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BAP updated guidelines: evidence-based guidelines for the pharmacological management of substance abuse, harmful use, addiction and comorbidity: recommendations from BAP

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Abstract

The *British Association for Psychopharmacology* guidelines for the treatment of substance abuse, harmful use, addiction and comorbidity with psychiatric disorders primarily focus on their pharmacological management. They are based explicitly on the available evidence and presented as recommendations to aid clinical decision making for practitioners alongside a detailed review of the evidence. A consensus meeting, involving experts in the treatment of these disorders, reviewed key areas and considered the strength of the evidence and clinical implications. The guidelines were drawn up after feedback from participants. The guidelines primarily cover the pharmacological management of withdrawal, short- and long-term substitution, maintenance of abstinence and prevention of complications, where appropriate, for substance abuse or harmful use or addiction as well management in pregnancy, comorbidity with psychiatric disorders and in younger and older people.

Keywords

Substance misuse, addiction, guidelines, pharmacotherapy, comorbidity

Introduction

The first *British Association for Psychopharmacology* evidence-based guidelines for 'the pharmacological management of substance misuse, addiction and comorbidity' were published in 2004 (Lingford-Hughes et al., 2004). This is a substantial revision of that original document but using the same criteria (Table 1) and taking into account a number of recent documents from the National Institute for Health and Clinical Excellence (NICE) and other organisations which significantly enhanced the knowledge base. As before, the guidelines are not intended to provide an equivalent comprehensive review of psychosocial interventions since this is a major topic in its own right. In addition, the word 'patient' is used throughout the document for consistency, although it is acknowledged that in many treatment centres, 'client' or 'user' is the preferred term.

Scope of these guidelines

Our aim is to provide helpful and pragmatic guidelines for clinicians such as psychiatrists and GPs involved in prescribing to people with substance abuse or harmful use or addiction alone and with psychiatric comorbidity. However, the update should also be of interest to other practitioners in the substance misuse field, non-specialists, patients and their families. This revision was undertaken to update the guidelines in the light of new evidence focussing on areas not covered by guidelines published since the original BAP guidelines (e.g. from NICE). We have searched for new evidence concerning pharmacological management of alcohol, nicotine, opioids, benzodiazepines, stimulants and associated comorbidity with mental health problems and substance use or abuse in pregnancy. In addition we have covered pharmacotherapy for younger and older people, for those with personality disorder, as well as for 'club drugs' and cannabis and polydrug users. We review pharmacotherapies in common clinical use as well as those with limited but promising evidence and highlight important areas of 'key uncertainty'. We have reviewed the evidence in as brief a format as possible and refer readers to the other guidelines such as NICE, where more detail is provided. Whilst some avenues have developed, it is notable that many key uncertainties remained unchanged since 2004.

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Other invited participants at the consensus meeting who contributed to the discussion and commented on the guidelines were Drummond C, Farrell M, Gilvarry E, Strang J. John, a user representative, read and commented on the written guidelines. Prof W van den Brink reviewed the written guidelines.

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Table 1. Categories of evidence and strength of recommendations

Categories of evidence for causal relationships and treatment
Ia: evidence from meta-analysis of randomised controlled trials
Ib: evidence from at least one randomised controlled trial
IIa: evidence from at least one controlled study without randomisation
IIb: evidence from at least one other type of quasi-experimental study
III: evidence from non-experimental descriptive studies, such as comparative studies, correlation studies and case-control studies
IV: evidence from expert committee reports or opinions and/or clinical experience of respected authorities
Proposed categories of evidence for observational relationships
I: evidence from large representative population samples
II: evidence from small, well-designed, but not necessarily representative samples
III: evidence from non-representative surveys, case reports
IV: evidence from expert committee reports or opinions and/or clinical experience of respected authorities
Strength of recommendation
A: directly based on category I evidence
B: directly based on category II evidence or extrapolated recommendation from category I evidence
C: directly based on category III evidence or extrapolated recommendation from category I or II evidence
D: directly based on category IV evidence or extrapolated recommendation from category I, II or III evidence
S: Standard of care

Table 2. Classification of substance abuse, harmful use and dependence

DSM IV	**ICD-10 F10 – F19**
Substance abuse (1 or more criteria for over 1 year) and never met criteria for dependence A. recurrent substance use resulting in a failure to fulfil major role obligations at work, school or home B. recurrent substance use in situations in which it is physically hazardous C. recurrent substance-related legal problems D. continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance	Harmful Substance use: Actual damage should have been caused to the mental or physical health of the user in the absence of diagnosis of dependence syndrome.
Substance dependence (3 criteria or more over 1 year) A. tolerance: a need for markedly increased amounts of the substance to achieve intoxication or desired effect or markedly diminished effect with continued use of the same amount of the substance B. withdrawal: the characteristic withdrawal syndrome for the substance or the same (or a closely related) substance is taken to relieve or avoid withdrawal symptoms C. the substance is often taken in larger amounts or over a longer period than was intended D. there is a persistent desire or unsuccessful efforts to cut down or control substance use E. a great deal of time is spent in activities necessary to obtain the substance, use of the substance or recovering from its effects F. important social, occupational or recreational activities are given up or reduced because of substance use G. the substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance	Substance dependence (3+ in last year) A. a strong desire or sense of compulsion to take alcohol B. difficulties in controlling alcohol-taking behaviour in terms of its onset, termination, or levels of use C. a physiological withdrawal state when alcohol use has ceased or been reduced, as evidenced by: the characteristic withdrawal syndrome for alcohol; or use of the alcohol with the intention of relieving or avoiding withdrawal symptoms D. evidence of tolerance, such that increased doses of alcohol are required in order to achieve effects originally produced by lower doses (clear examples of this are found in alcohol-dependent individuals who may take daily doses sufficient to incapacitate or kill nontolerant users) E. progressive neglect of alternative pleasures or interests because of alcohol use, increased amount of time necessary to obtain or take alcohol or to recover from its effects F. persisting with alcohol use despite clear evidence of overtly harmful consequences.

We have not re-evaluated diagnostic categories since at the time of writing these guidelines DSM-V is being developed and will be published in 2013. The criteria for the dependence syndrome are similar in both ICD and DSM classification systems (Table 2). In most recent trials either DSM-IV or ICD-10 is used, though in older trials definitions of 'dependence' were less precise. DSM-V may return to using the term 'addiction' to distinguish this syndrome from 'dependence' which would apply to those tolerant to

medication but not abusing or escalating its use. The criteria for the categories 'harmful use' (ICD-10) and 'substance abuse' (DSM-IV) differ, with the emphasis on negative social consequences of substance use in the DSM classification, and on the physical and mental health consequences in the ICD-10 classification. It is currently proposed for DSM-V to combine substance abuse and dependence into one disorder: substance use disorder. Substance 'misuse' is a commonly used term in many studies and has been used in recent NICE guidance (NICE, 2011a, b). However it is not an official diagnostic term and may refer to harmful use, abuse or dependence. We have therefore used these more precise diagnostic terms wherever possible, but have had to use the term when describing studies where it is used and further discrimination is not possible.

We have not covered in depth how to safely prescribe the pharmacotherapies described here, since guidance is constantly updated. The reader is recommended to consult current resources such as British National Formulary (BNF), Summaries of Product Characteristics (SPC) (http://www.medicines.org.uk/emc/). We also suggest seeking appropriate support and supervision from peers and clinical governance if required, since many of the medications described do not hold a licence for the indication under discussion in UK, though may in other countries.

Methodology

A consensus meeting was held on 8 December 2009 involving experts in the field of addiction and comorbidity. These included reviewers who gave brief presentations of their key area, with an emphasis on systematic reviews (e.g. Cochrane Database) and randomised controlled trials (RCTs) where possible, although inevitably much of the information presented did not come from these sources. This was followed by a discussion of the important issues to identify consensus and areas of uncertainty regarding the quality of evidence and strength of recommendations. A draft of this review of the literature, which was updated during writing with any subsequently published literature, was then circulated to all participants and other interested parties. Feedback was incorporated, wherever possible, into this final version.

Identification of relevant evidence

The range of disorders covered in these guidelines did not allow for a systematic review or meta-analysis of all possible data from primary sources. Existing systematic reviews and RCTs were identified from MEDLINE and EMBASE searches, from the Cochrane Database as well as from guidelines and identification by experts in the field.

Evidence categories and strength of recommendations

Categories of evidence for causal relationships (including treatment) and strength of recommendations are given in Table 1 and are taken from Shekelle et al. (1999). The strength of recommendation reflects not only the evidence but also the importance of the study. For instance, it is possible to have methodologically sound (category I) evidence about an area of practice that is clinically irrelevant or has such a small effect that it is of little practical importance, and therefore attracts a lower strength of recommendation. More commonly, however, it has been necessary to extrapolate from the available evidence leading to weaker levels of recommendation (B, C or D) based upon category I evidence statements. For some of the treatments, the strength of the recommendation may refer to not using this treatment approach. Where recommendations are not strictly based on systematic evidence at all, but represent an important consensus (practical or ethical), we have indicated 'S' (standard of care). The recommendations are there to give clinicians options in using pharmacotherapeutic approaches. However, not all options may be appropriate for every individual or clinical situation, and consequently they should not be seen as prescriptive.

Treatment aims

There are several possible aims when planning treatment for substance use disorders, ranging from those pertinent to the individual, for example reduced risk of infection from stopping injecting, through to those concerning society, for example reduction in crime. We emphasise that a shared understanding of treatment aims between patient and prescriber are key, alongside the fact that adequate demonstrable planning with the patient concerning their goals is required by many commissioners and services. Clarity is important since the same pharmacotherapy may be used for substitution as well as withdrawal/detoxification, for example methadone or buprenorphine in opiate addiction.

These guidelines focus on pharmacotherapy which is primarily for those who are dependent rather than engaging in 'harmful use' or 'abuse'. We have not reviewed psychosocial treatments or other forms of treatment, for example acupuncture. NICE has undertaken several systematic reviews and meta-analyses in these areas, and there are other guidelines and Cochrane reviews available (e.g. Ferri et al., 2011; Knapp et al., 2007; White et al., 2011). There is limited evidence concerning the interaction between these two approaches or whether there is an optimal pharmacological–psychosocial combination. For those patients who meet criteria for harmful use (ICD-10 criteria, Table 2) or abuse (DSM-IV criteria, Table 2) but do not meet criteria for a dependence syndrome, psychosocial approaches are the mainstay of treatment, and pharmacotherapy currently has a more limited role compared with those with dependence. It may, of course, be appropriate to use pharmacotherapy to treat any comorbid psychiatric disorder. Pharmacological interventions for the substance use disorder itself are of most value in dependence, and are targeted at the following areas of patient management:

- withdrawal syndromes
- relapse prevention and maintenance of abstinence
- reduction of harms associated with illicit drug use by prescribing a substitute drug or drugs (e.g. methadone maintenance treatment in which aims may include cessation of injecting, reduction or cessation of illicit heroin use, and reduction or cessation of other high-risk behaviours)
- prevention of complications of substance use (e.g. use of thiamine to prevent Wernicke's encephalopathy and Korsakoff's syndrome)

In this guideline, we have tried to indicate clearly the aims of each treatment. Goals should be set and agreed between the patient and prescriber. We have not included the pharmacological treatments used in management of severe acute intoxication or overdose. Such management usually takes place in Accident and Emergency departments.

Alcohol

Management of withdrawal and detoxification

Acute alcohol withdrawal, its associated risks and management including settings and pharmacological management or 'medically assisted withdrawal', has been systematically reviewed for NICE guidelines, by groups led by Royal College of Physicians (NICE, CG100, 2010c) (Ia) and by Royal College of Psychiatrists (NICE, CG115, 2011a) (Ia) as well as by Cochrane (Amato et al., 2010; Minozzi et al., 2010) (Ia). The recommendations in both NICE guidelines are broadly in agreement with our previous recommendations supporting the use of benzodiazepines. One difference, however, was that the CG100 guidelines, whose remit was management within a general medical inpatient setting, recommended a 'symptom-triggered' regimen (see Hecksel et al. (2008) regarding issues of managing in general medical setting) (III). However, the CG115 guidelines emphasised that this approach was only for inpatients or residential settings if the appropriate level of monitoring was available. These NICE guidelines recommended a fixed-dose regimen for community-based withdrawal. A recent study not available for inclusion in either NICE guidelines reported that outpatient alcohol withdrawal could be managed effectively and safely using chlordiazepoxide either with a symptom triggered or a fixed-schedule regimen (Elholm et al., 2011). The median of total doses of chlordiazepoxide over 10 days were 725mg in symptom triggered (range: 50 – 2800) and 875mg in fixed-schedule (range: 100 – 1900). In addition, the CG100 guidelines recommended clomethiazole as an alternative for inpatients, although to be used cautiously. The CG115 guidelines did not recommend using clomethiazole in the community.

The use of anticonvulsants continues to receive attention, since reducing glutamate overactivity is now thought to be key in reducing risk of brain toxicity during withdrawal. Undergoing more than two detoxifications has been associated with poorer performance on some cognitive tasks although a causal link has not been proven (Duka et al., 2004; Loeber et al., 2010). Krupitsky et al. (2007) (Ib) reported that a range of antiglutamatergic approaches such as memantine (NMDA antagonist), topiramate (AMPA/kainate inhibitor) or lamotrigine (glutamate release inhibitor) were efficacious in treating alcohol withdrawal similarly to diazepam. A Cochrane review (Minozzi et al., 2010) (Ia) was cautious about anticonvulsants, stating that there was 'insufficient evidence in favour of anticonvulsants for treatment of alcohol withdrawal' although they seemed to have 'limited side effects' and 'might be effective for some symptoms', for example seizures. NICE, CG100, (2010c) (Ia) recommended using carbamazepine or benzodiazepines, although in the UK there is less clinical experience in using anticonvulsants. NICE, CG115, (2011a) (Ia) guidelines did not comment on use of carbamazepine.

Due to concerns about carbamazepine's safety and tolerability, alternative anticonvulsants, for example oxcarbazepine, levetiracetam, pregabalin, have been investigated. Studies may show benefits compared with placebo but no one anticonvulsant has emerged as preferential (e.g. Anton et al., 2009 (Ib); Barrons and Roberts, 2010 (Ia); Bonnet et al., 2010 (III); Di Nicola et al., 2010 (IIb); Martinotti et al., 2010 (Ib); Richter et al., 2010 (Ib)). The role for anticonvulsants in alcohol withdrawal therefore still remains unclear. However, the finding that using carbamazepine during withdrawal was followed by longer time to eventual return to drinking than with using the benzodiazepine, lorazepam (Malcolm et al., 2002) (Ib), raises the question of whether benzodiazepine withdrawal leaves the brain vulnerable to relapse. Consequently, determining how to measure impact on markers of neurotoxicity is critical to answer this important question.

Acamprosate has been shown to reduce the hyperglutamatergic state during alcohol withdrawal in animal models and may have neuroprotective potential (Mann et al., 2008) (IV). A clinical study showed acamprosate reduced glutamate levels in the brain 25 days after initiation of benzodiazepine-treated alcohol withdrawal (Umhau et al., 2010) (Ib). Starting acamprosate 8 days prior to detoxification and continuing for 15 days without other medication for withdrawal resulted in reduced arousal level measured with magnetoencephalography and improved decreased wake time after sleep onset and increased stage 3 and REM sleep latency (Boeijinga et al., 2004 (Ib); Staner et al., 2006 (Ib)). Gual and Lehert (2001) (Ib) and anecdotally, clinicians who routinely use acamprosate during detoxification in addition to usual medication for alcohol withdrawal report no unwanted events and suggest acamprosate improves symptoms. However, a full randomised placebo-controlled trial has yet to be completed. Another small (n = 16 vs. 18) trial designed to see if giving acamprosate in addition to medication for alcohol withdrawal rather than starting it at the end of the detoxification improved drinking outcomes, found no benefit in drinking outcomes, indeed this approach might worsen some (Kampman et al., 2009) (Ib).

There are a number of medications that may be useful not only in treating withdrawal but also in relapse prevention, and are further described in this section below. These include baclofen, some anticonvulsants (e.g. topiramate) and gamma-hydroxybutyric acid (GHB or sodium oxybate; see Relapse Prevention, Other medications below), but there is limited evidence currently (Caputo and Bernardi, 2010; Leone et al., 2010 (Ia); Liu and Wang, 2011 (Ia)). Clearly if a medication can be used to treat withdrawal and reduce the risk of complications and prevent lapses/relapses during early abstinence, it may have advantages to patients who would otherwise have to wait until after detoxification before starting relapse prevention medication.

Alcohol withdrawal-related seizures. Bråthen et al. (2005) (Ia) have produced consensus recommendations for diagnosis and management of alcohol-related seizures based on a systematic review of the evidence. They recommend longer-acting benzodiazepines, for example diazepam, or if not available lorazepam, since they are efficacious for primary and secondary seizure prevention. They concluded that there is insufficient evidence for other pharmacological approaches.

Recommendations: management of alcohol withdrawal and detoxification. Although many alcohol-withdrawal episodes take place without any pharmacological support, particularly in those patients with a mild level of alcohol dependence, in the presence of symptoms medication should be given. Detoxification should be planned as part of a treatment programme to increase the likelihood of patients successfully altering their subsequent drinking behaviour. Early identification and treatment of alcohol dependence can reduce the level of complications.

Treatment regimens

- Benzodiazepines are efficacious in reducing signs and symptoms of withdrawal (A); fixed-dose regimens are recommended for routine use with symptom-triggered dosing reserved for use only with adequate monitoring (D)
- Carbamazepine has also been shown to be equally efficacious to benzodiazepines (A)
- Clomethiazole is reserved for inpatient settings only after due consideration of its safety (A)

Seizures

- Benzodiazepines, particularly diazepam, prevent de novo seizures (A)
- Anticonvulsants are equally as efficacious as benzodiazepines in seizure prevention, but there is no advantage when combined (A)
- In preventing a second seizure in the same withdrawal episode, lorazepam but not phenytoin has been shown to be effective (A)

Delirium

- Benzodiazepines, particularly those with longer half-life prevent delirium (A) and should be used for treatment (B)

Key uncertainties

- What is the role of acamprosate or carbamazepine and other anticonvulsants in alcohol detoxification – uncomplicated and complicated?
- What is the appropriate regimen for maximum symptom control, reducing risk of complications, preventing neuroinflammation and brain damage?

Alcohol-related brain disorder

Wernicke–Korsakoff syndrome (WKS) is now considered to be a unitary disorder comprising acute Wernicke's encephalopathy (WE) which proceeds in a proportion of cases to Korsakoff's syndrome. Adequate assessment and diagnosis still remain a challenge despite WKS being well recognised as a complication of harmful alcohol use. Thiamine replacement is still the critical intervention for WKS, and increased vulnerability is associated with genetic susceptibility in association with poor diet (Sechi and Serra, 2007) (IV).

Acute – Wernicke's encephalopathy. It has been suggested that a presumptive diagnosis of WE should be made for any patient with a history of alcohol dependence who shows one or more of the following: evidence of ophthalmoplegia, ataxia, acute confusion, memory disturbance, unexplained hypotension, hypothermia, coma, or unconsciousness (Sechi and Serra, 2007) (IV). Alcohol or benzodiazepine or carbamazepine intoxication may complicate the presentation. Operational criteria for the diagnosis of WE have been proposed with only two of the classic triad (ophthalmoplegia, ataxia, confusion) and dietary deficiencies (Caine et al., 1997) (IV). Although they help in distinguishing the problem from other potentially coexisting conditions such as alcohol withdrawal or hepatic encephalopathy, they are not yet widely used. Patients commonly deemed 'at risk' of developing WE during a hospital admission or a planned detoxification are those whose drinking has exceeded 15 units per day for a month or more and where there is evidence of recent weight loss or vomiting or diarrhoea or malnutrition or peripheral neuropathy or chronic ill-health. This is based only on 'expert opinion', but derives also from the established causal relationship of WE to severe malnutrition and hyperemesis of pregnancy.

Recent systematic reviews of the evidence for how best to treat WE have been completed for Cochrane (Day et al., 2004) (Ia) and NICE (2010c) (Ia). There is still insufficient evidence from RCTs. Nevertheless there is growing consensus for using parenteral regimens in those with WE and also, importantly, for those at risk as described above (NICE, 2010c) (Ia). Our recommendations concerning importance of identifying these two populations, particularly those at risk, and their treatment have not changed from the previous BAP guidelines. Whether or not and, if so, for how long to give oral thiamine to apparently healthy but potentially malnourished alcohol-dependent individuals remains unclear, with NICE (2010c) (Ia) not recommending 'widespread use of thiamine' in alcohol-dependent people 'eating a normal diet'. We suggest if there is any suggestion that such 'healthy' alcohol-dependent individuals may not have a healthy diet or have reduced thiamine levels, oral thiamine should be considered.

Chronic or persisting – Korsakoff's syndrome. Alcohol-related brain disorders encompass a broad range of dysfunction including Korsakoff's syndrome (Kopelman et al., 2009) (IV). Research is increasingly being focussed on prevention, and the roles of increased brain glutamate, oxidative stress and neuroinflammation give us a number of targets for the future (Thomson et al., 2012). Once cognitive impairment or Korsakoff's syndrome is evident and adequate thiamine replacement has been given, little additional pharmacotherapy to ameliorate cognitive impairment has been shown to be effective. For Korsakoff's syndrome, there has been little progress in finding an efficacious pharmacotherapy, with only a small trial of rivastigmine showing no effect published since the last guidelines (Luykx et al., 2008) (III). Maintaining abstinence is key, and pharmacotherapy may be used for this (see below).

Recommendations: alcohol-related brain disorder. A high index of suspicion must be maintained at all times regarding WE since it rarely presents with all signs and symptoms. The following recommendations are based on uncontrolled trials and from empirical clinical practice.

- In healthy uncomplicated alcohol-dependent/heavy drinkers (i.e. those at low risk), oral thiamine >300 mg/day should be given during detoxification (D)
- If patient is at high risk of WE (e.g. malnourished, unwell) prophylactic parenteral treatment should be given, using 250 mg thiamine (one pair of ampoules Pabrinex®) i.m. or i.v. once daily for 3–5 days or until no further improvement is seen (D)
- If WE is suspected or established, parenteral thiamine (i.m. or i.v.) of >500 mg should be given for 3–5 days (i.e. two pairs of ampoules Pabrinex® three times a day for 3-5 days), followed by one pair of ampoules once daily for a further 3–5 days depending on response (D)

Key uncertainties

- What is the appropriate dose, route and duration of thiamine administration in presumed or clinically obvious WE?
- To determine thiamine requirements during different stages of a patient's drinking, for example in those continuing to drink heavily, during alcohol withdrawal in otherwise healthy patients.
- To understand more about other neurobiological processes involved in WE.
- How best to treat Korsakoff's syndrome and manage the persisting symptoms long term?

Preventing lapse and relapse, promoting and maintaining abstinence

Since the last guidelines the debate about what is a reasonable or appropriate outcome regarding drinking behaviour continues. Abstinence is generally reported as 'continuous complete abstinence', cumulative abstinence or % time abstinent. There is no single definition of other drinking outcomes, nor is it clear which accrue health and social benefits. Relapse can be defined as five drinks in US studies (drink = 14 g alcohol = 8.1 UK units; note that the amount of alcohol in a 'unit' or 'drink' differs worldwide) in men and four drinks (6.5 units) in women on a single occasion, with any lesser episode of alcohol consumption categorised as a 'lapse'. In other studies, controlled drinking is reported as mean daily self-reported consumption of 5 units or less (men) or 3 units or less (women) and no single day exceeding 8 units (men) or 6 units (women). What level of alcohol drinking confers an acceptable low risk will depend on individual circumstances (Gmel et al., 2003). For those with cirrhosis and decompensated liver failure any drinking, even small amounts, is likely to be harmful (Tilg and Day, 2007). Complete abstinence gives them the best chance of recovery so they should be encouraged towards abstinence, though reduced drinking may be acceptable as an intermediate treatment goal in developing medicinal products for treatment of alcohol dependence (European Medicines Agency's guidelines, 2010). In addition, for those who have lost control of their drinking, reductions maybe hard to achieve and maintain, so a period of abstinence is also generally advocated. For those that are unwilling or unable to become abstinent, reduced drinking may be an appropriate intermediate goal on the way to abstinence, although ideally clinical benefit should also be evident. For others with less adverse health consequences or not dependent, some drinking may be acceptable.

Participants in the majority of trials are abstinent prior to starting pharmacotherapy, and generally the trial's aim is to maintain abstinence. Some studies have noted that having abstinence as a goal is associated with a good response (e.g. Anton et al., 2006; Mason and Lehert, 2010; Koeter et al., 2010) (Ib). In addition, all pharmacotherapies discussed here have been studied as an adjunct to psychosocial interventions, and use of medication alone is not currently advocated. Whether there is an optimal combination of a particular type of psychosocial intervention and pharmacotherapy has not been widely studied, so patients should engage with whichever psychosocial approach they find beneficial or is available.

When taking evidence from trials to UK practice, it is important to consider a trial's inclusion/exclusion criteria and where they were conducted. In particular, recent trials of pharmacotherapy in US settings do not necessarily come to the same conclusion as those conducted in European studies (Garbutt, 2009). In US trials patients may be recruited via advertisement, may be less dependent, able to stop drinking without medication, less anxious, and not want abstinence, which contrasts with European trials where patients are generally recruited from specialist alcohol services and tend to be highly dependent, require medically assisted alcohol withdrawal and a majority are aiming for abstinence. However, such differences can be used to inform clinicians what types of patients are more likely to benefit from that medication.

Reviewing the place of medication in relapse prevention, NICE (2011a) has recently recommended that '*after a successful withdrawal for people with moderate and severe alcohol dependence, consider offering acamprosate or oral naltrexone in combination with an individual psychological intervention (cognitive behavioural therapies, behavioural therapies or social network and environment-based therapies) focused specifically on alcohol misuse'*. In addition, *'for harmful drinkers and people with mild alcohol dependence who have not responded to psychological interventions alone, or who have specifically requested a pharmacological intervention, consider offering acamprosate or oral naltrexone in combination with an individual psychological intervention (cognitive behavioural therapies, behavioural therapies or social network and environment-based therapies) or behavioural couples therapy*'. We endorse the recommendation that pharmacotherapy should be the default position, such that the decision *not* to prescribe is made actively for those patients presenting with harmful alcohol use or abuse that have not benefited from psychosocial interventions and for everyone with dependence, rather than only thinking of medication for more complex patients. The range of medications are described below. We have considered a broader range of pharmacological approaches than NICE (2011a).

Acamprosate. Acamprosate acts as a functional glutamatergic NMDA antagonist, and since alcohol dependence and particularly withdrawal are associated with a hyperglutamatergic system, it can reduce this (Mann et al., 2008; Mason and Heyser, 2010). Acamprosate is generally well tolerated, with gastrointestinal disturbance (e.g. nausea, diarrhoea) being the most common side-effect reported (Mason and Heyser, 2010; NICE, 2011a) (Ia). It can be given safely to a wide number of patients with physical comorbidity, although with caution or even contraindicated in those with severe liver and renal impairment (see SPC).

There are a number of good-quality systematic reviews and meta-analyses of trials of acamprosate including those by Cochrane (Rösner et al., 2010a) (Ia), NICE (2011a) (Ia), Health Technology Board of Scotland (Slattery et al., 2003) (Ia), Swedish Board (Berglund et al., 2003) (Ia), and the Spanish Agency for Health Technology Assessment (Bouza et al., 2004) (Ia) in addition to those by Mann et al. (2004), Kranzler and van Kirk (2001), Mason and Ownby (2000), Rösner et al. (2008) and Mason and Heyser (2010) (Ia). These reviews broadly come to the same conclusion that compared with placebo, acamprosate is moderately effective in increasing the amount of abstinence after detoxification; for example Rösner et al. (2010a) (Ia) report RR 0.86 (95% CI 0.81–0.91), and NICE CG115 (2011a) (Ia) report RR = 0.83 (95% CI = 0.77–0.88). The 'number needed to treat' (NNT) was calculated as 9–11 (e.g. Rösner et al., 2010a; Slattery et al., 2003) (Ia). Notably, later systematic reviews and meta-analyses report smaller effect sizes due to three reasonably sized recent negative

studies conducted in the USA and Australia (COMBINE, Anton et al., 2006 (see below); Mason et al., 2006; Morley et al., 2006) (Ib). However, some of these studies included low-severity patients with few withdrawal symptoms, that is, patients who may be less likely to respond to acamprosate.

While the most potent consistent effect of acamprosate is to improve abstinence, some but not all meta-analyses or reviews have found evidence that acamprosate can reduce 'heavy drinking' in patients who have relapsed (Chick et al., 2003; NICE 2011a) (Ia) as was also found for naltrexone by Rösner et al. (2010b) (Ia).

When to start and how long to prescribe for? In most trials of acamprosate, patients were abstinent from alcohol for several days, and currently it is recommended that this drug should be started as soon as possible after detoxification. This recommendation was influenced by the UK study which did not find acamprosate to be superior to placebo; this might have been due to the greater mean length of time after detoxification that acamprosate was started compared with other studies (Chick et al., 2000) (Ib). A secondary analysis of COMBINE has shown that a longer period of pretreatment abstinence resulted in a poorer response with acamprosate (Gueorguieva et al., 2011) (Ib). Given this evidence and acamprosate's potential neuroprotective effect, we recommend it should be started during detoxification, despite Kampman et al. (2009) (Ib) reporting in a preliminary trial that some drinking outcomes may worsen.

Currently the SPC recommends acamprosate be given for 1 year. Mann et al. (2004) (Ia) reported from their meta-analysis that acamprosate's effect size for abstinent rates increased with time from 1.33 at 3 months, to 1.5 at 6 months and 1.95 at 12 months. NICE (2011a) recommends medication should be prescribed for 6 months but stopped if drinking persists after 4–6 weeks. Pragmatically it is sensible not to continue prescribing any medication without review if drinking behaviour is not changing.

The benefits of acamprosate in maintaining abstinence have been shown to persist for 3–12 months after stopping treatment, with a 9% lower risk to return to any drinking in patients who received acamprosate than those who received placebo (RR = 0.91; 95% CI 0.87–0.96) and a 9% higher continuous abstinence duration (MD 8.92; 95% CI 5.08–12.77; Rösner et al., 2010a) (Ia). The NNT for an additional prevention of drinking until the post-treatment evaluation was estimated at NNTB 12.5 (95% CI 9.09–25.00).

Who to give it to? Given that many people do not respond to acamprosate, are there any predictors to guide the clinician? While acamprosate has been referred to as 'anti-craving', recent trials have failed to show such an effect (Richardson et al., 2008 (Ib)). One trial reported a slight anxiolytic effect (Chick et al., 2000) (Ib) and insomnia, common in the early weeks of abstinence, seems to be helped by acamprosate (Staner et al., 2006) (Ib). Recently secondary analyses of the COMBINE dataset suggest those with subsyndromal anxiety and/or a significant past psychiatric history may particularly benefit from acamprosate, as do 'very frequent drinkers', but those who manage to stop drinking >14 days pretreatment may do worse (Gueorguieva et al., 2011; Mason and Lehert, 2010) (Ib). Mason et al. (2006) (Ib) had previously reported that acamprosate was effective in those motivated for abstinence. However, while individual studies may report post-hoc associations between clinical variables and outcome, meta-analyses of trials have not found robust predictors for 'treatment-matching'. Verheul et al. (2005) (Ia) used data from seven European trials and reported that high physiological dependence at baseline, negative family history of alcoholism, late age of onset, serious anxiety symptomatology at baseline, severe craving at baseline, and female gender did not predict response to acamprosate.

Since acamprosate's proposed mechanism of action is to correct glutamate–GABA imbalance, it has been hypothesised that since those more severely dependent are more likely to have such an imbalance, they are more likely to respond to acamprosate. There is some supporting evidence, since Morley et al. (2010) (Ib) reported an interaction between dependence severity and acamprosate treatment, such that higher levels of dependence severity at baseline predicted a beneficial response to acamprosate. In addition, failure of the two US trials to find acamprosate effective would fit with this hypothesis, since participants were less severely dependent (COMBINE, Anton et al., 2006; Mason et al., 2006) (Ib). However, evidence from meta-analyses has not been found in support of this (NICE, 2011a; Verheul et al., 2005) (Ia). Verheul et al. (2005) (Ia) indeed concluded that acamprosate is potentially effective for anyone with alcohol dependence. At the time of writing these guidelines, a large prospective study set up to define if there are any subgroups who respond to either acamprosate or naltrexone, 'project PREDICT' has yet to formally publish its results (Mann et al., 2009) (Ib).

Psychosocial intervention. Whether one psychosocial approach is preferable to another when prescribing acamprosate has not been investigated except in the COMBINE study, where acamprosate lacked efficacy with each of the three modes of psychosocial support offered (Anton et al., 2006) (Ib). One study reported no additional benefit of minimal and brief psychosocial interventions to acamprosate (de Wildt et al., 2002). Nevertheless, we suggest that a patient should be advised to engage with whatever approach they find available and acceptable.

Naltrexone. Naltrexone is a non-selective opioid antagonist. There is growing evidence for a role of the endogenous opioid system and its receptors in addiction (see Lingford-Hughes et al., 2010). The mu opioid receptor modulates dopaminergic cell firing in the ventral tegmental area, and therefore blocking the mu opioid receptor with naltrexone prevents any increase in dopaminergic activity. Consequently, naltrexone reduces alcohol's rewarding effects and also motivation to drink or 'craving' (Drobes et al., 2004; NICE, 2011a) (Ia). A role of the endogenous opioid system in impulsive behaviour is being increasingly characterised, with reduced opioid activity associated with lower levels of impulsivity. Consistent with this, naltrexone has been shown be effective in some impulse-control disorders such as pathological gambling, in particular those with a family history of alcoholism (Grant et al., 2008) (Ib).

Naltrexone as an oral tablet is licensed in the USA and some European countries to improve drinking behaviour. Whilst not licensed in the UK, it can be used and NICE (2011a) recommended that oral naltrexone, or acamprosate, be offered to those who are moderately to severely dependent, and to those less dependent or drinking harmfully if failing to improve. Early trials used dose of 50 mg/day, although more recent US studies have used 100 mg/day. In the UK, 50 mg/day is more typically used, and it is unclear whether or how much extra benefit is accrued from higher doses.

There have been several meta-analyses and systematic reviews which broadly have the same conclusion that oral naltrexone significantly reduces return to heavy drinking, probably by reducing

'lapse to relapse', but does not necessarily improve cumulative or continuous abstinence rates. The meta-analysis by NICE (2011a) (Ia) revealed that compared with placebo, naltrexone significantly reduced relapse to heavy drinking (RR = 0.83, 95% CI = 0.75–0.91). A Cochrane review found naltrexone reduced the risk of heavy drinking to 83% of the risk in the placebo group RR = 0.83 (95% CI 0.76–0.90) and decreased drinking days by about 4%, MD -3.89 (95% CI -5.75 to -2.04 (Rösner et al., 2010b)) (Ia). The most common side-effects are nausea and sedation (Rösner et al., 2010b) (Ia).

When to start and how long to prescribe for? Naltrexone can be used safely while someone is still drinking, but in trials for relapse prevention it is started soon after stopping drinking. Most trials conducted were for 3 or 6 months. One study has reported that those who had naltrexone for 24 weeks rather than 12 weeks had better drinking outcomes (Longabaugh et al., 2009 (Ib)). It is not clear if there is an optimal length of time; however, 6 months of treatment is reasonable, with stopping the medication if drinking persists for 4–6 weeks. Early studies of naltrexone suggest its beneficial effects did not persist for 14 or 16 weeks after stopping (Anton et al., 2001; O'Malley et al., 1996) (Ib). However, more recent evidence from the COMBINE study reported continued benefit persisting for up to a year (Donovan et al., 2008) (Ib).

Who to give it to? As for acamprosate, naltrexone does not help everyone and post-hoc analyses of trials have been undertaken to indicate who might respond. While several studies including more severely dependent individuals have suggested that naltrexone may be less effective in this group (e.g. Krystal et al., 2001; Morley et al., 2006, 2010) (Ib), meta-analyses have not supported this; indeed, the reverse has been found (e.g. NICE, 2011a) (Ia). Nevertheless, naltrexone has been shown to be beneficial in 'heavy drinkers' as well as 'dependent drinkers' (see below). A beneficial response has been reported as more likely in those with a positive family history (Monterosso et al., 2001; Rohsenow et al., 2007; Rubio et al., 2005) (Ib). Gueorguieva et al. (2007, 2010) (Ib) applied their 'trajectory modelling' to several naltrexone trials, including those that did not find in favour of naltrexone, and reported that naltrexone increased the probability of a lower risk trajectory such as abstainer or 'nearly daily drinking'. There have been several secondary analyses of the COMBINE dataset. In the medical management condition, naltrexone improves outcome in 'type A' (after Babor, less severe, later onset, weak/absent family history, less psychiatric comorbidity), but no such advantage was seen in type B alcoholics (Bogenschutz et al., 2009) (Ib). African Americans may not respond as well to naltrexone, although benefit has been shown for American Indian and Alaskan natives (O'Malley et al., 2008; Ray and Oslin, 2009) (Ib).

Concerning gender, Greenfield et al. (2010) (Ib) reported no gender differences in response to naltrexone in the COMBINE study. In comorbid cocaine/alcohol dependence, naltrexone (150 mg/day) resulted in reduced cocaine and alcohol use in men but not women; indeed, their cocaine use increased (Pettinati et al., 2008b) (Ib).

A functional polymorphism, Asp40 allele, of the mu opioid receptor gene has been shown to predict naltrexone treatment response in alcohol-dependent individuals (Anton et al., 2008; Kim et al., 2009; Oroszi et al., 2009; Oslin et al., 2003) (Ib), but its impact may be moderated by other efficacious treatment or patient variables such as motivation, since such an association has not always been found (Gelernter et al., 2007) (Ib).

The impact of depressive symptoms or depression on naltrexone's effectiveness is not clear, with evidence from some trials suggesting their presence is associated with greater improvements (Kiefer et al., 2003; Krystal et al., 2008; Morley et al., 2010) (Ib). For further discussion about effectiveness of naltrexone in depressed patients, see Comorbidity section.

Naltrexone + psychosocial interventions. The interaction between a number of different psychosocial interventions and naltrexone has been investigated, with no clear advantage of one approach. Several studies have suggested cognitive behavioural therapy (CBT) has a beneficial interaction with naltrexone and to be superior to supportive therapy (Balldin et al., 2003) (Ib), motivational enhancement therapy (Anton et al., 2005) (Ib), and equal to medical management (O'Malley et al., 2003) (Ib). Supportive therapy has been shown to be better than coping skills therapy (O'Malley et al., 1992) (Ib). In the COMBINE study, comparable outcomes resulted from combined behavioural intervention (CBI) alone, naltrexone, and the combination of CBI and naltrexone (Anton et al., 2006) (Ib). Broad spectrum treatment (BST) has been shown to result in better drinking outcomes than motivational enhancement therapy (MET) only with 24 rather than 12 weeks of naltrexone (Longabaugh et al., 2009) (Ib). However, many people may not be able to or want to access such intensive or comprehensive psychosocial treatment. It is therefore of interest that naltrexone has been shown to be effective with 'medical management' which involves regular but short meetings with a practitioner, often a nurse, monitoring compliance and supporting abstinence (Anton et al., 2006; O'Malley et al., 2003) (Ib).

Other opioid antagonists. There are injectable forms of naltrexone which have been designed to overcome poor adherence. An extended-release monthly injectable formulation of naltrexone (XR-NTX) is licensed in the USA and is being used in the UK by some for the treatment of alcohol dependence. In a 6 month trial, XR-NTX (380 mg monthly) significantly reduced the rate of heavy drinking compared with placebo (Garbutt et al., 2005) (Ib). A dose-dependent effect was apparent, since 190 mg monthly reduced the rate of heavy drinking, but not significantly. The effect was more pronounced in those who were abstinent for at least 4 days at the start compared with those who were still drinking (O'Malley et al., 2007) (Ib). The effect of the injection is seen within 2 days (Ciraulo et al., 2008) (Ib). Side-effects are similar to those of the oral preparation and include nausea; however, injection site pain and reactions have been reported, possibly related to poor injection technique, and some required medical treatment (Garbutt, 2009). Unfortunately, no direct comparison between immediate-release oral naltrexone and extended-release injectable naltrexone is available, and it is not possible to make an evidence-based benefit–risk assessment (Roozen et al., 2007).

An alternative oral medication is nalmefene, which is an opioid antagonist with a differing pharmacological profile to naltrexone at the three opioid receptor subtypes (Bart et al., 2005). Nalmefene can be given safely in alcohol dependence and can significantly prevent relapse to heavy drinking (Mason et al., 1994, 1999) (Ib). It may have a better safety profile than naltrexone with less risk of liver toxicity. Mason et al. (1999) (Ib) did not find a difference in reduction in drinking or side-effects between 20 mg/day and 80 mg/day, and Anton et al. (2004) (Ib) reported 5 mg, 10 mg and 20 mg/day were reasonably well tolerated.

European trials are being conducted in the hope of characterising the role and dose for nalmefene in treating alcohol dependence, and results are expected in the near future.

