Aripiprazole, alcohol and substance abuse: a review

M. BRUNETTI[1,2], L. DI TIZIO[2], S. DEZI[2], G. POZZI[3], P. GRANDINETTI[3,4], G. MARTINOTTI[1,2]

[1]Institute of Advanced Biomedical Technologies, University of Chieti, Italy
[2]Department of Neuroscience and Imaging, School of Medicine, University of Chieti, Italy
[3]Institute of Psychiatry and Psychology, Department of Neuroscience, School of Medicine, Catholic University of the Sacred Heart, Rome, Italy
[4]Department of Psychiatry and Psychotherapy, Ludwig Maximilians University, Munich, Germany

Abstract. – Aripiprazole is an atypical antipsychotic used for schizophrenia, manic and mixed episodes associated with bipolar I disorder and as adjunctive therapy for major depressive disorder. It functions as a partial agonist at dopamine D2 and 5-HT1A receptors, and as an antagonist at the 5-HT2A receptor.

The most recent results obtained from scientific research showed that dopaminergic mechanisms are involved in motivation, reward, and reinforcement of substance abuse. The use of aripiprazole and partial dopamine agonists could represent a novel strategy for normalizing dopamine neurotransmission. Many studies in the last few years have highlighted aripiprazole as a potential candidate for the treatment of different types of substance dependence. This review aims to describe recent scientific research using aripiprazole in different substance abuse disorders (i.e., alcoholism, cocaine, amphetamine and nicotine use). Furthermore, the efficacy of aripiprazole compared to other pharmacological therapies will be described.

Given the low number of studies, the frequent absence of placebo or active comparators, and the low statistical power of the studies, a clear conclusion about the use of aripiprazole in alcohol/substance dependence cannot be drawn. Therefore, we suggest the need for further studies, preferably randomized and placebo-controlled.

Key Words:
Aripiprazole, Substance abuse, Dopamine agonist.

Introduction

The Food and Drug Administration (FDA) approved the use of Aripiprazole (ARI) for schizophrenia, for the management and maintenance of manic and mixed episodes associated with bipolar I disorder and as adjunctive therapy for major depressive disorder[1].

Aripiprazole is an atypical antipsychotic. It is a quinolinone derivative that has a receptor binding profile with a different mechanism of action compared to the other atypical antipsychotic drugs[2].

The novel pharmacodynamics of aripiprazole shows an important interaction with a great number of G protein-coupled receptors[3]. Aripiprazole exhibits high affinity for dopamine D2 and D3, 5-HT1A (5-hydroxytryptamine 1A) and 5-HT2A (5-hydroxytryptamine 2A) receptors, moderate affinity for the 5-HT reuptake site, and moderate affinity for dopamine D4, 5-HT2C, 5HT7, α1-adrenergic and histamine H1 receptors. Aripiprazole functions as a partial agonist at dopamine D2 and 5-HT1A receptors, and as an antagonist at the 5-HT2A receptor[3]. It also presents an anti-inflammatory effect via the inhibition of microglial activation[4], with a promising effect on the cytokine production as showed by the newer antidepressants[5]. Aripiprazole was shown to be efficacious in different psychiatric disorders[6-8] with a favorable adverse event profile[9,10].

In the domain of substance use disorders, a novel strategy for normalizing dopamine neurotransmission could be represented by the use of aripiprazole and partial dopamine agonists which may help to reverse dopamine depletion, observed during withdrawal states, due to their flexible activity[11]. Considering the efficacy in decreasing alcohol consumption, craving for alcohol and psychiatric symptom intensity of other atypical antipsychotics acting on the dopaminergic/serotonergic systems, such as olanzapine[12] and quetiapine[13], aripiprazole should be given greater consideration for the treatment of substance abuse[12,14].

Corresponding Author: Paolo Grandinetti, MD; e-mail: paolo.grandinetti@edu.rm.unicatt.it

Alcoholism

Non-pharmacological treatments such as psychotherapy, cognitive-behavioral therapy, group therapy, or residential treatment programs have not yet obtained effective results with the alcohol use disorders[15]. In United States and Europe, only a few medications are approved for the treatment of alcohol dependence, but these medications were only moderately successful[16]. Recently, due to the better understanding of the neurobiological substrates of alcohol dependence, new pharmacological treatments appeared[17-20], and one of the main objectives of the scientific community is the integration of new pharmacotherapies with non-pharmacological treatment approaches[15].

Disulfiram, Naltrexone and Acamprosate[21] are the three medications currently approved for the treatment of alcohol dependence in US, whereas in some EU countries there are other options, as for Gamma hydroxybutyrate in Italy and Austria.

Disulfiram, an aldehyde dehydrogenase inhibitor, blocks the oxidation of ingested alcohol at the acetaldehyde stage and prevents its metabolism to acetate. For this reason, even small amounts of alcohol in a disulfiram treated patient, cause tachycardia, hypotension, diaphoresis, flushing, dyspnea, nausea and vomiting as a consequence of acetaldehyde accumulation[22].

