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Pharmacotherapy and clinical considerations for alcohol use disorder

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ABSTRACT

Alcohol use disorder is both disabling to affected individuals and a public health concern associated with significant medical, psychological, and social ramifications. Despite advances in our understanding of the neurobiology of alcohol use disorder, relatively few pharmacotherapies are approved for use and are critically under-prescribed to individuals with alcohol use disorder. This review aims to synthesize literature on currently approved first-line and second-line medications and provide clinical considerations for their use. First-line medications – acamprosate, disulfiram, naltrexone, and nalmefene – have demonstrated varying levels of effectiveness in reducing alcohol consumption or promoting abstinence. Second-line medications such as topiramate, baclofen, and gabapentin provide an option for individuals with alcohol use disorder who do not respond to first-line treatments; however, evidence for their efficacy is weaker than that of frontline options. The implementation of pharmacotherapy in clinical practice and the development of personalized medicine are of particular concern, given most individuals with alcohol use disorder are not offered medication. Ongoing research efforts into novel medications and the integration of pharmacotherapy with psychosocial interventions hold the potential to enhance treatment outcomes and alleviate the global burden of alcohol use disorder.

KEYWORDS

ACAMPROSATE
ALCOHOL USE DISORDER
BACLOFEN
DISULFIRAM
NALTREXONE
TOPIRAMATE
PHARMACOTHERAPY

INTRODUCTION

Alcohol consumption is associated with a myriad of physical and mental health consequences and is implicated in 5.1% of the global burden of disease[1]. Critically, alcohol is the leading risk factor for premature mortality and disability and accounts for 5.3% of all deaths worldwide1. Problematic alcohol use can result in alcohol use disorder (AUD), a chronic relapsing disorder characterized by compulsive alcohol-seeking and consumption despite negative consequences[2]. Strikingly, AUD forms one of the most undertreated mental disorders in developed countries[3]. Treatment typically comprises psychosocial intervention; however, rates of

relapse are significantly lower when psychosocial intervention is combined with pharmacotherapy[4]. These findings allude to the importance of pharmacotherapy in the treatment of AUD and the achievement of abstinence or controlled consumption. The purpose of the current review is to provide an overview of approved and emerging pharmacotherapies and clinical considerations for the treatment of AUD.

NEUROBIOLOGY OF ALCOHOL USE DISORDER

To effectively treat AUD, it is imperative to consider the neurobiological underpinnings of addiction and the resulting biological consequences of chronic alcohol consumption. AUD is characterized by reduced control over drinking that is associated with alterations in neural regions involved in the execution of motivated behaviours and the control of emotion. Dopaminergic pathways are heavily implicated in alcohol use and are key in reinforcing alcohol-seeking behaviours. That is, the effects of alcohol are mediated by the release of dopamine in the mesolimbic dopamine system, which projects from the ventral tegmental area (VTA) to the nucleus accumbens (NAc)[5]. Simply, alcohol indirectly elicits the release of dopamine into the NAc and prefrontal cortex, which in turn heightens the motivation to seek and consume. Unlike other addictive substances, which have specific molecular targets, the effect of alcohol is underpinned by the complex interaction of multiple neurotransmitter systems. First, dopaminergic cells in the VTA are under tonic inhibition by γ-amino butyric acid (GABA) neurons. Elevated levels of dopamine in the NAc and prefrontal cortex following alcohol exposure may be attributed to the disinhibition of dopamine neurons due to the downregulation of GABAergic neurons in the VTA[6]. One mechanism by which GABAergic synaptic transmission may be inhibited is through the activation of μ-opioid receptors on GABAergic neurons[7]. It has been suggested that the initial increases in dopaminergic activity may not be contingent on this disinhibition; however, the prolonged reinforcing effects of alcohol likely depend on the persistent disinhibitory effect of GABA neurons, which maintain reinforcement and support continued alcohol consumption[8]. Increased dopaminergic cell firing is also purported to be brought about through enhanced glutamate release in response to acute alcohol ingestion[9]. Moreover, glutamatergic synapses on dopaminergic neurons are purported to modulate the reinforcing properties of alcohol[10]. Alcohol has also been found to stimulate endorphin release, thereby activating the opioid system, which has been linked to the hedonic effects of acute alcohol intake[11-13]. In turn, endorphins trigger dopamine release within the NAc through the disinhibition of dopaminergic neurons in the VTA[14]. Finally, clinical evidence demonstrates that alcohol modulates nicotinic acetylcholine receptor function in the mesolimbic system[15] and increases the release of serotonin, which is purported to stimulate dopaminergic activity of both the VTA and NAc[16]. Taken together, there is a complex interplay of multiple neurotransmitter systems underlying the rewarding effects of acute alcohol ingestion.