Opioid antagonists and 'heavy drinking'. Due to naltrexone's proposed mechanism of action in reducing the pleasurable effects of alcohol, naltrexone has also been investigated in those who are still drinking. In addition, an alternative strategy to daily dosing is to use opioid antagonists in a targeted way, that is 'as needed', to reduce heavy drinking. In alcohol dependence, naltrexone taken only when craving is effective in maintaining reduced drinking (Heinälä et al., 2001) (Ib). In male, but not female, heavy drinkers 'targeted' naltrexone taken when drinking was imminent, rather than daily naltrexone or placebo, reduced 'drinks per day' by almost 20% (Kranzler et al., 2009) (Ib). With minimal psychosocial intervention, nalmefene (10 mg or 40 mg) taken prior to 'imminent drinking' has been shown to significantly reduce heavy drinking days, very heavy drinking days and total alcohol consumption (Karhuvaara et al., 2007) (Ib).

Comparing acamprosate and naltrexone. There are four published trials comparing acamprosate with naltrexone, of which two also studied them combined. The earlier European trials reported that naltrexone (50 mg/day) was superior to acamprosate (1998 mg/day) or placebo, and the combination conferred no additional benefit to naltrexone but improved outcomes compared with acamprosate (Kiefer et al., 2003; Rubio et al., 2001) (Ib).

A large nine-arm trial in the USA, COMBINE, examined whether acamprosate (3 g) or naltrexone (100 mg) individually or together provided any benefit in addition to standard 'medical management' or more intensive combined behavioral intervention (CBI) (Anton et al., 2006) (Ib). The primary outcomes were % days abstinent from alcohol and time to first heavy drinking day. While all groups showed improvements in drinking outcomes, naltrexone with medical management alone or in combination with CBI resulted in greater improvements than placebo or medical management alone, whereas acamprosate showed no evidence of additional efficacy in any combination. Naltrexone or CBI added to medical management resulted in a similar level of improvement, with no additional benefit of all three together. An Australian trial where patients received either acamprosate (1998 mg) or naltrexone (50 mg/day) or placebo alongside manualised compliance therapy found no superiority of either over placebo (Morley et al., 2006) (Ib). Another Australian trial reported that a combination of acamprosate and naltrexone with CBT resulted in the greatest benefit compared with either medication alone, with CBT or CBT alone (Feeney et al., 2006) (IIb).

In summary, taking into account the potential difference between European patient samples and the sample included in the COMBINE study, it appears there is no overall superiority of naltrexone over acamprosate that would apply to the UK patient population. From their review, Rösner et al. (2008) (Ia) concluded that 'acamprosate was found to be more effective in preventing a lapse, whereas naltrexone was better in preventing a lapse from becoming a relapse'.

Disulfiram. Disulfiram has been used for many years to help people remain abstinent. Disulfiram blocks aldehyde dehydrogenase, causing accumulation of acetaldehyde if alcohol is consumed, resulting in nausea, flushing, and palpitations. This deters people from drinking (Fuller and Roth, 1979) (Ib). Disulfiram also blocks dopamine-b-hydroxylase in the brain, so increasing dopamine and reducing noradrenaline, and this may contribute to its clinical effects in alcoholism or cocaine addiction (see later; Schroeder et al., 2010).

The fact that the disulfiram–alcohol reaction can have potentially severe adverse consequences often makes practitioners cautious of using disulfiram. However, recent studies report that disulfiram can be used safely in a wide range of patients, including those with psychosis (see comorbidity section later) and hepatitis C (Martin et al., 2004) (III). For more information about the safety of disulfiram, see Chick (1999) and Malcolm et al. (2008). To optimise compliance, witnessing (now the preferred term to 'supervision') disulfiram intake has been shown to be an important contributor to effectiveness, since otherwise disulfiram is no better than basic support (Chick et al., 1992) (Ib).

Many of the trials of disulfiram were conducted some decades ago and were therefore not as rigorously undertaken as those for newer medications. In addition, due to the alcohol–disulfiram reaction, patients entering trials of disulfiram have to be aware they could be taking disulfiram. Systematic reviews of older trials report that disulfiram is no better than placebo in preventing lapse to drinking (NICE 2011a; Slattery et al., 2003) (Ia). More recent trials of disulfiram have compared it with newer medications such as naltrexone, acamprosate or topiramate (de Sousa and de Sousa, 2004, 2005; de Sousa et al., 2008; Laaksonen et al., 2008) (Ib). When taking medication for 12 weeks, disulfiram has been shown to be superior to naltrexone or acamprosate in prolonging time to first drink and number of 'heavy drinking days' (Laaksonen et al., 2008) (Ib). All medication was 'supervised' by someone. However, in a subsequent 12-week phase of targeted medication taken in 'a craving situation', there were no differences between disulfiram, naltrexone and acamprosate (Laaksonen et al., 2008) (Ib). Two open but randomised pragmatic trials of disulfiram in a private clinic in Mumbai reported that disulfiram (250 mg/day) was superior to either naltrexone (50 mg/day) or topiramate (150 mg/day) in lengthening time to relapse and maintaining abstinence (de Sousa and de Sousa, 2004, 2005; de Sousa et al., 2008) (IIa).

NICE (2011a) (Ia) recommended that disulfiram should be tried after acamprosate or naltrexone, or where the patient indicates a preference for it. There is no evidence to guide how long to prescribe disulfiram, but clearly it can only be started once alcohol free for at least 24 hr. Patients must also be warned about potential for a reaction with alcohol for up to 7 days after stopping disulfiram. An open prospective study lasting 9 years reported that 2 years of treatment with disulfiram or calcium carbimide resulted in overall abstinence rates of 50%; however, not all patients could take disulfiram or calcium carbimide so received 'sham' treatment, and the authors emphasised the importance of its psychological ingredient (Krampe et al., 2006) (IIb)

While in the UK the usual daily disulfiram dose is 200 mg once a day, it can be given in higher doses. For instance, in trials with comorbid alcohol and cocaine dependence, 500 mg/day was used (Carroll et al., 1998) (Ib). In addition, disulfiram can be given in larger doses less frequently than daily, which might be advantageous if asking patients to attend a service and have their medication supervised or witnessed. However, Ulrichsen et al. (2010) (IIb) reported that 800 mg of supervised disulfiram given twice a week over 26 weeks was no better than just attending twice a week without taking disulfiram. Notably, over half of recruits failed to be randomised since some definitely wanted disulfiram and others failed to show up.

Baclofen. Baclofen is a GABA-B agonist that is licensed for controlling muscle spasms; it does not hold a licence for use in alcohol dependence, although it is being used by some clinicians. Preclinical evidence demonstrated that GABA-B receptors are key modulators of dopaminergic neuronal firing and baclofen can reduce ethanol self-administration. An Italian RCT of baclofen in cirrhotic alcohol-dependent patients wanting to be abstinent showed baclofen significantly increased the number maintaining abstinence compared with placebo (71% vs. 29%; Addolorato et al., 2007) (Ib). By comparison, another RCT in the USA reported no superiority of baclofen over placebo in reducing 'heavy drinking' or increasing abstinence (Garbutt et al., 2010) (Ib). This difference in effectiveness may relate to the fact that the cirrhotic patients tended to be more severely dependent, anxious, required medication for detoxification, and wanted sobriety, which contrasted with those in the US study. Baclofen reduced anxiety in both populations. It has therefore been suggested that those with greater anxiety and withdrawal symptoms are more likely to benefit from baclofen. In addition, the more comprehensive psychosocial treatment in the US study for both groups may have confounded differences in outcome, whereas there was less available in the Italian study.

Both of these studies used baclofen 10 mg tds (total 30 mg/d). However, secondary analysis of a trial suggests that 20 mg tds may be superior to 10 mg tds (Addolorato et al., 2011) (Ib). This would be consistent with other studies of baclofen in methamphetamine, cocaine and nicotine dependence, where higher doses of 60 mg/day and 80 mg/day have been studied. Of note, a high-profile case report detailed a patient taking up to 270 mg/day to control his alcohol consumption and craving before reducing to a lower 'maintenance' level (Ameisen, 2005).

Baclofen is generally well tolerated and can be safely given to patients with liver impairment (Leggio et al., 2010), where a lower dose may be sufficient. However baclofen-induced hepatitis in an alcohol-dependent patient has been reported (Macaigne et al., 2011). There are reports of reversible psychiatric disturbance when higher (120 mg/day, 275 mg/day) doses are used (see Dore et al., 2011; Leo and Baer, 2005).

Anticonvulsants

Topiramate. Topiramate is an anticonvulsant with multiple pharmacological actions. Its use in substance use disorders including alcohol dependence has recently been reviewed (de Sousa, 2010; Johnson and Ait-Daoud, 2010; Shinn and Greenfield, 2010). Topiramate does not currently hold a licence for such use.

In RCTs, topiramate (up to 300 mg/day) has been shown to improve the percentage of heavy drinking days, harmful drinking consequences, physical health and quality of life (Johnson et al., 2004, 2007, 2008) (Ib). Unlike other medication trials that start with abstinence, here topiramate was started in some patients while they were still drinking but aiming for abstinence.

There have been two trials comparing naltrexone and topiramate. Starting after detoxification, the number of alcohol-dependent patients that remained abstinent over 12 weeks was significantly greater in those receiving topiramate (titrated to 300 mg/day) compared with either naltrexone or placebo (Baltieri et al., 2008) (Ib). No differences were found between naltrexone and placebo. Notably, a greater number in the topiramate group engaged with Alcoholcs Anonymous (AA) than in the other groups. In a 6-month open randomised trial, both naltrexone (50 mg/day) and topiramate (titration to 200 mg/day, then increased to 400 mg/day if still craving or drinking; mean dose during study was ~200 mg/day) were equally effective, with almost half maintaining abstinence (Flórez et al., 2011) (Ib). In one study, topiramate was less efficacious than disulfiram (de Sousa et al., 2008; see above) (IIb).

However, trials of topiramate have reported some problematic side effects compared with placebo, such as paraesthesia (50.8% vs. 10.6%), 'taste perversion' (23.0% vs. 4.8%), anorexia (19.7% vs. 6.9%), and difficulty with concentration (14.8% vs. 3.2%) (from Johnson et al., 2007) (Ib). Such adverse events resulted in 12% of patients in the topiramate group dropping out, and people with alcohol dependence may be particularly susceptible to paraesthesia (Luykx and Carpay, 2010). This adverse event profile has likely limited clinicians using topiramate. Many of these problematic side effects are related to fast titration to high doses, and a slow titration to 300 mg/day over 6–8 weeks has been advocated (Johnson and Ait-Daoud, 2010). However 300 mg/day may still be too high for some patients.

Pregabalin. Pregabalin (flexible dosing 150–450 mg/day; average 275.8 + 95.6 mg/day) has been shown to result in similar abstinent or heavy drinking days as naltrexone (50 mg/day) (Martinotti et al., 2010) (Ib). Pregabalin was well tolerated; however, one person (3.2%) withdrew from the study due to confusion.

Specific serotonin reuptake inhibitors. Since serotonergic dysfunction has been implicated in alcohol dependence, particularly in early onset, trials have investigated the effect of specific serotonin reuptake inhibitors (SSRIs) in harmful alcohol use, abuse and dependence. However, in those without comorbid depression, their use cannot be recommended. There is no adequate evidence that they improve outcomes and in type 2 alcoholics (early onset, positive family history, impulsive/antisocial personality traits) receiving psychosocial interventions, they have been shown to worsen outcomes (Chick et al., 2004; Kranzler et al., 1996; Pettinati et al., 2000) (1b).

More recently, SSRIs have been conceptualised as reducing stress-induced relapse, but adding sertraline (100 mg) to naltrexone (50 mg) does not further improve drinking outcomes compared with naltrexone alone (Farren et al., 2009; O'Malley et al., 2008) (Ib). These patients were not depressed, and a more recent study suggests this combination may be beneficial in depressed alcoholics (Pettinati et al., 2010; see comorbidity section) (Ib). An open study with only 11–12 patients per group compared escitalopram (20 mg/day) alone with naltrexone (50 mg/day) or with gamma hydroxybutyric acid (GHB) (75 mg/kg) or with naltrexone and GHB (Stella et al., 2008) (IIb). Improvements were seen in all groups, with the smallest effect seen in escitalopram alone, and with the triple combination being the most effective after 6 months.

Other medications. There are a number of trials of other pharmacotherapies in alcoholism, although these are often small, open, single studies or not placebo-controlled. For example, antagonising dopaminergic activity with newer generation antipsychotics such as aripiprazole has shown some limited efficacy (Anton et al., 2008; Martinotti et al., 2009). GHB, a GABA-B agonist which also acts on GHB receptors in the brain and is used to treat narcolepsy, has also shown efficacy in treating alcohol withdrawal and relapse prevention (see review by Addolorato et al., 2009). It has a licence in some European countries, but concerns about its abuse potential currently limits its use in the

UK (Leone et al., 2010) (Ia); however, the advent of a new solid formulation (Alcover) may make this less of an issue (see Chick and Nutt, 2012). Finally, the 5HT3 antagonist, ondansetron, has shown promise, particularly in early onset alcoholism (Johnson, 2010). The mechanistic concepts behind these and other approaches to addiction treatments are discussed in Nutt et al., 2012.

Recommendations: preventing relapse, maintaining abstinence

- Acamprosate can be used to improve abstinence rates (A). It should be continued if the person starts drinking, since there is evidence that acamprosate reduces alcohol consumption (A), at least for a period to assess whether there is overall patient benefit attributable to acamprosate.
- Naltrexone can be used to reduce risk of lapse becoming a relapse, but there is less evidence to support its use in maintaining abstinence (A). Naltrexone may therefore be a better choice if someone is 'sampling' alcohol regularly but wishes to be abstinent.
- For acamprosate and naltrexone there is no consistent evidence to suggest which types of patient will respond, and relapse prevention medication should be offered to/considered for everyone who is alcohol dependent wanting to be abstinent (A).
- Disulfiram is effective if intake is witnessed. Disulfiram can be offered as a treatment option for patients who intend to maintain abstinence, and for whom there are no contraindications (B).
- Baclofen should be considered if a patient wants to be abstinent, has high levels of anxiety and has not benefited from or is unable to take acamprosate, naltrexone or disulfiram (C).
- SSRIs should be avoided, or used with caution in type 2 alcoholism (B).

Key uncertainties

- Who is likely to benefit from which pharmacotherapy?
- Is there a role for prescribing medication such as opioid antagonists to alter drinking behaviour in harmful alcohol drinking or alcohol abuse rather dependence?
- What is the role of sodium oxybate in managing alcohol withdrawal and relapse prevention?
- How long to continue the prescription, particularly if the patient has resumed drinking?
- Are any particular forms of psychosocial intervention better than others in the context of pharmacotherapy?

Opioid dependence

Opioid maintenance treatments

Methadone maintenance treatment: MMT

Background. Methadone, a mu opioid receptor agonist with a much longer half-life than heroin, is the most widely used and researched treatment for heroin dependence. Despite its widespread use, longer-term methadone maintenance continues to be disputed. Opinions and practice are strongly influenced by political/social context. There are a number of updated systematic reviews recently published, and a technology appraisal of both methadone and buprenorphine maintenance treatments was completed by NICE in 2007 (TA114) (NICE, 2007c) (Ia). This considered 31 systematic reviews and 27 RCTs, dated up to 2005, the majority of which concerned methadone maintenance. Studies were based in a variety of settings, and the quality of studies included was moderate to good. Most studies were of fixed-dose regimes with supervised consumption, although some later studies were of flexible dosing regimes. The doses used in the studies ranged from 20–150 mg daily. The main outcome measures of interest were retention in treatment and reduction in use of illicit opioid drugs. Since the publication of the NICE technology appraisal, there have been three new or updated Cochrane reviews, comparing methadone maintenance treatment (MMT) with no opioid replacement treatment (Mattick et al., 2009) (Ia); comparing buprenorphine maintenance treatment (BMT) with placebo and with MMT (Mattick et al., 2008) (Ia); and comparing agonist treatment alone with agonist treatment plus psychosocial treatment (Amato et al., 2011a) (Ia).

The research evidence remains firmly based on programmes with supervised consumption, whereas in practice, many treatment programmes provide methadone without supervision of consumption. Methadone is available in oral (liquid and tablet) formulations and as an injectable preparation. The injectable preparation is considered in the section below on injectable opioid maintenance treatment. Tablet formulations are not recommended in recent UK treatment guidelines because of the risk of injection of crushed tablets and increased risk of diversion (Department of Health, 2007). However, studies of the effectiveness of oral maintenance therapy do not address different formulations, probably because the dangers of misuse and diversion are low in treatment programmes in which consumption is supervised.

Goals of treatment. The goals of treatment are initially retention in treatment and the reduction of illicit drug use and of associated risks and harms, including reductions in heroin use (by self-report and by analysis of urine or hair samples), injecting, mortality, criminal activity and use of other drugs, and improved physical and psychological health. Maintenance is in itself a treatment; however it is often a stage in a long-term care plan with the ultimate goal of abstinence.

Effectiveness. Compared with no opioid replacement, MMT appears significantly more effective for retaining patients in treatment and for the reduction of heroin use (six RCTs), but not significantly more effective in reducing criminal activity (three RCTs); there was a trend towards reduction in mortality (four RCTs) (Mattick et al., 2009) (Ia). However, it was discussed that the RCTs were not suitable to measure the effects on morbidity, mortality and criminality, and that large-scale cohort studies show substantial effects on these outcomes. The impact of opioid substitution treatment on HIV infection has been assessed in a Cochrane review (Gowing et al., 2011). This concluded that oral substitute treatment reduces drug-related behaviours with a high risk of HIV transmission, but has less effect on sex-related behaviours (IIa). Overall, although the number of well-conducted RCTs of methadone maintenance treatment is small, the findings are supported by many observational studies (Marsch, 1998) (I).

Dosing. Methadone doses ranging from 60–100 mg daily are more effective than lower doses (<39 mg) in retaining patients in treatment and in reducing use of heroin and cocaine during treatment (Faggiano et al., 2003) (Ia). There are risks associated with methadone induction, and starting doses should be significantly lower (see Department of Health, 2007, and section on comparison of methadone and buprenorphine below).

Additional therapies. The optimal mode of delivery of methadone is unknown. The majority of research studies are based on supervised consumption, so the advantages of supervision over unsupervised dosing are therefore not established. Many programmes involve substantial additional therapies, ranging from regular counselling to integrated programmes including family therapy, psychiatric care and help with employment. An updated Cochrane review (Amato et al., 2011a) examined the effectiveness of agonist maintenance treatment combined with a specific psychosocial treatment versus the effectiveness of agonist maintenance treatment alone (with standard counselling). Thirty four RCTS were included, with a total of 3777 subjects. An earlier version of this review showed a reduction in heroin use with addiction of a psychosocial treatment, but the updated version with added studies found no evidence of reduction in heroin use or number of patients abstinent at the end of follow-up. There is no clear evidence of enhancement of agonist maintenance treatments by specific psychosocial treatments (IIa).

Buprenorphine maintenance treatment: BMT

Background. Buprenorphine is a long-acting mu opioid receptor partial agonist with improved safety over methadone. BMT is a more recently established approach than methadone, but there is a growing evidence base supporting equivalent effectiveness to methadone in maintenance treatment. A Cochrane review compared buprenorphine maintenance with placebo and with MMT (Mattick et al., 2008) (Ia). This review included 24 studies, all RCTs. In addition, the NICE technology appraisal of methadone and buprenorphine, referred to in the section on MMT, was published in 2007 (NICE, 2007c) (Ia). The goals of BMT are the same as those of MMT: the reduction of illicit drug use and associated risks and harms.

Effectiveness. Compared with no opioid agonist replacement, BMT is more effective in retaining patients in treatment at low, medium and high doses, but only medium (8–15 mg) and high (>15 mg) doses are effective in suppressing heroin use (Mattick et al., 2008) (Ia). In this systematic review buprenorphine was also compared with MMT, and appeared to be less effective in retaining patients in treatment than medium or high-dose methadone. However, this may relate to slower induction practice (described in the section on buprenorphine and methadone below). In summary, buprenorphine maintenance is an effective treatment for opioid dependence (Ia). A discussion of the advantages and disadvantages of MMT and BMT compared with each other is provided in a separate section below.

Dosing. Doses of 8–16 mg buprenorphine are superior to lower doses (Ia), 16 mg is superior to 8 mg (Ib), and doses of 12–24 mg are preferable for maintenance treatment (IV).

Comparison of methadone maintenance and buprenorphine maintenance treatments

Effectiveness. The Cochrane meta-analysis conducted to evaluate the outcomes for MMT versus BMT (Mattick et al., 2008) (Ia) consisted mostly of studies of fixed-dose regimes for methadone and buprenorphine, but this does not reflect clinical practice in many settings. In addition, most studies were done with buprenorphine and not with the combination of buprenorphine and naloxone. However, eight studies were included that reported flexible dosing, five of which were double-blind studies. A meta-analysis of these five studies showed lower rates of retention of patients for BMT RR 0.83 (95% CI 0.72–0.95) compared with MMT. The total number of patients in these pooled studies was 788, with very little heterogeneity (I^2=19.0%, p=29). However, over half of the patients in the pooled analysis were accounted for by one study n=405 (Mattick et al., 2003) (Ib). During this study, conducted between 1996 and 1998, patients were inducted onto BMT much more slowly than is now standard clinical practice. The authors note that the small difference in retention rates between BMT and MMT developed in the first 2 weeks of treatment, with the retention curves essentially parallel thereafter. There was no significant difference between MMT and BMT on heroin use as confirmed by urinalysis.

Evidence from large representative population samples is also informative when making clinical choices between buprenorphine and methadone for maintenance. Burns et al. (2009) (III) reported on treatment retention rates from the extensive health database in New South Wales, Australia. Retention in treatment was better for patients maintained on methadone (69% of patients remained in continuous treatment at 3 months, 57% at 6 months, and 44% at 1 year) than buprenorphine (39% at 3 months, 29% at 6 months, and 21% at 1 year). The hazard ratio of a patient leaving treatment with BMT compared with MMT was 1.89 (1.79–1.99: $p < 0.001$). Patients commencing on BMT were more likely to switch medications at least once ($p < 0.001$) and have multiple treatment episodes ($p < 0.001$) than those on MMT. However, the authors note that during this time buprenorphine was a novel treatment, whereas methadone maintenance was a well-established practice and induction with buprenorphine was often not performed properly (first dose after withdrawal symptoms occurred followed by fast titration to an effective dosage).

Safety. The Australian health database described above was analysed with data from the Australian National Deaths Index to investigate mortality for individuals on opioid replacement therapy (Degenhardt et al., 2009) (III). The time period studied captured 1644 deaths when patients and clinicians had a choice between BMT and MMT. Induction onto methadone treatment was significantly more hazardous with a crude mortality ratio (CMR) of 26.3 compared with buprenorphine treatment (CMR 2.5: relative risk 0.09, $p = 0.04$). However, cessation CMR was also high (17.3 both groups) and with higher drop-out rates for BMT, the overall standardised mortality ratio (SMR) was equal (7.3). Again it is possible that both these differences could be accounted for by too gentle induction regimes for buprenorphine.

In a study of the prevalence of corrected QT (QTc) interval prolongation during methadone and buprenorphine treatment, 4.6% of subjects on methadone had corrected QT intervals > 500 ms, 15% > 470 ms and 28.9% > 450 ms. All subjects on buprenorphine had QTc < 450 ms. There was a positive dose-dependent association between QTc interval and methadone dose. All eight patients with QTc > 500 ms were prescribed 120 mg or more of methadone (Anschersen et al., 2009) (III). Further information, debate and guidance is available elsewhere (e.g. Department of Health, 2007; Krantz et al., 2009).

The NICE technology appraisal of buprenorphine and methadone (NICE, 2007c) (Ia) acknowledges the effectiveness of both

MMT and BMT. The authors recommend that the choice of drug should be determined on a case-by-case basis, taking into account a person's history of opioid dependence, their commitment to a particular management strategy, and the risk benefits of each treatment. If both treatments are suitable, the NICE recommendation is to choose methadone; this recommendation is influenced by the current superior performance of methadone in cost-effectiveness analyses.

Summary. Both buprenorphine maintenance and methadone maintenance are effective treatments for individuals dependent on opioids. There is strong evidence that MMT increases the likelihood of a patient remaining in treatment. However, methadone maintenance appears to be a more risky treatment during induction. In addition, the risk of cardiac effects (prolonged QTc interval) appears higher with methadone, although this risk appears to be mainly associated with high-dose (>100 mg/day) methadone only, and the risk of related adverse events is not known. This may be of particular interest for patients who are prescribed other drugs that might prolong the QTc interval, such as antipsychotics. Further research is needed with more rapid induction regimes for buprenorphine treatment to see whether this removes some of the difference in retention rates in the early stages of treatment.

Buprenorphine with naloxone. Buprenorphine is also available as a sublingual tablet combined with naloxone in a 4:1 ratio (Suboxone®). The active ingredient in sublingual administration is just buprenorphine as the naloxone is not very well absorbed, and open-label trials show that the product is free from opioid antagonist effects on sublingual administration (Amass et al., 2004) (Ib). This product has been used in successful studies in maintenance and detoxification (Amass et al., 2004; see Ling et al., 2010) (I), including in adolescents and young people (Woody et al., 2008) (I).

If the tablet is misused by crushing and used by intravenous injection or intranasally, the naloxone is also active and will cause opioid withdrawal symptoms in opioid users. The product is therefore intended to discourage injection without interfering with effectiveness with sublingual administration. There is evidence from naturalistic setting post-dispensing surveillance studies that diversion of buprenorphine/naloxone does occur, but that it is less prevalent than diversion of buprenorphine alone (McCormick et al., 2009; Mammen and Bell, 2009) (III)). There is evidence that the buprenorphine/naloxone combination is less likely to be injected than buprenorphine alone, although some individuals do inject it (Degenhardt et al., 2009) (III).

Slow-release oral morphine. A small number of short-term cross-over studies (in special populations, e.g. patients intolerant to methadone) of slow-release oral morphine (SROM) have been published. These show similar efficacy to methadone, but no long-term data are available (Bond et al., 2011; Eder et al., 2005; Mitchell et al., 2004; Winklbaur et al., 2008) (Ib). However, experiences in Austria show that SROM is frequently abused and dominates the black market (Beer et al., 2010).

Dihydrocodeine. A single RCT from the UK of dihydrocodeine (30 mg equivalent to 2.5 mg methadone) and methadone showed dihydrocodeine had a similar treatment retention rate to methadone. There was no difference in other measured outcomes, but there was a lot of switching in the dihydrocodeine group to methadone (Robertson et al., 2006) (Ib).

Injectable opioid maintenance treatment

Background. Injectable opioid treatment (IOT), also known as heroin-assisted treatment (HAT), has a long history, which is remarkable for variations between national jurisdictions. It was used in many parts of the UK during the twentieth century, although many had commented on the lack of evidence underpinning treatment. This lack of evidence was reflected in our previous BAP guidelines, which stated that IOT could be a possible second-line approach for those resistant to methadone to improve recruitment and retention (Lingford-Hughes et al., 2004). During the past few years a number of studies have expanded the evidence base considerably (Ferri et al., 2011) (Ia). In addition to the main findings below, it is of note that study reports contain detailed description of what constitutes optimised oral treatment, and that patients randomised to optimised oral treatment also show improvement over baseline, in a group often selected for treatment resistance.

Goals of treatment. The general goals of treatment are those of other forms of substitute prescribing for treatment of opioid dependence; namely, the reduction of illicit heroin use, of injecting and other risk behaviours, and of associated harms. The focus differs from oral methadone maintenance in terms of selection of patients. Because there is considerable evidence supporting oral methadone maintenance, the use of injectable drugs has been considered mainly for those who have failed to benefit from optimal oral treatment, or who have not been attracted to or retained in treatment by oral methadone maintenance programmes (though see Haasen et al., 2010 below) (Ib).

Effectiveness: injectable diamorphine. Several open-label RCTs of on-site diamorphine provision compared with oral methadone have added to the literature base in recent years (Haasen et al., 2007 (Ib); March et al., 2006 (Ib); Oviedo-Joekes E, et al., 2009 (NAOMI) (Ib); Strang et al., 2010 (RIOTT) (Ib); van den Brink et al., 2003 (Ib)). The findings of these studies are consistent across the different treatment contexts. There is increased retention in IOT/HAT compared with control groups; reductions in self-reported illicit heroin use, and improved outcomes in terms of quality of life or health outcome measures. One study reported improved outcomes in relation to reduced consumption of alcohol (Haasen et al., 2009) (Ib). The Cochrane review by Ferri et al. (2011) (Ia) concluded that evidence suggested heroin alongside methadone for long-term, treatment refractory opioid users reduced illicit substance use and criminal activity and possibly reduced mortality and increased retention in treatment. However, due to the higher rate of serious adverse events, injectable heroin is an option for those that have failed previous maintenance treatments.

A number of the studies have reported longer-term follow-up outcomes – the study from the Netherlands demonstrates continued retention at 4 years of 55.7% (95% CI: 47.6–63.8%), and response according to the multifactorial dichotomous measure was significantly better for patients continuing 4 years of HAT compared with patients who discontinued treatment: 90.4% versus 21.2% (difference 69.2%; odds ratio (OR) = 48.4, 95% CI: 17.6–159.1). Those who continued HAT treatment also had fewer health problems and were more likely to have stopped illicit drug

and excessive alcohol use (Blanken et al., 2010) (III). The German study also demonstrates improved long-term retention (Verthein et al., 2008) (III).

Inclusion criteria are typically those who have failed on oral opioid treatment, although the recent German study (Haasen et al., 2010) (Ib) included a group that was not currently on oral treatment. Controlled studies are now necessary to examine whether diamorphine treatment could be considered as one of several options in treating severely opioid-dependent patients, regardless of previous maintenance treatment experience.

Research reports also include cost utility analyses. The study in the Netherlands (Dijkgraaf et al., 2005) (Ib) analysed costs of addiction treatment, other health treatment, law enforcement and victim costs and found increased quality-adjusted life years (QALYs) per patient-year and a cost saving in the diamorphine group. However, the outcomes reported remain limited by a relative reliance on self-reported illicit drug use, with only two studies including biological measures. The illicit drug outcome in the German trial included urine and hair data but supplemented with self-report where these were not available. The recently reported UK study, RIOTT, had a reduction in urine tests positive for illicit heroin as the primary outcome measure.

Some studies provide data about the frequency of serious adverse events (Rehm et al., 2001, 2005) (III), with a lower mortality rate among the treatment group in a Swiss study compared with mortality of Swiss opioid users in the general population.

Effectiveness: injectable methadone. The UK study, RIOTT (Strang et al., 2010) (Ib), included an arm in which participants were randomised to receive injectable methadone. These subjects did not show the benefits demonstrated in the injectable heroin arm. Previous studies comparing injectable heroin and methadone have been observational studies without randomisation; this is the first randomised comparison.

Effectiveness: injectable hydromorphone. The North American study included an arm in which participants received hydromorphone to inject, rather than diamorphine. Results were equivalent, and the place of oral hydromorphone is being evaluated in a follow-up trial. (SALOME, Oviedo-Joekes et al., 2010) (Ib).

Recommendations: opioid maintenance treatment for opioid dependence

Methadone maintenance treatment

- MMT is an appropriate treatment option for opioid-dependent patients. It is effective in reducing heroin use, injecting, and sharing of injecting equipment (A).
- MMT is more effective at doses in the range 60–120 mg than at lower doses. Following safe induction of methadone treatment (see Department of Health Guidelines), consideration should be given to higher maintenance doses (A).

Buprenorphine maintenance treatment

- BMT is an appropriate treatment option for opioid-dependent patients. It is effective in reducing heroin use (A).
- Buprenorphine should be prescribed at doses of 8 mg or higher when used for maintenance treatment (B), and preferably at doses over 12 mg (D).
- Where concerns over diversion are paramount, buprenorphine/naloxone combinations may be preferred (B).

Choice of methadone or buprenorphine maintenance treatment

- Both methadone and buprenorphine are effective treatments. Opioid-dependent patients should be offered either medication, guided by patient choice and safety considerations. (A).

Additional therapies

- MMT or BMT should be provided in conjunction with psychosocial interventions such as regular counselling (B).

Injectable opioid maintenance treatments

- Highly supervised injectable diamorphine maintenance treatment should be considered for patients who have failed to respond to optimised MMT or BMT (B).
- We do not recommend injectable methadone treatment at present, although further studies are warranted (C).

Key uncertainties – opioid maintenance treatment for opioid dependence

- How does BMT compare with MMT when high doses and faster induction are used?
- How significant is the difference in safety of induction of methadone and buprenorphine treatment?
- What is the clinical significance of the differences in cardiac effects of methadone and buprenorphine?
- Is there a role for injectable opioid maintenance treatment for people with severe opioid dependence who have not already tried oral MMT or BMT?

Management of withdrawal from opioid drugs

Background. There are good-quality systematic reviews of the main pharmacotherapeutic approaches: methadone at tapered doses (Amato et al., 2005) (Ia), buprenorphine tapering (Gowing et al., 2009a) (Ia) and symptomatic treatment with α2 adrenergic agonists (Gowing et al., 2009b) (Ia). There is also a small number of small RCTs of SROM and one of dihydrocodeine. In addition, there is a systematic review of studies addressing the role of psychosocial treatments in supporting pharmacological treatment regimes for withdrawal (Amato et al., 2011b) (Ia). The main outcomes studied are severity of withdrawal symptoms, completion of withdrawal and adverse effects of the withdrawal regimen. With a wide variety of pharmacotherapeutic options, patient choice can help to guide a clinical decision. In 2007, a NICE clinical guideline on opioid detoxification was published (NICE, 2007b) (Ia).

Goals of treatment. The goals of treatment are to alleviate withdrawal symptoms and to complete withdrawal without

adverse effects. In evaluating the outcome of the withdrawal process, it is important to distinguish the outcome of withdrawal itself from longer-term measures such as continued abstinence from heroin. Heroin dependence is often a chronic relapsing disorder.

Effectiveness: methadone at tapered doses. The Cochrane review by Amato et al., (2005) (Ia) considered 20 studies including methadone versus adrenergic agonists (11 studies), methadone versus other opioids (five studies) and methadone versus anxiolytics (two studies). Methadone at tapered doses is effective in reducing withdrawal symptoms. Comparing methadone with any other pharmacological treatment for opioid withdrawal, there was no difference in treatment completion (14 studies, RR 1.08, 95% CI 0.95–1.24) or abstinence at 1 month follow-up (two studies, RR 1.17, 95% CI 0.72–1.92). The withdrawal symptoms experienced differed according to the medication used and the detoxification programme followed. Gowing et al. (2009a) (Ia) reported there was a trend towards more successful completion with buprenorphine compared with methadone (see below).

Effectiveness: buprenorphine. In the Cochrane review by Gowing et al. (2009a) (Ia), buprenorphine appeared equivalent to methadone at tapered doses in reducing the severity of withdrawal symptoms. The withdrawal symptoms may resolve more quickly with buprenorphine. There was a trend for better completion rates with buprenorphine (four studies, RR 1.18, 95% CI 0.93–1.49). Buprenorphine was better than α2 agonists at ameliorating withdrawal symptoms. Buprenorphine was associated with lower mean peak withdrawal scores (four studies, SMD -0.45, 95% CI -0.64 to -0.25, $p < 0.001$) and lower mean overall withdrawal scores (two studies, SMD -0.59, 95% CI -0.79 to -0.39). Completion of detoxification was more likely with buprenorphine than α2 agonists (10 studies, RR 1.64, 95% CI 1.31–2.06).

Effectiveness: α2 adrenergic agonists. Withdrawal symptoms and withdrawal completion rates are similar for α2 adrenergic agonists and methadone at tapered doses (Cochrane review of 24 studies including 21 RCTs: Gowing et al., 2009b) (Ia) but α2 adrenergic agonists appear inferior to buprenorphine in alleviation of withdrawal symptoms and in withdrawal completion. Nevertheless, they are effective and may be an appropriate choice for patients who prefer not to have an opioid drug. Lofexidine is preferable to clonidine because of its more favourable side-effect profile: in particular, lofexidine causes hypotension less frequently than clonidine.

Effectiveness: slow release oral morphine. A randomised, double-blind, double dummy, parallel group design study compared SROM with methadone for detoxification from opioid maintenance treatment. Subjects had a tapered dose reduction of SROM or methadone over 16 days. Completion rates were 51% (SROM) versus 49% (methadone) (difference between groups 95% CI -12% to 16%). There was no significant difference in craving or signs and symptoms of withdrawal (Madlung-Kratzer et al., 2009) (Ib).

Additional therapies or approaches. A Cochrane review (Amato et al., 2011b) (Ia) of 11 studies of five different psychosocial interventions and two detoxification medications (buprenorphine and methadone) found adding any psychosocial treatment to any detoxification treatment showed benefit in terms of reduced drop-outs (six studies, RR 0.71, 95% CI 0.59–0.85), use of opiates during treatment (four studies, RR 0.82, 95% CI 0.71–0.93) and at follow-up (three studies, RR 0.66, 95% CI 0.53–0.82) and clinical absences during the treatment RR 0.48 (95%CI 0.38–0.59).

Recommendations: management of withdrawal from opioid drugs

- There is a robust evidence base for three approaches to opioid detoxification: methadone at tapered doses, buprenorphine, or an α2 adrenergic agonist (usually lofexidine) (A).
- The choice of agent will depend on what treatment patients are already receiving, for example methadone or buprenorphine and individual preference. However, if short duration of treatment is desirable, or in patients with mild or uncertain dependence, α2 adrenergic agonists may be preferable (A).
- SROM is not recommended for opioid detoxification (B).
- Ultra-rapid detoxification is not recommended (A).
- Pharmacological management of withdrawal should be supported by psychosocial treatment (A).

Key uncertainties

- The comparative effectiveness of buprenorphine versus methadone.
- Optimal treatment regimens for management of withdrawal using buprenorphine need to be established.

Opiate dependence: relapse prevention and maintaining abstinence

There has been very little investigation of the role of pharmacotherapy in relapse prevention or maintaining abstinence compared with alcohol or stimulants. Naltrexone is the only pharmacotherapy that has received much attention, but one trial of baclofen (60 mg/day) in abstinent opioid addicts showed promise in promoting abstinence, reducing withdrawal and depressive symptoms (Assadi et al., 2003).

Oral naltrexone. A good-quality systematic review by Cochrane (Minozzi et al., 2011 (Ia)) and a NICE technology appraisal (NICE, 2007d) (Ia) have been recently published of naltrexone maintenance treatment to support maintenance of abstinence from opioid drugs in formerly dependent patients following detoxification. Naltrexone is prescribed for oral use as a 50 mg tablet. The studies on which these guidelines are based have been of patients prescribed the oral preparation. However, since the mid-1990s, naltrexone subcutaneous implants and intramuscular depots have been developed, although they are not yet licensed in the UK as pharmacological products.

The Cochrane reviewers (Minozzi et al., 2011) (Ia) concluded that there was no significant difference in treatment retention for people treated with naltrexone with or without adjunctive psychosocial therapy compared with placebo with or without psychosocial therapy (six studies, RR 1.43, 95%CI 0.72–2.82). There was a significant reduction in illicit heroin use as assessed by urinalysis (six studies RR 0.72; 95% CI 0.58–0.90) but the difference was not statistically significant when comparing

the studies of naltrexone versus placebo only. Naltrexone with psychosocial treatment showed reduced re-incarceration rates compared with psychosocial treatment alone (two studies RR 0.47, 95%CI 0.26–0.84) but the sample size was small.

The NICE technology appraisal (NICE, 2007d) (Ia) considered the Cochrane review together with 13 RCTs and three non-randomised comparative studies. None of the studies were conducted in the UK, the studies were of poor to moderate quality, and randomisation was not adequately reported in the RCTs. The degree of supervision of medication in the studies was variable. Nine of the RCTs studied the effectiveness of strategies to improve retention on naltrexone, such as incentive vouchers, psychosocial therapies and pharmaceutical agents. The main outcomes reported were retention in treatment, relapse rates and re-incarceration rates. Given that outcomes for retention and abstinence were likely to be higher in clinical practice than reported in the RCTs, as in practice treatment is targeted at highly motivated people seeking abstinence, NICE concluded that naltrexone is an appropriate treatment option in detoxified formerly opioid-dependent people who have high motivation and with adequate supervision.

Naltrexone implants and injectable sustained release naltrexone. An RCT of 56 patients given a 6-month naltrexone implant versus usual aftercare found naltrexone was associated with significantly fewer days of heroin use in the 6-month follow-up period (Kunøe et al., 2009) (Ib). In an RCT of 60 patients, Comer et al. (2006) (Ib) found improved retention in treatment for injectable sustained-release naltrexone compared with placebo, and that retention was higher for those given higher dose naltrexone. Superior effects on abstinence from illicit drugs were not demonstrated. An RCT of 70 patients reported that a naltrexone implant significantly reduced relapse to heroin use and resulted in higher blood naltrexone levels compared with oral (Hulse et al., 2009) (Ib). In a comparison of two separate trials (one of oral naltrexone and one of injectable sustained-release naltrexone), Brooks et al. (2010) (IIb) concluded that patients with severe baseline heroin use showed better outcomes when treated with oral naltrexone and intensive psychosocial therapy (behavioural naltrexone therapy), while those with less severe baseline heroin use showed better outcomes with injectable naltrexone. However, these conclusions are uncertain as they are drawn from a comparison of the interventions in two separate, though concurrent, trials (Brooks et al., 2010) (IIb). Others have reported that many patients did not accept a second injection (Kunøe et al., 2010), and plasma levels of naltrexone implants have been shown not to remain at the targeted levels for the intended time (Hulse et al., 2009).

