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Aripiprazole for relapse prevention and craving in alcohol use disorder: current evidence and future perspectives

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**ABSTRACT**

**Introduction:** Among other approaches, the modulation of the dopaminergic pathway has been advocated in the therapeutic management of Alcohol Use Disorders (AUD). A potential avenue toward the modulation of the dopaminergic pathway across varying substance disorders seems to be provided by aripiprazole, a second-generation antipsychotic characterized by a peculiar pharmacodynamics signature.

**Areas covered:** In this review, the authors provided a qualitative synthesis and a critical perspective on the efficacy of aripiprazole in relapse prevention and craving in AUD. A systematic search was carried out through MEDLINE/Embase/PsycINFO/Cochrane Library from inception until September 2015, combining free terms and MESH headings for the topics of AUD and aripiprazole as following: ((((Alcohol use Disorder) OR (Alcohol use)) AND aripiprazole).

**Expert opinion:** Based both on a qualitative synthesis and a critical interpretation of the evidence, the authors submit that aripiprazole would promote alcohol abstinence and reduce the alcohol seeking behaviour possibly via dopaminergic and serotonergic modulations at the fronto-subcortical circuits underpinning alcohol reward and craving, impulsive behaviour as well as reduce alcohol-related anxiety/low mood and anhedonia. However, due to the lack of published studies, a conclusive statement about any direct effect of aripiprazole in the prevention of craving and/or alcohol consumption is not possible.

1. Introduction

Addictive disorders, including substance use disorders (SUD) share common neurobiological underpinnings for reward, yet differing with regard to specific effects on neurotransmitters, despite a substantial converge on a common circuitry at the limbic system.\cite{1} Heterogeneous mechanisms of action involving glutamate, gamma-aminobutyric acid (GABA), serotonin, endogenous opioids, and endocannabinoids have been accounted in the neurobiology of alcohol use disorders (AUD). In addition, considerable evidence emphasizes the crucial role of dopaminergic projections of the ventral tegmental area (VTA) of the midbrain to the nucleus accumbens (NAc) pathway in increasing overall dopaminergic transmission, thus mediating the acute rewarding effects of alcohol as well as the chronic changes in reward associated with addiction.\cite{2}

The dopaminergic system is prominently involved in the prediction or anticipation and motivation components of reward.\cite{3} According to the incentive-sensitization theory proposed by Robinson and Berridge,\cite{4} drug addiction and craving may occur due to a sensitization of the mesolimbic dopaminergic system. The intake of addictive drugs may determine long-lasting structural changes in the brain architecture (‘neuroadaptation’) which may be responsible of a sensitization of those brain systems involved in the process of incentive salience/motivational (or drug ‘wanting’) subcomponent of the reward.\cite{4,5}

Furthermore, it has been reported that dopamine fibers projecting from the VTA to the NAc are activated in response to unpredicted rewards\cite{6} and in response to cues that predict rewards. These observations suggest that dopamine may mediate the process by which the positive incentive value is transferred from the actual reward to the cues that predict it.\cite{6} Therefore, dopamine in the ventral striatum appears to be implicated in the reinforcement learning of rewards, as it regulated the prediction and anticipation of rewards.\cite{7} Ventral striatal dopamine also mediates the motivational component of reward. Indeed, depletion of dopamine in the NAc or treatment by dopamine antagonists have been demonstrated to decrease behavioral responses for large reward, although increasing responses for smaller rewards.\cite{8} The studies so far conducted indicate that ventral striatal dopamine...
should be necessary to provide incentive motivation for rewards when the efforts required obtaining them is increased. These effects are mediated by both D<sub>1</sub> and D<sub>2</sub> dopamine receptors, since knockout of both these receptors has been associated to increased anhedonia. Deficits in dopamine neurotransmission in the ventral striatum may impair reinforcement learning, that is: prediction and anticipation of rewards, and may disrupt motivation to obtain large but too demanding rewards, which translates in increased avolition conducts.

