European Review for Medical and Pharmacological Sciences 2024; 28: 2095-2106

Dual disorder: does expert clinical experience support the rationale for cariprazine use?

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Abstract. – Comorbid substance use disorder (SUD) in patients with schizophrenia (dual disorder, DD) is a frequent occurrence in the psychiatric clinical practice and is positively associated with poorer outcomes. Despite a very high co-prevalence, clinical guidelines for SUD and severe mental illnesses tend to give limited consideration to co-existing disorders regarding diagnosis and management.

This article is the result of a meeting held in February 2023 to discuss common challenges and best clinical practice initiatives for patients with schizophrenia and DD in different treatment settings.

The authors identified issues in the clinical approach to DD in schizophrenia spectrum disorders and suggested the most suitable management based on their experience as a group of experts, identifying possible improvement areas.

In conclusion, the panel recommends that individuals with DD should be cared for in a single center. Pharmacologic treatment in individuals with DD needing both control of symptoms related to schizophrenia spectrum disorders and substance withdrawal should ideally be based on using a non-sedative antipsychotic with anti-craving activity.

Key Words:
Dual disorder, Schizophrenia, Substance use disorder, Antipsychotic, Cariprazine.

Introduction

The frequent co-occurrence of a psychiatric illness with a substance use disorder (SUD) has increasingly gained clinicians' attention over the

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past three decades. It has been recognized as a clinical condition referred to as dual disorder (DD) or dual diagnosis[1-4]. The term DD is preferable to dual diagnosis as the second one refers to two categorically different/separate diagnoses and implies no or little interrelationship. SUD is present in up to 75% of patients with other psychiatric disorders, and more than 70% of patients seeking treatment for an addictive disorder have at least one additional mental illness[5,6]. However, even higher rates were reported[7] when tobacco use was taken into account. The risk of bipolar disorder is 4.1-fold increased among individuals with alcohol use disorder and is 5.0-fold greater in illicit drug users compared to non-users[8]. Likewise, the overall risk of developing schizophrenia is substantially increased in people with a SUD diagnosis; cannabis and alcohol have been reported[9] to have the strongest association, with a 5.2- and 3.4-fold increased risk, respectively. Conversely, a diagnosis of schizophrenia has also been reported[10] to be associated with a 3.7-fold increased risk of developing an SUD. Additionally, patients with DD have been recognized as a population at high risk of adverse outcomes, recurrence, and poor prognosis. Comorbid SUD in patients with schizophrenia has been positively associated[1,11-14] with poorer outcomes in terms of psychotic symptoms, relapse rates, hospitalizations, compliance, violence, suicidal behavior, overall health, money management, and use of crisis-oriented services.

Treating DD patients is generally more challenging and difficult than managing patients with either a SUD or another mental illness, as suggested by a meta-analysis[15] of studies from 1990 to 2017, which found that the prevalence rates of DD were relatively stable over that time period. Patients with DD are at high risk of social exclusion and stigma, making it challenging to connect with healthcare professionals and caregivers, further reducing treatment adherence and contributing to poorer outcomes[16].

In addition, effective psychosocial and pharmacological interventions for patients with DD in general, and for those with schizophrenia and co-occurring SUD, are currently still very limited due to various factors, including the poor understanding of the underpinnings of DDs, the frequent exclusion of patients with a SUD from randomized controlled clinical trials, the organization of therapeutic resources, or the different patients' perception of their illness and expectations on treatment goals[17-19]. Not surprisingly, despite the very high prevalence of DD, clinical guidelines for managing either SUD or severe mental illnesses tend to give limited consideration to diagnosing and managing DDs[20]. Since real-world evidence and clinical experience may support clinicians in choosing the best treatment option for an individual patient, a group of experts with wide clinical experience in managing DD patients gathered to share views and practices arising from daily clinical care. Specifically, this group of experts addressed the potential additional beneficial role of novel pharmacological agents, such as partial D3 agonists (e.g., cariprazine), in treating DD.

This paper aimed to describe the authors' shared and agreed opinion on the clinical approach and the best treatment approaches for patients with DD in schizophrenia spectrum disorders, focusing on medication efficacy and safety, healthcare organization, and clinical program effectiveness, as well as identifying gaps in knowledge and possible areas of improvement.

