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REVIEW

World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Substance Use and Related Disorders, Part 1: Alcoholism

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Abstract

These practice guidelines for the biological treatment of substance use disorders were developed by an international Task Force of the World Federation of Societies of Biological Psychiatry (WFSBP). The goal during the development of these guidelines was to review systematically all available evidence pertaining to the treatment of substance use disorders, and to reach a consensus on a series of practice recommendations that are clinically and scientifically meaningful based on the available evidence. These guidelines are intended for use by physicians evaluating and treating people with substance use disorders and are primarily concerned with the biological treatment of adults suffering from substance use disorders. The data used to develop these guidelines were extracted primarily from various national treatment guidelines for substance use disorders, as well as from meta-analyses, reviews and randomized clinical trials on the efficacy of pharmacological and other biological treatment interventions identified by a search of the MEDLINE database and Cochrane Library. The identified literature was evaluated with respect to the strength of evidence for its efficacy and then categorized into four levels of evidence (A–D). This first part of the guidelines covers the treatment of alcohol dependence; Part 2 will be devoted to the treatment of drug dependence.

Key words: *Alcoholism, pharmacotherapy, acamprosate, naltrexone, topiramate, carbamazepine, disulfiram, ondansetron, benzodiazepine*

Introduction

Alcohol dependence is a widespread psychiatric disorder with lifetime prevalence estimates of 7–12.5% in most Western countries (Pirkola et al. 2006; Hasin et al. 2007), though with clear evidence of variability of prevalence (Rehm et al. 2005). Alcohol misuse and dependence are defined by a cluster of somatic, psychological and behavioural symptoms. In the US, a recent estimate of the 1-year population prevalence of alcohol use disorders (i.e., alcohol abuse or dependence) was 8.5% (Grant et al. 2004).

The biological treatment of alcoholism includes therapies for alcohol intoxication, withdrawal symptoms, alcohol-related neuropsychiatric disorders,

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and for the initiation and maintenance of abstinence (i.e., relapse prevention). Over the past two decades, a number of medications have been tested for these indications.

Alcohol's effects on neurotransmitters

Alcohol is metabolized by the alcohol dehydrogenases (ADHs) to acetaldehyde, which is rapidly converted by acetaldehyde dehydrogenases (ALDHs) to acetate. Acetaldehyde is a toxic compound that is responsible for many unpleasant effects of alcohol, especially the 'flushing response' seen among susceptible individuals. There are a number of isoforms of both enzymes which significantly modify alcohol metabolism, tolerance and risk for development of alcohol dependence. Blockade of ALDHs by different drugs, especially disulfiram (see below), was until recently one of the few pharmacological interventions for alcohol dependence. There is now compelling evidence from controlled clinical trials that a variety of compounds that interact with the opioid, serotonergic, and γ-aminobutyric acid (GABA)/glutamate systems are safe and efficacious medications for treating alcohol withdrawal, alcohol dependence, or both.

Alcohol is a simple molecule that affects many different neurotransmitters systems including, but not limited to, dopamine, serotonin, glutamate, opioids, and GABA. There is a very substantial body of literature on the neuropharmacology of alcohol, including neurochemical and neuroimaging studies. Some of the methodological problems that limit interpretation of the results of these studies are that:

1. acute and chronic effects of alcohol may differ substantially;
2. dose-dependent effects of alcohol are often overlooked;
3. changes induced by alcohol's metabolic products (e.g., acetaldehyde) and other ingredients of alcoholic beverages are difficult to evaluate;
4. alcohol has clear neurotoxic effects, resulting in cell damage;
5. few studies have been conducted in long-term abstinent alcoholics or high-risk patients.

Over the last decades considerable efforts have been made to elucidate the neurobiological basis of alcoholism. Evidence comes from animal studies as well as from neurochemical and neuroimaging studies in humans (for reviews see Johnson and Ait-Daoud 2000; Petrakis 2006; Knapp et al. in press). Alcohol does not act via a single receptor but affects multiple neurotransmitter systems and receptors. In brief, acute alcohol intake has consistently been shown to enhance GABAergic neurotransmission. There also is cross-tolerance between alcohol and GABAergic drugs. The clinical picture of alcohol intoxication, which includes sedation, ataxia and drowsiness, can be explained by its effects on GABAergic neurotransmission. PET studies have revealed reduced GABA-receptor function in alcohol dependence (Lingford-Hughes et al. 2005). Recent genetic studies also show that the vulnerability for alcoholism may be mediated in part through variation in the genes encoding GABA receptor subunits (Covault et al. 2004; Dick et al. 2004; Edenberg et al. 2004; Lappalainen et al. 2005; Fehr et al. 2006; Soyka et al. 2008). In alcohol withdrawal, GABAergic dysfunction contributes to restlessness, seizures and other signs and symptoms.

There is also substantial evidence that alcohol enhances dopaminergic transmission in the mesolimbic brain (Johnson and Ait-Daoud 2000). The abuse liability of alcohol appears to be mediated by dopaminergic pathways that originate in the ventral tegmental area and progress via the nucleus accumbens to the cortex (Weiss and Porrino 2002; Koob 2003). In addition, alcohol was found to increase serotonin levels and to antagonize glutamatergic neurotransmission (see below). Recently the interaction of the endocannabinoid system and alcohol has attracted more attention (Economidou et al. 2006).

Methods

These guidelines are intended for use in clinical practice by clinicians who diagnose and treat patients with substance use disorders. The aim of these guidelines is to improve the quality of care and to aid physicians in clinical decisions. Although these guidelines are based on the available published evidence, the treating clinician is ultimately responsible for the assessment and the choice of treatment options, based on knowledge of the individual patient. These guidelines do not establish a standard of care nor do they ensure a favourable clinical outcome if followed. The primary aim of the guidelines is to evaluate the role of pharmacological agents in the treatment and management of substance use disorders, with a focus on the treatment of adults. Because such treatments are not delivered in isolation, the role of specific psychosocial and psychotherapeutic interventions and service delivery systems is also covered, albeit briefly.

The aim of these guidelines is to bring together different views on the appropriate treatment of substance use disorders from experts representing all continents. To achieve this aim, an extensive literature search was conducted using the Medline

and Embase databases through March 2007, supplemented by other sources, including published reviews. The guidelines presented here are based on data from publications in peer-reviewed journals. The evidence from the literature research was summarized and categorized to reflect its susceptibility to bias (Shekelle 1999). Daily treatment costs were not taken into consideration due to the variation worldwide in medication costs. Each treatment recommendation was evaluated and is discussed with respect to the strength of evidence for its efficacy, safety, tolerability and feasibility. It must be kept in mind that the strength of recommendation is due to the level of efficacy and not necessarily of its importance. Four categories were used to determine the hierarchy of recommendations (related to the described level of evidence):

***Level A*:** There is good research-based evidence to support this recommendation. The evidence was obtained from at least three moderately large, positive, randomised, controlled, double-blind trials (RCTs). In addition, at least one of the three studies must be a well-conducted, placebo-controlled study.