Specifically, a three-pathway psychobiological model of craving was proposed for alcohol.[10] This multi-factorial model (i.e. neurobiological and psychological factors) of craving for AUD suggests three craving pathways: reward, relief and obsessive. Reward craving (i.e. desire for the rewarding, stimulating and/or enhancing effects of alcohol) may result from either dopaminergic/opioidergic dysregulation or a reward seeking personality style or a combination of both.[10] Relief craving (i.e. desire for the reduction of tension or arousal) may result from either GABAergic/glutamatergic dysregulation or a stress reactivity personality style. While an obsessive craving (i.e. a lack of control over intrusive thoughts about drinking) is mediated either by a serotonin deficiency or a disinhibiting/low constraint personality style.[10] According to this model, some medications in the field of anti-craving drug therapy were also proposed.[11]

Stating the crucial role of dopaminergic transmission, it is therefore unsurprising that both dopamine agonist, partial agonist and antagonist drugs have been proposed also for the management of AUD.[12] Among other classes of drugs, second generation antipsychotics (SGAs) have been proposed for SUD, including AUD,[13] with evidence in support of the practice.[14,15] In contrast to the SGAs, first generation antipsychotics (FGAs) have been associated with negative findings and a higher risk of relapse when compared with placebo, especially for flupentixol.[16]

FGA are predicted to induce a severe perturbation of dopamine neurotransmission in the striatum. FGAs are potent and relatively selective blockers of D<sub>2</sub> receptors, reaching high level of striatal D<sub>2</sub> receptor occupancy even at intermediate-low doses. It has been observed that striatal D<sub>2</sub> receptors mediate ‘No-Go’ behaviors, while alcohol consumption increases dendritic branching and AMPA receptor activity in D<sub>1</sub>-expressing striatal neurons.[17] Notably, blockade of D<sub>1</sub> but not D<sub>2</sub> receptors attenuates alcohol consumption.[17] In addition, low striatal dopamine release and D<sub>2</sub> receptor binding has been reported in brain imaging studies in AUD.[18] Low dopamine binding to D<sub>2</sub> receptors has been demonstrated to be predictive of increased craving for alcohol and greater propensity to relapse.[19]

Taken together, these reports let hypothesize that antipsychotic agents with high D<sub>2</sub> receptor blocking potential could induce a state of iatrogenic low striatal dopamine release and low dopamine binding to D<sub>2</sub> receptor, which may interfere with reward processes on one side and may per se increase craving on the other. Conversely, the great part of SGA has lower D<sub>2</sub> receptor blocking propensity, reaching therapeutic efficacy at lower levels of striatal D<sub>2</sub> receptor occupancy.[20]

Moreover, some of the SGA are regarded to provide a loose binding to D<sub>2</sub> receptors (a phenomenon known as fast-dissociation).[20] Furthermore, their antagonistic activity at 5-HT<sub>2A</sub> receptors reduces the dopaminergic transmission, by suggesting that SGA could less potently affect reward processes, thus preventing craving to occur.

Nonetheless, stating the relatively recent introduction of the SGA class, characterized by low dissociation constants and high 50% fast-off time[20] and their off-label use in the management of SUD, little is known on the matter, especially concerning the most relatively recently introduced compounds, as aripiprazole.

Aripiprazole is the first 5-HT<sub>1A</sub> and D<sub>2</sub> partial agonist introduced in the SGA class (Box 1). It also displays a high binding affinity for the D<sub>2</sub>, 5-HT<sub>1A</sub>, 5-HT<sub>2A</sub>, 5-HT<sub>2B</sub> and 5-HT<sub>7</sub> receptors, and limited/negligible affinity for D<sub>1</sub>, D<sub>3</sub>, D<sub>4</sub>, 5-HT<sub>1B</sub>, 5-HT<sub>3</sub>, 5-HT<sub>6</sub> subtypes and serotonin transporter. Affinity is only moderate at 5-HT<sub>1D</sub> and 5-HT<sub>2C</sub> receptors. Aripiprazole has also moderate affinity at adrenergic α<sub>1A</sub>, α<sub>1B</sub>, α<sub>2A</sub> and α<sub>2C</sub> receptors and at histaminergic H<sub>1</sub> receptors. Affinity is negligible at cholinergic, GABAergic, glutamatergic, and opioidergic receptors.[13,21,22] It has been reported to occupy approximately 95% of D<sub>2</sub> receptors in the striatum.[23] Aripiprazole has variable biological effects, depending on the biological system taken into account and on the levels of competing dopamine. Accordingly, it may act as a prevalent D<sub>2</sub> receptor antagonist when the synaptic levels of dopamine are elevated and as a prevalent D<sub>2</sub> receptor partial agonist when the levels of dopamine are low.[24] This biphasic mechanism may depend on the prevalence of agonistic 5-HT<sub>1A</sub> receptors-mediated effects at low doses and the prevalence of inhibition of mesocortical dopaminergic neurons activity at high doses.[24] The peculiar effect exerted by aripiprazole could be underpinned by its effect in stabilizing dopamine receptors through a modulation of functioning, rather than their sole blockade or stimulation. As both cortical (prefrontal) and dorsal striatal mechanisms are involved in the reward, aripiprazole may own a promising mechanism to modulate impulsiveness, mood and anxiety as well as the craving swings usually observed in patients with AUD.

