Medication Development for Alcohol Use Disorder: A Focus on Clinical Studies

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Abstract

Compared to other medical disorders, including other brain diseases, the number of medications approved for alcohol use disorder (AUD) is very small. Disulfiram, naltrexone (oral and long-acting), and acamprosate are approved by the US Food and Drug Administration (FDA) to treat patients with AUD. These medications are also approved in other countries, including in Europe, where the European Medicines Agency (EMA) also approved nalmefene for AUD. Furthermore, baclofen was recently approved for AUD in France. These approved medications have small effect sizes, which are probably the consequence of the fact that they only work for some patients, yet a personalized approach to match the right medication with the right patient is still in its infancy. Therefore,

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research is needed to expand the armamentarium of medications that clinicians can use to treat their patients, as well as to better develop personalized approaches. This book chapter reviews other medications, beyond those approved by the FDA, that have shown efficacy in clinical trials, as well as medications which are still in the early stages of evaluation in human studies.

Keywords
Alcohol use disorder · Clinical studies · Medication development · Pharmacotherapy

1 Introduction

Addictions, including alcohol use disorder (AUD), represent a chronic brain disorder characterized by a compulsive-like seeking behavior and consumption of excessive amounts of alcohol despite the knowledge of its negative consequences. As many other medical disorders, AUD represents a heterogenous disease and is the product of complex gene × environment interactions. There have been significant advances in the neuroscience field that have shed light on the neurobiological pathways that underline the development and maintenance of AUD. As reviewed in the previous chapter (McCool and McGinnis 2019), we have now a much better understanding of the molecular and neurobiological basis of AUD, and this knowledge has been instrumental in identifying important druggable targets. Studying these targets has resulted, in turn, in the development of medications that, combined with psychosocial and behavioral interventions, may help patients with AUD to reduce or quit drinking and prevent relapse.

In the USA, three medications have been approved by the US Food and Drug Administration (FDA) for the treatment of AUD: disulfiram, naltrexone (oral and extended-release injectable), and acamprosate. These medications are also approved in other countries, including in Europe, where the European Medicines Agency (EMA) also approved nalmefene for AUD. Furthermore, baclofen was recently approved for AUD in France. As it is often the case in medication development, especially in the neuroscience field, clinical trials testing these medications have from time to time generated conflicting results, therefore questioning the efficacy of these medications. Nonetheless, several meta-analyses do support the efficacy of these medications to treat patients with AUD. In particular, one of the most recent and comprehensive meta-analyses indicates that both acamprosate and oral naltrexone are associated with reduction in return to drinking, with no significant differences between these two medications (Jonas et al. 2014).

Compared to other medical disorders, including other brain diseases, the number of medications approved for AUD is very small. Furthermore, their effect sizes (e.g., numbers needed to treat) are small, which is probably the consequence of the fact that these medications only work for some patients; however, a personalized approach to match the right medication with the right patient is still in its infancy (e.g., for a recent systematic review on potential subgroups who may respond better to naltrexone, see Garbutt et al. 2014). Therefore, research is needed to expand the

armamentarium of medications that clinicians can use to treat their patients, as well as to better develop personalized approaches. Efforts made to test other medications beyond those approved by the FDA are reviewed in this book chapter. Specifically, here we briefly review medications that have exhibited efficacy in alcohol treatment clinical trials and examples of medications which are still in the early stages of evaluation in human studies.

1.1 Medications That Have Shown Efficacy in Research Clinical Studies for AUD[1]

1.1.1 ABT-436 (Vasopressin V1b Receptor Antagonist)

Preliminary animal studies suggest that blocking the type 1b receptor (V1b) of the antidiuretic hormone vasopressin results in a reduction in alcohol drinking (Edwards et al. 2011; Zhou et al. 2011). Following on these preclinical findings, ABT-436 800 mg/day, a novel selected V1b receptor antagonist, was evaluated in a 12-week multi-site randomized clinical trial (RCT) of 150 alcohol-dependent individuals (Ryan et al. 2017). ABT-436 significantly increased the percent of days abstinent compared with placebo, while there were no significant differences in heavy drinking days nor on other measures of drinking or alcohol craving. Furthermore, in subgroup analyses, individuals reporting higher baseline levels of stress responded better to ABT-436 than to placebo. Tolerability and safety of ABT-436 in this RCT were excellent. Diarrhea was the only side effect to be significantly more frequent in the ABT-436 group than the placebo group, although only four participants stopped ABT-436 as a result of gastrointestinal complaints. The ABT-436 group, compared with the placebo group, had greater rates of anxiety and nausea, although these differences were only at a statistical trend level. Overall, additional future studies with this compound are warranted, but unfortunately, the manufacturer discontinued development of this compound.

1.1.2 Aripiprazole

Aripiprazole is an atypical, antipsychotic drug, approved by the FDA to treat schizophrenia and bipolar disorder and as adjunct treatment for major depression (Litten et al. 2016). Aripiprazole has multiple pharmacological mechanisms, including acting as a partial agonist for the dopamine D_2 and serotonin 5-HT_{1A} receptors and as an antagonist to the 5-HT_2 receptor (Fleischhacker 2005). Common side effects of aripiprazole include fatigue, insomnia, restlessness, somnolence, anxiety, and disturbances in attention.

Human laboratory studies suggest that aripiprazole may affect drinking behavior. Kranzler et al. (2008) reported that aripiprazole (2.5 mg and 10 mg per day) increased alcohol sedating effects and, to a lesser degree, reduced the euphoric effects ($N = 18$). Voronin et al. (2008) showed that, compared to placebo,

[1]Listed in alphabetical order.

aripiprazole (up to 15 mg per day) reduced alcohol drinking but had no effect on self-reported "high," intoxication, or alcohol craving ($N = 30$). Furthermore, Myrick et al. (2010) conducted a neuroimaging study ($N = 30$) which indicated that aripiprazole (15 mg per day) blunted alcohol cue-induced brain activity in the right ventral striatum. A recent human laboratory study of 99 alcohol-dependent individuals found that aripiprazole (15 mg per day) had no main effect on alcohol drinking during the naturalistic outpatient period (Anton et al. 2017). However, aripiprazole significantly decreased alcohol self-administration among individuals with low self-control and delayed the return to drinking in those with high impulsivity compared with placebo (Anton et al. 2017), suggesting the need for precision medicine to elucidate the efficacy of aripiprazole. Further supporting the importance of this future direction, an additional neurogenetic analysis from the same human laboratory study suggested that polymorphisms in the dopamine transporter 1 (DAT1) and other dopamine-related genes may moderate aripiprazole effects on alcohol cue-elicited striatal activation and alcohol self-administration (Schacht et al. 2018).

In a 12-week multi-site RCT ($N = 295$), aripiprazole (titrated up to 30 mg per day) was effective in reducing the number of drinks per drinking day compared with the placebo group and also reduced the blood concentrations of carbohydrate-deficient transferrin (CDT), a biomarker of excessive alcohol use, at weeks 4 and 8 (Anton et al. 2008). However, aripiprazole was not superior to placebo in percent of days abstinent, number of heavy drinking days, and time to first drinking day (Anton et al. 2008). In addition, 15 mg per day may be an optimal dose to test, given the higher dropout rate in the active group, compared to placebo, especially with the 30 mg dose.

At present, a 12-week RCT is under way in outpatients with bipolar I or II disorder (depressed or mixed mood state) and alcohol use disorder, with active alcohol use (NCT02918370).

1.1.3 Baclofen

Several animal studies support that the $GABA_B$ agonist baclofen, currently approved by the FDA for the treatment of muscle spasticity, may play a role in AUD (for a review, see Colombo and Gessa 2018). From a biobehavioral mechanism standpoint, several human laboratory studies suggest that baclofen may affect alcohol drinking by changing the subjective effects of alcohol. These observations have been reported in human laboratory studies with acute baclofen administration (40 mg or 80 mg) in nondependent heavy drinkers ($N = 18$; Evans and Bisaga 2009), as well as in a pilot human laboratory study ($N = 14$; Leggio et al. 2013) and in a relatively larger follow-up human laboratory study ($N = 34$, Farokhnia et al. 2017, 2018) with alcohol-dependent heavy drinkers treated with baclofen 30 mg per day for approximately a week.

