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Original article

Long Acting Injectable Aripiprazole in the treatment of psychotic subjects comorbid with alcohol and substance use disorders: an open label observational study

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Abstract

***Background*: Among patients affected by a severe mental illness, comorbid addictive disorders are very common, despite they are under diagnosed and poorly treated. Dual-diagnosis patients are usually difficult to treat and they show a very low level of compliance. Oral formulation of Aripiprazole has shown to be efficacious in reducing craving and preventing relapses in subjects with alcohol use disorders and other forms of addiction. Our aim was to explore the effectiveness of Aripiprazole Long-Acting Injection in dual-diagnosis patients presenting with psychotic symptoms.**

***Methods*: In this observational, non-interventional study, we collected clinical and demographic data of outpatients presenting with psychotic symptoms comorbid with addictive disorder and receiving aripiprazole long acting monthly injection. Data about Timeline Follow-Back, Global Assessment of Functioning (GAF) and Brief Psychiatric Rating Scale (BPRS), performed before treatment initiation, during treatment and after treatment discontinuation, have been collected.**

***Results*: 18 patients completed the study (Table 1). At T0, BPRS and GAF scores were respectively 60.86 ± 12.11 and 44.38 ± 12.93. At T1, BPRS and GAF scores were respectively 48.57 ± 11.90 and 55.31 ± 13.43. Reduction in BPRS scores and improvement in GAF scores after treatment were statically significant (P<0.001). Twelve (66.7%) patients quit assuming substances during treatment. No pathological prolongation of QTc rates was observed.**

***Conclusions*: Our preliminary results suggest that aripiprazole long-acting intramuscular formulation may represent a valid opportunity for psychotic symptoms comorbid with Substance-related and Addictive Disorder. The mechanism of action of the drug, its pharmacokinetic properties, and the improvements in compliance might explain its potentialities in dual-disorders.**

KEY WORDS: aripiprazole, LAI, psychosis, dual diagnosis, addiction.

Introduction

Among patients affected by a severe mental illness, comorbid addictive disorders are very common, despite they are underdiagnosed and poor treated (1, 2). As known for a long time, patients with a psychiatric diagnosis are 2.7 times more likely to have behavioral, alcohol or substance addiction (3). Furthermore, for those with psychotic spectrum disorders (including Bipolar Disease with Psychosis) the odds of having an addictive comorbid disorder is also higher (4-6): the rate of psychotic-addictive disorders comorbidity is assessed between 40% and 70% (7, 8) and increases over time, especially in young patients at the onset of their disorder (9), presenting higher comorbidity rates. Despite the high prevalence of mental-addictive disorder comorbidity, dual-diagnosis is frequently underestimated (1), with subjects using alcohol and substances usually excluded from clinical trials.

Dual-diagnosis patients are usually difficult to treat and the prognosis is considered poor: comorbid patients usually show a very low level of compliance, and are frequently exposed to drop-out and lack of efficacy for the available antipsychotic drugs (2, 7, 10). Furthermore, they present higher rates of relapses and hospitalization, and the disease course tends to be chronic and unfavourable(2, 3, 5, 11). Nevertheless, only 10% of dual-diagnosis patients receive treatment for both mental and addictive disorders (12).

Among other classes of drugs, second generation antipsychotics (SGAs) have been proposed for Substance use Disorders (SUDs) with evidence in support of the practice (13). In contrast to the SGAs, first generation antipsychotics (FGAs) have been associated with negative findings and higher risk of relapse when compared with placebo, especially for flupentixol (14). FGAs are potent and relatively selective blocker of D_2 receptors, reaching high level of striatal D_2 receptor occupancy even at intermediate-low doses. Notably, blockade of D_1 but not D_2 receptors attenuates alcohol and substance consumption (15). Taken together, these reports let hypothesize that antipsychotic agents with high D_2 receptor blocking potential could induce a state of iatrogenic low striatal dopamine release, 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_2 receptor blocking propensity, reaching therapeutic efficacy at lower levels of striatal D_2 receptor occupancy (16). Moreover, some of the SGA are regarded to provide a loose binding to D_2 receptors (fast-dissociation) (16). Also, second generation antipsychotics are known to enhance serotonergic transmission by their antagonist action on 5-HT_{2A} receptors. These features suggest that second generation antipsychotics could less potently affect reward processes, thus preventing craving to occur, with good evidences for aripiprazole in subjects with alcohol use disorders and other forms of addiction (17, 18).

As far as we know there are no studies in dual-diagnosis patients treated with Long-Acting Injectable antipsychotics, although the issue of compliance, commonly addressed by this class of drugs, represent a central point in these subjects, as reported in different real life studies (19, 20).

