Pharmacotherapy of Alcohol Use disorder. A Review of Current Literature

Robert Joseph MIELA[1], Wiesław Jerzy CUBAŁA[1], Katarzyna JAKUSZKOWIAK-WOJTEN[1], Dariusz Wojciech MAZURKIEWICZ[2]

[1]Department of Psychiatry, Medical University of Gdańsk, Poland
[2]St. Mark's Place Institute for Mental Health, New York, USA

SUMMARY

Aim. The objective of this review is to provide an updated analysis of currently approved as well as emerging pharmacotherapeutic options for the management of alcohol use disorder (AUD).

Methods: Relevant papers were selected for review following extensive, language, location and date unrestricted, electronic and manual searches of published literature regarding pharmacotherapeutic modalities in alcohol use disorder.

Results. Acamprosate, disulfiram, naltrexone, nalmefene, sodium oxybate and baclofen are the only approved pharmacotherapeutic options for the treatment of alcohol use disorder. Acamprosate and naltrexone have been evaluated in numerous clinical trials and represent evidence-based treatments in AUD. Nalmefene use, however, is controversial. Controversy also surrounds sodium oxybate, currently approved in Italy and Austria. The GABA (γ-aminobutyric acid) receptor agonist baclofen has shown mixed results; it is currently licensed for the treatment of AUD in France only. Supervised disulfiram is a second-line treatment approach. Compounds developed and licensed for various neuropsychiatric disorders are potential alternatives. Encouraging results have been reported for topiramate, gabapentin and also varenicline, which might be useful in patients with comorbid nicotine dependence. Metadoxine, pregabalin, ondansetron, already have a therapeutic profile and are currently evaluated with respect to efficacy in AUD. OSU6162 represents a novel compound under investigation.

Conclusion. Pharmacotherapeutic management of alcohol use disorder has been shown to be moderately efficacious with reasonably few safety concerns. Though it is grossly underutilized, ongoing studies of novel pharmacotherapeutic modalities, inclusive of pharmacogenetics, in alcohol use disorders are promising.

Key words: alcohol use disorder, pharmacotherapy

INTRODUCTION

In 1952, the American Psychiatric Association Committee on Nomenclature and Statistics published the first edition of the Diagnostic and Statistical Manual. The DSM-I featured descriptions of 106 disorders, featuring alcoholism with acute and chronic specifiers. Subsequent editions classified alcohol-related use as; excessive, episodic, habitual, intoxication, abuse and dependence. In 2013, the DSM-5 integrated the two previous DSM-IV disorders, alcohol abuse and alcohol dependence, into a single entity designated as alcohol use disorder (AUD) with mild, moderate, and severe sub-classifications. Modern pharmacotherapy for AUD has its roots in the failure of National Prohibition in the United States and the rise of the disease model of alcoholism. Beginning in the early 1950s, the US Food and Drug Administration (FDA) approved pharmacotherapy for alcohol use disorder was introduced. Nevertheless, the scope of therapeutic options for those with AUD remains limited, as most studies examining outcomes of individuals attending treatment find that 70–80% will relapse in the first year, with the highest rate of relapse taking place in the first 3 months. Those that remain abstinent from alcohol for the first year following treatment initiation have a relatively low risk of relapse [1]. It seems crucial, that the ongoing improvements in the efficacy of treatment, including pharmacotherapy, be diligently evaluated and updated. The present review will summarize the data on currently approved medications and also discuss recent findings concerning off-label evidence-based alcohol use disorder pharmacotherapies.

Pharmacotherapeutic agents currently approved for treatment of AUD

Disulfiram, acamprosate and naltrexone are the pharmaceutical agents licensed for the maintenance of abstinence/relapse prevention in abusive drinkers in the majority of countries advocating the use of pharmacotherapy for the management of alcohol use disorder. Sodium oxybate has been approved for the treatment of alcohol withdrawal

Corresponding author: Katarzyna Jakuszkowiak-Wojten, PhD; Department of Psychiatry, Medical University of Gdańsk Dębinki St. 7 build. 25, 80-952 Gdańsk, Poland; Phone: +48 58 349 26 50 ; E-mail: k.jakuszkowiak@gumed.edu.pl

syndrome and for relapse prevention in Italy and in Austria [2, 3, 4]. Similarly, nalmefene is approved in some countries, for use in people who are drinking at high-risk levels who wish to reduce their alcohol consumption but not necessarily abstain [5]. Baclofen is authorized by the French Health Agency, under a specific measure known as a "temporary recommendation for use" as a second-line drug to prevent relapse or reduce drinking in people with alcohol dependence.

Disulfiram

Disulfiram was discovered in the 1920's and received FDA approval for use in the treatment of alcohol use disorder in 1951. The oral preparation is licensed for relapse prevention in North America, much of Europe, the UK, Australia and parts of Asia. Despite its apparent efficacy, when used in compliant and/or supervised patients, overall, its use remains controversial. Alcohol is metabolized in the liver, via the enzyme alcohol dehydrogenase, to acetaldehyde and then to acetate via the enzyme acetaldehyde dehydrogenase (ALDH). Disulfiram is an ALDH inhibitor. The accumulation of high levels of acetaldehyde following alcohol ingestion in patients taking disulfiram results in the development of a constellation of symptoms such as flushing, nausea, vomiting, tachycardia, hypotension, dyspnea, dizziness and headache [6]. These symptoms appear approximately 5–15 min after alcohol consumption and last from 30 min to several hours. The intensity of the reaction varies with the amount of alcohol consumed and can prove fatal. The fear of the unpleasant effects provoked by alcohol is believed to be the primary mechanism facilitating abstinence from alcohol [5, 7]. Its efficacy also could be related to secondary central nervous system actions, through modulation of catecholamine neurotransmission. Specifically, at clinical doses, disulfiram inhibits the enzyme dopamine-β-hydroxylase, which converts dopamine to norepinephrine, potentially leading to increases in dopamine levels [8].

Not surprisingly, disulfiram has shown potential in maintaining abstinence and reducing relapse, but its effectiveness requires supervision due to a high rate of medication noncompliance. The utility of disulfiram is further decreased due to its various contraindications with drugs metabolized by cytochrome p450 enzymes including imipramine, warfarin, phenytoin, various benzodiazepines, omeprazole, and others. Furthermore, disulfiram is known to produce other unintentional side effects including various types of neuritis, hepatotoxicity, fulminant hepatitis, confusion, and psychosis. More severe adverse effects of disulfiram include myocardial infarction, congestive heart failure, respiratory depression, and rarely, death. Disulfiram is not recommended for individuals with a history of psychosis, cardiovascular disease, pulmonary disease, previous renal failure, diabetes, or those over the age of 60. Thus, despite over 60 years as an approved medication, disulfiram is not recommended as a first-line treatment for alcohol dependence [9]. NICE guidance suggests that disulfiram should be used as a second-line treatment after acamprosate or naltrexone or if a strong preference for its use is expressed. Treatment should be started at least 24 h after the last alcoholic drink with an initial and average maintenance dose of 250 mg per day. Warnings should be provided about the nature and seriousness of the interaction with ingested alcohol and the presence of alcohol in foodstuffs, perfumes and aerosol sprays. Supervision should be sought whenever possible. Treatment, if successful and relatively free from side-effects, may be continued long-term [10,11,12].

Studies of disulfiram are heterogeneous. Since its discovery, no consensus has been reached as to trial methodology and the efficacy of disulfiram as a treatment for alcohol use disorder [13]. It has long been held that it cannot be appraised fairly in double-blind, randomized, clinical trials (RCTs) because the psychological fear of provoking an unpleasant disulfiram-alcohol reaction is key to its effectiveness. According to the guidelines of the Cochrane Handbook for Systematic Reviews of Interventions, a lack of blinding of participants and personnel in randomized trials increases the risk of bias [14]. Notwithstanding, a number of systematic reviews and meta-analyses of the available trial data have been undertaken with some degree of consensus on treatment efficacy [15, 16]. The most comprehensive of these included a total of 22 RCTs, published between 1973 and 2010, comparing the efficacy of disulfiram to no treatment, placebo or other pharmacological treatments, irrespective of blinding or supervision of medication. Based on the results of the open-label studies, where compliance was assured by supervision, disulfiram is a safe and efficacious treatment compared to no treatment or to other pharmacological agents. However, no evidence of efficacy was found in blinded RCTs or where there was no supervision [5, 17].

