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Current pharmacological treatment approaches for alcohol dependence

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Introduction: At present, the substances acamprosate, naltrexone and disulfiram are available for pharmacotherapy in alcohol dependence, but clinical studies found only modest effect sizes of these treatment options.

Areas covered: This article focuses on current pharmacological treatment approaches for alcohol dependence, which have been evaluated in randomized, placebo-controlled trials (RCTs).

Expert opinion: Besides the opioid system modulator nalmefene, which has recently been approved as a medication for the reduction of alcohol consumption, several compounds have been investigated in patients with alcohol dependence using a randomized, placebo-controlled design. In these studies, the antiepileptic drugs topiramate and gabapentin were found to be effective in improving several drinking-related outcomes, whereas levetiracetam failed to show efficacy in the treatment of alcohol dependence. Clinical studies using (low-dose) baclofen, a selective GABA-B receptor agonist, produced conflicting results, so that results of further trials are needed.

Varenicline has also shown mixed results in two RCTs, but might possibly be useful in patients with comorbid nicotine dependence. The α1 adrenergic antagonist prazosin is currently under investigation in alcohol dependence with and without comorbid posttraumatic stress disorder (PTSD). Finally, first clinical evidence suggests that the 5-HT3 antagonist ondansetron might possibly be used in future within a pharmacogenetic treatment approach in alcohol dependence.

Keywords: alcohol dependence, pharmacotherapy, reduced drinking, relapse prevention


1. Introduction

Alcohol use disorders (AUDs) represent common and serious diseases, which in most cases require intensive medical treatment; up to 40% of hospitalized patients suffer from AUDs [1]. An alcohol detoxification is often the first step in the treatment of alcohol dependence and mainly addresses the complications of the underlying disease. After detoxification, the vast majority of alcohol-dependent patients (up to 85%) suffer from relapses [2]. Improvement of the treatment outcome can be achieved by combining psychosocial with pharmacological interventions. However, since alcohol dependence represents a heterogeneous disorder that results from gene × environment interactions, which differ from patient to patient, it seems unlikely that one single medication will show efficacy in all alcohol-dependent patients [3]. Currently, the anti-craving substances acamprosate and naltrexone as well as the aversion therapeutic agent disulfiram are available for pharmacotherapy of alcohol dependence. Acamprosate was thought to modulate glutamatergic transmission by inhibition of N-methyl-D-aspartate (NMDA) and metabotropic glutamate (mGluR5) receptors [4]. However, a recent study suggests that acamprosate...
might act through calcium [5]. In a meta-analysis including 24 clinical trials [6], acamprosate has been shown to significantly reduce the risk of relapse to 86% of the risk of the placebo group to increase cumulative abstinence duration by 11% compared to placebo. In terms of tolerability, diarrhea was the only side effect that occurred more frequently in patients treated by acamprosate than placebo. With regard to the opioid antagonist naltrexone, a meta-analysis including 47 clinical trials [7] found a significant risk reduction for relapse to heavy drinking (defined as ≥ 5 standard drinks/day for men; ≥ 4 standard drinks/day for women, 1 standard drink = 12 g of alcohol) to 83% of the risk of the placebo group and a reduction of drinking days by 4% compared to placebo. Gastrointestinal and sedative effects were the most common side effects of naltrexone. However, these meta-analyses found only modest effect sizes of these treatment approaches, with a number needed to treat (NNT) of 9 for both acamprosate and naltrexone. Moreover, some large trials failed to replicate the positive effects of acamprosate [8,9].

The aldehyde dehydrogenase inhibitor disulfiram has been evaluated in numerous trials in alcohol dependence showing inconsistent results [10,11]. Most of these studies possessed relevant methodological limitations [10]; only three trials investigated (unsupervised) disulfiram using a randomized, double-blind, placebo-controlled design. One study in a small sample of adolescent patients reported a higher abstinence rate (54 vs 15%) and a higher cumulative abstinence duration (69 vs 30 days) for disulfiram [12]. In contrast, two large studies could not show unsupervised disulfiram to be superior with regard to total abstinence compared to placebo [13,14]. Interestingly, disulfiram has shown preliminary efficacy in reducing craving and relapse rates in cocaine dependence [15]. These effects might possibly be related to the ability of disulfiram to inhibit the dopamine beta-hydroxylase (DBH), leading to an increase in dopamine concentrations while decreasing the concentrations of norepinephrine in the brain [16-18].