Meeting Topics

The present document is the result of a full-day meeting held in February 2023 in Barcelona with the support of Recordati S.p.A. and aimed to discuss common challenges and best clinical practice initiatives for patients with schizophrenia and DD in different treatment settings. The need for improved communication between clinicians and a practical consensus statement was identified. The meeting was attended by 11 psychiatrists and addiction specialists with expertise in managing patients with DD from Germany, Greece, Italy, Norway, Portugal, Spain, Sweden, and Switzerland.

The meeting was organized in different sections, where participants had the opportunity to discuss different concepts sequentially with enough time to maximize the participants' interaction, to exchange ideas and experiences, and subsequently reach agreements and conclusions on a specific subject. Topics discussed included the definition of DD, the assessment and diagnosis of individual patients with DD, and the management and treatment organization of DD in schizophrenia spectrum disorders, focusing on both the psychotic symptoms and all different aspects of the interventions for the coexisting SUD. Finally, the potential role of dopamine partial agonists and, specifically, of the partial D3 agonist cariprazine was also discussed.

The present paper, which has been reviewed and discussed within the group of participating experts, results from the debates held during the meeting and the exchange of information and proposals that arose during and after the meeting. As a result of this process, the successive drafts and the final document were circulated for written approval by all participants of the Expert Meeting. To prepare the document, non-systematic searches of clinical epidemiological studies, randomized controlled trials, and reviews were conducted in Medline, as well as from cross-referencing and identification by the experts. Additional details of the clinical presentation, assessment and management of patients with schizophrenia spectrum dual disorders were provided by clinical experience and practice by the group of experts. The results and conclusions shown here represent the general views agreed by the participants.

Issues in the Current Clinical Approach to DD

Definition of DD

As a basis for discussion, an operational definition of DD, which is compatible with the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision (DSM-5-TR) and International Classification of Diseases 11th Revision (ICD-11)[2,21,22] definitions, was chosen: "The simultaneous or sequential existence or concurrence, throughout the life cycle, of two or more independent but necessarily interacting psychiatric disorders, at least one of which is an addictive disorder". This definition encompasses the use of substances susceptible to causing SUD and is independent of the number of substances, the amount and the frequency of use. This wide definition of DD is derived from the authors' clinical experience that any substance use in a psychiatric patient with other psychiatric disorders represents a particular condition, different from SUD or psychiatric illness alone, with the need for specific management. The term DD is preferable to dual diagnosis as the latter refers to two categorically different/separate diagnoses, implying no or little interrelationship.

Diagnosis of DD

The high rate of SUD in patients with any psychiatric disorder implies the absolute necessity of exploring recent or lifetime substance use as part of the assessment, regardless of the clinical setting, and may require a urine drug screen, particularly in patients attending the emergency department. A comprehensive approach to DD, considering psychiatric illness and substance use equally, is necessary following diagnosis.

The interplay between substance effects and psychiatric syndromes, such as depression, anxiety, hyperactivity, or negative symptoms, is complex. SUD may be a consequence of common vulnerability factors in psychotic subjects, the first manifestation of a mental disorder followed by schizophrenia or a consequence of a self-medication attempt, or preceding and increasing the vulnerability to develop schizophrenia in ultra-high-risk subjects with first episode[17].

For instance, patients frequently refer to using alcohol or cannabis to relieve stress, while tobacco has an antidepressant effect, and smokers increase cigarette consumption when depressed[23,24].

The number of substances used by people with DD is variable. From their clinical experience, the panel feels that the most frequent comorbidity in DD is a depressive syndrome of varying origin with tobacco smoking. Comorbidity of depression with alcohol use is also frequent, as supported by the literature[25]. However, a large majority of patients with dual depression use tobacco, alcohol, and delta-9-tetrahydrocannabinol (THC); the addition of a stimulant, such as methamphetamine or cocaine, or a sedative, such as benzodiazepines, is also frequent.

A better understanding of the condition and an improved organization of services might facilitate diagnosis and treatment in general clinical practice. The diagnosis of SUD in a patient with a mental disorder is sometimes omitted or postponed because the clinician fails to address it or assess it adequately, but also frequently because the patient does not easily agree to be referred to a different service or does not accept a second stigma (so omitting the use of substances). Conversely, in the panel's experience, some patients attribute all psychiatric symptoms to substance use, accepting the stigma of SUD while rejecting that of psychiatric illness.

