Current and Promising Pharmacotherapies, and Novel Research Target Areas in the Treatment of Alcohol Dependence: A Review

Steven M. Edwards[1], George A. Kenna[1], Robert M. Swift[1,2] and Lorenzo Leggio[1,3,*]

[1]*Center for Alcohol and Addiction Studies, Brown University, Providence, RI, USA,* [2]*Veterans Administration Medical Center, Providence, RI, USA,* [3]*Institute of Internal Medicine, Catholic University of Rome, Rome, Italy*

Abstract: Harmful alcohol use is a risk factor in more than 60 diseases and injuries resulting in approximately 2.5 million deaths per year worldwide. In the United States (US) and Europe, there are only a few medications approved for alcohol dependence (AD) however, these medications have only been moderately effective and there is a crucial need for more effective treatments. This review briefly summarizes research on currently approved medications for AD, as well as promising medications like topiramate, baclofen and ondansetron. Topiramate is likely the most promising new treatment for AD, however, further research is needed to determine the optimal dose and appropriate length of treatment. Baclofen, a $GABA_B$ agonist, is a promising medication as a treatment for AD, especially for patients with AD and severe liver disease. Ondansetron has shown promising results as a potential medication for AD, but only within a certain subtype of individuals. This review also discusses more recent findings on other potential pharmacotherapies for AD, such as serotonin-specific reuptake inhibitors (SSRIs; i.e. sertraline), aripiprazole and prazosin, as well as on some examples of other potentially interesting new neuropharmacological targets (i.e. cannabinoid receptors, CRF, NPY, ghrelin). Finally, the present review also discusses the attempts to personalize medication for AD treatment by alcohol typology and pharmacogenetics.

Keywords: Alcohol Dependence, Alcohol Pharmacotherapy, Alcohol Typology, Pharmacogenetics.

INTRODUCTION

Harmful alcohol use is a factor in more than 60 diseases and injuries and results in approximately 2.5 million deaths per year worldwide [1]. As highlighted by the World Health Organization [2], the disease burden attributable to alcohol consumption is significant worldwide and, in many countries, public health problems caused by harmful use of alcohol represent a substantial health, social and economic burden. Therefore, interventions that reduce alcohol dependence (AD) may have important public health implications.

While not always considered a 'medical problem', AD is a chronic relapsing condition with a multifactorial etiology that includes genetic, neurobiological, and environmental components [3]. Diagnosis of AD is defined by meeting at least 3 of the following conditions during a 12-month period: tolerance, withdrawal symptoms, ingestion of alcohol in larger amounts or over a longer period than intended, persistent desire or one or more unsuccessful attempts to reduce or control alcohol ingestions, expenditure of much time in activities necessary to get and drink alcohol or to recover from its effects, abandonment of important social, occupational, or recreational activities because of alcohol ingestion, continued alcohol ingestion despite the knowledge of having a persistent or recurrent social, psychological, or physical problem that is caused or exacerbated by it [4].

Current treatments of AD include psychological, social and pharmaceutical interventions. Alcohol affects several neurotransmitter systems, including dopamine (DA), serotonin (5-HT), gamma-amino butyric acid (GABA), glutamic acid, opioid, and many others [5,6]. These systems are potential targets for drug therapy in the treatment of AD. The growing understanding of the neurobiology of AD has led to the development of pharmacotherapies that can complement psychosocial treatments [7,8]. The National Institute of Health (NIH) emphasizes that addictions (including AD) are brain disorders and the National Institute on Alcohol Abuse and Alcoholism (NIAAA) strongly recommends consideration of pharmacotherapies for all alcoholic patients [9].

*Address correspondence to this author at the Center for Alcohol and Addiction Studies Brown University Medical School Box G S 121-4; Providence, RI 02912, USA; Tel: 401 863-6638; Fax: 401 863-6647;
E-mail: Lorenzo_Leggio@brown.edu

For example, in the US, currently there are only four medications approved by the Food and Drug Administration (FDA) to treat AD: disulfiram, oral and intramuscular (I.M.) naltrexone, and acamprosate (Table **1**). Data suggests however, that their overall efficacy is modest [10]. Therefore, there is a critical need in the field to identify new medications that may be effective in treating AD individuals. In this regard, several medications are currently under investigation, and their main results will be reviewed (see also Table **1**).

DISULFIRAM

Disulfiram reinforces an individual's desire to stop drinking by providing a psychological disincentive associated with the increase in acetaldehyde, resulting in hypotension, flushing, nausea and vomiting, when patients consume alcohol [11]. By contrast to the pharmacological effects of the other approved pharmacotherapies, the psychological effect of disulfiram makes it a difficult drug to test in a double-blind placebo controlled drug trial. As a result, disulfiram has demonstrated mixed results as a treatment for AD [12].

Disulfiram has been investigated in several clinical trials and has been used for over 50 years in clinical settings as a pharmacotherapy for AD. In the largest clinical trial (n=605 men), AD patients were divided into 3 groups based on the following 3 possible treatments: 250 mg daily disulfiram (n=202), 1 mg disulfiram (n=204), and multivitamin (n=199). This study showed no statistical difference in total abstinence between the groups, however, in patients who relapsed, those in the group taking 250mg a day drank significantly less than the other 2 groups [13]. There have been other studies showing that patients who receive disulfiram report more total days of abstinence from alcohol as well as lower levels of gamma-glutamyltransferase (GGT) when compared to placebo groups [14,15].

While most reactions to drinking alcohol when taking disulfiram are temporary, at worse, disulfiram can induce hepatotoxicity and liver failure [16]. Additionally, 28% of the reported cases of disulfiram-induced hepatotoxicity resulted in death [17]. This is of special concern considering that AD patients may already be present with a wide spectrum of alcohol-related liver diseases. Disulfiram has been shown to inhibit dopamine beta-hydroxylase [18,19], which facilitates increased DA levels, presumably in the

1381-6128/11 $58.00+.00

Table 1. Current and Promising Pharmacotherapies in the Treatment of Alcohol Dependence

Drug	Pharmacological Mechanism of Action	Notes of Interest
Disulfiram	• Blockade of the oxidation of acetaldehyde by enzyme ALDH • Inhibition of DBH, the enzyme that catalyzes the conversion of DA to NE (?)	Approved for AD
Oral and I.M. Naltrexone	• Opiod receptor antagonist (μ- and κ-opioid receptors, and to a lesser extent δ-opioid receptors)	Approved for AD
Acamprosate	• Blockade of glutamatergic NMDA receptors • Activation of $GABA_A$ receptors	Approved for AD
Topiramate	• Increase of $GABA_A$-facilitated neuronal activity • Antagonism of AMPA and kainate glutamate receptors • Inhibition of L-type calcium channels, and limiting the activity of voltage-dependent sodium channels • Inhibition of CA-II and CA-IV	Remarkable effect size but research needed for optimal dose
Baclofen	• $GABA_B$ agonist	Of interest for patients with AD and severe liver impairment.
Ondansetron	• Antagonism of 5-HT_3 receptor • Possible antagonism of 5-HT_{1A}, 5-HT_{1B}, α1 NE and μ-opioid receptors	Effective for certain genotypes
SSRIs	• Selective inhibition of 5-HT reuptake	Effective for certain typologies
Aripiprazole	• partial dopamine agonist, in particular high affinity for the D2 receptors (e.g. partial agonism of DA autoreceptors at D2L receptors) • partial agonism of the 5-HT1A receptor; antagonism of the 5-HT2A receptor; and inverse agonism of the 5-HT2B receptor	Research needed for optimal dose
Prazosin	• Blockade of the NE α_1 receptor	Of interest for patients with AD and PTSD

ALDH: aldehyde dehydrogenase; DBH: dopamine β-hydroxylase; DA: dopamine; NE: norepinephrine; AD: Alcohol Dependence; I.M.: intramuscular; NMDA: N-methyl-D-aspartate; $GABA_A$: gamma-aminobutyric acid type A; AMPA: alpha-amino-3-hydroxy-5-methyl-4- isoxazole-propionic acid; CA-II and CA-IV: carbonic anhydrase isoenzymes; $GABA_B$: gamma-aminobutyric acid type B; SSRIs: Selective serotonin reuptake inhibitors; 5-HT serotonin; PTSD: Post-traumatic stress disorder.

dopaminergic brain areas related to alcohol reinforcement. Interestingly, Fuller and Gordis [20] report that disulfiram may play an important role for treatment of AD if administered under supervision. This supervision approach has been supported by a meta-analysis [21] and a recent review [22].

