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Serotonergic Systems in the Pathophysiology of Ethanol Dependence: Relevance to Clinical Alcoholism

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Abstract

Alcoholism is a progressive brain disorder that is marked by increased sensitivity to the positive and negative reinforcing properties of ethanol, compulsive and habitual use despite negative consequences, and chronic relapse to alcohol drinking despite repeated attempts to reduce intake or abstain from alcohol. Emerging evidence from preclinical and clinical studies implicates serotonin (5-hydroxytryptamaine; 5-HT) systems in the pathophysiology of alcohol dependence, suggesting that drugs targeting 5-HT systems may have utility in the treatment of alcohol use disorders. In this review, we discuss the role of 5-HT systems in alcohol dependence with a focus on 5-HT interactions with neural circuits that govern all three stages of the addiction cycle. We attempt to clarify how 5-HT influences circuit function at these different stages with the goal of identifying neural targets for pharmacological treatment of this debilitating disorder.

Keywords

Serotonin; SSRIs; alcohol; 5-HT_{2C} receptors; withdrawal; anxiety

Alcoholism is a heterogeneous disorder with that represents a common endpoint for multiple diverging etiologies. In this review, we develop the hypothesis that genotypic differences in serotonin (5-hydroxytryptamine; 5-HT) function contribute in different ways to these various “pathways to alcoholism”. 5-HT hypofunction, for instance, is associated with early-onset alcoholism that leads to impulsive alcohol drinking. 5-HT hyperfunction, on the other hand, is associated with anxiety and may play a role in drinking for the purposes of self-medication. As dependence takes root, the neurotoxic effects of alcohol lead to widespread dysregulation of brain 5-HT systems that contribute to the excessive and compulsive alcohol use, enhanced sensitivity to the negative reinforcing aspects of alcohol, and susceptibility to relapse after periods of abstinence. Global reduction in 5-HT markers reflects a loss of 5-HT neurons and axons that may increase ethanol consumption and reduce stress resilience, thereby promoting relapse. On the other hand, there are compensatory,

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region-specific increases in synaptic 5-HT function or 5-HT receptors in the extended amygdala that can increase negative affect and anxiety during withdrawal, potentially leading to relapse. Together, these findings provide compelling evidence that 5-HT systems are critically involved in all stages of alcohol dependence, from the initiation of drinking to withdrawal and relapse. Given the complexity of 5-HT circuitry and the multiplicity of 5-HT receptor subtypes involved at different stages of the disease, caution should be taken when prescribing drugs such as selective serotonin reuptake inhibitors (SSRIs) that increase synaptic 5-HT across the board. Converging lines of evidence suggest that pharmacological strategies focused on targeting specific 5-HT receptors subtypes may enable more precise control of circuit elements that regulate different phases of the addiction cycle and improve treatment outcomes.

1. Overview of Alcoholism

Alcohol abuse is a significant public health burden and a leading cause of death among adults in the United States[1,2]. Adolescents who abuse alcohol or those with a family history of alcoholism are at increased risk of developing alcohol dependence, a chronic relapsing disorder that affects an estimated 16.9 million Americans and is notoriously difficult to treat[3]. Current pharmacotherapies for alcohol use disorders target a wide range of systems and include naltrexone (a μ-opioid receptor antagonist), acamprosate and topiramate (both of which act to augment GABAergic transmission and inhibit glutamatergic signaling). The overall effectiveness of these treatments is somewhat limited due to the complex etiology of the disorder, which has been classified into two discrete subtypes according to the severity of discrete symptoms and age of onset[4]. In Cloninger type 2-like or early-onset alcoholism (age of onset<25 years), a strong hereditary influence is present along with antisocial or impulsive personality traits[5]. Interestingly, a functional polymorphism in the serotonin (5-hydroxytryptamine; 5-HT) transporter (5-HTT) gene has been associated with early-onset alcoholism and may play a causative role in the pathophysiology of this disorder[6,7]. Mutations in the 5-HTT linked polymorphic region (5-HTTLPR) result in two allele variants that differ in their transcriptional activity; the short (S) allele and the long (L) allele. Early-onset alcoholism is associated with homozygosity for the L allele, which confers high 5-HTT expression and activity in the dorsal raphe nucleus (DRN). Elevated 5-HT clearance from the synaptic cleft results in lower basal 5-HT levels[8–10], which in turn increases the propensity to consume alcohol[11]. Indeed, individuals homozygous for the L allele exhibit fewer negative side effects from alcohol and stronger cravings, increasing the likelihood that they will drink to excess[12,13].

Cloninger type 1-like or late-onset alcoholism (age of onset≥25 years) is characterized by psychosocial impairment, a high degree of comorbid depression and anxiety, and low genetic predisposition. This type of alcoholism is classically associated with deficits in dopaminergic function rather than any specific serotonergic anomaly, although widespread dysregulation of serotonergic markers (including 5-HTT) in the striatum, amygdala and nucleus accumbens (NAc) is evident in both alcoholic subtypes[14–16]. However, these perturbations are likely the direct consequence of excessive stimulation of serotonergic pathways through repeated cycles of intoxication and withdrawal. Individuals with late-onset alcoholism typically have one or more S alleles, which confers lower levels of 5-HTT and

higher basal 5-HT function. As a result, these individuals are less sensitive to the 5-HT enhancing effects of alcohol but may derive some benefit from its anxiolytic properties, particularly in social or other anxiety-provoking situations. On the other hand, higher 5-HT function may contribute to a hypodopaminergic state that makes these individuals uniquely sensitive to the dopamine-enhancing effects of alcohol. Furthermore, their 5-HT status confers enhanced sensitivity to withdrawal and an increased incidence of relapse[17,18]. Together, these data suggest that low 5-HT function may play a role in the initiation of alcohol intake and facilitate the positive reinforcing properties of alcohol in early-onset alcoholics, whereas high 5-HT function may contribute to the negative reinforcing aspects or withdrawal symptoms in late-onset alcoholics.