Chronic exposure to alcohol results in changes in the sensitivity of these motivational systems, leading to increased tolerance and eventual dependence. Long-term alcohol use induces a depressant state, resulting in compensatory increases in glutamatergic activity and reductions in GABAergic activity. These neuroadaptations result in potentiated dopaminergic activity in central reward areas, including the NAc and VTA[17]. Over time, this produces tolerance to the effects of alcohol and a propensity for withdrawal following alcohol cessation. The state of withdrawal decreases dopamine release in the NAc, prompting alcohol-seeking and intake to reinstate and maintain dopaminergic levels. Upon repeated cycles of intoxication and withdrawal, alcohol-induced neuroadaptations may fail to restore the activity of the reward system[18]. Disruption of these neuromodulatory systems results in alterations in corticostriatal synapses, which sustain alcohol-seeking behaviours. Additionally, deficits in neuroplasticity caused by prolonged alcohol consumption may diminish behavioural flexibility and lead to perseveration (Renteria R, Baltz ET, Gremel CM. Chronic alcohol exposure disrupts top-down control over basal ganglia action selection to produce habits. Nat Commun 2018;9(1):211.). In addition to modulating these motivational systems, chronic alcohol use can result in increased anxiety and craving for alcohol, particularly during periods of alcohol withdrawal[19]. That is, alcohol exposure dysregulates stress-responsive neurotransmitter systems such as glucocorticoids and adrenaline/noradrenaline[20]. Increased glutamatergic activity, as well as increased corticotrophin-releasing factor within the extended amygdala, are also purported to underlie withdrawal symptoms of anxiety and irritability[21]. As such, emerging pharmacotherapies for AUD have focused on modulating the stress/reward system via oxytocin, corticotrophin-releasing factor and vasopressin.

FRONTLINE MEDICATION

Acamprosate

Acamprosate is a derivative of the endogenous amino acid N-acetyl homotaurine, a molecule with analogy to many amino acids, most notably glutamate and GABA. While the exact mechanism of acamprosate remains under contention, current evidence suggests that it interacts with glutamate and GABA neurotransmission to restore the balance between neuronal excitation and inhibition that is disrupted by chronic alcohol exposure. Specifically, acamprosate is purported to exert its effects on N-methyl-D-aspartic acid (NMDA) receptors and metabotropic glutamate receptor 5 (mGlu5), and more indirectly on GABAA receptor transmission. Acamprosate has been found to be effective in reducing craving and maintaining abstinence from alcohol. Research has demonstrated increased odds of abstinence at 12 months following treatment with acamprosate compared with placebo (1.86, 95% CI = 1.49 to 2.33)[22] and a number needed to treat (NNT) of 12 over placebo for reducing the risk of returning to drinking[23]. Additionally, acamprosate has been shown to reduce the risk of drinking following detoxification by 86% and increases the number of abstinent days by approximately three additional days a month[24]. There is some evidence that polymorphisms in the gene coding for GATA-binding protein 4 (*GATA4*) are associated with patient response to acamprosate, specifically risk of relapse and pharmacological response[25]. It has been suggested that acamprosate should be initiated following a period of detoxification, as this has been found to result in better clinical outcomes[26]. Due to the risk of accumulation with prolonged use, acamprosate is contraindicated for patients with severe renal impairment[27]. Acamprosate demonstrates good tolerability and is generally administered for 3-12 months. The recommended dosing regimen is two tablets three times a day, reduced to four tablets per day in adults weighing less than 60kg, which is relatively cumbersome. Common side effects, such as gastrointestinal disturbances, are typically mild and transient.

