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Introduction to the Special Issue “Pharmacotherapies for the Treatment of Alcohol Abuse and Dependence” and a Summary of Patents Targeting other Neurotransmitter Systems

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Abstract

This paper introduces the Special Section: Pharmacotherapies for the Treatment of Alcohol Abuse and Dependence and provides a summary of patents targeting neurotransmitter systems not covered in the other four chapters. The World Health Organization notes that alcoholic-type drinking results in 2.5 million deaths per year, and these deaths occur to a disproportionately greater extent among adolescents and young adults. Developing a pharmacological treatment targeting alcohol abuse and dependence is complicated by (a) the heterogeneous nature of the disease(s), (b) alcohol affecting multiple neurotransmitter and neuromodulator systems, and (c) alcohol affecting multiple organ systems which in turn influence the function of the central nervous system. Presently, the USA Federal Drug Administration has approved three pharmacotherapies for alcoholism: disulfiram, naltrexone, and acamprosate. This chapter provides a summary of the following systems, which are not covered in the accompanying chapters; alcohol and acetaldehyde metabolism, opioid, glycinergic, GABA-A, neurosteroid, dopaminergic, serotonergic, and endocannabinoid, as well as patents targeting these systems for the treatment of alcoholism. Finally, an overview is presented on the use of pharmacogenetics and pharmacogenomics in tailoring treatments for certain subpopulations of alcoholics, which is expected to continue in the future.

Keywords

Addiction; alcohol-use disorders; agonist; allosteric modulator; antagonist; hormone; metabolism; neuromodulator

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CONFLICTS OF INTEREST

None of the authors have real or perceived conflicts of interest with this material.

PREVALENCE OF ALCOHOL ABUSE AND DEPENDENCE

The effects of alcohol abuse and dependence cost the United States ~\$185 billion each year [1]. A recent White Paper published by the Research Society on Alcoholism (RSA) indicates that over half of adult Americans have a family history of alcoholism or alcohol abuse, and that nearly one-third of Americans over 18 have a life-time diagnosis of alcohol abuse or dependence [2]. Previous estimates of the ratio of men to women having an alcohol use disorder have varied between 2:1 and 3:1 [3], with more recent data suggesting the “gender gap” has been narrowing in older and younger populations [3–5]. The Centers for Disease Control and Prevention (CDC) rank alcohol drinking as the third leading cause of preventable death [6]. For example, the mortality of women with substance-associated diseases is four times that of breast cancer [7], and a causal relationship has been shown between alcohol use and at least 50 different medical conditions [8].

Today’s youth are initiating alcohol use earlier and experiencing more alcohol-related problems than ever before [9, 10], and this is true for both men and women [4, 11]. Recent estimates indicate that 80% of high school seniors, in the United States, have consumed alcohol and half of these initiated drinking before the eighth grade [12], with early onset of alcohol use serving as a strong predictor of future alcohol dependence [13, 14]. In college, binge drinking is becoming more prevalent and, as with younger individuals, it is a strong predictor for future alcohol-related problems for both men and women in North America [15–19] as well as Europe [20]. Although most of these statistics were obtained from populations in North America, alcohol abuse and dependence are serious public health concerns on an international scale. A brief survey of recent studies on alcohol abuse and dependence, as well as their correlates, among adolescents and young adults in Argentina [21], Australia [22–24], Bosnia and Herzegovina [25], Brazil [26, 27], Great Britain [28], Canada [29], Chile [30], China [31], Europe [20], France [32, 33], Germany [34, 35], Honduras [36], Hong Kong [37, 38], Hungary [39, 40], India [41, 42], Japan [43, 44], Mexico [45], Mongolia [46], Netherlands [47], Poland [48, 49], Puerto Rico [50, 51], Saudi Arabia [52], South Africa [53, 54], Southern and Eastern Europe [55], Spain [56, 57], Sweden [58], Switzerland [59, 60], and Turkey [61] makes this abundantly clear.

Pattern of drinking (*e.g.* binge drinking, which is characterized by periods of large volumes of ethanol intake per day separated by periods of abstinence, versus constant ethanol consumption, which is generally characterized by lower volumes of intake per day) and total volume consumed are important diagnostic criteria for the onset of alcoholism in adult individuals [62, 63]. Additionally, these criteria have been used to develop different typologies and/or drinking profiles for alcoholics [64–71]. Importantly, it is often the case that the effectiveness of a particular treatment appears to depend upon where an individual ranks on the continuum of a respective typology [67, 72–74]. Therefore, age-of-onset, pattern of drinking and family history are factors that have predictive validity for a life-time diagnosis of alcohol abuse or dependence and, in some cases, these factors have predictive validity as to the effectiveness of treatments for these disorders as well.

ALCOHOL ABUSE, DEPENDENCE AND THE “ADDICTIVE PROCESS”

In general, alcohol abuse and dependence are parts of a chronic, progressive, relapsing disorder that progresses in stages from experimentation to dependence [75–81]. The disease progresses, such that the rewarding, euphoric and positive-reinforcement aspects of alcohol intake drive the disease-process in early stages and the dysphoric and associated negative-reinforcement aspects of alcohol abuse drive the disease-process in later stages. Ethanol is positively reinforcing when alcohol intake produces a euphoria/high or a perceived positive sense of well-being (*e.g.* increases in perceived confidence). Ethanol is negatively

reinforcing when alcohol intake removes dysphoria (*e.g.* anxiety) or a negative sense of well-being (*e.g.* “hangover” and physiological withdrawal). Once dependence is acquired, ethanol’s negative-reinforcement aspects tend to overshadow its positive-reinforcement aspects making the disease very difficult to treat. Since alcohol abuse and dependence continue to be serious public health problems, more effective treatments are needed.