In summary, given the high relapse rates and the suffering of dependent patients, further research is urgently needed to develop more effective pharmacotherapies for the treatment of alcohol dependence.

2. New pharmacological treatment approaches

2.1 Approved medications

2.1.1 Nalmefene

Nalmefene, an opioid system modulator structurally related to naltrexone, possesses antagonistic properties at the µ- and δ-receptor and partial agonistic properties at the κ-receptor [19]. It has already been evaluated in several randomized, placebo-controlled trials (RCTs) in alcohol dependence [20,22]. With the exception of one study [23], all trials reported a reduction of heavy drinking during the treatment with nalmefene. Recently, the results of two large multicenter RCTs have been published [24,25]; in both studies, alcohol-dependent patients received an ‘as-needed’ treatment with nalmefene (-18 mg/day) or placebo over 24 weeks.

The first study in a sample of 604 patients reported a greater reduction of heavy-drinking days (-2.3 days/month) and total alcohol consumption (-11.0 g/day) in the nalmefene group compared to placebo [24]. Side effects were more common in the nalmefene group and included nausea, dizziness, fatigue, sleep disorder, insomnia, hyperhidrosis and vomiting. Thirty-eight serious adverse events (AEs) were reported (18 nalmefene vs 20 placebo). The authors reported more dropouts due to side effects in the nalmefene group (23 vs 7%).

The second study in 718 patients found a significant reduction in heavy-drinking days (group diff.: -1.7 days/month), but no significant reduction in total alcohol consumption (group diff.: -5.0 g/day, p = 0.088) [25]. The most common side effects were dizziness, nausea and insomnia, with an incidence two times higher in the nalmefene group compared to placebo. The rate of dropouts due to side effects did not differ between the groups (6.7 nalmefene vs 5.9% placebo). Serious AEs occurred in 25 patients (8 nalmefene vs 17 placebo).

In February 2013, nalmefene has been approved by the European Medicines Agency (EMA) for the reduction of alcohol consumption in alcohol-dependent patients who have a high drinking-risk level without physical withdrawal symptoms and who do not require immediate detoxification [26].

2.2 Off-label medications (Table 1)

2.2.1 Levetiracetam

Levetiracetam is a second-generation antiepileptic drug that has recently been investigated in several preclinical and
Table 1. Study characteristics and outcomes of randomized, placebo-controlled trials investigating off-label medications in alcohol dependence.

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Duration</th>
<th>Dose</th>
<th>Efficacy</th>
<th>Tolerability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levetiracetam</td>
<td></td>
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</tr>
<tr>
<td>Richter et al. [39]</td>
<td>201</td>
<td>16 weeks</td>
<td>Target dose: 2000 mg/day</td>
<td>Levetiracetam = placebo: rate of severe relapse, time to severe relapse, abstinence rate</td>
<td>No differences in AEs and SAEs</td>
</tr>
<tr>
<td>Fertig et al. [40]</td>
<td>130</td>
<td>16 weeks</td>
<td>Target dose: 2000 mg/day</td>
<td>Levetiracetam = placebo: percent of heavy-drinking days, percent of subjects with no heavy-drinking days</td>
<td>Levetiracetam: fatigue, no differences in SAEs</td>
</tr>
<tr>
<td>Topiramate</td>
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</tr>
<tr>
<td>Johnson et al. [46]</td>
<td>150</td>
<td>12 weeks</td>
<td>25 – 300 mg/day</td>
<td>Topiramate &gt; placebo: drinks per day, drinks per drinking day, fewer heavy-drinking days, days abstinent</td>
<td>Topiramate: dizziness, paraesthesia, psychomotor slowing, memory or concentration impairment, weight loss, no SAEs</td>
</tr>
<tr>
<td>Johnson et al. [47]</td>
<td>371</td>
<td>14 weeks</td>
<td>up to 300 mg/day</td>
<td>Topiramate &gt; placebo: percentage of heavy-drinking days</td>
<td>Topiramate: paraesthesia, taste perversion, anorexia, difficulty with concentration/attention, pruritus; no differences in SAEs</td>
</tr>
<tr>
<td>Baltieri et al. [48]</td>
<td>155</td>
<td>12 weeks</td>
<td>Target dose: 300 mg/day</td>
<td>Topiramate = naltrexon &gt; placebo: time to first relapse, cumulative abstinence duration, weeks of heavy drinking</td>
<td>No differences in AEs, no SAEs</td>
</tr>
<tr>
<td>Rubio et al. [49]</td>
<td>76</td>
<td>12 weeks</td>
<td>up to 250 mg/day</td>
<td>Topiramate &gt; placebo: drinks per drinking day, percentage of heavy-drinking days, percentage of abstinent days</td>
<td>No detailed report</td>
</tr>
<tr>
<td>Gabapentin</td>
<td></td>
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</tr>
<tr>
<td>Furieri et al. [50]</td>
<td>60</td>
<td>4 weeks</td>
<td>600 mg/day</td>
<td>Gabapentin &gt; placebo: drinks per day, percentage of heavy-drinking days, percentage of abstinent days</td>
<td>No differences in AEs, no SAEs</td>
</tr>
<tr>
<td>Mason et al. [51]</td>
<td>150</td>
<td>12 weeks</td>
<td>900 and 1800 mg/day</td>
<td>Gabapentin 1800 mg/day &gt; gabapentin 900 mg/day &gt; placebo: rate of abstinence, rate of no heavy drinking</td>
<td>No differences in AEs, no drug-related SAEs</td>
</tr>
<tr>
<td>Baclofen</td>
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<tr>
<td>Addolorato et al. [61]</td>
<td>39</td>
<td>4 weeks</td>
<td>30 mg/day</td>
<td>Baclofen &gt; placebo: abstinence rate, cumulative abstinence duration</td>
<td>No differences in AEs, no SAEs</td>
</tr>
<tr>
<td>Addolorato et al. [62]</td>
<td>84</td>
<td>12 weeks</td>
<td>30 mg/day</td>
<td>Baclofen &gt; placebo: abstinence rate, cumulative abstinence duration</td>
<td>No differences in AEs, no SAEs</td>
</tr>
</tbody>
</table>