In clinical trials, following a positive small 4-week RCT with baclofen 30 mg per day in alcohol-dependent patients ($N = 39$; Addolorato et al. 2002), a relatively larger 12-week RCT ($N = 84$) was conducted in alcohol-dependent patients with liver cirrhosis (Addolorato et al. 2007). This latter RCT indicated that baclofen

30 mg per day was significantly more effective, as compared to placebo, in increasing total alcohol abstinence, increasing the number of days abstinent, and reducing alcohol craving. An additional analysis also showed that, despite the smaller sample analyzed ($N = 24$), baclofen still was significantly effective in promoting total alcohol abstinence in a subgroup of patients with alcohol dependence, liver cirrhosis, and hepatitis C infection (Leggio et al. 2012). In contrast, another 12-week RCT conducted in 80 patients with alcohol dependence (without liver disease) did not find differences between baclofen 30 mg per day and placebo in any of the alcohol-related outcomes (Garbutt et al. 2010).

The mixed results of these studies suggest that baclofen might be an effective medication only in those patients with higher severity of alcohol dependence (Leggio et al. 2010). Consistent with this hypothesis, a 12-week RCT ($N = 30$) with baclofen (80 mg per day) in alcohol-dependent individuals who also were smokers indicated that baclofen, compared with placebo, significantly increased the number of days abstinent from alcohol and tobacco co-use, and this effect was stronger in those patients with higher severity of alcohol dependence (Leggio et al. 2015). Furthermore, it is possible that the fact that baclofen was effective in those alcohol-dependent patients with liver cirrhosis (Addolorato et al. 2007), but not in those without (Garbutt et al. 2010), may indirectly reflect the different severity of alcohol dependence of these patients. Two recent RCTs support this interpretation. Specifically, a 12-week RCT with baclofen 30 mg per day in 180 veteran patients with hepatitis C virus (HCV) coinfection did not find differences between baclofen and placebo on alcohol-related outcomes; notably, the baseline levels of alcohol were quite low in this trial, reflecting an overall low severity of dependence (Hauser et al. 2017). In contrast, another 12-week RCT ($N = 104$) found a significant effect of baclofen (either 30 mg per day or 75 mg per day, without a dose-response effect) on alcohol-related outcomes in patients (with and without alcoholic liver disease), and the effect of baclofen was stronger in those alcohol-dependent patients with alcoholic liver disease than those without (Morley et al. 2018a).

Some anecdotal case reports suggested that significantly higher doses of baclofen, compared to those used in previous RCTs, may be effective in facilitating alcohol abstinence, i.e., up to 140 mg per day (Bucknam 2007) or even up to 300 mg per day (Ameisen 2005). Despite the anecdotal nature of these reports, they prompted significant mass media interest and attention in the scientific community, culminating in a few RCTs that tested high doses of baclofen. Muller et al. (2015) conducted an RCT with baclofen up to 250 mg per day in 56 alcohol-dependent individuals and found that baclofen, compared to placebo, increased the abstinence rate and cumulative abstinence duration. In contrast, Beraha et al. (2016) conducted an RCT of baclofen in 151 alcohol-dependent individuals who were administered a relatively high dose (150 mg per day), a lower dose (30 mg per day), or placebo and found no differences in time to first relapse or abstinence rates among the three groups. In another multi-site 24-week RCT, baclofen (180 mg per day) or placebo was administered to 320 alcohol-dependent individuals (Reynaud et al. 2017). Although the baclofen and placebo group did not differ significantly for abstinence or drinks per day, baclofen was more effective than placebo in reducing drinking in

individuals who were drinking heavily at baseline. In conclusion, whether higher doses are more effective remains unclear and controversial, although higher doses may have a greater risk of adverse events, the most common being somnolence, sleep disorders, asthenia, and dizziness. The French drug administration agency recently approved the use of baclofen for AUD, but it limited the approved dose to up to 80 mg per day (Medical Press 2018).

Two RCTs have recently been completed but results have not been published yet. A 16-week RCT conducted in the USA compared placebo to baclofen 30 mg per day and baclofen 90 mg per day in a community sample of alcohol-dependent patients (NCT01980706). Another RCT conducted in France with alcohol-dependent patients managed by primary care physicians compared placebo to baclofen up to 300 mg per day during a 52-week period (NCT01604330).

Notably, a recent international consensus statement highlighted the potential efficacy of baclofen, calling for additional larger studies with baclofen but also emphasizing the importance of tailoring doses based on safety, tolerability, and efficacy (Agabio et al. 2018).

1.1.4 Gabapentin

Gabapentin is approved by the FDA for the treatment of seizures, neuropathic pain, and restless legs syndrome. Its mechanism of action is thought to be related to its inhibition of voltage-gated calcium channels, which indirectly modulate GABA activity (Sills 2006).

An initial human laboratory study with 33 alcohol-dependent individuals indicated that gabapentin (1,200 mg per day) was effective in reducing alcohol craving and improving sleep quality (Mason et al. 2009).

A few short-term small RCTs have indicated the potential efficacy of gabapentin in AUD patients (Furieri and Nakamura-Palacios 2007; Brower et al. 2008). It has been also suggested that gabapentin may work best in patients with significant withdrawal symptoms. Specifically, compared to placebo, gabapentin (up to 1,200 mg per day for about 6 weeks and combined with flumazenil 20 mg per day for first 2 days) led to an increase in the percent of days abstinent and a longer delay to heavy drinking in 60 alcohol-dependent patients; however, this effect was limited to those patients with more alcohol withdrawal symptoms before treatment (Anton et al. 2009).

Two larger single-site RCTs ($N = 150$ in each trial) further support the role of gabapentin in AUD. The first was a 16-week RCT which combined and compared gabapentin to naltrexone and showed that the combined medication group experienced a longer delay to heavy drinking, less heavy drinking days, and fewer drinks per drinking days than the group taking naltrexone alone or receiving placebo (Anton et al. 2011). Additionally, the patients with the combined gabapentin/naltrexone reported significantly better sleep than the other two groups (Anton et al. 2011). The second trial was a 12-week RCT of gabapentin testing two doses: 900 mg per day and 1,800 mg per day. In this second trial, compared to placebo, gabapentin significantly improved the rates of abstinence and no heavy drinking with greater efficacy in the 1,800 mg per day group than the 900 mg per day group

(Mason et al. 2014). Furthermore, gabapentin reduced alcohol craving and improved mood and sleep (Mason et al. 2014).

More recently, results from another RCT conducted in Thailand further supported the efficacy of gabapentin (Chompookham et al. 2018). Specifically, 112 alcohol-dependent patients were treated with either placebo or gabapentin (at least 300 mg per day) for 12 weeks. Gabapentin significantly reduced the percent of heavy drinking days per week and the weekly drinking days (Chompookham et al. 2018). On the other hand, no superiority of gabapentin compared to placebo was found in a large recent RCT in the USA. The latter was a multi-site 6-month RCT in 346 alcohol-dependent patients treated with placebo or gabapentin enacarbil extended-release, a prodrug formulation of gabapentin designed to increase its bioavailability. This trial did not show efficacy of gabapentin enacarbil, compared to placebo, in any of the alcohol-related primary or secondary outcomes (Falk et al. 2019a). A pharmacokinetic analysis, suggested that specific formulation used in this RCT may have resulted in lower than expected absorption of the active medication (Falk et al. 2019a).

Common side effects of gabapentin in these trials included fatigue, insomnia, and headaches. Furthermore, it is important to mention that, while gabapentin is considered to have no abuse potential, a recent report indicates that gabapentin potentially may be misused in individuals with substance use disorder, especially those who abuse opioids (Smith et al. 2016).

Finally, a 16-week RCT is currently ongoing to investigate if gabapentin up to 1,200 mg per day has efficacy in a sample of patients with DSM-5 criteria for AUD and for history of alcohol withdrawal (NCT02349477).

1.1.5 Ondansetron

Ondansetron is a selective serotonin 5-HT_3 receptor antagonist approved by the FDA for the treatment of nausea and vomiting. Initial human laboratory studies indicated that ondansetron reduces the desire to drink and augments the biphasic (i.e., stimulating and sedating) effects of alcohol ($N = 16$ in Johnson et al. 1993; $N = 15$ in Kenna et al. 2009; $N = 12$ in Swift et al. 1996).

In early clinical trials, an RCT by Sellers et al. (1994) tested ondansetron (0.25 mg or 2 mg per day) in 71 alcohol-dependent individuals and found that, compared to placebo, ondansetron significantly decreased alcohol intake in a subgroup of individuals with relatively lower baseline drinking (10 or less drinks per drinking day). Notably, an unexpected reversed dose effect was observed such that the 0.25 mg dose was more efficacious than the 2 mg dose. A subsequent larger 11-week RCT ($N = 271$) tested ondansetron 2 μg/kg, 8 μg/kg, or 32 μg/kg per day in alcohol-dependent individuals divided as early- and late-onset of alcoholism (25-year-old or younger vs. >25-year-old). This trial showed efficacy of ondansetron only in early-onset patients, with 8 μg/kg being the most effective dose (Johnson et al. 2000).