NEUROBEHAVIORAL AND NEUROCHEMICAL CHARACTERISTICS ASSOCIATED WITH ALCOHOL ABUSE AND DEPENDENCE

Clinical and basic research indicate that 1) lower sensitivity to ethanol’s effects is positively associated with high ethanol consumption, thus an individual drinks more ethanol for the effects achieved in others [82, 83]; 2) the ability to display greater levels and quicker development of tolerance (a reduction in ethanol’s effects after prior treatment with ethanol) to ethanol’s effects is associated with excessive ethanol consumption and the development of alcoholism, thus an individual drinks more ethanol to achieve the same effect as obtained in the past [84]; and 3) the expression of low- to moderate-dose ethanol-induced stimulation is associated with an individual’s propensity to abuse alcohol, as often modeled in rodents by increased motor activity or approach behavior [85–87], aggression [88], as well as social facilitation [89, 90]. For difficulties in establishing consilience/translatability between the rodent and clinical literature on ethanol-induced stimulation along with other behavioral correlates see Crabbe *et al.* [91]. Regarding neurochemistry, clinical and basic research indicate that alcohol abuse and dependence are related to alterations in the following systems: acetylcholine (ACh) [92–94], glutamate/*N*-methyl-D-aspartate (GLU/NMDA) [95, 96], gamma-aminobutyric-acid (GABA) [97–99], dopamine (DA) [100], serotonin (5-HT) [101, 102], opioid [103], neuropeptide-Y (NPY) [104], corticotropin releasing factor (CRF) [105], substance P [106], nociceptin/orphanin FQ (NOP, N/OFQ) [107], neurotrophic factors such as BDNF [108], hypothalamic-pituitary-adrenal (HPA) [109–112] and endocannabinoid [113] systems. Therefore, substantial preclinical research has been conducted in developing and testing models of the above characteristics (*e.g.* selective breeding or gene knockouts) and subsequently testing putative treatments for alcohol abuse and dependence in these models [114–122].

CHAPTERS WITHIN THIS SPECIAL SECTION

First, Agabio and colleagues [123], detail the development and testing of positive allosteric modulators of the GABA_B receptor in both preclinical and clinical trials. GABA is the major inhibitory neurotransmitter with major projections throughout the central nervous system (CNS). GABA_B receptors in neurons are coupled *via* a G-protein to adenylyl cyclase in neurons and membrane potassium and calcium channels. Their activation decreases adenylyl cyclase activity, increases potassium conductance, and decreases calcium conductance. Thus, GABA_B receptors inhibit neuronal excitability and neurotransmitter release. The prototypic GABA_B receptor agonist, baclofen remains one of the most potent and selective agents for stimulation of the GABA_B receptor. Recently, a binding site for positive allosteric modulation of the GABA_B receptor has been identified. This site is topographically distinct from the orthosteric binding site of the neurotransmitter GABA and associated agonists. The pharmacological activation of this modulatory binding site by positive allosteric modulators of the GABA_B receptor (GABA_B PAMs) augments the affinity of the GABA_B receptor for GABA and agonists and synergistically potentiates their effects. Because GABA_B PAMs are devoid of substantial intrinsic agonistic activity in the absence of GABA, they provide more physiological means of activating the GABA_B receptor *in vivo* than agonists, *per se*. Therefore, by targeting only endogenously activated receptors, GABA_B PAMs are expected to produce fewer side effects and lower tolerance, with research supporting this hypothesis (for references see Agabio *et al.* [123]). Given baclofen, and associated agonists, decrease

alcohol drinking and craving and alleviate the negative symptoms associated with alcohol withdrawal; GABA_B PAMs should provide a suitable alternative to baclofen in the treatment of alcohol abuse and dependence. In their paper, Agabio *et al.* review a substantial preclinical literature supporting this conjecture.

In the second paper, Barron and colleagues [124] detail the development and testing of polyamine binding site (*e.g.* NMDAR-NR2B subunit) antagonists that attenuate ethanol relapse-like drinking and ethanol withdrawal-induced neurotoxicity. Glutamate is the major excitatory neurotransmitter in the CNS and glutamatergic neurons are distributed throughout the brain. There are both metabotropic and ionotropic GLU receptors (mGluRs and iGluRs, respectively). While mGluRs are involved in alcohol's action, the role of iGluRs in alcohol's effects has received far more attention. Three basic receptor families have been identified, including the NMDAR, the α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA) and the kainic acid receptor (KAR). Fast synaptic transmission within this system is mediated by AMPA and KAR, while NMDARs and mGluRs are responsible for glutamate-mediated neurotransmission and modulation of transmitter release. Group I mGluRs (mGluR1 and mGluR5) appear important in regulating the effects of alcohol and drugs of abuse. In addition, all three of the iGluR classes are inhibited by alcohol at physiologically relevant concentrations (for references see Barron *et al.* [124]). Given the above, it is not surprising that antagonism of GLU receptors blocks many of alcohol's effects. In particular, NMDAR antagonists reduce ethanol self-administration, relapse, conditioned approach behavior and sensitization of the motor activating effects of low dose ethanol as well as attenuate neurotoxicity within the CNS observed during ethanol withdrawal. Polyamines are simple cationic compounds, derived from the amino acid arginine; which is subsequently converted to putrescine, with putrescine being the precursor of two other major polyamines, spermine and spermidine. These polyamines are ubiquitous in brain, involved in multiple neuronal functions, bind to the NR2B subunit in particular and modulate ethanol's effects within the CNS (for references see Barron *et al.* [124]). In their paper, Barron *et al.* review a class of polyamine binding site inhibitors that display equal or greater effectiveness in (a) blocking relapse to ethanol drinking and (b) affording neuroprotection during ethanol withdrawal when compared with more common NMDAR antagonists (*e.g.* acamprosate and memantine).

