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Long-acting second-generation and oral antipsychotics for substance use disorders and psychotic symptoms: Prescribing attitudes among Italian psychiatrists

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Abstract

Purpose: To explore Italian psychiatrists' attitudes toward the off-label use of second generation antipsychotics (SGAs) in patients with substance use disorder and psychotic symptoms.

Design and Methods: A sample of 300 Italian psychiatrists associated with the Italian Society of Neuropsychopharmacology was randomly selected to complete a survey about the off-label prescription of SGAs.

Findings: Oral aripiprazole (32.7%), olanzapine (30.2%), and quetiapine (25.2%) were considered "appropriate." Long-acting antipsychoticss were generally considered "inappropriate."

Practice Implications: Our findings reflect a substantial level of uncertainty and a lack of coherent clinical guidance within the realm of dual diagnosis treatment.

Therefore, they emphasize the need to develop specific guidelines to improve the management of pharmacotherapy among this population.

KEYWORDS
off-label, psychotic symptoms, second-generation antipsychotics, substance abuse

1 | INTRODUCTION

The term dual disorder (DD) is usually utilized to define the coexistence of two disorders, in which one is considered to be the first in order of time and clinical relevance. The comorbidity of substance use disorders (SUDs) and psychotic symptoms is a clinical condition frequently observed in emergency departments and psychiatric inpatient units.[1] In fact, it has been estimated that around 25%–50% of patients diagnosed with psychosis or schizophrenia spectrum disorder have also co-occurrent SUDs.[2] The prevalence of SUDs is 25.1% in patients with schizophrenia (with the highest prevalence of nonalcohol drug-use disorder among young men affected) and 20.1% in subjects with bipolar disorder.[3] Looking at early psychosis, comorbid SUDs is highly represented, with a prevalence ranging from 25% to 60%.[4,5] There is growing recognition that SUDs are associated with the emergence of psychosis, which develops during the use of the substance and may or may not subside following withdrawal or abstinence.

If the role of substances as a triggering psychotic factor in certain individuals appears to be clear, it must be reported that some of these induced psychotic syndromes remain transitory with localized dissociative syndromes, defined by the Diagnostic and Statistical Manual for Mental Disorders (DSM-5) as substance-induced psychosis lasting for less than one month. The DSM-5 defines a substance-induced psychotic disorder (SIPD) as delusions and/or hallucinations related to the physiological effects of a substance based on evidence from history, physical examination, or laboratory findings.[6] SIPD can produce a full range of psychotic symptoms, such as hallucinations, delusions, psychomotor changes, impaired cognition, disorganized speech, and (hypo)manic symptomatology. According to the DSM-5, between 7% and 25% of people who present with an initial episode of psychosis have SIPD.[6] People with heavy substance use, especially marijuana, amphetamine, psychedelics, cocaine, and novel psychoactive substances, are at higher risk,[7–11] whereas the effect of alcohol and opiates is milder in terms of specific psychotic symptoms.[12] A recent study showed that after the first SIP episode, 26% of the sample received a diagnosis of full-blown schizophrenia within 5 years, with the use of cannabis and the abuse of multiple substances being mostly associated with a worse prognosis.[13] Caton et al.[14] reported that SIPD show specific characteristics that may differ from schizophrenia. For instance, both visual hallucinations and violent behavior seem more common in SIPD than schizophrenia. Moreover, there is a higher prevalence of suicidal thoughts during the previous year, a more frequent family history of SUDs, and higher levels of insight. It has been reported that patients with schizophrenia spectrum disorder and comorbid SUDs were more likely to experience chronic disease, worse relapses, and more frequent access to emergency units.[15] In these conditions, the use of substances negatively impacts on family and social life, work, and school. SUDs are associated with severe impairment or distress and may cause financial problems. According to the literature, other relevant consequences related to DDs are higher rates of violent crimes,[16,17] sexually transmitted and blood-borne infections,[18] homelessness,[19] and suicide[20] than for people without a severe mental illness.