2. Serotonin in the positive reinforcing aspects of ethanol intake

2.1.1 Effects of 5HT on ethanol intake

The idea that individual differences in ethanol preference are determined by genetic variations in serotonergic tone is supported by the fact that individuals with the LL genotype have an earlier age of onset of drinking and a poorer prognosis for recovery from alcohol dependence. These findings are corroborated in rodent studies of alcohol-preferring (P) and non-preferring (NP) rats. P rats exhibit widespread deficits in levels of 5-HT and its metabolite 5-hydroxyindoleacetic acid (5H1AA), fewer 5-HT cell bodies and fibers, and increased 5-HT_{1A} receptor binding in the cortex and hippocampus[19–23]. Additionally, in mice with a congenital deficiency in tryptophan hydroxylase 2, the enzyme that converts tryptophan to 5-HT, elevated ethanol consumption and preference coincide with a reduced sensitivity to its sedative effects[11]. In addition to mediating reward, 5-HT may also potentiate ethanol-induced sedation by augmenting GABAergic transmission in the brainstem. Taken together, these studies indicate that deficits in 5-HT function increase the propensity to consume alcohol in both humans and rodents.

Additional evidence from 5-HT depletion studies supports the hypothesis that low 5-HT tone drives ethanol consumption. For instance, neurotoxins such as 5,6-dihydroxytryptamine (DHT) and 5,7-DHT selectively destroy 5-HT neurons in the DRN and increase alcohol consumption[24–28]. However, studies with p-chlorophenylalanine (pCPA) and p-chloroamphetamine (pCA), which deplete brain 5-HT by inhibiting tryptophan hydroxylase, the enzyme that converts tryptophan to 5-hydroxytrptophan (5-HTP), have yielded conflicting results[29]. Both compounds were found to reduce ethanol consumption due to compensatory increases in synaptic 5-HT function or toxic accumulation of acetaldehyde during ethanol intake, leading to conditioned taste aversion. These secondary and off-target effects of 5-HT depleting drugs make a compelling case for using a more refined approach to investigate the contributions of 5-HT function to alcohol abuse. Optogenetic and chemogenetic strategies are two emerging technologies that enable us to target discrete neural circuits in the brain and may pave the way for continuing this line of research in the future.

Conversely, genetic and pharmacological manipulations that increase synaptic serotonin typically reduce ethanol intake. Mice with a homozygous deletion of the 5-HTT consume less ethanol[30]. Selective serotonin reuptake inhibitors (SSRIs), which are widely

prescribed in the treatment of depression and anxiety disorders, generally decrease ethanol consumption in animal studies and short-term human studies[31,32]. However, in long-term clinical studies SSRIs have had mixed results, potentially due to variations in treatment response between alcoholic subtypes. Late-onset alcoholics tend to response more favorably to SSRI treatment, while in early-onset alcoholics, or those with the LL genotype, SSRIs increase ethanol drinking[33–36]. These genotypic differences in drinking outcomes may reflect variations in 5-HT tone. In early onset alcoholics, for instance, low 5-HT tone may result in hypersensitivity of 5-HT receptors in the NAc that signal reward, which would tend the increase the reinforcing properties of alcohol. Likewise, P rats exhibit reduced 5-HT innervation of the medial and posterior NAc[21] which has been strongly implicated in reward processing[37].

2.2. Ethanol effects on 5HT signaling in mesocorticolimbic reward circuits

Acute ethanol administration increases 5-HT levels in the NAc and likely contributes to its reinforcing properties[38–40]. The NAc receives dense 5-HT input from the DRN with widespread innervation of the NAc shell and core[41]. Although the canonical view is that dopamine signaling is the primary substrate of reward in the nucleus accumbens, a recent study found that optogenetic stimulation of 5-HT inputs from the DRN to the NAc were potently rewarding, suggesting that 5-HT signaling also mediates reinforced behavior[37]. The stimulatory effects of ethanol on 5-HT are even more pronounced in alcohol-preferring rats, suggesting a strong link between the reinforcing properties of ethanol and its ability to precipitate 5-HT release. Interestingly, acute ethanol decreases the firing rate of putative 5-HT neurons and increases inhibitory drive in the DRN[42–44], so the stimulatory actions on synaptic 5-HT release appear to be mediated by local circuits in the NAc rather than direct activation of 5-HT neurons. A recent study also demonstrates that escalations in alcohol intake after repeated exposures to ethanol are mediated by 5-HT_{2C} receptor signaling in the NAc shell, which is potentiated in ethanol-dependent mice[40]. Thus, the reinforcing effects of ethanol appear to be augmented in the early stages of dependence in these animals, which may drive increased consumption.

These acute effects of ethanol stand in stark contrast to the effects of chronic ethanol, which is marked by a progressive loss of 5-HT axons and a global reduction in 5-HTT binding, particularly in early-onset alcoholics. This results in a hyposerotonergic state that may accelerate the development of alcohol dependence in this vulnerable group[45]. Similar results have been found in monkeys[46]. Additionally, chronic ethanol exposure over 5 days decreased basal 5-HT levels in P rats but not in NP rats[47]. Thus, deficits in 5-HT transmission induced by repeated ethanol exposure may increase the desire to drink, particularly in those with a genetic profile of low serotonergic tone.

2.3. Overview of 5-HT receptors subtypes

5-HT receptors are classified into seven families based on sequence homology, pharmacological characteristics and effector coupling[48]. All except one, the 5-HT_3 receptor, are members of the G protein-coupled receptor (GPCR) superfamily. The 5-HT_1 receptor family includes the 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{1E} and 5-HT_{1F} receptors, of which only the 5-HT_{1A} and 5-HT_{1B} have been extensively studied in the context of alcohol dependence.

The 5-HT_1 family of receptors are Gi/o coupled receptors that have in common an inhibitory influence on adenylyl cyclase activity[49]. In addition to this, the 5-HT_{1A} receptor also regulates the function of a number of different ion channels, notably the G protein-coupled inwardly-rectifying potassium channel (GIRK), which induces a hyperpolarizing current when activated. In the DRN, 5-HT neurons send a short negative feedback circuit that inhibits their own activity through activation of somatodendritic 5-HT_{1A} autoreceptors. However, the 5-HT_{1A} receptor is also expressed as a postsynaptic heteroreceptor in terminal fields throughout the brain. The other key player in alcohol dependence, the 5-HT_{1B} receptor, is also negatively coupled to adenylyl cyclase and has an overall inhibitory influence on neurotransmitter release[50]. Unlike the 5-HT_{1A}, the 5-HT_{1B} receptor consists of consists mainly of presynaptic autoreceptors and heteroreceptors that inhibit release of a variety of neurotransmitters including 5-HT, GABA, dopamine and glutamate. This makes the 5-HT_{1B} receptor extremely versatile in modulating synaptic function in the brain. From an addiction standpoint, 5-HT_{1B} receptors expressed at GABAergic terminals play a crucial role in the disinhibition of dopamine neurons in the VTA that orchestrate drug and other reward-seeking behaviors.