NALTREXONE

One of alcohol's many actions includes the release of β-endorphins from neurons. A higher concentration of β-endorphin results in an inhibition of GABA neurons that facilitate the disinhibition of DA neurons located in the ventral tegmental area (VTA), that in turn project to the nucleus accumbens (NAc). In addition to direct stimulation of the NAc to release DA, this mediated action also results in the release of DA at the NAc. This increased DA activity is related to the positively reinforcing effects of alcohol and is thought to be associated with the development of alcohol dependence [23,24]. Naltrexone, an opioid receptor antagonist, was found to increase the release of DA [25].

Naltrexone was approved for AD treatment in 1994 after successful trials reported AD patients significantly reduced alcohol craving and consumption when taking naltrexone [26,27]. Subsequent clinical studies with oral naltrexone have produced some conflicting results [28]; however, there are more positive studies and several meta-analytic studies supporting the efficacy of naltrexone, particularly in reducing heavy drinking (defined as 4 or more drinks per day for women and 5 or more drinks per day for men), though with small effect sizes [29-31]. Naltrexone has also shown efficacy against placebo in increasing time to relapse and time to first drink [32]. The largest multisite clinical trial, the COMBINE study (n = 1383) tested the efficacy of medications (i.e., naltrexone and acamprosate), behavioral interventions (Medical Management [MM] and Cognitive Behavioral Intervention [CBI], and their combinations in AD patients in a 16 week multi-site study. While all groups showed a substantial reduction in drinking, participants who received naltrexone with MM, CBI or both, showed a significant increase in the drinking outcomes. However, at one year follow-up the results were similar, and no longer significant [33].

Some predictors of a positive response to naltrexone have been identified, including a high level of craving, a positive family history of alcoholism [34] and possessing a polymorphism (Asn40Asp) in the mu opioid receptor gene [35,36]. Moreover, human laboratory studies - as reviewed in [37] - have demonstrated that naltrexone counteracts the stimulant/reinforcing effect of alcohol while enhancing the sedative effect; reduces subjective ratings of alcohol cue-elicited craving; and reduces alcohol self-administration.

Long-acting forms of naltrexone that are administered monthly by I.M. injection have been developed, as patient adherence improves clinical outcomes [38,39]. An I.M. injection of a depot formulation of naltrexone, when combined to a motivational enhancement therapy, increased abstinent days and time to first drinking

day in a 3-month multicenter trial in 315 subjects [40]. Subjects who received the naltrexone depot reported significantly fewer drinking days during treatment and a significantly greater abstinence rate than the placebo group (18% vs. 10%). A second long-acting injectable formulation of naltrexone was developed and tested, after an initial pilot study [41], in a multi-center double blind placebo-controlled randomized trial (DBPCRCT); results of this trial showed an effect of of naltrexone in decreasing the rate of heavy drinking, although no effect was found in reducing the number of heavy drinking days in women [42]. In this multi-center trial [42], two doses (180mg, 360mg) were tested and there was a dose-response effect in reducing heavy drinking.

Naltrexone can cause hepatotoxicity, especially in patients with significant liver problems [43]. Sustained release naltrexone may produce less hepatotoxicity than oral naltrexone, because the injected, sustained release drug does not undergo first pass metabolism in the liver. However, FDA approval of both oral and I.M. naltrexone for AD includes a black-box warning about the risk of liver damage.

ACAMPROSATE

Acamprosate, a glutamatergic antagonist and GABA agonist, is thought to normalize the glutamatergic excitation that occurs in alcohol withdrawal through a mechanism of action that is not clearly understood [44,45]. Most of the early large clinical trials were completed in Europe where these trials resulted in strong effect sizes for improving drinking outcomes, i.e. acamprosate effectively maintained complete abstinence in detoxified AD patients. In particular, three European multi-center DBPCRCTs showed that acamprosate, in addition to psychosocial treatment, promoted alcohol abstinence [32,46-48]. Meta-analyses confirmed the efficacy of acamprosate in improving rates of abstinence and increasing time to first drink [29,49]. For example, Mann *et al*. [49] reported effect sizes in abstinent rates at 3, 6, and 12 months were 1.33, 1.50, and 1.95, respectively. A more recent trial with 374 AD patients reported that genetic variations in GATA-binding protein 4 (GATA4) might influence relapse and treatment response to acamprosate in AD patients via modulation of atrial natriuretic peptide (ANP) plasma levels [50].

However, other trials in the US and Europe have failed to find similar strength effects calling for further studies into typologies and the severity of alcoholism [33,51-53]. In particular, differences in the US and European trials could be attributed to differences in study design and population. A recent Cochrane review of 24 randomized clinical trials (n = 6915) showed that acamprosate, compared to placebo, significantly reduced the "risk of any drinking" and increased the cumulative abstinence duration (CAD). On the other hand, no significant effect of acamprosate was found in reducing heavy drinking. The Cochrane review concluded that acamprosate is safe and effective in promoting continuous abstinence after detoxification in AD patients [54].

TOPIRAMATE

Topiramate is an anticonvulsant that increases $GABA_A$-facilitated neuronal activity and antagonizes AMPA and kainate glutamate receptors with a consequent reduction of DA release in the NAc. Moreover, topiramate modulates ionotropic channels, inhibiting L-type calcium channels, limiting the activity of voltage-dependent sodium channels and facilitating potassium conductance, all of which contribute to the hyperactivity and resulting anxiety of withdrawal. Another mechanism of action for topiramate is weak inhibition of the carbonic anhydrase isoenzymes, CA-II and CA-IV, in the brain and in the kidney [55].

In a 12-week, DBPCRCT (n=150), AD patients taking topiramate as well as receiving a medication adherence therapy, significantly decreased the number of drinks consumed per day and increased the number of their abstinent days. Topiramate was also effective in reducing certain components of alcohol craving: obsessive thoughts about alcohol, automaticity of drinking, and interference due to drinking, as assessed by the Obsessive and Compulsive Drinking Scale [56].

A large multi-site (n=371) DBPCRCT administered up to 300mg/day of topiramate compared to placebo for 14 weeks [57]. In addition to topiramate (or matched placebo), all participants received a weekly manual-guided compliance intervention, Brief Behavioral Cognitive Enhancement Therapy (BBCET) provided by a healthcare professional, and used to facilitate medication adherence. This study demonstrated that topiramate was effective, as compared to placebo, in reducing alcohol drinking outcomes (e.g. heavy drinking days) through the course of the study [58]. Additionally, this trial showed a statistically significant effect that favoured topiramate for improved physical health, reduced alcohol craving, and increased psychosocial well-being [59]. Though its use for AD is off-label, topiramate represents a new pharmacotherapy option for AD.

Interestingly, in the US multi-site trial [59], the therapeutic effect was evident by week 4 (titration to 300mg took 5 weeks); suggesting further research is needed to determine the optimal dose necessary [60]. In particular, given that there was a trend toward an increased frequency of adverse events with dose of topiramate, a dose of topiramate that is lower but still effective in reducing alcohol drinking may be of clinical value [59]. In this regard, a preliminary human laboratory study suggests that topiramate 200mg/day is able to reduce the stimulating effects of alcohol ingestion compared to placebo [61]. Finally, one recent but very important development regarding topiramate was a change in the pregnancy classification to category D, by the US FDA. This change was prompted as new data reviewed by the North American Drug Pregnancy Registry found that infants exposed to topiramate as a single therapy for epilepsy in the first trimester of pregnancy had a 1.4% prevalence of oral clefts compared to 0.38% to 0.55% for infants exposed to other antiepileptic medications, and 0.07% for infants of mothers who did not have epilepsy and had not been exposed to antiepileptics [62].

BACLOFEN

A variety of animal studies (reviewed in: [63]) have suggested that the $GABA_B$ receptor agonist, baclofen, is able to affect several aspects of AD and alcohol-seeking behaviors. Baclofen blocks DA release in central reward areas, such as ventral striatum and prefrontal cortex; interestingly, a recent human study reported that baclofen increased cerebral blood flow in these reward areas, as shown by a brain functional Magnetic Resonance Imaging (fMRI) [64]. Consistent with the animal data [63], baclofen has been investigated as a potential new medication for the treatment of AD. A preliminary DBPCRCT [65] showed that baclofen increased CAD and reduced alcohol craving and anxiety.

These observations were also replicated in open-label studies [66,67], and more importantly, another DBPCRCT confirmed the efficacy of baclofen in increasing CAD and reducing alcohol craving, in AD patients with liver cirrhosis, a population usually excluded from alcohol pharmacological trials because the risk to worsen liver disease [68]. The safety of baclofen in patients with alcohol liver disease has been recently confirmed by a small study, where baclofen was administered for 5-8 months in patients with alcoholic hepatitis [69]. Together, these data suggested that baclofen may represent a promising pharmacotherapy for AD patients affected by alcoholic liver disease. If confirmed by larger studies, the efficacy and safety of baclofen in treating AD patients with significant medical problems may have important public health implications.