Naltrexone is an opioid receptor antagonist. It reduces heavy drinking by diminishing the rewarding neurobiological effects of alcohol[23]. It acts, in the ventral tegmental area and the nucleus accumbens, on dopamine reward pathways and reduces both dopamine release[24] and endogenous opioids release[25] in response to alcohol.

In 2004 the Food and Drug Administration approved the use of acamprosate, or N-acetyl homotaurine, a N-methyl-D-aspartate receptor modulator which is, together with psychosocial support, a good treatment in detoxified alcohol-dependent patients during maintenance therapy[26].

According to a recent review by Edwards, Kenna et al, serotonin-specific reuptake inhibitors (i.e., sertraline), prazosin, topiramate, baclofen and ondansetron, and aripiprazole could represent new neuropharmacological treatment for alcohol dependence[27].

Aripiprazole and Alcohol use Disorders

For many years researchers have tried novel strategies to normalize dopamine neurotransmission, using partial dopamine agonists, with the aim of reversing dopamine depletion typically observed during ethanol abstinence[11].

The first two studies that investigated the efficacy of aripiprazole in alcohol dependence were performed by Martinotti et al in 2007 and by Anton in 2008. In the first study the Authors observed the efficacy of aripiprazole in decreasing alcohol use in substance abusers, lessening craving and attenuating severity of psychopathological symptoms. Thirteen detoxified alcohol-dependent subjects were treated with flexible doses of aripiprazole for 16 weeks; six patients maintained an alcohol free condition for the entire study period but all the subjects experienced a reduction of craving in both OCDS and VAS and a decrease of the SCL-90 General Severity Index (GSI)[28].

Anton et al[29] in a randomized, multicenter, double-blind, placebo-controlled study, showed the efficacy and safety of aripiprazole, compared to placebo. The study showed that, aripiprazole-treated subjects reported a more positive response than placebo-treated subjects both in subjective effects and in craving.

Voronin et al[30] tested the effects of aripiprazole on alcohol consumption in thirty alcoholics. Patients were divided into two groups; 15 were treated with aripiprazole (15 mg) and 15 were treated with placebo for eight days. The utility of aripiprazole was observed during the first six days of treatment and, on day 8, during a free choice limited access alcohol consumption paradigm following an initial drink of alcohol in a bar-lab setting. This study showed that aripiprazole was well tolerated and reduced the desire to drink again after the first drink, which was used as bait, and broke the link between priming drink induced stimulation and further drinking, especially in more impulsive patients. With this study Voronin et al[30] suggested that aripiprazole would improve impulse control (self control for alcohol) by enhancing the function of frontal cortex in patients with alcohol dependence.

Recently different researchers have tried to determine if a combination of different drugs had a greater efficacy than either single drug taken alone in reducing alcohol use in alcohol dependent patients. In 2009 Kenna et al[19] investigated the safety and tolerability of the aripiprazole-topiramate combination in alcohol drinkers. All participants were treated with 300 mg of topiramate and 30 mg of aripiprazole for 36 days resulting in a reduction of alcohol use by participants. Moreover there was no evidence of adverse effects from the combination of these two drugs

and, therefore, the Authors concluded that the combination could be administered safely with a modest amount of alcohol.

Other researchers have conducted specific studies in dual-diagnosis patients assuming a possible correlation between alcoholism and psychiatric disorders. A randomized, double-blind, comparison trial with naltrexone investigated the efficacy of aripiprazole on alcohol-drinking indices, craving and improvement of psychiatric symptoms[31]. In this study craving and withdrawal rating scales were applied. Psychiatric symptoms were evaluated through the Symptom Check List 90-Revised. The number of subjects remaining alcohol free for the entire study period (16 weeks) and the number of relapsing subjects was not significantly different in the two groups, but the survival function showed that patients treated with aripiprazole remained abstinent from any amount of alcohol for a longer time with respect to those treated with naltrexone. Also, patients treated with naltrexone showed a better outcome, in terms of craving scores, compared to those treated with aripiprazole.

In recent years, neuroimaging studies aimed at investigating aripiprazole effects on brain activation were also conducted. Myrick et al[32] using fMRI, observed brain activation in alcoholics. Non-treatment-seeking alcoholics were randomly assigned aripiprazole (15 mg) or placebo for 14 days. Then each patient underwent functional magnetic resonance imaging, they were given a sip of alcohol before measuring changes in regional brain activity while they were viewing alcoholic and nonalcoholic-beverage randomized pictures. During the scanner sessions subjects rated their urge to drink. The Authors showed an increased activation in the right ventral striatum for placebo-treated subjects, while there was a lower activation in the same areas in the aripiprazole treated patients. Moreover, during the 14-day medication period, a reduction of heavy drinking was observed in aripiprazole-treated subjects. The study provides both novel and valuable information regarding the effect of aripiprazole on cue-induced brain activation and voluntary drinking during treatment. The important findings provided from this study clarified the role of the ventral striatum for brain dopamine balance: the mesolimbic pathway was clearly a critical point implicated in the dopaminergic system and in the maintenance of heavy drinking in alcoholics.