The 5-HT_2 receptor family includes the 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C} which are Gq-coupled receptors that stimulate phosphoinositide-specific phospholipase C (PI-PLC) signaling [51,52]. Here we will focus primarily on the 5-HT_{2A} and 5-HT_{2C} receptors as they appear to contribute to the modulation of ethanol drinking behavior by 5-HT. Both types of receptors are expressed postsynaptically and have a net depolarizing effect on neurons. The 5-HT_{2A} receptor is highly convergent with midbrain dopamine neurons[53,54] and appears to be a positive modulator of dopamine signaling and drug-seeking behavior[55]. The 5-HT_{2C} receptor, on the other hand, is highly expressed in GABAergic interneurons in the VTA and NAc[56] and has an inhibitory effect on dopamine signaling[57,58]. In addition to these actions on dopamine release, 5-HT_{2C} receptors expressed in the NAc core have been shown to reduce dopamine signaling at the postsynaptic level by inhibiting phosphorylation of DARPP-32[59].

The 5-HT_3 receptor is a member of the Cys-loop family of ligand-gated ion channels and consists of composed of a ion-conducting pore that is permeable to Na^+, Ca^{2+} and K^+. Once activated, an inward current causes rapid depolarization of neurons[60]. This receptor is unique in that is appears to be a direct substrate of ethanol and is thought to mediate at least some of its reinforcing properties. Expression of these receptors in dopamine neurons of the posterior VTA stimulate dopamine releases in terminal fields of the PFC and ventral pallidum[61,62]

Another 5-HT receptor that has been investigated for the treatment of neuropsychiatric disorders and addiction is the 5-HT_7 receptor, which is a Gs-coupled receptor that is positively coupled to downstream adenylyl cyclase signaling. Activation of postsynaptic 5-HT_7 receptors has a depolarizing effects on neurons in the BNST. Presynaptic 5-HT7 receptors located in the amygdala may regulate release of 5-HT and dopamine in this region, which could impact anxiety-like behavior. In the following sections, we will discuss the role of individual 5-HT receptor subtypes in the positive reinforcing aspects of ethanol dependence.

2.3.1. Role of 5-HT$_{1A}$ receptors—Pharmacological studies reveal a complex relationship between 5-HT$_{1A}$ receptor signaling and ethanol consumption. Several studies indicate that systemic 5-HT$_{1A}$ receptor agonists (e.g. 8-OH-DPAT) have a biphasic effect on ethanol intake that is dose dependent, with high doses reducing ethanol preference and intake[63,64] and lower doses potentiating ethanol consumption[65]. It has been suggested that these divergent drinking outcomes reflect differences in sensitivity of somatodendritic 5-HT$_{1A}$ autoreceptors and postsynaptic 5-HT$_{1A}$ heteroreceptors[66]. Low doses preferentially activate 5-HT$_{1A}$ autoreceptors in the DRN compared to high doses that nonselectively bind to both types of receptors. Hence, the ability of low doses of 8-OH-DPAT to increase drinking may be the direct result of activation of 5HT$_{1A}$ autoreceptors in the DRN that inhibiting firing of 5-HT neurons. In support of this idea, site-directed injection of 8-OH-DPAT into the DRN (2.5 μg) or median raphe nucleus (MRN) (5 μg) increased intake of a 12% ethanol solution in a limited access paradigm[67]. In agreement with these findings, a positive correlation was observed between basal 5-HT$_{1A}$ receptor levels in the DRN and subsequent ethanol consumption in rhesus monkeys in a continuous access, two-bottle choice paradigm over a period of at least 9 months[68]. Similar results were obtained in mice trained to consume ethanol[69]. In total, these results suggest a positive association between elevated 5-HT$_{1A}$ autoreceptor signaling in the DRN and ethanol consumption.

Conversely, activation of postsynaptic 5-HT$_{1A}$ heteroreceptors appears to reduce ethanol drinking and other consummatory behaviors, possibly by inhibiting dopamine release. A relatively high dose of systemically administered 8-OH-DPAT (0.1 mg/kg-0.2 mg/kg) decreased the firing rate of dopamine neurons in the VTA[70] and dopamine release in the NAc[71], suggesting that 5HT$_{1A}$ receptor mediated reductions in dopamine signaling may suppress ethanol drinking in studies using similar doses[66]. Site-directed injection of 8-OH-DPAT into the NAc suppressed all consummatory behavior in a manner similar to systemic injections[72], whereas intra-VTA injection did not mimic the effects of systemic 8-OH-DPAT on dopamine neuron firing[70]. Together, these studies indicate that high doses of 5-HT$_{1A}$ receptor agonists may reduce ethanol intake through pharmacological actions at postsynaptic 5-HT$_{1A}$ receptors in the NAc.

In light of these pharmacological studies, it stands to reason that the impact of chronic alcohol on 5-HT$_{1A}$ receptors may in turn influence ethanol drinking behavior. In rhesus monkeys, chronic ethanol is accompanied by widespread upregulation of the 5-HT$_{1A}$ receptor in the cortex, hippocampus, amygdala, and dorsolateral prefrontal cortex (dlPFC), although there was no correlation with ethanol consumption for any of these regions[68]. These data indicate dissociation between ethanol-induced upregulation of postsynaptic 5-HT$_{1A}$ receptors and the motivation to drink alcohol. Another study in macaques, which used an operant self-administration paradigm for 12 months and caloric controls, observed an increase in 5-HT$_{1A}$ receptor binding in the posterior dentate gyrus polymorphic layer but not in other regions of the hippocampus using in vitro autoradiography[73]. Human alcoholics, on the other hand, display reduced levels of 5-HT$_{1A}$ receptors in the perigenual anterior cingulate cortex (pACC), a region that exerts top-down control over emotional processing in the amygdala[74]. This effect is especially pronounced in late-onset alcoholics and may play an essential role in stress-induced relapse drinking in these individuals.