In contrast to previous studies, another 12-week clinical trial [70] found no significant differences between baclofen and placebo in reducing heavy drinking and craving, or in increasing percentage

of abstinence. A possible explanation of the difference in outcomes across trials could be the different severity of AD of the enrolled patients [71-73]. In particular, a recent analysis of previous positive and negative baclofen studies in AD has shown a difference in baseline alcohol drinking, withdrawal severity and anxiety [73]. As such, future studies are needed to identify subtypes of AD patients who respond to baclofen. Moreover, all previous studies used baclofen at the dose of 10mg three times a day (t.i.d.). However, a recent preliminary study shows a dose-response effect of baclofen 20mg t.i.d. vs. baclofen 10mg t.i.d. [74], thus suggesting that testing higher doses of baclofen represents another possible direction to pursue.

ONDANSETRON

The 5-HT system plays a key role in regulating the severity of alcohol drinking [75]. Ondansetron, a 5-HT_3 antagonist, is thought to work by affecting the function of the 5-HT transporter (5-HTT) resulting in down-regulation of the dopaminergic neurons decreasing the reward from alcohol [76].

A randomized, placebo-controlled study tested the efficacy of 6 weeks of ondansetron (0.25 mg twice a day (b.i.d.) or 2.0 mg b.i.d.), in the treatment of 71 alcohol-dependent males and provided preliminary evidence of the role of ondansetron in reducing alcohol drinking [77]. Subsequently, another clinical trial tested the role of ondansetron in AD. The researchers divided participants into early-onset (EOA) and late-onset (LOA) groups [EOA is defined as the initial onset of alcoholism at the age of 25 years or younger compared to LOA in which initial alcoholism after the age of 25]. This study showed positive results for patients who received ondansetron (1,4, and 16mcg/kg b.i.d.) compared with those received placebo in reducing drinks per day and drinks per drinking day. Ondansetron, 4 mcg/kg b.i.d., was more effective than placebo in increasing total days abstinent and percentage of days abstinent [78]. Furthermore, when compared to placebo, ondansetron (4 mcg/kg b.i.d.) resulted in a significant reduction in alcohol craving, in EOA but not in LOA [79].

More recently, a large study (n=304) was completed with testing ondansetron in AD where groups were divided by genotype in the 5' regulatory region of the 5-HTT gene: LL, LS, or SS. In addition to standardized cognitive behavioral therapy, participants were randomized to receive either 4 mcg/kg twice daily or placebo. Individuals with the LL genotype significantly reduced their drinks per day and increased their days of abstinence compared to LL individuals on placebo. Also, among participants receiving ondansetron, those with the LL genotype significantly reduced their drinking compared to the LS and SS individuals [80]. These findings are consistent with a pilot human laboratory study [81], where drinking was evaluated under laboratory conditions (i.e. alcohol self-administration). Specifically, Kenna and colleagues [81] reported that AD individuals taking .25mg twice a day of ondansetron with the LL genotype reported a significant reduction in drinking. By contrast, the researchers found no correlation in a reduction in drinking with ondansetron in individuals with the LS or SS genotype [81].

SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIS)

Selective serotonin reuptake inhibitors (SSRIs) work by inhibiting the reuptake of 5-HT into the presynaptic cell resulting in then increased level of 5-HT made available to bind to the postsynaptic receptor. Preclinical studies have shown that SSRIs such as, fluoxetine, sertraline, and citalopram increase serotonergic function and reduce consumption of alcohol in animals [82].

However, these results have only been partially supported by clinical trials as a treatment for AD. For example, in a DBPCRCT (n=101), fluoxetine (60mg/day) was compared to placebo; both groups also received cognitive behavioral therapy. While there was no significant difference in drinking between groups, fluoxetine actually exacerbated drinking with the type B alcoholics (a subtype characterized by high levels of premorbid vulnerability, alcohol-related problems and earlier onset of alcoholism), defined by more severe AD, earlier start drinking age and a more negative outlook on life [83]. Subsequently, Pettinati and colleagues tested sertraline 200 mg /day vs. placebo in a 14-week study (n=100) differentiated by patients with or without a diagnosis of lifetime depression [84]. Sertraline reduced alcohol drinking in patients without a diagnosis of comorbid lifetime depression. Pettinati *et al* [84] then differentiated the analysis by alcoholic subtype (A or B). Comparatively, type A alcoholics are marked by a later onset of alcoholism, less psychopathology, and less other drug use than type B alcoholics. Like the study by Kranzler *et al*. [83], the researchers found that type B alcoholics actually drank more when taking the SSRI when compared to placebo. Conversely, type A alcoholics who received sertraline significantly reduced their alcohol drinking when compared to placebo [84].

Following previous studies that reported LOAs reduced drinking when taking a SSRI [84], Kranzler and colleagues sought to compare the effects in LOAs vs. EOAs moderated by the 5-HTTLPR polymorphism of the 5-HT transporter. AD patients received either 200 mg/day sertraline (n=63) or placebo (n=71). There were no main effects among S' (S or LG) allele carriers. However, in L' homozygotes (LA/LA) carriers, the medication effect varied by age of onset as LOAs who received sertraline reported a significant reduction in drinking, whereas EOA patients reduced drinking when taking placebo [85]. This last study suggests that L' homozygotes carriers might represent those individuals, whose alcohol consumption is affected by SSRIs, a feature consistent with the biological knowledge that L' homozygous alleles result in several higher 5-HT transporter mRNA transcriptions than S' alleles.

Examining the specific effects of citalopram on alcohol drinking behavior, Naranjo and colleagues [86] conducted a DBPCRCT (n=61) testing 40mg/day of citalopram for 12 weeks. Participants were diagnosed with mild to moderate AD. Compared to women (n=27), men (n=34) who received citalopram significantly reduced their average drinking per day when compared to placebo. This suggests that while citalopram may have a role for reducing alcohol use in male AD patients [86], larger studies are needed to confirm these findings. In summary, although positive preclinical studies showed much promise for SSRIs, these results have not been consistent in human clinical trials for the treatment of AD.

ARIPIPRAZOLE

As originally proposed by Kenna [87], aripiprazole may represent a treatment for AD. Aripiprazole binds with a high affinity for the D2 family of receptors (e.g. partial agonism of DA autoreceptors at D2L receptors). Furthermore, aripiprazole holds additional pharmacological actions, i.e. partial agonism of the 5-HT1A receptor; antagonism of the 5-HT2A receptor; and inverse agonism of the 5-HT2B receptor [87]. Human laboratory studies examining the mechanism of action demonstrated that aripiprazole attenuates the sedative effects of alcohol [88], and reduces drinking, especially in more impulsive alcoholics [89]. Moreover, an fMRI study demonstrated that aripiprazole significantly attenuates neural activity in the ventral striatum in response to alcohol cues [90].

A 12-week, DBPCRCT with 295 AD individuals found that aripiprazole initially decreased heavy drinking days compared to placebo, but this significant effect was attenuated when the target dose of 30 mg was reached [91]. This trial also showed greater side effects and study discontinuation in the aripiprazole arm, as compared to placebo [91]. Interestingly, an open-label study of aripiprazole [92] suggests that lower doses of aripiprazole (5-15mg per day) may be better tolerated and still reduce drinking.

PRAZOSIN

Preclinical and clinical evidence demonstrate an important role of the norepinephrine (NE) system in AD, thus several preclinical studies have been investigating the potential role of the NE system as a neuropharmacological target for AD [93-97].

Though early work suggested that the NE reuptake inhibitor desipramine prolonged the time to relapse in depressed alcoholics [98,99] research on alcohol pharmacotherapy has been slow to focus on the NE system. Following the unpublished clinical observation that many patients affected by Post-Traumatic Stress Disorder (PTSD) and treated with the NE alpha 1-blocker prazosin reduced or even stopped drinking, researchers started preclinical and clinical research aimed at testing prazosin for AD. An experiment demonstrated that prazosin reduces alcohol self-administration and is more potent in ethanol-dependent rats than in non-dependent, suggesting that prazosin blocks dependence-induced increases for responding to alcohol by rats [100]. Subsequently, an experiment demonstrated that both acute and chronic prazosin treatment decreases ethanol consumption in alcohol preferring rats [101]. Based on this preclinical evidence, a 6-week pilot DBPCRCT was recently performed [102]. After a 2-week titration, 24 AD subjects were treated with placebo or prazosin 16 mg/day (4 mg QAM, 4 mg QPM, and 8 mg QHS), the highest dose usually used in clinical practice, i.e. for hypertension. Participants also received Medical Management sessions. During the last 3 weeks of this study, (when participants were at the targeted dose), the prazosin group had a statistically significant reduction in drinking days per week, and a trend of reduction in drinks per week compared to placebo. Larger studies are currently ongoing to test the role of prazosin in AD, as well as in AD and PTSD comorbidity.

