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NORADRENERGIC TARGETS FOR THE TREATMENT OF ALCOHOL USE DISORDER

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Abstract

The role of norepinephrine (NE) in the development of alcohol use disorder (AUD) has been studied over the past several decades. However, the NE system has been largely ignored for many years as a potential target for medication development for AUD. More recently, preclinical and clinical studies have demonstrated the potential value of targeting NE signaling for developing new pharmacological treatments for AUD. This review contributes to a Special issue of *Psychopharmacology* focused on promising targets for alcohol addiction. Specifically, this review coalesces preclinical and clinical neuroscience that re-evaluate the noradrenergic system, and in particular the alpha-1 receptor, as a potential target for AUD.

1. Introduction

Stress has been implicated in a wide range of health and psychiatric illnesses ranging from anxiety and depression to alcohol use disorder (AUD) (Koob and Kreek, 2007). Stress is a key factor contributing to escalation from social drinking to excessive drinking and the development of AUD (Sarnyai et al., 2001); reducing stress has a protective effect (Fox et al., 2007). Furthermore, there is a considerable scientific literature that supports the role of alcohol in the dysregulation of the stress system, generally resulting in enhanced stress responses (Kreek and Koob, 1998, Koob and Le Moal, 1997). There is evidence that stress can affect the rewarding effect of alcohol which, in turn, can detrimentally affect drinking behaviors (Haass-Koffler et al., 2017b). Finally, stress does not halt when individuals stop

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drinking. Indeed, stress and anxiety increase in AUD individuals who stop drinking. Both stress and anxiety contribute to alcohol craving and withdrawal, which in turn may lead to relapse in alcohol drinking [for a review, *see*: (Haass-Koffler et al., 2014)].

While the role of stress in AUD is well established, none of the currently FDA-approved medications in the U.S., or EMA-approved medications in Europe (Soyka and Muller, 2017), specifically target the stress system. Disulfiram affects the pharmacokinetics of alcohol and induces unpleasant effects that act as a deterrent from consuming alcohol. Acamprosate, naltrexone, and nalmefene act on neurobiological targets involved in AUD and affect important AUD-related phenotypes (craving, reward, and/or withdrawal), but do not necessarily, or directly, affect stress.

One potential pharmacological target for the stress component of AUD is norepinephrine (NE). Noradrenergic neurons innervate key limbic and forebrain areas involved in arousal, reinforcement, and stress response processes involved in developing and maintaining AUD (Koob, 2008). Noradrenergic neuron cell bodies are clustered in seven discrete nuclei in the brainstem and pons, whose axons project widely throughout the brain and spinal cord. The largest and best characterized of these nuclei is the locus coeruleus (A6), which has been shown to be involved in stress (Weiss et al, 1994), anxiety (McCall, et. al., 2017), alcohol (West et al., 2016), and opioid responses (Van Bockstaele, et. al., 2010). Studies on NE in the amygdala, the bed nucleus of the stria terminalis (BNST) (Kash, 2012), and the paraventricular nucleus of the hypothalamus (Alonso et al., 1986), key anatomical circuitries implicated in the neurobiology of addiction, further support the role of NE in the development of AUD (Koob, 2009). The excessive noradrenergic activation, which accompanies alcohol withdrawal and stress responses, produces anxiety and hyperarousal, for review see (Kent et al., 2002), and has been implicated in relapse drinking and other alcohol related behaviors, for review see (Becker, 2012). Yet, the potential for the NE system to be a pharmacological target for AUD medication development has been largely neglected.