In the third paper, Rahman and Prendergast [125] detail the development and testing of cholinergic functional antagonists at nicotinic receptors (nAChR) which attenuate excessive alcohol intake. Nicotinic AChRs are located throughout the brain. There are 12 neuronal nAChR subunits (α 2— α 10 and β 2— β 4), which assemble to form diverse functional nAChRs. Thus, nAChRs are a super family of ligand gated ion channels, with heteromeric receptors assembled with both α (α 2— α 6) and β subunits. The most abundant nAChRs are in the CNS, with greater than 90% of these nAChRs containing α 4- β 2* subunits (*, denotes that there are multiple β 2 subunits). Homomeric nAChRs include a single subunit type (α versus β), such as the α 7 nAChR subtype. The α 6 nAChR is present in a restricted number of CNS regions primarily at limited levels in a number of DA-rich regions within the meso-cortico-limbic neurocircuit, which suggests the α 6 nAChR may be a good candidate (*e.g.* fewer secondary effects) targeting alcohol abuse and dependence. Alcohol activates the meso-limbic DA system as measured by increased extracellular DA levels in the nucleus accumbens (Acb). Research thus far indicates ligands for nAChRs attenuate alcohol drinking behavior by acting at key DA-terminals within the meso-cortico-limbic system (for references see Rahman and Prendergast [125]). In their review, Rahman and Prendergast discuss the development and testing of molecules (*e.g.* competitive and noncompetitive antagonists as well as partial agonists) targeting nAChRs for the treatment of alcohol abuse and dependence using *in vivo*, *in vitro*, preclinical and clinical assays.

In the fourth paper, Rezvani *et al.* [126] detail the development and testing of molecules targeting different neuronal systems including sodium channels, mitochondrial aldehyde dehydrogenase (mALDH), 5-HT₂ receptors, histamine H₃ receptors, and $\alpha_4\beta_2$ nicotinic receptors. A number of antiepileptic and anticonvulsant agents have been tested for the treatment of alcoholism. These agents include topiramate, carbamazepine, valproate, gabapentin, lamotrigine, and zonisamide. Carisbamate (Registry Number 194085-75-1), an adjunctive treatment for epilepsy, which modulates voltage-activated sodium channels, voltage-activated calcium currents, is an allosteric modulator of some GABA receptors, and inhibits NMDA receptor currents has been tested by Rezvani *et al.* as well. Disulfiram/antabuse, is the oldest FDA-approved treatment to facilitate alcohol abstinence, acts as an aldehyde dehydrogenase inhibitor and may affect multiple metabolic pathways. However, GS-455534 (Gilead, Inc.) selectively inhibits mitochondrial ALDH2 at very low concentrations while having no effect on ALDH1, mono-amine oxidase, and a variety of other enzymes that are inhibited by disulfiram. Thus, GS-455534 has a lower side-effects profile than the prototypic ALDH inhibitor disulfiram. Anxiolytics (*e.g.* benzodiazepines) are often used during early abstinence when withdrawal symptoms are common, thus promoting continued abstinence. JNJ-5234801 (Johnson & Johnson) is an anxiolytic that appears to exert its effects through the 5-HT_{2A} and 5-HT_{2C} receptors. Importantly, JNJ-5234801, unlike benzodiazepines, at anxiolytic doses does not impair learning and memory, does not induce sedation or skeletal muscle relaxation, and does not have adverse interactions with alcohol when it is present. Histaminergic-3 (H₃) receptors are autoreceptors localized on non-histaminergic neurons throughout the mesocorticolimbic system and regulate the release of a variety of neurotransmitters. Thus, H₃ antagonist-induced reductions in ethanol self-administration, H₃ agonist-induced increases in ethanol self-administration and the fact that mice lacking the H₃ receptor exhibit lower alcohol-preference than their wild-type counterparts may be due to histaminergic modulation of DAergic activity within this neurocircuit. Therefore, JNJ-39220675 (Johnson & Johnson), a selective H₃ antagonist, was tested for its effects on ethanol intake and preference. Lastly, a new compound, Sazetidine-A, a highly selective $\alpha_4\beta_2$ nAChR desensitizer, has been developed by a group of scientists at Georgetown University. Given Sazetidine-A reduces nicotine self-administration this compound was also tested for its effects on ethanol drinking behavior (for references see Rezvani *et al.* [126]). In their review, Rezvani and colleagues discuss their findings that all 5 of these compounds reduce high alcohol consumption and a preference for alcohol over water.

OTHER NEUROBIOLOGICAL SYSTEMS MEDIATING THE DEVELOPMENT AND EXPRESSION OF ALCOHOLISM

U.S. Federal Drug Administration (FDA)-approved treatments for alcohol abuse and dependence

