Psychopharm

Journal of Psychopharmacology
18(3) (2004) 293–335

ISSN 0269-8811
SAGE Publications Ltd, London, Thousand Oaks, CA and New Delhi
10.1177/0269881104048516

Evidence-based guidelines for the pharmacological management of substance misuse, addiction and comorbidity: recommendations from the *British Association for Psychopharmacology*

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The *British Association for Psychopharmacology* guidelines for the treatment of substance misuse, 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, in substance misuse, addiction and comorbidity with psychiatric disorders.

Introduction

The *British Association for Psychopharmacology* (BAP) aims to advance education and research in the science of psychopharmacology and includes people from clinical and experimental disciplines. To this end, the Association arranges scientific meetings, fosters research and teaching, encourages publication of results of research and provides guidance and information to the public on matters relevant to psychopharmacology. In recent years, the Association has begun to produce a range of consensus statements on the evidence-based treatment of clinical disorders.

The first BAP guidelines on 'Treating depressive disorders with antidepressants' were published in 1993, followed by revised guidelines in 2000 (Montgomery *et al*., 1993; Anderson *et al*., 2000). Guidelines for treating bipolar disorder were published in 2003 after a consensus meeting in 2002 (Goodwin, 2003). The BAP recognized that, because psychopharmacology is at the heart of all drug, nicotine and alcohol misuse and dependence, and often its treatment, such evidence-based guidelines were a priority. In addition, because substance misuse is very common in patients with psychiatric illness and more attention is being paid to its neurobiology and pharmacotherapy, it is timely to review the evidence of how to manage such comorbidity. These 'substance misuse, addiction and comorbidity' guidelines will be followed by guidelines for the treatment of anxiety in 2005. The aim is to regularly update all the guidelines in a 5-year cycle. All guidelines are available through the BAP website (http://www.bap.org.uk).

These guidelines primarily focus on the pharmacological management of all major substances of abuse and their comorbidity with psychiatric disorders, and provide a comprehensive review of

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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 randomized controlled trials
Ib:	Evidence from at least one randomized controlled trial
IIa:	Evidence from at least one controlled study without randomization
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

the evidence following explicit criteria (Table 1). However, these guidelines were not intended to provide an equivalent comprehensive review of psychosocial interventions because this is a considerable 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' is used instead.

During the review process, it was noticeable that there is a dearth of high quality research from which evidence based guidelines can be drawn. However, this is offset by a wealth of clinical experience over many years. Nevertheless, in some cases, it is hard to advocate particular regimens over another. We see this as the beginning of a process. The production of such guidelines should stimulate more research to fill the gaps.

Scope and target of the guidelines

The aim of this document was to produce helpful and useable guidelines for clinicians covering a wide range of substances including alcohol, nicotine, opioids, stimulants and comorbidity with psychiatric problems. In addition, we have reviewed management of substance misuse in pregnancy. Although ambitious, we believe that it is important to cover all the substances commonly treated with pharmacotherapy in clinical treatment settings in one document to further enhance its usefulness. The contents of the guidelines are primarily relevant to psychiatrists and general practitioners treating patients with addiction or comorbidity. We have concentrated on treatments that can be provided by most specialist clinical treatment services in the UK. We have reviewed the evidence in as brief a format as possible,

Another important role of collating and reviewing the evidence is to identify the gaps in our knowledge and stimulate further research. To this end, areas of key uncertainty are highlighted within each section.

Areas that are not covered

We have not included substances for which there is a lack of pharmacological treatment for misuse or dependence (e.g. ecstasy, cannabis, other 'club drugs' and solvents).

These guidelines neither provide a comprehensive review, nor cover guidelines concerning psychosocial interventions. However, it is not possible to review pharmacological treatments in isolation from psychosocial interventions and, accordingly, we have described key psychosocial interventions at various points in the document.

The evidence that we present is derived mainly from studies that have excluded the elderly, adolescents or children, and so care must be taken in extrapolating these recommendations to such populations (see Crome, 1997; Crome and Day, 1999; Crome *et al*., 2004).

We have not included the pharmacological treatments used in the management of severe acute intoxication or overdose, which can affect first-time drug or alcohol users as well as those with an established substance use disorder. Such management usually takes place in Accident and Emergency departments.

Methodology

A consensus meeting was held on 14 November 2003 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 randomized 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 discussion and review of the literature was then circulated to all participants and other interested parties. Feedback was incorporated, wherever possible, into the final version. The views of all

participants shaped this document; however, the authors, Lingford-Hughes, Welch and Nutt, take responsibility for the final version.

Identification of relevant evidence

The range of disorders covered in these guidelines did not allow for a systematic review of all possible data from primary sources. Existing systematic reviews and RCTs were identified from MEDLINE and EMBASE searches, and from the Cochrane Database, as well as from previous published guidelines and those identified 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 example, 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. However, more commonly, 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), but we do not review these points in depth.

Diagnostic categories

There is a spectrum of substance use behaviours and, over time, observers have taken different approaches to understanding and describing them. The dependence syndrome was first proposed for alcohol (Edwards and Gross, 1976), and the criteria for diagnosis are now incorporated in both International Classification of Disease (ICD) (WHO, 1992) and Diagnostic and Statistics Manual for Mental disorders (DSM) (American Psychiatric Association, 1994) classification systems. The latest versions of both these systems (ICD-10 and DSM-IV) use the same approach to both alcohol and drugs of abuse (including nicotine), and both systems make a distinction between the dependence syndrome and other harmful patterns of substance use (definitions and diagnostic criteria are given in Table 2). The criteria for the dependence syndrome are similar in the two systems. 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 psychiatric consequences in the ICD-10 classification. In recent years, the concept of 'addiction' has been resurrected to assist in clarifying the differences between physical dependence and drug abuse and to emphasize the serious often life-changing nature that drug and alcohol abuse can result in (Nutt, 2003).

Validity of diagnostic categories

As the concept of the dependence syndrome first developed as a description of a pattern of cognitive, behavioural and physiological symptoms seen in consumers of alcohol, its applicability to other drugs of misuse has been questioned. There is relatively little controversy regarding its use for opioid and benzodiazepine drugs, as both can produce a clear increase in tolerance and characteristic withdrawal syndromes. However, its use for drugs such as cannabis, nicotine, cocaine and amphetamines has generated debate. A large study of alcohol, opioid, cocaine and cannabis users conducted by the World Health Organization in 12 countries (Nelson *et al*., 1999) found the 'dependence' and 'abuse' constructs to be broadly generalizable across all four categories of substance, though the use of this two-dimensional model was found to fit cocaine use less well than alcohol, opioid and cannabis use. This study also showed that specific criteria played a greater or lesser role in defining the construct in the different user groups. A smaller study of daily tobacco smokers (Johnson *et al*., 1996) also supported a two-factor model, with the two factors described as 'dependence' and 'failed cessation'. Recent research on cannabis use has supported the validity of the dependence syndrome, although the definition of a withdrawal syndrome remains unclear (Smith, 2002).

Although a diagnosis of 'the dependence syndrome' is generally now well defined in studies, earlier ones did not necessarily observe this, nor is it easy to extract the data from these studies.

Treatment aims

In planning treatment for substance use disorders, there are many possible aims. 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 pharmacological treatments currently have limited application. Of course, it may be appropriate to use drug treatments to treat any comorbid psychiatric disorder. Pharmacological interventions aimed at treating the substance use disorder itself are most often used in patients who have developed the features of the dependence syndrome, and are targeted at the following areas of patient management:

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

Table 2 Classification of substance abuse and dependence

DSM-IV

Substance abuse (one 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

Substance dependence (three 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

ICD-10 F10–F19

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+ 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 to achieve the 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

Special considerations in the treatment of substance use disorder

Substance use disorders occur in a complex psychosocial and cultural context and result in a variety of harms, including interpersonal, occupational and legal problems. Some pharmacological treatments (particularly those aimed at harm reduction) are sometimes evaluated in terms of outcomes that are not clearly health-related. For example, the impact of both methadone maintenance treatment and injectable opioid prescribing programmes on criminal behaviour has been of interest. Although a reduction in criminal behaviour is clearly desirable, the medical practitioner's role is to ensure that the treatment has demonstrable health benefits.

In the treatment of substance misuse, the provision of pharmacological treatment is guided not only by clinical criteria, but also by the need to avoid abuse and diversion of prescribed drugs. We do not cover aspects of delivery of drug treatment in detail in this review, but draw attention to special measures (such as supervised consumption of medication) where they are key features in the evidence base for particular treatments. Before prescribing, it is recommended that a pharmacopoeia such as the British National Formulary (www.bnf.org.uk) be consulted.

Licensing

In these guidelines, some pharmacotherapies described do not have a UK license for the indication discussed. It is important to realise that, in this area of medicine, the absence of a license usually means that a license has not been applied for, rather than that the pharmacotherapy is not safe or appropriate. There is no contra-indication to prescribing a drug off-license provided there is a body of evidence that supports its efficacy (Healy and Nutt, 1998). In many cases, these guidelines can be considered as providing appropriate evidence.

ALCOHOL

(i) Management of withdrawal and detoxification

Background

Goals of treatment

Many alcohol withdrawal episodes take place without any medical or pharmacological treatment. In those patients where detoxification is planned, the balance between giving medication unnecessarily and giving sufficient to appropriately minimize withdrawal symptoms has to be struck. However, in addition, consideration should also be given to prevention of complications, such as seizures and delirium tremens (DTs), during each withdrawal episode and also in future withdrawal episodes. Successive episodes of alcohol withdrawal are associated with increased withdrawal severity and rate of complications and with cognitive impairment (Schuckit *et al*., 1995; Malcolm *et al*., 2000; Duka *et al*., 2003).

In determining the most appropriate management of alcohol detoxification, consideration needs to be given to the intended goal. Is it symptom suppression, no complications, completion of regimen without drinking alcohol or abstinence subsequently, and for how long? All of these have been used, making comparisons between studies difficult.

Where and when to detoxify?

The consensus meeting and these guidelines do not address these important topics in depth. The reader is directed to Raistrick (2001) for further information. It is important to consider the following questions:

(1) What are the medical risks?
(2) What setting is appropriate?
(3) What does the service user want from detoxification?
(4) How to integrate into the bigger treatment picture?

Deciding when to detoxify someone is important because detoxification without adequate aftercare in place is less likely to lead to sustained abstinence. As stated, an increasing number of detoxifications are associated with increasingly severe withdrawal states and, in addition, the patient's self-efficacy decreases.

Community-based detoxification is now common and can be delivered in the home or from a service centre. Generally, the model involves daily contact with a nurse to assess withdrawal and monitor for complications, with prescribing from either the general practitioner or psychiatric or addiction team. There is wide variation in the availability of inpatient facilities for alcohol detoxification, making it hard to be prescriptive about who needs admission, but those with previous severe complications (e.g. fits, DTs), who are medically or psychiatrically unwell, live alone, with poor support and have previously failed, should be considered for inpatient detoxification.

Treatment regimens

Several meta-analyses and systematic reviews have concluded that benzodiazepines are better than placebo as the treatment of choice for alcohol withdrawal as assessed by severity of withdrawal, reduction in incidence of delirium and seizures, adverse effects of medication, completion of detoxification and entrance into rehabilitation (Mayo-Smith, 1997; Lejoyeux *et al*., 1998; Williams and McBride, 1998; Holbrook *et al*., 1999; Kosten and O'Connor, 2003; Shand *et al*., 2003) (1a). In all of these publications, concerns were expressed about the methodology of many of the studies.

- ***Benzodiazepine***

Studies comparing different benzodiazepines demonstrate that they appear equally efficacious in reducing signs and symptoms of withdrawal (1a). Medication is typically given for approximately 7 days. It has been suggested that the choice of which benzodiazepine to use routinely is not critical, but to consider that particular drugs may suit different circumstances (e.g lorazepam or oxazepam in patients with liver failure). Longer-acting benzodiazepines may be more effective in preventing seizures and delirium but this needs to be weighed up against their accumulation in the elderly and in those with liver failure (Mayo-Smith, 1997; Kosten and O'Connor, 2003) (1a).

Alcohol withdrawal severity varies widely and the amount of benzodiazepine required for symptom amelioration can also vary. There is no fixed, standardized dose for all patients, but a typical regimen for covering uncomplicated withdrawal is 20 mgs q.d.s. of chlordiazepoxide, reducing over approximately 7 days. Additional titration using prn medication to achieve complete symptom suppression in first 2 days can also be used.

There are alternative ways of giving benzodiazepines other than a reducing regimen over approximately 7 days, but these are less widely used. 'Front-loading' involves giving a loading dose of diazepam and thereafter further doses are given approximately every 90 min until light sedation is achieved. No further medication is given and the long-half life of diazepam covers the withdrawal. Sellers *et al*. (1983) showed such a regimen using 20 mg diazepam was more effective than placebo. Skilled supervision and monitoring is required for the initial stages.

Another manner of delivering the patient's benzodiazepine is through symptom-triggered therapy. Saitz *et al*. (1994) compared a fixed regimen versus a symptom triggered one using chlordiazepoxide and found faster control and less benzodiazepine was used in the symptom-triggered regimen (100 mg versus 425 mg) (1a). However, this study excluded those patients with a history of complications. Daeppen *et al*. (2002) reported similar findings with oxazepam and included patients with a history of seizures and delirium (1b). Given that prevention of withdrawal symptoms should be the goal and this is likely to reduce the risk of complications in further withdrawal episodes, such 'symptom-triggered' regimens may be problematic. In addition, such a regimen requires skilled monitoring.

- ***Chlormethiazole***

Chlormethiazole has also been shown to be superior to placebo (Williams and McBride, 1998) (1a), but its use in outpatient settings is no longer recommended due principally to the greater

risk of respiratory depression if alcohol is drunk, as well as other concerns including its variable bioavailability, addictive potential and 'street value' (McInnes, 1987; Duncan and Taylor, 1996). However, in inpatient settings with skilled staff and monitoring, i.v. chlormethiazole can be used in severe withdrawal (Morgan, 1995).

• *Carbamazepine*

Although, in the UK, benzodiazepines are the most widely used pharmacotherapy, carbamazepine alone is used elsewhere in the world. In their review, Williams and McBride (1998) concluded that carbamazepine might be a first-line alternative to benzodiazepines. Carbamazepine appears to be effective throughout the range of alcohol withdrawal symptoms, including severe withdrawal, and is not contra-indicated in liver failure. In their respective meta-analyses, Holbrook *et al*. (1999) and Mayo-Smith (1997) concluded that carbamazepine appeared as efficacious as relatively low doses of oxazepam if used in an approximately 7-day reducing regimen in mild-to-moderate withdrawal (1a). In a recent double-blind, randomized controlled comparison of lorazepam and carbamazepine, Malcolm *et al*. (2002) reported that the two regimens were equivalent in regard to withdrawal symptomatology. However, in those with two or more previous detoxifications carbamazepine was associated with lower levels of drinking in the following 12 days. Carbamazepine has not been evaluated for treating delirium tremens and, with regard to the role of carbamazepine in preventing seizures, the evidence is limited (see below).

Seizures: prevention and treatment

Preventing an alcohol withdrawal-related seizure is an important clinical goal. The incidence of seizures quoted is 1–15% in alcohol-dependent patients. The likelihood of having another seizure increases in any subsequent episode of alcohol withdrawal (Ballenger and Post, 1978). It was proposed that this was due to a kindling process whereby episodes of alcohol withdrawal sensitise the brain leading to increased likelihood of a seizure with each future episode. Indeed, this appears to happen for all alcohol withdrawal related symptoms, not just seizures (Malcolm *et al*., 2000).

Hillbom *et al*. (2003) recently assessed the efficacy of different drug regimens in preventing seizures by studying controlled clinical trials in patients with and without a past history of seizures. In the trials studied, the average seizure rate calculated by Hillbom *et al*. (2003) was 8%, which was reduced to 3% with drug therapy. Their meta-analysis of these trials demonstrated that benzodiazepines, particularly long-acting ones such as diazepam, significantly reduced seizures occurring *de novo* (1a). Anticonvulsants alone were equally as effective to benzodiazepines (1a); however, both drugs taken together conferred no advantage in primary seizure prevention (1a).

In regard to preventing a secondary seizure in the same withdrawal episode, Hillbom *et al*. (2003) performed a meta-analysis of three studies of phenytoin (Alldredge *et al*., 1989; Chance, 1991; Rathlev *et al*., 1994) (1a) and showed this to be ineffective (1a). However, lorazepam has been shown to be effective in a single study (D'Onofrio *et al*., 1999) (1b). Other reviewers have made equivalent observations (Mayo-Smith, 1997).

Continuing with an anticonvulsant if it has been used to treat an alcohol withdrawal related seizure is not recommended (Hillbom *et al*., 2003).

Delirium

There is little evidence on the efficacy of different medications in preventing or treating delirium. Benzodiazepines have been shown to be more effective than placebo (Mayo-Smith, 1997) in preventing delirium (1a). Kosten and O'Connor (1998) suggest that, as with seizures, benzodiazepines with a longer half-life were more effective in reducing the incidence of delirium. A diazepam load can be used to treat delirium.

Other complications of alcohol withdrawal

In hypertension, a β-blocker such as propranolol could be used. Slower detoxification regimens have been used in hypoglycaemia and psychiatric illness.

In intoxicated patients with incipient alcohol withdrawal, there are no controlled studies evaluating properties of any medication for withdrawal. Clinically, withdrawal medication is often not given until blood alcohol levels have reduced or withdrawal symptoms are manifest due to concerns of over-sedation and increased confusion. Recently, Lucht *et al*. (2003) compared a combination of carbamazepine/tiapride with diazepam and with chlormethiazole. The combination of carbamazepine and tiapride was safe in intoxicated (blood alcohol content > 1 g/l) patients compared with diazepam. Side-effects of ataxia and diplopia, were attributed to the high dose of carbamazepine used (1200 mg/day).

Other pharmacotherapeutic strategies

• *Adrenergic α_2 agonists*

Noradrenergic overactivity is thought to be present in alcohol withdrawal as in opioid withdrawal. Studies of clonidine found it to be effective in ameliorating alcohol withdrawal (Williams and McBride, 1998; Mayo-Smith, 1997) (1a) but the most recent double-blind, randomized placebo-controlled trial found no advantage of adding the α_2 agonist, lofexidine, to their chlordiazepoxide regimen (Keaney *et al*., 2001) (1b).

• *Magnesium*

Alcoholism is associated with hypomagnesia however, a double-blind, randomized, placebo-controlled trial of magnesium (2 g, 6 hourly) in addition to a benzodiazepine did not show any improvement in withdrawal nor in reduction of seizures (Wilson and Vulcano, 1984) (1b).

• *Antipsychotics*

Antipsychotics such as phenothiazines (chlorpromazine, promazine) and butyrophenones (haloperidol) have been shown in a meta-analyses to reduce signs and symptoms of alcohol withdrawal (Mayo-Smith, 1997; Kosten and O'Connor, 2003) (1a). However, they do not reduce the risk of seizures, nor delirium, as effectively as benzodiazepines and they increase the likelihood of seizures compared with placebo. Antipsychotics are now generally used to reduce agitation in alcohol withdrawal. It is suggested that

Recommendations – management of alcohol withdrawal and detoxification

Although many alcohol withdrawal episodes take place without any pharmacological support, in the presence of symptoms, medication should be given. Ideally, detoxification should be planned as part of a treatment programme to increase the likelihood of successfully altering their drinking behaviour.

Treatment regimens

- Benzodiazepines are efficacious in reducing signs and symptoms of withdrawal, and are recommended as the treatment of choice (A)
- Carbamazepine has also been shown to be efficacious and can be chosen as an alternative to benzodiazepines (A)
- Chlormethiazole is reserved for inpatient settings only after due consideration (A)

Seizures

- Benzodiazepines, particularly diazepam, reduce *de novo* seizures and are recommended for treatment of withdrawal previously complicated by seizures (A)
- Carbamazepine is equally efficacious in seizure prevention and can be chosen as an alternative to benzodiazepines, but there is no advantage in using both together (A)
- To prevent a second seizure in same withdrawal episode, the evidence supports the use of lorazepam but does not support the use of phenytoin (A)

Delirium

- Benzodiazepines, particularly those with longer half-life, prevent delirium (A) and are recommended for treatment of this complication of alcohol withdrawal (B)

Miscellaneous

- The evidence does not support use of α_2 agonists, magnesium or antipsychotics to reduce symptoms of alcohol withdrawal, and we do not recommend their use

Key uncertainties

- What is the appropriate outcome for withdrawal from alcohol (e.g. drinking behaviour at 3 or 12 months after detoxification)?
- What is the role of carbamazepine or other anticonvulsants in alcohol detoxification – uncomplicated and complicated – or in people who have a history of misusing benzodiazepines?
- What is appropriate regimen for maximum symptom control, reducing risk of complications, preventing brain damage?

this should only be performed after appropriate review of the amount of benzodiazepines given.

(ii) Vitamin replacement: thiamine

Background

Wernicke's encephalopathy

Vitamin deficiency in alcoholism is common. There is a particular need to replenish thiamine stores due to its critical role as a co-factor for metabolic enzymes. Thiamine deficiency causes Wernicke's encephalopathy (WE) and is most commonly seen in heavy drinkers with a poor diet. Consideration regarding treatment needs to be given as to whether a patient is at low risk, at high risk or has suspected or actual WE. Knowledge about appropriate thiamine replacement is based on uncontrolled trials and empirical practice. In addition, there is no consistency in post-treatment assessment and the duration of observations varies.

The role of thiamine supplementation in 'healthy uncomplicated' (i.e. low risk) alcohol-dependent patients undergoing detoxification is unclear. Based on clinical practice, current recommendations are for 100–200 mg daily by mouth for up to 1 month (Raistrick, 2001). The Royal College of Physicians (2001) has recommended that for patients undergoing alcohol detoxification in the community 200 mg four times a day of oral thiamine and vitamin B strong tablets (30 mg/day) is the treatment of choice for the duration of the detoxification. Both supplements could be continued if there is evidence of cognitive impairment (thiamine 50 mg four times a day) or poor diet (vitamin B co strong 30 mg/day). It is important to consider compliance.

Diagnosing WE is crucial and it has been argued that there should be a high index of suspicion for subclinical presentations because the classic triad of confusion, ataxia and nystagmus is only present in 10% of patients and 80% of patients are not diagnosed before post mortem (Cook *et al*., 1998). There are no diagnostic laboratory tests. WE is initially reversible but, if untreated or with inadequate thiamine replenishment can result in irreversible brain damage (Korsakoff's syndrome) in 84% of survivors and is associated with significant mortality (approximately 20%) (Victor *et al*., 1989; Cook *et al*., 1998).

In patients at high risk of WE and once WE has been diagnosed, or is suspected, parenteral (i.m. or i.v.) administration must be used. Oral supplementation is not appropriate to address thiamine deficiency because only approximately 1 mg will be absorbed

Recommendations – management of vitamin deficiency, Wernicke's encephalopathy

A high index of suspicion must be maintained at all times regarding Wernicke's encephalopathy (WE) because 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. at low risk), oral thiamine should be given at a minimum dose of 300 mg/day during detoxification (D)
- If the patient is at high risk of WE, prophylactic treatment should be given, using 250 mg thiamine (one pair of ampoules Pabrinex®) i.m. or i.v. once daily for 3–5 days (D)
- If WE is suspected or established, parenteral thiamine (i.m. or i.v.) of > 500 mg should be given for 3–5 days (e.g. two pairs of ampoules Pabrinex® three times a day for 3 days, followed by one pair of ampoules once daily for 3–5 days) depending on response (D)

Key uncertainties

- What is the appropriate dose, route (i.m. or i.v.) and duration of thiamine administration in presumed or clinically obvious WE?
- To determine thiamine requirements during alcohol withdrawal in otherwise healthy patients and at different times during the patient's 'drinking career'
- To understand more about other neurobiological processes involved in WE
- What is the role of other vitamin deficiences in the presentation of alcohol-related WE?

from a single tablet greater than 30 mg in a malnourished patient due to impaired absorption (Thomson, 2000). This amount barely covers thiamine turnover, let alone replenishes depleted stores. Therefore, both prophylaxis and treatment should be based on parenteral vitamin therapy. In particular thiamine should be given before any i.v. glucose.

Pabrinex® is the only source of parenteral thiamine available in the UK and also contains nicotinamide, pyridoxine (vitamin B_6), riboflavin (vitamin B_2) and vitamin C. Most of these constituents may have a direct part to play in the treatment of WE or brain damage due to nicotinic acid deficiency (Thomson *et al*., 2002).

There is a high incidence of WE occurring during the alcohol withdrawal syndrome and it is recommended that all patients considered to be at risk of thiamine deficiency (e.g. those that miss meals or have clinical signs of malnutrition) (Sgouros *et al*., 2004) should receive prophylactic treatment with 250 mg thiamine (one pair of ampoules of Pabrinex®) i.m. or i.v. once daily for 3–5 days (Royal College of Physicians, 2001). If this is delivered in the community, procedures should be followed to ensure safe administration (see British National Formulary).

Doses of thiamine from 100 mg to 250 mg i.v. or i.m. daily have been reported as effective in treating WE but not reliably so (Reuler *et al*., 1985) (IV). Doses of up to 1 g of parenteral thiamine may be required (Lindberg and Oyler, 1990). In the absence of well-conducted studies, the current recommendation to treat suspected or diagnosed WE in alcohol-dependent patients is a minimum of 500 mg (i.e. two pairs of Pabrinex® ampoules) given parenterally three times a day for at least 2 days, followed by one pair of ampoules once daily for 5 days (Royal College of Physicians, 2001; Thomson *et al*., 2002). For full guidance about dosing, duration and safety considerations, see Thomson *et al*. (2002). When looking for a response, ophthalmoplegia responds quickest, generally within hours, but cognitive impairment takes longer to respond, if at all. The neurobiology of cognitive impairment is likely to be complex and other pharmacological strategies may be needed to result in improvement (see Korsakoff's syndrome). It is important to recognize that alcohol-related WE and Korsakoff's syndrome are different entities to those induced by thiamine alone and responds to much lower doses of thiamine therapy.

Pabrinex® replaced Parentrovite©, which was associated with a small risk of anaphylaxis when given as a bolus rather than infusion, requiring i.v. preparations to be given with facilities available to treat anaphylaxis. This warning still remains for Pabrinex®. However, the risk for Parentrovite© was low (four reports per 1 million pairs of ampoules when used i.v. and one report per 5 million pairs of ampoules when used i.m.) and many hospitals report years of parenteral thiamine use without serious problems (Thomson *et al*., 2002). This risk appears to have resulted in fears about using parenteral preparations and, consequently, the inappropriate use of oral thiamine preparations. However, given the nature of WE, the benefit to risk ratio still favours parenteral thiamine.