Concerns have been raised whether naltrexone is associated with higher mortality due to suicide or overdoses. One study reported that risk of death appeared low during naltrexone treatment; however, it was higher post-treatment compared with methadone (Gibson and Degenhardt, 2007) (III). Studies using the implant have shown reduced opioid overdoses (Hulse et al., 2005) (III)) and similar mortality to methadone (Ngo et al., 2008) (III)).

Recommendations: naltrexone for treatment of opioid dependence

- Oral naltrexone treatment should be considered for formerly opioid-dependent people who are highly motivated to remain abstinent (D).

Key uncertainties

- How can naltrexone be used most effectively?
- What is the role for injectable or depot naltrexone?
- Is there a role for other pharmacotherapies?

Benzodiazepine dependence

Background

These guidelines address two differing patient populations: the ‘therapeutic dose’ users, which includes patients who have been prescribed benzodiazepines usually on a long-term basis for a disorder such as anxiety or insomnia but who do not abuse their prescription, and the other patients who misuse their prescription and/or use illicit benzodiazepines, often in high doses. This may include benzodiazepines purchased via the internet (Levine, 2007). Individuals in either category may be dependent. Abuse of benzodiazepines is often associated with other substance abuse (e.g. to ‘come down’ from stimulants or to enhance the effect of opioids). It is important to establish the presence or absence of dependence to help determine whether pharmacological treatment is appropriate. Problems consistent with ICD-10 or DSM-IV dependence criteria in addition to physiological withdrawal symptoms should be elicited. Use patterns in high-dose abusers include once-daily dosing to maximise effect, seeking euphoric or sedative effects, escalating dosages, ‘binge’ use and very high self-reported doses. The withdrawal syndrome can be severe.

The literature and evidence base on the management of ‘therapeutic dose’ dependence is far more extensive and systematic than for the management of benzodiazepine dependence in illicit, high-dose users. Transferring the management principles from the ‘therapeutic dose’ literature to illicit drug users is affected not only by the differing clinical picture, but also by the need to avoid abuse and diversion of any prescribed medication (Fenton et al., 2010; Seivewright, 2000).

Management of benzodiazepine dependence in ‘therapeutic dose’ users

Management often takes place in primary care and can include minimal interventions, gradual dose reduction and gradual dose reduction with additional psychological or pharmacological treatments. A stepped approach can be considered, moving through minimal interventions to gradual dose reduction and then additional therapies aimed at specific symptoms. Minimal or brief interventions include GPs sending a letter advising patients of the need to reduce their benzodiazepine prescription, and provision of booklets on self-help strategies. In primary care populations, minimal interventions were more effective than routine care in achieving cessation of benzodiazepine use (three studies, OR = 4.37, CI 2.28–8.40) increasing the success rates from 5% to 22% (Parr et al., 2008)(1a))

Gradual dose reduction alone. Dose-reduction schedules frequently last several weeks, although there is wide variation from abrupt discontinuation to discontinuation over a year or more (Oude Voshaar et al., 2006a) (Ia). Gradual dose reduction is preferable to abrupt discontinuation of benzodiazepine (Denis et al., 2006) (Ia).

Switching from a short half-life benzodiazepine to a long half-life benzodiazepine before gradual taper does not receive much support (Denis et al., 2006 (Ia); Murphy and Tyrer, 1991 (Ib)), but may be useful if reduction of short half-life benzodiazepine causes problematic withdrawal symptoms. In primary care patients who had failed to cease benzodiazepine use with minimal intervention, gradual dose reduction was more effective than routine care in achieving cessation of use (51% vs. 15%) (Oude Voshaar et al., 2003) (1b). At 15-month follow-up 36% of those who received gradual dose reduction were abstinent based on benzodiazepine prescription data, compared with 15% of those who received routine care (Oude Voshaar et al., 2006b) (Ib). The British National Formulary contains advice on gradual benzodiazepine reducing regimes (see BNF).

Gradual dose reduction and additional psychological therapies

Additional psychological therapies increase cessation rates compared with both routine care (three studies, OR = 3.38, CI 1.86–6.12) and gradual dose reduction alone (seven studies, OR = 1.82, CI 1.25–2.67) (Parr et al., 2008) (Ia). The psychological interventions employed in these studies generally included some form of group CBT. Compared with gradual dose reduction alone, additional psychological intervention seemed particularly beneficial in patients using benzodiazepines for insomnia and panic disorder (1b). In a primary care study Baillargeon et al. (2003) (Ib) reported that 77% of patients with chronic insomnia withdrew from benzodiazepines with gradual dose reduction and group CBT compared with 38% with gradual dose reduction alone (OR = 5.3, CI 1.8–16.2). The effect persisted at 12-month follow-up. Morin et al. (2004) (Ib) found similar results in their study of older adults with chronic insomnia. Patients who received gradual dose reduction plus CBT were more likely to be benzodiazepine-free after the initial intervention (85%), compared with those who received gradual dose reduction alone (48%) or CBT alone (54%). For panic disorder patients attempting to stop benzodiazepines, successful discontinuation was significantly greater in the gradual dose reduction plus CBT group, than the gradual dose reduction alone group (76% vs. 25%, $p < 0.005$) (Otto et al., 1993) (Ib). A pilot study of CBT delivered via the internet for cessation of benzodiazepine use found good acceptability amongst participants but limited take-up (Parr et al., 2011) (IIb).

Gradual dose reduction plus additional pharmacotherapy has shown no benefit compared with gradual dose reduction alone in a meta-analysis (14 studies, OR = 1.30, CI 0.97–1.73) (Parr et al., 2008) (Ia). The 14 studies involved 11 different pharmacotherapies. Four of the pharmacotherapies showed significant effects on benzodiazepine discontinuation rates in single studies (1b). Garfinkel et al. (1999) (IIb) reported discontinuation rates of 77% with the addition of melatonin compared with 25% with gradual dose reduction alone. Rickels et al. (1999) (Ib) added sodium valproate, trazodone or placebo to a benzodiazepine taper. At 5 weeks post-taper, 79% of sodium valproate and 67% of trazodone, but only 31% of placebo patients were benzodiazepine free. These differences were not maintained at 12 weeks post-taper. Adjunctive paroxetine in patients without major depression increased discontinuation rates compared with gradual dose reduction alone (46% vs. 17%) (Nakao et al., 2006) (Ib). However, in patients in primary care with depression, adding paroxetine to gradual dose reduction did not increase benzodiazepine discontinuation rates above gradual dose reduction and placebo, with two-thirds in each group ceasing benzodiazepine use. In both groups depressive ratings improved with no significant effect of paroxetine, but paroxetine did have a beneficial effect on anxiety symptoms (Zitman and Couvée, 2001) (Ib). Within the meta-analysis the odds ratio for these two paroxetine studies was significant (OR = 1.73, CI 1.01–2.96) (Parr et al., 2008) (Ib).

Two studies of imipramine with conflicting results were not reported in the meta-analysis. In patients with generalised anxiety disorder and long-term benzodiazepine use, imipramine increased discontinuation rates compared with placebo (83% vs. 37%, $p < 0.01$). Buspirone also increased discontinuation rates but non-significantly compared with placebo (68% vs. 37%, $p < 0.06$) (Rickels et al., 2000)(1b). However, in patients with panic disorder and long-term benzodiazepine use, imipramine or buspirone did not significantly increase discontinuation rates (Rynn et al., 2003) (Ib).

Flumazenil (a benzodiazepine antagonist) reduced withdrawal symptoms and craving compared with an oxazepam taper over 8 days in benzodiazepine-dependent patients. Flumazenil-treated patients also had greater abstinence rates post detoxification (Gerra et al., 2002) (Ib). A flumazenil infusion has also been shown to be a safe and effective treatment for benzodiazepine withdrawal (Hood et al., 2009) (III).

Management of benzodiazepine dependence in high-dose and/or illicit drug users

There is little evidence to guide practitioners in the management of this often difficult-to-treat population. Patients should be assessed to determine why they are using benzodiazepines, and alternative treatment strategies employed for problems such as anxiety and insomnia. The presence of alcohol or other illicit drug abuse or dependence should be determined.

Benzodiazepine abuse is frequent amongst heroin users and those in opioid substitution treatment (Gelkopf et al., 1999; Gossop et al., 1998; Jaffe et al., 2004). Ongoing current benzodiazepine use is associated with concurrent poorer clinical outcomes in this population (Darke et al., 2010) (III). Prescribing of benzodiazepines during opioid substitution treatment is common, despite a lack of research to support this (Reed et al., 2011) (III). Such prescribing can often slip into de facto maintenance despite the lack of evidence for this. Use of benzodiazepines in combination with opioids is associated with increased opioid toxicity and performance deficits (Lintzeris et al., 2006; Nielsen et al., 2007) (III). A history of prescription of benzodiazepines was associated with mortality in Scottish patients receiving methadone in primary care (McCowan et al., 2009) (III).

Vorma et al. (2002) (Ib) evaluated gradual dose reduction with CBT versus an unspecified standard withdrawal regime in high-dose benzodiazepine users. There was no significant difference in discontinuation rates (13% experimental group vs. 27% control group, OR 0.4 (0.1–1.5), $p = 0.20$). Over half the users in each group were able to reduce their dose by > 50% (54% vs. 59%). Reductions to therapeutic dose levels were maintained (Vorma et al., 2003) (Ib)). McGregor et al. (2003) (Ib) conducted an RCT of fixed gradual dose reduction (5–10 mg reduction per day) versus symptom-triggered diazepam taper methods during inpatient benzodiazepine withdrawal treatment in 44 high-dose benzodiazepine users. There were no significant differences in abstinence rates (27% gradual dose reduction vs. 18% symptom triggered). Both groups showed a

reduction in benzodiazepine dosage of 86% to around 14 mg which was maintained at 1 month post-discharge. Liebrenz et al. (2010) have proposed the need to evaluate agonist substitution treatment in high-dose benzodiazepine dependence, where individuals have not been able to undergo withdrawal. However, they recognise this needs to be balanced against the risks, particularly in regard to negative effects on cognition and memory.

In an open study in methadone-maintained benzodiazepine-dependent patients, clonazepam was substituted for their benzodiazepine of choice. Patients were then either detoxified from or maintained on clonazepam, and outcome measured was self-reported illicit benzodiazepine use. Illicit benzodiazepine use was reduced in the maintenance group compared with the detoxification group (Weizman et al., 2003) (III). Wickes et al. (2000) (III) described five case studies of clobazam maintenance in methadone-maintained patients with mixed results. Clobazam was reported by the patients as being less sedating than diazepam.

Other small studies in benzodiazepine-dependent methadone-maintained patients have examined community reduction and contingency management. McDuff et al. (1993) (III) reported that 12 out of 22 patients misusing primarily alprazolam completed an outpatient reduction procedure which averaged 7.8 weeks. Contingency management with rewards for benzodiazepine-free urines showed some success. However, results were not maintained at the end of the contingency phase (Stitzer et al., 1982) (III).

In clinical practice some services have used carbamazepine for inpatient benzodiazepine detoxification in opioid dependence, particularly when the benzodiazepine use has been illicit. There is some evidence to support carbamazepine in attenuating the withdrawal symptoms from benzodiazepines (Di Costanzo and Rovea, 1992; Garcia-Borreguero et al., 1991; Schweizer et al., 1991) (IIb).

In practical terms for illicit drug users, there should be an extended assessment of their benzodiazepine use, dependence and needs with resistance to requests for immediate prescriptions. Opioid treatment should be optimised in opioid-dependent benzodiazepine users and benzodiazepine needs reassessed after this has been achieved. Much benzodiazepine use – even apparently dependent benzodiazepine use – resolves if this strategy is followed. Benzodiazepines should be detected in serial drug screens. If a benzodiazepine prescription is to be issued, there should be a clear treatment plan outlining the goals and time frame of treatment. A single, long-acting benzodiazepine should be prescribed and initiated on a daily dispensing basis. There is no need to match the high self-reported illicit doses. Prescribing need only be moderate dose, often far lower than claimed usage even in the presence of concerns about withdrawal seizures (Williams et al., 1996) (III). Doses greater than 30 mg diazepam equivalent per day should rarely be prescribed (Department of Health, 2007). Reduction schedules should be negotiated at the outset. In high-dose users, reducing to a 'therapeutic' benzodiazepine dose level may be an appropriate first aim (McGregor et al., 2003; Vorma et al., 2002, 2003) (Ib), because of the high relapse or drop-out rates with detoxification. Once this has been achieved and there is sufficient psychosocial stability, further reductions or detoxification can occur. For drug users on 'maintenance' benzodiazepine prescriptions, the treatment should be reviewed, including medication compliance with drug screening, and ideally a gradual dose reduction plan put in place.

Z-drugs - zaleplon, zolpidem and zopiclone

There is limited evidence on the prevalence of Z-drug abuse and dependence, although dependence has been reported (Hajak et al., 2003; Jaffe et al., 2004; Victorri-Vigneau et al., 2007) (III). In case of dependence, withdrawal should include tapering of dose as with benzodiazepines. Broader guidance about their use is also available from NICE (NICE, TA77 (Ia)).

Recommendations: benzodiazepine dependence

Establishing the presence or absence of physiological withdrawal symptoms and the dependence syndrome is important in determining whether pharmacological treatment is appropriate.

Management of benzodiazepine dependence in 'therapeutic dose' users

- In early/mild dependence minimal interventions such as advisory letters, other information provision or General Practitioner advice should be offered (A).
- Where dependence is established, gradual dose reduction of prescribed benzodiazepine is recommended (A).
- Switching from a short half-life benzodiazepine to a long half-life benzodiazepine before gradual taper should be reserved for patients having problematic withdrawal symptoms on reduction (D).
- Additional psychological therapies increase the effectiveness of gradual dose reduction particularly in individuals with insomnia and panic disorder. Consideration should be given to targeted use of these interventions (B).
- Additional pharmacological therapies do not appear to increase the effectiveness of gradual dose reduction. However, use of additional pharmacotherapy such as antidepressants, melatonin, valproate, and flumazenil should be considered on an individual basis (C).

Management of benzodiazepine dependence in high-dose and/or illicit drug users

- Maintenance prescribing in illicit drug users cannot be recommended on the basis of existing evidence, although it may reduce illicit benzodiazepine use in some patients (D).
- Carbamazepine may be used instead of benzodiazepines to control withdrawal symptoms (C).
- Doses greater than 30 mg diazepam are rarely necessary, and this is sufficient to prevent benzodiazepine withdrawal symptoms including withdrawal seizures in very high-dose benzodiazepine users (D).
- Drug screens should be monitored for benzodiazepine and other drug use (D).
- Reduction of high-dose use to a therapeutic dose level may be a useful therapeutic objective in some dependent users (D).
- Clinicians should remember the potential risks of benzodiazepine prescribing in patients co-dependent on alcohol and/or opioids (D).

Key uncertainties

- What is the optimal speed or duration of gradual dose reduction?
- Is a stepped care model from simpler to more complex interventions for benzodiazepine detoxification helpful?
- Can additional psychological interventions be delivered effectively by alternatives to face-to-face contact?
- In illicit drug users, is there a role for benzodiazepine agonist maintenance therapy?
- Do modified detoxification strategies for high-dose users (e.g. partial reduction and stabilisation at therapeutic dose prior to completing reduction) work?

Stimulant drugs: cocaine (including crack), methamphetamine and amphetamine

Research on pharmacotherapy for stimulant drugs has focused mainly on the treatment of dependent users of the various forms of cocaine and amphetamine. Treatment goals are usually the management of withdrawal and the maintenance of abstinence, although the value of substitution treatment with harm reduction goals is also considered. Overall, the evidence supporting pharmacological treatment is weak.

Management of withdrawal from stimulant drugs

Amphetamine. A Cochrane review identified four studies from which it was concluded that neither mirtazapine nor amineptine were significantly effective in treating amphetamine withdrawal (Shoptaw et al., 2009) (Ia). Concerning mirtazapine, one RCT suggested that mirtazapine may reduce hyperarousal and anxiety symptoms associated with amphetamine withdrawal (Kongsakon et al., 2005) (Ib). However a more recent study failed to find any benefit of mirtazapine over placebo (Cruickshank et al., 2008) (Ib).

Cocaine. In a double-blind placebo-controlled trial of amantadine, propranolol and both in combination, for treatment of patients with severe cocaine withdrawal symptoms, 119 patients were randomly allocated to the four treatment groups (Kampman et al., 2006) (Ib). None of the three active treatments (propranolol, amantadine or their combination) was significantly more effective than placebo in promoting abstinence from cocaine. Among patients highly adherent to study medication, propranolol treatment was associated with better treatment retention and higher rates of cocaine abstinence compared with placebo.

Cocaine dependence: preventing relapse, maintaining abstinence

Psychostimulant drugs. Recently a Cochrane review has been published regarding efficacy of psychostimulant drugs for treatment of cocaine dependence (Castells et al., 2010) (Ia). Sixteen studies were included, with a total of 1345 patients. Drugs investigated included dextroamphetamine, mazindol, methylphenidate, modafinil and bupropion, methamphetamine and selegiline. Psychostimulant drugs did not improve treatment retention or reduce cocaine use. There was a statistical trend in favour of psychostimulant drugs in improving sustained abstinence from cocaine. Considering all outcomes for individual drugs, only the proportion of patients achieving sustained abstinence from cocaine was higher with dextroamphetamine, bupropion and modafinil at a statistical trend of significance.

Dopamine agonists. Dopamine agonists (amantadine, bromocriptine and pergolide) have been investigated in 17 randomised studies with 1224 participants, with urine tests for cocaine use and retention in treatment as the main outcomes of interest. A meta-analysis (Amato et al., 2011c) (Ia) found no significant difference between interventions. In a study of patients with severe cocaine withdrawal symptoms, amantadine was not found to be effective in retaining patients in treatment either alone or in combination with propranolol (Kampman et al., 2006) (Ib). The evidence does not support the use of dopamine agonists.

Anticonvulsants. A Cochrane review included 17 trials with a total of 1194 patients (Minozzi et al., 2008) (Ia). Overall, anticonvulsants were not found to be effective in improving treatment retention, in reducing use of cocaine or craving for cocaine. Anticonvulsants studied included carbamazepine (six studies), tiagabine (three studies), lamotrigine and valproate (one study each) for which no significant differences in outcomes were found compared with placebo (1b). There were three studies of gabapentin and two of phenytoin in which placebo was superior to anticonvulsant (1b). Topiramate (one study) may be beneficial in patients capable of achieving some level of abstinence (Kampman et al., 2004) (1b).

Disulfiram. Initial studies of the effectiveness of disulfiram for patients dependent on both cocaine and alcohol were thought to reflect efficacy for alcohol dependence (Carroll et al., 1998, 2000) (Ib), but later studies showed an independent effect on cocaine use. Disulfiram reduced cocaine use in a placebo-controlled trial when given with either interpersonal psychotherapy (IPT) or CBT. A combination of disulfiram with CBT was most effective in reducing cocaine use for those patients who were not alcohol dependent. Disulfiram appears to reduce the rewarding effects of cocaine use (Baker et al., 2007) (III). Other trials of disulfiram have been based on patients with concurrent alcohol dependence or opioid dependence (maintained on methadone or buprenorphine); for those with concurrent alcohol and cocaine dependence, a combination of disulfiram and naltrexone was most likely to result in three consecutive weeks of abstinence from alcohol and cocaine (Pettinati et al., 2008a) (Ib).

Antidepressants. A range of antidepressant drugs has been investigated for treating cocaine dependence or problematic use, including desipramine (17 trials, 75–300 mg); fluoxetine (five trials, 20–60mg); nefazodone (<400 mg) and ritanserin (10 mg) (two trials each); bupropion (three trials, 300 mg) and one trial each with imipramine (150–300 mg), buspirone (30 mg), gepirone 16 mg), paroxetine (20 mg), citalopram (20 mg), venlafaxine (<150 mg), selegiline (20 cm^2 patch containing 1.0 mg/cm^2), tryptophan (8 g/day), sertraline (110 mg) and imipramine (150–300 mg). Some 37 randomised studies with (3551 participants) have been meta-analysed (Pani et al., 2011) (Ia). Studies of patients with concurrent opioid dependence were studied separately, but yielded similar results. Desipramine performed no better than placebo in

terms of retention in treatment, although there was a non-significant trend in favour of desipramine in terms of cocaine-free urines. One trial favoured imipramine over placebo in terms of clinical self-report, and one trial suggested that fluoxetine maintained people in treatment. However, there was no significant effect when selecting studies using operationally defined diagnostic criteria. Pani et al. (2011) concluded that the evidence did not support the efficacy of antidepressants. There has since been a small open trial of reboxetine which showed some improvement but also adverse effects (Szerman et al., 2005) (III). In summary, there is no evidence to support the use of antidepressants for cocaine dependence (1a).

Antipsychotic drugs. A meta-analysis and systematic review included seven small studies (293 participants), with risperidone, olanzapine and haloperidol (Amato et al., 2007) (Ia). No significant differences were found for any of the efficacy measures comparing any antipsychotic drug with placebo. The studies of haloperidol and olanzapine were too small to give conclusive results (Amato et al., 2007).

Baclofen. Initial studies demonstrating reduced craving and cocaine use in patients with high baseline cocaine use have not been supported by a multicentre RCT of baclofen (60 mg/day) in an 8-week programme for severely dependent users (Kahn et al., 2009) (1b). The effectiveness of baclofen at higher doses is unknown (see alcohol section), as is effectiveness as a relapse prevention agent in patients already cocaine-abstinent.

Cocaine vaccine. Cocaine vaccines are in development: high levels of anti-cocaine antibodies can sequester cocaine and facilitate inactivation. The cocaine vaccine has been studied in methadone-maintained opioid-dependent patients. Only 38% achieved target levels of IgG, but there were significantly more cocaine-free urines in these patients. The blockade achieved was only short term, and further work on the vaccine is required (Martell et al., 2009) (Ib).

Amphetamine dependence: preventing relapse, maintaining abstinence

Antidepressants. Randomised double-blind trials have investigated fluoxetine, amlodipine, imipramine and desipramine. Fluoxetine may decrease craving in the short term, and imipramine may increase adherence to treatment in the medium term. No reduction in amphetamine use or other benefits were identified (Srisurapanont et al., 2001) (Ia).

Dexamphetamine. Substitute prescribing with dexamphetamine or methylphenidate for treatment of amphetamine dependence has been reported as possibly beneficial in small studies (Elkashef et al., 2008) (IV). Descriptive studies (see Lingford-Hughes et al., 2004) suggest benefits in terms of reduction in amphetamine use and in injecting; however, all are small, and five are retrospective and rely on self-reported outcomes. In one pilot RCT (Shearer et al., 2001) (Ib) 41 long-term dependent amphetamine users were randomised to dexamphetamine (up to 60 mg) or weekly counselling only. Reductions in use were seen in both groups without discernable differences, but the study lacked power.

Modafinil. Shearer et al. (2009) (Ib) studied 80 methamphetamine-dependent subjects allocated randomly to modafinil (200 mg/day) (n = 38) or placebo (n = 42) under double-blind conditions. There were no differences in methamphetamine abstinence, craving or severity of dependence, although medication-compliant subjects tended to provide more 'clean' urine samples over the 10-week treatment period (p = 0.07). There were significant reductions in systolic blood pressure (p = 0.03) and in weight gain (p = 0.05) in modafinil-compliant subjects compared with placebo.

Methylphenidate and aripiprazole. Tiihonen et al. (2007) (Ib) compared aripiprazole (15 mg/day), slow-release methylphenidate (54 mg/day), and placebo in 53 individuals with intravenous amphetamine dependence over 20 weeks. Patients who received methylphenidate had significantly fewer amphetamine-positive urine samples than patients who had received placebo (OR = 0.46, 95% CI 0.26–0.81). In contrast, aripiprazole patients had significantly more amphetamine-positive urine samples than the placebo group (OR = 3.77, 95% CI 1.55–9.18). The study was terminated early because of these effects of aripiprazole.

Disulfiram. Because of its potential in treating cocaine dependence, the effect of disulfiram on amphetamine use was studied in 10 subjects (Sofuoglu et al., 2008) (IIb) where it was found to enhance the subjective effects of dextroamphetamine, including anxiety, subjective 'high' feeling, 'bad drug effects' and 'drug liking'.

Naltrexone. One RCT reported that naltrexone (50 mg/day) significantly increased the number of amphetamine-negative urines compared with placebo (Jayaram-Lindström et al., 2008) (Ib).

Recommendations: stimulant drugs

- There is no convincing evidence supporting the use of pharmacological treatment for amphetamine and cocaine abuse and dependence. Psychosocial interventions such as CBT and contingency management remain the mainstay of treatment (S).
- We do not recommend the use of dopamine agonists, antidepressants or anticonvulsants (A).
- Disulfiram is not yet an established treatment for cocaine use, but clinicians should be alert to further studies as the current small evidence base is of interest (C).
- There is no clear evidence to support substitute prescribing of dexamphetamine for treatment of cocaine or amphetamine dependence, but definitive studies are warranted and clinicians should be alert to further studies (D).

Key uncertainties

- When to use pharmacological strategies?
- Which are optimal psychosocial interventions?
- Is there a role for disulfiram, and if so, what is the appropriate dose?

- Is there a role for baclofen at higher doses, or in relapse prevention?
- Is there a role for naltrexone?
- Is there a role for propranolol?

'Club' drugs

Ecstasy (MDMA)

Ecstasy dependence is rare, and there are no specific trials examining it. Depressive symptoms in MDMA users may lead to an antidepressant being prescribed, but it is likely to be ineffective in many (see comorbid section).

A MixMag 2009 Survey revealed that 19% (227/1197) MDMA users had ever been prescribed antidepressants, 9.5% (113/1180) had ever taken MDMA while on antidepressants and 8.8% in the last 12 months. This is of concern due to risks of interaction, 5HT syndrome, as well as poor efficacy. As for other comorbid disorders, the advice is to delay diagnosis of depressive disorder until 2–4 weeks abstinent.

Recommendations: Ecstasy

- There is absence of any evidence for a role for pharmacotherapy in treating Ecstasy dependence or withdrawal. Psychosocial approaches are recommended (S).
- Assessment of whether the individual has a depressive disorder should occur in absence of Ecstasy use (S).

Key uncertainties

- Whether long-term use incurs any impact on neurotransmitter systems, for example the serotonergic system, that could be prevented or ameliorated with pharmacotherapy?

Gamma-hydroxybutyric acid (GHB) and its precursors

Pharmacological treatments for users of gamma-hydroxybutyric acid (GHB) and its precursor drugs gamma-butyrolactone (GBL) and 1,4-butanediol are currently directed at management of the withdrawal syndrome. This is similar to that of alcohol, but sometimes with particularly marked neuropsychiatric symptoms and autonomic instability that can be life-threatening. For a comprehensive review of GHB abuse, dependence and withdrawal, see Gonzalez and Nutt, (2005), McDonough et al. (2004) and Wojtowicz et al. (2008) and the case series of 19 patients undergoing GBL withdrawal (Bell and Collins, 2011) (III). Some patients have required urgent intensive care as a result of severe delirium, seizures and rhabdomyolysis. Currently there are no clear predictors of who might develop such difficulties, and so facilities to admit patients for acute medical care should always be available.

The majority of case reports are with benzodiazepines but high initial doses (40–120 mg diazepam in first 24 h, sometimes more) are usually needed (Bell and Collins, 2011; McDonough et al., 2004). There are case reports of the use of other sedative agents, mainly pentobarbital, in patients resistant to treatment with benzodiazepines (McDonough et al., 2004; Schneir et al., 2001; Sivilotti et al., 2001) (III). A recent study reported a titration and tapering procedure in 23 moderate to severe GHB-dependent inpatients whereby pharmaceutical GHB replaced illicit GHB, which was then tapered over 1 week (de Jong et al., 2012) (III). Patients experienced low withdrawal symptoms and none developed psychosis or delirium. Given that GHB/GBL have GABA-B agonist activity, baclofen may be used in withdrawal in much the same way that benzodiazepines are used in alcohol withdrawal, particularly as it is much safer than barbiturates (see case report LeTourneau et al., 2008) (III). Bell and Collins (2011) have reported a case series of 19 patients treated for withdrawal from GBL, most of whom were outpatients. They used high-dose diazepam (mean dose in the first 24 h 75 mg) together with baclofen (10 mg tds). Sixteen patients completed withdrawal, although several had lapses to GBL use during treatment. One patient developed delirium that required admission to an inpatient detoxification unit. Insomnia, anxiety and depression were common persisting symptoms for some weeks after withdrawal.

Recommendations: GHB/GBL

- Planned outpatient withdrawal from GHB/GBL should be approached with caution and particular attention given to previous withdrawals, comorbid dependence (particularly to benzodiazepines), physical and psychiatric health and social support (S).
- Successful management of withdrawal has been achieved using high-dose benzodiazepine regimes, either alone or in conjunction with baclofen. This approach is the treatment of choice at present (C).
- Although outpatient treatment is possible, there are several case reports of severe withdrawal syndromes with life-threatening complications. Consideration should therefore be given to inpatient admission for management of withdrawal and ability to admit patients for acute medical care should always be available (S).

Key uncertainties

- What is the optimal assessment and treatment regimen to prevent complications of withdrawal?
- What are the indicators for suitability for inpatient or outpatient withdrawal?
- What is the potential utility of GHB/sodium oxybate in managing withdrawal?

Cannabis

Dependence on cannabis is third behind that to tobacco and alcohol in terms of population prevalence, with up to 1% of the European population meeting criteria (Wittchen et al., 2011). Research related to pharmacological treatment of cannabis abuse and dependence focuses mainly on alleviation of withdrawal symptoms to aid quit attempts (Budney et al., 2004; Cui et al., 2001; Hart, 2005). The symptoms are primarily emotional and behavioural, although appetite change, weight loss, and physical discomfort are also reported. An assessment scale for cannabis withdrawal has recently been developed by Allsop and colleagues (2011). Pharmacological approaches and studies have recently been reviewed (van den Brink, 2012).

Treating cannabis withdrawal

Oral tetrahydrocannabinol (THC or dronabinol). There are two small randomised, double-blind placebo-controlled trials of oral tetrahydrocannabinol (THC) (Budney et al., 2007; Haney et al., 2004) (Ib) which reduced withdrawal symptoms, including reduction in sleep problems and anxiety. Doses ranged from 30–90 mg daily. Reductions in craving and depressed mood were greater with higher doses.

Haney et al. (2008) compared oral THC (60 mg) with placebo, with lofexidine (2.4 mg) and with a combination of THC and lofexidine treatment under laboratory conditions with mixed results. The combination of lofexidine and oral THC produced the most robust improvements in sleep and decreased withdrawal symptoms, craving, and relapse. In a more recent, larger study (Levin et al., 2011) (Ib) 156 cannabis-dependent adults were enrolled in a randomised, double-blind, placebo-controlled, 12-week trial of dronabinol 20 mg twice a day or placebo started after 1 week of abstinence. There was no significant difference between treatment groups in the proportion of participants who achieved 2 weeks of abstinence. Dronabinol was well tolerated, improved treatment retention and provided better relief from withdrawal symptoms than placebo.

Lithium carbonate. There are two small open-label studies of the use of lithium carbonate (Bowen et al., 2005; Winstock et al., 2009) (IIb) that suggest potential benefit in alleviating cannabis withdrawal and a RCT is underway.

Anticonvulsants. No clear benefit has been found in two small randomised double-blind placebo controlled trials of divalproex sodium. Haney et al. (2004) found it reduced craving, but increased ratings of irritability, anxiety and tiredness, whereas Levin et al. (2004) found no benefit (Ib).

Antidepressant drugs. The antidepressant drugs bupropion, fluoxetine and mirtazapine have been tested in placebo-controlled trials. In two studies of bupropion (Carpenter et al., 2009 (106 subjects); Haney et al., 2001 (10 subjects)) (Ib) no benefit was found, and bupropion worsened irritability, sleep disturbance and depressed mood. Riggs et al. (2007) (III) found no benefit from fluoxetine in depressed adolescents with substance use disorders. In a small placebo-controlled laboratory study of mirtazapine, Haney et al. (2010) found mirtazapine improved sleep and food intake but not other withdrawal symptoms or relapse to cannabis use.

To date there appears to be no substantial evidence for antidepressant prescribing to aid cannabis withdrawal. Depressed mood is more common in cannabis users and therefore clinicians are likely to consider antidepressant use. It is possible however that prescribing some antidepressants such as SSRIs and bupropion may exacerbate anxiety and insomnia in the early stages of withdrawal.

Cannabinoid receptor antagonists. A study of rimonabant was discontinued because of significant medication side effects (Montebello R, personal communication). It is unknown whether other antagonists would have a similar effect.

Baclofen. In a small human laboratory study of baclofen in cannabis intoxication, withdrawal and relapse (Haney et al., 2010), baclofen decreased craving for tobacco and cannabis in a dose-dependent fashion, but had little effect on mood during abstinence and did not decrease relapse. Baclofen also worsened cognitive performance.

Buspirone. In a single controlled trial of buspirone (50 participants), there was a significant difference in favour of buspirone in terms of negative urine drug screens achieved (McRae-Clark et al., 2009) (Ib).

Hypnotic medications. Sleep difficulties are commonly reported by people attempting to quit cannabis use. Some practitioners use a low-dose benzodiazepine to aid sleep in the short term during cannabis withdrawal, although there is a risk of abuse and dependence. A laboratory study of extended-release zolpidem (Vandrey et al., 2011) demonstrated that zolpidem attenuated the effects of cannabis withdrawal on sleep architecture, and improved sleep efficiency but not sleep latency.

Recommendations: cannabis withdrawal

- At present there is no clear evidence base for pharmacological treatment of cannabis withdrawal and no pharmacological treatment can be recommended (D).
- We do not recommend the use of antidepressant drugs for the treatment of cannabis withdrawal (D).

Key uncertainties

- Which pharmacotherapeutic approaches for the management of cannabis withdrawal should be given priority, for example, oral THC, lithium, buspirone?
- What are the optimal dose, dosing frequency, and participant characteristics for the use of oral THC?
- What are the risks and benefits of short-term hypnotic prescribing (such as benzodiazepines or zolpidem)?
- Are combination medication regimens aimed at individual symptoms helpful?
- What might be the role of cannabinoid receptor-specific agents?
- What is the clinical utility of psychometrically validated scales for assessing the symptomatology and severity of cannabis withdrawal?
- Which approaches are most helpful for those with comorbid mental illness, physical health and other substance use disorders such as co-occurring cigarette smoking?
- What is role of medication in preventing relapse?

Polydrug use

In clinical practice, it is common for patients to abuse or even to have developed dependence on more than one drug. One approach is to apply evidence-based treatments for each drug simultaneously or sequentially. However, it would be helpful to have a clear evidence base for a treatment strategy for polydrug users, so we have examined treatment studies including patients who were using more than one drug in the month prior to starting treatment.

Opioids and cocaine

Comparison of methadone and buprenorphine maintenance. Cocaine reduces serum methadone concentration (Tennant and

Shannon, 1995), and although some patients may respond to an increase in methadone dose, the cocaine use itself should be addressed. Three RCTs have compared methadone with buprenorphine maintenance treatment for patients using both opioids and cocaine. One RCT (Schottenfeld et al., 2005) (Ib) found that methadone at an average dose of 80 mg was superior to buprenorphine average dose 15 mg, whereas two studies showed no difference between the two treatments in opioid or cocaine-free urines at 26 weeks (Strain et al., 1994) and 24 weeks (Schottenfeld et al., 1997) (Ib).

Use of two drugs for treatment of opioid dependence and cocaine use. There have been a number of randomised placebo-controlled trials adding a treatment for cocaine use to methadone or buprenorphine treatment. These have been largely negative in terms of reducing cocaine use. These include adding bupropion to methadone maintenance (Margolin et al., 1995) (Ib), desipramine to methadone or buprenorphine (Kosten et al., 2003; Oliveto et al., 1999) (Ib), and gabapentin to methadone (González et al., 2007) (Ib).

By contrast, significant reductions in cocaine use have been found in two studies of disulfiram (250 mg/day) combined with methadone maintenance (Petrakis et al., 2000) (Ib) and buprenorphine maintenance (George et al., 2000) (Ib). A more recent double-blind, placebo-controlled RCT of disulfiram for treatment of cocaine abuse in methadone-stabilised patients found increasing cocaine use in patients treated with low-dose disulfiram (62.5 mg or 125 mg daily) and decreasing cocaine use only in patients given high-dose disulfiram (250 mg; Oliveto et al., 2011) (Ib).

Two studies adding tiagabine to methadone maintenance treatment (González et al., 2003, 2007) (Ib) have found significant reductions in cocaine use at 12-week follow-up. One study of bupropion and/or contingency management added to methadone showed significant reductions in cocaine use at 25 weeks only in the group receiving methadone plus bupropion plus contingency management (Poling et al., 2006) (Ib).

There is a published 24-week phase RCT of a cocaine vaccine in methadone maintenance patients (Martell et al., 2009) (Ib). Five vaccinations were given over 12 weeks; 38% of patients achieved high IgG levels with significant reduction in cocaine use, although this treatment would be expected to remain effective for 2 months only.

Opioids and alcohol

A systematic review of the effect of methadone maintenance treatment on alcohol consumption (Srivastava et al., 2008) (Ia) examined 15 studies: three found an increase, three found a decrease, and nine found no difference in the alcohol consumption. Nava and colleagues (2008) (IIb) compared high-dose methadone (200 mg) with high-dose buprenorphine (32 mg) in an open RCT of 218 patients over 1 year. Those on buprenorphine reported less craving and lower alcohol consumption than those on methadone. There is evidence from the studies of cocaine and opioid users described above that disulfiram reduces alcohol consumption in conjunction with methadone if patients are prepared to stop drinking alcohol.

Opioids and benzodiazepines

Studies mainly examine detoxification from both substances in inpatient settings but there are no RCTs. de Wet and colleagues (2004) (III) reported that opioid patients using benzodiazepines experienced more severe withdrawal symptoms, including opioid-specific withdrawal symptoms, than users of opioids alone during inpatient detoxification. A pilot study of 27 patients comparing buprenorphine plus carbamazepine with oxazepam plus carbamazepine (Schneider et al., 2000) (III) showed similar completion rates for both groups but superior symptom relief in the buprenorphine/carbamazepine group.

Reed and colleagues (2007) (IIb), in a preliminary study of patients undergoing inpatient detoxification, found superior completion rates and less severe withdrawal symptoms in opioid and benzodiazepine-dependent patients where buprenorphine was used for management of withdrawal rather than methadone. Kristensen and colleagues (2006) (IIb) compared a buprenorphine and valproate regime with a clonidine and carbamazepine regime in an open-label study of inpatient detoxification from both opioids and benzodiazepines. Earlier symptom relief was achieved with the buprenorphine/valproate combination.

Studies in community settings are limited. A study of benzodiazepine detoxification for those regularly using benzodiazepines, mostly alprazolam, reported 12 out of 22 methadone patients were successful (McDuff et al., 1993) (IIb). Weizman and colleagues (2003) (III) compared detoxification from benzodiazepines using clonazepam with clonazepam maintenance treatment in patients engaged in a methadone maintenance programme. Low-dose maintenance appeared more successful than detoxification in preventing illicit benzodiazepine use (66 patients followed for 1 year).

Alcohol and cocaine

This is a common comorbidity and challenging to treat.

Naltrexone. Naltrexone appears ineffective in reducing either alcohol or cocaine use in alcohol and cocaine users when used at daily doses of 50 mg (Hersh et al., 1998; Schmitz et al., 2004) (Ib) or 100 mg (Schmitz et al., 2009) (Ib). Higher doses of naltrexone, such as 100 mg/day and 150 mg/day, may have beneficial effects in combined dependence, particularly in men (McCaul, 1996; Oslin et al., 1999; Pettinati et al., 2008b) (Ib). Those with higher severity of cocaine but not alcohol dependence were less likely to achieve abstinence from cocaine (Ahmadi et al., 2009). Early benefit at 2 months was lost at 6 months (McCaul, 1996) (Ib). Schmitz et al. (2009) found no differences between naltrexone (100 mg/day) and placebo added to contingency management. Poor compliance and engagement in treatment is consistently found.

Disulfiram. Disulfiram at daily doses of 250–500 mg appears to improve treatment retention and duration of abstinence from both alcohol and cocaine (Carroll et al., 1998) (Ib) with a sustained response at 12 months for cocaine, but not alcohol (Carroll et al., 2000) (Ib). The effect of disulfiram on reducing cocaine is independent of its effect on alcohol consumption, although those that did best stopped or reduced their drinking.

Naltrexone/disulfiram combination. Pettinati et al. (2008a) (Ib) conducted an RCT of disulfiram (250 mg/day) alone, naltrexone (100 mg/day) alone, disulfiram/naltrexone in combination, and placebo (208 patients). Medication adherence was low in all groups. Patients taking disulfiram either alone or in combination

were more likely to abstain from alcohol and cocaine. Patients taking the combination of disulfiram and naltrexone were the most likely to achieve three consecutive weeks abstinence from alcohol and cocaine. All medications were well tolerated, with no serious adverse events.