Adrenergic receptors expressed in the central nervous system, and at the noradrenergic autonomic nerve endings, regulate efferent sympathetic pathway activity and the release of NE (Berlan et al., 1992). The two main classes of adrenergic receptors are alpha and beta (Ahlquist, 1948), which have been cloned and are subdivided into alpha-1_A, alpha-1_B, alpha-1_D, alpha-2_A, alpha-2_B, alpha-2_C, beta1, beta-2, and beta-3 (Sica, 2005). Table 1 describes the major noradrenergic receptor subtypes. The adrenergic receptors are G-protein linked receptors that are well characterized functionally (Rosenbaum et al., 2009). Alpha1-, beta-1, beta-2 adrenoceptors are located in the membrane of postsynaptic neurons. Alpha-1 adrenoceptors also are localized postsynaptically in smooth muscle adjacent to nerve terminals and mediate arteries and veins vasoconstriction (Sica, 2005). In addition to the alpha-1/beta-1/beta-2 postsynaptic adrenoceptors, there are alpha-2 autoreceptors located on the noradrenergic nerve terminals. Presynaptic inhibitory alpha-adrenoceptors regulate the release of norepinephrine through a negative feedback mechanism (Langer, 1980, Qin et al., 2008). The alpha-2_A and alpha-2_C subtypes are expressed in the central nervous system. Their stimulation by norepinephrine results in sympatholytic effects e.g. hypnosis, analgesia and sedation (Giovannitti et al., 2015). They inhibit adenylyl cyclase, reduce cyclic

adenosine monophosphate and induce hyperpolarization of noradrenergic neurons and suppression of neural firing (Pichot et al., 2012).

Hundreds of highly specific agonists (Giovannitti et al., 2015) and antagonists (Sica, 2005) of the adrenergic receptors have been developed and several of these medications are in routine clinical use for control of blood pressure, heart rate, bronchospasm, etc. The diversity of adrenergic receptors, and the many drugs available to stimulate or block the receptors, suggest that NE is an exploitable target for the development of medications for AUD.

Studies examining the intercept between NE and alcohol have been conducted using two general approaches. In one approach, the effects of alcohol administration or withdrawal on NE levels have been studied, while the other approach has focused on the effects of pharmacological manipulations of the NE system on alcohol consumption. Examples of both approaches are provided next. Alcohol withdrawal is characterized by anxiety, adrenergic hyperactivity, central nervous system hyperactivity and intense craving to use alcohol. Both preclinical and clinical studies suggest a role of noradrenergic systems in alcohol withdrawal (Trzaskowska et al., 1986, Riihioja et al., 1997). For example, in the periphery and in the central nervous system, NE levels are elevated in animals during alcohol withdrawal (Kovacs et al., 2002). Similarly, in alcohol-dependent patients in alcohol withdrawal, NE levels are elevated in the cerebrospinal fluid (Hawley et al., 1981) and in plasma (Patkar et al., 2003, Fitzgerald, 2013).

The acute effects of alcohol administration on NE levels are complex, and depend on alcohol dose, route of administration and anatomical specificity of different brain regions (Yamanaka, 1982). The systemic or localized administration of alcohol (1–2 g/kg) directly onto a single neuron in the rat locus coeruleus (a major brainstem noradrenergic cell nucleus) produces a suppression in the neuronal firing rate (Strahlendorf and Strahlendorf, 1983). In Wistar rats, acute alcohol administration (1.5 and 4.0 g/kg of ethanol 30 min prior to sacrifice for moderate and severe intoxication) significantly reduced NE levels, with a decrease in the activity of dopamine-beta-hydroxylase in the hippocampus (Yamanaka and Egashira, 1982). The decrease in NE levels became more significant during alcohol withdrawal, particularly in the medulla oblongata and the striatum (Yamanaka and Egashira, 1982). The large noradrenergic input in the bed nucleus of the stria terminalis seems to inhibit glutamate release via activation of alpha-2 receptors (Egli and Winder, 2003, Egli et al., 2005), and has been associated with activation of the hypothalamic–pituitary–adrenal s axis, anxiety and stress-induced relapse to drug seeking (Kash, 2012). The NE input in the bed nucleus of the stria terminalis is, however, more complex, since NE can also enhance glutamatergic transmission via both beta-1 and beta-2 receptors (Egli et al., 2005). The effect of alcohol (*in vivo*, four-day vapor exposure in C57BL/6J mice) on NE modulation in the bed nucleus of the stria terminalis lead specifically to a reduced magnitude for the alpha-1 mediated post-synaptic long-term depression (McElligott et al., 2010). Interestingly, the alpha-1 receptor antagonists (discussed later in this review) have cast positive results, both at preclinical and clinical levels, for the development of AUD therapies.

