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Pharmacotherapy for Alcohol Use Disorder: Enhancing Health and Treatment Outcomes

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ABSTRACT

Introduction and Objective: Alcohol Use Disorder (AUD) combines alcohol abuse and dependence into a single condition characterized by an inability to control alcohol consumption despite its negative consequences. Treatment for AUD includes both pharmacological and behavioral therapies aimed at achieving complete abstinence. This paper reviews pharmacological treatment options and their clinical effectiveness. Given the increasing prevalence of AUD globally, including in Poland, understanding the availability, efficacy, and cost of these treatments is essential to improve patient outcomes.

Review methods: This review analyzes current literature on pharmacological treatments for AUD, including medications approved by FDA and EMA. Sources include peer-reviewed articles and clinical trials.

Results: Naltrexone and nalmefene have been shown to be effective in reducing alcohol consumption

and cravings, while acamprosate and topiramate are particularly effective in relapse prevention and maintaining abstinence. Gabapentin is effective in treating alcohol withdrawal symptoms, while baclofen, mifepristone, and N-acetylcysteine show promising results but require further research. Ondansetron has been documented as effective in treating young patients with early-onset AUD, and varenicline effectively reduces alcohol cravings in individuals with nicotine dependence. The disulfiram implant is ineffective in treating alcohol dependence and maintaining abstinence, with its action primarily based on the fear of a disulfiram reaction.

Conclusions: Pharmacological treatments for AUD, combined with behavioral therapy, help reduce alcohol consumption or maintain abstinence. Individualized therapy selection is crucial, taking into account the patient's health status and the presence of other conditions. Further research is required to optimize treatment, both in terms of pharmacological mechanisms and better tailoring the therapy to the specific needs of individual patients.

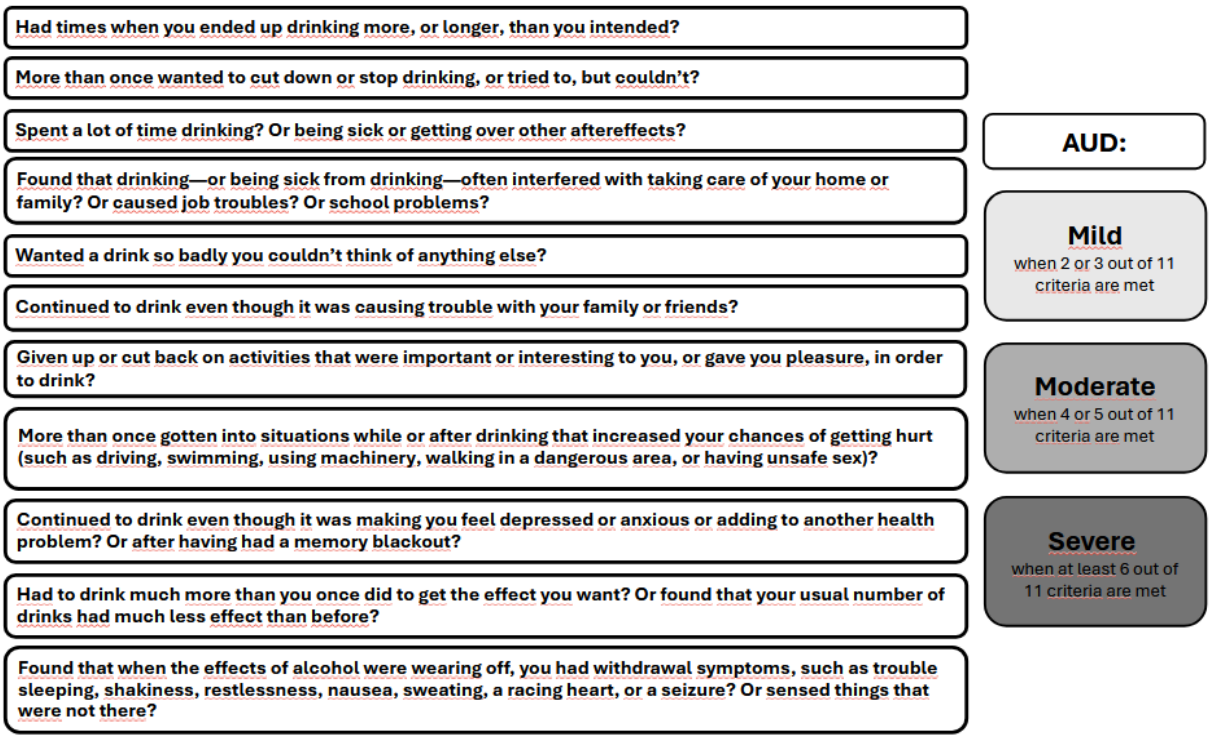
Keywords: naltrexone, nalmefene, acamprosate, disulfiram, gabapentin, topiramate; baclofen, N-acetylcysteine, mifepristone, ondansetron, varenicline

