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WFSBP TREATMENT GUIDELINES

Guidelines for biological treatment of substance use and related disorders, part 1: Alcoholism, first revision

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ABSTRACT

These practice guidelines for the biological treatment of alcohol use disorders are an update of the first edition, published in 2008, which was developed by an international Task Force of the World Federation of Societies of Biological Psychiatry (WFSBP). For this 2016 revision, we performed a systematic review (MEDLINE/PUBMED database, Cochrane Library) of all available publications pertaining to the biological treatment of alcoholism and extracted data from national guidelines. The Task Force evaluated the identified literature with respect to the strength of evidence for the efficacy of each medication and subsequently categorised it into six levels of evidence (A–F) and five levels of recommendation (1–5). Thus, the current guidelines provide a clinically and scientifically relevant, evidence-based update of our earlier recommendations. These guidelines are intended for use by clinicians and practitioners who evaluate and treat people with alcohol use disorders and are primarily concerned with the biological treatment of adults with such disorders.

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1. Introduction

Alcohol dependence is a common psychiatric disorder with lifetime prevalence estimates of up to 10% globally and 7–10% in most Western countries (Grant et al. 2004; Kessler et al. 2005; Pirkola et al. 2006; Hasin et al. 2007), although one study found clear evidence for high variability in 12-month prevalence rates (Rehm et al. 2005). The prevalence of alcohol dependence in the adult population worldwide is estimated to be 4.9% (men: 7.8%, women: 1.5%) (Gowing et al. 2015). Recent data from the United States suggest that the 12-month and lifetime prevalence of alcohol use disorder (AUD) is 13.9 and 29.1%, respectively (using criteria of the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5; American Psychiatric Association 2013)) (Grant et al. 2015). In ICD-10 and DSM-IV, alcohol misuse or harmful use and dependence are defined by a cluster of somatic, psychological and behavioural symptoms. The recently published DSM-5 (American Psychiatric Association 2013) has replaced the categorical distinction between abuse and dependence with a dimensional approach. It specifies 11 criteria for substance use disorders; two or three positive symptoms constitute a mild substance use disorder, four or five a moderate one and six or more a severe one.

Multiple lines of evidence, including studies in primary care, indicate that AUDs are dramatically underreported and most patients do not get adequate treatment (Rehm et al. 2015). Although moderate alcohol consumption without heavy-drinking episodes may have a beneficial effect on the risk of ischaemic heart disease (Roerecke & Rehm 2014), the effect is far outweighed by the substantial psychiatric, somatic, social and economic burden caused by AUDs (Connor et al. 2015; Schoepf & Heun 2015; Whiteford et al. 2015).

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AUDs account for 9.6% of disability-adjusted life years (DALYs) worldwide (Whiteford et al. 2013). Individuals with an AUD also show an excess mortality rate (Rehm et al. 2010; Laramee et al. 2013; Roerecke & Rehm 2013). The World Health Organisation (WHO) estimates that 3.3 million deaths worldwide are alcohol related (representing 5.9% of all deaths) and that mortality is especially high in less-educated people (Mackenbach et al. 2015). In some Eastern and Northern European countries alcohol-related causes account for 10% or more of the socioeconomic inequality in total mortality (Mackenbach et al. 2015).

The biological treatment of alcoholism includes therapies for alcohol intoxication, withdrawal symptoms, alcohol-related neuropsychiatric disorders (including seizures and psychosis) and comorbid psychiatric disorders and for the initiation and maintenance of abstinence (i.e., relapse prevention) or reduction of alcohol intake. Over the past 75 years, a number of medications have been tested for these indications and some have emerged as evidence-based treatments for AUDs.

The effects of alcohol on neurotransmitters appear to mediate the risk for alcohol use disorder: a brief update

Alcohol is metabolised 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 of the unpleasant effects of alcohol, especially the 'flushing response' seen among susceptible individuals. Both enzymes have multiple isoforms that differ significantly in their effects on alcohol metabolism, tolerance and risk for the development of alcohol dependence. For a long time, blockade of ALDHs by different drugs, especially disulfiram (see below), was the only pharmacological intervention for alcohol dependence.

Alcohol is a simple molecule that affects many different neurotransmitter systems. Given its complex molecular basis, the effects of alcohol are not completely understood. Unlike other drugs or medications, alcohol is dosed in grams, not milligrams, and thus seems to have a low affinity for many neuroreceptors. Over the last few decades, considerable evidence of the effects of alcohol has emerged from animal studies and from neurochemical and neuroimaging studies in humans (for reviews see Johnson & Ait-Daoud 2000; Koob & Le Moal 2006; Petrakis 2006; Nutt & Nestor 2013; Noronha et al. 2014). Alcohol does not act via a single receptor but affects multiple neurotransmitter systems and receptors, largely as a function of its effects on the neuronal lipid bilayer, in which receptors are embedded.

The mechanisms of action of alcohol include effects on GABA, the endogenous opioid system, glutamate, the endocannabinoid system, noradrenaline, dopamine and serotonin (Koob & Le Moal 2006; Spanagel 2009; Spanagel & Vengeliene 2013) and also on neuroendocrine systems, including the hypothalamic-pituitary-adrenal (HPA) axis (Hillemacher et al. 2015). 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. There is also substantial evidence that alcohol enhances dopaminergic transmission in the mesolimbic forebrain (Johnson & 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 & Porrino 2002; Koob 2003). In recent years, the opioidergic system has come to be viewed as a 'hedonic' system that is also involved in the development of AUDs (Ciccocioppo et al. 2002; Jarjour et al. 2009), in principle by mediating the reinforcing effects of alcohol (Gianoulakis 2004). In addition, alcohol increases serotonin levels and antagonises glutamatergic neurotransmission (see below). Alcohol has also been shown to interact with the endocannabinoid system (Economidou et al. 2006).

Controlled clinical trials have now provided compelling evidence that a variety of compounds that interact with the opioid, serotonergic and gamma-aminobutyric acid (GABA)/glutamate systems are safe and efficacious medications for treating alcohol withdrawal, alcohol dependence or both. Some of the methodological problems that limit interpretation of the results of these studies are as follows: the acute and chronic effects of alcohol may differ substantially; dose-dependent effects of alcohol on neurotransmitters are often overlooked; changes induced by the metabolic products of alcohol (e.g., acetaldehyde) and other ingredients of alcoholic beverages are difficult to evaluate; alcohol has clear neurotoxic effects, resulting in cell damage similar to that caused by hypovitaminosis, malnutrition or other associated disorders; and few studies have been conducted in long-term abstinent alcohol-dependent or high-risk patients.

The neural correlates and neurocircuitry of alcohol dependence have also been extensively studied. Key structures involved in the pathophysiology of alcohol

dependence are the limbic system, including the ventral tegmental area and nucleus accumbens, and the orbito- and prefrontal cortices. Dopamine release in limbic areas, including the nucleus accumbens, appears to be the principle neurotransmitter effect that underlies the reinforcing effects of alcohol. The prefrontal cortex is crucial for cognitive control and the orbitofrontal cortex for motivation (Nutt & Nestor 2013). PET studies have revealed reduced GABA receptor function in alcohol dependence (Lingford-Hughes et al. 2005). Recent genetic studies also show that vulnerability to 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. 2008b). In alcohol withdrawal, GABAergic dysfunction contributes to restlessness and seizures, among other signs and symptoms.

2. Methods

These guidelines are intended for use by clinicians who diagnose and treat patients with AUDs. The aim of these guidelines is to improve the quality of care and to aid in clinical decision making. Although these guidelines are based on published evidence, the treating clinician is ultimately responsible to assess and select the most appropriate treatments, 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 guidelines primarily cover the role of pharmacological agents in the treatment of AUDs, with a focus on treating 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.

To achieve these goals, we bring together different views on the appropriate treatment of AUDs from experts representing all continents and an extensive literature search that was conducted using the Medline and Embase databases through October 2015—supplemented by other sources, including published reviews and national guidelines. The guidelines are based on data from publications in peer-reviewed journals, which were summarised and categorised to reflect their susceptibility to bias (Shekelle et al. 1999). Daily treatment costs were not taken into consideration because of the variation worldwide in medication costs. Each treatment recommendation was evaluated by the Task Force 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 based on the level of efficacy and not on the clinical significance of the treatment.

2.1 Methods of literature research and data extraction

To update the first set of guidelines, we performed a systematic review (MEDLINE/PubMed database) with the search terms 'alcohol', 'alcoholism', 'therapy' and 'pharmacotherapy' to identify all available publications pertaining to the biological treatment of alcoholism published in English or with an English abstract between January 2010 and October 2015. In addition, we used the following guidelines, consensus papers and sources in the development of these guidelines: American Psychiatric Association, 'Practice Guideline for the Treatment of Patients with Substance Use disorders, Second Edition' (Kleber et al. 2007); German Association for Psychiatry, Psychotherapy and Psychosomatics (DGPPN), 'S-3 guideline for diagnosis and treatment of alcohol use disorders' (Mann et al. 2016a); National Institute for Clinical Excellence (NICE), 'Alcohol-use disorders: Diagnosis, assessment and management of harmful drinking and alcohol dependence' (NICE 2011); French Alcohol Society and European Federation of Addiction Societies (Rolland et al. 2016); British Association for Psychopharmacology (Lingford-Hughes et al. 2012); Cochrane Library 'Meta-analyses on the efficacy of different drugs and interventions in alcoholism' (Ntais et al. 2005; Rösner et al. 2010a; Rösner et al. 2010b; Sarai et al. 2013; Liu & Wang 2015). Findings from recent meta-analyses (Maisel et al. 2013; Jonas et al. 2014; Donoghue et al. 2015) on the efficacy of anti-craving drugs were also incorporated.

2.2 Rating of recommendations

The recommendations were developed by the authors on the basis of the identified publications and arrived at by consensus with the WFSBP Task Force on Addiction Disorders, which consists of 24 international experts in the field. The rating levels (see Bandelow et al. 2008) are shown in Table 1.

3. Treatment of alcohol withdrawal syndrome and alcohol withdrawal delirium (delirium tremens)

Alcohol withdrawal syndrome (AWS) occurs with some frequency among individuals with a diagnosis of alcohol dependence (Connor et al. 2015) and presents

Table 1. Categories of evidence and recommendation grades. Reproduced with permission from Bandelow et al. (2008).