Another factor that may delay the diagnosis is an underdiagnosis of certain mental illnesses, such as bipolar disorder, attention deficit hyperactivity disorder (ADHD), or post-traumatic stress disorder, particularly in adolescents[26,27]. Therefore, a better liaison between child and adolescent mental health services and addiction units would be required, particularly considering that DD in-

dividuals start using substances at a younger age and show a much more severe and overall worse outcome[27,28].

The Problem with Tobacco

Tobacco is often used to cope with psychotic symptoms as nicotine has cognitive-enhancing effects and might improve attention and working memory (cognitive symptoms of schizophrenia) as well as ameliorate antipsychotic side effects[29]. Indeed, the alpha7 nicotinic receptor has emerged as a potential therapeutic target to treat cognitive deficits in schizophrenia[30].

However, the specific detrimental effects of tobacco use on mental illness are well known[31], but smoking is not easily acknowledged as SUD, being a socially accepted habit, although a major risk factor for cardiovascular and respiratory diseases[32]. In the USA, the prevalence of current use of any tobacco product in 2021 was at least two times higher among adults with serious psychological distress than in the general population[33]. A recent cross-sectional study[34] with 29,045 community-dwelling adults in the USA (among whom 2.9% had received a lifetime diagnosis of psychosis) also found that people with psychosis had a higher adjusted prevalence of tobacco use in the previous month [41.3% *vs.* 27.7%; adjusted risk ratio (RR)=1.49; 95% CI: 1.36-1.63]. Among those who had used cigarettes in the previous month, subjects with psychosis had a higher adjusted mean nicotine dependence score (54.6 *vs.* 49.5; $p<0.001$) and were more likely to have attempted to quit smoking (60.0% *vs.* 54.1%; adjusted RR=1.11; 95% CI: 1.01-1.21). These data show that, although tobacco use has decreased in recent years in the general population and individuals with psychiatric illnesses[35], it is still highly prevalent in this group[36].

It has to be noted that in a US national cohort[37] of adults with schizophrenia, excess deaths were mostly attributed to cardiovascular and respiratory diseases. This highlights the need to modify risk factors, such as tobacco use, in this vulnerable population with an increased cardiometabolic and respiratory burden. In addition, there are important pharmacological interactions associated with tobacco smoking. It is well known[38,39] that cigarette smoking, due to its content of polycyclic aromatic hydrocarbons, lowers the plasma levels of some antipsychotics by inducing cytochromes P450 (CYP) 1A2 and 2B6. Indeed, tobacco may increase drug metabolism, reducing the effectiveness of some antipsychotics, such as clozapine and olanzapine[40,41]. This problem is particularly relevant at the time of hospitalization and discharge, as tobacco use may be abruptly interrupted and reinitiated at these times, resulting in marked changes in serum drug concentrations and, by this, treatment efficacy and the emergence of side effects.

While smoking cessation treatment is increasingly offered to patients with various psychiatric disorders, tobacco smokers with schizophrenia are still less likely to receive a tobacco cessation intervention by clinicians[42]. Indeed, although tobacco cessation in patients with a psychotic illness has been associated with better overall outcomes, including improved psychotic symptoms, cognitive function and quality of life[43], several obstacles persist, including the little adaptation of standard tobacco cessation programs to the patient's needs with respect to the coexisting mental health problem, as well as difficulties in obtaining and maintaining patients' compliance.

As far as pharmacologic treatment is concerned, varenicline is recommended for smoking cessation, based on many clinical trials[44-52], but is no longer available in Europe. Cytisine, a partial agonist that binds with high affinity to the α4β2 nicotinic acetylcholine receptor, may emerge as a future promising option[53]. Additionally, improving the negative symptoms of schizophrenia by using the third-generation antipsychotic cariprazine may be useful in treating those patients whose tobacco and other substance use is mainly sustained by anhedonia and lethargy. Although high-level evidence on the efficacy of cariprazine in tobacco cessation is not yet available, preclinical studies have suggested a rationale for this approach, and preliminary clinical experiences have been published[54-57].