Korsakoff's syndrome

Korsakoff's syndrome is the chronic form of WE and is characterized by loss of short-term memory and confabulation with relative preservation of other intellectual functions, thus distinguishing it from alcoholic dementia.

A series of case reports or small trials have been reported showing improvement, unless stated, with clonidine and fluvoxamine (Mrazek *et al*., 1999), fluvoxamine alone (O'Carroll *et al*., 1994, no improvement; Martin *et al*., 1995, improvement), reboxetine (Reuster *et al*., 2003), memantine (Rustembegovic *et al*., 2003) or donepezil (Iga *et al*., 2001, improvement in one case; Sahin *et al*., 2002, ineffective in non-alcoholic Kosakoff's syndrome) (II).

Recommendations – management of Korsakoff's syndrome

- Given the lack of evidence, it is not possible to make specific recommendations regarding pharmacological approaches

Key uncertainties

- What are appropriate therapies for Korsakoff's syndrome?

(iii) Preventing relapse: promoting and maintaining abstinence

Background

All pharmacotherapies discussed here have been studied as an adjunct to psychosocial interventions. In addition, most studies include patients aiming for abstinence, although a range of outcome measures are generally used, including reduced amount of alcohol consumed.

Acamprosate

Acamprosate is a taurine derivative and inhibits glutamatergic NMDA receptor function *in vitro* (this receptor system is up-regulated in alcoholism). Although its mechanism of action *in vivo* is not clear, one hypothesis is that it suppresses the 'urge to drink' in response to learned cues (Littleton, 1995; Verheul *et al*., 1999). Acamprosate is generally well tolerated, with gastrointestinal disturbance (e.g. nausea, diarrhoea) being the most common side-effect reported.

There have been a number of meta-analyses and systematic reviews of the double-blind, placebo-controlled trials, although a different but overlapping range of trials were included in each one (Slattery *et al*., 2003, $n = 17$; Kranzler and Van Kirk, 2001, $n = 11$; Mason, 2003, $n = 16$, Mann *et al*., 2004, $n = 20$). References for individual studies can be derived from these reviews. All have found acamprosate to be better than placebo (1a). Various outcome measures have been used, such as improvement in γ-glutamyl-transpeptidase (GGT), abstinence (total and cumulative), fewer days drinking, greater time to relapse, treatment retention and craving (1a). Because the majority of studies were conducted in patients aiming for abstinence rather than controlled drinking, their motivation to be abstinent is likely to be an important factor in the studies. Rates of abstinence with acamprosate range from approximately 25% to 50% at 3, 6 and 12 months and are generally about twice that seen with placebo. As with other such analyses, it was commented that comparing studies can be difficult due to different outcomes (e.g. abstinence, length of treatment) and different inclusion and exclusion criteria.

In a meta-analysis conducted for the Health Technology Board (HTB) of Scotland (Slattery *et al*., 2003), acamprosate was shown to be effective compared with placebo [odds ratio (OR) = 1.73; 95% CI 1.36–2.2 and a 'number needed to treat' of 11 to prevent one relapse]. Similar results were found by the Swedish Technology board in their meta-analyses (Berglund *et al*., 2003).

More recently, Chick *et al*. (2003) undertook reanalysis of 15 placebo-controlled trials of acamprosate and determined that acamprosate reduced the amount and frequency of alcohol consumed compared with placebo by approximately 50%.

• *Psychosocial interventions*

Because a psychosocial intervention was present in all studies, acamprosate alone has not been shown to be effective. It is questionable whether it should be prescribed in the absence of a patient willing to engage with a psychosocial approach. An observational study (Soyka and Sass, 1994) showed that individual psychotherapy, group psychotherapy, cognitive behavioural therapy (CBT)/coping strategy and brief interventions appeared equivalent as an adjunct to acamprosate. More recently, Feeney *et al*. (2002) have shown that acamprosate and CBT is more effective than CBT alone.

• *When to start and how long to prescribe for?*

In the trials, patients are generally detoxified from alcohol, although one study showed that it could be safely used during medicated alcohol withdrawal (Gual and Lehert, 2001) (1b). Currently, the manufacturer's recommendation is to start acamprosate as soon after detoxification as possible. One study showing no advantage of acamprosate over placebo may have been due to a longer period between detoxification and starting acamprosate than in other studies (Chick *et al*., 2000a) (1b). Pre-clinical data suggesting that acamprosate may be neuroprotective support the principle that acamprosate should be started with or soon after detoxification (Koob *et al*., 2002).

It appears that the benefits of acamprosate may continue after stopping the drug. Three of four studies including a follow-up period have shown persisting higher rates of abstinence in patients treated with acamprosate compared with placebo, 1–2 years after stopping acamprosate (Ladewig *et al*., 1993, no difference; Sass *et al*., 1996; Whitworth *et al*., 1996; Poldrugo, 1997) (1b).

• *Who to give it to?*

In view of the fact that not everyone benefits from acamprosate, there have been several attempts to define the characteristics of a 'responsive' alcohol-dependent patient. To date, there is no clear evidence to suggest which type of patient may benefit, although it has been suggested that a classical, primary type of alcohol-dependent patient appears more likely to benefit than one with a psychiatric or organic disorder or with social problems, or one that is an episodic drinker (Lesch and Walter, 1996; Chick *et al*., 2000a) (1b). A recent review (Verheul *et al*., 2004) did not find that gender, age of onset, severity of dependence, predicted treatment efficacy.

Acamprosate and disulfiram

In one study, the addition of disulfiram to acamprosate improved outcome compared with acamprosate alone (Besson *et al*., 1998) (1b).

Naltrexone

Naltrexone is an opioid antagonist that is licensed in the USA and some European countries for treatment of alcohol dependence, but not in the UK (although it can be prescribed). Similar to acamprosate, naltrexone is used to maintain abstinence as an adjunct to psychosocial intervention. It is hypothesized that naltrexone reduces the pleasurable effects of alcohol by blocking the effects of opioids released by alcohol that enhance dopamine release in the mesolimbic system (Ulm *et al*., 1995).

As with acamprosate, studies have been mostly conducted in patients who have undergone detoxification from alcohol and are in abstinence-focussed programmes.

Naltrexone has been shown to be superior to placebo in the following outcomes: abstinence, relapse rates, time to first drink, reduction in number of drinking days, reduction in craving and improvement in GGT. For the HTB for Scotland, 12 positive of 17 published clinical trials were analysed (Slattery *et al*., 2003). It was concluded that naltrexone was more effective than placebo as an adjunct to psychosocial interventions but that there was a wide variation in study design (OR = 1.46 (95% CI 1.12–1.9) and NNT of 11 (1a). Another meta-analysis of seven RCTs showed that naltrexone was associated with lower relapse rates, reduced drinking levels and higher abstinence rates compared with placebo (Streeton and Whelan, 2001) (1a). A Cochrane review (Srisurapanont and Jarusuraisin, 2003a) concluded that 50 mg of naltrexone was effective in the short-term treatment of alcohol dependence in improving drinking outcomes, but there was no evidence to support its use over acamprosate or disulfiram (1a).

However, not all trials of naltrexone have found a statistically significant benefit over placebo for drinking outcome measures (Volpicelli *et al*., 1997; Chick *et al*., 2000b; Kranzler *et al*., 2000; Krystal *et al*., 2001; Gastpar, 2002) (1b). The reasons given to explain this have been length of abstinence before starting naltrexone or the type of psychosocial intervention delivered. In addition, naltrexone may not show efficacy in chronic severe alcohol dependence (Krystal *et al*., 2001) (1b).

In the original naltrexone trials, one of the main outcome measures was 'relapse to heavy drinking' (i.e. > 5 drinks/day or drinking on more than 5 days/week) rather than abstinence. By contrast, the acamprosate trials mostly used complete abstinence (i.e. having no alcohol in 1 day as their outcome measure). The naltrexone studies therefore found that individuals who resume at least some drinking are those who benefit most from being on the active drug (Volpicelli *et al*., 1997). Indeed, one review (Garbutt *et al*., 1999) reported that naltrexone reduces the risk of relapse to heavy drinking and the frequency to drinking compared with placebo but does not substantially enhance abstinence. Therefore, the main effect of naltrexone may be to reduce drinking, or prevent a 'lapse' becoming a full-blown relapse. It follows that naltrexone should not be stopped if drinking resumes.

Compared with acamprosate, naltrexone has a higher rate of side-effects such as nausea and headache. Nausea is associated with shorter duration of abstinence, lighter drinking, younger age, being female and can be lessened by starting at 25 mg (O'Malley, 2000) (1b). In addition, it is not suitable for anyone taking opioids [e.g. for analgesia, or in an opioid (methadone, buprenorphine) maintenance programme]. When used in larger doses than the current 50 mg dose, naltrexone has been associated with hepatotoxicity, and blood monitoring is advisable. Although concerns have been raised that naltrexone may cause dysphoria because it blocks the opioid system involved in the 'pleasure–reward' system, a recent review found no clinical evidence of this (Miotto *et al*., 2002).

Unsurprisingly, predictors of better drinking outcomes are compliance and good attendance (Volpicelli *et al*., 1997) and two studies suggest that patients with high levels of craving or poor cognitive abilities tend to benefit (Volpicelli *et al*., 1995; Jaffe *et al*., 1996) (1b).

• *Psychosocial interventions*

In terms of what type of psychotherapy or psychosocial intervention is best with naltrexone, CBT or coping skills has been shown to be better than psychosocial treatment alone or supportive therapy (O'Malley *et al*., 1992; Anton *et al*., 1999; Heinala *et al*., 2001) (1b).

• *When to start and how long to prescribe for?*

Similar to acamprosate, it is not clear how long to prescribe naltrexone for, and the trials tend to be short in duration (e.g. 12 weeks). O'Malley *et al*. (2003) reported that naltrexone, given for a further 6 months to those patients that had responded to it when combined with CBT over 10 weeks, conferred no advantage over placebo plus maintenance CBT. However, continued naltrexone in a primary care setting did result in better improvement compared with placebo. It is also not clear whether the favourable effects of naltrexone are maintained after it is stopped, with two follow-up studies showing that the benefits are lost within a few weeks and outcomes at 6 months are then similar to psychosocial interventions (O'Malley, 1996; Anton *et al*., 2001) (1b). This emphasizes the importance of psychosocial interventions.

Acamprosate versus naltrexone

Kranzler and Van Kirk (2001) conducted a meta-analysis comparing acamprosate and naltrexone. Nine naltrexone and 11 acamprosate studies were included. There were no differences between the drugs on a number of different outcomes (% abstinent, % retention) and both were better than placebo (1a).

Two studies have directly compared naltrexone and acamprosate. An open, non-blind, randomized comparison found that naltrexone was better than acamprosate in achieving abstinence, reducing craving, number of drinks and number of days to relapse (Rubio *et al*., 2001) (IIb). A double-blind, RCT compared placebo with acamprosate and naltrexone, and with combined acamprosate and naltrexone (Kiefer *et al*., 2003) (1b). Acamprosate and naltrexone alone were more efficacious than placebo in increasing time to first drink and heavy drinking. However, the combination was more effective in preventing relapse than acamprosate alone but not naltrexone.

Disulfiram

Disulfiram has been used for many years to promote abstinence. It blocks a liver enzyme, aldehyde dehydrogenase, resulting in the accumulation of acetaldehyde leading to signs and symptoms such as flushing, nausea, vomiting, headache, tachycardia and palpitations if alcohol is consumed. If a large amount of alcohol is consumed, a severe reaction, including hypertension, collapse and death, can occur. Fear of this reaction is important to the drug's efficacy and patients should be adequately informed and advised to carry a card (Fuller and Roth, 1979). Alcohol should not have been taken for 24 h before starting disulfiram and not for a week after stopping. However, there is a wide variation in the reaction produced, and patients might not experience an intense reaction on consuming alcohol whereas others experience pronounced flushing after application of aftershave or perfume containing alcohol.

Despite its long and widespread use in alcohol dependence treatment, there are few controlled clinical trials. In recent reviews, disulfiram was reported to reduce the number of drinking days and reduce the quantity of alcohol consumed, but not increase abstinence (Hughes and Cook, 1997; Garbutt *et al*., 1999) (1b). However, there was diversity in the subjects studied and methodologies used, making comparisons and recommendations difficult.

Witnessing, or supervising, the taking of disulfiram is important for its efficacy (Chick *et al*., 1992; Hughes and Cook, 1997; Slattery *et al*., 2003) (1a). When prescribed with no supervision, disulfiram is no better than basic support. There is little evidence to guide how long patients should receive disulfiram but, generally, 3–6 months is advocated, or for as long any benefits are maintained.

Evidence does not support the use of disulfiram implants, although there are now newer formulations that may deliver higher doses of disulfiram (Hughes and Cook *et al*., 1997; Garbutt *et al*., 1999) (1b).

Other pharmacotherapies

A number of other pharmacotherapies have been studied for their efficacy in maintaining abstinence. Often the trials are open, not placebo-controlled or replicated, making recommendations difficult. We did not set out to provide a comprehensive review of all medications tried in alcohol dependence and the reader is directed to Garbutt *et al*. (1999), Swift (1999), Johnson and Ait-Daoud (2000) and Johnson *et al*. (2003).

• Specific serotonin reuptake inhibitors

Because serotonergic dysfunction has been implicated in the neurobiology of alcohol misuse and dependence, specific serotonin reuptake inhibitors (SSRIs) have been investigated (McBride and Li, 1998). Comorbidity with depression will be discussed subsequently; however, in the absence of depression or anxiety, there is limited evidence and one review stated that their use could not be recommended (Garbutt *et al*., 1999).

In heavy social drinkers, citalopram (40 mg/day) and fluoxetine (60 mg/day) have been shown to improve some drinking outcomes over a short period at higher doses than normally prescribed (Naranjo *et al*., 1987, 1990; Balldin *et al*., 1994) (1b). Studies with citalopram (40 mg/day) in alcohol dependence without major depression have shown no significant improvement for longer than 1 week (Naranjo *et al*., 1995) or improved self-report of abstinence or in GGT (Tiihonen *et al*., 1996) (1b). Nevertheless, the variability observed in outcomes may be due to the type of patients studied. Re-analyses of trials have showed that SSRIs may improve drinking outcomes in type 1 alcoholism (later age of onset, anxious traits) but may worsen outcome in type 2 alcoholism (early age of onset, family history positive, impulsive/antisocial personality traits) (Kranzler *et al*., 1996; Pettinati *et al*., 2000; Chick *et al*., 2004) (1b).

Recommendations – preventing relapse: promoting and maintaining abstinence

There is good evidence to support the use of some medications in improving drinking behaviour as an adjunct to psychosocial interventions. There is no good evidence about who might respond to this approach.

- Acamprosate and naltrexone can be used to improve abstinence rates (total and cumulative, reduced days drinking, greater time to relapse, improved treatment retention and craving). There is no consistent evidence to suggest which types of patient will respond. We recommend that acamprosate and naltrexone be considered as treatment options for patients attempting to maintain abstinence from alcohol (A)
- Disulfiram is also effective if intake is supervised. Disulfiram can be offered as a treatment option for patients who intend to maintain abstinence, and for whom there are no contraindications (B)
- SSRIs should be avoided or used with caution in type 2 alcoholism (C)

Key uncertainties

- Who is likely to benefit from which pharmacotherapy?
- Is there a role for prescribing naltrexone to alter drinking behaviour in alcohol misuse rather dependence?
- How long to prescribe for, particularly if the patient has started drinking?
- Are any particular forms of psychosocial intervention better than others?
- Is acamprosate neuroprotective in humans undergoing repeated withdrawals?

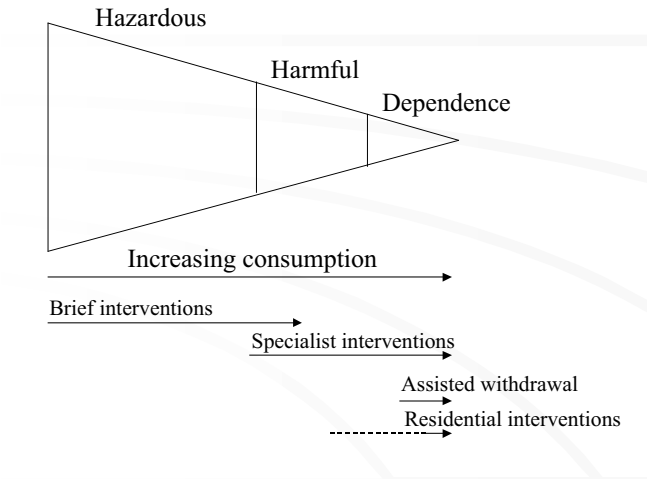

Figure 1 Relationship between levels of alcohol consumption and appropriate interventions

Psychosocial interventions

This is an immense topic in its own right. These guidelines aim to concentrate on the pharmacological management of substance misuse and, necessarily, this section is concise. Concerns were been expressed about the type of and highly selected groups of patients entering studies of psychosocial interventions and how generalizable the results are. Aside from brief interventions, most of the studies were performed in the USA and therefore may not translate in to other treatment systems. Use of manuals, setting for treatment delivery and the quality of the therapist all need to be taken in to consideration when interpreting outcomes. In the clinical setting, a mixture of approaches is likely to be used.

Although the pharmacotherapy described above is aimed at the dependent patient, psychosocial interventions span the entire range of drinking behaviour (Fig. 1). Those that are drinking at hazardous to harmful levels will benefit from brief interventions that can be delivered in a non-specialist setting. Once harmful drinking has been reached, as well as dependence, more specialist interventions are generally required.

There are several recent systematic reviews of treatment of alcohol problems. Recently, an update of the 'Mesa Grande Project', a long-term and ongoing systematic review of controlled clinical trials for treatment for alcohol use disorders where the methodological strength of the study is taken into account, has been published (Miller and Wilbourne, 2002) (Table 3). It provides a list of interventions that have been studied and does include pharmacotherapy; however, criticisms have been leveled at its review process. For example, no distinction is made between types of patients or level of alcohol consumption. The ranking reflects cumulative evidence and not necessarily relative efficacies.

The HTB for Scotland (Slattery *et al*., 2003) reviewed evidence for a number of interventions and models, including CBT, behavioural self-control training (BSCT), motivational enhancement therapy (MET), coping skills training, marital/family therapy, and intensive case management. Their meta-analysis showed that BSCT, MET, marital/family therapy and coping/skills training had similar beneficial effect sizes. Similar conclusions were reached by Shand *et al*. (2003) on reviewing the evidence for psychosocial interventions for the Australian Guidelines for the Treatment of Alcohol Problems.

The Swedish Technology board (Berglund *et al*., 2003) has also undertaken a review. Amongst its conclusions are that psychosocial treatments, such as CBT, 12-step approaches, motivational approaches, structured interactional therapy with a psychodynamic reference framework and partner and family therapy, show similar benefits. There was only weak evidence for subgroups. Inpatient and outpatient results were similar. It is important to address problems with psychiatric illness and lifestyle concurrently with abuse.

• *Specific psychosocial interventions*

There have been a number of systematic reviews of brief interventions (BI) (Holder *et al*., 1991; Bien *et al*., 1993; Freemantle *et al*., 1993; Miller *et al*., 1995; Wilk *et al*., 1997; Poikolainen, 1999; Moyer *et al*., 2002). There can be considerable variation in what is

Table 3 Mesa Grande results: a selection from review where there were three or more studies available

Rank	Treatment modality	CES	No of studies	Rank	Treatment modality	CES	No of studies
1	Brief intervention	280	31	11	Cognitive therapy	21	10
2	Motivational enhancement	173	17	12.5	Client-centred counselling	20	7
3	Acamprosate	116	5	12.5	Disulfiram	20	24
4	Opiate antagonist	100	6	16.5	Acupuncture	14	3
5	Social skills training	85	25	18	Self-help	11	5
6	Community reinforcement	80	4	23	Family therapy	−5	3
7	Behaviour contracting	64	5	24.5	12-step facilitation	−13	3
8	Behaviour marital therapy	60	8	30	Hypnosis	−41	4
9	Case management	33	6	35	Relapse prevention	−87	20
10	Self-monitoring	25	6	39.5	Alcoholics Anonymous	−108	7

CES, Cumulative evidence score = MQS (methodological quality scores) × OLS (outcome logic scores) such that a high score indicates a predominance of evidence that the treatment modality exerts some benefit on drinking outcomes. The top 10 ranked treatments are listed followed by other commonly used treatments. The ranking reflects cumulative evidence and not necessarily relative efficacies (Miller and Wilbourne, 2002).

Table 4 Characteristics suggested of a brief intervention in alcohol misuse

Goal of reduced or non-problem drinking as opposed to abstinence
Being delivered by a non-specialist
Being directed at non-dependent drinkers as opposed to dependent
Addressing individual's motivation to change drinking habits
Being self, as opposed to professionally, directed
Having particular ingredients (e.g. FRAMES) (Bien *et al.*, 1993) [F: feedback of risk; R: encouraging responsibility for change; A: advice; M: menu of alternative options; E: empathy; S: enhancing self-efficacy]

understood by a BI. A BI refers to an opportunistic intervention occurring in non-specialist settings and is primarily directed at patients who are drinking excessively but are not complaining about, or seeking treatment for, their alcohol use. For example, they may be identified through screening or from abnormal liver function tests. The characteristics of a BI are detailed inTable 4.

BIs have been shown to result in a 20–30% reduction in excessive drinking. There is some evidence of cost effectiveness, most of the evidence is from primary care, and BIs show greater effects in opportunistically screened, early stage drinkers rather than dependent drinkers. Indeed, if more severely affected patients are included in comparisons, BI is not more effective than control conditions. Moreover, in treatment seeking groups, BI is significantly less effective compared with longer treatment interventions.

Therefore, such opportunistic BIs are distinct from 'brief' treatment strategies used by specialists in treatment seeking alcohol-dependent populations. There are a wide variety of treatment approaches used, some with limited theoretical rationale, or a combination of approaches, which makes it difficult to group and compare studies. In addition, some interventions are not a single type (e.g. CBT) but rather a model underlying many psychosocial interventions, or are specific techniques versus modalities (e.g. 12-step facilitation versus Minnesota model residential programmes).

CBT is not included in Mesa Grande but was included in Project MATCH (see below). However, the CBT approach incorporates many treatment interventions. For example, considerable overlap may exist with coping skills or social skills training. A recent review concluded that although CBT was effective, there was no support that this was occurring via its theoretical route of increasing coping and behavioural skills (Morgenstern and Longabaugh, 2000).

A meta-analysis on outcomes of BSCT, which aims for controlled drinking rather than abstinence, has been performed by Walters (2000). Support for the effectiveness of the BSCT approach in promoting controlled drinking was evident. The HTB for Scotland came to similar conclusions (Slattery *et al*., 2003)

MET or motivational interviewing (MI) has become one of the most popular forms of treatment. A meta-analysis suggested that MI was best as an adjunct to more intensive treatment (Dunn *et al*., 2001). The meta-analysis performed for HTB similarly found evidence to support MI as an effective part of more extensive psychosocial treatment (Slattery *et al*., 2003).

Although there have been no systematic reviews of social or coping skills training, they are common elements to other interventions. Family or marital therapy has also been shown to be beneficial compared with individual therapy; however, 'family therapy' includes a wide range of interventions (O'Farrell and Fals-Stewart, 2001).

Cue exposure has also been used as a treatment alongside coping skills training. Several controlled clinical trials have found this combination to be effective, but attribute the success to the coping skills element rather than the cue exposure (Monti *et al*., 1993; Rohsenow *et al*., 2001).

Alcoholics Anonymous (AA) is the most ubiquitous form of self-help group available worldwide. Project MATCH found AA attendance predicted a better long-term outcome, particularly in those lacking a non-drinking support network (Project MATCH, 1998). However, a meta-analysis of randomized and non-randomized trials showed that attending AA resulted in worse outcomes than comparator treatments or no treatment (Kownacki and Shadish, 1999). Critically, this result was heavily influenced by trials in which patients were mandated to attend AA. In light of this, Slattery *et al*. (2003) gave a strong recommendation that patients should be introduced to AA, and encouraged to attend, but not mandated to attend.

- ***Which intervention to give to which patient?***

It has been suggested that 'treatment matching' might improve outcome. Project MATCH in the USA was a large multisite randomized clinical trial conducted to test this hypothesis. The psychosocial treatments explored were CBT, MET and 12-step facilitation and were matched to a variety of clinical characteristics (Project MATCH, 1998). There was little evidence for matching improving outcome, and therefore there is no support for using patient characteristics to decide which treatment to offer. A major study in the UK has just been completed and publication of the results is pending. UKATT is a multicentre, randomized, controlled trial comparing Motivational Enhancement Therapy and Social Behaviour and Network Therapy in treating alcohol problems (UKATT *et al*., 2001).

BENZODIAZEPINE ABUSE AND DEPENDENCE

Background

These guidelines address two distinct populations of patients. The first includes patients who have taken benzodiazepines long-term for a disorder such as anxiety or insomnia but who do not abuse their prescription. The other population includes patients who abuse their prescription or buy their benzodiazepines. Individuals in either category may be dependent. Usually, treatment focuses on safe withdrawal and cessation of use.

Abuse is defined as 'maladaptive pattern of recurrent usage producing interpersonal or social problems, and/or physical risks in specific situations'. Such use of benzodiazepines is generally associated with other substance abuse in characteristic combinations (e.g. using them to 'come down' from stimulants or to 'boost'

Recommendations – benzodiazepine misuse and dependence

Determination of presence or absence of physical dependence and the dependence syndrome is important in determining whether pharmacological treatment is appropriate.

Management of benzodiazepine dependence in non-abusing patients with a licit prescription

- In early/mild dependence, minimal interventions such as advisory letters, other information provision, general practitioner advice or short courses of relaxation should be offered (B)
- Where dependence is established, graded discontinuation of prescribed benzodiazepine is recommended (B)
- The appropriate treatment goals for most patients are safe withdrawal and cessation of use (S)
- Additional psychological therapies do not appear to increase effectiveness of graded discontinuation but should be considered on their own merits (C)

Illicit benzodiazepine misusers

- Management in illicit drug users is less clear with no robust evidence to support maintenance prescribing. We cannot recommend maintenance prescribing 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 from high doses of benzodiazepines (C)

Key uncertainties

- Pharmacological treatment strategies are focussed on the management of the dependence syndrome, and the diagnosis of dependence can be difficult to make in those who also misuse or are dependent on illicit drugs
- The optimal speed or duration of dose reduction is unknown
- The value of antidepressants to prevent emergent depression during withdrawal?

the effects of methadone). Dependence is generally associated with tolerance, withdrawal symptoms and compulsive usage. The withdrawal syndrome can be severe, including a life-threatening delirium. A diagnosis of dependence should only be considered when a range of problems occur in addition to physiological withdrawal symptoms as specified in ICD-10 or DSM-IV (e.g. priority of drug-seeking behaviour). Determination of the presence or absence of a dependence syndrome is important in determining whether pharmacological treatment is appropriate. It is notable that the rate of physical dependence on benzodiazepines among illicit drug misusers has been found to be relatively low (Williams *et al*., 1996; Ross and Darke, 2000).