Category of Evidence		Description
A		**Full Evidence From Controlled Studies is based on:** two or more double-blind, parallel-group, randomised controlled studies (RCTs) showing superiority to placebo (or in the case of psychotherapy studies, superiority to a 'psychological placebo' in a study with adequate blinding) **and** one or more positive RCT showing superiority to or equivalent efficacy compared with established comparator treatment in a three-arm study with placebo control or in a well-powered non-inferiority trial (only required if such a standard treatment exists) In the case of existing negative studies (studies showing non-superiority to placebo or inferiority to comparator treatment), these must be outweighed by at least two more positive studies or a meta-analysis of all available studies showing superiority to placebo and non-inferiority to an established comparator treatment. Studies must fulfil established methodological standards. The decision is based on the primary efficacy measure.
B		**Limited Positive Evidence From Controlled Studies is based on:** 1 or more RCTs showing superiority to placebo (or in the case of psychotherapy studies, superiority to a 'psychological placebo') **or** a randomised controlled comparison with a standard treatment without placebo control with a sample size sufficient for a non-inferiority trial **and** no negative studies exist
C		**Evidence from Uncontrolled Studies or Case Reports/Expert Opinion**
	C1	**Uncontrolled Studies. Evidence is based on:** 1 or more positive naturalistic open studies (with a minimum of 5 evaluable patients) **or** a comparison with a reference drug with a sample size insufficient for a non-inferiority trial **and** no negative controlled studies exist
	C2	**Case Reports. Evidence is based on:** 1 or more positive case reports **and** no negative controlled studies exist
	C3	Evidence is based on the opinion of experts in the field or clinical experience
D		**Inconsistent Results** Positive RCTs are outweighed by an approximately equal number of negative studies
E		**Negative Evidence** The majority of RCTs studies or exploratory studies shows non-superiority to placebo (or in the case of psychotherapy studies, superiority to a 'psychological placebo') or inferiority to comparator treatment
F		**Lack of Evidence** Adequate studies proving efficacy or non-efficacy are lacking.
Recommendation Grade		**Based on**
1		**Category A evidence and good risk–benefit ratio**
2		**Category A evidence and moderate risk–benefit ratio**
3		**Category B evidence**
4		**Category C evidence**
5		**Category D evidence**

with a broad range of symptoms from mild 'hangover' to delirium tremens (Brust 2014). AWS usually develops within hours or days of the initiation of abstinence or a significant reduction in alcohol consumption by 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.

The DSM-5 (American Psychiatric Association 2013) criteria for alcohol withdrawal are the presence of two or more of the following symptoms developing within hours to a few days of the cessation of or reduction of heavy alcohol use: autonomic hyperactivity (sweating, fast pulse); increased hand tremor; insomnia; nausea and vomiting; transient hallucination or illusions; psychomotor agitation; anxiety; and grand mal seizures. The ICD-10 criteria are similar to those of the DSM-5. Most signs and symptoms of alcohol withdrawal are non-specific, i.e., tremor, elevated pulse rate and blood pressure, perspiration, agitation, nervousness, sleeplessness, anxiety and depression. As reflected in the diagnostic criteria, the signs and symptoms occur typically within the first hours after discontinuation of alcohol consumption and may last for up to 1 week, seldom for longer. In addition, more serious symptoms can occur that may warrant specific interventions, including hallucinations, delirium tremens, alcohol-related psychotic symptoms and seizures. A number of rating scales are available to measure the intensity of alcohol withdrawal symptoms. The most frequently used measure of alcohol withdrawal

severity is the Clinical Institute Withdrawal Assessment–Alcohol, revised (CIWA-Ar, Sullivan et al. 1989) scale. A number of detailed evidence-based guidelines have been published concerning the management of AWS (Mayo-Smith 1997; Berner et al. 2004; Lingford-Hughes et al. 2004; Kleber et al. 2007).

The treatment of alcohol withdrawal focuses on the relief of immediate symptoms, prevention of complications and initiation of rehabilitation. Although outpatient detoxification is a safe treatment option for many patients with mild-to-moderate AWS (Soyka et al. 2005; Soyka et al. 2006), patients with severe symptoms, extremely high alcohol intake, significant somatic or psychiatric symptoms or delirium tremens (see below) 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; Sachdeva et al. 2015) and repletion of nutrient, fluid or mineral deficiencies plays an important role in the treatment of AWS but will not be discussed here in detail. Vitamin deficiencies are common in patients with heavy alcohol intake. Supplementation is recommended, especially of B vitamins, including thiamine, to prevent the development of Wernicke-Korsakoff syndrome (see Section 7). Four trials involving 317 patients have been performed using magnesium to treat alcohol withdrawal, but a Cochrane analysis did not find a clear benefit (Sarai et al. 2013). Thus, the use of magnesium should be limited to cases of hypomagnesemia.

The major aims of pharmacotherapy of AWS are to sedate patients to control agitation, anxiety and related symptoms and prevent cardiovascular complications resulting from high blood pressure and a rapid pulse rate. Pharmacological treatment of AWS is pragmatic. Numerous pharmacological agents have been used to treat AWS, but few have sufficient empirical evidence supporting their efficacy. Results from placebo-controlled studies show that benzodiazepines (BZDs), beta-adrenergic receptor antagonists, calcium channel blockers, anticonvulsants and clonidine reduce withdrawal symptoms (Berglund et al. 2003). Clomethiazole, which is not available in the United States, is also frequently used to treat AWS. Although no placebo-controlled trials are available, antipsychotics, especially haloperidol, can be given in combination with a BZD for treatment of severe agitation (Mayo-Smith et al. 2004) (*Level C*) or psychotic symptoms (Ungur et al. 2013). Antipsychotics, particularly less potent ones lower 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. Beta-adrenergic blockers or alpha2 agonists may be of value in patients with persistent hypertension (Ungur et al. 2013).

Alcohol withdrawal delirium is the most serious and dangerous manifestation of AWS and is a medical emergency. 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 and is more frequent in critically ill patients in whom early and aggressive titration of medication is recommended (Awissi et al. 2013). Frequent symptoms and signs of alcohol withdrawal delirium are autonomic instability, fever, fluid loss, electrolyte imbalances, hypoglycaemia, liver failure, pancreatitis, sepsis, meningitis intracranial haemorrhage and Wernicke-Korsakoff syndrome (Brust 2014). Control of agitation is essential in alcohol withdrawal delirium. To address the agitation, patients should be sedated and kept in light somnolence for the duration of the delirium.

3.1 Benzodiazepines

Worldwide, BZDs are the drugs of first choice in the treatment of AWS and alcohol withdrawal delirium. BZDs act via allosteric effects at the GABA-A receptor and are cross-tolerant with alcohol. Multiple placebo-controlled studies support the clinical efficacy of BZDs. They are clinically effective in reducing key symptoms of 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 (*Level A, Recommendation grade [RG] 1*). BZDs can be categorised according to their catabolism. Longer-acting BZDs are oxidised by the hepatic microsomes into active and inactive metabolites. Shorter-acting BZDs like lorazepam and oxazepam, which are not oxidised but simply conjugated in the liver before excretion, may be preferred in patients with impaired liver function to avoid cumulative effects or over-sedation. It is a matter of debate whether short- 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 1997). A Cochrane review found BZDs to be effective for alcohol withdrawal, particularly seizures, compared to placebo (Ntais et al. 2005). BZDs have been touted as

superior to many other drugs for this indication (Mayo-Smith 1997; Berglund et al. 2003), though the Cochrane review (Ntais et al. 2005) was unable to draw definite conclusions about the effectiveness and safety of BZDs against other drugs, because of the heterogeneity of the trials.

There are different treatment strategies and techniques for the use of BZDs 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 diazepam, for example, may be preferable. While many clinicians favour a symptom-triggered approach and an individualised 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. However, many patients will require less medication than that. Other possible dosage regimens include diazepam 10 mg every 6 h or lorazepam 2 mg or chlordiazepoxide 50 mg every 4–6 h (*Level C, RG 2*). The optimal dosage depends on the severity of AWS and is based on the patient's individual characteristics. A recent study showed that symptom-triggered dosing of lorazepam resulted in the use of lower doses of medication and a shorter duration of treatment than a fixed taper of the drug (Sachdeva et al. 2014) (*Level C, RG2*). Short-acting BZDs may be more suitable for the detoxification of elderly patients (*Level C, RG2*).

Sedative-hypnotic agents, usually BZDs, are also recommended to treat alcohol-withdrawal delirium (*Level A*), as evidenced by a limited number of studies (Mayo-Smith et al. 2004). A 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 to treat alcohol withdrawal 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.

It should be noted that a major limitation in the use of BZDs is their abuse liability. Therefore, a number of alternative strategies for the treatment of the AWS have been studied and are discussed below.

3.2 Other GABAergic compounds

A variety of other GABAergic compounds are used to treat AWS (Johnson et al. 2005). Gamma-hydroxybutyric acid (GHB; also called sodium oxybate) is a naturally occurring, short-chain, four-carbon fatty acid that is an endogenous neurotransmitter (Schep et al. 2012; Brennan & Van Hout 2014). GHB was found to be comparable in efficacy to BZDs and clomethiazole (Gallimberti et al. 1992; Addolorato et al. 1999; Nimmerrichter et al. 2002). The drug is approved to treat alcohol withdrawal and for maintenance treatment in Austria and Italy but has a substantial abuse potential and is potentially dangerous because of its amnestic effects (hence its use as a 'date-rape drug'). Patients with borderline personality disorder or other addictions may not be suitable candidates for GHB and strict medical surveillance is recommended because of its abuse potential (Keating 2014) (*Level C1, RG4*). The role of GHB as an anti-craving drug is less clear and controversial (see below). GHB has a relatively short half-life, so that frequent dosing is necessary. Both the abuse potential of GHB ('liquid ecstasy') and the frequency with which it is taken in overdose have raised significant concerns regarding its therapeutic use (McDonough et al. 2004; Brennan & Van Hout 2014). In addition, withdrawal from GHB can be very severe.

Gabapentin in higher doses was found to be as clinically effective as lorazepam (Myrick et al. 1998; Myrick et al. 2009) (see 3.5 'Anticonvulsants' below). Other drugs, such as the GABA-B agonist baclofen, have not been studied adequately to recommend them for use in the treatment of the AWS (*Level D, RG4*). A recent Cochrane review specifically of baclofen stated that the evidence for recommending it for the treatment of AWS is insufficient (Liu & Wang 2015).

3.3 Glutamatergic compounds

Impairment of glutamatergic neurotransmission has been shown to play a major part in the development of AWS. There is preliminary evidence that lamotrigine, which inhibits glutamate release; memantine, which is an NMDA receptor antagonist; and topiramate, which antagonises the AMPA/kainate receptor, may be useful in treating AWS (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.