A recent meta-analysis reported that SIPD is associated with a substantial risk for transition to schizophrenia, particularly following cannabis-induced psychosis.[21] High transition rates are partly related to the progression of the psychotic disorder (i.e., SIPD develops into a primary psychotic disorder) and partly a result of the narrowed definition of SIPD, which may favor misdiagnosis. In this respect, the new definition of "substance-related exogenous psychosis," has recently been proposed to indicate persistent psychoses associated with substance use.[22]

However, there has been little effort to deliver a common clinical and procedural framework for patients with DD, and separate policies have focused on either severe mental health problems or addiction, with a clear lack of specific pharmacological approaches.[23]

The practice of prescribing off-label antipsychotics among Italian psychiatrists had already been reported in the literature but, in recent years, there has been a substantial increase in their prescription.[24] Although there are no specific therapeutic indications by the Pharmaceutical Regulatory Agencies, antipsychotics are largely used off-label for the management of SUDs with psychotic symptoms (i.e., DD/psychosis) and SUDs alone.[25] Efficacy has been demonstrated above all on impulse symptoms and anger feelings which are very common in patients with these disorders.[26,27] To date, several studies have been conducted on the efficacy of aripiprazole or paliperidone, oral or LAI formulation, on DD or SUDs with psychotic symptoms or SUDs alone.[28–32] Illicit drug use or addiction, besides reduction of treatment adherence, can interfere with the efficacy of antipsychotics by worsening symptoms of the disease and/or interacting with the pharmacodynamic aspects of antipsychotics.[33] However, the presence of several psychiatric symptoms could lead to an increase or a worsening of SUDs comorbid and viceversa. Lastly, treatment-resistant schizophrenia is reported in approximately 30% of cases and SUDs is considered a contributing factor.[34]

The current survey aimed to explore Italian psychiatrists' attitudes to off-label use of second generation antipsychotics (SGAs) and long-acting injectable (LAI) antipsychotics in patients with SUDs and psychotic symptoms.

2 | METHODS

We randomly selected a sample of 300 Italian psychiatrists associated with the Italian Society of Neuropsychopharmacology working in Northern, Central, and Southern Italy, and sent by email a survey about the prescription of SGAs in patients with SUDs and psychotic symptoms.

The questionnaire was divided into three parts. The first part included questions about the socio-demographic characteristics of the psychiatrist respondents (i.e., gender; age; job placement; worksite, such as hospital, outpatient clinic, university clinic, or therapeutic community; and years of clinical practice). The second part of the questionnaire included questions about the following (a) informed consent before prescribing off-label SGAs; (b) the frequency of off-label SGA use (the choices were "very often," "often", "occasionally," or "rarely/never"); and (c) the main motivation driving them to prescribe off-label SGAs in clinical practice (the choices were nonresponse or side effects to usual treatment, patient preference, indication from other regulatory agencies or positive evidence from published literature, listed from the most relevant to the least relevant). The third part of the questionnaire was focused on assessing the use of SGAs for specific psychiatric disorders for which antipsychotics are usually employed, for either on- or off-label indications of bipolar disorder, bipolar depression, long-term treatment bipolar disorder, major depressive disorder, anxiety disorders, borderline personality disorder, obsessive-compulsive disorder, post-traumatic stress disorder, sleep disorders, SUDs with behavioral/psychotic symptoms, neurodevelopment disorders with behavioral/psychotic symptoms, and neurocognitive disorders with behavioral/psychotic symptoms. The psychiatrists were asked to rate the appropriateness of using single SGAs according to a Likert scale as follows: "highly inappropriate" (treatment that I would never use), "inappropriate" (treatment that I would rarely use), "doubtful" (treatment that I would use sometimes according to the preferences of the patient/family or when other treatment options have failed), "appropriate" (treatment that I use frequently) and "highly appropriate" (my treatment of choice).[35,36]

Institutional Review Board approval was not considered necessary, because the study did not involve patients, as mentioned in the two previous reports.[35,36] Although including human subjects and being a cross-sectional online survey, permission was obtained by the Italian Society of Neuropsychopharmacology review board. Informed consent was collected for the anonymous publication of data.