Moreover it was demonstrated that the frontal-subcortical circuits subserve reward/craving and impulsive behavior[33]. In patients who developed a dependence it was shown that these areas were affected by a dysregulation, given the putative activity of aripiprazole on these areas, this drug could be beneficial for the treatment of alcoholism. Furthermore, supporting this hypothesis, it was demonstrated that in animal models of alcoholism aripiprazole produced an overall decrease in drinking behavior[34].

In 2012, a study on mice investigated the effect of aripiprazole on ethanol-induced psychological and physiological dependence and anxiety-like behavior. This study observed the effect of aripiprazole on the development and expression of ethanol-induced place preference with the result that aripiprazole-treatment yielded a positive outcome, suggesting that aripiprazole can be effective for reversing ethanol-induced place preference and anxiety-like behavior.

Cocaine

Cocaine remains the second most commonly used illicit drug in Europe. Although prevalence levels and trends differ considerably between countries, almost everywhere the use of this drug remains limited, excepted for a small number of western European countries where high levels of cocaine use are observed. There is also a substantial diversity among cocaine users, divided into occasional users, who usually snort cocaine powder and most avid consumers, who inject cocaine or use crack cocaine[35].

The available drugs for the treatment of cocaine abuse or dependence are relatively ineffective[36]. The different hypotheses that researchers have recently formulated relating to the various mechanisms implicated in cocaine addiction suggest several promising pharmacological approaches[37]. The most promising medications for dependency seem to be agents such as GABA agents (topiramate, tiagabine, baclofen and vigabatrin) and agonist replacement agents (modafinil, disulfiram, methylphenidate). Furthermore, the results from trials of first- and second-generation neuroleptics were not promising. Nevertheless, in order to clarify remaining uncertainties, larger, randomized, placebo-controlled studies are needed[36,38].

It is also important to note that other drugs already studied for other indications, like Disulfiram[39] and Vigabatrin[40] were shown to have an efficacy and an anti-cocaine vaccine has also shown promise[41].

Finally, optimal therapeutic platforms that combined pharmacotherapies with behavioral therapies[37] and psychosocial treatments were useful in supporting the pharmacotherapy of cocaine abuse[36].

Aripiprazole and Cocaine Use Disorders

Several studies were conducted with the aim of testing the safety, tolerability, and subject-rated effects of acute intranasal cocaine administration during aripiprazole maintenance. In 2007 in a randomized, placebo-controlled study, Stoops et al[42] observed eight cocaine dependent subjects maintained with 10 mg oral aripiprazole and placebo. Their results indicated that aripiprazole did not have considerable effects, although it did modify temperature-increase and subject-rated effects of cocaine with dose. In 2008, Lile et al[43] performed a similar study to evaluate the prototypical stimulant-like effects of cocaine compared with placebo, finding that aripiprazole increased these effects.

A few years later, in 2011, the same Researchers[44] tested discriminative stimulus, subject-rated and cardiovascular effects of cocaine alone and in combination with aripiprazole, demonstrating that acutely administered aripiprazole attenuated discriminative stimulus. This efficacy of treatment in acute was in agreement with previous studies that tested aripiprazole in combination with acutely administered d-amphetamine. It seems clear, therefore, that, according to this study the ability of aripiprazole to modify stimulant effects of drugs depended on the duration of treatment. These results agreed with Meini et al[45] who recently conducted a 12-week clinical trial on cocaine dependence patients, comparing aripiprazole and ropinirole in order to determine their safety, tolerability and effects. The Authors demonstrated that aripiprazole was more efficacious than ropinirole in reducing cocaine use while cocaine craving decreased with aripiprazole treatment as well as ropinirole treatment. Nevertheless, a different point of view was provided in 2011 by Haney et al[46] that in their study, showed that aripiprazole seemed to increase cocaine self administration in humans to compensate for a blunted subjective cocaine effect.

Amphetamine and Methamphetamine

Amphetamines and ecstasy are usually the most commonly used illicit drugs in many European countries, though they have become the second most commonly used illicit substance after cannabis in a few other countries always in Europe[35].

Although cognitive behavior interventions, cognitive behavior therapy, family education, support, and counseling may give some advantages, there are no randomized controlled trials indicating that psychosocial treatment was really effective in decreasing intravenous amphetamine use[47].

Various neuronal mechanisms implicated in methamphetamine dependence suggest several pharmacological approaches. As reported in a focused review of 2010 pharmacological approaches using high number of drugs to methamphetamine dependence was not effective, but modafinil, bupropion and naltrexone, in double-blind placebo-controlled trials showed some promising effects. In addition studies employing agonist replacement medications, with d-amphetamine and with methylphenidate, have shown to be effective, but a pharmacotherapy options to manage abstinence have not been identified[37]. This observation was shared by Brackins et al[48], who conducted a literature review on pharmacological treatments for methamphetamine use and addiction. The Authors pointed out that Aripiprazole trials appeared more frequently than the other medications within the reviewed literature. This work indicates that, at the moment, no single medication demonstrated a consistent efficacy in amphetamines.