Acute alcohol exposure (one injection 2 g/kg as 5% solution i.p.) has been shown to modulate NE synthesis (Corrodi et al., 1966), to increase NE release (Socaransky et al., 1985), and to downregulate central alpha-2 adrenergic receptors (Thiele et al., 2000). Yohimbine, an alpha-2 adrenoceptor antagonist increases NE cell firing and NE release into extracellular fluid (Abercrombie et al., 1988) by blocking pre-synaptic inhibition; yohimbine increases anxiety and has been extensively used as pharmacological stressor. A double-blind, placebo-controlled design with 12 healthy volunteers compared the effects of acute administration of either alcohol or yohimbine (McDougle et al., 1995). Both alcohol and yohimbine increase NE levels compared to placebo, as measured by increases in the plasma NE metabolite 3-methoxy-4-hydroxyphenylethylene glycol (MHPG). As expected, yohimbine increased anxiety, plasma cortisol, and blood pressure compared to placebo. Alcohol increased plasma MHPG significantly more than yohimbine; however, yohimbine significantly increased anxiety, plasma cortisol, and blood pressure more than alcohol. The combined administration of alcohol and yohimbine, however, had a synergistic effect in increasing both the subjective measures of alcohol intoxication and MHPG level, compared with the single administration of alcohol or yohimbine alone.

The role of NE in AUD is also supported by studies focused on the effects of pharmacological manipulations of the NE system on alcohol consumption. For example, alcohol consumption using a two-bottle, free-choice paradigm [alcohol and water either for 5 alternate days (25 or 40 mg/kg i.p.) or for 5 consecutive days (45 mg/kg i.p.)] is decreased by both the disruption of noradrenergic function, and the administration of dopamine beta-hydroxylase inhibitors that decrease NE synthesis in alcohol-preferring P rats (Amit et al., 1977). Furthermore, the alpha-2-antagonist yohimbine, which increases norepinephrine release, increases alcohol reinstatement and excessive alcohol drinking in both preclinical (Simms et al., 2012, Marinelli et al., 2007) and clinical (Umhau et al., 2011) settings. In healthy volunteers, the administration of the NE synthesis inhibitor, alpha-methyl-p-tyrosine, reduced alcohol-induced euphoria and stimulation (Ahlenius et al., 1973).

In summary, both animal and human studies have shown that dysregulation of the noradrenergic systems that mediate arousal, stress and withdrawal are key components of the pathophysiology of AUD, and pharmacotherapies that target the adrenergic receptors may be useful for treatment of this detrimental disorder.

2. Pharmacological approaches for the development of therapies for Alcohol Use Disorder (AUD)

There are FDA-approved oral medications that target the NE system used for indications such as hypertension, tachycardia, etc. These medications represent an opportunity to test novel pharmacological approaches for AUD that can be quickly repurposed for treatment of AUD. Next, we summarize recent efforts via animal and human studies directed at targeting the alpha-1, alpha-2 and beta receptors in AUD.

2.1. The role of alpha-1 receptor

Several selective alpha-1 blockers are FDA-approved for hypertension and benign prostatic hyperplasia and, therefore, are readily available to be tested not only in animal models, but also in humans. Both prazosin and doxazosin have been tested, in this regard, as promising treatments for AUD. As chemical congeners, these medications share the same piperazine ring structure, and have a non-selective action on all three alpha-1-subtypes, *i.e.*, alpha-1_A, alpha-1_B and alpha-1_D (Gross et al., 1989), Table 2. The alpha-1 prototype antagonist prazosin is active in the CNS, as it is highly lipophilic and easily crosses the blood-brain barrier. Doxazosin is less lipophilic but still holds central effects. Blockade of the alpha-1B subtypes (located in the brain) by prazosin and doxazosin contributes to the central side-effects, such as dizziness and fatigue, thus demonstrating indirectly the CNS penetration of these drugs (Michel et al., 2000, Gross et al., 1989, Hofner and Jonas, 2002). Preclinical studies also demonstrate CNS-actions of doxazosin, administered peripherally (McLeod and Cairncross, 1995).

