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ORIGINAL RESEARCH ARTICLE

Once-Monthly Long-Acting Injectable Aripiprazole for the Treatment of Patients with Schizophrenia and Co-occurring Substance Use Disorders: A Multicentre, Observational Study

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Abstract

Aim To evaluate the efficacy and impact of long-acting injectable (LAI) aripiprazole in patients with schizophrenia with a coexisting substance use disorder (SUD).

Patients and methods A multicenter, observational, descriptive and retrospective study was conducted in patients with a DSM-5 diagnosis of schizophrenia who had a coexisting SUD and were treated with LAI-aripiprazole. Disease severity was evaluated with the Clinical Global Impression (CGI) severity scale for schizophrenia, daily functioning and disability were evaluated with the World Health Organisation Disability Assessment Scale (WHODAS-2.0), and the severity of the addiction was evaluated with the Severity of Dependence Scale (SDS).

Results The sample included 40 patients. Overall, after 6 months of treatment with LAI-aripiprazole at a dose of 400 mg/4 weeks in 77.5% of the patients, we observed significant improvement in the psychopathological symptoms, with a reduction of over 30% in the scores of the five CGI-severity scales. The WHODAS-2.0 mean (standard deviation) score was also significantly reduced from 57.6 (8.2) to 42.3 (4.3) points ($p < 0.001$). Regarding SUDs, after 6 months of treatment, substance use was stopped in 5 of the 9 patients with cocaine use disorder and in 3 of the 16 patients with alcohol abuse disorder. A significant reduction in the severity of the dependence was observed only in the subgroups of participants with cocaine and alcohol use disorders.

Conclusion Our study suggests that once-monthly LAI-aripiprazole retains its antipsychotic efficacy in patients with schizophrenia and a coexisting SUD and could be useful for the management of cocaine or alcohol use disorders in this population.

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Key Points

Once-monthly LAI, aripiprazole is efficacious for managing psychotic symptoms in patients with schizophrenia with coexisting substance use disorders.

In patients with psychosis and co-occurring alcohol or cocaine use disorder, LAI aripiprazole could be useful for reducing the severity of the use disorder and eventually for stopping consumption.

These promising results should be confirmed by randomized clinical trials that include a long-term follow-up and an evaluation of the impact of the treatment on specific outcomes, such as sustained abstinence and the so-called "good functioning".

1 Introduction

Substance use disorders (SUDs) are common in patients with schizophrenia. A recent meta-analysis showed that the prevalence of any SUD among patients with schizophrenia or first-episode psychosis was 42%, with the most common SUDs being those related to illicit drugs (28%), cannabis (26%), alcohol (24%) and stimulants (7%) [1]. The prevalence of tobacco smoking in patients with schizophrenia varies across countries, but overall, the rate of current schizophrenia patient smokers is up to 6-fold higher than the rate reported in the general population [2]. Although less studied, the prevalence of pathological gambling has been reported to be approximately 10% among patients with schizophrenia [3]. The presence of SUDs among patients diagnosed with schizophrenia is associated with a higher severity of symptoms, an increased risk of non-adherence, an increased risk of extrapyramidal symptoms, more frequent relapse and inpatient psychiatric admissions, and a higher occurrence of disruptive behaviors [4–11].

Treatment of patients with schizophrenia and a coexisting SUD is particularly challenging. According to current guidelines, the best treatment approach is the combination of antipsychotics and psychosocial interventions for addictive behaviors [12, 13]. Although there are few advantages of one antipsychotic treatment over another, when treating patients with psychosis and coexisting SUDs, the use of second-generation antipsychotics may be preferred over first-generation antipsychotics due to their better tolerability profile, including a lower liability for inducing extrapyramidal side effects [12]. In addition, first-generation antipsychotics, due to potent dopaminergic blockade, can induce a worsening of craving, as reported with haloperidol and smoking [14].