Treatment-resistant AWS is rather rare, in which case high doses of sedatives are used (Wong et al. 2015). For cases of BZD-resistant AWS, some reports

based on case series have recommended the use of short-term narcotics (Wong et al. 2015).

3.4 Clomethiazole

Clomethiazole, a thiamine derivative, was introduced into clinical practice in the early 1960s. It is a potent anticonvulsant hypnotic widely used in Europe to treat AWS, but it is not approved for use in the United States. Although it has been used to treat delirium (Majumdar 1991), no randomised 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 closely monitored because of the risk of adverse cardiac effects.

A few studies have compared the effects of clomethiazole with those of BZDs or other drugs. Bonnet et al. (2011) conducted a prospective observational comparison of clomethiazole and clonazepam and found that both score-driven treatments were equally safe and effective. Despite the conclusion by Majumdar (1991) that clomethiazole is safe and equal or superior to BZDs, a 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, RG2*) but is not available in many countries.

3.5 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 (CBZ) and valproate suggest that they are viable alternatives to BZDs for treating AWS. Anticonvulsants are 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; Stuppaeck et al. 1992; Malcolm et al. 2001; Malcolm et al. 2002) and clomethiazole (Ritola & Malinen 1981; Seifert et al. 2004) for treating the symptoms of AWS (*Level B*). The usual dosage of CBZ is 600–1200 mg/day. CBZ has also been used in combination with tiapride for the outpatient treatment of AWS (Soyka et al. 2002; Soyka et al. 2006) (*Level C*). In addition to reducing symptoms of AWS, CBZ reduced drinks per drinking day and time to first drink in abstinent alcohol-dependent individuals (Mueller et al. 1997; Malcolm et al. 2002). A comprehensive review concluded that CBZ and oxcarbazepine are efficacious in treating moderate-to-severe symptoms of AWS in an inpatient setting, but evidence for the prevention of alcohol withdrawal seizures and delirium tremens is inconclusive (Barrons & Roberts 2010) (*Level C, RG 4*).

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 the severity of withdrawal symptoms compared with placebo (Reoux et al. 2001). A retrospective chart analysis suggested that valproate may offer some advantages over CBZ in treating AWS (Eyer et al. 2011). Both CBZ and valproate are contraindicated in patients with hepatic or haematological disorders.

An inpatient study showed that topiramate was as efficacious as lorazepam in the treatment of AWS, while allowing the patient to remain on that medication during the transition to outpatient care. There was also no evidence that topiramate had abuse potential or that it increased the risk of relapse commonly seen in alcohol-dependent people treated with BZDs (Choi et al. 2005). A small, open-label study showed topiramate to be potentially useful and well tolerated in preventing tonic-clonic seizures associated with alcohol withdrawal (Rustembegovic et al. 2002). The adjunctive use of another anticonvulsant, levetiracetam, reduced the BZD requirements of patients with AWS (Youland et al. 2014).

3.6 Clonidine

There is some clinical and empirical justification for the use of alpha2-adrenocepter agonists in AWS, although only in specific cases (Albertson et al. 2014), such as in patients with symptoms of severe adrenergic hyperactivity. Under these circumstances, use of a sympatholytic such as clonidine or an alpha-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 blood pressure 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 C2, RG4*). The sympatholytic lofexidine is used to treat

opioid withdrawal, and studies in patients with severe AWS would be of interest (Albertson et al. 2014).

4. 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 patient may require intervention to ensure adequate respiratory function. High intravenous doses (5 mg) of the BZD 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 & Askenasi 1991), but these results require confirmation in controlled clinical trials (*Level F*).

5. Diagnosis and management of alcohol-related seizures

There is a complex relationship between chronic heavy drinking or its abrupt cessation and the occurrence of seizures (Brathen et al. 1999; Leone et al. 2002). According to the guidelines of the European Federation of Neurological Science (EFNS) Task Force on Diagnosis and Treatment of Alcohol-Related Seizures (Brathen et al. 2005), one-third of seizure-related admissions occur in the context of alcohol withdrawal. Up to 15% of patients with alcohol dependence experience 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 likelihood of experiencing seizures is at least three times higher among alcohol-dependent patients. Alcohol consumption acutely increases the seizure threshold. However, after chronic heavy drinking the seizure threshold is lowered upon cessation of drinking. Alcohol seizures typically occur within the first 6–48 h after the abrupt cessation of heavy drinking. The 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 shown a high frequency of symptomatic or partial seizures (Brathen et al. 1999; Leone et al. 2002).

After the initial management of seizures in patients with a new onset of seizure, neuroimaging, i.e., CT or MRI, is warranted to search for a structural cause (Brathen et al. 2005). Because 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 alcohol-dependent patients, including the effects of alcohol on calcium and chloride flux through ion-gated glutamate and GABA receptors, respectively. Some drugs such as antipsychotics may also lower seizure threshold. 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, with some recent data from animal studies pointing the role of seizure susceptibility being mediated via calcium channels (N'Gouemo et al. 2010, 2015). Although status epilepticus after an alcoholic seizure is rare, its serious consequences warrant prompt treatment to prevent it.

After an alcoholic seizure, the patient should be observed in hospital for at least 24 h. Routine drug therapy for the prevention of seizures is not necessary in patients with no history of withdrawal seizures and mild-to-moderate withdrawal symptoms. A meta-analysis of controlled trials for primary prevention of alcohol withdrawal seizures demonstrated a highly significant reduction of seizures with BZDs and epileptic drugs and an increased risk with antipsychotics (Hillbom et al. 2003). Diazepam and lorazepam are recommended for such preventive efforts (*Level A, RG1*). A meta-analysis of randomised, placebo-controlled trials for the secondary prevention of seizures after alcohol withdrawal showed lorazepam, but not phenytoin, to be effective (Hillbom et al. 2003). Because withdrawal seizures typically do not recur in abstinent patients, there is no reason to continue anticonvulsant treatment in these patients to prevent seizures (Hillbom et al. 2003) (*Level C*).

6. 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. Auditory hallucinations are most common, but visual hallucinations and delusions of persecution also occur. 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). More recent studies suggest a less favourable overall outcome than prior studies (Jordaan & Emsley 2014). In some cases, differentiating alcohol psychosis from schizophrenia can be difficult (Soyka 1990), though there is no evidence for a common genetic basis for alcohol psychosis and schizophrenia (Glass 1989a). Although PET findings indicate a dysfunction of the thalamus in patients with alcohol psychosis (Soyka et al. 2005), the pathophysiology remains unclear. Regional blood flow was increased in the left caudate and left frontal lobe after antipsychotic treatment and clinical improvement; overall, the data indicate a reversible generalised cerebral dysfunction (Jordaan et al. 2012).

There are no controlled studies of the pharmacotherapy of alcohol psychosis and no established therapy. Given the often vivid psychotic symptomatology and risk of aggressive or suicidal reactions, antipsychotic treatment is warranted in most patients with alcohol psychosis (Jordaan & Emsley 2014), perhaps optimally in combination with BZDs (*Level C2*). There is no evidence for an increased risk of seizures in patients with alcohol psychosis treated with antipsychotics, especially not with 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.

7. Wernicke-Korsakoff syndrome

The metabolism of glucose requires thiamine (vitamin B1) as an essential co-factor. A deficiency of thiamine results in the Wernicke-Korsakoff syndrome (WKS) (Thomson et al. 2002) (*Level A, RG1*), which is especially likely in malnourished chronic heavy drinkers with signs of hypovitaminosis. Prophylactic parenteral thiamine should be given before starting any carbohydrate-containing intravenous fluids to avoid precipitating acute WKS. Symptoms of WKS (ophtalmoplegia, ataxia, changes in consciousness) must not be overlooked. A presumptive diagnosis of WKS should be made for any patient with a history of alcohol dependence who shows one or more of the following: ophtalmoplegia, ataxia, acute confusion, memory loss or disturbances, unexplained hypotension, hypothermia, coma or unconsciousness.

Intravenous treatment with thiamine is vital in this setting and must be initiated immediately after the diagnosis is made. There is no consensus on the optimal duration of treatment, dose or mode of administration (Latt & Dore 2014) and a Cochrane review showed that there was insufficient evidence from randomised controlled trials (RCTs) to inform these questions (Day et al. 2013). The British Association for Psychopharmacology guidelines recommend that a dose of >500 mg of thiamine should be given for 3–5 days if WKS is suspected or the diagnosis is established (Lingford-Hughes et al. 2012). Even with prompt treatment, mortality in this disorder is still high. There is no established pharmacological treatment to improve the memory impairment in WKS. The role of neuropsychological rehabilitation is not well defined, though there are some benefits of a number of memory rehabilitation strategies (Svanberg & Evans 2013).

8. Treatment of alcohol dependence

8.1 Goals of treatment

Alcohol dependence or AUD primarily manifest as impaired control over drinking. 'Stable' abstinence is usually achieved only after several years of abstaining from alcohol (Vaillant 1996) and both naturalistic and long-term clinical 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, although abstinence is the primary goal recommended by most clinicians, 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; Kranzler et al. 2003a; Garbutt et al. 2005; Johnson et al. 2007).

Many clinicians and self-help organisations such as Alcoholics Anonymous (AA) consider alcohol dependence to be a chronic and disabling disorder for which they advocate long-term or lifelong abstinence. Although treatments have been advocated that are aimed at regaining control over drinking ('controlled drinking') in alcohol-dependent patients, 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 the effects of self-control training focussed on cognitive-behavioural therapy (CBT) 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.

In patients who are not motivated for abstinence-oriented interventions it is acceptable to follow a harm-reduction strategy to promote a reduction in drinking, but abstinence from alcohol remains the primary long-term goal for moderate-to-severe alcohol dependence. Today, the reduction of alcohol consumption is considered to be an adequate, sometimes intermediate goal in many treatment guidelines and is accepted by the European Medicines Agency (EMA) as a legitimate outcome goal in the pharmacological treatment of alcoholism (EMA 2010).

8.2 Psychosocial treatment

Psychosocial treatments can reduce alcohol consumption and increase abstinence rates and are the most widely used treatments for AUDs. Psychosocial treatments can also increase patients' motivation for abstinence, enhance non-alcohol-related outcomes and increase adherence to pharmacological treatment of AUDs. These treatments usually involve family, community and employment resources and encourage patients to reduce their alcohol use, participate in counselling programmes and self-help groups and increase sober and rewarding activities. The main aims of the treatment are to improve physical health, reduce alcohol-related social problems and reduce or eliminate the use of alcohol completely. Psychosocial interventions can be conducted at an individual, family or group level.