3 | RESULTS

A total of 202 Italian psychiatrists associated with the Italian Society of Neuropsychopharmacology completed the questionnaire (67% of those contacted). Gender was equally distributed, and the mean age was 44.1 ± 11.1 years. One hundred and fifty-two psychiatrists (75.2%) were full-time employees of the National Health System, 108 (53.5%) worked in inpatient units, 75 (37.1%) worked in outpatient clinics, and 16 (7.9%) worked in therapeutic communities, indicating that the interviewed sample was adequately representative of psychiatrists' job placements in Italy. Of these, 55.4% were experienced, with at least 10 years of working experience in the public and private context (Table 1).

TABLE 1 Characteristics of the surveyed sample

	N = 202
Gender, *N* (%)	
Male	101 (50.0)
Female	101 (50.0)
Age, mean ± *SD*	44.1 ± 11.1
Duration of service, *N* (%)	
<5 years	42 (20.8)
5–10 years	48 (23.8)
>10 years	112 (55.4)
Role at workplace, *N* (%)	
Resident in Psychiatry	29 (14.4)
National Health System psychiatrist	152 (75.2)
Professor/Researcher	21 (10.4)
Type of workplace, *N* (%)	
Psychiatric inpatient unit	45 (22.3)
Psychiatric outpatient unit	73 (36.1)
Service for substance abuse/dependence	2 (1.0)
University Clinic	63 (31.2)
Therapeutic Community	16 (7.9)
Other	3 (1.5)

The findings indicated that the psychiatrists' attitudes towards the use of off-label treatments of SUDs with psychotic symptoms widely varied. Oral olanzapine and risperidone were both considered "highly appropriate" by only 2% of the respondents, and dubious by 47.5% and 46.5% of the survey participants, respectively. Oral aripiprazole was considered "appropriate" by 32.7% of the respondents, followed by oral olanzapine (30.2%) and oral quetiapine (25.2%). Oral clozapine, asenapine and ziprasidone were considered "highly inappropriate" for SUDs with behavioral/psychotic symptoms (65.4%, 55%, and 79.7%, respectively; Table 2).

LAI antipsychotics were generally considered "highly inappropriate" for SUDs associated with psychotic symptoms (Table 3).

4 | DISCUSSION

The findings of our survey showed that for more than 50% of the respondents off-label prescription of SGAs represents a common practice.[35,36]

This finding coherently fits with the worldwide trend of increasing off-label prescription of SGAs observed in recent years. A systematic review of pharmaco-epidemiological studies published between 2000 and 2015 reported that off-label prescribing schemes comprise 40% to 75% of all SGA prescriptions in adults with mood and anxiety disorders, insomnia, and psychomotor agitation as the main unlicensed indications.[37]

TABLE 2 Attitudes of off-label SGAs in the treatment of substance use disorders with psychotic symptoms

Drugs	*N* (%)
Aripiprazole	
Highly inappropriate	21 (10.4)
Inappropriate	31 (15.3)
Doubt	82 (40.6)
Appropriate	66 (32.7)
Highly appropriate	2 (1.0)
Asenapine	
Highly inappropriate	111 (55.0)
Inappropriate	27 (13.4)
Doubt	52 (25.7)
Appropriate	12 (5.9)
Highly appropriate	0 (0.0)
Clozapine	
Highly inappropriate	132 (65.4)
Inappropriate	32 (15.8)
Doubt	32 (15.8)
Appropriate	6 (3.0)
Highly appropriate	0 (0.0)
Olanzapine	
Highly inappropriate	22 (10.9)
Inappropriate	19 (9.4)
Doubt	96 (47.5)
Appropriate	61 (30.2)
Highly appropriate	4 (2.0)
Paliperidone	
Highly inappropriate	65 (32.2)
Inappropriate	28 (13.9)
Doubt	73 (36.1)
Appropriate	35 (17.3)
Highly appropriate	1 (0.5)
Quetiapine	
Highly inappropriate	62 (30.7)
Inappropriate	19 (9.4)
Doubt	70 (34.7)
Appropriate	51 (25.2)
Highly appropriate	0 (0.0)
Risperidone	
Highly inappropriate	37 (18.3)
Inappropriate	30 (14.9)
Doubt	94 (46.5)
Appropriate	37 (18.3)
Highly appropriate	4 (2.0)
Ziprasidone	
Highly inappropriate	161 (79.7)
Inappropriate	9 (4.5)
Doubt	26 (12.8)
Appropriate	6 (3.0)
Highly appropriate	0 (0.0)

