical conditions and costs. *Alcohol Clin Exp Res* 2005; **29**: 989–98.
- Dawson DA, Grant BF, Stinson FS, et al. Recovery from DSM-IV alcohol dependence: United States, 2001–2002. *Addiction* 2005; **100**: 281–92.
- Schuckit MA, Smith TL, Danko GP, et al. Prospective evaluation of the four DSM-IV criteria for alcohol abuse in a large population. *Am J Psychiatry* 2005; **162**: 350–60.
- Hasin D, Grant BF, Cottler L, et al. Nosological comparisons of alcohol and drug diagnoses: a multisite, multi-instrument international study. *Drug Alcohol Depend* 1997; **47**: 217–26.
- Hasin D, Li Q, McCloud S, Endicott J. Agreement between DSM-III, DSM-III-R, DSM-IV and ICD-10 alcohol diagnoses in US community-sample heavy drinkers. *Addiction* 1996; **91**: 1517–27.
- Rush AJ Jr, Pincus HA, First MB, et al. Handbook of Psychiatric Measures: Task Force for the Handbook of Psychiatric Measures. Washington, DC, USA: American Psychiatric Association, 2000.
- Saremi A, Hanson RL, Williams DE, et al. Validity of the CAGE questionnaire in an American Indian population. *J Stud Alcohol* 2001; **62**: 294–300.
- Reinert DF, Allen JP. The alcohol use disorders identification test: an update of research findings. *Alcohol Clin Exp Res* 2007; **31**: 185–99.
- Berner MM, Kriston L, Bentele M, Harter M. The Alcohol Use Identification Test for detecting at-risk drinking: a systematic review and meta-analysis. *J Stud Alcohol Drugs* 2007; **68**: 461–73.
- Hietala J, Kiovisto H, Anttila P, Niemela O. Comparison of the combined marker GGT-CDT and the conventional laboratory markers of alcohol abuse in heavy drinkers, moderate drinkers and abstainers. *Alcohol Alcohol* 2006; **41**: 528–33.
- Parker AJR, Marshall EJ, Ball DM. Diagnosis and management of alcohol use disorders. *BMJ* 2008; **336**: 496–501.
- Irwin M, Baird S, Smith T, Schuckit MA. Use of laboratory tests to monitor heavy drinking by alcoholic men discharged from a treatment program. *Am J Psychiatry* 1988; **145**: 595–99.
- Conigrave KM, Degenhardt LJ, Whitfield JB, et al. CDT, GGT, and AST as markers of alcohol use: The WHO/ISBRA Collaborative Project. *Alcohol Clin Exp Res* 2002; **26**: 332–39.
- Anton RF, Youngblood M. Factors affecting %CDT status at entry into a multisite clinical treatment trial: experience from the COMBINE study. *Alcohol Clin Exp Res* 2006; **30**: 1878–83.
- Schellenberg F, Schwan R, Mennetrey L, et al. Dose-effect relation between daily ethanol intake in the range 0–70 grams and %CDT value: validation of a cut-off value. *Alcohol Alcohol* 2005; **40**: 532–34.
- Alte D, Lüdemann J, Piek M, et al. Distribution and dose response of laboratory markers to alcohol consumption in a general population: Results of the Study of Health in Pomerania (SHIP). *J Stud Alcohol* 2003; **64**: 75–82.
- Niemela O. Biomarkers in alcoholism. *Clin Chim Acta* 2007; **377**: 39–49.
- Maddrey WC. Alcohol-induced liver disease. *Clin Liver Dis* 2000; **4**: 115–31.
- Mann K, Schafer DR, Langle G, Ackermann K, Croissant B. The long-term course of alcoholism, 5, 10 and 16 years after treatment. *Addiction* 2005; **100**: 797–805.
- Lemke S, Schutte K, Brennan P, Moos R. Sequencing the lifetime onset of alcohol-related symptoms in older adults: is there evidence for disease progression? *J Stud Alcohol* 2005; **66**: 756–65.