A variety of psychosocial alcohol interventions (including psychotherapy) have been found to be effective (for a review see Ferri et al. 2006; Kaner et al. 2007; Lui et al. 2008; McQueen et al. 2009; Klimas et al. 2014). These interventions include strategies to enhance the motivation for recovery; CBT, including broad-spectrum treatment with a CBT focus and other related approaches; 12-step treatment; and various forms of family, social network, family therapy and social competence training. The data supporting other treatments, including psychodynamically oriented ones are less convincing. The most frequently used and best-investigated psychosocial interventions are described below.

Motivational interviewing (MI) is an evidence-based counselling method that aims to enhance intrinsic motivation and induce behaviour change by helping patients explore and resolve their ambivalence about change. Smedslund et al. (2011) conducted a Cochrane meta-analysis of 59 studies of MI in a total of 13,342 patients with substance abuse (29 trials were specific to alcohol). Compared to a no-treatment control, MI significantly reduced substance use post intervention and in short- and medium-term follow-ups. However, no significant differences were found between MI and treatment as usual for substance use disorders or other active treatments (Smedslund et al. 2011). MI can reduce the use of alcohol compared to no intervention, but overall effect sizes are small.

Brief interventions that provide advice or behavioural counselling are also effective primary-care treatments for patients with alcohol misuse. However, results from randomised trials show mixed results for the efficacy of screening and brief interventions in primary and inpatient care and emergency departments (Substance Abuse and Mental Health Services Administration 1999; Schmidt et al. 2015). Furthermore, the definition of 'brief intervention' varies and other terms to describe this approach include minimal interventions, 'brief counselling' and 'simple advice'. Brief interventions include structured treatment programmes or more informal suggestions by a professional to reduce alcohol use.

CBT is a common, established, and structured form of psychotherapy that aims to modify behaviours that are underpinned by conditioned learning (Beck 1993). CBT seeks to help patients to change their thoughts and emotions, find new ways to behave, and change maladaptive behaviour or social environments. A meta-analysis of 53 studies found a modest effect on outcomes for alcohol and other substance use disorders compared to no treatment or control conditions (Magill & Ray 2009). A more recent meta-analysis of 12 studies found a small but clinically significant effect of combined CBT/MI treatment compared with treatment as usual (Riper et al. 2014). However, studies have not shown an improved outcome from the combination of CBT and medications for relapse prevention in alcohol dependence (Anton et al. 2006; Mann et al. 2013b).

Self-help groups are a common component in the treatment of patients with an AUD. Different models of self-help exist, but in general, participants work in groups, increasing social support and working toward abstinence. The most famous self-help programme is AA, which is based on a 12-step approach ('Twelve Steps to Recovery'). The members of AA regularly attend group meetings with members who share their philosophy and belief in a spiritual basis for recovery. Despite methodological problems that are present in trials of AA participation, a meta-analysis of studies in patients with AUDs reported similar outcomes for AA participation as other psychosocial interventions or 12-step approaches (Ferri et al. 2006).

Residential treatment provides an alcohol-free environment and 24-h medical care. So far, no well-designed clinical trials have compared the effectiveness of residential treatment for AUDs to that of other treatments. Furthermore, residential treatment

programmes vary in their intensity and the kinds of treatment they offer. However, from a clinical point of view, residential treatments seem beneficial in patients with moderate-to-severe alcohol dependence and patients with psychiatric or medical comorbidity or both. Furthermore, residential treatments may be beneficial for patients who require a change of environment, have greater functional impairment or are in general at very high risk of relapse. The availability of residential treatment varies widely and the costs of such treatment are often covered by health insurance in only some countries.

Psychosocial therapies are important components of the treatment of AUDs. However, the range of psychosocial therapies in different countries is substantial and the heterogeneity makes a scientific comparison of the different psychosocial interventions difficult. For this reason, more evidence from RCTs is needed to assess the effectiveness of psychosocial interventions for the treatment of AUDs. Treatment options should be offered to patients on the basis of their individual needs and preferences.

8.3 Pharmacological treatment

Disulfiram has been used to treat alcohol dependence for over six decades. In the last 25 years, a number of other drugs have been introduced as treatments for alcohol dependence, including acamprosate and naltrexone (Kleber et al. 2007). A number of reviews and meta-analyses have addressed this topic (Hughes & Cook 1997; Garbutt et al. 1999; Kenna et al. 2004a,b; Soyka & Roesner 2006).

8.3.1 Disulfiram

In the 19th century, disulfiram was used for vulcanisation during rubber production and resulted in intolerance to alcohol in individuals exposed to the substance. E.E. Williams first described the occurrence of this adverse reaction in 1937, noting its possible therapeutic utility. A few years later, the Danish researchers Hald and Jacobsen began to test the compound clinically (Hald & Jacobsen 1948). In 1949, disulfiram was the first medication approved specifically by the US Food and Drug Administration to treat alcohol dependence, and it has since been used worldwide for that indication. However, case reports of deaths during the 1950s and 1960s and the aversive mechanism of action of disulfiram triggered contentious debates on the drug, leading to a significant decline in its use in many countries (Amadoe & Gazdar 1967).

Disulfiram is a thiuram derivative and an irreversible inhibitor of ALDH, which is responsible for the conversion of acetaldehyde to acetate during alcohol metabolism in the liver. Drinking while taking disulfiram results in an elevated concentration of acetaldehyde and precipitation of the aversive disulfiram-alcohol reaction (DAR). The DAR is unpleasant and occasionally dangerous, with a variety of signs and symptoms including nausea, flushing, vomiting, sweating, hypotension and palpitations. The rationale for using the medication is the anticipation of patient of an aversive DAR if alcohol is consumed (Suh et al. 2006). Disulfiram is typically prescribed at a dosage of 200–500 mg/day (Suh et al. 2006).

In addition to inhibiting ALDH, disulfiram inhibits other enzymes such as dopamine-ß-hydroxylase (DBH), which catalyses the oxidation of dopamine to noradrenaline. However, while this could explain the putative efficacy of the drug in the treatment of cocaine dependence (Carroll et al. 2004; Suh et al. 2006), in alcohol-dependent patients DBH inhibition probably has only a subordinate role in promoting abstinence from alcohol (Mutschler et al. 2012).

A number of clinical studies of the efficacy of disulfiram in treating alcohol dependence have been conducted but there has been little consistency in the findings (Fuller et al. 1986; Hughes & Cook 1997; Garbutt et al. 1999; Krampe et al. 2006) (*Level C*). 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 significantly fewer drinking days than the other two treatment conditions. Most other studies of disulfiram have not used a rigorous clinical trial methodology, and compelling evidence that disulfiram increases abstinence rates is lacking (for review see Hughes & Cook 1997). Garbutt et al. (1999) concluded that the evidence for the efficacy of disulfiram is inconsistent (*Level B, RG3*). Recent open-label studies and a comprehensive review showed better outcome for patients treated with disulfiram than acamprosate, topiramate or naltrexone (De Sousa 2004, 2005; De Sousa et al. 2008; Krampe & Ehrenreich 2010). Furthermore, a recent meta-analysis of various outcome measures (continuous abstinence, number of days drinking, time to first relapse) in a total of 22 RCTs found a significant overall effect for disulfiram (Skinner et al. 2014). This meta-analysis also confirmed the superiority of the therapeutic effects of disulfiram under supervised ingestion compared with non-supervised ingestion. Because poor adherence is a major limitation of disulfiram treatment (Mutschler

et al. 2013), the use of supervised disulfiram treatment has been advocated (Sellers et al. 1983; Suh et al. 2006). Efforts have been made to develop long-lasting, implantable formulations of disulfiram to improve adherence. However, at present, this treatment cannot be recommended (Suh et al. 2006).

Taken together, because of side effects, including the potentially dangerous DAR, and poor adherence, disulfiram is best considered a second-line medication in relapse prevention (*Level B, RG3*). However, in severely affected patients, supervised disulfiram treatment is a treatment option with a good effect size.

8.3.2 Acamprosate

Recent Cochrane reviews (Rösner et al. 2010a,b) concluded that acamprosate and naltrexone are safe and effective in patients with alcohol dependence, with small-to-moderate effect sizes. Acamprosate is contraindicated in patients with severe renal impairment (i.e., estimated creatinine clearance (CrCl) $<$ 30 ml/min), and gastrointestinal adverse events may prevent use or limit dose maximisation.

Although the exact mechanism, including the molecular targets, by which acamprosate diminishes alcohol consumption and the likelihood of relapse is not entirely clear, there is some evidence that it acts predominantly via glutamatergic receptors. The effects of alcohol on the glutamatergic system are complex. Acutely, alcohol reduces glutamatergic neurotransmission via NMDA receptor blockade, although it also promotes glutamate release in several important pathways in the brain. In addition to its effects on NMDA receptors, the effects of alcohol on the glutamatergic system are also mediated by AMPA and kainate receptors (Moghaddam & Bolinao 1994; Costa et al. 2000; Crowder et al. 2002; Krystal & Tabakoff 2002). Previous research showed that acamprosate modulates glutamatergic neurotransmission, counteracting hyper-glutamatergic states (Littleton 1995; Spanagel & Zieglgansberger 1997). Acamprosate has been shown to reduce 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 the metabotropic glutamate receptor, thereby blocking the excitotoxicity produced by ethanol (Harris et al. 2003). More recent data from Spanagel et al. (2014), who have studied acamprosate extensively, did not provide evidence for a glutamatergic mechanism of action of the drug. Rather, these investigators found that the calcium in the molecule was the only active component. However, this issue is controversial and is not supported by clinical data (Mann et al. 2016b). There is also evidence that, after stimulation of glutamate receptors, acamprosate blocks enhanced extracellular dopamine release 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 exert its therapeutic effects through changes in dopamine-mediated alcohol reinforcement (Spanagel & Weiss 1999).

Acamprosate has poor oral bioavailability; therefore, the clinical dosage is comparatively high: 1998 mg (two 333 mg tablets three times daily in patients with a body weight $>$60 kg; two 333 mg tablets twice daily in lighter-weight 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 (Rösner et al. 2010a).