Disulfiram

Disulfiram inhibits the enzyme aldehyde dehydrogenase which is required for the metabolism of alcohol. If alcohol is consumed while under treatment, acetaldehyde accumulates, resulting in an aversive reaction involving tachycardia, flushing, nausea, and vomiting. The expectancy of this highly disagreeable physiological response to alcohol thus acts as a drinking deterrent. As such, disulfiram may only be appropriate for patients who are seeking to achieve abstinence rather than a reduction in consumption. Additional pharmacodynamic mechanisms of action for disulfiram have been proposed. That is, studies on cocaine dependence have found that disulfiram inhibits dopamine beta-hydroxylase, resulting in reduced synaptic norepinephrine release[28,29]. There is little evidence, however, to support a direct pharmacological effect of disulfiram in preventing alcohol relapse[30]. The disulfiram-ethanol reaction varies in intensity and, in more severe cases, may rarely result in cardiovascular collapse, respiratory depression, convulsions, and death (1 in 50,000 patients). A rare but potentially fatal hepatoxicity can occur. Therefore, biochemical monitoring in the first 3 months of treatment is mandatory, particularly in those with pre-existing abnormal liver enzymes. Disulfiram is contraindicated for patients with significant cardiovascular, pulmonary, or liver disease.

Studies on the efficacy of disulfiram have somewhat lacked concordance. This has been attributed to differences in methodology, such as a lack of double-blinding due to the required expectancy effects. That is, the efficacy of disulfiram is highly dependent on the patients' knowledge of the effect of the medication when taken in combination with alcohol[31]. Indeed, a meta-analysis demonstrated that disulfiram was more effective than placebo in open-label trials, while there was no difference in effectiveness in randomized controlled trials[30]. Clinical evidence suggests that disulfiram is most effective in patients who are highly compliant and when administered under direct supervision[32]. Generally, two or three doses per week may be sufficient and most feasible for monitoring. In some cases, more than one tablet per day is required to prevent drinking.

Naltrexone

Naltrexone is a μ-opioid receptor antagonist that reduces dopamine levels in the NAc by attenuating the release of endogenous opioids following alcohol consumption. In reducing dopamine release, naltrexone works to diminish the rewarding effects of alcohol[26]. Meta-analyses have shown that naltrexone was superior to placebo in reducing heavy drinking and preventing relapse, particularly when the initiation of treatment was preceded by a period of abstinence[26]. Moreover, naltrexone has demonstrated an NNT of 12 over placebo for preventing the return to heavy drinking[23]. Dosing is recommended to commence following resolution of any acute withdrawal (generally 3-7 days after the last drink), and side effects are less likely if commenced at half dose for a few days. Naltrexone is not suitable for patients on opioid therapy or for those who require opiate-based analgesia. Further, it is contraindicated for patients with acute hepatitis or severe liver failure.

Naltrexone is generally well tolerated and is usually administered for a minimum of 3-6 months. Common side effects include nausea and headache; however, these typically subside within the first few days. Due to hepatoxicity and the potential rise of liver enzymes, liver function tests are recommended periodically. If opioid analgesia is required (e.g., elective surgery), naltrexone should be discontinued 48-72 hours prior to opioid administration.

Nalmefene

Nalmefene is an opioid receptor antagonist and is similar in chemical structure to naltrexone[33]. Unlike naltrexone, which exerts its effects predominantly on the μ-opioid receptor, nalmefene is both a κ-opioid receptor antagonist and a partial κ-opioid receptor agonist[34]. It has been suggested that the additional activity at the κ-opioid receptor underlies the therapeutic potential of nalmefene. Chronic alcohol consumption results in up-regulation of the dynorphin/κ-opioid receptor system, which has been proposed to contribute to the negative reinforcing effects of alcohol consumption[35]. That is, amplified κ-opioid receptor system signalling leads to aversive withdrawal symptoms, which prompt excessive alcohol consumption and relapse[34]. As a partial κ-opioid receptor agonist, nalmefene acts as a functional antagonist by attenuating dynorphin/κ-opioid receptor system hyperactivity[36]. Indeed, preclinical studies in rodents show that nalmefene is more effective in reducing alcohol intake compared to naltrexone[37]. In addition to its greater affinity for opioid receptors, nalmefene is suggested to be more advantageous than naltrexone due to its bioavailability[38] and absence of a dose-dependent relationship with liver toxicity[39].

Evidence regarding the effectiveness of nalmefene in treating AUD is generally favourable. Meta-analyses have demonstrated a small effect of nalmefene in reducing heavy drinking days[23,34,40], total alcohol consumption[40] and drinks per drinking day[23]. A more recent network meta-analysis by Palpacuer, Duprez[41] examined the effect of nalmefene for the control of drinking, including participants who were actively drinking prior to treatment enrolment. Nalmefene was found to be superior to placebo in reducing total alcohol consumption. While no direct comparisons have been made between nalmefene and other alcohol pharmacotherapies, an indirect meta-analysis found nalmefene to be superior to naltrexone in reducing alcohol intake[42].

