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Review Article

Perspectives on the pharmacological management of alcohol use disorder: Are the approved medications effective?

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ABSTRACT

Introduction: In the last decades, many medications have been tested for the treatment of Alcohol Use Disorder (AUD). Among them, disulfiram, acamprosate, naltrexone, nalmefene, sodium oxybate and baclofen have been approved in different countries, with different specific indications. Topiramate is not approved for the treatment of AUD, however, it is suggested as a therapeutic option by the American Psychiatric Association for patients who do not tolerate or respond to approved therapies.

Areas covered: In this narrative review we have analyzed the main studies available in literature, investigating the efficacy and safety of these medications, distinguishing whether they were oriented towards abstinence or not. Randomized controlled studies, analyzing larger populations for longer periods were the main focus of our analysis.

Conclusions: The medications currently available for the treatment of AUD are quite effective, yet further progress can still be achieved through the personalized strategies. Also, these medications are still markedly underutilized in clinical practice and many patients do not have access to specialized treatment.

1. Introduction

Alcohol use disorder (AUD) is characterized by a large consumption of alcoholic beverages, which can determine the onset of alcohol-related diseases and an overall increase of morbidity and mortality. AUD is the third leading risk factor for morbidity and mortality both in Europe [1] and in the U.S. [2]. About 3 million deaths per year worldwide are indeed related to AUD and a considerable proportion of these deaths occur in young people, between the ages of 15 and 30 [3]. In this age group binge drinking represents the most common pattern of alcohol intake, consisting of over five drinks for men or over four drinks for women in a single occasion [4]. In the U.S., about 249 billion dollars were spent in 2010 for alcohol related issues and binge drinking accounted for 191.1 billion dollars of both direct and indirect costs [5].

The most effective management strategy for AUD is a combination of psychosocial interventions and pharmacological therapy [6]. The most commonly used psychosocial interventions are twelve-step facilitation therapy, motivational enhancement therapy (MET) and cognitive-behavioral therapy (CBT). In the last decades, several medications have been investigated to treat AUD, in addition to psychosocial interventions. Some of these medications have proven to be safe and effective in promoting alcohol abstinence and/or reduction of alcohol intake, even preventing relapse, and have been approved to be used in AUD, even though the exact panel of approved medications may vary across countries.

Disulfiram, acamprosate and naltrexone have been approved both in U.S. by the Food and Drug Administration (FDA) and in Europe by the European Medicines Agency (EMA), while nalmefene has been approved only in Europe by the EMA. Other drugs have only been approved by single States, such as sodium oxybate in Italy by the Italian Medicines Agency (AIFA) and Austria by the Austrian Agency for Health and Food Safety (AGES), and baclofen in France by the the Agence Nationale de Sécurité du Médicament (ANSM). In addition, topiramate, ondansetron, gabapentin and varenicline have started being used off-label in patients with AUD, and initial results have been encouraging [7]. Topiramate, in particular, even though not approved, is suggested by the American Psychiatric Association as a therapeutic option for patients who do not respond or tolerate conventional therapies [8].

The aim of this narrative review is to describe the efficacy of these medications in reducing alcohol cravings and intake, and/or to achieve

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total alcohol abstinence and prevent relapse in patients with AUD. Their main indications in the treatment of AUD as abstinence and not-abstinence oriented medications are also reported. Alcohol use disorder, pharmacological treatment, acamprosate, baclofen, disulfiram, nalmefene, naltrexone, topiramate were used as keywords. Literature search included all studies published between the 1950s to the present, focusing mainly on the ones published in the last 10 years, with randomized-controlled designs, larger study samples and longer duration.

2. Disulfiram

Disulfiram was approved for the treatment of AUD by the FDA in 1951. The efficacy of this medication is mainly related to the patients' knowledge of the effect of disulfiram, when it is combined with alcohol: unpleasant and severe adverse effects take place and include nausea, vomiting, flushing, hypotension, sweating, palpitations and even cardiovascular failure. This reaction, also known as "acetaldehyde syndrome", is due to the inhibition of acetaldehyde dehydrogenase by disulfiram with the consequent increase of blood acetaldehyde concentration. In addition, disulfiram showed efficacy in reducing cocaine use and gambling disorder through the inhibition of dopamine beta-hydroxylase and thus increasing dopamine levels [9]; this same mechanism could further explain its influence on alcohol craving and intake in patients with AUD.

A recent meta-analysis, including 22 studies, showed a higher success rate of disulfiram compared to controls. However, only open-label trials showed a significant superiority over controls, while randomized controlled trials (RCTs) with double-blind design failed to show a significant efficacy of the drug [9]. One of the first randomized studies which tested disulfiram involved 128 patients with AUD, who were randomized in three groups of treatment (disulfiram at regular dose of 250 mg, disulfiram at inactive dose of 1 mg and no drug treatment) [10]. Although the authors did not observe significant differences in terms of total alcohol abstinence and total drinking days among the three groups of patients, a trend of alcohol abstinence was found in the two groups who received disulfiram. This study paved the way for other trials and over the years several studies showed the usefulness of disulfiram to promote alcohol abstinence and to prevent relapse.

In a one-year multicenter study, the same authors randomized an even larger sample, consisting of 605 patients, randomizing them in three groups (disulfiram 250 mg vs disulfiram 1 mg vs no treatment) [11]. A significantly higher number of abstinence days and an overall reduction of the frequency in alcohol intake after relapse were found in the 250-mg disulfiram group. No significant difference in total alcohol abstinence was found among the 3 groups.

In a RCT Tønnesen et al. (1999) compared 16 patients who were administered disulfiram (800 mg disulfiram taken during controlled supervision twice weekly until the week before surgery) and were able to achieve and maintain total alcohol abstinence before colorectal surgery, to 19 patients with AUD who were not treated with disulfiram and which continued with their drinking habits until surgery. At the end of the study, patients treated with disulfiram developed significantly less post-operative morbidity [12].

