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Medications for alcohol use disorders: An overview

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ABSTRACT

Patients who suffer from alcohol use disorders (AUDs) usually go through various socio-behavioral and pathophysiological changes that take place in the brain and other organs. Recently, consumption of unhealthy food and excess alcohol along with a sedentary lifestyle has become a norm in both developed and developing countries. Despite the beneficial effects of moderate alcohol consumption, chronic and/or excessive alcohol intake is reported to negatively affect the brain, liver and other organs, resulting in cell death, organ damage/failure and death. The most effective therapy for alcoholism and alcohol related comorbidities is alcohol abstinence, however, chronic alcoholic patients cannot stop drinking alcohol. Therefore, targeted therapies are urgently needed to treat such populations. Patients who suffer from alcoholism and/or alcohol abuse experience harmful effects and changes that occur in the brain and other organs. Upon stopping alcohol consumption, alcoholic patients experience acute withdrawal symptoms followed by a protracted abstinence syndrome resulting in the risk of relapse to heavy drinking. For the past few decades, several drugs have been available for the treatment of AUDs. These drugs include medications to reduce or stop severe alcohol withdrawal symptoms during alcohol detoxification as well as recovery medications to reduce alcohol craving and support abstinence. However, there is no drug that completely antagonizes the adverse effects of excessive amounts of alcohol. This review summarizes the drugs which are available and approved by the FDA and their mechanisms of action as well as the medications that are under various phases of preclinical and clinical trials. In addition, the repurposing of the FDA approved drugs, such as anticonvulsants, antipsychotics, antidepressants and other medications, to prevent alcoholism and treat AUDs and their potential target mechanisms are summarized.

1. Introduction

Alcoholism is a chronic, relapsing disorder defined by compulsive alcohol seeking, loss of control over drinking and in a negative emotional state when not drinking. The major health issue that results from binge drinking is gut leakage and organ damage. For instance, chronic and excessive alcohol drinking negatively influences gut microbiota, stimulates gut leakage with elevated endotoxin, which can promote advanced liver disease, including inflammation, fibrosis, cirrhosis and eventually results in hepatocellular carcinoma (Schnabl & Brenner,

Abbreviations: AUD, Alcohol use disorder; FDA, Food and Drug Administration; MOR, Mu opioid receptor; DOR, Delta opioid receptor; KOR, Kappa opioid receptor; NMDA, *N*-methyl-D-aspartate; GABA, Gaba amino butyric acid; DSM-IV, Diagnostic and statistical measurement IV; PACS, Penn Alcohol Craving Scale; AMPA, Amino-3-hydroxy-5methyl-4-isoxazolepropionic acid; PSNHDD, Percent subject with no heavy drinking days; HDD, Heavy drinking days; ASHSP, American Society of Health System Pharmacists; VGCC, Voltage gated calcium channel; msP, Marchigian Sardinian; AWS, Alcohol withdrawal syndrome; RCT, Randomized clinical trial; MDD, Major depressive disorder; ARI, Aripiprazole; FLX, Fluoxetine; 5-HT2A, 5-hydroxytryptamine receptor 2A; 5-HT7, 5-hydroxytryptamine receptor 7; CYP2D6, Cytochrome P450 2D6; CYP3A4, Cytochrome P450 3A4; EtPR, Ethanol preferring rat; EtNPR, Ethanol non-preferring rat; CASA, Chronic alcohol self-administration; SSRI, Selective serotonin receptor inhibitor; SNRI, Serotonin and norepinephrine receptor inhibitor; PFC, Prefrontal cortex; PTSD, Post-traumatic stress disorder; ADHD, Attention deficit hyperactivity disorder; NTX, Naltrexone; VAR, Varenicline; NAc, Nucleus accumbens; nAChR, Nicotinic acetylcholine receptor; DID, Drinking in dark; PCC, Poison control center; OCDS, Obsessive Compulsive Drinking Scale; TAC, Total alcohol consumption; BPD, Borderline personality disorder; CRF1, Corticotropin releasing factor-1; CB1, Cannabinoid receptor-1; PET, Positron emission tomography; ICV, Intracerebroventricular; VBST, Ventral bed nucleus of stria terminalis; BLA, Basolateral amygdala; AD, Alcohol dependent; FHDA, Family history density of alcoholism; PDE, Phosphodiesterase; PPAR, Peroxisome proliferative activated receptor; PR, Progressive ratio; CTA, Conditioned taste aversion; CPP, Conditioned place preference; WGCNA, Weighted gene co-expression network analysis; BDNF, Brain derived neurotrophic factor; HPA, Hypothalamus pituitary adrenal; OTR, Oxytocin receptor; GHS-RIA, Ghrelin receptor; GHRP6, Growth hormone releasing peptide-6; OXR, Orexin receptor; HCRT1, Hypocretin receptor-1; VTA, Ventral tegmental area; CIE, Chronic intermittent ethanol; HAD, High alcohol drinking; AVP, Arginine vasopressin; CDR, Cognitive test battery; HAM-D-17, Hamilton depression rating scale; MASQ, Mood and anxiety symptoms questionnaire; ACTH, Adeno-corticotropic hormone; CRH, Corticotropin releasing hormone

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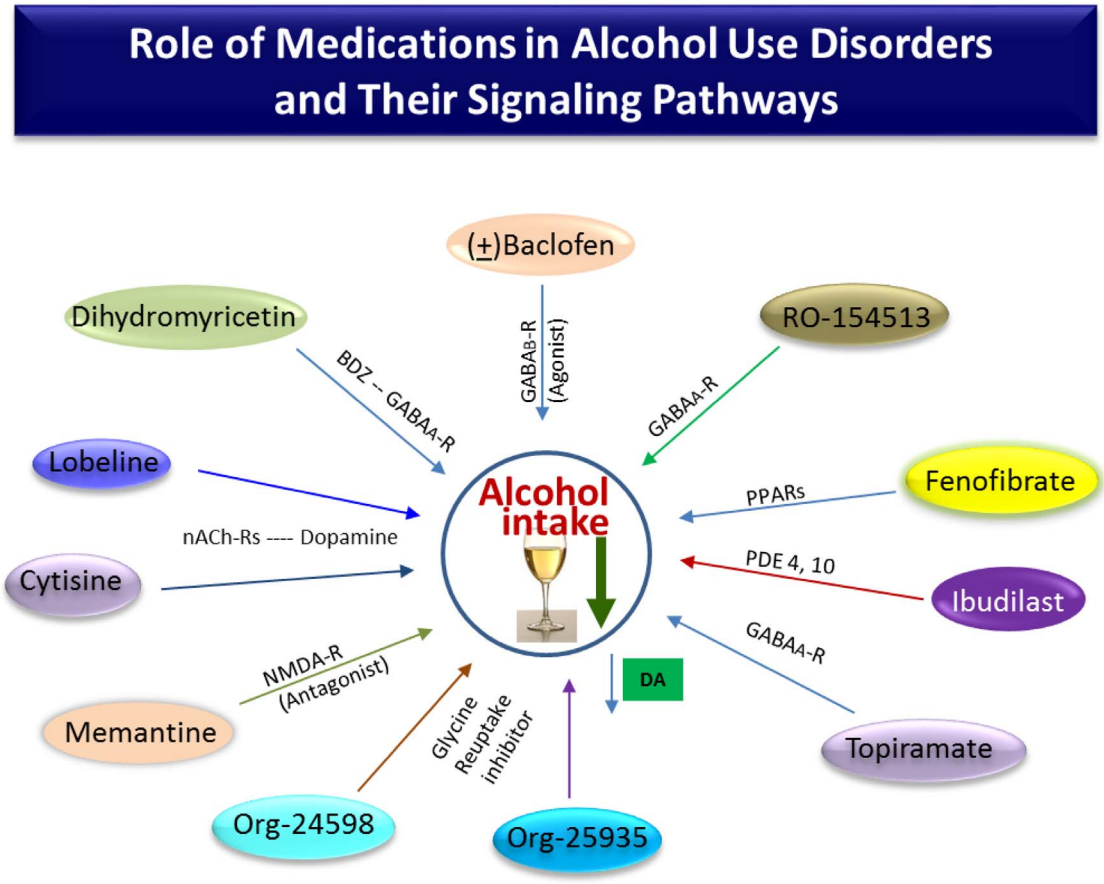

Fig. 1. Schematic diagram of the FDA-approved drugs and other medications, such as anticonvulsants and some off-label medications that are used or repurposed for the treatment of AUDs. This scheme also shows the underlying pathways through which these medications exert their inhibitory effects on alcohol intake and/or craving.

2014). In addition to the liver, alcohol contributes to more than 200 diseases, including alcoholic dementia, injury-related health conditions and cancers, falls and automobile-related accidental injuries (NIAAA, 2016a). Binge drinking, in the United States, is defined as a pattern of alcohol consumption that brings the blood alcohol concentration (BAC) level to 0.08 g/dL or above within 2 h (CDC, 2016). According to the national surveys, more than 90% of American adults who drink excessively reported binge drinking in the past 30 days (NIAAA, 2016b). Many binge drinkers may not be alcohol dependent, but their binge drinking habits make them susceptible to several health problems.

These problems related to AUD vary from individual to individual, based on genetic makeup, metabolism, age, gender, ethnicity, environment, lifestyle, etc. Since every individual responds differently to alcohol drinking, there is always a great concern for their susceptibility and outcome severity. For instance, having 2 or more drinks a day increases the risk of developing breast cancer by 25% (Smith-Warner et al., 1998). A meta-analysis of 53 studies reported that, in women, 4 or more drinks per day increases the risk of breast cancer by 46% and this risk increases by 7% for each additional 10 g of alcohol consumed (Hamajima et al., 2002). However, heavy alcohol consumption directly affects brain function and has been shown to induce mental disorders including mood, anxiety, psychotic, sleep and dementia disorders (Shivani, Goldsmith, & Anthenelli, 2002). In addition to mood and behavior changes, alcohol can negatively influence thought, memory, and coordination. Excessive alcohol use can also affect other organs, such as the gut, liver, pancreas, and heart contributing to endotoxemia, advanced liver disease, pancreatitis, irregular heartbeat, stroke, high blood pressure and cardiomyopathy. In this article, we have focused on the effects of alcohol on the central nervous system (CNS) and medications for the treatment of AUDs. Covering other organs and organ systems as well as injuries mediated by AUD are beyond the scope of this review (for more details: Clemens, Wells, Schneider, & Singh, 2014; Massey, Beier, Ritzenthaler, Roman, & Arteel, 2015; Molina, Gardner, Souza-Smith, & Whitaker, 2014; Patel et al., 2015; Souza-Smith et al., 2016). Despite the preclinical and clinical studies for the treatment of AUD during the past decades, only a few drugs have been approved by the U.S. Food and Drug Administration (FDA). These approved drugs were beneficial for some people, but not for others. Therefore, the highest priority for the NIAAA is to promote the development of less expensive, fast acting and more potent medications with less side effects. Additionally, to achieve these goals, there are several druggable medications coming on the market from time to time that are in different phases of preclinical and clinical trials. Litten et al. have evaluated the clinical efficacy and safety of the potential medications for AUD treatment (Litten, Wilford, Falk, Ryan, & Fertig, 2016).

Significant progress has been made during the past two decades in understanding the biological mechanisms underlying AUD, and there are more than 30 druggable targets on which preclinical and clinical trials are underway (Noronha, Cui, Harris, & Crabbe, 2014; clinicaltrials.gov). Altogether there are 249 clinical trials that were completed around the world and among them 179 were conducted in the United States of America for the treatment of AUD. Currently, there are 105 ongoing clinical trials that are recruiting for the studies around the world and 75 of them are in the United States at the time of writing this review article (clinicaltrials.gov). The targets currently under investigation are important and are sensitive to stress, withdrawal and addiction. Other physiological systems, such as the immune system, have been shown to influence alcohol seeking and drinking behavior could be exploited for the development of AUD medications (Blednov, Black, Benavidez, Stamatakis, & Harris, 2016a, 2016b; Cui, Grandison,

& Noronha, 2011). We have discussed most of the medications and their preclinical and clinical trials in other sections based on their categorization and the mechanisms of action. In this section, we will focus on some individual medications that are in various preclinical and clinical trials.

Chronic alcoholism has become a major health issue both in developed and developing countries with heavy social, medical and economic burdens. Despite the available pharmacotherapies for the treatment of AUDs, there are no such medication and treatment methods that give a hundred percent cure rate. Many of these drugs and medicines are known to exhibit some deleterious side effects or are only effective in some conditions. The currently used FDA approved drugs include Disulfiram, Naltrexone, and Acamprosate. These drugs were also approved by different regulatory agencies in many countries and have been used to treat AUDs for the past few decades with variable success rates. Improved medications for the treatment of binge, chronic alcohol drinking and alcohol related socio-medical problems are greatly needed. Reviews of the current literature show that many drugs and medications such as anticonvulsants, antipsychotic and antidepressants are under preclinical and clinical trials for the treatment of AUDs. Previously we have reviewed on the status of FDA approved and some other medications for the treatment of AUDs (Heilig & Egli, 2006). In the present article, we have focused on the existing medications and the repurposing of the FDA approved medications for the prevention and treatment of AUDs with a list of potential medication candidates, as summarized in Figs. 1 & 2, and Tables 1 & 2. In addition to this, the novel medications with potential therapeutic use and in various stages of development are discussed.