The literature on management of 'ordinary-dose' benzodiazepine dependence mainly relates to individuals prescribed these drugs for psychiatric disorders, and is far more extensive and systematic than that concerning illicit drug users. In practice, the advisability of applying management principles from this literature to illicit drug users is affected not only by clinical criteria, but also by the need to avoid abuse and diversion of prescribed supplies (Van Valkenburg and Akiskal, 1999; Seivewright, 2000).

Management of benzodiazepine dependence in non-abusing patients with a licit prescription

This often takes place in primary care and frequently involves a pragmatic combination of approaches. There is abundant literature that identifies the elements of preparation, switch to a long-acting compound, graded reduction, and additional psychological and/or pharmacological treatments (Lader and Morton, 1991; Mant and Walsh, 1997; Seivewright, 1998; Couvee *et al*., 2003) (1b).

• *Minimal interventions*

Minimal interventions include advisory letters, provision of other information, single consultations with a general practitioner, short courses of relaxation, etc. (Cormack *et al*., 1989; Jones, 1990; Bashir *et al*., 1994) (1b). Such approaches have been calculated to achieve cessation of benzodiazepine use in approximately 20% of cases (Couvee *et al*., 2003).

• *Graded discontinuation alone*

There are a number of studies of discontinuation schedules lasting several weeks (Tyrer *et al*., 1983; Murphy and Tyrer, 1991; Habraken *et al*., 1997; Oude-Voshaar *et al*., 2003) but a wide range has been used, from a 7-day schedule (Petrovic *et al*., 1999) to discontinuation over many years (Ashton, 1987) (1b).

Overall, the short-term cessation rate has been calculated at 66%, with little influence of switching to a long-acting compound, length of taper, or allowing reductions to be symptom-guided (Couvee *et al*., 2003). Data on longer-term outcome of benzodiazepine discontinuation is limited, but some degree of relapse appears common (Holton and Tyrer, 1990; Zitman and Couvee, 2001) (1b).

• *Additional psychological therapies*

Additional psychological therapies have been used, such as anxiety management training (e.g. Elsesser *et al*., 1996), CBT (Otto *et al*., 1993; Vorma *et al*., 2002) and supportive therapies (Charney *et al*., 2000) (1b). However, overall, these do not appear to definitely increase the effectiveness of graded discontinuation (Couvee *et al*., 2003).

• Additional pharmacological treatments

Medications studied include anticonvulsants (Rickels *et al*., 1990; Schweizer *et al*., 1991), antidepressants (Tyrer *et al*., 1996; Rickels *et al*., 1999), β-blockers (Tyrer *et al*., 1981), buspirone (Ashton *et al*., 1990; Udelman *et al*., 1990; Morton and Lader, 1995) and melatonin (Garfinkel *et al*., 1999) (1b). Varying results have been achieved in reducing withdrawal symptom severity and/or improving discontinuation rates, but no compound has been clearly established as effective in repeated RCTs (Schweizer and Rickels, 1998; Couvee *et al*., 2003).

Management in illicit benzodiazepine users

There is a dearth of literature to guide management in this often difficult to manage population. The patient should be assessed as to why they are requesting benzodiazepines; for example, are they suffering from anxiety or insomnia which can be treated by non-benzodiazepine medications? In addition, whether alcohol or illicit drug misuse or dependence is present should be determined.

Maintenance prescribing occurs more commonly in practice in opioid maintenance patients than might appear to be advisable (Seivewright *et al*., 1993; Greenwood, 1996; Best *et al*, 2002). Such prescribing has been found in preliminary studies to reduce other benzodiazepine use (Wicks *et al*., 2000; Weizman *et al*., 2003) (III).

Contingency management with rewards for benzodiazepine-free urines in opioid substitution treatment has been tried with some success (Stitzer *et al*., 1992) (III).

Concerns about withdrawal seizures can influence prescribing both for maintenance and detoxification. It has been consistently shown that prescribing for detoxification need only be moderate-dose, often far lower than claimed usage (Harrison *et al*., 1984; Williams *et al*., 1996) (IIb). Carbamazepine may be particularly useful in controlling withdrawal symptoms from high benzodiazepine doses (Ries *et al*., 1989; Schweizer *et al*., 1991) (IIb).

NICOTINE DEPENDENCE

Background

Nicotine dependence is recognized 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. In comparison with treatment of dependence on other substances, the treatment of nicotine dependence has been investigated in a large number of well-conducted RCTs. High quality systematic reviews have been conducted (NICE, 2002; Silagy *et al*., 2003) and various treatment guidelines have been published (McRobbie and Hajek, 2000; United States Department of Health and Human Services, 2000; West *et al*., 2000). The information in this review is based largely on these sources and references for individual studies can be derived from them.

Goals of treatment

The main harmful effects of nicotine dependence arise from long-term health effects of 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, as relapse rates after this time are low, at approximately 8% per year for the first few years and less than this subsequently.

The main forms of pharmacological treatment covered are nicotine replacement therapy and the atypical antidepressant bupropion, but we have also included a brief section on other pharmacotherapies.

Nicotine replacement therapy (NRT)

Products

NRT is currently produced as:

- Transdermal patch (varying doses, 16 h and 24 h duration)
- Gum (2 mg and 4 mg)
- Inhalator/inhaler
- Nasal spray (0.5 mg per dose, usually administered two doses at a time)
- Sublingual tablet (2 mg)
- Lozenge (1, 2 and 4 mg)

Clinical effectiveness

Nicotine replacement therapy increases the chance of achieving abstinence for at least 6 months [OR = 1.74, CI 1.64–1.86; probability difference 6.7% (16.9% versus 10.2%)]. These figures arise from 96 high quality RCTs (Silagy *et al*., 2003) with biochemical verification of smoking status at follow-up (usually from expired air carbon monoxide) (Ia). Effectiveness per treatment episode in terms of permanent cessation is modest but important. There is some evidence to suggest that combinations of NRT products are more effective overall than single products (five trials with heterogeneous samples and results, Silagy *et al*., 2003) (Ia). Such combinations have been found to be safe. There is insufficient evidence to support attempts to match types of smoker to different NRT products, or to show that in unselected patients any one form of NRT is more effective than another.

Dosing

In highly dependent smokers 4 mg gum is more effective than 2 mg gum (three trials, Silagy *et al*., 2003) (Ia). Higher dose patches are more effective than lower dose patches (six trials, Silagy *et al*., 2003) (Ia). There is no clear evidence that the 24-h patch is more effective than the 16-h patch (Silagy *et al*., 2003), and tapering patch dose after 8 weeks does not improve effectiveness (Silagy *et al*., 2003).

Safety

NRT delivers pure nicotine, which is just one of the components smokers already obtain from cigarettes. NRT use does not pose a cancer risk and is safe in patients with stable coronary heart disease (Joseph and Fu, 1996) and lung disease (Murray *et al*., 1996). NRT may have a harmful effect on the fetus, but it is believed that it does

Recommendations – nicotine dependence

Nicotine replacement therapy (NRT)

- All NRT products are effective. NRT should be offered to patients requesting help for smoking cessation (A)
- Combinations of NRT products can safely be used (e.g. patch plus inhalator) and may be more effective (B)
- Higher dose products are more effective for heavily dependent smokers (4 mg gum, or standard rather than low dose patches) (B)
- Additional behavioural support (as provided in specialist smokers' clinics) improves overall success rates but is not required for the pharmacotherapy *per se* to be effective. We recommend the provision of additional behavioural support: however, lack of availability of such support should not deter practitioners from offering NRT (A)
- NRT can be used safely in patients with cardiac disease (A)
- Although effectiveness is not established in these patients groups, NRT can be considered on an individual basis for pregnant women and for young people (under 18 years)

Bupropion

- Bupropion is an effective intervention and should be offered as a treatment option for patients requesting help with smoking cessation, unless any of the contraindications apply (A)
- Bupropion is not licensed for adolescents or pregnant women, and is contraindicated for people with a history of seizures or eating disorders

Key uncertainties

- Comparisons of the effectiveness of bupropion, NRT, and the two treatments in combination warrant further study
- How long to continue with NRT when a quit attempt has failed?
- The value of NRT as a harm reduction strategy in patients who do not intend to abstain completely is unknown

so to a lesser extent than smoking (see section below 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

Additional behavioural support improves overall success rates but does not appear to be required to NRT *per se* to be effective (Silagy *et al*., 2003). There is insufficient evidence to state whether NRT plus bupropion (see bupropion below) is more effective than either NRT or bupropion alone (two trials, one showed bupropion to be superior; Hughes *et al*., 2004).

Specific patient groups

Evidence is lacking for effectiveness in specific patient groups:

- Pregnant smokers (see section on pregnancy)
- Adolescents (no adequate studies)
- Hospital inpatients (studies inconclusive)
- Psychiatric patients (see section on comorbidity)

However, opinion tends to favour presumption of effectiveness on the basis of studies on other populations.

Bupropion

Although nicotine replacement has become the most widely used pharmacotherapy for nicotine dependence, some smokers may prefer a treatment that is not nicotine-based (Hughes *et al*., 2004). The atypical antidepressant bupropion has been well studied and is the only non-nicotine medication licensed as an aid to smoking cessation (Hughes *et al*., 2004). 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.

Clinical effectiveness

Results of a meta-analysis of 10 placebo-controlled RCTs (n = 3800) (Hughes *et al*., 2004) showed bupropion to be more effective than placebo (OR = 2.16, CI 1.5–3.1). Continuous abstinence at 12 months was found in 19% of patients taking bupropion compared with 9% taking placebo. The effect appears to be independent of a past history of depression (Hayford *et al*., 1999).

Safety

Bupropion is contraindicated for patients with history of seizures or eating disorder. Rates of *de novo* seizures are low (approximately 0.1%) (Dunner, 1998; manufacturers data) and predominantly occur when higher doses are used (e.g. 450 mg/day) and may be minimized by slow dose escalation. Bupropion has not been established as safe in pregnancy, or for patients aged under 18 years.

Additional therapies

There is insufficient evidence to state whether NRT plus bupropion is more effective than either NRT or bupropion alone (Hughes *et al*., 2004).

Specific patient groups

Bupropion has similar efficacy in patients with medical comorbidity (e.g. lung or cardiovascular disease) as in those without (Tashkin *et al*., 2001; Tonstad *et al*., 2003) Bupropion is not recommended for use in adolescents or pregnant women.

Recommendations – nicotine dependence with alcohol and/or drug dependence

- Behavioural programmes and NRT may be effective in increasing smoking abstinence rates in patients in treatment programmes for their dependence on alcohol (B) and/or illicit drugs (B)
- Consideration should be given to offering all patients help to quit since addressing smoking has not been shown to have an adverse effect on recovery from alcohol or illicit drug misuse (B)

Key uncertainties

- Large randomized trials are needed of pharmacological and behavioural interventions in smokers with current alcohol and illicit drug dependence
- Is a higher dose of nicotine needed for patients misusing alcohol or illicit drugs?

Other pharmacotherapies for smoking cessation

There have also been five trials of the tricyclic antidepressant, nortriptyline, of which meta-analysis indicates that it aids smoking cessation. There have also been trials of SSRIs such as fluoxetine, but the limited published evidence does not provide support for use in smoking cessation (Hughes *et al*., 2004).

Comparison of NRT and bupropion

There have only been two RCTs comparing NRT with bupropion, one of which showed a superior effect of bupropion (Hughes *et al*., 2004). Bupropion is unsuitable for some patient groups (e.g. pregnant women, people with a history of seizures or eating disorders) for which nicotine replacement may be considered. Bupropion has a side-effect profile that may make it less acceptable than NRT. NRT can be purchased 'over-the-counter' for quit attempts, but bupropion must be prescribed. There are therefore several advantages to NRT in comparison with bupropion, but some patients may prefer a pharmacotherapy that is not based on nicotine, and it is possible that bupropion or a combination of bupropion and NRT may be more effective than NRT alone.

Nicotine and other substance misuse

The prevalence of smokers in patients who misuse alcohol and illicit substances is approximately three-fold higher than that of the general population (Romberger and Grant, 2004). In addition, approximately 80% of alcohol-dependent patients are reported to smoke cigarettes, and alcoholism is 10-fold more common in smokers than non-smokers. In illicit drug users, estimates of cigarette smoking are also approximately 80% (Richter *et al*., 2002).

• *Alcohol*

The treatment of cigarette smoking in alcohol dependence has only been specifically addressed in a few studies and has recently been reviewed (Hurt and Patten, 2003).

Behavioural programmes have been evaluated in patients with a past history of alcohol dependence and those in early abstinence and can be as successful as in the general population. In abstinent alcohol-dependent outpatients, an RCT reported that behavioural counselling (BC) with physical exercise resulted in the highest rate of abstinence (60%), whereas BC and nicotine gum (52%) and nicotine anonymous meetings (31%) were less effective (Martin *et al*., 1997) (1b). However, no differences were seen at 6 months (21–27%) and 12 months (27%). Only 4% relapsed to alcohol use and alcohol relapse did not differ by treatment group or smoking status.

Patten *et al*. (2002) performed an RCT of BC compared with BC and CBT aimed at improving their mood in patients with a history of alcohol dependence (1b). Those patients with higher depression scores (Hamilton rating scale for depression) were more likely to achieve short-term abstinence with BC plus CBT than those receiving BC only.

It appears that a history of alcoholism does not reduce the effectiveness of nicotine substitution in smoking cessation (Hughes *et al*., 2003). A post-hoc analysis of an RCT of nicotine patch and behavioural intervention found that smoking abstinence rates in those with current or past history of alcohol problems were lower at 4 and 8 weeks, but not at 26 weeks, compared with those with no such problems (Hays *et al*., 1999). It was suggested that the lack of efficacy might be due to a requirement for higher doses of nicotine in patients with active or past alcohol problems (1b).

• *Alcohol and illicit substance misuse*

Several studies have shown that nicotine substitution and specific smoking cessation programmes can improve smoking behaviour in drug- and/or alcohol-dependent patients in treatment programmes, in residential, in- and outpatient settings (Campbell *et al*., 1995; Saxon *et al*., 1997; Bobo *et al*., 1998; Campbell *et al*., 1998) (Ib). Importantly, addressing their smoking does not have an adverse effect on their recovery from alcohol or illicit drug misuse.

Two studies suggest that although patients may stop smoking after specific interventions, this is independent of their use of other drugs and alcohol. A non-randomized controlled trial of behavioural intervention for cigarette smoking in inpatients in a drug and alcohol addiction programme, reported increased abstinence rates from 10% to 22% (Hurt *et al*., 1994) (IIa). At 1 year, although no patients in the control group had stopped smoking, 12% of the behavioural intervention group had. Notably, the rates for abstinence for the other drugs and alcohol were the same in the two groups. Similarly, behavioural treatments for smoking cessation resulted in abstinence rates at 12 months to 10% compared with 0% with no treatment in alcohol- and drug-dependent smokers in a residential rehabilitation programme (Burling *et al*., 2001) (IIa). There was no significant difference between the groups regarding drug and alcohol abstinence.

Recommendations – management of withdrawal from opioid drugs

There is a substantial evidence base for three main types of pharmacotherapy: methadone, buprenorphine and α2 adrenergic agonists (e.g. clonidine and lofexidine). All are effective in reducing withdrawal symptoms.
The choice of agent may be guided by the following:

Desired duration of treatment

- If short duration of treatment is desirable, α2 adrenergic agonists are preferable to methadone (A)
- Buprenorphine can be used for short-term opioid withdrawal and has a better outcome than clonidine (B)
- Methadone treatment is more successful if carried out slowly or with a linear dose reduction (B)

Adverse effects

- Buprenorphine is preferable to α2 adrenergic agonists if there are concerns about bradycardia or hypotension (B)

Withdrawal severity

- Buprenorphine results in lower severity of withdrawal symptoms than α2 adrenergic agonists (A)

Specific patient groups

- Methadone can be used during pregnancy, and there are emerging studies regarding the use of buprenorphine. α2 adrenergic agonists should not be prescribed in pregnancy (see pregnancy section)

Key uncertainties

- Further information is needed on the comparative effectiveness of buprenorphine
- Optimal treatment regimens for management of withdrawal using buprenorphine need to be established

OPIOID DEPENDENCE

Management of withdrawal from opioid drugs: evidence base

There are high quality systematic reviews of the three main pharmacotherapeutic approaches: methadone at tapered doses (Amato *et al*., 2003); buprenorphine (Gowing *et al*., 2003a) and α_2 adrenergic agonists (Gowing *et al*., 2003b). The main outcomes studied are severity of withdrawal symptoms, completion of withdrawal and adverse effects of the withdrawal regimen. With a variety of pharmacotherapeutic options, patient choice can help to guide a clinical decision. 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 (Amato *et al*., 2003).

Methadone

The systematic review by Amato *et al*. (2003) considered 43 studies, of which 21 (1357 subjects) were included in the analysis. The reviewers found a wide variation in duration, design and treatment objectives of studies, making comparisons difficult.

Eleven studies compared methadone with α_2 adrenergic agonists; two with other opioid agonists; and one with chlordiazepoxide. Six studies concerned different rates of methadone reduction.

Comparisons with α_2 adrenergic agonists showed no substantial clinical difference in retention in treatment [three studies, relative risk (RR) 0.80; 95% CI 0.64–1.00] (Ia); degree of withdrawal discomfort (five studies no difference, four studies worse and one study better for α_2 agonist) (Ia); or detoxification success rates (seven studies, RR 1.14; 95% CI 0.92–1.41) (Ia).

Some studies have focused on different methadone regimens. Severity of withdrawal was lower if patients were well informed (Green and Gossop, 1988), if methadone was stopped abruptly (Lal and Singh, 1976) and if a linear rather than exponential reduction was followed (Strang and Gossop, 1990). Lower rates of treatment dropout were found if patients were well-informed (Green and Gossop, 1988), if the regimen was physician- rather than self-regulated (Fulwiler *et al*., 1979), if the regimen included contingency management (Hall *et al*., 1979) and if counselling was provided (Rawson *et al*., 1983). No difference in treatment dropout was found between exponential and linear reduction regimens (Strang and Gossop, 1990). Other studies showed that methadone produced less severe withdrawal and fewer dropouts than with placebo (San *et al*., 1992) or propoxyphene (Tennant *et al*., 1975). No difference was found between methadone and LAAM on most outcomes (Sorensen *et al*., 1982). Significantly more severe early withdrawal symptoms were found with chlordiazepoxide compared with methadone, but there was no significant difference later in withdrawal severity (Drummond *et al*., 1989).

Reports of adverse effects of treatment were too variable to allow meta-analysis (Amato *et al*., 2003). These included reports of more frequent hypotension with α_2 adrenergic agonists (found in four of six studies); bradycardia with methadone compared to compared with chlordiazepoxide (Drummond *et al*., 1989); and more complaints on abrupt cessation than with a tapering dose (Lal and Singh, 1976).

Slow tapering of methadone has been studied by Senay *et al*. (1977, 1981). In both studies, the slower regimen resulted in less craving and withdrawal discomfort, reflected in improved completion rates (3 month regimen was better than 3 week regimen; 7.5 month regimen was better than 2.5 month regimen).

In summary, methadone is similar to other pharmacological

treatments for withdrawal in terms of retention and overall effectiveness at reducing withdrawal symptoms and subsequent heroin abstinence rates

Buprenorphine

A systematic review of studies comparing buprenorphine with other withdrawal regimens (Gowing *et al*., 2003a) considered 37 studies of which only 6 were included in their final review. The studies were heterogeneous in design and all measured withdrawal severity and completion differently. Since the last revision of this Cochrane review, there has been a large RCT comparing buprenophine with clonidine and benzodiazepines (Lintzeris *et al*., 2002a).

Buprenorphine has potential to ameliorate withdrawal from heroin and possibly methadone, but there is insufficient information to quantify outcomes, and the small number of studies and risk of bias in the studies make it difficult to draw any conclusions regarding appropriate treatment protocols (Gowing *et al*., 2003a) (1a). Buprenorphine appears to be superior than clonidine for management of withdrawal in terms of heroin use during withdrawal, completion of withdrawal, alleviation of withdrawal symptoms and treatment retention after withdrawal (Linzteris *et al*., 2002a) (Ib). The relative efficacy of outpatient compared with inpatient withdrawal is uncertain. More adverse effects were reported for clonidine than for buprenorphine (Ib). Suggested dosing regimens for outpatient and inpatient opioid withdrawal using buprenorphine are given in Lintzeris (2000b) and Lintzeris *et al*. (2003).

α-2 adrenergic agonists

A systematic review of the use of α_2 adrenergic agonists has been carried out by Gowing *et al*. (2003b). Sixty-one studies were considered, and 22 included (1691 subjects). Twelve studies compared α_2 adrenergic agonists with reducing doses of opioid agonists; four compared different α_2 adrenergic agonists (clonidine, lofexidine) with each other; two compared clonidine with placebo; and the remaining studies were heterogeneous. Clonidine was the first α_2 agonist found to be effective in opioid detoxification; however, lofexidine with its improved side-effect profile obtained a license for this indication.

Comparing α_2 adrenergic agonists with reducing doses of methadone: the duration of treatment was longer with methadone (three studies, Ib), but there was no significant difference in completion rates (nine studies, one showed higher completion rates for methadone) (Ia). Withdrawal severity is similar or marginally greater with α_2 adrenergic agonists (Ib). Withdrawal occurs and resolves earlier in treatment with α_2 adrenergic agonists than with methadone (Ib). There are more adverse events for clonidine than for methadone (Ib), although blood pressure reduction is less for lofexidine than for clonidine.

Opioid maintenance

Methadone maintenance treatment: evidence base

Background

Methadone maintenance treatment is the most researched treatment for heroin dependence, and is used in many countries. Despite its widespread use, it is a controversial approach and its philosophy and effectiveness continue to be disputed (Mattick *et al*., 2003a). Opinions and practice are strongly influenced by social context; for an overview of the UK, see Tober and Strang (2003). There are published Cochrane reviews regarding the effectiveness of methadone maintenance therapy versus no opioid replacement therapy (Mattick *et al*., 2003a) and regarding the effectiveness of methadone maintenance at different dosages (Faggiano *et al*., 2003) (1a). Other reviews include those by Farrell *et al*. (1994) and Marsch (1998). Although this is the most thoroughly researched treatment for opioid dependence, there are only a small number of structured trials.

Methadone maintenance programmes vary widely in terms of the nature and quantity of psychosocial support delivered in addition to the medication, and in terms of the degree of supervision of methadone consumption. The research evidence has been based on programmes with supervised consumption of methadone whereas, in practice, many treatment programmes are based on unsupervised 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 maintenance prescribing. Tablet formulations are not recommended in recent UK treatment guidelines because of the risk of injection of crushed tablets (Drug Misuse and Dependence: Guidelines on Clinical Management, DOH, 1999). However, studies of the effectiveness of oral maintenance therapy do not address different formulations, probably because the danger of misuse is low in treatment programmes in which consumption is supervised.

Goals of treatment

The goals of treatment are initially the reduction of illicit drug use and of associated risks and harms. These include reduction or cessation of heroin use and of injecting, which are commonly reported outcomes, but can encompass reduction of a broad range of physical and social harms. Outcome measures in research studies include heroin use (by self-report and urinalysis), retention in treatment, mortality, criminal activity, physical and psychological health, and use of other drugs. Maintenance is in itself a treatment; however, it may also be a useful stage in a long-term care plan with the ultimate goal of abstinence.

Effectiveness

Compared with no opioid replacement, methadone maintenance appears significantly more effective for retaining patients in treatment (three RCTs, RR = 3.05; 95% CI 1.75–5.35) and for the suppression of heroin use (three RCTs, RR = 0.32; 95% CI 0.23–0.44) (Mattick *et al*., 2003a) (1a). In this Cochrane review, methadone maintenance has not been shown to reduce criminal activity (three RCTs, RR = 0.39; 95% CI 0.12–1.25) (Mattick *et al*., 2003a) (1a). Three studies have provided evidence regarding prevention of deaths. These show a trend favouring methadone treatment over no pharmacological treatment (Mattick *et al*., 2003a) (1a). Information on injecting behaviour and on prevention of HIV seroconversion is available from large-scale observational studies (Cochrane reviews in progress, Ward, 1992). The impact of methadone treatment in changing sexual behaviour appears to be limited to reducing sex for drugs or money (Gowing *et al*., 2004)

Recommendations – methadone maintenance treatment for opioid dependence

- Methadone maintenance treatment is an appropriate treatment option for opioid-dependent patients who are unwilling to undergo withdrawal or have had repeated unsuccessful attempts at withdrawal. Methadone maintenance treatment should be offered to such patients. It is effective in reducing heroin use, injecting, and sharing injecting equipment (A)
  - Methadone maintenance treatment is more effective at doses in the range 60 mg to 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)
  - Methadone maintenance treatment should be provided in conjunction with psychosocial interventions such as regular counselling (B)

Key uncertainties

- How important is supervised consumption in terms of clinical outcomes?
- In which settings can methadone maintenance treatment be provided effectively?

(1a). Overall, although the number of well-conducted controlled trials is small, the findings of these trials are supported by observational studies (included in reviews by Farrell *et al*., 1994 and Marsch *et al*., 1998).

Dosing

Methadone doses ranging from 60 mg to 100 mg per day are more effective than lower dosages in retaining patients (meta-analysis of 10 studies, plus examination of observational studies) and in reducing use of heroin (three RCTs) and cocaine (three studies) during treatment (Faggiano *et al*., 2003) (1a).

Additional therapies

The most desirable mode of delivery of methadone is unknown. The majority of research studies are based on supervised consumption of methadone, and the advantages of supervision over unsupervised dosing are therefore unknown. Many methadone maintenance programmes involve substantial additional therapies, ranging from regular counselling to integrated programmes including family therapy, psychiatric care and help with employment. One trial by McLellan *et al*. (1993) compared methadone maintenance treatment alone with two levels of additional psychosocial support: one provided regular counselling and the other provided regular counselling plus the other elements of an integrated programme, described above (1b). The most intensive treatment was the most effective, and the intermediate programme was the most cost-effective. Methadone maintenance treatment appears to be effective in primary care (Gossop *et al*., 1999) (III). More research into the importance of the treatment setting and mode of delivery is needed. In particular, there has been an emphasis in UK policy on development of treatment in the primary care setting, and this needs further evaluation.

Buprenorphine maintenance treatment: evidence base

Goals of treatment

The goals of treatment are the same as those of methadone maintenance treatment; the reduction of illicit drug use and of associated risks and harms.