In 2003 Niederhofer et al. tested the long-term efficacy of disulfiram in a RCT in which 26 adolescents were randomized to receive disulfiram or placebo for 90 days. Mean cumulative abstinence duration was significantly higher in the disulfiram group [13].

Over the years, the efficacy of disulfiram was also compared to other medications used for the treatment of AUD. In two comparative open label studies, disulfiram was more effective than naltrexone in terms of total alcohol abstinence, both in adults [14] and adolescents [15]. Moreover, time to first relapse was significantly delayed in patients treated with disulfiram, compared to patients treated with naltrexone in both studies. Patients who were administered naltrexone, however, showed fewer cravings than the disulfiram group.

Laaksonen et al. (2008) compared disulfiram, acamprosate and naltrexone in a randomized, open label, multicenter naturalistic study, conducted for 119 weeks [16]. Disulfiram was more effective than naltrexone and acamprosate in reducing alcohol intake, increasing number of abstinence days and delaying time to first relapse and to first drinking. There were no differences between naltrexone and acamprosate in the outcomes of the study.

In a comparative open label randomized study, disulfiram was more effective than acamprosate in increasing the percentage of total alcohol abstinent patients, while also delaying the time to first relapse [17]. Patients who were administered acamprosate, however, showed fewer cravings than the disulfiram group.

In an open label randomized trial, the same investigators compared the efficacy of disulfiram and topiramate in preventing alcohol relapse. Disulfiram was more effective than topiramate to increase the percentage of total alcohol abstinent patients and to delay the time to first relapse [18]. Patients allocated with topiramate showed less craving than the disulfiram group.

Finally, in an open label randomized study, disulfiram was compared with naltrexone and sodium oxybate [19]. In this study, no significative difference was found among the treatments, both in maintaining abstinence and in reducing alcohol intake. No differences in biological markers of AUD or in craving reduction was found among patients administered different medications.

Overall, although RCTs failed to consistently show a significant efficacy of the medication compared to placebo in terms of total alcohol abstinence, disulfiram seems to be useful and indicated in helping to maintain abstinence and/or prevent relapse. The main reason at the basis of RCTs failure could be related to the proposed mechanism of action of the medication. In particular, disulfiram is effective if the patient is afraid of the effects related to the combination between the medication and alcohol. The perspective of developing acetaldehyde syndrome is at least in part what causes both the absence of significant differences in outcomes between the medication and placebo groups in RCTs, and the positive results of open-label trials. As reported by Skinner et al. [9], blinded designs distribute the threat of disulfiram evenly among the arms of a study, whereas open-label designs allow the psychological threat to be present in only the disulfiram arm, compared to controls. In addition, the same meta-analysis showed a higher efficacy of disulfiram in AUD when its administration takes place in protected and supervised environments, such as hospitals or at home through administration by a family member [9]. Although third party supervision could be a bias in evaluating the efficacy of the medication, strong support has been shown to increase patient compliance with a consequent reduction in alcohol consumption. Also, studies in which placebo and disulfiram were both administered under third party supervision, showed that disulfiram was more effective in reducing alcohol consumption, thus the bias does not appear to be relevant.

Finally, with regards to the safety profile, disulfiram could lead to the development of different adverse events including fatigue, nausea, and vomiting, skin rush, neurological and cardiac changes, hepatotoxicity until to liver failure, particularly in patients with liver disease [9].

2.1. Acamprosate

Acamprosate is a synthetic compound, with a chemical structure related to that of taurine and c-aminobutyric acid (GABA) [20]. The mechanism of action behind its efficacy in the treatment of AUD has not been definitively established, although the medication is approved for AUD both in the U.S. since 2004 and in the EU since 2013. Preclinical evidence suggests that acamprosate may restore the imbalance between neuronal excitation and inhibition that occurs in chronic alcohol exposure [20,21]. In particular, acamprosate could rebalance the excitatory glutamate and inhibitory GABA neurotransmission [22] through its action on the N-methyl-D-aspartic acid (NMDA) receptors and metabotropic glutamate receptor 5 (mGlu5) [21].

Studies that took place in the 80 s have shown the efficacy of acamprosate in both reducing alcohol intake and in maintaining abstinence.

The efficacy of acamprosate in reducing ethanol consumption was firstly shown in preclinical studies, performed both in murine [23], and in rat [24,25] models.

The first RCT showing the efficacy of acamprosate in the treatment of patients with AUD were performed in France at the beginning of the 80 s [26]. In this study, a total of 85 patients with severe AUD patients were randomized to receive acamprosate or placebo. The main outcome was total alcohol abstinence, during the three months of treatment.

A significantly higher percentage of abstinent patients was found in the acamprosate group, compared to the placebo group. No significant difference in side effects was observed between patients receiving acamprosate or placebo.

Subsequently, several RCTs have been designed to evaluate the efficacy of acamprosate to achieve and maintain the total alcohol abstinence. Acamprosate showed to be better than placebo in over 272 patients treated for one year and evaluated for two years [27], in 448 patients treated for 12 months [28], in 118 patients treated for 48 weeks and evaluated for two years [29], in 296 patients treated for 6 months [30], and in 160 patients treated for 12 weeks [31]. Acamprosate proved to be effective also in reducing alcohol intake. In particular, a study of 15 placebo-controlled trials, in which the main outcome was complete abstinence, showed that the overall weekly consumption of alcohol was significantly decreased also in patients who relapsed [32]. The efficacy of the medication increases with time, as suggested by a meta-analysis study [33].