- Schuckit MA, Smith TL, Pierson J, et al. Externalizing disorders in the offspring from the San Diego Prospective Study of alcoholism. *J Psychiatric Research* 2008; **46**: 644–52.
- Babor TF, Hofmann M, DelBoca FK, et al. Types of alcoholics, I: Evidence for an empirically derived typology based on indicators of vulnerability and severity. *Arch Gen Psychiatry* 1992; **49**: 599–608.
- Kuperman S, Chan G, Kramer JR, et al. Relationship of age of first drink to child behavioral problems and family psychopathology. *Alcohol Clin Exp Res* 2005; **29**: 1869–76.
- Harford T, Ye-Yi H, Hilton M. Alcohol abuse and dependence in college and noncollege samples: a ten-year prospective follow-up in a national survey. *J Stud Alcohol* 2006; **67**: 803–09.
- Clark DB. The natural history of adolescent alcohol use disorders. *Addiction* 2004; **99**: 5–22.
- Schuckit MA. Comorbidity between substance use disorders and psychiatric conditions. *Addiction* 2006; **101**: 76–88.
- Li T-K. The biological bases of nicotine and alcohol co-addiction. *Biol Psychiatry* 2007; **61**: 1–3.
- Hughes JR, Kalman D. Do smokers with alcohol problems have more difficulty quitting? *Drug Alcohol Depend* 2006; **82**: 91–102.
- Maisto S, Clifford P, Stout R, Davis C. Drinking in the year after treatment as a predictor of three-year drinking outcomes. *J Stud Alcohol* 2006; **67**: 823–32.

- 37 Bodin M, Romelsjö A. Predictors of abstinence and nonproblem drinking after 12-step treatment in Sweden. *J Stud Alcohol* 2006; **67**: 139–46.
- 38 Cox WM, Rosenberg H, Hazel C, et al. United Kingdom and United States healthcare providers recommendations of abstinence versus controlled drinking. *Alcohol Alcohol* 2004; **39**: 130–34.
- 39 Moos RF, Moos BS. Rates and predictors of relapse after natural and treated remission from alcohol use disorders. *Addiction* 2006; **101**: 212–22.
- 40 Rumpf HJ, Bischof G, Hapke U, Meyer C, John U. Stability of remission from alcohol dependence without formal help. *Alcohol Alcohol* 2006; **41**: 311–14.
- 41 Norstrom T. Per capita alcohol consumption and all-cause mortality in Canada, 1950–1998. *Addiction* 2004; **99**: 1274–78.
- 42 Rivara FP, Garrison MM, Ebel B, McCarty CA, Christakis DA. Mortality attributable to harmful drinking in the United States, 2000. *J Stud Alcohol* 2004; **65**: 530–36.
- 43 Schuckit MA, Smith TL. An evaluation of the level of response to alcohol, externalizing symptoms, and depressive symptoms as predictors of alcoholism. *J Stud Alcohol* 2006; **67**: 215–27.
- 44 Timberlake DS, Hopfer CJ, Rhee SH, et al. College attendance and its effect on drinking behaviors in a longitudinal study of adolescents. *Alcohol Clin Exp Res* 2007; **31**: 1020–30.
- 45 Nurnberger JI Jr, Bierut LJ. Seeking the connections: alcoholism and our genes. *Sci Am* 2007; **296**: 46–53.
- 46 Cook TAR, Luczak SE, Shea SH, et al. Association of ALDH2 and ADH1B genotypes with response to alcohol in Asian Americans. *J Stud Alcohol* 2005; **66**: 196–204.
- 47 Kendler K, Kuo PWT, Kalsi G, et al. A joint genomewide linkage analysis of symptoms of alcohol dependence and conduct disorder. *Alcohol Clin Exp Res* 2006; **30**: 1972–77.
- 48 Dick DM, Bierut L, Hinrichs A, et al. The role of GABRA2 in risk for conduct disorder and alcohol and drug dependence across developmental stages. *Behav Genet* 2006; **36**: 577–90.