Prazosin was tested in non-dependent rats and in rats made alcohol-dependent, via a 4-week intermittent vapor exposure period in which animals were exposed to ethanol vapor for 14h/day. (Walker et al., 2008). Interestingly, prazosin reduced alcohol dependence-induced operant responding during acute withdrawal in a specific manner in the dependent, but not in the non-dependent rats. Additional studies supported a role of prazosin in AUD by showing that, in rats selectively bred for alcohol preference (P rats), prazosin suppressed alcohol drinking using a two-bottle choice paradigm (Rasmussen et al., 2009) and alcohol intake in an animal model of alcohol relapse (Froehlich et al., 2015). In combination with cyproheptadine (a potent antagonist of the 5-HT2 receptors), prazosin was able to reverse alcohol preference in DBA2 mice (Trovero et al., 2016). Finally, using a yohimbine challenge and a foot shock paradigm, prazosin blocked foot shock- and yohimbine-induced reinstatement of alcohol seeking in Wistar rats (Le et al., 2011).

Following on this preclinical work, prazosin has been tested in individuals affected by AUD. Prazosin was tested in a 6-week pilot randomized clinical trial in treatment seeking individuals with AUD (N = 24) (Simpson et al., 2009). After two-week titration, when prazosin reached target dose (16 mg/day administered, thrice a day), the prazosin group, compared to placebo, reported fewer drinking days per week (DD) and fewer drinks per week. The medication was well tolerated, with no adverse events between the two groups (Simpson et al., 2009).

Prazosin was further tested in alcohol-dependent patients ($N = 17$) using an experiment with guided imagery exposure to stress, alcohol cues, and neutral-relaxing/control conditions. Prazosin decreased stress- and cue-induced alcohol craving, suggesting that it may normalize the stress dysregulation associated with early recovery from alcoholism (Fox et al., 2012). Considering the high comorbidity between AUD and PTSD, and previous work indicating a role for prazosin in the treatment of PTSD (Raskind et al., 2013), an outpatient 6-week, double-blind, randomized controlled pilot trial with prazosin was conducted in patients with comorbid AUD and PTSD. Prazosin reduced drinking outcomes from baseline compared to placebo, but did not change PTSD symptoms. In terms of safety, individuals in the prazosin arm reported more hypotensive side effects than those in the placebo arm

(Simpson et al., 2015). In contrast, in a randomized clinical trial of veterans with PTSD and alcohol dependence, symptoms of PTSD and alcohol consumption were not significantly different between the prazosin and placebo groups (Petrakis et al., 2016).

In humans, the long half-life ($t_{1/2}$) of doxazosin represents an attractive pharmacological property, especially for AUD, as it allows for once a day dosing, as opposed to the need for multiple daily dosing as in the case of prazosin. In fact, lack of medication compliance is a critical challenge in randomized clinical trials for AUD, as well as in clinical practice with patients with AUD (Swift et al., 2011). Also, because doxazosin absorption is not affected by food, and does not produce metabolites with hypotensive activity (Kaye et al., 1986), in clinical practice, doxazosin is preferred to treat hypertension or benign prostatic hyperplasia, over short-acting α_1-blockers, such as prazosin (Akduman and Crawford, 2001). Based on these pharmacological properties, given the promising results obtained with prazosin in AUD, doxazosin was also tested in AUD. In alcohol preferring P rats (O'Neil et al., 2013), doxazosin significantly reduced alcohol intake, did not affect locomotor activity, and resulted in a lower plasma alcohol concentration, suggesting that the doxazosin-induced reduction in alcohol drinking was not dependent on motor impairment or an alteration in alcohol clearance (O'Neil et al., 2013). Furthermore, as prazosin, doxazosin is also effective in reducing yohimbine-induced reinstatement in alcohol-seeking rats (Funk et al., 2016).