2.3.2. Role of 5-HT$_{1B}$ receptors—The 5-HT$_{1B}$ receptor gene, in particular the HTR1B G861C polymorphism and the short-tandem repeat locus D6S284, has been linked to impulsivity and aggressive behaviors that typify antisocial or early-onset alcoholism[75,76]. In mice, homozygous deletion of the 5-HT$_{1B}$ receptor gene promotes impulsivity and, in some cases, ethanol consumption[77]. Likewise, alcohol preferring rats have a lower density of 5-HT$_{1B}$ receptors in the cortex, lateral and medial septum, and lateral nucleus of the amygdala[78]. Together, these studies indicate that low 5-HT$_{1B}$ receptor expression may predispose to alcohol dependence.

In agreement with these genetic studies, systemic administration of 5-HT$_{1B}$ receptor agonists generally reduces ethanol intake in an operant self-administration paradigms[79,80]. The mechanism of action for these effects is unclear, although evidence suggests that 5-HT$_{1B}$ receptors in the NAc core may be involved, as site-directed administration of a 5-HT$_{1B}$ receptor agonist into the NAc core also decreased ethanol seeking behavior[81]. The NAc core receives glutamatergic inputs from the PFC[82] and 5-HT inputs from the DRN that promote reward seeking behavior, so 5-HT$_{1B}$ receptor agonists may reduce ethanol seeking behavior by shutting down these inputs. These effects appear to be region-specific, as viral overexpression of 5-HT$_{1B}$ receptors in projection neurons of the NAc shell promote rather than reduce ethanol seeking behavior[83,84]. In this case, GABAergic projections to the VTA that provide inhibitory control over midbrain dopamine neurons appear to be involved. Overexpression of 5-HT$_{1B}$ receptors in these neurons would tend to reduce GABA release in the VTA, thereby disinhibiting VTA dopamine neurons and increasing dopamine release. This supported by studies showing that activation of 5-HT$_{1B}$ receptors in the VTA increases dopamine release in the VTA and NAc[85,86], which would be expected to promote ethanol seeking behavior.

These findings are particularly interesting in light of PET imaging studies showing increased 5-HT$_{1B}$ receptor expression in the ventral striatum of human alcoholics[87], which may promote both the initiation of ethanol drinking and the excessive drinking that typifies dependence[83]. The neural processes underlying escalations in drinking (e.g. after CIE-induced dependence) appear to involve increased glutamatergic drive in the NAc[88]. In a recent study, bilateral infusion of the non-selective glutamate transporter blocker threo-b-benzyloxyaspartate (TBOA), which augments glutamate levels, induced dependence-level voluntary ethanol drinking in non-dependent mice. On the other hand, the metabotropic glutamate receptor 2/3 (mGluR2/3) agonist LY379268, which reduces extracellular glutamate, decreased drinking in dependent mice. Given that 5-HT$_{1B}$R agonists also reduce glutamate levels in the NAc, these drugs may have utility in the clinical management of alcoholism, particularly in Type II alcoholics that have a propensity toward alcohol-heightened aggression[89].

2.3.3 Role of 5-HT$_{2A}$ receptors—In a recent study, alcohol dependence was associated with a polymorphism in the *5htr2a* gene which could indicate a role for the 5-HT$_{2A}$ receptor in the pathophysiology of this disease[90]. Pharmacological blockade of 5-HT$_{2A}$ receptors in the posterior VTA reduced ethanol self-administration in rats[91], suggesting a facilitatory role for these receptors in ethanol-seeking behaviors. In support of this, global downregulation of the 5-HT$_{2A}$ receptor using antisense attenuates ethanol intake[92], although similar effects

are seen using site-specific administration into the lateral division of the central amygdala (CeA). Together, these data strongly suggest that 5-HT_{2A} receptors in the VTA and CeA can promote ethanol seeking behaviors.

Accumulating evidence suggests that 5-HT_{2A} receptors can mediate different behavioral outcomes in a regionally specific manner. In a recent study, 5-HT_{2A} receptors in the BLA were found to negatively modulate ethanol seeking behavior by inhibiting principal neurons in the BLA that send excitatory inputs to the NAc that have a well-characterized role in reward[93,94]. Other lines of evidence indicate that the insular cortex may also play an inhibitory role. Maternal separation stress, which represents an early life stressor that can predispose to alcohol dependence, reduces 5-HT_{2A} receptor expression in the anterior insular cortex and enhances ethanol consumption[95]. These results raise the possibility that regional deficits in 5-HT_{2A} receptor signaling may enhance vulnerability to alcohol dependence in individuals exposed to early life stress.

2.3.4. Role of 5-HT_{2C} receptors—There is a substantial body of literature implicating 5-HT_{2C} receptors in the etiology of substance abuse disorders. Systemically administered 5-HT_{2C} receptor agonists consistently reduce self-administration of cocaine[96,97], nicotine[98] and alcohol[99,100]. The putative mechanism of action for these behavioral outcomes involves the inhibitory actions of 5-HT_{2C} receptors on VTA dopamine neurons and subsequent dopamine release in the NAc shell[57,58], which reduces the reinforcing properties of drugs of abuse. This is supported by optogenetic studies in which activation of VTA GABAergic neurons was found to interrupt reward-seeking behavior[101]. However, one potential confound of these pharmacological studies is that 5-HT_{2C} receptor agonists also reduce consummatory behavior via 5-HT_{2C} receptors in the hypothalamus, which makes results difficult to interpret.

Strikingly, drugs that stimulate 5-HT_{2C} receptor signaling at the level of the NAc shell elicit behaviors opposite to that of systemic administration[102]. In a recent study, 5-HT_{2C} receptor antagonists infused directly into the NAc shell reduced drinking in mice with a history of chronic intermittent ethanol (CIE)[40]. This study also reported ethanol-induced remodeling of 5-HT inputs to the NAc that resulted in enhanced 5-HT release and 5-HT_{2C} receptor expression in this region, which may account for the escalated drinking in CIE-exposed mice. In a subsequent study, this group also reported increased 5-HT_{2C} receptor editing in the NAc and DRN of C57BL/6J mice that exhibit escalated drinking following CIE[103]. This apparent dissociation between behavioral outcomes associated with 5-HT_{2C} receptor in the VTA and NAc may be related to their opposing effects on GABA release. In the VTA, activation of 5-HT_{2C} receptors expressed in GABAergic interneurons enhance GABA release[104] and inhibit reward signaling. In the NAc, however, GABA release is attenuated[105]. Taken together, these studies suggest that 5-HT, via 5-HT_{2C} receptors, inhibits GABA signaling in the NAc which in turn potentiates reward[37]. Thus, functional adaptations in regional expression of 5-HT_{2C} receptors may drive the transition from drinking as a more goal-directed, recreational activity to the excessive, immoderate use of alcohol that characterizes ethanol dependence.