AEs: Adverse events; SAEs: Serious adverse events.
<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Duration</th>
<th>Dose</th>
<th>Efficacy</th>
<th>Tolerability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Garbutt et al. [63]</td>
<td>80</td>
<td>12 weeks</td>
<td>30 mg/day</td>
<td>Baclofen = placebo: percentage of heavy-drinking days, percentage abstinent days</td>
<td>No differences in AEs, no SAEs</td>
</tr>
<tr>
<td>Addolorato et al. [64]</td>
<td>42</td>
<td>12 weeks</td>
<td>30 and 60 mg/day</td>
<td>Baclofen = placebo: heavy-drinking days, abstinent days, time to first lapse, time to first relapse. Secondary analysis: baclofen 60 mg/day &gt; baclofen 30 mg/day &gt; placebo: number of drinks per day</td>
<td>No differences in AEs, no SAEs</td>
</tr>
<tr>
<td>Varenicline</td>
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<tr>
<td>Plebani et al. [69]</td>
<td>40</td>
<td>13 weeks</td>
<td>2 mg/day</td>
<td>Varenicline = placebo: alcohol use</td>
<td>No differences in AEs, no SAEs</td>
</tr>
<tr>
<td>Litten et al. [70]</td>
<td>200</td>
<td>13 weeks</td>
<td>2 mg/day</td>
<td>Varenicline &gt; placebo: percent heavy-drinking days, drinks per day, drinks per drinking day, number of cigarettes smoked</td>
<td>Varenicline: nausea, abnormal dreams, constipation; no differences in SAEs</td>
</tr>
<tr>
<td>Prazosin</td>
<td></td>
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<tr>
<td>Simpson et al. [72]</td>
<td>24</td>
<td>6 weeks</td>
<td>16 mg/day</td>
<td>Prazosin &gt; placebo: number of drinking days, number of drinks</td>
<td>No differences in AEs, no SAEs</td>
</tr>
<tr>
<td>Ondansetron</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Johnson et al. [74]</td>
<td>271</td>
<td>11 weeks</td>
<td>2, 8 or 32 µg/kg per day</td>
<td>Ondansetron (all dosages) &gt; placebo in early-onset AD: number of drinks per day, drinks per drinking day</td>
<td>No differences in AEs, no SAEs</td>
</tr>
<tr>
<td>Johnson et al. [75,76]</td>
<td>283</td>
<td>11 weeks</td>
<td>8 µg/kg per day</td>
<td>Ondansetron = placebo; with subgroups according to genotype: ondansetron &gt; placebo: drinks per drinking day, percentage of days abstinent, percentage of heavy-drinking days [76]</td>
<td>Ondansetron: fatigue, no medication-related SAEs</td>
</tr>
<tr>
<td>Correa Filho and Baltieri [77]</td>
<td>102</td>
<td>12 weeks</td>
<td>16 mg/day</td>
<td>Ondansetron = placebo: percentage of abstinent days, percentage of heavy-drinking days</td>
<td>No differences in AEs, no SAEs</td>
</tr>
</tbody>
</table>