One reason of these results could be methodological, given that the typical stimulant abuser is often a polysubtsance dependent and for this reason is a more difficult subject; this factor was not always included in clinical trials[49].

Furthermore, this review revealed that all the considered studies included several methodological limitations that need to be overcome in future studies if effective pharmacotherapy options to enhance abstinence are to be found[48].

Aripiprazole and Disorders Induced by Amphetamine and Methamphetamine

During the last ten years, several studies verified the effectiveness of aripiprazole in amphetamine dependence treatment.

A study was conducted in 2007 with the purpose of comparing the effectiveness of aripiprazole, methylphenidate, and placebo in the treatment of amphetamine dependence. Urinalysis was used as an objective measure of primary outcome. The results of this study provided an

unfavorable result for the use of aripiprazole in the treatment of amphetamine dependence. When compared to placebo group, in fact, ARI treatment was found to correspond to a greater number of amphetamine-positive urine samples[47]. With the same goal in 2008, in a double-blind in-patient clinical pharmacology study, Newton et al[50] investigated the tolerability and effectiveness of aripiprazole, with the aim of assessing the interactions between intravenous methamphetamine and oral aripiprazole. The Authors concluded that aripiprazole treatment had negligible effects on the pharmacokinetics of methamphetamine since "higher ratings on Addiction Research Center Inventory subscales reflecting euphoria, significant reductions in ratings of 'bad effects' and reductions on the ARCI subscale for sedation effects following Meth dosing" were found.

More recently, using a different perspective in comparison to the previous studies, Sevak et al[51] studied discriminative-stimulus, subject-rated, and physiological effects of methamphetamine in humans pretreated with aripiprazole. The study assessed the effects of a range of doses of methamphetamine (0, 2.5, 5, 10, and 15 mg), alone and in combination with 0 and 20 mg of aripiprazole. The results thus obtained differed from the conclusions of previous studies. In their patients the discriminative-stimulus and cardiovascular effects together with the subject-rated drug effects, were significantly attenuated by administration of aripiprazole. A different study by Narendran et al[52] using positron emission tomography (PET), measured the amphetamine-induced dopamine (DA) release. These Authors evaluated the action of specific ligands in the human cerebellum by detecting a change in [^{11}C]FLB 457 V(T) following aripiprazole which ranged from –33 to –42% in the regions of interest (ROIs). The result of this study suggested an important interaction between aripiprazole and specific binding sites in the cerebellum that could be used in future drug treatments.

Finally, in 2011, a complex study by Steed et al[53] analyzed the ability of the serotonin reuptake inhibitor fluvoxamine to alter methamphetamine-induced hyperactivity. In this work aripiprazole was used just for comparative purposes, together with haloperidol, terguride, and clozapine. The results of this study emphasized that 1mg/kg of aripiprazole was the minimal effective dose necessary to attenuate methamphetamine-induced locomotor activity.

Nicotine

Tobacco addiction, the second-leading cause of death worldwide, is correlated with approximately 5 million deaths each year. Currently, there are about 1.3 billion smokers; most (84%) live in developing countries[54]. "With the present smoking trends, tobacco will kill 10 million people each year by 2020"[55].

Due to the complexity of the type of dependence, nicotine replacement therapies have been developed. These therapies gradually release nicotine into the body to facilitate withdrawal while allowing the smoker to break the behavioral habits associated with the cigarette itself. Nicotine gum is available in 2-mg and 4-mg pieces and is sold without a prescription[56]. Nicotine patches are a system designed to deliver nicotine transdermally over a 16- or 24-hour period maintaining nicotine levels for a longer period than any other system[57].

Another agent (non-nicotine based) that can be used to facilitate smoking cessation is bupropion. In clinical trials bupropion was well tolerated, the only adverse events more common with bupropion than placebo were insomnia and dry mouth and it prevented weight gain even if it should be noted that the drug was effective only in a long term therapy[58].

Varenicline, a partial α4β2 and full α7 nicotinic receptor agonist, was approved by the FDA in 2006 for the treatment of nicotine dependence. Its activity seems related to the inhibition of nicotine self-administration, through the action on dopamine balance in the nucleus accumbens[56]. In three studies comparing varenicline with buproprion and placebo, "varenicline 1 mg resulted in 52-week continuous abstinence rates of 21% to 23% (95% confidence intervals ranging from 17% to 28%), whereas buproprion and placebo produced rates of 14% to 16% (95% confidence interval 11%-20%) and 4% to 10% (95% confidence interval 1%-13%)", respectively[60].

Aripiprazole and Nicotine Consumption

The central dopaminergic system has a central role in the mechanism of reinforcement of the nicotine effects and consequently in the urge to smoke. In literature before 2010 two cases of smokers who responded positively to aripiprazole were reported.