2. FDA approved medications for alcohol use disorders

As mentioned previously, the medications that are approved by the FDA for the treatment of AUDs are Disulfiram, Acamprosate, Naltrexone and injectable extended-release Naltrexone (Revia or Vivitrol). Disulfiram, discovered in the year 1920 (Adams & Ludwig, 1930), and approved by the FDA in 1951, is still used for the treatment of chronic alcoholism conditions. It inhibits the enzyme mitochondrial aldehyde dehydrogenase with a low Km (Michaelis Constant) for acetaldehyde. Disulfiram in the presence of alcohol, even in small amounts, produces flushing, throbbing headache, respiratory difficulty, nausea, copious vomiting, sweating and thirst. Chest pain, palpitation, blurred vision, and confusion are other symptoms that are obvious. Severe side effects may include: respiratory depression, cardiovascular collapse, arrhythmias, myocardial infarction, acute congestive heart failure, unconsciousness, convulsions, and death (NIH, 2016). The major metabolite of disulfiram (diethyldithiocarbamate) is an inhibitor of dopamine-β-hydroxylase, an enzyme that catalyzes the metabolism of dopamine to norepinephrine, resulting in psychosis, although this might be a rare effect depending on a family history of psychosis (Mohapatra & Rath, 2017). Similarly, severe axonal polyneuropathy involving cranial nerves that developed within weeks after a regular dosage of 500 mg/day disulfiram was observed (Santos, Martins-Campos, & Morais, 2016). A recent meta-analysis on the efficacy of disulfiram for the treatment of alcohol dependence showed disulfiram as a controversial medication. The results of 22 included studies revealed that disulfiram was superior in comparison to control and in open-label RCTs. In contrast, disulfiram didn't show any efficacy in blinded-RCTs in comparison to controls. However, disulfiram was more

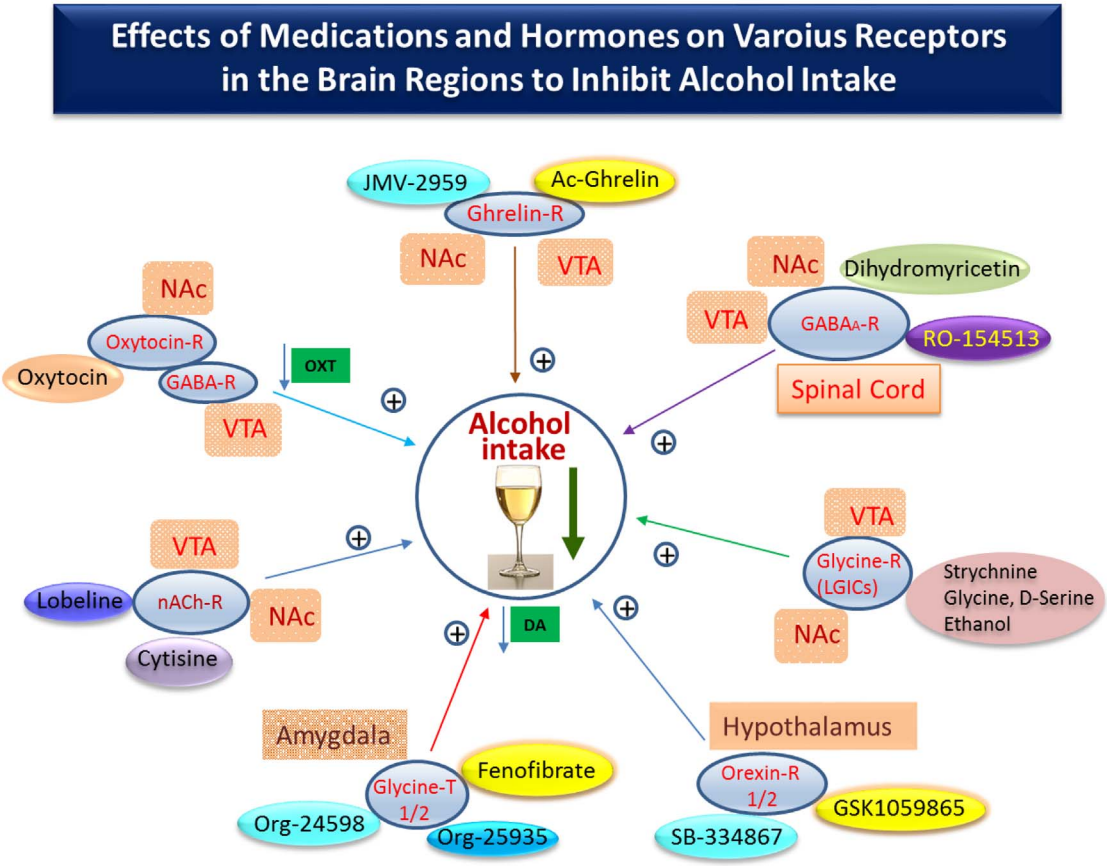

Fig. 2. Schematic diagram showing drugs, hormones and their receptors in the brain inhibiting alcohol intake. The FDA-approved medications and others undergoing pre-clinical and clinical trials are shown. The inhibitory effects of alcohol intake are mediated through the hormone ghrelin, oxytocin and opioid receptors that are expressed in VTA, NAc, hypothalamus and amygdala of the brain. In addition to the FDA-approved drugs, the new medications, that exert their effects through interactions with various receptors, including GABAA, Glycine and nACh receptors, have therapeutic potentials for the treatment of AUDs.

Table 1
Medications and their effects in human studies.

Medication	Mode of action	Results in humans	References
FDA approved drugs			
Disulfiram	Inhibit mitochondrial aldehyde dehydrogenase	Reduced alcohol consumption in open-label RCTs, but not in blinded RCTs	Skinner et al. (2014), Adams and Ludwig (1930), Santos et al. (2016)
Naltrexone	Opioid receptor agonists	Reduced alcohol consumption and full abstinence	Plosker (2015), Mason (2001), Nutt (2014)
Acamprosate	Enhance NMDA receptor functions Inhibit GluR functions at higher doses	Reduced heavy alcohol and chronic escalation drinking	Rösner et al. (2010), Niciu and Arias (2013)
Anticonvulsants			
Gabapentin	Modulates glutamate decarboxylase enzyme involved in GABA biosynthesis	Reduced alcohol dependence, relapse and craving and induce complete abstinence	Taylor (1997), Stock et al. (2013), Mason et al. (2014)
Topiramate	Activate voltage gated Na and AMPA/ Kainate channels GABA-A type receptor	Reduced alcohol drinking, relapse and induce abstinence	Porter et al. (2012), Baltieri et al. (2008), Falk et al. (2010)
Pregabalin	α2δ subunit of voltage gated Calcium channel, not GABA-A or B receptor	Reduced alcohol relapse rate, AWS, craving and psychiatric symptoms	Martinotti, di Nicola, Frustaci, et al., 2010; Martinotti, Di Nicola, Tedeschi, et al., 2010), Förg et al. (2012), Addolorato and Leggio (2010)
Antipsychotics			
Quetiapine	Antagonist of serotonin Dopamine & Adrenergic receptors, partial agonist on 5-HT1A receptors	Reduced alcohol intake in open-label/retrospective study in AD patients, reduced akathisia and depression, improved sleep, but was not effective multisite RCT placebo control trial in heavy alcohol drinking patients	Monnelly et al. (2004), Martinotti et al. (2008), Kurlawala and Vatsalya (2016), Litten et al. (2012)
Aripiprazole	Partial dopamine agonist, and antagonist Of 5-HT2A & 5-HT7 receptors	Reduced alcohol craving in MDD patients, inhibits cue-induced heavy drinking, decreased number of drinks in low but not in high impulsivity patients, caused side effects	Han et al. (2013), Myrick et al. (2010), Anton et al. (2017)
Antidepressants			
Duloxetine	Serotonin, norepinephrine, and dopamine reuptake inhibitor, CYP2D6 inhibitor	Induced liver injury in psychiatric MDD patients and in patients with preexisting chronic liver disease and alcohol consumption, and elderly patients	Froehlich et al. (2016), Kang et al. (2011), Voican et al. (2014)
Venlafaxine	Serotonin, norepinephrine, and dopamine reuptake inhibitor	No effect in anxiety disorder, depression, induced liver injury, hepatitis, jaundice in many patients	Stadlmann et al. (2012), Detry et al. (2009), Yildirim et al. (2009)
Other medications			
Baclofen	Agonist of GABA-B receptors	Mixed or not effective in reducing alcohol intake, craving, abstinence and conflicting results with alcohol dependence	Imbert et al. (2015), Beraha et al. (2016), Ponizovsky et al. (2015), Reynaud et al. (2017)
Ondansetron	Selective antagonist of 5-HT3 receptors	Reduced alcohol intake in early onset alcoholics, reduced depression, anxiety, and hostility	Kranzler et al. (2003), Johnson et al. (2003)
Nalmefene	Opioid receptor antagonist	Reduced alcohol dependence, heavy drinking days, Borderline personality disorders and AUD	Mason et al. (1999), Di Nicola et al. (2017), Martín-Blanco et al. (2017)

Table 2
Medications and hormones and their effects in human studies.

	Mechanism of action	Results in humans	References
Medication			
Pexacerfont	CRF receptor-1 antagonist	No positive effects on alcohol craving, emotional responses and anxiety, and stress related psychiatric disorders	Kwako et al. (2015), Shaham and de Wit (2016), Sanders and Nemeroff (2016), Spierling and Zorilla (2017)
Prazosin	α1-Adrenoreceptor antagonist	Reduced alcohol intake, symptoms of PTSD, and sleep	Skelly and Weiner (2014), Simpson et al. (2015), Petrakis et al. (2016)
Org-25935	Glycine reuptake inhibitor	Not effective	Liem-Moolenaar et al. (2013)
Ibudilast	Phosphodiesterase inhibitor	Attenuated the stimulant and mood altering effects of alcohol in comparison to placebo in a randomized, crossover, double-blind Placebo-controlled laboratory study.	Ray et al. (2017)
Fenofibrate	PPARα agonist	Not effective	(Clinicaltrials.gov; NCT02158273)
Memantine	NMDA receptor antagonist	Not effective, many negative side effects	Evans et al. (2007)
ABT-436	Arginine-vasopressin receptor antagonist	Reduced HPA activity, antidepressant activity, reduced cortisol levels, increased abstinence	Katz et al. (2016, 2017), Ryan et al. (2017)
Hormones			
Oxytocin	GABA receptor agonist	Decrease AWS, reverse tolerance	Pedersen et al. (2013)
Ghrelin	Ghrelin receptor agonist	Increased alcohol craving in alcohol-dependent individuals, during abstinence	Lee, Rohn, Tanda, and Leggio (2016), Koopmann et al. (2012)
Orexin	Orexin receptor agonist	Increased orexin levels in alcohol-dependent patients, decreased during abstinence, biomarker of alcohol relapse	Ziółkowski et al., 2016, von der Goltz et al. (2011)
Varenicline Cytisine/ Lobeline	Nicotine Acetylcholine receptor agonist/antagonist	Reduced alcohol craving, diastolic blood pressure, increased learning memory, decrease alcohol craving in heavy smokers	Verplaetse et al. (2016), McKee et al. (2009), Mitchell et al. (2012), Litten et al. (2013)

effective than the control in comparison to other medications (Skinner, Lahmek, Pham, & Aubin, 2014). Despite the controversial results, this was the only medication physicians could offer to their alcoholic patients to overcome alcoholism for more than four decades.

In 1994, FDA approved another oral medication Naltrexone for the treatment of alcoholism and opioid dependence. Naltrexone binds to the opioid receptors and attenuates the pleasant sensations associated with alcohol drinking. This medication is also reported to reduce alcohol craving. In 2006 the extended release formulation of naltrexone was approved by FDA and since then it has been in use. The closely related medications, which are used for the same purpose are Methylnaltrexone and Nalmefene. Naltrexone is marketed under the trade names Revia and Vivitrol and used for the treatment of alcoholism (Data.Medicaid.gov, 2016; Naltrexone: ATC/DDD Index – WHO, 2016). Naltrexone and its active metabolite 6β naltrexol are agonists at the μ-opioid (MOR), the κ-opioid (KOR) and to a lesser extent, to the δ-opioid receptor (DOR) (Niciu & Arias, 2013). It has been shown to prevent heavy drinking, decreasing the volume and the number of alcohol drinking days (Rösner et al., 2010). Acute administration of a combination of naltrexone and Mesyl Salvinorin B (MSB, a long-acting deacetylated metabolite of a hallucinogenic recreational drug Salvinorin A) reduced alcohol intake profoundly after 3-week chronic escalation drinking (CED) at doses lower than those individual effective doses (Zhou, Cowley, Ben, Prisinzano, & Kreek, 2017). Even though it is effective in managing alcohol and opioid consumption, the overall benefits of naltrexone have been described as modest (Donoghue et al., 2015; Garbutt, 2010).

Another medication Acamprosate, was approved by the FDA in the year 2006 and has been used along with counselling in the treatment of alcohol dependence (Plosker, 2015). It is sold under the brand name Campral and is thought to stabilize the balance of neurotransmitters in the brain that would otherwise be disrupted by alcohol withdrawal (Williams, 2005). Reports indicate that acamprosate works to best advantage in combination with psychosocial support and can help facilitate reduced consumption as well as full abstinence (Mason, 2001; Nutt, 2014). Acamprosate, at high concentrations well above those that occur clinically (1–3 μM), has been reported to inhibit glutamate receptor-activated responses (1 mM), enhance *N*-methyl-D-aspartate (NMDA) receptor function (300 μM), and exhibit weak antagonism of the NMDA receptor with partial agonism of the polyamine site of the NMDA receptor. Thus, the use of acamprosate as an adjunct to psychosocial interventions in alcohol-dependent patients provides modest but potentially valuable improvements in alcohol-consumption outcomes (Plosker, 2015).

In addition to the FDA approved medications, there are many other medications available. These agents include Fluoxetine, Duloxetine, Tiagabine, Levetiracetam, Gabapentin, Pregabalin, Sertraline, Citalopram, Ritanserin, Aripiprazole, Ondansetron, Quetiapine, Nalmefene and Topiramate. Many supporting reports are available for the potential usage of these medications in the treatment of AUDs, although they are not approved by the FDA yet. Some of them are discussed in detail in the following section.

3. FDA approved medications with potential to be repurposed for alcohol use disorders

3.1. Anticonvulsants

3.1.1. Gabapentin

Gabapentin [1-(aminomethyl) cyclohexaneacetic acid] was approved in 1993 to treat partial seizures in epilepsy (Gabapentin, ASHSP, 2015). It is also used for the treatment of neuropathic pain in diabetic neuropathy, post-herpetic neuralgia (Moore, Wiffen, Derry, Toelle, & Rice, 2014), central neuropathic pain, hot flashes and restless leg syndrome (Attal et al., 2010; Wijemanne & Jankovic, 2015). Sleepiness and dizziness are the common side effects and patients with kidney problems should use lower doses. It is unclear whether it is safe to use during pregnancy or breastfeeding (Gabapentin Pregnancy and Breastfeeding, 2016). Gabapentin resembles to the endogenous neurotransmitter GABA and does not bind GABA receptors at concentrations at or below 1 mM (Patel & Dickenson, 2016; Product Monograph, 2014). It modulates the enzymatic activities of glutamate decarboxylase and branched chain aminotransferase, both of which are known to be involved in GABA biosynthesis. Gabapentin has been reported to enhance the synthesis of GABA and increase non-synaptic GABA neurotransmission in vitro (Taylor, 1997). It has been shown to bind to the α2δ-1 subunit of voltage gated calcium ion channels, which contribute to its pain attenuation effects on diabetic neuropathy and post-herpetic neuralgia. Other neurophysiological findings indicate that gabapentin also interacts with NMDA receptors, protein kinase C, and inflammatory cytokines (Kukkar, Bali, Singh, & Jaggi, 2013).

Preclinical evaluation of gabapentin shows sensitivity to moderate alcohol doses and alcohol self-administration in rats with history of moderate alcohol drinking. Gabapentin (0, 10, 30, 60 mg/kg i.g.) pretreatment potentiated the interoceptive effects of both experimenter-administered and self-administered alcohol in discrimination-trained rats. Gabapentin doses (30 and 120 mg/kg) showed partial alcohol-like discriminative stimulus when given alone. In the self-administration trained rats, gabapentin pretreatment (60 mg/kg) resulted in escalation in alcohol self-administration suggesting that gabapentin may mediate the potentiation of alcohol effects by increasing alcohol self-administration in non-dependent populations (Besheer, Frisbee, Randall, Jaramillo, & Masciello, 2016).

A randomized, double-blind study, involving US veterans meeting DSM-IV diagnostic criteria for alcohol dependence, showed that gabapentin reduced alcohol craving. Seventeen out of the 26 patients received gabapentin (1200 mg orally for 3 days, followed by 900, 600, and 300 mg for 1 day each) and nine of them received chlordiazepoxide (100 mg orally for 3 days, followed by 75, 50, and 25 mg for 1 day each). In ambulatory veterans with symptoms of alcohol withdrawal, gabapentin treatment resulted in significantly greater reduction in sedation on the Epworth Sleepiness Scale (ESS) and a trend to reduced alcohol craving on Penn Alcohol Craving Scale (PACS) by the end of treatment compared to chlordiazepoxide treatment. Despite the limitation of the small sample size, this study showing a reduction in sleepiness and less alcohol craving warrants a replicate study with a larger sample group (Stock, Carpenter, Ying, & Greene, 2013). A recent clinical study lasting for 12 weeks was conducted between 2004 and 2010 at a single-site, outpatient clinical research facility adjoining a general medical hospital. Gabapentin (particularly the 1800-mg dosage) was used to evaluate gabapentin as a pharmacological treatment option for alcohol dependence in primary care. A 12 week, double-blind, placebo-controlled, randomized dose-ranging trial of 150 men and women showed that it was effective in treating alcohol dependence and relapse-related symptoms of insomnia, dysphoria, and craving. There were linear gabapentin dose effects on increasing rates of complete abstinence. Compared with placebo, gabapentin, 1800 mg, increased the relative benefits of complete abstinence from heavy drinking (Mason et al., 2014). The role of gabapentin to reduce alcohol craving and consumption was evaluated in a subacute human laboratory study by employing a double-blind, placebo-controlled treatment in 35 non-treatment seeking alcoholic subjects. Gabapentin (1200 mg/day or 0 mg/day) was given for 8 days. This study suggests that there was no overall effect of gabapentin on drinking or craving and that it was well tolerated (Myrick, Anton, Voronin, Wang, & Henderson, 2007).