INTRODUCTION

The latest edition of the American Psychiatric Association's classification system, the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), introduces a new diagnostic category called alcohol use disorder (AUD). This diagnosis combines two categories from the previous edition: alcohol abuse and alcohol dependence. AUD is defined as a condition characterized by an inability to stop or control alcohol consumption despite negative social, professional, or health-related consequences [1]. The diagnostic criteria for AUD, along with its severity classifications, are presented in Figure 1. Treatment for AUD can involve both pharmacological and non-pharmacological (behavioural) approaches, with the primary goal being complete abstinence [2]. The European Medicines Agency (EMA) has also accepted harm reduction as an intermediate treatment goal, including reducing the number of heavy drinking days (defined as consuming more than 40g of alcohol per day for women and more than 60g for men), lowering the overall quantity of alcohol consumed, and reducing risk levels according to WHO criteria [2, 3]. WHO defines low risk as up to 20g of alcohol per day for

women and up to 40g for men, moderate risk as 21–40g for women and 41–60g for men, high risk as 41–60g for women and 61–80g for men, and very high risk as more than 60g for women and more than 80g for men per day [2].

Figure 1. Levels of Severity and Diagnostic Criteria for AUD According to DSM-5- AUD can be diagnosed when the patient has met at least 2 out of 11 criteria within the past year [4].



In the United States, it is estimated that approximately 29 million people aged 12 years and older suffered from Alcohol Use Disorder (AUD) in 2023 (16.8 million men and 12.0 million women) [5, 6, 7, 8]. However, only 7.6% of these individuals received treatment for the disorder, and just 0.9% used pharmacological treatment [1, 6]. Furthermore, in 2019, only 1.6% of people with AUD in the U.S. used medications with proven effectiveness [3, 5]. In Poland, the exact number of individuals addicted to alcohol or suffering from AUD is not known. According to a 2022 report, in Poland, 15% of men and 5% of women consume alcohol at least once a day [9]. It is worth noting that alcohol consumption in Poland increased during the COVID-19 pandemic compared to the pre-pandemic period [10]. Furthermore, alcohol consumption remained elevated post-pandemic, and it is suspected that the number of individuals dependent on alcohol may have risen [10]. Historical data from 2011, provided by Mr. Krzysztof Brzózka, the former Director of the State Agency for Solving Alcohol Problems (Państwowa Agencja Rozwiązywania Problemów Alkoholowych, PARPA), estimated that between 600,000 and 900,000 people were dependent on alcohol at that time [11]. The

population of Poland was larger in 2011 than in 2023. Based on this, we will assume that the number of people dependent on alcohol in Poland has remained similar since 2011. With a population of 37.6365 million in 2023, these figures correspond to 1.6% and 2.4% of the population, respectively [12].

Polish law allows a single doctor working in Primary Health Care (PHC) to oversee up to 2,500 patients. Assuming a PHC doctor manages the maximum number of patients, with an equal split between men and women, this doctor would statistically oversee 40 to 60 individuals dependent on alcohol. Additionally, they would care for approximately 188 men and 63 women (a total of 251 patients) who consume alcohol daily. These 251 individuals are particularly at risk of developing AUD or may already suffer from it.

TREATMENT OF AUD

In treating patients with AUD, both pharmacological and behavioral therapies should be considered. Pharmacological treatment is not recommended without concurrent behavioral therapy [6, 13]. Similarly, behavioral therapy should not exclude the use of pharmacological methods [6, 13]. Specifically, pharmacological treatment is recommended for patients with moderate or severe AUD [1, 14], while for mild AUD, pharmacotherapy may be considered at the clinician's discretion [1]. Before initiating AUD treatment, clinicians should assess the need for managing withdrawal syndrome (also known as abstinence syndrome). Mild and moderate withdrawal symptoms can be managed on an outpatient basis, while severe cases or those with complications require hospital treatment [1].