AEs: Adverse events; SAEs: Serious adverse events.
clinical studies in alcohol dependence [27,28]. The precise mechanism of action of levetiracetam is still unclear. It has no significant affinity to gamma-aminobutyric acid (GABA) or glutamate receptors and does not directly interact with the benzodiazepine binding site [29-31]. Levetiracetam was reported to bind to the synaptic vesicle protein 2A, which is involved in synaptic vesicle function and calcium-dependent regulation of neurotransmitter release during repetitive stimulation [30,32-35]. In alcohol-dependent mice, levetiracetam has been shown to reduce the alcohol withdrawal syndrome [36]. Two open-label trials provided some evidence that levetiracetam might also be safe and efficacious in the in- and outpatient treatment of alcohol withdrawal syndrome [28,57], whereas one RCT failed to show superiority of levetiracetam in the treatment of alcohol withdrawal syndrome compared to placebo [38]. With regard to relapse prevention in alcohol-dependent patients, two RCTs have been conducted to date. In a multicenter, 16-week RCT, the efficacy and safety of levetiracetam have been investigated in a sample of 201 recently detoxified alcohol-dependent patients using target dosages of 2000 mg per day [39]. At study end, no significant differences between the levetiracetam and the placebo group were observed for the endpoints ‘rate of severe relapse’ (defined as any alcohol consumption of > 60 g/day for men and > 48 g/day for women; 45 vs 40%), ‘time to severe relapse’ (77.4 vs 76.4 days) and ‘abstinence rate’ (35 vs 34%). The overall incidence of AEs did not differ between the levetiracetam and the placebo group (73 vs 71%); also, no differences in serious AEs between both groups were found (2 vs 3%). The study retention rate was similar in the levetiracetam and the placebo group (82 vs 75%). In a further multisite, 16-week RCT, levetiracetam XR (extended-release) has been evaluated in 130 very heavy drinking alcohol-dependent patients (defined as 10 or more drinks/drinking day for men, 8 or more drinks/drinking day for women at least 40% of the days during the last month) with a target dose of 2000 mg/day [40]. No significant differences between the levetiracetam XR and the placebo group were found in terms of percent of heavy-drinking days (LSMEAN 45.8 vs 41.2), percent of subjects with no heavy-drinking days (14 vs 18%) or in other secondary drinking outcomes. Except for fatigue (with a prevalence rate in the levetiracetam XR group of 53 vs 24% in the placebo group), the number of AEs did not differ between both groups. A total of 13 serious AEs occurred during the study period (3 in the levetiracetam XR group, 10 in the placebo group). The study retention rate was similar in the levetiracetam and the placebo group (78 vs 85%).

2.2.2 Topiramate

The anticonvulsant topiramate has been hypothesized to antagonize the rewarding effects of alcohol by inhibition of mesolimbic dopamine release, mediated through the facilitation of GABAergic function via a non-benzodiazepine site on the GABA-A receptor and antagonism of α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and kainate glutamate receptors [41-43]. In preclinical studies, topiramate has been shown to suppress ethanol drinking and to reduce stress-induced increases in alcohol consumption in mice [44,45]. Until now, four RCTs have been conducted in patients with alcohol dependence. In a first 12-week RCT [46], 150 patients received either topiramate in escalating dosages of 25 - 300 mg per day or placebo; both groups also received a standardized medication compliance management program. At study end, topiramate was significantly more effective than placebo in improving several drinking outcomes: patients receiving topiramate had 2.9 fewer drinks per day, 3.1 fewer drinks per drinking day, 28% fewer heavy-drinking days and 26% more days abstinent in comparison to patients who received placebo. AEs that were reported more frequently in the topiramate than in the placebo group were dizziness (28 vs 10%), paraesthesia (57 vs 19%), psychomotor slowing (27 vs 12%), memory or concentration impairment (19 vs 5%) and weight loss (55 vs 27%). The study completion rate did not differ between both groups. No serious AEs have been reported.