Level B: There is fair research-based evidence to support this recommendation. The evidence was obtained from at least two moderately large, positive, randomised, double-blind trials (this can be either two or more comparator studies or one comparator-controlled and one placebo-controlled study) or from one moderately large, positive, randomised, double-blind study (comparator-controlled or placebo-controlled) and at least one prospective, moderately large (sample size equal to or greater than 50 participants), open-label, naturalistic study.

Level C: There is minimal research-based evidence to support this recommendation. The evidence was obtained from at least one randomised, double-blind study with a comparator treatment and one prospective, open-label study/case series (with a sample of at least 10 participants), or at least two prospective, open-label studies/case series (with a sample of at least 10 participants) showing efficacy.

Level D: Evidence was obtained from expert opinions (from authors and members of the WFSBP Task Force on Addiction Disorders) supported by at least one prospective, open-label study/case series (with a sample of at least 10 participants).

No level of evidence or Good Clinical Practice (GCP): This category includes expert opinion-based statements for general treatment procedures and principles.

The guidelines were developed by the authors and arrived at by consensus with the WFSBP Task Force on Addiction Disorders, consisting of 22 international experts in the field.

Treatment of the alcohol withdrawal syndrome and delirium tremens

The alcohol withdrawal syndrome (AWS) occurs with some frequency among individuals with a diagnosis of alcohol dependence. The AWS develops within the first hours or days of abstinence or after a significant reduction of alcohol consumption in an individual with severe physical dependence. In many cases, this condition resolves without complications and does not require pharmacological treatment. However, in some cases it can progress to a more serious or even life-threatening condition.

Diagnostic and Statistical Manual of Mental Disorders, 4th edition Text Revision (DSM-IV-TR) (American Psychiatric Association 2000) criteria for alcohol withdrawal are:

- cessation of or reduction of heavy alcohol use;
- two or more of the following symptoms developing within hours to a few days: Autonomic hyperactivity (sweating, fast pulse); increased hand tremor; insomnia; nausea and vomiting; transient hallucination or illusions; psychomotor agitation; anxiety; grand mal seizures.

Most symptoms of alcohol withdrawal are nonspecific: tremor, elevated pulse rate and blood pressure, perspiration, agitation, nervousness, sleeplessness, anxiety, and depression. They occur typically within the first hours after discontinuation of alcohol consumption and may last for a few days up to a week, seldom for longer. In addition, more serious symptoms can occur that may warrant specific interventions: hallucinations, delirium tremens, alcohol-related psychotic symptoms, and seizures. There are a number of rating scales to measure intensity of alcohol withdrawal symptoms. The most frequently used scale is the Clinical Institute Withdrawal Assessment-Alcohol-Revised scale (CIWA-Ar, Sullivan et al. 1989). There are a number of detailed evidence-based guidelines concerning management of AWS (Mayo-Smith et al. 1997; Mundle et al. 2003; Berner et al. 2004; Lingford-Hughes et al. 2004; American Psychiatric Association 2007).

The treatment of alcohol withdrawal focuses on the relief of immediate symptoms, prevention of complications, and the initiation of rehabilitation. Although outpatient detoxification is a safe treatment option for many patients with mild-to-moderate AWS (Soyka et al. 2005, 2006), patients with severe symptoms, extremely high alcohol intake,

significant somatic or psychiatric symptoms, or delirium tremens should be treated as inpatients. Risk factors for severe withdrawal syndromes and delirium tremens are concurrent physical illness, long and intensive consumption of large amounts of alcohol and a previous history of similar conditions.

Supportive care (Whitfield et al. 1978; Shaw et al. 1981) and repletion of nutrient, fluid or mineral deficiencies plays a very important role in the treatment of AWS, but will not be discussed here in detail. Vitamin deficiencies are very common in patients with heavy alcoholic intake. Supplementation, especially of B vitamins including thiamine to prevent the development of Wernicke-Korsakoff syndrome (see Section 7), is recommended. The major aims of pharmacotherapy are sedation of patients to control increased excitability as manifested by agitation, anxiety and related symptoms and prevention of cardiovascular complications due to high blood pressure and pulse rate.

Numerous pharmacological agents have been used for the treatment of alcohol withdrawal, but few have sufficient empirical evidence supporting their efficacy. Results from placebo-controlled studies suggest that benzodiazepines (BZDs), β-adrenergic receptor antagonists, calcium channel blockers, anticonvulsants, and clonidine reduce withdrawal symptoms (Berglund et al. 2003). Clomethiazole, which is not available in the US, is also frequently used for the treatment of AWS. The few studies conducted in patients with delirium tremens show that benzodiazepines, used for treatment of AWS, are also useful for delirium tremens (Mayo-Smith et al. 2004).

Benzodiazepines

Worldwide, benzodiazepines (BZDs) are the drugs of first choice in the treatment of AWS. BZDs act via allosteric effects at the GABA receptor and are cross-tolerant with alcohol. There is good empirical evidence from a number of placebo-controlled studies of the clinical efficacy of BZDs. They are also superior to many other drugs for this indication (Berglund et al. 2003; Mayo-Smith 1997). BZDs are clinically effective in reducing key symptoms of the AWS such as anxiety, agitation, and symptoms of autonomic hyperactivity (e.g., perspiration, tremor, palpitations). They also reduce overall withdrawal severity and the incidence of delirium and seizures. The most commonly used BZDs are diazepam, chlordiazepoxide, oxazepam, lorazepam and alprazolam. It is a matter of debate whether short-acting or long-acting BZDs are preferable. Many clinicians favour the longer-acting agents because they provide a smoother course of withdrawal, may require less frequent dosing, and are more forgiving of a missed dose (Mayo-Smith et al. 1997). BZDs can be categorised according to their catabolism. Longer-acting BZDs are oxidized by the hepatic microsomes into active and inactive metabolites. Shorter-acting BZDs like lorazepam and oxazepam, which are not oxidized, but simply conjugated in the liver before excretion, may be preferred in patients with severe liver disorder in order to avoid cumulative effects or over-sedation.