- 49 Jones KA, Porjesz B, Almasy L, et al. A cholinergic receptor gene (CHRM2) affects event-related oscillations. *Behav Genet* 2006; **36**: 627–39.
- 50 Laucht M, Becker K, Blomeyer D, Schmidt M. Novelty seeking involved in mediating the association between the dopamine D4 receptor gene exon III polymorphism and heavy drinking in male adolescents: results from a high-risk community sample. *Biol Psychiatry* 2007; **61**: 87–92.
- 51 Schuckit MA. Vulnerability factors for alcoholism. In Davis K, ed. *Neuropsychopharmacology: the fifth generation of progress*. Baltimore, MD, USA: Lippincott Williams & Wilkins 2002, 1399–1411.
- 52 Hinckers AS, Laucht M, Schmidt MH, et al. Low level of response to alcohol as associated with serotonin transporter genotype and high alcohol intake in adolescents. *Biol Psychiatry* 2006; **60**: 282–87.
- 53 Schuckit MA, Smith TL, Kalmijn J. The search for genes contributing to the low level of response to alcohol: patterns of findings across studies. *Alcohol Clin Exp Res* 2004; **28**: 1449–58.
- 54 Volkow N, Wang G, Begleiter H, et al. High levels of dopamine D2 receptors in unaffected members of alcoholic families. *Arch Gen Psychiatry* 2006; **63**: 999–1008.
- 55 Duranceaux NCE, Schuckit MA, Eng MY, et al. Associations of variations in alcohol dehydrogenase genes with the level of response to alcohol in non-Asians. *Alcohol Clin Exp Res* 2006; **30**: 1470–78.
- 56 Dickson P, James M, Heath A, et al. Effects of variation at the ALDH2 locus on alcohol metabolism, sensitivity, consumption, and dependence in Europeans. *Alcohol Clin Exp Res* 2006; **30**: 1093–1100.
- 57 Krystal J, Staley J, Mason G, et al. Gamma-aminobutyric acid type A receptors and alcoholism. *Arch Gen Psychiatry* 2006; **63**: 957–68.
- 58 Enoch M, Schwartz L, Albaugh B, Virkkunen M, Goldman D. Dimensional anxiety mediates linkage of GABRA2 haplotypes with alcoholism. *Am J Med Genet* 2006; **141**: 599–607.
- 59 Schumann G, Saam C, Heinz A, Mann K, Treutlein J. The NMDA receptor system: genetic risk factor for alcoholism. *Nervenarzt* 2005; **76**: 1355–62.
- 60 Kalivas K, Volkow N. The neural basis of addiction: a pathology of motivation and choice. *Am J Psychiatry* 2005; **162**: 1403–13.
- 61 van den Wildenberg E, Wiers R, Dessers J, et al. A functional polymorphism of the u-opioid receptor gene (OPRM1) influences cue-induced craving for alcohol in male heavy drinkers. *Alcohol Clin Exp Res* 2007; **31**: 1–10.
- 62 Pastor R, Aragon C. The role of opioid receptor subtypes in the development of behavioral sensitization to ethanol. *Neuropsychopharmacology* 2006; **31**: 1489–99.
- 63 Barr C, Newman T, Becker M, et al. Serotonin transporter gene variation is associated with alcohol sensitivity in rhesus macaques exposed to early-life stress. *Alcohol Clin Exp Res* 2005; **27**: 812–17.
- 64 Weinschenker D, Schroeder JP. There and back again: a tale of norepinephrine and drug addiction. *Neuropsychopharmacology* 2007; **32**: 1433–1451.
- 65 Blednov YA, Cravatt BF, Boehn SL II, et al. Role of endocannabinoids in alcohol consumption and intoxication: studies of mice lacking fatty acid amide hydrolase. *Neuropsychopharmacology* 2007; **32**: 1570–82.
- 66 Hamilton SP, Slager S, Baisre de Leon A, et al. Evidence for a genetic linkage between a polymorphism in the adenosine 2A receptor and panic disorder. *Neuropsychopharmacology* 2004; **29**: 558–65.