Aripiprazole is an atypical antipsychotic that, in contrast to first-generation and other second-generation antipsychotics, acts as a partial agonist of D2 receptors, modulating their activity instead of *blocking* it [15]. Since aripiprazole is a partial agonist, it produces substantially less functional antagonism of D2 receptor-mediated neurotransmission than full antagonists [15]. Dopaminergic dysfunction is well known to be involved in addiction. Thus, drugs such as aripiprazole, which can modulate the dopaminergic system, might be beneficial for reducing craving, rewarding effects, and relapse [16]. These characteristics, together with its well-established efficacy for the treatment of schizophrenia, the lower risk of extrapyramidal side effects compared to first-generation antipsychotics, and the lower risk of metabolic side effects compared to most second-generation antipsychotics [17], make aripiprazole an attractive alternative for the treatment of patients with schizophrenia with coexisting SUDs. Evidence from randomized clinical trials and laboratory studies has suggested that oral aripiprazole could be efficacious for the management of alcohol [18, 19] or cocaine dependence [20, 21]. However, other clinical [22] and laboratory studies [23–25] have reported negative results. Focusing on dual disorders, a randomized neuroimaging study suggested that oral aripiprazole combined with escitalopram may be useful for the treatment of patients with major depression and alcohol dependence [26]. Moreover, although published evidence on the efficacy of aripiprazole in patients with schizophrenia and co-occurrent SUDs is scarce, a randomized study comparing oral aripiprazole with perphenazine in a sample of patients with schizophrenia and cocaine dependence reported a reduction in cocaine craving associated with aripiprazole [27].

While highlighting the need for more research, partly due to the high level of noncompliance in dual disorder patients, some authors have proposed the preferred use of long-acting injectable (LAI) formulations in the management of patients with schizophrenia and a co-occurrent SUD [12, 13, 28]. In the case of LAI aripiprazole, to date, the published evidence is limited to a naturalistic trial that showed better outcomes with LAI aripiprazole than with LAI paliperidone in patients with comorbid psychosis and SUDs [29] and a small case series [30]. The aim of this retrospective study was to evaluate the efficacy and impact of long-acting injectable aripiprazole in patients with schizophrenia with a coexisting SUD.

2 Patients and Methods

This multicenter, observational, descriptive and retrospective study was conducted at five sites in Spain between October 2017 and February 2018; the five participant sites were Hospital Universitario Gregorio Marañón (Madrid, Spain). Instituto Adicciones (Madrid, Spain), Hospital Universitario Vall d´Hebron (Barcelona, Spain), Hospital Universitari Dr. Peset (Valencia, Spain), and Complejo Asistencial Universitario Salamanca (Salamanca, Spain). The study was revised and approved by the Ethics Committee of the Hospital General Universitario Gregorio Marañón (Madrid, Spain)(Protocol code: FPD-ARI-2017-01), and all patients gave their written informed consent for using their data with investigational purposes.

Patients with a diagnosis of schizophrenia and a coexisting SUD according to the DSM-5 who had received treatment with LAI aripiprazole were eligible for the study. Due to its naturalistic design, patients could have received other medications, including other antipsychotics.

Information was collected on sociodemographic and clinical characteristics, as well as on disease severity using the Clinical Global Impression (CGI) severity scale for schizophrenia, on daily functioning and disability with the World Health Organization Disability Assessment Schedule (WHODAS 2.0), and on addiction severity using

the Severity of Dependence Scale (SDS) before starting treatment with LAI aripiprazole. The CGI severity scale, WHODAS 2.0 and SDS scores were also recorded at 3 and 6 months after treatment initiation.

The CGI severity scale for schizophrenia is an instrument that was devised to evaluate the severity and treatment response among patients with a diagnosis of schizophrenia [31]. It comprises five items based on a 7-point Likert scale that focus on positive, negative, depressive, cognitive, and overall symptom severity. This scale is considered a simple and reliable measure to evaluate the clinical status and course of the disease during routine clinical practice [32]. The WHODAS 2.0 evaluates six domains of functioning as experienced in the previous 30 days: mobility, self-care, life activities, understanding and communicating, interpersonal interactions, and participation in society [33]. This 12-item instrument assesses each domain with two items that are measured on a 3-point scale in which 1 indicates no disability and 2 and 3 indicate mild to moderate and severe to extreme disability, respectively. Therefore, the higher the score is, the greater the disability. We used the validated Spanish version of the WHODAS 2.0 [34]. The Severity of Dependence Scale (SDS) is a reliable and valid 5-item screening instrument that provides a score indicating the severity of dependence on several types of substances [35]. Each of the five items is scored on a 4-point scale (0–3). The total score is obtained through the sum of the ratings of the 5 items. The higher the score is, the higher the severity of substance dependence. We used the validated Spanish version of the SDS [36, 37].