In parallel, and before this animal work was published, a proof-of-concept RCT was conducted to test the hypothesis that doxazosin may represent a safe and effective medication to reduce alcohol consumption in patients with AUD (Kenna et al., 2016). This was a 10-week, between-subject, double-blind, and placebo-controlled preliminary RCT with doxazosin, 16 mg once a day, in an outpatient setting with treatment-seeking AD patients. Although the main drinking outcome of this study showed no significant differences between groups, an *a priori* moderator analysis showed that doxazosin reduced drinking and craving in AD patients with high family history density alcoholism (Kenna et al., 2016). This reduction is in line with the preclinical study mentioned before, which showed that doxazosin decreased alcohol consumption in P rats (O'Neil et al., 2013), a well-characterized model of genetically-predisposed excessive, voluntary alcohol drinking (Li et al., 1979). From a translational perspective, in humans, doxazosin significantly reduced alcohol drinking in alcohol-dependent patients with high family history density alcoholism and, by contrast, increased drinking in those with low family history density alcoholism (Kenna et al., 2016).

Measurable biomarkers to assess therapeutic response are desirable and critical features in medication development for AUD (Litten et al., 2010). A proposed biomarker of alpha-1-blockade response is pre-treatment blood pressure. A recent randomized clinical trial testing prazosin in patients with PTSD demonstrated that baseline systolic blood pressure predicts prazosin's efficacy, suggesting that prazosin may be more efficacious in PTSD patients with higher pre-treatment blood pressure (Raskind et al., 2016). Blood pressure is regulated by norepinephrine activation via alpha 1 receptors in the peripheral arterioles, and it may represent a peripheral surrogate for alpha-1 receptor central tone (Reid, 1986). Systolic blood pressure as a moderator of doxazosin's effect on alcohol drinking outcomes was observed in AD patients (Kenna et al., 2016). Specifically, this study revealed the potential

role of pre-treatment systolic blood pressure, as a moderator of doxazosin's response on alcohol consumption, in treatment seeking individuals with AUD. That is, doxazosin was significantly more effective, compared to placebo, in reducing alcohol consumption in those alcohol-dependent patients with higher pre-treatment blood pressure (Haass-Koffler et al., 2017c). Patients with lower BP not only did not benefit from doxazosin, but also had a trend towards increased drinking compared to placebo. Of note, family history density alcoholism and BP were independent moderators and did not correlate with each other (Haass-Koffler et al., 2017c). Taken together, these results suggest that the beneficial effects of doxazosin are specific for sub-types of AUD patients (with higher family history density alcoholism and/or higher blood pressure). These preliminary findings represent a platform for additional larger studies towards developing personalized medicine approaches in AUD (Wilcox, 2017). Additional trials are underway on the combined use of prazosin and naltrexone for veterans with AUD (NCT 02322047), prazosin augmentation of outpatient treatment of AUD in active duty soldiers with PTSD (NCT02226367), doxazosin in AUD (NCT02989493), and in the comorbidity of PTSD and AUD (NCT02492334 and NCT 02500602).