Nalmefene is approved by the European Medicines Agency, and while not currently available in Australia, it has also been approved by the Australian Therapeutic Goods Administration for the management of AUD. It is the first pharmacotherapy to be approved for the control of drinking with an 'as needed' approach and, therefore, appears to be most suitable for patients with alcohol misuse or low dependence on alcohol[43]. The National Institute for Health and Care Excellence recommends the use of nalmefene to reduce alcohol consumption in combination with psychosocial intervention, while current Australian guidelines state that further research is required[44]. It is important to note, however, that research used to support the licensing of nalmefene has been heavily criticized. In particular, the evidence base demonstrates very small risk reductions relative to placebo at a surrogate endpoint, consistently high dropout rates, and post-hoc subgroup analyses of patients drinking at high or very high levels at the time of randomization[45,46]. Further, there currently exist no randomized controlled trials comparing nalmefene to naltrexone, making it difficult to confirm the added benefit of nalmefene[46]. Taken together, evidence for the efficacy of nalmefene remains inferior relative to other first-line medications.

SECOND-LINE MEDICATION

Topiramate

Topiramate is an anticonvulsant medication that is purported to attenuate dopamine release in the mesolimbic dopaminergic pathway by enhancing GABA neurotransmission[47] and/or inhibiting glutamatergic neurotransmission (via AMPA/kainate receptors)[48]. By suppressing dopamine in the NAc, topiramate is suggested to alter the reinforcing effects of acute alcohol consumption. A growing body of evidence supports the use of topiramate for the treatment of AUD. Indeed, topiramate is increasingly being prescribed for AUD, where its use now exceeds that of acamprosate, disulfiram and injectable naltrexone combined in the United States veterans' health care system[49]. Meta-analyses of placebo-controlled studies have discerned superior effects of topiramate over placebo in maintaining abstinence[50,51], reducing heavy drinking[23,50,51], and reducing drinking days and drinks per drinking day[23]. More recently, a Bayesian meta-analysis concluded that topiramate was more effective than placebo in reducing heavy drinking, lowering craving and maintaining longer periods of abstinence[52]. Studies directly comparing topiramate to first-line pharmacotherapies for AUD are sparse. In their meta-analysis, Blodgett, Del Re[51] determined topiramate to have a larger effect size than naltrexone and acamprosate in reducing heavy drinking and maintaining abstinence. Further, a network meta-analysis found topiramate to be superior to nalmefene, naltrexone and acamprosate[41]. Despite the apparent efficacy of

topiramate in reducing consumption, there are several significant side effects associated with its use, particularly at higher doses and without gradual dose titration. Patients most commonly experience paraesthesia, fatigue, weight loss, taste perversion, nausea, and cognitive impairment[53]. Therefore, a low-dose titration is typically recommended, increasing at weekly intervals as tolerated.

The FDA suggests topiramate as a therapeutic option for patients with AUD who do not respond or tolerate other approved medications[54]. Considering the body of evidence in support of its efficacy, topiramate appears to be a promising pharmacotherapy for AUD.

Baclofen

Baclofen is a selective GABAB receptor agonist used primarily in the treatment of spasticity associated with neurological conditions. GABAB receptors are located on dopaminergic neurons and glutamatergic afferent neurons in the VTA. By activating these receptors, baclofen inhibits the action of dopaminergic neurons[55]. That is, baclofen suppresses alcohol-stimulated dopamine release in the NAc, thus attenuating the reinforcing effects of alcohol consumption. Currently, baclofen is approved in France for the treatment of AUD following failure of other available pharmacotherapies. Due to relatively minor hepatic metabolism and some evidence of safety, it has been recommended that baclofen be considered as a first-line treatment for patients with advanced liver disease, where other pharmacotherapy is contraindicated[56,57].