Understanding DD Severity

In the panels' experience, it is important to stress that the concomitance of SUD with another psychiatric disorder is a breeding ground for more severe conditions and worse outcomes. DD severity may vary not only with substance type, frequency and quantity of use but also with the associated psychiatric disorder's severity, type, and functional impact. Patients with psychotic disorders in the context of DD have poorer compliance, experience more side effects of antipsychotics (e.g., extrapyramidal symptoms), and may profit less from psychosocial treatment due to parallel substance use compared to patients with mental illness alone. Moreover, patients

with bipolar mania, severe personality disorders, ADHD, and organic psychosis with concomitant SUD are often more difficult to treat because adherence and motivation are usually low.

Patients need to be aware of the seriousness of their condition in order to share treatment goals and be motivated to get treatment. The patient's perception of functionality and the impact of substance use on general health are appropriate parameters for assessing the severity of DD in clinical practice. As long as physical health is not impaired, many patients consider substance consumption a socially accepted habit. Therefore, the motivational interviewing technique is a valuable tool to trigger insight and adherence. Additionally, it is essential to assess the patient's perception of his/her mental illness as it may be completely different from the one of the treating physicians.

Treatment Issues

DD management is challenging because of the inferior response to many treatments for the mental disorder, the continuous need to maintain abstinence, and the high incidence of relapse and re-hospitalization. Several factors contribute to worse outcomes. Medication adherence is a common problem. Many psychiatric patients are inclined to reduce the amount of medication they are prescribed. Partial adherence, which is even more frequent than complete non-adherence, may result in unnecessary antipsychotic dose increases or medication changes and the addition of concomitant antipsychotic drugs, leading to more relapse and hospitalizations[58,59]. As previously mentioned, a second problem may arise from the pharmacologic interaction of substances with medications.

In long-term management, cessation of substance use is challenging and must face patients' disinclination to comply due to several situations. Noteworthy, many patients use substances to deal with psychiatric symptoms and will not accept to quit. Some substances can potentially elevate flattened affect and/or ameliorate a lack of motivation and improve dysphoric states. Initiation of programs for cessation requires cognitive competencies, motivation, and the willingness to maintain good relationships with the therapeutic team. All these competencies may often be lacking in a patient recently hospitalized for acute psychosis, especially if the experience with medication was bad, e.g., extrapyramidal motor symptoms or oversedation. Patients with DD are also often socially marginalized[16], with poor education, employment, housing, and family relationships.

Patients with psychosis often require sedation, particularly when experiencing aggressive or agitated states. Highly sedative antipsychotics are sometimes not avoidable but may impair cognition and subsequently affect insight and cooperativeness and, consequently, compliance[60,61]. Variable degrees of cognitive dysfunction may be present, depending on age, type of cognitive function measured, and type of psychoactive substance used[62].

Although the clinical presentation of DD is complex and its management involves several areas of competence, these patients should ideally be managed by a single team with an integrated approach, dealing with the diagnosis and treatment of SUD and psychiatric illnesses, as well as social support and relapse prevention programs. Many healthcare systems in Europe, albeit in varying modalities, offer separate facilities for adult psychiatry, developmental psychiatry, substance use, and social support. This type of organization reflects the ICD-11 definition of DD, which focuses on only one area, that of substance use (referred to addiction care centers) or mental disorders (referred to psychiatric facilities)[63].

Examples of problems and challenges arising from this type of scattered organization are as follows:

- A good patient-physician relationship is necessary to facilitate adherence to management and requires, especially in DD patients, the participation of several healthcare professionals.
- Patients should accept their diagnosis and treatment, and a less specialized institution may be apt to reduce the fear of stigma.
- The use of cannabis in adolescents is generally considered a risk factor for the development of psychosis[64], but addiction care centers are seldom interested in early detection and intervention in psychosis, even though early management of psychosis may improve prognosis; similarly, child and adolescent mental health services commonly pay little attention to addiction problems.
- In the panels' experience, with an increase in the degree of specialization, the diagnosis of either SUD or an underlying psychiatric disorder might be overlooked. Understanding the underlying pathophysiology may help to detect a concurrent mental disorder; for example, adolescents who report "feeling focused" when using methamphetamine or cocaine should be screened for ADHD.