The recent success of Lorcaserin (Belviq®) in the treatment of clinical obesity has sparked interest in the off-label use of this selective 5-HT_{2C} receptor agonist for substance abuse disorders such as nicotine and alcohol dependence[106,107]. However, to date there have been no behavioral studies investigating Lorcaserin in a chronic intermittent ethanol model, which may speak more clearly to their clinical utility in the treatment of alcohol dependence. Most of the studies in which 5-HT_{2C} receptor agonists had an inhibitory effect on drinking used operant self-administration paradigms that model the early stages of drinking in which the reinforcing actions of ethanol are likely mediated by dopamine[99,100]. In non-dependent drinking, the inhibitory influence of 5-HT_{2C} receptor agonists over dopaminergic signaling in the VTA and NAc likely accounts for the observed reductions in ethanol self-administration in these models. The CIE model captures some of the elements of ethanol dependence by incorporating repeated cycles of ethanol exposure and withdrawal, which induce escalated drinking. In these more advanced stages of drinking, blockade of 5-HT_{2C} receptors may decrease ethanol consumption. Interestingly, it appears that in a two-bottle choice paradigm in which rats are given ethanol access for 5 consecutive days for 3 cycles, systemic 5-HT_{2C} receptor antagonists did decrease drinking[108], suggesting that the inhibitory contributions of 5-HT_{2C} receptors in VTA and NAc core interneurons may be overcome by upregulation of 5-HT_{2C} receptors in the NAc shell in this model. Overall, these conflicting studies warrant further investigation into role of 5-HT_{2C} receptors at different stages of ethanol dependence.

2.3.5. Role of 5-HT_3 receptors—The 5-HT_3 receptor is a direct neural substrate of ethanol's acute actions on dopamine signaling and likely mediates the reinforcing properties of ethanol, particularly in the initiation of ethanol drinking which relies on intact dopamine signaling. Antagonists of the 5-HT_3 receptor predictably reduce voluntary ethanol drinking in rodents during long (12 or 24 h) exposures[109,110], but surprisingly had no effect in limited access (1 or 4 h) paradigms[64,111,112]. In operant self-administration models, 5-HT_3 receptor antagonists injected in the posterior VTA effectively reduced acquisition of ethanol intake[113], although ethanol responding increased in the post-injection period suggestive of a rebound effect. In the maintenance phase, 5-HT_3 receptor antagonists had the opposite effect and increased ethanol intake, indicating that dopamine is differentially involved in the acquisition and maintenance of ethanol consumption. However, when ethanol access was unpredictable, 5-HT_3 receptor antagonists once again decreased ethanol consumption[114]. These data indicate that when ethanol is novel or unpredictable, 5-HT_3 receptor mediated facilitation of dopamine in the VTA promotes ethanol intake. In established or maintenance drinking, on the other hand, further increases in dopamine signaling reduce ethanol intake. In clinical alcoholism, which is marked by periods of heavy drinking followed by abstinence and withdrawal that are largely determined by unpredictable environmental and biological factors, 5-HT_3 receptor antagonists may be useful in reducing alcohol consumption.

2.3.6. Role of 5-HT_7 receptors—The 5-HT_7 receptor has until recently been largely neglected in addiction studies, but a interesting and important role for these receptors is beginning to emerge[115]. The 5-HT_7 receptor gene has been linked to traits that predict drug-taking behavior such as impulsivity and novelty seeking. In high responder (HR) rats that exhibit increased novelty- and drug-seeking behaviors, reduced 5-HT_7 receptor mRNA has

been observed in the dorsal hippocampus, intralaminar nucleus, and paraventricular thalamic nucleus[116]. These HR rats also exhibit deficits in a novel object exploration task that can be induced in low responder (LR) mice with a 5-HT_7 receptor antagonist. Impulsivity, a core trait of early-onset alcoholics, is also heightened following systemic administration of a 5-HT_7 receptor antagonist[117]. Furthermore, systemic injection of methylphenidate, a drug used to treat attention deficit/hyperactivity disorder (ADHD), not only suppressed impulsive behavior but increased 5-HT_7 receptor expression in the NAc and PFC. These data suggest that 5-HT_7 receptor signaling in the mesocorticolimbic pathways may be an important neural substrate in impulse control. Methylphenidate also increases 5-HT_7 receptor mRNA in the striatum[118], a key structure implicated in compulsive and perseverative behaviors that are markedly enhanced in alcohol dependence. Pharmacological activation of the 5-HT_7 receptor has been shown to increase neurite length in the primary striatal culture and may have a protective function that suppresses impulsive behavior.[117]

The apparent link between impulsivity and reduced 5-HT_7 receptor function seems to suggest that similar deficits would occur in animal models of ethanol dependence or clinical alcoholism. Surprisingly, one study has found that CIE actually increases 5-HT_7 receptor expression in the NAc and DRN of mice[40]. However, it should be noted that systemic administration of a 5-HT_7 receptor antagonist did not affect ethanol intake in these mice, so the functional role of this enhanced 5-HT_7 receptor expression is currently unknown. Future studies investigating the role of 5-HT_7 receptors in the striatum or PFC in ethanol consumption may be more informative.

Emerging evidence from clinical studies reveals a relationship between alcohol dependence and genetic polymorphism in the *5htr7* gene[119,120]. One *5htr7* polymorphism on chromosome 10q23 was found to be associated with a reduction in event-related brain oscillations (EROs), which serves as an endophenotype for a variety of neuropsychiatric disorders[119]. This particular polymorphism was positively correlated with alcoholism, and reduced theta EROs were found among alcoholic individuals homozygous for the polymorphism. In another study, several *5htr7* polymorphisms were associated with alcoholism using the Alcohol Use Disorders Identification Test (AUDIT)[120]. Together, these data provide compelling evidence that 5-HT_7 receptors are critically involved in alcohol dependence.