TABLE 3 Attitudes of off-label SGAs LAI in the treatment of substance use disorders with psychotic symptoms

Drugs	*N* (%)
Aripiprazole LAI	
Highly inappropriate	114 (56.4)
Inappropriate	15 (7.4)
Doubt	46 (22.8)
Appropriate	27 (16.4)
Highly appropriate	0 (0.0)
Olanzapine pamoate LAI	
Highly inappropriate	141 (69.9)
Inappropriate	13 (6.4)
Doubt	34 (16.8)
Appropriate	13 (6.4)
Highly appropriate	1 (0.5)
Risperidone LAI	
Highly inappropriate	117 (57.9)
Inappropriate	16 (7.9)
Doubt	49 (24.3)
Appropriate	18 (8.9)
Highly appropriate	2 (1.0)
Paliperidone LAI	
Highly inappropriate	109 (54.0)
Inappropriate	15 (7.4)
Doubt	53 (26.2)
Appropriate	23 (11.4)
Highly appropriate	2 (1.0)

However, according to our data, Italian psychiatrists' clinical opinions on the prescription of SGAs for SUDs with psychotic symptoms are defined as skeptical and cautious. Indeed, albeit to varying degrees, the use of SGAs was mostly rated as "doubtful" or "clearly inappropriate." This finding reflects a level of uncertainty and a lack of coherent clinical guidance within the realm of DD treatment considering that the scientific approach seems to be the most credited by Italian psychiatrists since the "presence of strong published evidence in the literature" was the main motivation for prescribing off-label SGAs.

Looking at prescribing attitudes for oral SGAs, aripiprazole (32.7%), olanzapine (30.2%), and quetiapine (25.2%) were the only antipsychotics that received a rating of "appropriate" from more than 25% of the respondents.

Aripiprazole appeared to be the first-line choice, followed by other SGAs. This finding confirms that SGAs are indeed widely prescribed for SUDs and psychotic symptoms, and those with lower metabolic impact are favored. This prescribing attitude may be determined by specific characteristics of aripiprazole. First, aripiprazole showed efficacy on craving reduction and relapse prevention for alcohol and SUDs without the presence of psychotic features.[31,38] Second, it has a peculiar mechanism of action as a partial agonist.

It is now commonly agreed that dopamine is a major neurotransmitter in terms of reward dependence, even if there is some controversy regarding its clinical modulation in the treatment and prevention of SUDs.[32] The peculiar effect exerted by aripiprazole could be underpinned by its effect in stabilizing dopamine receptors by modulating functioning rather than solely blockading or stimulating. Craving states could be paradoxically increased by a long-term, tight blockade of D_2 receptors in the striatum, resulting in an increase in substance relapses. Aripiprazole action as a partial agonist could represent a promising mechanism for addressing craving swings usually observed in subjects with SUDs. Therefore, partial dopamine agonists may represent a tool to reverse the dopamine depletion seen during alcohol abstinence due to their multireceptorial activity. Moreover, regarding the serotonin system, the 5-HT_{1A} partial agonist effect of aripiprazole may also modulate the prefrontal cortex to improve impulse control through projections from the raphe nucleus to the ventral tegmental area and nucleus accumbens.[39] Taken together, these considerations suggest that dopamine release induced by aripiprazole might be associated with the increased activation of the anterior cingulate which, in turn, may control cravings for alcohol and substances.