3.1.2. Topiramate

2,3:4,5-Bis-*O*-(1-methylethylidene)-β-D-fructopyranose sulfamate, marketed under the trade name Topamax, is an anticonvulsant, used for the treatment of epilepsy in adults as well as in children (Topamax, FDA, 2011) and used for treating migraines. Minor side effects include

dizziness, weight loss or gain, paresthesia, anemia, nausea, dilated pupil, somnolence, dizziness, agitation and abnormally uncoordinated body moments, and may become fatal in combination with multi-drug exposure (Lofton & Klein-Schwartz, 2005; Wills et al., 2014). Topiramate mediates its effects through multiple mechanisms, including activation of voltage-gated sodium channels, high voltage-activated calcium channels, GABA-A type receptor, AMPA/kainate receptors and carbonic anhydrase isozymes (Porter, Dhir, Macdonald, & Rogawski, 2012). However, post-translational modifications such as phosphorylation of these proteins are also reported to exhibit their indirect effect (Meldrum & Rogawski, 2007). Among them, sodium channels are thought to be a major target due to the role they play in seizures.

In addition to its role as an anticonvulsant medication, topiramate has been used in AUD with moderate to good success rates. For instance, Junqueira-Ayres et al. studied the effects of topiramate on anxiety and AWS. They reported that when topiramate (40 mg/kg, i.g.) was given acutely and chronically to rats that showed anxiety like behavior after alcohol withdrawal, it significantly reduced anxiety indicating the anti-anxiolytic effect of topiramate (Junqueira-Ayres et al., 2017). They also reported that there were no signs of tolerance and dependence. Echeverry-Alzate et al., studied the effects of topiramate on operant ethanol self-administration along with cocaine in Wistar rats ($N = 128$) by treating with topiramate (2.5–40 mg/kg, i.p.). Topiramate inhibited cocaine-induced increased response to ethanol dose dependently without mediating any motor impairment by itself when topiramate administered before alcohol access, but not when topiramate was administered before cocaine and did not block cocaine-induced psychomotor stimulation. Topiramate reduced blood ethanol levels but has no effect on cocaine metabolism. Ethanol increased gene expressions of DNA and RNA methyltransferases, whereas histone aeacetylase-2 and glutamate receptor kainite-1 were increased by cocaine treatment. The upregulation of dopamine and opioid receptor genes were reported when topiramate and cocaine were co-administered, suggesting that topiramate regulates the expression of genes in response to alcohol and cocaine-induced behavior and inhibits the cocaine-induced increase in operant ethanol self -administration (Echeverry-Alzate et al., 2004).

In a clinical trial, the effects of low dose topiramate were studied for the treatment of alcohol dependence. In an open-label controlled study, thirty patients received 75 mg of topiramate per day in addition to psychotherapeutic treatment, in comparison to the control group. After 4–6 weeks of monitoring for the symptoms of depression, anxiety and craving, they found that patients who received topiramate showed a marked improvement in depressive, anxiety and obsessive-compulsive drinking symptoms in comparison to controls. In addition, the relapse rate was shown to be lower in the patients receiving topiramate, suggesting that a low dose of topiramate was effective in reducing craving, symptoms of depression and anxiety (Paparrigopoulos, Tzavellas, Karaiskos, Kourlaba, & Liappas, 2011).

Baltieri et al., conducted a comparative study of topiramate and naltrexone for the treatment of alcohol dependence. In a 12-week, double-blind, placebo-controlled trial, patients received either topiramate (300 mg/day), naltrexone (50 mg/day), or placebo. In comparison to those receiving naltrexone and placebo patients receiving topiramate showed reduced relapse time, cumulative abstinence duration and diminished drinking, suggesting that topiramate is more efficient than naltrexone in preventing of alcoholism relapse (Baltieri, Daro, Ribeiro, & de Andrade, 2008). Similarly, topiramate and naltrexone were evaluated for percent of subjects with no heavy drinking days (PSNHDDs) in two large alcohol clinical trials, namely COMBINE and a multi-site topiramate trial. In these trials, PSNHDDs and other traditional end points were drawn for topiramate, naltrexone, acamprosate and placebo groups. PSNHDD effect sizes were significant for both topiramate and naltrexone. A 2-month grace period for naltrexone and a 1-month grace period for topiramate have been shown to be greater than the majority of traditional outcome measures. Subjects with no HDDs during treatment fared better than those with some HDDs on drinking outcomes and alcohol-related consequences (Falk et al., 2010). Despite the beneficial effects of topiramate in reducing relapse, alcohol dependence, anxiety and craving, this medication has not been approved for the treatment of alcohol dependence in either Europe or USA and needs further investigations (Michalak & Biala, 2016). The recent studies from Anthenelli et al., showed that topiramate was not effective in the patients who were alcohol dependent male smokers. Topiramate was only effective in preventing and reducing alcohol consumption in current alcohol drinkers and prevents relapse in recently detoxified alcoholics, indicating that topiramate has some potential to treat non-alcohol dependent male smokers (Anthenelli et al., 2017).

3.1.3. Pregabalin

[(3*S*)-3-(aminomethyl)-5-methylhexanoic acid], is a medication marketed under the brand name Lyrica, for the treatment of epilepsy, neuropathic pain, fibromyalgia, and generalized anxiety disorders (Frampton, 2014; Patel & Dickenson, 2016; Pregabalin, ASHSP, 2015). In addition, pregabalin can be used for treating restless leg syndrome (Kirsch, 2013), prevention of migraines, social anxiety disorders (Pregabalin Lyrica Part I, 2015) and alcohol withdrawal (Mirijello et al., 2015). Common side effects include: sleepiness, confusion, memory, poor motor coordination, dry mouth, vision, weight gain and potentially serious side effects include angioedema and drug misuse. There is an increased risk of suicide and addiction, if taken in high doses over a longer period (Pregabalin, ASHSP, 2015). Pregabalin, a close analogue of the inhibitory neurotransmitter GABA and a gabapentinoid (Bryans & Wustrow, 1999; Lapin, 2001), is a GABAergic anticonvulsant and a depressant of the CNS. Although pregabalin is an analogue of GABA, it does not bind directly to $GABA_A$, $GABA_B$, benzodiazepine, or opioid receptors, and does not block sodium channels, instead it binds with high affinity to the $\alpha_2\delta$-1 $\alpha_2\delta$-2 subunit-containing voltage-gated calcium channels (VGCC) (Li et al., 2011). The $\alpha_2\delta$-1 and $\alpha_2\delta$-2 subunits are expressed throughout the brain regions such as; cerebral cortex, hippocampus, cerebellum including DRG neurons. Binding of pregabalin correlates partially with some excitatory GABAergic neurons and some with inhibitory interneurons (Dolphin, 2012) and exerts distinctive functions in the CNS (Cole et al., 2005). Pregabalin increases the density of GABA transporter proteins and increases the rate of functional GABA transport (DailyMed, 2015).

Stopponi et al. used genetically selected alcohol-preferring Marchigian Sardinian (msP) rats, and evaluated the effect of pregabalin on alcohol drinking and relapse with alcohol seeking, induced by stress or environmental conditioning factors (Stopponi et al., 2012). The results showed that treatment with pregabalin (0, 10, 30 and 60 mg/kg) given orally selectively reduced home cage alcohol drinking in msP rats. In the alcohol reinstatement model, pregabalin (0, 10 and 30 mg/kg) abolished alcohol seeking behavior elicited by the pharmacological stressor yohimbine, suggesting its role in the treatment of alcohol addiction. The effects of pregabalin were evaluated on nitroglycerin (NTG)-induced hyperalgesia in male Sprague-Dawley rats. Pretreatment of rats with pregabalin (10–30 mg/kg, s.c.) 30 min prior to NTG (10 mg/kg, i.p) injection alleviated NTG-induced hyperalgesia and suppressed peripheral calcitonin-gene-related peptide (CGRP) (Di et al., 2015). Previously, the anticonvulsant effects of pregabalin were evaluated in mice. Adult mice were chronically exposed to ethanol and upon withdrawal examined for the behavioral signs of seizure activity such as handling-induced convulsions (HIC) or abnormalities in EEG activity recorded from cortical and subcortical regions. Pregabalin (50–200 mg/kg, i.p.) administered after 1 and 4 h of withdrawal dose dependently reduced HIV and EEG activity in comparison to vehicle-treated mice, suggesting that pregabalin might be a potential therapeutic agent for the management of alcohol detoxification (Becker, Myrick, & Veatch, 2006).

Martinotti et al., studied in a randomized double-blind comparison trial the effects of pregabalin and naltrexone by recruiting seventy-one

patients and investigated the alcohol drinking indices (alcohol craving and relapse prevention) and psychiatric symptoms. Detoxified patients were randomized into two groups that received either pregabalin (150–450 mg) and naltrexone (50 mg) for 16 weeks. The results showed the pregabalin effects are similar to naltrexone in improving alcohol drinking indices, relapse rate and craving scores. In addition, pregabalin was more favorable in reducing the specific symptoms of anxiety, hostility and psychoticism and showed better outcome in patients reporting a comorbid psychiatric disorder (Martinotti, di Nicola, Frustaci, et al., 2010; Martinotti, Di Nicola, Tedeschi, et al., 2010). In another study, Addolorato & Leggio, 2010, has compared the effects of pregabalin with other medications for the treatment of AWS. In this study, 111 alcoholic patients suffering with AWS were randomized and given pregabalin (450 mg/day), tiapride (800 mg/day) and lorazepam (10 mg/day) for 14 days. Among these medications, pregabalin showed significant reduction in AWS and many patients remained alcohol-free, suggesting that pregabalin has pharmacotherapeutic potential for AWS (Addolorato & Leggio, 2010). In a randomized double-blind placebo-controlled trial during inpatient alcohol detoxification, alcohol dependent patients received pregabalin or placebo on a fixed dose schedule starting with 300 mg/day for 6 days. Both pregabalin and placebo showed similar efficacy according to alterations of scores of the AWS, clinical institute withdrawal assessment for alcohol revised (CIWA-Ar) scores and neuropsychological scales. The frequency of adverse events and dropouts did not differ between the treatment groups and demonstrated the relative safety of pregabalin in the treatment of AWS (Förg et al., 2012).

3.2. Antipsychotics

3.2.1. Quetiapine

Quetiapine, marketed under the trade name Seroquel, is an atypical antipsychotic medication approved for the treatment of schizophrenia, bipolar disorder, and major depressive disorder. It was approved by FDA in the year 1997. There are now several generic versions that are available and have been used for these disorders. Quetiapine exhibits antagonistic effects on serotonin, dopamine, and adrenergic receptors, and shows a potent antihistamine effect with clinically negligible anticholinergic properties. Quetiapine binds strongly to the serotonin receptors and acts as partial agonist on 5-HT_{1A} receptors (Guzman, 2013). Some of the antagonized receptors (serotonin, norepinephrine) are actually auto-receptors and blocking these receptors increases the release of neurotransmitters.

Celikyurt et al., evaluated the effects of quetiapine in adult male Wistar rats on AWS. Quetiapine was compared with other medications after giving ethanol (7.2% v/v for 21 days). Quetiapine (8 & 16 mg/kg, i.p.), risperidone (1 & 2 mg/kg, i.p.) and ziprasidone (0.5 & 1 mg/kg, i.p.) were given and measured ethanol withdrawal symptoms after 1, 2, 4 and 6 h. All three drugs showed significant reduction in AWS and reduced incidence of audiogenic seizures, suggesting that quetiapine and risperidone were more effective than ziprasidone in attenuating AWS in rats and might help in controlling AWS in ethanol-dependent patients (Celikyurt et al., 2011).

The efficacy of quetiapine was evaluated by Kurlawala & Vatsalya, for the treatment of akathisia (involuntary body movements) in a very heavy alcohol drinking patients. It has been shown to alleviate symptoms of akathisia in a clinical trial. Treatment with quetiapine progressively lowered the occurrence of akathisia in alcohol dependent patients with no symptoms of depression, and over time in heavy drinkers who had clinically significant symptoms of depression (Kurlawala & Vatsalya, 2016). Several preliminary open-label and retrospective studies reported that quetiapine reduced alcohol intake in alcohol-dependent patients (Martinotti et al., 2008; Monnelly, Ciraulo, Knapp, LoCastro, & Sepulveda, 2004). In contrast, Kampman et al., reported that patients characterized by the late age onset of drinking problem and low severity of alcohol dependence did not benefit from quetiapine (Kampman et al., 2007). Litten et al., conducted a multisite RCT by enrolling 224 alcohol-dependent patients who reported very heavy drinking across five clinical sites. Two weeks after randomization, patients received a titrated target dose of quetiapine fumarate extended-release (Seroquel XR) 400 mg/day during weeks 3 to 11 and a tapered dose in the final week. They found no difference between the quetiapine treated patients and placebo group in terms of percent heavy drinking days and other alcohol drinking outcomes. However, quetiapine significantly reduced depressive symptoms and improved sleep (Litten et al., 2012).

Quetiapine was evaluated in another randomized, double-blind, placebo-controlled trial of patients with bipolar disorder, depression and alcohol dependence. Ninety outpatients with bipolar disorder (I and II) with depression and mixed mood state and alcohol dependence patients who were randomized and given quetiapine (600 mg/day) for 12 weeks did not show significance differences in reducing alcohol consumption in patients with bipolar disorders (Brown et al., 2014). These data suggest that, despite quetiapine showing promising results in preliminary human studies, it was not effective in a single site (Martinotti et al., 2008; Monnelly et al., 2004) and multisite RCT (Litten et al., 2012; Litten et al., 2016).

3.2.2. Aripiprazole

Aripiprazole, is an atypical antipsychotic medication sold under the brand name Abilify. It is a partial dopamine agonist used to treat schizophrenia and bipolar disorder. Aripiprazole (ARI), is also used for the treatment of major depressive disorder (MDD), tic disorders and autism. Side effects include neuroleptic malignant syndrome, tardive dyskinesia, high blood pressure in diabetics and dementia (Ramsberg, Asseburg, & Henriksson, 2012). ARI functions as a D2 and 5-HT1A receptor partial agonist and as an antagonist of the 5-HT2A and 5-HT7 receptor (Burstein et al., 2005; Jordan et al., 2002; Lawler et al., 1999). It has moderate affinities for histamine and α-adrenergic receptors and serotonin transporters. It is metabolized by the hepatic enzymes CYP2D6 and CYP3A4. The CNS dopamine system is implicated in both reward processing/memory and the inhibitory control mechanisms at the subcortical and cortical regions of the brain.