The three drugs that have been approved for the treatment of alcoholism in the United States are disulfiram, naltrexone and acamprosate (for thorough reviews, see [127–129]). Disulfiram is an aversive therapy that has been used in the treatment of alcohol addiction since the 1940's. It interferes with the metabolism of acetaldehyde by aldehyde dehydrogenase, leading to elevated levels of acetaldehyde which results in a number of physiologically aversive symptoms. These symptoms include facial flushing, tachycardia, hypotension, hyperthermia and ataxia [130]. Given these symptoms, disulfiram's practical efficacy in preventing relapse to alcohol abuse is modest at best. Naltrexone was the second compound to be approved for alcoholism treatment in the U.S. Although it primarily targets the mu-opioid receptor, it is a pan-opioid antagonist blocking the mu-, delta- and kappa-opioid receptors. While naltrexone's efficacy in preventing relapse has been debated, it does appear to be effective in certain subpopulations of alcoholics depending upon their genetic

profile [131–135]. Moreover, several depot (*i.e.* long-lasting) naltrexone medications have been developed to facilitate patient compliance and naltrexone's efficacy. Acamprosate was approved by the U.S. FDA for treating alcoholism in 2004 and has been used in Europe to treat alcohol addiction for quite some time. Acamprosate's pharmacological effects are mediated by the NMDA and mGluR5 glutamate receptors. Acamprosate's efficacy is attributed, in part, to its ability to reduce negative affect and interfere with craving during abstinence from alcohol drinking. As outlined below, the majority of patents granted for the treatment of alcohol abuse and dependence include one or more of these compounds (*i.e.* disulfiram, naltrexone, or acamprosate) or their derivatives. Therefore, while significant progress has been made in developing treatments for alcohol addiction, there is still a great need for novel, efficacious medicinal treatments for alcoholism, and it is clear that preclinical and clinical research must continue to address this important public health concern.

Disulfiram and other modulators of alcohol and acetaldehyde metabolism

The body catabolizes alcohol, primarily in the liver, via several pathways [136]. The most common pathway for this metabolism is the oxidation of ethanol, by the enzyme alcohol dehydrogenase, to acetaldehyde and subsequent breakdown to acetate by aldehyde dehydrogenase [137]. An aldehyde dehydrogenase 2 (ALDH2) polymorphism reduces hepatic, mitochondrial ALDH2 activity and causes the alcohol-induced flushing response seen in certain Native American and Asian subpopulations [138]. This flushing response is characterized by facial flushing, tachycardia, hypotension, hyperthermia and ataxia [130]. The alcohol aversive agent disulfiram (Antabuse®) exerts its effect via blocking ALDH2 activity as well. Due to its aversive nature, patient adherence to disulfiram treatment is very poor, although court-ordered treatment can increase adherence substantially [139].

Patents of treatments involving collagen forming agents [140, 141] and/or N-terminal D (–) penicillamine peptides [142] act as sequestering agents and are generally used under conditions of alcohol poisoning. In another case, metadoxine has been patented which is a pyridoxine-pyrrolidone carboxylate and acts as an ethanol scavenger [143]. D-glyceric acid (or its salt and esters) also has been patented for its ability to accelerate alcohol oxidation, which is paralleled by an enhancement of acetaldehyde oxidation to metabolically harmless acetic acid [144]. Traditional medicines also have been patented to reduce ethanol concentrations in the blood [145]. Paradoxically, despite its aversive nature, inhibition of ALDH remains a prominent method of treatment for alcoholism. One focus of patented ALDH treatments is making the treatment less aversive. This can be done through combinatorial therapy and the development of new ALDH inhibitors that induce less aversive symptoms compared with disulfiram.

A number of patents have been granted that combine an aldehyde dehydrogenase inhibitor and one of a number of other compounds such as a monoamine oxidase B inhibitor (*e.g.* selegiline: [146–152]), a benzodiazepine [153], a pan-opioid antagonist [154] or medicaments including tryptophan and benserazide [155–157] to treat alcohol addiction. Another patented combinatorial therapy targeting alcohol metabolism is a compound including taurine and racemic (race-methionine) [158]. A major metabolite of this combination is taurocholic acid which is involved in the metabolic conversion of alcohol. In addition, race-methionine has both anti-oxidant properties and increases liver lecithin, which concurrently reduces liver fat a medical issue in chronic alcoholics.

Although functionally similar to disulfiram, patented treatments [N,N'-bis-(3-aminopropyl)-cyclohexane-1,4-diamine] with oral administration of tetrametanesulfonate monohydrate [159–161] or quinazolinone derivatives [162] do not appear to be as aversive as disulfiram. Alteration of ALDH activity also can be accomplished at the level of gene expression [163].

Cyanamide and cyanamide-metabolites have been patented to disrupt ALDH [164, 165], with both of these patents reducing high-dose effects of cyanamide (*i.e.* toxicity) by functionally slow, “controlled” release of cyanamide. *Radix Puerariae* (Kudzu root) has been patented to treat alcoholism [166, 167]. This root contains daidzin (daidzein), an isoflavone which inhibits mitochondrial ALDH2 and leads to disulfiram-like alcohol reactions [166, 167]. In addition, new isoflavones targeting the ALDH1 system also have been patented to treat alcoholism [168–171]. Among these are C-Glycosylisoflavones having an alky-laminoalkoxyl substituent [172, 173], which provides an alternative aldehyde dehydrogenase system on which to focus. Despite disulfiram-like reactions, the herbal nature of daidzin and isoflavones suggest that the magnitude of these disulfiram-like responses will be less than that induced by disulfiram itself.

Naltrexone and other modulators of the opioid system

The endogenous opioid system is made up of three receptor types: the mu-, delta-, and kappa-receptors. Endomorphins [174], endorphins [175] and dynorphins [176, 177] are the endogenous ligands with selectivity for these receptor types respectively [178]. These ligands originally were recognized as antinociception agents [178]; however, extensive research implicates a role for them in reward and reinforcement [175, 177, 179, 180], neuronal proliferation and maturation [181], as well as other central and peripheral physiological and behavioral processes [175, 179, 182]. The field of chemical dependency treatment still relies heavily on pan-opioid (ligands with affinity for mu-, delta-, and kappa-opioid receptors) antagonists for treating alcoholics, including depot solutions of naltrexone or similar opioid antagonists [183–188]. Naltrexone’s effectiveness appears to be due, in part, to a polymorphism in the gene for the opioid receptor mu-1 (Oprm1) [27–29]. Polymorphisms in the genes for the opioid kappa-1 (Oprk1) and opioid delta-1 (Oprd1) receptors, found in some alcoholics [26, 30], also may influence naltrexone’s effectiveness. Therefore, the genetic make-up of an individual determines to some degree the efficacy of pharmacological treatments targeting opioid receptors.