Despite these promising results and the subsequent FDA approval in the U.S., contrasting data have been reported on the efficacy of acamprosate as a long-term strategy for the relapse prevention [6,34;35]. The National Institute on Alcohol Abuse and Alcoholism Combined Pharmacotherapies and Behavioral Interventions for Alcohol Dependence (COMBINE) trial tested naltrexone, acamprosate and placebo treatments on 1383 patients with AUD over a four-month period: primary outcomes were time to first drink and cumulative abstinence proportion [6]. The COMBINE study concluded that naltrexone, with or without intensive counseling, was the most useful treatment for relapse prevention, while acamprosate failed to show significant efficacy compared to placebo, either alone or in combination with naltrexone. On the other hand, a subsequent meta-analysis, which also included the data from the COMBINE study, showed that acamprosate is an effective medication for the treatment of patients with AUD [36]. As suggested by the authors, the difference in terms of acamprosate efficacy in most of the European studies, compared to the COMBINE trial, could be related to several factors: different sample size, duration of studies, severity of dependence, detoxification before treatment [36]. Moreover, different craving subtypes could play a role; acamprosate may be effective in those patients who use alcohol to reduce distress, including the distress caused by withdrawal [36] and in patients in which the relief craving is considered the main psychological drive for alcohol consumption [37].

In addition, the different response to acamprosate among patients could be sustained by genetic factors, as suggested by Kiefer et al. (2011) [38]. In particular, polymorphisms in the gene coding for GATA-binding protein 4 (GATA 4), could influence both alcohol relapse and pharmacological response to acamprosate in patients with AUD, through modulation of atrial natriuretic peptide plasma levels [38].

Despite these contrasting results, available data suggests that acamprosate can be considered a safe and effective treatment. The Cochrane review, including 24 RCTs with 6915 participants, showed that acamprosate is highly effective in several outcome measures other than abstinence; its use was associated with a reduction in the return to any drinking and significantly increased the cumulative abstinence duration [39].

Moreover, in another meta-analysis, acamprosate showed a significant efficacy when compared to placebo, in terms of higher percentage of abstinence days, higher compliance to treatment, lower percentage of relapses in "heavy drinking" and lower drop-out rate [40].

In conclusion, acamprosate showed to be effective in maintaining alcohol abstinence in detoxified patients.

Future clinical studies are needed to identify more clearly which subpopulations of alcohol-dependent patients may benefit more of this medication.

From a safety point of view, acamprosate seems to have a good safety profile, and mostly minor gastrointestinal adverse events like nausea, vomit and diarrhea have been reported in treated patients [40].

2.2. Naltrexone

Naltrexone is a competitive opioid receptor antagonist approved as a treatment for AUD by the FDA since 1994. This medication is the first anti-craving medication approved for the treatment of AUD.

The efficacy of naltrexone in reducing the amount of alcohol intake and relapse to heavy drinking is related to its neuropharmacological profile. The antagonism against μ-opioid receptors, and against the κ-opioid and δ-opioid receptors to a lesser extent, is able to contrast the pleasant effects of alcohol. In particular, the blockade of opioid receptors reduces the dopamine release induced by alcohol consumption in the nucleus accumbens [41–43] with the consequent decrease of reward craving.

The endogenous opioid systems and their receptors were discovered as early as the 1970s. The knowledge of their role was enhanced by the development of two small-molecule competitive antagonists, derived from the analgesic opioid oxymorphone: naloxone, which is only bioavailable upon parenteral administration, and naltrexone, which is instead bioavailable upon oral administration.

In one of the first preclinical studies, naltrexone was effective in reducing alcohol intake in rhesus monkeys [44]. The efficacy of the drug was subsequently confirmed in several preclinical studies and in different animal models [45].

The first clinical open study on naltrexone showed a lack of enjoyment from drinking alcohol in actively drinking individuals with alcohol addiction [46]. These results were confirmed in a subsequent RCT [47], in which male veterans in an outpatient treatment program were randomized to receive either 50 mg naltrexone daily or placebo. This dose of naltrexone was selected because it had been used in treatment of heroin addiction and had been shown to block the high caused from heroin. All patients received counselling and group therapy (Alcoholics Anonymous). This study concluded that patients receiving naltrexone reported a lower alcohol relapse rate, less alcohol craving, and less reward from alcohol if they drank, compared to the placebo group [47]. The results of this study were confirmed in a subsequent study conducted at Yale University by O'Malley and colleagues [48] and, therefore, FDA added AUD the indications for the use of naltrexone.

Moreover, literature data suggests that naltrexone reduces drinking primarily by dampening cravings and alcohol's reinforcing effects; retrospective patient reports in the initial clinical trials suggested that naltrexone reduced day-to-day cravings and subjective high following alcohol consumption [49]. The most recently published studies in literature found naltrexone blunted craving in response to alcohol [50, 51] and dampened the reinforcing effects of alcohol [51,52].

These encouraging results were also confirmed in adolescents, in a randomized, double-blinded, placebo-controlled crossover study, which compared naltrexone (50 mg/daily) versus placebo in 22 adolescents with alcohol use problems aged between 15 and19 [53]. The authors demonstrated that naltrexone reduced the likelihood of drinking and heavy drinking, blunted cravings, blunted alcohol-induced stimulation, and increased sedation in a brief medication period, excluding treatment-seeking youths. Behavioral intervention did not take place, in order to isolate the pharmacological effects of naltrexone.

In the last decades, clinical observations revealed that some patients with AUD show no response to naltrexone, whereas others improved

dramatically. An effort to identify the characteristics of a naltrexone responder showed that a strong family history of AUD (genetically determined opioid activation transmission) and self-report of strong alcohol craving were the main indicators of naltrexone responsiveness [54].

However, the heterogeneity of naltrexone response among patients with AUD could partly be explained by genetic factors that influence subjective feelings of a 'high' from a standard alcohol dose and the level of alcohol self-administration; a common functional variant - Asn40Asp - was indeed discovered in the Opioid Receptor Mu 1 (OPRM1) gene, which encodes the mu-opioid receptors, the target for naltrexone [55].