Acamprosate

Until the early 1990s, disulfiram was the predominant pharmaceutical agent indicated for AUD. By the late 1990s, acamprosate had been introduced and became the most likely drug to be prescribed. On July 29th, 2004, it became approved by the FDA for alcohol use disorder. Acamprosate is licensed for the maintenance of abstinence in alcohol-dependent people in a wide range of countries including North America, most of Europe, UK, Australia, parts of Asia and Africa and, most recently, Japan.

Researchers have proposed that acamprosate's actions may be mediated through antagonism of the N-methyl d-aspartate (NMDA) glutamate receptor site or via modulation of glutamate neurotransmission at metabotropic-5-glutamate receptors. Furthermore, in vitro data suggests that acamprosate has an affinity for type A and type B GABA receptors. However, recent findings suggest that these hypothesized mechanisms of action are not evidenced in the therapeutic dose range that normally is used to reduce alcohol use [18]. Moreover, it has been suggested that acamprosate has no direct neurotransmitter target and that the therapeutic effects associated with its use are due to the co-administered calcium moiety. These findings have yet to be substantiated [5, 19, 20].

The results of a large number of RCTs and meta-analyses have shown that treatment with acamprosate, in conjunction with psychosocial support, significantly increases the proportion of alcohol-dependent patients who remained completely abstinent from alcohol at 6 months. A meta-analysis of 17 RCTs, involving 4087 participants, showed that 36.1% of patients receiving acamprosate achieved this

endpoint compared with 23.4% of those receiving placebo. Overall the number needed to treat (NNT) to achieve continuous abstinence was 7.8 at 6 months and 7.5 at 12 months [21]. A Cochrane review, including 24 RCTs with 6915 participants, showed a significant beneficial effect of acamprosate on a number of outcome measures other than abstinence; thus, its use was associated with a reduction in the return to any drinking with a NNT of nine; a reduction in the risk of any drinking to 86% of the placebo rate and an increase in the number of abstinent days by approximately three per month [22].

Acamprosate is not metabolized in the liver and has no impact on drugs subject to hepatic metabolism or those which affect the cytochrome P450 system. Thus, it does not interact with alcohol and it is generally safe in patients with impaired hepatic function. However, as it is excreted predominantly via the kidney, it should be used with care in people with renal insufficiency. Pharmacovigilance data in 1.5 million patients indicate no serious adverse events; the most commonly reported side-effect is diarrhea, and, occasionally, headaches, dizziness and pruritus being described. It does not have addictive potential and appears safe in overdose. Acamprosate is contraindicated in patients with severe renal impairment and in those who are hypersensitive to the drug or any of its components. Guidelines in the UK, France, the USA and Australia recommend that acamprosate is used as first line treatment for alcohol use disorder. It should be started as soon as possible after assisted withdrawal from alcohol in a daily divided dose of 1998 mg in people weighing >60 kg and of 1332 mg in those weighing <60 kg. There is no need to adjust the dose in people with mild to moderate hepatic impairment, although dose adjustment is recommended for people with moderate renal impairment. Treatment should continue for 6 months or longer in those deriving benefit who wish to continue; it can be continued if patients lapse but should be stopped if drinking persists beyond 4–6 weeks [5, 23].

Naltrexone

Naltrexone was initially synthesized in 1963 and used in the management of opioid dependence since 1984. In 1995, the FDA approved naltrexone as a treatment for AUD. The oral preparation is licensed for relapse prevention in alcohol-dependent people in a wide range of countries including the USA, much of Europe, the UK, Australia and Asia. Naltrexone and its active metabolite 6β-naltrexol act as opioid receptor antagonists, particularly at the μ and κ-opioid receptor. Its excretion is primarily renal [24, 25]. Naltrexone's efficacy in reducing alcohol drinking is believed to be mediated through interactions between the endogenous opioid system and dopamine systems, specifically through antagonism of the μ-opioid receptors. Evidence from animal models indicates that alcohol increases the release of β-endorphins modulating the dopaminergic mesolimbic pathway known to be involved in alcohol reward and that naltrexone administration blocks this release [8].

A substantial number of RCTs have been undertaken to examine the efficacy of naltrexone for the treatment of alcohol dependence. These have been the subject of a number of systematic reviews and meta-analyses employing varying inclusion criteria and drinking outcomes, nevertheless, with broadly comparable results. Thus, in alcohol-dependent people who have been withdrawn from alcohol, naltrexone, in combination with psychosocial support, has a modest, albeit significant beneficial effect on relapse rates, and in reducing alcohol intake. A Cochrane systematic review and meta-analysis, including 40 placebo-controlled RCTs of naltrexone, involving approximately 4500 participants, showed that treatment with naltrexone significantly reduced the risk of a return to heavy drinking to 83% of the placebo rate with a NNT of nine [26]. Treatment was also associated with a 4% reduction in the number of drinking days; a 3% reduction in the number of heavy drinking days; and a reduction in the amount of alcohol consumed, on drinking days, by about 11 g. It did not, however, have a significant effect on the return to any drinking [27]. The effect on overall abstinence rates was not determined. The results of a number of other meta-analyses confirm the effects of naltrexone in reducing the risk of a relapse to heavy drinking and the number of drinks consumed on drinking days. Some found that its use was, in addition, associated with a significant, albeit modest effect on the return to any drinking and overall abstinence rates [27, 28].

The metabolism of naltrexone takes place in the liver via the enzyme dihydrodiol dehydrogenase predominantly to 6β-naltrexol; the metabolites are further conjugation with glucuronide. Naltrexone is not metabolized via the cytochrome P450 system, therefore interactions with drugs subject to hepatic metabolism are likely to be minimal. Notably, increased plasma naltrexone concentrations have been reported in patients with cirrhosis. Naltrexone has no addictive potential, and it does not interact with alcohol. The most commonly reported side-effects are nausea, vomiting, dizziness, abdominal pain, reduced appetite, insomnia, anxiety; these are dose-dependent and appear to be worse in women [29]. Hepatotoxicity has been reported in association with the use of naltrexone in doses of >300 mg/day to treat obesity. However, reviews of the available safety data have confirmed that hepatic toxicity is very unlikely to occur with the standard daily dose of 50 mg. The most important safety consideration in relation to naltrexone is its reaction with opioid drugs. Opioid receptor blockade persists for 48–72 h after the last oral dose; thus, in an emergency non-opioid analgesia would have to be used for pain relief. If future use of opioids is anticipated, for example, for elective surgery, then naltrexone should be discontinued ahead of time [23]. Naltrexone is contraindicated in individuals taking or likely to take opioids. It is also contraindicated in people with acute hepatitis and acute or chronic liver failure. It should be used with caution in people with serum transaminase activities exceeding three times the upper reference range and in patients with renal failure.

At present, there is no consistent advice about monitoring of liver function tests in people receiving this drug but NICE guidance recommends that this should be considered in the elderly and the obese and that the drug should be discontinued immediately if the user feels unwell. Guidelines in the USA, UK, France and Australia recommend that naltrexone should be considered as a first-line treatment for alcohol use disorder. Opioids should be stopped 7–10 days beforehand but treatment can be started while patients are still drinking and during medically-assisted withdrawal from alcohol. An initial

dose of 25 mg/day is recommended increasing over a period of 2 weeks to a maintenance dose of 50 mg/day. Treatment should be continued for 6 months or longer in those deriving benefit who wish to continue. It can be continued if patients lapse but should be stopped if drinking persists beyond 4–6 weeks [5, 23].

Combined treatment with acamprosate and naltrexone

Since the therapeutic efficacy of acamprosate and naltrexone are moderate, the effect of combining the two treatments has been studied. In a study conducted by Keifer et al., where 160 severely dependent drinkers were randomised to acamprosate, naltrexone, acamprosate/naltrexone combined or placebo for 12 weeks, all participants received specific relapse prevention intervention. Both acamprosate and naltrexone and their combination had a positive treatment effect relative to placebo. The naltrexone/acamprosate combination was more effective than acamprosate alone but comparable in effect to naltrexone alone [30]. Anton et al., randomized 1383 much less severely dependent drinkers to the same four arms of treatment for 16 weeks. Participants were further randomized to receive one of two different types of behavioral therapy. Outcomes improved in all participant groups but were significantly better in those receiving naltrexone together with intensive behavioral therapy; combining treatments had no additional beneficial effect. Meta-analysis of these two trials confirmed that there were no significant differences in outcome favoring combined treatment [31].