For the statistical analysis, quantitative variables were described with the mean and standard deviation, and qualitative variables were described with the absolute and relative frequencies. Changes after treatment initiation in the outcome measures were analyzed using a paired Student's *t* test. Changes were considered statistically significant at $p < 0.05$. All analyses were performed with IBM® SPSS® Statistics Version 25 for the Mac OS.

3 Results

3.1 Demographic and Clinical Characteristics

A consecutive sample of 40 patients with a mean age of 38 years who were predominantly male and mostly single or divorced were included in the study (Table 1). The most frequent medical comorbidities were hepatitis (20%) and HIV infection (10%). Half of the patients had multiple episodes of schizophrenia, a majority were currently in partial remission, and over half were mildly to moderately ill, as evaluated with the CGI scale (Table 2). Thirty-two (80%) of the patients had previous inpatient admissions, with a mean of 3.7 admissions. For the vast majority of patients, treatment with LAI aripiprazole was initiated at a dose of 400 mg every 4 weeks. Many patients were prescribed other psychotropic medications, as well, most commonly benzodiazepines and antidepressants, while 9 (22.5%) patients were also taking oral antipsychotics (six were taking quetiapine, two were taking olanzapine, and one was taking levomepromazine). Eighteen (45%) patients were receiving psychotherapy, which consisted of individual sessions of cognitive behavioral guidance.

The most frequent current and lifetime SUD diagnoses involved tobacco, alcohol, cannabis or cocaine. Drug use was initiated at a mean age of 14–25 years for the different substances (Table 3). Very few patients received specific pharmacological treatment for the SUD (Table 2).

3.2 Efficacy Results

At the end of the follow-up, 31 (77.5%) patients were receiving 400 mg/4 weeks, 5 (12.5%) were receiving 300 mg/4 weeks, 3 (7.5%) were receiving 400 mg/3 weeks, and 1 patient (2.5%) was receiving 400 mg/2 weeks of LAI aripiprazole; 34 (85%) patients were receiving other psychotropics, including 1 patient receiving an antipsychotic (quetiapine). Almost half of the patients were also receiving some kind of psychotherapy intervention.

Table 1 Sociodemographic characteristics and medical comorbidities

Characteristic	*N* = 40
Age (years), mean (SD)	37.7 (9.9)
Sex (male) [*n* (%)]	31 (77.5)
Marital status [*n* (%)]	
Single/never married	21 (52.5)
Married/living with a partner	12 (30.0)
Divorced	7 (17.5)
Working status [*n* (%)]	
Active	11 (27.5)
Unemployed	5 (12.5)
Permanent disability	13 (32,5)
Retired	6 (15%)
Housewife	1 (2.5)
Other	2 (5.0)
Medical comorbidity [*n* (%)]	
Hepatitis	8 (20.0)
HIV infection	4 (10.0)
Hypertension	2 (5.0)
Obesity	2 (5.0)
Diabetes mellitus	1 (2.5)
Tuberculosis	1 (2.5)
Other	7 (17.5)