Effectiveness

The effectiveness of buprenorphine maintenance treatment has been examined in a Cochrane review (Mattick *et al*., 2003b).

In comparison with placebo, there is evidence that buprenorphine is superior in terms of retention in treatment at low or moderate doses (four trials) (Ia) and at high dose (one trial) (Ib). It is superior to placebo in terms of reduction in opioid positive urines at moderate doses (two trials) (Ia) and high doses (one trial) (Ib) but not at low doses (two trials) (Ia). Three trials have examined reductions in use of benzodiazepines and/or cocaine: one showing

Recommendations – buprenorphine maintenance for opioid dependence

- Buprenorphine is an effective intervention for use in the maintenance treatment of opioid dependent patients who are unwilling to undergo withdrawal or who have had repeated unsuccessful attempts at withdrawal. It can be offered as an alternative to methadone maintenance treatment, though may not be as effective as high dose methadone maintenance treatment (A)
- Higher daily doses of buprenorphine (at least 8 mg and probably as high as 16 mg) are more effective in maintenance treatment (A)

Key uncertainties

- The comparative effectiveness of high dose (16–32 mg) buprenorphine maintenance treatment compared with high-dose methadone has not been examined
- Further comparisons of buprenorphine and methadone in terms of reduction in mortality and relative effects on immune function need to be determined

Recommendations – naltrexone for treatment of opioid dependence

- The evidence base to support a general recommendation for the use of naltrexone to prevent relapse to opioid dependence is currently inadequate. The potential benefits of treatment can be weighed up on an individual basis (S)
- Naltrexone may be a useful adjuvant in therapy, for highly motivated patients and for those who fear severe consequences if they do not stop opioid use (e.g. health care professionals) (C)
- Services aimed at patients involved with the criminal justice system should consider offering naltrexone as a treatment option (A)
- Naltrexone implants and depot injections are untested in Phase III randomized controlled trials and cannot be recommended at this time

Key uncertainties

- How naltrexone can be used most effectively?

that low dose buprenorphine does not reduce positive tests for cocaine or benzodiazepines (Ib); one showing that buprenorphine is inferior to placebo in relation to reducing benzodiazepine use (Ib) and one showing that buprenorphine is superior to placebo in relation to reducing cocaine use.

In comparison to methadone maintenance treatment, buprenorphine produces comparable outcomes to lower dose (e.g. 30–60 mg) methadone. Higher dose methadone maintenance treatment (> 60 mg) appears more effective than buprenorphine, but adequate comparisons of higher dose (16–32 mg) buprenorphine with high dose methadone maintenance treatment (60–120 mg) are lacking. There is category Ia evidence that 8–16 mg is superior to lower doses; category Ib evidence that 16 mg is superior to 8 mg and category IV evidence that daily doses of 12–24 mg are preferable for maintenance treatment).

There is some (category III) evidence to suggest that there is reduced mortality in buprenorphine maintenance treatment compared with methadone maintenance treatment (Auriacombe *et al*., 2001).

Naltrexone maintenance treatment: evidence base

Goal of treatment

The goal of naltrexone treatment is maintenance of abstinence from opioid drugs in formerly dependent patients following detoxification.

Products

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, after the mid-1990s, various practitioners have developed their own naltrexone implants although these have not been registered pharmaceutical products. There has been more recent development of injectable i.m. depot (sustained release) products, for which phase II and III trials are under way. This product may have more appeal because there is no need for a surgical implantation procedure.

Effectiveness

A systematic review published by the Cochrane Library (Kirchmayer *et al*., 2003) included 11 studies, of which nine were randomized. There was evidence of reduced reincarceration of patients given naltrexone plus behaviour therapy compared with those given behaviour therapy alone (1a). There were no other significant results of note. The reviewers described the significant heterogeneity of study populations, which made comparison of studies very difficult. Several studies that did not meet criteria for the systematic review were noted to show trends favouring naltrexone treatment. Naltrexone is probably a useful adjunct to treatment in highly motivated individuals (Ling, 1978).

There are no controlled trials of either naltrexone implants or naltrexone depot preparations. There is a descriptive study of outcome of 101 patients given naltrexone implants (Foster *et al*., 2003) and a pilot study of 12 patients given depot naltrexone preparations at doses of 192 mg and 384 mg (Comer *et al*., 2002) (III). Further studies of the depot preparation are awaited.

Injectable opioid maintenance treatment: evidence base

Background

The prescribing of injectable opioids has a complex history. Injectable opioids were provided in the early UK clinics for treatment of heroin dependence, but this practice subsequently declined, with oral methadone becoming the dominant drug for maintenance treatment. Injectable prescribing remains of interest as a possible approach for treatment of individuals who are resistant to methadone treatment, and for those who are very hard to attract and retain in treatment. It has also attracted political interest as a possible strategy for crime reduction. Two injectable products have been investigated: diamorphine (heroin) and methadone.

Despite the recent high profile discussion of potential expansion of prescribing of injectable opioid drugs as part of the UK, there are very few informative studies. The place of injectable drugs in the treatment of opioid dependence needs to be considered in relation to the stronger evidence base for oral methadone maintenance treatment. In this context, injectable drugs are considered as a possible second-line treatment where well-supported oral substitution treatment (usually methadone maintenance) is unsuccessful. The context in which the injectable drugs have been provided has varied from provision of unsupervised doses to take home, to fully supervised clinics from which no take-home supplies are issued. The context is important both in assessing clinical out-

Recommendations – injectable opioid maintenance treatment

- The current evidence base supporting the use of injectable opioid drugs for maintenance treatment is inadequate as a basis for recommendations though it could be considered for some patients in whom methadone maintenance is failing

Key uncertainties

- Injectable opioid maintenance treatment is of interest as a strategy for recruitment and retention in treatment of those who have failed to respond to optimal oral methadone maintenance treatment, but its effectiveness has not been established
- As with oral methadone maintenance, the degree of supervision of use of medication may be an important factor affecting outcome and needs further study
- The use of injectable opioid drugs in conjunction with oral methadone treatment (as in the study by van den Brink *et al*., 2003) is worthy of further study
- More research is needed into the use of smoking heroin as a substitute in non-injecting patients

comes and in considering the potential for abuse and diversion of prescribed medication.

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 is considered mainly for those who have failed to benefit from optimal oral treatment, or who have not been attracted or retained in treatment by oral methadone maintenance programmes.

Products

Two products have been studied:

- Diamorphine (heroin, or 'dry amps')
- Methadone ('wet amps')

Effectiveness: injectable diamorphine

Diamorphine (heroin) treatment has been evaluated in a systematic review for which four studies (577 patients) met criteria for inclusion (Ferri *et al*., 2004) (1a). Only three concerned injectable diamorphine (the fourth concerned inhaled heroin). One trial (Hartnoll *et al*., 1980) showed heroin treatment to be superior to methadone treatment in terms of retention in treatment at 12 months (1b). However, other benefits were unclear, and the value of treatment retention alone is questionable. The other studies, based in Switzerland (Perneger *et al*., 1998) and the Netherlands (Van den Brink *et al*., 2003) took place in the context of supervised treatment facilities from which no take-away injectable medication was supplied (1b). In the Swiss trial, injectable heroin treatment was compared with oral methadone maintenance treatment. In the Dutch trial, patients were given oral methadone alone, or a combination of injectable heroin and oral methadone. From these studies, given the differences in context, it is difficult to draw any generalizable conclusions about the effectiveness of heroin maintenance, although both found that heroin treatment improved outcomes on several measures (Ferri *et al*., 2004).

Effectiveness: injectable methadone

There has been one trial comparing injectable methadone with oral methadone maintenance treatment (Strang *et al*., 2000) (1b) in which no significant differences in treatment outcomes were identified.

Treatment models involving coercion

Background

Programs involving coercion are currently of particular interest in the UK, where Drug Treatment and Testing Orders (DTTO) have become an established part of statutory treatment provision for drug users who have committed crimes. Such orders can encompass a range of pharmacological treatment approaches, and models vary nationally, but all have substantial psychosocial elements. Some information on the evidence for DTTO programmes and similar approaches is included to guide practitioners using pharmacological treatments in this context.

Goals of treatment

The prevention of reoffending is a prominent goal in such programmes, alongside the more usual treatment goals concerning personal and public health.

Recommendations – coercion in treatment of substance misuse/dependence

- The limited evidence is inadequate to support any recommendations

Key uncertainties

- The role of coercion and the best model of delivering it

Effectiveness: treatment programmes involving coercion

Treatment programmes involving coercion generally encompass several elements, and it can be difficult to identify the important elements in an apparently effective total programme. In such programmes, different weight may be placed on crime reduction as an important outcome compared with other outcomes. Coercion may be present in treatment regimens in settings other than the criminal justice system. For example, there is category IV evidence supporting supervised treatment for doctors with substance use disorders (Brooke *et al*., 1993), and category Ib evidence showing improvements in treatment programmes for employees (Walsh *et al*., 1991). One study assessed the patient's perception of the level of coercion involved in treatment (Hser *et al*., 1993) and showed no relationship with treatment outcome (III).

In relation to the criminal justice system, the majority of studies have been from the USA. These include a number of studies amounting to category IIa evidence (Desland and Batey, 1992; Desmond and Maddux, 1996; Fugelstad *et al*., 1998; Vito and Tewksbury, 1998; Heale and Lang, 2001; Bavon, 2001; Wild *et al*., 2002), but selection of comparison groups have been poor, and the generalizability of the studies beyond the USA is questionable. These studies show no consistent benefit from coercion on any outcomes (in addition to no evidence of harm).

Effectiveness: drug treatment and testing orders (UK)

Evaluation of the pilot areas for the UK DTTO programmes (Turnbull *et al*., 2000) showed a reduction in reported spending on drugs, but reduction in drug use from urinalysis was not seen (III).

STIMULANT DRUGS

Goals of treatment

Research on pharmacotherapy for stimulant drug use focuses mainly on the treatment of dependent users of the various forms of cocaine or amfetamine. Treatment goals are usually the management of withdrawal and the maintenance of abstinence, although the value of substitute prescribing with harm reduction goals is also considered. Van den Brink and van Ree (2003) recently reviewed pharmacological treatments. Although the evidence supporting pharmacological treatment is weak, and psychosocial treatments such as cognitive behaviour therapy and contingency management are recommended as the main treatment approaches, there is also a lack of high quality reviews of the effectiveness of these psychosocial approaches.

Cocaine dependence

Dopamine agonists

The role of dopamine agonists (amantadine, bromocriptine and pergolide) has been investigated in 17 randomized studies with 1224 participants, with urine tests for cocaine use and retention in treatment as the main outcomes of interest. A meta-analysis of these studies (Soares *et al*., 2003) found no significant difference between interventions. The evidence does not support the use of dopamine agonists (Ia).

Antidepressants

A range of antidepressant drugs has been investigated, including desipramine (12 trials, dose range 150–300 mg), fluoxetine (two trials, dose range 20–60 mg), ritanserin (one trial, dose 10 mg), gepirona (one trial, 16 mg), buproprion (one trial, 300 mg) and imipramine (one trial, 150–300 mg). Eighteen randomized studies with 1177 participants have been the subject of meta-analysis and systematic review (Lima, 2003b). Studies of patients who were also opioid dependent were examined separately, but yielded similar results.

Desipramine performed no better than placebo in terms of retention in treatment, although there was a non-significant trend favouring desipramine over placebo in terms of cocaine-negative urine specimens. One trial favoured imipramine over placebo in terms of clinical response by self-report, and one trial suggested patients on fluoxetine were less likely to drop out. In summary, there is no current evidence to support the use of antidepressants in the treatment of cocaine dependence (Ia).

Carbamazepine

Five studies with 455 people randomized have been subject to meta-analysis (Lima *et al*., 2003a). No differences between carbamazepine and placebo were found in terms of urine testing for cocaine use. The evidence does not support the use of carbamazepine in the treatment of cocaine dependence.

Dexamfetamine

One pilot randomized double-blind, placebo-controlled trial has been reported (Shearer *et al*., 2003) (1b). The study participants were 33 cocaine-dependent injecting drug users, 16 randomized to 60 mg dexamfetamine and 14 to placebo for 14 weeks. Preliminary findings in terms of treatment retention, urinalysis results and self-reports were not statistically significant but favoured the active treatment. A definitive evaluation of the utility of dexamfetamine is feasible and warranted.

Disulfiram

Disulfiram reduced cocaine use in a placebo-controlled trial in which disulfiram treatment was supported by either interpersonal psychotherapy (IPT) or CBT (Carroll *et al*., 2004a) (1b). In this trial, CBT was superior to IPT. Other trials of disulfiram have been based on patients with concurrent alcohol, or opioid dependence (maintained on methadone or buprenorphine), but the results obtained are of interest (Carroll *et al*., 1998; Carroll *et al*., 2000; George *et al*., 2000a; Petrakis *et al*., 2000) (1b). The effect on cocaine use appears to be independent of their alcohol use.

Other drug trials

Other drug trials have investigated mazindol (two trials), lithium (one trial), naltrexone (one trial), phenytoin (one trial) and risperidone (one trial). The evidence does not support the use of these drugs in the routine treatment of cocaine dependence (Lima *et al*., 2002) (1a).

More recently, olanzapine has been shown not to reduce cocaine use, and in fact may even make it worse (Kampan *et al*., 2003) (1b).

Recommendations – stimulant drugs

- There is a lack of evidence supporting pharmacological treatment for amphetamine and cocaine abuse and dependence. Psychosocial interventions such as cognitive behaviour therapy and contingency management the mainstay of treatment (S)
- We do not recommend the use of dopamine agonists, antidepressants or carbamazepine, because these treatments are unsupported by the evidence (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 dexamfetamine 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?
- Definitive studies are warranted about the role of medication in stimulant misuse

Amfetamine dependence

Amineptine

Two randomized, double-blind, placebo-controlled trials of the use of amineptine favoured amineptine in terms of improved discontinuation rate, but no direct effect on withdrawal symptoms or craving. Amineptine has since been withdrawn because of abuse potential (Srisurapanont *et al*., 2003) (1a).

Fluoxetine, amlodipine, imipramine and desipramine

Four randomized double-blind trials have investigated the above drugs. Fluoxetine may decrease craving in the short term, and imipramine may increase adherence to treatment in the medium-term. No reduction in amfetamine use or other benefits were identified (Srisurapanont *et al*., 2003b) (1a).

Dexamfetamine

Substitute prescribing of dexamfetamine for treatment of amfetamine dependence has been reported in one pilot randomized controlled trial (Shearer *et al*., 2001) (1b). In this study, 41 long-term dependent amfetamine users were randomized to dexamfetamine (up to 60 mg) or weekly counselling only. Reductions in use were seen in both groups with no discernable differences, but the study had low power. Six descriptive studies have been reported (Fleming and Roberts, 1994; Pates *et al*., 1996; McBride *et al*., 1997; Klee and Morris, 1997; Merrill and Tetlow, 1998; White, 2000), all of which are small (III). Five are restrospective and rely on self-reported outcomes. However, all suggest benefits in terms of reduction in amfetamine use and in injecting.

Psychosocial interventions for stimulant misuse

Psychosocial interventions are the mainstay of treatment strategies for patients with stimulant misuse and dependence. These guidelines have not undertaken a comprehensive review of studies performed and no meta-analyses are available.

Behavioural therapies, in particular contingency management approaches, have been demonstrated to be effective in cocaine dependence, including in those who are methadone maintained opioid addicts. Higgins *et al*. (2003) reported on their latest findings using a contingency management, involving vouchers exchangeable for retail items contingent on cocaine abstinence, alone or with an intensive behaviour therapy intervention known as community reinforcement approach (CRA) (1b). Cocaine addicts receiving vouchers and CRA did better, with regard to cocaine use, than CRA alone during the study, although longer-lasting improvements in decreased depressive symptomatology, fewer hospitalizations and legal problems were seen 6-month follow-up. Roozen *et al*. (2004) systematically reviewed the effectiveness of CRA in cocaine addiction as well as alcohol and opioid addiction. They concluded that there was strong evidence showing that CRA with incentives was effective in cocaine addiction, but only limited for CRA in an opioid detoxification or methadone maintenance programme.

Cognitive therapy has also been shown to be effective (Carroll *et al*., 1994a,b) for cocaine misusers and for those in methadone maintenance programmes (Condelli *et al*., 1991) (1b). More recently, contingency management has been compared with cognitive therapy in cocaine dependent methadone maintained opioid addicts (Rawson *et al*., 2002). Both treatment strategies were effective, with contingency management providing better effects during treatment, although cognitive therapy was comparable at 6 months and 1 year. The combination was not more efficacious (1b).

In 1999, the results from the National Institute on Drug Abuse Collaborative Cocaine Treatment Study were published (Crits-Christoph *et al*., 1999) (1b). This US study aimed to determine the most effective psychosocial therapy for cocaine dependence and compared, individual drug counselling therapy plus group drug counselling (GDC), cognitive therapy plus GDC, supportive-expressive plus GDC, or GDC alone over 6 months. Individual drug counselling plus GDC, which incorporated 12-step philosophy, was the most effective in reducing cocaine use. The authors proposed that the success of the individual therapy might be the result of focussing on stopping current drug use.

Recommendations – alcohol and pregnancy

- Women should be advised not to drink alcohol or at maximum, one drink/day (S)
- Adequate screening should be routine (S)
- Psychosocial interventions should be offered and be the mainstay of treatment (B)
- Patients with symptomatic withdrawal should be offered medical cover for their detoxification, ideally as an inpatient (D)
- Medication to sustain abstinence should be avoided (D)

Key uncertainties

- Risks of alcohol withdrawal versus the benzodiazepine prescribed versus continued alcohol consumption to the fetus and whether any trimester carries more risk than at other times?
- Risk of medication such as acamprosate, naltrexone or disulfiram in pregnancy?

The guidelines will now deal with particular populations of patients.

PREGNANCY

The general principles of best practice underwrite additional special requirements of pregnancy that involve not only the woman, but also the fetus. Most research considers outcomes in neonate, but the treatment of women is often not specified. These guidelines address primarily management of the pregnant mother. Clearly, there may be ethical considerations about performing rigorous controlled clinical trials (e.g. RCTs) in this population. However, there is a wealth of clinical experience to guide appropriate treatment strategies. Again, the focus is on pharmacotherapy and not the appropriate delivery of care, for which the reader is directed to Jansson *et al*. (1996) and Haller *et al*. (1997).

Assessment and antenatal care

Pregnant substance misusers may be late entering antenatal care. Screening and recognition of substance misuse, including alcohol, is not uniform and often goes unrecognized. Treating a substance-misusing pregnant woman raises the issue of whether this should be mandatory, with no research to inform this difficult topic. Prenatal care and substance misuse treatment should ideally be delivered on the same site/clinic with a need for integrated programmes.

Alcohol

The majority of women drink whilst pregnant, even though the risk of alcohol-related problems modifies many people's consumption but not all. Drinking seven or more drinks per week, or more than five on 1 day, has been linked to an increased risk of an alcohol-affected infant (Stratton *et al*., 1996). Rates for fetal alcohol syndrome (FAS) range from 0.05% to 0.3% of births and, for alcohol-related birth defects, by as much as 0.5% (Stratton *et al*., 1996). For a description and discussion of FAS, the reader is referred to Sokol *et al*. (2003).

The following are from the guidelines from the Royal College of Obstetrics and Gynaecology in the UK (Taylor, 1999). 'There is no conclusive evidence of adverse effects in either growth or IQ at levels of consumption below 120 g ms (15 units) per week. Nonetheless it is recommended that women should be careful about alcohol consumption in pregnancy and limit this to no more than one standard drink per day'. Nevertheless, women are advised not to drink alcohol during pregnancy.

Hankin *et al*. (2000) reviewed the literature about the identification and treatment of pregnant alcohol abusing women. In addition, many of these women have poor social conditions and nutritional status, adding to the risk to their and the fetus's health. Lastly, many continue to smoke, and a proportion will also be abusing illicit drugs. The review identified some of the following issues for consideration.

• *Psychosocial interventions*

Education has impact and an important role. Motivational interviewing showed positive results for heavy drinkers, as did CBT and brief interventions (Peterson and Lowe, 1992; Chang *et al*., 1999; Handmaker *et al*., 1999; Hankin *et al*., 2000) (1b).

Clearly, there are many gaps in the evidence base to suggest one treatment strategy over another. It appears that identification is the first crucial step that may not occur but, once a problem is identified, similar strategies as described above for alcohol misuse and dependence are likely to be effective.

• *Detoxification*

Regarding alcohol detoxification, no research data is available. It does not appear that pregnancy increases the occurrence of severe withdrawal symptoms although, clearly, if the woman undergoes alcohol withdrawal, so does the fetus (Thomas and Riley, 1998). This could lead to death in both mother and/or fetus. An intoxicated mother will deliver a baby whose onset of alcohol withdrawal may be delayed due to slow metabolism of alcohol.

It is the opinion of this consensus group that pharmacological cover with benzodiazepines should be given in the presence of alcohol withdrawal symptoms (I.V). In addition, an inpatient admission is advisable (I.V). However, the amount of benzodiazepines given should be kept to a minimum to reduce potential teratogenicity. However, pharmacological options are not recommended in US guidelines due to the absence of adequate safety and efficacy data (Mayo-Smith, 1997).

Recommendations – nicotine and pregnancy

- Psychosocial interventions should be offered since they are effective (A)
- Risk : benefit ratio should be considered for offering nicotine replacement therapy (C)
- Bupropion should be avoided

• Maintaining abstinence

Similarly, we are unaware of any data or information relating to the use of pharmacotherapy to maintain abstinence and, accordingly, these drugs are not generally recommended in pregnancy. Psychosocial interventions are therefore recommended (see above).

Nicotine

A Cochrane review of smoking cessation interventions in pregnancy reported that these appeared to reduce smoking, low birthweight and pre-term births, but no effect was detected for very low birth weight or perinatal mortality (Lumley *et al*., 1999) (1a).

• NRT and bupropion

Although a general principle is to avoid pharmacotherapy and nicotine is known to have adverse effects, if psychosocial interventions fail, the overall risk : benefit ratio of using NRT should be considered. However, it is not clear if NRT is effective in pregnancy, with one RCT showing no difference with controls and another finding that effectiveness of NRT beyond the first trimester in pregnant women who smoke heavily is questionable, but NRT may be helpful in a minority of women (Wisborg *et al*., 2000; Kapur *et al*., 2001) (1b).

There is no published information available on the safety of bupropion, and it is best avoided.

Opioids: substitution and maintenance

The desired goals of maintenance during pregnancy are to prevent withdrawal syndrome and toxic opioid levels with their associated risks to the fetus, in addition to the other benefits listed above, such as reduced infection. Furthermore, provision of a daily dose of a substitute can facilitate critical antenatal care, rather than insisting on abstinence and risking loss of contact. There have been several studies of the outcome of maternal opioid dependence on the outcome of the pregnancy. Management of the pregnant addict is included in the Drug Misuse and Dependence Guidelines on Clinical Management (Department of Health, 1999) and has been recently reviewed (Johnson *et al*., 2004).

• Methadone

Until recently, the only recommended maintenance therapy was methadone. Methadone maintenance treatment (MMT) together with comprehensive antenatal care can result in a significant improvement in maternal and neonatal outcomes such as longer pregnancy and fewer complications (Archie, 1998; Kandall *et al*., 1999) (IIb). Wang (1999) reviewed methadone in pregnancy and found that there was no evidence showing that methadone has adverse effects; indeed, birth weights were higher with methadone than heroin even though 90% on MMT continue other drug use. Neonatal abstinence syndrome (NAS) may not be insignificant.

There has been extensive debate about what dose to prescribe, with some studies showing higher methadone levels associated with positive effects (such as higher birth weight, more antenatal care) and negative effects (such as higher NAS) (Archie, 1998). All pregnant women need close monitoring of their dose. Generally, in opioid addicts already maintained on methadone, the level can remain the same, but patients may need to increase in the third trimester (Drozdick *et al*., 2002) (III). Split dosing can be used in the third trimester.

• Buprenorphine

Johnson *et al*. (2003) reviewed the use of buprenorphine in pregnancy including 14 published case reports, five prospective studies and two open-label controlled studies resulting in the birth of 309 infants (IIb). A range of buprenorphine doses have been used (0.4–24 mg), there were low rates of prematurity, and NAS was similar or less than that following methadone exposure. Due to its partial agonist action, buprenorphine may interfere with opioid analgesia in labour.

Recommendations – opioids and pregnancy

- Methadone maintenance results in improved maternal and fetal health and should be offered to opioid dependent pregnant women (B)
- Less data are available for buprenorphine maintenance but it appears similar benefits are seen for mother and fetus as for methadone (B)
- Detoxification should be avoided in the first trimester, is preferred in the second and used with caution in third.
- Methadone is the best known substitute pharmacotherapy in pregnancy and will usually be the first choice; however, recent experience with buprenorphine is encouraging. Clinicians may therefore consider continuing buprenorphine in patients doing well on established treatment. Potential problems with opioid analgesia during labour must be anticipated

Key uncertainties

- Does methadone or buprenorphine have any advantages over the other in terms of maternal or fetal/neonatal outcomes?

Recommendations – stimulants and pregnancy

- Limited evidence to make any recommendations except 'stop'
- Substitution therapy is not recommended despite no studies (S)

Key uncertainties

- What to offer?

Opioids: detoxification

Detoxification or withdrawal has been thought to be undesirable in the first trimester due to risk of miscarriage and in the third trimester due to the risk of fetal stress and premature labour. If it has to be undertaken, the second trimester is preferred. A reduction of 1 mg of methadone per day has been suggested (Archie, 1998) (I.V) or 2.5–5 mg weekly, 2-weekly or whatever can be tolerated (DOH Guidance for the Clinical Management of Drug Misusers Guidelines, 1999) (I.V).

A retrospective review of 101 opioid addicts maintained on methadone who underwent a 21-day inpatient detoxification in second or third trimester reported no increased risk to fetus, with no miscarriages and only one pre-term delivery (Luty *et al*., 2003). In the first trimester, one miscarriage occurred out of the five patients withdrawn which, although not statistically significant, does support the view that detoxification here is associated with an increased risk of miscarriage.

Stimulants

Cocaine is most commonly written about and the reader is directed to meta-analyses of the effects and outcomes of cocaine use in pregnancy (Lutiger *et al*., 1991; Addis *et al*., 2001). Notably, some of the effects attributed to cocaine may in fact be due to other confounders such as alcohol misuse.

Zlotnick *et al*. (1996) reported on their 5-month outpatient programme for pregnant women (III). Those who received family therapy were four times more likely to maintain abstinence. Non-abstinent women generally had a 'using' partner. This is an important issue, relevant to all substance misuse and often seen in clinical practice. The partner should also be offered treatment. Substitute prescribing is not recommended.