Nalmefene

On 13 December 2012, nalmefene, an opioid antagonist, was approved by the European Medicines Agency (EMA) for the reduction of alcohol consumption in adult patients with alcohol dependence, a high-risk drinking level, no physical withdrawal symptoms and not requiring immediate detoxification [32]. Nalmefene is an opioid system modulator which is structurally similar to naltrexone but it has a different receptor profile as a μ and δ-opioid receptor antagonist and a partial κ-opioid receptor agonist. It was first introduced into clinical practice for the treatment of alcohol dependence in the early 1990s. However, a meta-analysis of the three RCTs available from that time, which utilized daily doses in the 20–80 mg range, showed that although nalmefene had some beneficial effect on drinking outcomes, none of these was significant. Subsequently, the drug was remarketed and licensed, on the basis of a small number of additional industry sponsored initiatives, for use in people who were drinking harmfully and wanted to reduce, though not necessarily stop, their alcohol consumption. However, this so-called „harm reduction" approach to AUD remains controversial [33, 34]. In November 2014, NICE, despite concerns raised by its own Evidence Review Group, recommended nalmefene, taken in a dose of 18 mg daily, as needed, together with psychosocial support, as a treatment option for people drinking at high-risk levels who, although alcohol-dependent, did not need medically-assisted withdrawal from alcohol and wished to reduce rather than stop alcohol. In France, nalmefene is recommended as the first-line medication for reducing alcohol consumption in people who are alcohol-dependent [5, 11].

More than 3,000 patients have been exposed to nalmefene in clinical studies. Adverse events were frequently reported in these studies and were slightly more frequent in the nalmefene arms (81% and 68% in ESENSE 1 and ESENSE 2, respectively) than in the placebo arms (67% and 59% in ESENSE 1 and ESENSE 2, respectively).

The most common adverse reactions were nausea, vomiting, dry mouth, weight loss, decreased appetite, tachycardia, palpitation, dizziness, headache, somnolence, tremor, disturbance in attention, paresthesia, hypoesthesia, malaise, sleep disorders, confusion, restlessness, decreased libido, muscle spasms, hyperhidrosis. Hallucinations and dissociation also reported. The majority of these reactions were mild or moderate, associated with treatment initiation, and of short duration. Co-administration with potent inhibitors of UGT2B7, may significantly increase the exposure to nalmefene. This is unlikely to present a problem with occasional use, but if long-term concurrent treatment with a potent UGT2B7 inhibitor is initiated, a potential for an increase in nalmefene exposure cannot be excluded. Conversely, concomitant administration with UGT inducers, may potentially lead to subtherapeutic nalmefene plasma concentrations. If nalmefene is taken concomitantly with opioid agonists, for example, certain types of cough and cold medicinal products, certain antidiarrheal medicinal products, and opioid analgesics, the patient may not benefit from the opioid agonist. Simultaneous intake of alcohol and nalmefene does not prevent the intoxicating effects of alcohol [35]. A slightly higher percentage of patients discontinued treatment because of adverse events in the nalmefene arms compared with the placebo arms (23% and 6.7% in the nalmefene arms versus 7% and 5.9% in the placebo arms of the ESENSE 1 and 2 studies, respectively). No difference was observed in terms of serious adverse events. Notwithstanding, regulators and advisory bodies in other European countries, for example, Germany and Sweden, have not recommended nalmefene for this indication [36, 37]. The drug is not licensed for use in the USA or Australia.

Palpaceur et al., have recently undertaken a meta-analysis of the efficacy and safety of nalmefene for the treatment of alcohol use disorder. They included all available RCTs of nalmefene irrespective of publication status, primary outcomes, and licensed indications. Overall, there was some evidence of a beneficial effect of nalmefene on the number of heavy drinking days per month and on total alcohol consumption but there were more withdrawals for safety reasons in the nalmefene-treated groups and the findings were not robust. There was no evidence of a beneficial effect of nalmefene on the health outcomes examined. The authors concluded that, at best, nalmefene has limited efficacy in reducing alcohol consumption but they were clearly aware of the limitations of their review and made specific recommendations for future studies. The licensing and subsequent recommendations for the therapeutic use of nalmefene have been widely criticized [38, 39, 40] (Table 1).

Sodium Oxybate

Sodium oxybate has been used to treat AUD in Italy since 1992, and in Austria since 1999. Sodium oxybate (SMO) or the sodium salt of γ-hydroxy-butyric acid, GHB, is a short-chain fatty acid that occurs naturally in the mammalian

Table 1. **Essential details of pharmacotherapeutic agents most commonly licensed for the treatment of Alcohol Use Disorder**

Drug	Order	Mode of Action	Contra-indications	Precautions	Side-effects	Dosage	Duration	Comments
Disulfiram	Second-line	ADH inhibitor	Cardiovascular disease Systemic hypertension Severe personality disorder Suicidal risk or psychosis Pregnancy & breast-feeding Caution in the presence of renal failure, hepatic or respiratory disease, diabetes mellitus and epilepsy	Caution due to seriousness of the interaction with ingested alcohol, alcohol in foodstuffs, perfumes, aerosol sprays	Headaches rowsiness Lethargy Peripheral neuropathy Optic neuritis Hepatotoxicity Psychosis	200 mg/day	Long term if required	Start 24 h after last drink Treatment most effective if supervised or witnessed
Acamprosate	First-line	GABA agonist Glutamate antagonist	Severe renal impairment (creatinine clearance <30 mL/min)	Does not eliminate or diminish withdrawal symptoms.	Diarrhoea Anorexia Flatulence Nausea Pruritus Dry mouth Paraesthesia Fatigue	Weight: > 60 kg 1998 mg/day < 60 kg 1332 mg/day Reduce in moderate renal failure	6 months, or longer	Safe for use in mild to moderate hepatic failure
Naltrexone	First-line	μ and κ-opioid receptor antagonist	Acute hepatitis Acute / chronic liver failure Use of / likely use of opioids Caution: if serum transaminase activities exceeding three times the upper reference range and in patients with renal failure.	Warning: Naltrexone blockade persists for 48–72 h after the last oral dose	Nausea Vomiting Dizziness Abdominal pain Anorexia Headache Daytime sleepiness Hepatotoxicity with high doses	Start with: 25 mg/day Maintenance 50 mg/day	6 months, or longer	Stop opioids 7–10 days before prescribing
Nalmefene	First-line (in France only)	μ and δ-opioid receptor antagonist, partial κ-opioid receptor agonist	Severe hepatic impairment Severe renal impairment Patients with a recent history of acute alcohol withdrawal syndrome (including hallucinations, seizures, and delirium tremens) Galactose intolerance Pregnancy Breastfeeding Current or recent opioid use	Discontinue in opioid administration Caution in psychiatric comorbidity seizure disorder including alcohol withdrawal seizures Caution with UGT2B7 enzyme inhibitors / inducers	Nausea, vomiting, dry mouth, weight loss, decreased appetite, tachycardia, palpitation, dizziness, headache, somnolence, tremor, disturbance in attention, paraesthesia, hypoaesthesia, malaise, sleep disorders, confusion, restlessness, decreased libido, muscle spasms, hyperhidrosis, hallucinations, dissociation	18 mg/day	No longer than 6 months	GP to monitor patient at monthly intervals for adverse effects, adherence treatment, attendance at psychosocial support, and reduction in alcohol consumption

brain, in particular in the thalamus, hypothalamus, and basal ganglia. SMO is structurally similar to the inhibitory neurotransmitter γ-amino-butyric acid (GABA), binding to GABAB receptors. Its functions are as both a precursor and a metabolite of the GABA system [41]. It is thought that the alcohol-mimicking effect of SMO is related to the effects of the dopamine increase mediated by GABAB receptors in the mesocorticolimbic circuitry. Most evidence suggests that mesolimbic dopaminergic neurons, originating in the ventral tegmental area and projecting their neurons into the nucleus accumbens, play a pivotal role in the regulation of alcohol craving, being stimulated by alcohol consumption [3, 42].