The U.S. Food and Drug Administration (FDA) has approved three medications for treating AUD: naltrexone, acamprosate, and disulfiram. In contrast, EMA has approved four medications: the three FDA-approved options plus nalmefene. None of these medications are reimbursed in Poland. However, before excluding them for cost reasons, it is worth knowing their prices, which will be discussed later in this paper. All of these medications are available in oral form. Additionally, naltrexone is available in an extended-release intramuscular formulation (not available in Poland), and disulfiram is available as subcutaneous implant tablets. Naltrexone and acamprosate are generally considered first-choice medications for AUD [1, 15], though some sources also include nalmefene in this group [6, 13].

Other medications have demonstrated efficacy in treating AUD and may be used when registered medications are unsuitable or when naltrexone and acamprosate are not viable options for a specific patient [1, 2, 7]. Among these, we can mention gabapentin, topiramate,

and baclofen. Notably, among all countries, only France has officially registered baclofen for AUD treatment [3, 16]. However, baclofen has been used in AUD treatment for over a decade in several other countries, particularly in Europe and Australia [16].

Before discussing medications in detail: naltrexone, nalmefene, acamprosate, disulfiram, gabapentin, topiramate, baclofen, N-acetylcysteine, mifepristone, ondansetron, and varenicline, it is important to note that alcohol consumption activates the endogenous opioid system, while alcohol withdrawal disrupts the transmission of gamma-aminobutyric acid type A (GABA A), N-methyl-D-aspartic acid (NMDA), and glutamate [1].

NALTREXONE

Naltrexone is an antagonist of the μ, δ, and κ opioid receptors [17]. By acting through these receptors, it disrupts opioid activity, which affects dopamine transmission in the mesolimbic pathway associated with the sensation of pleasure. This disruption inhibits the rewarding effects of alcohol consumption and ultimately reduces alcohol intake [1, 3, 6]. This medication significantly decreases the number of drinks consumed per day, the subjective pleasure experienced, the craving for alcohol, and the number of drinking days [3, 5, 6]. Clinical trials have also shown that naltrexone reduces the likelihood of relapse into alcohol use by 50% compared to a placebo [1, 3, 5, 6]. Additionally, studies indicate that naltrexone is more effective in reducing alcohol intake in individuals who use nicotine compared to non-users [1]. Naltrexone is a recommended medication for AUD patients who are actively drinking alcohol [1]. It is also preferred for patients with aspartate aminotransferase/alanine aminotransferase (AST/ALT) levels between 3 and 5 times the upper limit of normal, despite its hepatic metabolism [1, 7]. However, naltrexone is contraindicated in patients with acute hepatitis or liver failure [3, 7]. Other contraindications include concurrent use of opioid pain relievers, opioid agonists, the presence of physiological symptoms of opioid dependence, or a positive urine test for opioids [1, 6]. If a patient has previously used opioids, a waiting period of 7- 14 days is recommended before starting naltrexone therapy.

Naltrexone therapy is generally well tolerated [3]. Side effects are typically mild and may include nausea, vomiting, and dizziness [3, 5, 7]. The recommended dose is 50 mg once daily, which can be increased to 100 mg if necessary. Treatment is typically administered for 12 weeks, and it should not exceed six months [13]. The monthly cost of naltrexone therapy at a dose of 50-100 mg is approximately 97-558 PLN [14, 18].

NALMEFENE

Nalmefene is an antagonist of μ and δ opioid receptors and a partial agonist of the κ opioid receptor [3, 15, 17]. As an antagonist of the μ and δ opioid receptors, it functions similarly to naltrexone [3]. However, as a κ receptor agonist, nalmefene affects the nucleus accumbens, which is associated with dopamine, potentially reducing alcohol consumption and the motivation to drink during abstinence periods [3]. A study involving 18 patients with AUD (who consumed 76.9 ± 52 g of pure alcohol daily), using a double-blind, placebo-controlled design with an 18 mg dose of nalmefene, and functional magnetic resonance imaging (fMRI) to assess effects, concluded that nalmefene influences the ventral striatum [15]. Existing studies have shown that on-demand nalmefene (taken as needed) is more effective than a placebo in reducing the number of heavy drinking days, with this effect becoming evident after 12 weeks [3, 6, 15, 17]. Furthermore, it reduces the frequency of alcohol intake, craving, and reactivity to alcohol-related cues [6, 15].