COMORBIDITY WITH PSYCHIATRIC DISORDERS

Background and general comments

Symptoms of psychiatric disorders such as depression, anxiety and psychosis are common in patients misusing drugs and/or alcohol. In addition, these psychiatric disorders increase the risk of substance misuse. Patients may also be physically unwell. Such patients are often the most challenging to engage and treat and their prognosis is frequently poor. There are currently few placebo-controlled trials resulting in little robust evidence to guide management of such comorbidity. In addition, there is little to guide treatment in the adolescent or old age populations.

These guidelines concentrate on the psychopharmacology of treating such comorbid disorders. As previously discussed, all studies include a psychosocial intervention. For more information models of delivering care to this comorbid population, the reader is referred to Crawford (2001), Banerjee *et al*. (2001) and the Health Advisory Service (2001).

Although it is common to refer to a patient's psychiatric disorder or substance misuse disorder as primary or secondary, this may have limited use clinically. The key issue is to recognize that substance misuse may be contributing to their psychiatric problems. Although removing or minimizing the contribution of substance misuse is an important aim, it is often difficult to achieve. In addition, attributing a psychiatric disorder purely to substance misuse 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. As can be seen from some of the evidence below, improvements in a psychiatric disorder or substance misuse does not necessarily result in progress in the other.

In reviewing the literature, there were a wide variety of types of studies and outcomes reported. Few studies are RCTs or even trials, with many being reports of case series. The majority of studies do not use 'intention to treat' analysis. Most have small samples (e.g. n = 16–100) and short duration (days to weeks). In some studies, the primary outcome measure often related to the psychiatric disorder, and secondary outcomes are substance related. It was often not clear what the goal was regarding their substance use (e.g. reduction or abstinence), nor the extent and nature of psychosocial interventions. Several studies reported reduction in psychiatric symptoms (e.g. depression) but the patients did not necessarily have an ICD/DSM diagnosis of depression. Many studies looking at treating comorbidity in illicit drug misusers not only have the caveats described above, but also indicate that subjects were abusing a range of substances. However, this does reflect real-life clinical situations. Some studies only reported on the 'safety' of medication in comorbid patients whereas others reported on their efficacy in abstinence.

Assessment

It is important to distinguish between substance-induced and substance-related psychiatric disorders. It is advisable to allow 3–4 weeks of abstinence before making diagnosis of a psychiatric disorder, but this is often impractical. A complete substance history should be obtained, with urinalysis and blood tests (e.g. to detect liver dysfunction secondary to alcohol or hepatitis) if possible.

A comprehensive history including age of onset of disorders, chronology, persistence of psychiatric illness during abstinence, and family history should help determine whether an additional diagnosis to their substance misuse is present. In addition, the safety of prescribing a particular medication must be determined not only with regard to drug–drug interactions, but also with respect to how the medication is delivered or monitored, considering particularly deliberate self-harm behaviour.

Depression

Alcohol

After assessment, the first treatment required may be medically-assisted alcohol withdrawal to help determine the contribution of alcohol misuse to their psychiatric presentation (see the section above on alcohol).

A meta-analysis of placebo-controlled trials has recently been performed of the treatment of depression in patients with alcohol or drug dependence (Nunes and Levin, 2004) (1a). They concluded that antidepressant medication exerts a modest beneficial effect for depressive symptoms in such patients although concurrent therapy for their dependence is needed. Even when the antidepressant was effective in treating depression, the associated improvement in substance use was minimal. Waiting at least 1 week to diagnose depression improved the response rate, presumably by screening out those with depressive symptoms solely related to their alcohol use. Therefore, the prescribing of antidepressants to patients with continuing alcohol or drug use requires careful consideration and regular review for effectiveness, compliance and adverse effects.

• *Tricyclic antidepressants (TCAs)*

There have been a number of controlled trials looking at the effect of TCAs in alcohol dependence and depression reviewed by Ciraulo and Jaffe (1981) and Liskow and Goodwin (1987) (1b). They concluded that TCAs showed no benefit, although the majority of studies had methodological problems.

Imipramine has been investigated more recently. Nunes *et al.* (1993), conducted an open-label trial of imipramine followed by a double-blind, placebo-controlled study period for the responders only (1b). At the end of this 6-month period, the lower number of relapses in patients who received imipramine compared with those receiving placebo just failed to achieve significance. Relapses were associated with return of depression. It was suggested that a subgroup of alcohol dependent patients would benefit from receiving antidepressant medication. McGrath *et al.* (1996) conducted an RCT of imipramine in drinking alcohol-dependent patients with a current depressive disorder aiming for abstinence (1b). Imipramine improved depression but not drinking outcomes. However, there was a positive relationship seen between improved mood and drinking behaviour, which was more marked in the imipramine group.

An RCT found that nortriptyline resulted in no improvement in anxiety or depression or drinking outcomes compared with placebo (Powell *et al.*, 1995) (1b). Mason *et al.* (1996) reported that an RCT of desipramine in abstinent alcohol dependence with and without depression showed that desipramine reduced the severity of depression and risk of relapse to heavy drinking in depressed patients (1b). In non-depressed patients, desipramine resulted in fewer relapses, although less than in the depressed group.

• *Specific serotonin reuptake inhibitors (SSRIs)*

In studies of SSRIs in alcohol misuse comorbid with depression, the doses of SSRIs used are often greater than that routinely prescribed (e.g. 40–60 mg fluoxetine, 200 mg sertraline). All of the SSRIs, except escitalopram, have been studied.

In alcohol dependence, it should be noted that patients were started on their SSRI when abstinent, they were motivated and aimed to sustain abstinence. Use of SSRIs to promote abstinence in the non-depressed patient is covered in the section above on alcohol.

As described above, whereas depressive symptomatology may improve, drinking behaviour does not necessarily do so. Fluoxetine did not affect drinking behaviour, but depressive scores improved with fluoxetine for those with current depression (Kranzler *et al.* 1995; Kabel and Petty 1996) (1b). In one RCT, sertraline has been shown to be effective in reducing depressive symptomatology in

Recommendations – depression with alcohol misuse or dependence

- Overall, antidepressants may improve mood but not necessarily alcohol behaviour in depressed alcohol dependent patients. Selective serotonin reuptake inhibitors (SSRIs) appear effective in improving drinking behaviour and depression only in severely depressed patients. We therefore recommend that antidepressant prescribing is suitable only for clearly depressed patients and should be undertaken with caution (B)
- Tricyclic antidepressants (TCAs) are not recommended due to potentially serious interactions between TCAs and alcohol, including cardiotoxicity and death in overdose (S)

Key uncertainties – alcohol and depression

- What doses of SSRIs are required and for how long?
- Evaluation of other antidepressants such as mirtazepine or venlafaxine
- Evaluation of combinations of antidepressants with naltrexone or acamprosate.
- The relationship between different types of psychosocial treatment (e.g. MET; CBT; TSF) to address their alcohol use and depression with pharmacotherapy
- What is the best treatment for resistant depression in this comorbid population?

Recommendations – depression with opioid dependence

- There are limited studies from which to derive recommendations but from studies with tricyclic antidepressants (TCAs), antidepressants may improve mood but not necessarily drug related behaviour in depressed opioid addicts. They should be therefore be used with caution and with regular review (B)
- TCAs are not recommended due to potentially serious interactions including cardiotoxicity and death in overdose (S)

Key uncertainties

- Efficacy of selective serotonin reuptake inhibitors and newer antidepressants?
- The effect of opioid substitution treatment, buprenorphine or methadone, on mood?
- Value of psychosocial interventions?

patients with alcoholism, still depressed 2 weeks after detoxification (Roy, 1998) (1b). However, drinking outcomes were not described. Two RCTs of nefazodone in depressed and non-depressed alcohol dependent patients, showed that nefazodone did not improve drinking outcomes but, where patients were depressed, an improvement in depressive symptomatology was seen (Kranzler *et al*., 2000; Roy-Byrne *et al*., 2000) (1b).

However, one RCT has reported that fluoxetine improved drinking outcomes and depressive symptomatology compared with placebo in depressed, suicidal alcohol dependent patients over 12 weeks (Cornelius *et al*., 1997) (1b). The groups were initially inpatients and appear to be more severely alcohol-dependent and depressed than in other studies. At follow-up, 1 year later, those who received fluoxetine and were mostly still taking fluoxetine continued to do better (Cornelius *et al*., 2000).

An RCT of sertraline in alcohol dependence was reanalysed to address whether a lifetime diagnosis of depression predicted a better response to an SSRI (Pettinati *et al*., 2001) (1b). In patients with such a lifetime diagnosis, sertraline did not improve drinking outcomes or their depressive symptoms, even in those concurrently depressed. However, in those alcohol-dependent patients without a history of depression, improvement was evident. Gerra *et al*. (1992) suggested that fluoxetine may only be of benefit in non-depressed, family history positive alcohol dependent patients.

Opioids and depression

There have been several RCTs in depression and opioid addiction although, in many of the studies, cocaine misuse/addiction was also present. In their recent meta-analysis of the treatment of depression in alcohol or drug dependence, opioid-dependent patients were included; for general conclusions, see the section above on alcohol and depression (Nunes and Levin, 2004) (1b).

• *TCAs*

Nunes and Quitkin (1997) and Kosten *et al*. (1998) reviewed treatment with TCAs (mostly doxepin) in depressed opioid addicts, who were not abusing cocaine. They concluded that TCAs decreased depression but not necessarily drug use, when it was measured (Woody *et al*., 1975; Kleber *et al*., 1983; Titievsky *et al*., 1982; Woody *et al*., 1982) (1b).

In an early study, imipramine did not improve depression compared with placebo (Kleber *et al*., 1983) (1b). However, a larger RCT reported that imipramine improved depression, which was associated with reduced substance misuse (e.g. heroin, cocaine, alcohol, etc.) (Nunes *et al*., 1998) (1b). However, the effect on substance misuse was not as robust as for depression, nor was the association between the two, leading the authors to recommend treating the patient's depression, but not to expect the substance misuse to improve.

Cocaine and depression

The relationship between these two disorders is complex and there is concern that depression in cocaine addicts fuelling further drug use or risk of deliberate self-harm. As with other drugs of abuse, but perhaps more particularly, achieving abstinence or minimizing misuse of cocaine is critical in attempting to improve mood. Antidepressants may directly compensate for the cocaine-related reduction in neurotransmitters such as dopamine, serotonin and noradrenaline.

Studies evaluating antidepressant pharmacotherapy for comorbid cocaine dependence and unipolar depression have produced inconsistent results. In some studies, if depression was not a specific inclusion criteria, ratings of depressive symptomatology were used as one of the outcome measures. In their recent meta-analysis of the treatment of depression in alcohol or drug dependence, cocaine-dependent patients were included and for general conclusions see above section on alcohol and depression (Nunes and Levin, 2004) (1a).

• *TCAs*

Desipramine is the most widely studied antidepressant, with efficacy shown in the initial open-label trial (Gawin *et al*., 1989) (1b). However, later controlled trials including depressed and non-depressed patients did not report a significant advantage of desipramine over placebo (Weddington *et al*., 1991; Carroll *et al*., 1994a,b) (1b). Psychosocial interventions were also part of the study. For example, in one RCT, cocaine abusers received desipramine or placebo with relapse prevention or clinical management (Carroll *et al*., 1994a,b) (1b). In this study, depressed patients had a greater reduction in cocaine use than non-depressed patients and had a better response to relapse prevention than to clinical management. In a later study, Carroll *et al*. (1995) compared depressed versus non-depressed outpatient cocaine abusers in a 12-week randomized controlled trial of desipramine and cognitive-behavioural relapse prevention (CBRP) treatment, alone and in combination (1b). Desipramine improved mood better than placebo

Recommendations – depression with cocaine dependence

- For all pharmacological studies, the importance of psychosocial interventions is emphasized and should be addressed because there is no robust evidence showing pharmacotherapy is effective (A)
- Desipramine and fluoxetine show no significant advantage over placebo in cocaine dependence alone or in cocaine misusing methadone maintained opioids addicts (B)
- Tricyclic antidepressants are not recommended due to potentially serious interactions including cardiotoxicity and death in overdose (S)

Key uncertainties

- Whether antidepressants play a role in treatment of depression and cocaine misuse?

but this was not accompanied by reduced cocaine use. The CBRP did not affect depressive symptomatology but did result in better retention and longer periods of abstinence from cocaine than supportive clinical management.

Imipramine has been reported to reduce cocaine craving and euphoria and depression but the effect on cocaine use was less impressive (Nunes *et al*., 1995) (1b). Although not significantly different, depressed ('primary and secondary') patients responded better than the non-depressed group with regard to cocaine use.

• *SSRIs*

As with desipramine, fluoxetine has showed some promise for treating cocaine misuse with or without comorbid depression but not consistently (Covi *et al*., 1985; Batki *et al*., 1991; Grabowski *et al*., 1995; Batki *et al*., 1996) (1b). However, these trials did not specifically address the issue of depressed versus non-depressed cocaine addicts. An RCT compared placebo with fluoxetine alongside CBT in cocaine-dependent depressed patients (Schmitz *et al*., 2001) (1b). Although depressive symptomatology improved, there was no medication effect and, initially, the placebo group had fewer cocaine-positive urines.

• *Others*

There are no RCTs or controlled clinical trials of newer antidepressants. A small number of depressed cocaine-dependent patients who had not responded to desipramine in another RCT, were given venlafaxine. It was safe and well tolerated, associated with reduced depressive symptomatology and cocaine use (McDowell *et al*., 2000) (III).

• *Particular subgroups*

(i) Methadone or buprenorphine maintained opioid addicts with cocaine misuse

Desipramine has been reported to be no better than placebo with respect to cocaine use in methadone maintained opioid addicts (Arndt *et al*., 1992; Kolar *et al*., 1992; Kosten *et al*., 1992) (1b). Ziedonis and Kosten (1991) reanalysed their placebo-controlled study and found that desipramine or amantadine in depressed methadone-maintained opioid addicts was associated with reduced cocaine use and that their mood did not worsen as seen in the placebo group (1b).

Fluoxetine has been shown to be ineffective in improving cocaine use or depression in either non-depressed or depressed methadone-maintained opioid addicts (Grabowski *et al*., 1995; Petrakis *et al*., 1998) (1b). More recently, a double-blind, placebo-controlled trial investigated the efficacy of sertraline in treating depression in non-abstinent methadone-maintained opioid addicts (Carpenter *et al*., 2004) (1b). No significant reduction was seen in cocaine or heroin use, or improvement in depression. However, those in a 'positive' environment, as defined by Addiction Severity Index, had better outcomes than those in 'negative' ones.

An RCT of buproprion in methadone maintained cocaine dependent patients also found no medication effect; however, reduced cocaine use was evident in the depressed patient subgroup (Margolin *et al*., 1995) (1b).

(ii) Alcohol dependence with cocaine misuse

Cornelius *et al*. (1998) conducted an analysis of patients in their trial of fluoxetine in depressed alcohol dependent patients who were misusing cocaine. Fluoxetine resulted in no improvement in this group in cocaine, alcohol use or depression (1b).

A RCT with 50 mg naltrexone in comorbid alcohol and cocaine use found no advantage of naltrexone over placebo (Hersh *et al*., 1998) (1b). Oslin *et al*. (1999) performed an open trial of 150 mg naltrexone in addition to their psychosocial programme in patients addicted to both alcohol and cocaine (1b). They reported improvement in cocaine and alcohol use, although the attrition rate was high (47%).

Nicotine

Nicotine is by far the most commonly abused drug in patients with psychiatric disorders, with prevalence rates ranging from 71% to 100% (El-Guebaly *et al*., 2002a; Farrell *et al*., 2001). In addition, patients often smoke heavily (Lasser *et al*., 2000). This undoubtedly leads to increased morbidity and mortality in this population and is generally over-looked in treatment programmes.

El-Guebaly *et al*. (2002a,b) critically reviewed smoking cessation studies performed in patients with psychiatric disorders. There was not enough uniformity in the studies to allow meta-analysis. A combination of a psychoeducational and pharmacotherapeutic approach was commonly used. Making psychiatric hospitals largely smoke-free was judged not to have dramatically reduced the number of patients smoking. It was noted that cigarettes may be used as a reward in behavioural programmes. The quit rates were broadly similar to those in other samples.

Dysphoria, depression and history of a depression appear

Recommendations – depression with nicotine dependence

- There are limited studies on which to base recommendations
- NRT and bupropion are of benefit to patients with a history of depression and should be offered to patients requesting help with smoking cessation (B)

Key uncertainties

- Large randomized controlled trials are needed to establish effectiveness of treatments in patients with depression?

related to difficulty in quitting smoking, particularly if depressive symptoms are present in early abstinence (Hall *et al*., 1996; Pomerleau *et al*., 2001) (1b). A recent review reported abstinence rates in studies including those patients with depression, ranged from 31% to 72% at the end of treatment and 11.8% to 46% 12 months later (El-Guebaly *et al*., 2002a). Brown *et al*. (2001) reported that standard smoking cessation CBT, together with CBT for depression, was more effective in smokers with recurrent major depressive disorder (MDD) than standard CBT alone (1b).

• *NRT*

The results from studies on the effect of NRT on smoking cessation in patients with a history of MDD have been mixed (Hall *et al*., 1994, 1996; Kinnunen *et al*., 1996; Thorsteinsson *et al*., 2001) (1b).

• *Antidepressants, bupropion*

The effect of antidepressant medication has also been studied. In patients with a history of MDD but who were not currently depressed, nortriptyline improved abstinence rates independent of depression history better than placebo, and CBT was more effective than the control (Hall *et al*., 1998) (1b). Buproprion has been shown to improve abstinence rates independent of a history of MDD or alcoholism in patients who did not fulfil criteria for MDD, but some had depressive symptomatology [Beck Depression Inventory (BDI) > 10] (Hayford *et al*., 1999) (1b). An increase in BDI score was associated with relapse to smoking. Finally, a subanalysis of data from an RCT of fluoxetine as an adjunct to the nicotine inhalator showed effectiveness in depressed but not nondepressed patients (Blondal *et al*., 1999) (1b).

Anxiety

Alcohol

Because anxiety is a feature of alcohol withdrawal, waiting until the acute withdrawal period is over for a clearer assessment is critical (Brown *et al*., 1991). There is limited knowledge about treating this comorbid condition (Scott *et al*., 1998).

There have been four RCTs of buspirone in alcohol dependence comorbid with generalized/non-panic anxiety disorder or high levels of anxiety. Results are mixed with some effect on both outcomes seen in three studies and no effect on drinking or on anxiety in the other (Malcolm *et al*., 1992; Tollefson *et al*., 1992; Kranzler *et al*., 1994; Fawcett *et al*., 2000) (1b). Another RCT found buspirone did not improve drinking outcomes in non-anxious patients (Malec *et al*., 1996) (1b). In a pilot study, Randall *et al*. (2001a) reported that paroxetine was superior to placebo in improving anxiety in patients with social phobia and alcohol dependence, but its effects on drinking were less consistent (1b).

Often in treating any comorbid substance misuse disorder, the dilemma is whether to treat one then the other or to treat together? A randomized study of CBT to treat either the alcohol dependence alone or together with CBT for social anxiety found that whereas anxiety and drinking improved in both groups, treatment of both resulted in a poorer outcome for drinking behaviour (Randall *et al*., 2001b) (1b). Another study compared outpatient CBT with 12-step facilitation therapy in female alcohol dependent patients with social anxiety disorder. Abstinence was achieved for longer with CBT than 12-step therapy; however, the reverse was seen in male alcohol dependent patients with social anxiety disorder (Randall *et al*., 2000) (1b).

Recommendations – anxiety with alcohol misuse, dependence

- Patients should first undergo alcohol detoxification (S)
- Buspirone has not been shown to improve anxiety or alcohol outcomes and is not recommended (B)
- In patients who are anxious and misuse alcohol, we recommend that a selective serotonin reuptake inhibitor (SSRI) antidepressant is first-line pharmacotherapy and that assessment by a specialist addiction service is recommended prior to using a benzodiazepine to treat their anxiety (B)

Key uncertainties

- Efficacy of SSRIs and newer antidepressants
- Role of anxiety in other substance misuse disorders
- Role of pharmacological treatment in patients misusing alcohol

Recommendations – bipolar disorder with substance misuse and dependence

- Given the lack of evidence, it is not possible to make specific recommendations regarding pharmacological approaches

Key uncertainties

- More knowledge is required about the role of different mood stabilizers in improving substance misuse either directly or indirectly through improving their bipolar illness

• Particular populations

Alcohol misuse, anxiety and prescribing benzodiazepines

Prescribing benzodiazepines for anxiety in patients who currently misuse alcohol, or have done so previously, is not generally recommended. Abstinent alcohol dependent patients may be at greater risk of benzodiazepine abuse and dependence due to greater rewarding effects (Ciraulo *et al*., 1997). Those patients who are severely dependent, with antisocial personality disorder or with polysubstance abuse are most at risk of abusing benzodiazepines. However, there is evidence to suggest that for those who are less severely dependent, benzodiazepine prescribing may not result in abuse; however, their use in this population requires careful consideration of risk: benefit ratios (Ciraulo *et al*., 1988; Ciraulo and Nace, 2000; Posternak and Mueller, 2001) (III).

Bipolar disorder

Alcohol misuse and dependence is common in bipolar disorder (Regier *et al*., 1990). Despite this, there is little evidence to guide practitioners. There is a recent helpful review concerning treatment (Sonne and Brady, 2002). Although not directly addressing substance misuse outcome, trials have noted that valproate may have greater acceptability than lithium due to its side-effects in patients with substances use disorder and bipolar disorder (Weiss *et al*., 1998) (III). In addition, because patients are not warned not to drink alcohol when taking lithium, this may affect their compliance.

A small open-label study in cocaine abusing patients with bipolar disorder reported that lamotrigine, alone or in addition to usual pharmacotherapy, was associated with significant improvement in mood and drug cravings but not cocaine use (Brown *et al*., 2003) (III). Quetiapine as an adjunct to usual treatment in patients with bipolar disorder and cocaine dependence resulted in improved mood and cocaine cravings and reduced cocaine use in an open-label trial of 17 outpatients (Brown *et al*., 2002) (III).

Schizophrenia and schizoaffective disorder

Misuse of drugs and alcohol in patients with schizophrenia is common, with 47% of patients with schizophrenia misusing substances (Regier *et al*., 1990). After cigarettes, the most commonly abused substance is alcohol occurring in approximately one-third of patients (Regier *et al*., 1990; Cantwell *et al*., 1999). There have been no published RCTs of pharmacotherapy in schizophrenia with comorbid substance abuse with substance use specifically as an outcome measure. For more information on the neurobiological basis, a review of evidence-based practice (in US) and pharmacological treatment of schizophrenia and comorbid substance misuse, the reader is referred to Drake *et al*. (2001) and Green *et al*. (2002).

• Typical antipsychotics

In a review, Siris (1990) commented that typical antipsychotics do not appear to reduce substance abuse and may even contribute to their use in patients with schizophrenia. Nevertheless, Levin *et al*. (1998) conducted an open study of flupentixol given to eight patients with schizophrenia and cocaine abuse after having tapered them off their usual antipsychotic over 10 weeks (III). It was well tolerated, with psychotic and depressive symptoms and abuse of cocaine all improving.

• Atypical antipsychotics

There is limited data available for atypical antipsychotics. In patients with schizophrenia or schizoaffective disorder, olanzapine has been associated with abstinence or marked improvements in substance use, including for alcohol, cocaine, marijuana, amfetamines and hallucinogens (Conley *et al*., 1998; Littrell *et al*., 2001; Noordsy *et al*., 2001) (III). However, a recent review of patients in a study comparing olanzapine with haloperidol found that those patients in their first episode of schizophrenia who were abusing substances (alcohol, cannabis, other) were less likely to respond to either neuroleptic (Green *et al*., 2004) (III). In those abusing alcohol, olanzapine but not haloperidol, was associated with a reduced response with regard to their psychotic symptomatology than in those who were not abusing alcohol.

Smelson *et al*. (2002) conducted an open-label pilot study of risperidone over 6 weeks in abstinent cocaine dependent patients with schizophrenia who were not abusing other drugs except nicotine (III). Eight patients were cross-tapered to risperidone and compared with 10 patients on typical antipsychotics. They reported that risperidone was associated with less cocaine use and less cue reactivity than those on typical antipsychotics, with a trend towards improved negative but not positive symptoms. However, a retrospective small study comparing clozapine and risperidone found abstinence from alcohol and cannabis was more likely with clozapine (54%) than risperidone (13%) at 1 year (Green *et al*., 2003) (III).

• Clozapine

The majority of studies concerning substance misuse and anti-psychotic medication in schizophrenia have been published about clozapine. There are several case reports, a retrospective survey, naturalistic surveys and trials that suggest clozapine reduces substance use in psychotic patients (Albanese *et al*., 1994; Buckley, 1994a,b; Marcus and Snyder, 1995; Buckley, 1998a,b?; Tsuang *et al*., 1999; Drake *et al*., 2000; Zimmet *et al*., 2000). Clozapine is associated with improvements by as much as 85% for comorbid patients' use of substances, including alcohol, marijuana and cocaine, and no patients show an increase in substance use (IIb).

Recommendations – schizophrenia with substance misuse and dependence

- Given the dearth of information, it is difficult to draw up recommendations
- Typical antipsychotics do not appear to improve substance misuse and may even contribute to it, so we recommend that their use be avoided where possible (D)
- Atypical antipsychotics appear to have a more favourable outcome though there are no controlled data to support this supposition (D)
- Clozapine has been reported to reduce substance misuse and improve psychosis but this data is still preliminary (D)

Key uncertainties – schizophrenia with substance misuse and dependence

- Do low dose typical antipsychotics contribute to substance misuse?
- Are atypical better than typical antipsychotics in reducing substance misuse and/or treating the comorbidity, and if so why?
- Randomized controlled trials specifically designed to look at this comorbidity are required
- Is clozapine superior to other atypical antipsychotics?

It has been hypothesized that clozapine-related improvements in psychosis, mood, cognition and lower levels of side-effects, e.g. extra-pyramidal, underlie these improvements.

• *Miscellaneous: naltrexone*

Petrakis *et al*. (2004) conducted an RCT studying the effects of naltrexone in addition to their neuroleptic medication in alcohol abusing patients with schizophrenia (Ib). Patients also received relapse prevention interventions. Naltrexone was associated with fewer drinking days, fewer heavy drinking days and less craving without worsening their schizophrenia. The lack of any benefit in their schizophrenia may have been due to the short length of the study (12 weeks).

• *Nicotine*

Patients with schizophrenia have higher rates of smoking than the general population with current estimates of up to approximately 90% of patients (i.e. three times the rate in the general population) (Kelly and McCreadie, 2000; Farrell *et al*., 2001).