2.2. The role of alpha-2 receptors

Clonidine is the oldest alpha-2 receptor agonist FDA-approved for hypertension and it was investigated several decades ago as a treatment for alcohol withdrawal (Bjorkqvist, 1975). Clonidine crosses the blood-brain barrier and acts as an agonist on alpha-2 receptors located in brainstem tractus solitaries. Clonidine decreases NE release from presynaptic terminals and postsynaptically decreases sympathetic conduction (Aghajanian and VanderMaelen, 1982), therefore it lowers noradrenergic signaling. Clonidine reduces blood pressure by acting centrally at the presynaptic alpha-2 receptors in the brainstem by decreasing calcium levels thus inhibiting NE release. Clonidine is effective in treating noradrenergic hyperactivity in opioid withdrawal (Gold et al., 1980). Furthermore, more recently, clonidine was shown to reduce alcohol drinking in alcohol-preferring rats (P line) (Rasmussen et al., 2014a). In a pilot with eight male volunteers, clonidine reduced significantly sedation after a period of heavy alcohol intake (Berggren et al., 2003) and in a study with 17 individuals with alcohol-dependence in full sustained remission showed that there is a long recovery period in alpha-2-adrenoceptor function, especially for clonidine-induced increase in level of sedation (Berggren et al., 2002). In humans, clonidine, as compared to chlormethiazole (a GABA positive allosteric modulator often used in Europe to treat alcohol withdrawal (Mirijello et al., 2015)), was more effective in improving alcohol withdrawal symptoms in humans (Adinoff, 1994). Alpha-2_A adrenoreceptors have shown to be involved in the reinstatement of alcohol seeking in alcohol-dependent rats by using pretreatment of lofexidine (agonist) and yohimbine (antagonist). Intraperitoneal administration of lofexidine was able to attenuate stress-induced reinstatement of alcohol seeking and decrease alcohol self-administration. Yohimbine strongly reinstated alcohol seeking after extinction and induced increase in alcohol self-administration in rats trained to self-administer alcohol (Le et al., 2005). However, a randomized clinical trial demonstrated that adjunct therapy with lofexidine does not provide benefit when administered with chlordiazepoxide (benzodiazepine class) in the treatment of alcohol withdrawal (Keaney et al., 2001).

Guanfacine is a medication used to treat hypertension and attention deficit hyperactivity disorder, and it is a selective alpha-2_A receptor agonist. It was tested in rats trained to self-administer alcohol (12% w/v, 1 h/day), and after extinction of alcohol-reinforced lever pressing, and attenuated yohimbine-induced reinstatement of alcohol seeking similarly as prazosin, but only at the higher dose tested (Le et al., 2011). Also, guanfacine reduced alcohol consumption in high (4.3 ± 0.2 g/kg per 24 h), but not low (1.9 ± 0.2 g per kg/24 h) alcohol-consuming rats, and the repeated drug administration prolonged the effect in reducing alcohol intake (Fredriksson et al., 2015). The same study reported that guanfacine attenuated the alcohol deprivation effect, alcohol seeking, and priming-induced reinstatement of alcohol seeking. Electrophysiology studies showed that the alcohol-related behavioral effects are regulated by dysregulation of glutamatergic neurotransmission in the medial prefrontal cortex. Notably, subchronic treatment with guanfacine normalized alcohol-induced dysregulated glutamatergic neurotransmission in the medial prefrontal cortex (Fredriksson et al., 2015). The use of guanfacine in reducing craving and improving cognitive control in women with AUD, compared to men, is currently under clinical investigation in a 10-week out-patient, clinical trial (NCT03137082).

Another alpha-2 receptor antagonist is idazoxan, a selective alpha-$2_{A/C}$-adrenergic receptor antagonist (Doxey et al., 1983, Doxey et al., 1984, Lister et al., 1989). Idazoxan attenuates social interaction and locomotor behaviors induced by alcohol (Durcan et al., 1989b), and suppresses alcohol-induced exploratory behavior and hypothermia (Durcan et al., 1989a, Durcan et al., 1989c). Idazoxan neutralizes the interaction between alcohol and clonidine on loss of righting reflex in rats (Mao and Abdel-Rahman, 1996), and reduces the anxiolytic effect produced by alcohol (Taksande et al., 2010). In naïve alcohol-exposed animals, idazoxan reduced the positive reinforcing effects of alcohol (Lister et al., 1989). These results in non-alcohol-dependent rodents are in line with a human laboratory study in non-dependent social drinkers, which indicated that idazoxan altered subjective effects of alcohol intoxication and hemodynamic parameters possibly by affecting the biphasic effects of alcohol (Haass-Koffler et al., 2015). A pharmacokinetics/pharmacodynamics model that linked alcohol concentration and alcohol effects (Wright et al., 2011), adopted in this study, showed that idazoxan was able to affect the biphasic effects of alcohol by altering alcohol pharmacokinetic parameters, such as reduce maximus concentration (C_{max}) and delay of time of maximum concentration (t_{max}) (Haass-Koffler et al., 2015, Haass-Koffler et al., 2017a).