The use of aripiprazole in AUD has been also documented in animal models of alcohol with both evidence in support and

<table>
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<th>Box 1. Drug summary</th>
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<tr>
<td><strong>Drug name</strong></td>
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<tr>
<td><strong>Phase</strong></td>
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<td><strong>Indication</strong></td>
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<td><strong>Pharmacology</strong></td>
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<td><strong>Route of administration</strong></td>
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<tr>
<td><strong>Chemical structure</strong></td>
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<tr>
<td><strong>Pivotal trial(s)</strong></td>
</tr>
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Aripiprazole is effective in reducing locomotor activity,[25,26] but only at a notably higher dose or after repeated treatment.[25] In addition, mice pre-treated with aripiprazole, showed a decreased hyperlocomotion in the presence of ethanol compared to placebo.[26] Furthermore, it is able to reduce or abolish anxiety-like behaviors and ethanol-induced place preference as well as produce an overall decrease in drinking behaviors.[27] A preclinical animal model of chronic alcohol self-administration demonstrated that oral administration of aripiprazole (1, 3, and 10 mg/kg) on 4% alcohol intake reduced alcohol consumption, significantly only at 10 mg/kg \( p < 0.01 \). This study reported that chronic alcohol intake would increase aripiprazole exposure, by suggesting that aripiprazole dose might have to be decreased.[28]

Moreover, thought rigorous and updated, the most recent systematic review and meta-analysis about the use of SGA, including aripiprazole, in the treatment of AUD, adopted stringent inclusion and exclusion criteria, namely, ‘RCTs only’; ‘no comorbid psychiatric condition’; ‘absence of any concomitant drug’, just to mention few.[12,29] Balancing high-powered qualitative and quantitative extractions of the evidence with open-label human studies, is therefore recommended, at this time, in order to allow a critical perspective toward the development of experimental drugs to be tested in RCTs. This seems particularly relevant, especially considering the overall paucity of the evidence available on the matter, including non-controlled reports and the need to divert the attention also towards special settings/population.

The present comprehensive critical review aims at providing both qualitative synthesis and critical interpretation of the current evidence about the efficacy of aripiprazole in the relapse prevention and craving attenuation in AUD.

2. Materials and methods

The present review was carried out in accordance to the methods recommended by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[30]

2.1. Information sources and search strategy

Studies were identified searching the electronic databases MEDLINE, PsycINFO, and the Cochrane Library. We combined the search strategy of free text terms and exploded MESH headings for the topics of alcohol use disorder and aripiprazole as following: (Alcohol use Disorder) OR (Alcohol use) AND aripiprazole. The strategy was first developed in MEDLINE and then adapted for use in the other databases. Studies published in English through 21 September 2015 were included. In addition, further studies were retrieved from reference listing of relevant articles and consultation with experts in the field and or manual search.

2.2. Inclusion criteria, study population and study design

We considered studies that included aripiprazole treatment for AUD subjects if diagnostic criteria used were specified. Participants of both genders, 18 years of age or older were considered. Both population-based and hospital-based studies were included. Among hospital-based studies, inpatients, day-hospital, and outpatient subjects were included while emergency care records were excluded as considered non-representative. All experimental and observational study designs were included apart from case reports. Narrative and systematic reviews, letters to the editor, and book chapters were excluded.

2.3. Study selection and data extraction

Identified studies were independently reviewed for eligibility by three authors (GM, LO, and MF) in a two-step-based process; a first screening was performed based on title and abstract while full texts were retrieved for the second screening. At both stages, disagreements by reviewers were resolved by consensus. Data were identified, selected and then extracted by two authors (MF and LO) and supervised by a third author (GM) using an ad hoc developed data extraction spreadsheet. With the initial set of keywords, some 79 studies were identified. Of these, 10 were excluded because duplicated. Of these remaining 15 relevant studies, 54 were excluded because did not meet the inclusion criteria or not consistent with the aims of the review. Finally, the data extraction spreadsheet was piloted on eight randomly selected papers and modified accordingly. Four open-label studies and four randomized clinical trials (RCT) were included and properly retrieved (as shown in Tables 1 and 2). Figure 1 provides a synthetic flow chart of the multi-step selection procedure as was followed.