Acamprosate has been studied in more than 5,000 alcohol-dependent patients in RCTs in 14 different countries (Rösner et al. 2010a; Maisel et al. 2013; Jonas et al. 2014). The drug significantly reduced relapse rates in alcohol-dependent patients in a number of RCTs (see Table 2) (*Level A, RG1*). Meta-analyses provide clear evidence of the efficacy of acamprosate for the maintenance of abstinence (Rösner et al. 2010a; Maisel et al. 2013; Jonas et al. 2014; Donoghue et al. 2015). All meta-analyses support the efficacy of acamprosate in improving outcomes in treatment of alcoholism, with small-to-moderate effect sizes (see Table 2). The most robust effect of acamprosate was seen in a German multi-centre study, which found a 1-year abstinence rate of 41% in the patient group compared to 22% in the placebo group, an effect that persisted for 1 year after discontinuation of study medication (Sass et al. 1996). However, a multi-centre trial conducted in the United States (Mason et al. 2006) did not show an intent-to-treat effect of acamprosate (although secondary analyses provided some support for the drug over placebo), while the US COMBINE trial and a similar German study failed to show an effect of acamprosate on relapse prevention, either alone or in combination with naltrexone (Anton et al. 2006; Mann et al. 2013b).

8.3.3 Opioid receptor antagonists

There is broad evidence that alcohol interacts functionally with the opioidergic system, which in recent years has come to be viewed as a 'hedonic' system

Table 2. Meta-analyses of acamprosate studies.

Authors and year of publication	Patients	Studies	NNT/effect sizes to prevent return to any drinking	NNT/effect sizes to prevent return to heavy drinking
Jonas et al. 2014	7519	27	12 (acamprosate $n = 4847$)	not associated with improvement
Rösner et al. 2010a	6492	18	9.09 (acamprosate $n = 3563$, placebo $n = 2929$)	not associated with improvement
Maisel et al. 2013	4349	16	Effect sizes: $g = 0.359$, $k = 15$	Effect sizes: alcohol $g = 0.072$, $k = 5$
Donoghue et al. 2015	5236	22	Overall effect: $Z = 5.51$ (acamprosate $n = 2091$, placebo $n = 2042$)	–

NNT, number needed to treat; *k*, number of studies; *g*/*Z*, overall effect size.

Table 3. Meta-analyses of naltrexone studies.

Authors and publication year	Patients	Studies	NNT/effect sizes to prevent return to any drinking	NNT/effect sizes to prevent return to heavy drinking
Jonas et al. 2014	9140	16/19	20 (naltrexone $n = 2347$)	12 (naltrexone $n = 2875$)
Rösner et al. 2010b	694	2	Overall effect: $Z = 1.03$ (naltrexone $n = 345$; placebo $n = 349$)	not associated with improvement
Maisel et al. 2013	5434	45	Effect sizes: g = 0.116, $k = 36$	Effect sizes: $g = 0.189$, $k = 39$
Donoghue et al. 2015	4199	27	Overall effect: $Z = 2.04$ (naltrexone $n = 946$; placebo $n = 947$)	Overall effect: $Z = 3.74$ (naltrexone $n = 1999$; placebo $n = 1689$)

NNT, number needed to treat; *k*, number of studies; *g*/*Z*: overall effect size.

that mediates the reinforcing effects of alcohol by indirectly modulating dopamine release (Nutt 2014). Three major classes of opioid receptors exist: mu (μ), kappa (κ) and delta (δ). Alcohol stimulates the release of the endogenous opioid receptor ligands beta-endorphin, enkephalins and dynorphin (Koob 2003; Marinelli et al. 2004; Dai et al. 2005; Marinelli et al. 2005; Marinelli et al. 2006; Nutt 2014). In animal models, antagonism of opioid receptors resulted in decreased alcohol intake (Hubbell et al. 1986; Oswald & Wand 2004).

Mu receptors mediate the analgesic effects of alcohol and have a special role in its rewarding effects (Gianoulakis 2004; Oswald & Wand 2004). Opioid receptor antagonists decrease alcohol consumption (Oswald & Wand 2004) (for a review see Hubbell et al. 1988; Nutt 2014). Opioid receptors interact with dopaminergic neurons via GABAergic interneurons and thereby mediate dopamine release (Koob & Le Moal 2006). Further, midbrain dopamine neurons in the ventral tegmental area and their projections to the nucleus accumbens and then to the ventral striatum support the anticipation and effects of reward (Adcock et al. 2006). Functional neuroimaging data show an inverse relationship between mu-opioid receptor binding and alcohol craving (Bencherif et al. 2004; Heinz et al. 2005).

On the basis of evidence that endogenous opioid peptides, such as β-endorphin, are involved in both the rewarding effects of ethanol and the risk for alcoholism (Gianoulakis et al. 1989; Gianoulakis et al. 1996; Cowen et al. 2004), naltrexone and nalmefene, opioid receptor antagonists with no intrinsic agonist properties, have been studied for the treatment of alcohol dependence.

8.3.3.1 Naltrexone Naltrexone is a non-selective antagonist at mu, kappa, and delta opioid receptors. Early studies with naltrexone found that it reduced craving for alcohol, the reinforcing properties of alcohol, alcohol-induced euphoria and the chances of continued drinking following a slip or lapse, consistent with its blockade of the contribution of the endogenous opioid system to the 'priming effect' of alcohol (Volpicelli et al. 1995; O'Malley et al. 1996b). However, the beneficial effects of naltrexone were found to diminish gradually after the 12-week medication treatment period (O'Malley et al. 1996a; Anton et al. 2001).

Many, but not all, subsequent studies of naltrexone showed it to be efficacious in the treatment of alcohol dependence (see Table 3) (*Level A, RG1*). The efficacy of naltrexone has been confirmed in several published meta-analyses. Recent meta-analyses by Maisel et al. (2013), Jonas et al. (2014) and Donoghue et al. (2015) all found that naltrexone reduced the risk of relapse to heavy drinking or alcohol consumption rather than increasing abstinence rates. This was also the conclusion of a Cochrane analysis (Rösner et al. 2010b).

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 participants remaining abstinent throughout the 12-week study period (Kranzler et al. 2004). A second extended-release 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 ($P = .02$). The effect was significant in men (48% reduction), but not in women. The 190-mg formulation produced a 17% reduction in heavy drinking, but this did not reach statistical significance ($P = .07$). A secondary analysis of this study showed that in the 82 participants with 4 days or more of voluntary abstinence before beginning treatment, the rate of continuous abstinence during the study was 32% in the group receiving the 380-mg active formulation compared with 11% in the placebo group ($P = .02$) (*Level B*). In the initially abstinent subsample, the extended-release naltrexone 380-mg group also showed a substantially longer time to the first heavy-drinking day (>180 days vs 20 days; $P = .04$) and greater improvement in gamma-glutamyl transpeptidase levels ($P = .03$) (O'Malley et al. 2007). Depot naltrexone is not available in Europe.

Comparative studies of acamprosate and naltrexone and the two in combination: Few studies have directly compared acamprosate, naltrexone and a combination of the two. In one study, naltrexone, acamprosate and the combination were significantly more efficacious than placebo (Kiefer et al. 2003). The acamprosate/naltrexone combination group had a significantly lower relapse rate than either the placebo or acamprosate groups, but it did not differ statistically from the naltrexone group. In addition, there was a non-significant trend for a better outcome with naltrexone than with acamprosate in the time to the first drink and time to relapse to heavy drinking. The US COMBINE Study (COMBINE Study Research Group 2003a,b) compared naltrexone, acamprosate and their combination; patients receiving medication also received medical management (consisting of nine brief sessions to promote sobriety and improve treatment compliance) and nearly half were also randomised to receive intensive psychotherapy (up to 20 sessions of Combined Behavioural Intervention). The study showed that naltrexone was efficacious, but neither acamprosate alone nor acamprosate in combination with naltrexone was superior to placebo (Anton et al. 2006). Mann et al. (2013b) obtained null findings for both naltrexone and acamprosate in a multi-centre study conducted in Germany comparing the two medications. A single-site, open-label, non-randomised study from Australia showed that the combination of acamprosate and naltrexone was superior to either medication alone (Feeney et al. 2006).

In conclusion, there is abundant evidence supporting the use of oral naltrexone for treating alcohol dependence (*Level A, RG1*). However, the optimal dosage and duration of treatment are two important clinical questions that remain to be adequately addressed, along with the most appropriate patient population and optimal treatment goal (i.e., harm reduction/reduction of heavy drinking days vs. abstinence). New approaches to the use of naltrexone, including long-acting injectable formulations, promise to enhance the clinical use of the medication.

8.3.3.2 Nalmefene Unlike naltrexone, nalmefene is not only an antagonist at the mu- and delta-opioid receptors but a partial agonist at the kappa opioid receptor (for review see Soyka 2016). The function of the kappa receptor is not entirely clear, but it may be relevant to the motivational aspects of alcoholism (Walker & Koob 2008; Walker et al. 2012; Walker et al. 2011). In 2013, the EMA approved nalmefene for the treatment of alcoholism, specifically to reduce alcohol consumption in adult patients with alcohol dependence who have a high risk level, are without physical withdrawal, and do not require immediate detoxification (EMA 2014).

Six clinical trials of the efficacy of nalmefene have been published (*Level A, RG1*). In the initial trial, Mason et al. (1999) found no efficacy for either the 20- or 80-mg/day dosages, although when combined the nalmefene-treated groups had a significantly lower rate of heavy drinking than the placebo group. A second study showed no efficacy of nalmefene 5, 20 or 40 mg/day on any measure of treatment outcome (Anton et al. 2004). Karhuvaara et al. (2007) reported the results of a multi-centre, randomised trial of targeted nalmefene combined with a minimal psychosocial intervention in which alcohol-dependent individuals 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. When, after 28 weeks, a subgroup of nalmefene-treated participants was randomised to continue on nalmefene or to receive placebo, those

who received placebo were more likely to return to heavy drinking.

More robust evidence of nalmefene's efficacy comes from three placebo-controlled RCTs in Europe that studied nalmefene exclusively as an as-needed medication to reduce drinking, rather than for the maintenance of abstinence (Gual et al. 2013; Mann et al. 2013a; van den Brink et al. 2014). Rather than using the 18-mg nalmefene or placebo tablet as a fixed dosage, participants decided daily whether to take the medication, on an as-needed basis.

In one of the studies, Mann et al. (2013a) compared nalmefene with placebo treatment for 6 months in 579 patients with alcohol dependence. The nalmefene group used the study medication on 48.0% of days, compared with 63.9% of days for the placebo group. The nalmefene group showed a significantly greater reduction of total daily alcohol consumption (–11.0 g/day, $P = .0003$) and heavy drinking days (–2.3 days, $P = .0021$) than the placebo group. Treatment-emergent adverse events were noted in 81.5% of the nalmefene group and 66.9% of the placebo group. The number of patients who discontinued treatment was significantly higher in the nalmefene group, mostly because of adverse events. The most frequent treatment-emergent adverse events associated with discontinuation were nausea, dizziness, fatigue and headache.