Like naltrexone, nalmefene is an attractive option for patients who aim to reduce their alcohol consumption and those reluctant to engage in abstinence-based treatment [3]. It is metabolised by the liver and excreted via the kidneys [19]. The most commonly reported side effects include dizziness, nausea, vomiting, insomnia, and headache [3]. Nalmefene should be taken as needed before high-risk drinking alcohol situations [13, 15, 17]. It is recommended at a dose of 18 mg/day on an as-needed basis for 6-12 months, although this period may be extended [19]. Furthermore, this dosage is the most common in literature. Noteworthy results come from a 24-week prospective, randomized clinical trial involving 867 patients [17]. In this trial, nalmefene was administered in two doses-10 mg and 20 mg- along with psychosocial support. The results confirmed the efficacy of both doses in alcohol dependence treatment compared to placebo, with fewer side effects among participants taking the 10 mg dose. Assuming nalmefene is taken daily at 18 mg, the monthly cost of such therapy is approximately 550 PLN, or 275 PLN if taken every other day [14, 18].

ACAMPROSATE

The precise mechanism of action of acamprosate is not fully understood. However, it is believed to act on the glutamatergic system as a partial co-agonist of the NMDA receptor and to modulate GABA-A receptor transmission [1, 3]. These mechanisms may help reduce neuronal hyperexcitability that occurs with sudden alcohol withdrawal and prolonged alcohol abstinence [1, 3]. Acamprosate reduces the risk of relapse to any drinking by 86% compared to placebo

and increases the duration of abstinence [1, 3, 5]. In clinical trials comparing acamprosate to placebo, it has been shown to increase the percentage of individuals who maintained total abstinence from alcohol, the mean cumulative duration of abstinence, the percentage of alcohol-free days, and the median time to first alcohol consumption [1].

On the other hand, a meta-analysis involving 7,519 participants showed that treatment with acamprosate reduced the risk of relapses for those who had abstained from alcohol but did not reduce the frequency of heavy drinking episodes [3]. Moreover, acamprosate shows the greatest efficacy in individuals who are highly motivated for treatment [1]. Acamprosate may also have neuroprotective effects, which can be beneficial for patients with heavy alcohol consumption [3]. However, in the 2006 COMBINE trial, which required 4 days of pre-trial abstinence and compared acamprosate, naltrexone, and behavioural therapies, acamprosate did not show a significant benefit over placebo [3].

Acamprosate is recommended for achieving and maintaining total abstinence rather than for reducing alcohol consumption [3]. It may be a good option for patients with significant liver dysfunction, as it is not metabolised by the liver- it is excreted via the kidneys [1]. Moreover, to date, there have been no reported risks of hepatotoxicity associated with its use [1, 3]. Treatment with acamprosate is generally well tolerated and has minimal side effects [1, 3, 5]. The most frequently reported side effect in clinical trials was diarrhoea [1, 5]. If severe diarrhoea occurs, temporarily reducing the dose may be beneficial [1]. Acamprosate is contraindicated in patients with an eGFR less than 30 ml/min/1.73 m^2 [1]. Therefore, kidney function should be assessed prior to initiating acamprosate therapy. Additionally, a 7-day period of alcohol abstinence is optimal before beginning treatment [1]. The recommended dose of acamprosate is 333 mg (two tablets) three times daily, totaling 1,998 mg per day, with a monthly therapy cost of approximately 247 PLN [1, 14, 18]. The duration of treatment can range from several months to several years [5].

DISULFIRAM

Disulfiram is an aldehyde dehydrogenase inhibitor that blocks alcohol metabolism, leading to an accumulation of acetaldehyde when alcohol is consumed. Acetaldehyde, a toxic metabolite, triggers an aversive reaction known as the "disulfiram reaction," which includes symptoms such as nausea, vomiting, sweating, facial flushing, palpitations, hypotension, tachycardia, shortness of breath, dizziness, blurred vision, and confusion [1, 3, 5]. Additionally, disulfiram has been shown to reduce serum dopamine-β-hydroxylase (DBH) levels, an enzyme whose activity is

associated with withdrawal symptoms [3]. However, disulfiram's efficacy in treating AUD is largely due to the fear of the disulfiram reaction upon alcohol consumption [1, 3, 5]. This is concluded based on meta-analyses that have shown that disulfiram can reduce alcohol consumption in open-label studies, but it has not been as effective in blinded randomized controlled trials [1, 3].