In a second, 14-week, multicenter RCT [47], topiramate has been evaluated in 371 alcohol-dependent patients with dosages up to 300 mg per day. In this trial, topiramate was more effective in reducing the percentage of heavy-drinking days from baseline to week 14 than placebo (mean difference 8.4%). Furthermore, topiramate significantly decreased the percentage of heavy-drinking days compared to placebo (mean difference: 16.2%). AEs that occurred more frequently in the topiramate group were paraesthesia (51 vs 11%), taste perversion (23 vs 5%), anorexia (20 vs 7%), difficulty with concentration/attention (15 vs 3%) and pruritus (10 vs 1%). Four participants of both treatment groups experienced a serious adverse event. At study end, the retention rates in both groups differed significantly (topiramate 61 vs placebo 77%), and the attrition rates due to AEs were 19% for the topiramate group and 4% for the placebo group.

In a third 12-week RCT, the efficacy and safety of topiramate (target dose 300 mg/day) have been compared with naltrexone (50 mg/day) and placebo in 155 alcohol-dependent patients who had received a 1-week detoxification prior to the initiation of the relapse prevention treatment [48]. Topiramate was superior to placebo in terms of ‘time to first relapse’ (7.8 vs 5.0 weeks), ‘cumulative abstinence duration’ (8.2 vs 5.6 weeks) and ‘weeks of heavy drinking’ (3.4 vs 5.9). No significant differences between topiramate and naltrexone were found. The overall incidence of AEs did not differ between the groups, and no serious AEs were reported. Dropout rates were significantly lower in the topiramate group compared to placebo (36 vs 57%).

Rubio and colleagues conducted a fourth RCT using topiramate for 12 weeks with a daily dose of 250 mg/day in a sample of 76 alcohol-dependent patients [49]. Patients of the topiramate group consumed fewer drinks per drinking day (6.5 vs 8.8), had a lower percentage of heavy-drinking days
which plays a crucial role in the development of behaviors in rodents. The GABA-B receptor is located within experimental evidence have demonstrated a role of GABA-B drinking behavior in rats\(^{56,57}\), the increase in alcohol intake found to suppress acquisition and maintenance of alcohol dependence \(^{55}\). In preclinical studies, baclofen was after a period of alcohol abstinence in rats\(^{58}\), and oral self-administration of alcohol in rats and mice trained to lever-press for alcohol\(^{59,60}\). In alcohol-dependent patients, four RCTs using baclofen have been published until now. In a first clinical trial, 39 alcohol-dependent patients received 30 mg of baclofen per day or placebo for 4 weeks\(^{61}\). Compared to placebo, there was a higher proportion of patients who achieved and maintained alcohol abstinence during the study in the baclofen group (70 vs 21%). Furthermore, the cumulative abstinence duration was significantly higher in the baclofen group (19.6 vs 6.3 days). The occurrence of AEs did not differ between both groups, and also, no serious AEs were reported. The study retention rate was similar in both groups.

A second RCT assessed the efficacy and safety of 30 mg of baclofen per day in 84 patients with alcohol dependence and comorbid liver cirrhosis during a 12-week study period\(^{62}\). In this trial, a significantly higher number of patients achieved and maintained abstinence in the baclofen group in comparison to the placebo group (71 vs 29%). The cumulative abstinence duration was significantly higher in the group of patients who received baclofen (62.8 vs 30.8 days). Tolerability of the study medication was similar in both groups, and no serious AEs were reported. The study retention rate did not differ between the baclofen and the placebo groups.

A third RCT has been conducted in 80 alcohol-dependent patients using 30 mg of baclofen per day or placebo for 12 weeks\(^{63}\). With regard to the endpoints ‘percentage of heavy-drinking days’ and ‘percentage abstinent days,’ no differences between the baclofen and the placebo group were found (26 vs 26%; 50 vs 51%). The rates of reported AEs and the study completion rate did not differ between both treatment groups. No serious AEs occurred during the study period.

In a fourth 12-week RCT, baclofen has been investigated in 42 alcohol-dependent patients using target dosages of 30 and 60 mg per day in comparison to placebo\(^{64}\). Regarding the endpoints ‘heavy-drinking days,’ ‘abstinent days,’ ‘time to first lapse’ and ‘time to first relapse,’ no significant differences between the groups were found. In a secondary analysis, patients receiving 30 mg of baclofen per day had a 53% reduction in the number of drinks per day and patients receiving 60 mg of baclofen had a 68% reduction in the number of drinks per day compared to placebo. Occurrence of AEs and study completion rates were similar in all treatment groups, and no serious AEs have been reported.

In line with a recent review of baclofen for the treatment of substance use disorders\(^{65}\), final conclusions regarding its efficacy and safety for the treatment of alcohol dependence can currently not be drawn due to the divergent results from past RCTs.