Experience with Cariprazine in DD

Cariprazine is a novel third-generation antipsychotic, acting as a partial agonist of the D3 and D2 dopamine receptors, with higher binding affinity for D3 and serotonin 1A (5-HT1A) and serotonin 2A (5-HT2A) receptors[65]. Cariprazine is approved for the treatment of schizophrenia in Europe and also for manic or mixed episodes of bipolar I disorder and bipolar depression in the USA. Due to this unique pharmacodynamic profile, it has been successfully tested in patients with schizophrenia and concomitant SUD[54-57], albeit not yet licensed in this indication. Cariprazine has a low potential for sedation but rather an activating effect[66]. This feature may be very useful in patients with DD who need to be cognitively fit to access cessation programs. Cariprazine has the potential to stabilize mood and decrease negative symptoms, thus enabling participation in programs for SUD treatment[55]. Additionally, cariprazine has anti-craving effects and reduces impulsivity[67-69]. Its activity on D3 receptors prompts modulation of the dopamine system in the mesolimbic regions and prefrontal cortex, which are involved in these symptoms[67]. Finally, the partial agonist activity on 5HT1A confers activity on anxiety and depression, which are frequent comorbid symptoms and disorders[66]. This is relevant information for clinicians as published guidelines had found only low-level evidence for pharmacological treatment of substance use concomitant with schizophrenia[70]. For patients with schizophrenia and cannabis or alcohol use, so far, no second or third-generation antipsychotic has been recommended to improve psychotic symptoms or reduce substance use. Adjuvant bupropion has been recommended[70] to reduce nicotine use and support abstinence.

The panel took notice of two protocols for acute DD inpatient treatment. At Teramo Hospital, Italy, intramuscular aripiprazole ≥4.5 mg was used together with cariprazine, regardless of agitation, followed by cariprazine alone after acute symptom control. The risk of akathisia[71] does not appear to be increased compared to aripiprazole alone. Other medications were used as needed, including benzodiazepine, levopromazine, and anti-seizure medication, mainly if the patient asked for the treatment of specific symptoms.

Caripiprazine was also used in Blakstad Hospital of Vettre, Norway, with doses of 1.5-3 mg of cariprazine, as shown in Figure 1. Cariprazine facilitates adherence to antipsychotic therapy in the long term and the treatment of SUD, showing an anti-craving effect. Using cariprazine already

