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Review Article

Rationale for use of aripiprazole for alcohol dependence treatment

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Abstract

Given the broad implications for alcoholism in many societies, the major aims of drug development in the field of pharmacotherapy for alcohol dependence involve finding medications that are effective complements to behavioral interventions without limiting side effects. At present, only two drugs are approved as antidipsotropics in the United States. Previous findings for dopaminergics in general and antipsychotics in particular, indicated promise in reducing alcohol use, yet their utility is limited by unpleasant or life-threatening side effects. Animal and human data suggest that aripiprazole –a dopamine/5-HT system stabilizer– possesses several important mechanisms of action that target specific dopamine and 5-HT receptors, with a more acceptable side effect profile. Based on aripiprazole's multidimensional mechanism of action, it is suggested that the medication may be a worthwhile candidate to test in an alcohol-dependent sample.

Introduction

Alcoholism affects most societies, and the World Health Organization (WHO) estimates that approximately 62 million people suffer from alcoholism worldwide (1). The impact of alcohol use in the United States is extensive. Almost 14 million American adults abused alcohol or were dependent on it in 1992, and approximately 10% of Americans will be affected by alcohol dependence sometime during their lives (2-4). As a result, alcohol use, abuse and dependence in the U.S. contribute to over 100,000 lives lost per year, with an estimated economic burden of $165.5 billion in 1995 (1, 5).

Alcoholism is a chronic disease influenced by genetic, psychosocial and environmental factors. Alcoholics cannot control their drinking, even when it results in adverse medical conditions, personal or professional losses. At present, treatment is limited, consisting primarily of psychological, social and pharmacotherapeutic interventions (6). Although treatment outcomes have improved for some, much work remains to address unsuccessful treatment for many others (7).

Studies consistently demonstrate the importance of dopamine for the reinforcement and reward associated with chemical dependence, including alcoholism (8). However, most pharmacotherapy trials for treating alcohol dependence have focused on indirect-acting agents that moderate dopamine, such as opiate antagonists, serotonergics, glutamatergics or medications with mixed mechanisms of action (*e.g.*, topiramate). While recent studies in animals and humans consistently suggest that dopaminergic agents may be an important class of pharmacotherapies for alcohol dependence, side effects have limited their use (9). Finding drugs that directly influence the dopamine system with minimal side effects may represent significant future additions to the pharmacotherapy armamentarium of clinicians for alcohol dependence treatment.

Currently approved medications

Inroads to the successful introduction of pharmacological interventions for alcohol dependence have been slow. At present, two medications are approved by the U.S. Food and Drug Administration (FDA) for the treatment of alcohol dependence: disulfiram and naltrexone. Disulfiram was approved by the FDA in 1950 and is an irreversible acetaldehyde dehydrogenase inhibitor that blocks the normal metabolism of alcohol, creating acetaldehyde overload and resulting in hypotension, flushing and vomiting. Fuller and colleagues (10) compared 1 and 250 mg of disulfiram to placebo in a large group of veterans. Though there were no significant differences between the groups, if relapsed, those who took the 250 mg dose of disulfiram subsequently drank less. Notably, regardless of group, those who were compliant with taking their medication drank significantly less.

The second drug, naltrexone, approved in 1994, is a β-endorphin antagonist and has been broadly studied for alcohol dependence since the early 1990s. When challenged with alcohol, β-endorphin release disinhibits GABAergic neurons that normally tonically inhibit dopamine neurons. These dopamine neurons project to the nucleus accumbens (NA) via the ventral tegmentum. Naltrexone blocks this pathway. The clinical result is an attenuation of positive reinforcement and reward in some individuals who have a predisposed dysregulatory response to β-endorphins facilitated by alcohol (11, 12). Naltrexone has been reported to reduce the positive effects of alcohol (13), and measures of craving or the urge to drink in heavy drinkers (14). Several studies report naltrexone have reported it to be more effective than placebo in reducing relapse rates and decreasing the percentage of drinking days (15-17), yet other studies have failed to demonstrate a significant difference compared to placebo (18, 19). Given that the findings from studies with disulfiram are mixed and treatment effects for naltrexone are small at best, the need for discovering medications that provide more effective treatments for this patient population is substantial (20, 21).