Sriram Ramaswamy et al[61] reported the first in 2006. A case of "a man with a major depressive disorder that during his hospital stay, initiated

aripiprazole therapy and that subsequently discharged on aripiprazole and other medication noticed a lack of "high" from the cigarettes as well as fewer cravings for nicotine use, his Modified Fagerstrom Tolerance Questionnaire score decreased to zero and the patient attributed these results to aripiprazole. He continued to be nicotine abstinent for the next 2 weeks until he ran out of aripiprazole, while off aripiprazole therapy, he relapsed and went back to smoking. Approximately a week later, he resumed aripiprazole therapy and was simultaneously able to quit smoking again".

Another study was reported by Arbaizar[62] in 2008, that described a decrease in tobacco consumption after treatment with topiramate and aripiprazole. The mentioned case concerns "a 34-year-old man who compulsively smoked 80 to 100 cigarettes each day and that after receiving treatment with topiramate and aripiprazole, dramatically reduced his tobacco consumption".

Starting from these cases and other clinical evidence, in the last two years some clinical studies were conducted on heavy smokers and smoking schizophrenic patients. A recent study in 2010 investigated the urge to smoke in two particular moments of the day, at awakening and immediately following meals, in heavy smokers treated for 2 weeks with 10-mg aripiprazole, demonstrating that in treated patients an important decrease of waking and postprandial urges to smoke were observed[63].

In another study[64], this time in patients with a positive history of smoking but also having a previous diagnosis of schizophrenia, the effects of haloperidol and three atypical antipsychotics (risperidone, olanzapine, and aripiprazole) on the reduction of the urge to smoke were evaluated. These patients were interviewed about the need to smoke and cigarette craving at baseline and following eight weeks of treatment. Patients included in the haloperidol group reported that the urge to smoke increased, whereas patients belonging to atypical antipsychotics groups and specifically patients treated with aripiprazole, reported a reduction both in nicotine dependence and cigarette craving.

Conclusions

From the most recent literature, despite the lack of definitive results, it seems clear that the biological basis of dependence is related to several factors.

The most recent results obtained from scientific research showed that dopaminergic mechanisms are involved in motivation, reward, and reinforcement of substance abuse. It is becoming increasingly clear that in addicted subjects a decreased dopamine function produces a congruent decreasing in the sensitivity to non-drug-related stimuli and a reduction in the inhibitory frontal function. These last two aspects contribute to compulsive drug intake and compromise inhibitory control[65]. To this respect Voronin et al[30] suggested that aripiprazole would improve impulse control (self control for alcohol and substance) by enhancing the function of frontal cortex.

Regarding the serotonin system, the 5-HT1A partial agonist effect of aripiprazole may modulate prefrontal cortex to improve impulse control through the projections from the raphe nucleus to the ventral tegmental area and nucleus accumbens (Walsh and Cunningham, 1997)[66]. Taken together, these findings suggest that dopamine release induced by aripiprazole might be associated with increased activation of anterior cingulate which may control craving for alcohol and substances.

Many studies in the last few years highlighted aripiprazole as a potential treatment candidate for different types of dependence, with good evidence in alcohol, cocaine, amphetamine and tobacco use disorders, as described in this review. Moreover, in our opinion, aripiprazole could also represent a possible alternative in subjects with poly-substance-abuse, a condition characterized by higher level of psychiatric, and in those substance/alcohol abusers with high level of impulsivity and novelty seeking[67,68]. However, given the low number of studies, the frequent absence of placebo or active comparators, and the low statistical power of these studies, a clear conclusion cannot be drawn. Therefore we suggest that further studies are required, mainly randomized placebo-controlled, to determine the real efficacy of this molecule in the treatment of dependence.

References

1) STAHL SM. Dopamine system stabilizers, aripiprazole, and the next generation of antipsychotics, part 2: illustrating their mechanism of action. J Clin Psychiatry 2001; 62: 923-924.

2) CROXTALL JD. Aripiprazole: a review of its use in the management of schizophrenia in adults. CNS Drugs 2012; 26: 155-183.

3) SHAPIRO DS. Aripiprazole, a novel atypical antipsychotic drug with a unique and robust pharmacology. Neuropsychopharmacology 2003; 28: 1400-1411.

4) KATO T, MIZOGUCHI Y, MONJI A, HORIKAWA H, SUZUKI SO, SEKI Y, IWAKI T, HASHIOKA S, KANBA S. Inhibitory effects of aripiprazole on interferon-gamma-induced microglial activation via intracellular Ca2+ regulation in vitro. J Neurochem 2008; 106: 815-825.

5) DE BERARDIS D, CONTI CM, SERRONI N, MOSCHETTA FS, OLIVIERI L, CARANO A, SALERNO RM, CAVUTO M, FARINA B, ALESSANDRINI M, JANIRI L, POZZI G, DI GIANNANTONIO M. The effect of newer serotonin-noradrenalin antidepressants on cytokine production: a review of the current literature. Int J Immunopathol Pharmacol 2010; 23: 417-422.

6) KLEMP M, TVETE IF, SKOMEDAL T, GAASEMYR J, NATVIG B, AURSNES I. A review and Bayesian meta-analysis of clinical efficacy and adverse effects of 4 atypical neuroleptic drugs compared with haloperidol and placebo. J Clin Psychopharmacol 2011; 31: 698-704.