Overall, despite solid evidence supporting the efficacy of this medication, naltrexone has not come into widespread clinical use, and physicians are still skeptic about its efficacy [56].

Recently, a systematic review on the efficacy of naltrexone showed very promising data in terms of reduction of daily alcohol intake, craving control (even if generally less consistent as for heavy drinking outcomes), incidence of relapse to heavy drinking, contrasting the pleasant effects of alcohol and contributing to reduction in alcohol reward [57]. In conclusion, high levels of reward craving, a positive family history of AUD and the presence of a specific polymorphism in the opioid receptor gene appear to predict a positive response to naltrexone [58].

The most common side effects of naltrexone are headaches, nausea, dyspepsia, anorexia, anxiety, and sedation. A recent meta-analysis on naltrexone, nalmefene, acamprosate, baclofen and topiramate showed that naltrexone and nalmefene were associated with a significant increase in withdrawals from the study for safety reasons, which raises concerns about a plausible attrition bias [59].

2.3. Nalmefene

Nalmefene is an opioid modulator with a distinct μ, δ and k receptor binding profile (MOR, DOR and KOR), acting as μ and δ antagonist and as partial agonist of the k receptor [60,61]. Furthermore, nalmefene shows high affinity for μ and k receptors and medium affinity for δ receptors [61].

Nalmefene is the first and only medication to be approved in European Union (EMA, 2013) for reducing alcohol consumption in adult patients with AUD, who have a high drinking risk level (DRL) according to WHO (DRL >60 g/day in men and >40 g/day in women) [62], without physical withdrawal symptoms and who do not require immediate detoxification.

As per administration schedule, nalmefene should be taken as needed: patients have taken a tablet on the days they perceive an increased risk of drinking, preferably 1–2 h before drinking alcohol. Also, continuous psychosocial support, focused on treatment adherence and reducing alcohol consumption, should be offered too.

Nalmefene should be initiated only in patients who continue to have a high DRL two weeks after initial assessment [60].

Three European RCTs (ESENSE 1, ESENSE 2 and SENSE) evaluated the efficacy of nalmefene on a monthly basis in reducing heavy drinking days (HDDs) and total alcohol consumption (TAC) [62,64,65]. The number of HDDs was defined as a day with alcohol consumption ≥60 g for men and ≥40 g for women. TAC was defined as mean daily alcohol consumption in g/day over a month (=28 days). The secondary endpoints were a change in HDDs and TAC from baseline to month six [63,64].

These studies showed significant efficacy of nalmefene in reducing TAC [63] and the number of HDDs [63,64].

In a post-hoc subgroup analyses [66] in the ESENSE1 and ESENSE2 studies, made up of patients with high DRL at screening and at randomization, nalmefene has significant effects on co-primary outcomes. At month 6, nalmefene was significantly superior to placebo in reducing the number of HDDs and TAC, with a significant between-group difference at each month. Therefore, efficacy of nalmefene was larger in these patients than in the total population.

Supportive evidence on the long-term efficacy of nalmefene is based on the results of the SENSE study [65], a 52-week RCT in which a fixed dose (18 mg) of nalmafene. The co-primary efficacy endpoints were the change in number of HDDs and TAC from baseline to month 6 and month 13

In a subgroup analysis of patients with high DRL at screening and at randomization, there was a significant effect in favor of nalmefene on TAC at month 6, and on both HDDs and TAC at month 13. Furthermore, nalmefene showed a significant efficacy in reducing both HDDs and TAC at most time points over the full study period.

More recently, a 24-week, open-label, Italian study [67] evaluated the efficacy of Nalmefene in patients with stabilized psychiatric comorbidity, through as-needed dosing. At month 6, there was a significant reduction in both comorbid and non-comorbid patients in the number of HDDs and TAC to baseline. Moreover, about 40% of patients achieved complete abstinence and/or showed no HDD.

The main reported adverse events in patients treated with nalmefene are mostly mild to moderate and included gastrointestinal and neurological symptoms, in particular dizziness, nausea, and insomnia [66]. However, nalmefene was associated with a significant increase in withdrawals from the study for safety reasons [59].

2.4. Baclofen

Baclofen is a selective GABA-B receptor agonist, with primary kidney metabolism; it was firstly tested in preclinical animal models of AUD, then in clinical studies in patients without liver disease, with promising results; its use was then evaluated in patients with advanced liver disease.

In animal models, administration of baclofen was effective in reducing intensity of ethanol withdrawal signs, alcohol intake, alcohol deprivation effects (a model of human relapse) and alcohol motivational properties [68–71]. The first preclinical evidence [68] was used to design clinical trials, to further understand its applications in humans. A four-week open-label pilot was firstly performed in ten male alcohol-dependent patients, in which 10 mg of baclofen were administered three times a day orally for 4 weeks in addition to weekly psychological support counseling. A reduction in alcohol cravings and a suppression of alcohol intake was observed from the first week of drug administration [72]. These findings were subsequently strengthened by the same group in a RCT in which 39 patients with AUD were randomized to receive 10 mg of baclofen or placebo three times a day for four weeks, in addition to weekly psychological support counseling. A significantly higher percentage of patients achieving and maintaining abstinence was observed in the baclofen group compared to the placebo group. Baclofen reduced daily alcohol intake within the first week of treatment. Cumulative abstinence duration was also significantly higher in patients taking baclofen than in patients treated placebo [73].

Several open-label [74–76] and cohort studies [77,78] later confirmed the usefulness of this medication. The primary value of these open and cohort studies, given the lack of a blind design and a placebo group, was to demonstrate that baclofen administration to AUD patients was feasible, useful and tolerated.

The first RCT that showed a possible dose-related efficacy of baclofen randomized 48 patients to receive either 10 mg of baclofen thrice a day, 20 mg thrice a day or placebo for 12 weeks. Both doses were significantly effective compared to placebo to reduce alcohol intake; the effect of 20 mg baclofen three times a day was greater than that of 10 mg. [79].