\textbf{2.2.3 Gabapentin}

Gabapentin, a non-benzodiazepine anticonvulsant GABA analog, has been evaluated in two clinical trials in alcohol dependence. A 4-week RCT in 60 patients investigated the compound using dosages of 300 mg twice per day\(^{50}\). Compared to placebo, patients receiving gabapentin showed a significant reduction in number of drinks per day and percentage of heavy-drinking days. Also, the percentage of abstinent days was significantly increased in this group. Side effects occurred in the form of insomnia, sleepiness and headache with no differences between the groups. No serious AEs were reported. The retention rate was higher in the gabapentin group compared to placebo.

In a recent 12-week RCT, gabapentin was administered in 150 alcohol-dependent patients with dosages of 900 and 1800 mg per day, respectively\(^{51}\). Patients receiving gabapentin showed a significantly higher rate of abstinence in comparison to placebo (17% in the 1800 mg/day group vs 11% in the 900 mg/day group vs 4% in the placebo group) with an NNT of 8 for 1800 mg/day. With regard to the co-primary endpoint ‘no heavy drinking’ rate, gabapentin was also superior compared to placebo (48% in the 1800 mg/day group vs 30% in the 900 mg/day group vs 23% in the placebo group; NNT = 5 for 1800 mg/day). Side effects such as headache, fatigue and insomnia were reported, but no significant differences between the treatment groups were found. Also, no serious drug-related AEs occurred during the study. The retention rates were similar in all groups.

\textbf{2.2.4 Baclofen}

Baclofen, a selective GABA-B receptor agonist, is approved for the treatment of spasticity resulting from various neurological conditions\(^{52}\). In the past years, several lines of experimental evidence have demonstrated a role of GABA-B receptors and baclofen in affecting different alcohol-related behaviors in rodents. The GABA-B receptor is located within the mesolimbic reward system of the brain and has been hypothesized to modulate dopaminergic neurotransmission\(^{53,54}\), which plays a crucial role in the development of alcohol dependence\(^{55}\). In preclinical studies, baclofen was found to suppress acquisition and maintenance of alcohol-drinking behavior in rats\(^{56,57}\), the increase in alcohol intake after a period of alcohol abstinence in rats\(^{58}\), and oral self-administration of alcohol in rats and mice trained to lever-press for alcohol\(^{59,60}\). In alcohol-dependent patients, four RCTs using baclofen have been published until now. In a first clinical trial, 39 alcohol-dependent patients received 30 mg of baclofen per day or placebo for 4 weeks\(^{61}\). Compared to placebo, there was a higher proportion of patients who
lower rate of cigarette smoking was detected for the varenicline group compared to placebo. Common side effects were headache, sleep disturbances, nausea and diarrhea, with no significant differences between the groups. No serious AEs were reported.

In a recent multicenter RCT, varenicline has been investigated in a sample of 200 alcohol-dependent patients [70]. Patients received 2 mg/day of varenicline or placebo for 13 weeks in combination with a computerized behavioral intervention. Compared to placebo, the varenicline group had lower weekly percent heavy-drinking days (adjusted mean diff.: 10.4), less drinks per day (4.4 vs 5.3) and drinks per drinking day (5.8 vs 6.8). Moreover, a lower number of cigarettes smoked per day was found for the varenicline group (7.4 vs 11.7). Side effects like nausea, abnormal dreams and constipation occurred with significantly higher rates in the varenicline group compared to the placebo group. Four serious AEs were reported (two in the varenicline, two in the placebo group). The retention rates were similar in both treatment groups (88% varenicline vs 84% placebo).

### 2.2.6 Prazosin

Based on the findings from preclinical studies showing that the α1 adrenergic antagonist prazosin reduces self-administration of ethanol in rats [71], the substance has been evaluated in a 6-week RCT in a small sample of 24 alcohol-dependent patients using a target dose of 16 mg/day. [72]. Patients who received prazosin reported fewer drinking days per week and fewer drinks per week during the final 3 weeks of the study. The average total number of drinking days was 0.9 for the prazosin group and 5.7 for the placebo group, and average total number of drinks was 2.6 for the prazosin group and 20.8 for the placebo group. Side effects were dizziness, lack of energy and drowsiness, with no differences between the groups. No serious AEs occurred during the treatment period. The retention rates were similar in both groups. Currently, several RCTs investigate the efficacy and safety of prazosin in alcohol dependence with and without comorbid PTSD.