7) KATZMAN MA. Aripiprazole: a clinical review of its use for the treatment of anxiety disorders and anxiety as a comorbidity in mental illness. J Affect Disord 2011; 128(Suppl 1): S11-20.

8) FAGIOLINI A, NITTI M, FORGIONE RN, MARRA FS, CASAMASSIMA F. Aripiprazole for the treatment of bipolar disorder: a review of current evidence. Expert Opin Pharmacother 2011; 12: 473-488.

9) KANE JM, BARNES TR, CORRELL CU, SACHS G, BUCKLEY P, EUDICONE J, MCQUADE R, TRAN QV, PIKALOV A 3RD, ASSUNÇÃO-TALBOTT S. Evaluation of akathisia in patients with schizophrenia, schizoaffective disorder, or bipolar I disorder: a post hoc analysis of pooled data from short- and long-term aripiprazole trials. J Psychopharmacol 2010; 24: 1019-1029.

10) BERSANI G, GHERARDELLI S, CLEMENTE R, DI GIANNANTONIO M, GRILLI A, CONTI CM, EXTON MS, CONTI P, DOYLE R, PANCHERI P. Neurologic soft signs in schizophrenic patients treated with conventional and atypical antipsychotics. J Clin Psychopharmacol 2005; 25: 372-375.

11) BONO G, BALDUCCI C, RICHELMI P, KOOB GF, PULVIRENTI L. Dopamine partial receptor agonists reduce ethanol intake in the rat. Eur J Pharmacol 1996; 296: 233-238.

12) HUTCHISON KE, RAY L, SANDMAN E, RUTTER MC, PETERS A, DAVIDSON D, SWIFT R. The effect of olanzapine on craving and alcohol consumption. Neuropsychopharmacology 2006; 31: 1310-1317.

13) MARTINOTTI G, ANDREOLI S, DI NICOLA M, DI GIANNANTONIO M, SARCHIAPONE M, JANIRI L. Quetiapine decreases alcohol consumption, craving, and psychiatric symptoms in dually diagnosed alcoholics. Human Psychopharmacol: Clini Experi 2008; 23: 417-424.

14) KAMPMAN KM, PETTINATI HM, LYNCH KG, WHITTINGHAM T, MACFADDEN W, DACKIS C, TIRADO C, OSLIN DW, SPARKMAN T, O'BRIEN CP. A double-blind, placebo-controlled pilot trial of quetiapine for the treatment of Type A and Type B alcoholism. J Clin Psychopharmacol 2007; 27: 344-351.

15) OLIVE MF. Pharmacotherapies for alcoholism: the old and the new. CNS Neurol Disord Drug Targets 2010; 9: 2-4.

16) MANN K. Pharmacotherapy of alcohol dependence: a review of the clinical data. CNS Drugs 2004; 18: 485-504.

17) MARTINOTTI G, DI NICOLA M, TEDESCHI D, MAZZA M, JANIRI L, BRIA P. Efficacy and safety of pregabalin in alcohol dependence. Adv Ther 2008; 25: 608-618.

18) MARTINOTTI G, DI NICOLA M, FRUSTACI A, ROMANELLI R, TEDESCHI D, GUGLIELMO R, GUERRIERO L, BRUSCHI A, DE FILIPPIS R, POZZI G, DI GIANNANTONIO M, BRIA P, JANIRI L. Pregabalin, tiapride and lorazepam in alcohol withdrawal syndrome: a multi-centre, randomized, single-blind comparison trial. Addiction 2010; 105: 288-299.

19) KENNA GA, LEGGIO L, SWIFT RM. A safety and tolerability laboratory study of the combination of aripiprazole and topiramate in volunteers who drink alcohol. Hum Psychopharmacol 2009; 24: 465-472.

20) ADDOLORATO G, LEGGIO L, FERRULLI A, CARDONE S, BEDOGNI G, CAPUTO F, GASBARRINI G, LANDOLFI R. Baclofen Study Group. Dose-response effect of baclofen in reducing daily alcohol intake in alcohol dependence: secondary analysis of a randomized, double-blind, placebo-controlled trial. Alcohol Alcohol 2011; 46: 312-317.

21) BASER O, CHALK M, RAWSON R, GASTFRIEND DR. Alcohol dependence treatments: comprehensive healthcare costs, utilization outcomes, and pharmacotherapy persistence. Am J Manag Care 2011; 17(Suppl 8): S222-234.

22) SAVAS MC, GULLU JH. Disulfiram ethanol reaction– the significance of supervision. Ann Pharmacother 1997; 31: 374-375.

23) ANTON RF. Naltrexone for the management of alcohol dependence. N Engl J Med 2008; 359: 715-721.

24) BENJAMIN D, GRANT ER, POHORECKY LA. Naltrexone reverses ethanol induced dopamine release in the nucleus accumbens in awake freely moving rats. Brain Res 1991; 621: 137-140.

25) HERZ A. Endogenous opioid systems and alcohol addiction. Psychopharmacology 1997; 129: 99-111.