2.4 Other drugs of abuse

So far we have shown that 5-HT actions on mesocorticolimbic circuits via discrete 5-HT receptor subtypes can influence ethanol intake, but these effects can be generalized to most other drugs of abuse[121]. Experimental manipulations that reduce brain 5-HT typically augment behavioral and dopamine responses to cocaine in humans and rodents[122–126], and there is some evidence to suggest that reduced 5-HT activity increases sensitivity to the effects of nicotine and opiates[127,128]. The literature regarding the effects of 5-HT enhancing drugs on cocaine-related behaviors is incongruous with that of ethanol. Overall, SSRIs potentiate the reinforcing, discriminative and locomotor activating effects of cocaine in rodents via facilitatory actions on dopamine release in the NAc shell[129–132]. On the other hand, 5-HT precursors appear to do the opposite[133,134], which supports the original

hypothesis that 5-HT has an inhibitory effect on drug seeking behavior. The discrepant results obtained with SSRIs may reflect that both drugs compete for binding at the 5-HTT, whereas cocaine also has high affinity for DAT. By effectively reducing the number of 5-HTT binding sites, SSRIs increase cocaine binding to DAT which in turn enhances dopamine release. However the story in primates is incongruous with that in rodents, as SSRIS appear to decrease cocaine discrimination in monkeys[135] and reduce subjective effects of cocaine in healthy volunteers and cue reactivity in cocaine users[136,137], which is in line with their effects on ethanol intake. In total, these studies suggest that 5-HT generally inhibits drug seeking behavior, most likely via actions on 5-HT_{1A}, 5-HT_{1B}, or 5-HT_{2C} receptors.

3. Serotonin in compulsive and habitual ethanol use

Alcoholism is associated with marked alterations in 5-HT systems that interact with genetic and environmental risk factors to reinforce maladaptive drinking patterns. Sensitization to the positive and negative reinforcing aspects of alcohol, combined with desensitization to its aversive and sedative properties, may fuel the desire to drink to excess, which marks the beginning of compulsive alcohol use. The dorsal striatum (i.e. caudate, putamen and ventral pallidum) has been implicated in the transition from goal-oriented behaviors to stimulus-response associations that characterize the formation of habits[138]. Repeated stress or alcohol use also accelerates deterioration of the hippocampus, the structure involved in action selection based on reinforced outcomes, which precipitates the process of reverting to a more striatal-based stimulus response strategy that is relatively inflexible and insensitive to reward devaluation. Drug craving in general is associated with activation of the right caudate and putamen[139], indicating that these structures may be critically involved in compulsive alcohol-seeking behavior.

Accumulating evidence suggests that 5-HT exerts an inhibitory influence over neurons in the caudate through actions at multiple receptor subtypes[140]. The presence of 5-HT_{1B} receptors on corticostriatal terminals results in suppression of evoked glutamate release[141]. Furthermore, stimulation of both fast-spiking and tonically active interneurons, which provide inhibitory input to striatal output neurons, are mediated by 5-HT_{2C}, 5-HT_6 and 5-HT_7 receptors in the dorsal striatum[142–144]. These inhibitory effects of 5-HT in the dorsal striatum may be protective, as low extracellular 5-HT has been associated with compulsive behavior[145]. Alcoholism is associated with a reduction in 5-HTT binding in the caudate[14]; hence the progressive loss of 5-HT innervation of the dorsal striatum by repeated alcohol exposure may in result in hyperactivity of the dorsal striatum which in turn facilitates craving and compulsive alcohol seeking.

The dorsal striatum also modulates the activity of the orbitofrontal cortex (OFC) through direct pathway projections, a region that has been implicated in drug craving in humans[139]. Additionally, hyperactivity of the OFC is associated with persistent responding to reinforced cues even when paired with an aversive stimulus[146]. Thus, striatal influence over the activity of the orbitofrontal cortex (OFC) and basolateral amygdala (BLA) are likely to be substrates for the continued use of alcohol even in the face of adverse social and legal consequences.

As a result, individuals sensitized to alcohol-related cues will drink in the absence of positive reinforcement and even in spite of negative outcomes.

4. Serotonin in the negative reinforcing aspects of ethanol

One of the defining features of alcoholism is the presence of a withdrawal syndrome that can manifest as early as 2 hours after the last drink and persist for several weeks[147]. Symptoms range from mild anxiety and shakiness to more severe complications such as seizures and delirium tremens. The efficacy of SSRIs in treating specific symptoms in the first 8 hours of ethanol withdrawal (e.g. locomotor hyperactivity, stereotyped behavior, tremor, wet dog shakes, agitation, and audiogenic seizures) has been documented in preclinical studies[148–150]. The mechanism of action for these ameliorative effects may involve reduction of cortical excitability through 5-HT mediated enhancement of GABAergic signaling[151]. SSRIs can also be effective in the clinical management of alcoholism, particularly in Type I or late-onset alcoholics with internalizing personality traits (e.g. low novelty seeking, high harm avoidance and high reward dependence) that are more likely to use alcohol for its anxiety-relieving and mood enhancing effects[152–154]. Together, these studies indicate that 5-HT hypofunction may contribute to the physical symptoms that occur during the early stages of withdrawal (2–8 hours). This is the likely outcome of 5-HT_{1A} autoreceptor hypersensitivity induced by chronic ethanol[69,155], which has an inhibitory effect of 5-HT synthesis and release

Here we will focus on the emotional aspects of withdrawal (e.g. anxiety, negative affect, and cravings) which together represent a powerful incentive to resume drinking and are referred to as the negative reinforcing properties of alcohol. Brain 5-HT systems are implicated in the pathophysiology of anxiety and affective disorders and continue to be one of the main targets for conventional pharmacotherapy. Ethanol-induced adaptations in 5-HT systems tend to exacerbate withdrawal-induced symptoms of anxiety and depression and may be one of the primary motivating factors that lead to relapse.

4.1. Role of 5-HT in anxiety during ethanol withdrawal

Heightened anxiety during ethanol withdrawal has been attributed to hyperactivity of brain stress systems[156], notably corticotropin-releasing factor (CRF) signaling[157–159], which has dose-dependent bi-phasic effect on 5-HT activity that is dependent on the functional balance of CRF_1 and CRF_2 receptors in the DRN[160–163]. Physical stress increases 5-HT efflux in NAc[164], possibly due to CRF-mediated increases in 5-HT neuronal firing in the DRN. In a recent study, withdrawal from chronic intermittent ethanol (CIE) was found to increase the firing rate of neurons in the dorsomedial and ventromedial portions of the DRN that are enriched in 5-HT neurons and receive limbic inputs from the CeA and the bed nucleus of the stria terminalis (BNST)[44]. It should be noted that these experiments were conducted during late withdrawal (24-h into withdrawal), so the initial decrease in 5-HT function during early withdrawal is apparently resolved by this time. This hyperactivity of $5\text{-}HT^{DRN}$ neurons appears to be critically involved in the anxiety-promoting effects of ethanol withdrawal, which are reversed by both systemic[165] and intra-DRN administration of a 5-HT_{1A} receptor agonist[166]. Furthermore, SSRIs can promote anxiety in early-onset

alcoholics that abstain from alcohol, indicating an anxiogenic role for elevated synaptic 5-HT during ethanol withdrawal in these individuals[167]. Interestingly, juvenile exposure to CIE exacerbates the anxiety associated with ethanol withdrawal[159], suggesting that anxiety may have a substantial influence over the developmental course of alcoholism in individuals that begin drinking at an earlier age.