(i) Behavioural programmes and NRT

A behavioural programme derived from the American Lung Association (ALA; includes psychoeducation, positive reinforcement and anxiety reduction) resulted in an abstinence rate in patients with schizophrenia of 42% after 7 weeks, which fell to 12% by 6 months (Addington *et al*., 1998) (IIb). George *et al*. (2000b) compared this programme in a randomized trial with another manualised programme designed for patients with schizophrenia; both included a nicotine patch (1b). There was no difference in the smoking abstinence rates between the two interventions after 12 weeks; however, those on atypical antipsychotics sustained abstinence for longer compared with those receiving typical antipsychotics (55.6% versus 22.2%). The study also suggested that olanzapine and risperidone were better than clozapine or quetiapine. At 6-month follow-up, more were abstinent who had the ALA programme (17.6% versus 10.7%) and were taking atypical antipsychotics (16.7% versus 7.4%).

Elsewhere, naturalistic studies following patients switched to clozapine from their typical antipsychotic have reported reduced smoking (George *et al*., 1995; McEvoy, 1995, 1999) (III).

(ii) Buproprion

In several studies in patients with schizophrenia, bupropion has been shown to increase abstinence from smoking as an adjunct to a variety of behavioural programmes including CBT, ALA programme and supportive therapy. A pilot double-blind, placebo-controlled study of bupropion SR (150 mg/day) as an adjunct to CBT, increased abstinence rates from 11% to 66% (Evins *et al*., 2001) (Ib). Another study reported that buproprion SR (300 mg/day) with supportive therapy reduced the level of smoking in patients with schizophrenia (Weiner *et al*., 2001) (IIb). In an RCT, buproprion SR (300 mg/day) as an adjunct to group therapy improved abstinence rates in patients with schizophrenia who wanted to quit (George *et al*., 2002) (Ib). Bupropion quadrupled the abstinence rates to 50% but, after 6 months, the rates had declined to 18.8% in the buproprion group versus 6.3% in the placebo group (not significantly different). The results of this study were similar to their study on nicotine substitution; those patients on atypical antipsychotics did better and improvement was seen in negative symptoms with no change in positive ones.

Acknowledgements

The participants are indebted to Susan Chandler who organized the logistics of the meeting. The authors would also like to thank Ian Anderson for his advice and comments and Jenny Colyer for her secretarial assistance with the references. The following were participants at the Consensus Meeting and had the opportunity to comment on these guidelines: Mr Eric Appleby, Chief Executive, Alcohol Concern; Dr Eilish Gilvarry, Chair of Substance Misuse Faculty, Royal College of Psychiatrists; Mr Bill Nelles, Methadone Alliance; Dr Annette Dale-Perera, National Treatment Agency. Professor Dai Stephens, BAP Council; Dr Clare Stanford, BAP Council and Professor Charles Marsden, BAP Council attended the consensus meeting. In addition, the expense of the meeting was in part defrayed by the charging participating pharmaceutical companies some of whom sent representatives to the Consensus meeting and had the opportunity to comment on these guidelines, Link Pharmaceuticals, Schering-Plough, Reckitt Benckiser, Britannia Pharmaceuticals, Martindale and Lilly. Contributors at the Consensus meeting were asked to declare any interests of potential conflict in line with BAP and J Psychopharm policy. These are held on file by the BAP.

References

American Psychiatric Association (1994) Diagnostic and Statistics Manual for Mental disorders (DSM-IV). American Psychiatric Association, Washington, DC

Addington J, el-Guebaly N, Campbell W, Hodgins D, Addington D (1998) Smoking cessation treatment for patients with schizophrenia. Am J Psychiatry *155*: 974–978

Addis A, Moretti M E, Ahmed S F, Einarson T R, Koren G (2001) Fetal effects of cocaine: an updated meta-analysis. Reprod Toxicol *15*: 341–369

Albanese M J, Khantzian E J, Murphy S L, Green A I (1994) Decreased substance use in chronically psychotic patients treated with clozapine. Am J Psychiatry *151*: 780–781

Alldredge B K, Lowenstein D H, Simon R P (1989) Placebo-controlled trial of intravenous diphenylhydantoin for short-term treatment of alcohol withdrawal seizures. Am J Med *87*: 645–648

Amato L, Davoli M, Ferri M, Ali R (2003) Methadone at tapered doses for the management of opioid withdrawal (Cochrane Review). In: The Cochrane Library. John Wiley & Sons, Ltd, Chichester

Amato L, Davoli M, Ferri M, Gowing L, Perruci C (2004) Effectiveness of interventions on opiate withdrawal treatment: an overview of systematic reviews. Drug Alcohol Depend *73*: 219–226

Anderson I M, Nutt D J, Deakin J F (2000) Evidence-based guidelines for treating depressive disorders with antidepressants: a revision of the 1993 British Association for Psychopharmacology guidelines. British Association for Psychopharmacology. J Psychopharmacol *14*: 3–20

Anglin M D (1988) The efficacy of civil commitment in treating narcotic addiction. NIDA Res Monogr *86*: 8–34

Anton R F, Moak D H, Waid L R, Latham P K, Malcolm R J, Dias J K (1999) Naltrexone and cognitive behavioral therapy for the treatment of outpatient alcoholics: results of a placebo-controlled trial. Am J Psychiatry *156*: 1758–1764

Anton R, Moak D, Latham P, Randolph W, Malcolm R, Dias J, Roberts J (2001) Posttreatment results of combining naltrexone with cognitive-behavior therapy for the treatment of alcoholism. J Consult Clin Psychopharm *21*: 72–77

Archie C (1998) Methadone in the management of narcotic addiction in pregnancy. Curr Opin Obstet Gynecol *10*: 435–440

Arndt I, Dorozynsky L, Woody G, McLellan A, O'Brien C (1992) Desipramine treatment of cocaine dependence in methadone-maintained patients. Arch Gen Psychiatry *49*: 888–893

Ashton C, Rawlins M, Tyrer S (1990) A double-blind placebo-controlled study of buspirone in diazepam withdrawal in chronic benzodiazepine users. Br J Psychiatry *157*: 232–238

Ashton H (1987) Benzodiazepine withdrawal: outcome in 50 patients. Br J Addict *82*: 665–671

Auriacombe M, Franques P, Tignol J (2001) Deaths attributable to methadone versus buprenorphine in France. JAMA *285*: 45

Balldin J, Berggren U, Engel J, Eriksson E, Hard E, Soderpalm B (1994) Effect of citalopram on alcohol intake in heavy drinkers. Alcohol Clin Exp Res *18*: 1133–1136

Ballenger J C, Post R M (1978) Kindling as a model for alcohol withdrawal syndromes. Br J Psychiatry *133*: 1–14

Banjeree S, Clancy C, Crome I (2001) Co-existing problems of mental disorder and substance misuse (dual diagnosis). An information Manual. Final Report to the Department of Health. Royal College of Psychiatrists' Research Unit, London

Bashir K, King M, Ashworth M (1994) Controlled evaluation of brief intervention by general practitioners to reduce chronic use of benzodiazepines. Br J Gen Pract *44*: 408–412

Batki S L, Manfredi L B, Sorensen J L, Jacob P, Dumontet R, Jones R T (1991) Fluoxetine for cocaine abuse in methadone patients: preliminary findings. NIDA Res Monogr *105*: 516–517

Batki S L, Washburn A M, Delucchi K, Jones R T (1996) A controlled trial of fluoxetine in crack cocaine dependence. Drug Alcohol Depend *41*: 137–142

Bavon A (2001) The effect of the Tarrant County drug court project on recidivism. Eval Program Plan *24*: 13–22

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

Besson J, Aeby F, Kasas A, Lehert P, Potgieter A (1998) Combined efficacy of acamprosate and disulfiram in the treatment of alcoholism: a controlled study. Alcohol Clin Exp Res *22*: 573–579

Best D, Noble A, Man L, Gossop M, Finch E, Strang J (2002) Factors surrounding long-term benzodiazepine prescribing in methadone maintenance clients. J Subst Abuse Treat *7*: 175–179

Bien T H, Miller W R, Tonigan J S (1993) Brief interventions for alcohol problems: a review. Addiction *88*: 315–335

Blondal T, Gudmundsson L, Tomasson K, Jonsdottir D, Hilmarsdottir H, Kristjansson F, Nilsson F, Bjornsdottir U (1999) The effects of fluoxetine combined with nicotine inhalers in smoking cessation – a randomized trial. Addiction *94*: 1007–1015

Bobo J, McIlvain H, Lando H, Dale Walker R, Leed-Kelly A (1998) Effect of smoking cessation counselling on recovery from alcoholism: findings from a randomized community intervention trial. Addiction *93*: 877–887

Brooke D, Edwards G, Andrews T (1993) Doctors and substance misuse: types of doctors, types of problems. Addiction *88*: 655–663

Brown E S, Nejtek V A, Perantie D C, Bobadilla L (2002) Quetiapine in bipolar disorder and cocaine dependence. Bipolar Disord *4*: 406–411

Brown E S, Nejtek V A, Perantie D C, Orsulak P J, Bobadilla L (2003) Lamotrigine in patients with bipolar disorder and cocaine dependence. J Clin Psychiatry *64*: 197–201

Brown R, Kahler C, Niaura R, Abrams D, Sales S, Ramsey S, Goldstein M, Burgess E, Miller I (2001) Cognitive-behavioral treatment for depression in smoking cessation. J Consult Clin Psychol *69*: 471–480

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

Buckley P (1998a) Substance abuse in schizophrenia: a review. J Clin Psychiatry *59*: 26–30

Buckley P (1998b) Novel antipsychotic medications and the treatment of comorbid substance abuse in schizophrenia. J Subst Abuse Treat *15*: 113–116

Buckley P, Thompson PA, Way L, Meltzer H Y (1994a) Substance abuse and clozapine treatment. J Clin Psychiatry *55* (Suppl B): 114–116

Buckley P, Thompson P, Way L, Meltzer H Y (1994b) Substance abuse among patients with treatment-resistant schizophrenia: characteristics and implications for clozapine therapy. Am J Psychiatry *151*: 385–389

Burling T, Burling A, Latini D (2001) A controlled smoking cessation trial for substance-dependent inpatients. J Consult Clin Psychol *69*: 295–304

Campbell B K, Wander N, Stark M J, Holbert T (1995) Treating cigarette smoking in drug-abusing clients. J Subst Abuse Treat *12*: 89–94

Campbell B K, Krumenacker J, Stark M J (1998) Smoking cessation for clients in chemical dependence treatment. A demonstration project. J Subst Abuse Treat *15*: 313–318

Cantwell R, Brewin J, Glazebrook C, Dalkin T, Fox R, Medley I, Harrison G (1999) Prevalence of substance misuse in first-episode psychosis. Br J Psychiatry *174*: 150–153

Carpenter K, Brooks A, Vosburg S, Nunes E (2004) The effect of sertraline and environmental context on treating depression and illicit substance use among methadone maintained opiate dependent patients: a controlled clinical trial. Drug Alcohol Depend *74*: 123–134

Carroll K M, Rounsaville B J, Gordon L T, Nich C, Jatlow P, Bisichini R, Gawin F (1994a) Psychotherapy and pharmacotherapy for ambulatory cocaine abusers. Arch Gen Psychiatry *51*: 177–187

Carroll K M, Rounsaville B J, Nich C, Gordon L T, Wirtz P W, Gawin F (1994b) One-year follow-up of psychotherapy and pharmacotherapy for cocaine dependence. Delayed emergence of psychotherapy effects. Arch Gen Psychiatry *51*: 989–997

Carroll K M, Nich C, Rounsaville B J (1995) Differential symptom reduction in depressed cocaine abusers treated with psychotherapy and pharmacotherapy. J Nerv Ment Dis *183*: 251–259

Carroll K M, Nich C, Ball S A, McCance E, Rounsavile B J (1998) Treatment of cocaine and alcohol dependence with psychotherapy and disulfiram. Addiction *93*: 713–727

Carroll K M, Nich C, Ball S A, McCance E, Frankforter T L, Rounsaville B J (2000) One-year follow-up of disulfiram and psychotherapy for cocaine-alcohol users: sustained effects of treatment. Addiction *95*: 1335–1349

Carroll K M, Fenton L R, Ball S A, Nich C, Frankforter T L, Shi J, Rounsaville B J (2004a) Efficacy of disulfiram and cognitive behavior therapy in cocaine-dependent outpatients: a randomized placebo-controlled trial. Arch Gen Psychiatry *61*: 264–272

Carroll K, Nich C, Rounsaville B (2004b) Differential symptom reduction in depressed cocaine abusers treated with psychotherapy and pharmacotherapy. J Nerv Ment Dis *183*: 251–259

Chance J F (1991) Emergency department treatment of alcohol withdrawal seizures with phenytoin. Ann Emerg Med *20*: 520–522

Chang G, Wilkins-Haug L, Berman S, Goetz M A (1999) Brief intervention for alcohol use in pregnancy: a randomized trial. Addiction *94*: 1499–1508

Charney D, Paraherakis A, Gill K (2000) The treatment of sedative-hypnotic dependence: evaluating clinical predictors or outcome. J Clin Psychiatry *61*: 190–195

Chick J, Gough K, Falkowski W, Kershaw P, Hore B, Mehta B, Ritson B, Ropner R, Torley D (1992) Disulfiram treatment of alcoholism. Br J Psychiatry *161*: 84–89

Chick J, Howlett H, Morgan M, Ritson B (2000a) 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, Anton R, Chechinski K, Croop R, Drummond D, Farmer R, Labriola D, Marshall J, Moncrieff J, Morgan M, Peters T, Ritson B (2000b) A multicentre, randomized, double-blind, placebo-controlled trial of naltrexone in the treatment of alcohol dependence or abuse. Alcohol Alcohol *35*: 587–593

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

Chick J, Aschauer H, 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

Ciraulo D A, Jaffe J H (1981) Tricyclic antidepressants in the treatment of depression associated with alcoholism. J Clin Psychopharmacol *1*: 146–150

Ciraulo D A, Nace E P (2000) Benzodiazepine treatment of anxiety or insomnia in substance abuse patients. Am J Addict *9*: 276–279

Ciraulo D A, Barnhill J G, Ciraulo A M, Sarid-Segal O, Knapp C, Greenblatt D J, Shader R I (1997) Alterations in pharmacodynamics of anxiolytics in abstinent alcoholic men: subjective responses, abuse liability, and electroencephalographic effects of alprazolam, diazepam, and buspirone. J Clin Pharmacol *37*: 64–73

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

Comer S, Collins E, Kleber H, Nuwayser E, Kerrigan J, Fischman M (2002) Depot naltrexone: long-lasting antagonism of the effects of heroin in humans. Psychopharmacology *159*: 351–360

Condelli W S, Fairbank J A, Dennis M L, Rachal J V (1991) Cocaine use by clients in methadone programs: significance, scope, and behavioral interventions. J Subst Abuse Treat *8*: 203–212

Conley R, Kelly D, Gale E (1998) Olanzapine response in treatment-refractory schizophrenic patients with a history of substance abuse. Biol Psychiatry *33*: 95–101

Cook C C, Hallwood P M, Thomson A D (1998) B Vitamin deficiency and neuropsychiatric syndromes in alcohol misuse. Alcohol Alcohol *33*: 317–336

Cormack M, Woens R, Dewey M (1989) The effect of minimal interventions by general practitioners on long-term benzodiazepines use. J Royal Coll Gen Pract *39*: 408–411

Cornelius J, Salloum I, Ehler J, Jarrett P, Cornelius M, Perel J, Thase M, Black A (1997) Fluoxetine in depressed alcoholics. Arch Gen Psychiatry *54*: 700–705

Cornelius J, Salloum I, Thase M, Haskett R, Daley D, Jones-Barlock A, Upsher C, Perel J (1998) Fluoxetine versus placebo in depressed alcoholic cocaine abusers. Psychopharmacol Bull *34*: 117–121

Cornelius J, Salloum I, Haskett R, Daley D, Cornelius M, Thase M, Perel (2000) Fluoxetine versus placebo in depressed alcoholics: a 1-year follow-up study. Addict Behav *25*: 307–310

Couvee J, Oude-Voshaar R, van Balkom A, Zitman F (2003) Strategies to discontinue long term benzodiazepine use: a systematic review. In Couvee J (ed), Towards a treatment of chronic benzodiazepine users suffering from depression. Glaxo SmithKline BV, The Netherlands,

Covi L, Hess J, Kreiter N, Haertzen C (1995) Effects of combined fluoxetine and counseling in the outpatient treatment of cocaine abusers. Am J Drug Alcohol Abuse *21*: 327–344

Crawford V (2001) Co-existing problems of mental disorder and substance misuse (dual diagnosis): a review of relevant literature. Final report to the Department of Health. Royal College of Psychiatrists' Research Unit, London

Crits-Christoph P, Siqueland L, Blaine J, Frank A, Luborsky L, Onken L S, Muenz L R, Thase M E, Weiss R D, Gastfriend D R, Woody G E, Barber J P, Butler S F, Daley D, Salloum I, Bishop S, Najavits L M, Lis J, Mercer D, Griffin M L, Moras K, Beck A T (1999) Psychosocial treatments for cocaine dependence: National Institute on Drug Abuse Collaborative Cocaine Treatment Study. Arch Gen Psychiatry *56*: 493–502

Crome I B (1997) Alcohol problems in the older person. J Roy Soc Med *90* (Suppl 32): 16–22

Crome I B, Day E (1999) Substance misuse and dependence: Older people deserve better services. Rev Clin Gerontol *9*: 327–342

Crome I B, McCardle P, Gilvarry E, Bailey S (2004) Treatment. In Crome I, Ghodse H, Gilvarry E, McCardle P (eds), Young people and substance misuse, pp. 140–162. Gaskell, London

D'Onofrio G, Rathlev N K, Ulrich A S, Fish S S, Freedland E S (1999) Lorazepam for the prevention of recurrent seizures related to alcohol. N Engl J Med *340*: 915–919

Daeppen J-B, Gache P, Landry U, Sekera E, Schweizer V, Gloor S, Yersin B (2002) Symptom-triggered versus fixed-schedule doses of benzodiazepine for alcohol withdrawal. Arch Intern Med *162*: 1117–1121

Department of Health, The Scottish Office, The Welsh Office and DHSS Northern Ireland (1999) Drug Misuse and Dependence: Guidelines on Clinical Management. [available at www.doh.gov.uk]

Desland M L, Batey R G (1992) A 12-month prospective comparison of court-diverted with self-referred heroin users. Drug Alcohol Rev *11*: 121–129

Desmond D P, Maddux J F (1996) Compulsory supervision and methadone maintenance. J Subst Abuse Treat *13*: 79–83

Drake R E, Xie H, McHugo G J, Green A I (2000) The effects of clozapine on alcohol and drug use disorders among patients with schizophrenia. Schizophr Bull *26*: 441–449

Drake R, Essock S, Shaner A, Carey K, Minkoff K, Kola L, Lynde D, Osher F, Rickards L (2001) Implementing dual diagnosis services for clients with severe mental illness. Psychiatr Serv *52*: 469–476

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

Drummond D C, Turkington D, Rahman M Z, Mullin P J, Jackson P (1989) Chlordiazepoxide versus methadone in opiate withdrawal: a preliminary double blind trial. Drug Alcohol Depend *23*: 63–71

Duka T, Townshend J M, Collier K, Stephens D N (2003) Impairment in cognitive functions after multiple detoxifications in alcoholic inpatients. Alcohol Clin Exp Res *27*(10): 1563–1572

Duncan D, Taylor D (1996) Chlormethiazole or chlordiazepoxide in alcohol detoxification. Psychiatr Bull *20*: 599–601

Dunn C, Deroo L, Rivara F (2001) The use of brief interventions adapted from motivational interviewing across behavioural domains: a systematic review. Addiction *96*: 1725–1742

Dunner D, Zisook S, Billow A, Batey S, Johnston J, Ascher J (1998) A prospective safety surveillance study for bupropion sustained-release in the treatment of depression. J Clin Psychiatry *59*: 366–373

Edwards G, Gross M (1976) Alcohol dependence: provisional description of a clinical syndrome. BMJ *1*: 1058–1061

El Guebaly N, Cathcart J, Currie S, Brown D, Gloster S (2002a) Public health and therapeutic aspects of smoking bans in mental health and addiction settings. Psychiatr Serv *53*: 1617–1622

El Guebaly N, Cathcart J, Currie S, Brown D, Gloster S (2002b) Smoking cessation approaches for persons with mental illness or addictive disorders. Psychiatr Serv *53*: 1166–1170

Elsesser K, Sartory G, Maurer J (1996) The efficacy of complaints management training in facilitating benzodiazepine withdrawal. Behav Res Ther *34*: 149–156

Evins A, Mays V, Rigotti N, Tisdale T, Cather C, Goff D (2001) A pilot trial of bupropion added to cognitive behavioral therapy for smoking cessation in schizophrenia. Nicotine Tob Res *3*: 397–403

Faggiano F, Vigna-Taglianti F, Versino E, Lemma P (2003) Methadone maintenance at different dosages for opioid dependence (Cochrane Review). In: The Cochrane Library. John Wiley & Sons, Ltd, Chichester

Farrell M, Ward J, Mattick R, Hall W, Stimson GV, des JD, Gossop M, Strang J (1994) Methadone maintenance treatment in opiate dependence: a review. BMJ 309: 997–1001

Farrell M, Howes S, Bebbington P, Brugha T, Jenkins R, Lewis G, Marsden J, Taylor C, Meltzer H (2001) Nicotine, alcohol and drug dependence and psychiatric comorbidity. Results of a national household survey. Br J Psychiatry *179*: 432–437

Fawcett J, Kravitz H, McGuire M, Easton M, Ross J, Pisani V, Fogg L, Clark D, Whitney M, Kravitz G, Javaid J, Teas G (2000) Pharmacological treatment for alcoholism: revisiting lithium and considering buspirone. Alcohol Clin Exp Res *24*: 666–674

Feeney G, Young R, Connor J, Tucker J, McPherson A (2002) Cognitive behavioural therapy combined with the relapse-prevention medication acamprosate: are short-term treatment outcomes for alcohol dependence improved? Austr NZ J Psychiatry *36*: 622–628

Ferri M, Davoli M, Perruci C (2004) Heroin maintenance for chronic heroin dependence (Cochrane Review). In: The Cochrane Library. John Wiley & Sons, Ltd, Chichester

Fleming PM, Roberts D (1994) Is the prescription of amphetamine justified as a harm reduction measure? J Royal Soc Health *114*: 127–131

Foster J, Brewer C, Steele T (2003) Naltrexone implants can completely prevent early (1 month) relapse after opiate detoxification: a pilot study of two cohorts totalling 101 patients with a note on naltrexone blood levels. Addiction Biol *8*: 211–217

Freemantle N, Gill P, Godfrey C, Long A, Richards C, Sheldon TA, Song F, Webb J (1993) Brief interventions and alcohol use. Qual Health Care *2*: 267–273

Fryer J, Lukas R (1999) Noncompetitive functional inhibition at diverse, human acetylcholine receptor subtypes by bupropion. J Pharmacol Exp Ther *288*: 88–92

Fugelstad A, Agren G, Romelsjo A (1998) Changes in mortality, arrests, and hospitalizations in nonvoluntarily treated heroin addicts in relation to methadone treatment. Subst Use Misuse *33*: 2803–2817

Fuller R K, Roth H P (1979) Disulfiram for the treatment of alcoholism. An evaluation in 128 men. Ann Intern Med *90*: 901–904

Fulwiler R L, Hargreaves W A, Bortman R A (1979) Detoxification from heroin using self versus physician regulation of methadone dose. Int J Addict *14*: 289–298

Garbutt J C, West S L, Carey T S, Lohr K N, Crews F T (1999) Pharmacological treatment of alcohol dependence: a review of the evidence. JAMA *281*: 1318–1325

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

Gastpar M, Bonnet U, Boning J, Mann K, Schmidt L, Soyka M, Wetterling T, Kielstein V, Labriola D, Croop R (2002) Lack of efficacy of naltrexone in the prevention of alcohol relapse: results from a German multicenter study. J Clin Psychopharmacol *22*: 592–598

Gawin F H, Kleber H D, Byck R, Rounsaville B J, Kosten T R, Jatlow P I, Morgan C (1989) Desipramine facilitation of initial cocaine abstinence. Arch Gen Psychiatry *46*: 117–121

George T P, Chawarski M C, Pakes J, Carroll K M, Kosten T R, Schottenfeld R S (2000a) Disulfiram versus placebo for cocaine dependence in buprenorphine-maintained subjects: a preliminary trial. Biol Psychiatry *47*: 1080–1086

George T P, Ziedonis D M, Feingold A, Pepper W T, Satterburg C A, Winkel J, Rounsaville B J, Kosten T R (2000b) Nicotine transdermal patch and atypical antipsychotic medications for smoking cessation in schizophrenia. Am J Psychiatry *157*: 1835–1842

George T P, Sernyak M J, Ziedonis D M, Woods S W (1995) Effects of clozapine on smoking in chronic schizophrenic outpatients. J Clin Psychiatry *56*(8): 344–346

George T P, Vessicchio J C, Termine A, Bregartner T A, Feingold A, Rounsaville B J, Kosten T R (2002) A placebo controlled trial of bupropion for smoking cessation in schizophrenia. Biol Psychiatry *52*: 53–61

Gerra G, Caccavari R, Delsignore R, Bocchi R, Fertonani G, Passeri M (1992) Effects of fluoxetine and Ca-acetly homotaurinate on alcohol intake in familial and nonfamilial alcohol patients. Curr Ther Res *52*: 291–295

Goodwin G M (2003) Evidence-based guidelines for treating bipolar disorder: recommendations from the British Association for Psychopharmacology. J Psychopharmacol *17*: 149–173

Gossop M, Marsden J, Stewart D, Lehmann P, Strang J (1999) Methadone treatment practices and outcome for opiate addicts treated in drug clinics and in general practice: results from the National Treatment Outcome Research Study. Br J Gen Pract *49*: 31–34

Gowing L, Ali R, White J (2003a) Buprenorphine for the management of opioid withdrawal (Cochrane Review). In: The Cochrane Library. John Wiley & Sons, Ltd. Chichester

Gowing L, Farrell M, Ali R, White J (2003b) Alpha2 adrenergic agonists for the management of opioid withdrawal (Cochrane Review). In: The Cochrane Library. John Wiley & Sons, Ltd, Chichester

Gowing L, Farrell M, Bornemann R, Ali R (2004) Substitution treatment of

injecting opioid users for preventing transmission of HIV infection (Cochrane Review). In: The Cochrane Library. John Wiley & Sons, Ltd, Chichester (in press)

Grabowski J, Rhoades H, Elk R, Schmitz J, Davis C, Creson D, Kirby K (1995) Fluoxetine is ineffective for treatment of cocaine dependence or concurrent opiate and cocaine dependence: two placebo-controlled double-blind trials. J Consult Clin Psychopharmacol *15*:163–174

Green A, Salomon M, Brenner M, Rawlins K (2002) Treatment of schizophrenia and comorbid substance use disorder. Curr Drug Targets – CNS Neurol Disord *1*: 129–139

Green A, Burgess E, Dawson R, Zimmet S, Strous R (2003) Alcohol and cannabis use in schizophrenia: effects of clozapine versus risperidone. Schizophr Res *60*: 81–85

Green A, Tohen M, Hamer R, Strakowski S, Lieberman J, Glick I, Clark W, HGDH Research Group (2004) First episode schizophrenia-related psychosis and substance use disorders: acute response to olanzapine and haloperidol. Schizophr Res *00*: 125–135

Green L, Gossop M (1988) Effects of information on the opiate withdrawal syndrome. Br J Addict *83*: 305–309

Greenwood J (1996) Six years' experience of sharing the care of Edinburgh's drug users. Psychiatr Bull *20*: 8–11

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

Habraken H, Soenen K, Blondeel L, Van Elsen J, Bourda J, Coppens E, Willeput M (1997) Gradual withdrawal from benzodiazepines in residents of homes for the elderly: experience and suggestions for future research. Eur J Clin Pharmacol *51*: 355–358

Hall S M, Bass A, Hargreaves W A, Loeb P (1979) Contingency management and information feedback in outpatient heroin detoxification. Behav Ther *10*: 443–451.