The selective effect of ondansetron in the early-onset subpopulation raised the question of whether pharmacogenetics may further shed light on the potential selective role of ondansetron in AUD. For example, the *SLC6A4* gene encodes the

serotonin transporter, 5-HTT, and the *SLC6A4* promoter contains a functional polymorphic region (5′-regulatory region of the 5-HTT; 5′-HTTLPR) with a long form (L) that possesses an additional 44 base pairs that are absent in the short variant (S). Alcohol-dependent individuals with the LL genotype, compared with those with the SS genotype, have significantly less 5-HT uptake and reduced paroxetine binding capacity (Javors et al. 2005; Johnson et al. 2008). Notably, 5′-HTTLPR polymorphisms have been associated with several psychiatric disorders including AUD. Johnson et al. (2011) performed a 11-week RCT of ondansetron (8 μg/kg per day) in 283 alcohol-dependent individuals randomized to 3 different genotypes: LL, LS, and SS genotypes of the main results of this trial showed that LL genotype patients treated with ondansetron had significantly lower drinks per drinking day and higher percentage of days abstinent, as compared to those treated with ondansetron but with the LS/SS genotypes and to those treated with placebo (Johnson et al. 2011). In a subsequent analysis from the same RCT, Johnson et al. (2013) found additional functional genetic polymorphisms in the *HTR3A* and *HTR3B* genes that encode the 5HT3 receptor, including AC polymorphism in the rs17614942 portion in the *HTR3B* gene and AG and GG polymorphisms in the rs1150226 and rs1176713 portions of the *HTR3A* gene, respectively. Ondansetron was more effective than placebo in reducing the number of drinks per drinking day and the number of heavy drinking days and increasing the percent of days abstinent in people carrying one or more of these genetic variants. However, it is important to keep in mind that the potential functionality of rs1150226 and rs1176713 of *HTR3A* and rs17614942 of *HTR3B* is unknown, and therefore their putative molecular mechanisms need to be elucidated. It has been speculated that all three of these polymorphisms may alter mRNA expression levels (Johnson et al. 2013). Finally, consistent with Johnson et al. (2011), Kenna et al. (2014a) conducted a laboratory study of ondansetron and sertraline in 77 nontreatment-seeking alcohol-dependent individuals and found that ondansetron was effective in reducing the amount of drinking per drinking day in LL genotype individuals. The same team also found that female, but not male, participants who had the LL genotype, and equal or greater than seven exon III repeats on the dopamine receptor D4 gene (DRD4), had significantly reduced alcohol intake after taking ondansetron (0.5 mg per day for 3 weeks) (Kenna et al. 2014b). Notably, expression of the 7-repeat allele of DRD4 is associated with a blunted effect of dopamine on cAMP levels in comparison to the 4-repeat allele, with almost a threefold increase in dopamine concentration required to achieve the same level of dopamine-induced cAMP inhibition as the 4-repeat allele (Asghari et al. 1995; Oak et al. 2000). A meta-analysis suggests DRD4 VNTR variation may be a risk factor for problematic alcohol use; however there is a critical need for studies with larger and more inclusive samples that account for sex and genetic ancestry to fully understand this relationship (Daurio et al. 2019).

From a safety standpoint, ondansetron has been typically very well-tolerated in these clinical trials with alcohol-dependent individuals. An FDA safety precaution warns that cardiac QT prolongation is possible at doses typically used for its approved indication (nausea and vomiting; https://www.fda.gov/Drugs/DrugSafety/ucm271913.htm). However, this side effect may not be evident at the lower doses used in the trials with AUD individuals.

The promising pharmacogenetic effect of ondansetron is currently under further investigation in an ongoing multi-site 16-week RCT testing ondansetron (0.33 mg, twice daily) versus placebo in alcohol-dependent patients prospectively randomized based on selected genotypes at the serotonin transporter and receptor genes (NCT02354703).

1.1.6 Prazosin and Doxazosin

Prazosin is a selective α-1 adrenergic receptor antagonist approved by the FDA to treat hypertension and benign prostatic hyperplasia. The off-label use of prazosin in patients with PTSD led to the anecdotal observation that some patients taking prazosin reduced or even stopped drinking alcohol, hence raising the question whether prazosin may be useful in AUD patients. A small treatment 8-week RCT ($N = 24$; Simpson et al. 2009) and a preliminary human laboratory study ($N = 17$; Fox et al. 2012), both conducted in alcohol-dependent individuals, suggested the potential efficacy of prazosin up to 16 mg per day, compared to placebo, in reducing alcohol drinking and craving. Subsequently, Simpson et al. (2015) and Petrakis et al. (2016) conducted two RCTs of prazosin (16 mg per day) in alcohol-dependent patients with comorbid PTSD: one study was a 6-week RCT in 30 patients and found a significant effect of prazosin in reducing alcohol-related outcomes (Simpson et al. 2015). The other was a 13-week RCT in 96 patients and did not find an effect of prazosin versus placebo on the alcohol-related outcomes (Petrakis et al. 2016). Furthermore, neither study found prazosin improving PTSD symptoms.

More recently, Simpson et al. (2018) conducted a relatively larger RCT ($N = 92$) with alcohol-dependent patients (without PTSD) randomized to either prazosin up to 16 mg per day or placebo. Results indicated that the rates of drinking and heavy drinking over time decreased to a larger extent in the prazosin group compared to placebo. Consistent with previous reports, some side effects like drowsiness were more common in the prazosin group.

Similar to prazosin, the α-1 adrenergic receptor antagonist doxazosin is also approved by the FDA to treat hypertension and benign prostatic hyperplasia. However, compared to prazosin, doxazosin has a longer half-life; hence it requires only once-a-day dosing compared with prazosin's two to three dosages per day. Furthermore, frequency of side effects (e.g., drowsiness, dizziness, fatigue) is lower in doxazosin than prazosin; and, unlike prazosin, doxazosin may be taken with or without food (Leggio and Kenna 2013). These properties of doxazosin have made doxazosin a potential intriguing candidate for AUD, given that medication adherence is a critical challenge both in RCTs and in clinical practice. For this reason, Kenna et al. (2015) conducted a 10-week RCT of doxazosin (up to 16 mg per day) in 41 alcohol-dependent individuals. While no significant differences were found in the drinking outcomes between the doxazosin and placebo groups in the whole sample, in a priori subgroup analysis, doxazosin-treated patients with higher density of family history of alcoholism presented with a significant decrease in drinks per week and heavy drinking days per week. Furthermore, in a later analysis from the same RCT, Haass-Koffler et al. (2017) found that doxazosin, compared with placebo, reduced drinks per week and heavy drinking days per week in a subgroup of

patients who had higher baseline standing blood pressure. Notably, these latter results have been recently replicated in a 6-week RCT with prazosin ($N = 36$; 16 mg per day) in AUD (Wilcox et al. 2018). Additional work is needed to identify optimal personalized approaches for the use of alpha-1 receptor blockers for AUD (Haass-Koffler et al. 2018b).

1.1.7 Topiramate and Zonisamide

Topiramate is approved by the FDA for treatment of seizures and migraines. Furthermore, the FDA recently approved the combination of topiramate and phentermine for obesity. Topiramate antagonizes α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and kainate receptors, facilitates GABA activity, blocks L-type calcium channels, reduces voltage-dependent sodium channel activity, and inhibits carbonic anhydrase (Arnone 2005).

Human laboratory studies with individuals not seeking treatment for alcohol problems showed that topiramate at doses of 200 mg per day or 300 mg per day reduced alcohol craving, alcohol drinking (heavy drinking or drinking days), and the stimulating effects of alcohol (Miranda et al. 2008, 2016; Haass-Koffler et al. 2018a). Small RCTs with treatment-seeking individuals with AUD also support a role of topiramate in reducing several alcohol drinking outcomes at doses of 300 mg per day (Knapp et al. 2015) and 100 mg per day (Martinotti et al. 2014).