HIV human immunodeficiency virus, *SD* standard deviation

Table 2 Psychiatric history and treatment

Characteristic	$N=40$
Schizophrenia diagnosis (course specifiers) [*n* (%)]	
First episode, currently in partial remission	9 (22.5)
Multiple episodes, currently in acute episode	5 (12.5)
Multiple episodes, currently in partial remission	20 (50.0)
Multiple episodes, currently in full remission	4 (10.0)
Continuous	1 (2.5)
Unspecified	1 (2.5)
Previous admissions	
Yes [*n* (%)]	32 (80.0)
Total number, mean (SD)	3.7 (3.3)
Number in previous year, mean (SD)	0.8 (0.9)
WHODAS 2.0, total score	57.5 (8.2)
CGI severity [*n* (%)]	
Normal, not ill	0 (0.0)
Minimally ill	5 (12.5)
Mildly ill	10 (25.0)
Moderately ill	13 (32.5)
Markedly ill	6 (15.0)
Severely ill	6 (15.0)
Among the most severely ill	0 (0.0)
LAI aripiprazole: initial dose [*n* (%)]	
400 mg/2 weeks	1 (2.5)
400 mg/3 weeks	3 (7.5)
400 mg/4 weeks	33 (82.5)
300 mg/4 weeks	3 (7.5)
Other psychotropics[a] [*n* (%)]	
Any	34 (85.0)
Antidepressants	13 (32.5)
Lithium	1 (2.5)
Benzodiazepines	19 (47.5)
Oral antipsychotics	9 (22.5)
Anticonvulsants	11 (27.5)
SUD pharmacologic treatments [*n* (%)]	
Opioid agonists	3 (7.5)
Naltrexone	1 (2.5)
Nalmefene	3 (7.5)
Disulfiram	2 (5.0)
Varenicline	1 (2.5)
Psychotherapy [*n* (%)]	18 (45.0)

SD standard deviation

[a]Patients could be receiving more than one treatment

Table 3 Substance use disorder characterization

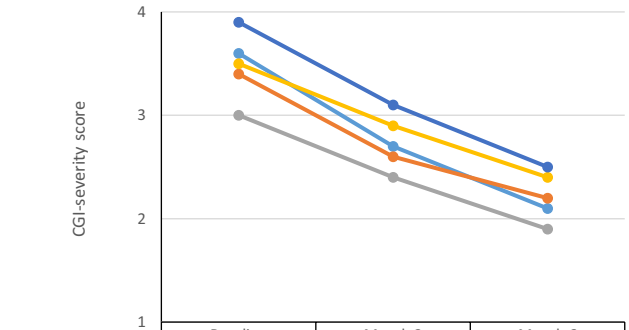
Characteristic[a]	$N=40$
Tobacco	
Lifetime [*n* (%)]	36 (90.0)
Current [*n* (%)]	35 (87.5)
Age of onset (years), mean (SD)	14.3 (1.5)
Alcohol	
Lifetime [*n* (%)]	26 (65.0)
Current [*n* (%)]	16 (40.0)
Age of onset (years), mean (SD)	15.6 (2.6)
Caffeine	
Lifetime [*n* (%)]	11 (27.5)
Current [*n* (%)]	11 (27.5)
Age of onset (years), mean (SD)	15.9 (2.5)
Cannabis	
Lifetime [*n* (%)]	26 (65.0)
Current [*n* (%)]	17 (42.5)
Age of onset (years), mean (SD)	16.0 (3.4)
Opioids (heroin)	
Lifetime [*n* (%)]	7 (17.5)
Current [*n* (%)]	3 (7.5)
Age of onset (years), mean (SD)	19.9 (3.5)
Opioids (methadone)	
Lifetime [*n* (%)]	2 (5.0)
Current [*n* (%)]	1 (2.5)
Age of onset (years), mean (SD)	24.5 (0.7)
Sedatives	
Lifetime [*n* (%)]	5 (12.5)
Current [*n* (%)]	5 (12.5)
Age of onset (years), mean (SD)	24.2 (8.2)
Cocaine	
Lifetime [*n* (%)]	18 (45.0)
Current [*n* (%)]	9 (22.5)
Age of onset (years), mean (SD)	19.6 (2.6)
Pathological gambling	
Lifetime [*n* (%)]	4 (10.0)
Current [*n* (%)]	1 (2.5)
Age of onset (years), mean (SD)	25.2 (2.4)

SD standard deviation

[a]Patients could exhibit more than disorder

Overall, treatment with LAI aripiprazole was associated with a significant improvement in the psychopathological symptoms as evaluated with the five CGI severity scales (Fig. 1). Across all scales, a reduction of over 30% in the CGI severity score was observed after 6 months of treatment with LAI aripiprazole. The mean (standard deviation) score of the WHODAS 2.0 was significantly reduced from 57.6 (8.2) at treatment initiation to 42.3 (4.3) after 6 months of treatment ($p<0.001$). The reductions in the scores of the CGI scales and WHODAS 2.0 were statistically significant at month 3.