2.3. The role of beta receptors

Since noradrenergic activation in the central nervous system is also mediated by postsynaptic beta-adrenergic receptors, propranolol, a non-selective beta-blocker, FDA-approved for treating cardiovascular disorders, was tested as a potential treatment for AUD, both in preclinical and clinical settings. Notably, propranolol, together with metoprolol, are lipophilic and therefore has relatively greater central effects. By contrast, other β-blockers (e.g.: nadolol and atenolol) are less lipophilic and therefore have less blood–brain barrier penetrance, therefore their administration leads to more peripheral than central effects.

Preclinical work demonstrated that beta-adrenoceptor activation is required for alcohol enhancement of lateral paracapsular GABAergic synapses in the rat basolateral amygdala. Interestingly this effect was selective for beta-1 antagonists but not for beta-2 or beta-3 receptor antagonists (Silberman et al., 2012). Because enhancement of lateral paracapsular GABAergic synapses inhibition can reduce anxiety-like behaviors, these findings have hypothesized a possible alcohol anxiolytic mechanism that may contribute to the development of AUD (Silberman et al., 2012). For example, in Long Evans alcohol-dependent rats, propranolol did not alter 24-hour free-choice alcohol drinking (Begleiter, 1974), and in Wistar rats made alcohol-dependent via chronic intermittent (14 h ON/10 h OFF) alcohol vapor inhalation, and trained to respond for alcohol in an operant conditioning paradigm on fixed-ratio-1 and progressive ratio reinforcement schedules, propranolol was able to ameliorate alcohol withdrawal-induced, acute operant responding for alcohol (Gilpin and Koob, 2010). Since only centrally acting propranolol, but not peripherally acting nadolol, suppresses operant alcohol-reinforced responding in alcohol-dependent rats, it is believed that this effect is mediated by central actions of propranolol (Gilpin and Koob, 2010). Notably, the combination of prazosin with propranolol reduced alcohol consumption during both alcohol withdrawal and following prolonged abstinence. The combination of these two medications was more effective than single drug treatment in P rats, when given a two-hour free-choice between alcohol and water (Rasmussen et al., 2014b).

In humans, a double-blind comparative study of propranolol and diazepam with patients suffering from moderate alcohol withdrawal showed that both medications were equipotent in reducing physical withdrawal symptoms and anxiety symptoms. Propranolol, however was ineffective in preventing major motor seizures (Bailly et al., 1992). A double blind, placebo-controlled randomized clinical trials of the beta-blocker atenolol, in 180 outpatients with mild alcohol withdrawal, showed decreased withdrawal severity, craving, and treatment failure with atenolol, compared to placebo (Horwitz et al., 1989). In spite of potential effects of noradrenergic medications to mitigate alcohol withdrawal, benzodiazepines represent the gold standard treatment for alcohol withdrawal syndrome, given they are the only class of medications proven to be effective in treating alcohol withdrawal syndrome and in preventing its most serious complications, like seizure and delirium tremens (Saitz, 2017). In current clinical practice, alpha-1 agonists, including clonidine, and beta-blockers, including propranolol, are used only as adjunct pharmacological treatments to benzodiazepines for alcohol withdrawal symptoms, especially in patients with cardiovascular complications such as tachycardia and hypertension (Mirijello et al., 2015).