Other medications are also currently being tested. Used in Europe for almost 20 years, acamprosate has been consistently demonstrated to be significantly better than placebo in reducing drinking frequency and cumulative drinking days (20). Acamprosate is not approved in the U.S., however results from a large trial should provide the data necessary for FDA consideration (22). Several other medications, such as topiramate (23) and ondansetron (24), are also currently being evaluated for the treatment of alcohol dependence.

Dopaminergic mechanisms and agents in alcohol dependence

An extensive literature supports the involvement of dopamine in motivation, reward and reinforcement (8). Litten and Allen (25), in a review of medications for alcohol dependence treatment, suggested that the potential of dopaminergics to reduce alcohol consumption remains largely unexplored. A strong body of evidence suggests that alcohol activates dopamine release at the nucleus accumbens and surrounding extended amygdala (26). The action of alcohol on the mesolimbic dopaminergic reward pathway is considered to be strongly associated with susceptibility to alcoholism, and the development of craving and loss of control (27, 28). The psychological dependence on alcohol is attributed to the acquisition of excessive motivational properties associated with alcohol-related cues (8, 29). Indeed, the action of medications such as naltrexone, and even ondansetron, to reduce drinking, ultimately modulates dopamine release (30, 31).

Dopaminergics in animal and human studies

Growing evidence focuses on dopamine agonists and antagonists, reflecting the importante of the dopaminergic system and the reinforcing effects of alcohol. In genetic animal models of alcoholism, reduced dopamine levels and dopamine D_2 receptor populations have been found in alcohol-preferring rats (32, 33). The behavioral significance is supported by decreased ethanol self-administration in rats following administration of dopamine antagonists (34) or blockade of dopamine receptors in the nucleus accumbens (35). Similarly, after administration of the D_2 agonists bromocriptine and quinpirole, declines in alcohol intake in alcohol-preferring and high-alcohol-drinking rats were also demonstrated (36, 37).

Studies in humans provide additional support for a relationship between alcohol dependence and dopamine function. In alcoholics, postsynaptic receptor function has been assessed by measuring growth hormone levels in response to the D_1 and D_2 receptor agonist apomorphine. Subsequent to apomorphine administration, maximum growth hormone response was significantly reduced in alcoholics who were abstinent for 2 months and more than 6 years compared to the control group (38, 39). Growth hormone response to apomorphine challenge has also been compared in controls and alcoholics who were either family history-positive (FHP) or family history-negative (FHN) for alcoholism (40). A blunted growth hormone response in the FHP but not FHN group was significantly different compared to the placebo group. As a result of this line of research, it is suggested that reduced dopamine D_2 receptor function may be a marker for alcoholism (39).

Antipsychotics used for the treatment of alcohol dependence

Both reward prediction associated with alcohol cues that influence dopamine release by the mesolimbic pathway and salient attribution to irrelevant stimuli interpreted as positive symptoms of schizophrenia seem to share similar dopaminergic dysfunction (41). Potentially, this

relationship may explain the disproportionate prevalence of comorbid substance abuse and schizophrenia when compared to the general population (4). The use of antipsychotics in alcoholics may therefore signify the correlation of an important common pathway affecting both disorders.

Dopamine antagonists such as haloperidol, tiapride, olanzapine and clozapine have all demonstrated various degrees of efficacy, such as reducing craving and alcohol consumption or increasing abstinence (42-45). In a double-blind, placebo-controlled trial involving 16 participants diagnosed with alcohol abuse or dependence, patients were pretreated with either saline or the D_2 antagonist haloperidol (42). Measures of craving and impaired control were significantly reduced in the group using the D_2 antagonist. The efficacy of tiapride, another D_2 antagonist, was demonstrated in a placebo-controlled clinical trial, as drinking levels of 54 alcohol-dependent participants in the group receiving tiapride were significantly lower than in the placebo group (43). Olanzapine, a $D_2/D_4/5\text{-}HT_2$ antagonist, also reduces craving for alcohol. Although a dose of 5 mg of olanzapine did not influence the rewarding effects of alcohol, it did moderate alcohol cues and the urge to drink (45, 46). In a subsequent study in 67 participants, compared to cyproheptadine, olanzapine reduced craving after exposure to alcohol cues and after a priming dose of alcohol for participants with a D_{4L} receptor variant only (47). Clozapine, the original atypical neuroleptic, is a medication with multiple actions on D_1, D_2 and D_4 receptors, as well as 5-HT, adrenergic, cholinergic and histamine systems. In a retrospective study in 151 schizophrenic patients with alcohol and drug use disorders, 36 of whom received clozapine, 79% of the patients who received clozapine were in remission from a diagnosis of alcohol use disorder for 6 months or longer, while just over 33% of those not taking clozapine were in remission (45).