Furthermore, two larger RCTs (a single-site 12-week trial with 150 alcohol-dependent patients and a multi-site 14-week trial with 371 alcohol-dependent individuals) further indicate that topiramate, up to 300 mg per day, resulted in a significant reduction in craving, drinks per day, and heavy drinking days and a significant increase in abstinent days (Johnson et al. 2003, 2007). Side effects included dizziness, paresthesia, psychomotor slowing, memory or concentration impairment, nervousness, taste perversion, pruritus, and weight loss (Johnson et al. 2003, 2007). By contrast, topiramate did not show efficacy in another 12-week RCT testing topiramate 200 mg per day in 129 alcohol-dependent male smokers who were abstinent for 6 months at study entry (Anthenelli et al. 2017). Overall, these RCTs suggest that topiramate may be more effective in initiating and facilitating abstinence in current drinkers rather than in preventing relapse in individuals who are already abstinent (Swift 2003; Litten et al. 2018).

Additional studies suggest a potential pharmacogenetic effect for topiramate in AUD. An initial pilot human laboratory study showed that heavy drinkers with the CC genotype of a single nucleotide polymorphism (SNP), rs2832407, of the GRIK1 gene encoding the glutamate kainate GluK1 receptor had significantly fewer topiramate-related side effects and lower topiramate blood concentrations (Ray et al. 2009). More recently, a 12-week RCT with 138 alcohol-dependent individuals showed that topiramate 200 mg per day led to a significant reduction in heavy drinking days and a significant increase in abstinent days, and these effects were moderated by the rs2832407 SNP, such that topiramate was effective in the CC genotype, but not in the AC and AA genotypes (Kranzler et al. 2014).

Like topiramate, zonisamide is FDA-approved as an adjunct treatment for partial seizures and has similar pharmacological actions, i.e., blocking voltage-sensitive

sodium channels and T-type calcium channels, facilitating GABA activity, and serving as a weak inhibitor of carbonic anhydrase (Kothare and Kaleyias 2008). Compared to topiramate, the side effect profile of zonisamide seems more favorable (Kothare and Kaleyias 2008), hence the interest in testing it for AUD. In an initial placebo-controlled human laboratory study of risky drinkers, zonisamide reduced alcohol craving and alcohol self-administration (Sarid-Segal et al. 2009). Similarly, a 12-week RCT with 40 alcohol-dependent patients indicated that, compared to placebo, zonisamide, up to 500 mg per day, significantly reduced the number of heavy drinking days, drinks per week, and alcohol craving (Arias et al. 2010). Finally, Knapp et al. (2015) conducted a multigroup 14-week RCT with 85 alcohol-dependent individuals comparing zonisamide (400 mg per day), topiramate (300 mg per day), levetiracetam (200 mg per day), and placebo. This study indicated comparable results for both zonisamide and topiramate in reducing percent of drinking days per week, drinks per day, and heavy drinking per week (levetiracetam was only effective in decreasing the percent of heavy drinking days per week). Moreover, zonisamide had a more favorable side effect profile than topiramate.

Larger RCTs are currently ongoing to test the efficacy of zonisamide in AUD (NCT02900352; NCT02368431) and to test the pharmacogenetic-based efficacy of topiramate in AUD (NCT02371889).

1.1.8 Varenicline

Varenicline, a partial agonist at α4β2 and a full agonist at α7, nicotinic acetylcholine receptors (Mihalak et al. 2006), is currently approved by the FDA for smoking cessation. Several proof-of-concept human laboratory studies in alcohol-dependent individuals have indicated that varenicline reduced drinking, alcohol craving, alcohol self-administration, and the subjective reinforcing effects of alcohol ($N = 20$ in McKee et al. 2009; $N = 77$ in Roberts et al. 2017a; $N = 60$ in Roberts et al. 2017b; and $N = 35$ in Schacht et al. 2014). Small treatment randomized clinical trials have also tested varenicline (titrated up to 2 mg per day) in heavy drinkers with AUD. These preliminary studies found that, compared to placebo, varenicline reduced alcohol craving ($N = 30$ in Fucito et al. 2011; $N = 40$ in Plebani et al. 2013), heavy drinking days (Fucito et al. 2011), and drinks per week ($N = 64$; Mitchell et al. 2012).

More recently, these studies led to a larger 13-week multi-site RCT of varenicline (2 mg per day) in alcohol-dependent individuals ($N = 200$), approximately 40% of whom were smokers (Litten et al. 2013). Compared to placebo, varenicline significantly reduced alcohol craving and alcohol consumption outcomes, including heavy drinking days, drinks per day, and drinks per drinking day. Furthermore, a subgroup analysis suggested that varenicline was most effective in individuals with less severe AUD and in those who reduced their smoking (Falk et al. 2015). However, another multi-site 12-week RCT ($N = 160$) conducted in Sweden did not show the same efficacy in favor of varenicline. Specifically, there were no differences in self-reported drinking outcomes or reduction in smoking between the varenicline and placebo groups. However, there were significant reductions in alcohol craving, the number of reported AUD symptoms (measured using the Alcohol Use Disorders

Identification Test [AUDIT]), and blood levels of phosphatidyl ethanol (PEth), a specific biomarker of alcohol consumption (de Bejczy et al. 2015).

Given that varenicline is approved for smoking cessation, a recent two-site RCT in the USA tested its efficacy in patients with alcohol use disorder and comorbid smoking seeking alcohol treatment and further evaluated its secondary effects on smoking abstinence. A total of 131 patients were treated with either varenicline 2 mg per day or placebo (O'Malley et al. 2018). There were no differences between the two groups on the percentage of heavy drinking days in the whole group, although a subgroup analysis indicated that varenicline may reduce the percentage of heavy drinking days in men more than in women. Furthermore, varenicline increased smoking abstinence in the overall sample (O'Malley et al. 2018).

Consistent with this latter trial, the potential role of varenicline for tobacco and alcohol use comorbidity has been also investigated in combination with naltrexone. Indeed, based on the promising results of an initial human lab study with heavy drinking, daily smokers (Ray et al. 2014), a larger RCT is ongoing to test concomitant smoking cessation and alcohol use reduction using a three group medication design consisting of varenicline alone (2 mg per day), naltrexone alone (50 mg per day), and the combination of both varenicline and naltrexone at the same doses as in the monotherapy conditions (NCT02698215).

Varenicline is generally well-tolerated with typically mild to moderate side effects which include nausea, constipation, and abnormal dreams. Notably, the FDA recently removed the box warning on varenicline about possible neuropsychiatric side effects but issued a warning that varenicline may change the way patients respond to alcohol, affecting their ability to tolerate its effects. Moreover, in rare accounts, seizures have been reported in patients taking varenicline (https://www.fda.gov/Drugs/DrugSafety/ucm436494.htm).

1.2 Other Promising Medications or Compounds for AUD

In addition to the medications above, preclinical or preliminary proof-of-concept human studies support the potential role of other medications on novel compounds for the treatment of AUD (for details, see also Litten et al. 2018). Examples are the glucocorticoid receptor antagonist mifepristone (Richardson et al. 2008; Simms et al. 2012; Vendruscolo et al. 2012; Vendruscolo et al. 2015), the hormone oxytocin (for reviews, see Kenna et al. 2012; Lee et al. 2016), the nonselective phosphodiesterase inhibitor ibudilast (Bell et al. 2013; Ray et al. 2017), D-cycloserine (a partial agonist at the glycine modulatory site of the glutamate NMDA receptor; Seif et al. 2015; Watson et al. 2011; Hofmann et al. 2012; MacKillop et al. 2015, Kiefer et al. 2015), *N*-acetylcysteine (Morley et al. 2018b), and blockade of the receptor of the hormone ghrelin (Lee et al. 2018; see also reviews: Zallar et al. 2017; Morris et al. 2018; Farokhnia et al. 2019).

2 Conclusions

This is an exciting time for medication development for AUD and addiction in general. As basic neuroscience research starts to unfold the mechanisms that underline the development and maintenance of AUD, new targets are identified. These targets may lead to the development of novel medications to be tested for their safety and efficacy in patients with AUD. As such, the discovery of novel and more effective targets is clearly a high priority. This is of paramount importance, given that at present, we only have three medications approved by the FDA for AUD.

However, the history of these approved medications, as well as of the additional medications tested in the past decades and reviewed in this chapter, also tells us that no medication will work for all patients with AUD. AUD is a complex and heterogenous disorder; hence it is conceivable that different medications may work best in certain subgroups of patients. Indeed, the challenge rests on identifying precision medicine approaches where the right medication is matched with the right patient (Litten et al. 2015, 2016, 2018). The literature reviewed above provides some examples, including pharmacogenetics (e.g., ondansetron and topiramate); family history or physiological markers (prazosin and doxazosin); severity of dependence and/or medical comorbidity, like liver disease (baclofen); and severity of alcohol withdrawal (gabapentin). However, it is very unlikely that a single factor is able to predict a positive outcome for a specific medication. Rather, it is conceivable that multiple factors will need to be taken into account toward the identification of effective precision medicine approaches (Heilig and Leggio 2016; Litten et al. 2018).