SMO was tested in preclinical and clinical settings for the treatment of alcohol withdrawal syndrome (AWS). A meta-analysis performed in 2010 by the Cochrane Collaboration showed that SMO (50–100 mg/kg/day) is more effective than placebo in reducing the CIWA-Ar score with an equal efficacy to benzodiazepines and clomethiazole without any differences in the onset of side effects. Recently, the GATE 1 study (phase IV, multicenter, multinational, randomized, double-blind, with parallel groups) showed that SMO presents a similar efficacy to oxazepam, one of the gold standard benzodiazepines, in the treatment of uncomplicated AWS [43]. Due to the ability of SMO to inhibit voluntary alcohol consumption, SMO is used for the treatment of AUD with encouraging results in maintaining total alcohol abstinence. In particular, 50–60% of treated patients achieve and maintain alcohol abstinence at the end of the first three months of treatment. In addition, SMO is at least as effective as naltrexone or disulfiram in the maintenance of abstinence in alcohol-dependent patients [44]. SMO was shown to be significantly more effective than placebo in reducing the number of daily drinks ($p < 0.00001$) and in reducing relapses into heavy drinking ($p < 0.00032$) in a controlled clinical trial. In a two-phase trial exploring the efficacy of dose-fractioning of SMO treatment, 17.4% of patients did not achieve complete abstinence but they significantly reduced their daily drinking ($p < 0.05$) at the end of the first three-month phase. An open multicenter study found a reduction of biomarkers of alcohol abuse after SMO treatment, and the group of patients who did not achieve complete abstinence did reduce their average alcohol intake. Maremmani et al. described a long-term treatment with SMO in a population of treatment-resistant patients; although the size of the group was limited, the partial responder group who reduced their alcohol intake for an average of 40% was larger than the total responders who achieved complete abstinence from alcohol (14.3% vs. 11.4%) [45, 46, 47, 48].

SMO has also been evaluated in combination with other drugs. An open, randomized, comparative study evaluated the efficacy of SMO in combination with naltrexone in maintaining alcohol abstinence compared to SMO and naltrexone alone. These data confirm that the two drugs combine their different actions synergistically without suppressing the favorable effects of each other. In SMO treatment-resistant chronic alcoholics (30–40%), the combination with disulfiram was proposed. SMO-disulfiram combines the adverse effect of disulfiram with the anti-reward effect of SMO [49, 50]. There is some preliminary evidence that SMO can be effective in reducing alcohol intake in patients who fail to maintain total alcohol abstinence. It also seems that, for less motivated patients to achieve total alcohol abstinence immediately, the reduction in alcohol intake could be the primary end-point of SMO treatment, suggesting a role in „harm reduction" treatment. Unfortunately, the endpoints defined by published trials are varied and non-comparable: heavy drinking days, daily alcohol intake, total amount of alcohol intake, or cumulative days of abstinence. Thus, more studies to confirm these data and to explore the efficacy of SMO in patients considering alcohol reduction as their primary goal are warranted [3].

SMO is primarily eliminated by the liver by the enzyme GHB dehydrogenase, and by a still not fully ascertained process of beta-oxidation. Only a modest quantity of SMO remains unmodified (2–5%) and eliminated with urine with a relatively short window of detection (3–12 h). A dose of 50 to 100 mg/kg/day, fractioned into three to six daily administrations, is considered a safe approach in the use SMO. About 30% of alcohol-dependent patients treated with SMO can develop side effects, represented by nausea, vomiting, diarrhea, dizziness, sedation, enuresis and paresthesia. These events do not, in general, require discontinuation of treatment, as the dizziness subsides spontaneously after the first doses, while sedation and paresthesia abate within 2–3 weeks. In addition, no side effects due to the combination of SMO 50 mg/kg/day and alcohol were observed in those SMO-treated patients who were still drinking during treatment. A recent randomized, double-blind, crossover trial in healthy volunteers aimed at exploring the pharmacodynamic interaction of the solid immediate release formulation of SMO and alcohol, showed that SMO and alcohol have separate adverse effect profiles and that the objective effects of SMO are much less marked than those of alcohol, without any deleterious interaction. Caution should be maintained in concomitant use of with divalproex sodium which may result in a 25% mean increase in systemic exposure to SMO [3, 51, 52, 53].

Concerns have been raised about the risk of developing addiction to, misuse, or abuse of SMO. However, clinical trials have shown that episodes of craving for, and abuse of, SMO in alcohol-dependent cohort are limited (~10% of cases), and are mainly confined to patients with AUD associated with polydrug addiction and psychiatric co-morbidity, in particular, borderline personality disorder [54, 55]. GHB as a "street drug", sold for recreational use, is mostly reported in Anglo-Saxon countries, with some cases reported in Italy. Recreational use represents the primary cause of GHB-related death. Risk factors are unknown: dose/concentration, frequently combined use with other drugs, difficulties with dose titration, and narrow safety margins between a recreational dose and lethal dose. Cardiorespiratory depression is a documented dose-related effect of GHB, and it is likely to be the principal cause of death in GHB overdose. Whereas it is well known that a GHB blood concentration of 500 mg/L causes death due to cardiorespiratory depression, it is impossible to clearly define a "lethal" dose. Reduced vigilance leading to trauma and driving impairment are other possible causes of GHB-related death. With regard to SMO treatment for AUD, there are no published data concerning related deaths [3, 56, 57, 58].

Baclofen

In 2014, baclofen, in doses up to 300 mg/day, was authorized by the French Health Agency (FHA) as a second-line drug to prevent relapse or reduce drinking in people with alcohol dependence. This authorization, which is a specific measure known as a "temporary recommendation for use" (TRU) requires a centralized collection of follow-up data. Baclofen is a selective γ-aminobutyric acid GABAB receptor agonist which was originally approved for the treatment of spasticity associated with multiple sclerosis and spinal cord lesions. Activation of GABAB receptors reduces anxiety and it was for this reason that it was identified as a potential treatment for alcohol withdrawal and dependence. A number

of placebo-controlled RCTs of baclofen, 30–60 mg/day, have been undertaken but with widely different results [5)] A series of trials undertaken by one Italian group, including a trial in patients with cirrhosis, showed significantly higher abstinence rates in participants receiving baclofen compared with placebo, together with improvements in other drinking outcomes. However, studies undertaken in the USA, Australia and Israel showed no beneficial effects of baclofen over placebo on any drinking outcome, although a post hoc analysis of the Australian data showed that baclofen conferred some benefit, in terms of relapse behavior, in a subgroup of patients with a comorbid anxiety disorder [59, 60]. The divergent results of these studies have not been fully explained. One suggestion is that they may relate to the relatively low doses of baclofen used in the trials undertaken to date. Baclofen is rapidly absorbed and excreted primarily unchanged by the kidney but there is significant inter-subject variation in its pharmacokinetics, which could potentially be reflected in differences in population responses. This view was supported by the self-reported experience of a French physician who treated his own alcohol dependence and anxiety disorder with baclofen in a dose of 270 mg/day [61]. The consequent media interest resulted in an unprecedented demand, in France, for off-label treatment with high dose baclofen (Table 2).

Studies utilizing high doses of baclofen are now being reported. A German group randomized 56 alcohol-dependent people to either baclofen titrated to 270 mg/ day or placebo. The mean daily dose of baclofen achieved during the 12 week high dose phase of the trial was 180 mg and during this phase abstinence rates were higher in those receiving baclofen than placebo (68.2% vs. 23.8%, p = 0.014); baclofen also had a significant beneficial effect on overall abstinence rates during the 20 week trial (42.9% vs. 14.3% p = 0.04) [62, 63]. However, there was no relationship between the individualized doses of baclofen and drinking behavior outcomes suggesting that the efficacy of baclofen does not have a clear dose threshold. A multicentre RCT95 undertaken in the Netherlands randomly assigned 151 alcohol-dependent individuals to 6 weeks titration and 10 weeks maintenance with either low-dose baclofen (30 mg/day), high-dose baclofen (up to 150 mg/ day; mean 94 mg/day), or placebo. No significant differences were observed between the groups in the time to first relapse; the proportions who relapsed; the proportions who attained continuously abstinence; the cumulative abstinence duration; or the dropout rates [64, 65].

The results of two French high-dose baclofen studies, which will be pivotal in determining whether the TUR currently in place will be removed by the FHA or made official, have been reported but in abstract form only.

In the first of these, the ALPADIR study, 320 alcohol-dependent outpatients attending French specialist alcohol treatment clinics were randomized to baclofen (target dose 180 mg/day attained by 66%) or placebo using a 7-week titration, and 17 weeks maintenance paradigm. The proportions of patients who were continuously abstinent throughout the trial were similar in both groups viz. baclofen 11.9%; placebo 10.5%. Post hoc subgroup analyses showed more evidence of benefit in the heaviest drinkers and when the outcome variable selected was the overall reduction in consumption. The second of these French studies, the multicenter BACLOVILLE study, was designed to explore pragmatic risk reduction in a general practice. A total of 320 attendees diagnosed as having an alcohol use disorder were randomized to treatment with baclofen, individually titrated to a maximum dose of 300 mg/day, or placebo for 12 months. There was no requirement for participants to be withdrawn from alcohol or to receive psychosocial support. The primary outcome, which was the proportion of patients who achieved WHO defined safe drinking levels (1–20 g/day for women and 1–40 g/day for men) was attained by 56.8% of the baclofen group and 36.5% of the placebo group (risk reduction 1.56 [95% CI: 1.15–2.11]; p = 0.004) [5, 64, 65].