Side effects of dopaminergics

Although recent studies in animals and humans provide evidence that dopaminergic agents may be an important class of pharmacotherapy for alcohol dependence, side effects have limited their use (9). Neurological movement disorders occur with haloperidol, tiapride may induce neurological side effects, neuroleptic malignant syndrome and increase the likelihood of seizures, olanzapine has been associated with significant weight gain, increased triglyceride levels and diabetes, and clozapine is associated with weight gain and agranulocytosis (48-53). Furthermore, the use of certain antipsychotics with substantial side effects by schizophrenics may actually contribute to greater substance use in an effort to self-medicate (54, 55). The importance of dopamine in the addiction process, however, would suggest that treatments using dopamine antagonist-type medications with more acceptable side effect profiles may constitute an important area for future research.

Pharmacology of partial dopamine agonists

A fairly new class of drugs known as partial dopamine agonists (PDAs) shows high binding affinity for dopamine receptors but low intrinsic activity (56). Under conditions of hyperdopaminergic tone, dopamine agonists block the majority of available dopamine, while under conditions of hypodopaminergic tone, dopamine agonists facilitate some dopamine stimulation of the receptors (57). In short, the action of this class is variable depending on the substrate and level of dopaminergic synaptic activity.

Partial dopamine agonists and effects on drinking

The actions of PDAs on substance use have been studied in animal models. Terguride, for example, was shown to act as a dopamine receptor antagonist in rats trained to self-administer cocaine (58). Terguride also blocks amphetamine self-administration in rats (59) and cocaine- and food-maintained behavior in monkeys (60). Consistent with the reduction in reinforcement associated with other drugs, terguride also significantly reduces ethanol intake in rats, suggesting that PDAs reduce the reinforcing effects of ethanol in rats (58). The unique mechanism of PDAs may become even more important under conditions of a rebound reduction of dopaminergic activity in the mesolimbic area that may be associated with ethanol abstinence (61, 62). Partial dopamine agonists may provide a means to reverse dopamine depletion observed during ethanol abstinence, and because of their flexible activity, may represent a novel strategy for normalizing dopamine neurotransmission along the behavioral continuum of alcoholism (58).

Serotonergic (5-HT) mechanisms and agents in alcohol dependence

The effect of alcohol on 5-HT

Studies of the role of 5-HT in the effects of alcohol in the brain show that alcoholics and experimental animals that consume large amounts of alcohol show differences in levels of 5-HT compared to nonalcoholics (63). Considerable experimental evidence suggests that 5-HT plays a crucial role in the impulsivity and craving often seen in alcoholics (64), and is at least in part responsible for alcohol dependence (65, 66). Several hypotheses suggest a relationship between 5-HT and alcoholism (67). For example, impulsive alcohol use is associated with hyposerotonergic levels and increased dopamine activity (65); symptoms of anxiety may be related to hyposerotonergic states that underlie the use of alcohol to self-medicate (68); the use of alcohol to increase 5-HT activity in a hyposerotonergic brain may interact with dopamine and contribute to the rewarding properties of alcohol (69); and medications that affect 5-HT might have an effect on appetite behavior through the renin-angiotensin system (67).

Differences in alcohol use may be related to subtypes of 5-HT receptors: reward, consumption, tolerance and reinforcement

Several 5-HT receptors have been shown to contribute to alcohol use in animals (63). Moreover, in humans, in addition to and operating concurrently with dopamine release, alcohol has complex actions in the brain through numerous sub-types of 5-HT systems (70). Relative to alcohol, 5-HT_{1A} receptors may be associated with alcohol consumption and the development of tolerance, 5-HT_2 receptors may contribute to reward, and 5-HT_3 receptors may be involved in the development of reinforcement through synaptic projections on the mesolimbic dopamine system (63). Alcohol increases brain levels of 5-HT, affecting these receptors. In addition, the 5-HT metabolite 5-hydroxyindoleacetic acid (5-HIAA) has been found to be lower in the cerebrospinal fluid of individuals with suicidal behavior, impulsivity, depression and alcoholism, suggesting a potential role for dysregulation of 5-HT in some alcoholics (71, 72).