There are different treatment strategies and techniques for the use of BZD in the treatment of AWS. In most cases, oral treatment with BZDs is sufficient and effective. In severely disturbed or physically ill patients, especially those with delirium tremens, intravenous administration of, e.g., diazepam may be preferable. While many clinicians favour a symptom-triggered approach and an individualized dosage, Sellers et al. (1983) proposed a fixed dosage scheme with diazepam 'loading,' involving administration of 20 mg every hour until the patient's symptoms subside. Other possible dosage regimens are diazepam 10 mg every 6 h, or lorazepam 2 mg or chlordiazepoxide 50 mg (*Level C*). The optimal dosage depends on the severity of AWS.

It should be noted, however, that a major problem with the BZDs is their abuse liability. Therefore, a number of alternate strategies for the treatment of the AWS have been studied. (These are discussed below).

Treatment of alcohol withdrawal delirium. Alcohol-withdrawal delirium is the most serious and dangerous manifestation of the AWS. It has a prevalence rate of approximately 5% (3–15%) among individuals who manifest withdrawal symptoms (Hansen et al. 2005). It usually lasts 48–72 h but can persist for a much longer period. Control of agitation is essential in alcohol withdrawal delirium. The patient should be sedated and kept in light somnolence for the duration of the delirium. Sedative-hypnotic agents, usually BZDs, are recommended for treatment (*Level A*). A recent meta-analysis of nine prospective controlled trials found BZDs to be more effective than antipsychotics in reducing the duration of delirium and mortality risk (Mayo-Smith et al. 2004). Several different BZDs, most commonly diazepam or lorazepam, and different dosing regimens have been recommended for the treatment of delirium. Severe cases of delirium require intravenous therapy to ensure adequate dosing. The BZD dosage required to treat delirium can be extremely high: up to 1000 mg of diazepam equivalents/day.

Although there are no placebo-controlled trials available, antipsychotics, especially haloperidol, can

be given in combination with a BZD for treatment of severe agitation (Mayo-Smith et al. 2004, *Level C*). Less potent antipsychotics may have a greater risk of lowering the seizure threshold. There are no studies of the utility and risks of second-generation antipsychotics for the treatment of agitation in the context of the AWS. β-Adrenergic blockers may be of value in patients with persistent hypertension. Magnesium should be provided in cases of hypomagnesemia.

Other GABAergic compounds. Recently, a variety of other GABAergic compounds have been advocated for treatment of AWS (Johnson et al. 2005). γ-Hydroxybutyric acid (GHB) is a naturally occurring short-chain 4-carbon fatty acid that proved to be of comparable efficacy to BZDs or clomethiazole (Addolorato et al. 1999; Gallimberti et al. 1989; Nimmerrichter et al. 2002, *Level C*). Its role as a so-called anti-craving drug is less clear (see below). GHB has a relatively short half-life, so that more frequent dosing is necessary. The abuse potential of GHB ('liquid ecstasy') has raised significant concern (McDonough et al. 2004). In addition, GHB withdrawal can be very severe. Other drugs, such as gabapentin or baclofen, have not been studied adequately to recommend them for use in the treatment of the AWS (*Level D*).

Glutamatergic compounds. Impairment of glutamatergic neurotransmission has been shown to play a major part in the development of alcohol withdrawal symptoms. There is preliminary evidence that the glutamate release inhibitor, lamotrigine; the NMDA receptor antagonist, memantine; and the AMPA/kainate receptor inhibitor, topiramate may be useful in the treatment of alcohol withdrawal (Rustembegovic et al. 2002; Choi et al. 2005; Krupitsky et al. 2007, *Level C* for topiramate; *Level D* for lamotrigine and memantine). L-type voltage-gated calcium channel antagonists (diltiazem, verapamil, nimodipine) are probably not effective.

Clomethiazole. Clomethiazole, derived from thiamine, was introduced into clinical practice in the early 1960s. It is a potent anticonvulsant hypnotic widely used in Europe to treat the AWS. It is not approved for use in the US. Although the drug has been used to treat delirium (Majumdar 1990), no randomized studies have been conducted in full-blown delirium tremens (Berglund et al. 2003). Some studies have shown a substantial decrease in mortality in patients treated with clomethiazole. The drug has GABA-mimetic and glycine-potentiating effects, a half-life of only 4 h, and no hepatic toxicity, and can be given both orally and intravenously. However, it has a substantial abuse potential and a relatively narrow therapeutic range, limiting its use in outpatients. Intravenous administration should be intensively monitored because of the risk of adverse cardiac effects.

There are few studies comparing the effects of clomethiazole with those of BZDs or other drugs. Despite the conclusion by Majumdar (1990), that clomethiazole is safe and equal or superior to BZDs, a recent meta-analysis (Mayo-Smith et al. 2004) did not favour this medication. Nonetheless, the drug remains well established in Europe for the treatment of AWS (*Level B*).

Anticonvulsants

BZDs have some limitations in clinical use, including abuse liability, pharmacological interaction with alcohol, and adverse cognitive and psychomotor effects. A number of studies demonstrating the efficacy and safety of anticonvulsants such as carbamazepine and valproate suggest that they provide safe alternatives to benzodiazepines for the treatment of alcohol withdrawal. They are considered to be relatively safe, free from abuse liability, and usually do not potentiate the psychomotor or cognitive effects of alcohol (Ait Daoud et al. 2006).

Controlled studies have shown CBZ to be superior to placebo (Bjorkquist et al. 1976; Berglund et al. 2003) and as effective as BZDs (Malcolm et al. 1989, 2001, 2002; Stuppaeck et al. 2002) or clomethiazole (Ritola and Malinen 1981; Seifert et al. 2004) for the treatment of the symptoms of AWS (*Level B*). The usual dosage of carbamazepine is 600–1200 mg/day. There is no evidence that CBZ is effective in alcohol withdrawal delirium. CBZ has also been used in combination with tiapride for outpatient treatment of AWS (Soyka et al. 2002, 2006, *Level C*). In addition to reducing symptoms of AWS, carbamazepine reduced drinks per drinking day and time to first drink in abstinent alcoholics (Mueller et al. 1997; Malcolm et al. 2002) (*Level C*).

A study of individuals with moderate alcohol withdrawal showed that sodium valproate treatment was well tolerated, reduced the need for BZD treatment, and decreased the likelihood of progression in severity of withdrawal symptoms compared with placebo (Reoux et al. 2001).

Both carbamazepine and valproate are contraindicated in patients with comorbid hepatic complications or hematological disorders.

A recent inpatient study showed that topiramate was as efficacious as lorazepam at treating alcohol withdrawal, while allowing transition of the patient to outpatient care on the same regimen (Choi et al. 2005), without the potential for abuse or the

increased risk of relapse commonly seen in alcoholics treated with BZDs. An open-label study showed topiramate to be efficacious and well tolerated in the treatment of tonic-clonic seizures associated with alcohol withdrawal (Rustembegovic et al. 2002).