In this survey, clozapine was globally considered as "highly inappropriate," despite its role in treatment-resistant schizophrenia.[40] This could also be interpreted as a reason for its adverse event profile in situations where comorbid SUDs can be worsened.[41]

Around one-half of participants responded that they use LAI in clinical practice, with a clear preference for the use of atypical agents in this formulation. Among LAI formulations for the treatment of subjects suffering from SUDs with psychotic symptoms, aripiprazole is favored, as recently reported in an open-label study.[32] Cuomo et al.[29] demonstrated this tendency by showing better results for LAI aripiprazole compared to paliperidone palmitate. However, these preliminary data were not consistent with a recent survey in which Italian psychiatrists reported that among LAI antipsychotics, paliperidone palmitate should be considered the first choice for psychotic patients with SUDs.[25] In addition, recent data from the Paliperidone Palmitate Research in Demonstrating Effectiveness study indicated that a cohort of patients with schizophrenia, SUDs and a history of recent incarceration reported better outcomes with paliperidone palmitate LAI than the oral formulation, leaving room for the specific role of paliperidone LAI for DDs.[28] Moreover, Emond et al.[30] reported that 3 months of paliperidone palmitate treatment showed promising results in the treatment of those dimensions associated with SUDs, alcohol included.

Although the presence of psychotic symptoms among patients with SUDs is a worldwide concern, to the best of our knowledge, no other articles have examined psychiatrists' attitudes towards antipsychotic prescriptions in this condition, including LAI antipsychotics.[42]

Although an adequate drug treatment for these clinical situations is fundamental, several critical issues commonly found in clinical practice should be discussed. First of all, patients with SUDs and comorbid psychiatric symptoms do not show a great compliance in taking drugs. Second, they may be particularly sensitive to develop side effects (e.g., extrapyramidal, cardiovascular, and metabolic effects). Psychiatrists should carefully pay attention to the adverse metabolic effects of some SGAs,[43] especially the risk of reward deficiency syndrome (RDS) in substance-user psychotic patients treated with a fully blocking D_2 antagonist. Second-generation LAI antipsychotics have a safer pharmacological profile and guarantee greater adherence. Therefore, their prescription may exclude false-positive treatment-resistant patients, by possibly increasing the availability of the antipsychotics at the receptor level.

The limitations of the present study are mostly related to the characteristics of respondents. First, the survey was administered to adult psychiatrists without any differentiation based on their training and experience in treating SUDs. Second, in Italy, subjects with SUDs are not always treated in general psychiatric settings but often referred to specialized services. Thus, it would be interesting to discriminate psychiatrists' attitudes towards SGAs prescription in subjects with SUDs according to their expertise in this area and their workplace. Third, all respondents to the survey were members of the Italian Society of Neuropsychopharmacology. Since they represent a sample of psychiatrists who are probably more familiar with the latest evidence on psychopharmacology, the opinions expressed are only partially representative of the community of Italian psychiatrists.[35,36] Last, we administered a self-report questionnaire, which validity might be hampered by the subjectivity of self-rating and the lack of validation. Our survey represents a new tool, developed to be used in the contest of the Italian mental health care system and may not be representative of daily clinical practice.

5 | CONCLUSION

Considering the results of our survey, the presence of psychotic symptoms in patients with SUDs represents a well-known problem in clinical practice. However, the off-label use of SGAs remains limited, even though recent data support their use.[44] Therefore, It is necessary to identify therapeutic strategies that overcome these obstacles to efficacy, considering also tolerability and, especially, the potentially negative metabolic consequences of SGAs. Therefore, this survey may help to better understand the prescribers' doubts and the clinical reasoning underlying the off-label use of SGAs in patients with SUDs and psychotic symptoms and to identify new treatment paradigms.

6 | IMPLICATIONS FOR PSYCHIATRIC NURSING PRACTICE

The findings of the present paper emphasize the urgent need to develop specific guidelines for the management of psychopharmacology in patients with SUDs and psychotic symptoms. Moreover, they may increase the knowledge about this important topic and the off-label use of pharmacological treatment. Psychiatric nurses should be aware of the appropriate pharmacological strategies and psychiatrists' prescribing attitudes towards patients with DDs.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

DATA AVAILABILITY STATEMENT

Shared data availability only upon request.

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