3. Results

3.1. Clinical lab studies

Voronin et al. [31] primarily evaluated the efficacy and safety of aripiprazole as well as its possible mechanism of action on alcohol consumption, by enrolling 30 non-treatment seeking alcoholics in a clinical laboratory study. Subjects received double-blind treatment with up to 15 mg daily of aripiprazole \( (n = 15) \) or placebo \( (n = 15) \) for 8 days. After the priming drink in the bar lab, there was no significant difference between placebo and aripiprazole groups on the subjective high assessment scale (SHAS), which represents a measure of intoxication and alcohol induced adverse effects \( p = 0.79 \) and on overall alcohol urge questionnaire (AUQ) scores. Aripiprazole-treated subjects experienced more insomnia \( p = 0.017 \) and nervousness \( p = 0.042 \) compared to placebo group. Subjects who had lower self-control (more impulsivity) compared to those who had higher self-control (less impulsivity) were more likely to have fewer drinks per day when on aripiprazole compared to placebo \( p = 0.03 \).

An alcohol administration design was performed in order to assess, as primary outcomes, the safety and tolerability of 300 mg of topiramate and 30 mg of aripiprazole in heavy drinking volunteers, in an open-label trial.[32] Thirteen participants not seeking treatment for alcoholism were randomized and submitted to an alcohol challenge session (ACS). Each week participants were monitored for adverse effects, changes
Table 1. Summary of included studies examining effects of aripiprazole in alcohol use disorder.

<table>
<thead>
<tr>
<th>Study</th>
<th>Participants</th>
<th>Dose (mean) mg/day</th>
<th>Study design (weeks)</th>
<th>Primary outcomes (scales)</th>
<th>Secondary outcomes (scales)</th>
</tr>
</thead>
<tbody>
<tr>
<td>[31]</td>
<td>30 (25/5) 27.5 ± NA [NA]</td>
<td>ARI (15) vs PBO</td>
<td>RCT (1) Clinical laboratory study</td>
<td>Safety and tolerability of the interaction between ARI and alcohol (POMS; BAES; SHAS; AUQ)</td>
<td>Attenuating craving (OCDS; ACQ; AUQ)</td>
</tr>
<tr>
<td>[32]</td>
<td>13 (11/2) 38 ± NA [22–58]</td>
<td>ARI (30) plus TPR (300)</td>
<td>Open-label (4)</td>
<td>Safety and tolerability of the combination of aripiprazole and topiramate with alcohol (AIMS; SAFTED)</td>
<td>Craving attenuation (OCDS; AUQ)</td>
</tr>
<tr>
<td>[33]</td>
<td>30 (22/8) 28.9 ± 7 [NA]</td>
<td>ARI (15) vs PBO</td>
<td>RCT (2)</td>
<td>Analysis of established brain imaging paradigm to explore the effect of ARI vs placebo on alcohol cue-induced brain activation and drinking (fMRI)</td>
<td>Attenuating craving (OCDS)</td>
</tr>
<tr>
<td>[34]</td>
<td>35 (23/12) 39.6 ± 7.6 [NA]</td>
<td>ARI (5–15) – flexible plus ESC (10–20) OR ESC (10–20) 5–15 (7.7) – flexible</td>
<td>Open-label (6)</td>
<td>Clinical changes and craving attenuation (MAST; BDI; AUQ; CGI-S)</td>
<td>Changes in BOLD signal during 6-week therapy (fMRI)</td>
</tr>
<tr>
<td>[36]</td>
<td>13 (11/2) 37.9 ± 7.8 [NA]</td>
<td>5–15 (7.7) – flexible</td>
<td>Open-Label (16)</td>
<td>Craving attenuation (VAS; OCDS)</td>
<td>Safety and tolerability (ECG; urinalysis, haematological/clinical chemical analysis; AEs)</td>
</tr>
<tr>
<td>[37]</td>
<td>295 (202/93) 47.3 ± 8.7</td>
<td>ARI (30) vs PBO</td>
<td>RCT (12)</td>
<td>Percent of days abstinent (TLFB)</td>
<td>Abstinent days</td>
</tr>
<tr>
<td>[38]</td>
<td>75 (60/15) 40.3 ± 11.8 [NA]</td>
<td>ARI (5–15) vs NAL (50)</td>
<td>RCT (16)</td>
<td>Safety and efficacy of ARI on alcohol drinking indices (CIWA-Ar; CGI-S)</td>
<td>Craving attenuation (VAS; OCDS)</td>
</tr>
</tbody>
</table>