Clonidine. In patients with symptoms of severe adrenergic hyperactivity, use of a sympatholytic may be necessary. Under these circumstances, either clonidine or a β-adrenergic blocker such as atenolol (Kraus et al. 1985; Horwitz et al. 1989) may be effective, especially in patients with a systolic blood pressure over 160 mmHg or diastolic over 100 mmHg. These drugs should be avoided in patients who are dehydrated, have active volume losses, or have evidence of sick sinus syndrome or high-grade conduction blocks (*Level C*).

Management of alcohol intoxication

The severely intoxicated patient should be monitored in a safe environment. The presence of other drugs should be assessed by laboratory tests, especially in severely intoxicated or sedated patients. Clinical management includes the administration of thiamine and fluids. The obtunded patient may require intervention to ensure adequate respiratory function. High doses (5 mg) of the benzodiazepine receptor antagonist flumazenil are reported to hasten the recovery from ethanol-induced heavy sedation or coma in open-label case series (Martens et al. 1990; Lheureux and Askenasi 1991), but these results require confirmation in controlled clinical trials.

Diagnosis and management of alcohol-related seizures

The relationship between alcohol and seizures is complex (Brathen et al. 1999; Leone et al. 2003). According to the recent guidelines of the European Federation of Neurological Science (EFNS) Task Force on Diagnosis and Treatment of Alcohol-Related Seizures, alcohol-related seizures account for one-third of seizure-related admissions. Up to 15% of patients with alcohol dependence suffer from seizures (Hillbom et al. 2003). There is little consensus as to the optimal evaluation and management of alcohol-related seizures (Brathen et al. 2005). While the prevalence of epilepsy in alcohol-dependent patients is only slightly higher than in the general population (Hillbom et al. 2003), the prevalence of seizures among alcohol-dependent patients is at least three times higher than in the general population. Alcohol consumption acutely increases the seizure threshold. However, following chronic heavy drinking, the seizure threshold is lowered upon cessation of drinking. Alcohol seizures typically occur within the first 6–48 h following abrupt cessation of heavy drinking. First onset of alcohol-related seizures is typically in middle-aged individuals. Most alcohol-related seizures are of the grand-mal type, although partial seizures and epileptiform EEG abnormalities are not uncommon. Some, but not all, clinical series have also found a high frequency of symptomatic or partial seizures (Brathen et al. 1999; Leone et al. 2003).

A first seizure should prompt neuroimaging to search for a structural cause, i.e., CT or MRI (Brathen et al. 2005). Since most alcohol-related seizures are of the grand mal type, any other type of seizure, e.g. focal type or partial-onset seizures, may indicate underlying pathology such as cerebrovascular disease (intracranial haemorrhage or infarctions), or concurrent metabolic, toxic, infectious, traumatic, or neoplastic disease. A number of pathophysiological mechanisms may explain the increased risk of seizures in alcoholics, including alcohol's effects on calcium and chloride flux through ion-gated glutamate and GABA receptors. Chronic alcohol exposure results in adaptive changes in the CNS, including a higher alcohol tolerance. There is no clear evidence for a genetic predisposition to alcohol withdrawal seizures, which likely reflects the difficulty of conducting research in this area. Although *status epilepticus* following an alcoholic seizure is rare, its serious consequences warrant prompt treatment to prevent it.

After an alcoholic seizure, the patient should be observed in a hospital for at least 24 h. For patients with no history of withdrawal seizures and mild-to-moderate withdrawal symptoms, routine drug therapy for prevention of seizures is not necessary. A meta-analysis of controlled trials for primary prevention of alcohol withdrawal seizures demonstrated a highly significant reduction of seizures with benzodiazepines and epileptic drugs and an increased risk with antipsychotics (Hillbom et al. 2003). Diazepam and lorazepam are recommended for such preventive efforts (*Level A*). A meta-analysis of randomised, placebo-controlled trials for the secondary prevention of seizures after alcohol withdrawal showed lorazepam to be effective but phenytoin to be ineffective (Hillbom et al. 2003). Because withdrawal seizures typically do not re-occur in abstinent patients, there is no reason for continuing antiepileptic treatment in these patients. (Hillbom et al. 2003) (*Level C*).

Alcohol psychosis

Chronic alcohol consumption can result in a psychotic disorder, most commonly with hallucinatory features. In the older psychiatric literature, this schizophrenia-like syndrome was called alcohol hallucinosis. Patients suffer from predominantly auditory but also visual hallucinations and delusions of persecution. In contrast to alcohol delirium, the sensorium in these patients is clear. Alcohol psychosis occurs rarely, although more often than previously believed (Tsuang et al. 1994). Although the prognosis is good, 10–20% of patients with alcohol psychosis will develop a chronic schizophrenia-like syndrome (Glass 1989b). In these cases, differentiating alcohol psychosis from schizophrenia can be difficult (Soyka 1990). The pathophysiology of alcohol psychosis is not clear. There is no evidence for a common genetic basis for alcohol psychosis and schizophrenia (Glass 1989a). Recent PET findings indicate a dysfunction of the thalamus in patients with alcohol psychosis (Soyka et al. 2005).

There are no studies of the pharmacotherapy of alcohol psychosis and no established therapy. Taking the often vivid psychotic symptomatology into account, with the risk of aggressive or suicidal reactions, antipsychotic treatment is warranted in most patients, perhaps optimally in combination with benzodiazepines (*Level D*). There is no evidence for an increased risk of seizures in patients with alcohol psychosis treated with antipsychotics, especially haloperidol (Soyka et al. 1992). Abstinent patients with full remission of symptoms have a good prognosis, so there is no need for ongoing treatment with antipsychotic medication.

Wernicke–Korsakoff syndrome

The metabolism of glucose requires thiamine (vitamin B1) as a co-factor. Therefore, supplementation with thiamine is vital to prevent Wernicke–Korsakoff Syndrome (Thomson et al. 2002) (*Level A*), especially in malnourished patients with signs of hypovitaminosis. Prophylactic parenteral thiamine should be given before starting any carbohydrate-containing intravenous fluids to avoid precipitating acute Wernicke's syndrome. Symptoms of morbus Wernicke (ophthalmoplegia, ataxia, loss of consciousness) must not be overlooked. Intravenous treatment with thiamine is vital in this setting and must be initiated immediately after the diagnosis is made. Even with prompt treatment, mortality in this disorder is still high. There is no established pharmacological treatment of Korsakoff psychosis to improve the memory impairment.