These four high-dose baclofen studies are not directly comparable as they differ considerably in aspects of patient selection, study design and duration, dosage schedules, and outcome variables. In addition, the reporting of the two French studies is still incomplete. Thus, overall conclusions about the efficacy of baclofen as a treatment for alcohol dependence cannot be made at this time. Baclofen and alcohol are both central nervous depressants so there are considerable safety concerns around the use of this drug. Fatigue, transient drowsiness, nausea, confusion, headache, insomnia, constipation, urinary frequency, euphoria were more frequent, particularly in the high-dose studies. Vomiting, muscular hypotonia, accommodation disorders, respiratory depression, seizures, and coma have been reported in overdose. Several case reports of baclofen-induced mania have recently been presented in the literature. Reports of further adverse event such as confusion, major sedation, and sleep apnea are increasing in parallel with increased use of this drug. Hallucinations and seizures have occurred on abrupt withdrawal. Because baclofen is primarily excreted unchanged by the kidneys,

Table 2. **Pharmacotherapeutic agents approved for the treatment of Alcohol Use Disorder in some European countries**

Drug	Mode of Action	Dosage	Side-effects	Precautions
Sodium Oxybate	GABAB receptor agonist	50 mg/kg/day	Nausea, vomiting, diarrhea, dizziness, sedation, asthenia, enuresis	Caution should be maintained in concomitant use of with divalproex sodium
Baclofen	GABAB receptor agonist	30–300 mg/day	Nausea, confusion, headache, insomnia, constipation, urinary frequency, euphoria	Caution in severe renal impairment (creatinine clearance <30 mL/min) Caution in Phenylketourea contains phenylalanine

it should be given with caution and it may be necessary to reduce the dosage in patients with impaired renal function. Phenylketonuric patients should be informed that baclofen contains phenylalanine [66, 67, 68, 69].

Emerging pharmacotherapies for Alcohol Use Disorder

Several other agents have been proposed and are currently under investigation as potential treatment options for AUD. The majority already have a therapeutic profile and are being repurposed for use in this field. Of these, topiramate and metadoxine, gabapentin and pregabalin are the best known.

Topiramate

Topiramate's actions have been associated with antagonism of AMPA/kainate glutamate receptors and voltage-dependent sodium channels, as well as agonism of extrasynaptic GABAA receptors. In animal models, topiramate has been shown to reduce alcohol use and alcohol withdrawal-induced convulsions [8]. Like many other drugs proposed for the treatment of alcohol dependence, it is thought to reduce mesolimbic dopaminergic activity. A small number of RCTs of topiramate vs. placebo, no treatment or an active comparator for the treatment of alcohol dependence have been undertaken and subjected to systematic review with or without meta-analysis [70, 71]. A systematic review of topiramate vs. placebo including seven RCTs, involving 1125 participants, demonstrated significant, though moderate, benefits of topiramate for abstinence and heavy drinking outcomes. A more generic Cochrane review of anticonvulsants in the management of alcohol dependence included a separate analysis of six placebo-controlled RCTs of topiramate, involving 970 participants, and showed a modest but significant beneficial effect on heavy drinking and the number of drinks per drinking day, but a rather less robust effect on the number of abstinent days. Topiramate is a mild inhibitor of CYP2C19 and a mild inducer of CYP3A4. In a dose of 300 mg/day, it appears to be relatively well-tolerated with the most common adverse effects being dizziness, paresthesia, anorexia, mild-to-moderate taste disturbances and metabolic acidosis. Rarely, topiramate causes serious ophthalmologic effects. However, all the trials undertaken to date are short-term; with long-term treatment, there is potential, given the drug's safety profile, for the emergence of other side-effects [5, 71].

Metadoxine

Metadoxine (pyridoxal L-2-pyrrolidone-5- carboxylate) is an ion pair salt of pyridoxine and L-pyroglutamate. It is approved in several European countries, India, the Russian Federation and Brazil for treating acute alcohol intoxication, based on its ability, when given as a single 900 mg intravenous dose, to facilitate the elimination of alcohol from blood and tissues. Metadoxine has also been used to treat alcohol dependence based on its properties as a selective serotonin receptor subtype 5-HT2B antagonist and a monoamine-independent GABA modulator. In an open-label study, patients treated with metadoxine, 1500 mg/day in divided doses, were significantly more likely to maintain abstinence at 3 months than untreated controls (44.8% vs. 21.6%; $p < 0.004$). In another randomized, open-label study in patients with severe alcoholic hepatitis survivors who received metadoxine, in addition to standard therapy, were significantly more likely to maintain abstinence at 6 months than those who did not (74.5% vs. 59.4%, $p = 0.02$). Metadoxine may reduce the effects of levodopa and is contraindicated in pregnancy and lactation. Most common side effects consist of diarrhea, skin rash, numbness, and drowsiness [72, 73, 74].

Gabapentin

Gabapentin, 1-(aminomethyl) cyclohexa- neacetic acid is an anticonvulsant used for spasticity and epilepsy. Gabapentin is structurally related to GABA. However, it does not bind to GABAA or GABAB receptors, and it does not appear to influence synthesis or uptake of GABA. High-affinity gabapentin binding sites have been located throughout the brain; these sites correspond to the presence of voltage-gated calcium channels specifically possessing the α2-δ subunit. This channel appears to be located presynaptically and may modulate the release of excitatory neurotransmitters. In a 28-day placebo-controlled trial (n = 60), gabapentin significantly reduced the number of drinks per day and mean percentage of heavy drinking days, and increased the percentage of days of abstinence. Gabapentin may be more effective in patients experiencing withdrawal symptoms and may improve outcomes over naltrexone alone during early stages of abstinence. Ongoing clinical trials in the USA are promising, raising the likelihood of approval for the use in AUD [75, 76, 77, 78].

Pregabalin

Pregabalin, (S)-3-(aminomethyl)-5-methylhexanoic acid, along with gabapentin, derive their chemical structure and consequently their USAN generic names from GABA. Nevertheless, both drugs are inactive at GABA receptors including GABAA, benzodiazepine, TBPS and GABAB binding sites. In many respects, pregabalin is pharmacologically similar in its mechanism to gabapentin. Both of these compounds have bulky aliphatic chemical substitutions at the 3-position of the GABA backbone which changes their pharmacological properties significantly in comparison to GABA. Pregabalin binds to the α2-δ subunit of voltage-gated calcium channels within the CNS and modulates calcium influx at the nerve terminals, thereby inhibiting excitatory neurotransmitter release including glutamate, norepinephrine, serotonin, dopamine and substance P. A randomized trial showed no differences in alcohol abstinence between pregabalin and the comparator, naltrexone whereas hitherto no placebo-controlled study has been reported [79, 80].

Novel treatments with an evidence base evaluated for Alcohol Use Disorder

Varenicline

Varenicline is a partial neuronal α4 β2 nicotinic receptor agonist; prevents nicotine stimulation of mesolimbic dopamine system associated with nicotine addiction. Also binds to the 5-HT3 receptor with moderate affinity. Varenicline stimulates dopamine activity but to a much smaller degree than nicotine does, resulting in decreased craving and withdrawal symptoms. It reduces alcohol intake in preclinical models and is of particular interest due to the high comorbidity of nicotine and

alcohol use disorder. While varenicline was associated with significantly reduced alcohol drinking and alcohol craving compared to placebo in both alcohol-dependent smokers and non-smokers, another trial failed to detect any effect in a similar population [81, 82, 83, 84].

Ondansetron

Ondansetron, a 5-HT3 receptor antagonist used as an anti-emesis prophylaxis before chemotherapy, has shown efficacy in reducing alcohol drinking in subgroups of patients with an early onset type of alcohol use disorder in which serotonergic dysfunction may play a role. In one RCT, ondansetron was shown to significantly reduce self-reported drinking. Patients who received ondansetron 4 mcg per kg twice per day had fewer drinks per day. They also had a greater percentage of days of abstinence (70 vs. 50% with placebo) and a greater total number of days abstinent per study week (6.7 vs. 5.9 with placebo) in patients with early-onset alcoholism. Its clinical usefulness remains to be determined in replication trials [75, 85].