Alcohol dependence increases the risk of depression in patients, causing damage and deficiencies in brain function, resulting in cognitive function impairment. However, many studies have suggested the antidepressant effects of ARI in animal model and in humans. Burda-Malarz et al., assessed the antidepressant effect of ARI by employing Porsolt's forced swimming test and Morris water maze test in alcohol-preferring rats (EtPRs). Administration of ARI (6 mg/kg i.p.), fluoxetine (FLX; 5 mg/kg p.o.) and combined administration of both drugs in these behavioral tests in alcohol-dependent rats showed no antidepressant and procognitive effects of either ARI or FLX in EtPRs after acute and chronic treatment. In fact, combined administration of both drugs leads to spatial memory deterioration in the animal study (Burda-Malarz et al., 2014a). In another study by using alcohol non-preferring rats (EtNPRs), both ARI and FLX either administered alone or in combination did not show any antidepressant and precognitive effects. Combined administration of both drugs led to anxiogenic effect and spatial memory deterioration in EtNPRs (Burda-Malarz et al., 2014b). The role of ARI as a potential medication for the treatment of alcohol-dependence with psychotic disorders was evaluated in a preclinical chronic alcohol self-administration (CASA) animal model. During oral administration of ARI at doses 1, and 3 mg/kg on 4% alcohol intake, ARI did not reduce alcohol intake substantially (13 and 28%, respectively). However, ARI at 10 mg/kg dose significantly reduced alcohol intake. Striatal D_2R occupancy and brain exposure of ARI were considerably higher in CASA rats when compared to normal rats, suggesting that ARI could be a potential medication to treat the patients dually diagnosed with alcohol abuse and psychotic disorders (Nirogi et al., 2013).

Han et al., reported that the combination of Escitalopram (a selective SSRI) with ARI improved depressive symptoms and reduced

craving for alcohol and cue-induced brain activity in patients with co-morbid alcohol dependence and major depressive disorder (MDD). Thirty five subjects with co-morbid alcohol dependence and MDD were recruited in this study and divided into two groups. One received ARI + escitalopram (ARI 5–15 mg + escitalopram 10–20 mg/day for 6 weeks) and other escitalopram alone. Both escitalopram alone and ARI + escitalopram group were shown to reduce Beck Depression Inventory and clinical global index-severity (CGI-S) scores, however, reduced alcohol craving in ARI + escitalopram group. These findings suggest that the effects of ARI on anterior cingulate cortex might mediate the successful treatment of alcohol dependence in patients with MDD (Han, Kim, Choi, Min, & Renshaw, 2013). Myrick et al., evaluated the effects of aripiprazole on alcohol cue-induced brain activation and drinking in alcoholics. 30 subjects with no-treatment seeking alcoholics were URN randomized (biased-coin approach) into control and treatment groups and given 15 mg/day for 14 days. Brain activity analysis revealed increased activation in placebo-treated subjects in the right ventral striatum, however activation in this area in aripiprazole-treated subjects were attenuated resulting in significantly less heavy drinking sessions during the treatment period. These results suggest that aripiprazole attenuates heavy drinking mediated by cue-induced brain activation and voluntary drinking (Myrick et al., 2010).

The effects of ARI on the aspects of impulsivity were evaluated in non-treatment-seeking AUD individuals based on their level of impulsivity and self-control in a well-validated clinical trial. Ninety-nine subjects with heavy drinking and meeting DSM-IV criteria were randomized into two groups. The ARI group received 15 mg/day for 8 days. There was no effect of ARI or interaction on a Barratt Impulsiveness Scale (BIS-11) score during the natural drinking period in both the groups, however, it was effective on bar-lab drinking. ARI also reduced the total number of drinks consumed among individuals with low self-control and increased latency to consume more drinks among those with high impulsivity. This paradigm forced a choice between immediate drinking reward and delayed monetary reward, suggesting ARI-induced targeting of cortical dopamine/serotonin balance might show clinical benefits of reduced drinking among individuals with impulsivity/low self-control (Anton, Schacht, Voronin, & Randall, 2017).

3.3. Antidepressants

3.3.1. Duloxetine

Duloxetine, sold under the brand name Cymbalta (Drugs.com, 2016), a selective serotonin and norepinephrine re-uptake inhibitor (SNRI), is mostly prescribed for major depression and generalized anxiety disorder, fibromyalgia and neuropathic pain (Duloxetine Monograph, ASHSP, 2015). According to a 2014 Cochrane review, duloxetine was reported beneficial for the treatment of diabetic neuropathy and fibromyalgia (Lunn, Hughes, & Wiffen, 2014). Nevertheless, the French medical journal Prescrire branded duloxetine as a good drug with considerable risk of side effects (*Prescrire International*, 2014). Duloxetine increases DA specifically in the prefrontal cortex (PFC), where there are few DA reuptake pumps, through the inhibition of NE re-uptake pumps (Stahl, 2013). However, duloxetine has no significant affinity for dopaminergic, cholinergic, histaminergic, opioid, glutamate, and GABA reuptake transporters and can therefore be a selective reuptake inhibitor of the 5-HT and NE transporters. Circulating metabolites of duloxetine do not contribute significantly to the pharmacologic activity (Bymaster & Lee, 2005; Stahl & Grady, 2005).

In a comparative study by using putative noradrenergic signaling inhibitors (prazosin, propranolol, and duloxetine) in adult male Long Evans rats, Skelly & Weiner have reported that prazosin (1.5 mg/kg/day) and duloxetine (1.5 mg/kg/day) significantly decreased ethanol self-administration by reducing anxiety-like behavior (Skelly & Weiner, 2014). They have also reported that exposure to stress, particularly during adolescence, may increase the risk of developing psychotic conditions, anxiety and post-traumatic stress disorders (PTSD), resulting in excessive alcohol intake in adulthood. By utilizing anxiolytic medications, these investigators confirmed that adolescent social isolation increases anxiety-like behavior and enhances ethanol intake. They suggested that disrupted noradrenergic signaling may contribute to escalating ethanol drinking following social isolation, associated with early life stress, making these noradrenergic drugs potential therapeutic agents (Skelly, Chappell, Carter, & Weiner, 2015). Previously, Ji et al., has reported the effects of duloxetine and other medications in voluntary and self -administration of alcohol in male Wistar rats in daily limited access two-bottle choice and operant drinking sessions. Injections of duloxetine (0–8 mg/kg every 3 to 4 days, i.p.), naltrexone (0–450 mg/kg every 3 to 4 days, i.p.) and MPZP (0–20 mg/kg every 3 to 4 days, i.p.) were given to Wistar rats. The results showed duloxetine dose dependently suppressed two-bottle choice alcohol binge drinking and operant alcohol responding as well as operant supersac drinking, but did not affect two-bottle choice supersac drinking. The other drugs showed moderate to no effects on alcohol or supersac consumption (Ji, Gilpin, Richardson, Rivier, & Koob, 2008).

Recently, the effects of antidepressants including duloxetine and other SSRIs were evaluated in an observational study based on a multicenter drug surveillance (Arzneimittelsicherheit in der Psychiatrie) program in German speaking countries such as; Austria, Germany, and Switzerland. They recorded the severe drug reactions in psychiatric inpatients (n = 184,234) in 80 psychiatric hospitals and found 149 cases of drug-induced liver injury (DILI). Many antidepressants including fluoxetine, paroxetine and duloxetine are inhibitors of CYP2D6 and induce DILI (Friedrich et al., 2016), especially in elderly patients (Voican et al., 2014). Similar observations were reported by Kang et al., in South Korea. Three patients, a 22 years old Korean male with depression, a 65 year old Korean female with MDD and a 37 year old Korean male with MDD were given duloxetine (30–60 mg/day) during the course of treatment in the clinic. Duloxetine was administered to these patients along with the other medications for the treatment of depression showed higher levels of ALT, AST and ALP in liver function tests, suggesting that duloxetine administration can induce liver injury in patients with MDD and in patients with preexisting chronic liver disease or alcohol consumption (Kang et al., 2011).

3.3.2. Venlafaxine

Venlafaxine, marketed as Effexor, Effexor XR, Lanvexin, Viepax and Trevilor, is used as an antidepressant medication. This medicine belongs to an SNRI group of inhibitors (Bymaster et al., 2001; Muth et al., 1986; Yardley et al., 1990) that increase the concentrations of the neurotransmitters serotonin and NE in the body and the brain. Currently it is used for the treatment of MDD, generalized anxiety disorder (GAD), panic disorder and social phobia (Joint Formulary Committee, 2013; Rossi, 2013). Its metabolite (*O*-desmethylvenlafaxine) also acts as another antidepressant drug called desvenlafaxine and sold under the brand name Pristiq (Pae, 2011). Venlafaxine works on both serotoninergic and adrenergic systems, and reduces the cataplexy (a form of muscle weakness) episodes in patients with the sleep disorder narcolepsy (Grothe, Schecjner, & Albano, 2004). It is also reported as a serotonin-norepinephrine-dopamine reuptake inhibitor (SNDRI) based on its dose-dependent effects on various neurotransmitter systems (ClinicalTrials.gov, 2008; Goeringer, McIntyre, & Drummer, 2001; Wellington & Perry, 2001).

Cognitive impairments are associated with depression and decrease grey matter volume in brain that may affect cognitive function and brain structure (Droppa et al., 2017). In addition, venlafaxine indirectly affects the opioid receptors (mu-, kappa1–kappa3- and delta-opioid receptor subtypes) as well as the alpha2-adrenergic receptor. Additionally, intraperitoneal injection of venlafaxine was shown to induce naloxone-reversible antinociceptive effect in a dose-dependent manner. These findings suggest venlafaxine's seemingly superior efficacy in severe depression conditions (Schreiber, Bleich, & Pick, 2002). Trouvin

et al., demonstrated in their eleven randomized clinical trials that, in nine out of eleven clinical trials venlafaxine was found to be effective against neuropathic pain with mild to moderate adverse events, suggesting that venlafaxine is associated with greater improvement in depression severity (Trouvin, Perrot, & Lloret-Linares, 2017). In another clinical trial, Ciraulo et al., evaluated the efficacy of venlafaxine in comorbid AUD and anxiety disorders. A randomized controlled trial comprising of 81 patients divided into 4 groups such as cognitive behavioral treatment (CBT), progressive muscle relaxation therapy (PMR), placebo-CBT and placebo-PMR with or without venlafaxine (225 mg/day) was conducted. After 11 weeks of treatment on CBT and PMR conditions, venlafaxine did not modulate anxiety and drinking in three groups, however, there was significant decrease in heavy drinking in placebo-CBT group (Ciraulo et al., 2013). Some open-label and three double-blind studies have suggested the efficacy of venlafaxine in the treatment of attention deficit hyperactivity disorder (ADHD) and PTSD (Ghanizadeh, Freeman, & Berk, 2013; Pae, Lim, Ajwani, Lee, & Patkar, 2007). In contrast, there are several other reports that showed the toxicity of this medication to liver and other disease conditions such as cholestatic hepatitis (Stadlmann et al., 2012), jaundice and liver failure (Detry et al., 2009), and hepatotoxicity in patient with ulcerative colitis (Yildirim et al., 2009).

Recent studies with guanfacine, an α-2-adrenoreceptor agonist and FDA-approved ADHD medication, reported to attenuate stress-induced relapse of several drugs of abuse including alcohol. The effects of guanfacine (0.6 mg/kg injection once a week, 7 days apart) on voluntary alcohol intake, the alcohol deprivation effect, alcohol seeking behavior and cue priming-induced reinstatement was evaluated in Wistar rats that had voluntarily consumed alcohol around two months. Guanfacine decreased alcohol intake in high alcohol-consuming rats in comparison to naltrexone. Repeated guanfacine treatment induced a long-lasting decrease in alcohol intake and attenuated the alcohol deprivation effect, alcohol seeking and cue/priming-induced reinstatement of alcohol seeking. Even though higher doses (1.5, 1 mg/kg doses) guanfacine used by other groups (Opitz, 1990: Smith & Aston-Jones, 2011) and results from the same group that used 1 mg/kg of guanfacine clearly decreased alcohol intake in a pilot study and in the open field test. But this effect was due to sedative and nonspecific effect due to higher doses. However, with 0.6 mg/kg, the nonspecific effects of sedation decreased as guanfacine increased significant water intake, but not in alcohol-naïve rats, suggesting that guanfacine mediated effects are specific that improve prefrontal connectivity through modulation of glutamatergic neurons (Fredriksson et al., 2015).

In another study, Ivermectin (a semi-synthetic macrocyclic lactone; an anti-parasitic agent), that has been to shown to reduce alcohol intake in mice (Wyatt et al., 2014; Yardley et al., 2012), was used in a randomized, placebo-controlled crossover clinical trial. Eleven patients with AUD participated in a cue exposure paradigm received 30 mg oral every day (QD) followed by 0.08 g/dl intravenous alcohol administration. When compared with placebo, Ivermectin did not reduce cue-induced craving and did not significantly affect the subjective response to alcohol (Roche et al., 2016). Furthermore, a previous study indicated that ivermectin does not appear to cross the blood-brain barrier, minimizing its role in treating AUDs (Geyer, Gavrilova, & Petzinger, 2009). However, MacKillop et al. reported that D-cycloserine (D-4-amino-3-isoxazolidone: an antibiotic compound that is also a partial agonist for NMDA receptor) enhanced extinction to cue-elicited craving for alcohol in individuals with AUDs (MacKillop et al., 2015). Although, D-cycloserine has been shown to attenuate reacquisition of CPP in mice (Groblewski, Lattal, & Cunningham, 2009) and reduce priming-based reinstatement in rats (Vengelience et al., 2008) and are consistent with other addictive drugs (Myers & Carlezon, 2010). However, these effects on alcohol related extinction have not been reproduced in humans (MacKillop et al., 2015).

The role of the endocannabinoid system in the AUD has been evaluated by many laboratories. By using animal and cell culture models, it has been demonstrated that chronic ethanol exposure causes an increase in endocannabinoid levels and downregulate cannabinoid receptor-1 (CB1) (Basavarajappa & Hungund, 2001). In rodents, treatment with a CB1 receptor antagonist SR141716A (Rimonabant), or genetic deletion of CB1 receptors was shown to reduce voluntary alcohol drinking (Hungund, Szakall, Adam, Basavarajappa, & Vadasz, 2003; Naassila, Pierrefiche, Ledent, & Daoust, 2004; Vinod et al., 2008), ethanol-stimulated dopamine release in the NAc, operant self-administration of ethanol (Cippitelli et al., 2005; Cippitelli et al., 2007; Cippitelli et al., 2008; Economidou et al., 2006), sensitization to the locomotor effects of ethanol (Marinho et al., 2015), and reinstatement/relapse of ethanol-motivated behavior. Similarly, down-regulation of CB1 receptors has been reported in multiple regions of the human alcoholic brains as evaluated by positron emission tomography (PET) (Normandin et al., 2015). Despite the beneficial effects in rodent studies, the clinical utility of the Rimonabant was limited due to neuropsychiatric side effects and is not in use for AUD research.

3.4. Other medications

3.4.1. Baclofen [β-(4-chlorophenyl)-γ-aminobutyric acid (β-(4-chlorophenyl)-GABA)]

Baclofen is an agonist of $GABA_B$-receptors, and is used in alcohol-dependent patients at higher doses for the treatment of alcohol craving. A retrospective study of baclofen self-poisoning was reported by the western France Poison Control Center (PCC), suggesting that baclofen, when prescribed in high doses, may lead to severe poisoning, particularly in patients with psychiatric illnesses (Boels et al., 2017).