In addition to its excitatory effects on central 5-HT neurons, ethanol withdrawal has been shown to alter 5-HT signaling in two projection areas that are critically involved in withdrawal-induced anxiety, the CeA and BNST[166,168]. The 5-HT_{2C} receptor has a well-established role in anxiety and is a likely candidate for the anxiogenic effects of 5-HT during ethanol withdrawal[169]. Numerous studies have verified that systemically administered 5-HT_{2C} receptor antagonists mitigate withdrawal-related anxiety in rodents[158,170]. Site-directed injection of a 5-HT_{2C} receptor antagonist into the CeA also attenuated withdrawal-induced anxiety[166], indicating that 5-HT_{2C} receptors in the CeA may be critically involved. However, another study found that injection of a 5-HT_{2C} receptor agonist into the basolateral amygdala (BLA), but not the CeA, exacerbated anxiety associated with cocaine abstinence[171]. These discrepant results may reflect differences in the behavioral assays that were used to measure anxiety. In the former study, social interaction was used as a measure of anxiety, while the latter study used the elevated plus maze (EPM). Taken together, these studies suggest that the CeA and BLA mediate distinct aspects of anxiety, with the CeA playing a more prominent role in anxiety with a social component. In another recent study, withdrawal from CIE selectively increased anxiety in a social approach test without affecting general anxiety in the open field[168], highlighting the unique role of alcohol as a “social lubricant”. CIE was also associated with enhanced 5-HT_{2C}R signaling in the ventral BNST which, together with 5-HT_{2C} receptor signaling in the CeA, may regulate the anxiogenic aspects of ethanol withdrawal.

As suggested above, chronic alcohol has a significant impact on the neural circuitry governing normal social functioning, resulting in social withdrawal. In zebrafish, deficits in social approach behavior were found in adults after embryonic exposure to ethanol for 7 days[172]. Human alcoholics also exhibit reductions in 5-HTT in regions of the brain that govern social cognition, including the posterior insula, posterior cingulate, and parahippocampal gyrus[173]. Alcoholics in withdrawal are also uniquely sensitive the anxiety-relieving properties of ethanol, particularly in social contexts. A recent found that in heavy social drinkers, alcohol effectively reduces coupling between the prefrontal cortex (PFC) and the amygdala[174], a pathway that has been coined the “aversive amplification circuit” in reference to its role in anxiety and negative affective bias[175]. Withdrawal from CIE also potentiates the ability of exogenously applied ethanol to increase GABAergic transmission in the DRN[44], which inhibits the activity of 5-HT neurons. Thus, ethanol withdrawal enhances sensitivity to the anxiolytic aspects of ethanol that may predispose individuals to relapse.

In summary, hyperexcitability of 5-HT neurons in the DRN during late withdrawal play a crucial role in anxiety by activating circuits in the extended amygdala via 5-HT_{2C} receptors. Pharmacological interventions that suppress 5-HT neurons or reduce excitability in the BNST and/or CeA may be effective in treating withdrawal-related anxiety. 5-HT_{1A}

receptor agonists accomplish both of these things by stimulating 5-HT_{1A} autoreceptors in the DRN and post-synaptic 5-HT_{1A} receptors in the BNST, which are primarily inhibitory and anxiolytic[176,177]. Buspirone, a partial 5-HT1AR agonist, is one such candidate that has been shown to reduce withdrawal-related anxiety in mice[44] and in human alcoholics with comorbid anxiety[178]. A similar effect may also be achieved with 5-HT_{1B} agonists, which have been shown to inhibit glutamate transmission in the BNST[179].

4.2. Role of 5-HT in anhedonia during withdrawal

The negative mood states that accompany ethanol withdrawal have been attributed to adaptations in the mesocorticolimbic pathway that occur as the result of excessive and prolonged alcohol consumption. Ethanol withdrawal leads to profound deficits in reward processing (i.e. anhedonia) that typifies clinical depression[180]. Intracranial self-stimulation (ICSS) is an operant procedure that is used to measure reward thresholds, with lower thresholds representing a hedonic state that can be brought about by drugs of abuse and higher thresholds representing an anhedonic state that can be elicited by drug withdrawal. Monoamine releasing drugs (e.g. amphetamine) that selectively target dopamine have been shown to facilitate ICSS responding and reduce reward thresholds while serotonin releasers (e.g. fenfluramine) reduce ICSS and increase thresholds[181,182], implicating 5-HT in the anhedonic states that accompany ethanol withdrawal.

In contrast to its effects on 5-HT neuronal firing and 5-HT signaling in regions of the extended amygdala (e.g. the CeA and BNST), acute ethanol withdrawal resulted in a robust and progressive decrease in extracellular 5-HT in the nucleus accumbens that is restored by subsequent ethanol intake[183]. Notably, paroxetine combined with a 5-HT_{1A} antagonist ameliorated reward deficits during amphetamine and nicotine withdrawal[184], indicating a crucial role for 5-HT in withdrawal-induced anhedonia. These serotonergic deficits may promote anhedonia directly by reducing excitatory inputs to the NAc[40] or by indirect modulation of dopamine release[185], which is also depleted during ethanol withdrawal. Deficits in dopamine function may also account for the reduced novelty-seeking that is observed during protracted ethanol withdrawal[186].