OSU6162

OSU6162 belongs to a novel class of dopamine stabilizers characterized by the ability to suppress, stimulate, or not influence dopamine activity depending on the prevailing dopaminergic tone. It exhibits partial agonist action at both dopamine D2 receptors and 5-HT2A receptors. In rats, OSU616 reduces voluntary ethanol consumption, ethanol withdrawal symptoms, operant ethanol self-administration, and cue-induced reinstatement of ethanol, and blunts ethanol-induced dopamine output in nucleus accumbens of ethanol-naive rats. A clinical trial of OSU6162 on cue-induced alcohol craving in humans is currently in progress [75, 86, 87] (Table 3).

Additional compounds are predicted to be effective based on a battery of animal models. Using such models, a short list of targets has accumulated sufficient preclinical validation to merit clinical development. These include the cannabinoid CB1 receptor, receptors modulating glutamatergic transmission (mGluR2, 3 and 5), and receptors for stress-related neuropeptides corticotropin releasing factor (CRF), neuropeptide Y (NPY) and nociceptin. Similarly, preclinical studies with D-Penicillamine, as well as Mesyl Salvinorin B (MSB), a potent selective κ-opioid receptor (KOP-r) agonist, as novel pharmacological strategies to treat AUD are currently underway. In the past few years, many studies have focused on scrutinizing genetic polymorphisms that alter a person's vulnerability to developing AUD as well as the efficacy and response to treatment. Association of these polymorphisms in shaping the response to medications, or pharmacogenetics, has only begun recently. And although only a handful of published studies address AUD pharmacogenetics, those that have, demonstrate a clear advantage over prescribing a common pill to all. Considering the fact that the "ideal" and effective pharmacotherapeutic modality for all phenotypes of alcohol use disorder patients does not exist, the future challenge will be to identify a more personalized approach. Finally, according to Clinical Practice Research Datalink study, published by Thompson et al. 2017, only 4,677 (11.7%) of the cohort of 39,980 people with an incident diagnosis of alcohol dependence aged 16 years or older between 1 January 1990 and 31 December 2013, received relevant pharmacotherapy in the 12 months following diagnosis in the UK [88]. Similarly, only about 9% of individuals meeting diagnostic criteria for alcohol use disorder receive pharmacologic treatment in a given year in the USA [89].

Table 3. **Emerging and novel pharmacotherapies in Alcohol Use Disorder**

Drug	Mode of action
Topiramate	GABAA receptor agonist AMPA/kainate glutamate receptors antagonist voltage-dependent sodium channels antagonist
Metadoxine	GABA modulator 5-HT2B antagonist
Gabapentin	Voltage-gated Caα2-δ-channel agonist
Pregabalin	Voltage-gated Caα2-δ-channel agonist
Varenicline	α4 β2 neuronal nicotinic receptor partial agonist 5-HT3 receptor agonist
Ondansetron	5-HT3 receptor antagonist
OSU6162	D2 partial agonist 5HT2A partial agonist

CONCLUSION

Alcohol has a complex neuropharmacology and can affect many different brain neurotransmitter systems. Several pharmacological agents that interact with specific neurotransmitter systems affected by alcohol have shown efficacy in the treatment of alcohol use disorder and many exciting investigational agents are on the horizon. The evidence indicates that best choices for prevention of relapse are acamprosate and naltrexone with concurrent counseling through professional or self-help programs. The evidence is lacking for combination pharmacotherapy, but research is underway. Because of its lack of effectiveness and problems with adverse effects and compliance, disulfiram is not recommended as first-line treatment in the primary care setting. Controversy surrounds Nalmefene and Sodium oxybate. Baclofen has shown mixed results. Encouraging results have been reported for topiramate, gabapentin and also varenicline, which might be useful in patients with comorbid nicotine dependence. Metadoxine and ondansetron, already have a therapeutic profile and are currently evaluated with respect to efficacy in AUD. OSU6162 represents a novel compound under investigation. Thus, enhancing existing treatment modalities, conducting trials on off-label pharmacotherapies, furthering the investigation and investment in pharmacogenetics, and facilitating access to treatment emerge as the most crucial priorities in the management of prevalence of AUD.