POSSIBLE FUTURE TARGETS FOR AD.

There are a myriad of different neuropharmacological targets for AD that are under investigation, mostly at a preclinical level (for an extensive review, see [103]). Here, we only report a few examples.

Cannabinoid Receptors

Involved in the physiological processes of mood, appetite, pain-sensation, and memory, the endocannabinoid system plays an important role in the behavioral effects of alcohol [104]. There are currently two known subtypes of cannabinoid receptors: CB1 and CB2. CB1 is mainly expressed in the brain, but also is found in the lungs, liver, and kidneys whereas the CB2 receptor is mainly expressed in the immune system. In the brain, CB1 receptors are densely found in the VTA and the NAc. As part of the reward system of the brain, targeting these particular receptors could prove beneficial in reducing the craving of alcohol.

In animal studies, administration of certain CB1 agonists significantly stimulates ethanol intake in ethanol-preferring rats. In contrast, blocking of this receptor decreases alcohol consumption (reviewed in: [103,104]). One potential CB1 antagonist, rimonabant has shown promise as a potential blocker of this receptor and decreasing ethanol intake in animal studies [105]. However, rimonabant has failed to replicate the animal study findings, in either a multi-site alcohol treatment study [106] or in a human laboratory study with an alcohol self-administration experiment [107]. Further research is needed to understand the inconsistencies between preclinical research and clinical studies. Moreover, rimonabant has been associated with an increase risk of suicide, therefore further increasing the concern of clinical research on this area [108].

Corticotropin-Releasing Factor (CRF)

Corticotropin-releasing factor (CRF), (also called corticotropin-releasing hormone; CRH), is a 41-amino acid peptide involved in the stress response. CRF appears to be related to two of the main stress response systems: hypothalamic-pituitary-adrenal (HPA)-axis and the locus coeruleus-norepinephrine (LC-NE) system suggesting a central role for CRF in coordination and control of the biological stress pathways of substance abuse. Within the HPA-axis, release of CRF from the paraventricular nuclei stimulates the secretion of adrenocorticotropic hormone (ACTH) from the anterior pituitary. ACTH then stimulates the adrenal glands to release cortisol. Cortisol controls many functions including inhibiting further release of CRF in a negative feedback loop. This stress response is hypothesized to play a main role in the development and facilitation of alcohol and substance abuse disorders [109] as well as involved in a behavioral component of alcohol relapse [110]. Preclinical data suggests acute ethanol withdrawal increases CRF levels in the central nucleus of amygdala [111] and in the bed nucleus of the stria terminalis [112] facilitating stress and anxiety responses. A large body of evidence demonstrates that upregulated activity of the CRF system confers susceptibility for excessive self-administration of alcohol and relapse (reviewed [103]). Furthermore, some studies have shown a link between genetic polymorphisms in CRF1 and risky-drinking behaviors [113,114], suggesting that the impact of stress on heavy drinking could be more evident among individuals carrying a particular genotypic variant of CRF1 gene.

Neuropeptide Y (NPY)

Neuropeptide Y (NPY) is a 36-amino acid peptide neurotransmitter secreted by the hypothalamus. NPY is one of the most abundant neuron modulators in the central nervous system and is involved in controlling hunger, thirst, fatigue, and body temperature. NPY effects are mediated by G-protein-coupled receptors. Currently, there are 4 identified receptor subtypes: Y1, Y2, Y4 and Y5 [115].

Preclinical studies using genetically modified mice found NPY levels in the central and medial nuclei of the amygdala were inversely correlated to ethanol intake [116]. NPY infusion normalizes the decreased expression of NPY and decreases the anxiety-like and drinking behaviors. This deficiency in NPY signaling may be involved in regulation of the anxiety-like and drinking behaviors. [117].

Recent studies have shown an association with the NPY2R and NPY5R receptor genes and alcohol withdrawal. Therefore, it is plausible that individuals with these particular receptor genes experience alcohol withdrawal differently than those without those genes. Further research is needed to determine the importance of these receptors and the specific role they play in alcohol withdrawal.

Ghrelin

Ghrelin is a 28-amino acid gut peptide involved in food-seeking behaviour, specifically stimulating appetite and food intake. Ghrelin stimulates appetite by interacting with the hypothalamic arcuate nuclei (ARC). The ARC is critical in controlling food and alcohol-seeking behaviour. In addition to being concentrated in the ARC, the ghrelin receptor, GHS-R, is also highly expressed in the so-called reward system of the VTA, hippocampus, substantia nigra, and dorsal and medial raphe nuclei. Interacting with this reward system could be vital in understanding the role in the craving effect of alcohol. Several animal studies show that antagonism of the ghrelin system might represent an innovative way to treat AD [118-121]. Human studies show a correlation between blood ghrelin levels, alcohol drinking and alcohol craving [122]. Future research might turn into new treatments targeting the ghrelin system [123], but at present alcohol research on ghrelin is at an early stage.

Neurokinin Receptors

Substance P is a neurotransmitter involved in the stress response, exerting mainly through the neurokinin-1 receptor (NK1R). Preclinical studies with the genetic deletion or pharmacological blockade of NK1R have shown to inhibit the behavioral responses

to psychological stressors [124]. A study by George and colleagues utilizing mice genetically-deficient in NK1R reported a significant decrease in voluntary alcohol consumption and an increase in sensitivity to the sedative effects of alcohol suggesting a possible role for NK1R blockade in the treatment of AD [125]. Thorsell and colleagues replicated these findings in mice by a method of NK1R antagonism suggesting a direct, rather than developmental role for the NK1R receptor in alcohol intake [126]. In recently detoxified alcoholic patients (n=50) enrolled in a DBPCRCT testing spontaneous alcohol craving, craving assessed in a human laboratory setting, stress-related hormones (i.e. cortisol) and brain responses (i.e. fMRI), a NK antagonist (LY686017) showed beneficial effects of LY686017, as compared to placebo [125]. Finally, a recent study with 271 alcoholics and 337 healthy controls found that specific polymorphisms of the NK1R were significantly associated with the development of AD [127].

PERSONALIZING PHARMACOTHERAPIES FOR AD

With only small effect sizes of the current approved medications for AD, there is not only a great need to find new therapies, but also a need to delineate more optimally tailored treatment of AD using currently approved therapies. Two current efforts of typology research and utilizing genetics for pharmacotherapy show promise in personalizing AD treatment.

Typologies of AD

The goal of typology research is to gather fundamental patient information in hopes of creating AD subtypes to better utilize treatment for patients [128]. Attempts have been made, though none have proven extremely effective or may be considered state-of-the-art.

In 1960, Jellinek first distinguished between 5 subtypes of drinking: alpha, beta, delta, gamma, and epsilon. The alpha subtype shows no physical addiction, but use alcohol as a means to cope with stress. Like the alpha type, the beta subtype shows no physical addiction, but suffer from a severe alcohol related disease (e.g. polyneuropathy, liver cirrhoses, gastritis). The delta and gamma subtype distinguished by Jellinek were the only two of his five clusters that would carry a diagnosis of AD. The gamma subtype represents the drinkers who are able to abstain, but suffer from a loss of control once they consume alcohol whereas the delta includes these characteristics, but also has an inability to abstain from drinking. Epsilon subtype is defined by dipsomania, an uncontrollable craving for alcohol [129].

Building upon Jellinek's typology some researchers have created a binary typology like the Cloninger and Babor whereas, Lesch, Windle and Scheidt favored a multifactor typology, as detailed next.

Opting for a personality-based typology, Cloninger and colleagues created a dichotomous typology of Type I and II for AD. Type I alcoholics are characterized by self-medicators and generally respond better to treatment. These alcoholics have the ability to at least temporarily abstain from drinking, whereas Type II alcoholics are exclusively male and suffer from the inability to abstain and often drink for pleasure. They are thought to inherit the disease from their father [130]. Using a cluster analysis of 321 AD individuals, Babor and colleagues created 17 factors that included personality trains, psychiatric disorders, severity of AD, family history, and consequences of alcohol consumption. Babor then created a two-cluster solution of Type A and Type B alcoholics [131].

Overlapping between the Babor and Cloninger typologies, a simpler classification of age of onset of AD was formed: EOA and LOA [132]. As reported earlier in this review, EOA and LOA classification has proved useful in studies with serotonergic medications.