Long-acting formulations [186] and microsphere or other packaging agents [189–194]) with pan-opioid antagonists continue to be patented for treating alcohol abuse and dependence. In addition, non-oral routes of administration for pan-opioid antagonists have been patented, including trans-dermal [195, 196], transmucosal [197–203]; and intramuscular [204, 205]. There also is patented work on pro-drugs (*i.e.* the antagonist is a metabolic product of the treatment compound) for these pan-opioid antagonists, such as nalmefene [197, 198]. Some patents combine both an opioid agonist [*e.g.* noribogaine: 206, 207; oxycodone: 208] for treating pain and/or withdrawal symptoms and a pan-opioid antagonist [209–211]. Partial, such as buprenorphine [212–215] and methadone [216, 217], and full, such as fentanyl [218], opioid agonists have been patented to treat alcohol abuse and dependence. Novel compounds fitting these categories [219, 220] have been patented as well. Methods of taste-masking recognized treatments for alcoholism (*e.g.* opioid antagonists or topiramate) also have been patented [221–224].

Patents with naltrexone, nalmefene or nazalone often combine these antagonists with ligands targeting other systems. For instance, a pan-opioid antagonist can be combined with anxiolytic drugs for alcohol withdrawal such as GABA-A antagonists [*e.g.* competitive antagonist flumazenil: 225], agonists [226] or general anti-convulsants [227–229]. A number of other system combinations include a pan-opioid antagonist and a GABA-B [230], adrenergic [226, 231–236], serotonergic [229, 231–247], dopaminergic [231–238, 242–250], glutamatergic [229, 240, 241, 249], corticosteroid-associated [250], carbonic anhydrase [237, 238], monoamine uptake [232–235], selective serotonin reuptake [251, 254], or multiple system [255] modulator(s). More selective opioid antagonists/modulators also have

been developed and patented for treating alcoholism [256] such as those for the mu- [257, 258], delta- [259–265] and kappa- [266–268] opioid receptors. On the other hand, delta-mixed agonist/antagonist [260, 269–274] and agonists [275] have been patented to treat alcoholism as well. In addition, mixed opioid receptor modulators such as those for both the mu- and delta-receptor [262, 276, 277] also have been patented for treating alcoholism. In addition, N-acylated imidazo-3-amines and imidazo-5-amines [257, 278] and aminomethyl-phenyl-cyclohexane [279] putative ligands for opiate receptors with analgesic effects have been patented as well.

Acamprosate and other modulators of the glutamatergic system

The glutamatergic system and associated patents are covered in Barron *et al.* ([124] This Issue).

Glycinergic system

The glycine receptor (GlyR) is an ion channel that allows the influx of Cl⁻ ions to mediate inhibitory neurotransmission, in a manner similar to the GABA-A receptor. Taurine also acts as an endogenous ligand at the GlyR and appears to mediate some of ethanol's effects at this receptor [280–284]. The GlyR is made up of one of four alpha-subunits (alpha1-alpha4) and a beta-subunit as a heteromeric receptor, although homomeric alpha GlyRs also have been identified. Gephyrin is required to anchor the GlyR at the post-synaptic membrane but appears to only bind to the beta-subunit indicating the need for the heteromeric alpha1-beta and alpha2-beta GlyRs. GlyRs are located both pre- and post-synaptically at GABA-A and glutamate (NMDA as well as AMPA) associated synapses [284, 285]. Glycine (sometimes called GlyB) also has a binding site associated with the NMDA receptor and acts as a co-agonist at this binding site [284, 285]. This binding site also facilitates NMDA receptor internalization [284]. There are two glycine transporters (GlyT1 and GlyT2). GlyT1 is located on astrocytes and pre-synaptically at excitatory synapses, whereas GlyT2 is located pre-synaptically at inhibitory synapses [284, 285]. Alpha4-beta GlyRs also have been identified on glia [286]. The GlyR, or its binding site, has been implicated in motoneuron disease, associated dysfunctional startle response, vision, hearing, seizures, white matter pathology, nociception, learning/synaptic plasticity, memory, schizophrenia and addiction [280, 282–289].

Ethanol potentiates GlyR currents, whereas benzodiazepines and certain neurosteroids inhibit alpha2-associated GlyR currents [281, 282, 284, 290]. Interestingly, endocannabinoids appear to modulate GlyR activity at inhibitory synapses [283]. Related to addiction, ethanol appears to modulate GlyR activity on GABAergic interneurons and neurons in the nucleus accumbens with the latter projecting to the ventral tegmental area [288]. Primarily glycine uptake inhibitors have been patented for the treatment of alcohol addiction. For instance, both GlyT1 [291–294] and general glycine transport inhibitors (N-(piperidinyl)(phenyl)methyl benzamide derivatives, N-heterocyclymethyl-benzamide derivatives and N-heterocyclymethyl-benzamide derivatives) [295–301] have been patented. Finally, selective competitive antagonists (N-substituted-4-uredo-5,7-dihalo-2-carboxy quinolone compounds) at the glycine site of N-methyl-D-aspartate (NMDA) receptors have been patented for treating alcohol dependence as well [302–305].