26) MARK TL, KASSED CA, VANDIVORT-WARREN R, LEVIT KR, KRANZLER HR. Alcohol and opioid dependence medications: prescription trends, overall and by physician specialty. Drug Alcohol Depend 2009; 99: 345-349.

27) EDWARDS S, KENNA GA, SWIFT RM, LEGGIO L. Current and promising pharmacotherapies, and novel research target areas in the treatment of alcohol dependence: a review. Curr Pharm Des 2011; 17: 1323-1332.

28) MARTINOTTI G, DI NICOLA M, JANIRI L. Efficacy and safety of aripiprazole in alcohol dependence. Am J Drug Alcohol Abuse 2007; 33: 393-401.

29) ANTON RF, KRANZLER H, BREDER C, MARCUS RN, CARSON WH, HAN J. A randomized, multicenter, double-blind, placebo-controlled study of the efficacy

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

30) Voronin K, Randall P, Myrick H, Anton R. Aripiprazole effects on alcohol consumption and subjective reports in a clinical laboratory paradigm–possible influence of self-control. Alcohol Clin Exp Res 2008; 32: 1954-1961.

31) Martinotti G, Di Nicola M, Di Giannantonio M, Janiri L. Aripiprazole in the treatment of patients with alcohol dependence: a double-blind, comparison trial vs. naltrexone. J Psychopharmacol 2009; 23: 123-129.

32) Myrick H, Li X, Randall PK, Henderson S, Voronin K, Anton RF. The effect of aripiprazole on cue-induced brain activation and drinking parameters in alcoholics. J Clin Psychopharmacol 2010; 30: 365-372.

33) Vergne DE, Anton RF. Aripiprazole: a drug with a novel mechanism of action and possible efficacy for alcohol dependence. CNS Neurol Disord Drug Targets 2010; 9: 50-54.

34) Shibasaki M, Kurokawa K, Mizuno K, Ohkuma S. Effect of aripiprazole on anxiety associated with ethanol physical dependence and on ethanol-induced place preference. J Pharmacol Sci 2012; 118: 215-224.

35) European Monitoring Centre for Drug and Drug Addiction (EMCDDA). Annual report on the state of the drugs problem in Europe. Luxembourg: Office for official Publications of the European Communities, 2011.

36) Preti A. New developments in the pharmacotherapy of cocaine abuse. Addict Biol 2007; 12: 133-151.

37) Karila L, Weinstein A, Aubin HJ, Benyamina A, Reynaud M, Batki SL. Pharmacological approaches to methamphetamine dependence: a focused review. Br J Clin Pharmacol 2010; 69: 578-592.

38) Kalivas PW. Neurobiology of cocaine addiction: implications for new pharmacotherapy. Am J Addict 2007; 16: 71-78.

39) Pani PP, Trogu E, Vacca R, Amato L, Vecchi S, Davoli M. Disulfiram for the treatment of cocaine dependence. Cochrane Drugs and Alcohol Group Published Online: 20 Jan 2010

40) Brodie JD, Case BG, Figueroa E, Dewey SL, Robinson JA, Wanderling JA, Laska EM. Randomized, double-blind, placebo-controlled trial of vigabatrin for the treatment of cocaine dependence in mexican parolees. Am J Psychiatry 2009; 166: 1269-1277.

41) Wee S, Hicks MJ, De BP, Rosenberg JB, Moreno AY, Kaminsky SM, Janda KD, Crystal RG, Koob GF. Novel cocaine vaccine linked to a disrupted adenovirus gene transfer vector blocks cocaine psychostimulant and reinforcing effects. Neuropsychopharmacology 2012; 37: 1083-1091.

42) Stoops WW, Lile JA, Lofwall MR, Rush CR. The safety, tolerability, and subject-rated effects of acute intranasal cocaine administration during aripiprazole maintenance. Am J Drug Alcohol Abuse 2007; 33: 769-776.

43) Lile JA, Stoops WW, Hays LR, Rush CR. The safety, tolerability, and subject-rated effects of acute intranasal cocaine administration during aripiprazole maintenance II: increased aripipirazole dose and maintenance period. Am J Drug Alcohol Abuse 2008; 34: 721-729.

44) Lile JA, Stoops WW, Glaser PE, Hays LR, Rush CR. Discriminative stimulus, subject-rated and cardiovascular effects of cocaine alone and in combination with aripiprazole in humans. J Psychopharmacol 2011; 25: 1469-1479.

45) Meini M, Moncini M, Cecconi D, Cellesi V, Biasci L, Simoni G, Ameglio M, Pellegrini M, Forgione RN, Rucci P. Aripiprazole and ropinirole treatment for cocaine dependence: Evidence from a pilot study. Curr Pharm Des 2011; 17: 1376-1383.

46) Haney M, Rubin E, Foltin RW. Aripiprazole maintenance increases smoked cocaine self-administration in humans. Psychopharmacology (Berl) 2011; 216: 379-387.