Given the main role aripiprazole oral formulation in the treatment of subjects with alcohol and substance addiction comorbid with psychiatric disorders, the potentialities of aripiprazole LAI in psychotic patients with dual diagnosis are therefore significant, as reported in some trials where these typologies of subjects were not excluded from the recruitment (21) or in other studies where aripiprazole LAI showed to be efficacious in some personality dimension that are commonly described in psychotic subjects comorbid with alcohol and/or substance abuse (22). Moreover, schizophrenic patients included in the QUALIFY study (21) who were using recreational drugs during treatment with aripiprazole once-monthly showed improvement in Quality of Life Scale (QLS) (23). Aripiprazole may also guarantee further benefits in terms of cardiac parameters (7), frequently altered in subjects with Alcohol and Substances Use Disorders, as recently showed by a study where aripiprazole did not provoke any QTc alteration in comparison with other antypsychotics (24).

To the best of our knowledge, no study specifically evaluated the role of Aripiprazole LAI in dual-diagnosis patients. Our aim was to explore its effectiveness in dual-diagnosis patients presenting with psychotic symptoms, both in term of psychiatric symptoms, functioning and addiction withdrawal. Our second aim was to evaluate QTc alteration in these patients.

Subjects and Methods

Setting

Data were collected in a prospective, observational, non-interventional study. The study was approved by the local Ethics Committee and conducted according to the national and local regulatory requirements, Good Clinical Practice guidelines and the Declaration of Helsinki of 1975, as revised in 1983. We collected data in the Outpatient Clinic of Mental Health Department of Chieti (Italy) and in the Addiction Outpatient Unit of Villa Maria Pia Clinic, Rome (Italy). All personal data had been anonymously extracted from records and identified via specific individual codes. Datasets had been anonymized by removing all direct and indirect identifiers.

Subjects

We collected clinical and demographic data of outpatients presenting with psychotic symptoms comorbid with alcohol or substance use disorder and receiving aripiprazole long acting monthly injection. All patients included met the following criteria: 1. 18-65 years old; 2. Alcohol or substance abuse disorder according with DSM-5; 3. Presenting psychotic symptoms; 4. Being treated with aripiprazole long-acting injection as monotherapy. Data about patients with liver and/or kidney diseases, younger than 18 or older than 65 years were excluded in order to reduce confounding factors.

Treatment

All patients receiving monthly injection at the time of the collection were included. Prescription of Aripiprazole Long-Acting was not influenced by researchers. As suggested by guide lines, treatment was started with Aripiprazole oral formulation administered 10-30 mg/day depending on the clinician's perception. Oral treatment was continued until symptoms stabilization, then Aripiprazole LAI has been administered at 400 mg monthly as intramuscular injection, together with the oral formulation for the first 14 days and then in monotherapy. The association with a mood stabilizer and benzodiazepines has been allowed.

Data collection

Demographic information included sex, age, body mass and height, marital status, years of study and occupational status. Symptoms severity and diagnosis have been extracted by records. Estimation of alcohol and substance abuse before, during and after treatment was obtained with the Timeline Follow-Back (25, 26) stored in medical records. Total and item per item scores of Global Assessment of Functioning (GAF) and Brief Psychiatric Rating Scale (BPRS), performed before treatment initiation, during treatment and after treatment discontinuation, have been collected. We considered baseline as the last psychiatric evaluation before treatment initiation and T1 as the first evaluation after treatment discontinuation or modification. At least one electrocardiography has been extracted from records and collected to evaluate QTc prolongation during treatment.

Statistical Analysis

All data were expressed as mean (*M*) ± Standard Deviation (*SD*) and categorical data as percentages. Normal distribution of data was tested with Kolmogoroff-Smirnov test. Clinical assessments and psychometric questionnaires scores performed before and after treatment were compared using *t*-tests for paired samples. ANCOVA analysis has been performed to evaluate the effect of addiction withdrawal and demographic factors on outcomes (BPRS and GAF amelioration). Statistical analysis was performed using SPSS version 22.0 (Macintosh). Statistical significance was accepted if a *p*-value < 0.05 (two-sided) was obtained.

Results

A total of 18 patients were included in the study. Demographic parameters of the study sample are summarized in Table 1. All patients presented with psychotic symptoms (Figure 1: 13 psychotic disorders, 5 mood disorders with psychotic features) comorbid with alcohol or substance use disorder (Figure 1). Addictive behaviours and type of abused substances are reported in Figure 2. All patients received Aripiprazole LAI for at least 4 weeks (n. weeks: 26.43 ± 31.30).