GABAergic systems

The GABA-B receptor and its actions are discussed cogently in the chapter by Agabio and colleagues [123, This Issue]. Therefore, background information on this system will not be discussed here. The GABA-A receptor is composed of a Cl⁻ ion channel and is the primary target for GABA, the major inhibitory neurotransmitter in the brain [306]. A number of subunits have been identified for the GABA-A receptor including alpha (1–6), beta (1–3),

gamma (1–3), delta, rho (1–3), epsilon as well as theta to form heteromeric receptors [306]. Ligand classes associated with the GABA-A receptor include GABA, benzodiazepines, picrotoxin, barbiturates, neurosteroids and volatile anesthetics [306]. Regarding uptake, there are four GABA transporters (GAT1-14) [306]. The GABAergic system has been shown to mediate depression, seizures, strokes, Alzheimer's disease, Down syndrome, anxiety, schizophrenia, pain, and addiction [136, 307–313]. Ethanol acts as a functional agonist at the GABA-A receptor and increases pre-synaptic GABA release, with an associated decrease in GABA-A function after chronic ethanol exposure in some behavioral assays [95, 289]. There is evidence that other neurotransmitter systems, such as the GABA-B receptor and neurosteroids, are implicated in this effect as well [95, 314]. In addition, chronic ethanol functionally down-regulates benzodiazepine potentiation of GABA activity at the GABA-A receptor [315]. It also is important to note that sex-differences in GABA-A receptors may influence ethanol [316] and neurosteroid [317] effects. Given that ethanol interacts with the GABAergic system, it is not surprising that genes implicated in alcoholism include GABA-associated proteins, such as the *Gabra2* gene [318–327].

Combinations of a GABA-A alpha1 antagonist (*e.g.* flumazenil) and an anti-addiction compound [*e.g.* naltrexone: 225]; or a GABA-A positive allosteric modulator and a PKC-epsilon inhibitor [328] have been patented to treat alcoholism. GABA-A functional agonists or potentiators (a barbiturate-like compound [329]; ligands for the benzodiazepine binding site [330–333]; bicyclic and tricyclic heteroaromatic derivatives [334]), and other GABA modulators (pregabalin or gabapentin [335, 336]; pyridazino[4,5-*b*]-indole-1-acetamide derivatives [337]; pyrido[3,4-*b*]indole-4-carboxamide derivatives [338]; or their precursors [339–341]) have been patented as well. Treatments with selectivity for particular GABA receptor subunits also have been patented, such as alpha2-delta [342]; alpha2, alpha3, alpha5 [343]. GABA-B allosteric modulators have been patented for alcohol abuse and alcohol dependence as discussed in Agabio and colleagues (This Issue [123, 344–349]. In addition, gamma hydroxybutyric (GHB) acid amides [350–353], GHB oligomers [354–356], and GHB-like methoxybutyramide derivatives [357–359] also have been patented to treat alcoholism. Gamma hydroxybutyric (GHB) acid modulates GABA-receptor activity and may have its own receptor in the brain [360]. Finally, gamma vinyl GABA, a GABA-transaminase blocker treatment which increases CNS-GABA levels, has been patented to treat alcohol dependence [361]. An antiepileptic (levetiracetam) that does not bind to glutamatergic or GABAergic receptors but to synaptic vesicle 2 (SV2) protein in the brain also has been patented [362].

Regarding treatment of neurodegeneration and regeneration as an adjunctive treatment, patents for nitrate esters that modify both GABAergic and glutamatergic activity have been granted [363, 364]. Topiramate, or its derivatives, which also modifies activity in both of these systems has been patented a number of times [237, 238, 251, 365, 366] as well as other novel compounds influencing both systems [367]. There is evidence that the P2X7 receptor modulates both GABA and glutamate release [368], with the manipulation of its activity patented for the treatment of alcoholism [369].

Neurosteroid systems

Generally, neurosteroids are discussed in the context of the GABA-A receptor complex where they act as potent allosteric modulators [314, 317, 370]. This section will describe these compounds within this context. There are three general categories of neurosteroids: pregnane neurosteroids, androstane neurosteroids, and sulfated neurosteroids [317]. Neurosteroids have been implicated in a number of physiological and behavioral processes such as anesthesia, sedation, seizures, anxiety, sex-associated physiology, mood disorders, aggression, learning, memory, synaptic plasticity, reward and addiction [314, 371–373].

Acute ethanol and/or stress increases central neurosteroid levels and enhances GABA-A receptor activity [314, 370, 374]. A number of patents for treating alcoholism that involve the androstane category of neurosteroids have been granted [375, 376] including dehydroepiandrosterone [DHEA: 377]. Substantial research indicates that the brain synthesizes estrogen [373]. Moreover, estrogen-associated steroids protect against ethanol withdrawal-induced lipid peroxidation and mitochondrial dysfunction in the brain [378, 379] with the GABAergic system implicated in these effects [380]. Therefore, a number of treatments have been patented for alcohol dependence that modulate (positively and negatively) estrogen levels [381–384].

Dopaminergic system

Dopamine (DA) is a catecholaminergic neurotransmitter with five receptor sub-types: D1 and D5 (which stimulate adenylate cyclase) and D2, D3, and D4 receptors (which inhibit adenylate cyclase). DA is cleared from the extracellular space by the DA transporter (DAT) and enzymatic catabolism [385–387]. Central DAergic activity is implicated in a number of physiological and behavioral processes including eating disorders, migraine, maternal behavior, Parkinson's disease, psychosis, learning, memory, cognition, attention deficit disorder, reward and reinforcement, aggression, as well as impulse control [388–397]. In addition, DA neurotransmission is associated with the rewarding properties of drugs of abuse, including alcohol [398–403]. Moreover, DA activity promotes alcohol self-administration in human and non-human subjects [403–409]. The application of pharmacologically relevant levels of ethanol to ventral tegmental area (VTA) brain slices increases DA neuron firing [410, 411] which *in vivo* subsequently increases extracellular DA levels in one of the mesolimbic projection regions, such as the nucleus accumbens [412–414].