Hall S, Munoz R, Reus V (1994) Cognitive-behavioral intervention increases abstinence rates for depressive-history smokers. J Consult Clin Psychol *62*: 141–146

Hall S, Munoz R, Reus V, Sees K, Duncan C, Humfleet G, Hartz D (1996) Mood management and nicotine gum in smoking treatment: a therapeutic contact and placebo-controlled study. J Consult Clin Psychol *64*: 1003–1009

Hall S, Reus V, Munoz R, Sees K, Humfleet G, Hartz D, Frederick S, Triffleman E (1998) Nortiptyline and cognitive-behavioral therapy in the treatment of cigarette smoking. Arch Gen Psychiatry *55*: 683–690

Haller D, Knisely J, Elswick R, Dawson K, Schnoll S (1997) Perinatal substance abusers; factors influencing treatment retention, J Subst Abuse Treatment *14*(6): 513–519

Handmaker N S, Miller W R, Manicke M (1999) Findings of a pilot study of motivational interviewing with pregnant drinkers. J Stud Alcohol *60*: 285–287

Hankin J, McCaul ME, Heussner J (2000) Pregnant, alcohol-abusing women. Alcohol Clin Exp Res *24*: 1276–1286

Harrison M, Busto U, Naranjo C, Kaplan H, Sellers E (1984) Diazepam tapering in detoxification for high dose benzodiazepine abuse. Clin Pharmacol Ther *36*: 527–533

Hartnoll R, Mitcheson M, Battersby A, Brown G, Ellis M, Fleming P, Hedley N (1980) Evaluation of heroin maintenance in controlled trial. Arch Gen Psychiatry *37*: 877–884

Hayford K, Patten C, Rummans T, Schroeder D, Offord K, Croghan I, Glover E, Sachs D, Hurt R (1999) Efficacy of bupropion for smoking cessation in smokers with a former history of major depression or alcoholism. Br J Psychiatry *174*: 173–178

Hays J, Schroeder D, Offord K, Croghan I, Patten C, Hurt R, Jorenby D, Fiore M (1999) Response to nicotine dependence treatment in smokers with current and past alcohol problems. Ann Behav Med *21*: 244–250

Heale P, Lang E (2001) A process evaluation of the CREDIT (Court Referral and Evaluation for Drug Intervention and Treatment) pilot programme. Drug Alcohol Rev *20*: 223–230

Health Advisory Service (2001) Substance misuse and mental health comorbidity (dual diagnosis). Standards for Mental Health Services. Health Advisory Service, London, available from www.nta.nhs.uk

Healy D, Nutt D J (1998) Prescriptions, licenses and evidence. Psychiatr Bull *22*: 680–684

Heinala P, Alho H, Kiianmaa K, Lonnqvist J, Kuoppasalmi K, Sinclair J (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 J, Kranzler H (1998) Naltrexone treatment of comorbid alcohol and cocaine use disorders. Psychopharmacology *139*: 44–52

Higgins S T, Sigmon S C, Wong C J, Heil S H, Badger G J, Donham R, Dantona R L, Anthony S (2003) Community reinforcement therapy for cocaine-dependent outpatients. Arch Gen Psychiatry *60*: 1043–1052

Hillbom M, Pieninkeroinen I, Leone M (2003) Seizures in alcohol-dependent patients. CNS Drugs *17*: 1013–1030

Holbrook A M, Crowther R, Lotter A, Cheng C, King D (1999) Meta-analysis of benzodiazepine use in the treatment of acute alcohol withdrawal. CMAJ *160*: 649–655

Holder H, Longabaugh R, Miller W R, Rubinois A V (1991) The cost effectiveness of treatment for alcoholism: a first approximation. J Stud Alcohol *52*: 517–540

Holton A, Tyrer P (1990) Five year outcome in patients withdrawn from long term treatment with diazepam. BMJ *300*: 1241–1242

Hser Y I, Anglin D, Powers K (1993) A 24-year follow-up of California narcotics addicts. Arch Gen Psychiatry *50*: 577–584

Hughes J, Cook C (1997) The efficacy of disulfiram: a review of outcome studies. Addiction *92*: 381–395

Hughes J R, Novy P, Hatsukami D K, Jensen J, Callas P W (2003) Efficacy of nicotine patch in smokers with a history of alcoholism. Alcohol Clin Exp Res *27*: 946–954

Hughes J, Stead L, Lancaster T (2004) Antidepressants for smoking cessation (Cochrane Review). In: The Cochrane Library. John Wiley & Sons, Ltd, Chichester

Hurt R, Patten C (2003) Treatment of tobacco dependence in alcoholics. Recent Dev Alcohol *16*: 335–359

Hurt R D, Eberman K M, Croghan I T, Offord K P, Davis L J Jr, Morse R M, Palmen M A, Bruce B K (1994) Nicotine dependence treatment during inpatient treatment for other addictions: a prospective intervention trial. Alcohol Clin Exp Res *18*: 867–872

Iga J I, Araki M, Ishimoto Y, Ohmori T (2001) A case of Korsakoff's syndrome improved by high doses of donepezil. Alcohol Alcohol *36*: 553–555

Jaffe A J, Rounsaville B, Chang G, Schottenfeld R S, Meyer R E, O'Malley S S (1996) Naltrexone, relapse prevention, and supportive therapy with alcoholics: an analysis of patient treatment matching. J Consult Clin Psychol *64*: 1044–1053

Jansson L M, Svikis D, Lee J, Paluzzi P, Rutigliano P, Hackerman F (1996) Pregnancy and addiction. A comprehensive care model. J Subst Abuse Treat *13*: 321–329

Johnson B A, Ait-Daoud N (2000) Neuropharmacological treatments for alcoholism: scientific basis and clinical findings. Psychopharmacology (Berl) *149*: 327–344

Johnson B A, Aid-Daoud N, Bowden C, DiClemente C, Roache J, Lawson K, Javors M, Ma J (2003) Oral topiramate for treatment of alcohol dependence: a randomised controlled trial. Lancet *361*: 1677–1685

Johnson E, Breslau N, Anthony J (1996) The latent dimensionality of DIS/DSM-III-R nicotine dependency: exploratory analyses. Addiction *91*: 583–588

Johnson R E, Jones H E, Fischer G (2003) Use of buprenorphine in pregnancy: patient management and effects on the neonate. Drug Alcohol Depend. *70*: S87-S101

Jones D (1990) Weaning elderly patients off psychotropic drugs in general practice: a randomised controlled trial. Health Trends *22*: 164–166

Joseph A, Fu S (2003) Safety issues in pharmacotherapy for smoking in patients with cardiovascular disease. Prog Cardiovas Dis *45*: 429–441

Kabel D, Petty F (1996) A placebo-controlled, double-blind study of fluoxetine in severe alcohol dependence: adjunctive pharmacotherapy during and after inpatient treatment. Alcohol Clin Exp Res *20*: 780–784

Kampman K, Pettinati H, Lynch K G, Sparkman T, O'Brien C (2003) A pilot trial of olanzapine for the treatment of cocaine dependence. Drug Alcohol Depend *70*: 265–273

Kandall S R, Doberczak T M, Jantunen M, Stein J (1999) The methadone-maintained pregnancy. Clin Perinatol *26*: 173–183

Kapur B, Hackman R, Selby P, Klein J, Koren G (2001) Randomized, double-blind, placebo-controlled trial of nicotine replacement therapy in pregnancy. Curr Ther Res Clin Exp *62*:274–278

Keaney F, Strang J, Gossop M, Marshall E, Farrell M, Welch S, Hahn B, Gonzalez A (2001) A double-blind randomized placebo-controlled trial of lofexidine in alcohol withdrawal: lofexidine is not a useful adjunct to chlordiazepoxide. Alcohol Alcohol *36*:426–430

Kelly C, McCreadie R (2000) Cigarette smoking and schizophrenia. Adv Psychiatr Treat 6: 327–331

Kiefer F, Jahn H, Tarnaske T, Helwig H, Briken P, Holzbach R, Kampf P, Stracke R, Baehr M, Naber D, Wiedemann K (2003) Comparing and combining naltrexone and acamprosate in relapse prevention of alcoholism: a double-blind, placebo-controlled study. Arch Gen Psychiatry *60*: 92–99

Kinnunen T, Doherty K, Militello F, Garvey A (1996) Depression and smoking cessation: characteristics of depressed smokers and effects of nicotine replacement. J Consult Clin Psychol *64*: 791–798

Kirchmayer U, Davoli M, Verster A (2003) Naltrexone maintenance treatment for opioid dependence (Cochrane Review). In: The Cochrane Library. John Wiley & Sons, Ltd, Chichester

Kleber H, Weissman M, Rounsaville B, Wilber C, Prusoff B, Riordan C (1983) Imipramine as treatment for depression in addicts. Arch Gen Psychiatry *40*: 649–653

Klee H, Morris J (1997) Amphetamine misuse: the effects of social context on injection related risk behaviour. Addict Res *5*: 329–342

Kolar A, Brown B, Weddington W, Haertzen C, Michaelson B, Jaffe J (1992) Treatment of cocaine dependence in methadone maintenance clients: a pilot study comparing the efficacy of desipramine and amantadine. Int J Addict *27*: 849–868

Koob G, Mason B, De Witte P, Littlejohn J, Siggins G (2002) Potential neuroprotective effects of acamprosate. Alcohol Clin Exp Res *26*: 586–592

Kosten T (1994) Buprenorphine for benzodiazepine-abusing heroin addicts. Am J Psychiatry *15*: 151

Kosten T, O'Connor P (2003) Management of drug and alcohol withdrawal. N Engl J Med *348*: 1786–1794

Kosten T, Morgan C, Falcione J, Schottenfeld R (1992) Pharmacotherapy for cocaine-abusing methadone-maintained patients using amantadine or desipramine. Arch Gen Psychiatry *49*: 894–898

Kosten T, Markou A, Koob G (1998) Depression and stimulant dependence: neurobiology and pharmacology. J Nerv Ment Dis *186*: 737–745

Kownacki R, Shadish W (1999) Does Alcoholics Anonymous work? The results from a meta-analysis of controlled experiments. Subst Use Misuse *34*: 1897–1916

Kranzler H (2000) Pharmacotherapy of alcoholism: gaps in knowledge and opportunities for research. Alcohol Alcohol *35*: 537–547

Kranzler H R, 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, Del Boca F, Babor T, Korner P, Brown J, Bohn M (1994) Buspirone treatment of anxious alcoholics. A placebo-controlled trial. Arch Gen Psychiatry *51*: 720–731

Kranzler H, Burleson J, Korner P, Del Boca F, Bohn M, Brown J, Liebowitz N (1995) Placebo-controlled trial of fluoxetine as an adjunct to relapse prevention in alcoholics. Am J Psychiatry *152*: 391–397

Kranzler H, Burleson J, Brown J, Babor T (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 H, Modesto-Lowe V, Van Kirk J (2000) Naltrexone versus nefazodone for treatment of alcohol dependence: a placebo-controlled trial. Neuropsychopharmacology *22*: 493–502

Krystal J, Carmer J, Krol W, Kirk G, Rosenheck R (2001) Naltrexone in the treatment of alcohol dependence. N Engl J Med *345*: 1734–1771

Lader M, Morton S (1991) Benzodiazepine problems. Br J Addict *86*: 823–828

Ladewig D, Knecht T, Leher P, Fendl A (1993) [Acamprosate – a stabilizing factor in long-term withdrawal of alcoholic patients]. Ther Umsch *50*: 182–188

Lal B, Singh G (1976) Experiences of a methadone detoxification programme for opium addicts. Drug Alcohol Depend *1*: 391–398

Lasser K, Boyd J W, Woolhandler S, Himmelstein D U, McCormick D, Bor D H (2000) Smoking and mental illness: A population-based prevalence study. JAMA *284*: 2606–2610

Latt N, Jurd S, Houseman J, Wutzke S (2002) Naltrexone in alcohol dependence: a randomised controlled trial of effectiveness in a standard clinical setting. MJA *176*: 530–534

Lejoyeux M, Solomon J, Ades J (1998) Benzodiazepine treatment for alcohol-dependent patients. Alcohol Alcohol *33*: 563–575

Lesch O M, Walter H (1996) Subtypes of alcoholism and their role in therapy. Alcohol Alcohol *31* (Suppl 1): 63–67

Levin F, Evans S, Coomaraswammy S, Collins E, Regent N, Kleber H (1998) Flupenthixol treatment for cocaine abusers with schizophrenia: a pilot study. Am J Drug Alcohol Abuse *24*: 343–360

Lima M S, de Oliveira Soares B G, Reisser A A, Farrell M (2002) Pharmacological treatment of cocaine dependence: a systematic review. Addiction *97*(8): 931–949

Lima A, Lima M, Soares B, Farrell M (2003a) Carbamazepine for cocaine dependence (Cochrane Review). In: The Cochrane Library. John Wiley & Sons, Ltd, Chichester

Lima M, Reisser A, Soares B, Farrell M (2003b) Antidepressants for cocaine dependence (Cochrane Review). In: The Cochrane Library. John Wiley & Sons, Ltd, Chichester

Lindberg M C, Oyler R A (1990) Wernicke's encephalopathy. Am Fam Physician *41*: 1205–1209

Ling W (1978) Naltrexone: the clinical investigator's dilemma. NIDA Res Monogr 308–314

Lintzeris N, Bell J, Bammer G, Jolley D, Rushworth L (2002a) A randomised controlled trial of buprenorphine in the ambulatory management of heroin withdrawal. Addiction *97*: 1395–1404

Lintzeris N (2002b) Buprenorphine dosing regimes in the management of outpatient heroin withdrawal. Drug Alcohol Rev *21*(1): 39–45

Lintzeris N, Bammer G, Rushworth L, Jolley D, Whelan G (2003) Buprenorphine dosing regime for inpatient heroin withdrawal: a symptom triggered dose titration study. Drug Alocohol Dependence *70*(3): 287–294

Liskow B, Goodwin D (1987) Pharmacological treatment of alcohol intoxication, withdrawal and dependence: a critical review. J Stud Alcohol *48*: 356–370

Littleton J (1995) Acamprosate in alcohol dependence: how does it work? Addiction *90*: 1179–1188

Littrell K, Petty R, Hilligoss N, Peabody C, Johnson C (2001) Olanzapine treatment for patients with schizophrenia and substance abuse. J Subst Abuse Treat *21*: 217–221

Lucht M, Kuehn K, Armbruster J, Gaensicke M, Barnow S, Tretzel H, Freyberger H (2003) Alcohol withdrawal treatment in intoxicated versus non-intoxicated patients: a controlled open-label study with tiapride/carbamazepine, clomethiazole and diazepam. Alcohol Alcohol *38*: 168–175

Lumley J Oliver S, Waters E (1999) Interventions for promoting smoking cessation during pregnancy (Cochrane Review). In: The Cochrane Library. John Wiley & Sons, Ltd, Chichester

Lutiger B, Graham K, Einarson T R, Koren G (1991) Relationship between gestational cocaine use and pregnancy outcome: a meta-analysis. Teratology *44*: 405–414

Luty J, Nikolaou V, Bearn J (2003) Is opiate detoxification unsafe in pregnancy? J Subst Abuse Treat *24*: 363–367

Malcolm R, Myrick H, Roberts J, Wang W, Anton R F, Ballenger J C (2002) The effects of carbamazepine and lorazepam on single versus multiple previous alcohol withdrawals in an outpatient randomized trial. J Gen Intern Med *17*(5): 349–355

Malcolm R, Anton R, Randall C, Johnston A, Brady K, Thevos A (1992) A placebo-controlled trial of buspirone in anxious inpatient alcoholics. Alcohol Clin Exp Res *16*: 1007–1013

Malcolm R, Roberts J, Wang W, Myrick H, Anton R (2000) Multiple previous detoxifications are associated with less responsive treatment and heavier drinking during an index outpatient detoxification. Alcohol *22*: 159–164

Malec E, Malec T, Gagne M, Dongier M (1996) Buspirone in the treatment of alcohol dependence: a placebo-controlled trial. Alcohol Clin Exp Res *20*: 307–312

Mann K, Lehert P, Morgan M Y (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

Mant A, Walsh R (1997) Reducing benzodiazepine use. Drug Alcohol Rev *16*: 77–84

Marcus P, Snyder R (1995) Reduction of comorbid substance abuse with clozapine. Am J Psychiatry *152*: 959

Margolin A, Kosten T, Avants S, Wilkins J, Ling W, Beckson M, Arndt I, Cornish J, Ascher J, Li S-H, Bridge P (1995) A multicenter trial of bupropion for cocaine dependence in methadone-maintained patients. Drug Alcohol Depend *40*: 125–131

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

Martin J, Calfas K, Patten C, Polarek M, Hofstetter C, Noto J, Beach D (1997) Prospective evaluation of three smoking interventions in 205 recovering alcoholics: one-year results of Project SCRAP-Tobacco. J Consult Clin Psychol *65*: 190–194

Martin P R, Adinoff B, Lane E, Stapleton J M, Bone G A, Weingartner H, Linnoila M, Eckardt M J (1995) Fluvoxamine treatment of alcoholic amnestic disorder. Eur Neuropsychopharmacol *5*: 27–33

Mason B (2003) Acamprosate and naltrexone treatment for alcohol dependence: an evidence-based risk-benefits assessment. Eur Neuropsychopharmacol *13*: 469–475

Mason B, Kocsis J, Ritvo E, Cutler R (1996) A double-blind, placebo-controlled trial of desipramine for primary alcohol dependence stratified on the presence or absence of major depression. JAMA *275*: 761–767

Mattick R, Breen C, Kimber J, Davoli M (2003a) Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence (Cochrane Review). In: The Cochrane Library. John Wiley & Sons, Ltd, Chichester

Mattick R, Kimber J, Breen C, Davoli M (2003b) Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence (Cochrane Review). In: The Cochrane Library. John Wiley & Sons, Ltd, Chichester

Mayo-Smith M (1997) Pharmacological management of alcohol withdrawal. JAMA *278*: 144–151

McBride W J, Li T K (1998) Animal models of alcoholism: neurobiology of high alcohol-drinking behavior in rodents. Crit Rev Neurobiol *12*: 339–369

McBride A J, Sullivan JT, Blewett A (1997) Amphetamine prescribing as a harm reduction measure: a preliminary study. Addict Res *5*: 95–112

McDowell D, Levin F, Seracini A, Nunes E (2000) Venlafaxine treatment of cocaine abusers with depressive disorders. Am J Drug Alcohol Abuse *26*: 25–31

McEvoy J, Freudenreich O, McGee M, VanderZwaag E L, Rose J (1995) Clozapine decreases smoking in patients with chronic schizophrenia. Biol Psychiatry *37*: 550–552

McEvoy J, Freudenreich O, Wilson W (1999) Smoking and therapeutic response to clozapine in patients with schizophrenia. Biol Psychiatry *46*: 125–129

McGrath P, Nunes E, Stewart J, Goldman D, Agosti V, Ocepek-Welikson K, Quitkin F (1996) Imipramine treatment of alcoholics with primary depression. Arch Gen Psychiatry *53*: 232–240

McInnes G (1987) Chlormethiazole and alcohol: a lethal cocktail. BMJ *294*: 592

McLellan A, Amdt I, Metzger D, Woody G, O'Brien C (1993) The effects of psychosocial services in substance abuse treatment. JAMA *269*: 1953–59

McRobbie H, Hajek P (2001) Nicotine replacement therapy in patients with cardiovascular disease: guidelines for health professionals. Addiction *96*: 1547–1551

Merrill J, Tetlow V A (1998) Prescribing for amphetamine users: evaluation of a dexamphetamine substitution programme. In: Beyond Oral Methadone: Expanded Pharmacotherapies for the Treatment of Drug Dependence. New York Academy of Medicine, New York

Miller W R, Brown J M, Simpson T L, Handmaker N S, Bien T H, Luckie L F, Montgomery H A, Hester R K, Tonigan J S (1995) What works? A methodological analysis of the alcohol treatment outcome literature. In Hester R K, Miller W R (eds), Handbook of alcoholism treatment approaches: effective alternatives, pp. 12–44. Allyn & Bacon, Boston, MA

Miller W R, Wilbourne P L (2002) Mesa Grande: a methodological analysis of clinical trials of treatments for alcohol use disorders. Addiction *97*: 265–277

Miotto K, McCann M, Basch J, Rawson R, Ling W (2002) Naltrexone and dysphoria: fact or myth? Am J Addict *11*: 151–160

Montgomery S A, Cowen P J, Deakin W, Freeling P, Hallstrom C, Katona C, King D, Leonard B, Levine S, Phanjoo A, Peet M, Thompson C (1993) Guidelines for the treating depressive illness with antidepressants. A statement from the British Association for Psychopharmacology. J Psychopharmacol *7*: 19–23.

Monti P M, Rohsenow D J, Rubonis A V, Niaura R S, Sirota A D, Colby S M, Goddard P, Abrams D B (1993) Cue exposure with coping skills treatment for male alcoholics: a preliminary investigation. J Consult Clin Psychol *61*: 1011–1019

Monti P *et al*. (2001) Research: naltrexone and coping-skills training can limit relapse. Alcohol Drug Abuse Week *13*: 3–4

Morgan M Y (1995) The management of alcohol withdrawal using chlormethiazole. Alcohol Alcohol *30*: 771–774

Morgenstern J, Longabaugh R (2000) Cognitive-behavioural treatment for alcohol dependence: a review of evidence for its hypothesized mechanisms of action. Addiction *95*: 1475–1490

Morton S, Lader M (1995) Buspirone treatment as an aid to benzodiazepine withdrawal. J Psychopharmacol *9*: 331–335

Moyer A, Finney J W, Swearingen C E, Vergun P (2002) Brief interventions for alcohol problems: a meta-analytic review of controlled investigations in treatment-seeking and non-treatment-seeking populations. Addiction *97*: 279–292

Mrazek M, Menges C, Steffes J, Thelen B, Erkwoh R (1999) [Therapeutic experiences with alcohol-related Korsakoff syndrome]. Nervenarzt *70*: 790–794

Murphy S, 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

Murray R P, Bailey W C, Daniels K, Bjornson W M, Kurnow K, Connett J E, Nides M A, Kiley J P (1996) Safety of nicotine polacrilex gum used by 3094 participants in the Lung Health Study. Lung Health Study Research Group. Chest *109*: 438–445

Naranjo C, Sellers E, Sullivan J, Woodley D, Kadlec K, Sykora K (1987) The serotonin uptake inhibitor citalopram attenuates ethanol intake. Clin Pharmacol Ther *41*: 266–274

Naranjo C, Kadlec K, Sanhueza P, Woodley-Remus D, Sellers E (1990) Fluoxetine differentially alters alcohol intake and other consummatory behaviors in problem drinkers. Clin Pharmacol Ther *47*: 490–498

Naranjo C, Bremner K, Lanctot K (1995) Effects of citalopram and a brief psycho-social intervention on alcohol intake, dependence and problems. Addiction *90*: 87–99

National Institute for Clinical Excellence (2002) Nicotine replacement therapy [NRT] and bupropion for smoking cessation. London Technology Appraisal Guidance no. 38, London

Nelson C, Rehm J, Ustun T, Grant B, Chatterji S (1999) Factor structures for DSM-IV substance disorder criteria endorsed by alcohol, cannabis, cocaine and opiate users: results from the WHO reliability and validity study. Addiction *94*: 583–588

Noordsy D, O'Keefe C, Mueser K, Xie H (2001) Six-month outcomes for patients who switched to Olanzapine treatment. Psychiatr Serv *52*: 501–507

Nunes E, Quitkin F (1997) Treatment of depression in drug-dependent patients: effects on mood and drug use. In: Drug-dependent individuals with comorbid mental disorders. NIDA Research Monograph, number 172: 61–84

Nunes E, Levin F (2004) Treatment of depression in patients with alcohol or other drug dependence: a Meta-analysis. JAMA *291*: 1887–1896

Nunes E, McGrath P, Quitkin F, Stewart J, Harrison W, Tricamo E, Ocepek-Welikson K (1993) Imipramine treatment of alcoholism with comorbid depression. Am J Psychiatry *150*: 1248

Nunes E, McGrath P, Quitkin F, Ocepek-Welikson K, Stewart J, Koenig T, Wager S, Klein D (1995) Imipramine treatment of cocaine abuse: possible boundaries of efficacy. Drug Alcohol Depend *39*: 185–195

Nunes E, Quitkin F, Donovan S, Deliyannides D, Ocepek-Welikson K, Koenig T, Brady R, McGrath P, Woody G (1998) Imipramine treatment of opiate-dependent patients with depressive disorders. Arch Gen Psychiatry *55*: 153–160

Nutt D J (2003) Death and dependence: current controversies over the selective serotonin reuptake inhibitors. J Psychopharmacol *17*: 355–364

O'Carroll R E, Moffoot A P, Ebmeier K P, Goodwin G M (1994) Effects of fluvoxamine treatment on cognitive functioning in the alcoholic Korsakoff syndrome. Psychopharmacology (Berl) *116*: 85–88

O'Farrell T J, Fals-Stewart W (2001) Family involved alcoholism treatment. An update. Recent Dev Alcohol *15*: 329–356

O'Malley S S, Jaffe A J, Chang G, Schottenfeld R S, Meyer R E, Rounsaville B (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, Rode S, Schottenfeld R, Meyer R, Rounsaville B (1996) Six-month follow-up of naltrexone and psychotherapy for alcohol dependence. Arch Gen Psychiatry *53*: 217–231