NA: not available; AUD: alcohol use disorder; VAS: visual analog scale; OCDS: obsessive-compulsive drinking scale; CGI-S: clinical global impairment severity scale; QOL: quality of life index; SCL-90: symptoms checklist-90 items; AC: anticonvulsants; AD: antidepressants; AP: antipsychotics; ARI: aripiprazole; PBO: placebo; TPR: topiramate; ADS: alcohol dependence scale; AUDIT: alcohol use disorders identification test; TLFB: timeline follow-back CIWA-Ar: clinical institute withdrawal assessment for alcohol-revised; HAM-D: Hamilton depression scale; AIMS: abnormal involuntary movement scale; SAFTED: systematic assessment of side effects in clinical trials; AUQ: alcohol urge questionnaire; fMRI: functional magnetic resonance imaging; POMS: profile of mood states; ACQ: alcohol craving questionnaire; BAES: biaxial alcohol effects scale; NAL: naltrexone; SAAST: self-administered alcohol screening test; BIS-11: Barratt impulsiveness scale-version 11; BAES: biaxial alcohol effects scale; SHAS: subjective high assessment scale; AUQ: alcohol urge questionnaire; MAST: Michigan alcohol screening test; BDI: Beck depression inventory.
During the ACS sessions, participants were administered alcohol (about three beers) and asked to complete a few short assessments after each drink including adverse effects. Findings demonstrated no evidence that adverse effects of aripiprazole and topiramate are additive; therefore, their

<table>
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<th>Table 2. Summary of aripiprazole effects on alcohol use disorder dimensions.</th>
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<tr>
<td>Study</td>
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<td>[38]</td>
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</table>

NS: not significant; N/A: not available; VAS: visual analog scale; OCDS: obsessive-compulsive drinking scale; CGI-S: clinical global impairment severity scale; QOL: quality of life index; SCL-90: symptoms checklist-90 items; TLFB: timeline follow-back; AUQ: alcohol urge questionnaire; A: aripiprazole; ESC: escitalopram.

in mood, and evaluation of concomitant medication use. During the ACS sessions, participants were administered alcohol (about three beers) and asked to complete a few short assessments after each drink including adverse effects. Findings demonstrated no evidence that adverse effects of aripiprazole and topiramate are additive; therefore, their

Figure 1. Adapted PRISMA 2009 flow diagram from [61].
combination was generally safe and well tolerated. Second, it was evaluated if lower as well as higher doses of these medications were comparatively effective in reducing alcohol urge and consumption. Findings demonstrated a statistically significant reduction of alcohol use by participants ($p = 0.08$).[32]

### 3.2. Neuroimaging studies

A study by Myrick et al. [33] investigating, as primary goal, the effect of aripiprazole vs placebo on ventral striatum activation and in the attenuation of alcohol cue-induced brain activation caused by medication treatment as well as the effects on decreased alcohol use, using fMRI. Thirty non-treatment-seeking alcoholics were recruited and randomized to either aripiprazole (15 mg/day) or placebo in a double-blind manner for a 14-day period. After this period, subjects underwent an fMRI brain scan with alcohol cue stimulation, in order to measure changes in regional brain activity while they were viewing alcoholic and nonalcoholic-beverage randomized pictures. No significant differences between the groups were observed regarding to alcohol craving ratings. Placebo-treated patients showed activation in limbic regions including right ventral striatum while aripiprazole-treated subjects did not show the ventral striatum activation ($p < 0.01$). Aripiprazole-treated subjects showed a reduction of heavy drinking days compared to placebo group ($p = 0.027$).

A 6-week open-label study [34] carried out on 35 subjects affected with comorbid major depressive disorder (MDD) and AUD were randomized to only escitalopram (10–20 mg/day) or aripiprazole plus escitalopram (flexible 5–15 mg/day of aripiprazole plus 10–20 mg/day of escitalopram). Depressive symptoms, craving for alcohol and alcohol use, as primary outcomes, were assessed by Beck depression inventory (BDI), the Korean alcohol urge questionnaire (AUQ-K) and the clinical global impairment-symptomatology (CGI-S). The BDI and CGI-S scores were reduced in the aripiprazole plus escitalopram group compared to only escitalopram group (respectively, $p = 0.13$ and $p = 0.30$). The AUQ-K scores were significantly decreased in the aripiprazole plus escitalopram group ($p = 0.02$). No significant differences were evidenced in the number of patients responding to depression treatment ($p = 0.15$) either in the number of patients who remained alcohol free ($p = 0.66$), between the two groups. Response to antidepressant treatment (as reduction in follow-up BDI scores to less than 50% of initial BDI scores) were similar in both groups. Craving for alcohol was decreased in the aripiprazole plus escitalopram group compared to only escitalopram one. At baseline and following 6 weeks of treatment, patients were assessed by 1.5 Tesla functional magnetic resonance imaging (fMRI) in order to evaluate their brain activity in response to alcohol drinking cue presentation. Findings that patients with comorbid AUD and MDD showed decreased activity in BOLD signal and metabolism in the anterior cingulate cortex (ACC) in response to alcohol drinking scenes, supported the evidence that anterior cingulate represents an important hub mediating depressive symptoms and negative mood, suggesting the role of this brain region in craving for alcohol. The authors also underlined that the activity of anterior cingulate in the aripiprazole plus escitalopram group increased following the 6-week treatment period. These findings may suggest that dopamine release induced by aripiprazole might control craving for alcohol during alcohol-cue stimulation in patients with MDD, via activation of anterior cingulate.