Regarding the SUDs, 4 of the 9 patients with a cocaine use disorder and 13 of the 16 patients with an alcohol use disorder at baseline were still consuming at 6 months of follow-up. In addition, all 3 patients with a heroin use disorder were abstinent at the end of the follow-up period (Fig. 2a). The only group of addictions that showed a



	Baseline	Month 3	Month 6
Positive	3.6	2.7	2.1
Negative	3.4	2.6	2.2
Depressive	3	2.4	1.9
Cognitive	3.5	2.9	2.4
Overall severity	3.9	3.1	2.5

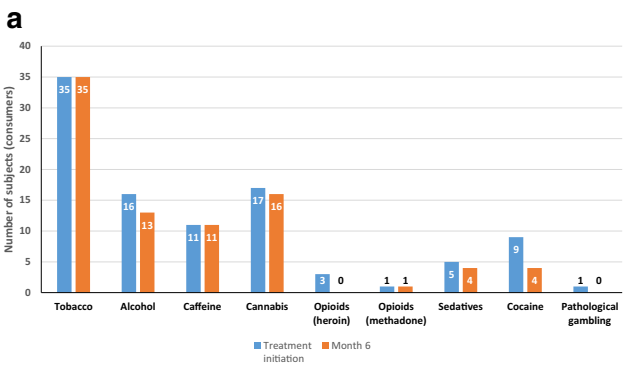
Fig. 1 Change in the Clinical Global Impression severity scores since treatment initiation. CGI severity scores range from 1 to 7; *Y* axis values represent scores 1–4 to improve the visibility of the data. All changes from baseline to month 3 and month 6 for all scales were statistically significant ($p < 0.001$)

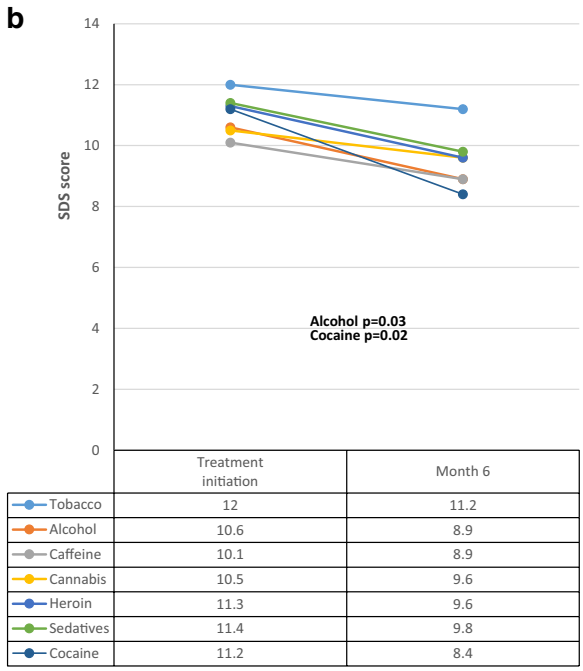
significant reduction in the severity of the dependence were the subgroups of alcohol (from a score [SD] of 10.6 [3.9]–8.9 [3.2]) and cocaine use disorders (from a score [SD] of 11.2 [4.9]–8.4 [3.5]) (Fig. 2b).

4 Discussion

The results of this observational retrospective study suggest that once-monthly LAI aripiprazole is efficacious for managing psychotic symptoms in patients with schizophrenia with coexisting SUDs. In addition, in psychotic patients with an alcohol or cocaine use disorder, LAI aripiprazole could be useful for reducing the severity of the use disorder and eventually achieving abstinence.