Gual et al. (2013) evaluated the as-needed use of nalmefene in 718 patients. In this 6-month study, the nalmefene group took study medication on a mean of 57.0% of days, compared to 65.2% in the placebo group. The co-primary efficacy analyses showed a significant greater reduction in heavy drinking days in the nalmefene group than the placebo group (group difference: –1.7 days/month, $P = .012$). In contrast to the Mann et al. (2013b) study, in the Gual et al. (2013) study the incidence of adverse events leading to dropout was similar in the two treatment groups. Treatment-emergent adverse events were recorded in 68.0% of the nalmefene group and 59.1% of the placebo group.

Van den Brink et al. (2013) published a secondary analysis of these two studies with an emphasis on patients who did not reduce their consumption after the initial assessment or before treatment began. The pooled analysis consisted of 667 patients (332 placebo, 335 nalmefene) and showed that nalmefene was significantly more effective than placebo in reducing the number of heavy drinking days and total alcohol consumption.

A third RCT was conducted by van den Brink et al. (2014). A total of 675 patients were randomised to receive 52 weeks of as-needed treatment with nalmefene 18 mg or placebo. In this study, the baseline alcohol level of 70 g/day was lower than that in the other two other RCTs (Gual et al. 2013; Mann et al. 2013a). Retention rates were similar in the two medication groups: a total of 112 participants (68%) in the placebo group and 310 (62%) in the nalmefene group completed the study. At month 6, primary outcome parameters did not differ between the groups, but at month 13 nalmefene was superior to placebo with respect to the reduction in both heavy drinking days (–1.6 days/month, $P = .017$) and total alcohol consumption (–6.5 g/day, $P = .036$). In patients with high/very high alcohol consumption, the reduction of total alcohol consumption was significant at both months 6 and 13. Serious adverse events were rare and were similar in frequency in the placebo (5.4%) and nalmefene groups (6.9%).

No head-to-head comparisons have been performed between naltrexone and nalmefene; an indirect meta-analysis gave modest evidence for some benefits of nalmefene over naltrexone (Soyka et al. 2016). RCTs are needed to address this question.

8.3.5 Alternative and second-line medications

8.3.5.1 Baclofen Baclofen, an agonist at the GABA-B receptor, is approved for use in spasticity associated with neurological disorders and has been studied for the treatment of alcohol dependence (Addolorato et al. 2009; Addolorato & Leggio 2010). Although the drug has long been off patent (Rolland et al. 2012), the drug was promoted by Olivier Ameisen, who published a self-report and monograph that described his recovery from alcoholism after taking high-dose baclofen (Ameisen 2005, 2008). In March 2014, it was temporarily approved by the French Drug Agency for the treatment of alcohol dependence in the case of resistance to previous medications. Special guidelines were issued in relation to contraindications and the requirement for gradual titration and dosage (maximal dose of 300 mg/day). Prescribers are required to register their patients through the French Drug Agency website. In September 2014, 3750 patients were registered and the first results were published on the website (http://ansm.sante.fr). Among the patients in whom treatment with baclofen was started, 12% were abstinent at baclofen introduction and 32% at the first follow-up visit. Among those who were receiving baclofen before March 2014 and in whom baclofen was maintained, 46% were abstinent. Craving was reduced in 75% of the newly treated patients. Nine percent of all patients complained of at least one side

effect that could be related to baclofen and 1% reported experiencing a severe side effect (mainly epilepsy (0.2%) and psychiatric symptoms (2.9%) such as anxiety, depressive symptoms or suicidal ideas).

Some preclinical evidence shows that baclofen suppresses alcohol intake (Addolorato et al. 2000). It is rapidly and extensively absorbed from the gastrointestinal tract after oral administration and peak plasma concentrations are generally observed 2–3 h after ingestion. Baclofen's elimination half-life is 2–6 h and it is usually administered three to four times daily (Novartis 1998). Baclofen is excreted primarily unchanged by the kidneys, making it a useful agent in patients with impaired hepatic function or a high potential for hepatic cytochrome P450-mediated drug-drug interactions.

A number of randomised clinical trials conducted in Italy (Addolorato et al. 2000; Addolorato et al. 2002; Addolorato et al. 2007; Addolorato et al. 2011) and a randomised trial conducted in the United States (Garbutt et al. 2010) generated divergent results using 30 mg/day of baclofen (for review see Agabio and Colombo 2014; Soyka & Lieb 2015). In brief, the data from the Italian group that performed the majority of the studies support the efficacy of baclofen, while the US study, a randomised, placebo-controlled, double-blind trial in 80 patients with an AUD, found that baclofen was not effective in reducing alcohol consumption (Garbutt et al. 2010).

There is some notable public support, in part via Internet forums, for the use of baclofen to treat alcoholism and some larger studies with baclofen were initiated, some of which have been completed. It is unclear whether baclofen can be viewed as 'partial substitution' (mimicking some of tthe effects of alcohol) in alcohol dependence (Pastor et al. 2013; Rolland et al. 2013). A multi-centre, randomised, placebo-controlled, double-blind study evaluated two different dosages of baclofen (30 and 60 mg/day) but failed to achieve the planned level of participation (Addolorato et al. 2011). Disappointing results were also reported in a double-blind, placebo-controlled study in 69 patients that compared baclofen 30 and 60 mg/day with placebo in a 12-week trial (Morley et al. 2014), as well as in a recent small Russian pilot study using 50 mg/day (Krupitsky et al. 2015). Interestingly, a recent study conducted at the Berlin Charité gave evidence for efficacy of baclofen in reducing alcohol intake (Muller et al. 2015). The results of two larger randomised French studies (one with a maximal dosage of 180 mg/day and another one with no maximal dose recommendation) are expected to be published soon and may provide more evidence of baclofen's ability to reduce alcohol consumption.

In general, baclofen may prolong the time to first drink, reduce the number of drinking days and facilitate maintenance of abstinence. The most common positive effect observed is the reduction of craving, which usually requires a dosage of at least 150 mg/day (personal data on a cohort of 100 patients). However, some safety concerns exist, especially for high-dose baclofen treatment. This is of greatest concern when the drug is administered at dosages up to 300 mg/day, as the most prominent adverse effect, sedation, is dose dependent (Rolland et al. 2015) (Level B, RG1). Other concerns include risk of withdrawal symptoms including seizure risk and delirium (Franchitto et al. 2014, Kapil et al. 2014). Baclofen may be an interesting option in alcohol-dependent patients with liver dysfunction (Addolorato et al. 2007)

8.3.5.2 Ondansetron Ondansetron is a selective 5-HT3 receptor antagonist that is approved to treat chemotherapy- and opioid-induced nausea and vomiting. When administered in low dosage (i.e., 1–16 μg/kg/day), ondansetron diminished drinking and increased abstinence among patients with an early onset of problem drinking (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 alcohol-dependent patients (Kranzler et al. 2003b). In a laboratory study, Kenna et al. (2014) found that ondansetron was superior to sertraline in reducing alcohol consumption in non-treatment-seeking alcohol-dependent individuals. Ondansetron, in combination with topiramate, was effective in reducing drinking in rodent studies (Lynch et al. 2011; Moore et al. 2014) and has shown promise in a subset of patients with alcohol dependence (Ait-Daoud et al. 2001). Variation in the serotonin transporter gene may modify treatment response to serotonergic medications such as ondansetron (Muller et al. 2014; Thompson & Kenna 2016), which is discussed in detail below. Taken together, these data suggest that ondansetron, possibly in combination with topiramate, is a potential medication for treating alcohol dependence (Level D).

8.3.5.3 Anticonvulsants *Gabapentin:* Gabapentin is used to treat epilepsy and neuropathic pain. It inhibits presynaptic voltage-gated Na^{+} and Ca^{2+} channels and prevents the release of various neurotransmitters, including glutamate (Dooley et al. 2000; Cunningham et al. 2004). Gabapentin has some efficacy in treating

alcohol withdrawal (Myrick et al. 1998; Bonnet et al. 1999; Bozikas et al. 2002; Voris et al. 2003; Rustembegovic et al. 2004; Mariani et al. 2006) (for review see Leung et al. 2015) and may reduce alcohol-induced CNS hyperexcitability (Watson et al. 1997).

The efficacy of gabapentin in the treatment of alcohol dependence has been studied in a number of trials. In a Cochrane review (Pani et al. 2014), gabapentin was found to have statistically significant positive effects on heavy drinking. No significant differences were found between placebo and gabapentin with respect to abstinence or craving. Mason et al. (2014), in a 12-week dose-ranging RCT of oral gabapentin (dosages of 0 (placebo), 900 mg/day or 1800 mg/day; $n = 150$, concomitant manual-guided counselling), found that gabapentin significantly improved the rates of abstinence and 'no heavy drinking'. The abstinence rate was 4.1% in the 900-mg group and 17.0% in the 1800-mg group. However, the findings from this study need to be interpreted in the context of the low rate of study completion (57%), which could have biased the findings despite a comparable rate of study completion in the drug and placebo groups. In contrast to the clinical trial findings, animal data suggest that gabapentin has some alcohol-like discriminative effects, and pre-treatment with gabapentin increases alcohol self-administration in rats (Besheer et al. 2016). As for other GABAergic drugs there are some case reports and series of gabapentin abuse, dependence and withdrawal (Mersfelder & Nichols 2016). Gabapentin is a drug with some potential for use in alcohol treatment (*Level D*).

Other anticonvulsants: CBZ, valproate and topiramate have been studied to treat alcohol dependence (for a review see Ait-Daoud et al. 2006). CBZ reduced drinks per drinking day and time to first drink in abstinent alcohol-dependent patients (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*).

Of the anticonvulsants, topiramate has been studied the most in clinical populations, although few animal studies have been published to date (Gabriel & Cunningham 2005; Farook et al. 2007; Hargreaves & McGregor 2007; Nguyen et al. 2007; Lynch et al. 2011; Moore et al. 2014). A single-site clinical trial of topiramate 300 mg/day 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 more than placebo (Johnson et al. 2003). A 14-week, multi-centre trial of topiramate 300 mg/day, combined with counselling to enhance medication compliance, found it to be superior to placebo in reducing the percentage of heavy drinking days as well as in a variety of other drinking outcomes (Johnson et al. 2007) (*Level B*). However, topiramate 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 of dosage increase (i.e., titration to the target dosage in the single-site study occurred over 8 weeks, compared to 6 weeks in the multi-centre study). A systematic meta-analysis of the effect of topiramate in AUD included seven RCTs with a total of 1,125 participants (Blodgett et al. 2014). It showed small-to-moderate effects of topiramate, primarily on abstinence rates and to a lesser degree on heavy drinking. The authors noted that the effects of topiramate were greater than those associated with naltrexone or acamprosate treatment. Likhitsathian et al. (2013) conducted a 12-week RCT in 106 alcohol-dependent outpatients. Although they found no medication effect on any treatment outcomes, the study completion rate was low (52.8% of the topiramate group and 47.2% of the placebo group), which limits interpretation of the findings. Batki et al. (2014) studied the effects of topiramate in veterans with PTSD and AUD and found some preliminary evidence that topiramate reduces alcohol consumption and craving and PTSD symptoms. Topiramate may be associated with transient cognitive impairment and a variety of other adverse effects.