A more recent cluster analysis by Windle and Scheidt [133] suggests a four-factor classification model. The four alcoholic subtypes include mild course, polydrug, negative affect and chronic antisocial behavior. The mild course subtype is characterized by LOA, fewer years of drinking and childhood conduct problems, lower levels of consumption, impairment and withdrawal symptoms. The polydrug subtype is characterized by the highest polydrug use. The negative affect subtype is comprised of AD individuals with the highest number of major depressive disorder and generalized disorder symptoms. The chronic antisocial subtype is characterized by the highest levels of consumption, the most years of drinking and the highest levels of adult antisocial behavior [133].

Another four subtype model was created in Europe by Lesch and colleagues. Types I, II, III, IV were created after a 5 year follow-up study of 444 AD patients where physiological, clinical, and behavioral characteristics were collected. Lesch Type I alcoholics are characterized by individuals who suffer from a severe alcohol withdrawal syndrome and tend to use alcohol to prevent or weaken withdrawal symptoms. Lesch Type II is comprised of individuals who drink alcohol as a means of self-medication due to the sedative effect of alcohol and exhibit extensive behavioral changes when under the influence of alcohol. Lesch Type III is characterized by the use of alcohol as anti-depressant. Individuals with pre-morbid cerebral defects, behavioral disorders, and high social burdens before the age of 14 characterize Lesch Type IV [134].

In summary, it is unclear if there will be a dominant alcohol subtype theory; however, current typologies have shown to be compatible with research findings. As noted, serotonergic medications have been shown to only be effective within a certain subtype [78,84] and even harmful [85] in some cases. With additional research, it is hoped to delineate specific subtypes in hopes of better targeting treatments for AD patients.

Genetically Targeted Pharmacotherapy

As reviewed by Kranzler and Edenberg [135], the convergence of research in AD treatment and genetics of AD is leading to the possibility of matching patients with certain treatments. For example, naltrexone is a modestly effective treatment for AD, although ineffective for certain AD individuals. Recent studies have sought to fully understand the role that certain opioid receptor genes play. For example, patients genotyped at the A(+118)G (Asn40Asp) who were taking naltrexone (compared to placebo) and had either one or two Asp40 alleles, were significantly less likely to return to heavy drinking and had significantly lower rates of relapse than patients with Asn40 homozygotes [35]. The COMBINE study also found a positive moderating effect on the Asp40 allele in reducing the percentage of heavy drinking days [36]. In regard to dopaminergic genes, a number of studies have focused on the variation of in the DRD4, which encodes the D4 DA receptor [136]. The L allele of DRD4 has been associated with craving or drinking alcohol in some studies [137-140], but other studies found no association [141,142].

CONCLUSION

While only moderately effective, there are only a few medications approved for the treatment of AD, and as reviewed here there are many new promising medications and potential research target areas. In addition, pharmacogenetic and typology research show promise in personalizing AD treatment for patients.

However, it is unlikely there will ever be one medication that 'cures' AD, therefore we need to continue our efforts in identifying pharmacotherapies that can be the best fit for a specific patient. Moreover, we need to continue investigating the role the psychosocial environment plays in combination with pharmacotherapy. Pharmacotherapy for AD should be considered an adjunct therapy to psychosocial interventions, and this combinational therapy should best address the high relapse rates of AD.

REFERENCES

[1] World Health Organization Global Status Report on Alcohol. Geneva: World Health Organization; 2011

[2] World Health Organization Global Status Report on Alcohol. Geneva: World Health Organization; 2006

[3] O'Connor PG. Alcohol abuse and dependence. In: Goldman L, Ausiello D, eds. Cecil Medicine. 23rd ed. Philadelphia, Pa: Saunders Elsevier; 2007: chap 31.

[4] Diagnostic and statistical manual of mental disorders, Revised 4th ed.; DSM-IV. Washington, D.C.; American Psychiatric Association 2000.

[5] Faingold CL, N'gouemo P, Riaz A. Ethanol and neurotransmitter interactions: from molecular to integrative effects. Prog Neurobiol 1998; 55: 509-35.

[6] Koob GF, Roberts AJ, Schulteis G, *et al*. Neurocircuitry targets in ethanol reward and dependence. Alcohol Clin Exp Res 1998; 22: 3-9.

[7] O'Malley SS, Carroll KM. Psychotherapeutic considerations in pharmacological trials. Alcohol Clin Exp Res 1996; 20(7 Suppl): 17A-22A.

[8] Pettinati HM, Volpicelli JR, Pierce JD, O'Brien CP. Improving naltrexone response: an intervention for medical practitioners to enhance medication compliance in alcohol dependent patients. Journal of Addictive Diseases 2000; 19(1): 71-83.

[9] National Institute for Alcohol Abuse and Alcoholism. Helping patients who drink too much. A clinician's guide [guide on the internet]. Updated 2005 edition [cited 2011 Mar 3]. Available from: http://pubs.niaaa.nih.gov/publications/Practitioner/CliniciansGuide2005/clinicians_guide.htm.

[10] Kranzler HR, van Kirk J. Efficacy of naltrexone and acamprosate for alcoholism treatment: a meta-analysis. Alcohol Clin Exp Res 2001; 25(9): 1335-41.

[11] Swift, R. Emerging approaches to managing alcohol dependence. Am J Health Syst Pharm 2007; 64(5 Suppl 3): S12-22.

[12] Garbutt JC, West SL, Carey TS, Lohr KN, Crews FT. Pharmacological treatment of alcohol dependence: a review of the evidence. JAMA 1999; 281: 1318-25.

[13] Fuller RK, Branchey L, Brightwell DR, *et al.* Disulfiram Treatment of Alcoholism. A Veterans Administration cooperative study. JAMA 1986; 256(11): 1449-55.

[14] Carroll KM, Nich C, Ball SA, McCance E, Frankforter TL, Rounsaville BJ. One-year follow-up of disulfiram and psychotherapy for cocaine-alcohol users: sustained effects of treatment. Addictions 2000; 95(9): 1335-49.

[15] Chick J, Gough K, Falkowski W, *et al*. Disulfiram treatment of alcoholism. Br J Psychiatry 1992; 161: 84-9.

[16] Eneanya DI, Bianchine JR, Duran DO, Andresen BD. The actions of metabolic fate of disulfiram. Annu Rev Pharmacol Toxicol 1981; 21: 575-96.

[17] Neuman MG, Monteiro M, Rehm J. Drug interactions between psychoactive substances and antiretroviral therapy in individuals infected with human immunodeficiency and hepatitis viruses. Subst Use Misuse 2006; 41: 1395-463.

[18] Goldstein M, Anagnoste B, Lauber E, McKeregham MR. Inhibition of dopamine-beta-hydroxylase by disulfiram. Life Sci 1964; 3: 763-7.

[19] Vaccari A, Saba PL, Ruiu S, Collu M, Devoto P. Disulfiram and diethyldithiocarbamate intoxication affects the storage and release of striatal dopamine. Toxicol Appl Pharmacol 1996; 139: 102-8.

[20] Fuller RK, Gordis E. Does Disulfiram Have A Role In Alcoholism Treatment Today? Addiction 2004; 99(1): 21-4.

[21] Berglund M. A better widget? Three lessons for improving addiction treatment from a meta-analytical study. Addiction 2005; 100: 742-50.

[22] Krampe H, Ehrenreich H. Supervised disulfiram as adjunct to psychotherapy in alcoholism treatment. Curr Pharm Des 2010; 16(19): 2076-90.

[23] Robinson TE, Berridge KC. The neural basis of drug craving: an incentive-sensitization theory of addiction. Brain Res Rev 1993; 18: 247–91.

[24] Gessa GL, Muntoni F, Collu M, Vargiu L, Mereu G. Low doses of ethanol activate dopaminergic neurons in the ventral tegmental area. Brain Res 1985; 346: 201-3.

[25] Benjamin D, Grant E, Pohorecky LA. Naltrexone reverses ethanol-induced dopamine release in the nucleus accumbens in awake, freely moving rates. Brain Res 1993; 621: 137-40.

[26] Volpicelli JR, Alterman AI, Hayashida M, O'Brien CP. Naltrexone in the treatment of alcohol dependence. Arch Gen Psychiatry 1992; 49: 876-80.

[27] O'Malley SS, Jaffe AJ, Chang G, Schottenfield RS, Meyer RE, Rounsaville B. Naltrexone and coping skills therapy for alcohol dependence: a controlled study. Arch Gen Psychiatry 1992; 49: 881-7.

[28] Krystal JH, Cramer JA, Krol WF, Gail F, Kirk MS, Rosenheck RA. Naltrexone in the Treatment of Alcohol Dependence. NEJM 2001; 345: 1734-9.