Behavioral despair, another critical component of depression, is also heightened in the forced swim test (FST) following ethanol withdrawal and has been attributed to reductions in hippocampal neurogenesis[187]. SSRIs generally increase hippocampal neurogenesis and restore normal affective and cognitive function, indicating that 5-HT hypofunction in the hippocampus may also contribute to the depressogenic effects of ethanol withdrawal. Despite these findings, sertraline was found to be generally ineffective at treating depression or alcohol consumption in alcohol-dependent subjects with comorbid depression[188], although it should be noted that none of the subjects were abstinent from alcohol, making it difficult to assess its efficacy in treating withdrawal-related depression.

In summary, it appears that ethanol withdrawal exerts divergent effects on 5-HT signaling in mesolimbic reward circuits as opposed to anxiety circuits in parts of the extended amygdala. This may reflect differences in the functional expression of CRF receptors in 5-HT^{DRN} neurons that project to these regions, or in synaptic release properties in the terminal fields themselves. The disparate roles of 5-HT in these distinct emotional aspects of

withdrawal emphasize the need for thorough clinical assessment and subtyping of alcoholics in treatment. For instance, alcoholics that present with anxiety may respond favorably to buspirone and other 5-HT_{1A} receptor agonists while those with depression may be better treated with an SSRI combined with a 5-HT_{1A} receptor antagonist.

5. Serotonin in Alcohol Cravings and Relapse

Alcohol withdrawal is typically attended by cravings for alcohol that can be primed or exacerbated by certain environmental triggers (e.g. alcohol, alcohol-related cues and contexts, stress) that in turn precipitate relapse. Monoamine depletion (i.e. 5-HT and dopamine) increased cued induced alcohol craving in alcoholics[189], suggesting that the conditions generated by alcohol withdrawal may increase sensitivity to alcohol-related cues, possibly by disinhibiting regions of the NAc associated with drug wanting (“craving”). Meta-Chlorophenylpiperazine (mCPP), a 5-HT_2 receptor agonist, also increased craving in abstinent alcoholics[190]. Several lines of evidence have implicated the medial prefrontal cortex (mPFC), a region rich in 5-HT_{2A} receptors in cue and context-induced relapse[191,192]. Recently, it was also shown that 5-HT_{2A} receptors are also enriched in glutamatergic projections from the PFC to the NAc[193], a circuit that is critically involved in behavioral sensitization to drugs of abuse[194]. Taken together, these studies indicate that enhanced 5-HT_{2A} receptor signaling in the mPFC and NAc may be an important neural substrate underlying cue and context-induced reinstatement. Accordingly, functional polymorphisms in the 5-HT_{2A} receptor enhance relapse rates in alcoholics[195].

The alcohol deprivation effect (ADE) closely models relapse by reintroducing alcohol after a period of abstinence, resulting in a temporary increase in alcohol consumption that is related to changes in the rewarding value of alcohol[196,197]. Although this issue has not been entirely resolved, recent evidence suggests that ADE may be driven by an increase in the reinforcing properties of ethanol as indicated by an increase in the breakpoint in a progressive-ratio schedule of reinforcement[198]. One potential neural substrate underlying this effect is the 5-HT_{2C} receptor in the NAc, which is upregulated following CIE in mice[40]. Accordingly, acute administration of SSRIs reduce ADE[199], possibly by suppressing midbrain dopamine activity. On the other hand, chronic treatment with SSRIs potentiated ethanol intake. One possible explanation is that chronic SSRI treatment leads to the development of tolerance to the dopamine suppressing effect and facilitation of 5-HT_{2C} receptor mediated reward signaling in the NAc.

Pharmacological manipulations that inactivate 5-HT neurons in the median raphe nucleus (MRN) can also precipitate reinstatement of alcohol seeking behavior in rodents in the absence of environmental cues, indicating a critical role for these neurons in mediating relapse[200,201]. Given the role of the MRN in promoting stress resilience[202], 5-HT^{MRN} neurons are likely involved in relapse triggered by environmental stress. 5-HT^{MRN} projections to the hippocampus, for instance, suppress hippocampal theta rhythms generated by conditioned aversive stimuli[203]. In agreement with this, both fluoxetine and dexfenfluramine attenuate footshock induced reinstatement to alcohol seeking behavior[204,205]. Blockade of 5-HT_3 receptors also attenuated stress-induced reinstatement. At the presynaptic level, 5-HT_3 receptor antagonism would reduce local 5-HT release in the

DRN, releasing 5-HT^{DRN} neurons from 5-HT$_{1A}$ receptor mediated inhibition. This would tend to increase 5-HT release in regions that promote stress resilience and have an inhibitory effect on stress-induced relapse.

Alternatively, 5-HT$_3$ receptor antagonists may prevent stress-induced relapse via interactions with dopamine systems. Previous studies have shown footshock promotes relapse via enhance dopamine signaling[206]. 5-HT$_3$ receptor antagonists specifically inhibit stress-induced dopamine release in NAc and frontal cortex[207–209] and thus represent a promising target for pharmacological treatment of alcoholism[210,211].

6. Conclusion

Overall, 5-HT has widespread influence over the neural circuits governing all aspects of alcohol dependence, from the early stages of binge and intoxication to the later stages of withdrawal and relapse. Despite preclinical evidence indicating that SSRIs reduce ethanol intake, clinical studies have indicated that their usefulness is limited, particularly in early-onset alcoholics. On the other hand, SSRIs may improve the early symptoms of withdrawal, which are comprised mostly of physical symptoms, but they can exacerbate anxiety during late withdrawal that may lead to relapse. Given that SSRIs are widely prescribed in the treatment of anxiety and depression, caution should be exercised in prescribing these drugs to patients with a history of alcohol dependence. In general, the heterogeneity of alcohol use disorders coupled with the complexity of 5-HT systems suggests that serotonergic agents may differentially modulate neural systems involved in distinct phases of the addiction cycle. As such, drugs that reduce ethanol intake during the binge/intoxication stage may not be beneficial in the management of withdrawal symptoms and relapse, and vice versa. For instance 5-HT$_{2C}$ receptor agonists generally decrease ethanol consumption and may be beneficial for non-dependent drinkers, but they have the potential to exacerbate anxiety during withdrawal and may precipitate relapse. 5-HT$_{1A}$ receptor agonists, on the other hand, may exacerbate drinking in non-dependent subjects but reduce anxiety during withdrawal, making this a useful adjunct for patients that use alcohol to self-medicate for anxiety. On the other hand, 5-HT$_3$ receptor antagonists have proven beneficial during the early phases of binge drinking and in the prevention of stress-induced relapse, making this a more versatile drug that may hold promise for the treatment of alcoholism.

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