### 3.3. Open-label trials

A preliminary open-label study was carried out on 11 detoxified alcohol-dependent patients, in order to investigate the short-term efficacy of aripiprazole, by evaluating alcohol relapse rates and craving attenuation.[35] Subjects were orally treated with flexible doses of aripiprazole (5–15 mg/day) for a 16-week period. A significant progressive reduction of craving in both the visual analog scale (VAS) ($p = 0.002$) and obsessive-compulsive drinking scale (OCDS) ($p = 0.048$), with a more significant effect on the compulsive component ($p = 0.032$) was observed both at the first follow-up and at the end of the study. An open-label trial investigated, as primary outcomes, the safety and tolerability of the aripiprazole–topiramate combination on thirteen heavy drinking subjects not seeking treatment for alcoholism. Subjects were titrated up to 300 mg of topiramate and 30 mg of aripiprazole daily for 36 days.[35] In another study, flexible doses of aripiprazole have been administered to 13 detoxified alcohol-dependent patients in a 16-week period.[36] Primary outcomes consist in investigate the short-term efficacy of aripiprazole in alcoholics in terms of alcohol relapse prevention, craving attenuation and improvement of psychiatric symptoms. Secondary outcomes comprised measurements of safety and tolerability. Aripiprazole-treated patients experienced a statistically significant reduction of craving as measured by OCDS scores ($p = 0.042$), particularly on the compulsive component ($p = 0.032$), and VAS ($p = 0.002$). Furthermore, a significant improvement on the clinical global impairment (CGI) severity scale ($p = 0.001$), quality of life (QOL) index ($p = 0.011$) and on SCL-90 general severity index ($p = 0.038$), was observed. Withdrawal symptoms were significantly reduced during the study ($p = 0.011$). Finally, authors reported, among the most frequently reported side effects, nausea, and vomiting.[36]

### 3.4. RCT

A 12-week multicenter, double blind, parallel group, placebo-controlled RCT aimed at comparing the efficacy and safety of oral aripiprazole (2–30 mg daily) vs placebo in the maintenance of abstinence in 295 alcohol-dependent patients (146 placebo and 149 aripiprazole), without concurrent substance abuse or dependence (i.e. cocaine, heroin, etc.) or concurrent Axis I/II disorders. Aripiprazole was started at 2 mg/day and titrated to 5 mg/day (days 3 and 4); 10 mg/day at the day 7 visit; 15 mg/day (days 10 and 11); 20 mg/day at day 14; 25 mg/day at day 21; and 30 mg/day at day 28 until the term of study. The primary efficacy outcome, i.e. the percentage of days abstinent over 12
weeks, as assessed by the timeline follow-back (TLFB) method, was reported similar between aripiprazole and placebo (58.7% vs 63.3%; \( p = 0.227 \)). Among the secondary outcomes, the percentage of subjects with an increase of 50% or more in abstinent days, the percentage of subjects without a heavy drinking day (i.e. more than five drinks daily for men or four for women) and the time to first drinking day, were not significantly different between two groups (respectively, \( p = 0.228; p = 0.978; p = 0.067 \)). While the percentage of subjects completely abstinent from alcohol throughout the study is significantly higher in placebo group \( (p = 0.016) \). The average number of drinks/drinking days was significant lower for aripiprazole \( (p < 0.001) \). OCDS and the drinker inventory of consequences-2 R version \( (DrInC-2 \ R) \), as behavioral measures of alcohol abuse and dependence, showed no significant differences between two groups. While statistically significant differences were reported in alcohol dependence scale \( (ADS) \) (aripiprazole superior to placebo; \( p = 0.004 \)) and quick inventory of depressive symptomatology-self report version \( (QIDS-SR16) \) (placebo superior to aripiprazole; \( p = 0.009 \)). Higher discontinuation rates were reported in aripiprazole group \( (40.3\%) \) vs placebo \( (26.7\%) \), mainly due to adverse events \( (AEs) \), e.g. insomnia \( (6.9\%) \), anxiety \( (3.4\%) \), and restlessness \( (2.7\%) \). Aripiprazole-treated subjects discontinued significantly earlier the study compared to placebo group \( (p = 0.008) \), particularly when aripiprazole dose exceeded 15 mg daily. Treatment-related \( AEs \) were reported higher with aripiprazole than with placebo \( (82.8\% vs 63.6\%) \), particularly including fatigue \( (p < 0.0001) \), insomnia, restlessness \( (p < 0.0001) \), somnolence \( (p = 0.002) \), anxiety \( (p = 0.001) \) and disturbance in attention \( (p = 0.007) \). The extrapyramidal \( AEs \) related to aripiprazole reported included akathisia \( (6.2\% vs 0.7\%) \), tremor \( (3.4\% vs 2.8\%) \) and dyskinesia \( (1.4\% vs 0\%) \). Overall, aripiprazole-treated patients reported more positive subjective treatment effects and less overall severity of AUD compared to placebo group.[37]