Treatment of alcohol dependence

Goals of treatment

Alcohol dependence is primarily manifest as impaired control over drinking. Both naturalistic and clinical long-term studies have indicated that relapse to heavy drinking can occur even after decades of abstinence (Berglund et al. 2003). Relapse to heavy drinking has also been shown in animal models even after long periods of (forced) abstinence (Schumann et al. 2003). Consequently, abstinence is the primary goal recommended by most clinicians, though there is growing interest in harm reduction strategies that aim to reduce heavy drinking, even among patients for whom the goal of treatment may not be abstinence (Johnson et al. 2003, 2007; Kranzler et al. 2003a; Garbutt et al. 2005).

Most clinicians and self-help organizations such as Alcoholics Anonymous consider alcohol dependence to be a chronic and disabling disorder for which they advocate long-term or lifelong abstinence. Although treatments that favour techniques aimed at regaining control over drinking ('controlled drinking') in alcohol-dependent patients have been advocated, the available data call into question whether this is an effective long-term strategy, at least for patients with moderate-to-severe alcohol dependence. Studies of the long-term course of alcoholism indicate that most individuals are unable to maintain controlled drinking (Vaillant 1996). Studies of effects of cognitive-behavioural therapy (CBT)-focused, self-control training in patients with limited alcohol problems show some positive effects in comparison with no treatment (for a review, see Berglund et al. 2003), but the effect in alcohol-dependent individuals remains controversial. Following a harm-reduction strategy for patients not motivated for abstinence-oriented interventions to promote a reduction in drinking is acceptable in such situations (Good Clinical Practice), but abstinence from alcohol remains the primary long-term goal for moderate-to-severe alcohol dependence.

Psychosocial treatment

A variety of psychosocial interventions (including psychotherapy) have been found to be effective in alcohol treatment (for review, see Holder et al. 1991, 2000; Miller 1992; Miller et al. 1995; Berglund et al. 2003). Long-term abstinence rates following alcohol treatment rarely exceed 40%; many studies have shown less favourable treatment results (Berglund et al. 2003; Bottlender et al. 2006). It is difficult to demonstrate the superiority of one active approach to alcohol treatment over another (Project MATCH Research Group 1997, 1998; Bottlender et al. 2006;

Schmidt et al. 2007). Nonetheless, comprehensive reviews of treatment studies (see Holder et al. 1991, 2000; Miller 1992; Miller et al. 1995; Berglund et al. 2003) reveal that, generally speaking, alcohol treatment is more effective than no treatment.

Interventions that have been found to be effective include strategies aimed at the enhancement of motivation for recovery, CBT, including broad spectrum treatment with a CBT focus and other related forms, 12-step treatment, various forms of family, social network, and marital therapy, and social competence training. The data for psychodynamically oriented treatments and others are less convincing (Bottlelender et al. 2006).

Pharmacotherapy can be used in conjunction with psychosocial treatment to increase abstinence rates or reduce relapse rates, treat other alcohol-related disorders (see above), or treat comorbid psychiatric disorders. In this context, psychotherapeutic or psychosocial interventions have been used to increase motivation for abstinence, improve motivation for medication compliance, and to enhance outcomes generally.

Ledgerwood et al. (2005) provide a comprehensive discussion of the use of combined medication and psychotherapy for treatment of alcohol use disorders. They consider six different psychotherapeutic approaches that have been used in studies of the pharmacotherapy of alcohol dependence: brief interventions, motivational enhancement therapy, CBT, behavioural treatments (e.g., contingency management, community reinforcement approaches), behavioural marital therapy, and 12-step facilitation. Although these approaches have been used widely together with pharmacotherapy, there are few controlled trials examining the interaction of psychotherapy and pharmacotherapy in alcohol dependence, and no standard psychotherapy has been established in this respect. The COMBINE Study (Anton et al. 2006) represents a major effort to examine this important area of research in alcohol treatment, but it underscores the difficulty and high cost of such trials, since evaluation of interactive effects of medication and psychosocial interventions requires large samples to provide adequate statistical power.

Treatment of comorbid psychiatric disorders

Few controlled treatment studies have been conducted in patients with co-existing psychiatric disorders, a topic that has received more attention in recent years. The limited research database indicates that in these patients treatment of alcohol dependence should be integrated with treatment of the comorbid psychiatric disorder (Berglund et al. 2003).

Mood disorders

Community- and population-based epidemiological studies consistently find a greater than 2-fold greater prevalence of depressive disorders in individuals with alcohol dependence compared to the general population (Regier et al. 1990; Agosti and Levin 2006). A review of 35 studies found that the median prevalence of current or lifetime alcohol problems in individuals with depression was 16 and 30%, respectively, compared to 7 and 16–24% in the general population (Sullivan et al. 2004). Other studies show a modest association of unipolar depression and alcohol dependence (Schuckit et al. 1997). Alcoholism in depressive patients is of special importance for the course of depression, suicide/death risk, and social functioning (Hasin et al. 1996; Agosti and Levin 2006).

The differential diagnosis between depression and alcohol-induced disorders can be difficult to make. Depressive symptoms can sometimes be differentiated into primary (preceding the onset of alcoholism) and secondary (following alcoholism onset) based upon the chronological ordering of the disorders. Because many secondary depressive symptoms may take time to resolve in abstinent patients, reliable differential diagnosis can sometimes be made only after some weeks or even months of abstinence.

There is consistent evidence for an excess rate of alcoholism in patients with bipolar disorder, with a prevalence that is up to 6-fold that seen in the general population (Regier et al. 1990; Kessler et al. 1997).

In general, the same guidelines can be used for the biological treatment of affective disorder in alcoholic patients as for non-alcoholics (for WFSBP guidelines, see Bauer et al. 2002), although a few special considerations are warranted. Apart from diagnostic problems, drug interactions with alcohol are of special relevance. Tricyclic antidepressants in combination with alcohol may lead to toxic reactions, sedation, blackouts or seizures. This risk is substantially lower for newer antidepressants, especially selective serotonin reuptake inhibitors (SSRIs). Compliance may be poorer among alcoholics than non-alcoholics, an important issue to be addressed by the clinician. For safety reasons, treatment with lithium requires excellent compliance.