### 2.2.7 Ondansetron

The selective 5-hydroxytryptamine 3 (5-HT₃) receptor antagonist ondansetron is an antiemetic drug that has been shown to reduce ethanol consumption in rodents [73]. In a first RCT, 271 patients received ondansetron in dosages of 1, 4 or 16 µg/kg twice per day for 11 weeks [74]. Compared to placebo, ondansetron decreased the number of drinks per day (1.9, 1.6 and 1.9 vs 3.3) and drinks per drinking day (4.8, 4.3 and 5.2 vs 6.9) in early-onset (< 25 years of age) but not in late-onset alcohol-dependent patients. Common side effects were headache, constipation, tachycardia and pruritus; no differences between the treatment groups were observed, and also, no serious AEs were reported. The dropout rates did not differ between the treatment groups.

A pharmacogenetic RCT investigated the efficacy of ondansetron (4 µg/kg twice per day) versus placebo in 283 alcohol-dependent patients over 11 weeks [75]. In this study, patients were subgrouped based on their 5'-HTTLPR and rs1042173 genotypes in the serotonin transporter (5-HTT) gene SLC6A4. The authors reported that carriers of SLC6A4-LL/TT who were treated with ondansetron had fewer standard drinks per drinking day (-2.6) and a percentage of days abstinent 17% higher in comparison to noncarriers of that genotype. However, no significant effect of ondansetron compared to placebo was found when patients were not subgrouped according to these genotypes. With regard to side effects, only fatigue occurred more frequently in the ondansetron group compared to placebo. Further side effects included insomnia, headache, appetite disturbances and diarrhea, with no significant differences between the groups. No medication-related serious AEs were reported. The retention rate did not differ among the treatment groups.

A further analysis within the same trial found that also polymorphisms of the HTR3A and HTR3B genes (which encode the 5-HT₃ receptor subunits A and B) predicted treatment response to ondansetron [76]. For patients carrying one or more of the genotypes rs1150226-AG and rs1176713-GG in HTR3A and rs17614942-AC in HTR3B, a mean difference in drinks per drinking day (2.5), percentage of heavy-drinking days (20.6%) and percentage of days abstinent (18.2%) for ondansetron versus placebo was found.

A recent 12-week RCT assessed the efficacy and safety of ondansetron in 102 alcohol-dependent patients using dosages of 16 mg/day [77]. No significant difference between the groups regarding the percentage of abstinent days (76 placebo vs 89% ondansetron) was found. Also, there was no significant difference regarding percentage of heavy-drinking days (10 placebo vs 6% ondansetron). Side effects occurred in the form of headache, dyspepsia and constipation, with no differences between the groups. No serious AEs were reported. The dropout rates did not differ significantly between the groups.

Table 1 shows the study characteristics and outcomes of RCTs investigating off-label medications in alcohol dependence.

### 3. Expert opinion

Based on the findings from two meta-analyses [6,7], the anti-craving substances acamprosate and naltrexone seem to represent efficacious and safe treatment options for alcohol dependence, but the reported effect sizes are only moderate.

Although disulfiram has been evaluated in several clinical studies, no clear conclusions can currently be drawn due to methodological limitations of these studies.

As a further treatment option, the opioid system modulator nalmefene has shown efficacy in several RCTs [22,24,25] and has recently been approved by the EMA for the reduction of alcohol consumption in alcohol-dependent patients. Thus, patients who are not able or willing to abstain from alcohol can be included in treatment programs aimed to reduce...
alcohol intake and dosing as needed, thereby offering a way to reduce harm in those patients.

RCTs (single- and multisite) using levetiracetam with dosages up to 2000 mg per day for the treatment of alcohol withdrawal syndrome or for the prevention of alcohol relapse could not show its efficacy in comparison to placebo [38-40]. Thus, there is currently no good evidence for its use as an off-label medication in the treatment of alcohol dependence.

In contrast, topiramate has repeatedly been shown to be effective in improving several drinking outcomes in four well-designed RCTs using dosages of up to 300 mg per day [46-49]. However, its widespread use in alcohol-dependent patients might be limited by the reported, frequently occurring side effects such as weight loss and cognitive impairments. Another disadvantage of topiramate in a clinical setting might be the long titration phase (up to 8 weeks for a dose of 300 mg/day). On the other hand, an improvement of physical and psychosocial well-being in alcohol-dependent patients receiving topiramate has been reported [78]. Taken together, the off-label use of topiramate can be considered as evidence based, but its future role in the treatment of alcohol dependence needs to be determined.