Clinically-directed research indicates that polymorphisms in the genes for the DA-1 (*Drd1* [415, 416]), -2 (*Drd2* [417, 418]), and -4 (*Drd4* [418–420]) receptors, as well as genes for dopa decarboxylase (*Ddc* [421]), catechol-O-methyl-transferase (*Comt* [421]), monoamine oxidase type A (*Maoa* [422]) and a member of the solute carrier 6/dopamine transporter 1 (*Slc6a3/Dat1*) family [421–424] may influence the development and expression of alcohol abuse and dependence. Therefore, pharmacological modulation of the DA receptor and DAT has been a target for treating alcoholism. DA-D2 receptor agonists have been evaluated and patented to treat alcohol abuse and dependence for quite some time [425]. This work parallels basic research indicating these compounds may attenuate the reinforcing properties of alcohol [406]. Along with the D2 receptor, the D3 receptor also has been implicated in alcohol craving [426] and has been a target for patented medications [427].

Combination treatments that include a DA receptor or DAT modulator and a modulator of other neurotransmitter systems have been patented as well. One combination is that of a D2 receptor antagonist with a serotonin-3 (5-HT₃) receptor antagonist [428]. This combination is proposed to reduce untoward side-effects of D2 blockade (*e.g.* extra-pyramidal signs associated with certain antipsychotics). The 5-HT₃ receptor modulates the VTA-DA projections to target regions in the mesocorticolimbic system and play an important role in ethanol reinforcement/reward [429, 430]. A similar combination is that of partial agonists for the D2 and 5HT-1A receptors (bifeprunox and aripiprazole [431]). Another patented combination is that of a D4 negative modulator with an inverse or partial agonist for the 5-HT_{2A} receptor [432, 433]. A third combination includes a D2 antagonist with a 5-HT_{1A} agonist [434, 435]. A fourth combination is that of a weak D2 antagonist that blocks the alpha₂-adrenergic receptor as well [436]. Another avenue of treatment for alcoholism is the use of compounds that mimic its ability to increase mesolimbic DA-activity, with preclinical evidence indicating that DAT blockers substitute for ethanol's DA-releasing effects in the

nucleus accumbens [437]. Thus, the use of DAT inhibitors to treat alcohol addiction has been patented [438–440], with greater efficacy expected during early abstinence.

Alcohol can induce neuronal damage and has been implicated in changes to membrane characteristics that alter receptor binding [441] and signaling cascades. Thus, patents have been granted to protect neurons in the mesolimbic system [442, 443]. Similarly, patents have been granted for compounds which seek to increase the ratio of Dopamine AMPHETAMINE INHIBITOR (DAMPIN) to dopamine or cyclic adenosine monophosphate-regulated neuronal phosphoprotein (DARPP-32) in dopamine circuits, in order to reduce protein kinase A activity [444–449]. As described in [448], DAMPIN is a splice variant of DARPP-32 that lacks the first 37 amino acids of DARPP-32. Also, whereas DARPP-32 is phosphorylated by PKA signaling thus inhibiting protein phosphatase 1 (PP1); DAMPIN, as a splice variant, is not phosphorylated by PKA signaling and does not inhibit PP1. Interestingly, both DARPP-32 and DAMPIN have Cdk5 phosphorylation sites which result in inhibition of PKA signaling. In general, these compounds modify dopaminergic responses to drugs, including alcohol, and reduce dopamine-mediated inhibition of sodium-potassium adenosine triphosphatase; thus helping maintain resting membrane potential and dopaminergic activity. Adenosine receptors appear to control DAergic transmission [450] and treatments targeting the A2a receptor have been patented to treat alcohol addiction [451, 452].

Serotonergic system

Serotonin (5-hydroxytryptamine; 5-HT) is a monoaminergic neurotransmitter synthesized from the amino acid tryptophan. It has 7 target receptor superfamilies (5-HT₁₋₇), some of which include multiple subtypes. Serotonin is primarily cleared from extracellular space by selective transporters (5-HTT or SERT) or enzymatic metabolism. Central serotonin has been implicated in a number of physiological and behavioral processes, including appetite [453, 454], impulse control [455], sleep [456, 457], and cognitive functions [458]. In particular, this neurotransmitter is associated with neuropsychiatric disorders, and a number of anti-depressant pharmaceuticals act through modulation of the central serotonin system [459]. In addition, substantial clinical and pre-clinical evidence indicates that serotonin is involved in some of the reinforcing and/or rewarding effects of drugs of abuse, including alcohol [460].

Clinical research indicates that genetic polymorphisms or differences in expression of genes that encode serotonin receptors and transporters [461–465] may influence the development and treatment of alcoholism in some individuals. Therefore, pharmacological modulation of serotonin receptors and transporter activity, as well as the enzymes that break down synaptic serotonin, has proven to be a common focus in research and medications development aimed at treating alcohol abuse and dependence. Patents that address selective serotonin transporter blockers and the genes that encode for them have great promise in the treatment of alcohol abuse [229, 237, 238, 359, 466–480], and are an ongoing focus of alcohol research [481, 482]. 5HT uptake [483] and 5HT-2A receptor [484] inhibitors in combination with alpha-adrenergic antagonists or SERT and norepinephrine transporter (NET) blockers [485–491] have been patented as well. In addition, compounds that modulate serotonin's amino acid pre-cursor tryptophan have been issued to address alcohol cessation via disulfiram-like aversion therapy [492] or inhibition of tryptophan hydroxylase [493].