Perhaps because of the multiple 5-HT receptor subtypes, studies using serotonergic medications have provided mixed results. For example, although buspirone is a dopamine D_2 antagonist, its primary action is as a 5-HT_{1A} partial agonist with anxiolytic properties. As noted, 5-HT_1 receptors may be involved in alcohol consumption, intoxication and tolerance (63). While studies have reported that subjects receiving buspirone scored significantly better than placebo on alcohol use measures (68, 73, 74), patients also suffered from coexisting anxiety disorders. When results were controlled for these disorders, buspirone was no more effective than placebo (75). Reviews therefore suggest that the results of trials using buspirone are inconclusive (20, 76).

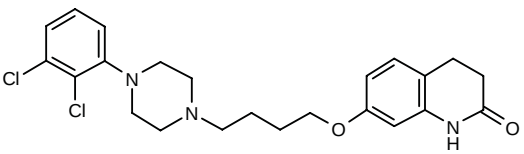
Results of clinical trials using serotonin specific reuptake inhibitors (SSRIs) have in general also been mixed (20). Despite reductions of drinking in lab studies with experimental animals, in human drinking sessions and in alcoholics with major depression, most double-blind placebo-controlled studies using SSRIs have not reduced drinking or improvement in any other relevant measures (77-79). Recent research suggests, however, that subtypes of alcoholics may respond differently to SSRIs. For example, although Kranzler and colleagues (80) demonstrated that 60 mg of fluoxetine was no better than placebo in reducing alcohol consumption, two alcoholic subtypes –type A and B– were found to respond differently to the medication: type A not at all and type B was made worse. Type A has a later onset of dependence (after 25 years of age), few pathological or drinking-related problems or childhood risk factors. The type B alcoholic is an early-onset type occurring before the age of 25, with more severe psychopathology, antisocial and impulsive tendencies, childhood risk factors and significant problems with alcohol. As an extension of the previous study (80), Pettinatti *et al*. used 200 mg of sertraline and initiated the study by subgrouping alcoholics a priori into early- and late-onset groups (81). This study confirmed that early-onset alcoholics actually drank significantly more when taking SSRIs, but the results conflicted with the Kranzler study (80), and demonstrated that late-onset alcoholics drank significantly less. Again this finding suggests that different subtypes of alcoholics may respond differently to serotonergics.

Some individuals who become alcohol-dependent before the age of 25 years, with a family history-positive genetic link for alcohol dependency, may be more prone to have a homozygous variant of a 5-HT transporter (SERT), resulting in more rapid 5-HT removal and attenuated dopaminergic function (82). Ondansetron, a 5-HT_3 antagonist and antiemetic, has functionally opposite affects to SSRIs and blocks 5-HT, and has been reported to be a potentially new treatment for the same biologically predisposed group (type B) who do not respond to SSRIs. 5-HT may increase the rewarding effects of alcohol by its action at 5-HT_3 receptors. One theory suggests that robust homozygous variant SERT reuptake in early-onset alcoholics removes 5-HT from the synapse three times faster than normal, contributing to an upregulation of 5-HT_3 receptors. These postsynaptic receptors synapse on ventral tegmental dopaminergic neurons, projecting to the nucleus accumbens via the mesolimbic tract. With alcohol use in predisposed individuals, the result is an increased release of dopamine, associated with facilitated reinforcement. A 5-HT_3 antagonist blocks 5-HT_3 receptors, decreasing dopamine release and reinforcement (82). The clinical outcome of this effect is hypothesized to be a downregulation of the dopaminergic neurons that project to the nucleus accumbens, enhanced dopaminergic function and decreased reward from alcohol use (83).