Another important aspect to consider is that various RCTs have often used different primary outcomes to define the efficacy of a specific medication. While it may be important to tailor the specific outcome to the medication under investigation (e.g., whether its mechanism of action is more likely to lead to reduction in heavy alcohol drinking, abstinence, or release prevention), on the other hand, standardization may also be critical. This is particularly important from a regulatory standpoint in terms of acceptable outcomes for pivotal RCTs, especially given growing evidence that non-abstinence-oriented outcomes may be quite beneficial, e.g., percentage of subjects with no heavy drinking days (Falk et al. 2010) and reductions in World Health Organization (WHO)-based drinking risk levels (Falk et al. 2019b).

Last, but not least, medications for AUD are dramatically underutilized; therefore, basic science and human research efforts will need to be accompanied with translational practice approaches, where effective novel medications and precision medicine approaches are effectively translated from the research settings to the clinical practice.

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References

Addolorato G, Caputo F, Capristo E, Domenicali M, Bernardi M, Janiri L, Agabio R, Colombo G, Gessa GL, Gasbarrini G (2002) Baclofen efficacy in reducing alcohol craving and intake: a preliminary double-blind randomized controlled study. Alcohol Alcohol 37:504–508

Addolorato G, Leggio L, Ferrulli A, Cardone S, Vonghia L, Mirijello A, Abenavoli L, D'Angelo C, Caputo F, Zambon A, Haber PS, Gasbarrini G (2007) Effectiveness and safety of baclofen for maintenance of alcohol abstinence in alcohol-dependent patients with liver cirrhosis: randomised, double-blind controlled study. Lancet 370:1915–1922

Agabio R, Sinclair JMA, Addolorato G, Aubin HJ, Beraha EM, Caputo F, Chick JD, de La Selle P, Franchitto N, Garbutt JC, Haber PS, Heydtman M, Jaury P, Lingford-Hughes AR, Morley KC, Müller CA, Owens L, Pastor A, Paterson L, Pélissier F, Rolland B, Stafford A, Thompson A, van den Brink W, de Beaurepaire R, Leggio L (2018) The use of baclofen to treat patients with alcohol use disorder: the Cagliari statement. Lancet Psychiatry 5:957–960

Ameisen O (2005) Complete and prolonged suppression of symptoms and consequences of alcohol-dependence using high-dose baclofen: a self-case report of a physician. Alcohol Alcohol 40:147–150

Anthenelli RM, Heffner JL, Wong E, Tibbs J, Russell K, Isgro M, Dinh E, Wehrle C, Worley MJ, Doran N (2017) A randomized trial evaluating whether topiramate aids smoking cessation and prevents alcohol relapse in recovering alcohol-dependent men. Alcohol Clin Exp Res 41:197–206

Anton RF, Kranzler H, Breder C, Marcus RN, Carson WH, Han J (2008) A randomized, multicenter, double-blind, placebo-controlled study of the efficacy and safety of aripiprazole for the treatment of alcohol dependence. J Clin Psychopharmacol 28:5–12

Anton RF, Myrick H, Baros AM, Latham PK, Randall PK, Wright TM, Stewart SH, Waid R, Malcolm R (2009) Efficacy of a combination of flumazenil and gabapentin in the treatment of alcohol dependence: relationship to alcohol withdrawal symptoms. J Clin Psychopharmacol 29:334–342

Anton RF, Myrick H, Wright TM, Latham PK, Baros AM, Waid LR, Randall PK (2011) Gabapentin combined with naltrexone for the treatment of alcohol dependence. Am J Psychiatry 168:709–717

Anton RF, Schacht JP, Voronin KE, Randall PK (2017) Aripiprazole suppression of drinking in a clinical laboratory paradigm: influence of impulsivity and self-control. Alcohol Clin Exp Res 41:1370–1380

Arias A, Feinn R, Oncken C, Covault J, Kranzler HR (2010) Placebo-controlled trial of zonisamide for the treatment of alcohol dependence. J Clin Psychopharmacol 30:318–322

Arnone D (2005) Review of the use of topiramate for treatment of psychiatric disorders. Ann Gen Psychiatry 4:5

Asghari V, Sanyal S, Buchwaldt S, Paterson A, Jovanovic V, van Tol HH (1995) Modulation of intracellular cyclic AMP levels by different human dopamine D4 receptor variants. J Neurochem 65:1157–1165

Bell RL, Lopez MF, Cui C, Egli M, Johnson KW, Franklin KM, Becker HC (2013) Ibudilast reduces alcohol drinking in multiple animal models of alcohol dependence. Addict Biol 20:38–42

Beraha EM, Salemink E, Goudriaan AE, Bakker A, de Jong D, Smits N, Zwart JW, van Geest D, Bodewits P, Schiphof T, Defourny H, van Tricht M, van den Brink W, Wiers RW (2016) Efficacy and safety of high-dose baclofen for the treatment of alcohol dependence: a multicenter, randomized, double-blind controlled trial. Eur Neuorpsychopharmacol 26:1950–1959

Brower KJ, Myra Kim H, Strobbe S, Karam-Hage MA, Consens F, Zucker RA (2008) A randomized double-blind pilot trial of gabapentin versus placebo to treat alcohol dependence and comorbid insomnia. Alcohol Clin Exp Res 32(8):1429–1438

Bucknam W (2007) Suppression of symptoms of alcohol dependence and craving using high-dose baclofen. Alcohol Alcohol 42:158–160

Chompookham P, Rukngan W, Nilaban S, Suwanmajo S, Yoosom P, Kalayasiri R (2018) A randomized trial of low-dose gabapentin for post hospitalization relapse prevention in a Thai clinical sample of alcohol dependence. Psychiatry Res 270:34–40

Colombo G, Gessa GL (2018) Suppressing effect of baclofen on multiple alcohol-related behaviors in laboratory animals. Front Psych 9:475

Daurio AM, Deschaine SL, Modabbernia A, Leggio L (2019) Parsing out the role of dopamine D4 receptor gene (DRD4) on alcohol-related phenotypes: a meta-analysis and systematic review. Addict Biol:e12770. https://doi.org/10.1111/adb.12770

de Bejczy A, Lof E, Walther L, Gutertstam J, Hammarbeg A, Ansanovska G, Franck J, Isaksson A, Soderpalm B (2015) Varenicline for treatment of alcohol dependence: a randomized, placebo-controlled trial. Alcohol Clin Exp Res 39:2189–2199

Edwards S, Guerrero M, Ghoneim OM, Roberts E, Koob GF (2011) Evidence that vasopressin V1b receptors mediate the transition to excessive drinking in ethanol-dependent rats. Addict Biol 17:76–85

Evans SM, Bisaga A (2009) Acute interaction of baclofen in combination with alcohol in heavy social drinkers. Alcohol Clin Exp Res 33:19–30

Falk D, Wang XQ, Liu L, Fertig J, Mattson M, Ryan M, Johnson B, Stout R, Litten RZ (2010) Percentage of subjects with no heavy drinking days: evaluation as an efficacy endpoint for alcohol clinical trials. Alcohol Clin Exp Res 34:2022–2034

Falk DE, Castle IJP, Ryan M, Fertig J, Litten RZ (2015) Moderators of varenicline treatment effects in a double-blind, placebo-controlled trial for alcohol dependence: an exploratory analysis. J Addict Med 9:296–303

Falk DE, Ryan ML, Fertig JB, Devine EG, Cruz R, Brown ES, Burns H, Salloum IM, Newport DJ, Mendelson J, Galloway G, Grant T, Kampman K, Brooks C, Green AI, Brunette MF, Rosenthal RN, Dunn KE, Strain EC, Ray L, Shoptaw S, Ait-Daoud Tiouririne N, Gunderson EW, Random J, Scott C, Leggio L, Caras S, Mason B, Litten RZ, The National Institute on Alcohol Abuse and Alcoholism Clinical Investigations Group (NCIG) Study Group (2019a) Gabapentin enacarbil extended-release for alcohol use disorder: a randomized, double-blind, placebo-controlled, multisite trial assessing efficacy and safety. Alcohol Clin Exp Res 43:158–169