3. Conclusions

Decades of preclinical and clinical research support an important role of the NE system in the pathophysiology of AUD and suggest that medications that target the NE system could be utilized for the treatment of AUD. In particular, medications that block post-synaptic alpha-1 receptors (prazosin and doxazosin) or post-synaptic beta receptors (propranolol), or that act on presynaptic alpha-2 autoreceptors (clonidine, guanfacine), are shown to reduce alcohol-related behaviors, including alcohol consumption in pre-clinical and clinical settings.

The wide distribution of NE in the body and its diversity of physiological functions including metabolic, cardiovascular, and behavioral effects, suggests that pharmacological treatments for AUD, that focus on the NE system, will require more specificity and better targeting toward specific systems involved in AUD. Moreover, the findings that blood pressure moderates the effects of alpha-1 blockers on PTSD and AUD, suggests that individual factors may contribute to personalized response. This aspect provides additional support for a personalized medicine approach to AUD pathology. Additionally, as most human studies have small sample sizes, there is also a need to conduct larger clinical trials to further test promising medications targeting the NE system. In addition to larger sample sizes, future clinical studies and mechanistic preclinical experiments should address psychiatric comorbidities that are common in AUD. For example, 2 × 2 fully factorial trials should test prazosin or doxazosin, as compared to placebo, in AUD patients with and without PTSD. If these studies should confirm the lack of medication effects in patients with AUD/PTSD, mechanistic studies could be conducted to shed light on possible mechanisms involved which hypothetically could range from differences in the engagement of specific neurobiological pathways to pharmacological effects (e.g. receptor down-regulation). Finally, future clinical trials could be designed with the goal of minimizing significant placebo effects related to the specific research setting to investigate whether the putative medication effect may translate to clinical practice.

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Table 1

Major noradrenergic receptor subtypes

Receptor	Subtype	Action	G-coupled mechanism
Alpha-1	A, B, D	Smooth muscle, mucosa, gastrointestinal (GI) contraction, vasoconstriction and mydriasis. Activation produces anorexia, decreases cellular excitability in the temporal cortex and decreases glutamatergic excitatory postsynaptic potential	Gq: phospholipase C (PLC) activated, inositol triphosphate (IP3), diacylglycerol (DAG), increase calcium output
Alpha-2	A, B, C	Smooth muscle contraction/relaxation, NE inhibition, platelet activation, inhibition of insulin release and induction of glucan from pancreas, negative feedback in neuronal synapses, presynaptic inhibition of NE release in the CNS	Gi: adenylate cyclase inactivation (cAMP) decrease
Beta-1	-	Increase cardiac output (positive chronotropic, dromotropic and inotropic effects,) increased amylase secretion, renin secretion from kidney and ghrelin from stomach.	Gs: adenylate cyclase activation (cAMP) increase
Beta-2	-	Smooth muscle relaxation, glycogenolysis and gluconeogenesis, stimulate insulin secretion from the pancreas, increases renin secretin from kidney. The Beta-2 receptor in the brain is involved in immune communication and in the flight-fight response	G_i and Gs: adenylate cyclase activation (cAMP) increase
Beta-3	-	Enhances lipolysis, promotes relaxation in the muscle in the bladder. Some beta-3 agonists have anti-stress properties in animal models	Gs: adenylate cyclase activation(cAMP) increase

Table 2

Alpha 1 blockers

	Prazosin	Doxazosin
FDA-approval	hypertension (HTN) benign prostatic hyperplasia (BPH)	
Alpha (α)-1 subtypes	α_{1A}, α_{1B}, α_{1D}	
Maximum daily dose	16 mg	
Daily administration	2–3 times	once
Half-life ($t_{1/2}$)	2.5 hours	~22 hours
Absorption	reduced by food	not affected by food
Metabolism	liver 4 active metabolites possess hypotensive activity	liver
Side-effects	first-dose phenomenon, hypotension, syncope, drowsiness, tiredness, headache	similar to prazosin, but less frequent, especially blood pressure-related side-effects