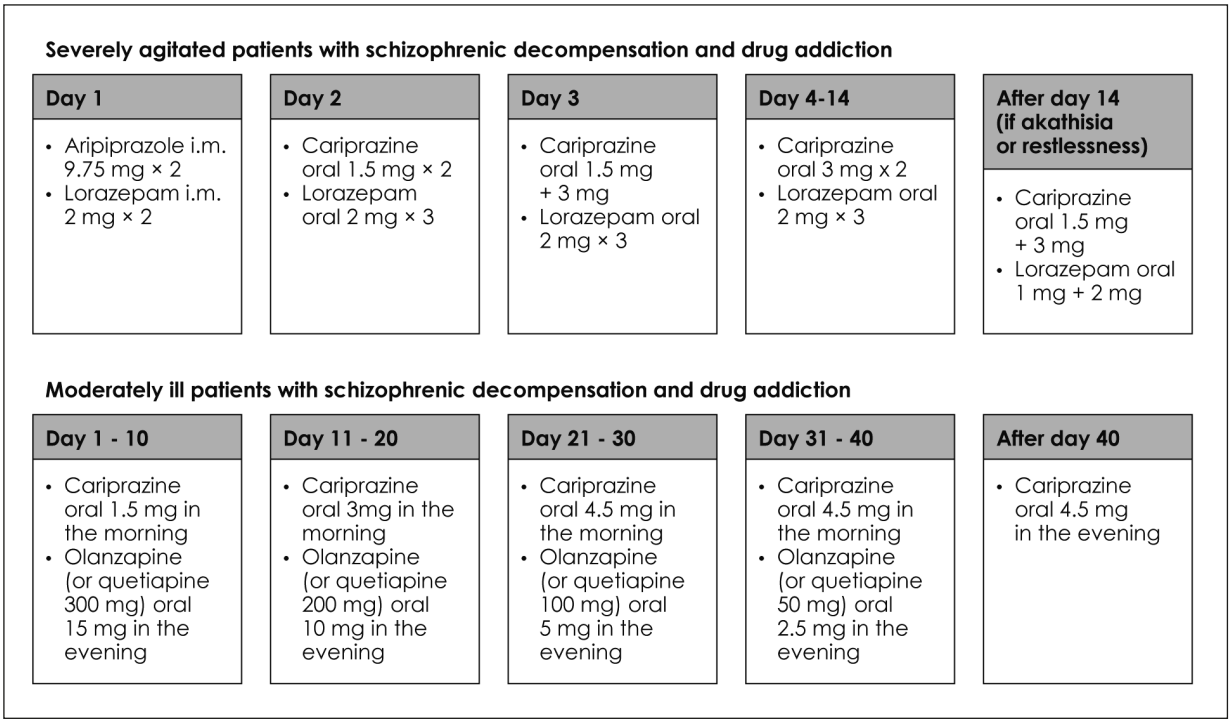

Figure 1. Treatment protocols for DD inpatient treatment used in Blakstad Hospital of Vettre, Norway.

in the agitated patient has been particularly recommended in combination with benzodiazepines and olanzapine in the early phase of hospitalization when cariprazine will be the continuation medication of choice. The panel suggested that this scheme should be tested in a clinical trial comparing olanzapine plus cariprazine *vs.* olanzapine alone in acute psychosis, with benzodiazepine rescue medication in the first 2 weeks.

Continuation treatment of DD is necessary after hospital discharge, and depot formulations are effective and often preferred for adherence to treatment[72]. With oral medication, dosing frequency may be an issue for patients who refuse depot formulations, as the caregiver must check that the patient takes the medication at home. With its long effective half-life (up to 1 week), missing a dose of cariprazine is not a major concern, and weekly administration has been reported[73,74].

Recommendations for Improved Management of DD

Close cooperation of adult psychiatrists, child and adolescent psychiatrists, SUD centers, and primary care can facilitate early detection of DD. Professionals in all these areas should educate themselves about DD and how to detect early prodromal symptoms of psychosis in young patients.

A diagnostic tool should be routinely used; the panel recommends the Psychiatric Research Interview for Substance and Mental Disorders (PRISM)[75,76]. It is a semi-structured interview for DD, translated and validated in different languages.

Gender-specific aspects need to be considered when diagnosing and treating DD. Women with SUD experience more stigma and thus may avoid seeking medical help.

Cognition should be assessed when DD is suspected, as many patients cope with antipsychotic-related cognitive problems with nicotine, skunk-like cannabis, or other substances. Cognition assessment is one tool to consolidate the diagnosis of DD in psychiatric practice. If core domains such as working memory and attention are affected in a psychotic patient, a diagnosis of genuine schizophrenia or severe affective disorder can be considered, whereas these areas are usually not impaired in drug-induced psychosis. Assessing cognitive capability is also important, as substance cessation and psychotherapy programs have a higher chance of failure if cognition is severely affected.

When choosing treatment, psychiatrists should be aware that patients with DD are more prone to experiencing adverse events. Treatment for DD should be carried out in a single center that is competent not only for substance use but also for mental illness and related medical problems.

The goals of DD management include not only initial treatment of acute psychotic episodes, followed by control of positive and negative symptoms in the long-term and withdrawal of substances, but also general health care and restoration of good quality of life. Recognizing and valuing the patient's perspective of desirable health outcomes supports motivation and adherence. In addition to controlling symptoms, treatment-seeking patients aim to 'reclaim a life', connect and interact with their social surroundings, enjoy life and contribute as active citizens[16]. These goals are not of high priority in acutely psychotic patients but are important after remission. They are often difficult to achieve because patients often need to change their attitude toward their illness, identify intermediate goals, and understand and accept non-pharmacological interventions. First of all, achievable outcomes should be prioritized. Ensuring survival in aggressive or suicidal patients is the primary, urgent goal, while the quality of life is addressed later, but these two successive steps should be considered right from treatment initiation in a comprehensive plan.

Accounting for the type of psychoactive substance(s) used helps choose appropriate pharmacological treatment. This tailored treatment increases the chance of efficacy of the first drug prescribed and is usually helpful in improving compliance in the long term. If sedative antipsychotics are administered in acutely aggressive patients with DD, they should be discontinued as soon as possible, and early and concomitant use of a non-sedating antipsychotic may facilitate adherence in the long-term treatment after discharge. A short and controlled course of benzodiazepine can also be considered in DD patients to achieve sedation as needed and reduce withdrawal symptoms. Treatment of choice should help manage substance use in the long run, having some effect on reducing craving or at least should have a lower propensity to cause side effects that can lead to scaling up substance use as self-medication.