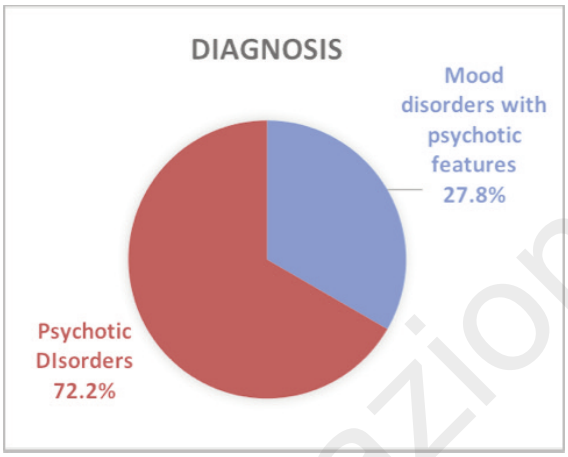

Figure 1. Main psychiatric diagnosis.

Psychometric Assessment

There were significant differences in BPRS and GAF scores between baseline and T1 (*p's* < 0.001): we observed a significant amelioration of symptoms severity and functioning, as reported in Table 2 and figure 3. These results were not confirmed by single-items analysis.

There were no significant effects of time expressed as weeks of treatment (*p's* > 0.05). Covariate analysis for gender, diagnosis, marital and occupational status, revealed that no demographic factors was significantly associated with BPRS or GAF outcomes (*p's* > 0.05).

Addictive behaviour

According to TLFB, 12 patients quitted their addictive behaviour at the second evaluation (T1) and 2 of them did not referred any changing in consumption, 6 patients did not complete their TLFB at the second evaluation. We separately analysed the two groups of patients (addiction: patients who quitted VS patients who continued). Estimation of improvement in psychiatric symptoms and functioning, expressed as Delta score (score at the end of the study - score at baseline) of BPRS and GAF scores, did not differ between the two groups.

Furthermore, there were no significant main effects for addiction quitting on GAF scores amelioration (*p* > 0.05), but there was a trend towards significance in

Table 1. Demographic data.

Gender (n; %)	10 (55.6%) males; 8 (44.4%) females
Age (years)	36.56 ± 9.34
Marital Status (n; %)	14 (77.8%) singles; 3 (16.7%) married
Occupational Status (n; %)	9 (50%) unemployed; 9 (50%) employed
Race (n; %)	18 (100%) Caucasians
Years of study (years)	12.25 ± 2.2

Age and Years of study are expressed as Mean ± SD; all other data as number of subjects and percentage.

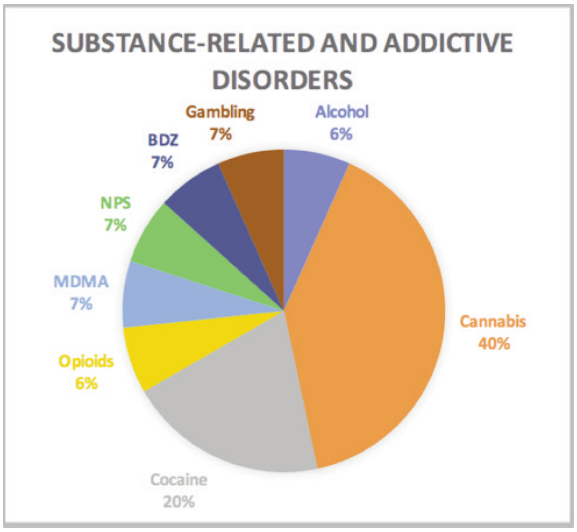

Figure 2. Addiction behavior.
NPS: novel psychoactive substances; BDZ: benzodiazepines; MDMA: amphetamines.

reducing BPRS scores (F = 3.604, $p = 0.084$).

QTc assessment

No patients showed QTc interval prolongation after treatment, as shown by ECG evaluation performed at T1 (0.402 ± 0.018).

Discussion

In this observational, prospective, naturalistic study we intended to collect some preliminary data on the safety and efficacy of Aripiprazole Long Acting monthly injection in psychotic patients comorbid with addictive disorders. We chose a naturalistic study to directly assess LAI prescription practice in two different Italian outpatients' units.

In accordance with our hypotheses, the main findings of this study show an improvement in both psychiatric symptoms and functioning among dual diagnosis patients treated with Aripiprazole Long-Acting injection. These positive results were not influenced by duration of treatment: reduction of psychotic symptomatology and increase in functioning were reported also in patients who completed only 4 weeks of treatment. This is the first study in which the effects of aripiprazole LAI were assessed in dual diagnosis individuals and these preliminary evidences support a possible role of aripiprazole in this high-risk population. These data are consistent with what was previously observed with Aripiprazole oral formulation in dual-diagnosis subjects (17, 27-30), and confirm some incidental data emerged from previous trial with LAI-Aripiprazole (23).