A randomized, double-blind, confrontation trial with naltrexone investigating as primary outcome the efficacy of aripiprazole on alcohol-drinking indices, was carried out on 75 detoxified alcohol dependent subjects in a 16-week period. Patients were subsequently randomized into groups, receiving 50 mg of naltrexone and flexible dose \( (5–15 \ mg/\ day) \) of aripiprazole, respectively. The number of subjects remained alcohol free for the length of study, the number of subjects relapsed, the mean number of abstinent days and heavy drinking days were not significantly different in the two groups. The aripiprazole-treated patients showed a significant reduction in VAS \( (p < 0.05) \) while naltrexone-treated patients had significant reduction in the OCDS \( (p < 0.001) \), OCDS sub-score obsessive \( (p < 0.001) \) and compulsive \( (p < 0.001) \) and in the VAS \( (p < 0.05) \). Withdrawal symptoms, as assessed by CIWA, were significantly reduced in both groups \( (p < 0.0001) \). Aripiprazole-treated patients reported significant improvement on the CGI severity scale \( (p < 0.01) \) while naltrexone-group was not associated with a significant improvement \( (p = 0.072) \).[38]

### 4. Conclusion

Abnormalities in dopaminergic neural transmission have been strongly hypothesized to contribute to the pathophysiology of AUD through an amplification of motivational (craving) as well as reward aspects.[39–43] Furthermore, the mesolimbic dopamine pathway that projects from the VTA to a structure within the ventral striatum, the NAc, has been implicated as a major site for the reinforcing actions of many addictive drugs including alcohol.[38,44,45] It has been proposed that during initial attempts of abstinence, the dopaminergic system may be down-regulated (low dopamine levels) determining a low hedonic tone.[46–48]

The presence of anhedonia, defined as diminished interest or pleasure in response to rewarding stimuli, as it reflects deficits in hedonic capacity and is closely linked to the reward processes (i.e. reward evaluation, motivation to seek reward and decision-making), could facilitate the level of craving and drug-seeking behavior.[8,46] On the other hand, relapse drinking or initiation has been associated with increased dopamine concentrations at the striatum.[49,50] Therefore, all drugs acting in the modulation of the dopaminergic system may theoretically reduce craving and prevent relapse, by promoting abstinence, in alcohol-dependent patients.[40,51] Therefore, in this context of altered brain dopamine function, aripiprazole might provide a novel therapeutic approach in the different stages of the pathogenesis of alcoholism, by attenuating both craving (during the abstinent phase) and anxiety, depression and impulsivity, potentially responsible of relapse, and worsening of drinking behaviors.[31,34,52]

Nevertheless, clinical studies published so far reported mixed and unclear findings. In fact, despite the main goal of the present review was at providing an overview of current evidence on efficacy of aripiprazole in relapse prevention and craving attenuation in AUD, the paucity of available data reported to date on the matter, precludes any conclusive statement about any direct or otherwise definitive efficacy of aripiprazole in alcohol craving and prevention relapse. Future research studies should assess the clinical and brain activities after administration of aripiprazole in patients with AUD with or without other substance use and/or abuse. Further controlled randomized trials should be carried out in order to assess the short- and long-term efficacy of aripiprazole in alcoholics in terms of alcohol relapse prevention, craving attenuation and improvement of psychiatric symptoms.