Several RCTs were then designed to assess the efficacy and safety of high doses of baclofen. The BACLAD study used a dose escalation design and showed the efficacy of baclofen at dosages of 30–270 mg/day in increasing total alcohol abstinence and cumulative abstinence duration, compared to placebo. The mean dose of baclofen was 180 mg/day [80]. In the ALPADIR study a significant decrease of craving and a trend in alcohol intake reduction were both observed when patients were

administered the target dose of 180 mg/day [81]. In the Bacloville study, a significant abstinence rate and/or a reduction of alcohol intake to low risk level (defined as < 40 g/day in men and < 20 g/day in women) was reported in patients with AUD who received titrated baclofen up to 300 mg/day, compared to placebo [82]. Finally, a recent RCT tested 30 and 90 mg/day of baclofen, compared to placebo, and examined the role of gender both on the efficacy and tolerability [83]. Baclofen increased abstinent days and reduced heavy drinking days, compared to placebo; gender was a moderator of response. In particular, men responded marginally to 90 mg/day compared to placebo, but not to 30 mg/day; women, instead, showed a positive response to 30 mg/day and only a marginal response to 90 mg/day which was not well tolerated in this population [83].

Some meta-analyses have reported contrasting data. A significant efficacy of baclofen in increasing abstinence rate was reported by Lesouef et al. [84], Pierce et al. [85] and Rose et al. [86]. On the contrary, Bschor et al. [87] and Minozzi et al. [88] failed to find an increased abstinence rate in patients treated with baclofen, although a significant reduction of alcohol intake was reported [88]. Different factors could potentially explain the contrasting data. Agabio et al. [89] recently showed that anxiety could, indeed, play a central role on the outcome of treatment with baclofen in patients with AUD. In a meta-analysis of 13 studies, a significant higher abstinence rate was found in baclofen treated patients who presented with higher baseline anxiety levels, compared to placebo and, most interestingly, to patients with lower baseline anxiety.

The most interesting aspect of this medication seems to be the possibility of its use in patients with advanced liver disease, which are usually excluded from anti-craving treatment. Baclofen is mainly eliminated by the kidney and only in a small percentage by the liver, thus its efficacy and safety has been thoroughly investigated in this typology of patients with AUD. The first RCT included 84 AUD patients with liver cirrhosis. Patients were randomized to receive baclofen (10 mg three times daily.) or placebo for 12 weeks. Compared to placebo, a significant higher percentage of patients treated with baclofen achieved and maintained total alcohol abstinence. Cumulative abstinence duration was significantly higher in the group treated with baclofen, and it was particularly evident in patients with more advanced liver cirrhosis, as indicated by the Child-Pugh score. A significant reduction of craving was found in the baclofen group, compared toto the placebo group. The medication was safe and well tolerated and no event leading to medication cessation was reported [90]. These data were recently replicated in a multi-centric RCT, named BacALD [91]. The efficacy and safety of 2 fixed-doses, 10 mg and 25 mg, thrice a day were evaluated in patients with AUD, with or without liver disease. Compared to placebo, the study reported a significant higher percentage of days of alcohol abstinence in the baclofen group and a significant delay in the first lapse and relapse overall in the subgroup of patients with liver disease. No difference between the two doses was found in terms of efficacy, while some minor side effects (sedation and shortness of breath) were significantly present in those taking the higher dose [91].

The usefulness and safety of this medication in patients with liver diseases were further demonstrated by several cohort studies, in which more than 300 patients were treated [92–94]. At present baclofen is included in both European [95] and American [96] clinical guidelines for the management of **alcohol-associated** liver disease.

Overall, baclofen seems to be effective and manageable in the treatment of patients with AUD. As reported in a recent position paper, baclofen should be considered a second-line treatment in patients who have not responded to other approved pharmacotherapies for AUD, yet it could be considered as a first-line treatment in patients with advanced liver disease, even though off-label [97].

Finally, no significant difference in terms of dropout rate and compliance to treatment in patients treated with baclofen or placebo was reported in a recent meta-analysis [88].

Baclofen was recently approved in France by ANSM (the French FDA) at the maximum dose of 80 mg/day.

Some neurological adverse events like headache, tiredness, weakness and somnolence have been reported in baclofen treated patients, although they are usually mild and transient [91].

2.5. Sodium oxybate

Sodium oxybate (SMO) has been approved as an oral solution in Italy and Austria for the treatment of alcohol withdrawal syndrome (AWS) since 1991 and for the maintenance of abstinence since 1999 [98]. SMO is the sodium salt of γ-hydroxybutyric acid (GHB), a short-chain fatty acid, which is naturally present in the mammalian brain. GHB binds with low affinity to GABA subtype B receptors and with high affinity to GHB-specific receptors [99]. The pharmacological profile of GHB has similarities to that of alcohol, thus, one proposed mechanism of SMO in the treatment of individuals with AUD is its alcohol-mimicking effect in the brain [99]. SMO efficacy in the maintenance of abstinence in patients with AUD has been tested in a series of open label and blinded randomized controlled trials (RCTs).

Seven RCTs, overall including 1085 patients, investigated oral SMO 50 mg/kg/day efficacy in the maintenance of abstinence, with treatment periods ranging from three to 12 months [100]. In a pilot double-blind, placebo controlled RCT, with 82 patients, SMO was significantly more effective in increasing the number of abstinent days, reducing the number of daily drinks and the intensity of alcohol craving [101]. SMO efficacy in the maintenance of abstinence and in longer abstinence duration in relapsing patients was also showed in a Phase III double-blind, placebo controlled RCT conducted on 314 patients [102]. A further phase IIb double-blind, placebo controlled RCT confirmed the efficacy of SMO compared to placebo in increasing both abstinence rate and the percentage of abstinent days. In this trial, 496 alcohol-dependent patients from nine European countries and 68 different sites were enrolled and treated for three months. A post hoc analysis showed that the medication was particularly effective in patients with severe AUD [100].