Evidence for the efficacy of baclofen in reducing alcohol consumption is somewhat equivocal. The first randomized controlled trial on the effectiveness and safety of baclofen in patients with advanced liver disease found baclofen to be more effective than placebo in maintaining abstinence with no hepatic side effects reported[58]. These results were later validated in a confirmatory study which found a significant effect of baclofen on time to lapse, relapse and percentage days abstinent but not drinks per drinking day nor the number of heavy drinking days[59]. Some meta-analyses have determined baclofen to be superior to placebo in increasing abstinence rates and reducing the risk of relapse[60,61], with an NNT of 8 for abstinence[62]. These effects, however, were found to be greater when total alcohol consumption before inclusion was higher, suggesting it may be more effective for heavy drinkers. Regarding reductions in total alcohol consumption and heavy drinking, meta-analyses have generally found no significant effect of baclofen relative to placebo[62,63]. Where a small effect of baclofen on total consumption was found, this was attributed to the results of one small study[41]. Indeed, a more recent meta-analysis determined that baclofen had no effect on heavy drinking days and number of drinks consumed per drinking day[61]. There is, however, evidence to suggest that baclofen may be more effective in patients with comorbid anxiety or higher baseline anxiety levels[64,65].

Generally, low-dose baclofen has been found to be more effective than high-dose baclofen, which is likely due to low tolerability of the high dose[60]. Indeed, baclofen has been found to be associated with adverse effects, including psychological disturbances and sedation, even at low doses[59]. Baclofen overdose is associated with prolonged coma, seizures and may be fatal. It should not be prescribed in patients at risk of self-harm, a problem known to be associated with AUD. There is currently no consensus regarding the dose. Most studies have used a total daily dose of 30-75 mg with stepwise titration and step-down at the end of treatment. Higher doses have been recommended by some experienced clinicians; however, this approach has not been validated by formal trials[66]. There is a small risk of withdrawal symptoms, including seizures, so it is recommended that baclofen be tapered rather than ceased abruptly. Taken together, it appears that the superiority of baclofen over placebo has not been well-established, there are practical challenges to safe prescribing, and the strength of the evidence base is lower than that of currently approved pharmacotherapies for AUD.

Gabapentin

Gabapentin is an amino acid with a structural analogy to GABA. It is approved for the management of epileptic seizures and neuropathic pain. Gabapentin binds to the alpha-2-delta type 1 subunit of voltage-gated calcium channels. In doing so, it inhibits the influx of calcium ions through these channels, which subsequently reduces postsynaptic excitability and the release of excitatory neurotransmitters. While not directly interacting with GABAA and GABAB receptors, gabapentin increases whole-brain GABA concentration, likely through its attenuation of excitatory neurotransmission. Gabapentin was first tested for the management of alcohol withdrawal symptoms and later examined as a potential treatment for reducing consumption or promoting abstinence in individuals with AUD. It is currently endorsed by the American Psychiatric Association for patients who do not benefit from acamprosate and naltrexone; however, the FDA has not approved the use of gabapentin for the treatment of AUD.

Relatively few studies have examined the efficacy of gabapentin in treating AUD. A meta-analysis of placebo-controlled trials revealed a significant effect of gabapentin in reducing the percentage of heavy drinking

days relative to placebo[67]. This effect, however, was not upheld when correcting for non-independent comparisons with placebo. Further, gabapentin was not found to be superior to placebo on other measures such as abstinence, relapse to heavy drinking, percentage of days abstinent and drinks consumed per drinking day. A more recent meta-analysis found gabapentin to be superior to placebo in improving total abstinence but not heavy drinking[68]. Beyond these meta-analyses, a recent double-blind randomized controlled trial of 145 patients with AUD found a significant effect of gabapentin on increasing the number of patients with total abstinence and a reduction in heavy drinking days[69]. Of note, gabapentin had a positive effect on reducing heavy drinking days and increasing total abstinence in individuals with high alcohol withdrawal prior to the trial. In individuals who demonstrated low alcohol withdrawal, there were no significant differences between gabapentin and placebo on these measures. Thus, gabapentin may be more efficacious in patients with AUD with a history of withdrawal symptoms.

While research on the use of gabapentin for AUD is still in its infancy relative to other pharmacotherapies, there are several factors regarding its tolerability and safety that should nonetheless be considered. Gabapentin bioavailability is saturable and decreases at higher doses. The drug is not metabolized by the liver with limited potential for drug-drug interactions, making it suitable for use in AUD where hepatic disease is common. Although research has generally found no significant adverse interaction with alcohol, there is evidence of a dose-dependent relationship between gabapentin and alcohol-induced tachycardia[70]. Therapeutic doses are typically well tolerated; however, side effects such as dizziness, somnolence, and ataxia have been reported[69]. Further, abrupt discontinuation can be associated with withdrawal syndrome and so dose-tapering is recommended[71]. Of concern, gabapentin has demonstrated

Table 1. Current first-line and second-line pharmacotherapies for alcohol use disorder.