Treatment with antidepressants in alcoholics may be most useful in combination with psychotherapeutic interventions such as cognitive behavioural therapy (Brown et al. 1997). A number of placebo-controlled clinical trials have been conducted on the efficacy of antidepressants (Ciraulo and Jaffe 1981; McGrath et al. 1996; Cornelius et al. 1997; Pettinati

et al. 2001; Kranzler et al. 2006). In a recent review and meta-analysis, Nunes and Levin (2004) identified 14 placebo-controlled studies with a total of 848 patients with comorbid depression and alcohol or other drug dependence: five studies of tricyclic antidepressants, seven of SSRIs, and two of antidepressants from other classes. Data indicated that antidepressant medication exerts a modest beneficial effect for patients with both disorders (*Level B*). SSRIs performed less well overall than tricyclics or other classes of antidepressants (*Level B*). This finding was in part due to a high placebo response rate in some of the SSRI studies, and must be balanced against the risk of interactions, as addressed above. When medication was effective in treating depression, there was also some effect on alcohol use, but few patients achieved abstinence. These findings indicate that the treatment of depression alone is not sufficient in these dual-diagnosis patients, but must be combined with alcohol-specific interventions. Although there is some limited evidence for SSRIs to reduce alcohol consumption, the overall evidence for non-depressive patients to benefit from this treatment is limited (LeFauvre et al. 2004; Nunes and Levin 2004). A recent meta-analysis by Torrens et al. (2005) concluded that in alcohol dependence without comorbid depression, the use of any antidepressant is not justified.

In a recent placebo-controlled trial among alcohol-dependent individuals with comorbid bipolar disorder, valproate treatment was associated with improved drinking outcomes (Salloum et al. 2005). There are no other published studies on this subject (*Level D*).

Anxiety disorders

Community-based epidemiological studies show a 2.2-fold increased risk for anxiety disorders among individuals with alcohol dependence compared to the general population (Agosti and Levin 2006). There is a lifetime prevalence of 6–20% for anxiety disorders among alcoholics. Social and specific phobias have the highest risk (Kessler et al. 1997; Grant et al. 2005; Conway et al. 2006). Differential diagnosis can be difficult due to overlapping symptoms. Self-medication of anxiety symptoms with alcohol may partially explain the high comorbidity rate. Cognitive-behavioural interventions have been found to be effective in these patients (Randall et al. 2001).

Few pharmacotherapeutic trials have been conducted in patients with alcohol dependence and anxiety disorder. One study found paroxetine to reduce anxiety symptoms in patients with comorbidity (Randall et al. 2001) (*Level D*). A review of five published studies showed a positive effect of buspirone on treatment retention and anxiety (*Level B*) (Malec et al. 1996). The effect on alcohol consumption was less clear.

Schizophrenia

Up to 34% of schizophrenic patients have an alcohol use disorder and 47% have a drug use disorder (Regier et al. 1990; Soyka 1996). Dual-diagnosis patients have a higher risk of psychotic relapse and rehospitalisation, poor medication adherence, and are at risk of suicide and aggressive behaviour (Green et al. 2002).

Case series and chart reviews suggest that second-generation antipsychotics, especially clozapine, are more effective than first-generation drugs in reducing substance use by patients with schizophrenia (Drake et al. 2000; Green et al. 2002; Green 2005; Noordsy et al. 2001). In the absence of controlled clinical trials, it is difficult to recommend any specific medication for these types of patients (*Level D*). Patients with schizophrenia and comorbid substance use have a higher risk for adverse effects of antipsychotic treatment, especially tardive dyskinesia (Miller et al. 2005) and extrapyramidal symptoms (Potvin et al. 2006), suggesting an advantage for second-generation antipsychotics (*Level C*). They may also adversely affect the reward system less than first-generation antipsychotics (Chambers et al. 2001). For patients with prominent depressive symptoms, antidepressants can be given concomitantly (Siris 1990).

With respect to anti-craving compounds, based on limited evidence, the use of naltrexone and disulfiram has been recommended in patients with psychotic spectrum disorders (Petrakis et al. 2006a). Since disulfiram also blocks dopamine-β-hydroxylase, the risk of a psychotic relapse resulting from reduced metabolism of dopamine must be considered.

Pharmacological relapse prevention

Disulfiram was the first medication approved specifically for the treatment of alcoholism. In the last decade or so, a number of additional agents for the treatment of alcohol dependence have been introduced into clinical practice, including acamprosate and naltrexone (American Psychiatric Association 2007). A number of reviews and meta-analyses have been published addressing this topic (Hughes and Cook 1997; Garbutt et al. 1999; Kenna et al. 2004a,b; Mann et al. 2004; Kranzler 2006; Soyka and Roesner 2006, Roesner et al. 2008).

Disulfiram. Disulfiram, an irreversible inhibitor of acetaldehyde dehydrogenase (ALDH), has was approved for alcohol dependence treatment by the US Food and Drug Administration in 1949. Drinking while taking disulfiram results in an elevated concentration of acetaldehyde and precipitation of the disulfiram-alcohol reaction (DAR). The DAR is unpleasant and occasionally dangerous, with a variety of symptoms including nausea, flushing, vomiting, sweating, and hypotension, among others. The rationale for using the medication is to deter the patient from drinking alcohol again. Disulfiram is usually given at a dosage of 200–500 mg/day.

Data on the efficacy of disulfiram are mixed (*Level C*) (Chick et al. 1992, Hughes and Cook 1997; Garbutt et al. 1999). The largest placebo-controlled study of the drug compared disulfiram 250 mg with disulfiram 1 mg and placebo (Fuller et al. 1986). The study failed to show an effect of disulfiram on the likelihood of abstinence over the 1-year treatment period. However, among individuals who relapsed to drinking, treatment with disulfiram 250 mg was associated with a significantly lower number of drinking days compared with the other two treatment conditions. Most of the other studies of disulfiram that have been conducted have not used a rigorous clinical trial methodology, and compelling evidence that disulfiram increases abstinence rates is lacking (for review, see Hughes and Cook 1997). Garbutt et al. (1999) concluded that the efficacy evidence for disulfiram is inconsistent and that there is more often negative evidence on other outcome measures such as relapse (*Level C*). Recent open-label studies showed a better outcome for patients treated with disulfiram compared to acamprosate or naltrexone (de Sousa and de Sousa 2004, 2005). A recent, randomized trial in patients with comorbid psychiatric disorders showed that treatment with disulfiram (open-label administration with no placebo control) and naltrexone (double-blind, placebo-controlled administration) were of equal efficacy (Petrakis et al. 2005, 2006b).

Poor adherence is a major problem with disulfiram treatment; most patients discontinue treatment within a few months (Azrin et al. 1982). Therefore, the use of supervised disulfiram treatment has been advocated. A comprehensive review of 13 controlled and five uncontrolled studies of the drug concluded that supervised disulfiram reduced drinking and improved the rate of retention in treatment compared with unsupervised disulfiram or a no-disulfiram control group (Brewer et al. 2000). Disulfiram is best considered a second-line medication in relapse prevention, which can be combined with either acamprosate or naltrexone.