The anticonvulsant gabapentin has been evaluated positively in two independent RCTs using dosages up to 1800 mg/day [50,51]. Both trials also reported a high tolerability of gabapentin in alcohol-dependent patients. Thus, this compound possibly represents a further pharmacological treatment option in alcohol dependence, but these findings have to be replicated in future studies to draw final conclusions.

With regard to baclofen, four RCTs have reported a high tolerability in alcohol-dependent patients (also in patients with comorbid liver cirrhosis [62] – the EASL clinical practical guidelines recommend its use in patients with advanced alcoholic liver disease [79]) but conflicting results in terms of efficacy [61-64]. These inconsistent findings might possibly be related to the rather low dosages of baclofen used in these trials (30 – 60 mg/day). Based on the preclinical observations of a dose-dependent effect of baclofen on alcohol consumption in rats treated with dosages up to 3 mg/kg [80] as well as two case reports in alcohol-dependent patients receiving high-dose baclofen with up to 270 mg/day [81,82], three ongoing RCTs investigate the efficacy and safety of high-dose baclofen (up to 300 mg/day) in alcohol-dependent patients (Clinicaltrials.gov: NCT01266655; NCT01738282; NCT01604330). Since the evidence for baclofen in the treatment of alcohol dependence is low and its risk profile (high-dose baclofen) has not been extensively studied until now, the broadened use of baclofen can, currently, not be recommended.

Varenicline, a substance approved for smoking cessation, has shown mixed results in two recent RCTs in alcohol dependence [69,70]. If varenicline were to be found to be effective in future trials, this approach might be a useful extension of the currently available medications, given that nicotine dependence represents one of the most common comorbidities in alcohol-dependent patients [83].

Prazosin has shown efficacy in a pilot trial within a small sample of patients with alcohol dependence [72]. Currently, several clinical trials are ongoing to investigate its efficacy in patients with and without comorbid PTSD.

The antiemetic drug ondansetron has been assessed in three RCTs [74-77], showing efficacy in patients with early-onset alcohol dependence in one trial [74] and in two pharmacogenetic studies within one trial, when patients were subgrouped according to their genotypes of the serotonin transporter (5-HTT) gene and the 5-HT3 receptor subunits A and B genes [75,76]. Without subgrouping, no differences between the treatment groups were found. A further trial investigating ondansetron in alcohol dependence reported negative results [77]. Thus, first clinical evidence suggests that ondansetron might be a further pharmacological strategy for alcohol dependence when used within a pharmacogenetic treatment approach.

Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.
Current pharmacological treatment approaches for alcohol dependence

Bibliography

Papers of special note have been highlighted as either of interest (●) or of considerable interest (●●) to readers.


● An interesting study on the mechanism of action of acamprosate suggesting that calcium is the active component of acamprosate.


● This large multi-center trial assessed the efficacy of pharmacological and behavioural interventions as well as their combinations.


• A comprehensive review of disulfiram for the treatment of addictive diseases.


● This article discusses the possible mechanisms(s) of action of disulfiram in the treatment of cocaine dependence focusing on its ability to inhibit dopamine β-hydroxylase (DBH).


31. Margineanu DG, Kligaard H. Levetiracetam has no significant effect on alcohol.
41. Johnson BA. Recent advances in the development of treatments for alcohol and cocaine dependence: focus on topiramate and other modulators of GABA or glutamate function. CNS Drugs 2005;19(10):873-96
43. Moghaddam B, Boliniao ML. Glutamatergic antagonists attenuate ability of dopamine uptake blockers to increase extracellular levels of dopamine: implications for tonic influence of glutamate on dopamine release. Synapse 1994;18(4):337-42
44. Farook JM, Lewis B, Littleton JM, Barron S. Topiramate attenuates the stress-induced increase in alcohol consumption and preference in male C57BL/6J mice. Physiol Behav 2009;96(1):189-93
60. Besheer J, Lepoutre V, Hodge CW. GABA(B) receptor agonists reduce operant ethanol self-administration and enhance ethanol sedation in C57BL/6J mice. Psychopharmacology (Berl) 2004;174(3):358-66

• The first RCT using low-dose baclofen in a sample of alcohol-dependent patients with comorbid liver cirrhosis.


73. Tomkins DM, Le AD, Sellers EM. Effect of the 5-HT3 antagonist ondansetron on voluntary ethanol intake in rats and mice maintained on a limited access procedure. Psychopharmacology (Berl) 1995;117(4):479-85


• This study shows the efficacy of ondansetron within a pharmacogenetic treatment approach.


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