Drug	Order	Mechanism of action	Recommended dose
Acamprosate	First-line	Derivative of N-acetyl homotaurine; modulates GABA and glutamate function via mGlu5, NMDA and GABAA receptors	1998 mg/day (6 tablets/day) For adults <60 kg, 1332 mg/day (4 tablets/day)
Disulfiram	First-line	Inhibits aldehyde dehydrogenase; acetaldehyde accumulates following alcohol consumption leading to an aversive reaction	200-400 mg/day (1-2 tablets/day)
Naltrexone	First-line	μ-opioid receptor antagonist; reduces dopamine levels in NAc	Starting dose, 25 mg/day (1/2 tablet/day) Maintenance dose, 50 mg/day (1 tablet/day)
Nalmefene	First-line[a]	μ-opioid receptor antagonist and partial κ-opioid receptor agonist	18 mg/day (1 tablet/day)
Topiramate	Second-line	Enhances GABA and/or inhibits glutamate neurotransmission (via AMPA/kainate receptors); attenuates dopamine release	Titrated dose up to 200 mg/day (2 divided doses/day)
Baclofen	Second-line[b]	Selective $GABA_B$ receptor agonist; inhibits action of dopamine neurons	No consensus
Gabapentin	Second-line	Increases whole-brain GABA by binding to alpha-2-delta type 1 subunit of voltage-gated calcium channels	No consensus

[a]Nalmefene has been approved by the European Medicines Agency and the Australian Therapeutic Goods Administration
[b]Baclofen has been approved by the French Health Safety Agency
GABA = γ-amino butyric acid; mGlu5 = metabotropic glutamate receptor 5; NAc = nucleus accumbens; NMDA = *N*-methyl-D-aspartic acid

abuse potential, particularly at high dosages. This has been particularly documented in high-risk populations, notably individuals dependent on opioids[72]. Additionally, gabapentin has been found to be associated with respiratory failure when administered in conjunction with other central nervous system depressants. Indeed, co-prescription of gabapentin and opioids has been found to increase the risk of mortality in a dose-dependent manner[73]. It is thus important to consider the safety profile of gabapentin, particularly for use in polysubstance and opioid users.

EMERGING PHARMACOTHERAPIES

As AUD exhibits heterogeneity in its manifestation, and responses to existing treatments are variable, it is hoped that the development of drug therapies with diverse pharmacology may yield improved outcomes. Of note, psychedelic drugs that act as agonists at cortical serotonin 2A (5-HT2A) receptors have aroused substantial interest as novel treatments for a range of psychological conditions, including AUD[74]. In particular, psilocybin has recently shown efficacy in reducing heavy drinking days compared to active placebo in a large randomized controlled clinical trial of participants with AUD[75]. While a precise mechanism of action remains unclear, psilocybin appears to interact with a variety of neurocognitive systems that are known to be impaired in addiction[76]. Specifically, preclinical evidence is suggestive of anti-craving effects[77], and human studies have demonstrated reductions in stress sensitivity[78], alcohol craving[79] and improved cognitive flexibility[80]. Additional psychological benefits with relevance to AUD may include improvements in self-regard, affect regulation and social connectedness[79,81]. While the preliminary evidence for psychedelics like psilocybin in AUD is promising, conclusions remain limited due to the paucity of high-quality randomized controlled trials. Further, methodological challenges inherent to clinical trials of psychedelics include prominent expectancy effects and difficulties maintaining adequate blinding, which remain to be conclusively addressed[82,83]. Finally, there are a number of other promising investigational agents currently limited to clinical trial settings. These are considered in more detail elsewhere and include varenicline, ibudilast, suvorexant, N-acetylcysteine, methylenedioxymethamphetamine (MDMA), cannabidiol and glucagon-like peptide-1 (GLP-1) agonists[84]. While such steps are encouraging, current inadequacies in treatment justify ongoing investment and research into novel drug candidates to further expand the pharmacological repertoire available in the treatment of AUD.