Falk DE, O'Malley SS, Witkiewitz K, Anton RF, Litten RZ, Slater M, Kranzler HR, Mann KF, Hasin DS, Johnson B, Meulien D, Ryan M, Fertig J, Alcohol Clinical Trials Initiative (ACTIVE) Workgroup (2019b) Evaluation of drinking risk levels as outcomes in alcohol pharmacotherapy trials: a secondary analysis of 3 randomized clinical trials. JAMA Psychiatry 76:374–381

Farokhnia M, Schwandt ML, Lee MR, Bollinger JW, Farinelli LA, Amodio JP, Sewell L, Lionetti TA, Spero DE, Leggio L (2017) Biobehavioral effects of baclofen in anxious alcohol-dependent individuals: a randomized, double-blind, placebo-controlled, laboratory study. Transl Psychiatry 7:e1108

Farokhnia M, Deschaine SL, Sadighi A, Farinelli LA, Lee MR, Akhlaghi F, Leggio L (2018) A deeper insight into how GABA-B receptor agonism via baclofen may affect alcohol seeking and consumption: lessons learned from a human laboratory investigation. Mol Psychiatry. https://doi.org/10.1038/s41380-018-0287-y

Farokhnia M, Faulkner ML, Piacentino D, Lee MR, Leggio L (2019) Ghrelin: from a gut hormone to a potential therapeutic target for alcohol use disorder. Physiol Behav 204:49–57

Fleischhacker WW (2005) Aripiprazole. Expert Opin Pharmacother 6:2091–2101

Fox HC, Anderson GM, Tuit K, Hansen J, Kimmerling A, Siedlarz KM, Morgan PT, Sinha R (2012) Prazosin effects on stress-and cue-induced craving and stress response in alcohol-dependent individuals: preliminary findings. Alcohol Clin Exp Res 36:351–360

Fucito LM, Toll BA, Wu R, Romano DM, Tek E, O'Malley SS (2011) A preliminary investigation of varenicline for heavy drinking smokers. Psychopharmacology 215:655–663

Furieri FA, Nakamura-Palacios EM (2007) Gabapentin reduces alcohol consumption and craving: a randomized, double-blind, placebo-controlled trial. J Clin Psychiatry 68(11):1691–1700

Garbutt JC, Kampov-Polevoy AB, Gallop R, Kalka-Juhl L, Flannery BA (2010) Efficacy and safety of baclofen for alcohol dependence: a randomized, double-blind, placebo-controlled trial. Alcohol Clin Exp Res 34(11):1849–1857

Garbutt JC, Greenblatt AM, West SL, Morgan LC, Kampov-Polevoy A, Jordan HS, Bobashev GV (2014) Clinical and biological moderators of response to naltrexone in alcohol dependence: a systematic review of the evidence. Addiction 109(8):1274–1284

Haass-Koffler CL, Goodyear K, Zywiak WH, Magill M, Eltinge SE, Wallace PM, Long VM, Jayaram-Lindstrom N, Swift RM, Kenna GA, Leggio L (2017) Higher pressure in associated with greater alcohol drinking reduction in alcohol-dependent individuals treated with doxazosin. Drug Alcohol Depend 177:23–28

Haass-Koffler CL, Goodyear K, Zywiak WH, Leggio L, Kenna GA, Swift RM (2018a) Comparing and combining topiramate and aripiprazole on alcohol-related outcomes in a human laboratory study. Alcohol Alcohol 53(3):268–276

Haass-Koffler CL, Swift RM, Leggio L (2018b) Noradrenergic targets for the treatment of alcohol use disorder. Psychopharmacology 235(6):1625–1634

Hauser P, Fuller B, Ho SB, Thuras P, Kern S, Dieperink E (2017) The safety and efficacy of baclofen to reduce alcohol use in veterans with chronic hepatitis C: a randomized controlled trial. Addiction 112(7):1173–1183

Heilig M, Leggio L (2016) What the alcohol doctor ordered from the neuroscientist: theragnostic biomarkers for personalized treatments. Prog Brain Res 224:401–418

Hofmann SG, Huweler R, MacKillop JM, Kantak K (2012) Effects of D-cycloserine on craving to alcohol cues in problem drinkers: preliminary findings. Am J Drug Alcohol Abuse 38:101–107

Javors MA, Seneviratne C, Roache JD, Ait-Daoud N, Bergeson SE, Walss-Bass MC, Akhtar FZ, Johnson BA (2005) Platelet serotonin uptake and paroxetine binding among allelic genotypes of the serotonin transporter in alcoholics. Prog Neuro-Psychopharmacol Biol Psychiatry 29:7–13

Johnson BA, Campling GM, Griffiths P, Cowen PJ (1993) Attention of some alcohol-induced mood changes and the desire to drink by 5-HT3 receptor blockade: a preliminary study I healthy male volunteers. Psychopharmacology 112:142–144

Johnson BA, Roache JD, Javors MA, DiClemente CC, Cloninger CR, Prihoda TJ, Bordnick PS, Ait-Daoud N, Hensler J (2000) Ondansetron for reduction of drinking among biologically predisposed alcoholic patients: a randomized controlled trial. JAMA 284(8):963–971

Johnson BA, Ait-Daoud N, Bowden CL, DiClemente CC, Roache JD, Lawson K, Javors MA, Ma JZ (2003) Oral topiramate for treatment of alcohol dependence: a randomised controlled trial. Lancet 361:1677–1685

Johnson BA, Rosenthal N, Capece JA, Wiegund F, Mao L, Beyers K, McKay A, Ait-Daoud N, Anton RF, Ciraulo DA, Kranzler HR, Mann K, O'Malley SS, Swift RM (2007) Topiramate for treating alcohol dependence: a randomized controlled trial. JAMA 198(14):1641–1651

Johnson BA, Javors MA, Roache JD, Seneviratne C, Bergeson SE, Ait-Daoud N, Dawes MA, Ma JZ (2008) Can serotonin transporter genotype predict serotonergic function, chronicity, and severity of drinking? Prog Neuro-Psychopharmacol Biol Psychiatry 32:209–216

Johnson BA, Ait-Daoud N, Seneviratne C, Roach JD, Javors MA, Wang XQ, Liu L, Penberthy JK, Di Clemente CC, Li MD (2011) Pharmacogenetic approach at the serotonin transporter gene as a method of reducing the severity of alcohol drinking. Am J Psychiatry 168:265–275

Johnson BA, Seneviratne C, Wang XQ, Ait-Daoud N, Li MD (2013) Determination of genotype combinations that can predict the outcome of the treatment of alcohol dependence using the 5-HT_3 antagonist ondansetron. Am J Psychiatry 170:1020–1031

Jonas DE, Amick HR, Feltner C, Bobashev G, Thomas K, Wines R, Kim MM, Shanahan E, Gass CE, Rowe CJ, Garbutt JC (2014) Pharmacotherapy for adults with alcohol use disorders in outpatient settings: a systematic review and meta-analysis. JAMA 311(18):889–900

Kenna GA, Zywiak WH, McGeary JE, Leggio L, McGeary C, Wang S, Grenga A, Swift RM (2009) A within-group design of nontreatment seeking 5-HTTLPR genotyped alcohol-dependent subjects receiving ondansetron and sertraline. Alcohol Clin Exp Res 33:315–323

Kenna GA, Swift RM, Hillemacher T, Leggio L (2012) The relationship of appetitive, reproductive and posterior pituitary hormones to alcoholism and craving in humans. Neuropsychol Rev 22 (3):211–228

Kenna GA, Zywiak WH, Swiftt RM, McGeary JE, Cliifford JS, Shoaff JR, Vuittonet C, Fricchione S, Brickley M, Beaucage K, Haass-Koffler CL, Leggio L (2014a) Ondansetron reduces naturalistic drinking in nontreatment-seeking alcohol-dependent individuals with the LL 5′-HTTLPR genotype: a laboratory study. Alcohol Clin Exp Res 38:1567–1574

Kenna GA, Zwiak WH, Swift RM, McGeary JE, Clifford JS, Shoaff JR, Fricchione S, Brickley M, Beaucage K, Haass-Koffler CL, Leggio L (2014b) Ondansetron and sertraline may interact with 5-HTTLPR and DRD4 polymorphisms to reduce drinking in non-treatment seeking alcohol-dependent women: exploratory findings. Alcohol 48:515–522