One noteworthy finding of this research is that the absence of substance/alcohol consumption was associated with an increase in symptoms amelioration in people already treated with aripiprazole. This result, albeit nonsignificant owing to the small sub-sample, suggests a potential role for Aripiprazole in the treatment of psychotic symptoms comorbid with addictive disorders.

Another relevant result of this study is that cardiac parameters remained stable during treatment. This data is consistent with a recent study where Aripiprazole did not provoke any QTc alteration in comparison with other antypsychotics (24), and is relevant considering that of alcohol and drug users a population of subjects usually considered at risk for the development of cardiac abnormalities (31-33). The safety profile of Aripiprazole suggests its suitability for use also when the use of other substance cannot be ruled out.

Trying to speculate on the possible factors influencing this positive results for aripiprazole LAI, that of the psychodynamic interaction of the drug represents the main hypothesis, given the dopamine partial agonist activity of Aripiprazole able to preserve the reward system (23). Furthermore, aripiprazole is a partial dopamine and 5-HT1A agonists: it seems to improve impulses control and craving for alcohol and substances by modulation prefrontal cortex, ventral tegmental area (VTA) and Nucleus Accumbens (NAc) (17, 18). The long acting formulation could fguarantee a further benefit in terms of pharmacokinetic/concentration stability of the drug, and a dramatic improvement in compliance.

Although the open-label mature of the study do not allow to trace any firm conclusion about the efficacy of LAI Aripiprazole in the prevention of relapse and in maintenance of abstinence, we can consider this drug with a potential for: 1. Subjects with primary psychiatric conditions, especially schizophrenia, mood disorders with psychotic features, dissociative disorders, and borderline personality (27, 29), where the presence of an addictive disorder can complicate the clinical presentation; 2. Subjects with poly-substance-abuse, characterized by higher levels of impulsiveness, sensation seeking, early onset of alcohol misuse, antisocial behaviors, reward craving, with high

Table 2. Psychometric assessment between baseline and T0.

	Baseline	T1	p-value
GAF	44.38 ± 12.93	55.31 ± 13.43	< 0.001**
BPRS	60.86 ± 12.11	48.57 ± 11.90	< 0.001**

GAF: Global Assessment of Functioning; BPRS: Brief Psychiatric Rating Scale.

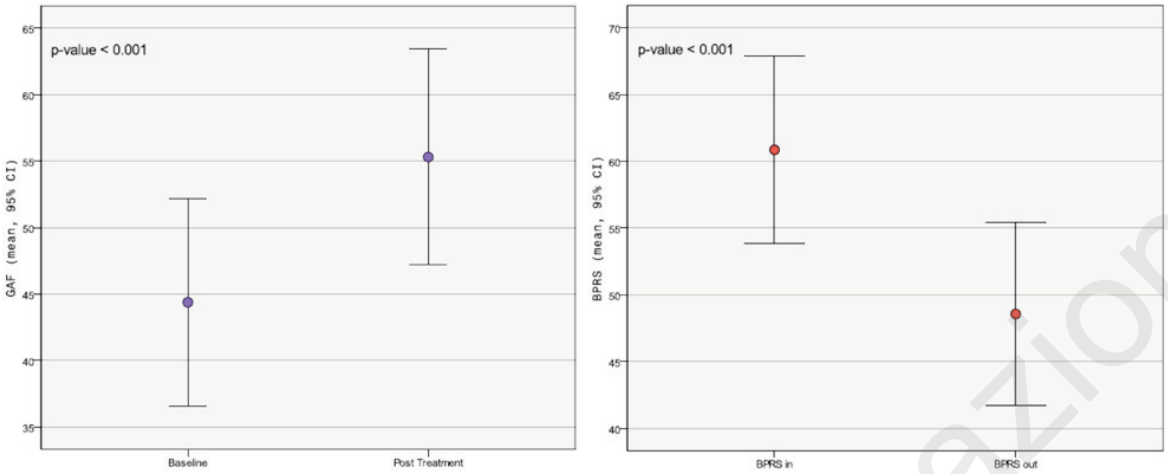

Figure 3. Psychometric assessment between baseline and T0.

rates of concurrent psychiatric symptoms, especially when polyabuse of alcohol and novel psychoactive substances occurs (34-37), and when compliance for a patient can represent a very difficult target to achieve.
The limitations of this study are represented by: 1. The open-label design; 2. The low number of participants; 3. The not homogeneous duration of the study; 4. The absence of an active comparator.

Conclusions

Our preliminary results suggest that Aripiprazole Long-Acting intramuscular formulation may offer a valid opportunity for a life-time control for psychotic symptoms in subjects with Schizophrenia and Mood Disorders with psychotic features comorbid with Substance-related and Addictive Disorder, clinical conditions that nowadays represent the typical phenomenology of a young patient at the onset of its psychotic disorder. These results may be further investigated in clinical trials involving larger sample of patients.

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