SMO was also significantly more effective than naltrexone in the maintenance of abstinence in two open label RCTs [103,104]. Meta-analyses also provided evidence of SMO's efficacy in maintaining abstinence, compared to placebo and naltrexone [100,105]. In a subgroup meta-analysis, SMO consistently showed significantly higher and clinically relevant effect sizes in patients with severe disease: RR [95% CI] in abstinence rate of 2.86 [1.41; 5.81] vs placebo and of 2.62 [1.30; 5.30] vs naltrexone [100].

The safety profile of SMO in the treatment of AUD has been investigated in 46 different clinical studies, including 3067 patients, who were exposed to the medication mostly in an outpatient setting. Data showed that SMO has a good safety profile, which was confirmed by pharmacovigilance data resulting from 299,013 patients exposed to SMO in Austria and Italy. Main adverse events were transitory dizziness and vertigo. Serious adverse events were rare. No death attributable to SMO has been reported. Risks of abuse or dependence were low in patients without psychiatric comorbidities or multidrug use [98].

2.6. Topiramate

Although topiramate is not an FDA-approved medication for the treatment of AUD, it is suggested by the American Psychiatric Association (APA) as a therapeutic option for patients with AUD who do not respond or tolerate other approved medications [106,107]. Topiramate acts as an antagonist of glutamate activity, improving GABAergic function and reducing cerebral dopamine release [108]. In several studies topiramate showed its efficacy in promoting alcohol abstinence and in reducing alcohol intake.

The first RCT included 150 patients, who were treated with an escalating dose of 25–300 mg per day of topiramate or placebo for 12 weeks. A significant reduction of alcohol intake and craving was found

in the topiramate group, compared to the placebo group [109]. The same researchers confirmed the efficacy of the medication in another RCT [110]. The medication was effective in reducing the number of heavy drinking days and improving the quality of life of patients. Moreover, a secondary analysis of the data from this RCT showed that topiramate was effective in helping patients reach "safe" levels of alcohol intake (< or = 1 drink for women and < or = 2 drinks for men). In particular, it was associated to a significant increase of success in maintaining lower risk drinking for seven days, and a reduction of the risk to exceed this "lower risk" drinking in the following days, compared to placebo [111].

In a subsequent RCT Johnson et al. tested topiramate (up to 300 mg/day) vs. placebo in 371 patients for 14 weeks, showing a significative reduction of heavy drinking days in the topiramate group, with a higher rate of alcohol abstinent patients, compared to placebo [112]. The most commonly reported adverse events in this study were anorexia, paresthesia, and taste perversion. However, the medication was generally safe and the analysis of the data of this RCT showed that topiramate administration was associated with improvements in both physical and psychosocial health [113]. Several studies confirmed the efficacy of topiramate in reducing alcohol intake and frequency of heavy drinking [114,115], in modulating impulsivity [116] and in improving abstinence rate [117].

The efficacy of topiramate in patients with AUD could be influenced by genetic variability. The presence of a single nucleotide polymorphism (rs2832407) in GRIK1 could increase the response to topiramate [118] although, at present, there is contrasting evidence [119].

Over the years, the efficacy of topiramate was also compared to that of other medications used for the treatment of AUD. Florez et al. (2008) compared topiramate (200–400 mg/day) with naltrexone (50 mg/day) in a 6-month randomized trial on 102 patients who were heavy drinkers. At the end of the study, no significative differences were found between the two groups in terms of alcohol intake reduction: topiramate showed a larger trend in reducing alcohol craving [120]. In a RCT study, 155 patients were randomized to receive topiramate, naltrexone or placebo. Both topiramate and naltrexone showed a significant efficacy in increasing alcohol abstinence and in reducing heavy drinking days. Topiramate showed a slightly higher efficacy to delay time to first relapse [121]. In a subsequent comparative study, Florez et al. showed a significant efficacy of topiramate (200 mg/day), compared to naltrexone (50 mg/day), in reducing alcohol consumption and alcohol craving [122].

Martinotti et al. (2014) confirmed the efficacy of topiramate in 52 detoxified patients with AUD at a dose of 100 mg/die in reducing alcohol intake (particularly in terms of drinking days and daily alcohol consumption) and craving, while also showing an improvement in anxiety and depression [123].

Knapp et al. (2015) compared the efficacy of topiramate, levetiracetam and the zonisamide (another anticonvulsant medications). With respect to placebo, patients treated with topiramate or zonisamide showed a significant reduction of alcohol intake, percentage of drinking days, and percentage of heavy drinking days, suggesting that other anticonvulsants could be an effective treatment of AUD [124].

A recent study of Haas-Koffler CL et al. (2018) tested topiramate in combination with aripiprazole to evaluate the two mechanisms of action in synergy [125]. In this study, topiramate appear an effective treatment for alcohol use disorder and demonstrated to be superior both alone and in combination with aripiprazole [125].

A recent large meta-analysis included seven RCTs investigating topiramate in a total of 1125 patients [126]. Topiramate was effective in improving abstinence and reducing heavy drinking. A trend of craving reduction was also observed. Although this study showed a higher dropout rate in patients treated with topiramate due to side effects, no other differences in dropout rate between topiramate and placebo were found [127].

In conclusion, topiramate seems to be safe and effective in the

Table 1
Outcomes, NNT and effect size for each of the described medications.