O'Malley S, Krishnan-Sarin S, Conor F, O'Connor P (2000) Naltrexone-induced nausea in patients treated for alcohol dependence: clinical predictors and evidence for opioid-mediated effects. J Clin Psychopharmacol *20*: 69–76

O'Malley S, Rounsaville B, Farren C, Namkoong K, Wu R, Robinson J, O'Connor P (2003) Initial and maintenance naltrexone treatment for alcohol dependence using primary care versus specialty care. Arch Intern Med *163*: 1695–1703

Oslin D, Pettinati H, Volpicelli J, Wolf A, Kampman K, O'Brien C (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, Reiter S, Meltzer B, Rosenbaum J (1993) Discontinuation of benzodiazepine treatment: efficacy of cognitive-behavioural therapy for patients with panic disorder. Am J Psychiatry *50*: 1485–1490

Oude-Voshaar R, Gorgels W, Mol A, VanBalkom A, Van de Lisdonk E, Breteler M, Van den Hoogen H, Zitman F (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

Pates R, Coombes N, Ford N (1996) A pilot programme in prescribing dexamphetamine for amphetamine users (part 1). J Subst Misuse *1*: 80–84

Patten C, Drews A, Myers M, Martin J, Wolter T (2002) Effect of depressive symptoms on smoking abstinence and treatment adherence among smokers with a history of alcohol dependence. Psychol Addict Behav *16*: 135–142

Perneger T V, Giner F, del Rio M, Mino A (1998) Randomised trial of heroin maintenance programme for addicts who fail in conventional drug treatments. BMJ *317*: 13–18

Peterson P L, Lowe J B (1992) Preventing fetal alcohol exposure: a cognitive behavioral approach. Int J Addict *27*: 613–626

Petrakis I, Carroll K, Nich C, Gordon L, Kosten T, Rounsaville B (1998) Fluoxetine treatment of depressive disorders in methadone-maintained opioid addicts. Drug Alcohol Depend *50*: 221–226

Petrakis I, Carroll K, Nich C, Gordon L, McCance-Katz E, Frankforter T, Rounsaville B (2000) Disulfiram treatment for cocaine dependence in methadone-maintained opioid addicts. Addiction *95*: 219–228

Petrakis I, O'Malley S, Rounsaville B, Poling J, McHugh-Strong C, Krystal J (2003) Naltrexone augmentation of neuroleptic treatment in alcohol abusing patients with schizophrenia. Psychopharmacology *00*: 1–13

Petrovic M, Pevernagie D, Dan Den N, Mariman A, Miachaelsen W, Afshcrift M (1999) A programme for short-term withdrawal from benzodiazepines in geriatric hospital inpatients: success rate and effect on subjective sleep quality. Int J Geriatr Psychiatry *14*: 754–760

Pettinati H, Volpicelli J, Kranzler H, Luck G, Rukstanlis M, Cnaan A (2000) Sertraline treatment for alcohol dependence: interactive effects of medication and alcoholic subtype. Alcohol Clin Exp Res *24*: 1041–1049

Pettinati H, Volpicelli J, Luck G, Kranzler H, Rukstalis M, Cnaan A (2001) Double-blind clinical trial of sertraline treatment for alcohol dependence. J Clin Psychopharmacol *21*: 143–153

Poikolainen K (1999) Effectiveness of brief interventions to reduce alcohol intake in primary health care populations: a meta-analysis. Prev Med *28*: 503–509

Poldrugo F (1997) Acamprosate treatment in a long-term community-based alcohol rehabilitation programme. Addiction *92*: 1537–1546

Pomerleau C, Brouwer R, Pomerleau O (2001) Emergence of depression during early abstinence in depressed and non-depressed women smokers. Addict Dis *20*: 73–80

Posternak M A, Mueller T I (2001) Assessing the risks and benefits of benzodiazepines for anxiety disorders in patients with a history of substance abuse or dependence. Am J Addict *10*: 48–68

Powell B, Campbell J, Landon J, Liskow B, Thomas H, Nickel E, Dale T, Penick E, Samuelson S, Lacoursiere R (1995) A double-blind, placebo-controlled study of nortriptyline and bromocriptine in male alcoholics subtyped by comorbid psychiatric disorders. Alcohol Clin Exp Res *19*: 462–468

Project MATCH Research Group (1998) Matching alcoholism treatments to client heterogeneity: treatment main effects and matching effects on drinking during treatment. Project MATCH Research Group. J Stud Alcohol *59*: 631–639

Raistrick D (2001) Alcohol withdrawal and detoxification. In Heather N, Peters T, Stockwell T (eds), International handbook of alcohol dependence and problems, pp. 523–539. John Wiley & Sons Ltd, Chichester, UK

Randall C L, Thomas S E, Thevos A K (2000) Gender comparison in alcoholics with concurrent social phobia: implications for alcoholism treatment. Am J Addict *9*: 202–215

Randall C L, Thomas S, Thevos A K (2001a) Concurrent alcoholism and social anxiety disorder: a first step toward developing effective treatments. Alcohol Clin Exp Res *25*: 210–220

Randall C L, Johnson M R, Thevos A K, Sonne S C, Thomas S E, Willard S L, Brady K T, Davidson J R (2001b) Paroxetine for social anxiety and alcohol use in dual-diagnosed patients. Depress Anxiety *14*: 255–262

Rathlev N K, D'Onofrio G, Fish S S, Harrison P M, Bernstein E, Hossack R W, Pickens L (1994) The lack of efficacy of phenytoin in the prevention of recurrent alcohol-related seizures. Ann Emerg Med *23*: 513–518

Rawson R A, Mann A J, Tennant F S Jr, Clabough D (1983) Efficacy of psychotherapeutic counselling during 21-day ambulatory heroin detoxification. NIDA Res Monogr *43*: 310–314

Rawson R A, Huber A, McCann M, Shoptaw S, Farabee D, Reiber C, Ling W (2002) A comparison of contingency management and cognitive-behavioral approaches during methadone maintenance treatment for cocaine dependence. Arch Gen Psychiatry *59*: 817–824

Regier D A, Farmer M E, Rae D S, Locke B Z, Keith S J, Judd L L, Goodwin F K (1990) Comorbidity of mental disorders with alcohol and other drug abuse. Results from the Epidemiologic Catchment Area (ECA) Study. JAMA *264*: 2511–2518

Reuler J B, Girard D E, Cooney T G (1985) Current concepts. Wernicke's encephalopathy. N Engl J Med *312*: 1035–1039

Reuster T, Buechler J, Winiecki P, Oehler J (2003) Influence of reboxetine on salivary MHPG concentration and cognitive symptoms among patients with alcohol-related Korsakoff's syndrome. Neuropsychopharmacology *28*: 974–978

Richter K P, McCool R M, Okuyemi K S, Mayo M S, Ahluwalia J S (2002) Patients' views on smoking cessation and tobacco harm reduction during drug treatment. Nicotine Tob Res *4* (Suppl 2): S175–S182

Rickels K, Case W, Schweizer E, Garcia-Espagna F, Fridman R (1990) Benzodiazepine dependence: management of discontinuation. Psychopharmacol Bull *26*: 63–68

Rickels K, Schweizer E, Garcia E, Case G, DeMartinis N, Greenblatt D (1999) Trazodone and valporate in patients discontinuing long-term benzodiazepine therapy: effects on withdrawal symptoms and taper outcome. Psychopharmacology *141*: 1–5

Ries P, Roy-Byrne P, Ward N, Neppe V, Cullison S (1989) Carbamazepine treatment for benzodiazepine withdrawal. Am J Psychiatry *146*: 536–537

Rohsenow D J, Monti P M, Rubonis A V, Gulliver S B, Colby S M, Binkoff J A, Abrams D B (2001) Cue exposure with coping skills training and communication skills training for alcohol dependence: 6- and 12-month outcomes. Addiction *96*: 1161–1174

Romberger D, Grant K (2004) Alcohol consumption and smoking status: the role of smoking cessation. Biomed Pharmacother *58*: 77–83

Roozen H, Boulogne J, Tulder M, van den Brink W, De Jong CA, Kerkhof A J (2004) A systematic review of the effectiveness of the community reinforcement approach in alcohol, cocaine and opioid addiction. Drug Alcohol Depend *74*: 1–13

Ross J, Darke S (2000) The nature of benzodiazepine dependence among heroin users in Sydney, Australia. Addiction *95*: 1785–1793

Roy-Byrne P, Pages K, Russo J, Jaffe C, Blume A, Kingsley E, Cowley D, Ries R (2000) Nefazodone treatment of major depression in alcohol-dependent patients: a double-blind, placebo-controlled trial. J Clin Psychopharmacol *20*: 129–136

Roy A (1998) Placebo-controlled study of sertraline in depressed recently abstinent alcoholics. Biol Psychiatry *44*: 633–637

Royal College of Physicians (2001) Alcohol – can the NHS afford it? Royal College of Physicians, London

Rubio G, Jimenez-Arriero M, Ponce G, Palomo T (2001) Naltrexone versus acamprosate: one year follow-up of alcohol dependence treatment. Alcohol Alcohol *36*: 419–425

Rustembegovic A, Kundurovic Z, Sapcanin A, Sofic E (2003) A placebo-controlled study of memantine (Ebixa) in dementia of Wernicke–Korsakoff syndrome. Med Arh *57*: 149–150

Sahin H A, Gurvit I H, Bilgic B, Hanagasi H A, Emre M (2002) Therapeutic effects of an acetylcholinesterase inhibitor (donepezil) on memory in Wernicke-Korsakoff's disease. Clin Neuropharmacol *25*: 16–20

Saitz R, Mayo-Smith M F, Roberts M S, Redmond H A, Bernard D R, Calkins D R (1994) Individualized treatment for alcohol withdrawal. A randomized double-blind controlled trial. JAMA *272*: 519–523

San L, Cami J, Fernandez T, Olle J M, Peri J M, Torrens M (1992) Assessment and management of opioid withdrawal symptoms in buprenorphine-dependent subjects. Br J Addict *87*: 55–62

Sass H, Soyka M, Mann K, Zieglgansberger M (1996) Relapse prevention by acamprosate. Arch Gen Psychiatry *53*: 673–680

Saxon A, McGuffin R, Dale Walker R (1997) An open trial of transdermal nicotine replacement therapy for smoking cessation among alcohol and drug-dependent inpatients. J Subst Abuse Treat *14*: 333–337

Schmitz J, Averill P, Stotts A, Moeller F, Rhoades H, Grabowski J (2001) Fluoxetine treatment of cocaine-dependent patients with major depressive disorder. Drug Alcohol Depend *63*: 207–214

Schuckit M A, Tipp J E, Reich T, Hesselbrock V M, Bucholz K K (1995) The histories of withdrawal convulsions and delirium tremens in 1648 alcohol dependent subjects. Addiction *90*: 1335–1347

Schweizer E, Rickels K (1998) Benzodiazepine dependence and withdrawal: a review of the syndrome and its clinical management. Acta Psychiatr Scand *98*: 95–101

Schweizer E, Rickels K, Case W, Greenblatt D (1991) Carbamazepine treatment in patients discontinuing long-term benzodiazepine therapy. Effects on withdrawal severity and outcome. Arch Gen Psychiatry 8: 448–452

Scott J, Gilvarry E, Farrell M (1998) Managing anxiety and depression in alcohol and drug dependence. Addict Behav *23*: 919–931

Seivewright N (1998) Theory and practice in managing benzodiazepine dependence and abuse. J Subst Misuse 3: 170–177

Seivewright N (2000) More than methadone? The case for other substitute drugs. Community treatment of drug misuse: more than methadone, pp. 49–81. Cambridge University Press, Cambridge, UK

Seivewright N, Donmall M, Daly C (1993) Benzodiazepines in illicit drug

scene – the UK picture and some treatment dilemmas. Int J Drug Policy *4*: 42–48

Sellers E M, Naranjo C A, Harrison M, Devenyi P, Roach C, Sykora K (1983) Diazepam loading: simplified treatment of alcohol withdrawal. Clin Pharmacol Ther *34*: 822–826

Senay E C, Dorus W, Goldberg F, Thornton W (1977) Withdrawal from methadone maintenance. Rate of withdrawal and expectation. Arch Gen Psychiatry *34*: 361–367

Senay E C, Dorus W, Showalter C V (1981) Short-term detoxification with methadone. Ann NY Acad Sci *362*: 203–216

Sgouros X, Baines M, Bloor R N, McAuley R, Ogundipe L O, Willmott S (2004) Evaluation of a clinical screening instrument to identify states of thiamine deficiency in inpatients with severe alcohol dependence syndrome. Alcohol Alcohol *39*(3): 227–232

Shand F, Gates J, Fawcett J, Mattick RP (2003) The treatment of alcohol problems: a review of the evidence. National Drug and Alcohol Research Centre. Department of Health and Ageing, Australia

Shearer J, Wodak A, Mattick R P, van B I, Lewis J, Hall W, Dolan K (2001) Pilot randomized controlled study of dexamphetamine substitution for amphetamine dependence. Addiction *96*: 1289–1296

Shearer J, Wodak A, van B I, Mattick R P, Lewis J (2003) Pilot randomized double blind placebo-controlled study of dexamphetamine for cocaine dependence. Addiction *98*: 1137–1141

Shekelle P G, Woolf S H, Eccles M, Grimshaw J (1999) Clinical guidelines: developing guidelines. BMJ *318*: 593–596

Silagy C, Lancaster T, Stead L, Mant D, Fowler G (2003) Nicotine replacement therapy for smoking cessation (Cochrane Review). In: The Cochrane Library. John Wiley & Sons, Ltd, Chichester

Siris S G (1990) Pharmacological treatment of substance-abusing schizophrenic patients. Schizophr Bull *16*: 111–122

Slattery J, Chick J, Cochrane M, Godfrey C, Kohli H, Macpherson K, Parott S, Quinn S, Single A, Tochel C, Watson H (2003) Prevention of relapse in alcohol dependence. Health Technology Assessment Report 3. Health Technology Board for Scotland, Glasgow

Smelson D, Losonczy M, Davis C, Kaune M, Williams J, Ziedonis D (2002) Risperidone decreases craving and relapses in individuals with schizophrenia and cocaine dependence. Can J Psychiatry *47*: 671–675

Smith N (2002) A review of the published literature into cannabis withdrawal symptoms in human users. Addiction *97*: 621–632

Soares B, Limas M, Reisser A, Farrell M (2003) Dopamine agonists for cocaine dependence (Cochrane Review). In: The Cochrane Library. John Wiley & Sons, Ltd, Chichester

Sokol R J, Delaney-Black V, Nordstrom B (2003) Fetal alcohol spectrum disorder. JAMA *290*: 2996–2999

Sonne S C, Brady K T (2002) Bipolar disorder and alcoholism. Alcohol Res Health *26*: 103–108

Sorensen J L, Hargreaves W A, Weinberg J A (1982) Withdrawal from heroin in three or six weeks. Comparison of methadyl acetate and methadone. Arch Gen Psychiatry *39*: 167–171

Soyka M, Sass H (1994) Acamprosate: a new pharmacotherapeutic approach to relapse prevention in alcoholism – preliminary data. Alcohol Alcohol 2: 531–536

Srisurapanont M, Jarusuraisin N (2003a) Opioid antagonists for alcohol dependence. (Cochrane Review) In: The Cochrane Library. John Wiley & Sons, Ltd, Chichester

Srisurapanont M, Jarusuraisin N, Kittirattanapaiboon P (2003b) Treatment for amphetamine dependence and abuse (Cochrane Review). In: The Cochrane Library. John Wiley & Sons, Ltd, Chichester

Stitzer M, Bigelow G, Liebson I, Hawthorne J (1992) Contingent reinforcement for benzodiazepine-free urines: evaluation of a drug abuse treatment intervention. J Appl Behav Anal *15*: 493–503

Strang J, Gossop M (1990) Comparison of linear versus inverse exponential methadone reduction curves in the detoxification of opiate addicts. Addict Behav *15*: 541–547

Strang J, Marsden J, Cummins M, Farrell M, Finch E, Gossop M, Stewart D, Welch S (2000) Randomized trial of supervised injectable versus oral methadone maintenance: report of feasibility and 6-month outcome. Addiction *95*: 1631–1645

Stratton K, Howe C, Battaglia F (1996) Fetal alcohol syndrome: diagnosis, epidemiology, prevention and treatment. National Academy Press, Washington DC

Streeton C, Whelan G (2001) Naltrexone, a relapse prevention maintenance treatment of alcohol dependence: a meta-analysis of randomized controlled trials. Alcohol Alcohol *36*: 544–552

Swift R (1999) Drug therapy for alcohol dependence. N Engl J Med *340*: 1482–1490

Tashkin D, Kanner R, Bailey W, Buist S, Anderson P, Nides M, Gonzales D, Dozier G, Patel M K, Jamerson B (2001) Smoking cessation in patients with chronic obstructive pulmonary disease: a double-blind, placebo-controlled, randomised trial. Lancet *357*: 1571–1575

Taylor D J (1999) Alcohol Consumption in Pregnancy (9). Royal College of Obstetricians and Gynecologists. http://www.rcog.org.uk/

Tennant F S Jr, Russell B A, Casas S K, Bleich R N (1975) Heroin detoxification. A comparison of propoxyphene and methadone. JAMA *232*: 1019–1022

Thomas J D, Riley E P (1998) Fetal Alcohol Syndome. Does alcohol withdrawal play a role? Alcohol Res Health *22*: 47–53

Thomson A D (2000) Mechanisms of vitamin deficiency in chronic alcohol misusers and the development of the Wernicke–Korsakoff syndrome. Alcohol Alcohol Suppl *35* (Suppl 1): 2–7

Thomson A, Cook C, Touquet R, Henry J (2002) The Royal College of Physicians report on alcohol: guidelines for managing Wernicke's encephalopathy in the accident and emergency department. Alcohol Alcohol *37*: 513–521

Thorsteinsson H, Gillin J, Patten C, Golshan S, Sutton L, Drummond S, Clark C, Kelsoe J, Rapaport M (2001) The effects of transdermal nicotine therapy for smoking cessation on depressive symptoms in patients with major depression. Neuropsychopharmacology *24*: 350–358

Tiihonen J, Ryynanen O-P, Kauhanen J, Hakola H, Salaspuro M (1996) Citalopram in the treatment of alcoholism: a double-blind placebo-controlled study. Pharmacopsychiatry *29*: 27–29

Titievsky J, Seco G, Barranco M, Kyle E (1982) Doxepin as adjunctive therapy for depressed methadone maintenance patients: a double-blind study. J Clin Psychiatry *43*: 454–456

Tober G, Strang J (2003) Methadone matters: evolving practice of community methadone treatment of opiate addiction. Taylor & Francis, New York

Tollefson G, Montague-Clouse J, Tollefson S (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, Farsang C, Klaene G, Lewis K, Manolis A, Perruchoud A P, Silagy C, Van Spiegel P I, Astbury C, Hider A, Sweet R (2003) Bupropion SR for smoking cessation in smokers with cardiovascular disease: a multicentre, randomised study. Eur Heart J *24*: 946–955

Tsuang J, Eckman T, Shaner A, Marder S (1999) Clozapine for substance-abusing schizophrenic patients. Am J Psychiatry *156*: 1119–1120

Turnbull P J, McSweney T, Webster R, Edmunds M, Hough M (2000) Drug treatment and testing orders: final evaluation report. Home Office Research Study 212. Home Office, London

Tyrer P, Rutherford D, Huggett T (1981) Benzodiazepine withdrawal symptoms and propranolol. Lancet *1*: 520–522

Tyrer P, Owen R, Dawling (1983) Gradual withdrawal of diazepam after long-term therapy. Lancet *1*: 1402–1406

Tyrer P, Ferguson B, Hallstrom C, Michie M, Tyrer S, Cooper S, Caplan R, Barczak P (1996) A controlled trial of dothiepin and placebo in treating benzodiazepine withdrawal symptoms. Br J Psychiatry *168*: 457–461

Udelman H, Udelman D (1990) Concurrent use of buspirone in anxious patients during withdrawal from alprazolam therapy. J Clin Psychiatry *51*: 46–50

UKATT Research Team (2001) United Kingdom Alcohol Treatment Trial (UKATT): hypotheses, design and methods. Alcohol Alcohol *36*:11–21

Ulm R, Volpicelli J, Volpicelli L (1995) Opiates and alcohol self-administration in animals. J Clin Psychiatry *56*:5–14

United States Department of Health and Human Services (2000) Reducing tobacco use. A report of the Surgeon General. Executive summary. MMWR Recommunication Rep. United States Department of Health & Human Services *49*: 1–27

Van den Brink W, van Ree J (2003) Pharmacological treatments for heroin and cocaine addiction. Eur Neuropsychopharmacol *13*: 476–487

Van den Brink W, Hendriks V, Blanken P, Koeter M, van Zwieten B, van Ree J (2003) Medical prescription of heroin to treatment resistant heroin addicts: two randomised controlled trials. BMJ 327–310

Van Valkenburg C, Akiskal H (1999) Which patients presenting with clinical anxiety will abuse benzodiazepines? Hum Psychopharmacol *14*: S45-S51

Verheul R, van den B W, Geerlings P (1999) A three-pathway psychobiological model of craving for alcohol. Alcohol Alcohol *34*: 197–222

Verheul R, Lehert P, Geerlings P J, Koeter M W, van den Brink W (2004) Predictors of acamprosate efficacy: results from a pooled analysis of 7 European trials including 1485 alcohol-dependent patients. Psychopharmacology, in press

Victor M V, Adams R C, Collins G H (1989) The Wernicke-Korsakoff syndrome and related neurologic disorders due to alcoholism and malnutrition. FA Davis., Philadelphia, PA

Vito G F, Tewksbury R A (1998) The impact of treatment: The Jefferson county (Kentucky) drug court program. Fed Probat *62*: 46–51

Volpicelli J R, Clay K L, Watson N T, O'Brien C P (1995) Naltrexone in the treatment of alcoholism: predicting response to naltrexone. J Clin Psychiatry *56* (Suppl 7): 39–44

Volpicelli J, Rhines K, Volpicelli L, Alterman A, O'Brien C (1997) Naltrexone and alcohol dependence. Arch Gen Psychiatry *54*: 737–742

Vorma H, Naukkarinen H, Sarna S, Kuoppasalmi K (2002) Treatment of outpatients with complicated benzodiazepine dependence: comparison of two approaches. Addiction *97*: 851–859

Walsh D C, Hingson R W, Merrigan D M, Levenson S M, Cupples L A, Heeren T, Coffman G A, Becker C A, Barker T A, Hamilton S K (1991) A randomized trial of treatment options for alcohol-abusing workers. N Engl J Med *325*: 775–782

Walters G D (2000) Behavioural self-control training for problem drinkers: a meta-analysis of randomized control studies. Behav Ther *31*: 135–149

Wang E C (1999) Methadone treatment during pregnancy. J Obstet Gynecol Neonatal Nurs *28*: 615–622

Weddington W, Brown B, Haertzen C, Hess J, Mahaffey J, Kolar A, Jaffe J (1991) Comparison of amantadine and desipramine combined with psychotherapy for treatment of cocaine dependence. Am J Drug Alcohol Abuse *17*: 137–152

Weiner E, Ball M, Summefelt A, Gold J, Buchanan R (2001) Effects of sustained-release bupropion and supportive group therapy on cigarette consumption in patients with schizophrenia. Am J Psychiatry *158*: 635–637

Weiss R D, Greenfield S F, Najavits L M, Soto J A, Wyner D, Tohen M, Griffin M L (1998) Medication compliance among patients with bipolar disorder and substance use disorder. J Clin Psychiatry *59*: 172–174

Weizman T, Gelkopf M, Melamed Y, Adelson M, Beleich A (2003) Treatment of benzodiazepine dependence in methadone maintenance treatment patients: a comparison of two therapeutic modalities and the role of psychiatric comorbidity. Aust NZ J Psychiatry *37*: 458–463

West R, McNeill A, Raw M (2000) Smoking cessation guidelines for health professionals: an update. Thorax *55*: 987–999

White R (2000) Dexamphetamine substitution in the treatment of amphetamine abuse: an initial investigation. Addiction *95*: 229–238

Whitworth A, Fischer F, Lesch O, Nimmerrichter A, Oberbauer H, Platz G, Potgieter A, Walter H, Fleischhacker W (1996) Comparison of acamprosate and placebo in long-term treatment of alcohol dependence. Lancet *347*: 1438–1443

WHO (1992) The ICD-10 classification of mental health and behavioural disorders – clinical descriptions and diagnostic guidelines. WHO, Geneva

Wicks W, Darke S, Ross J (2000) Clobazam maintenance among methadone maintenance patients with problematic benzodiazepine use: five case studies. Drug Alcohol Rev *19*: 401–405

Wild T C, Roberts A B, Cooper E L (2002) Compulsory substance abuse treatment: an overview of recent findings and issues. Eur Addict Res *8*: 84–93

Wilk A I, Jensen N M, Havighurst T C (1997) Meta-analysis of randomized control trials addressing brief interventions in heavy alcohol drinkers. J Gen Intern Med *12*: 274–283

Williams D, McBride A (1998) The drug treatment of alcohol withdrawal symptoms: a systematic review. Alcohol Alcohol *33*: 103–115

Williams H, Oyefeso A, Ghodse A (1996) Benzodiazepine misuse and dependence among opiate addiction treatment. Irish J Psychol Med *13*: 62–64

Wilson A, Vulcano B (1984) A double-blind, placebo-controlled trial of magnesium sulfate in the ethanol withdrawal syndrome. Alcohol Clin Exp Res *8*: 542–545

Wisborg K, Henriksen T B, Jespersen L B, Secher N J (2000) Nicotine patches for pregnant smokers: a randomized controlled study. Obstet Gynecol *96*: 967–971

Woody G, O'Brien C, Rickels K (1975) Depression and anxiety in heroin addicts: a placebo-controlled study of doxepin in combination with methadone. Am J Psychiatry *132*: 447–450

Woody G E, O'Brien C P, McLellan A T, Marcovici M, Evans B D (1982) The use of antidepressants with methadone in depressed maintenance patients. Ann NY Acad Sci *398*: 120–127

Ziedonis D, Kosten T (1991) Pharmacotherapy improves treatment outcome in depressed cocaine addicts. J Psychoact Drugs 4: 417–425

Zimmet S, Strous R, Burgess E, Kohnstamm S, Green A (2000) Effects of clozapine on substance use in patients with schizophrenia and schizoaffective disorder: a retrospective survey. J Clin Psychopharmacol *20*: 94–98

Zitman F, Couvee 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

Zlotnick C, Franchino K, St Claire N, Cox K, St John M (1996) The impact of outpatient drug services on abstinence among pregnant and parenting women. J Subst Abuse Treat *13*: 195–202