- 67 Borghese CM, Ali DN, Bleck V, et al. Acetylcholine and alcohol sensitivity of neuronal nicotinic acetylcholine receptors: mutations in transmembrane domains. *Alcohol Clin Exp Res* 2002; **26**: 1764–72.
- 68 Witkiewitz K. Lapses following alcohol treatment: modeling and falls from the wagon. *J Alcohol Drugs* 2008; **69**: 594–604.
- 69 Thomson AD, Marshall EJ. The natural history and pathophysiology of Wernicke's encephalopathy and Korsakoff's psychosis. *Alcohol Alcohol* 2006; **41**: 151–58.
- 70 Nelson EC, Heath AC, Bucholz KK, et al. Genetic epidemiology of alcohol-induced blackouts. *Arch Gen Psychiatry* 2004; **61**: 257–63.
- 71 Pitel AL, Beaunieux H, Witkowski T, et al. Genuine episodic memory deficits and executive dysfunctions in alcoholic subjects early in abstinence. *Alcohol Clin Exp Res* 2007; **31**: 1169–1178.
- 72 Bartsch AJ, Homola G, Biller A. Manifestations of early brain recovery associated with abstinence from alcoholism. *Brain* 2007; **130**: 36–47.
- 73 Van Reen E, Jenni OG, Carskadon MA. Effects of alcohol on sleep and the sleep electroencephalogram in healthy young women. *Alcohol Clin Exp Res* 2006; **30**: 974–81.
- 74 Conroy DA, Arnedt JT, Brower KJ, et al. Perception of sleep in recovering alcohol-dependent patients with insomnia: relationship with future drinking. *Alcohol Clin Exp Res* 2006; **30**: 1992–99.
- 75 Peters TJ, Kotowicz J, Nyka W, et al. Treatment of alcoholic polyneuropathy with vitamin B complex: a randomized controlled trial. *Alcohol Alcohol* 2006; **41**: 636–42.
- 76 Fatjó F, Sancho-Bru P, Fernández-Solá J, et al. Up-regulation of myocardial L-type Ca²⁺ channel in chronic alcoholic subjects without cardiomyopathy. *Alcohol Clin Exp Res* 2007; **31**: 1099–105.
- 77 Uyarel H, Ozdol C, Gencer AM, Okmen E, Cam N. Acute alcohol intake and QT dispersion in healthy subjects. *J Stud Alcohol* 2005; **66**: 555–58.
- 78 Polednak AP. Recent trends in incidence rates for selected alcohol-related cancers in the United States. *Alcohol Alcohol* 2005; **40**: 234–38.
- 79 Ramstedt M. Alcohol and pancreatitis mortality in the population level: experiences from 14 western countries. *Addiction* 2004; **99**: 1255–61.
- 80 Szucs S, Sarvary A, McKee M, Adany R. Could the high level of cirrhosis in central and eastern Europe be due partly to the quality of alcohol consumed? An exploratory investigation. *Addiction* 2005; **100**: 536–42.
- 81 Rosenbloom MJ, Sullivan EV, Sassoon SA, et al. Alcoholism, HIV infection, and their comorbidity: factors affecting self-rated health-related quality of life. *J Stud Alcohol Drugs* 2007; **68**: 115–25.
- 82 Romero-Gomez M, Grande L, Nogales MC, et al. Chronic alcohol use enhances the hepatitis C virus load in the liver. *Alcohol Research* 2002; **7**: 66.
- 83 Kaukonen JP, Luthje IN, Luthje P, et al. Acute alcohol use among patients with acute hip fractures: a descriptive incidence study in southeastern Finland. *Alcohol Alcohol* 2006; **41**: 345–48.
- 84 Palmieri VO, Cicco G, Minerva F, et al. Red blood cells (RBC) deformability and aggregability: alterations in alcoholism. *Adv Exp Med Biol* 2006; **578**: 125–31.

- 85 Alati R, Mamun AA, Williams GM. In utero alcohol exposure and prediction of alcohol disorders in early adulthood. *Arch Gen Psychiatry* 2006; **63**: 1009–16.