Kenna GA, Haass-Koffler CL, Zywiak WH, Edwards SM, Brickley MB, Swift RM, Leggio L (2015) Role of the α1 blocker doxazosin in alcoholism: a proof-of-concept randomized controlled trial. Addict Biol 21:904–914

Kiefer F, Kirsch M, Bach P, Hoffmann S, Reinhard I, Jorde A, von der Goltz C, Spanagel R, Mann K, Loeber S, Vollstadt-Klein S (2015) Effects of D-cycloserine on extinction of mesolimbic cue reactivity in alcoholism: a randomized placebo-controlled trial. Psychopharmacology 232(13):2353–2362

Knapp CM, Ciraulo DA, Sarid-Segal O, Richardson MA, Devine E, Streeter CC, Oscar-Berman M, Surprise C, Colaneri L, Putnam M, Waters M, Richambault C (2015) Zonisamide, topiramate, and levetiracetam: efficacy and neuropsychological effects in alcohol use disorders. J Clin Psychopharmacol 35:1–9

Kothare S, Kaleyias J (2008) Zonisamide: review of pharmacology, clinical efficacy, tolerability, and safety. Expert Opin Drug Metab Toxicol 4:493–506

Kranzler HR, Covault J, Pierucci-Lagha A, Chan G, Douglas K, Arias AJ, Oncken C (2008) Effects of aripiprazole on subjective and physiological responses to alcohol. Alcohol Clin Exp Res 32:1–7

Kranzler HR, Covault J, Feinn R, Armeli S, Tennen H, Arias AJ, Gelernter J, Pond T, Oncken C, Kampman KM (2014) Topiramate treatment for heavy drinkers: moderation by a *GRIK1* polymorphism. Am J Psychiatry 171:445–452

Lee MR, Rohn MCH, Tanda G, Leggio L (2016) Targeting the oxytocin system to treat addictive disorders: rationale and progress to date. CNS Drugs 30(2):109–123

Lee MR, Tapocik JD, Ghareeb M, Schwandt ML, Dias AA, Le AN, Cobbina E, Farinelli LA, Bouhlal S, Farokhnia M, Heilig M, Akhlaghi F, Leggio L (2018) The novel ghrelin receptor inverse agonist PF-5190457 administered with alcohol: preclinical safety experiments and a phase 1b human laboratory study. Mol Psychiatry. https://doi.org/10.1038/s41380-018-0064-y

Leggio L, Kenna GA (2013) Commentary: doxazosin for alcoholism. Alcohol Clin Exp Res 37:191–193

Leggio L, Garbutt JC, Addolorato G (2010) Effectiveness and safety of baclofen in the treatment of alcohol dependent patients. CNS Neurol Disord 9:33–44

Leggio L, Ferrulli A, Zambon A, Caputo F, Kenna GA, Swift RM, Addolorato G (2012) Baclofen promotes alcohol abstinence in alcohol dependent cirrhotic patients with hepatitis C virus (HCV) infection. Addict Behav 37(4):561–564

Leggio L, Zywiak WH, McGeary JE, Edwards S, Fricchione SR, Shoaff JR, Addolorato G, Swift RM, Kenna GA (2013) A human laboratory pilot study with baclofen in alcoholic individuals. Pharmacol Biochem Behav 103:784–791

Leggio L, Zywiak WH, Edwards SM, Tidey JW, Swift RM, Kenna G (2015) A preliminary double-blind, placebo-controlled randomized study of baclofen effects in alcoholic smokers. Psychopharmacology 232:233–243

Litten RZ, Ryan ML, Fertig JB, Falk DE, Johnson B, Dunn KE, Green AI, Pettinati HM, Ciraulo DA, Sarid-Segal O, Kampman K, Brunette MF, Strain EC, Tiouririne NA, Ransom J, Scott C, Stout R (2013) A double-blind, placebo-controlled trial assessing the efficacy of varenicline tartrate for alcohol dependence. J Addict Med 7:277–286

Litten RZ, Ryan ML, Falk DE, Reilly M, Fertig JB, Koob GF (2015) Heterogeneity of alcohol use disorder: understanding mechanisms to advance personalized treatment. Alcohol Clin Exp Res 39:579–584

Litten RZ, Falk DE, Ryan ML, Fertig JB (2016) Discovery, development, and adoption of medications to treat alcohol use disorder: goals for the phases of medications development. Alcohol Clin Exp Res 40:1368–1379

Litten RZ, Falk DE, Ryan ML, Fertig J, Leggio L (2018) Advances in pharmacotherapy development: human clinical studies. Handb Exp Pharmacol 248:579–613

MacKillop J, Few LR, Stojek MK, Murphy CM, Malutinok SF, Johnson FT, Hofmann SG, McGeary JE, Swift RM, Monti PM (2015) D-cycloserine to enhance extinction of cue-elicited craving for alcohol: a translational approach. Transl Psychiatry 5(4):e544

Martinotti G, DiNicola M, De Vita O, Hatzigiakoumis DS, Guglielmo R, Santucci B, Aliotta F, Romanelli R, Verrastro V, Petruccelli F, Di Giannantonio M, Janiri L (2014) Low-dose topiramate in alcohol dependence: a single-blind, placebo-controlled study. J Clin Psychopharmacol 34:709–715

Mason BJ, Light JM, Williams LD, Drobes DJ (2009) Proof-of-concept human laboratory study for protracted abstinence in alcohol dependence: effects of gabapentin. Addict Biol 14(1):73–83

Mason BJ, Quello S, Goodell V, Shadan F, Kyle M, Begovic A (2014) Gabapentin treatment for alcohol dependence: a randomized clinical trial. JAMA Intern Med 174:70

McCool BA, McGinnis MM (2019) Adolescent vulnerability to alcohol use disorder: neurophysiological mechanisms from preclinical studies. Handb Exp Pharmacol. https://doi.org/10.1007/164_2019_296

McKee SA, Harrison ELR, O'Malley SS, Krishnan-Sarin S, Shi J, Tetrault JM, Picciotto MR, Petrakis IL, Estevez N, Balchunas E (2009) Varenicline reduces alcohol self-administration in heavy-drinking smokers. Biol Psychiatry 66:185–195

Medical Press (2018) France clears use of anti-spasm drug to treat alcoholism. https://medicalxpress.com/news/2018-10-france-anti-spasm-drug-alcoholism.html. Accessed 31 May 2019

Mihalak KB, Carroll FI, Luetje CW (2006) Varenicline is a partial agonist at α4β2 and a full agonist at α7 neuronal nicotinic receptors. Mol Pharmacol 70:801–805

Miranda R, MacKillop J, Monti PM, Rohsenow DJ, Tidey J, Gwaltney C, Swift R, Ray L, McGeary J (2008) Effects of topiramate on urge to drink and the subjective effects of alcohol: a preliminary laboratory study. Alcohol Clin Exp Res 32:489–497

Miranda R, MacKillop J, Treloar H, Blanchard A, Tidey JW, Swift R, Chun T, Rohsenow DJ, Monti PM (2016) Biobehavioral mechanisms of topiramate's effects on alcohol use: an investigation pairing laboratory and ecological momentary assessments. Addict Biol 21:171–182

Mitchell JM, Teague CH, Kayser AS, Bartlett SE, Fields HL (2012) Varenicline decreases alcohol consumption in heavy-drinking smokers. Psychopharmacology 223:299–306

Morley KC, Baillie A, Fraser I, Furneaux-Bate A, Dore G, Roberts M, Abdalla A, Phung N, Haber PS (2018a) Baclofen in the treatment of alcohol dependence with or without liver disease: multisite, randomised, double-blind, placebo-controlled trial. Br J Psychiatry 212(6):362–369

Morley KC, Baillie A, van den Brink W, Chitty KE, Brady K, Back SE, Seth D, Sutherland G, Leggio L, Haber PS (2018b) N-acetyl cysteine in the treatment of alcohol use disorder in patients with liver disease: rationale for further research. Expert Opin Investig Drugs 27 (8):667–675

Morris LS, Voon V, Leggio L (2018) Stress, motivation, and the gut-brain axis: a focus on the ghrelin system and alcohol use disorder. Alcohol Clin Exp Res 42:1378

Muller CA, Geisel O, Petz P, Higl V, Kruger J, Stickel A, Beck A, Wernecke KD, Hellweg R, Heinz A (2015) High-dose baclofen for the treatment of alcohol dependence (BACLAD study): a randomized, placebo-controlled trial. Eur Neuropsychopharmacol 25:1167–1177