An advantage of third-generation antipsychotics, including cariprazine, is that different dosages have different effects. In schizophrenia, higher dosages (4.5-6 mg) are effective against acute positive symptoms, whereas lower dosages, 3 mg or less, may be used in maintenance to address negative symptoms or stabilize mood. Cariprazine, when initiated in the acute phase, reinstitutes the central dopaminergic balances, and it may also help patients sustain substance use.

Close consultation is needed between all healthcare professionals and caregivers interacting with a patient with DD. Communication should be promoted through sharing clinical reports and interdisciplinary boards to discuss cases. All involved should also educate carers about the specific needs of these patients. Maintaining overall health also requires the management of medical comorbidities and the monitoring of adverse events. This task is mainly assigned to primary care, but the patient with DD is not easily persuaded to adhere to scheduled follow-ups and laboratory tests. A good liaison between the specialist team and the family physician and a conjointly agreed treatment plan is essential.

Explaining objectives, benefits and risks to patients and their caregivers is mandatory and likely to improve the therapeutic alliance. Due to the lack of evidence-based clinical trials and the complexity of these patients[77], the experience of clinicians and real-world management should be taken into account in future protocols.

Conclusions

Patients with DD are a special population requiring dedicated management. It is important to acknowledge DD as a complex disorder. Therefore, the panel recommends that patients with DD should be cared for in a single center, involving all the necessary expertise, with an integrated approach. Pharmacologic treatment of patients with DD needing both psychotic symptom control and substance withdrawal should ideally be based on using a non-sedative antipsychotic with some anti-craving activity, enabling psychological and psychosocial treatments. Such drugs could be already started in the emergency setting, added to benzodiazepines for short-term sedation or to other antipsychotics, and continued in the long term. Prescribing a non-sedating antipsychotic, such as cariprazine, may improve patient acceptability, facilitate adherence to recovery plans, reduce craving for substances to counteract sedation and may enable participation in activities of daily living, such as driving.

Acknowledgements

Editorial assistance was provided by Valentina Attanasio, Laura Brogelli, PhD, and Aashni Shah (Polistudium srl, Milan, Italy). This activity was supported by Recordati Industria Chimica e Farmaceutica S.p.A, Milan, Italy.

Funding

The group meeting was supported by an unrestricted educational grant from Recordati Industria Chimica e Farmaceutica S.p.A.

Conflicts of Interest

Heinz Grunze has received honoraria for advisory board participation or speaker's fees in the last three years from Janssen-Cilag and Recordati. Denis Kenzin has received speaker's fees from Recordati in the last three years. Johan Sahlsten Schölin has been invited to advisory boards and received honoraria as a speaker from Recordati and Gedeon Richter. Domenico De Berardis has received honoraria for advisory board participation or speaker's fees from Angelini, Janssen-Cilag, Lundbeck, and Recordati in the last three years. Elias Wagner has been invited to advisory boards from Recordati and Boehringer Ingelheim. Jon Johnsen was a consultant and received honoraries from Eli-Lilly, Janssen, Lundbeck, Otsuka, Recordati, Takeda, and Sunovion. Carlos Roncero has received fees to give lectures for Janssen-Cilag, Indivior, Gilead, MSD, Exceltis, Abbvie, Takeda, Rubio, Casein-Recordati, Carnot, Angellini and Camurus. He has received financial compensation for his participation as a consultant or a board member of Lundbeck, Gilead, MSD, INDIVIOR, Exceltis, Camurus, Abbvie, Idorsia, Rovi, and Recordati board. He has carried out the PROTEUS project, which was funded by a grant from Indivior and the COSTEDOPIA project, which was funded by INDIVIOR. He received two medical education grants from Gilead and medical writing support from Abbvie. All the authors received an unrestricted grant from Recordati Industria Chimica e Farmaceutica S.p.A to participate in the DuDAG meeting.

Authors' Contributions

Conception: HG; manuscript drafting: JMB, HG; manuscript editing and approval to submit: JMB, MB, DK, CR, JS, DDB, JJ, GT, EW, GF, HG.

Informed Consent and Ethics Approval

Not applicable.

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Availability of Data and Materials

Not applicable.

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