Initial studies suggest that ondansetron and theoretically other 5-HT_3 antagonists may be important adjunctive treatments for the early-onset alcoholic subgroup. Based on previous studies using SSRIs (80, 81), Johnson *et al*. (83) subtyped their participants a priori into groups of early- or late-onset alcoholics, and compared placebo to subtherapeutic doses of 1, 4 and 16 μg/kg twice a day of ondansetron. The findings demonstrated that the group taking the dose of 4 μg/kg drank significantly less than the placebo group. In sum, as demonstrated in studies with serotonergics, the variable responses based on individual characteristics such as age of onset of alcoholism suggest that alcoholics may respond differently based on various 5-HT subtypes.

Aripiprazole: partial dopamine agonist and mixed 5-$HT_{1A/2A}$ receptor medication

Aripiprazole [I] is approved in the United States for schizophrenia (84). The compound exhibits high affinity for dopamine D_2 and D_3, 5-HT_{1A} and 5-HT_{2A} receptors (K_i = 0.34, 0.8, 1.7 and 3.4 nM, respectively), moderate affinity for dopamine D_4, 5-HT_{2C} and 5-HT_7, α1-adrenergic and histamine H_1 receptors (K_i = 44, 15, 39, 57 and 61 nM, respectively), and moderate affinity for the 5-HT



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reuptake site (K_i = 98 nM). Aripiprazole has no appreciable affinity for cholinergic muscarinic receptors (IC_{50} > 1000 nM). Aripiprazole functions as a partial agonist at dopamine D_2 and 5-HT_{1A} receptors, and as an antagonist at the 5-HT_{2A} receptor (84).

Pharmacokinetics of aripiprazole

The activity of aripiprazole is presumed to be due primarily to the unchanged compound and to a lesser extent to its metabolite dehydroaripiprazole (DAPZ), which has an affinity for D_2 receptors similar to aripiprazole. The mean half-lives of aripiprazole and DAPZ are 75 and 94 h, respectively. Steady state is reached in 14 days. Aripipirazole is well absorbed and can be given with or without food. Elimination is primarily via the hepatic enzymes CYP2D6 and CYP3A4. Because of the effect of these cytochrome P-450 isozymes, drug-drug interactions may occur (*i.e.*, drugs that inhibit CYP3A4 or CYP2D6 isozymes will inhibit aripiprazole elimination and increase blood levels; drugs that induce CYP3A4 or CYP2D6 isozymes could increase aripiprazole metabolism, resulting in lower blood levels). Despite these theoretical interactions, there is little evidence that aripiprazole causes any clinically significant interaction with other drugs metabolized by cytochrome P-450 isozymes (83). In general, no dose adjustment is required based on the age of the patient, gender, race, smoking status, hepatic or renal function.

Aripiprazole is a partial dopamine agonist

As with many other typical and atypical antipsychotics, aripiprazole binds with high affinity to the D_2 family of receptors (85). The action of aripiprazole contrasts with currently marketed dopaminergics, however, as it may exert its effects through a partial agonist effect at dopamine D_{2L} autoreceptors (86, 87). As noted (88), reduced D_2 function may play a key role in alcoholism. Aripiprazole administration in rats results in decreased extracellular dopamine levels and release in the frontal lobe and striatum (89), consistent with presynaptic agonism. Aripiprazole also displays dopamine-antagonist properties, and was found to block apomorphine-induced stereotypy and locomotor activity in rats (85). While no studies in animals or man have tested the utility of aripiprazole for the treatment of alcohol dependence, other PDAs have been shown to reduce stimulant and alcohol use in animals (58, 59, 90).

Aripiprazole is a mixed 5-$HT_{1A/2A}$ receptor medication

The prefrontal cortex contains a robust population of 5-HT_{1A} and 5-HT_{2A} receptors, located principally on pyramidal neurons (87). Aripiprazole is both a partial agonist at presynaptic 5-HT_{1A} receptors, associated with an anxiolytic action, and a 5-HT_{2A} receptor antagonist, an effect associated with improvements in cognition and control of agitation, aggression and depression. However, it does not have a significant 5-HT_{2C} receptor-antagonist effect, which is associated with weight gain such as with clozapine and olanzapine (91-94). 5-HT_{2A} receptors are abundant in the limbic forebrain, frontal cortex and nucleus accumbens (95). Chronic administration of most antidepressants with 5-HT_{2A}-antagonist activity induces downregulation of 5-HT_{2A} receptors, believed to be an important mechanism of action of these drugs (95). Aripiprazole is also an inverse agonist at the 5-HT_{2B} receptor (87), an action known to be beneficial in the treatment of migraine headaches (96). Notably, a direct agonist effect at this receptor has been implicated in valvular heart disease associated with the weight loss drug dexfenfluramine (97).