Recent studies suggested the bidirectional effects of baclofen enantiomers where R(+)-baclofen, suppressed alcohol intake and R(−) baclofen stimulated alcohol intake in mice. To further evaluate the enantioselectivity of baclofen on the reinforcing effects of alcohol in rats, Lorrai and his group used selectively bred Sardinian alcohol-preferring (sP) rats. In sP rats, 3 mg/kg (±)-baclofen reduced the number of lever responses for alcohol administration and estimated amount of self-administered alcohol by approximately 60% in comparison to vehicle treatment. Treatment with 1.5 mg/kg R(+)-baclofen decreased both outcome measures to an extent like that of the decreasing effect of 3 mg/kg (±)-baclofen. Conversely, treatment with all doses of S (−)-baclofen failed to modulate alcohol self-administration (Lorrai, Maccioni, Gessa, & Colombo, 2016).

Morley et al., conducted a double blind, placebo-controlled, randomized clinical trial by enrolling sixty-nine patients randomized to receive placebo, 30 or 60 mg baclofen for 12 weeks. Both doses of baclofen were beneficial in reducing alcohol-dependent comorbid anxiety and are well tolerated without any serious adverse events (Morley et al., 2014). In another clinical trial, baclofen has been investigated to reduce craving, voluntary alcohol intake and withdrawal syndrome of alcoholic patients. Sixty-seven outpatients enrolled in this study were examined during 3 months after treatment initiation. Baclofen was administered by the oral route. Craving level was assessed by the Obsessive-Compulsive Drinking Scale (OCDS). A population pharmacokinetic (PK) pharmacodynamic analysis of the OCDS variation following baclofen administration was performed. Demographic data, biological data, and tobacco consumption were evaluated for their influence on the outcome parameter. Baclofen treatment decreased craving in all patients, however, there was a wide interindividual variability in response (Imbert, Alvarez, & Simon, 2015). Previously randomized, placebo-controlled trials with low-to-medium doses of baclofen (30–60 mg) showed inconsistent results, but case studies suggested a dose-response effect with positive outcomes in patients on high doses of baclofen (up to 270 mg). Its prescription was permitted temporarily for the treatment of alcohol dependence (AD), now it is widely prescribed in France. It has been reported that although adverse events were frequent, they were generally mild and transient. One medication-related serious adverse event occurred in the high-dose

baclofen group, suggesting a large-scale prescription of baclofen for the treatment of AD seems premature and should be reconsidered (Beraha et al., 2016).

Similarly, limited clinical trials and case-reports yielded conflicting results regarding the efficacy of baclofen (a $GABA_B$ agonist) in the treatment of alcohol dependence. A double-blind, placebo-controlled, randomized clinical trial was conducted in Israel comparing 50 mg/day of baclofen or placebo over 12 weeks, in addition to a standard psychosocial intervention program with 26-week and 52-week follow-up observations. No inter-group differences were found in the percentages of heavy drinking and abstinent days. A significant reduction in levels of distress, depression and craving with improved HRQL occurred for both arms, whereas self-efficacy and social support remained unchanged in both groups. Unlike previous positive trials in Italy and a negative trial in the USA, they found no evidence of superiority of baclofen over placebo (Ponizovsky, Rosca, Aronovich, Weizman, & Grinshpoon, 2015). Furthermore, Reynaud et al., recently reported that baclofen (180 mg/day) did not significantly improve alcohol abstinence in a clinical study consisting of 320 alcohol-dependent patients (i.e., 158 baclofen-treated patients and 162 placebo group) for 7-week titration followed by 17-weeks maintenance baclofen doses, although there was a tendency for reduced alcohol consumption and craving assess by Obsessive-Compulsive Drinking Scale in baclofen-treated patients. These reports with mixed outcome results suggest that more trials are needed to either verify or discard a possible clinical efficacy of baclofen for alcohol dependence (Reynaud et al., 2017).

3.4.2. Ondansetron

Ondansetron is a selective 5-HT3 receptor antagonist, with low affinity to dopamine receptors, approved by FDA in the year 1991 and sold under the trade name Zofran. It is generally used for the treatment of nausea and vomiting during chemotherapy and radiation therapy in many cancer patients. It is also used by the pregnant women for morning sickness.

The effects of ondansetron (0–0.01 mg/kg) and topiramate (0–10 mg/kg) were evaluated alone or in combination for the treatment of alcohol dependence in alcohol preferring (P) rats and Wistar rats ($N = 20$ each) in a 24 h access free choice paradigm. Acute administration of topiramate alone or in combination reduced alcohol consumption in heavy drinking P rats but not in lighter-drinking P rats and Wistar rats, suggesting that combination of topiramate and ondansetron has a potential to treat relapse and alcohol drinking in heavy alcohol drinkers (Lynch, Bond, Breslin, & Johnson, 2011). In another study, the mechanisms of ondansetron (0.001 mg/kg) and topiramate (10 mg/kg)-mediated beneficial effects through modulation of alcohol's reinforcing effects in male alcohol preferring (P) rats ($N = 22$) responding for alcohol under a progressive-ratio (PR), with acute treatment for one day and chronic administration for ten days, were examined. Low dose acute treatment with topiramate and ondansetron similarly reduced PR responding for alcohol following acute treatment and during initial phase of chronic treatment, however, repeated administration with the combination showed sustained reduction of alcohol suggesting that combination of topiramate and ondansetron produced a sustained reduction in alcohol's reinforcing effects (Moore et al., 2014).

Recently, ondansetron has been shown to decrease alcohol consumption in patients with AUDs. In a double-blind, randomized, placebo-controlled clinical trial, 217 patients who received ondansetron 1, 4 and 16 μg/kg twice a day for 11 weeks showed fewer drinks in comparison to placebo control (Johnson et al., 2000). They suggested that 4 μg/kg ondansetron twice a day was effective in patients with early onset alcoholism and craving (Johnson, Roache, Ait-Daoud, Zanca, & Velazquez, 2002). In an open-label study, Kranzler et al. also reported that 4 μg/kg ondansetron twice a day was suitable for the treatment of alcohol dependence in early-onset alcoholics (Kranzler, Pierucci-Lagha, Feinn, & Hernandez-Avila, 2003). A higher dosage of ondansetron (16 μg/kg twice a day) combined with cognitive behavior therapy decreased depression, anxiety, and hostility (Johnson, Ait-Daoud, Ma, & Wang, 2003). In another randomized trial, men taking ondansetron (8 mg twice per day) had fewer heavy drinking days compared with those taking placebo, although they did not have increased abstinence rates. The combination of ondansetron (4 μg/kg twice a day) and naltrexone (25 mg twice a day) may be effective in treating early AUD (Corrêa Filho & Baltieri, 2013).

3.4.3. Nalmefene

Is an opiate derivative similar to opioid antagonist naltrexone, sold under the trade name Selincro and Nalmetrene. It has numerous potential pharmacological advantages in comparison to naltrexone for the treatment of alcohol dependence. Nalmefene has a longer half-life, greater oral bioavailability and no dose dependent liver toxicity compared to naltrexone.

Recently nalmefene was reported to prevent alcohol-induced neuroinflammation and preference alcohol drinking in PND35 (TLR4 knockout) female adolescent mice in comparison to wild type adolescent mice. Nalmefene (0.1 mg/kg, i.p.) was given following CIE ethanol exposure for two consecutive days and astroglial cells were used to study the TLR4 mediated pro-inflammatory immune signaling. Nalmefene treatment prevented the upregulation of pro-inflammatory cytokines (IL-β, IL-17A, TNFα) and chemokines (MCP-1, MIP-1, KC) and other mediators (iNOS, COX-2) inhibiting apoptotic events in PFC and NAc. In addition, nalmefene also inhibited the alcohol-induced escalation of alcohol preference and intake, suggesting that nalmefene reduces neuroinflammation by blocking pro-inflammatory TLR4 response in modulating alcohol drinking (Montesinos, Gil, & Guerri, 2017).

Previously the effects of nalmefene and other opioid agonist were evaluated in male Wistar rats that self-administer ethanol in standard operant conditioning method or exposed to 4-week intermittent ethanol vapor exposure for 14 h per day for 4 weeks. After confirming the alcohol dependence, nalmefene (0–0.1 mg/kg, s.c.) and naltrexone (0–1 mg/kg, s.c.) were administered to Wistar rats. The results revealed that nalmefene and naltrexone induced a significant dose-dependent decrease in the number of lever presses in both groups of animals, however, in alcohol-dependent animals, nalmefene was significantly effective in reducing alcohol intake suggesting that k-opioid receptors are involved in alcohol dependence-induced ethanol self-administration that dysregulate dynorphin/k-opioid receptors (Walker, Rasmussen, Raskind, & Koob, 2008).

In an outpatient study, individuals suffering from AUD were given 18 mg of nalmefene per day for 24 weeks and the changes in heavy drinking days (HDDs), total alcohol consumption (TAC, grams/day) and the changes in drinking risk level and craving (Obsessive-Compulsive Drinking Scale and visual analog scale for craving) were measured. Among them, 64% of individuals, who had one or more stabilized psychiatric comorbidity, showed significant reduction in HDDs, TAC and craving measures with no differences between subjects with and without psychiatric comorbidity (Di Nicola et al., 2017). Borderline personality disorder (BPD) symptoms in AUD patients have been reported to improve by using nalmefene. Eight-weeks of nalmefene treatment reduced alcohol consumption in individuals with BPD and comorbid AUD (Martín-Blanco et al., 2017). Previously, Mason et al., have shown that treatment with nalmefene was effective in preventing relapse to heavy drinking in comparison to placebo. In a double-blind placebo-controlled trial, patients were given two doses of oral nalmefene (20- or 80-mg/day for 12 weeks) for alcohol dependence. Placebo treated patients showed significant relapse to heavy drinking (2.4 times greater) in comparison to nalmefene treated subjects (Mason, Salvato, Williams, Ritvo, & Cutler, 1999).

These preclinical animal models have shown promising results in evaluating other medications and cannot draw any negative conclusions on their efficacy. For example, the α-2 adrenoreceptor agonists such as clonidine and lofexidine were translated in human studies

against stress-induced drug craving (Mantsch, Baker, Funk, Lê, & Shaham, 2016; Sinha et al., 2011). Similarly, gabapentin reduced both the anxiogenic-like behavior and the increased ethanol self-administration observed in withdrawn, ethanol-dependent rats, but not non-dependent rats (Besheer et al., 2016; Roberto et al., 2008). Recently, the glucocorticoid receptor antagonist mifepristone reduced ethanol intake in alcohol dependent rodents during abstinence but not in non-alcohol dependent rodents (Simms, Haass-Koffler, Bito-Onon, Li, & Bartlett, 2012; Vendruscolo et al., 2012; Yang, Wang, Rice, Munro, & Wand, 2008). In addition, mifepristone was reported to reduce alcohol-cued craving in the laboratory-based study as well as in a double-blind, placebo-controlled study in alcohol-dependent human subjects. Individuals who received mifepristone (600 mg/day, orally for one week) exhibited a substantial decrease in alcohol-cued craving and alcohol consumption during the one week of treatment phase and one week post-treatment phase (NCT01548417 - Clinicaltrials.gov; Vendruscolo et al., 2015). Thus, all of these preclinical models and clinical trial do show predictive sensitivity to determine effective treatments. Recently, Palpacuer et al. performed a meta-analysis of double-blind RCTs to assess the efficacy of AUD medications such as nalmefene, naltrexone, acamprosate, baclofen and topiramate in non-abstinent adults diagnosed with AUD. Thirty-two RCTs involving 6036 patients data were analyzed for total alcohol consumption (TAC). Based on these analyses, they conclude that there is no reliable evidence of pharmacologically controlled drinking for the treatment of patients suffering from alcohol dependence or AUD. They showed low to medium efficacy in reducing alcohol drinking with variable and inconsistent results and sometimes with more adverse effects (Palpacuer et al., 2017).

4. Novel AUD medications and their signaling pathways

We now focus on the novel medications and their signaling mechanisms by which they exert their effects on AUDs. These novel medications were developed to minimize the alcohol induced side effects and improve the quality of life. These groups of medications include novel as well as FDA-approved medications that are being repurposed for the prevention and treatment of AUDs. In some studies, the combination of these drugs was reported to exhibit potent effects than when they are used alone. The drug combination strategy appears promising for AUD treatment and other behavioral deficits. The following medications are in different phases of clinical trials and have a great potential for the treatment of the AUD (Fig. 2). These candidate compounds are listed below.

4.1. Corticotropin-releasing factor-1

Corticotropin-releasing factor-1 (CRF1), is an endogenous peptide hormone, released in response to various chronic stressors and affects many physiological functions. The CRF1 receptor antagonists have been developed and were tested in many preclinical studies showing strong signs of potential clinical efficacy. For instance, antalarmin (10 μm/L), NIH-3 (10 μm/L) and R121919 (1 μm/L) the three CRF1 receptor antagonists blocked ethanol-induced GABA release in both naïve and ethanol-dependent rats in central amygdala (CeA) GABAergic neurons. Intra-CeA administration of a CRF_1 antagonist reversed dependence-related elevations in extracellular GABA and blocks ethanol-induced increases in GABA in both ethanol-dependent and naive rats. Chronic CRF_1 antagonist treatment blocked withdrawal-induced increases in alcohol drinking by dependent rats and tempered moderate increases in alcohol consumption by nondependent rats in intermittent testings (Roberto et al., 2010). In another study, by using a two-bottle choice paradigm, the effect of the stressor and CRF on ethanol deprivation-induced ethanol intake and anxiety-like behavior in alcohol-preferring P rats was evaluated. Injection of SSR125543 (10 μg) into the NAc inhibited the restrain stress-induced voluntary alcohol intake without affecting anxiety-like behavior, whereas injection into the amygdala or dorsal root neurons prevented the anxiety-like behavior and did not affect drinking (Knapp et al., 2011). In contrast, by using the 20% ethanol intermittent access model of Sardinian alcohol-preferring P rats, Sabino and her colleagues have shown that alcohol consumption was decreased by naltrexone and SCH 39166 (a dopamine D1 receptor antagonist), but not by R121919, indicating that this reduction in alcohol consumption was due to opioid- and dopamine-receptor mediated, but not due to CRF1 system (Sabino, Kwak, Rice, & Cottone, 2013). In agreement with this study, Giardino & Ryabinin also reported that CRF1 receptor antagonists did not exert specific effects on ethanol intake in the drinking-in-dark (DID) model of binge alcohol consumption. Treatment of C57BL/6J mice with CRF1-selective antagonists CP-376395 (10 to 20 mg/kg i.p.) or NBI 27914 (10 to 30 mg/kg, i.p.) have shown some nonspecific increase of sucrose (10%) intake and alcohol (15%) decrease in the presence of pharmacological and genetic disruption of CRF1 activity (Giardino & Ryabinin, 2013).