Myrick H, Li X, Randall PK, Henderson S, Voronin K, Anton RF (2010) The effect of aripiprazole in cue-induced brain activation and drinking parameters in alcoholics. J Clin Psychopharmacol 30:365–372

Oak JN, Oldenhof J, van Tol HH (2000) The dopamine D4 receptor: one decade of research. Eur J Pharmacol 405:303–327

O'Malley SS, Zweben A, Fucito LM, Wu R, Piepmeier ME, Ockert DM, Bold KW, Petrakis I, Muvvala S, Jatlow P, Gueorguieva R (2018) Effect of varenicline combined with medical management on alcohol use disorder with comorbid cigarette smoking: a randomized clinical trial. JAMA Psychiat 75:129–138

Petrakis IL, Desai N, Gueorguieva R, Arias A, O'Brien E, Jane JS, Sevarino K, Southwick S, Ralevski E (2016) Prazosin for veterans with posttraumatic stress disorder and comorbid alcohol dependence: a clinical trial. Alcohol Clin Exp Res 40:178–186

Plebani JG, Lynch KG, Rennert L, Pettinati HM, O'Brien CP, Kampman KM (2013) Results from a pilot clinical trial of varenicline for the treatment of alcohol dependence. Drug Alcohol Depend 133(2):754–758

Ray LA, Miranda R, MacKillop J, McGeary J, Tidey JW, Rohsenow DJ, Gwaltney C, Swift RW, Monti PM (2009) A preliminary pharmacogenetic investigation of adverse events from topiramate in heavy drinkers. Exp Clin Psychopharmacol 17:122–129

Ray LA, Courtney KE, Ghahremani DG, Miotto K, Brody A, London ED (2014) Varenicline, low dose naltrexone, and their combination for heavy-drinking smokers: human laboratory findings. Psychopharmacology 231:3843–3853

Ray LA, Bujarski S, Shoptaw S, Roche DJ, Heinzerling K, Miotto K (2017) Development of the neuroimmune modulator ibudilast for the treatment of alcoholism: a randomized, placebo-controlled, human laboratory trial. Neuropsychopharmacology 42(9):1776–1788

Reynaud M, Aubin HJ, Trinquet F, Zakine B, Dano C, Dematteis M, Trojak B, Paille F, Detilleux M (2017) A randomized, placebo-controlled study of high-dose baclofen in alcohol-dependent patients – the ALPADIR study. Alcohol Alcohol 52(4):439–446

Richardson HN, Lee SY, O'Dell LE, Koob GF, Rivier CL (2008) Alcohol self-administration acutely stimulates the hypothalamic-pituitary-adrenal axis, but alcohol dependence leads to a dampened neuroendocrine state. Eur J Neurosci 28:1641–1653

Roberts W, Harrison ELR, McKee SA (2017a) Effects of varenicline on alcohol cue reactivity in heavy drinkers. Psychopharmacology 234(18):2737–2745

Roberts W, Verplaetse TL, Moore K, Oberleitner L, Picciotto MR, McKee SA (2017b) Effects of varenicline on alcohol self-administration and craving in drinkers with depressive symptoms. J Psychopharmacol 31:906–914

Ryan ML, Falk DE, Fertig JB, Rendenbach-Mueller B, Katz DA, Tracy KA, Strain EC, Dunn KE, Kampman K, Mahoney E, Ciraulo DA, Sickles-Colaneri L, Ait-Daoud N, Johnson BA, Ransom J, Scott C, Koob GF, Litten RZ (2017) A phase2, double-blind, placebo-controlled randomized trial assessing the efficacy of ABT-436, a novel V1b receptor antagonist, for alcohol dependence. Neuropsychopharmacology 42:1012–1023

Sarid-Segal O, Knapp CM, Burch W, Richardson MA, Bahtia S, DeQuattro K, Afshar M, Richambault C, Sickels L, Devine E, Ciraulo D (2009) The anticonvulsant zonisamide reduces ethanol self-administration by risky drinkers. Am J Drug Alcohol Abuse 35:316–319

Schacht JP, Anton RF, Randall PK, Li X, Henderson S, Myrick H (2014) Varenicline effects on drinking, craving and neural reward processing among non-treatment-seeking alcohol-dependent individuals. Psychopharmacology 231:3799–3807

Schacht JP, Voronin KE, Randall PK, Anton RF (2018) Dopaminergic genetic variation influences Aripiprazole effects on alcohol self-administration and the neural response to alcohol cues in a randomized trial. Neuropsychopharmacology 43:1247–1256

Seif T, Simms JA, Lei K, Wegner S, Bonci A, Messing RO, Hopf FW (2015) D-serine and D-cycloserine reduce compulsive alcohol intake in rats. Neuropyschopharmacology 40 (10):2357–2367

Sellers EM, Toneatto T, Romach MK, Somer GR, Sobell LC, Sobell MB (1994) Clinical efficacy of the 5-HT_3 antagonist ondansetron in alcohol abuse and dependence. Alcohol Clin Exp Res 18 (4):879–885

Sills GJ (2006) The mechanisms of action of gabapentin and pregabalin. Curr Opin Pharmacol 6:108–113

Simms JA, Haass-Koffler CL, Bito-Onon J, Li R, Bartlett SE (2012) Mifepristone in the central nucleus of the amygdala reduces yohimbine stress-induced reinstatement of ethanol-seeking. Neuropsychopharmacology 37:906–918

Simpson TL, Saxon AJ, Meredith CW, Malte CA, McBride B, Ferguson LC, Gross CA, Hart KL, Raskind M (2009) A pilot trial of the alpha-1 adrenergic antagonist, prazosin for alcohol dependence. Alcohol Clin Exp Res 33:255–263

Simpson TL, Malte CA, Dietel B, Tell D, Pocock I, Lyons R, Varon D, Raskind M, Saxon AJ (2015) A pilot trial of prazosin, an alpha-1 adrenergic antagonist, for comorbid alcohol dependence and posttraumatic stress disorder. Alcohol Clin Exp Res 39:808–817

Simpson TL, Saxon AJ, Stappenbeck C, Malte CA, Lyons R, Tell D, Millard SP, Raskind M (2018) Double-blind randomized clinical trial of prazosin for alcohol use disorder. Am J Psychiatry 175:1216

Smith RV, Havens JR, Walsh SL (2016) Gabapentin misuse, abuse and diversion: a systematic review. Addiction 111:1160–1174

Swift RM (2003) Topiramate for the treatment of alcohol dependence: initiating abstinence. Lancet 361(9370):1666–1667

Swift RM, Davidson D, Whelihan W, Kuznetsov O (1996) Ondansetron alters human alcohol intoxication. Biol Psychiatry 40:514–521

Vendruscolo LF, Barbier E, Schlosburg JE, Misra KK, Whitfield TW, Logrip ML, Rivier C, Repunte-Canonigo V, Zorrilla EP, Sanna PP, Heilig M, Koob GF (2012) Corticosteroid-dependent plasticity medicates compulsive alcohol drinking in rats. J Neurosci 32:7563–7571

Vendruscolo LF, Estey D, Goodell V, Macshane LG, Logrip ML, Schlosburg JE, McGinn MA, Zamora-Martinez ER, Belanoff JK, Hunt HJ, Sanna PP, George O, Koob GF, Edwards S, Mason BJ (2015) J Clin Invest 125:3193–3197

Voronin K, Randall P, Myrick H, Anton R (2008) Aripiprazole effects on alcohol consumption and subjective reports in a clinical laboratory paradigm–possible influence of self-control. Alcohol Clin Exp Res 32:1954–1961

Watson BJ, Wilson S, Griffin L, Kalk NJ, Taylor LG, Munafo MR, Lingford-Hughes AR, Nutt DJ (2011) A pilot study of the effectiveness of D-cycloserine during cue-exposure therapy in abstinent alcohol-dependent subjects. Psychopharmacology 216:121–129

Wilcox CE, Tonigan JS, Bogenschutz MP, Clifford J, Bigelow R, Simpson T (2018) A randomized, placebo-controlled, clinical trial of prazosin for the treatment of alcohol use disorder. J Addict Med 12(5):339–345

Zallar LJ, Farokhnia M, Tunstall BJ, Vendruscolo LF, Leggio L (2017) The role of the ghrelin system in drug addiction. Int Rev Neurobiol 136:89–119

Zhou Y, Colombo G, Carai MAM, Ho A, Gessa GL, Kreek MJ (2011) Involvement of arginine vasopressin and V1b receptor in alcohol drinking in Sardinian alcohol-preferring rats. Alcohol Clin Exp Res 35:1876–1883