Recommendations:

Opioids and other harmful substance use, abuse or dependence

- There is currently inadequate evidence to favour either MMT or BMT for patients who use both opioids and cocaine or alcohol. Either treatment is appropriate for the management of the opioid dependence (A).
- Disulfiram may be helpful for patients committed to abstinence from alcohol (D).
- There is no evidence to support adding bupropion, desipramine, amantadine or gabapentin to methadone or buprenorphine maintenance treatment to reduce cocaine or alcohol use in opioid-dependent cocaine or alcohol users (B).
- Benzodiazepine withdrawal and opioid withdrawal can be carried out concurrently in an inpatient setting (B).
- Buprenorphine is superior to methadone for relief of opioid withdrawal symptoms when opioid and benzodiazepine withdrawal is carried out concurrently in an inpatient setting (B).

Alcohol and cocaine

- Disulfiram should be considered for patients with concurrent alcohol and cocaine abuse/dependence (C).
- A combination of disulfiram and naltrexone may be considered for patients with concurrent alcohol and cocaine abuse/dependence (D).

Key uncertainties

- The appropriate dose response of disulfiram remains to be established.
- What is the potential of tiagabine as a treatment for cocaine and opioid dependence?
- The potential of a cocaine vaccine needs further study.
- Is high-dose buprenorphine superior to high-dose methadone in terms of reduction of craving for alcohol and of alcohol consumption?
- There is inadequate evidence to guide the management of benzodiazepine withdrawal in opioid-dependent patients in community settings.

Nicotine dependence

Nicotine dependence is recognised in ICD-10 and DSM-IV as a psychiatric disorder. The defining features include failed attempts to abstain, powerful urges to use nicotine, and withdrawal symptoms on cessation. An estimated 80% of cigarette smokers are classifiable as dependent by DSM-IV criteria, and the treatment of nicotine dependence has been investigated in a large number of well-conducted RCTs. There are high-quality systematic reviews (Moore et al., 2009; Stead et al., 2008) (Ia) and treatment guidelines (USDHHS, 2008; West et al., 2000).

The main harmful effects of nicotine dependence arise from long-term health effects of tobacco constituents other than nicotine, and this is particularly true for smoking cigarettes. The benefits and sustainability of reductions in cigarette consumption are uncertain; therefore the primary goal of treatment is permanent cessation of smoking. An abstinent period of 6 months or longer is widely regarded as an acceptable marker for successful cessation, in that it permits a quite accurate prediction of permanent cessation: relapse after this time is estimated at around 50% over a lifetime (West et al., 2005). However, there has been more recent interest in the use of nicotine replacement products for patients attempting to reduce their cigarette consumption (Nicotine Assisted Reduction in Smoking) prior to planning a specific quit attempt, as well as for those who are ready to quit. In this strategy, the long-term goal remains permanent cessation, but a short-term goal may be to reduce smoking by at least 50%, with a review of the quitting goal after 3 months.

Nicotine replacement therapy

Nicotine replacement therapy (NRT) consists of products that allow smokers to obtain therapeutic doses of nicotine without other toxins, to provide a partial substitute for smoking and to aid smoking cessation. Nicotine from the product binds to nicotinic acetylcholinergic receptors in the central nervous system in a dose-dependent manner. This reduces urges to smoke and nicotine withdrawal symptoms, and partially blocks the rewarding effect of a cigarette if a lapse occurs.

Products and dosing. A variety of nicotine replacement products are available. These include nicotine-containing gum (2 mg and 4 mg), transdermal patches (varying doses), inhalator/inhaler, nasal spray (0.5 mg per dose, usually administered two doses at a time), sublingual tablet, mouth-spray, lozenge and now electronic cigarettes (though these are not typically seen as anti-smoking devices). These products have differing rates of delivery of nicotine. Transdermal patches provide the slowest delivery. The nasal spray and electronic cigarette provides the fastest delivery (tmax is around 10 min), although the gum, inhalator, lozenge, mouth-spray and sublingual tablet typically achieve peak levels within 30 min of use. In many countries, including the UK, products may be used singly or in combination (usually of the transdermal patch plus a faster-acting product). In some countries, such as the USA, combination use is not permitted, according to the label.

When used with a quit attempt, NRT should be started on, or up to 2 weeks prior to, the target quit date. It should be used for a minimum of 8 weeks, and then as long as is necessary. As described above, NRT can be used with the goal of smoking reduction, where there is a long-term goal of smoking cessation: the aim is to reduce cigarette consumption by at least 50%, and the quitting goal should be reviewed after 3 months.

Clinical effectiveness. All the above forms of NRT can help people who make a quit attempt to increase their chances of successfully stopping smoking. From the findings of a Cochrane review (Stead et al., 2008) (Ia) based on 111 trials with over 40,000 participants, NRTs have been estimated to increase the rate

of quitting by 50–70%. There is evidence (from six trials) that combining a nicotine patch with a rapid-delivery form of NRT (nicotine combination therapy) is more effective than a single type of NRT (nicotine monotherapy). Pooled evidence from four trials indicates that starting a nicotine patch for a brief period before the target quit date significantly increases the rate of cessation compared with initiating the patch on the quit day. Indirect comparisons of a large number of trials showed no difference in success rates between regimes involving abrupt cessation of nicotine patch use and those in which tapered doses of nicotine patch were used.

A further systematic review (Moore et al., 2009) (Ia) concentrated on studies of NRT used in patients who aim to reduce smoking but have no short-term goal to quit smoking. Seven RCTs were included, with a total of 2767 patients. The longer-term quit rate was approximately doubled in those who had received NRT compared with those who had used placebo. Most of the evidence comes from trials with regular behavioural support and monitoring. There is evidence that NRT can be effective when given without behavioural support (Hughes et al., 2011). However, general population studies have produced mixed findings (West and Fidler, 2011; West and Zhou, 2007) (IIb).

Dosing. In highly dependent smokers there appears to be a significant benefit of 4 mg gum compared with 2 mg gum (from four trials), but only marginal evidence of a benefit from higher doses of patch (from seven trials) (Stead et al., 2008) (Ia).

Safety. NRT delivers pure nicotine, which is just one of the components smokers already obtain from cigarettes. NRT does not pose a cancer risk and is safe in patients with stable coronary heart disease (Stead et al., 2008) (Ia). It is effective in helping smoking cessation in patients with chronic obstructive pulmonary disease (van der Meer et al., 2001) (Ia). NRT may present some risk to the foetus (Lumley et al., 2009) (Ia), but this may be less harmful to the foetus than smoking during pregnancy (see section on pregnancy). A minority of smokers transfer dependence from cigarettes to NRT. Such patients would probably resume smoking if they could not continue NRT use.

Additional therapies and context of treatment. Additional behavioural support improves overall success rates but does not appear to be required for NRT to be effective (Stead et al., 2008) (Ia). There is some evidence to suggest that abstinence rates are lower in those who buy NRT over the counter in comparison with those who obtain NRT by prescription (West and Fidler, 2011) (III).

Specific patient groups. NRT has not yet been shown to be effective in adolescents (two small trials, see Grimshaw and Stanton, 2006) (Ia).

Antidepressants

There are several reasons to believe antidepressants might help in smoking cessation. Nicotine withdrawal may produce depressive symptoms or precipitate a depressive episode; nicotine may have antidepressant effects that maintain smoking, and antidepressants may substitute for this effect; and some antidepressants may have a specific effect on neural pathways (e.g. inhibiting monoamine oxidase) or receptors, (e.g. blockade of nicotinic-cholinergic receptors) underlying nicotine addiction (Hughes et al., 2007) (Ia).

The atypical antidepressant bupropion has been well studied and is licensed as an aid to smoking cessation. It has dopaminergic and adrenergic actions, and also appears to act as an antagonist at the nicotinic acetylcholinergic receptor (Fryer and Lukas, 1999). Bupropion is produced as a sustained release tablet formulation. Results of a meta-analysis of 49 trials (Hughes et al., 2007) (Ia) show bupropion to be more effective than placebo in promoting continuous abstinence from smoking. This effect appears to be independent of its antidepressant action, and the effect is also independent of the patient's history of depression.

In their meta-analysis and Cochrane review, Hughes and colleagues (2007) (Ia) considered the following antidepressant drugs in addition to bupropion: nortriptyline; SSRIs including fluoxetine, paroxetine and sertraline; monoamine oxidase inhibitors; venlafaxine; and St John's Wort. There was clear evidence for effectiveness of nortriptyline and bupropion, and both are well tolerated. No significant effects were found for fluoxetine, paroxetine, sertraline, the monoamine oxidase inhibitor moclobemide, or for venlafaxine. There were no long-term trials of St John's Wort.

Anxiolytic drugs

Anxiolytic drugs have also been of interest to aid smoking cessation. The rationale for this is that anxiety symptoms are present in nicotine withdrawal, and that smoking is a behaviour that is sometimes used to relieve anxiety. In a meta-analysis and Cochrane review, Hughes and colleagues found one trial each for diazepam, meprobamate, metoprolol and oxprenolol, and two trials for buspirone (Hughes et al., 2000) (Ia). No trial showed a significant effect in helping smokers to quit, but confidence intervals were wide. The authors conclude that the role for anxiolytic drugs cannot be ruled out on current evidence.

Nicotine receptor partial agonists

Nicotine receptor partial agonists may help people to stop smoking by a combination of counteracting withdrawal symptoms (acting as an agonist) and reducing smoking satisfaction (acting as an antagonist, see Nutt et al., 2012). In the review and meta-analysis by Cahill et al. (2011) (Ia), 11 trials of varenicline were identified. Varenicline at standard dose increased the chances of successful long-term smoking cessation between two- and threefold compared with placebo or bupropion. Varenicline has been found in direct and indirect comparisons in RCTs to be more effective than bupropion or nicotine patches (Cahill et al., 2011; NICE, 2007e) (Ia). It has also been associated with higher success rates in routine clinical practice (Brose et al., 2011) (III). It is unclear whether varenicline is more effective than optimised NRT (for example patches plus a faster-delivery form of NRT). Lower-dose regimens of varenicline also increased success rates, while reducing the incidence of adverse events (the most common being nausea). Limited evidence suggests that varenicline may have a role to play in relapse prevention. There have been reports of possible serious adverse events, including depressed mood, agitation and suicidal thoughts, but their relationship to varenicline has not been substantiated (Gunnell et al., 2009; Tonstad et al., 2010) (III). Varenicline has not been established as safe in pregnancy, breastfeeding or adolescence. There is evidence that a very low-cost partial agonist which is available in some parts of Europe, cytisine, is effective in aiding cessation (West et al., 2011).

Nicotine vaccines

Nicotine vaccines are currently in development. These induce antibodies which bind to the nicotine molecule to prevent it entering the brain, and are intended as relapse prevention adjunctive treatment, rather than a cessation treatment. Data to date are suggestive of efficacy, but there is currently insufficient evidence for them to be recommended for use.

Recommendations: nicotine

- NRT, varenicline, bupropion, nortriptyline and cytisine are all effective in aiding smoking cessation. Prescriptions for one of these should be offered to all smokers (A).
- Optimal results can be expected with either varenicline or combination of NRT patch plus a faster-acting form of NRT (A).
- All smokers should also be encouraged to use behavioural support where this is available (for example in the UK National Health Service all smokers should have access to a trained stop-smoking practitioner), but unwillingness to use behavioural support should not preclude prescribing pharmacotherapy (A).
- All pharmacotherapies can safely be used in patients with stable cardiac disease (A).
- NRT should be considered to aid smoking reduction as a prelude to quitting in smokers not ready to make a quit attempt but willing to reduce (A).
- Although effectiveness is not established in these patient groups, NRT can be considered on an individual basis for pregnant women and for young people under 18 (D).
- Nortriptyline and cytisine are very low-cost, effective medications that may be of particular value in low to middle income countries (D).

Key uncertainties

- It is not clear whether varenicline is more effective than combination of NRT patch and a faster acting product.
- The benefits of combining multiple treatments need to be evaluated.
- There is uncertainty about whether NRT bought over the counter is currently proving effective in some populations.
- It is not clear whether cytisine is more or less effective than varenicline under a similar dosing schedule.

Pregnancy

In pregnancy, the general principles of best practice need to apply to the foetus as well as to the woman. There are a number of sources of evidence and good practice to guide practitioners despite the difficulties, ethical and otherwise, of conducting RCTs in this population. We focus here on pharmacotherapy, and the reader is directed elsewhere for broader management issues, for example NICE clinical guideline on pregnancy and complex social factors which included women who misuse alcohol and/or drugs (NICE, 2010b) (Ia), the Confidential Enquiries into Maternal Deaths reports (Centre for Maternal and Child Enquiries (CMACE), 2011), NICE guidance on antenatal and postnatal mental health (NICE, 2007a) (Ia) and smoking (NICE, 2010a) (Ia), and the Cochrane review on improving pregnancy outcomes by pre-pregnancy health promotion (Whitworth and Dowswell, 2009) (Ia). There are also Cochrane reviews of psychosocial interventions and opioid agonist maintenance treatment for pregnant women (Minozzi et al., 2008; Terplan and Lui, 2007) (Ia).

Problems with the evidence base include the facts that much comes from the USA and no RCTs were conducted in the UK, polysubstance misuse is the norm in the UK, numbers in RCTs are small, and the high prevalence of nicotine use as a potential confounder.

Assessment and antenatal care

Enabling pregnant substance users to access antenatal care is vital. In 2006–2008, 11% of all maternal deaths were in substance misusers (CMACE, 2011) and 44% of substance-misusing women received no/little antenatal care. Some 31% of maternal deaths from suicides were in substance misusers. Assessment tools such as T-ACE, TWEAK or AUDIT C have been shown to have the highest sensitivity for identifying prenatal risk of drinking (Burns et al., 2010).

Early information-sharing between the GP, maternity and addiction services is essential. All women who are substance users should have integrated specialist care that includes professionals in addiction, child safeguarding, specialist midwifery and obstetrics (CMACE, 2011; NICE, 2010b).

Women who are substance users and who attend drug treatment programmes are likely to have better antenatal care and better general health than those who do not engage with treatment services. Addiction services should fast-track pregnant women into treatment and engage substance-misusing partners (Department of Health, 2007).

Opioids

Opioid dependence is associated with increased maternal and neonatal complications. Maintenance treatment with an opioid substitute can prevent the adverse effects on the foetus of repeated withdrawals and periods of intoxication. The UK guidelines on clinical management of harmful drug use or abuse or dependence cover general management strategies for pregnant opioid-dependent women (Department of Health, 2007).

Methadone. MMT in pregnancy is associated with improved compliance with antenatal care, reduced maternal morbidity and improved neonatal outcomes (Burns et al., 2007; Fajemirokun-Odudeyi et al., 2006; Kandall et al., 1999) (IV). The most appropriate methadone dose in pregnancy is still debated. Some practitioners favour higher doses to limit illicit drug use and counteract the increased methadone clearance in pregnancy, which may necessitate a dose increase in the third trimester (Drozdick et al., 2002; Wolff et al., 2005). Others favour lower doses to try to reduce the incidence of neonatal abstinence syndrome (NAS) (Dashe et al., 2004) or using the lowest doses compatible with stability (Dryden et al., 2009). Splitting the daily dose in the third trimester can be a helpful strategy (III). A recent systematic review and meta-analysis did not find an association between high or

low-dose maternal MMT and severity of NAS (Cleary et al., 2010) (III). A prospective study of pregnant women prescribed up to 110 mg/day of methadone did not find an association between methadone dose and measures of NAS (Gray et al., 2010 (III)). However, a recent retrospective cohort study found a dose–response relationship between maternal methadone dose at delivery and NAS (Cleary et al., 2011).

Buprenorphine. There is increasing experience with buprenorphine during pregnancy. Improvements in perinatal outcomes were similar for methadone and buprenorphine in a prospective observational study (Lejeune et al., 2006 (III)). Of note, buprenorphine combined with naloxone is contraindicated in pregnancy (BNF, SPC), so all studies have used buprenorphine. In a Cochrane review of maintenance opioid agonist treatments in pregnancy (Minozzi et al., 2008 (Ia)) two studies compared methadone (at doses between 40–100 mg/day) with buprenorphine (at doses between 8–24 mg/day) (Fischer et al., 2006; Jones et al., 2005) (Ib). Comparing methadone with buprenorphine there was no difference in maternal treatment drop-out rates (two studies), NAS (two studies), use of heroin (one study) or APGAR scores (one study). Kakko et al. (2008) (III) found that buprenorphine was associated with lower levels of NAS and increased birth weight. A recent multicentre international RCT of buprenorphine and methadone in 175 pregnant opioid-dependent women (the MOTHER study) found that babies of mothers treated with buprenorphine had less severe neonatal abstinence symptoms requiring less medication and shorter stays in hospital (Jones et al., 2010) (1b).

Slow-release oral morphine. In a RCT comparing methadone with SROM there was no difference in maternal or neonatal outcomes for methadone and SROM except reduced maternal heroin use in the third trimester with morphine (Fischer et al., 1999) (IIb).

Detoxification. Detoxification or withdrawal has been thought to be risky in the first trimester due to risk of miscarriage and in the third trimester due to the risk of foetal stress and premature labour. If it has to be undertaken, the second trimester is preferred. A reduction of 2–3 mg of methadone every 3–5 days has been suggested, as long as illicit opiate use is not continuing (Department of Health, 2007). A slow reduction in the third trimester may be undertaken (Department of Health, 2007). Any potential benefit from dose reductions must be balanced against the risk of decreased methadone doses leading to relapse to illicit drug use.

Recommendations: opioids and pregnancy

- Methadone and buprenorphine (not buprenorphine/naloxone) maintenance treatment improves maternal and foetal outcomes, and substitution treatment should be offered to pregnant opioid-dependent women (B).
- The choice of medication should be based on individual need and preference following full assessment, and the dose of methadone prescribed should be that which maintains clinical stability (C).
- Buprenorphine may be associated with less NAS (B).
- Detoxification should be avoided in the first trimester, is preferred in the second and only with caution in third trimester (S).

Key uncertainties

- Can psychosocial interventions enhance outcomes in combination with substitution treatment?
- Are the findings for generally similar outcomes with methadone and buprenorphine maintained with larger studies?

Stimulants

A Cochrane review of psychosocial interventions for pregnant women examined nine trials of contingency management or motivational interviewing (Terplan and Lui, 2007) (Ia). The majority of women used opiates and cocaine. Contingency management may increase treatment retention but there is no clear effect on drug abstinence. There was no evidence to support motivational interviewing. RCTs focussing on obstetric and neonatal outcomes are needed. The Department of Health guidelines recommend offering psychological approaches including family intervention to pregnant women misusing stimulants (Department of Health, 2007). Substitute prescribing is not recommended.

Recommendations: stimulants and pregnancy

- There is not enough evidence to make any recommendations except ‘stop’ and use psychosocial interventions and not pharmacotherapy for relapse prevention (S).

Key uncertainties

- What psychosocial intervention is most effective in pregnancy?

Nicotine

All pregnant women who smoke or who have stopped in the last 2 weeks should be referred to smoking cessation services (NICE, 2010a). A Cochrane review (Lumley et al., 2009) (Ia) found smoking cessation interventions reduced smoking in late pregnancy (RR 0.94, 95% CI 0.93–0.96), reduced low birth weight (RR 0.83, 95% CI 0.73–0.95), and preterm birth (RR 0.86, 95% CI 0.74–0.98) plus increased mean birth weight by 39.26 g (95% CI 15.77–62.74 g). There were no significant differences for very low birth weight or perinatal mortality. Financial incentives to women to quit smoking were more effective than other interventions (RR 0.76, CI 0.71–0.81). Self-help smoking cessation interventions for pregnant smokers are effective (OR 1.83 95% CI 1.23–2.73) (Naughton et al., 2008) (Ia).

Pharmacotherapy. NRT should be considered if smoking cessation interventions without NRT have failed (NICE, 2010a). However, there is mixed evidence for the effectiveness of NRT in pregnancy, so it is not as effective as in the general population (Lumley et al., 2009; Oncken et al., 2008) (Ib). Bupropion and varenicline should not be prescribed to pregnant or breast-feeding women (NICE, 2010a).

Recommendations: nicotine and pregnancy

- Psychosocial interventions should be offered since they are effective (A).
- Offer NRT after risk–benefit analysis if other interventions have failed (B).

Key uncertainties

- Are financial incentives to stop smoking in pregnancy effective in a UK setting?

Alcohol

There is much controversy regarding how much alcohol is 'safe' to drink in pregnancy (Carson et al., 2010; NICE, 2008; O'Leary et al., 2007); however, there is no evidence of a threshold level of alcohol consumption during pregnancy above which alcohol is harmful to the baby. NICE (2008) states *"in the absence of clear evidence of a threshold it would appear that drinking no more than 1.5 units/day is not associated with harm to the baby but there remains a possibility that there is an increased miscarriage rate in association with alcohol consumption although the evidence is limited and of poor quality"*. There is limited evidence that binge drinking, as defined by drinking five or more standard drinks in a single episode, may be associated with neuro-developmental harm to the baby (NICE, 2008). UK government advice is currently not to drink during pregnancy or when trying to conceive (Department of Health, 2008). If a woman chooses to drink, they should drink no more than '1–2 units once or twice a week' and that binge drinking (> 7.5 units) on a single occasion may be harmful (Department of Health, 2008; NICE, 2008). In addition, a man is also recommended not to drink excessively to improve fertility.

Detoxification. We and others recommend the use of benzodiazepines for alcohol detoxification during pregnancy (e.g. Latt et al., 2009; Lingford-Hughes et al., 2004; Rayburn and Bogenschutz, 2004; TIP, 2006) (IV), preferably in an inpatient setting under specialist supervision (NICE, 2011a). Either chlordiazepoxide or diazepam can be used.

Relapse prevention. No relapse prevention medication has been evaluated in pregnancy suitable for a systematic Cochrane review (Smith et al., 2009) (Ia), and existing studies of pharmacological interventions in alcohol treatment exclude pregnant women. The BNF advises to avoid acamprosate in pregnancy and to avoid disulfiram in the first trimester. Naltrexone is licensed in UK to prevent relapse in opioid dependence and the BNF says it can be used if 'benefit outweighs risk'. In the USA, advice is to avoid any of these medications unless 'potential benefit outweighs risks' (TIP, 2009) (IV). In addition, appropriate birth control is recommended while on these medications.

There is therefore little research evidence for the efficacy or the safety of pharmacological treatments in pregnancy or breast feeding, and these are best avoided.

Recommendations: alcohol and pregnancy

- Women and men are advised not to drink alcohol when trying to conceive (S).
- Pregnant women with symptomatic withdrawal should be offered medical cover for their detoxification, ideally as an inpatient (D).
- Starting relapse prevention medication should be avoided, although if already successfully established on relapse prevention medication, patients' needs should be assessed on a case-by-case analysis (D).

Key uncertainties

- What are the risks of alcohol withdrawal versus the risks of benzodiazepine exposure to foetus, and does any trimester carry more risk than at other times?
- Risk of medication such as acamprosate, naltrexone or disulfiram versus risk of excessive drinking and its consequences in pregnancy and breast feeding.

Comorbidity

Symptoms of psychiatric disorders such as depression, anxiety and psychosis are the rule rather than the exception in patients misusing drugs and/or alcohol. In addition, these psychiatric disorders increase the risk of harmful substance use, abuse or dependence, and patients may be physically unwell. Such patients are often the most challenging to engage and treat, and their prognosis is frequently poor. The number of placebo-controlled trials is small, and although increasing steadily there remains little evidence to guide treatment, particularly in the adolescent or old age populations. There are now national guidelines to guide treatment of comorbidity in UK (NICE, 2011a, 2011b) (Ia), in Australia (Mills et al., 2009) (IV) as well as management within relevant BAP guidelines (see for example those for ADHD (not covered in these guidelines), schizophrenia, bipolar disorder at www.bap.org.uk) (IV). We therefore concentrate on the psychopharmacology of treating such comorbid disorders. As previously discussed, all studies include a psychosocial intervention.

While it is common to refer to a patient's psychiatric disorder or substance use disorder as primary or secondary, this may have limited use clinically. It is important to establish whether substance use may be contributing to their psychiatric problems. Such an assessment may be appropriate at every meeting, particularly if there are changes in their psychiatric presentation. While removing or minimising the contribution of harmful substance use is an important aim, it is often not achieved. In addition, misplaced attribution of the psychiatric disorder purely to substance use can occur, and may result in the patient achieving abstinence but not being reassessed, or never having their psychiatric problems adequately addressed because they never achieve abstinence. Pragmatically, both disorders may have to be treated concurrently, although improvement in one does not necessarily result in improvement in the other.

The literature contains a wide variety of types of studies and outcomes, but few RCTs or even trials, with many being case series. Most do not use 'intention to treat' analysis and have small samples (e.g. n = 16–100) and short duration (days to weeks). In some studies, the primary outcome measure is the psychiatric disorder, with secondary outcomes being substance related, and neither the goal regarding substance use, for example reduction or abstinence, nor the extent and nature of psychosocial interventions is discussed. Reductions in psychiatric symptoms, for

example depression, can be reported although patients did not necessarily have a diagnosis of depression.

In the following sections we primarily focus on studies where the impact of the medication on substance use outcomes is reported from the perspective of pharmacotherapy for the psychiatric disorder as well as for substance use disorder. Some pharmacotherapy has not been studied in patients with a comorbid psychiatric disorder. However, such absence of evidence due, in part, to difficulties in studying this population and lack of 'pharma' interest in conducting such large-scale trials should not deter prescribing, given its potential effectiveness.

Assessment

It is important to distinguish between substance-induced and substance-related psychiatric disorders. While it is advisable to allow at least 2 weeks of abstinence before making diagnosis of a psychiatric disorder, this is often impractical. A complete substance history should be obtained, including nicotine and so-called 'legal highs' as well as drugs bought off the internet, with urinalysis and blood tests. To establish how a patient's substance use and other psychiatric disorder are linked, the order of onset of their psychiatric disorder and substance use, family history and effect of previous treatments of comorbid psychiatric disorder should be determined.

Bipolar disorder

The limited evidence is presented in several systematic reviews and guidelines available, including BAP bipolar guidelines (Goodwin et al., 2009 (IV); NICE, 2011b (Ia), TIP, 2006 (IV); Spanish (Casas et al., 2008) (IV) and Australian guidelines (Mills et al., 2009) (IV); and comprehensive reviews by Vornik and Brown (2006) and Tiet and Mausbach (2007)).

After nicotine, the most commonly abused substance is alcohol. The majority of bipolar disorder patients report using substances, including alcohol, to reduce anxiety (e.g. Bizzarri et al., 2007). Given the overlap between and increased risk of mania and harmful alcohol use, abuse or dependence, detoxification from alcohol may be needed early in treatment of mania alongside mood stabilisation. Trials are generally conducted in a depressive or mixed phase, or maintenance phase.

Treating bipolar disorder. Existing standard pharmacological approaches appear effective in comorbid bipolar disorder and there is no robust evidence for better efficacy of any one particular pharmacological approach. Compliance may be affected by warnings about not drinking alcohol when taking a mood stabiliser. There is evidence for the use of carbamazepine, valproate and antipsychotics for improving alcohol-related outcomes.

The combination of lithium and valproate has been compared with lithium alone in two trials. Patients with BPD I and alcohol dependence completed a few days of stabilisation on lithium, after which valproate or placebo was added for 24 weeks (Salloum et al., 2005) (Ib) The lithium plus valproate group had a significantly lower proportion of heavy drinking days ($p = 0.02$) and a trend toward fewer drinks per heavy drinking day ($p = 0.055$) than the lithium plus placebo group, although manic and depressive symptoms improved equally in both groups. In the other trial, patients with BPD I or II and alcohol, cannabis or cocaine abuse or dependence entered a 6-month stabilisation 'open' phase with lithium and valproate, followed by a blinded 6-month 'maintenance' phase comparing this combination with lithium alone (Kemp et al., 2009) (Ib). Only 31 of the 145 patients were randomised in the maintenance phase, and the combination was not superior in improving any of their chosen outcome measures including 'time to treatment' for a mood episode or time to discontinuation with medication. However, in those that entered the maintenance phase, substance use was reduced so that more than half were no longer abusing alcohol or cannabis or cocaine. The combination of lithium and valproate resulted in greater improvements in drinking outcomes. Therefore both trials suggest a combination of lithium and valproate may be better than lithium alone for substance abuse; however, the combination is not superior in improving mood.

In two open-label studies, Brown and colleagues reported that the addition of lamotrigine improved mood – depression and mania – and reduced cocaine craving and use (Brown et al., 2003, 2006) (Ib).

Quetiapine has been the most-studied antipsychotic, with mixed results. An open trial of add-on quetiapine (flexible dosing, mean dose 229 mg/d) in patients with bipolar disorder and cocaine dependence reported 'substantial improvement in psychiatric symptoms and cocaine cravings' (Brown et al., 2002) (IIb). Further analysis of this trial examined those who had alcohol craving at baseline, of which about half were dependent or abused alcohol, and reductions in craving and alcohol consumption were seen (Longoria et al., 2004). An RCT comparing quetiapine (303 + 152 mg/day) with risperidone (3.1 + 1.2 mg/day) reported that both medications improved psychiatric symptoms and stimulant cravings (Nejtek et al., 2008) (Ib).

An RCT of add-on quetiapine (600 mg/day) found no improvement in alcohol use or craving in those with bipolar disorder and alcohol abuse or dependence (Brown et al., 2008) (Ib). An open trial that included patients with alcohol dependence and bipolar disorder ($n = 10$), or schizoaffective disorder ($n = 2$) and/or borderline personality disorder ($n = 10$) found that quetiapine alone improved psychiatric symptoms, and decreased alcohol consumption and craving (Martinotti et al., 2008) (IIb). A double-blind placebo-controlled trial reported no benefit of quetiapine (400 mg/day, up to 800 mg/day) as an adjunct to lithium or divalproex in reducing number of heavy drinking days, nor improvement in bipolar disorder (Stedman et al., 2010) (Ib).

In an open-label study of 20 patients with bipolar disorder or schizoaffective disorder, a switch to aripiprazole resulted in improved depression, mania and BPRS scores as well as reduction in cocaine and alcohol craving, and amount spent on alcohol, but not cocaine use (Brown et al., 2005) (IIb).

Relapse prevention medication in bipolar disorder: alcohol. A secondary analysis of the trial (Petrakis et al., 2005) (Ib) comparing disulfiram and naltrexone alone and in combination with placebo, in patients with a psychiatric comorbidity, compared those with psychosis spectrum, of which the majority (73%) had bipolar disorder, with the remaining non-psychotic participants (Petrakis et al., 2006b) (Ib). There was no significant difference between the psychotic and non-psychotic groups in retention or compliance; however, the 'psychotic group' complained about more side effects, drank more heavily and had less abstinence, but responded more to either naltrexone or disulfiram. In the 'psychotic group', placebo resulted in little change in their frequency

of heavy drinking days (12/84); however, there was a significant reduction in drinking with naltrexone (3/84), disulfiram (4/84) and the combination (6/84). There was no difference between the medications. Despite improvement in drinking, there was no significant change in psychiatric symptoms rated with PANSS.

There is evidence that naltrexone can reduce number of drinking days from a pilot RCT where it was added to a CBT programme aimed at bipolar disorder and alcohol dependence, delivered over 16 weeks alongside usual medication (Brown et al., 2009) (Ib).

An RCT in those with bipolar disorder and alcohol dependence compared acamprosate with placebo in addition to their mood-stabilising medication (Tolliver et al., 2012) (Ib). While acamprosate showed no benefit in drinking related outcomes, the study was small (n = 30), of short duration (8 weeks), and levels of alcohol drinking were low with more abstinent than drinking days at baseline. However, acamprosate was well tolerated and had no adverse effects on mood. An anxiety disorder was present in about 75% of the group and associations with increased depressive symptoms and greater alcohol consumption were reported (Prisciandaro et al., 2011, 2012). Anticonvulsants and antipsychotics were associated with greater alcohol use and lithium with lower alcohol consumption.

Relapse prevention medication in bipolar disorder: cocaine. Carbamazepine has been shown to result in a trend towards fewer cocaine-positive urines and reduction in depression in a group of patients with a mix of bipolar disorder and depressive disorders (Brady et al., 2002) (Ib).

Recommendations: bipolar disorder

- Treat different phases of bipolar disorder as recommended in guidelines, for example NICE, BAP; however, assess contribution of substance use to hypomania or mania and consider if medically assisted withdrawal is required (S).
- Review pharmacotherapy for bipolar disorder particularly if only on lithium, and consider adding sodium valproate (D).
- Offer naltrexone to help patients reduce their alcohol consumption (C).
- Offer acamprosate if naltrexone has not been effective to help patients remain abstinent (D).
- Consider disulfiram if patient wants abstinence and acamprosate and naltrexone have failed. The patient must be able to understand the risks of taking disulfiram and have their mood monitored (D).

Key uncertainties

- What is the best pharmacological approach for patients with comorbid bipolar disorder, in manic, depressive or maintenance phases?
- What is the best pharmacological approach for their comorbid harmful substance use, abuse or dependence?

Schizophrenia

Managing substance use in patients with schizophrenia is a significant challenge, and there are still limited empirical data to guide clinicians. The debate continues about the influence of substances, particularly cannabis, on causing schizophrenia de novo, increasing vulnerability and increasing relapse rates. There is some evidence to suggest that vulnerability to psychosis and substance use may be shared, rather than substances being taken to ameliorate psychotic symptoms or overcome side-effects of medication (Chambers et al., 2001). Nicotine is the most commonly abused substance, with up to 85% of patients with schizophrenia smoking cigarettes. Alcohol is the next most commonly abused substance, followed by cannabis. With the introduction of restrictions on smoking, more patients are being offered nicotine substitution and cessation programmes. Recent comprehensive and systematic reviews have described some of the challenges and management (Lubman et al., 2010; San et al., 2007; Wobrock and Soyka, 2009), and see other guidelines (Barnes et al., 2011; Mills et al., 2009; NICE, 2011b). A recent Cochrane review concluded that there was no good evidence for effectiveness of any one particular psychosocial treatment in psychotic spectrum disorders comorbid with substance abuse (Cleary et al., 2008) (Ia). Of note, a recent trial in the UK showed that integrated motivational interviewing and CBT in addition to standard care was no better than standard care alone in improving psychiatric or substance use outcomes (Barrowclough et al., 2010) (Ib). Another trial in the Netherlands found that training parents in 'motivational interviewing and interaction skills' focused on reducing cannabis use resulted in reduced cannabis use in their young adult offspring with schizophrenia compared with routine family support (Smeerdijk et al., 2011). However, there were no differences in the patients' general level of functioning and in reducing parents' stress and sense of burden. Throughout these guidelines we have used the terminology to describe antipsychotics as in the original paper, that is, typical or atypical or first or second-generation antipsychotic (FGA, SGA).

The importance of reducing substance abuse is illustrated by a prospective study that followed-up patients with schizophrenia and found much of the improvements in reducing relapse rates in patients compliant with their antipsychotic medication were diminished by substance abuse (Hunt et al 2002). Analysis of the CATIE study revealed that, compared with non-users, illicit drug users tended to stop their antipsychotic, and the advantage of olanzapine seen in non-users was attenuated (Swartz et al., 2008) (Ib). Significantly poorer outcomes were seen in those with moderate/severe drug use (Kerfoot et al., 2011) (Ib). This reinforces 'the need for concurrent substance abuse treatment'.

The majority of studies covering schizophrenia comorbid with harmful substance use, abuse or dependence are still not prospective RCTs but rather retrospective surveys, open trials or case series. We will focus on reports published since the last guidelines in 2004.

With regard to treating schizophrenia itself, recent evidence from CUtLASS1 and CATIE trials indicates that FGA are not inferior to SGA (Barnes et al., 2011) (IV). This has had a large impact on recommendations suggesting FGA were appropriate as 'first line' rather than favouring SGA over FGA, as happened after the introduction of many SGA (Barnes et al., 2011) (IV). The lack of extrapyramidal side effects of many SGAs may be now outweighed by their effects on physical health and associated impact on morbidity and mortality. Substance abuse also impacts adversely on physical health, and therefore reducing its impact, such as stopping smoking, is likely to have significant health benefits.

Treating schizophrenia

Oral medication. There is some evidence from older studies that typical antipsychotics or FGA do not reduce harmful substance use, abuse or dependence, and it is hypothesised that substances of abuse may be used to overcome extrapyramidal side effects and possible consequences of hypodopaminergia such as low mood and blunted affect (see review by Siris, 1990). However as described above, more recent trials report that SGA may not be superior to FGA for treating schizophrenia and similarly it is not clear in comorbidity.

There have been several trials comparing olanzapine with haloperidol. Green et al. (2004) (Ib) reported the substance use data from a double-blind randomised trial comparing olanzapine with haloperidol in patients in their first episode of schizophrenia. Patients who were abusing substances (alcohol, cannabis, other) were less likely to respond to either antipsychotic, and were less likely to complete treatment with haloperidol. At 12 weeks, olanzapine but not haloperidol, was associated with a reduced response with regard to their psychotic symptomatology in those abusing alcohol compared with those not abusing alcohol. No data regarding substance use at the 2 year end point was reported (Green et al., 2006). In other small trials, no clinically meaningful differences were found, (Sayers et al., 2005; Smelson et al., 2006) (Ib).

Similarly, in observational studies and case notes reviews of other SGAs some benefits for them over FGAs have been reported, but these are of uncertain clinical value; for example, Scheller-Gilkey et al. (2003) (III) found reduced use of alcohol but not other drugs. In a retrospective case notes review, Petrakis et al. (2006a) (III) found that the severity of substance use and substance-related problems had declined by follow-up in patients receiving atypical (olanzapine, quetiapine, risperidone) but not conventional antipsychotics, whether 'maintained' or 'switched to', but this was not significant.

With tobacco the situation might be different, in that Stuyt et al. (2006) (III) studied inpatients with dual-diagnosis of schizophrenia or schizoaffective disorder who were not allowed to smoke; about half of those on risperidone or ziprasidone stated that they were not going to smoke on discharge, whereas all those on olanzapine or depot said they intended to.

The CATIE study (Swartz et al., 2008) (Ib) found that although olanzapine led to less 'all cause discontinuation' in those not using illicit drugs, there was no difference in those abusing illicit drugs. By contrast, alcohol use and abuse in the absence of illicit substance use had little effect on time to discontinuation, since these patients tended to be older and more stable. They concluded by reinforcing the need for concurrent substance use disorder treatment. In an open uncontrolled trial in patients with schizophrenia, switching to quetiapine was associated with improvements in psychiatric symptoms and substance abuse (Potvin et al., 2006) (IIb).

In small studies, oral risperidone has been shown to be superior to 'typical antipsychotics' (Smelson et al., 2002) (IIb) or worse than clozapine in terms of substance use-related outcomes (Green et al., 2003) (III). Olanzapine showed a trend for a greater effect in reducing cocaine use, while risperidone resulted in more craving for cannabis (Akerele and Levin, 2007) (IIb). In young adults with a recent diagnosis of schizophrenia, no differences were reported between olanzapine and risperidone in subjective well-being, cannabis craving or reduction in number of joints smoked (van Nimwegen et al., 2008) (Ib).

Given that preclinical studies suggested that partial agonists at the DRD2/3 may have potential to treat substance use disorders, there was interest in aripiprazole, which has similar pharmacology. In six of 10 patients with schizophrenia and cocaine dependence who completed an 8-week trial of aripiprazole, reductions were seen in cocaine and alcohol craving, cocaine-positive urines and psychotic symptoms (Beresford et al., 2005; see also section on stimulants) (IIb).

Depot medication. Open, pilot trials of depot flupenthixol have shown that it was well tolerated in patients with schizophrenia and alcohol dependence or cocaine abuse, and resulted in improvements in cocaine and alcohol use but not necessarily psychiatric symptoms (Levin et al., 1998; Soyka et al., 2003) (IIb). In an open, randomised study, injectable risperidone was shown to be statistically superior to zuclopenthixol-depot regarding improvements in substance abuse and schizophrenia symptoms (Rubio et al., 2006) (Ib).

Clozapine. Although case reports and surveys (Green et al., 2003; Kim et al., 2008) (III) suggest that clozapine is beneficial for schizophrenia with substance use disorders, there are still no prospective randomised studies. A review of patients with schizophrenia discharged on clozapine found that there was no difference in time to readmission between those with and without a substance-use disorder, suggesting clozapine is beneficial in the abusing group (Kelly et al., 2003) (III). In a naturalistic survey, patients on clozapine stayed in the community longer despite drinking as much alcohol as patients on risperidone at baseline; however, no alcohol data were collected during follow-up period (Kim et al., 2008) (III). Clozapine has also been shown to result in fewer relapses to substance abuse compared with other antipsychotics (8% vs. 40%), but there was no difference in improvement in psychiatric symptoms (Brunette et al., 2006) (III).

Summary. There is currently insufficient evidence to recommend one antipsychotic over another or FGA versus SGA when treating schizophrenia with comorbid harmful substance use, abuse or dependence, either in relation to superiority in reducing substance use or improving psychiatric symptoms.

Relapse prevention medication in schizophrenia: alcohol.

There have been a number of trials of alcohol relapse-prevention medication in patients with schizophrenia, but there are none for illicit substances of abuse. Smoking cessation is discussed below.