- 86 Kodituwakku PW, Adams CM, Hay A, et al. Letter and category fluency in children with fetal alcohol syndrome from a community in South Africa. *J Stud Alcohol* 2006; **67**: 502–09.
- 87 Stecker T, Curran GM, Han X, Booth BM. Patterns of health services use associated with Veterans Affairs outpatient substance-use treatment. *J Stud Alcohol Drugs* 2007; **68**: 510–18.
- 88 Smith TL, Volpe FR, Hashima JN, Schuckit MA. Impact of a stimulant-focused enhanced program on the outcome of alcohol- and/or stimulant-dependent men. *Alcohol Clin Exp Res* 1999; **23**: 1772–79.
- 89 Bottlender M, Soyka M. Outpatient alcoholism treatment: predictors of outcome after 3 years. *Drug Alcohol Depend* 2005; **80**: 83–89.
- 90 McKellar JD, Harris AH, Moos RH. Predictors of outcomes for patients with substance-use disorders five years after treatment dropout. *J Stud Alcohol* 2006; **67**: 685–93.
- 91 Heather N, Brodie J, Wale S, et al. A randomized controlled trial of moderation-oriented cue exposure. *J Stud Alcohol* 2000; **61**: 561–70.
- 92 Carroll K, Ball S, Nich C, et al. Motivational interviewing to improve treatment engagement and outcome in individuals seeking treatment for substance abuse: a multisite effectiveness study. *Drug Alcohol Depend* 2006; **81**: 301–12.
- 93 Vasilaki E, Hosier S, Cox M. The efficacy of motivational interviewing as a brief intervention for excessive drinking: a meta-analytic review. *Alcohol Alcohol* 2006; **41**: 328–35.
- 94 Crawford MJ, Patton R, Touquet R, et al. Screening and referral for brief intervention of alcohol-misusing patients in an emergency department: a pragmatic randomised controlled trial. *Lancet* 2004; **364**: 1334–39.
- 95 Moyer A, Finney JW, Swearingen CE, et al. Brief interventions for alcohol problems: a meta-analytic review of controlled investigations in treatment-seeking and non-treatment-seeking populations. *Addiction* 2002; **97**: 279–92.
- 96 Mundt M, French M, Roebuck M, Manwell L, Barry K. Brief physician advice for problem drinking among older adults: an economic analysis of costs and benefits. *J Stud Alcohol* 2005; **66**: 389–94.
- 97 Babor T, Higgins-Biddle J, Dauser D, et al. Brief interventions for at-risk drinking: patient outcomes and cost-effectiveness in managed care organizations. *Alcohol Alcohol* 2006; **41**: 624–31.
- 98 Ståhlbrandt H, Johnsson KO, Berglund M. Two-year outcome of alcohol interventions in Swedish university halls of residence: a cluster randomized trial of a brief skills training program, twelve-step-influenced intervention, and controls. *Alcohol Clin Exp Res* 2007; **31**: 458–66.
- 99 Sannibale C, Fucito L, O'Connor D, Curry K. Process evaluation of an out-patient detoxification services. *Drug Alcohol Review* 2005; **24**: 475–81.
- 100 Reoux JP, Miller K. Routine hospital detoxification practice compared to symptom triggered management with an objective withdrawal scale (CIWA-Ar). *J Addiction* 2000; **9**: 135–44.
- 101 Lingford-Hughes AR, Welch S, Nutt DJ. Evidence-based guidelines for the pharmacological management of substance misuse, addiction and comorbidity: recommendations from the British Association for Psychopharmacology. *J Psychopharmacol* 2004; **18**: 293–335.
- 102 Humphreys K, Moos R. Encouraging posttreatment self-help group involvement to reduce demand for continuing care services: two-year clinical and utilization outcomes. *Alcohol Clin Exp Res* 2007; **31**: 64–68.
- 103 Witkiewitz K, Marlatt G. Relapse prevention for alcohol and drug problems. *Am Psychol* 2004; **59**: 224–35.