Efforts have been made to develop long-lasting, implantable formulations of disulfiram to improve adherence. There are few studies of this approach. A placebo-controlled trial (Johnsen and Morland 1991) failed to show efficacy of the disulfiram implant. At present, this treatment cannot be recommended.

Acamprosate. The exact mechanism, including the molecular targets, by which acamprosate diminishes alcohol consumption and the likelihood of relapse is not entirely clear. The effects of alcohol on the glutamatergic system are complex. Acutely, alcohol reduces glutamatergic neurotransmission via NMDA receptor blockade, though it also promotes glutamate release in several important pathways in the brain. In addition to its effects on NMDA receptors, alcohol's effects on the glutamatergic system are also mediated by AMPA and kainate receptors (Moghaddam and Bolino 1994; Coster et al. 2000; Crowder et al. 2002; Krystal and Tabakoff 2002). Acamprosate modulates glutamatergic neurotransmission, counteracting hyper-glutamatergic states (Littleton 1995; Spanagel and Zieglgansberger 1997). Recent work indicates that acamprosate reduces brain glutamate levels and alcohol consumption in mice that are mutated for the Per2 gene (Spanagel et al. 2005). Per2 is a clock gene that influences the glutamatergic system and modulates alcohol intake. In addition, acamprosate may act as an antagonist of the mGluR5 subtype of metabotropic glutamate receptor, thereby blocking the excitotoxicity produced by ethanol (Harris et al. 2003). There is also evidence that, following stimulation of glutamate receptors, acamprosate blocks enhanced extracellular dopamine levels in the nucleus accumbens, a key neurobiological structure in the development of addiction (Cano-Cebrian et al. 2003). Therefore, in addition to effects on glutamate systems, acamprosate may also exert therapeutic effects through changes in dopamine-mediated alcohol reinforcement (Spanagel and Weiss 1999).

Acamprosate has poor oral bioavailabilty; therefore, the dosage used clinically is comparatively high: 1998 mg (two 333-mg tablets three times daily in patients with a body weight greater than 60 kg; two 333-mg tablets twice daily in lighter patients). The drug is not known to have any psychotropic (e.g., sedative, antidepressant) effects or to interact with other psychotropic agents, either pharmacodynamically or pharmacokinetically. Acamprosate is usually well tolerated but should not be given to patients with hypercalcemia. The most frequent adverse effect is diarrhoea.

Acamprosate significantly reduced relapse rates in alcohol-dependent patients in a number of

placebo-controlled, double blind trials (*Level A*). Acamprosate has been studied in more than 5,000 alcohol-dependent patients in 19 double-blind, placebo-controlled clinical trials conducted in 14 different countries (Bouza et al. 2004; Mann et al. 2004). Meta-analyses provide clear evidence of the efficacy of acamprosate for the maintenance of abstinence (Kranzler and Van Kirk 2001; Bouza et al. 2004; Mann et al. 2004; Roesner et al. 2008). For example, in a meta-analysis of data from 11 European clinical trials that included more than 3,000 patients, acamprosate nearly doubled the likelihood of preventing relapse to drinking [odds ratio (OR) = 1.88, 95% confidence interval (CI) = 1.57, 2.25, $P < 0.001$] and increased the likelihood that patients would remain in treatment by nearly one-third (OR = 1.29, 95% CI = 1.13, 1.47, $P < 0.001$). Perhaps the most robust effect of acamprosate was seen in a German multi-centre study, where the abstinence rate after 1 year was 41%, compared to 22% in the placebo group, an effect that persisted during a 1-year period following the discontinuation of study medication (Sass et al. 1996). However, a multi-centre trial conducted in the US (Mason et al. 2006) did not show an intent-to-treat effect of acamprosate (though secondary analyses did provide support for the drug over placebo), while the recent COMBINE Trial failed to show an effect of acamprosate on relapse prevention, either alone, or in combination with naltrexone (Anton et al. 2006).

Opioid receptor antagonists. Based on evidence that endogenous opioid peptides, such as β-endorphin, are involved both in the rewarding effects of ethanol and risk for alcoholism (Gianoulakis et al. 1989, 1996), naltrexone and nalmefene, opioid receptor antagonists with no intrinsic agonist properties, have been studied for the treatment of alcohol dependence.

Naltrexone. Early studies with naltrexone found that it reduced craving for alcohol, alcohol's reinforcing properties, alcohol-induced euphoria, and the chances of continued drinking following a slip or lapse, suggesting that naltrexone blocked the endogenous opioid system's contribution to the 'priming effect' of alcohol (Volpicelli et al. 1995; O'Malley et al. 1996a). However, the beneficial effects of naltrexone were found to diminish gradually after the 12-week medication treatment period (O'Malley et al. 1996b; Anton et al. 2000).

Many, but not all, subsequent studies of naltrexone showed it to be efficacious in the treatment of alcohol dependence (*Level A*). The efficacy of naltrexone has been confirmed in several published meta-analyses (Kranzler and Van Kirk 2001; Streeton and Whelan 2001; Bouza et al. 2004; Srisurapanont and Jarusuraisin 2005; Roesner et al. 2008).

The meta-analysis by Bouza et al. (2004) included 19 studies of naltrexone involving 3,205 participants with alcohol dependence. The large majority of these studies were of short duration (i.e., $\leq$12 weeks). Using relapse to heavy drinking as an outcome, these studies yielded an OR = 0.62 [95% CI = 0.52, 0.75, $P < 0.00001$], reflecting a 38% lower likelihood of relapse with naltrexone treatment. The likelihood of total abstinence, while also favouring naltrexone, failed to reach statistical significance (OR = 1.26; 95% CI = 0.97, 1.64, $P = 0.08$). Secondary outcomes in this meta-analysis were also significantly better in the naltrexone-treated group, including time to relapse, percentage of drinking days, number of drinks per drinking day, days of abstinence, total alcohol consumption during treatment, and levels of γ-glutamyl transpeptidase and aspartate aminotransferase.