A placebo-controlled RCT of naltrexone reported fewer drinking days, fewer heavy drinking days and less craving with naltrexone without improving psychosis, although importantly not worsening it either (Petrakis et al., 2004) (Ib). A prospective open study found similar benefits (Batki et al., 2007) (IIb). In Petrakis et al. (2006b) naltrexone was also found to be of benefit, although only a few patients had schizophrenia.

With disulfiram, Mueser et al. (2003) and Petrakis et al. (2005, 2006b) (Ib) have reported benefits in reducing alcohol consumption with limited adverse events, despite its theoretical propensity to increase psychosis through its blockade of dopamine-beta-hydroxylase. For information about the safety of disulfiram see Chick (1999) and Malcolm et al. (2008).

There is one study comparing the effects acamprosate with placebo on cognitive functioning in 30 patients with schizophrenia (Ralevski et al., 2011) (Ib). There were no adverse effects,

including on cognitive functioning, and drinking improved in both groups.

There are only case reports of baclofen (25 mg tds; Agabio et al., 2007) (III) and acamprosate (666mg tds; Tek et al., 2008) (III) reducing alcohol consumption in single patients with schizophrenia.

Relapse prevention medication in schizophrenia: opioids. There is very little information on illicit opioid use. One open study in heroin-dependent patients with comorbid schizophrenia found those on olanzapine remained longer in treatment and revealed more negative urine analyses for illicit drugs compared with those on haloperidol treatment (Gerra et al., 2007) (II). Higher doses are generally needed for methadone-maintained patients with psychiatric comorbidity, with enrolment and stabilisation in such programmes having a beneficial effect on their psychiatric symptoms (Tenore, 2008) (IV). The potential interaction between methadone and antipsychotics, for example on QTc interval, will need to be considered.

Relapse prevention medication in schizophrenia: nicotine. Patients have high rates of smoking, which contributes to their higher rates of physical morbidity and mortality. However, recently there have been changes with restrictions on smoking in public places and hospitals, and the general health of patients with schizophrenia is receiving more attention. Whilst many patients with schizophrenia do quit smoking with pharmacological support from NRT or bupropion, quit rates are less than half of those seen in the general population.

An early RCT found that nicotine transdermal patches resulted in limited numbers stopping smoking, but those on atypical antipsychotics fared better than those on typical antipsychotics (George et al., 2000) (Ib). Tidey et al. (2002) (IIb) found that a nicotine patch (21 mg) did not further improve quit rates achieved with contingency management.

As an adjunctive to psychological support, bupropion has been shown to aid smoking cessation, to be safe and well tolerated, and there is some evidence to suggest that those on atypical antipsychotics are more likely to be able to quit (George et al., 2002; Weiner et al., 2001) (Ib).

Two RCTs have reported that combining bupropion SR or placebo with high-dose transdermal nicotine patch resulted in higher abstinence rates than nicotine substitution alone (Evins et al., 2007; George et al., 2008) (Ib). The combination was safe and well tolerated. Evins et al. (2007) found equivalent outcomes between those on typical and atypical antipsychotics. However, in both studies longer-term abstinence after the treatment period was no different between the groups, so it may be that longer treatment and support should be considered.

One pilot trial of galantamine (a cholinesterase inhibitor) reported that it had no effect on reducing smoking and nicotine dependence (Kelly et al., 2008) (Ib). One suggested reason why patients with schizophrenia smoke is to derive benefits from nicotine on cognition. A small prospective study of varenicline was undertaken to explore possible beneficial effects on cognition and smoking (Smith et al., 2009) (IIb). After 9 weeks, improvements in some cognitive tasks were seen, with a reduction in smoking also apparent without adverse psychiatric consequences. A preliminary study of mecamylamine (a nicotinic receptor antagonist) found that it increased the number of cigarettes smoked (McKee et al., 2009) (IIb).

A Cochrane review of smoking cessation in schizophrenia concluded that bupropion increased smoking abstinence rates. However, it did not find any evidence for benefit from NRT (Tsoi et al., 2010) (Ia). Of the psychosocial interventions, only contingency management could be supported.

Recommendations: schizophrenia

- The negative impact of harmful substance use, abuse or dependence on patients with schizophrenia requires that their substance use is assessed and treatment is also focussed on any harmful substance use, abuse or dependence (S).
- Antipsychotic medication should be optimised following existing guidance, for example NICE, BAP (D).
- Clozapine should be considered in patients with persisting harmful substance use, abuse or dependence, since it has been reported to reduce substance use and improve psychosis, but these data are still preliminary (D).
- Medication for patients' substance misuse should be considered, such as optimising opioid substitution, use of alcohol relapse prevention such as naltrexone or acamprosate, and smoking cessation using bupropion or varenicline (D).

Key uncertainties

- Prospective RCTs with substance-use related outcomes investigating antipsychotic medication in comorbid schizophrenia are required.
- Prospective RCTs investigating relapse prevention medication for alcohol misuse or nicotine are required.

Depression

Opioids and depression. Depressive symptoms are very common in opioids addicts, with about half meeting criteria for major depression: this may motivate them to present for treatment for opioid dependence. Often other substances such as alcohol and cocaine contribute to their depressed mood. Despite this comorbidity there is evidence that such patients do well in opioid treatment and certainly no worse than non-depressed patients (Ngo et al., 2011; Nunes et al., 2004) (III). Higher doses may be needed for methadone-maintained patients with depression, and enrolment and stabilisation in such programmes alone is likely to have a beneficial effect on their psychiatric symptoms (Tenore, 2008) (IV). This may be a direct effect of opioid agonism on the reward pathway as well as secondary consequences on their chaotic lifestyle. Buprenorphine may have advantages over methadone in treating depressed opioid addicts due to its kappa antagonism, although this has not been shown consistently (Dean et al., 2004 (IIb); Gerra et al., 2006 (III)). Nevertheless, in about 10–20%, depression will persist (Nunes et al., 2004) (IV).

Studies of comorbid opioid dependence and depression are in the meta-analysis by Nunes and Levin, (2004 (Ia)) and also in a comprehensive review (Nunes et al., 2004) (IV). Conclusions were similar to those for alcohol and depression (see below), with antidepressants not being robustly superior for mood or substance use over placebo. The meta-analysis by Torrens et al. (2005) (Ia) considered seven studies, all of which were of methadone-maintained patients, but no

significant difference in opioid use was reported by any study. However the meta-analysis using data from two studies of doxepin and imipramine was just significant (OR = 3.65, 95% CI 1.10–12.16). Only one study involving imipramine reported improvement in depression, and the meta-analysis using data from two studies of imipramine and sertraline showed no significant effect on mood (OR = 2.27, 95% CI 0.39–13.19). Kosten et al. (2004) (Ib) found that desipramine in combination with either methadone or buprenorphine did not improve mood in opioid and cocaine-dependent patients, and indeed the depressed desipramine/buprenorphine group had least improvement in opiate-free urines. A recent trial reported depressive symptoms improved in addicts starting on buprenorphine and addition of escitalopram showed no advantage in terms of depressive or opiate outcomes (Stein et al., 2010) (Ib).

Overall, antidepressant treatment within methadone maintenance programmes can improve depressive symptoms but robust effects on mood are not usual, nor are improvements in opioid or other drug use.

Lastly, although it is theoretically possible for naltrexone to worsen mood, this has not been seen clinically. Recent studies in newly abstinent heroin addicts have not found naltrexone induction and/or maintenance to worsen mood, but instead to improve it (Dean et al., 2006 (Ib); Mysels et al., 2011 (IIb)).

Alcohol and depression. Depressive and anxiety symptoms commonly co-occur in the withdrawal period, but mostly subside after 3–4 weeks of abstinence (Brown and Schuckit, 1988; Brown et al., 1991; Liappas et al., 2002). Factors leading to a diagnosis of depression include family history and a previous non-alcohol-related depressive episode. Stopping alcohol is important in fully determining its role in the patient's depression and anxiety.

Three meta-analyses examine pharmacotherapy of alcohol-use disorders and depressive disorders with broadly similar conclusions (Iovieno et al., 2011; Nunes and Levin, 2004; Torrens et al., 2005) (Ia). The meta-analysis by Nunes and Levin (2004) found significant or trend antidepressant effects in 8/14 studies (effect size of 0.38, 95% CI 0.18–0.58). Those with alcohol dependence were more likely to respond than for other drug addictions. The largest (71%) variance was explained by placebo response, with those studies reporting a placebo response of less than 25% more likely to find an antidepressant effect. A greater antidepressant effect was also more likely if the diagnosis of depression was made after at least a week of abstinence, which likely excluded those people with transient withdrawal-related symptoms. A lower response to antidepressants was associated with SSRIs, more women in sample and a concurrent manual-guided psychosocial intervention. The severity of depression did not influence outcome.

Those antidepressants with mixed pharmacology such as tricyclics (e.g. imipramine or desipramine) appear to be better than SSRIs (e.g. fluoxetine, sertraline) (Nunes and Levin, 2004) (Ia). A meta-analysis of four studies with SSRIs showed an OR = 1.85 (95% CI 0.73–4.68), and the three studies with other antidepressants showed an OR = 4.15 (95% CI 1.35–12.75) (Torrens et al., 2005) (Ia).

The effect on alcohol outcomes was mixed: Nunes and Levin (2004) (Ia) found that in those studies with depression effect sizes over 0.5, the effect size on substance outcome was 0.56 (95% CI 0.33–0.79), whereas almost no impact on substance use was seen in those studies with a lower depression effect size. Once again, antidepressants with mixed pharmacology performed better, resulting in significantly greater reductions in drinking (OR = 1.99, 95% CI 0.78–5.08), whilst SSRIs did not (OR = 0.93, 95% CI 0.45–1.91) (Torrens et al., 2005) (Ia).

Patients comorbid for substance abuse and depression should be treated for their depression, but improving mood and/or antidepressants may not necessarily reduce their substance abuse; therefore specific, appropriate substance-focussed treatment should also be delivered. While the meta-analyses suggest that antidepressants with mixed pharmacology tend to do better than SSRIs, there is little information on the newer drugs. An open study reported that mirtazapine (15–45 mg/day) was well tolerated in depressed alcoholics and resulted in reductions in depression, anxiety and alcohol craving over 8 weeks (Yoon et al., 2006) (IIb). One small double-blind RCT reported that both amitriptyline (titrated up to 125–150 mg/day) and mirtazapine (titrated up to 45–60 mg/day) resulted in similar improvements in depression, anxiety and alcohol craving, although drinking outcomes were not reported (Altintoprak et al., 2008) (Ib). Mirtazapine was better tolerated.

One 26-week trial has reported that escitalopram (20 mg/day) or memantine (20 mg/day) resulted in similar improvements in depression and anxiety in patients with major depressive disorder (Muhonen et al., 2008) (Ib). No differences were seen in cognition during the trial or between groups and impact on drinking was not reported.

Relapse prevention medication in depression. More recently, combinations of antidepressants and relapse prevention pharmacotherapy have been investigated. A study over 14 weeks conducted in depressed alcoholics compared sertraline (200 mg/day) and naltrexone (100 mg/day), each alone and in combination, with placebo (Pettinati et al., 2010) (Ib). CBT was also delivered. The combination resulted in a significantly better drinking outcome, about half abstinent, whereas only about a quarter achieved this in the other groups. Also, by the last 3 weeks the mood of those on the combination tended to be better. It was not clear why naltrexone alone failed to show an advantage in this study over placebo in drinking outcomes.

A secondary analysis of the trial comparing naltrexone, disulfiram alone and in combination, with placebo in a group of patients with alcohol dependence and psychiatric comorbidity compared those with and without current depression (Petrakis et al., 2005, 2007) (Ib). Just over half (55%) met the current DSM-IV criteria for major depression, and depression improved during the trial in all treatment groups. However, there was no relationship between current depression and medication on alcohol or psychiatric outcomes, or side-effect reporting. Therefore naltrexone and disulfiram can be used safely in depressed alcoholics with comparable efficacy with those not depressed.

Krystal et al. (2008) (Ib) undertook a secondary analysis of the VA naltrexone trial where naltrexone failed to show significant advantage over placebo. During the study, about 10% of people required antidepressants since their mood worsened. Although drinking outcomes were worse in those requiring antidepressants, those on naltrexone had better outcomes than those who received placebo. Indeed, the outcomes on those receiving naltrexone was not different between those that were on antidepressants or not. One interpretation is that combination of antidepressant and naltrexone is better than either drug alone, but only in patients who are depressed.

Given naltrexone's theoretical impact on worsening mood, a recent exploratory survey of alcohol-dependent patients treated with the extended release form of naltrexone suggests that its impact on alcohol pleasure is not generalised. In patients, some treated for years (average 3.5 years), pleasure of being with friends, good food, sex and listening to music were rated higher than for alcohol or gambling (O'Brien et al., 2011).

A post-hoc analysis of 11 RCTs of acamprosate and Hamilton depression rating scale to define those with and without depression revealed that acamprosate has an indirect modest beneficial effect on depression by increasing abstinence (Lejoyeux and Lehert, 2011) (Ib). The effect of acamprosate is not altered by the presence of depression, nor was there evidence that it adversely impacts on depression.

A recent audit of baclofen in 13 patients with depressive disorder, some of which also had an anxiety disorder, reported that seven patients achieved abstinence and one reduced consumption to a non-problematic level (Dore et al., 2011) (III). However, two patients took overdoses and sedation was an issue, likely due to the sedative drugs also being prescribed.

Nicotine and depression. As described in the nicotine section, there are strong links between smoking and depressive symptoms. Most trials examining the impact of depressive disorder have studied those with a past rather than current history, and those with symptoms rather than a disorder. One meta-analysis concluded that a lifetime history of major depression did not appear to be an independent risk factor for cessation failure in smoking cessation treatment (Hitsman et al., 2003) (Ia). Another systematic review and meta-analysis reported identifying only three RCTs that included those with current depression, and only one involved pharmacotherapy (Gierisch et al., 2012) (Ia).

One RCT reported that an intervention integrating motivational feedback plus medication and psychological intervention improved smoking outcomes in smokers in treatment for depression compared with brief contact (Hall et al., 2006) (Ib). All patients were given nicotine patches, the strength depending on how much they smoked, and if they failed to quit they could then receive nortriptyline or bupropion (12% in control, 18% in active intervention). One study included those with elevated depressive symptoms rather than a depressive disorder; the behavioural intervention did result in greater smoking cessation and improvement in depressive symptoms (MacPherson et al., 2010) (Ib). The remaining study reported that an exercise counselling intervention in depressed female smokers compared with health education was feasible (Vickers et al., 2009) (Ib).

Another RCT included both those with a current history or those with a past unipolar depressive disorder and compared bupropion with placebo in smokers being treated with standard group CBT and nicotine patch and not antidepressant medication (Evins et al., 2007) (Ib). The primary analysis did not show an advantage of bupropion over placebo; however, the drop-out rate was high (50%) and the effectiveness of other treatments may have led to a ceiling effect.

Taking into account the other studies that included those with depressive symptoms, Gierisch et al. (2012) concluded that patients with depression should be encourage to seek help from smoking cessation services that include both NRT and behavioural mood management.

Recommendations: depression

- Antidepressants may improve mood but not necessarily substance use in those who are depressed with harmful or dependent substance use. Generally mood will only improve in those with a significant depressive disorder, and use of antidepressants should be restricted to this population and then with caution and monitored (A).
- A comprehensive assessment is essential to determine how substance use and depression are linked (S).
- Tricyclic antidepressants (TCAs) are not recommended due to potentially serious interactions between TCAs and substances, including cardiotoxicity and death in overdose (S).
- Consider using an antidepressant with mixed serotonergic/noradrenergic pharmacology since they may be better in improving mood in contrast to SSRIs, which have not shown consistent benefits in improving mood (D).
- Medication for harmful substance use, abuse or dependence should be considered such as optimising opioid substitution, use of alcohol relapse prevention such as naltrexone or acamprosate, use of nicotinic replacement therapy for smoking cessation (D).

Key uncertainties

- Which is the best antidepressant to use and evaluation is needed of newer antidepressants such as mirtazapine and venlafaxine?
- What is the best combination of antidepressants and medication for treating depression and harmful substance use, abuse or dependence?
- What is the best combination of pharmacological and psychosocial approaches to address depression and harmful substance use, abuse or dependence?
- What is the best approach to those with resistant depression?

Anxiety

Anxiety is a common symptom of substance misuse, occurring in intoxication, withdrawal and abstinence, depending on the substance. Therefore a comprehensive assessment is vital in order to determine how these factors are related and the likelihood of an independent anxiety disorder. For instance, anxiety disorders are associated with alcohol abuse or greater non-medical opioid use and vice versa (Martins et al., 2011; Regier et al., 1990). Ideally, abstinence should be attained to aid assessment and diagnosis, and a medically assisted withdrawal may be required. Identifying anxiety is critical, since it can have profound negative effects on the ability of someone to engage with treatment and predicts poor outcome in cocaine and opioid dependence (Book et al., 2009; Lejuez et al., 2008). We describe the only available pharmacotherapy studies which are in alcohol use disorders.

Anxiety is a common symptom in people with harmful alcohol use, abuse, dependence and withdrawal, and alcohol is used as self-medication by many with anxiety disorders, especially social anxiety (Regier et al., 1990). Anxiety reduces during alcohol withdrawal and in the following few weeks (Brown et al., 1991, Liappas et al., 2002), but if it persists, relapse rates increase up to

twofold (Brown et al., 1991; Kushner et al., 2005). Some studies show improvement in substance use by treating comorbid anxiety (e.g. Fals-Stewart and Schafer, 1992; Tollefson et al., 1992) (Ib), although others found no effect on substance use (e.g. Bowen et al., 2000; Schade et al., 2005; Thomas et al., 2008) (Ib).

The use of benzodiazepines is controversial in those with alcohol dependence, although abuse may not be as widespread as many people fear (Chick and Nutt, 2012; Ciraulo et al., 1988; Ciraulo and Nace, 2000). Mueller et al. (2005) (III) found no difference in benzodiazepine usage between those who developed alcohol use disorder and those that did not, and benzodiazepine use did not predict relapse or recovery in those with alcohol use disorder.

In the context of anxiety disorders, it may be that many people do not get adequate treatment due to concerns about using benzodiazepines. It has been reported that abstinent alcohol-dependent patients may be at greater risk of benzodiazepine abuse and dependence, and patients who are severely dependent with antisocial personality disorder or with polysubstance abuse are most at risk of abusing benzodiazepines (Ciraulo and Nace, 2000) (IV). Therefore there should be a clear favourable risk:benefit ratio, but benzodiazepines do have a role in treating anxiety and alcohol use disorders.

A meta-analysis of five RCTs showed that buspirone was beneficial in improving anxiety but not alcohol consumption (Malec et al., 1996) (Ia). A series of studies investigating the effect of paroxetine in patients seeking treatment for social anxiety who also had comorbid alcohol use disorder found paroxetine (up to 60 mg/day) was superior to placebo in improving social anxiety disorder but not drinking (Book et al., 2008; Thomas et al., 2008) (Ib), although there was less drinking to 'self-medicate' (Thomas et al., 2008).

Post-traumatic stress disorder (PTSD) is a risk factor for harmful substance use, abuse or dependence, with 'self-medication' often cited as a significant contributor. Supporting this are studies, for example, which report improvements in PTSD resulting in improvements in substance use with minimal impact of improvements in substance use on PTSD (Hien et al., 2010) (Ib). In a secondary analysis of their comorbidity trial investigating naltrexone and disulfiram alone and combined (cf above, Petrakis et al., 2005), Petrakis et al. (2006c) (Ib) compared patients with (37%) and without (63%) PTSD and alcoholism. Either naltrexone or disulfiram alone or combined resulted in improved drinking outcomes compared with placebo in those with PTSD. There was a suggestion that disulfiram may be particularly beneficial, and this could be due to a reduction in noradrenaline dampening arousal.

A recent study of Iraq and Afghanistan veterans compared paroxetine (titrated to 40mg/d) with desipramine (titrated to 200mg/d) (i.e. serotonergic vs noradrenergic uptake inhibitor) with or without adjunctive naltrexone (Petrakis et al., 2012). Desipramine had comparable efficacy to paroxetine in treating PTSD but had superior efficacy in reducing alcohol consumption. Notably naltrexone did not show efficacy in this population for drinking outcomes compared to the previous secondary analysis (Petrakis et al., 2006c). This could have been due to the study design including that patients were specifically recruited for the recent study and were started or changed their antidepressant rather than on long-standing pharmacotherapies.

In patients with comorbid PTSD and alcohol dependence, sertraline (150 mg/day) was not superior to placebo in reducing alcohol consumption over 12 weeks, with both groups showing improvement in their drinking but not their PTSD (Brady et al., 2005) (Ib). Further analysis revealed that sertraline in those whose PTSD predated their alcohol dependence improved alcohol outcomes; however, in those that were more severely dependent, sertraline resulted in more drinking than placebo. This is similar to what is seen in early versus late-onset alcoholism (see alcohol section), and emphasises that SSRI medication should be used with caution in those with harmful alcohol use, abuse or dependence.

While prospective RCTs are not available for other alcohol relapse medication in those with comorbid anxiety disorders, both acamprosate and baclofen have shown some benefit in reducing anxiety in post-hoc analyses of trials in alcohol dependence (see alcohol section).

Recommendations: anxiety

- Ideally patients should first undergo alcohol detoxification (S).
- If detoxification is not possible, treatment of the anxiety disorder should still be attempted: follow guidelines to select most appropriate pharmacotherapy for management of their anxiety disorder (B).
- Assessment by a specialist addiction service is recommended prior to using a benzodiazepine to treat their anxiety (D).
- Medication for the patient's harmful substance use, abuse or dependence should be considered, such as optimising opioid substitution, use of alcohol relapse prevention such as naltrexone or acamprosate (D).

Key uncertainties

- Which is the best antidepressant/anxiolytic to use?
- What is the best combination of medications for treating anxiety and substance abuse or harmful use?
- What is the best combination of pharmacological and psychosocial approaches to address anxiety and harmful substance use, abuse or dependence?

Personality disorder and treatment for substance use disorders

Authoritative reviews of studies of the co-occurrence of personality disorders and substance use disorders have been published (e.g. Seivewright and Daly, 1997; Verheul, 2001). These concentrate mainly on studies with larger samples that have used interview methods of assessment and clear diagnostic criteria. In Verheul's review, median prevalence of any personality disorder of 56.5%, with antisocial personality disorder of 22.9%, followed by borderline personality disorder at 17.7%. A more recent London-based study (Bowden-Jones et al., 2004) had similar findings, with overall prevalence of personality disorder of 37% among patients in treatment for drug-use disorders and 53% among patients in treatment for alcohol-use disorders. Patients with dependent personality disorder may be at higher risk of development of dependence on benzodiazepines (e.g. Murphy and Tyrer, 1991).

Studies of pharmacological treatment for substance use disorders typically do not exclude people with personality disorders, hence it is likely they were included in most studies. 'Mainstream' studies of drug treatments for substance use disorders are therefore of relevance to patients with personality disorder.

There is a commonly held view that personality disorder predicts poor response to treatment for substance use disorders. However, there are a number of studies showing that although people with personality disorder may have greater pre- and post-treatment problem severity, they can improve as much as those without personality disorders (Verheul, 2001) (IV). This suggests that drug and alcohol users with personality disorders probably benefit from standard treatments for substance use disorders. These studies range across MMT for opioid dependence (Alterman et al., 1998; Cacciola et al., 1996; Darke et al., 1996) (III), treatments for alcohol dependence (Powell et al., 1992; Verheul et al., 1999) (III), as well as some based on mixed populations of substance use disorders (Cacciola et al., 1995; Cecero et al., 1999) (III). In one study of disulfiram and naltrexone for treatment of alcohol dependence (Ralevski et al., 2007) (Ib), patients with comorbid Axis I psychiatric disorders and either antisocial personality disorder or borderline personality disorder responded as well to treatment with either medication as patients without personality disorder. Moreover, Rohsenow et al. (2007) (Ib) found patients with antisocial traits had better alcohol outcomes in response to treatment with naltrexone than patients without antisocial traits.

Explicit reference to improvements in symptoms of personality disorder is rarely reported, and reported outcomes are often not limited to the presence or absence of substance misuse, but also include associated behaviours such as HIV risk behaviours, criminal activity, physical morbidity, overall mortality, and mortality from suicide (Caplehorn et al., 1996; Marsch, 1998, Ward et al., 1999) (III). Several studies show the risk of suicidal and harmful behaviour continues in patients with personality disorder, even when the treatment for substance abuse has been successful (van den Bosch and Verheul, 2007) (IV). This pattern was apparent in the 3-year follow-up of the Australian Treatment Outcome Study (Darke et al., 2007) (III) in which patients with borderline personality disorder maintained elevated risk levels across a number of domains, despite equivalent progress to patients without personality disorder in relation to abstinence from heroin and polydrug use.

Recommendations: personality disorder

- Patients with personality disorder can be offered the same range of treatment options as patients without personality disorder (B).
- High-risk behaviour persists in patients with borderline personality disorder despite successful treatment of harmful substance use, abuse or dependence, and such patients should also have treatment aimed at ameliorating the impact of the personality disorder (D).

Key uncertainties

- Whether any pharmacotherapy is particularly beneficial in personality disorder with harmful substance use, abuse or dependence?

Sleep

Insomnia is commonly seen in people who misuse substances and can occur during intoxication, withdrawal or become more evident during abstinence. Sleep problems are often cited by patients as a reason they began to drink heavily or relapse, and poor sleep has been shown to be associated with poorer outcomes (see Brower and Perron, 2010). As for other comorbidities, a comprehensive assessment is key to determine the relationship between sleep problems and substance use and to inform a management plan. Rather than use additional pharmacotherapy, review of their existing pharmacotherapy with advice about 'sleep hygiene' (Wilson et al., 2010) is likely to be the best approach.

Alcohol. Sleep problems may become first evident during alcohol detoxification, although adequate doses of benzodiazepines should minimise this. Both acamprosate and carbamazepine have been associated with improved sleep during withdrawal (Malcolm et al., 2002; Staner et al., 2006) (Ib). A placebo-controlled RCT of trazodone, an antidepressant often used for insomnia, found improved sleep quality in alcohol-dependent patients with insomnia (Friedmann et al., 2008) (Ib). However the improvement disappeared once they stopped taking trazodone after 12 weeks, and they drank more than the placebo group in the follow-up period.

Some but not all studies of acamprosate in relapse prevention have reported beneficial effects on sleep (Johnson et al., 2003; Mason and Heyser, 2010) (Ib). Unlike many other medications such as some antidepressants, acamprosate does not appear to adversely affect sleep. Other drugs such as gabapentin and quetiapine have been shown to have potential in improving sleep in abstinence (see Arnedt et al., 2007 for review) (IV).

Opioids. Sleep dysregulation is commonplace in opioid addicts (Zutler and Holty, 2011). While clinically sleep problems are more recognised during withdrawal, and are often protracted, especially from methadone, they may also be present during maintenance or substitute therapy. However, a laboratory study of sleep difficulties revealed they may not be associated with the methadone dose, but benzodiazepine abuse or chronic pain (Peles et al., 2009).

Stimulants. Stimulant withdrawal may be associated with hypersomnia, with insomnia more likely seen during abstinence. Modafinil has shown some promise in treating cocaine dependence (see above), and Morgan et al. (2010) (Ib) reported that it also improved diurnal sleep rhythm and sleep architecture.

Younger people: children and adolescence

The definition of young people may range from the age of 10–25 years. For this document, we are focussing on children and young people under the age of 18. Young people are still physically and mentally growing, and their brain, particularly their frontal lobes, continues developing into the early 20s. Thus the neurobiological impact and consequences of substances on this developing plastic brain is likely to be different to those on an adult, fully developed brain. The 'reward and motivation' system, such as the ventral striatum, develops at an earlier stage before the 'top-down' control from the prefrontal cortex is established (Somerville and Casey, 2010). In addition, it may be that the exposure of a developing plastic brain to substances may result in increased risk of acquiring a chronic addictive disorder (O'Brien 2007; Spear, 2007). There is also a potential increased risk of mental illness, for example cannabis and psychosis (Moore et al., 2007). Research

indicates that the experience of craving for, and withdrawal symptoms from, addictive substances are similar in adult and younger populations (Thomas et al., 2005).

Substance use is common in young people, with high levels of prevalence in the UK compared with elsewhere in Europe and USA (Frischer et al., 2003). Alcohol is the most common substance used (British Medical Association, 2003). About 1% of 14–16-year-olds in the United Kingdom drink alcohol nearly every day, and are therefore at high risk of alcohol use disorder. Recently, the WHO estimated that the main risk factor for disability-adjusted life years in 10–24-year-olds was alcohol, with illicit drug use also significantly contributing (Gore et al., 2011).

Young people generally present with problems with alcohol and/or cannabis to specialist drug and alcohol services. For recent guidance about assessment and prescribing in young people as well as underlying principles of care, responsibilities and consent see Gilvarry and Britton, (2009) (IV).

While emphasis is put on psychosocial, harm reduction and family interventions as appropriate approaches in young people, pharmacotherapy is an important component for some. As for adults, medication can be used for stabilisation, detoxification, relapse prevention and preventing complications. However, in younger people pharmacotherapy for relapse prevention is less commonly used and is not recommended for routine use (Gilvarry and Britton, 2009). This emphasises the need for a specialist multidisciplinary team, including specialists in addiction to initiate treatment and those to care for mental and physical health and social needs in young people.

A complicating factor is that pharmacotherapy is not generally licensed for use in 'younger' people, with age limits varying. For example, in the UK, acamprosate is licensed for over 18-year-olds, methadone is not licensed for children under age of 13, and buprenorphine is licensed for those aged 16 and over. Doses of medication may need to be adjusted from those for adults, given the difference in pharmacokinetics and pharmacodynamics between adults and younger people. Generally, guidance is that pharmacotherapy should only be used after careful assessment of risks and benefits, and in the context of a comprehensive treatment plan embracing various psychosocial approaches (Gilvarry and Britton, 2009; Upadhyaya and Deas, 2008) (IV). With only a few studies and the majority conducted in the USA with generally small numbers, mostly male participants, and short treatment or follow-up periods, there is little evidence on which to base guidance. Nevertheless, pharmacotherapy should be considered in young people with a diagnosis of dependence.

Alcohol

The assessment and management, including psychosocial and pharmacological approaches, of harmful alcohol use and dependence in children and young people has recently been reviewed (NICE, 2011a). The number of younger people dependent on alcohol that need pharmacotherapy to cover withdrawal is likely to be small. In the absence of any studies to inform guidance, approaches used in adults are an appropriate benchmark, although possibly with a lower threshold of admitting to hospital (NICE, 2011a) (Ia). Chlordiazepoxide has been recommended, with need to consider what dose is appropriate (Gilvarry and Britton, 2009) (IV).

A placebo-controlled RCT of acamprosate (1332 mg/day two tablets, one tablet, one tablet) in 26 16–19-year-olds with chronic or episodic alcohol dependence reported improved drinking outcomes in the acamprosate group during the 90-day study (Niederhofer and Staffen, 2003a) (Ib). They reported that the proportion of patients who remained abstinent was higher in the acamprosate group (seven vs. two) and that the mean cumulative abstinence duration was significantly greater in the acamprosate group (79.8 (SD 37.5) vs. 32.8 (SD 19.0)). Acamprosate was well tolerated with no difference in reported side effects to placebo.

A case report of naltrexone (50 mg/day) described reduced alcohol cravings and abstinence from alcohol and cannabis for 30 days in a 17-year-old (Wold and Kaminer, 1997) (III). An open-label pilot study of naltrexone (25 mg or 50 mg) in five outpatient treatment-seeking adolescents reported reduction in craving and drinking (Deas et al., 2005) (III). In this study, nausea was reduced if naltrexone was taken with food. A double-blind placebo-controlled study of naltrexone (50 mg/day) in 60 16–19-year-olds reported that significantly more patients on naltrexone remained abstinent during the 90 days, with cumulative abstinence of 70 days compared with 23 days (Niederhofer et al., 2003) (Ib). There was no significant difference in the two groups for side effects.

Disulfiram (250 mg/day) use in a 16 and in a 17-year-old resulted in prolonged abstinence for one young man but not the other, in whom compliance was poor (Myers et al., 1994) (III). A double-blind placebo-controlled study of disulfiram 200 mg daily (two 50 mg tablets mane, one 50 mg tablet at midday and one 50 mg tablet in the evening) in 26 16–19-year-olds reported disulfiram resulted in significantly greater abstinence (Niederhofer and Staffen, 2003b) (Ib). No significant difference was seen between the groups.

A prospective open-label trial of ondansetron (4 μg/kg) alongside weekly CBT in 12 treatment-seeking 14–20-year-olds found improvement in drinking outcomes over 8 weeks (Dawes et al., 2005) (IIb). However, there was no placebo group.

Opioids

The use of opioids, including 'street' and prescription opioids, appears to be on the rise in young people and has recently been reviewed (Subramaniam et al., 2009). Gilvarry and Britton (2009) (IV) provide guidance about prescribing opioid substitutes to young people. While in adults, stabilisation with an opioid substitute followed by long-term maintenance is common, this is a more controversial approach in young people with a limited history of opioid use and minimal adverse consequences. In such cases, substitution followed soon after by detoxification may be a more appropriate approach.

Optimal pharmacotherapy for detoxification has limited evidence, so advice for adults can be followed (Gilvarry and Britton, 2009, (IV); NICE, 2007 (Ia)). Buprenorphine, particularly with naloxone, is favoured by some due to its better tolerability, adverse event profile, and easier dose reduction to abstinence. An RCT compared buprenorphine with clonidine in detoxification of 36 opioid-dependent adolescents (13–18 years old; Marsch et al., 2005) (Ib). Buprenorphine improved retention in treatment for 1 month compared with clonidine (72% vs. 39%), provided more opiate-free urines (64% vs. 32%), and more started naltrexone afterwards (61% vs. 5%).

Another randomised trial compared two different regimens of buprenorphine–naloxone over 12 weeks in 150 15–21-year-olds (Woody et al., 2008) (Ib). It compared buprenorphine–naloxone, 24 mg per day for 9 weeks, then tapered to week 12 with

buprenorphine–naloxone prescribed up to 14 mg per day and then tapered to day 14 (called 'detox' group). Compared with the buprenorphine–naloxone group, the 'detox' group had more opioid-positive urines at weeks 4 (61% vs. 26%) and 8 (54% vs. 23%) but not 12 (51% vs. 43%) when both groups were not receiving any substitute prescription. Retention in treatment was better in the buprenorphine–naloxone group (70% vs. 20%). The majority in both groups resumed opioid use in the following 12 months. This study suggests that short-term treatment with buprenorphine–naloxone results in better outcomes than detoxification; however, once treatment stops, this gain is lost.

Concerning opioid maintenance, a recent Cochrane review of this approach identified two trials of maintenance treatment (Minozzi et al., 2009) (Ia). One was the Woody et al. (2008) (Ib) trial described above using buprenorphine–naloxone, and the other reported no difference between methadone and LAAM maintenance in 37 heroin addicts (Lehmann, 1973) (IIa).

For relapse prevention, the extended-release formulation of naltrexone (XR-naltrexone) requires monthly injections which can overcome compliance issues. In a case series of 16 individuals, average age 18 (range 16–20 years), XR-naltrexone was well tolerated, with 10 being retained for the 4-month treatment period (Fishman et al., 2010) (III). The majority of patients (11) were abstinent or had substantial reductions in opioid use, and nine met criteria for a 'good' outcome at 4 months. Importantly, there were no reports of overdoses despite many testing the blockade.

Nicotine

A recent Cochrane review of smoking cessation trials in young people reported the majority of trials included some form of motivational enhancement, and that complex psychological interventions showed promise (Grimshaw and Stanton, 2006) (Ia). A small trial of NRT alone, one with bupropion and one with bupropion alone failed to show efficacy in adolescent smokers (Killen et al., 2004; Moolchan et al., 2005; Muramoto et al., 2007) (Ib).

Other substances of abuse

There is no evidence to inform practice. For benzodiazepine dependence, maintenance prescribing is not recommended and detoxification with diazepam is recommended (Gilvarry and Britton, 2009) (IV). For all other substances of abuse, including stimulants, cannabis and Ecstasy, psychosocial approaches are considered the best approach and medication, if required for reducing problems such as insomnia, should only be used cautiously on a limited basis.

Comorbidity

As for adults, a coordinated approach for managing comorbidity of substance use disorder and another psychiatric disorder is required, perhaps even more so in younger people (Gilvarry and Britton, 2009; Lamps et al., 2008) (IV). High levels of such comorbidity at 60–88% have been reported in young people (Deas, 2006). Careful assessment is essential to understand the relationship between the two (or more) disorders and possible aetiology (NICE, 2011b) (Ia).

A pilot placebo-controlled trial of sertraline alongside CBT in 10 depressed alcohol-dependent adolescents reported that mood and drinking improved similarly in both groups (Deas et al., 2000) (Ib). Sertraline (25 mg/day increased to 100 mg by week 4) was well tolerated over the 12-week trial. An open-label 12-week trial of fluoxetine in depressed alcohol-dependent and alcohol-abusing adolescents reported significantly improved depression and drinking outcomes (Cornelius et al., 2001) (IIb). Fluoxetine was well tolerated. However, there was no placebo group, which limits drawing conclusions from this study.

A double-blind placebo-controlled trial over 6 weeks in 25 adolescents, mean age of 16 years, with bipolar disorder and secondary substance dependence reported that lithium was an efficacious treatment of both (Geller et al., 1998) (Ib). Alcohol and cannabis were the most common dependencies, although nicotine is not mentioned.

Recommendations: younger people. There is limited evidence on treatment of substance use disorders in younger people on which to base recommendations to guide specific pharmacological approaches. However, it is important that pharmacotherapy be considered, particularly in alcohol, opioid or nicotine dependence, and ideally by a specialist multidisciplinary service.

- Pharmacological treatment should follow the evidence base for the general adult population with appropriate dose adjustments for age-related pharmacokinetic and pharmacodynamic changes (C).
- Younger people with harmful substance use, abuse or dependence should have full routine health screens with identification and treatment of psychiatric or physical health problems (S).
- There should be a lower threshold for admission for inpatient assessment and treatment, for example for assisted alcohol withdrawal, opioid stabilisation in younger people (D).

Key uncertainties

- What is the long-term outcome after alcohol or opioid detoxification?
- What is the optimal opioid substitution regimen for opioid dependence in this age group?
- What is the effectiveness of alcohol relapse prevention medication in younger people?

Older adults

In 2001, people over 65 made up 16% of England's population and this is forecast to rise to 21% by 2026 (Falaschetti et al., 2002), increasing demands on the substance misuse treatment system over the next two decades (Gfroerer et al., 2003). A recent report is recommended reading (Crome, 2011). Some key points in this report are that psychiatric comorbidities of substance misuse are common in older people; older people are at increased risk of adverse physical effects of substance misuse, even at relatively modest levels of intake; older men are at greater risk of developing alcohol and illicit drug misuse problems than older women; and older women are at greater risk of developing problems associated with prescribed or over-the counter medication than men. In addition, the relationship between cognitive function and substance (particularly alcohol) use is complex, as is that between functional mental health problems (e.g. anxiety and depression) and substance

use, with the direction of causality often unclear. Lower safe levels of alcohol consumption (1.5 units/day; 11/week) are proposed. Older people can and do benefit from treatment, and in some cases have better outcomes than younger people (Moy et al., 2011).

There is a lack of evidence to guide practitioners on managing substance misuse in older adults. Elderly people are typically excluded from clinical trials of pharmacotherapy, despite the increasing need for an evidence base as the UK population ages. According to recent figures for England and Wales, 1.5% of the 55–59 year age group among the general population reported use of any illicit drug in the previous year, with 0.1% reporting use of a class A drug. This compares with 18.1% and 7.8%, respectively, for 20–24 year olds (Hoare and Moon, 2010).

There are difficulties in the detection and management of substance misuse problems in older adults. Reasons include inadequate drug and alcohol history-taking in the elderly, low referral rates to specialist drug and alcohol services, and greater use of prescription drugs with potential for misuse (Gottlieb, 2004; McInnes and Powell, 1994; Simoni-Wastila and Yang, 2006). Treatment should be within multidisciplinary settings with input from addiction specialists and specialists in older people's physical and mental health.

The normal physiological changes of ageing result in important pharmacokinetic and pharmacodynamic changes. Pharmacokinetic changes result from changes in body composition and hepatic and renal function. This results in an increased volume of distribution of lipid-soluble drugs and reduced hepatic and renal clearance. These changes lead to prolongation of plasma elimination half-life. From a pharmacodynamic perspective, age-dependent changes tend to increase sensitivity to drugs. Reduced homeostatic mechanisms may lengthen the time older adults require to regain steady-state levels following changes in drug therapy (Mangoni and Jackson, 2004). Pharmacological treatment should be started at a low dose and titrated slowly.

Drug misusers have higher mortality rates than the age-matched general population, and older drug users have additionally to deal with the increasing physical health problems of ageing. Older opioid users are at greater risk of death due to traumatic and somatic causes (Clausen et al., 2009). Clausen et al. (2009) also found that older opioid users were at higher risk of fatal overdose after leaving opioid maintenance treatment. Cardiovascular diseases and tumours (often hepatic) were the most common causes of death among drug users aged 55 or over in one long-term follow-up study (Stenbacka et al., 2010).