Disulfiram, when taken orally, supports temporary abstinence from alcohol [13]. However, the disulfiram implant has been shown to be ineffective both in treating alcohol dependence and in maintaining temporary abstinence [13].

Disulfiram is recommended primarily for supporting abstinence rather than reducing alcohol intake. It is not advised for use as a means to limit drinking [3]. The medication is generally well tolerated at recommended doses, with few side effects. However, potential adverse effects include hypertension, a reduced seizure threshold, encephalopathy, neuropathy (both cranial and peripheral), basal ganglia damage, catatonia, and psychosis [19, 20].

Disulfiram is contraindicated in individuals with ischemic heart disease, recent use of metronidazole, alcohol, or alcohol-containing preparations, and those with a history of psychosis or a family history of psychotic disorders [1]. It should also be avoided in patients with AST/ALT levels three to five times the upper limit of normal, with liver function tests advised before starting treatment. Cardiac function may also need assessment [1]. Healthcare providers must emphasize the importance of avoiding all forms of alcohol before initiating and throughout disulfiram therapy [1].

The recommended initial dose of disulfiram is 250–500 mg daily, typically administered as a single dose. After 1- 2 weeks, the dosage can be adjusted based on therapeutic response, with maintenance doses ranging from 125 mg to 500 mg daily. Treatment duration varies, ranging from several months to a few years depending on the patient [3, 5]. The monthly cost of disulfiram therapy ranges from approximately 13–51 PLN for doses of 125–500 mg [14, 18].

GABAPENTIN

Gabapentin is an anticonvulsant medication also used in the treatment of AUD [3]. Although its exact mechanism of action in AUD is not fully understood, it is believed to modulate GABA activity through indirect interaction with voltage-gated calcium channels [3]. Gabapentin has proven effective in treating both acute and chronic alcohol withdrawal symptoms, such as anxiety and sleep disturbances, with patients experiencing more severe withdrawal benefiting the most [1, 3]. Studies have demonstrated that gabapentin can reduce alcohol consumption and

cravings [1]. In a 28-day study involving 60 participants, gabapentin decreased the number of heavy drinking days, reduced the number of drinks consumed per day, and increased the percentage of alcohol-free days [3]. Another study, lasting one week and involving 33 participants, found that gabapentin significantly reduced alcohol cravings compared to a placebo [3].

A Cochrane review of 25 studies, including 2,641 participants, confirmed that anticonvulsants, including gabapentin, significantly reduced heavy drinking days and the number of drinks consumed per day compared to placebo [3]. However, a six-month, multi-center, randomized controlled trial using extended-release gabapentin did not show significant benefits in treating AUD [3]. These findings underscore the importance of the specific formulation of gabapentin, as not all forms of the medication yield the same results.

Gabapentin can be used to prevent withdrawal symptoms, reduce alcohol consumption, and promote abstinence [1, 3]. Notably, alcohol consumption is not a contraindication for its use [1]. However, gabapentin can induce euphoria when taken in combination with other substances, particularly opioids, benzodiazepines, and alcohol, and is associated with opioid overdose deaths. Therefore, caution is advised when prescribing gabapentin to patients using opioids [1]. Additionally, gabapentin is not metabolized by the liver, making it an attractive option for patients with liver dysfunction [1].

Common side effects of gabapentin include drowsiness, dizziness, peripheral edema, and ataxia or gait disturbances [3]. Other frequent side effects include headaches, fatigue, muscle pain, and gastrointestinal discomfort [1]. The initial dose is typically 300 mg per day, taken as a single dose. The dose gradually increased by 300 mg every 1-2 days until the patient reaches three doses per day, with a total daily dose not exceeding 3,600 mg. The optimal dose is 600 mg, taken three times daily, totaling 1,800 mg per day [1, 6].

TOPIRAMATE

Topiramate is an anticonvulsant medication [3]. While its exact mechanism of action in AUD is not fully understood, evidence suggests that it enhances GABAergic neurotransmission, inhibits glutamatergic pathways, and reduces dopaminergic activity in the brain's reward center. These effects likely contribute to a reduction in alcohol cravings and withdrawal symptoms [1, 3]. The drug has been shown to decrease the number of drinking days, the quantity of alcohol consumed per day, and the percentage of heavy drinking days, while increasing

the number of abstinent days [1, 3]. Notably, its efficacy in AUD appears to be independent of prior alcohol abstinence or detoxification [1].