[29] Bouza C, Angeles M, Munoz A, Amate JM. Efficacy and safety of naltrexone and acamprosate in the treatment of alcohol dependence: a systemic review. Addiction 2004; 99(7): 811-28.

[30] Srisurapanont M, Jarusaraisin N. Naltrexone for the treatment of alcoholism: a meta-analysis of randomized controlled trials. International Journal of Neuropsychopharmacology. 2005; 8: 1-14.

[31] Rosner S, Hackl-Herrwerth A, Leucht S, Vecchi S, Srisurapanont M, Soyka M. Opiod antagonists for alcohol dependence. Cochrane Database Syst Rev 2010; 12: CD001867.

[32] Kiefer F, Jahn H, Tarnaske T, *et al.* Comparing and combining naltrexone and acamprosate in relapse prevention of alcoholism: a double-blind, placebo-controlled study. Arch Gen Psychiatry 2003; 60(1): 92-9.

[33] Anton RF, O'Malley SS, Ciraulo DA, *et al.* Combined pharmacotherapies and behavioral interventions for alcohol dependence: the COMBINE study: a randomized controlled trial. JAMA 2006; 295(17): 2003-17.

[34] Monti PM, Rohsenow DJ, Swift RM, *et al*. Naltrexone and cue exposure with coping and communication skills training for alcoholics: treatment process and 1-year outcomes. Alcohol Clin Exp Res 2001; 25: 1634-47.

[35] Oslin DW, Berrettini W, Kranzler HR, *et al*. A functional polymorphism of the mu-opiod receptor gene is associated with naltrexone response in alcohol-dependent patients. Neuropsychopharmacology 2003; 28(8): 1546-52.

[36] Anton RF, Oroszi G, O'Malley SS, *et al.* An evaluation of mu-opiod receptor (OPRM1) as a predictor of naltrexone response in the treatment of alcohol dependence: results from the Combined Pharmacotherapies and Behavioral Interventions for Alcohol Dependence (COMBINE) study. Arch Gen Psychiatry 2008; 65: 135-44.

[37] Ray LA, Chin PF, Miotto K. Naltrexone for the treatment of alcoholism: clinical findings, mechanisms of action, and pharmacogenetics. CNS Neurol Disord Drug Targets 2010; 9(1): 13-22.

[38] Monti PM, Rohsenow DJ, Swift RM, *et al.* Naltrexone and cue exposure with coping and communication skills training for alcoholics: treatment process and 1-year outcomes. Alcohol Clin Exp Res 2001; 25: 1634-47.

[39] Weiss RD. Adherence to pharmacotherapy in patients with alcohol and opioid dependence. Addiction 2004; 99(11): 1382-92.

[40] Kranzler HR, Wesson DR, Billot L. Naltrexone depot for treatment of alcohol dependence: a multicenter, randomized, placebo-controlled clinical trial. Alcohol Clin Exp Res 2004; 28: 1051-9.

[41] Johnson BA, Ait-Daoud N, Aubin HJ, *et al.* A Pilot Evaluation of the Safety and Tolerability of Repeat Dose Administration of Long-Acting Injectable Naltrexone in Patients with Alcohol Dependence. Alcohol Clin Exp Res 2004; 28(9): 1356-61.

[42] Garbutt JC, Kranzler HR, O'Malley SS, *et al*. Efficacy and tolerability of long-acting injectable naltrexone for alcohol dependence: a randomized controlled trial. JAMA 2005; 293: 1617-25.

[43] Garbutt JC. Efficacy and tolerability of naltrexone in the management of alcohol dependence. Curr Pharm Des 2010; 16(19): 2091-7.

[44] Samson HH, Harris RA. Neurobiology of alcohol abuse. Trends Pharmacolo Sci 1992; 13: 206-11.

[45] Tsai G. Gastriend DR, Coyle JT. The glutamatergic basis of human alcoholism. Am J Psychiatry 1995; 152: 332-40.

[46] Paille FM, Guelfi JD, Perkins AC, Royer RJ, Steru L, Parot P. Double-blind randomized multicentre trial of acamprosate in maintaining abstinence from alcohol. Alcohol Alcohol 1995; 30: 239-47.

[47] Sass H, Soyka M, Mann K, Zieglgansberger W. Relapse prevention by acamprosate. Results from a placebo controlled study on alcohol dependence. Arch Gen Psychiatry 1996; 53: 673-80.

[48] Pelc I, Verbanck P, LeBon O, Gavrilovic M, Lion K, Lehert P. Efficacy and safety of acamprosate in the treatment of detoxified alcohol-dependent patients. A 90-day placebo controlled dose finding study. Br J Psychiatry 1997; 171: 73-7.

[49] Mann K, Lehert P, Morgan MY. The Efficacy of Acamprosate in the Maintenance of Abstinence in Alcohol-Dependent Individuals: Results of a Meta-Analysis. Alcohol Clin Exp Res 2004; 28: 51-63.

[50] Kiefer F, Witt SH, Frank J. Involvement of the atrial natriuretic peptide transcription factor GATA4 in alcohol dependence, relapse risk and treatment response to acamprosate. Pharmacogenomics J 2010; [Epub ahead of print].

[51] Mason BJ, Goodman AM, Chabac S, Lehert P. Effect of oral acamprosate on abstinence in patients with alcohol dependence in a double-blind, placebo-controlled trial: the role of patient motivation. J Psychiatr Res 2006; 40: 383-93.

[52] Chick J, Anton R, Checinski K, *et al.* A multicentre, randomized, double-blind, placebo-controlled trial of naltrexone in the treatment of alcohol dependence or abuse. Alcohol Alcohol 2000; 35: 587-93.

[53] Tempesta E, Janiri L, Bignamini A, Chabac S, Potgieter A. Acamprosate and relapse prevention in the treatment of alcohol dependence: a placebo-controlled study. Alcohol Alcohol 2000; 35(2): 202-9.

[54] Rosner S, Hackl-Herrwerth A, Leucht S, Lehert P, Vecchi S, Soyka M. Acamprosate for alcohol dependence. Cochrane Database Syst Rev 2010; 8(9): CD004332.

[55] Johnson BA. Recent advances in the development of treatments for alcohol and cocaine dependence: focus on topiramate and other modulators of GABA or glutamate function. CNS Drugs 2005; 19(10): 873-96.

[56] Johnson BA, Ait-Daoud N, Bowden CL, *et al.* Oral topiramate for treatment of alcohol dependence: a randomised controlled trial. Lancet 2003; 361(9370): 1677-85.

[57] Johnson BA, Rosenthal N, Capece JA, *et al.* Topiramate for treating alcohol dependence: a randomized controlled trial. JAMA 2007; 298: 1641-51.

[58] Johnson BA, Rosenthal N, Capece JA, *et al.* Improvement of physical health and quality of life of alcohol-dependent individuals with topiramate treatment. Arch Intern Med 2008; 168: 1188-99.

[59] Kenna G, Lomastro T, Schiesl A, Leggio L, Swift R. Review of Topiramate: An antiepileptic for the Treatment of Alcohol Dependence. Current Drug Abuse Reviews 2009; 2: 135-42.

[60] Swift RM. Topiramate for the treatment of alcohol dependence: initiating abstinence. Lancet 2003; 361(9370): 1666-7.

[61] Miranda RJ, MacKillop J, Monti PM, *et al.* Effects of topiramate on urge to drink and the subjective effects of alcohol: a preliminary laboratory study. Alcohol Clin Exp Res 2008; 32: 489-97.

[62] MedWatch:The FDA Safety Information and Adverse Event Reporting Program. Topamax (Topiramate): Label Change-Risk for development of cleft lip and/or cleft palate in newborns. US Food and Drug Administration.3/4/2011.

[63] Maccioni P, Carai MA, Kaupmann K, *et al.* Reduction of alcohol's reinforcing and motivational properties by the positive allosteric modulator of the GABA(B) receptor, BHF177, in alcohol-preferring rats. Alcohol Clin Exp Res 2009; 33: 1749-56.

[64] Franklin, TR, Wang, Z, Sciortino N, *et al.* Modulation of resting brain cerebral blood flow by the GABA B agonist, baclofen: A longitudinal perfusion fMRI study. Drug and Alcohol Depend 2011; [Epub ahead of print].

[65] Addolorato G, Caputo F, Capristo E, *et al*. Baclofen efficacy in reducing alcohol craving and intake: a preliminary double-blind randomized controlled study. Alcohol Alcohol 2002; 37: 504-8.

[66] Leggio L, Kenna GA, Swift R. New developments for the pharmacological treatment of alcohol withdrawal syndrome. A focus on non-benzodiazepine GABAergic medications. Prog Neuropsychpopharmacol Biol LPsychiatry 2008; 32: 1106-17.