MEDICATION	OUTCOMES	NNT	EFFECT SIZE (95% CI)
DISULFIRAM *	RETURN TO ANY DRINKING	NA	RD: −0.04 (−0.11 to 0.03)[a]
	RETURN TO HEAVY DRINKING	NA	NA
ACAMPROSATE *	RETURN TO ANY DRINKING	12 (8 to 26)	RD: −0.09 (−0.14 to −0.04)[a]
	RETURN TO HEAVY DRINKING	NA	RD: −0.01 (−0.04 to 0.03)[a]
NALTREXONE *	RETURN TO ANY DRINKING	20 (11 to 500)	RD: −0.05 (−0.10 to −0.002)[a]
	RETURN TO HEAVY DRINKING	12 (8 to 26)	RD: −0.09 (−0.13 to −0.04)[a]
NALMEFENE **	RETURN TO ANY DRINKING	NA	NA
	RETURN TO HEAVY DRINKING	NA	NA
	REDUCTION OF HDD	NA	g: −0.33 (−0.48 to −0.18) [b]
	REDUCTION OF TAC	NA	g: −0.35 (−0.51 to −0.20) [b]
BACLOFEN ***	RETURN TO ANY DRINKING	NA	NA
	RETURN TO HEAVY DRINKING	NA	NA
	% OF ABSTINENT DAYS	11 (7 to 35)	RD: 9.01 (2.85–15.16) [c]
	% OF ABSTINENT DAYS IN AUD PATIENTS WITH ANXIETY	4 (3 to 10)	RD: 23.47 (9.53–37.41) [c]
SODIUM OXYBATE ****	RETURN TO ANY DRINKING	5 (3 to 13)	RD: −0.19 (−0.30 to −0.08) [a]
	RETURN TO HEAVY DRINKING	2 (2 to 4)	RD: −0.43 (−0.60 to −0.25) [d]
TOPIRAMATE *****	RETURN TO ANY DRINKING	7 (4 to 100)	RD: −0.14 (−0.28 to −0.01)[a]
	RETURN TO HEAVY DRINKING	5 (3 to 24)	RD: −0.19 (−0.32 to −0.04)[d]

*Jonas DE, Amick HR, Feltner C, Bobashev G, Thomas K, Wines R, Kim MM, Shanahan E, Gass CE, Rowe CJ, Garbutt JC. Pharmacotherapy for adults with alcohol use disorders in outpatient settings: a systematic review and meta-analysis. JAMA 2014; 311:1889–90.

[a]RD evaluated as negative effect sizes favor intervention over placebo/control. For example, RD of −0.04 for disulfiram compared to placebo for return to any drinking indicates that 4% fewer participants treated with disulfiram (than with placebo) returned to any drinking; the RD of −0.09 for acamprosate compared to placebo for return to any drinking indicates that 9% fewer participants treated with acamprosate (than with placebo) returned to any drinking.

**Mann K, Torup L, Sørensen P, Gual A, Swift R, Walker B, van den Brink W. Nalmefene for the management of alcohol dependence: review on its pharmacology, mechanism of action and meta-analysis on its clinical efficacy. Eur Neuropsychopharmacol. 2016 Dec;26(12):1941–1949. doi: 10.1016/j.euroneuro.2016.10.008. Epub 2016 Nov 12. PMID: 27,842,940.

[b]negative effect sizes favor intervention over placebo/control. For example, the Hedges's g of −0.33 for nalmefene compared to placebo for the reduction of HDD indicates a greater reduction in the number of HDD in the groups treated with nalmefene than in the placebo groups; −0.35 for nalmefene compared with placebo for the reduction in TAC indicates a greater reduction in TAC in the groups treated with nalmefene than in the placebo groups.

***Agabio R, Baldwin DS, Amaro H, Leggio L, Sinclair JMA. The influence of anxiety symptoms on clinical outcomes during baclofen treatment of alcohol use disorder: A systematic review and meta-analysis. Neurosci Biobehav Rev 2021; 125:296–313.

[c]RD evaluated on the rate of abstinent days at the end of treatment.

****RD and NNT computed with STATA v14.2 based on reported data in.
van den Brink W, Addolorato G, Aubin HJ, Benyamina A, Caputo F, Dematteis M, Gual A, Lesch OM, Mann K, Maremmani I, Nutt D, Paille F, Perney P, Rehm J, Reynaud M, Simon N, Söderpalm B, Sommer WH, Walter H, Spanagel R. Efficacy and safety of sodium oxybate in alcohol-dependent patients with a very high drinking risk level. Addict Biol. 2018; 23:969–86. and in.

Guiraud J, Addolorato G, Aubin HJ, Batel P, de Bejczy A, Caputo F, Goudriaan AE, Gual A, Lesch O, Maremmani I, Perney P, Poulnais R, Raffaillac Q, Soderpalm B, Spanagel R, Walter H, van den Brink W, Treating alcohol dependence with an abuse and misuse deterrent formulation of sodium oxybate: Results of a randomised, double-blind, placebo-controlled study, Eur Neuropsychopharmacol 2021; 52: 18–30. and in.

Leone MA, 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 Feb 17;(2):CD006266. doi: 10.1002/14,651,858.CD006266.pub2. PMID: 20,166,080.

[a]RD evaluated as negative effect sizes favor intervention over placebo/control. RD of −0.19 for sodium oxybate compared with placebo indicates that 19% fewer participants treated with sodium oxybate (than with placebo) returned to any drinking.

[d]RD evaluated as negative effect sizes favor intervention over placebo/control. RD of −0.43 for sodium oxybate compared with placebo for return to heavy drinking indicates that 43% fewer participants treated with sodium oxybate (than with placebo) returned to heavy drinking.

***** RD and NNT computed with STATA v14.2 based on reported data in.

Cheng H, McGuinness L A, Elbers R G, MacArthur G J, Taylor A, McAleenan A et al. Treatment interventions to maintain abstinence from alcohol in primary care: systematic review and network meta-analysis BMJ 2020; 371:m3934. and in.

Feinn R, Curtis B, Kranzler HR. Balancing risk and benefit in heavy drinkers treated with topiramate: implications for personalized care. J Clin Psychiatry. 2016; 77:e278–82.