Two long-acting (up to 1 month), injectable (intramuscular) formulations of naltrexone have also been evaluated in clinical trials to improve adherence to the medication and to increase bioavailability by avoiding first-pass metabolism. One formulation (Drug Abuse Sciences, Inc.) was administered at a dosage of 300 mg in the first month and then 150 mg monthly for 2 months, in conjunction with motivational enhancement therapy. Although it did not reduce the risk of heavy drinking, the active formulation delayed the onset of any drinking, increased the total number of days of abstinence and doubled the likelihood of subjects remaining abstinent throughout the 12-week study period (Kranzler et al. 2004). A second formulation (Alkermes, Inc.) was evaluated in two dosage strengths (Garbutt et al. 2005) and in combination with a low-intensity psychosocial intervention. Compared with placebo treatment, the 380-mg formulation resulted in a 25% reduction in the event rate of heavy drinking ($P = 0.02$). There was a significant effect in men (48% reduction), but not in women. The 190-mg formulation produced a non-significant ($P = 0.07$) 17% reduction in heavy drinking.

Comparative studies of acamprosate and naltrexone. Three published studies have directly compared acamprosate, naltrexone, and their combination. In one study, naltrexone, acamprosate, and the two medications combined were significantly more efficacious than placebo (Kiefer et al. 2003). The combined medication group had a significantly lower relapse rate than either placebo or acamprosate, but it did not differ statistically from naltrexone. In addition, there was a non-significant trend for naltrexone to produce a better outcome than

acamprosate on the time to the first drink and time to relapse. The US COMBINE Study (COMBINE Study Research Group 2003a,b) compared naltrexone, acamprosate, and their combination, together with either medical management or an intensive psychotherapy. It found naltrexone to be efficacious, while neither acamprosate alone nor acamprosate in combination with naltrexone was superior to placebo (Anton et al. 2006). A single-site, open-label, non-randomized study from Australia showed that the combination of acamprosate and naltrexone was superior to either medication alone (Feeney et al. 2006).

Nalmefene. Three clinical trials of the efficacy of nalmefene have been published (*Level C*). One study found no efficacy at 20 or 80 mg/day, although when combined, the nalmefene-treated groups had significantly lower rates of heavy drinking compared to the placebo group (Mason et al. 1999). A second study found no efficacy for nalmefene at 5, 20 or 40 mg/day on any measure of treatment outcome (Anton et al. 2004). Recently, Karhuvaara et al. (2007), reported the results of a multi-centre, randomized trial of targeted nalmefene combined with a minimal psychosocial intervention, in which alcohol dependent subjects were encouraged to use 10–40 mg of the medication when they believed drinking to be imminent. Nalmefene was significantly better than placebo in reducing heavy drinking days, very heavy drinking days, and drinks per drinking day and in increasing abstinent days. After 28 weeks, when a subgroup of nalmefene-treated subjects was randomized to a withdrawal extension, subjects randomized to receive placebo were more likely to return to heavier drinking.

In conclusion, there is abundant evidence supporting the use of naltrexone for treatment of alcohol dependence (*Level A*). However, the optimal dosage and duration of treatment are two important clinical questions that remain to be adequately addressed, along with the patient population and treatment goal (i.e., harm reduction versus abstinence) that are most likely to yield beneficial effects. New approaches to the use of naltrexone, including long-acting injectable formulations, promise to enhance the clinical utility of the medication. Although it has shown some promise, additional research is required to evaluate more fully the utility of nalmefene in the treatment of alcohol dependence.

Ondansetron

The selective 5-HT_3 receptor antagonist ondansetron has shown promise in a subset of patients with alcohol dependence (Ait-Daoud et al. 2001). In one trial, the drug diminished drinking and increased abstinence among patients with an early onset of alcohol dependence (i.e., before age 25) (Johnson et al. 2000). In an open-label study in 40 patients, ondansetron 4 μg twice daily decreased drinks per day in early-onset, but not in late-onset alcoholics (Kranzler at al. 2003b). Taken together, these data suggest that ondansetron is a promising agent for use among early-onset alcoholics.

Anti-convulsants

Carbamazepine, valproate, and topiramate have been studied for the treatment of alcohol dependence (for a review, see Ait-Daoud et al. 2006). Carbamazepine reduced drinks per drinking day and time to first drink in abstinent alcoholics (Mueller et al. 1997; Malcolm et al. 2002) (*Level C*). Small studies of valproate in alcohol-dependent individuals suggest that it might reduce relapse to heavy drinking and promote abstinence (Brady et al. 2002; Longo et al. 2002) (*Level D*). Topiramate has been studied in more detail, although few animal studies have been published to date (Gabriel et al. 2005; Farook et al. 2007; Hargreaves and McGregor 2007; Nguyen et al. 2007). A single-site clinical trial of topiramate in alcohol-dependent individuals who were actively drinking showed that it reduced drinks per day, drinks per drinking day, and percentage of heavy drinking days, and increased the percentage of days abstinent, compared with placebo (Johnson 2003). Recently, the results of a 14-week, multicentre trial of topiramate, combined with counselling to enhance medication compliance, were published (Johnson et al. 2007) (*Level B*). That study showed the medication to be superior to placebo in reducing the percentage of heavy drinking days, as well as a variety of other drinking outcomes. However, the medication was associated with more adverse events and a higher rate of premature study discontinuation than placebo. The greater tolerability of topiramate in the single-site study may have resulted from a slower rate at which the dosage of the medication was increased (i.e., titration to the 300-mg target dosage in the single-site study occurred over 8 weeks, compared to 6 weeks in the multicentre study).

Other medications

A number of other drugs are currently being tested for the treatment of alcohol dependence, including the $GABA_B$ agonist baclofen (Heilig and Egli 2006). Other drugs modulating glutamatergic neurotransmission and receptors for stress-related neuropeptides (i.e., neuropeptide Y, corticotrophin releasing

factor) are also being studied. Drugs blocking the cannabinoid CB1 receptor may represent a novel mechanism of action for the treatment of addictive disorders (Gelfand and Cannon 2006). The CB1 antagonist SR141716A (rimonabant) is the first clinically available, potent, selective, and orally active antagonist of the CB1 receptor. Rimonabant reduces voluntary alcohol intake in an animal model of alcoholism (Basavarajappa and Hungund 2005). No clinical studies of rimonabant for alcohol dependence treatment have yet been published.

Disclosure statement

These treatment guidelines have been developed by psychiatrists who are in active clinical practice and/or primarily involved in research or other academic endeavours. It is possible that through such activities some task force members have received income related to treatments discussed in this guideline. Task force members are asked to disclose any potential conflict of interest that may bias (or appear to bias) their contribution, whether as an author or reviewer of the guidelines. Guideline drafts are reviewed not only by task force members but also by the Chairman of the WFSBP Committee on Scientific Publications, the Presidents of those national societies of biological psychiatry that belong to the WFSBP, and the WFSBP Executive Committee members. Revised versions of the guidelines address or integrate the comments of these multiple reviewers. The development of the WFSBP treatment guidelines is not financially supported by any commercial organization.

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Conflict of interest

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