Compounds that target serotonin receptors have received attention in the development of treatments for alcoholism. For example, the ability to modulate serotonin autoreceptors 5-HT_{1A} and 5-HT_{1B} (localized on the cell body or the nerve terminal, respectively [494, 495]) has been an area of focus for patented treatments targeting alcoholism (*e.g.* piperazine, pyrimidine or benzimidazolone derivatives [466, 477, 496–510]) due, in part, to clinical and pre-clinical evidence that this receptor subtype is involved in alcohol drinking and some of

the behavioral manifestations of alcoholism [461, 463, 511–514]. Other 5-HT1 receptors also have received attention in the field of alcohol addiction research [505]. A wealth of evidence also implicates 5-HT2 and 5-HT3 receptors in alcohol drinking and alcoholism. Two 5-HT2 receptors (5-HT2A and 2C), in particular, have been targeted in alcohol research due to clinical and pre-clinical findings that they promote alcohol drinking [515–519]. To that end, several patents have been directed at these receptor subtypes (*e.g.* pyrimidine derivatives [508, 520–529]). Modulation of the 5-HT2B receptor also has been patented for the treatment of alcohol abuse and dependence [530]. In addition, several patents have been issued for compounds that block 5-HT3A receptors (*e.g.* granisetron [531–534]) alone or in combination with an NMDA antagonist [535]. Some evidence suggests 5-HT3 receptor antagonists reduce alcohol drinking, craving, and relapse-like behaviors in humans and non-human animals [536–539]. Patents also have addressed other 5-HT receptors [540, 541], however these are less common.

Cholinergic system

The cholinergic system and associated patented treatments [*e.g.* 542] for alcoholism are discussed by Rahman and Prendergast [125, This Issue] as well as Rezvani and colleagues [126, This Issue].

Histaminergic system

The histaminergic system and associated patented treatments for alcoholism are discussed by Rezvani and colleagues [126, This Issue].

Endocannabinoid system

The endocannabinoid system acts as a neuromodulatory system triggered by neuronal activation or cellular stress. These neuromodulators/endocannabinoids once released are removed from the synaptic cleft through reuptake mechanisms or enzymatic degradation. There are two cannabinoid G-protein coupled receptors, CB1R and CB2R. CB1Rs are primarily found in the brain and located presynaptically where they inhibit neurotransmitter (*e.g.* GABA and glutamate) release. However, some CB1 agonists increase norepinephrine and serotonin neuro-transmission. CB2Rs are primarily located on immune-associated cells where they have immunosuppressive effects. Cellular stress tends to increase expression levels of CBRs and this effect appears to reduce symptom severity (*e.g.* neuropathic pain). Moreover, there is evidence for heterodimerization of CB1 receptors and D2, adenosine A2a, orexin-1, as well as opioid receptors. There are two primary endocannabinoid molecules, N-arachidonylethanolamine (anandamide) and 2-arachidonoylglycerol (2-AG). It is noteworthy that anandamide also binds to the vanilloid VR1 receptor [also called transient receptor potential vanilloid 1 (TRPV1)]. Treatments are not limited to CBRs and VR1 but include fatty acid amide hydrolase-1,2 (FAAH) inhibition which facilitates neuroprotection through increased anandamide levels. Therefore, patents targeting the VR1 receptor are included here. The endocannabinoid system mediates a number of physiological and behavioral processes such as feeding behavior, nociception, synaptic plasticity, thermoregulation, stroke, seizures, learning, memory, neurogenesis, schizophrenia, depression, mood and addiction (for reviews see [416, 543–556]).

Most patents for the treatment of alcohol abuse and dependence targeting the endocannabinoid system are CB1R antagonists, mostly pyrazoline derivatives [557–565]. Some patents combine the CB1R antagonist with other neurotransmitter system modulators [566–568]. Precursors for these pyrazoline compounds have been patented as well [569]. CB1R/CB2R agonists, inverse agonists and antagonists also have been patented together [570–572]. Modulators of the vanilloid VR1 receptor [573, 574] as well as mixed

modulators of the VR1 and CB1R/CB2R receptors [575, 576] have been patented for treating alcohol abuse and dependence.

CURRENT AND FUTURE DEVELOPMENTS

It is clear that alcohol abuse and dependence are complex disorders with characteristics common to other complex diseases [577]. These characteristics include (1) clinical heterogeneity; (2) polygenic inheritance, such that multiple genes are involved; (3) genetic heterogeneity, such that different polymorphisms of a certain gene/gene product may yield similar symptomology; (4) reduced genetic penetrance, such that not all individuals with particular genes or specific variations in the gene develop the disorder; (5) epistatic effects, such that the disorder results from interactions with alleles at different loci; and (6) phenocopies; such that the alcoholism phenotype is expressed despite lack of a clear genetic predisposition. Given the above, pharmacogenetic/pharmacogenomic strategies to treat alcohol abuse and dependence are being developed [578–586]. These approaches will need to be developed further, from two different directions. First, genotypic differences will have to be evaluated and, second, compounds that target the neuronal system will need to be evaluated in the preclinical and, subsequently, clinical settings. Some of this will be trial-and-error, but when an animal model that expresses both genotypic and phenotypic characteristics of the disorder is used, relatively high throughput screening can take place. Clinically, greater use of genetic screening via blood samples will provide important information about the effects of off-the-shelf compounds that have been approved for other disorders when treating alcohol abusing or dependent individuals with these comorbid conditions. Finally, the development of advanced neuroimaging techniques will provide vital information on the mechanisms, or site, of action for different compounds when evaluated in alcoholics, other substance abusers and associated controls. In conclusion, while significant inroads have been made in treating alcohol abuse and dependence; continued biochemical, genetic, behavioral research is required in both the preclinical and clinical setting.

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