Once-monthly LAI aripiprazole was associated with a reduction in symptoms of schizophrenia, as shown by the observed significant changes in all of the CGI severity schizophrenia subscales after 6 months of treatment. These reductions, albeit modest, were clinically relevant. Thus, the mean change from baseline in the CGI severity scores was more than 1 point for all symptoms, as well as in the overall severity, corresponding to more than a 30% decrease in all CGI severity scores. Moreover, disability also improved to a similar extent (i.e., a 27% reduction in the WHODAS 2.0 score), suggesting that this improvement in the symptoms of schizophrenia in these dually diagnosed patients is accompanied by an improvement in functioning. These results are difficult to put into perspective in terms of external evidence, since information on the use of LAI antipsychotics in patients with schizophrenia and a coexisting SUD is limited. In one of the few published reports, a





	Treatment initiation	Month 6
Tobacco	12	11.2
Alcohol	10.6	8.9
Caffeine	10.1	8.9
Cannabis	10.5	9.6
Heroin	11.3	9.6
Sedatives	11.4	9.8
Cocaine	11.2	8.4

Fig. 2 Time course of substance use disorders* under treatment with long-acting injectable aripiprazole. **a** Number of consumers. **b** Course of severity of dependence (SDS). Asterisk patients could exhibit more than disorder

randomized clinical trial comparing the efficacy and safety of LAI and oral formulations of risperidone, no differences were found between the two formulations of risperidone in the improvement of psychopathological symptoms [38]. LAI risperidone has also been compared with zuclopenthixol in patients with schizophrenia and comorbid substance abuse in a randomized, open-label, 6-month study that reported a 34% reduction in the Positive and Negative Syndrome scale total score, an effect size that is almost identical to that observed in the CGI overall severity score here (i.e., a 36% reduction) [39]. A randomized, 1-year follow-up study comparing LAI aripiprazole with LAI paliperidone in patients with psychosis, mostly schizophrenia, and SUD reported a large effect of the change from baseline in the CGI severity score, from 5.9 to 2.4 for LAI aripiprazole and from 5.7 to

2.6 for LAI paliperidone [29]. However, patients in the LAI aripiprazole group were much younger than those included in our study (a mean of 27 vs. 38 years old), and the number of previous hospitalizations was lower (a mean of 1.8 vs. 3.7 hospitalizations), suggesting that the patients in their study had a much less chronic disease. Considering these differences and the fact that their patients also exhibited a more severe symptoms of schizophrenia before starting treatment and a longer follow-up, it is not possible to compare the results of these studies.

LAI aripiprazole also showed a beneficial effect on some measures of substance use in patients with alcohol use disorder and especially in those with cocaine use disorder, with significant and clinically relevant reductions in the severity of the dependence. In addition, in the case of cocaine use disorder, a substantial number of patients achieved abstinence by the end of follow-up (i.e., from 9 patients who were consumers at treatment initiation to 4 patients by the end of follow-up). Previous studies of oral aripiprazole in patients with SUDs support these results. In a randomized placebo-controlled study, Moran et al. [21] showed that oral aripiprazole could delay relapse in recently abstinent cocaine users; however, somewhat unexpectedly, aripiprazole increased cocaine craving. In any case, the study was terminated early because of difficulties recruiting patients who met the abstinence criterion [21]. In a 12-week randomized pilot study in patients with cocaine dependence, oral aripiprazole was more efficacious than ropinirole in reducing cocaine use [40]. Specifically, in a short-term, double-blind randomized trial in patients with a dual diagnosis of schizophrenia and cocaine dependence, oral aripiprazole was as efficacious as perphenazine in the number of patients with cocaine-free urine samples and the frequency and duration of craving [27]. However, we must be cautious when interpreting these results and when suggesting the efficacy of LAI aripiprazole and other antipsychotics for the treatment of patients with schizophrenia and cocaine use disorder. Some laboratory studies have not supported the usefulness of aripiprazole for the management of cocaine use disorders [22, 24]. In addition, a systematic review of 14 placebo-controlled studies investigating the use of antipsychotics for cocaine dependence from the Cochrane Collaboration did not find significant differences in any of the outcome variables analyzed, including the number of patients using cocaine during treatment, continuous abstinence and craving [41], supporting the results of a previous meta-analysis on the use of antipsychotics for cocaine or psychostimulant use disorder [42]. Focusing on patients with a dual disorder diagnosis, another systematic review concluded that the efficacy of antipsychotics for cocaine dependence in patients with schizophrenia has not been robustly demonstrated [43]. Although the sample size precludes any conclusion, it is worthy to mention that the three patients with heroin use disorder at baseline achieved abstinence at the end of the follow-up.