REFERENCES

1. World Health Organization (2017). Dementia. [cited 6 May 2017]. Available from: http://www.1. Thompson A, Ashcroft D, Owens L, van Staa T, Pirmohamed M: Drug therapy for alcohol dependence in primary care in the UK: A Clinical Practice Research Datalink study. PLoS One. 2017; 12(3).
2. Busardo F.P, Kyriakou C, Napoletano S, Marinelli E, Zaami S: Clinical applications of sodium oxybate (GHB): from narcolepsy to alcohol withdrawal syndrome. European Review for Medical and Pharmacological Sciences 2015; 19: 4654-4663.
3. Skala K, Caputo F, Mirijello A, Vassallo G, Antonelli M, Ferrulli A, Walter H, Lesch O, Addolorato G. : Sodium oxybate in the treatment of alcohol dependence: from the alcohol withdrawal syndrome to the alcohol relapse prevention. Expert Opin Pharmacother. 2014 Feb;15(2):245-57 .
4. Caputo F, Vignoli T, Tarli C, Domenicali M, Zoli G, Bernardi M, Addolorato G: A Brief Up-Date of the Use of Sodium Oxybate for the Treatment of Alcohol Use Disorder. Int J Environ Res Public Health. 2016 Mar; 13(3): 290 .
5. Goh E.T, Morgan M.Y: Review article: pharmacotherapy for alcohol dependence – the why, the what and the wherefore. Aliment Pharmacol Ther 2017; 45: 865–882.
6. Fuller R.K, Branchey L, Brightwell D.R, et al.: Disulfiram treatment of alcoholism. A veterans administration cooperative study. JAMA 1986; 256: 1449–55.
7. Krampe H, Ehrenreich H: Supervised disulfiram as adjunct to psychotherapy in alcoholism treatment. Curr Pharm Des 2010; 16: 2076–90.
8. Krishnan-Sarin S, O'Malley S, Krystal J.H: Treatment Implications Using Neuroscience to Guide the Development of New Pharmacotherapies for Alcoholism. Alcohol Res Health. 2008; 31(4): 400–407.
9. Yahn S.L, Watterson L.R, Olive MF: Safety and Efficacy of Acamprosate for the Treatment of Alcohol Dependence. Substance Abuse: Research and Treatment 2013:7 1–12.
10. British National Formulary (BNF) 65 Mar-Sep 2013.
11. NICE Clinical Guideline CG 115 Alcohol-use disorders February 2011 www.nice.org.uk.
12. Summary of Product Characteristics Antabuse http://www.medicines.org.uk/emc/medicine/519/SPC/Antabuse+Tablets++200 mg.
13. Skinner M.D, Lahmek P, Pham H, Aubin H.J: Disulfiram Efficacy in the Treatment of Alcohol Dependence: A Meta-Analysis. PLoS One. 2014; 9(2).
14. Higgins J, Green S (2011) Cochrane Handbook for Systematic Reviews of Interventions.Version 5.1.0 The Cochrane Collaboration.
15. Jørgensen C.H, Pedersen B, Tønnesen H: The efficacy of disulfiram for the treatment of alcohol use disorder. Alcohol Clin Exp Res 2011; 35: 1749–58.
16. Jonas D.E, Amick H.R, Feltner C, et al.: Pharmacotherapy for adults with alcohol use disorders in outpatient settings: a systematic review and meta-analysis. JAMA. 2014 May 14;311(18):1889-900.
17. Skinner M.D, Lahmek P, Pham H, Aubin H.J. Disulfiram efficacy in the treatment of alcohol dependence: a meta-analysis. PLoS ONE 2014; 9.
18. Krishnan-Sarin S, O'Malley S, Krystal J.H: Treatment Implications. Using Neuroscience to Guide the Development of New Pharmacotherapies for Alcoholism. National Institute in Alcohol Abuse and Alcoholism. https://pubs.niaaa.nih.gov/publications/arh314/400-407.htm.
19. Spanagel R, Vengeliene V, Jandeleit B, et al.: Acamprosate produces its antirelapse effects via calcium. Neuropsychopharmacology 2014; 39: 783–91.
20. Kufahl P.R, Watterson L.R, Olive M.F: The development of acamprosate as a treatment against alcohol relapse. Expert Opin Drug Discov 2014; 9: 1355–69.
21. Mann K, Lehert P, Morgan M.Y: The efficacy of acamprosate in the maintenance of abstinence in alcoholdependent individuals: results of a meta-analysis. Alcohol Clin Exp Res 2004; 28: 51–63.
22. Rosner S, Hackl-Herrwerth A, Leucht S, et al.: Acamprosate for alcohol dependence. Cochrane Database Syst Rev 2010; 9: CD004332.
23. National Institute for Health and Care Excellence. Alcohol-Use Disorders: Diagnosis, Assessment and Management of Harmful Drinking and Alcohol Dependence. CG115. London: National Institute for Health and Care Excellence, 2011.
24. Drobes D.J, Anton R.F, Thomas S.E, et al. Effects of naltrexone and nalmefene on subjective response to alcohol among non-treatment-seeking alcoholics and social drinkers. Alcohol Clin Exp Res 2004; 28: 1362–70.
25. Anton R.F: Naltrexone for the management of alcohol dependence. N Engl J Med 2008; 359: 715–21.
26. Rosner S, Hackl-Herrwerth A, Leucht S, et al.: Opioid antagonists for alcohol dependence. Cochrane Database Syst Rev 2010; 12: CD001867.
27. Roozen H.G, de Waart R, van der Windt D.A, et al.: A systematic review of the effectiveness of naltrexone in the maintenance treatment of opioid and alcohol dependence. Eur Neuropsychopharmacol 2006; 16: 311–23.
28. Jarosz J, Miernik K, Wazchal M, Walczak J, Krumpl G: Naltrexone (50 mg) plus psychotherapy in alcohol-dependent patients: a metaanalysis of randomized controlled trials. Am J Drug Alcohol Abuse 2013; 39: 144–60.
29. Sinclair J.M, Chambers S.E, Shiles C.J, Baldwin D.S: Safety and tolerability of pharmacological treatment of alcohol dependence: comprehensive review of evidence. Drug Saf 2016; 39: 627–45.
30. Kiefer F, Jahn H, Tarnaske T, et al.: Comparing and combining naltrexone and acamprosate in relapse prevention of alcoholism: a double-blind, placebo controlled study. Arch Gen Psychiatry 2003; 60: 92–9.
31. Anton R.F, O'Malley S.S, Ciraulo D.A, et al.: Combined pharmacotherapies and behavioral interventions for alcohol dependence: the COMBINE study: a randomized controlled trial. JAMA 2006; 295: 2003–17.
32. Naudet F, Palpacuer C, Boussageon R, Laviolle B: Evaluation in alcohol use disorders – insights from the nalmefene experience. Naudet et al. BMC Medicine (2016) 14:119.
33. van den Brink W, Sørensen P, Torup L, et al.: Long-term efficacy, tolerability and safety of nalmefene as-needed in patients with alcohol dependence: a 1-year, randomised controlled study. J Psychopharmacol 2014; 28: 733–44.
34. Marlatt G.A, Witkiewitz K: Harm reduction approaches to alcohol use: health promotion, prevention, and treatment. Addict Behav 2002; 27: 867–86.
35. Greater Manchester Medicines Mannagement Group (GMMMG) Interface Prescribing Subgroup Nalmefene for Reduction of Alcohol Consumption in Adults Information for Primary Care . Approved: 19.11.2015 Review date: 19.11.2017.
36. Mann K, Bladström A, Torup L, et al.: Extending the treatment options in alcohol dependence: a randomized controlled study of as-needed nalmefene. Biol Psychiatry. 2013;73(8):706–713.
37. Gual A, He Y, Torup L, et al.: A randomised, double-blind, placebo-controlled, efficacy study of nalmefene, as-needed use, in patients with alcohol dependence. Eur Neuropsychopharmacol. 2013;23(11):1432–1442.
38. National Institute for Health and Care Excellence. Nalmefene for Reducing Alcohol Consumption in People with Alcohol Dependence: Evaluation Report. TA325. London: National Institute for Health and Care Excellence, 2014. Available at http:// www.nice.org.uk/guidance/ta325.
39. Stevenson M, Pandor A, Stevens J.W, et al.: Nalmefene for reducing alcohol consumption in people with alcohol dependence: an evidence review group perspective of a NICE single technology appraisal. Pharmacoeconomics 2015; 33: 833–47.
40. Palpacuer C, Laviolle B, Boussageon R, et al.: Risks and benefits of nalmefene in the treatment of adult alcohol ependence: a systematic literature review and meta-analysis of published and unpublished double-blind randomized controlled trials. PloS Med 2015; 12: e1001924.
41. Snead O.C, Gibson K.M: Gamma-hydroxybutyric acid. N. Engl. J. Med. 2005;352:2721–2732.
42. Mirijello A, Caputo F, Vassallo G, Rolland B, Tarli C, Gasbarrini A, Addolorato G: GABAB agonists for the treatment of alcohol use disorder. Curr. Pharm. Des. 2015;21:3367–3372.
43. Caputo F, Skala K, Mirijello A, Ferrulli A, Walter H, Lesh O, Addolorato G: Sodium oxybate in the treatment of alcohol withdrawal syndrome: A randomized double-blind comparative study versus oxazepam. The GATE 1 Trial. CNS Drugs. 2014;28:743–752.
44. Leone M.A., Vigna-Taglianti F., Avanzi G., Brambilla R., Faggiano F. Gamma-hydroxybutyrate (GHB) for treatment of alcohol withdrawal and prevention of relapses. Cochrane Database Syst. Rev. 2010;2.
45. Gallimberti L, Ferri M, Ferrara S.D, Fadda F, Gessa G.L: Gamma-hydroxybutyric acid in the treatment of alcohol dependance: A double-blind study. Alcohol. Clin. Exp. Res. 1992;16:673–676.
46. Addolorato G, Cibin M, Caputo F, Capristo E, Gessa G.L, Stefanini G.F, Gasbarrini G: Gamma-hydroxybutyric acid in the treatment of alcoholism: Dosage fractioning utility in non-responder alcoholic patients. Drug Alcohol Depend. 1998;53:7–10.
47. Addolorato G, Castelli E, Stefanini G.F, Casella G, Caputo F, Marsigli L, Bernardi M, Gasbarrini G: An open multicentric study evaluating 4-hydroxybutyric acid sodium salt in the medium-term treatment of 179 alcohol dependent subjects. GHB Study Group. Alcohol Alcohol. 1996;31:341–345.
48. Maremmani I, la Manna F, Tagliamonte A: Long-term therapy using GHB (sodium gamma hydroxybutyrate) for treatment-resistant chronic alcoholics. J. Psychoact. Drugs. 2001;33:135–142.
49. Caputo F., Addolorato G., Stoppo M, et al.: Comparing and combining gamma-hydroxybutyric acid (GHB) and naltrexone in maintaining abstinence from alcohol: An open randomised comparative study. Eur. Neuropsychopharmacol. 2007;17:781–789.
50. Maremmani A.G.I, Pani P.P, Rovai L, Pacini M, Dell'Osso L, Maremmani I: Long-term γ-Hydroxybutyric acid (GHB) and disulfiram combination therapy in GHB treatment-resistant chronic alcoholics. Int. J. Environ. Res. Public Health. 2011;8:2816–2827.
51. Palatini P, Tedeschi L, Frison G, et al.: Dose-dependent absorption and elimination of gamma-hydroxybutyric acid in healthy volunteers. Eur. J. Clin. Pharmacol. 1993;45:353–356.
52. Skala K, Caputo F, Mirijello A, et al.: Sodium oxybate in the treatment of alcohol dependence: From the alcohol withdrawal syndrome to the alcohol relapse prevention. Expert Opin. Pharmacother. 2014;15:245–257.
53. Leone M.A, Vigna-Taglianti F, Avanzi G, Brambilla R, Faggiano F: Gamma-hydroxybutyrate (GHB) for treatment of alcohol withdrawal and prevention of relapses. Cochrane Database Syst. Rev. 2010;2 .
54. Caputo F, Vignoli T, Grignaschi A, et al.: Pharmacological management of alcohol dependence: From mono-therapy to pharmacogenetics and beyond. Eur. Neuropsychopharmacol. 2014;24:181–191.
55. Pross N, Patat A, Vivet P, Bidaut M, Fauchoux N: Pharmacodynamic interactions of a solid formulation of sodium oxybate and ethanol in healthy volunteers. Br. J. Clin. Pharmacol. 2015;80:480–492.
56. Zvosec D.L, Smith S.W, Quinn Strobl T.P.A, Dyer J.E: Case series of 226 g-hydroxybutyrate–associated deaths: Lethal toxicity and trauma. Am. J. Emerg. Med. 2011;29:319–332.
57. Martinotti G., Lupi M., Carlucci L, et al.: Novel psychoactive substances: Use and knowledge among adolescents and young adults in urban and rural areas. Hum. Psychopharmacol. Clin. Exp. 2015;30:295–301.
58. Vento A.E., Martinotti G., Cinosi E, et al.: Substance use in the club scene of Rome: A pilot study. BioMed. Res. Int. 2014.
59. Addolorato G, Leggio L, Ferrulli A, et al. Effectiveness and safety of baclofen for maintenance of alcohol abstinence in alcohol-dependent patients with liver cirrhosis: randomised, double-blind controlled study. Lancet 2007; 370: 1915–22.
60. Addolorato G, Leggio L, Ferrulli A, et al.: Dose-response effect of baclofen in reducing daily alcohol intake in alcohol dependence: secondary analysis of a randomized, double-blind, placebo-controlled trial. Alcohol Alcohol 2011; 46: 312–7.
61. Rolland B, Cottencin O: Alcohol-dependence: The current French craze for baclofen. Article in Addiction . April 2012.
62. Agence Francaise du Medicament et des produits de sante Recommandation temporaire d'utilisation (RTU) pour le baclofene -Point d'information 2014. Available at http://ansm.sante.fr/S-informer/Actua lite/Une-recommandationtemporaired- utilisation-RTU-est-accordee-pourlebaclofene- Point-d-information .
63. Muller C.A, Geisel O, Pelz P, et al.: High-dose baclofen for the treatment of alcohol dependence (BACLAD study): a randomized, placebo controlled trial. Eur Neuropsychopharmacol 2015; 25: 1167–77.
64. ALPADIR study (NCT01738282). Efficacy and Safety of Baclofen for Maintenance of Abstinence in Alcohol Dependent Patients. Available at http://clinicaltrials.gov/show/ NCT01738282.
65. BACLOVILLE study (NCT01604330). Baclofen for the Treatment of Alcohol Drinkers. Available at http://clinicaltria ls.gov/ct2/show/NCT01604330 .
66. Rolland B, Labreuche J, Duhamel A, et al.: Baclofen for alcohol dependence: relationships between