Despite the encouraging results that were obtained in preclinical animal studies, a series of disappointing clinical results have been reported in the past two decades where the number of CRF1 receptor antagonists failed to successfully complete the double-blind, placebo-controlled trials of stress-related psychiatric disorders (Sanders & Nemeroff, 2016; Shaham & de Wit, 2016; Spierling & Zorilla, 2017). Pexacerfont (an oral, brain penetrant CRH antagonist), with positive results in animal models (Gehlert et al., 2007), did not show any significant effects in human clinical trials. Kwako et al., evaluated pexacerfont to suppress stress-induced alcohol craving and brain responses in treatment seeking alcohol-dependent patients in early abstinence. Alcohol-dependent patients enrolled in a double blind, randomized, placebo-controlled study at the NIH Clinical Center were given pexacerfont 300 mg/day for 7 days, followed by 100 mg/day for 23 days and assessed for alcohol craving in response to stressful and alcohol related cues. Pexacerfont treatment did not show any positive effects on alcohol craving, emotional responses and anxiety (Kwako et al., 2015). In a recent paper, Spierling & Zorilla reviewed possible reasons for the lack of effect in the human studies that include poor safety, efficacy, pharmacokinetic and physicochemical properties of the initial drugs, specificity problems with preclinical screens, the acute nature of screens vs. late presenting patients, and positive preclinical results limited to certain models (Spierling & Zorilla, 2017).

4.2. α1-adrenoreceptor antagonist

4.2.1. Prazosin

[4-(4-Amino-6,7-dimethoxy-2-quinazolinyl)-1-piperazinyl](2-furyl) methanone, is an α-1 adrenoceptor antagonist and sold under the trade names Minipress, Vasoflex, Lentropes, and Hypovase. It has been used to treat high blood pressure and PTSD (FDA, 2015; Prazosin-IUPHAR, 2016). It is also used for treating urinary hesitancy associated with prostatic hyperplasia. The antihypertensive characteristics of prazosin makes it a second-line choice (Shen, 2008) after thiazide diuretics such as chlorthalidone and hydrochlorothiazide (Medical Letter Inc., 2012), for the treatment of high blood pressure. The common side effects include dizziness, headache, drowsiness, weakness, palpitations and nausea. Another side effect could be orthostatic hypotension, especially after the first dose.

Previously it has been shown that blockade of α-1 adrenergic receptors suppresses excessive alcohol consumption after acute withdrawal in ethanol-dependent rats. In ethanol-dependent animals, prazosin (1.5 and 2.0 mg/kg) was effective in suppressing alcohol consumption, suggesting the involvement of noradrenergic receptors in the excessive alcohol drinking during acute withdrawal in ethanol-dependent rats (Walker et al., 2008). In nondependent rats, only 2.0 mg/kg dose was effective and at 0.25 mg/kg doze prazosin mediates anxiolytic effect on ethanol self-administration in nondependent rats. In general, stress-induced anxiety is a major risk factor for reinstatement to alcohol drinking. Medications such as SSRI and SNRI inhibitors,

buspirone, benzodiazepines, diphenhydramine, propranolol, tamoxifen, prazosin, doxazosin, that help to block the stress-induced anxiety may also reduce alcohol consumption. Among them, prazosin and doxazosin are known medications for the treatment of high blood pressure. Prazosin (1.0 or 1.5 mg/kg, i.p.) or vehicle was administered in alcohol preferring (P) rats and anxiety-like behavior was measured. Prazosin, given before stresses in the first two cycles of alcohol withdrawal, prevented increased anxiety-like behavior during the third alcohol deprivation, suggesting prior treatment of prazosin may prevent the increased anxiety during subsequent deprivation/abstinence that is a risk factor for relapse to alcohol drinking (Rasmussen, Kincaid, & Froehlich, 2017). Prazosin showed promising results in treating alcoholism by blocking α-1 adrenoreceptors in rats. Intracerebroventricular (ICV) administration of prazosin (2 and 6 nmol) or systemically (1 mg/kg) on antagonist yohimbine (1.25 mg/kg)-induced reinstatement of alcohol craving in rats was assessed by using footshock stress. Yohimbine-induced reinstatement of alcohol seeking was reduced substantially by the ICV and systemic prazosin (50 and 69% decreases) respectively. Similar results were obtained by employing a long-acting α-1 antagonist doxazosin that effectively block yohimbine-induced reinstatement of alcohol (Funk et al., 2016). In another study, long term treatment with a low dose of prazosin or duloxetine significantly decreased ethanol self-administration in adult male Long-Evans rats. Chronic infusion of prazosin (0.78–1.5 mg/day for 8–10 weeks) and duloxetine (0.75–1.5 mg/day for 8–10 weeks) decreased ethanol self-administration after three and four weeks of infusion indicating that chronic, but not acute treatment with low doses of putative inhibitors of α-1 adrenoreceptor and SNR1 may attenuate alcohol intake and reduce anxiety-like behavior after stress (Skelly & Weiner, 2014).

Simpson et al. reported that in a six-week double-blind randomized controlled pilot clinical trial, patients receiving 4–8 mg of prazosin showed greater reduction in percent days of drinking per week, however it did not show beneficial effects on PTSD symptoms (Simpson et al., 2015). In contrast, in a randomized, double-blind clinical trial, ninety-six veterans with PTSD and comorbid alcohol dependence received prazosin (16 mg) for 13 weeks. Even though symptoms of PTSD, sleep disturbances and alcohol consumption decreased over time, however, prazosin was not effective in treating either PTSD symptoms, improving sleep, or reducing alcohol consumption suggesting that comorbid condition affects the efficacy of prazosin (Petrakis et al., 2016).

Previously, a double-blind, placebo-controlled random trial consisting of seventeen alcohol dependent patients received prazosin (16 mg/day, over 4 weeks). All patients were exposed to 5-minute guided imagery, stress, alcohol cue, and neutral-relaxing/control conditions per day. When assessed, the prazosin group showed significantly lower alcohol craving, anxiety, and negative emotion following stress exposure, suggesting the beneficial effects of prazosin on decreasing stress- and cue-induced alcohol craving and normalizing the stress dysregulation associated with early recovery from alcoholism (Fox et al., 2012). Recently, Kenna et al. evaluated the α1-blocker doxazosin, which is similar to prazosin, in rodents and alcohol-dependent (AD) patients in a double-blind placebo-controlled randomized clinical trial by administering 16 mg/day (or maximum tolerable dose). Statistical analysis revealed that doxazosin considerably reduced alcohol drinking in AD patients with high family history density of alcoholism (FHDA) and by contrast increased drinking in those with low FHDA, indicating that doxazosin may be selectively effective in AD patients with high FHDA (Kenna et al., 2016). Similarly, the α2-adrenergic receptor antagonist idazoxan was evaluated for its role in managing AD patients. In a double-blind, single dose, placebo-controlled, crossover, randomized human laboratory study, ten social drinkers given 40 mg idazoxan or placebo showed reduced the peak blood alcohol level and time to peak in comparison to placebo, suggesting that idazoxan may alter the biphasic effects of alcohol by decreasing stimulation and increasing sedation (Haass-Koffler, Leggio, Davidson, & Swift, 2015).

4.3. Glycine reuptake inhibitors

Since glycine is known to elevate extracellular dopamine levels in the NAc and decrease alcohol consumption, a highly selective glycine reuptake inhibitor could be used to decrease alcohol consumption. Among these glycine reuptake inhibitors, Org-25935, initially developed for the treatment for schizophrenia, was studied in male Wistar rats, where it significantly decreased the alcohol consumption in a dose-dependent manner with its effects sustained for up to 40 days (Lidö, Stomberg, Fagerberg, Ericson, & Söderpalm, 2009; Molander, Lidö, Löf, Ericson, & Söderpalm, 2007).

In another study, NAc glycine modulates basal and ethanol-induced dopamine levels in the NAc as well as voluntary ethanol consumption. Systemic administration of the glycine transporter-1 (GlyT1) inhibitor Org-25935 also elevates dopamine levels in the NAc, prevents further ethanol-induced dopamine elevation robustly and dose-dependently decreased ethanol consumption in rats, providing supporting evidence for the glycine receptor as an important player in the dopamine reward circuitry and in ethanol's effects within this system (Lidö, Ericson, Marston, & Söderpalm, 2011). The same group developed another inhibitor Org-24598 which also reduced ethanol intake when it was compared with acamprosate (Lidö, Marston, Ericson, & Söderpalm, 2012). Overall, both Org-25935 and Org-24598 promoted a robust and long-lasting reduction in voluntary alcohol consumption and reversed compulsive relapse-like alcohol drinking (Molander et al., 2007; Vengeliene, Leonardi-Essmann, Sommer, Marston, & Spanagel, 2010). Org-25935 has demonstrated long-lasting properties of suppressing alcohol intake in rodent models with effects superior to most drug candidates for AUD (Spanagel & Kiefer, 2008). The compound has a good safety profile and neither animal studies nor human investigations indicate a positive hedonic profile (Liem-Moolenaar et al., 2013).

However, the attempts thus far to translate these promising results to AUD patients failed and the proof of concept trial was aborted before completion due to its failure in clinical trials as reported in European Union Clinical Trials Register (EudraCT:2006-003080-31). In addition, Org-25935 also demonstrated different outcome in different strains of rat models. For instance, in Alko-Alcohol (AA) rats Org-25935 reduced both ethanol and water intake and induced strong depressive effects on CNS, whereas it reduced alcohol intake in Wistar rats. Despite the lack of a successful clinical outcome, there is some interest in further studies in the development of a new generation of Gly-1 inhibitors (Lidö, Jonsson, Hyytiä, Ericson, & Söderpalm, 2017).

4.4. Phosphodiesterase inhibitors

Neuroinflammatory signaling pathways in the CNS are of current interest as potential pharmacotherapy targets for alcohol dependence. Ibudilast is a neuroimmune modulator that inhibits phosphodiesterase (PDE)-4 and PDE-10 and macrophage migration inhibitory factor (MIF). In a recent study, ibudilast reduced alcohol drinking and relapse in alcohol-preferring P rats, high-alcohol drinking HAD1 rats and a mouse model exposed to alcohol vapor. When administered twice daily, ibudilast reduced alcohol drinking in rats by approximately 50% and it also suppressed drinking in alcohol-dependent mice at doses which showed no effect in non-dependent mice. These findings support the usage of ibudilast as a potential treatment for alcohol dependent patients (Bell et al., 2016).

A randomized, crossover, double-blind, placebo-controlled laboratory study was conducted to investigate the benefits of ibudilast in 24 nontreatment-seeking individuals with current mild-to-severe AUD by measuring the subjective response to alcohol as well as secondary measures of cue- and stress-induced changes in craving and mood. After completion of two separate 7-day intensive outpatient protocols, and upon reaching a stable target dose, ibudilast (50 mg b.i.d.) was well tolerated; however, there were no beneficial effects on the primary measures of subjective response to alcohol. Ibudilast was associated

with mood improvements on the secondary measures of stress exposure and alcohol-cue exposure, as well as reductions in tonic levels of craving. Exploratory analyses revealed that among individuals with higher depressive symptomatology, ibudilast attenuated the stimulant and mood-altering effects of alcohol as compared to placebo. Together, these findings extend preclinical demonstrations of the potential utility of ibudilast for the treatment of AUD and suggest that depressive symptomatology should be considered as a potential moderator of efficacy for pharmacotherapies with neuroimmune modulators (Ray et al., 2017).

4.5. Peroxisome proliferator-activated receptor alpha agonist

In general, the fibrates are a class of medications used to treat hypercholesterolemia and dyslipidemia that target nuclear peroxisome proliferator-activated receptors (PPARs). Studies have shown the PPARα agonist fenofibrate also decreases voluntary alcohol (ethanol) consumption in mice (Blednov et al., 2016a; Ferguson, Most, Blednov, & Harris, 2014) and rats (Karahanian, Quintanilla, Fernandez, & Israel, 2014). Other agonists of PPARα are oleoylethanolamide (OEA), palmitoylethanolamide (PEA), clofibrate, gemfibrozil; WY14643, and MK886 as an antagonist reported to decrease voluntary ethanol consumption (Le Foll et al., 2013). On the other hand, PPARγ agonists such as pioglitazone, rosiglitazone and ciglitazone are known to reduce voluntary alcohol drinking (Le Foll et al., 2013). Reinforcing and motivational effects of ethanol were studied by using various doses of fenofibrate (Haile & Kosten, 2017). Fenofibrate (25, 50 and 100 mg/kg) in rats showed fenofibrate dose-dependently decreased ethanol self-administration providing further evidence for fenofibrate as a potential treatment for AUD in humans. The PPARα and γ subunits seem to play an important role in reducing the ethanol self-administration. By using the selective PPARα and α/γ agonists and antagonists, Blednov et al. examined the subunit dependence of this action in WT versus null mutant mice lacking PPARα. Fenofibrate (a PPARα agonist) and tesaglitazar (a PPARα/γ dual agonist) reduced ethanol consumption on continuous and intermittent 2-bottle choice drinking tests in male and female WT mice but not in male mice lacking PPARα, suggesting that PPARα plays an important role in decreased alcohol consumption (Blednov et al., 2016a, 2016b).

Blednov et al., also studied the roles of these PPAR agonists in ethanol-related behaviors and other actions such as preference for saccharin, ethanol-induced conditioned place preference (CPP), conditioned taste aversion (CTA), loss of righting reflex, and withdrawal, acoustic startle reflex, response to novelty, and ethanol clearance. Fenofibrate (150 mg/kg) and tesaglitazar (1.5 mg/kg) decreased the novelty response and increased acute ethanol withdrawal severity and ethanol-induced CTA. On the other hand, saccharin preference and ethanol-induced CPP were not altered, however, ethanol clearance was increased. Response to novelty seeking, acute withdrawal, and ethanol clearance showed sex-dependent differences and could explain the reduced ethanol consumption following fenofibrate administration. Thus, the complexities of ethanol-dependent and ethanol-independent behaviors that are altered by PPAR agonists provide evidence for novel behavioral actions of these drugs that may contribute to PPAR-mediated effects of alcohol drinking (Blednov et al., 2016b).

Previously, this group has demonstrated the cellular and molecular mechanisms of PPAR agonists in facilitating the reduced consumption of alcohol in rodents (Blednov et al., 2015; Ferguson et al., 2014). They used three PPAR agonists in a continuous access of two-bottle choice (2BC) drinking paradigm and found that tesaglitazar (PPARα/γ dual agonist: 1.5 mg/kg) and fenofibrate (PPARα agonist, 150 mg/kg) decreased ethanol consumption in male C57BL/6J mice while bezafibrate (PPARα/γ/β agonist, 75 mg/kg) did not. Comparing the unbiased genomic profiles of fenofibrate and tesaglitazar treatment with bezafibrate from the areas of brain regions known for alcohol dependence, PPAR agonists produced a strong neuronal signature in mouse brain. Weighted gene co-expression network analysis (WGCNA) revealed the co-expression of treatment-significant genes and the functional annotation of these gene networks suggested that PPAR agonists might act via neuropeptide and dopaminergic signaling pathways in the amygdala (Ferguson et al., 2014). In another study, PPARγ agonists were shown to reduce ethanol drinking in alcohol-preferring rats (Stopponi et al., 2011). Based on these reports, the effect of peroxisome proliferator-activating drugs acting on PPARα and PPARγ appears to be mediated by the potentiation effects of activated PPARγ in the brain and PPARα in the liver in reducing ethanol intake in animals (Karahanian et al., 2015).

A recently completed randomized, double-blind phase 2 clinical trial (Clinicaltrials.gov; NCT02158273) by Barbara et al., have used fenofibrate (TRICOR-145 mg/day, oral pill, for 9 days) in 50 subjects to measure alcohol craving. The four visual analog scale (VAS) questions; the intention to drink, loss of control, relief craving and urge intensity were measured. These studies did not show significant difference in fenofibrate treatment in comparison to control, indicating that despite the encouraging responses in animal studies, human studies didn't reproduce the beneficial effects of fenofibrate (Clinicaltrials.gov; NCT02158273).