Our results regarding the impact of once-monthly LAI aripiprazole on alcohol use disorder were also encouraging, showing a significant reduction in symptom severity and stopping alcohol use in some cases. As is the case for cocaine dependence, the results for oral aripiprazole treatment in patients with alcohol dependence are mixed [18, 25, 44]. Martinotti et al. [45], in a narrative review of the available evidence, stated that there is no conclusive evidence for the effects of aripiprazole on the prevention of craving or a reduction in alcohol consumption. The results for other antipsychotics do not support the efficacy of these medications for primary alcohol dependence [46]. Finally, the limited works investigating LAI aripiprazole in patients with schizophrenia and coexisting SUDs do not provide results for specific substance use disorders [29, 30].

It is also important to note that the Food and Drug Administration and other health authorities have issued a warning regarding the use of aripiprazole and the development of rare impulse control problems, including pathological gambling, binge-eating disorder, and hypersexuality [47]. While potent dopamine D2 receptor antagonist antipsychotics have been linked to elevated levels of substance dependence such as nicotine dependence in smokers with schizophrenia [48], in contrast, aripiprazole increases dopamine activity in the mesolimbic dopaminergic pathway, which is involved in the development of maladaptive behaviors, and has 5-HT1A partial agonist and 5-HT2A antagonist properties that may promote sexual activity; these actions could partially explain the occurrence of these impulse control disorders [49]. However, the trigger mechanism of addictive behavior is complex and cannot only be attributed to the pharmacodynamic effects of dopaminergic drugs. Individual vulnerabilities and environmental factors need to be considered in its occurrence [50]. In any case, this side effect is uncommon, and in our view, the benefits of enhancing dopamine activity in these dual disorders patients, through the D2 partial agonist properties of aripiprazole and its high D2 receptor affinity, to counteract psychopathological symptoms outweigh the risk of this side effect in this population with coexisting SUDs.

The use of antipsychotics is crucial for the treatment of patients with schizophrenia regardless of whether they have a co-occurrent SUD [12], and treatment with LAI may offer some advantages over oral formulations [12, 38] and is preferred by clinicians in routine clinical practice [51–53]; however, little is known about the efficacy of LAI antipsychotics for the management of dually diagnosed patients. In addition to its retrospective and uncontrolled design, our study has several limitations; these include the small sample size, especially for evaluating its efficacy in specific subgroups

of SUDs; the allowed concomitant use of psychotropics; and the limited information available on outcomes such as sustained abstinence, which are more predictive of the long-term usefulness of this intervention for the management of SUDs. Despite its important limitations, our study suggests that once-monthly LAI aripiprazole retains its antipsychotic efficacy in patients with schizophrenia and a coexisting SUD and could be effective for the management of alcohol or cocaine use disorders in this population. These promising results should be confirmed by randomized clinical trials that include a long-term follow-up and an evaluation of the impact of the treatment on specific outcomes, such as sustained abstinence, a reduction in the severity of SUDs and the so-called "good functioning" (i.e., a composite measure encompassing a lack of substance use and no reported legal, psychological, family, or employment problems) [54].

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Data Availability The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Compliance with Ethical Standards

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Conflict of Interest NS has received speaker honorarium from Lundbeck, Shire, Exeltis, Rubio, Indivior, and Adamed: IB-V has received Speaker honorarium from Servier, Exeltis, and Lundbeck; PV has received speaker-travel honorarium from Gilead, MSD, Abbvie, and Rubió. JM-R is advisory board member for Shire and has received speaker honorarium from Lundbeck, Janssen, and Shire; CP-T has received speaker honorarium from Janssen and Servier, and travel grants from Lundbeck and Qualigen; JCA has received travel grants from Lundbeck and Janssen; LG-L has received speaker honorarium from Janssen; MdM has received speaker-travel honorarium from Janssen, Qualigen, Lundbeck; FA declares no conflict of interest related with this manuscript.

Ethical Approval The study was revised and approved by the Ethics Committee of the Hospital General Universitario Gregorio Marañón (Madrid, Spain).

Informed Consent Informed consent was obtained from all individual participants included in the study.

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