A meta-analysis of seven randomized controlled trials, involving 1,125 participants with AUD, demonstrated that topiramate significantly increased the number of abstinent days and reduced heavy drinking days compared to placebo [3]. Furthermore, a 12-week randomized trial with 94 participants addicted to both alcohol and nicotine found that those receiving topiramate (300 mg/day) were more likely to abstain from smoking than those on placebo, as confirmed by serum cotinine levels, a biomarker of nicotine metabolism [21].

Alcohol consumption is not a contraindication for its use. Topiramate can be prescribed to actively drinking patients to facilitate abstinence or to prevent relapse in those who have completed alcohol detoxification [1, 3]. Common side effects include paresthesia, cognitive impairment, an increased risk of kidney stones, decreased sweating, acute visual disturbances (including myopia and acute angle-closure glaucoma), pruritus, anorexia, taste changes, and nervousness [1, 3].

The initial dose is typically 25 mg once daily, with gradual increases, e.g. by 50 mg every 7 days [1, 7]. The recommended maintenance dose ranges from 200 to 400 mg per day, divided into two doses [1]. In clinical trials, topiramate has been administered for durations between 12 weeks and 6 months [21, 22].

BACLOFEN

Baclofen has been used for over 50 years to treat muscle stiffness caused by central nervous system damage [16]. It is a GABA B receptor agonist, which acts on various brain regions to inhibit dopamine neuron firing induced by alcohol and suppress dopamine release in the nucleus accumbens [3, 16, 23]. These mechanisms reduce the reinforcing effects of alcohol and drugs [23].

The efficacy of baclofen in treating AUD remains ambiguous. Randomized clinical trials tailored to individual patient needs generally support its effectiveness [16]. However, studies using fixed-dose protocols report conflicting results [16]. A meta-analysis of 17 randomized controlled trials, involving 1,818 participants with AUD, found that baclofen reduces relapse risk by approximately 13% and increases the percentage of abstinent days by 9% [23]. In a 16-week randomized, placebo-controlled trial stratified by sex and alcohol consumption, baclofen at 30 mg/day showed a positive effect in women, while minimal effects were observed at 90

mg/day. Conversely, in men, a modest effect was noted at 90 mg/day, but no benefit was seen at 30 mg/day compared to placebo [24].

Baclofen is primarily eliminated by the kidneys (80%), with limited hepatic metabolism, so is particularly beneficial for individuals with liver function disorders [3, 16, 23]. Additionally, it may help patients with co-occurring AUD and drug addiction due to its versatile effects. Common side effects include drowsiness, headaches, dizziness, confusion, sweating, muscle rigidity, slurred speech, and sleep apnea. Most of these are mild and may be exacerbated by concurrent alcohol consumption [16]. Serious adverse effects, such as mania, delusions, seizures, or withdrawal syndrome, are rare (occurring in fewer than 1 in 10,000 patients) [16]. Tolerance to baclofen can develop, necessitating dose adjustments, which may intensify sedative effects, particularly in women [3].

Abrupt discontinuation or rapid dose reduction can cause a potentially life-threatening withdrawal syndrome [3, 16, 23, 25]. Additionally, the combined use of baclofen and alcohol amplifies the adverse effects of both substances [16].

In the treatment of AUD, baclofen is administered orally. While the optimal dose has not been definitively established, effective doses range from 5 mg to over 400 mg/day [16]. The recommended daily dose typically falls between 15 mg and 80 mg [23]. However, the French Society of Alcohology considers 300 mg/day to be the maximum allowable daily dose of baclofen [25]. If the desired therapeutic response is not achieved at 80 mg/day, it recommends referring patients to specialized, multidisciplinary addiction therapy [25]. The duration of treatment remains undefined, with some patients requiring long-term therapy [25]. Nevertheless, the effective dose should be maintained for at least six months before considering tapering [16]. Treatment usually begins at 15 mg daily, with gradual increases of 5–10 mg every three days, tailored to the patient's individual needs [16, 23]. Given its short half-life, baclofen should be taken 3–4 times per day [23].

N-ACETYLCYSTEINE

N-acetylcysteine (NAC) is a drug mainly used during lower airway infections such as influenza. It is a mucolytic medication, that is also effective in cystic fibrosis and chronic obstructive pulmonary disease [26,27]. Additionally it is used as an antidote for acetaminophen overdose [28].