baclofen and alcohol dosing and the occurrence of major sedation. Eur Neuropsychopharmacol 2015; 25: 1631–6.

67. Rolland B, Deheul S, Danel T, Bordet R, Cottencin O: A case of de novo seizures following a probable interaction of highdose baclofen with alcohol. Alcohol 2012; 47: 577–80.

68. Geoffroy PA, Auffret M, Deheul S, Bordet R, Cottencin O, Rolland B. Baclofen-induced manic symptoms: Case report and systematic review. Psychosomatics 2014; 55: 326–32.

69. Olivier PY, Joyeux-Faure M, Gentina T, et al.: Severe central sleep apnea associated with chronic baclofen therapy: a case series. Chest 2016; 149: e127–31.

70. Blodgett J.C, Del Re A.C, Maisel N.C, Finney J.W: A meta-analysis of topiramate's effects for individuals with alcohol use disorders. Alcohol Clin Exp Res 2014; 38: 1481–8.

71. Pani P.P, Trogu E, Pacini M, Maremmani I.: Anticonvulsants for alcohol dependence. Cochrane Database Syst Rev 2014; 2: Cd008544.

72. Guerrini I, Gentili C, Nelli G, Guazzelli M: A follow up study on the efficacy of metadoxine in the treatment of alcohol dependence. Subst Abuse Treat Prev Policy 2006; 1: 35–40.

73. Higuera-de la Tijera F, Servın- Caamano A.I, Serralde-Zuniga A.E, et al.: Metadoxine improves the threeand six-month survival rates in patients with severe alcoholic hepatitis. World J Gastroenterol 2015; 21: 4975–85.

74. Addolorato G, Ancona C, Capristo E, Gasbarrini G. Metadoxine in the treatment of acute and chronic alcoholism: a review. Int J Immunopathol Pharmacol 2003; 16: 207–14.

75. Franck J, Jayaram-Lindstrom N: Pharmacotherapy for alcohol dependence: status of current treatments. Current Opinion in Neurobiology 2013, 23:692–699.

76. Furieri F.A, Nakamura-Palacios E.M: Gabapentin reduces alcohol consumption and craving: a randomized, double-blind, placebo-controlled trial. J Clin Psychiatry 2007, 68:1691-1700.

77. Anton R.F, Myrick H, Baros A.M, Latham P.K, Randall P.K, Wright T.M, Stewart S.H, Waid R, Malcolm R: Efficacy of a combination of flumazenil and gabapentin in the treatment of alcohol dependence: relationship to alcohol withdrawal symptoms. J Clin Psychopharmacol 2009, 29:334-342.

78. Anton R.F, Myrick H, Wright T.M, Latham P.K, Baros A.M, Waid L.R, Randall P.K: Gabapentin combined with naltrexone for the treatment of alcohol dependence. Am J Psychiatry 2011, 168:709-717.

79. Martinotti G: Pregabalin in clinical psychiatry and addiction: pros and cons. Expert Opin Investig Drugs 2012, 21:1243-1245.

80. Martinotti G, Di Nicola M, Tedeschi D, Andreoli S, Reina D, Pomponi M, Mazza M, Romanelli R, Moroni N, De Filippis R, Di Giannantonio M, Pozzi G, Bria P, Janiri L: Pregabalin versus naltrexone in alcohol dependence: a randomised, double-blind, comparison trial. J Psychopharmacol 2010, 24:1367-1374.

81. Steensland P, Simms J.A, Holgate J, Richards J.K, Bartlett S.E: Varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, selectively decreases ethanol consumption and seeking. Proc Natl Acad Sci U S A 2007, 104:12518-12523.

82. Mitchell J.M, Teague C.H, Kayser A.S, Bartlett S.E, Fields H.L: Varenicline decreases alcohol consumption in heavy-drinking smokers. Psychopharmacology (Berl) 2012, 223:299-306.

83. Litten R.Z, Ryan M.L, Fertig J.B, Falk D.E, Johnson B, Dunn K.E, Green A.I, Pettinati H.M, Ciraulo D.A, Sarid-Segal O, Kampman K, Brunette M.F, Strain E.C, Tiouririne N.A, Ransom J, Scott C, Stout R: A double-blind, placebo-controlled trial assessing the efficacy of varenicline tartrate for alcohol dependence. J Addict Med 2013 Jul-Aug;7(4):277-86.

84. Soderpalm B, deBejczy A, Ericson M, Guterstam J, Hammarberg A, Franck J, Asanovska G, Lo f E: The ethanol– nAChR interaction and its relevance for modulating ethanol consumption in rodents and man. Alcohol Clin Exp Res 2012:S202.

85. Johnson B.A, Roache J.D, Javors M.A, DiClemente C.C, Cloninger C.R, Prihoda T.J, Bordnick P.S, Ait-Daoud N, Hensler J: Ondansetron for reduction of drinking among biologically predisposed alcoholic patients: a randomized controlled trial. JAMA 2000, 284:963-971.

86. Lahti R.A, Tamminga C.A, Carlsson A: Stimulating and inhibitory effects of the dopamine "stabilizer" (S)-OSU6162 on dopamine D2 receptor function in vitro. J Neural Transm 2007, 14:1143-1146.

87. Steensland P, Fredriksson I, Holst S, Feltmann K, Franck J, Schilstrom B, Carlsson A: The monoamine stabilizer (S)- OSU6162 attenuates voluntary ethanol intake and ethanol-induced dopamine output in nucleus accumbens. Biol Psychiatry 2012, 72:823-831.

88. Thompson A , Ashcroft D.M, Owens L, van Staa T.P, Pirmohamed M: Drug therapy for alcohol dependence in primary care in the UK: A Clinical Practice Research Datalink study. Published: March 20, 2017, https://doi.org/10.1371/journal.pone.0173272.

89. Alcohol-Use Disorders: Diagnosis, Assessment and Management of Harmful Drinking and Alcohol Dependence. NICE Clinical Guidelines, No. 115. National Collaborating Centre for Mental Health (UK).Leicester (UK): British Psychological Society; 2011.

Received 19 April 2018, accepted 24 July 2018
Straipsnis gautas 2018-04-19, priimtas 2018-07-24