[67] Flannery BA, Garbutt JC, Cody MW, *et al.* Baclofen for alcohol dependence: a preliminary open-label study. Alcohol Clin Exp Res 2004; 28: 1517-23.

[68] Addolorato G, Leggio L, Ferrulli A, *et al.* Effectiveness and safety of baclofen for maintenance of alcohol abstinence in alcohol-dependent patients with liver cirrhosis: randomised, double-blind controlled study. Lancet 2007; 370: 1915-22.

[69] Avanesyan A, Runyon BA. Utilization of baclofen in maintenance of alcohol abstinence in patients with alcoholic hepatitis in a real-life clinical setting. Hepatology 2010; 52: 1104A [AASLD abstract].

[70] Garbutt, JC, Kampov-Polevoy AB, Gallop R, Kalka-Juhl L, Flannery BA. Efficacy and safety of baclofen for alcohol dependence: a randomized, double-blind, placebo-controlled trial. Alcohol Clin Exp Res 2010; 34(11): 1849-57.

[71] Flannery BA, Garbutt JC. Comparison of U.S. and Italian human baclofen trials: why the difference? Alcohol Clin Exp Res 2008; 32(suppl 1): 276A.

[72] Garbutt, JC. The state of pharmacotherapy for the treatment of alcohol dependence. J Subst Abuse Treat 2009; 36: S15-23.

[73] Leggio L, Garbutt JC, Addolorato G. Effectiveness and safety of baclofen in the treatment of alcohol dependent patients. CNS Neurol Disord Drug Targets 2010; 9(1): 33-44.

[74] Addolorato G, Leggio L, Ferrulli A, *et al.* Dose-response effect of baclofen in reducing daily alcohol intake in alcohol-dependent subjects: secondary analysis of a randomized double-blind placebo controlled trial. Alcohol Alcohol 2011; [Epub ahead of print].

[75] Szumlinski KK, Diab ME, Friedman R, Henze LM, Lominac KD, Bowers MS. Accumbens neurochemical adaptations produced by binge-like alcohol consumption. Psychopharmacology (Berl) 2007; 190(4): 415-31.

[76] Kenna GA. Medications acting on the serotonergic system for the treatment of alcohol dependent patients. Curr Pharm Des 2010; 16(19): 2126-35.

[77] Sellers EM, Toneatto T, Romach MK, Somer GR, Sobell LC, Sobell MB. Clinical efficacy of the 5-HT3 antagonist ondansetron in alcohol abuse and dependence. Alcohol Clin Exp Res 1994; 18: 879-85.

[78] Johnson BA, Roache JD, Javors MA, *et al.* Ondansetron for reduction of drinking among biologically predisposed alcoholic patients: A randomized controlled trial. JAMA 2000; 284: 963-971.

[79] Johnson BA, Roache JD, Ait-Daoud N, Zanca NA, Velazquez M. Ondansetron reduces the craving of biologically predisposed alcoholics. Psychopharmacology (Berl) 2002; 160(4): 408-13.

[80] Johnson BA, Ait-Daoud N, Seneviratne C, *et al.* Pharmacogenetic Approach at the Serotonin Transporter Gene as a Method of Reducing the Severity of Alcohol Drinking. Am J Psychiatry 2011; 168(3): 265-75.

[81] Kenna GA, Zywiak WH, McGeary JE, *et al.* A within-group design of nontreatment seeking 5-HTTLPR genotyped alcohol-dependent subjects receiving ondansetron and sertraline. Alcohol Clin Exp Res 2009; 33(2): 315-23.

[82] Gulley JM, McNamara C, Barbera TJ , Ritz MC, George FR. Selective serotonin reuptake inhibitors: Effects of chronic treatment on alcohol-reinforced behavior in mice. Alcohol 1995; 12:177-181.

[83] Kranzler HR, Burleson JA, Korner P, *et al.* Placebo-controlled trial of fluoxetine as an adjunct to relapse prevention in alcoholics. Am J Psychiatry 1995; 152: 391-7.

[84] Pettinati HM, Volpicelli JR, Luck G, Kranzler HR, Rukstalis MR, Cnaan A. Double-blind clinical trial of sertraline treatment for alcohol dependence. J Clin Psychopharmacol 2001; 21(2): 143-53.

[85] Kranzler HR, Armeli S, Tennen H, *et al.* A double-blind, randomized trial of sertraline for alcohol dependence: moderation by age and 5-hydroxytryptamine transporter-linked promoter region genotype. J Clin Psychopharmacol 2011; 31(1): 22-30.

[86] Naranjo CA, Bremner KE, Lanctôt KL. Effects of citalopram and a brief psycho-social intervention on alcohol intake, dependence and problems. Addiction 1995; 90: 87-99.

[87] Kenna GA. Rationale for use of aripiprazole for alcohol dependence treatment. Drugs of the Future 2003; 28(12): 1227-35.

[88] Kranzler HR, Covault J, Pierucci-Lagha A, *et al.* Effects of aripiprazole on subjective and physiological responses to alcohol. Alcohol Clin Exp Res 2008; 32(4): 573-9.

[89] Voronin K, Randall P, Myrick H, Anton R. Aripiprazole effects on alcohol consumption and subjective reports in a clinical laboratory paradigm--possible influence of self-control. Alcohol Clin Exp Res 2008; 32(11): 1954-61.

[90] Myrick H, Li X, Randall PK, Henderson S, Voronin K, Anton RF. The effect of aripiprazole on cue-induced brain activation and drinking parameters in alcoholics. J Clin Psychopharmacol 2010; 30(4): 365-72.

[91] Anton RF, Kranzler H, Breder C, Marcus RN, Carson WH, Han J. A randomized, multicenter, double-blind, placebo-controlled study

of the efficacy and safety of aripiprazole for the treatment of alcohol dependence. J Clin Psychopharmacol 2008; 28(1): 5-12.

[92] Martinotti G, Di Nicola M, Di Giannantonio M, Janiri L. Aripiprazole in the treatment of patients with alcohol dependence: a double-blind, comparison trial vs. naltrexone. J Psychopharmacol 2009; 23(2): 123-9.

[93] Kook GF. A role for brain stress systems in addiction. Neuron 2008; 59: 11-34.

[94] Aston-Jones G, Cohen JD. An integrative theory of locus coeruleus–norepinephrine function: adaptive gain and optimal performance. Annu Rev Neurosci 2005; 28: 403–450.

[95] Ventura R, Alcaro A, Puglisi-Allegra S. Prefrontal cortical norepinephrine release is critical for morphine-induced reward, reinstatement and dopamine release in the nucleus accumbens. Cereb Cortex 2005; 15: 1877–86.

[96] Koob GF. Corticotropin-releasing factor, norepinephrine, and stress. Biol Psychiatry 1999; 46: 1167-80.

[97] Cecchi M, Khoshbouei H, Morilak DA. Modulatory effects of norepinephrine, acting on alpha 1 receptors in the central nucleus of the amygdala, on behavioral and neuroendocrine responses to acute immobilization stress. Neuropharmacology 2002; 43: 1139-47.

[98] Mason BJ, Kocsis JH. Desipramine treatment of alcoholism. Psychopharmacol Bull 1991; 27: 155–61.

[99] Mason BJ, Kocsis JH, Ritvo EC, Cutler RB. A double-blind, placebo-controlled trial of desipramine for primary alcohol dependence stratified on the presence or absence of major depression. JAMA 1996; 275: 761–7.

[100] Walker BM, Rasmussen DD, Raskind MA, Koob GF. Alpha1-noradrenergic receptor antagonism blocks dependence-induced increases in responding for ethanol. Alcohol 2008; 42: 91-7.

[101] Rasmussen DD, Alexander LL, Raskind MA, Froehlich JC. The alpha1-adrenergic receptor antagonist, prazosin, reduces alcohol drinking in alcohol-preferring (P) rats. Alcohol Clin Exp Res 2009; 33: 264-72.

[102] Simpson TL, Saxon AJ, Meredith CW, *et al.* A pilot trial of the alpha-1 adrenergic antagonist, prazosin, for alcohol dependence. Alcohol Clin Exp Res 2009; 33: 255-63.

[103] Leggio L, Cardone S, Ferrulli A, *et al.* Turning the clock ahead: potential preclinical and clinical neuropharmacological targets for alcohol dependence. Curr Pharm Des 2010; 16(19): 2159-18.

[104] Colombo G, Orru'A, Lai P, *et al.* The cannabinoid CB1 receptor antagonist, rimonabant, as a promising pharmacotherapy for alcohol dependence: preclinical evidence. Mol Neurobiol 2007; 36(1): 102-12.