NAC modulates glutamatergic synaptic activity. By decreasing stimulation of glutamate transmission, NAC can reduce cravings for stimulants such as cocaine [29] or alcohol [30].

There is a strong connection between using NAC and decrease in the frequency of cravings or consumption of alcohol [30].

Study conducted on rats, that previously where consuming alcohol (1.2 g/kg of 20% ethanol for 15 min per day) shows that administration of high dosage (100 mg/kg) of NAC- reduced their ethanol consumption, motivation, seeking and relapse drinking. The outcome of this study showed that the NAC-treated group of rats reduced alcohol intake by 81% compared to the placebo group [30].

A similar research was carried out on a group of mice subjected to daily alcohol exposure for 13 days, to develop heightened impaired sensitivity behaviour. Two hours before each ethanol disposition, mice were given injections of NAC. At the conclusion of the active research phase, brain samples were collected for analysis. Researchers came to the conclusion that administration of NAC inhibited alcohol-induced behavioural sensitization [31].

Related study was conducted, with control group and main group, on rats that consumed high amounts of alcohol for 30 days. After that period, based on which group rats were in, they were given NAC or saline for 4 days. On the 35th day of the research, rats were killed and the levels of inflammation and anti-inflammation cytokines were measured in the brain. The group that were given NAC had lower pro-inflammatory cytokines and there was a decrease in anti-inflammatory cytokines in the frontal cortex and hippocampus. It is significant to note that the serum levels of cytokines have not changed. These findings suggest a significant antioxidative effect of NAC on brain cells [32].

All of these studies suggest that NAC has a great potential to be used as a drug in Alcohol Use Disorder. Further research should be held to collect more data on the effectiveness of this therapy for individuals.

MIFEPRISTONE

Mifepristone (RU-486), a glucocorticoid receptor antagonist, works on the stress system by regulating the amygdala [33]. It is a FDA-approved medication for the termination of early pregnancy and for the treatment of hyperglycemia secondary to endogenous Cushing syndrome. Mifepristone has been studied as a potential treatment for neuropsychiatric disorders such as psychotic depression and AUD [34].

The present literature suggests validity of the mifepristone use in AUD but also emphasizes the need for subsequent studies to explore the mechanism by which mifepristone may affect alcohol-related outcomes, especially during stressful events [34].

Preclinically, both systemic and central amygdala injections of mifepristone were shown to suppress yohimbine stress-induced reinstatement of alcohol seeking, indicating that the central amygdala plays an important role in mifepristone's effects on ethanol-seeking [35].

On the other hand, in a study conducted on baboons [36] mifepristone did not alter alcohol-seeking or self-administration under the chain schedule of reinforcement. Mifepristone did not reduce alcohol-maintained behaviors when administered to baboons drinking 1g/kg daily [36].

Studies on the use of mifepristone in AUD conducted with humans appear to be promising. In a randomized placebo-controlled trial with 56 non-treatment seeking alcohol-dependent adults, individuals who received mifepristone (600 mg daily taken orally for 1 week) exhibited a substantial reduction in alcohol-cued craving. Naturalistic measures revealed reduced alcohol consumption during the 1-week treatment phase and 1-week post-treatment phase. The drug was well tolerated and improved liver-function markers [37].

A recent human laboratory study [34] showed that mifepristone, administered with yohimbine and alcohol, was safe in individuals with AUD. It was performed using a human laboratory paradigm designed to activate the noradrenergic system by a single oral dose of yohimbine (32.4 mg) paired with a cue-reactivity procedure, a priming alcohol dose and alcohol self-administration in an open bar laboratory. The main finding of the study was a significant reduction of the self-reported alcohol craving.

Moreover, mifepristone's effect in reducing yohimbine-induced alcohol craving was independent fromthe mifepristone-induced increase of cortisol level [34].

Further studies, possibly with higher doses, are warranted to evaluate mifepristone's alcohol consumption in patients with AUD and to best identify potential patients with AUD who may benefit from mifepristone treatment [34].

ONDANSETRON

Ondansetron is a selective 5-HT3 receptor antagonist. It is mainly used to treat nausea occurring during oncological treatment [38].