[a]RD evaluated as negative effect sizes favor intervention over placebo/control. RD of −0.14 for topiramate compared with placebo indicates that 14% fewer participants treated with topiramate (than with placebo) returned to any drinking.

[d]RD evaluated as negative effect sizes favor intervention over placebo/control. RD of −0.19 for topiramate compared with placebo for return to heavy drinking indicates that 19% fewer participants treated with topiramate (than with placebo) returned to heavy drinking.

NNT: number needed to treat.

NA: not applicable. NA entry means that the considered meta-analysis did not report results on the selected outcome, or that results were not significant (for NNT), or that that the effect measure was not one that allows direct calculation of NNT (eg, Hedges's g).

RD: risk difference.

HDD: heavy drinking days.

TAC: Total alcohol consumption.

g: Hedges's g.

treatment of patients with AUD, in particular in patients with obsessive craving and with automaticy of drinking [127]. A potential role of topiramate in patients with a previous history of epileptic seizures should also be investigated.

Topiramate has been linked to minor adverse events such as headache, fatigue, insomnia, anorexia, nausea, difficulty with memory and concentration. However, in rare cases serious adverse events like convulsions, loss of consciousness and cardiac arrest were reported [113].

3. Conclusion

This narrative review describes the medications available for the treatment of patients with AUD, and their different indications. Number Needed to Treat (NNT) and effect size with the different outcomes for each drug are reported in Table 1. Pro-and cons for each medications are reported in Table 2.

Acamprosate has shown the major efficacy in reducing alcohol use relapse in detoxified patients, so it should be considered as a possible treatment to maintain and extend alcohol abstinence [128]. Naltrexone is effective in reducing relapse to heavy drinking [128], while it does not seem to be indicated if the main goal is total alcohol abstinence. Nalmefene too shows its major efficacy in the reduction of heavy drinking days, although it seems to be more effective than naltrexone in reducing total alcohol consumption [58]. Moreover, nalmefene is currently the only approved medication to be taken as needed. Baclofen promotes total alcohol abstinence and prevents relapse. Patients with high level of anxiety [89] or with advanced liver disease [86] could be the target patients for this medication. In case of comorbidity of Alcohol Use Disorder and anxiety disorder, the use of pregabalin could also represent a further option of treatment [129]. Sodium oxybate has proved safe and effective in the prevention of relapses as well as in the treatment of alcohol withdrawal syndrome [102]. This medication could be a valid therapeutic option as a unique medication for both AWS treatment and the subsequent long term alcohol relapse prevention, avoiding changing medications and increasing the patients compliance. Topiramate seems to be effective in reducing alcohol intake and promoting abstinence [130]. In light of its antiepileptic effect, this drug could be useful for patients with a past history of epileptic seizures. Disulfiram seems to be useful and indicated for patients with AUD who need an external control to increase the motivation to maintain abstinence and to avoid relapse. The concern about the potential adverse events related to the combination between alcohol and disulfiram reinforces this motivation [131].

Table 2
Pros and Cons of the approved medications.

MEDICATION	PROS	CONS
Acamprosate	Effective in reducing alcohol relapse in detoxified patients. Approved by FDA and EMA	Contrasting data reported on the efficacy as a long-term relapse prevention
Naltrexone	Effective in reducing relapse to heavy drinking. Approved by FDA and EMA	High NNT in alcohol abstinence outcome
Nalmefene	Effective in reducing relapse to heavy drinking. Medication to take as needed. Approved by EMA	NNT not assessed
Baclofen	Effective in promoting abstinence and prevent relapse. Well tolerated in patients with advanced liver disease	Not yet approved by FDA and EMA
Sodium oxybate	Effective in promoting abstinence, in reducing Heavy Drinking and in the treatment of alcohol withdrawal syndrome	Not yet approved by FDA and EMA
Topiramate	Effective in promoting abstinence and in reducing Heavy Drinking. Treatment option for AUD patients with history of epileptic seizures	Not yet approved by FDA and EMA
Disulfiram	Useful to maintain alcohol abstinence and to avoid relapse. Approved by FDA and EMA	NNT not assessed

Combined therapy with these medications [31,104] and the identification of specific subgroups of patients that can benefit from specific medications [132–134], could enhance therapeutic success. However, currently the availability (in some health systems, these medications may not accessible), the cost, and the familiarity with a certain medication are the main factors influencing the choice of clinicians [135].

Also, it would be interesting to try to customize the treatment for the AUD based on gender; however, except for baclofen in which a gender difference was found in terms of dose and efficacy [83], there is currently no evidence in literature on differences in response to various pharmacological treatments on the basis of sex, as indicated by a recent systematic review by Newberry et al. (2019) [136]. Yet even a different drug formulation can influence the efficacy of the treatment based on gender; extended-release formulations of naltrexone showed a significant reduction of craving in women compared to men [137].

Finally, despite evidence of the efficacy and safety of therapies currently available for the treatment of AUD and their approvement by Medical Agencies, these medications are markedly underutilized in clinical practice [7] and many patients have not access to specialized treatment. As recently reported by the Surgeon General's report "Facing Addiction in America", only about 1 in 10 people with a substance use disorder receives any type of specialistic treatment [138].

On the contrary, effective medications for other psychiatric diseases, such as antidepressants, which have shown efficacy with similar NNT (5 to 9) [139], are widely used in clinical practice.

Increasing the training of clinicians may increase familiarity with the medications, reducing the lack of confidence in their efficacy, which is an important barrier for their prescription.

In conclusion, the most effective management strategy for AUD is the combination of psychosocial interventions and pharmacological therapy. Although the limit of the narrative design of this review, the currently available medications for the treatment of AUD have shown good overall efficacy, although further progress can be achieved through the combination between medications, and the individualization of target patients. Increasing the knowledge of these medications in clinicians can reduce the gap between patients needing treatment and those actually treated.

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