Opioids

The proportion of older adults attending treatment services is increasing. In 2009/10 in England 26% of the 206,889 in contact with structured drug treatment services were over 40 years old compared with 18% in 2005/6 (National Treatment Agency and Department of Health, 2010b). In addition, in recent years there have been increasing numbers of people above 40 years of age presenting for new treatment episodes to structured drug treatment services, mainly with problematical heroin use (National Treatment Agency and Department of Health, 2010b). Cochrane reviews of maintenance treatments for opioid dependence report participants to be 'approximately 30–40 years of age' (Mattick et al., 2008, 2009) (Ia).

Firoz and Carlson (2004) (III) compared outcomes for methadone treatment in 54 older adults (>55 years) with 705 adults under 55 years of age. The mean age for the older adults was 62 years (range 55–82). The older adults had improved outcomes on drug use measures at 9 months compared with the younger adults. The groups did not differ in medical or psychiatric problems.

Among entrants to a New York methadone programme, older adults were more likely to have had longer periods of treatment, less likely to report current heroin use and overall drug use, but were more likely to have a history of comorbid alcohol misuse (Rajaratnam et al., 2009) (III). Fareed et al. (2009) (III) conducted a retrospective chart review of older patients enrolled in a methadone maintenance programme. Patients who remained in treatment showed statistically significant improvements in drug use, psychiatric, medical and legal problems.

There is no direct evidence about methadone dosing regimens for maintenance treatment in older adults. Guidance from the pain management literature recommends opioid doses should be reduced, there should be a longer time interval between doses, and creatinine clearance should be monitored (Pergolizzi et al., 2008) (IV). As maintenance treatment utilises daily dosing of methadone, slower dose titration is advisable.

In the absence of a specific evidence base for buprenorphine and naltrexone in this population, treatment decisions should be based on extrapolations from the general opioid evidence base. Clinicians should be mindful of the changes of ageing and accompanying increases in comorbidity which may necessitate dose adjustments. Evidence from the alcohol literature can be used to inform about the safety of naltrexone. Buprenorphine may be the optimal choice for those with renal dysfunction requiring maintenance treatment (Pergolizzi et al., 2008) (IV).

Alcohol

Older adults are at increased risk of alcohol-related harm (O'Connell et al., 2003). The prevalence of alcohol dependence has been reported as 2.3% in 50–54-year-olds (Drummond et al., 2005). Of the 100,098 clients in contact with structured treatment services for a primary alcohol problem in 2008/9, 12,719 (13%) were over 55 years of age (National Treatment Agency and the Department of Health, 2010a). For a summary of the patterns of alcohol use, alcohol-related health problems and assessment and screening in the elderly see Dar (2006). NICE summarises the complexities of treating alcohol use disorders in older adults (NICE, 2011a).

There should be a lower threshold for admission for inpatient assisted alcohol withdrawal in older people (NICE, 2011a). Brower et al. (1994) reported a more protracted and severe alcohol withdrawal syndrome in the elderly compared with younger people with equal drinking severity. However, a prospective study of admissions to a specialist detoxification unit did not find a relationship between the severity of alcohol withdrawal and age (Wetterling et al., 2001).

Benzodiazepines remain the treatment of choice, but the doses may need to be reduced in older people (NICE, 2011a). Shorter acting benzodiazepines (e.g. oxazepam) may be preferred, especially where there is concern about accumulation leading to oversedation (Mayo-Smith et al., 2004) (III).

There is an absence of high-quality evidence on pharmacological interventions for maintaining abstinence in older people, and extrapolations should be made from the adult evidence base (NICE, 2011a). In trials of naltrexone treatment only 2.6% of

subjects were over 65 years of age, and in placebo-controlled clinical trials of acamprosate 1% were 65 years or older (Teter, personal communication).

There have been concerns about the increased risk of serious adverse effects in older adults prescribed disulfiram due to physical comorbidities and polypharmacy and the risks of precipitating a confusional state (Dufour and Fuller, 1995; Dunne, 1994; Schonfeld and Dupree, 1995 (IV)) and cardiovascular concerns if there was a drug–alcohol interaction (Barrick and Connors, 2002) (IV). However, Zimberg (2005) (IV) reports that disulfiram is safe and effective in a dose of 125 mg per day in elderly patients who are not suffering from significant cardiovascular or liver disease and who do not have significant cognitive impairment. Acamprosate is known to have a good safety profile except in renal insufficiency. Dose adjustment may be required in older adults due to age-related kidney disease. Naltrexone appears to be safe in older adults. A 12-week double-blind, placebo-controlled study of naltrexone (50 mg per day) in alcohol-dependent subjects over 50 years of age found no difference in frequency of adverse events, including changes in liver enzymes, between placebo and naltrexone-treated groups (Oslin et al., 1997) (Ib). In a randomised, double-blind, placebo-controlled efficacy trial of naltrexone (100 mg per day), older adults (over 55 years of age) were more likely to adhere to the medication regime than younger adults (OR = 3.28; 95% CI 1.19–9.08, $p = 0.022$) (Oslin et al., 2002) (Ib).

Nicotine dependence

Orleans et al. (1994) (III) reported the results of a 6-month telephone follow-up survey of smokers aged 65–74 years prescribed nicotine patches. Some 29% reported current abstinence (of at least 7 days duration) at 6-month follow-up. Miller et al. (2005) (III) also report a follow-up survey conducted 6 months after free distribution of NRT. Smokers who phoned a toll-free quit line were sent a 6-week course of NRT and had brief follow-up counselling calls. The highest quit rates were associated with those older than 65 years. Also, placebo-controlled trials of nicotine patches on patients with coronary artery disease have found no evidence for an increased risk of cardiac complications (Joseph et al., 1996; Tzivoni et al., 1998) (Ia).

In studies of immediate and sustained release bupropion in depression and smoking no overall differences in safety or effectiveness were observed between subjects over 65 years of age and younger subjects (Teter, personal communication). A maximum dose of 150 mg bupropion daily is recommended in the elderly. There is no specific dose reduction recommended in older adults for varenicline except where there is coexisting renal insufficiency (see BNF).

Benzodiazepines and hypnotics

There are ongoing concerns about inappropriate prescribing of benzodiazepines to older adults (Reay, 2009). Unlike research in opioid and alcohol dependence, many of the studies of benzodiazepine discontinuation have been conducted in elderly populations. These have usually involved patients in general practice or outpatient settings and patients who have 'therapeutic dose' dependence (Parr et al., 2008). In these studies minimal interventions (1a) and graded discontinuation (1b) have proven effectiveness. The addition of psychological interventions to graded discontinuation has shown increased effectiveness compared with gradual dose reduction alone, and may be particularly beneficial where there is problematical insomnia (Oude Voshaar et al., 2006b; Parr et al., 2008) (Ia).

Recommendations: older adults. There is limited evidence on treatment of harmful substance use, abuse or dependence in older adults on which to base recommendations to guide pharmacological approaches.

- Pharmacological treatment should follow the evidence base for the general adult population, with appropriate dose adjustments for age-related pharmacokinetic and pharmacodynamic changes and for psychiatric and physical comorbidities (C).
- Older adults with harmful substance use, abuse or dependence should have full routine health screens with identification and treatment of psychiatric and physical health problems (S).
- There should be a lower threshold for admission for inpatient assisted alcohol withdrawal in older people (D).
- 'Therapeutic dose' benzodiazepine users should be offered minimal interventions or graded discontinuation depending on the clinical picture (A).

Key uncertainties

- What is the long-term outcome after alcohol or opioid detoxification?
- What is the optimal opioid substitution regimen for opioid dependence in this age group?
- What is the efficacy of acamprosate and naltrexone in older adults?

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Conflicts of interest

Declaration of interests of the participants are held by the BAP office.

References

Addolorato G, Leggio L, Ferrulli A, et al. (2007) Effectiveness and safety of baclofen for maintenance of alcohol abstinence in alcohol-dependent patients with liver cirrhosis: randomised, double-blind controlled study. *Lancet* 370: 1915–1922.

Addolorato G, Leggio L, Ferrulli A, et al. (2009) The therapeutic potential of gamma-hydroxybutyric acid for alcohol dependence: balancing

the risks and benefits. A focus on clinical data. *Expert Opin Investig Drugs* 18: 675–686.

Addolorato G, Leggio L, Ferrulli A, et al. (2011) Dose-response effect of baclofen in reducing daily alcohol intake in alcohol dependence: secondary analysis of a randomized, double-blind, placebo-controlled trial. *Alcohol Alcohol* 46: 312–317.

Agabio R, Marras P, Addolorato G, et al. (2007) Baclofen suppresses alcohol intake and craving for alcohol in a schizophrenic alcohol-dependent patient: a case report. *Clin Psychopharmacol* 27: 319–320.

Ahmadi J, Kampman KM, Oslin DM, et al. (2009) Predictors of treatment outcome in outpatient cocaine and alcohol dependence treatment. *Am J Addict* 18: 81–86.

Akerele E and Levin FR (2007) Comparison of olanzapine to risperidone in substance-abusing individuals with schizophrenia. *Am J Addict* 16: 260–268.

Allsop DJ, Norberg MM, Copeland J, et al. (2011) The Cannabis Withdrawal Scale development: patterns and predictors of cannabis withdrawal and distress. *Drug Alcohol Depend* 119: 123–129.

Alterman AI, Rutherford MJ, Cacciola JS, et al. (1998) Prediction of 7 months methadone maintenance treatment response by four measures of antisociality. *Drug Alcohol Depend* 49: 217–223.

Altintoprak AE, Zorlu N, Coskunol H, et al. (2008) Effectiveness and tolerability of mirtazapine and amitriptyline in alcoholic patients with co-morbid depressive disorder: a randomized, double-blind study. *Hum Psychopharmacol* 23: 313–319.

Amass L, Ling W, Freese TE, et al. (2004) Bringing buprenorphine-naloxone detoxification to community treatment providers: the NIDA Clinical Trials Network field experience. *Am J Addict* 13(Suppl 1): S42–S66.

Amato L, Davoli M, Minozzi S, et al. (2005) Methadone at tapered doses for the management of opioid withdrawal. *Cochrane Database Syst Rev* 3: CD003409.

Amato L, Minozzi S, Pani PP, et al. (2007) Antipsychotic medications for cocaine dependence. *Cochrane Database Syst Rev* 3: CD006306.

Amato L, Minozzi S, Davoli M, et al. (2011a) Psychosocial combined with agonist maintenance treatments versus agonist maintenance treatments alone for treatment of opioid dependence. *Cochrane Database Syst Rev* 10: CD004147.

Amato L, Minozzi S, Davoli M, et al. (2011b) Psychosocial and pharmacological treatments versus pharmacological treatments for opioid detoxification. *Cochrane Database Syst Rev* 9: CD005031.

Amato L, Minozzi S, Pani PP, et al. (2011c) Dopamine agonists for the treatment of cocaine dependence. *Cochrane Database Syst Rev* 12: CD003352.

Amato L, Minozzi S, Vecchi S, et al. (2010) Benzodiazepines for alcohol withdrawal. *Cochrane Database Syst Rev* 3: CD005063.

Ameisen O (2005) Complete and prolonged suppression of symptoms and consequences of alcohol-dependence using high-dose baclofen: a self-case report of a physician. *Alcohol Alcohol* 40: 147–150.

Anschersen K, Clausen T, Gossop M, et al. (2009) Prevalence and clinical relevance of corrected QT interval prolongation during methadone and buprenorphine treatment: a mortality assessment study. *Addiction* 104: 993–999.

Anton RF, Kranzler H, Breder C, et al. (2008) A randomized, multicenter, double-blind, placebo-controlled study of the efficacy and safety of aripiprazole for the treatment of alcohol dependence. *J Clin Psychopharmacol* 28: 5–12.

Anton RF, Moak DH, Latham PK, et al. (2001) Posttreatment results of combining naltrexone with cognitive-behavior therapy for the treatment of alcoholism. *J Clin Psychopharmacol* 21: 72–77.

Anton RF, Moak DH, Latham P, et al. (2005) Naltrexone combined with either cognitive behavioral or motivational enhancement therapy for alcohol dependence. *J Clin Psychopharmacol* 25: 349–357.

Anton RF, Myrick H, Baros AM, et al. (2009) Efficacy of a combination of flumazenil and gabapentin in the treatment of alcohol dependence: relationship to alcohol withdrawal symptoms. *J Clin Psychopharmacol* 29: 334–342.

Anton RF, O'Malley SS, Ciraulo DA, et al. (2006) Combined pharmacotherapies and behavioral interventions for alcohol dependence: the COMBINE study: a randomized controlled trial. *JAMA* 295: 2003–2017.

Anton RF, Oroszi G, O'Malley S, et al. (2008) An evaluation of mu-opioid receptor (OPRM1) as a predictor of naltrexone response in the treatment of alcohol dependence: results from the Combined Pharmacotherapies and Behavioral Interventions for Alcohol Dependence (COMBINE) study. *Arch Gen Psychiatry* 65(2): 135–144.

Anton RF, Pettinati H, Zweben A, et al. (2004) A multi-site dose ranging study of nalmefene in the treatment of alcohol dependence. *J Clin Psychopharmacol* 24: 421–428.

Arnedt JT, Conroy DA and Brower KJ (2007) Treatment options for sleep disturbances during alcohol recovery. *J Addict Dis* 26: 41–54.

Assadi SM, Radgoodarzi R and Ahmadi-Abhari SA (2003) Baclofen for maintenance treatment of opioid dependence: a randomized double-blind placebo-controlled clinical trial. *BMC Psychiatry* 3: 16.

Baillargeon L, Landreville P, Verreault R, et al. (2003) Discontinuation of benzodiazepine among older insomniac adults treated with cognitive - behavioural therapy combined with gradual tapering: a randomized trial. *Can Med Assoc J* 169: 1015–1020.

Baker JR, Jatlow P and McCance-Katz EF (2007) Disulfiram effects on responses to intravenous cocaine administration. *Drug Alcohol Depend* 87: 202–209.

Balldin J, Berglund M, Borg S, et al. (2003) A 6-month controlled naltrexone study: combined effect with cognitive behavioral therapy in outpatient treatment of alcohol dependence. *Alcohol Clin Exp Res* 27: 1142–1149.

Baltieri DA, Daró FR, Ribeiro PL, et al. (2008) Comparing topiramate with naltrexone in the treatment of alcohol dependence. *Addiction* 103: 2035–2044.

Barnes TR; Schizophrenia Consensus Group of British Association for Psychopharmacology (2011) Evidence-based guidelines for the pharmacological treatment of schizophrenia: recommendations from the British Association for Psychopharmacology. *J Psychopharmacol* 25: 567–620.

Barrick C and Connors GJ (2002) Relapse prevention and maintaining abstinence in older adults with alcohol-use disorders. *Drugs Aging* 19: 583–594.

Barrons R and Roberts N (2010) The role of carbamazepine and oxcarbazepine in alcohol withdrawal syndrome. *J Clin Pharm Ther* 35: 153–167.

Barrowclough C, Haddock G, Wykes T, et al. (2010) Integrated motivational interviewing and cognitive behavioural therapy for people with psychosis and comorbid substance misuse: randomised controlled trial. *BMJ* 341: c6325.

Bart G, Schluger JH, Borg L, et al. (2005) Nalmefene induced elevation in serum prolactin in normal human volunteers: partial kappa opioid agonist activity? *Neuropsychopharmacology* 30: 2254–2262.

Batki SL, Dimmock JA, Wade M, et al. (2007) Monitored naltrexone without counselling for alcohol abuse/dependence in schizophrenia-spectrum disorders. *Am J Addict* 16: 253–259.

Beer B, Rabl W, Libiseller K, et al. (2010) Impact of slow-release oral morphine on drug abusing habits in Austria. *Neuropsychiatrie* 4: 108–117.

Bell J and Collins R (2011) Gamma-butyrolactone (GBL) dependence and withdrawal. *Addiction* 106: 442–447.

Beresford TP, Clapp L, Martin B, et al. (2005) Aripiprazole in schizophrenia with cocaine dependence: a pilot study. *J Clin Psychopharmacol* 25: 363–366.

Berglund M, Thelander S and Jonsson E (2003) *Treating alcohol and drug abuse. An evidence based review*. Weinheim: WILEY-VCH Verlag GmbH and Co.

Bizzarri JV, Sbrana A, Rucci P, et al. (2007) The spectrum of substance abuse in bipolar disorder: reasons for use, sensation seeking and substance sensitivity. *Bipolar Disord* 9: 213–220.

Blanken P, Hendriks VM, van Ree JM, et al. (2010) Outcome of long-term heroin-assisted treatment offered to chronic, treatment-resistant heroin addicts in the Netherlands. *Addiction* 105: 300–308.

Boeijinga PH, Parot P, Soufflet L, et al. (2004) Pharmacodynamic effects of acamprosate on markers of cerebral function in alcohol-dependent subjects administered as pretreatment and during alcohol abstinence. *Neuropsychobiology* 50: 71–77.

Bogenschutz MP, Scott Tonigan J and Pettinati HM (2009) Effects of alcoholism typology on response to naltrexone in the COMBINE study. *Alcohol Clin Exp Res* 33: 10–18.

Bond AJ, Reed KD, Beavan P, et al. (2011) After the randomised injectable opiate treatment trial: Post-trial investigation of slow-release oral morphine as an alternative opiate maintenance medication. *Drug Alcohol Rev* DOI: 10.1111/j.1465-3362.2011.00353.x. (Epub ahead of print).

Bonnet U, Hamzavi-Abedi R, Specka M, et al. (2010) An open trial of gabapentin in acute alcohol withdrawal using an oral loading protocol. *Alcohol Alcohol* 45: 143–145.

Book SW, Thomas SE, Dempsey JP, et al. (2009) Social anxiety impacts willingness to participate in addiction treatment. *Addict Behav* 34: 474–476.

Book SW, Thomas SE, Randall PK, et al. (2008) Paroxetine reduces social anxiety in individuals with a co-occurring alcohol use disorder. *J Anxiety Disord* 22: 310–318.

Bouza C, Angeles M, Muñoz A, et al. (2004) Efficacy and safety of naltrexone and acamprosate in the treatment of alcohol dependence: a systematic review. *Addiction* 99: 811–828.

Bowden-Jones O, Iqbal MZ, Tyrer P, et al. (2004) Prevalence of personality disorder in alcohol and drug services and associated comorbidity. *Addiction* 99: 1306–1314.

Bowen RC, D'Arcy C, Keegan D, et al. (2000) A controlled trial of cognitive behavioral treatment of panic in alcoholic inpatients with comorbid panic disorder. *Addict Behav* 25: 593–597.

Bowen R, McIlwrick J, Baetz M, et al. (2005) Lithium and marijuana withdrawal. *Can J Psychiatry* 50: 240–241.

Brady KT, Sonne S, Anton RF, et al. (2005) Sertraline in the treatment of co-occurring alcohol dependence and posttraumatic stress disorder. *Alcohol Clin Exp Res* 29: 395–401.

Brady KT, Sonne SC, Malcolm RJ, et al. (2002) Carbamazepine in the treatment of cocaine dependence: subtyping by affective disorder. *Exp Clin Psychopharmacol* 10: 276–285.

Bråthen G, Ben-Menachem E, Brodtkorb E, et al. (2005) EFNS guideline on the diagnosis and management of alcohol-related seizures: report of an EFNS task force. *Eur J Neurol* 12: 575–581.

British Medical Association, Board of Science and Education (2003) *Adolescent Health*. London: BMA Publishing Unit.

Brooks AC, Comer SD, Sullivan MA, et al. (2010) Long-acting injectable versus oral naltrexone maintenance therapy with psychosocial intervention for heroin dependence: a quasi-experiment. *J Clin Psychiatry* 71: 1371–1378.

Brose LS, West R, McDermott MS, et al. (2011) What makes for an effective stop-smoking service? *Thorax* 66(10): 924–926.

Brower KJ and Perron BE (2010) Sleep disturbance as a universal risk factor for relapse in addictions to psychoactive substances. *Med Hypotheses* 74: 928–933.

Brower KJ, Mudd S, Blow FC, et al. (1994) Severity and treatment of alcohol withdrawal in elderly versus younger patients. *Alcohol Clin Exp Res* 18: 196–201.

Brown ES, Carmody TJ, Schmitz JM, et al. (2009) A randomized, double-blind, placebo-controlled pilot study of naltrexone in outpatients with bipolar disorder and alcohol dependence. *Alcohol Clin Exp Res* 33: 1863–1869.

Brown ES, Garza M and Carmody TJ (2008) A randomized, double-blind, placebo-controlled add-on trial of quetiapine in outpatients with bipolar disorder and alcohol use disorders. *J Clin Psychiatry* 69: 701–705.

Brown ES, Jeffress J, Liggin JD, et al. (2005) Switching outpatients with bipolar or schizoaffective disorders and substance abuse from their current antipsychotic to aripiprazole. *J Clin Psychiatry* 66: 756–760.

Brown ES, Nejtek VA, Perantie DC, et al. (2002) Quetiapine in bipolar disorder and cocaine dependence. *Bipolar Disord* 4: 406–411.

Brown ES, Nejtek VA, Perantie DC, et al. (2003) Lamotrigine in patients with bipolar disorder and cocaine dependence. *J Clin Psychiatry* 64: 197–201.

Brown ES, Perantie DC, Dhanani N, et al. (2006) Lamotrigine for bipolar disorder and comorbid cocaine dependence: a replication and extension study. *J Affect Disord* 93: 219–222.

Brown SA and Schuckit MA (1988) Changes in depression among abstinent alcoholics. *J Stud Alcohol* 49: 412–417.

Brown SA, Irwin M and Schuckit MA (1991) Changes in anxiety among abstinent male alcoholics. *J Stud Alcohol* 52: 55–61.

Brunette MF, Drake RE, Xie H, et al. (2006) Clozapine use and relapses of substance use disorder among patients with co-occurring schizophrenia and substance use disorders. *Schizophr Bull* 32: 637–643.

Budney AJ, Hughes JR, Moore BA, et al. (2004) Review of the validity and significance of cannabis withdrawal syndrome. *Am J Psychiatry* 161: 1967–1977.

Budney AJ, Vandrey RG, Hughes JR, et al. (2007) Oral delta-9-tetrahydrocannabinol suppresses cannabis withdrawal symptoms. *Drug Alcohol Depend* 86: 22–29.

Burns E, Gray R and Smith LA (2010) Brief screening questionnaires to identify problem drinking during pregnancy: a systematic review. *Addiction* 105: 601–614.

Burns L, Mattick RP, Lim K, et al. (2007) Methadone in pregnancy: treatment retention and neonatal outcomes. *Addiction* 102: 264–270.

Burns L, Randall D, Hall WD, et al. (2009) Opioid agonist pharmacotherapy in New South Wales from 1985 to 2006: patient characteristics and patterns and predictors of treatment retention. *Addiction* 104: 1363–1372.

Cacciola JS, Alterman AI, Rutherford MJ, et al. (1995) Treatment response of antisocial substance abusers. *J Nerv Ment Dis* 183: 166–171.

Cacciola JS, Rutherford MJ, Alterman AI, et al. (1996) Personality disorders and treatment outcome in methadone maintenance patients *J Nerv Ment Dis* 184: 234–239.

Cahill K, Stead LF and Lancaster T (2011) Nicotine receptor partial agonists for smoking cessation. *Cochrane Database Syst Rev* 2: CD006103.

Caine D, Halliday GM, Kril JJ, et al. (1997) Operational criteria for the classification of chronic alcoholics: identification of Wernicke's encephalopathy. *J Neurol Neurosurg Psychiatry* 62: 51–60.

Caplehorn JR, Dalton MS, Haldar F, et al. (1996) Methadone maintenance and addicts' risk of fatal heroin overdose. *Subst Use Misuse* 31: 177–196.

Caputo F and Bernardi M (2010) Medications acting on the GABA system in the treatment of alcoholic patients. *Curr Pharm Des* 16: 2118–2125.

Carpenter KM, McDowell D, Brooks DJ, et al. (2009) A preliminary trial: double-blind comparison of nefazodone, bupropion-SR, and placebo in the treatment of cannabis dependence. *Am J Addict* 18: 53–64.

Carroll KM, Nich C, Ball SA, et al. (2000) One-year follow-up of disulfiram and psychotherapy for cocaine-alcohol users: sustained effects of treatment. *Addiction* 95: 1335–1349.

Carroll KM, Nich C, Ball SA, et al. (1998) Treatment of cocaine and alcohol dependence with psychotherapy and disulfiram. *Addiction* 93: 713–728.

Carson G, Cox LV, Crane J, et al. (2010) Alcohol use and pregnancy consensus clinical guidelines. *J Obstet Gynaecol Can* 32(8 Suppl 3): S1–S31.

Casas M, Franco MD, Goikolea JM, et al. (2008) Bipolar disorder associated to substance use disorders (dual diagnosis). Systematic review of the scientific evidence and expert consensus. *Actas Esp Psiquiatr* 36: 350–361.

Castells X, Casas M, Pérez-Mañá C, et al. (2010) Efficacy of psychostimulant drugs for cocaine dependence. *Cochrane Database Syst Rev* 2: CD007380.

Cecero JJ, Ball SA, Tennen H, et al. (1999) Concurrent and predictive validity of antisocial personality disorder subtyping among substance abusers. *J Nerv Ment Dis* 187: 478–486.

Chambers RA, Krystal JH and Self DW (2001) A neurobiological basis for substance abuse comorbidity in schizophrenia. *Biol Psychiatry* 50: 71–83.

Chick J (1999) Safety issues concerning the use of disulfiram in treating alcohol dependence. *Drug Saf* 20: 427–435.

Chick J and Nutt D (2012) Substitution therapy for alcoholism: time for a reappraisal? *J Psychopharmacol* 26: 205–212.

Chick J, Aschauer H and Hornik K (2004) Efficacy of fluvoxamine in preventing relapse in alcohol dependence: a one-year double-blind placebo controlled multicentre study with analysis by typology. *Drug Alcohol Depend* 74: 61–70.

Chick J, Gough K, Falkowski W, et al. (1992) Disulfiram treatment of alcoholism. *Br J Psychiatry* 161: 84–89.

Chick J, Howlett H, Morgan M, et al. (2000) United Kingdom multicentre acamprosate study (UKMAS): a 6-month prospective study of acamprosate versus placebo in preventing relapse after withdrawal from alcohol. *Alcohol Alcohol* 35: 176–187.

Chick J, Lehert P and Landron F (2003) Does acamprosate improve reduction of drinking as well as aiding abstinence? *J Psychopharmacol* 17: 397–402.

Ciraulo DN and Nace EP (2000) Benzodiazepine treatment of anxiety or insomnia in substance abuse patients. *Am J Addict* 9: 276–284.

Ciraulo D, Sands BF and Shader RI (1988) Critical review of liability of benzodiazepine abuse among alcoholics. *Am J Psychiatry* 145: 1501–1506.

Ciraulo DA, Dong Q, Silverman BL, et al. (2008) Early treatment response in alcohol dependence with extended-release naltrexone. *J Clin Psychiatry* 69: 190–195.

Clausen T, Waal H, Thoresen M, et al. (2009) Mortality among opiate users: opioid maintenance therapy, age and causes of death. *Addiction* 104: 1356–1362.

Cleary BJ, Donnelly J, Strawbridge J, et al. (2010) Methadone dose and neonatal abstinence syndrome – systematic review and meta-analysis. *Addiction* 105: 2071–2084.

Cleary B, Donnelly J, Strawbridge J, et al. (2011) Methadone and perinatal outcomes: a retrospective cohort study. *Am J Obstet Gynecol* 204: 139.e1–e9.

Cleary M, Hunt G, Matheson S, et al. (2008) Psychosocial interventions for people with both severe mental illness and substance misuse. *Cochrane Database Syst Rev* 1: CD001088.

CMACE, Centre for Maternal and Child Enquiries (2011) Saving Mothers' Lives: reviewing maternal deaths to make motherhood safer: 2006–08. The Eighth Report on Confidential Enquiries into Maternal Deaths in the United Kingdom. *Br J Obstret Gynaecol* 118 (Suppl. 1): 1–203.

Comer SD, Sullivan MA, Yu E, et al. (2006) Injectable, sustained-release naltrexone for the treatment of opioid dependence: a randomized, placebo-controlled trial. *Arch Gen Psychiatry* 63: 210–218.

Cornelius JR, Bukstein OG, Birmaher B, et al. (2001) Fluoxetine in adolescents with major depression and an alcohol use disorder: an open-label trial. *Addict Behav* 26: 735–739.

Crome I (2011) *Our invisible addicts. College report 165, Report of the Older Persons' Substance Misuse Working Group of the Royal College of Psychiatrists.* London: Royal College of Psychiatrists.

Cruickshank CC, Montebello ME, Dyer KR, et al. (2008) A placebo-controlled trial of mirtazapine for the management of methamphetamine withdrawal. *Drug Alcohol Rev* 27: 326–333.

Cui SS, Bowen RC, Gu GB, et al. (2001) Prevention of cannabinoid withdrawal syndrome by lithium: involvement of oxytocinergic neuronal activation. *J Neurosci* 21: 9867–9876.

Dar K (2006) Alcohol use disorders in elderly people: fact or fiction? *Adv Psychiatr Treat* 12: 173–181.

Darke S, Finlay-Jones R, Kaye S, et al. (1996) Anti-social personality disorder and response to methadone maintenance treatment. *Drug Alcohol Rev* 15: 271–276.

Darke S, Ross J, Mills K, et al. (2010) Benzodiazepine use among heroin users: Baseline use, current use and clinical outcome. *Drug Alcohol Rev* 29: 250–255.

Darke S, Ross J, Williamson A, et al. (2007) Borderline personality disorder and persistently elevated levels of risk in 36-month outcomes for the treatment of heroin dependence. *Addiction* 102: 1140–1146.

Dashe JS, Sheffield JS and Wendel GD (2004) Improving the management of opioid-dependent pregnancies. *Am J Obstet Gynecol* 190: 1806.

Dawes MA, Johnson BA, Ait-Daoud N, et al. (2005) A prospective, open label trial of ondansetron in adolescents with alcohol dependence. *Addict Behav* 30: 1077–1085.

Day E, Bentham P, Callaghan R, et al. (2004) Thiamine for Wernicke-Korsakoff Syndrome in people at risk from alcohol abuse. *Cochrane Database Syst Rev* 1: CD004033.

Dean AJ, Bell J, Christie MJ, et al. (2004) Depressive symptoms during buprenorphine vs. methadone maintenance: findings from a randomised, controlled trial in opioid dependence. *Eur Psychiatry* 19: 510–513.

Dean AJ, Saunders JB, Jones RT, et al. (2006) Does naltrexone treatment lead to depression? Findings from a randomized controlled trial in subjects with opioid dependence. *J Psychiatry Neurosci* 31: 38–45.

Deas D (2006) Adolescent substance abuse and psychiatric comorbidities. *J Clin Psychiatry* 67: 18–23.

Deas D, May MP, Randall C, et al. (2005) Naltrexone treatment of adolescent alcoholics: An open label pilot study. *J Child Adolesc Psychopharmaol* 15: 723–728.

Deas D, Randall CL, Roberts JS, et al. (2000) A double-blind, placebo-controlled trial of sertraline in depressed adolescent alcoholics: A pilot study. *Hum Psychopharmacol* 15: 461–469.

Degenhardt L, Randall D, Hall W, et al. (2009) Mortality among clients of a state-wide opioid pharmacotherapy program over 20 years: risk factors and lives saved. *Drug Alcohol Depend* 105: 9–15.

de Jong CA, Kamal R, Dijkstra BA, et al. (2012) Gamma-hydroxybutyrate detoxification by titration and tapering. *Eur Addict Res* 18: 40–45.

Denis C, Fatseas M, Lavie E, et al. (2006) Pharmacological interventions for benzodiazepine mono-dependence management in outpatient settings. *Cochrane Database Syst Rev* 3: CD005194.

Department of Health (England) and the devolved administrations (2007) *Drug misuse and dependence: UK guidelines on clinical management*. London: Department of Health (England) the Scottish Government, Welsh Assembly Government and the Northern Ireland Executive.

Department of Health (2008) *Pregnancy and Alcohol*. London: Department of Health.

de Sousa A (2010) The role of topiramate and other anticonvulsants in the treatment of alcohol dependence: a clinical review. *CNS Neurol Disord Drug Targets* 9: 45–49.

de Sousa A and de Sousa A (2004) A one-year pragmatic trial of naltrexone vs disulfiram in the treatment of alcohol dependence. *Alcohol Alcohol* 39: 528–531.

de Sousa A and de Sousa A (2005) An open randomized study comparing disulfiram and acamprosate in the treatment of alcohol dependence. *Alcohol Alcoholism* 40: 545–548.

de Sousa AA, De Sousa J and Kapoor H (2008) An open randomized trial comparing disulfiram and topiramate in the treatment of alcohol dependence. *J Subst Abuse Treat* 34: 460–463.

de Wet C, Reed LJ, Glasper A, et al. (2004) Benzodiazepine co-dependence exacerbates the opiate withdrawal syndrome. *Drug Alcohol Depend* 76: 31–35.

de Wildt WA, Schippers GM, Van Den Brink W, et al. (2002) Does psychosocial treatment enhance the efficacy of acamprosate in patients with alcohol problems? *Alcohol Alcohol* 37: 375–382.

Di Costanzo E and Rovea A (1992) [The prophylaxis of benzodiazepine withdrawal in the elderly: the effectiveness of carbamazepine. Double-blind study v. Placebo.] *Minerva Psychiatr* 33: 301–304.

Dijkgraaf MG, van der Zanden BP, de Borgie CA, et al. (2005) Cost utility analysis of co-prescribed heroin compared with methadone maintenance treatment in heroin addicts in two randomised trials. *BMJ* 330: 1297–1302.

Di Nicola M, Martinotti G, Tedeschi D, et al. (2010) Pregabalin in outpatient detoxification of subjects with mild-to-moderate alcohol withdrawal syndrome. *Hum Psychopharmacol* 25: 268–275.

Donovan DM, Anton RF, Miller WR, et al. (2008) Combined pharmacotherapies and behavioral interventions for alcohol dependence (The COMBINE Study): examination of posttreatment drinking outcomes. *J Stud Alcohol Drugs* 69: 5–13.

Dore GM, Lo K, Juckes L, et al. (2011) Clinical experience with baclofen in the management of alcohol-dependent patients with psychiatric comorbidity: a selected case series. *Alcohol Alcohol* 46: 714–720.

Drobes DJ, Anton RF, Thomas SE, et al. (2004) Effects of naltrexone and nalmefene on subjective response to alcohol among non-treatment-seeking alcoholics and social drinkers. *Alcohol Clin Exp Res* 28: 1362–1370.

Drozdick J, Berghella V, Hill M, et al. (2002) Methadone trough levels in pregnancy. *Am J Obstet Gynecol* 187: 1184–1188.

Drummond DC, Oyefeso A, Phillips T, et al. (2005) *Alcohol Needs Assessment Research Project: The 2004 National Alcohol Needs Assessment for England*. London: Department of Health.

Dryden C, Young D, Hepburn M, et al. (2009) Maternal methadone use in pregnancy: factors associated with the development of neonatal abstinence syndrome and implications for healthcare resources. *Br J Obstet Gynaecol* 116: 665–671.

Dufour M and Fuller RK (1995) Alcohol in the elderly. *Annu Rev Med* 46: 123–132.

Duka T, Gentry J, Malcolm R, et al. (2004) Consequences of multiple withdrawals from alcohol. *Alcohol Clin Exp Res* 28: 233–246.

Dunne FJ (1994) Misuse of alcohol or drugs by elderly people may need special management. *BMJ* 308: 608–609.

Eder H, Jagsch R, Kraigher D, et al. (2005) Comparative Study of the effectiveness of slow-release morphine and methadone for opioid maintenance therapy. *Addiction* 101: 1101–1109.

Elholm B, Larsen K, Hornnes N, et al. (2011) Alcohol withdrawal syndrome: symptom-triggered versus fixed-schedule treatment in an outpatient setting. *Alcohol Alcohol* 46: 318–323.

Elkashef A, Vocci F, Hanson G, et al. (2008) Pharmacotherapy of methamphetamine addiction: an update. *Subst Abuse* 29: 31–49.

European Medicine Agency (2010) Guideline on the development of medicinal products for the treatment of alcohol dependence. Available at: http://www.emea.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/03/WC500074898.pdf (accessed 1 March 2012).

Evins AE, Cather C, Culhane MA, et al. (2007) A 12-week double-blind, placebo-controlled study of bupropion SR added to high-dose dual nicotine replacement therapy for smoking cessation or reduction in schizophrenia. *J Clin Psychopharmacol* 27: 380–386.

Faggiano F, Vigna-Taglianti F, Versino E, et al. (2003) Methadone maintenance at different dosages for opioid dependence. *Cochrane Database Syst Rev* 3: CD002208.

Fajemirokun-Odudeyi O, Sinha C, Tutty S, et al. (2006) Pregnancy outcome in women who use opiates. *Eur J Obstet Gynecol Reprod Biol* 126: 170–175.

Falaschetti E, Malbut K and Primatesta P (2002) *Health Survey for England 2000: the general health of older people and their use of health services*. London: The Stationery Office.

Fals-Stewart W and Schafer J (1992) The treatment of substance abusers diagnosed with obsessive-compulsive disorder: an outcome study. *J Subst Abuse Treat* 9: 365–370.

Fareed A, Casarella J, Amar R, et al. (2009) Benefits of retention in methadone maintenance and chronic medical conditions as risk factors for premature death among older heroin addicts. *J Psychiatr Pract* 15: 227–234.

Farren CK, Scimeca M, Wu R, et al. (2009) A double-blind, placebo-controlled study of sertraline with naltrexone for alcohol dependence. *Drug Alcohol Depend* 99: 317–321.

Feeney GFX, Connor JP, Young RM, et al. (2006) Combined acamprosate and naltrexone, with cognitive behavioural therapy is superior to either medication alone for alcohol abstinence: A single centres' experience with pharmacotherapy. *Alcohol Alcoholism* 41: 321–327.

Fenton M, Keyes K, Martins S, et al. (2010) The role of a prescription in anxiety medication use, abuse and dependence. *Am J Psychiatry* 167: 1247–1253.

Ferri M, Davoli M and Perucci CA (2011) Heroin maintenance for chronic heroin-dependent individuals. *Cochrane Database Syst Rev* 12: CD003410.

Firoz S and Carlson G (2004) Characteristics and treatment outcome of older methadone-maintenance patients. *Am J Geriatr Psychiatry* 12: 539–541.

Fischer G, Jagsch R, Eder H, et al. (1999) Comparison of methadone and slow-release morphine maintenance in pregnant addicts. *Addiction* 94: 231–239.

Fischer G, Ortner R, Rohrmeister K, et al. (2006) Methadone versus buprenorphine in pregnant addicts: a double-blind, double-dummy comparison study. *Addiction* 101: 275–281.

Fishman MJ, Winstanley EL, Curran E, et al. (2010) Treatment of opioid dependence in adolescents and young adults with extended release naltrexone: preliminary case-series and feasibility. *Addiction* 105: 1669–1676.

Flórez G, Saiz PA, García-Portilla P, et al. (2011) Topiramate for the treatment of alcohol dependence: comparison with naltrexone. *Eur Addict Res* 17: 29–36.

Friedmann PD, Rose JS, Swift R, et al. (2008) Trazodone for sleep disturbance after alcohol detoxification: a double-blind, placebo-controlled trial. *Alcohol Clin Exp Res* 32: 1652–1660.

Frischer M, McArdle P and Crome I (2003) The epidemiology of substance misuse in young people. In: Crome I, Ghodse H, Gilvarry E and McArdle P (eds) *Substance misuse and young people*. London: Gaskell.

Fryer JD and Lukas RJ (1999) Antidepressants noncompetitively inhibit nicotinic acetylcholine receptor function. *J Neurochem* 72: 1117–1124.

Fuller RK and Roth HP (1979) Disulfiram for the treatment of alcoholism. An evaluation in 128 men. *Ann Intern Med* 90: 901–904.

Garbutt JC (2009) The state of pharmacotherapy for the treatment of alcohol dependence. *J Subst Abuse Treat* 36: S1–S15.

Garbutt JC, Kampov-Polevoy AB, Gallop R, et al. (2010) Efficacy and safety of baclofen for alcohol dependence: a randomized, double-blind, placebo-controlled trial. *Alcohol Clin Exp Res* 34: 1849–1857.

Garbutt JC, Kranzler HR, O'Malley SS, et al. (2005) Efficacy and tolerability of long-acting injectable naltrexone for alcohol dependence: a randomized controlled trial. *J Am Med Assoc* 293: 1617–1625.

Garcia-Borreguero D, Bronisch T, Yassouridis A, et al. (1991) Treatment of benzodiazepine withdrawal symptoms with carbamazepine. *Eur Arch Psychiatry Clin Neurosci* 241: 145–150.

Garfinkel D, Zisapel N, Wainstein J, et al. (1999) Facilitation of benzodiazepine discontinuation by melatonin: a new clinical approach. *Arch Intern Med* 159: 2456–2460.

Gelernter J, Gueorguieva R, Kranzler HR, et al. (2007) 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* 31: 555–563.

Gelkopf M, Bleich A, Hayward R, et al. (1999) Characteristics of benzodiazepine abuse in methadone maintenance treatment patients: a 1 year prospective study in an Israeli clinic. *Drug Alcohol Depend* 55: 63–68.