Its effectiveness in the treatment of AUD has been demonstrated in small study groups. It was particularly effective in two groups: in patients with early-onset AUD [39] and in people with the appropriate variant of the serotonin transporter (5HTT) [40].

When used at a dose of 4 μg/kg twice daily, it reduces alcohol cravings in alcohol-dependent people under 25 years of age [41].

Side effects of the use of ondansetron in the treatment of AUD include diarrhea, headache, fever, and prolongation of the QT interval. It should not be used in patients undergoing cardiac treatment for congenital long QT syndrome, hypertrophic cardiomyopathy or in people taking other medications associated with QT prolongation [42,43].

VARENICLINE

Alcohol and tobacco dependence are highly comorbid disorders, Varenicline is partial nicotinic agonist with high anity for the nicotinic acetylcholine receptors (nAChRs) and has shown evidence of efficacy not only in withdrawal symptoms with smoking cessation, but also in reducing alcohol consumption.[44, 45] In a randomized, double-blind, 16-week study in a group of heavy drinking smokers, varenicline significantly decreased alcohol consumption. Side effects of varenicline use such as suicidality and depression, were reported low in this study. [45] Another placebo-controlled study, was based on group of thirty heavy drinking smokers randomly assigned to receive extended 4-week pretreatment with varenicline or the usual 1-week pretreatment. Participants who received varenicline longer, reported significantly greater reductions in alcohol craving and numerically fewer heavy drinking days compared to those who received placebo [46]. Varenicline can produce a sustained decrease in alcohol consumption in individuals who also smoke. Results indicated that patients with alcohol dependence treated with varenicline showed improvement in percentage of very heavy drinking days, percentage of abstinent days, drinks per day, drinks per drinking day, and craving. However, these findings require replication in larger sample sizes for confirmation. [44, 47, 48].

CONCLUSIONS

Alcohol use disorder (AUD) concerns a huge part of the society worldwide with only a small percentage of them receiving professional help [5, 6, 7, 8, 10, 12]. Although there are various treatment methods of AUD available all over the world, some more and some less efficient than others, there is still a huge need for further research on alcohol abuse and alcohol dependence. Alcohol addiction is not only harmful for the health of individuals, has negative social and professional consequences but also subjects countries to both financial and economic loss [1]. Treatment for AUD includes behavioral as well as pharmacological measures. Therapeutic methods should be used simultaneously and not preclusively with the main goal being the complete abstinence [2, 6, 13]. The medications` availability and

reimbursement differ among countries and regions of the world [1, 6, 15, 13]. Each patient should be thoroughly examined by a physician. The drug and its dosage must be adjusted and aligned with an individual's overall health, their comorbidities, duration of alcohol addiction, potential need for treating a withdrawal syndrome, primary goal of the treatment etc. [1, 6, 13, 15].

In this research paper we focused on medications such as: naltrexone, nalmefene, acamprosate, disulfiram, gabapentin, topiramate, baclofen, N-acetylcysteine, mifepristone, ondansetron, and varenicline.

In patients with active alcohol use it's beneficial to reach out for naltrexone [1]. Nalmefene should be prescribed and taken on-demand as it reduces cravings, reactivity to alcohol-related cues, frequency of alcohol intake and lowers overall number of heavy drinking days [3, 6, 13, 15, 17]. Acamprosate and Topiramate are both beneficial when it comes to relapse prevention and maintaining complete abstinence [1, 3]. Disulfiram also promotes abstinence, however it works only temporarily [3,13].

Gabapentin is effective when it comes to treating chronic alcohol withdrawal symptoms as well as acute ones [1, 3]. N-acetylcysteine has proven to be effective when it comes to reducing consumption, number of relapses and strengthening motivation [30]. Ondansetron can be successfully used in patients under 25 years of age to reduce alcohol cravings [41]. Varenicline promotes decrease in alcohol consumption, cravings and episodes of heavy drinking. Apart from that it ceases symptoms related to smoking withdrawal [44, 45, 47, 48]. The efficacy of baclofen and mifepristone in treating AUD appear to be promising but there is a huge need for further studies [16, 34].

As shown above pharmacological treatment of alcohol use disorder can be effective and it’s crucial in order to achieve therapeutic success. However wide-reaching studies are needed for deepening the understanding of drugs’ actions and their efficacy during particular stages of AUD treatment.

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- **methodology:** K Moczyróg
- **software:** Not applicable
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- **resources:** Not applicable
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