- 104 Moos R, Finney J, Moos B. Inpatient substance abuse care and the outcome of subsequent community residential and outpatient care. *Addiction* 2000; **95**: 833–46.
- 105 Kranzler H, Koob G, Gastfriend D, Swift R, Willenbring M. Advances in the pharmacotherapy of alcoholism: Challenging misconceptions. *Alcohol Clin Exp Res* 2006; **30**: 272–81.
- 106 Srisurapanont M, Jarusuraisin N. Naltrexone for the treatment of alcoholism: a meta-analysis of randomized controlled trials. *Int J Neuropsychopharmacol* 2005; **8**: 267–80.
- 107 O'Malley SS, Garbutt JC, Gastfriend DR, Dong Q, Kranzler HR. Efficacy of extended release naltrexone in alcohol-dependent patients who are abstinent prior to treatment. *J Clin Psychopharmacology* 2007; **27**: 507–12.
- 108 Feeney G, Connor J, Young R, Tucker J, McPherson A. Combined acamprosate and naltrexone, with cognitive behavioural therapy is superior to either medication alone for alcohol abstinence: a single centres experience with pharmacotherapy. *Alcohol Alcohol* 2006; **41**: 321–27.
- 109 Mason B, Goodman A, Chabac S, Leher P. Effect of oral acamprosate on abstinence in patients with alcohol dependence in a double-blind, placebo-controlled trial: the role of patient motivation. *J Psychiatr Res* 2006; **40**: 383–93.
- 110 Kiefer F, Jahn H, Tarnaske T, et al. Comparing and combining naltrexone and acamprosate in relapse prevention of alcoholism: a double-blind, placebo-controlled study. *Arch Gen Psychiatry* 2003; **60**: 92–99.
- 111 Suh JJ, Pettinati HM, Kampman KM, O'Brien CP. The status of disulfiram: a half of a century later. *J Clin Psychopharmacol* 2006; **26**: 290–302.
- 112 Fuller FK, Gordis E. Does disulfiram have a role in alcoholism treatment today? *Addiction* 2004; **99**: 21–24.
- 113 Gelernter J, Gueorgulieva R, Kranzler HR, et al. Opioid receptor gene (OPRM1, OPRK1, and OPRD1) variants and response to naltrexone treatment for alcohol dependence: results from the VA Cooperative Study. *Alcohol Clin Exp Res* 2007; **31**: 555–63.
- 114 Krishnan-Sarin S, Krystal JH, Shi J, et al. Family history of alcoholism influences naltrexone-induced reduction in alcohol drinking. *Biol Psychiatry* 2007; **62**: 694–97.
- 115 Mann K, Leher P, Morgan MY. The efficacy of acamprosate in the maintenance of abstinence in alcohol-dependent individuals: results of a meta-analysis. *Alcohol Clin Exp Res* 2004; **28**: 51–63.
- 116 Krampe H, Stawicki S, Wagner T, et al. Follow-up of 180 alcoholic patients for up to 7 years after outpatient treatment: impact of alcohol deterrents on outcome. *Alcohol Clin Exp Res* 2006; **30**: 86–95.
- 117 Verge C, Lucena MI, López-Torres E, et al. Adverse hepatic reactions associated with calcium carbimide and disulfiram therapy: is there still a role for these drugs? *World J Gastroenterol* 2006; **21**: 5078–80.
- 118 Ho MP, Yo CH, Liu CM, Chen CL, Lee CC. Refractive hypotension in a patient with disulfiram-ethanol reaction. *Am J Med Sci* 2007; **333**: 53–55.
- 119 Johnson BA, Koob GF, Schuckit MA, et al. Understanding and treating alcohol dependence. *Alcohol Clin Exp Res* 2006; **30**: 567–84.
- 120 Steensland P, Simms JA, Holgate J, et al. Varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, selectively decreases ethanol consumption and seeking. *PNAS* 2007; **104**: 12518–23.
- 121 Johnson BA, Rosenthal N, Capece JA, et al. Topiramate for treating alcohol dependence: a randomized controlled trial. *JAMA* 2007; **298**: 1641–51.