4.6. NMDA receptor antagonist

Memantine, a non-competitive antagonist of NMDA receptors, (25 mg/kg) abolished ethanol self-administration in non-dependent (ND) rats and reduced self-administration by half in post-dependent (PD) rats during acute withdrawal. While this effect was observed only 6 h after treatment in ND rats, it was long lasting in PD rats (at least 30 h after injection). Furthermore, the results indicated that memantine did not modify the break-point for ethanol, suggesting that memantine acts by potentiating the pharmacological effect of ethanol but not by reducing the motivation for ethanol. Memantine was also ineffective in reducing relapse after protracted abstinence and may be used as a replacement therapy drug, but not as relapse-preventing drug (Alaux-Cantin, Buttolo, Houchi, Jeanblanc, & Naassila, 2015).

Memantine induces expression of BDNF in several brain regions, including the striatum (Jeanblanc, Coune, Botia, & Naassila, 2014). Based on the hypothesis that memantine could decrease ethanol consumption via activation of the BNDF signaling pathway, memantine was evaluated for reduction of self-administering of moderate or high amounts of ethanol (12.5 and 25 mg/kg) in Long Evans rats. They reported that memantine decreased ethanol self-administration and motivation of alcohol consumption, while inhibition or blockade of the BDNF signaling pathway prevented earlier, but not the delayed decrease in ethanol consumption induced by memantine. BDNF expression was differentially regulated between the early and delayed timepoints and an acute injection of memantine specifically reduced ethanol self-administration and motivation to consume ethanol for at least 30 h, proposing that the BDNF was responsible for the early effect, but the delayed effect was BDNF-independent (Jeanblanc et al., 2014).

Acute effects of memantine were evaluated in combination with alcohol in moderate alcohol drinkers on alcohol dependence and craving. In a double-blind three day long inpatient human study, 18 non-alcohol dependent volunteers were given memantine (0, 15, and 30 mg) which was administered 4 h before alcohol (1.5 g/l body water) was given. The results showed that, memantine pretreatment attenuated the craving for alcohol before alcohol administration, but not after alcohol consumption. In addition, memantine did not affect alcohol-induced performance impairment, physiological changes or pharmacokinetics, however it increased dissociative effects, confusion, subjective reports of dissociation and impaired motor coordination (Bisaga & Evans, 2004).

A placebo-controlled clinical trial completed by the same group (NCT00246415; Clinicaltrials.gov) has used memantine for alcohol dependence. 90 individuals who meet DSM-IV criteria for current

alcohol dependence were enrolled in this study to evaluate the safety and effectiveness of oral memantine (40 mg/day) in 16 weeks with a 12 week treatment phase study. Another 16 week double-blind outpatient pilot clinical trial was conducted by taking 44 treatment seeking individuals. Among them 34 patients were stratified to receive memantine (40 mg/day) or placebo and only 27 patients completed the entire 16 week trial. The results that emerged from longitudinal analysis showed significant reduction in drinks per day and drinks per drinking day, but no difference between the two groups. In addition, the percentage of heavy drinking days and rate of abstinent were observed in placebo group. Unfortunately, the memantine group had many side effects (26%) and had to either decrease the dose or drop out of the study indicating that there are negative effects of memantine for the treatment of alcohol dependent patients (Evans, Levin, Brooks, & Garawi, 2007).

4.7. Oxytocin

The effects of oxytocin (OT) have been reported by many laboratories in alcohol addiction as well as in some neuropsychiatric disorders and social behaviors (Baskerville & Douglas, 2010; Lee & Weerts, 2016). OT, a nine amino-acid (AA) peptide, is known to be synthesized in the magnocellular neurons of the paraventricular, supraoptic nuclei and the accessory magnocellular nuclei of the hypothalamus and released by the posterior pituitary into the peripheral circulation. Oxytocin receptor (OTR) is coupled to Gq types of G-protein coupled receptor (GPCR) in hypothalamus in the brain (e.g., cortical, limbic, and basal ganglia structures) where it exerts a variety of behavioral effects (Lee, Rohn, Tanda, & Leggio, 2016).

Recent studies have shown that OT influences a number of behavioral and physiological effects of alcohol, including tolerance, withdrawal, and motivational effects (Lee & Weerts, 2016). Systemic administration of OT reduces alcohol preference and intake in a variety of drinking models in rats (MacFadyen et al., 2016) and mice (King et al., 2017). Bowen et al. has demonstrated that OT specifically attenuates ethanol-induced motor impairment via GABAergic activity at δ-$GABA_A$ receptor (α4β1δ and α4β3δ) subunits without activating OTR. OT (1 μg, i.c.v.) given ahead of ethanol (1.5/kg, i.p.) attenuated ethanol-induced sedation and ataxia in the open field locomotor test. The inhibitory effect of oxytocin on the δ subunit-containing receptors appeared specific for ethanol, because the potentiating effects of a $GABA_A$ agonist that binds a different site from ethanol on the δ receptor were unaffected by oxytocin either in animal behavior tests or in the *Xenopus* expression system. Because *Xenopus* oocytes do not have the oxytocin receptor, these data indicate that oxytocin exerted its effects independently from the oxytocin receptor and suggest that the δ subunit of GABAA may be a target of oxytocin action (Bowen et al., 2015).

Direct injection of OT into the brain ventricles reduced alcohol consumption and alcohol-induced dopamine efflux in the NAc in rats (Peters, Bowen, Bohrer, McGregor, & Neumann, 2017). However, only few studies have examined the role of OTRs in mediating the neuropeptide's effects on motivational actions of alcohol. Recent studies involving viral-mediated overexpression of OTRs in the NAc core have implicated a role for these receptors in alcohol drinking and conditioned reward (Bahi, 2015; Bahi, Al Mansouri, & Al Maamari, 2016). McGregor and Bowen, found a long-lasting effect on the OT administration on ethanol preference in rats. Indeed, a single dose of OT (1 mg/kg) produced a progressive reduction in preference for the ethanol-containing beverage as compared to a non-ethanol-containing sweet solution and this effect lasted for up to 6 weeks. Additionally, treatment with OT at 1 mg/kg for 2 weeks before the start of a two-bottle free choice paradigm provided evidence that there was a significantly lower ethanol preference in OT-treated than in control rats (McGregor & Bowen, 2012). Modulation of the OTR via administration of the OTR agonist carbetocin or gene over-expression of OTRs via a lentiviral vector in NAc resulted in reduced acquisition and ethanol-primed reinstatement of CPP as well as increased rates of extinction (Bahi, 2015). OT is known to exert stress-buffering effects, and this may be of relevance to its role in influencing stress-alcohol interactions. For example, oxytocin decreases stress-induced HPA axis activation and behavioral (anxiety) responses (Neumann, Wigger, Torner, Holsboer, & Landgraf, 2000; Windle, Shanks, Lightman, & Ingram, 1997). Peters, Slattery, Flor, Neumann, & Reber, 2013, carried out the chronic subordinate colony (CSC) housing study to evaluate social stress paradigms which is considered as the pre-clinically validated psychosocial stress paradigm relevant to human psychiatric disorders. CSC stressed male mice when given increasing doses (0, 2, 4, 6 and 8%) of alcohol for 14 days showed a significant increase in alcohol consumption. Systemic administration of OT (10 mg/kg) or baclofen (2.5 mg/kg) reduced alcohol consumption, indicating that OT and baclofen attenuated chronic psychosocial stress-induced alcohol intake (Peters et al., 2013).

Recent studies have demonstrated OTRs are associated with genetic polymorphisms and aggression in humans and animal models (Gerra et al., 2017; Karpova, Mikheev, Marysheva, Bychkov, & Proshin, 2016; Yang et al., 2017). Previously, Pedersen and colleagues in a clinical study demonstrated that intranasal OT treatment attenuated alcohol withdrawal symptoms in treatment-seeking human subjects compared to placebo (Pedersen et al., 2013). Overall, studies to date suggest that OT plays a role in reversing tolerance and in reducing alcohol preference in a persistent manner, supporting OT as a potential treatment for AUD both in the short-term to manage AWS and in the long-term to reduce the rewarding effects of alcohol. Taken together, there is emerging evidence that OT may hold promise as a therapeutic candidate for treating AUDs and for stress-related alcohol drinking and relapse.

4.8. Ghrelin

Ghrelin, the orexigenic peptide, is an appetite-regulating peptide hormone released from the gut. Ghrelin controls the homeostatic system balancing energy expenditure and appetite in the hypothalamus. It is mainly synthesized and secreted by the entero-endocrine cells of the stomach and intestine as a precursor protein, preproghrelin (Tschop, Smiley, & Heiman, 2000). The peptide hormone is generated by proteolytic cleavage of preproghrelin and proghrelin to an active form with 28-amino acid residues. Only the acetylated form of ghrelin is functional, able to cross the blood-brain barrier and activate central growth hormone secretagogue receptors (ghrelin receptor- GHS-RIA) in the hypothalamus (Bednarek et al., 2000; Koopmann et al., 2012). Ghrelin receptors are highly expressed in hypothalamus and in the VTA. Expression of GHS-RIA in the hippocampus and substantia nigra, can also act on reward circuitry and modulate addictive disorders such as alcohol and tobacco addiction (Al'Absi, Lemieux, & Nakajima, 2014; Koopmann et al., 2015; Koopmann, Schuster, & Kiefer, 2016).

Recent studies have suggested that ghrelin modulates signaling of dopaminergic neurons. Preclinical studies also provided support for an important role of ghrelin in the neurobiology of addiction-related reward pathways, affecting the self-administration of alcohol and drugs. Intermittent access to a nutritionally complete high fat diet attenuates alcohol drinking in Long Evans rats (Sirohi, Van Cleef, & Davis, 2017). The impacts of binge-like feeding on alcohol intake and anxiety-like behavior were modulated by the plasma acyl-ghrelin level that was drastically increased in rats fed high fat diet intermittently, and it reduced alcohol intake in comparison to sucrose intake (Sirohi et al., 2017). In another study use of GHS-RIA antagonist JMV2959 suppressed the alcohol consumption and deprivation effects following long term voluntary alcohol consumption. After ten months of high alcohol consumption in rats, acute JMV2959 treatment significantly decreased alcohol intake without inducing tolerance and prevented the alcohol deprivation effects. In addition, there was a significant decrease in GHS-R1A receptor expression in the VTA, proposing that a negative correlation between GHS-R1A gene and alcohol intake exists (Suchankova,

Steensland, Fredriksson, Engel, & Jerlhag, 2013). Kaur & Ryabinin have demonstrated similar effects of ghrelin antagonist in decreasing the alcohol intake (Kaur & Ryabinin, 2010). C57BL/6J mice, when injected with 400 nmol of [D-Lys3]-Growth Hormone Releasing Peptide-6 (D-Lys3-GHRP-6, a selective ghrelin receptor antagonist) also called as DLS, showed reduced preference to alcohol with decreased alcohol intake in comparison to saline-treated control mice. They also showed the decreased blood alcohol levels in D-Lys3-GHRP-6 mice compared to control mice.

Animal and human studies have suggested that ghrelin modulates the neurobiology of alcohol dependence and alcohol craving (Leggio et al., 2012). In addition, Leggio et al. studied the role of ghrelin gene polymorphisms (Arg51Gln and Leu72Met) in alcohol-dependent individuals and reported the highest frequency of Leu72Met gene polymorphism in the alcohol-dependent group, further supporting the role of ghrelin in alcohol seeking behavior. In a double-blind placebo-controlled human study, intravenous administration of ghrelin 1 μg/kg or 3 μg/kg increased alcohol craving in alcohol-dependent heavy drinking individuals (Leggio et al., 2014). In contrast, clinical data failed to support an association between ghrelin and alcohol craving, possibly due to the fact that these studies have analyzed the pharmacologically inactive, preprohormone ghrelin instead of ghrelin in its active, acetylated form (Koopmann et al., 2012).

4.9. Orexin/hypocretin-1 receptor antagonist

Orexins (ORX), which are also called as hypocretins, are neuropeptides produced in the lateral hypothalamus regions of the brain and are responsible for appetite, wakefulness and arousal (Davis, Choi, & Benoit, 2011). There are two isoforms of orexins-A and -B or hypocretin-1 and -2 with 33 and 28- amino acid residues, respectively, and bind to orexin receptors/hypocretin receptors (ORXR-1 and 2 or HCRT1 and 2), a family of G-protein coupled receptors (De Lecea et al., 1998; Sakurai et al., 1998). The ORX system plays an important role in sleep regulation. Inactive mutation or gene deletion of the ORXR1 results in sleep disorders such as narcolepsy, or cataplexy (Chemelli et al., 1999; Lin et al., 1999). It is reported that the orexigenic neuropeptides secreted in the hypothalamus promote alcohol drinking and affect craving, withdrawal and relapse in relation to psychoactive substances. Animal models have shown that the expression of orexin mRNA levels increases after alcohol consumption and is decreased by using the ORXR1 antagonist SB-334867 (Cason et al., 2010; Merlo Pich & Melotto, 2014).

Recent studies have shown that the orexin system is associated with addiction and control motivational functions, making it a potential target for the treatment of alcohol and other drugs of abuse (Brown, Khoo, & Lawrence, 2013; Mahler, Smith, Moorman, Sartor, & Aston-Jones, 2012; Martin-Fardon & Weiss, 2014). ORXR antagonists, such as SB-334867, have shown great potential in reducing alcohol intake in laboratory animals (Bentzley & Aston-Jones, 2015; James, Yeoh, Graham, & Dayas, 2012). In alcohol preferring rats, decreased stress-induced reinstatement of alcohol seeking (Richards et al., 2008) and reduced relapse of alcohol-craving elicited by discriminative stimuli were observed (Martin-Fardon & Weiss, 2014). In another study, SB-334867 also decreased relapse to alcohol seeking/drinking after home cage deprivation in female alcohol-preferring rats when alcohol was available (Dhaher et al., 2010). These beneficial effects were in part mediated by the orexin receptor 1 (ORXR1) in the VTA and prelimbic cortex since the infusion of SB-334867 into these regions independently decreased cue-induced alcohol intake (Brown et al., 2016). Overall, ORXR1 antagonism decreased two-bottled choice preference selectively in high alcohol preferring rats (Moorman & Aston-Jones, 2009) and GSK1059865 decreased alcohol drinking preferentially in mice after chronic intermittent ethanol (CIE) (Lopez, Moorman, Aston-Jones, & Becker, 2016). In addition, OX1R antagonist suppressed compulsive-like alcohol consumption in C57BL/6 mice (Lei, Wegner, Yu, & Hopf, 2016). In another study, VTA and CeA have been demonstrated as important regions that regulate ORX1R in binge-like alcohol drinking behavior without affecting binge-like sucrose intake, indicating that ORXR circuits are specific for alcohol consumption (Olney, Navarro, & Thiele, 2017).

The brainstem nucleus incertus (NI) containing ORXR1 and ORXR2 are implicated in stress-induced reinstatement of alcohol seeking. However, yohimbine-induced reinstatement of alcohol seeking by activating orexinergic neurons in the hypothalamus was reported by Kastman et al., 2016. Orexigenic neurons directly innervate and excite NI relaxin-3 neurons (Blasiak et al., 2015) and ascending relaxin-3 neurons are implicated in alcohol seeking (Ryan et al., 2013). In alcohol preferring rats, bilateral injections of the ORXR2 antagonist TCS-OX2-29 attenuated yohimbine-induced reinstatement of alcohol seeking via ORXR2 as evidenced by the presence of higher levels of ORXR2 protein and mRNA that was complemented by the whole cell patch-clamp recordings in coronal rat brain slices. Taken together these data suggest that yohimbine-induced reinstatement of alcohol seeking is predominantly mediated by ORXR2 receptor (Kastman et al., 2016).