### 5. Expert opinion

Clinical studies are scarce in number and inconclusive, though clearly pointing out an overall favorable evidence in support of aripiprazole. However, the scanty available data limits the generalizability and statistical power of the findings here provided. A series of limitations have been here analyzed and discussed. First of all, most studies here retrieved recruited a small sample size without homogeneous inclusion/exclusion criteria, often not including multiple substance dependence or other axis I/II comorbid disorders. On the other hand, a sample including a high level of comorbidity may influence the outcomes. Second, the relatively short length of the studies may
limit the observation of relapse/recovery/abstinence. Furthermore, some studies do not take into account the different effects that specific ranges of aripiprazole dosages may exert on response, remission, relapse as well as side-effect pattern. Some studies evaluated efficacy of aripiprazole in combination with other drugs, such as escitalopram or topiramate, not specifically assessing the role of aripiprazole in AUD outcomes. In addition, primary outcomes (e.g. level of craving; prevention relapse rate; safety and tolerability in alcoholics patients, and so on) are often not homogeneous throughout the studies, by limiting the analysis of the data here retrieved. Finally, different study designs may limit comparability of data (‘measurement bias’). Furthermore, a lack of standardization of the outcome measures, dose range evaluation, and different population selections all can influence results.

The issue of the dosage is also crucial. Overall, aripiprazole, at low-medium dosages (ranging 5–15 mg daily), seems to reduce craving and alcohol consumption,[35,36,38] even though data are also contrasting [33] or likely influenced by the presence of co-administration with other drugs.[34] In particular, aripiprazole seems to be particularly effective in subjects who have high impulsivity/low self-control in natural drinking conditions[31] and in the improvement of comorbid psychiatric symptomatology.[34,38] Furthermore, some studies demonstrated that aripiprazole dosage should be decreased in subjects with chronic alcohol consume due to the risk of increasing aripiprazole exposure.[28,37] While higher doses of aripiprazole seem to be more likely associated with the onset of AEs (e.g. insomnia, anxiety, and restlessness), anhedonic states, and may induce worsening of craving and higher rates of drop-outs and relapse due to its antagonistic activity on D2.[32,37] Partial dopamine agonists, such as aripiprazole, may represent a tool to reverse dopamine depletion seen during ethanol abstinence and, due to their own multi-receptorial activity, may represent a novel strategy to balance dopamine neurotransmission along the behavioral continuum of alcoholism.[53] Regarding the serotonin system, the 5-HT1A partial agonist effect of aripiprazole may modulate the prefrontal cortex (PFC) to improve impulse control through the projections from the raphe nucleus to the VTA and NAc.[54] Taken together, these considerations suggest that dopamine release induced by aripiprazole might be associated with increased activation of anterior cingulate, which, on turn, may control craving for alcohol and substances. This is also the most likely issue accounting for the inconsistent results about the use of high dose aripiprazole as documented by the largest RCT performed to date.[37]

While current evidence to date do not allow any firm conclusion about the efficacy of aripiprazole in the prevention of craving and/or alcohol consumption and in the maintenance of abstinence, a list of specific kinds of patients could outlined to aid the prescribing clinicians: (1) subjects with comorbid psychiatric conditions, especially major depression, bipolar depression, psychotic disorders, dissociative disorders, and borderline personality.[34,36] For all these latter conditions, of dual diagnosis aripiprazole proved to be effective, although its direct effect on alcohol craving urge for confirmation studies[55]; (2) subjects with poly-substance-abuse, a condition characterized by high rates of concurrent psychiatric symptoms, especially when polyabuse of alcohol and novel psychoactive substances occur.[56,57] The safety profile of aripiprazole suggests its suitability for use also when the use of other substance cannot be ruled out; (3) subjects with a Cloninger II personality profile, characterized by higher levels of impulsiveness, sensation seeking, early onset of alcohol misuse, antisocial behaviors, reward craving.[58–60] In these conditions, aripiprazole showed some level of evidence in different studies.[31]

In conclusion, aripiprazole may represent a possible option in the broad, heterogeneous setting of AUD. Its direct effect on alcohol craving and relapse prevention need to be confirmed and we are still far from considering this drug as a drug of choice in alcoholism. However, waiting for further evidence on the matter, we can consider aripiprazole as the drug of choice in those cases of AUD where dual diagnosis, multiple substance abuse, and peculiar personality traits represent relevant phenomena.

Declarations of interest

L Orsolini, M Fornaro, R Vecchiotti and D De Berardis are employees of Polyedra, Teramo, Italy. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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Papers of special note have been highlighted as: • of interest  •• of considerable interest.

   • A brief overview on the incentive sensitization theory of addiction.

**A comprehensive review useful for an overview of neurochemical and clinical factors of craving in alcohol use disorder with a critical point on psychopharmacological alternatives according to the craving type.**