Geller B, Cooper TB, Sun K, et al. (1998) Double-blind and placebo-controlled study of lithium for adolescent bipolar disorders with secondary substance dependency. *J Am Acad Child Adolesc Psychiatry* 37: 171–178.

George TP, Chawarski MC, Pakes J, et al. (2000) Disulfiram versus placebo for cocaine dependence in buprenorphine-maintained subjects: a preliminary trial. *Biol Psychiatry* 47: 1080–1086.

George TP, Vessicchio JC, Sacco KA, et al. (2008) A placebo-controlled trial of bupropion combined with nicotine patch for smoking cessation in schizophrenia. *Biol Psychiatry* 63): 1092–1096.

George TP, Vessicchio JC, Termine A, et al. (2002) A placebo controlled trial of bupropion for smoking cessation in schizophrenia. *Biol Psychiatry* 52: 53–61.

George TP, Ziedonis DM, Feingold A, et al. (2000) Nicotine transdermal patch and atypical antipsychotic medications for smoking cessation in schizophrenia. *Am J Psychiatry* 157: 1835–1842.

Gerra G, Di Petta G, D'Amore A, et al. (2007) Combination of olanzapine with opioid-agonists in the treatment of heroin-addicted patients affected by comorbid schizophrenia spectrum disorders. *Clin Neuropharmacol* 30: 127–135.

Gerra G, Leonardi C, D'Amore A, et al. (2006) Buprenorphine treatment outcome in dually diagnosed heroin dependent patients: A retrospective study. *Prog Neuropsychopharmacol Biol Psychiatry* 30: 265–272.

Gerra G, Zaimovic A, Giusti F, et al. (2002) Intravenous flumazenil versus oxazepam tapering in the treatment of benzodiazepine withdrawal: a randomized, placebo-controlled study. *Addict Biol* 7: 385–395.

Gfroerer J, Penne M, Pemberton M, et al. (2003) Substance abuse treatment need among older adults in 2020. The impact of aging baby boom cohort. *Drug Alcohol Depend* 69: 127–135.

Gibson AE and Degenhardt LJ (2007) Mortality related to pharmacotherapies for opioid dependence: a comparative analysis of coronial records. *Drug Alcohol Rev* 26: 405–410.

Gierisch JM, Bastian LA, Calhoun PS, et al. (2012) Smoking cessation interventions for patients with depression: A systematic review and meta-analysis. *J Gen Intern Med* 27: 351–360.

Gilvarry E and Britton J (2009) *Guidance for the pharmacological management of substance misuse among young people*. National Treatment Agency for Substance Misuse. London: National Treatment Agency.

Gmel G, Gutjahr E and Rehm J (2003) How stable is the risk curve between alcohol and all-cause mortality and what factors influence the shape? A precision-weighted hierarchical meta-analysis. *Eur J Epidemiol* 18: 631–642.

Goodwin GM; Consensus Group of the British Association for Psychopharmacology (2009) Evidence-based guidelines for treating bipolar disorder: revised second edition – recommendations from the British Association for Psychopharmacology. *J Psychopharmacol* 23: 346-388.

Gossop M, Marsden J, Stewart D, et al. (1998) Substance use, health and social problems of clients at 54 drug treatment agencies: Intake data from the National Treatment Outcome Research Study (NTORS). *Br J Psychiatry* 173: 166–171.

Gonzalez A and Nutt DJ (2005) Gamma hydroxy butyrate abuse and dependency. *J Psychopharmacol* 19: 195–204.

González G, Desai R, Sofuoglu M, et al. (2007) Clinical efficacy of gabapentin versus tiagabine for reducing cocaine use among cocaine-dependent methadone-treated patients. *Drug Alcohol Depend* 87: 1–9.

González G, Sevarino K, Sofuoglu M, et al. (2003) Tiagabine increases cocaine-free urines in cocaine-dependent methadone-treated patients: results of a randomized pilot study. *Addiction* 11: 1625–1632.

Gore FM, Bloem PJ, Patton GC, et al. (2011) Global burden of disease in young people aged 10–24 years: a systematic analysis. *Lancet* 377: 2093–2102.

Gottlieb S (2004) Inappropriate drug prescribing in elderly people is common. *BMJ* 329: 367.

Gowing L, Ali R and White JM (2009a) Buprenorphine for the management of opioid withdrawal. *Cochrane Database Syst Rev* 3: CD002025.

Gowing L, Farrell M, Ali R, et al. (2009b) Alpha2 -adrenergic agonists for the management of opioid withdrawal. *Cochrane Database Syst Rev* 2: CD002024.

Gowing L, Farrell MF, Bornemann R, et al. (2011) Oral substitution treatment of injecting opioid users for prevention of HIV infection. *Cochrane Database Syst Rev* 8: CD004145.

Gray TR, Choo RC, Concheiro M, et al. (2010) Prenatal methadone exposure, meconium biomarker concentrations and neonatal abstinence syndrome. *Addiction* 105: 2151–2159.

Grant JE, Kim SW, Hollander E, et al. (2008) Predicting response to opiate antagonists and placebo in the treatment of pathological gambling. *Psychopharmacology* 200: 521–527.

Green AI, Burgess ES, Dawson R, et al. (2003) Alcohol and cannabis use in schizophrenia: effects of clozapine vs. risperidone. *Schizophr Res* 60: 81–85.

Green AI, Lieberman JA, Hamer RM, et al. (2006) Olanzapine and haloperidol in first episode psychosis: two-year data. *Schizophr Res* 86: 234–243.

Green AI, Tohen MF, Hamer RM, et al. (2004) First episode schizophrenia-related psychosis and substance use disorders: acute response to olanzapine and haloperidol. *Schizophr Res* 66: 125–135.

Greenfield SF, Pettinati HM, O'Malley S, et al. (2010) Gender differences in alcohol treatment: an analysis of outcome from the COMBINE study. *Alcohol Clin Exp Res* 34: 1803–1812.

Grimshaw GM and Stanton A (2006) Tobacco cessation interventions for young people. *Cochrane Database Syst Rev* 4: CD003289.

Gual A and Lehert P (2001) Acamprosate during and after acute alcohol withdrawal: a double-blind placebo-controlled study in Spain. *Alcohol Alcohol* 36: 413–418.

Gueorguieva R, Wu R, Donovan D, et al. (2010) Naltrexone and combined behavioral intervention effects on trajectories of drinking in the COMBINE study. *Drug Alcohol Depend* 107: 221–229.

Gueorguieva R, Wu R, Donovan D, et al. (2011) Baseline Trajectories of Drinking Moderate Acamprosate and Naltrexone Effects in the COMBINE Study. *Alcohol Clin Exp Res* 35: 523–531.

Gueorguieva R, Wu R, Pittman B, et al. (2007) New insights into the efficacy of naltrexone based on trajectory-based reanalyses of two negative clinical trials. *Biol Psychiatry* 61: 1290–1295.

Gunnell D, Irvine D, Wise L, et al. (2009) Varenicline and suicidal behaviour: a cohort study based on data from the General Practice Research Database. *BMJ* 339: b3805.

Haasen C, Verthein U, Degkwitz P, et al. (2007) Heroin-assisted treatment for opioid dependence: randomised controlled trial. *Br J Psychiatry* 191: 55-62.

Haasen C, Eiroa-Orosa FJ, Verthein U, et al. (2009) Effects of heroin-assisted treatment on alcohol consumption: findings of the German randomized controlled trial. *Alcohol* 43: 259–264.

Haasen C, Verthein U, Eiroa-Orosa FJ, et al. (2010) Is heroin-assisted treatment effective for patients with no previous maintenance treatment? Results from a German randomised controlled trial. *Eur Addict Res* 16: 124–130.

Hajak G, Muller W, Wittchen H, et al. (2003) Abuse and dependence potential for the non-benzodiazepine hypnotics zolpidem and zopiclone: a review of case reports and epidemiological data. *Addiction* 98: 1371–1378.

Hall SM, Tsoh JY, Prochaska JJ, et al. (2006) Treatment for cigarette smoking among depressed mental health outpatients: a randomized clinical trial. *Am J Public Health* 10: 1808–1814.

Haney M, Hart CL, Vosburg SK, et al. (2008) Effects of THC and lofexidine in a human laboratory model of marijuana withdrawal and relapse. *Psychopharmacology (Berl)* 197: 157-168.

Haney M, Hart CL, Vosburg SK, et al. (2004) Marijuana withdrawal in humans: effects of oral THC or divalproex. *Neuropsychopharmacology* 29: 158–170.

Haney M, Hart CL, Vosburg SK, et al. (2010) Effects of baclofen and mirtazapine on a laboratory model of marijuana withdrawal and relapse. *Psychopharmacology (Berl)* 211: 233–244.

Haney M, Ward AS, Comer SD, et al. (2001) Bupropion SR worsens mood during marijuana withdrawal in humans. *Psychopharmacology (Berl)* 155: 171–179.

Hart CL (2005) Increasing treatment options for cannabis dependence: a review of potential pharmacotherapies. *Drug Alcohol Depend* 80: 147–159.

Hecksel KA, Bostwick JM, Jaeger TM, et al. (2008) Inappropriate use of symptom-triggered therapy for alcohol withdrawal in the general hospital. *Mayo Clin Proceed* 83: 274–279.

Heinälä P, Alho H, Kiianmaa K, et al. (2001) Targeted use of naltrexone without prior detoxification in the treatment of alcohol dependence: a factorial double-blind, placebo-controlled trial. *J Clin Psychopharmacol* 21: 287–292.

Hersh D, Van Kirk JR and Kranzler HR (1998) Naltrexone treatment of comorbid alcohol and cocaine use disorders. *Psychopharmacology* 139: 44–52.

Hien DA, Jiang H, Campbell AN, et al. (2010) Do treatment improvements in PTSD severity affect substance use outcomes? A secondary analysis from a randomized clinical trial in NIDA's Clinical Trials Network. *Am J Psychiatry* 167: 95–101.

Hitsman B, Borrelli B, McChargue DE, et al. (2003) History of depression and smoking cessation outcome: A meta-analysis. *J Consult Clin Psychol* 71: 657–663.

Hoare J and Moon D (2010) *Drug Misuse Declared: Findings from the 2009/10 British Crime Survey*. Home Office Statistical Bulletin 13/10. London: Home Office.

Hood S, O'Neil G and Hulse G (2009) The role of flumazenil in the treatment of benzodiazepine dependence: Physiological and psychological profiles. *J Psychopharmacol* 23: 401–409.

Hughes JR, Peters EN and Naud S (2011) Effectiveness of over-the-counter nicotine replacement therapy: a qualitative review of nonrandomized trials. *Nicotine Tob Res* 13: 512–522.

Hughes JR, Stead LF and Lancaster T (2000) Anxiolytics for smoking cessation. *Cochrane Database Syst Rev* 4: CD002849.

Hughes JR, Stead LF and Lancaster T (2007) Antidepressants for smoking cessation. *Cochrane Database Syst Rev* 1: CD000031.

Hulse GK, Tait RJ, Comer SD, et al. (2005) Reducing hospital presentations for opioid overdose in patients treated with sustained release naltrexone implants. *Drug Alcohol Depend* 79: 351–357.

Hulse GK, Morris N, Arnold-Reed D et al. (2009) Improving clinical outcomes in treating heroin dependence. *Arch Gen Psychiatry* 66: 1108–1115.

Hunt GE, Bergen J and Bashir M (2002) Medication compliance and comorbid substance abuse in schizophrenia: impact on community survival 4 years after a relapse. *Schizophr Res* 54: 253–264.

Iovieno N, Tedeschini E, Bentley KH, et al. (2011) Antidepressants for major depressive disorder and dysthymic disorder in patients with comorbid alcohol use disorders: a meta-analysis of placebo-controlled randomized trials. *J Clin Psychiatry* 72: 1144–1151.

Jaffe J, Bloor R, Crome I, et al. (2004) A postmarketing study of relative abuse liability of hypnotic sedative drugs. *Addiction* 99: 165–173.

Jayaram-Lindström N, Hammarberg A, Beck O, et al. (2008) Naltrexone for the treatment of amphetamine dependence: a randomized, placebo-controlled trial. *Am J Psychiatry* 165: 1442–1448.

Johnson BA (2010) Medication treatment of different types of alcoholism. *Am J Psychiatry* 167: 630–639.

Johnson BA and Ait-Daoud N (2010) Topiramate in the new generation of drugs: efficacy in the treatment of alcoholic patients. *Curr Pharm Des* 16: 2103–2112.

Johnson BA, Ait-Daoud N, Akhtar FZ, et al. (2004) Oral topiramate reduces the consequences of drinking and improves the quality of life of alcohol-dependent individuals: a randomized controlled trial. *Arch Gen Psychiatry* 61: 905–912.

Johnson BA, O'Malley SS, Ciraulo DA, et al. (2003) Dose-ranging kinetics and behavioural pharmacology of naltrexone and acamprosate, both alone and combined, in alcohol-dependent subjects. *J Clin Psychopharmacol* 23: 281–293.

Johnson BA, Rosenthal N, Capece JA, et al. (2007) Topiramate for treating alcohol dependence: a randomized controlled trial. *JAMA* 298: 1641–1651.

Johnson BA, Rosenthal N, Capece JA, et al. (2008) Improvement of physical health and quality of life of alcohol-dependent individuals with topiramate treatment: US multisite randomized controlled trial. *Arch Intern Med* 168: 1188–1199.

Joint Formulary Committee *British National Formulary*. London: British Medical Association and Royal Pharmaceutical Society of Great Britain.

Jones HE, Johnson RE, Jasinski DR, et al. (2005) Buprenorphine versus methadone in the treatment of pregnant opioid-dependent patients: effects on the neonatal abstinence syndrome. *Drug Alcohol Depend* 79: 1–10.

Jones HE, Kaltenbach K, Heil SH, et al. (2010) Neonatal Abstinence Syndrome after methadone or buprenorphine exposure. *New Engl J Med* 363: 2320–2331.

Joseph AM, Norman SM, Ferry LH, et al. (1996) The safety of transdermal nicotine as an aid to smoking cessation in patients with cardiac disease. *New Engl J Med 335*: 1792–1798.

Kahn R, Biswas K, Childress AR, et al. (2009) Multi-center trial of baclofen for abstinence initiation in severe cocaine-dependent individuals. *Drug Alcohol Depend* 103: 59–64.

Kakko J, Heilig M and Sarman I (2008) Buprenorphine and methadone treatment of opiate dependence during pregnancy: comparison of fetal growth and neonatal outcomes in two consecutive case series. *Drug Alcohol Depend* 96: 69–78.

Kampman KM, Dackis C, Lynch KG, et al. (2006) A double-blind, placebo-controlled trial of amantadine, propranolol, and their combination for the treatment of cocaine dependence in patients with severe cocaine withdrawal symptoms. *Drug Alcohol Depend* 85: 129–137.

Kampman KM, Pettinati H, Lynch KG, et al. (2004) A pilot trial of topiramate for the treatment of cocaine dependence. *Drug Alcohol Depend* 75: 233–240.

Kampman KM, Pettinati HM, Lynch KG, et al. (2009) Initiating acamprosate within-detoxification versus post-detoxification in the treatment of alcohol dependence. *Addict Behav* 34: 581–586.

Kandall SR, Doberczak TM, Jantunen M et al. (1999) The methadone-maintained pregnancy. *Clin Perinatol* 26: 173–183.

Karhuvaara S, Simojoki K, Virta A, et al. (2007) Targeted nalmefene with simple medical management in the treatment of heavy drinkers: a randomized double-blind placebo-controlled multicenter study. *Alcohol Clin Exp Res* 31: 1179–1187.

Kelly DL, Gale EA and Conley RR (2003) Clozapine treatment in patients with prior substance abuse. *Can J Psychiatry* 48: 111–114.

Kelly DL, McMahon RP, Weiner E, et al. (2008) Lack of beneficial galantamine effect for smoking behavior: a double-blind randomized trial in people with schizophrenia. *Schizophr Res* 103: 161–168.

Kemp DE, Gao K, Ganocy SJ, et al. (2009) A 6-month, double-blind, maintenance trial of lithium monotherapy versus the combination of lithium and divalproex for rapid-cycling bipolar disorder and co-occurring substance abuse or dependence. *J Clin Psychiatry* 70: 113–121.

Kerfoot KE, Rosenheck RA, Petrakis IL, et al. (2011) Substance use and schizophrenia: adverse correlates in the CATIE study sample. *Schizophr Res* 132: 177–182.

Kiefer F, Jahn H, Tarnaske T, et al. (2003) Comparing and combining naltrexone and acamprosate in relapse prevention of alcoholism: a double-blind, placebo-controlled study. *Arch Gen Psychiatry* 60: 92–99.

Killen JD, Robinson TN, et al. (2004) Randomized clinical trial of the efficacy of bupropion combined with nicotine patch in the treatment of adolescent smokers. *J Consult Clin Psychol* 72: 729–735.

Kim JH, Kim D and Marder SR (2008) Time to rehospitalization of clozapine versus risperidone in the naturalistic treatment of comorbid alcohol use disorder and schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry* 32: 984–988.

Kim SG, Kim CM, Choi SW, et al. (2009) A micro opioid receptor gene polymorphism (A118G) and naltrexone treatment response in adherent Korean alcohol-dependent patients. *Psychopharmacology (Berl)* 201: 611–618.

Knapp WP, Soares BG, Farrel M, et al. (2007) Psychosocial interventions for cocaine and psychostimulant amphetamines related disorders. *Cochrane Database Syst Rev* 3: CD003023.

Koeter MW, van den Brink W and Lehert P (2010) Effect of early and late compliance on the effectiveness of acamprosate in the treatment of alcohol dependence. *J Subst Abuse Treat* 39: 218–226.

Kongsakon R, Papadopoulos K and Saguansiritham R (2005) Mirtazapine in amphetamine detoxification: a placebo-controlled pilot study. *Int Clin Psychopharmacol* 20: 253–256.

Kopelman MD, Thomson AD, Guerrini I, et al. (2009) The Korsakoff syndrome: clinical aspects, psychology and treatment. *Alcohol Alcohol* 44: 148–154.

Kosten T, Falcioni J, Oliveto A, et al. (2004) Depression predicts higher rates of heroin use on desipramine with buprenorphine than with methadone. *Am J Addict* 13: 191–201.

Kosten T, Oliveto A, Feingold A, et al. (2003) Desipramine and contingency management for cocaine and opiate dependence in buprenorphine maintained patients. *Drug Alcohol Depend* 70: 315–325.

Krampe H, Stawicki S, Wagner T, et al. (2006) Follow-up of 180 alcoholic patients for up to 7 years after outpatient treatment: impact of alcohol deterrents on outcome. *Alcohol Clin Exp Res* 30: 86–95.

Krantz MJ, Martin J, Stimmel B, Mehta D, Haigney MC; for the Center for Substance Abuse Treatment Cardiac Expert Panel (2009) QTc Interval Screening in Methadone Treatment: the CSAT Consensus Guideline. *Ann Intern Med* 150: 387–395.

Kranzler HR and Van Kirk J (2001) Efficacy of naltrexone and acamprosate for alcoholism treatment: a meta-analysis. *Alcohol Clin Exp Res* 25: 1335–1341.

Kranzler H, Burleson J, Brown J, et al. (1996) Fluoxetine treatment seems to reduce the beneficial effects of cognitive-behavioural therapy in type B alcoholics. *Alcohol Clin Exp Res* 20: 1534–1541.

Kranzler HR, Burleson JA, Del Boca FK, et al. (1994) Buspirone treatment of anxious alcoholics. A placebo-controlled trial. *Arch Gen Psychiatry* 51: 720–731.

Kranzler HR, Tennen H, Armeli S, et al. (2009) Targeted naltrexone for problem drinkers. *J Clin Psychopharmacol* 29: 350–357.

Kristensen O, Lølandsmo T, Isaksen A, et al. (2006) Treatment of polydrug-using opiate dependents during withdrawal: towards a standardisation of treatment *BMC Psychiatry* 6: 54–62.

Krupitsky EM, Rudenko AA, Burakov AM, et al. (2007) Antiglutamatergic strategies for ethanol detoxification: comparison with placebo and diazepam. *Alcohol Clin Exp Res* 31: 604–611.

Krystal JH, Cramer JA, Krol WF, Kirk GF, Rosenheck RA, Veterans Affairs Naltrexone Cooperative Study 425 Group (2001) Naltrexone in the treatment of alcohol dependence. *New Engl J Med* 345: 1734–1739.

Krystal JH, Gueorguieva R, Cramer J, Collins J, Rosenheck R and VA CSP No. 425 Study Team (2008) Naltrexone is associated with reduced drinking by alcohol dependent patients receiving antidepressants for mood and anxiety symptoms: results from VA Cooperative Study No. 425, "Naltrexone in the treatment of alcoholism". *Alcoh Clin Exp Res* 32: 85–91.

Kunøe N, Lobmaier P, Vederhus JK, et al. (2009) Naltrexone implants after in-patient treatment for opioid dependence: Randomised controlled trial. *Br J Psychiatry* 194: 541–546.

Kunøe N, Lobmaier P, Vederhus JK, et al. (2010) Retention in naltrexone implant treatment for opioid dependence. *Drug Alcohol Depend* 111: 166–169.

Kushner MG, Abrams K, Thuras P, et al. (2005) Follow-up study of anxiety disorder and alcohol dependence in comorbid alcoholism treatment patients. *Alcohol Clin Exp Res* 29: 1432–1443.

Laaksonen E, Koski-Jännes A, Salaspuro M, et al. (2008) A randomized, multicentre, open-label, comparative trial of disulfiram, naltrexone and acamprosate in the treatment of alcohol dependence. *Alcohol Alcohol* 43: 53–61.

Lamps CA, Sood AB and Sood R (2008) Youth with substance abuse and comorbid mental health disorders. *Curr Psychiatry Rep* 10: 265–271.

Latt N, Conigrave K, Saunders J, et al. (2009) *Addiction Medicine*. Oxford: Oxford University Press.

Leggio L, Garbutt JC and Addolorato G (2010) Effectiveness and safety of baclofen in the treatment of alcohol dependent patients. *CNS Neurol Disord Drug Targets* 9: 33–44.

Lehmann WX (1973) The use of 1-alpha-acetyl-methadol (LAAM) as compared to methadone in the maintenance and detoxification of young heroin addicts. *NIDA Res Monogr* 8: 82–83.

Lejeune C, Simmat-Durand L, Gourarier L, Aubisson S and the Groupe d'Etudes Grossesse et Addictions (2006) Prospective multicenter observational study of 260 infants born to 259 opiate-dependent mothers on methadone or high-dose buprenophine substitution. *Drug Alcohol Depend* 82: 250–257.

Lejuez CW, Zvolensky MJ, Daughters SB, et al. (2008) Anxiety sensitivity: a unique predictor of dropout among inner-city heroin and crack/cocaine users in residential substance use treatment. *Behav Res Ther* 46: 811–818.

Leo RJ and Baer D (2005) Delirium associated with baclofen withdrawal: a review of common presentations and management strategies. *Psychosomatics* 46: 503–507.

Leone MA, Vigna-Taglianti F, Avanzi G, et al. (2010) Gamma-hydroxybutyrate (GHB) for treatment of alcohol withdrawal and prevention of relapses. *Cochrane Database Syst Rev* 2: CD006266.

LeTourneau JL, Hagg DS and Smith SM (2008) Baclofen and gamma-hydroxybutyrate withdrawal. *Neurocrit Care* 8: 430–433.

Levin FR, Evans SM, Coomaraswammy S, et al. (1998) Flupenthixol treatment for cocaine abusers with schizophrenia: a pilot study. *Am J Drug Alcohol Abuse* 24: 343–360.

Levin FR, McDowell D, Evans SM, et al. (2004) Pharmacotherapy for marijuana dependence: a double-blind, placebo-controlled pilot study of divalproex sodium. *Am J Addict* 13: 21–32.

Levin FR, Mariani JJ, Brooks DJ, et al. (2011) Dronabinol for the treatment of cannabis dependence: A randomized, double-blind, placebo-controlled trial. *Drug Alcohol Depend* 116: 142–150.

Levine D (2007) 'Pharming': the abuse of prescription and over-the-counter drugs in teens. *Curr Opin Pediatr* 19: 270–274.

Lejoyeux M and Lehert P (2011) Alcohol-use disorders and depression: results from individual patient data meta-analysis of the acamprosate-controlled studies. *Alcohol Alcohol* 46: 61–67.

Liappas J, Paparrigopoulos T, Tzavellas E, et al. (2002) Impact of alcohol detoxification on anxiety and depressive symptoms. *Drug Alcohol Depend* 68: 215–220.

Liebrenz M, Boesch L, Stohler R, et al. (2010) Agonist substitution – a treatment alternative for high-dose benzodiazepine-dependent patients? *Addiction* 105: 1870–1874.

Ling W, Jacobs P, Hillhouse M, et al. (2010) From research to the real world: buprenorphine in the decade of the Clinical Trials Network. *J Subst Abuse Treat* 38(Suppl 1): S53–S60.

Lingford-Hughes A, Watson B, Kalk N, et al. (2010) Neuropharmacology of addiction and how it informs treatment. *Br Med Bull* 96: 93–110.

Lingford-Hughes A, Welch SJ and Nutt DJ (2004) Evidence-based guidelines for the pharmacological management of substance misuse, addiction and comorbidity: recommendations from the British Association for Psychopharmacology. *J Psychopharmacol* 18: 293–335.

Lintzeris N, Mitchell T, Bond A, et al. (2006) Interactions on mixing diazepam with methadone or buprenorphine in maintenance patients. *J Clin Psychopharmacol* 26: 274–283.

Liu J and Wang L (2011) Baclofen for alcohol withdrawal. *Cochrane Database Syst Rev* 1: CD008502.

Loeber S, Duka T, Welzel Márquez H, et al. (2010) Effects of repeated withdrawal from alcohol on recovery of cognitive impairment under abstinence and rate of relapse. *Alcohol Alcohol* 45: 541–547.

Longabaugh R, Wirtz PW, Gulliver SB, et al. (2009) Extended naltrexone and broad spectrum treatment or motivational enhancement therapy. *Psychopharmacology (Berl)* 206: 367–376.

Longoria J, Brown ES, Perantie DC, et al. (2004) Quetiapine for alcohol use and craving in bipolar disorder. *J Clin Psychopharmacol* 24: 101–102.

Lubman DI, King JA and Castle DJ (2010) Treating comorbid substance use disorders in schizophrenia. *Int Rev Psychiatry* 22: 191–201.

Lumley J, Chamberlain C, Dowswell T, et al. (2009) Interventions for promoting smoking cessation during pregnancy. *Cochrane Database Syst Rev* 3: CD001055.

Luykx HJ, Dorresteijn LD, Haffmans PM, et al. (2008) Rivastigmine in Wernicke-Korsakoff's syndrome: five patients with rivastigmine showed no more improvement than five patients without rivastigmine. *Alcohol Alcohol* 43: 70–72.

Luykx JJ and Carpay JA (2010) Nervous system adverse responses to topiramate in the treatment of neuropsychiatric disorders. *Expert Opin Drug Safe* 9: 623–631.

Macaigne G, Champagnon N, Harnois F, et al. (2011) Baclofen-induced acute hepatitis in alcohol-dependent patient. *Clin Res Hepatol Gastroenterol* 35: 420–421.

McCaul B (1996) Efficacy of naltrexone for alcoholics with and without comorbid opiate or cocaine dependence. *Alcohol Clin Exp Res* 20: 216A–218A.

McCormick CG, Henningfield JE, Haddox JD, et al. (2009) Case histories in pharmaceutical risk management. *Drug Alcohol Depend* 105(Suppl 1): S42–S55.

McCowan C, Kidd B and Fahey T (2009) Methadone maintenance treatment in primary care and its influence on mortality: a cohort study. *BMJ* 338: b2225.

McDonough M, Kennedy N, Glasper A, et al. (2004) Clinical features and management of gamma-hydroxybutyrate (GHB) withdrawal: a review. *Drug Alcohol Depend* 75: 3–9.

McDuff D, Schwartz R, Tommasello A, et al. (1993) Outpatient benzodiazepine detoxification procedure for methadone patients. *J Subst Abuse Treat* 10: 297–302.

McGregor C, Machin A and White J (2003) In-patient benzodiazepine withdrawal: comparison of fixed and symptom-triggered taper methods. *Drug Alcohol Rev* 22: 175–180.

McInnes E and Powell J (1994) Drug and alcohol referrals. Are elderly substance abuse diagnoses and referrals being missed? *BMJ* 308: 444–446.

McKee SA, Weinberger AH, Harrison EL, et al. (2009) Effects of the nicotinic receptor antagonist mecamylamine on ad-lib smoking behavior, topography, and nicotine levels in smokers with and without schizophrenia: a preliminary study. *Schizophr Res* 115: 317–324.

MacPherson L, Tull MT, Matusiewicz AK, et al. (2010) Randomized controlled trial of behavioral activation smoking cessation treatment for smokers with elevated depressive symptoms. *J Consult Clin Psychol* 78: 55–61.

McRae-Clark AL, Carter RE, Killeen TK, et al. (2009) A placebo-controlled trial of buspirone for the treatment of marijuana dependence. *Drug Alcohol Depend* 105: 132–138.

Madlung-Kratzer E, Spitzer B, Brosch R, et al. (2009) A double-blind, randomized, parallel group study to compare the efficacy, safety and tolerability of slow release oral morphine versus methadone in opioid-dependent in-patients willing to undergo detoxification. *Addiction* 104: 1549–1557.

Malcolm R, Myrick H, Roberts J, et al. (2002) The differential effects of medication on mood, sleep disturbance, and work ability in outpatient alcohol detoxification. *Am J Addict* 11: 141–150.

Malcolm R, Olive MF and Lechner W (2008) The safety of disulfiram for the treatment of alcohol and cocaine dependence in randomized clinical trials: guidance for clinical practice. *Expert Opin Drug Saf* 7: 459–472.

Malec TS, Malec EA and Dongier M (1996) Efficacy of buspirone in alcohol dependence: a review. *Alcohol Clin Exp Res* 20: 853–858.

Mammen K and Bell J (2009) The clinical efficacy and abuse potential of combination buprenorphine-naloxone in the treatment of opioid dependence. *Expert Opin Pharmacother* 10: 2537–2544.

Mangoni AA and Jackson SHD (2004) Age-related changes in pharmacokinetics and pharmacodynamics: basic principles and practical applications. *Br J Clin Pharmacol* 57: 6–14.

Mann K, Kiefer F, Smolka M, et al. (2009) PREDICT Study Research Team. Searching for responders to acamprosate and naltrexone in alcoholism treatment: rationale and design of the PREDICT study. *Alcohol Clin Exp Res* 33: 674–683.

Mann K, Kiefer F, Spanagel R, et al. (2008) Acamprosate: recent findings and future research directions. *Alcohol Clin Exp Res* 32: 1105–1110.

Mann K, Lehert P and Morgan MY (2004) The efficacy of acamprosate in the maintenance of abstinence in alcohol-dependent individuals: results of a meta-analysis. *Alcohol Clin Exp Res* 28: 51–63.

March JC, Oviedo-Joekes E, Perea-Milla E, et al. (2006) Controlled trial of prescribed heroin in the treatment of opioid addiction. *J Subst Abuse Treat* 31: 203–211.

Margolin A, Kosten TR, Avants SK, et al. (1995) A multicenter trial of bupropion for cocaine dependence in methadone-maintained patients. *Drug Alcohol Depend* 40: 125–131.

Marsch L (1998) The efficacy of methadone maintenance interventions in reducing illicit opiate use, HIV risk behaviour and criminality – a meta-analysis. *Addiction* 93: 515–532.

Marsch LA, Bickel WK, Badger GJ, et al. (2005) Comparison of pharmacological treatments for opioid-dependent adolescents: a randomized controlled trial. *Arch Gen Psychiatry* 62: 1157–1164.

Martell BA, Orson FM, Poling J, et al. (2009) Cocaine vaccine for the treatment of cocaine dependence in methadone-maintained patients: a randomized, double-blind, placebo-controlled efficacy trial. *Arch Gen Psychiatry* 66: 1116–1123.

Martin B, Alfers J, Kulig C, et al. (2004) Disulfiram therapy in patients with hepatitis C: a 12-month, controlled, follow-up study. *J Stud Alcohol* 65: 651–657.

Martins SS, Fenton MC, Keyes KM, et al. (2011) Mood and anxiety disorders and their association with non-medical prescription opioid use and prescription opioid-use disorder: longitudinal evidence from the National Epidemiologic Study on Alcohol and Related Conditions. *Psychol Med* 17: 1–12.

Martinotti G, Andreoli S, Di Nicola M, et al. (2008) Quetiapine decreases alcohol consumption, craving, and psychiatric symptoms in dually diagnosed alcoholics. *Hum Psychopharmacol Clin Exp* 23: 417–424.

Martinotti G, Di Nicola M, Di Giannantonio M et al. (2009) Aripiprazole in the treatment of patients with alcohol dependence: a double-blind, comparison trial vs. naltrexone. *J Psychopharmacol* 23: 123–129.

Martinotti G, Di Nicola M, Tedeschi D, et al. (2010) Pregabalin versus naltrexone in alcohol dependence: a randomised, double-blind, comparison trial. *J Psychopharmacol* 24: 1367–1374.

Mason BJ and Heyser CJ (2010) The neurobiology, clinical efficacy and safety of acamprosate in the treatment of alcohol dependence. *Expert Opin Drug Saf* 9: 177–188.

Mason BJ and Lehert P (2010) The effects of current subsyndromal psychiatric symptoms or past psychopathology on alcohol dependence treatment outcomes and acamprosate efficacy. *Am J Addict* 19: 147–154.

Mason BJ and Ownby RL (2000) Acamprosate for the treatment of alcohol dependence: a review of double-blind, placebo-controlled trials. *CNS Spectrum* 5: 58–69.

Mason BJ, Goodman AM, Chabac S, et al. (2006) 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* 40: 383–393.

Mason BJ, Ritvo EC, Morgan RO, et al. (1994) A double-blind, placebo-controlled pilot study to evaluate the efficacy and safety of oral nalmefene HCl for alcohol dependence. *Alcohol Clin Exp Res* 18: 1162–1167.

Mason BJ, Salvato FR, Williams LD, et al. (1999) A double-blind, placebo-controlled study of oral nalmefene for alcohol dependence. *Arch Gen Psychiatry* 56: 719–724.

Mattick RP, Ali R, White JM, et al. (2003) Buprenorphine versus methadone maintenance therapy: a randomized double-blind trial with 405 opioid-dependent patients. *Addiction* 98: 441–452.

Mattick RP, Breen C, Kimber J, et al. (2009) Methadone maintenance therapy versus no opioid replacement for opioid dependence. *Cochrane Database Syst Rev* 3: CD002209.

Mattick RP, Kimber J, Breen C, et al. (2008) Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. *Cochrane Database Syst Rev* 2: CD002207.

Mayo-Smith MF, Beecher LH, Fischer TL, et al. (2004) Management of alcohol withdrawal delirium: an evidence-based practice guideline. *Arch Intern Med* 164: 1405–1412.

Miller N, Frieden TR, Liu SY, et al. (2005) Effectiveness of a large-scale distribution programme of free nicotine patches: a prospective evaluation. *Lancet* 365: 1849-1854.

Mills KL, Deady M, Proudfoot H, et al. (2009) *Guidelines on the Management of Co-occurring Alcohol and Other Drug and Mental Health Conditions in Alcohol and Other Drug Treatment Settings*. Sydney: University of New South Wales.

Minozzi S, Amato L, Vecchi S, et al. (2011) Oral naltrexone maintenance treatment for opioid dependence. *Cochrane Database Syst Rev* 4: CD001333.

Minozzi S, Amato L and Davoli M (2009) Maintenance treatments for opiate dependent adolescent. *Cochrane Database Syst Rev* 2: CD006749.

Minozzi S, Amato L, Vecchi S, et al. (2008) Maintenance agonist treatments for opiate dependent pregnant women. *Cochrane Database Syst Rev* 2: CD006318.

Minozzi S, Amato L, Vecchi S, et al. (2010) Anticonvulsants for alcohol withdrawal. *Cochrane Database Syst Rev* 3: CD005064.

Mitchell TB, White JM, Somogyi AA, et al. (2004) Slow release oral morphine versus methadone: a crossover comparison of patient outcomes and acceptability as maintenance pharmacotherapy for opioid dependence. *Addiction* 99: 940–945.

Monterosso JR, Flannery BA, Pettinati HM, et al. (2001) Predicting treatment response to naltrexone: the influence of craving and family history. *Am J Addict* 10: 258–268.

Moolchan ET, Robinson ML, Ernst M, et al. (2005) Safety and efficacy of the nicotine patch and gum for treatment of adolescent tobacco addiction. *Pediatrics* 115: 407–414.

Moore D, Aveyard P, Connock M, et al. (2009) Effectiveness and safety of nicotine replacement therapy assisted reduction to stop smoking: systematic review and meta-analysis. *BMJ* 338: b1024.

Moore TH, Zammit S, Lingford-Hughes A, et al. (2007) Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review. *Lancet* 370: 319-28.

Morgan PT, Pace-Schott E, Pittman B, et al. (2010) Normalizing effects of modafinil on sleep in chronic cocaine users. *Am J Psychiatry* 167: 331–340.

Morin CM, Bastien C, Guay B, et al. (2004) Randomized clinical trial of supervised tapering and cognitive behavior therapy to facilitate benzodiazepine discontinuation in older adults with chronic insomnia. *Am J Psychiatry* 161: 332–342.

Morley KC, Teesson M, Reid SC, et al. (2006) Naltrexone versus acamprosate in the treatment of alcohol dependence: A multi-centre, randomized, double-blind, placebo-controlled trial. *Addiction* 101: 1451–1462.

Morley KC, Teesson M, Sannibale C, et al. (2010) Clinical predictors of outcome from an Australian pharmacological relapse prevention trial. *Alcohol Alcohol* 45: 520–526.

Moy I, Crome P, Crome I, et al. (2011) Systematic and narrative review of treatment for older people with substance problems. *Eur Geriatr Med* 2: 212–236.

Mueller TI, Pagano ME, Rodriguez BF, et al. (2005) Long-term use of benzodiazepines in participants with comorbid anxiety and alcohol use disorders. *Alcohol Clin Exp Res* 29: 1411–1418.

Mueser KT, Noordsy DL, Fox L, et al. (2003) Disulfiram treatment for alcoholism in severe mental illness. *Am J Addict* 12: 242–252.

Muhonen LH, Lahti J, Sinclair D, et al. (2008) Treatment of alcohol dependence in patients with co-morbid major depressive disorder – predictors for the outcomes with memantine and escitalopram medication. *Subst Abuse Treat Prevent Policy* 3: 20–26.

Muramoto ML, Leischow SJ, Sherrill D, et al. (2007) Randomized, double-blind, placebo-controlled trial of 2 dosages of sustained-release bupropion for adolescent smoking cessation. *Arch Pediatr Adolesc Med* 161: 1068–1074.

Murphy SM and Tyrer P (1991) A double-blind comparison of the effects of gradual withdrawal of lorazepam, diazepam and bromazepam in benzodiazepine dependence. *Br J Psychiatry* 158: 511–516.

Myers WC, Donahue JE and Goldstein MR (1994) Disulfiram for alcohol use disorders in adolescents. *J Am Acad Child Adolesc Psychiatry* 33: 484–489.

Mysels DJ, Cheng WY, Nunes EV, et al. (2011) The association between naltrexone treatment and symptoms of depression in opioid-dependent patients. *Am J Drug Alcohol Abuse* 37: 22–26.

Nakao M, Takeuchi T, Nomura K, et al. (2006) Clinical application of paroxetine for tapering benzodiazepine use in non-major-depressive outpatients visiting an internal medicine clinic. *Psychiatry Clin Neurosci* 60: 605–610.

NICE, National Institute for Health and Clinical Excellence (2004) *Zaleplon, zolpidem and zopiclone for the management of insomnia: NICE technology appraisal guidance 77*. London: National Institute for Health and Clinical Excellence.

NICE, National Institute for Health and Clinical Excellence (2007a) *Antenatal and postnatal mental health. Clinical management and service guidance. NICE clinical guideline 45.* London: National Institute for Health and Clinical Excellence.

NICE, National Institute for Health and Clinical Excellence (2007b) *Drug misuse: opiate detoxification management of drug misusers in the community and prison settings. NICE clinical guideline 57.* London: National Institute for Health and Clinical Excellence.

NICE, National Institute for Health and Clinical Excellence (2007c) *Methadone and buprenorphine for the management of opioid dependence: NICE technology appraisal guidance 114*. London: National Institute for Health and Clinical Excellence.

NICE, National Institute for Health and Clinical Excellence (2007d) *Naltrexone for the management of opioid dependence: NICE technology appraisal guidance 115*. London: National Institute for Health and Clinical Excellence.

NICE, National Institute for Health and Clinical Excellence (2007e) *Varenicline for smoking cessation: NICE technology appraisal guidance 123*. National Institute for Health and Clinical Excellence.

NICE, National Institute for Health and Clinical Excellence (2008) *Antenatal care: routine care for the healthy pregnant woman. CG62.* London: National Institute for Health and Clinical Excellence.

NICE, National Institute for Health and Clinical Excellence (2010a) *How to stop smoking in pregnancy and following childbirth. NICE public health guidance 26.* London: National Institute for Health and Clinical Excellence.