[105] Roberto M, Cruz M, Bajo M, Siggins GR, Parsons LH, Schweitzer P. The Endocannabinoid System Tonically Regulates Inhibitory Transmission and Depresses the Effect of Ethanol in Central Amygdala. Neuropsychopharmacology 2010; 35(9): 1962-72.

[106] Soyka M, Koller G, Schmidt P, *et al.* Cannabinoid receptor 1 blocker rimonabant (SR 141716) for treatment of alcohol dependence: results from a placebo-controlled, double-blind trial. J Clin Psychopharmacol 2008; 28(3):317-24.

[107] George DT, Herion DW, Jones CL, *et al*. Rimonabant (SR141716) has no effect on alcohol selfadministration or endocrine measures in nontreatment-seeking heavy alcohol drinkers. Psychopharmacology (Berl) 2010; 208(1): 37-44.

[108] US Food and Drug Administration Advisory Committee, FDA briefing document: Zimulti (rimonabant) Tablets, 20 mg, FDA, Rockville (2007) http://www.fda.gov/OHRMS/DOCKETS/AC/07/briefing/2007-4306b1-00-index.htm

[109] Sinha R. How does stress increase risk of drug abuse and relapse? Psychophamacology 2001; 158: 343-59.

[110] Clarke TK, Schumann G. Gene-environment interactions resulting in risk alcohol drinking behaviour are mediated by CRF and CRF1. Pharmacol Biochem Behav 2009; 93(3):230-6.

[111] Clarke TK, Schumann G. Gene-environment interactions resulting in risk alcohol drinking behaviour are mediated by CRF and CRF1. Pharmacol Biochem Behav 2009; 93(3):230-6.

[112] Olive MF, Koenig HN, Nannini MA, Hodge CW. Elevated extracellular CRF levels in the bed nucleus of the stria terminalis during ethanol withdrawal and reduction by subsequent ethanol intake. Pharmacol Biochem Behav 2002; 72(1-2): 213-20.

[113] Treutlein J, Kissling C, Frank J, *et al*. Genetic association of the human corticotrophin releasing hormone receptor 1 (CRHR1) with binge drinking and alcohol intake patterns in two independent samples. Mol Psychiatry 2006; 11(6): 594-602.

[114] Blomeyer D, Treutlein J, Esser G, Schmidt MH, Schumann G, Laucht M. Interaction between CRHR1 gene and stressful life events predicts adolescent heavy alcohol use. Biol Psychiatry 2008; 63(2):146-51.

[115] Stogner KA, Holmes PV. Neuropeptide-Y exerts antidepressant-like effects in the forced swim test in rats. Eur J Pharmacol 2000; 387(2):R9-10.

[116] Thiele TE, Marsh DJ, Ste Marie L, Bernstein IL, Palmiter RD. Ethanol consumption and resistance are inversely related to neuropeptide Y levels. Nature 1998; 396(6709): 366-9.

[117] Zhang H, Sakharkar AJ, Shi G, Ugale R, Prakash A, Pandey SC. Neuropeptide y signaling in the central nucleus of amygdala regulates alcohol-drinking and anxiety-like behaviors of alcohol-preferring rats. Alcohol Clin Exp Res 2010; 34(3): 451-61.

[118] Jerlhag E, Egecioglu E, Dickson SL, Andersson M, Svensson L, Engel JA. Ghrelin stimulates locomotor activity and accumbal dopamine-overflow via central cholinergic systems in mice: Implications for its involvement in brain reward. Addict Biol 2006; 11(1): 45-54.

[119] Jerlhag E, Egecioglu E, Dickson SL, Douhan A, Svensson L, Engel JA. Ghrelin administration into tegmental areas stimulates locomotor activity and increases extracellular concentration of dopamine in the nucleus accumbens. Addict Biol 2007; 12(1): 6-16.

[120] Jerlhag E. Systemic administration of ghrelin induces conditioned place preference and stimulates accumbal dopamine. Addict Biol 2008; 13(3-4): 358-63.

[121] Jerlhag E, Egecioglu E, Landgren S, *et al*. Requirement of central ghrelin signaling for alcohol reward. Proc Natl Acad Sci USA 2009; 106(27): 11318-23.

[122] Leggio L, Ferrulli A, Cardone S, *et al*. Ghrelin system in alcohol-dependent subjects: role of plasma ghrelin levels in alcohol drinking and craving. Addiction Biology 2011; (in press).

[123] Leggio L. Role of the ghrelin system in alcoholism: Acting on the growth hormone secretagogue receptor to treat alcohol-related diseases. Drug News Perspect 2010; 23(3): 157-66.

[124] Holmes A, Heilig M, Rupniak NM, Steckler T, Griebel G. Neuropeptide systems as novel therapeutic targets for depression and anxiety disorders. Trends Pharmacol Sci 2003; 24(11): 580-8.

[125] George D, Gilman, J, Hersh J, *et al.* Neurokinin 1 receptor as a possible therapy for alcoholism. Science 2008; 319: 1536-9.

[126] Thorsell A, Schank J, Singley E, Hunt S, Heilig M. Neurokinin-1 receptors (NK1R:s_, alcohol consumption, and alcohol reward in mice. Psychopharmacology 2010; 209: 103-11.

[127] Seneviratne C, Ait-Daoud N, Ma J, Chen G, Johnson BA, Li M. Susceptibility locus in neurokinin-1 receptor gene associated with alcohol dependence. Neuropsychopharmacology 2009; 34: 2442-9.

[128] Leggio L, Kenna GA, Fenton M, Bonenfant E, Swift RM. Typologies of Alcohol Dependence. From Jellinek to Genetics and Beyond. Neuropsychol Rev 2009; 19(1): 115-29.

[129] Jellinek EM. The Disease Concept of Alcoholism. New Brunswick: Hillhouse Press 1960.

[130] Cloninger CR, Bohman M, Sigvardsson S. Inheritance of alcohol abuse. Cross-fostering analysis of adopted men. Archives of General Psychiatry 1981; 38: 861-8.

[131] Babor TF, Hofmann MI, DelBoca FK, *et al.* (1992a). Types of alcoholics, I. Evidence for an empirically derived typology based on indicator of vulnerability and severity. Archives of General Psychiatry 1992; 49: 599–608.

[132] Dahmen N, Volp M, Singer P, Hiemke C, Szegedi A. Tyrosine hydroxylase Val-81-Met polymorphism associated with early-onset alcoholism. Psychiatr Genet 2005; 15: 13-16.

[133] Windle M, Scheidt D. Alcoholic Subtypes: are two sufficient? Addiction 2004; 99: 1508-19.

[134] Lesch OM, Kefer J, Lentner S, *et al.* The course of alcoholism. Long-term prognosis in different subtypes. Forensic Science International 1988; 36: 121-38.

[135] Kranzler HR, Edenberg HJ. Pharmacogenetics of alcohol and alcohol dependence treatment. Curr Pharm Des; 2010 16(19): 2141-8.

[136] Ray LA, Bryan A, Mackillop J, McGeary J, Hesterberg K, Hutchison KE. The dopamine D Receptor (DRD4) gene exon III polymorphism, problematic alcohol use and novelty seeking: direct and mediated genetic effects. Addict Biol 2009; 14(2): 238-44.

[137] Hutchison KE, McGeary J, Smolen A, Bryan A, Swift RM. The DRD4 VNTR polymorphism moderates craving after alcohol consumption. Health Psychol 2002; 21(2): 139-46.

[138] Hutchison KE, Wooden A, Swift RM, *et al*. Olanzapine reduces craving for alcohol: a DRD4 VNTR polymorphism by pharmacotherapy interaction. Neuropsychopharmacology 2003; 28(10): 1882-8.

[139] Hutchison KE, Ray L, Sandman E, Rutter MC, *et al*. The effect of olanzapine on craving and alcohol consumption. Neuropsychopharmacology 2006; 31(6): 1310-7.

[140] Mackillop J, Menges DP, McGeary JE, Lisman SA. Effects of craving and DRD4 VNTR genotype on the relative value of alcohol: an initial human laboratory study. Behav Brain Funct 2007; 3: 11.

[141] McGeary JE, Monti PM, Rohsenow DJ, Tidey J, Swift R, Miranda R Jr. Genetic moderators of naltrexone's effects on alcohol cue reactivity. Alcohol Clin Exp Res 2006; 30(8): 1288-96.

[142] van den Wildenberg E, Janssen RG, Hutchison KE, van Breukelen GJ, Wiers RW. Polymorphisms of the dopamine D4 receptor gene (DRD4 VNTR) and cannabinoid CB1 receptor gene (CNR1) are not strongly related to cue-reactivity after alcohol exposure. Addict Biol 2007; 12(2): 210-20.

Received: March 30, 2011 **Accepted: April 5, 2011**