Patients with alcohol dependence treated for relapse prevention showed significantly lower levels of ORX in their blood. 32 males suffering from alcohol dependence were enrolled in a pilot study. Upon measurement, the alcohol-dependent patients showed significantly higher levels of blood ORX than the control group. However, after 4 weeks of abstinence the levels of ORX decreased significantly similar to the levels of ORX in control subjects, suggesting that ORXR1 are potential target for the relapse prevention treatment and that ORX is a biomarker of alcohol relapse (Ziółkowski et al., 2016). Previous studies from von der Goltz et al., showed the involvement of ORX in the regulation of stress, affectivity and addictive behavior. 34 alcohol dependent patients were enrolled in this study and the blood ORX levels were measured before and after the 2 weeks of abstinence period. Results showed a positive correlation between ORX and global distress indices of the brief symptom inventory (BSI). In addition, the ACTH and cortisol levels were detected in the plasma, signifying the involvement of ORX in the affective dysregulation seen in alcohol dependent patients during alcohol withdrawal (von der Goltz et al., 2011).

4.10. Nicotinic acetylcholine receptor agonists

4.10.1. Varenicline (VAR)

Varenicline (VAR), varenicline tartrate, marketed as Chantix and Champix, is a prescription medication for the treatment of nicotine addiction. It works as a partial agonist and stimulates the nicotine receptors weakly, similar to cytisine, but not like bupropion, an agonist of nicotinic receptor which has a strong affinity to the nicotine receptor. According to the 2013 Cochrane overview and network meta-analysis, VAR is the most effective medication for tobacco cessation and the smokers on VAR are three times more likely to quit smoking compared with placebo treatment. It has not been tested in people under 18 years old or pregnant women (Coleman, Chamberlain, Davey, Cooper, & Leonardi-Bee, 2015), and is considered a class C pregnancy drug, with no increased risk of congenital anomalies and malformations (Cressman, Pupco, Kim, Koren, & Bozzo, 2012). VAR acts as a full agonist to the α7 nicotinic acetylcholine receptors and is a partial agonist to the α4β2, α3β4 and α6β2 subtypes (Mihalak, Carroll, & Luetje, 2006; Mineur & Picciotto, 2010; Tanuja, Hrachova, Chin, McIntosh, & Quik, 2012). In addition, it is a weak agonist to the α3β2 containing receptors and a partial agonist for the α4β2 receptors. This α4β2 competitive binding by VAR reduces the ability of nicotine to bind and stimulate the mesolimbic dopamine system, like the mode of action of buprenorphine in the treatment of opioid addiction (Elrashidi & Ebbert, 2014).

Recently, Froehlich et al., evaluated the effects of naltrexone (NTX) or VAR, alone or in combination, to reduce the genetic predisposition toward high alcohol drinking in P rats selectively bred for high alcohol

intake. When P rats were pretreated with the drug for 2 weeks prior to onset of alcohol access, only NTX (15.0 mg/kg BW) + VAR (1.0 mg/kg BW) in combination blocked the acquisition of alcohol drinking in alcohol-naïve P rats. Following termination of drug treatment, NTX + VAR and VAR alone continued to reduce alcohol drinking, suggesting that NTX + VAR may be effective in curtailing alcohol drinking in individuals with a high genetic risk of developing alcoholism (Froehlich et al., 2017). Low doses of VAR and NTX, when combined with a single medication, reduced alcohol intake in a rodent model of alcoholism. This approach showed the advantage of reducing potential side effects associated with each drug. Lowering the dose of NTX and VAR in a combined treatment approach, which maintains the efficacy while reducing the incidence of negative side effects, may increase patient compliance and improve clinical outcomes for alcoholics and heavy drinkers who want to reduce their alcohol intake (Froehlich et al., 2016).

In another study, whether the relapse to alcohol-seeking was triggered by re-exposure to an alcohol-associated environmental context was examined. Male, Long-Evans rats received Pavlovian conditioning sessions in which one auditory conditioned stimulus (CS +) was paired with 15% ethanol and a second group which did not receive conditioned stimulus (CS −) was not paired. Ethanol was delivered into a port for oral consumption and port entries triggered by each CS were recorded. To stimulate relapse, both cues were subsequently presented without ethanol in the prior conditioning context. Systemic VAR (0, 0.5 or 2.5 mg/kg, i.p.) blocked context-induced relapse to alcohol-seeking without affecting the ability to make a port entry. Neuropharmacological studies showed that context-induced relapse to alcohol-seeking was attenuated by bilateral microinfusion of VAR (0.3 μl/0–3.5 μg), in the NAc but not in the VTA, indicating that nicotinic acetylcholine receptors (nAChRs) in the NAc are critical to this effect (Lacroix, Pettorelli, Maddux, Heidari-Jam, & Chaudhri, 2017).

Thus, VAR has been found to decrease alcohol-motivated behaviors, however, recently the aversive events of the drugs have been reported. In this double-blind, placebo-controlled preliminary investigation, VAR (0, 1, or 2 mg/day) attenuated alcohol-related increases in subjective intoxication and decreases in executive cognitive function. VAR reduced alcohol craving and diastolic blood pressure, and increased associative learning, working memory, and perceptual motor function, suggesting the safe use of VAR with alcoholic individuals meeting the criteria for AUD (Verplaetse et al., 2016). Previously a double-blind placebo study examined the effect of VAR on alcohol self-administration in nineteen non-alcohol dependent heavy smokers. Results showed that VAR (2 mg/kg/day vs. placebo) for seven days significantly reduced the number of drinks and increased the likelihood of abstaining from drinking and attenuated alcohol craving (McKee et al., 2009). In another randomized, double-blind 16 week study with heavy drinking smokers (64 adults seeking treatment for smoking) were randomized to treatment. In agreement with the findings by other scientists (Fucito et al., 2011), VAR significantly decreased alcohol consumption in heavy drinking smokers (Mitchell, Teague, Kayser, Bartlett, & Fields, 2012). A multisite double-blind clinical trial (NCT03035708) with 200 individuals (men and women) with alcohol dependence population of smokers and nonsmokers were recruited across five clinical sites and given varenicline 2 mg/day for 13 weeks. Computerized behavioral intervention revealed that the VAR group had significantly decreased weekly percent heavy drinking days, drinks per day and alcohol craving in comparison to placebo group (Litten et al., 2013).

Recently, Roberts et al., 2017, evaluated the efficacy of VAR in alcoholic subjects who reported symptoms of depression. A double-blind, placebo-controlled study involving 60 adults subjects meeting DSM-IV criteria were enrolled in this trial and given VAR (1-2 mg/kg/day for one week). The results showed that subjects with higher depressive symptoms revealed a decrease in alcohol craving and alcohol drinking whereas subjects with fewer depressive symptoms reported to drink more suggesting that the levels of depressive symptoms moderate the efficacy of VAR (Roberts et al., 2017). VAR also reported to reduce cravings and decreases the pleasurable effects of cigarettes and other tobacco products, thus helping many tobacco addicts to quit smoking. It is used for smoking cessation and suggested to be more effective than bupropion and nicotine replacement therapy as seen in meta-analysis (Cahill, Stevensk, Perera, & Lancaster, 2013; Elrashidi & Ebbert, 2014; Mills, Wu, Spurden, Ebbert, & Wilson, 2009).

4.10.2. Cytisine and lobeline

The brain nicotinic acetylcholine receptors (nAChRs) are a super family of ligand gated ion channels with twelve neuronal nAChR subunits (α2-α10 and β2-β4) that are expressed throughout the brain. Preclinical and clinical studies have shown that nAChR ligands that target different nAChR subtypes, have different role in alcohol and nicotine addiction. These medications include: lobeline and cytisine which are small molecule drugs that modulate the brain nicotinic cholinergic system and support nAChR-based ligands as promising therapeutic agents for the treatment of alcohol and drug dependence (Rahman, Engleman, & Bell, 2015). In a pre-clinical trial, lobeline, a natural alkaloid derived from Lobelia inflate, decreased the preference for alcohol intake through the modulation of the nicotinic acetylcholine receptor. When assayed for its mutagenic and genotoxic effects (5 or 10 mg/kg) and ethanol (2.5 g/kg), it was found safe and the biochemical parameters were not altered, indicating the safety of lobeline to treat alcohol dependence (da Costa E Silva et al., 2014).

In another study, the effects of cytisine and lobeline, on the status of ethanol drinking by HAD-2 rats were investigated. Lobeline treatment (5.0 mg/kg dose) significantly reduced ethanol intake tested at all three time points, making the nAChR a promising target of pharmacotherapy development for the treatment of alcohol dependence and relapse (Bell, Eiler II, Cook, & Rahman, 2009). Farook et al., evaluated the effects of repeated (continuous and recurring) administration of lobeline on alcohol consumption (10% alcohol vs. water) in male C57BL/6J mice for alcohol preference using a 2-bottle choice procedure. In agreement with the previous report (Bell et al., 2009), lobeline substantially reduced alcohol intake and preference during the repeated administration phases, while total fluid intake remained unchanged (Farook, Lewis, Gaddis, Littleton, & Barron, 2009). Pretreatment with lobeline (4 or 10 mg/kg) or cytisine (1.5 or 3 mg/kg, s.c.) on continuous access drinking, substantially reduced ethanol intake drinking-in-the-dark (g/kg) post-2-h and 4-h treatment, in comparison to controls. Neither lobeline nor cytisine considerably affected water or sucrose solution (10% w/v) intake during drinking-in-the-dark or continuous drinking procedures, in comparison to control (Sajja & Rahman, 2011). These two compounds have different pharmacokinetic and pharmacodynamic properties at the brain nAChRs and modulate ethanol drinking behaviors and ethanol-induced dopamine functions in different rodent models. Lobeline was shown to have longer-lasting effects on ethanol consumption and metabolized slower than cytisine (Tutka & Zatonski, 2006) although cytisine was more potent (1.5 mg/kg) and faster acting (1–4 h) in comparison to lobeline dose (5 mg/kg) in 3 days (Bell et al., 2009).

In addition, Sajja & Rahman, have shown that cytisine inhibited chronic voluntary ethanol intake by inhibiting the levels of striatal ΔFosB up-regulation in C57BL/6J mice as demonstrated by behavioral and biochemical methods. Pretreatment with cytisine (0.5 or 1.5 mg/kg) substantially reduced ethanol intake and preference in both paradigms at 2 h and 24 h post-treatment. Furthermore, cytisine (0.5 mg/kg) significantly attenuated up-regulation of ΔFosB in the ventral and dorsal striatum following chronic ethanol consumption in intermittent access (IA) and chronic access (CA) paradigms (Sajja & Rahman, 2013). Despite the encouraging results in animal models, lobeline and cytisine, were not been used for the treatment of AUD in human studies.

4.11. Argenine-vasopressin-1B receptor antagonist

4.11.1. ABT-436

Generally, Arginine-vasopressin (AVP) Type 1B receptor antagonists showed relapse prevention in alcohol dependence studies by attenuating the neuroendocrine mediated behavioral responses to stress. ABT-436, a potent and selective AVP type 1B receptor (V1B) antagonist, has been demonstrated to attenuate basal hypothalamic-pituitary-adrenal (HPA) axis activity in humans. It has also exerted favorable effects in rat models of alcohol dependence. To further study the pharmacokinetic or pharmacodynamic interaction in between ABT-436 and alcohol, Katz et al. (2016) conducted a single-dose clinical study in twenty moderate alcohol drinkers. Each individual received the 4 possible combinations of a single 1000 mg ABT-436 dose (or matching placebo) and a single 0.5 g/kg alcohol dose (or placebo for alcohol) in a double-blind, randomized, 4-period crossover study. A computerized cognitive test battery (CDR System), Bond-Lader Visual Analog Scale, and a postural stability test were performed. The potential interaction of alcohol with ABT-436 and the pharmacological effect of ABT-436 were assessed by measuring serum cortisol. ABT-436 treatment reduced serum cortisol levels, however, no pharmacokinetic or pharmacodynamic interactions between ABT-436 and alcohol have been reported (Katz et al., 2016). Similarly, the effects of ABT-436 on the individuals with major depressive disorder (MDD) and its safety on the HPA-axis were evaluated in a one week randomized Phase 1b trial. MDD patients received 800 mg QD of ABT-436 or placebo for 7 days showed improved symptoms suggesting that further clinical studies are required for ABT-436 antidepressant activity (Katz, Locke, Greco, Liu, & Tracy, 2017).

The efficacy of ABT-436 was also evaluated in a 12 week clinical trial with alcohol-dependent participants. Men and women (n = 150) who met criteria for DSM-IV alcohol dependence were recruited across four sites. Participants received double-blind ABT-436 (800 mg/day) or placebo during weeks 2–12. Although the primary outcome, percentage of heavy drinking days, was decreased in participants receiving ABT-436 compared with the placebo group, it was not statistically significant. Also, participants receiving ABT-436 had a substantially greater percentage of abstinent days than those receiving placebo. No significant differences were found between treatment groups on any other measures of drinking, alcohol craving, or alcohol-related consequences. Smokers receiving ABT-436 burned significantly fewer cigarettes per week than those receiving placebo. In subgroup analyses, participants with relatively higher baseline stress levels responded better to ABT-436 than placebo on select drinking outcomes, indicating that there may be of some value in future testing medications targeting the vasopressin receptor in high stress, alcohol-dependent patients (Ryan et al., 2017).

5. Conclusion and future directions

In this review, we have systematically reviewed the recent findings that described the properties of drugs that have been used, currently are in use and the new drug candidates that are repurposed for the treatment of AUDs. These include many FDA-approved drugs such as anticonvulsants, antipsychotics, antidepressants, and other off-label medications. Some of these drugs have shown beneficial outcomes in various stages of clinical trials. Our current understanding of the alcohol and drug misuse has expanded during the last decade in terms of neural circuitry, behavior, and molecular pathways. Some of the medications showed significant potential in animal studies. However, the same medications in clinical trials had insignificant effects or sometimes even showed toxic effects resulting in organ injury. Based on the data that was reviewed and discussed in this article, newer and novel medications (Figs. 1 & 2) are available in the market for the treatment of AUDs with limited success rates and mild to severe side effects. The outcomes of these medications and hormones, both positive and negative in humans are summarized in Tables 1 & 2.

This has resulted from the advanced knowledge and experience of the fundamental mechanisms of action of alcohol and/or other drugs of misuse, across the diversified population. However, several gaps remain to be addressed on certain aspects of complex interactions between alcohol and other abused substances as well as genetic and environmental factors. For instance, genetic studies have identified several variants associated with altered activities of certain enzymes and receptors that are involved in AUDs interaction pathways. Based on the genetic and environmental factors, we should consider future studies with selectively enriched populations in testing the benefits of drug candidates for treating AUDs.

Since, AUDs continue to be a major socioeconomic and health concern all over the world, there is an urgent need for conducting more applied, translational research for better prevention and treatment strategies that will provide better options for the patients and have minimal side effects. Future directions should aim to continue basic and translational research to understand underlying mechanisms by which abused substances or misuses affect the brain at molecular, cellular and circuitry levels. The identification of common neurological mechanisms and their targets will lead to the development of new medications and other therapeutics for the targeted interventions in AUDs and other mental disorders.

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Conflict of interest statement

All authors declared no conflict of interest.

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