Multiple 5-HT_1 and 5-HT_2 receptors have been implicated in the reinforcing effects of alcohol. For example, amperozide, a 5-HT_{2A} antagonist, was found to cause persistent and irreversible suppression of alcohol intake in both cyanamide-induced and genetically selected alcohol-preferring and high-alcohol-drinking rats (98). Although in humans ritanserin, a nonspecific 5-HT_2 antagonist, was not significantly better than placebo in 423 alcohol-dependent patients, generalization to the entire class of 5-HT_2 antagonists, particularly those with broader mechanisms of action, should not preclude future research in this area (99). In rats, drugs that are considered second-generation amperozide-like drugs with both 5-HT_2 receptor-antagonist and 5-HT_{1A} receptor-agonist properties have also demonstrated the ability to decease acute ethanol reinforcement (94, 100,101). Alcohol drinking was significantly reduced in rats administered the mixed 5-HT_{1A} agonist/5-HT_{2A} antagonist FG-5893. Moreover, another 5-HT_{1A} agonist/5-HT_{2A}antagonist, FG-5938, also significantly reduced alcohol drinking in alcohol-preferring rats. These data suggest that compounds that are both 5-HT_{1A} agonists/5-HT_{2A}antagonists may be valuable therapeutic agents for the treatment of alcoholism.

Aripiprazole side effect profile compares favorably to other neuroleptics

Unlike the previously noted dopaminergics used in alcohol treatment studies, because of its unique mechanism of action, aripiprazole causes few extrapyramidal

side effects. In both short- (4 weeks) and long-term (52 weeks) trials comparing aripiprazole to haloperidol, aripiprazole was associated with fewer extrapyramidal side effects and lower tardive dyskinesia scores (102, 103). Aripiprazole also lacks strong histaminic activity suspected of causing sedation (104). In addition, aripiprazole causes relatively little elevation in prolactin levels, Q-T_c prolongation (102, 105) or weight gain in patients. Weight gain has been postulated to be associated with a polymorphic allele of the 5-HT_{2C} receptor (106), and aripiprazole is a partial agonist at this receptor, an action associated with antiobsessional and anorectic actions in humans (87). In a 28-week trial comparing olanzapine and aripiprazole, patients treated with aripiprazole lost weight on average and patients in the olanzapine group gained weight (107). Moreover, certain medications that cause weight reduction may also reduce alcohol consumption, such as naltrexone, topiramate and cannabinoid antagonists (15, 23, 108-110). While an important antipsychotic of last choice, a major limiting factor for clozapine use is the risk for agranulocytosis. Notably, the risk of agranulocytosis with aripiprazole is no greater than for the typical neuroleptics (104). While not innocuous, the most common side effects reported with aripiprazole include headache, weakness, nausea, vomiting and constipation. Other serious side effects reported with aripiprazole, while rare, include neuroleptic malignant syndrome and tardive dyskinesia (84).

Conclusions

The search for ideal medications to treat alcohol dependence seeks to attain qualities such as blocking the reinforcing effects of alcohol and reducing craving with minimal side effects (111). Although not discussed, pharmacogenomic research is beginning to provide greater understanding and insights into potential therapies that will target various alcoholic subtypes, providing more specific treatments. Given the extant literature, considerable evidence suggests that both PDAs and mixed 5-$HT_{1A/2A}$ receptor drugs independently show significant efficacy in reducing alcohol use in both animals and humans, without the limiting side effects associated with other closely related neuroleptics. Overall, these data indicate that aripiprazole and similarly acting drugs in development for schizophrenia, such as bifeprunox (112), which act as dopamine/5-HT system stabilizers (113), approach the optimal characteristics sought in medications to be considered for future testing in the treatment of alcohol dependence. Questions regarding aripiprazole's efficacy and effect on craving remain to be addressed in future alcohol dependence treatment trials.

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