NICE, National Institute for Health and Clinical Excellence (2010b) *Pregnancy and complex social factors: a model for service provision for pregnant women with complex social factors. NICE clinical guideline 110.* London: National Collaborating Centre for Women's and Children's Health.

NICE, National Institute for Health and Clinical Excellence (2010c) *Alcohol-use disorder: physical complications. NICE clinical guideline 100.* London: National Institute for Health and Clinical Excellence.

NICE, National Institute for Health and Clinical Excellence (2011a) *Alcohol dependence and harmful alcohol use. NICE clinical guideline 115.* London: National Institute for Health and Clinical Excellence.

NICE, National Institute for Health and Clinical Excellence (2011b) *Psychosis with coexisting substance misuse. NICE clinical guideline 120.* London: National Institute for Health and Clinical Excellence.

National Treatment Agency and Department of Health (2010a) *Statistics from the National Alcohol Treatment Monitoring System (NATMS) 1st April 2008 – 31st March 2009*. London: Department of Health.

National Treatment Agency and Department of Health (2010b) *Statistics from the National Drug Treatment Monitoring System (NDTMS) 1st April 2009 – 31st March 2010*. London: Department of Health.

Naughton F, Prevost AT and Sutton S (2008) Self-help smoking cessation interventions in pregnancy: a systematic review and meta-analysis. *Addiction* 103: 566–579.

Nava F, Manzato E, Leonardi C, et al. (2008) Opioid maintenance therapy suppresses alcohol intake in heroin addicts with alcohol dependence: preliminary results of an open randomized study *Progr Neuropsychopharmacol Biol Psychiatry* 32: 1867–1872.

Nejtek VA, Avila M, Chen LA, et al. (2008) Do atypical antipsychotics effectively treat co-occurring bipolar disorder and stimulant dependence? A randomized, double-blind trial. *J Clin Psychiatry* 69: 1257–1266.

Ngo HT, Tait RJ and Hulse GK (2008) Comparing drug-related hospital morbidity following heroin dependence treatment with methadone maintenance or naltrexone implantation. *Arch Gen Psychiatry* 65: 457–465.

Ngo HT, Tait RJ and Hulse GK (2011) Hospital psychiatric comorbidity and its role in heroin dependence treatment outcomes using naltrexone implant or methadone maintenance. *J Psychopharmacol* 25: 774–782.

Niederhofer H and Staffen W (2003a) Acamprosate and its efficacy in treating alcohol dependent adolescents. *Eur Child Adolesc Psychiatry* 12: 144–148.

Niederhofer H and Staffen W (2003b) Comparison of disulfiram and placebo in treatment of alcohol dependence of adolescents. *Drug Alcohol Rev* 22: 295–297.

Niederhofer H, Staffen W and Mair A (2003) Comparison of naltrexone and placebo in treatment of alcohol dependence of adolescents. *Alcohol Treat Quart* 21: 87–95.

Nielsen S, Dietze P, Lee N, et al. (2007) Concurrent buprenorphine and benzodiazepines use and self-reported opioid toxicity in opioid substitution treatment. *Addiction* 102: 616–622.

Nunes EV and Levin FR (2004) Treatment of depression in patients with alcohol or other drug dependence: a meta-analysis. *JAMA* 291: 1887–1196.

Nunes EV, Sullivan MA and Levin FR (2004) Treatment of depression in patients with opiate dependence. *Biol Psychiatry* 56: 793–802.

Nutt DJ, Lingford-Hughes A, Chick J (2012) Through a glass darkly: can we improve clarity about mechanism and aims of medications in drug and alcohol treatments? *J Psychopharmacol* 26: 199–204.

O'Brien C (2007) Brain development as a vulnerability factor in the aetiology of substance abuse and addiction. In: Romer D and Walker E (eds) *Adolescent psychopathology and the developing brain*. Oxford: Oxford University Press, pp. 388–400.

O'Brien CP, Gastfriend DR, Forman RF, et al. (2011) Long-term opioid blockade and hedonic response: preliminary data from two open-label extension studies with extended-release naltrexone. *Am J Addict* 20: 106–112

O'Connell H, Chin A-C, Cunningham C, et al. (2003) Alcohol use disorders in elderly people: redefining an age old problem in old age. *BMJ* 327: 664–667.

O'Leary CM, Heuzenroeder I, Elliott EJ, et al. (2007) A review of policies on alcohol use during pregnancy in Australia and other English-speaking countries, 2006. *Med J Aust* 186: 466–471.

Oliveto AH, Feingold A, Schottenfeld R, et al. (1999) Desipramine in opioid-dependent cocaine abusers maintained on buprenorphine vs methadone. *Arch Gen Psychiatry* 56: 812–820.

Oliveto A, Poling J, Mancino MJ, et al. (2011) Randomized, double blind, placebo-controlled trial of disulfiram for the treatment of cocaine dependence in methadone-stabilized patients. *Drug Alcohol Depend* 113: 184–191.

O'Malley SS, Garbutt JC, Gastfriend DR, et al. (2007) Efficacy of extended-release naltrexone in alcohol-dependent patients who are abstinent before treatment. *J Clin Psychopharmacol* 27: 507-512.

O'Malley SS, Jaffe AJ, Chang G, et al. (1992) Naltrexone and coping skills therapy for alcohol dependence. A controlled study. *Arch Gen Psychiatry* 49: 881–887.

O'Malley S, Jaffe A, Chang G, et al. (1996) Six-month follow-up of naltrexone and psychotherapy for alcohol dependence. *Arch Gen Psychiatry* 53: 217–231.

O'Malley SS, Robin RW, Levenson AL, et al. (2008) Naltrexone alone and with sertraline for the treatment of alcohol dependence in Alaska natives and non-natives residing in rural settings: a randomized controlled trial. *Alcohol Clin Exp Res* 32: 1271–1283.

O'Malley SS, Rounsaville BJ, Farren C, et al. (2003) Initial and maintenance naltrexone treatment for alcohol dependence using primary care vs specialty care: a nested sequence of 3 randomized trials. *Arch Intern Med* 163: 1695–1704.

Oncken C, Dornelas E, Greene J, et al. (2008) Nicotine gum for pregnant smokers. A randomized controlled trial. *Obstet Gynecol* 112: 859–867.

Orleans T, Resch N, Noll E, et al. (1994) Use of transdermal nicotine in a state-level prescription plan for the elderly. A first look at 'real-world' patch users. *JAMA* 271: 601–607.

Oroszi G, Anton RF, O'Malley S, et al. (2009) OPRM1 Asn40Asp predicts response to naltrexone treatment: a haplotype-based approach. *Alcohol Clin Exp Res* 33: 383–393.

Oslin DW, Berrettini W, Kranzler HR, et al. (2003) A functional polymorphism of the mu-opioid receptor gene is associated with naltrexone response in alcohol-dependent patients. *Neuropsychopharmacology* 28: 1546–1552.

Oslin D, Liberto JG, O'Brien J, et al. (1997) Naltrexone as an adjunctive treatment for older patients with alcohol dependence. *Am J Geriatr Psychiatry* 5: 324–332.

Oslin DW, Pettinati H and Volpicelli JR (2002) Alcoholism treatment adherence: older age predicts better adherence and drinking outcomes. *Am J Geriatr Psychiatry* 10: 740–747.

Oslin DW, Pettinati HM, Volpicelli JR, et al. (1999)The effects of naltrexone on alcohol and cocaine use in dually addicted patients. *J Subst Abuse Treat* 16: 163–167.

Otto M, Pollack M, Sachs G, et al. (1993) Discontinuation of benzodiazepine treatment: efficacy of cognitive-behavioral therapy for patients with panic disorder. *Am J Psychiatry* 150: 1485–1490.

Oude Voshaar R, Couvée J, Van Balkom A, et al. (2006a) Strategies for discontinuing long-term benzodiazepine use: meta-analysis. *Br J Psychiatry* 189: 213–220.

Oude Voshaar R, Gorgels W, Mol A, et al. (2003) Tapering off long-term benzodiazepine use with or without group cognitive behavioural therapy: three-condition, randomised controlled trial. *Br J Psychiatry* 182: 498–504.

Oude Voshaar R, Gorgels W, Mol A, et al. (2006b) Long-term outcome of two forms of randomised benzodiazepine discontinuation. *Br J Psychiatry* 188: 188–189.

Oviedo-Joekes E, Brissette S, Marsh DC, et al. (2009) Diacetylmorphine versus methadone for the treatment of opioid addiction. *New Engl J Med* 361: 777–786.

Oviedo-Joekes E, Guh D, Brissette S, et al. (2010) Double-blind injectable hydromorphone versus diacetylmorphine for the treatment of opioid dependence: a pilot study. *J Subst Abuse Treat* 38: 408–411.

Oviedo-Joekes E, March JC, Romero M, et al. (2010) The Andalusian trial on heroin-assisted treatment: a 2 year follow-up. *Drug Alcohol Rev* 29: 75–80.

Pani PP, Trogu E, Vecchi S and Amato L (2011) Antidepressants for cocaine dependence and problematic cocaine use. *Cochrane Database Syst Rev* 12: CD002950.

Parr J, Kavanagh D, Cahill L, et al. (2008) Effectiveness of current treatment approaches for benzodiazepine discontinuation: a meta-analysis. *Addiction* 104: 13–24.

Parr J, Kavanagh D, Young R, et al. (2011) Acceptability of cognitive-behaviour therapy via the internet for cessation of benzodiazepine use. *Drug Alcohol Rev* 30: 306–314.

Peles E, Schreiber S and Adelson M (2009) Documented poor sleep among methadone-maintained patients is associated with chronic pain and benzodiazepine abuse, but not with methadone dose. *Eur J Neuropsychopharmacol* 19: 581–588.

Pergolizzi J, Böger RH, Budd K, et al. (2008) Opioids and the management of chronic severe pain in the elderly: consensus statement of an international expert panel with focus on the six clinically most often used World Health Organization step III opioids (buprenorphine, fentanyl, hydromorphone, methadone, morphine, oxycodone). *Pain Pract* 8: 287–313.

Petrakis IL, Carroll KM, Nich C, et al. (2000) Disulfiram treatment for cocaine dependence in methadone-maintained opioid addicts. *Addiction* 95: 219–228.

Petrakis IL, Leslie D, Finney JW and Rosenheck R (2006a) Atypical antipsychotic medication and substance use-related outcomes in the treatment of schizophrenia. *Am J Addict* 15: 44–49.

Petrakis IL, Nich C and Ralevski E (2006b) Psychotic spectrum disorders and alcohol abuse: a review of pharmacotherapeutic strategies and a report on the effectiveness of naltrexone and disulfiram. *Schizophr Bull* 32: 644–654.

Petrakis IL, O'Malley S, Rounsaville B, et al. (2004) Naltrexone augmentation of neuroleptic treatment in alcohol abusing patients with schizophrenia. *Psychopharmacology (Berl)* 172: 291-–297.

Petrakis IL, Poling J, Levinson C, et al. (2005) Naltrexone and disulfiram in patients with alcohol dependence and comorbid psychiatric disorders. *Biol Psychiatry* 57: 1128–1137.

Petrakis IL, Poling J, Levinson C, et al. (2006c) Naltrexone and disulfiram in patients with alcohol dependence and comorbid post-traumatic stress disorder. *Biol Psychiatry* 60: 777–783.

Petrakis I, Ralevski E, Nich C, et al. (2007) Naltrexone and disulfiram in patients with alcohol dependence and current depression. *J Clin Psychopharmacol* 27:160–165.

Petrakis IL, Ralevski E, Desai N et al. (2012) Noradrenergic vs serotonergic antidepressant with or without naltrexone for veterans with PTSD and comorbid alcohol dependence. *Neuropsychopharmacology* 37: 996–1004.

Pettinati H, Volpicelli J, Kranzler H, et al. (2000) Sertraline treatment for alcohol dependence: interactive effects of medication and alcoholic subtype. *Alcohol Clin Exp Res* 24: 1041–1049.

Pettinati HM, Kampman KM, Lynch KG, et al. (2008a) A double blind, placebo-controlled trial that combines disulfiram and naltrexone for treating co-occurring cocaine and alcohol dependence. *Addict Behav* 33: 651–667.

Pettinati HM, Kampman KM, Lynch KG, et al. (2008b) Gender differences with high-dose naltrexone in patients with co-occurring cocaine and alcohol dependence. *J Subst Abuse Treat* 34: 378–390.

Pettinati HM, Oslin DW, Kampman KM, et al. (2010) A double-blind, placebo-controlled trial combining sertraline and naltrexone for treating co-occurring depression and alcohol dependence. *Am J Psychiatry* 167: 668–675.

Poling J, Oliveto A, Petry N, et al. (2006) Six-month trial of bupropion with contingency management for cocaine dependence in a methadone-maintained population. *Arch Gen Psychiatry* 63: 219–228.

Potvin S, Stip E, Lipp O, et al. (2006) Quetiapine in patients with comorbid schizophrenia-spectrum and substance use disorders: an open-label trial. *Curr Med Res Opin* 22: 1277–1285.

Powell BJ, Penick EC, Nickel EJ, et al. (1992) Outcomes of comorbid alcoholic men: a 1-year follow-up. *Alcohol Clin Exp Res* 16: 131–138.

Prisciandaro JJ, Brown DG, Brady KT, et al. (2011) Comorbid anxiety disorders and baseline medication regimens predict clinical outcomes in individuals with co-occurring bipolar disorder and alcohol dependence: Results of a randomized controlled trial. *Psychiatry Res* 188: 361–365.

Prisciandaro JJ, Desantis SM, Chiuzan C, et al. (2012) Impact of depressive symptoms on future alcohol use in patients with co-occurring bipolar disorder and alcohol dependence: a prospective analysis in an 8-week randomized controlled trial of acamprosate. *Alcohol Clin Exp Res* 36: 490–496.

Rajaratnam R, Sivesind D, Todman M, et al. (2009) The aging methadone maintenance patient: treatment adjustment, long-term success, and quality of life. *J Opioid Manage* 5: 27–37.

Ralevski E, Ball S, Nich C, et al. (2007) The impact of personality disorders on alcohol-use outcomes in a pharmacotherapy trial for alcohol dependence and comorbid Axis I disorders. *Am J Addict* 16: 443–449.

Ralevski E, O'Brien E, Jane JS, et al. (2011) Effects of acamprosate on cognition in a treatment study of patients with schizophrenia spectrum disorders and comorbid alcohol dependence. *J Nerv Ment Dis* 199: 499–505.

Ray LA and Oslin DW (2009) Naltrexone for the treatment of alcohol dependence among African Americans: results from the COMBINE Study. *Drug Alcohol Depend* 105: 256–258.

Rayburn WF and Bogenschutz MP (2004) Pharmacotherapy for pregnant women with addictions. *Am J Obstet Gynecol* 191: 1885–1897.

Reay G (2009) *An Inquiry into Physical Dependence and Addiction to Prescription and Over-the-Counter Medication*. London: The All-Party Parliamentary Drugs Misuse Group

Reed K, Bond A, Witton J, et al. (2011) *The Changing Use of Prescribed Benzodiazepines and Z-Drugs and of Over-The-Counter Codeine-Containing Products in England: a Structured Review of Published English and International Evidence and Available Data to Inform Consideration of the Extent of Dependence and Harm*. London: Department of Health.

Reed LJ, Glasper A, de Wet CJ, et al. (2007) Comparison of buprenorphine and methadone in the treatment of opiate withdrawal: possible advantages of buprenorphine for the treatment of opiate-benzodiazepine codependent patients? *J Clin Psychopharmacol* 27: 188–192.

Regier DA, Farmer ME, Rae DS, et al. (1990) Comorbidity of mental disorders with alcohol and other drug abuse. Results from the Epidemiologic Catchment Area (ECA) Study. *JAMA* 264: 2511–2518.

Rehm J, Frick U, Hartwig C, et al. (2005) Mortality in heroin-assisted treatment in Switzerland 1994-2000. *Drug Alcohol Depend* 79: 137–143.

Rehm J, Gschwend P, Steffen T, et al. (2001) Feasibility, safety and efficacy of injectable heroin prescription for refractory opioid addicts: a follow-up study. *Lancet* 358: 1417–1420.

Richardson K, Baillie A, Reid S, et al. (2008) Do acamprosate or naltrexone have an effect on daily drinking by reducing craving for alcohol? *Addiction* 103: 953–959.

Richter C, Hinzpeter A, Schmidt F, et al. (2010) Levetiracetam for the treatment of alcohol withdrawal syndrome: a multicenter, prospective, randomized, placebo-controlled trial. *J Clin Psychopharmacol* 30: 720–725.

Rickels K, DeMartinis N, Garcia-Espana F, et al. (2000) Imipramine and buspirone in treatment of patients with generalized anxiety disorder who are discontinuing long-term benzodiazepine therapy. *Am J Psychiatry* 157: 1973–1979.

Rickels K, Schweizer E, Garcia E, et al. (1999) Trazodone and valproate in patients discontinuing long-term benzodiazepine therapy: effects on withdrawal symptoms and taper outcome. *Psychopharmacology* 141: 1–5.

Riggs PD, Mikulich-Gilbertson SK, Davies RD, et al. (2007) A randomized controlled trial of fluoxetine and cognitive behavioral therapy in adolescents with major depression, behavior problems, and substance use disorders. *Arch Pediatr Adolesc Med* 161: 1026–1034.

Robertson JR, Raab GM, Bruce M, et al. (2006) Addressing the efficiency of dihydrocodeine versus methadone as an alternative maintenance

treatment for opiate dependence: a randomized controlled trial. *Addiction* 101: 1752–1759.

Rohsenow DJ, Miranda R Jr, McGeary JE, et al. (2007) Family history and antisocial traits moderate naltrexone's effects on heavy drinking in alcoholics. *Exp Clin Psychopharmacol* 15: 272–281.

Roozen HG, de Waart R and van den Brink W (2007) Efficacy and tolerability of naltrexone in the treatment of alcohol dependence: oral versus injectable delivery. *Eur Addic Res* 13: 201–206.

Rösner S, Hackl-Herrwerth A, Leucht S, et al. (2010a) Acamprosate for alcohol dependence. *Cochrane Database Syst Rev* 9: CD004332.

Rösner S, Hackl-Herrwerth A, Leucht S, et al. (2010b) Opioid antagonists for alcohol dependence. *Cochrane Database Syst Rev* 12: CD001867.

Rösner S, Leucht S, Lehert P, et al. (2008) Acamprosate supports abstinence, naltrexone prevents excessive drinking: evidence from a meta-analysis with unreported outcomes. *J Psychopharmacol* 22: 11–23.

Rubio G, Jiménez-Arriero MA, Ponce G, et al. (2001) Naltrexone versus acamprosate: one year follow-up of alcohol dependence treatment. *Alcohol Alcohol* 36: 419–425.

Rubio G, Martínez I, Ponce G,, et al. (2006) Long-acting injectable risperidone compared with zuclopenthixol in the treatment of schizophrenia with substance abuse comorbidity. *Can J Psychiatry* 51: 531–539.

Rubio G, Ponce G, Rodriguez-Jiménez R, et al. (2005) Clinical predictors of response to naltrexone in alcoholic patients: who benefits most from treatment with naltrexone? *Alcohol Alcohol* 40: 227–233.

Rynn M, Garcia-Espana F, Greenblatt D, et al. (2003) Imipramine and buspirone in patients with panic disorder who are discontinuing long-term benzodiazepine therapy. *J Clin Psychopharmacol* 23: 505–508.

Salloum IM, Cornelius JR, Daley DC, et al. (2005) Efficacy of valproate maintenance in patients with bipolar disorder and alcoholism: a double-blind placebo-controlled study. *Arch Gen Psychiatry* 62: 37–45.

San L, Arranz B and Martinez-Raga J (2007) Antipsychotic drug treatment of schizophrenic patients with substance abuse disorders. *Eur J Addict Res* 13: 230–243.

Sayers SL, Campbell EC, Kondrich J, et al. (2005) Cocaine abuse in schizophrenic patients treated with olanzapine versus haloperidol. *J Nerv Ment Dis* 193: 379–386.

Schade A, Marquenie LA, van Balkom AJLM, et al. (2005) The effectiveness of anxiety treatment on alcohol dependent patients with a comorbid phobic disorder: A randomized controlled trial. *Alcohol Clin Exp Res* 29: 794–800.

Scheller-Gilkey G, Woolwine BJ, Cooper I, et al. (2003) Relationship of clinical symptoms and substance use in schizophrenia patients on conventional versus atypical antipsychotics. *Am J Drug Alcohol Abuse* 29: 553–566.

Schmitz JM, Lindsay JA, Green CE, et al. (2009) High-dose naltrexone therapy for cocaine-alcohol dependence. *Am J Addict* 18: 356–362.

Schmitz JM, Stotts AL, Sayre SL, et al. (2004) Treatment of cocaine-alcohol dependence with naltrexone and relapse prevention therapy. *Am J Addict* 13: 333–341.

Schneider U, Paetzold W, Eronat V, et al. (2000) Buprenorphine and carbamazepine as a treatment for detoxification of opiate addicts with multiple drug misuse: a pilot study. *Addict Biol* 5: 65–69.

Schneir AB, Ly BT and Clark RF (2001) A case of withdrawal from the GHB precursors gamma-butyrolactone and 1,4-butanediol. *J Emerg Med* 21: 31–33.

Schonfeld L and Dupree LW (1995) Treatment approaches for older problem drinkers. *Int J Addict* 30: 1819–1842.

Schottenfeld RS, Chawarski MC, Pakes JR, et al. (2005) Methadone versus buprenorphine with contingency management or performance feedback for cocaine and opioid dependence. *Am J Psychiatry* 162: 340–349.

Schottenfeld RS, Pakes JR, Oliveto A, et al. (1997) Buprenorphine vs methadone maintenance treatment for concurrent opioid dependence and cocaine abuse. *Arch Gen Psychiatry* 54: 713–720.

Schroeder JP, Cooper DA, Schank JR, et al. (2010) Disulfiram attenuates drug-primed reinstatement of cocaine seeking via inhibition of dopamine β-hydroxylase. *Neuropsychopharmacology* 35: 2440–2449.

Schweizer E, Rickels K, Case WG, et al. (1991) Carbamazepine treatment in patients discontinuing long-term benzodiazepine therapy. Effects on withdrawal severity and outcome. *Arch Gen Psychiatry* 8: 448–452.

Sechi G and Serra A (2007) Wernicke's encephalopathy: new clinical settings and recent advances in diagnosis and management. *Lancet Neurol* 6: 442–455.

Seivewright N and Daly C (1997) Personality disorder and drug use: a review. *Drug Alcohol Rev* 16: 235–250.

Seivewright N (2000) More than methadone? The case for other substitute drugs. In: *Community Treatment of Drug Misuse: More than Methadone*. Cambridge, UK: Cambridge University Press, pp. 49–81.

Shearer J, Darke S, Rodgers C, et al. (2009) A double-blind, placebo-controlled trial of modafinil (200 mg/day) for methamphetamine dependence. *Addiction* 104: 224–233.

Shearer J, Wodak A, Mattick RP, et al. (2001) Pilot randomized controlled study of dexamphetamine substitution for amphetamine dependence. *Addiction* 96: 1289–1296.

Shekelle PG, Woolf SH, Eccles M, et al. (1999) Clinical guidelines: developing guidelines. *BMJ* 318: 593–596.

Shinn AK and Greenfield SF (2010) Topiramate in the treatment of substance-related disorders: a critical review of the literature. *J Clin Psychiatry* 71: 634–648.

Shoptaw SJ, Kao U, Heinzerling K and Ling W (2009) Treatment for amphetamine withdrawal. *Cochrane Database Syst Rev* 2: CD003021.

Simoni-Wastila L and Yang H (2006) Psychoactive drug abuse in older adults. *Am J Geriatr Pharmacother* 4: 380–394.

Siris SG (1990) Pharmacological treatment of substance-abusing schizophrenic patients. *Schizophr Bull* 16: 111–122.

Sivilotti ML, Burns MJ, Aaron CK, et al. (2001) Pentobarbital for severe gamma-butyrolactone withdrawal. *Ann Emerg Med* 38: 660–665.

Slattery J, Chick J, Cochrane M, et al. (2003) *Prevention of relapse in alcohol dependence. Health Technology Assessment Report 3*. Glasgow: Health Technology Board for Scotland.

Smeerdijk M, Keet R, Dekker N, et al. (2011) Motivational interviewing and interaction skills training for parents to change cannabis use in young adults with recent-onset schizophrenia: a randomized controlled trial. *Psychol Med* 8: 1–10.

Smelson DA, Losonczy MF, Davis CW, et al. (2002) Risperidone decreases craving and relapses in individuals with schizophrenia and cocaine dependence. *Can J Psychiatry* 47: 671–675.

Smelson DA, Ziedonis D, Williams J, et al. (2006) The efficacy of olanzapine for decreasing cue-elicited craving in individuals with schizophrenia and cocaine dependence: a preliminary report. *J Clin Psychopharmacol* 26: 9–12.

Smith EJ, Lui S and Terplan M (2009) Pharmacologic interventions for pregnant women enrolled in alcohol treatment. *Cochrane Database Syst Rev* 3: CD007361.

Sofuoglu M, Poling J, Waters A, et al. (2008) Disulfiram enhances subjective effects of dextroamphetamine in humans. *Pharmacol Biochem Behav* 90: 394–398.

Somerville LH and Casey BJ (2010) Developmental neurobiology of cognitive control and motivational systems. *Curr Opin Neurobiol* 20: 236–241.

Soyka M, Aichmüller C, v Bardeleben U, et al. (2003) Flupenthixol in relapse prevention in schizophrenics with comorbid alcoholism: results from an open clinical study. *Eur J Addict Res* 9: 65–72.

Spear L (2007) The developing brain and adolescent-typical behaviour patterns. In: Romer D and Walker E (eds) *Adolescent psychopathology and the developing brain*. Oxford: Oxford University Press, pp. 9–30.

Srisurapanont M, Jarusuraisin N and Kittirattanapaiboon P (2001) Treatment for amphetamine dependence and abuse. *Cochrane Database Syst Rev* 4: CD003022.

Srivastava A, Kahan M and Ross S (2008) The effect of methadone maintenance treatment on alcohol consumption: a systematic review. *J Subst Abuse Treat* 34: 215–223.

Staner L, Boeijinga P, Danel T, et al. (2006) Effects of acamprosate on sleep during alcohol withdrawal: A double-blind placebo-controlled polysomnographic study in alcohol-dependent subjects. *Alcohol Clin Exp Res* 30: 1492–1499.

Stead LF, Perera R, Bullen C, et al. (2008) Nicotine replacement therapy for smoking cessation. *Cochrane Database Syst Rev* 1: CD000146.

Stedman M, Pettinati HM, Brown ES, et al. (2010) A double-blind, placebo-controlled study with quetiapine as adjunct therapy with lithium or divalproex in bipolar I patients with coexisting alcohol dependence. *Alcohol Clin Exp Res* 34: 1822–1831.

Stein MD, Herman DS, Kettavong M, et al. (2010) Antidepressant treatment does not improve buprenorphine retention among opioid-dependent persons. *J Subst Abuse Treat* 39: 157–166.

Stella L, Addolorato G, Rinaldi B, et al. (2008) An open randomized study of the treatment of escitalopram alone and combined with gamma-hydroxybutyric acid and naltrexone in alcoholic patients. *Pharmacol Res* 57: 312–317.

Stenbacka M, Leifman A and Romelsjö A (2010) Mortality and cause of death among 1705 illicit drug users: A 37 year follow up. *Drug Alcohol Rev* 29: 21–27.

Stitzer M, Bigelow G, Liebson I, et al. (1982) Contingent reinforcement for benzodiazepine-free urines: evaluation of a drug abuse treatment intervention. *J Appl Behav Anal* 15: 493–503.

Strain EC, Stitzer ML, Liebson IA, et al. (1994) Comparison of buprenorphine and methadone in the treatment of opioid dependence. *Am J Psychiatry* 151: 1025–1030.

Strang J, Metrebian N, Lintzeris N, et al. (2010) Supervised injectable heroin or injectable methadone versus optimised oral methadone as treatment for chronic heroin addicts in England after persistent failure in orthodox treatment (RIOTT): a randomised trial. *Lancet* 375: 1885–1895.

Stuyt EB, Sajbel TA and Allen MH (2006) Differing effects of antipsychotic medications on substance abuse treatment patients with co-occurring psychotic and substance abuse disorders. *Am J Addict* 15: 166–173.

Subramaniam GA, Fishman MJ and Woody G (2009) Treatment of opioid-dependent adolescents and young adults with buprenorphine. *Curr Psychiatry Rep* 11: 360–363.

Swartz MS, Wagner HR, Swanson JW, et al. (2008) The effectiveness of antipsychotic medications in patients who use or avoid illicit substances: results from the CATIE study. *Schizophr Res* 100: 39–52.

Szerman N, Peris L, Mesías B, et al. (2005) Reboxetine for the treatment of patients with Cocaine Dependence Disorder. *Hum Psychopharmacol* 20: 189–192.

Tek C, Srihari V and Tek E (2008) Successful acamprosate treatment of alcohol dependence in schizophrenia. *Schizophr Res* 106: 373.

Tennant F and Shannon J (1995) Cocaine abuse in methadone maintenance patients is associated with low serum methadone concentrations. *J Addict Dis* 14: 67–74.

Tenore PL (2008) Psychotherapeutic benefits of opioid agonist therapy. *J Addict Dis* 27: 49–65.

Terplan M and Lui S (2007) Psychosocial interventions for pregnant women in outpatient illicit drug treatment programs compared to other interventions. *Cochrane Database Syst Rev* 4: CD006037.

Thomas SE, Drobes DJ and Deas D (2005) Alcohol cue reactivity in alcohol-dependent adolescents. *J Stud Alcohol* 66: 354–360.

Thomas SE, Randall PK, Book SW, et al. (2008) A complex relationship between co-occurring social anxiety and alcohol use disorders: what effect does treating social anxiety have on drinking? *Alcohol Clin Exp Res* 32: 77–84.

Thomson AD, Guerrini I, Bell D, et al. (2012) Alcohol-related brain damage: report from a Medical Council on Alcohol symposium, June 2010. *Alcohol Alcohol* 47: 84–91.

Tidey JW, O'Neill SC and Higgins ST (2002) Contingent monetary reinforcement of smoking reductions, with and without transdermal nicotine, in outpatients with schizophrenia. *Exp Clin Psychopharmacol* 10: 241–247.

Tiet QQ and Mausbach B (2007) Treatments for patients with dual diagnosis: a review. *Alcohol Clin Exp Res* 31: 513–536.

Tiihonen J, Kuoppasalmi K, Föhr J, et al. (2007) A comparison of aripiprazole, methylphenidate, and placebo for amphetamine dependence. *Am J Psychiatry* 164: 160–162.

Tilg H and Day CP (2007) Management strategies in alcoholic liver disease. *Nat Clin Pract Gastroenterol Hepatol* 4: 24–34.

TIP, Treatment Improvement Protocol Series 45 (2006) Center for Substance Abuse Treatment. *Detoxification and Substance Abuse Treatment*. HHS Publication No. (SMA) 06-4131. Rockville, MD: Substance Abuse and Mental Health Services Administration.

TIP, Treatment Improvement Protocol Series 49 (2009) Center for Substance Abuse Treatment. *Incorporating Alcohol Pharmacotherapies Into Medical Practice*. HHS Publication No. (SMA) 09-4380. Rockville, MD: Substance Abuse and Mental Health Services Administration.

Tolliver BK, Desantis SM, Brown DG et al. (2012) A randomized, double-blind, placebo-controlled clinical trial of acamprosate in alcohol-dependent individuals with bipolar disorder: a preliminary report. *Bipolar Disord*. 14: 54–63.

Tollefson GD, Montague-Clouse J and Tollefson SL (1992) Treatment of comorbid generalized anxiety in a recently detoxified alcoholic population with a selective serotonergic drug (buspirone). *J Clin Psychopharmacol* 12: 19–26.

Tonstad S, Davies S, Flammer M, et al. (2010) Psychiatric adverse events in randomized, double-blind, placebo-controlled clinical trials of varenicline: a pooled analysis. *Drug Saf* 33: 289–301.

Torrens M, Fonseca F, Mateu G, et al. (2005) Efficacy of antidepressants in substance use disorders with and without comorbid depression. A systematic review and meta-analysis. *Drug Alcohol Depend* 78: 1–22.

Tsoi DT, Porwal M and Webster AC (2010) Interventions for smoking cessation and reduction in individuals with schizophrenia. *Cochrane Database Syst Rev* 6: CD007253.

Tzivoni D, Keren A, Meyler S, et al. (1998) Cardiovascular safety of transdermal nicotine patches in patients with coronary artery disease who try to quit smoking. *Cardiovasc Drugs Ther* 12: 239–244.

Ulrichsen J, Nielsen MK and Ulrichsen M (2010) Disulfiram in severe alcoholism – an open controlled study. *Nord J Psychiatry* 64: 356–362.

Umhau JC, Momenan R, Schwandt ML, et al. (2010) Effect of acamprosate on magnetic resonance spectroscopy measures of central glutamate in detoxified alcohol-dependent individuals: a randomized controlled experimental medicine study. *Arch Gen Psychiatry* 67: 1069–1077.

Upadhyaya H and Deas D (2008) Pharmacological interventions for adolescent substance use disorders. In: Yifrah Kaminer Y and Oscar Bukstein O (eds) *Adolescent substance abuse, psychiatric comorbidity and high-risk behaviors*. Routledge, pp. 145–162.

USDHHS (2008) *US Department of Health and Human Services. Treating Tobacco Use and Dependence: 2008 Update of Clinical Practice Guideline*. Rockeville: USDHHS 2008.

van den Bosch LM and Verheul R (2007) Patients with addiction and personality disorder: Treatment outcomes and clinical implications. *Curr Opin Psychiatry* 20: 67–71.

van den Brink W (2012) Evidence-based pharmacological treatment of substance use disorders and pathological gambling. *Curr Drug Abuse Rev* In press.

van den Brink W, Hendriks VM, Blanken P, et al. (2003) Medical prescription of heroin to treatment resistant heroin addicts: two randomised controlled trials. *BMJ* 327: 310.

van der Meer RM, Wagena EJ, Ostelo RW, et al. (2001) Smoking cessation for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 1: CD002999.

Vandrey R, Smith MT, McCann UD, et al. (2011) Sleep disturbance and the effects of extended-release zolpidem during cannabis withdrawal. *Drug Alcohol Depend* 117: 38–44.

van Nimwegen LJ, de Haan L, van Beveren NJ, et al. (2008) Effect of olanzapine and risperidone on subjective well-being and craving for cannabis in patients with schizophrenia or related disorders: a double-blind randomized controlled trial *Can J Psychiatry* 53: 400–405.

Verheul R (2001) Co-morbidity of personality disorders in individuals with substance use disorders. *Eur Psychiatry* 16: 274–282.

Verheul R, Lehert P, Geerlings PJ, et al. (2005) Predictors of acamprosate efficacy: results from a pooled analysis of seven European trials including 1485 alcohol-dependent patients. *Psychopharmacology (Berl)* 178: 167–173.

Verheul R, van den Brink W, Koeter MW, et al. (1999) Antisocial alcoholic patients show as much improvement at 14-month follow-up as non-antisocial alcoholics. *Am J Addict* 8: 24–33.

Verthein U, Bonorden-Kleij K, Degkwitz P, et al. (2008) Long-term effects of heroin-assisted treatment in Germany. *Addiction* 103: 960–968.

Vickers KS, Patten CA, Lewis BA, et al. (2009) Feasibility of an exercise counseling intervention for depressed women smokers. *Nicotine Tob Res* 8: 985–995.

Victorri-Vigneau C, Dailly E, Veyrac C, et al. (2007) Evidence of zolpidem abuse and dependence: results of the French Centre for Evaluation and Information on Pharmacodependence (CEIP) network survey. *Br J Clin Pharmacol* 64: 198–209.

Vorma H, Naukkarinen H, Sarna S, et al. (2002) Treatment of out-patients with complicated benzodiazepine dependence: comparison of two approaches. *Addiction* 97: 851–859.

Vorma H, Naukkarinen H, Sarna S, et al. (2003) Long-term outcome after benzodiazepine withdrawal treatment in subjects with complicated dependence. *Drug Alcohol Depend* 70: 309–314.

Vornik LA and Brown ES (2006) Management of comorbid bipolar disorder and substance abuse. *J Clin Psychiatry* 67: 24–30.

Ward J, Hall W and Mattick RP (1999) Role of maintenance treatment in opioid dependence *Lancet* 353: 221–226.

Weiner E, Ball MP, Summerfelt A, et al. (2001) Effects of sustained-release bupropion and supportive group therapy on cigarette consumption in patients with schizophrenia. *Am J Psychiatry* 158: 635–637.

Weizman T, Gelkopf M, Melamed Y, et al. (2003) Treatment of benzodiazepine dependence in methadone maintenance treatment patients: a comparison of two therapeutic modalities and the role of psychiatric comorbidity. *Aust N Z J Psychiatry* 37: 458–463.

West R and Fidler J (2011) *Smoking and Smoking Cessation in England 2010*. London: Vasco-Graphics. Available from: www.smokinginengland.info (accessed 1 March 2012).

West R and Zhou X (2007) Is nicotine replacement therapy for smoking cessation effective in the "real world"? Findings from a prospective multinational cohort study. *Thorax* 62: 998–1002.

West R, Hajek P, Stead L, et al. (2005) Outcome criteria in smoking cessation trials: proposal for a common standard. *Addiction* 100: 299–303.

West R, McNeill A and Raw M (2000) National smoking cessation guidelines for health professionals: an update. *Thorax* 55: 987–99.

West R, Zatonski W, Cedzynska M, et al. (2011) Placebo-controlled trial of cytosine for smoking cessation. *New Engl J Med* 365: 1193–200.

Wetterling T, Driessen M, Kanitz R, et al. (2001) The severity of alcohol withdrawal is not age dependent. *Alcohol Alcohol* 36: 75–78.

White AR, Rampes H, Liu JP, et al. (2011) Acupuncture and related interventions for smoking cessation. *Cochrane Database Syst Rev* 1: CD000009.

Whitworth M and Dowswell T (2009) Routine pre-pregnancy health promotion for improving pregnancy outcomes. *Cochrane Database Syst Rev* 4: CD007536.

Wickes W, Darke S and Ross J (2000) Clobazam maintenance among methadone maintenance patients with problematic benzodiazepine use: five case studies. *Drug Alcohol Rev* 19: 401–405.

Williams H, Oyefeso A and Ghodse A (1996) Benzodiazepine misuse and dependence among opiate addicts in treatment. *Ir J Psychol Med* 13: 62–64.

Wilson SJ, Nutt DJ, Alford C, et al. (2010) British Association for Psychopharmacology consensus statement on evidence-based treatment of insomnia, parasomnias and circadian rhythm disorders. *J Psychopharmacol* 24: 1577–1601.

Winklbaur B, Jagsch R, Ebner N, et al. (2008) Quality of life in patients receiving opioid maintenance therapy. A comparative study of slow-release morphine versus methadone treatment. *Eur J Addict Res* 14: 99–105.

Winstock AR, Lea T and Copeland J (2009) Lithium carbonate in the management of cannabis withdrawal in humans: an open-label study. *J Psychopharmacol* 23: 84–93.

Wittchen HU, Jacobi F, Rehm J, et al. (2011) The size and burden of mental disorders and other disorders of the brain in Europe 2010. *Eur J Neuropsychopharmacol* 21: 655–679.

Wobrock T and Soyka M (2009) Pharmacotherapy of patients with schizophrenia and substance abuse. *Expert Opin Pharmacother* 10: 353–367.

Wojtowicz JM, Yarema MC and Wax PM (2008) Withdrawal from gamma-hydroxybutyrate, 1,4-butanediol and gamma-butyrolactone: a case report and systematic review. *Can J Emerg Med* 10: 69–74.

Wold M and Kaminer Y (1997) Naltrexone for alcohol abuse. *J Am Acad Child Adolesc Psychiatry* 36: 6–7.

Wolff K, Boys A, Rostami-Hodjegan A, et al. (2005) Changes to methadone clearance during pregnancy. *Eur J Clin Pharmacol* 61: 763–768.

Woody GE, Poole SA, Subramaniam G, et al. (2008) Extended vs short-term buprenorphine-naloxone for treatment of opioid-addicted youth: a randomized trial. *JAMA* 300: 2003–2011.

Yoon SJ, Pae CU, Kim DJ, et al. (2006) Mirtazapine for patients with alcohol dependence and comorbid depressive disorders: a multicentre, open label study. *Prog Neuropsychopharmacol Biol Psychiatry* 30: 1196–1201.

Zimberg S (2005) Alcoholism and substance abuse in older adults. In: Frances RJ, Miller SI and Mack AH (eds) *Clinical Textbook of Addictive Disorders, 3rd edn*. New York, NY: Guilford, pp. 396–410.

Zitman F and Couvée J (2001) Chronic benzodiazepine use in general practice patients with depression: an evaluation of controlled treatment and taper-off: report on behalf of the Dutch Chronic Benzodiazepine Working Group. *Br J Psychiatry* 178: 317–324.

Zutler M and Holty JE (2011) Opioids, sleep, and sleep-disordered breathing. *Curr Pharm Des* 17: 1443–1449.