47) Tiihonen J, Kuoppasalmi K, Föhr J, Tuomola P, Kuikanmäki O, Vorma H, Sokero P, Haukka J, Meririnne E. A comparison of aripiprazole, methylphenidate, and placebo for amphetamine dependence. Am J Psychiatry 2007; 164: 160-162.

48) Brackins T, Brahm NC, Kissack JC. Treatments for methamphetamine abuse: a literature review for the clinician. J Pharm Pract 2011; 24: 541-550.

49) Martinotti G, Carli V, Tedeschi D, Di Giannantonio M, Roy A, Janiri L, Sarchiapone M. Mono- and poly-substance dependent subjects differ on social factors, childhood trauma, personality, suicidal behaviour, and comorbid Axis I diagnoses. Addict Behav 2009; 34: 790-793.

50) Newton TF, Reid MS, De La Garza R II, Mahoney JJ III, Abad A, Condos R, Palamar J, Halkitis PN, Mojisak J, Anderson A, Li S, Elkashef A. Evaluation of subjective effects of aripiprazole and methamphetamine in methamphetamine-dependent volunteers. Int J Neuropsychopharmacol 2008; 11: 1037-1045

51) Sevak RJ, Vansickel AR, Stoops WW, Glaser PE, Hays LR, Rush CR. Discriminative-stimulus, subject-rated, and physiological effects of methamphetamine in humans pretreated with aripiprazole. J Clin Psychopharmacol 2011; 31: 470-480.

52) Narendran R, Mason NS, Chen CM, Himes M, Keating P, May MA, Rabiner EA, Laruelle M, Mathis CA, Frankle WG. Evaluation of dopamine D / specific binding in the cerebellum for the positron emission tomography radiotracer [¹¹C]FLB 457: implications for measuring cortical dopamine release. Synapse 2011; 65: 991-997.

53) Steed E, Jones CA, McCreary AC. Serotonergic involvement in methamphetamine-induced locomotor activity: a detailed pharmacological study. Behav Brain Res 2011; 220: 9-19.

54) Esson L, Leeder SR. The millennium development goals and tobacco control: an opportunity for

global partnership. Geneva: World Health Organization (WHO); 2004.

55) World Health Organization. Why is tobacco a public health priority? A Tobacco Free Initiative; Available at http://www.who.int/tobacco/health_priority/en. March 30, 2006.

56) Von Mulzer K, Dando S, Gustavsson G, Radley N, Sjöstedt G, Sydbom P, Waltermo A. Improved productcharacteristics of nicotine gums: an unexplored area for higher compliance with nicotine replacement therapy. MMW Fortschr Med 2011; 153(Suppl 3): 75-82.

57) Beard E, Vangeli E, Michie S, West R. The use of nicotine replacement therapy for smoking reduction and temporary abstinence: An interview study. Nicotine Tob Res 2012; 14: 849-856.

58) Holm KJ. Bupropion: a review of its use in the management of smoking cessation. Drugs 2000; 59: 1007-1024.

59) Spiller K, Xi ZX, Li X, Ashby CRJ, Callahan PM, Tehim A, Gardner EL. Varenicline attenuates nicotine-enhanced brain-stimulation reward by activation of $\alpha4\beta2$ nicotinic receptors in rats. Neuropharmacology 2009; 7: 60-66.

60) Gonzales D. Varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs sustained-release bupropion and placebo for smoking cessation: a randomized controlled trial. JAMA 200; 296; 47-55.

61) Ramaswamy S & Bhatia SC. Aripiprazole therapy for nicotine dependence Prim Care Companion J Clin Psychiatry 2006; 8: 47-49.

62) Arbaizar B. Decrease in tobacco consumption after treatment with topiramate and aripiprazole: a case report. J Med Case Reports 2008; 2: 198.

63) Liu Y, Bao YP, Sun HQ, Beveridge TJ, Li SX, Di XL, Yang FD, Lu L. Long-term treatment with aripiprazole on the waking and postprandial urges to smoke in Chinese heavy smokers. J Clin Psychopharmacol 2010; 30: 373-380.

64) Kim SH, Han DH, Joo SY, Min KJ. The effect of dopamine partial agonists on the nicotine dependency in patients with schizophrenia. Hum Psychopharmacol 2010; 25: 187-190.

65) Volkow ND, Fowler JS, Wang GJ. Dopamine in drug abuse and addiction: results from imaging studies and treatment implications. Mol Psychiatry 2004; 9: 557-569.

66) Walsh SL, Cunningham KA. Serotonergic mechanisms involved in the discriminative stimulus, reinforcing and subjective effects of cocaine. Psychopharmacology (Berlin) 1997; 34: 177-183.

67) Martinotti G, Cloninger CR, Janiri L. Temperament and character inventory dimensions and anhedonia in detoxified substance-dependent subjects. Am J Drug Alcohol Abuse 2008; 130: 41-58.

68) Martinotti G, Mandelli L, Di Nicola M, Serretti A, Fossati A, Borroni S, Cloninger CR, Janiri L. Psychometric characteristic of the Italian version of the Temperament and Character Inventory--revised, personality, psychopathology, and attachment styles. Compr Psychiatry 2008; 49: 514-22.