CLINICAL PRACTICE GUIDELINES

The American Psychiatric Association recommends that FDA-approved drugs (i.e., disulfiram, naltrexone and acamprosate) should be offered to patients with moderate-to-severe AUD[54]. The initial goals of treatment (e.g., reduction in consumption, abstinence) should be agreed upon by the patient and clinician, as this will ultimately inform the selection of treatment. It has been proposed that naltrexone and acamprosate should be offered to patients with moderate-to-severe AUD who do not display contraindications to these medications and who aim to achieve abstinence or a reduction in consumption. Acamprosate should not be administered to patients with severe renal impairment, while naltrexone should not be offered to patients with acute hepatitis or hepatic failure. Further, naltrexone should not be used to treat individuals with AUD who are using opioids or who anticipate the need for opioids. Evidence for the use of disulfiram is generally weaker; however, the drug remains an option for relapse prevention and can be effective when used as part of a comprehensive treatment program. Importantly, administration of disulfiram should be done so under supervision in order to ensure treatment compliance. The guidelines recommend the use of topiramate or gabapentin when patients display intolerance or have not responded to the FDA-approved pharmacotherapies. While there is an absence of evidence to inform the duration of treatment, pharmacotherapy is generally recommended for a minimum of 6 months[4]. Since trials for pharmacotherapies have typically included some form of psychosocial support, pharmacotherapies should be considered in conjunction with psychosocial interventions.

RECOMMENDED APPROACH TO TREATMENT

Based on the available evidence, it remains difficult to direct a personalized approach to treatment. While some studies have examined predictors of treatment response, these have typically done so using retrospective analyses. There is some evidence that naltrexone may be most efficacious for individuals who drink for the rewarding effect of alcohol and who are seeking to reduce heavy drinking, while acamprosate may be more beneficial for the maintenance of abstinence[26]. Critically, however, neither effect is large or consistent enough to inform a clinical recommendation, particularly given that most acamprosate trials have not included heavy drinking as an outcome measure. Regardless, clinical decision-making should be guid-

ed by individual patient factors such as side effects, prior experience, treatment goals, capacity for treatment adherence, concomitant physical conditions, and mental disorders. Individuals with comorbid disorders receiving pharmacotherapy for AUD should be more closely monitored for exacerbation of their comorbid symptoms. While most frontline medications appear to be safe in the context of concurrent mental disorders, caution should nonetheless be applied, particularly in the case of disulfiram and psychosis.

To advance personalized medicine, it is critical to develop effective methods to identify the medication most appropriate for a patient. Moreover, given that most individuals with AUD are not prescribed medication[85], there is the need to facilitate the use of alcohol pharmacotherapy in clinical practice. Although it has generally been proposed that pharmacotherapy and psychosocial interventions for AUD are most efficacious when combined, few studies have explored their interaction or determined the optimal intensity of psychosocial treatment[4]. This, therefore, precludes the development of definitive recommendations regarding their combined use in treating AUD. As such, the implementation of pharmacotherapy, together with appropriate psychosocial care, remains an important area for future research.

CONCLUSIONS

The treatment of AUD represents a complex challenge with significant public health implications. While psychosocial interventions have traditionally been the cornerstone of AUD treatment, the addition of pharmacotherapy has shown sufficient promise to merit widespread use. Potential targets for pharmacotherapy have been informed by advancements in understanding of the neurobiological underpinnings of AUD and the interplay of neurotransmitter systems involved in reward-seeking behaviours. Frontline medications typically target these systems and, in doing so, have demonstrated varying levels of efficacy in alleviating the core symptoms of AUD and assisting in reducing alcohol consumption or promoting abstinence. Critically, however, the number of medications currently approved for first-line use remains limited in number and efficacy. Second-line medications, such as topiramate, baclofen and gabapentin, offer additional options for individuals who do not respond well to first-line medications; however, further research is required to conclusively establish their efficacy. Of particular importance is the limited implementation of pharmacotherapy in clinical practice, as most individuals with AUD are currently not prescribed medication. The stigma associated with AUD remains an issue that prevents the identification, evaluation, and introduction of new treatments. Continued research efforts and the identification of novel medications, along with the integration of pharmacotherapy and psychosocial interventions in clinical practice, hold the potential to improve treatment outcomes and reduce the global burden of AUD.

Conflict of Interest:
The authors of this article declare that they have no conflict of interest.

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