A Cochrane analysis by Pani et al. (2014) assessed the efficacy of anticonvulsants for treating alcohol dependence and concluded that patients treated with topiramate had fewer drinks/drinking days ($n = 760$) and heavy drinking days and more abstinent days than those receiving placebo. The results indicated that, in general, however, the randomised evidence for the clinical utility of anticonvulsants to treat alcohol dependence is insufficient.

8.3.5.4 Varenicline Varenicline, an approved smoking cessation aid, has been evaluated in a number of clinical trials for its efficacy in AUD treatment (McKee et al. 2009; Fucito et al. 2011; Hays et al. 2011; Childs et al. 2012; Mitchell et al. 2012; Litten et al. 2013; Meszaros et al. 2013; Plebani et al. 2013) (for a review see Erwin & Slaton 2014).

Varenicline's mechanism in nicotine dependence is based on its partial agonist effects at $\alpha 4\beta 2$ and full

agonist effects at α7 nicotinic acetylcholine receptors located in the ventral tegmental area of the brain, which regulate dopaminergic pathways (Crunelle et al. 2010). Its mechanism of action in AUDs has not been fully elucidated, but decreased dopamine release in the nucleus accumbens in response to alcohol may play a role (Ait-Daoud et al. 2006; Crunelle et al. 2010; Crunelle et al. 2011; Mitchell et al. 2012; Nocente et al. 2013).

A recent systematic review (Erwin & Slaton 2014) included seven RCTs and one open-label study. Only one study showed an increased rate of neuropsychiatric adverse events (Mitchell et al. 2012). Two of the seven trials did not find differences in the overall frequency of adverse effects (McKee et al. 2009; Plebani et al. 2013), while four studies showed an increased rate of nausea, usually considered to be of mild intensity (Fucito et al. 2011; Childs et al. 2012; Litten et al. 2013; Meszaros et al. 2013). Overall, nausea was the most commonly reported adverse effect; others were headache, insomnia, abnormal dreams, constipation and vomiting. Most participants in the studies reviewed were comorbid smokers.

Varenicline treatment was associated with reduced alcohol consumption in four of the studies (McKee et al. 2009; Fucito et al. 2011; Mitchell et al. 2012; Litten et al. 2013). A fifth study showed a lower frequency of heavy drinking in the subgroup of smokers that was treated with varenicline (Plebani et al. 2013) and another demonstrated that varenicline potentiated the adverse effects of alcohol and decreased its reinforcing effects (Childs et al. 2012). There was no effect on abstinence rates in most studies, indicating that varenicline may be more effective in reducing alcohol intake once drinking is initiated than in relapse prevention (Erwin & Slaton 2014) (*Level D*).

8.3.5.5 Other medications A number of other drugs are currently being tested for the treatment of alcohol dependence, including those that modulate glutamatergic neurotransmission or receptors for stress-related neuropeptides (e.g., neuropeptide Y, corticotrophin releasing factor). Drugs that block the cannabinoid CB1 receptor are a novel mechanism of action for the treatment of addictive disorders (Gelfand & Cannon 2006). The CB1 antagonist SR141716A (rimonabant) was the first clinically available, potent, selective and orally active antagonist of the CB1 receptor. Rimonabant reduced voluntary alcohol intake in an animal model of alcoholism (Basavarajappa & Hungund 2005). The only clinical study of rimonabant for alcohol dependence treatment showed negative results (Soyka et al. 2008a) and the drug has been withdrawn because of safety concerns.

A recent meta-analysis (Kishi et al. 2013) found no evidence that antipsychotics in general are effective in primary alcohol dependence. Some data suggest possible efficacy of aripiprazole, which has D2 partial agonist, 5-HT1a agonist and 5-HT2A antagonist effects. There are also negative findings from a multi-centre trial of that medication for the treatment of alcohol dependence (Anton et al. 2008). No clear conclusion can be drawn on the basis of the few studies published so far (Brunetti et al. 2012; Martinotti et al. 2016). Quetiapine (see below) has also been discussed as a possible anti-craving drug (Ray et al. 2010), but data are disappointing in patients without psychiatric illness (Guardia et al. 2011).

9. Treatment of comorbid psychiatric disorders

Few controlled treatment studies have been conducted in patients with coexisting psychiatric disorders, a topic that has received more attention in recent years. There is an excess rate of psychiatric disorders in patients with AUD (Odlaug et al. 2016). The limited research database indicates that, in these patients, alcohol dependence treatment should be integrated with the treatment of the comorbid psychiatric disorder (Berglund et al. 2003).

9.1 Mood disorders

Community- and population-based epidemiological studies consistently find a greater than two-fold greater prevalence of depressive disorders in individuals with alcohol dependence than in the general population (Regier et al. 1990; Agosti & 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. 2005). Other studies show a modest association of unipolar depression and alcohol dependence (Schuckit et al. 1997). Alcoholism in depressed patients is of special importance for the course of depression, the risk of suicide and other causes of death and impaired social functioning (Hasin et al. 1996; Agosti & Levin 2006).

Differentiating independent depression from that which is alcohol induced can be difficult to do. Depressive symptoms are often differentiated into primary (preceding the onset of alcoholism) and secondary (following alcoholism onset) on the basis of the chronological ordering of the disorders. Because many

secondary depressive symptoms may take time to resolve in abstinent patients, often reliable differential diagnosis can be made only after weeks or months of abstinence. Patients with alcohol-induced depression have a better short-term outcome than patients with independent depression (Foulds et al. 2015).

There is consistent evidence for an excess rate of alcohol use disorder in patients with bipolar disorder, with a prevalence that is up to six-fold that seen in the general population (Regier et al. 1990; Kessler et al. 1997). The prognosis in patients with both disorders is often poor. There are few studies on the effects of anti-craving drugs to treat this patient group.

In general, the same guidelines can be used for the biological treatment of affective disorders in alcohol-dependent patients as for non-alcohol-dependent patients (for WFSBP guidelines see Bauer et al. 2013; Bauer et al. 2015), although a few special considerations are warranted. Apart from the difficulty of determining the order of onset of the disorders, drug interactions with alcohol are of special relevance. Tricyclic antidepressants in combination with alcohol may lead to sedation, blackouts or seizures. This risk is substantially lower for newer antidepressants, especially selective serotonin reuptake inhibitors (SSRIs). Medication adherence may be poorer among alcohol-dependent patients than among patients without alcohol dependence, an important issue to be addressed by the clinician. For safety reasons (risk of overdose), treatment with lithium requires excellent compliance. The same is true for other mood-stabilising drugs. Adequate treatment of bipolar disorder may also reduce comorbid alcohol or drug use in this population.

Patients with comorbid depression and alcoholism may have a poorer treatment response to antidepressants (Hashimoto et al. 2015). Treatment with antidepressants in alcohol-dependent patients may be most useful in combination with psychotherapeutic interventions such as CBT (Brown et al. 1997). A number of placebo-controlled clinical trials have been conducted of the efficacy of antidepressants (Ciraulo & Jaffe 1981; McGrath et al. 1996; Cornelius et al. 1997; Pettinati et al. 2001; Kranzler et al. 2006; Muhonen et al. 2008). In a review and meta-analysis of studies published at the time, 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. The 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 drug interactions, as addressed above.

Pettinati et al. (2010), in a study of depressed alcohol-dependent patients, found that treatment with the combination of naltrexone and sertraline resulted in a higher abstinence rate and a longer time to relapse to heavy drinking than either drug alone or double placebo. Further, the number of patients whose depression remitted during treatment in the combined treatment group was nominally greater than in the other groups. Adamson et al. (2015) recently reported negative findings for citalopram added to naltrexone treatment in patients with co-occurring alcohol dependence and major depression. When medication was effective in treating depression, there was also some effect on alcohol use, but few patients achieved abstinence. Although there is some limited evidence for SSRIs to reduce alcohol consumption, the overall evidence for non-depressed patients to benefit from this treatment is limited (Le Fauve et al. 2004; Nunes & Levin 2004). A meta-analysis by Torrens et al. (2005) concluded that in alcohol dependence without comorbid depression, the use of antidepressants is not justified.

In a placebo-controlled trial among alcohol-dependent individuals with comorbid bipolar disorder, valproate treatment was associated with improved drinking outcomes (Salloum et al. 2005). In an earlier study, quetiapine, a second-generation antipsychotic and multiple receptor antagonist at the 5-HT1A and 5-HT2A, dopamine D1 and dopamine 2, histamine H1 and adrenergic alpha 1 and alpha 2 receptors, when used as an add-on medication, decreased depressive symptoms, but not alcohol use, in patients with bipolar disorder (Stedman et al. 2010). A subsequent randomised, double-blind, placebo-controlled study of quetiapine for treatment of bipolar disorder, mixed or depressive phase, showed no effect of the active medication on alcohol consumption (Brown et al. 2014). No other relevant studies have been published on this topic (*Level F*).

9.2 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 & Levin 2006). There is a lifetime prevalence of 6–20% for anxiety disorders among alcohol-dependent individuals, with social and specific phobias having the highest risk (Kessler et al.

1997; Grant et al. 2005; Conway et al. 2006). Differential diagnosis can be difficult because of the overlap of anxiety and alcohol dependence symptoms, particularly given that alcohol withdrawal frequently presents with a high level of anxiety and agitation. 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 an anxiety disorder. One study found paroxetine to reduce social anxiety symptoms in patients with comorbidity (Randall et al. 2001) (*Level D*). A meta-analysis of five published studies showed a positive effect of buspirone on treatment retention and anxiety (Malec et al. 1996) (*Level B*). The effect on alcohol consumption was less clear.

9.3 Schizophrenia

Up to 34% of schizophrenia patients have an AUD and 47% have a drug use disorder (Regier et al. 1990; Soyka et al. 1993). Schizophrenic patients with co-occurring substance use disorders have a higher risk of psychotic relapse and rehospitalisation and poorer medication adherence and are at greater risk of suicide and aggressive behaviour than such schizophrenic patients without the comorbidity (Green et al. 2002).

Case series and chart reviews suggested 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; Noordsy et al. 2001; Green et al. 2003; Green 2005). Antipsychotics per se are not effective in treating primary alcohol dependence (Kishi et al. 2013), with the exception of aripiprazole in one study. An 18-month, randomised trial comparing four second-generation antipsychotics (olanzapine, risperidone, quetiapine, ziprasidone) and perphenazine in 1432 patients showed that no one drug was superior to the others in a secondary analysis of substance use behaviours, including alcohol consumption (Mohamed et al. 2015). In a randomised pilot trial in patients with concurrent alcohol and nicotine dependence in schizophrenia, varenicline reduced the number of standard drinks more than placebo (though the sample was too small to draw a meaningful conclusion). In this study, the active medication was poorly tolerated, especially because of gastrointestinal symptoms (Meszaros et al. 2013).

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 D*), although this is not supported by data from controlled trials (Hasan et al. 2015). Second-generation antipsychotics may also adversely affect the reward system less than first-generation antipsychotics (Chambers et al. 2001). The evidence is best for clozapine (*Level C2*). In the absence of controlled clinical trials, it is difficult to recommend any specific medication to treat schizophrenic patients with a co-occurring alcohol use disorder (*Level D*). A Cochrane analysis showed that there is not good evidence for the superiority of any psychosocial intervention over any other in dual-diagnosis patients (Cochrane analysis by Hunt et al. 2013). See Hasan et al. (2015) for a more detailed review,.

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. 2006). However, because disulfiram also blocks dopamine beta-hydroxylase, the risk of a psychotic relapse resulting from the reduced metabolism of dopamine must be considered.

10. Developments in pharmacogenetics

In the past decade, advances in human genetics have led to a growing number of studies of genetic variants as moderators of the effects of medications to treat alcohol dependence (Jones et al. 2015). These studies have shown that specific genotypes are associated with treatment response, though these findings remain to be replicated prospectively. The most promising findings have been those reported for the opioid antagonist naltrexone, serotonergic medications and topiramate. In some naltrexone studies, for example, carriers of a variant (118G or Asp40) allele in *OPRM1*, which encodes the μ-opioid receptor, had better treatment responses to naltrexone than did 118A (or Asn40) allele homozygotes (Oslin et al. 2003; Anton 2008). However, the only published prospective study in which patients were randomly assigned to receive naltrexone or placebo on the basis of genotype, there was no pharmacogenetic effect seen (Oslin et al. 2015. The lack of a moderating effect of the variant allele occurred despite the oversampling of Asp40 allele carriers, which yielded a larger number of individuals with the Asp40 allele ($N = 82$) than in any of the retrospective studies (Oslin et al. 2015). This finding suggests that any moderating effect of the single nucleotide polymorphism (SNP) is not clinically important.

Studies of serotonergic medications have examined the moderating effect of a functional polymorphism (5-HTTLPR) in *SLC6A4*, the gene encoding the serotonin transporter. Kranzler et al. (2013) found that the triallelic 5-HTTLPR polymorphism (which includes rs25531, a SNP in the long, or L, allele that yields L_A and L_G alleles) moderated the effects of sertraline and age of onset of alcohol dependence on the frequency of both drinking and heavy drinking. In participants homozygous for the L_A allele, those with late-onset alcohol dependence who received sertraline significantly decreased their drinking, while in patients with early-onset alcohol dependence, fewer drinking and heavy drinking days were seen with placebo than sertraline treatment. Johnson et al. (2011) found that two polymorphisms in *SLC6A4* moderated the response to ondansetron. The medication reduced drinking only in alcohol-dependent individuals with the 5-HTTLPR LL genotype. Further, a SNP in the 3′ untranslated region (3UTR) of *SLC6A4* interacted with the 5-HTTLPR polymorphism, such that the greatest reductions in drinking were in L-allele homozygotes that were also homozygous for the T allele of the 3UTR SNP. In a secondary analysis of this study, the same group (Johnson et al. 2013) genotyped SNPs in *HTR3A* and *HTR3B*, which encode the 5-HT3A and 5-HT3B receptor subunits, respectively. They used these SNPs to evaluate the optimal combination of genotypes to predict the response to ondansetron treatment. In addition to the two polymorphisms in *SLC6A4* that were reported previously to moderate ondansetron treatment response (Johnson et al. 2011), in individuals with one or more of three other genotypes (i.e., two related to *HTR3A* and one related to *HTR3B*) also showed a significantly greater therapeutic response. Johnson et al. (2013) calculated that the use of the five genotypes in these two studies could identify 34% of European ancestry individuals with alcohol dependence that are likely to respond very favourably to ondansetron treatment.

Both the severity of adverse events and the likelihood of a therapeutic response to topiramate in the treatment of heavy drinking may be moderated by genetic variation. As demonstrated in the multi-centre trial of topiramate for treating alcohol dependence (Johnson et al. 2007), a major limitation of the use of the medication is its adverse event profile, which includes cognitive impairment (Knapp et al. 2015). Topiramate, among its other pharmacologic effects, antagonises activity at glutamate receptors, specifically AMPA and kainate receptors (Gibbs et al. 2000; Skradski & White 2000). These effects are most potent and selective for glutamate receptors containing the GluK1 and GluK2 subunits (encoded by *GRIK1* and *GRIK2*, respectively) (Gryder & Rogawski 2003; Kaminski et al. 2004). To identify a potential genetic predictor of topiramate response, Kranzler et al. (2009) examined the association to alcohol dependence of seven SNPs in *GRIK1*. One of the SNPs, s2832407, a C-to-A non-coding change, was significantly associated with alcohol dependence in European Americans, with alcohol-dependent subjects showing an excess of the C allele. On the basis of these findings, Ray et al. (2009) conducted a secondary analysis of data from a pilot study of topiramate as a treatment for heavy drinkers (Miranda et al. 2008). The pharmacogenetic analysis showed that the severity of topiramate-related adverse effects in heavy drinkers was moderated by rs2832407.

Subsequently, in a placebo-controlled trial of topiramate 200 mg/day in 138 heavy drinkers whose goal was to reduce their drinking to safe levels, Kranzler et al. (2014a) found that topiramate significantly increased abstinent days and reduced heavy drinking days, gamma-glutamyltranspeptidase concentrations and alcohol-related problem scores. Further, the number of heavy drinking days was significantly reduced only in the subgroup of European ancestry patients with the rs2832407*CC genotype ($n = 122$). In A-allele carriers, the difference between topiramate and placebo was not significant. This pharmacogenetic effect persisted at 3- and 6-month post-treatment follow-up visits (Kranzler et al. 2014b). Although promising, these findings require replication before they can be recommended as the basis for personalised treatment of alcohol dependence with topiramate.

11. Other biological interventions

11.1 Neuromodulation in AUDs

New and innovative electrophysiological treatment options are available, namely deep brain stimulation (DBS) and repeated transcranial magnetic stimulation (rTMS), both of which show therapeutic potential by directly modulating dysfunctional brain networks in patients with AUDs.

11.1.1 Deep brain stimulation

DBS is a neurosurgical technique with proven effectiveness as an adjunctive therapeutic intervention in the treatment of severe neurological movement disorders (e.g., Parkinson disease). Preclinical studies investigated the effects of DBS in animal models of addiction to ethanol and illegal drugs, targeting brain areas that included the subthalamic nucleus, lateral habenula, medial prefrontal cortex, lateral hypothalamus and nucleus accumbens. The most commonly targeted brain

areas for DBS are the nucleus accumbens and subthalamic nucleus, and positive therapeutic effects of DBS on these brain regions have been described for AUD (Kuhn et al. 2007; Muller et al. 2009; Kuhn et al. 2011) and other substance use disorders (Kravitz et al. 2015).

Despite these initial promising results, almost all published studies on the use of DBS to treat AUDs were open-label or small case-control series or single case reports. Two registered randomised controlled DBS studies are currently recruiting patients with substance use disorders (Cologne/Germany and Amsterdam/Netherlands), but both research groups are experiencing problems in recruiting sufficient numbers of patients and it is not clear whether the studies will enrol the originally envisaged number of study participants (Luigjes et al. 2015). DBS may extend the current therapeutic options in severe cases of alcohol dependence. However, current evidence supporting DBS is limited to that derived from preclinical studies and human case reports or case series (*Level F*).

11.1.2 Repeated transcranial magnetic stimulation

rTMS is another electrophysiological therapeutic approach that may be of value in treating patients with an AUD (Bellamoli et al. 2014). TMS is non-invasive and therefore has many advantages compared to DBS, so it has a much greater potential to become an established therapy for AUD (Bellamoli et al. 2014). The magnetic field, delivered via a stimulation coil close the head, induces an electrical field in the brain and thereby activates cortical neurons. The main target for rTMS in the treatment of AUDs is the prefrontal cortical network, in particular the dorsolateral prefrontal and orbitofrontal cortices. These brain regions have important functions in the inhibitory control over the use of addictive substances. Other possible mechanisms of action of rTMS include the reduction of craving, modulation of the dopaminergic and HPA systems and of decision-making processes leading to a reduction in risk-taking behaviour (Knoch et al. 2006). To date, seven studies have investigated rTMS in patients with alcohol dependence (Mishra et al. 2010; Hoppner et al. 2011; Herremans et al. 2012; Rapinesi et al. 2014; Ceccanti et al. 2015; Girardi et al. 2015; Mishra et al. 2015), with some suggesting efficacy, particularly in the reduction of craving. Furthermore, high frequency rTMS also seems to have the potential to reduce alcohol consumption. However, the available studies are methodologically limited, with the main issues being the absence of reporting of long-term effects in most studies and the short-lived nature of the effects seen on craving and consumption. Moreover, some studies reported inconsistent outcomes for craving and consumption measures, illustrating the difficulties in operationalising the concept of craving and verifying alcohol consumption.

In conclusion, rTMS is a safe, non-invasive therapeutic method with some positive effects on craving and consumption in patients with AUDs. In addition, rTMS could be easily combined with other alcohol treatments as an augmentation therapy, with little risk of side effects. However, there is not yet consistent evidence of the efficacy of rTMS in treating alcohol dependence (*Level F*).

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Prof Kranzler has been an advisory board member, consultant, or continuing medical education speaker for Indivior, Lundbeck, and Otsuka. He is a member of the American Society of Clinical Psychopharmacology's Alcohol Clinical Trials Initiative, which is sponsored by AbbVie, Alkermes, Ethypharm, Indivior, Lilly, Lundbeck, Pfizer, and Xenoport.

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