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REVIEW

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Management of schizophrenia and comorbid substance use disorders: expert review and guidance

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Abstract

Background Schizophrenia and substance use disorders (SUDs) are often comorbid conditions that present clinical challenges due to their heterogeneity and the difficulties associated with poor physical health, low medication adherence, high relapse and hospitalization rates, and increased risk of mortality. This is often exacerbated by a fragmented health care system that treats addiction and mental illness separately, leading to delays in proper diagnosis and treatment.

Main text The aim of this narrative review, based on an extensive literature search and experts' clinical experience, is to synthesize evidence on the psychopathological and clinical characteristics of patients, the burden and management at the level of healthcare system, and possible gaps in the treatment of schizophrenia with comorbid SUD in order to understand and address the needs of patients. Treatment options, differences between antipsychotic medications, and the benefits of long-acting formulations and partial dopaminergic agonists are described. Partial dopamine agonists (aripiprazole, cariprazine, and brexpiprazole) have demonstrated good control of psychotic symptoms and SUDs with a favorable safety profile.

Conclusion Pharmacological interventions should be accompanied by psychosocial support within an integrated and multidisciplinary approach that promotes shared decision-making and a good therapeutic alliance between the entire medical team and the patient.

Keywords Schizophrenia, Substance use disorder, Comorbid disorders, Dual diagnosis, Antipsychotics, Care management

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Introduction

Schizophrenia is a serious and prevalent psychiatric illness that affects approximately 0.3% of the worldwide population [1, 2]. It is a disabling mental health condition characterized by positive symptoms (delusions, hallucinations, disorganized speech, and/or behavior), negative symptoms (apathy, social isolation, blunted affect), as well as motor alterations, and impaired cognitive and affective domains [3].

Dual disorders refer to the simultaneous occurrence of addiction and other mental health disorders [4]. A common dual disorder is the coexistence of substance use disorders (SUDs) and schizophrenia, which poses important challenges both at the diagnostic and therapeutic levels [5, 6]. Moreover, the SUD often complicates the psychopathological prognosis and makes clinical status heterogeneous and difficult to manage due to a tendency to poor adherence to treatment, high drop-out rates, legal problems, as well as greater risks for infections such as HIV and hepatitis [7–9]. Higher hospitalization and relapse rates, higher mortality, and decreased functionality have also been described [10, 11].

Schizophrenia and SUDs are frequently chronic conditions that require prolonged care beyond that provided by short-term programs and acute care services. The two disorders affect each other, and substantial variation in their severity and respective impacts makes each clinical situation different, with specific features and treatment needs. People with schizophrenia and comorbid SUD (SCHZ/SUD) often experience poor physical health and social support, and face double stigma and care access difficulties [12]. Failure to address the complex needs of this population can lead to high hospitalization rates and longer inpatient treatment, which increase healthcare burden and costs [13, 14]. Furthermore, people with SCHZ/SUD are prone to experience the wrong-door phenomenon, which occurs when a patient enters the system and bounces back and forth between mental health and addiction services without receiving the correct diagnosis and treatment [15]. This can result in the fragmentation of care, poor patient engagement, and treatment withdrawal, highlighting the need for an integrated and holistic approach [16].

Regarding treatment guidelines, limited data are available supporting the use of specific pharmacological or psychological interventions for people with SCHZ/SUDs [17], so they are usually treated with the same approach as patients without SUD. Because this patient profile is often excluded from clinical trials, high-quality evidence is lacking. The dual-paradigm approach requires consideration of the influence of one disorder on the other, reflecting common circuits and systems, and this is not addressed in the guidelines. The aim of this review is to examine the evidence regarding the clinical features, patients' and healthcare burdens, and critical areas in the management of SCHZ/SUD to establish a basis for understanding patient needs. We will cover the treatment options and provide expert-based guidance on feasible pharmacological and psychosocial interventions to improve patient prognosis.

Methods

A literature search was conducted using the PubMed and Cochrane Library databases for recent publications from January 1, 2018, to September 30, 2023, updated at the time of peer-review in September 2024, and restricted to English- and Spanish-language bibliography (see the initial scoping exercise to frame the search in Additional file 1). The following search terms were used, alone or in various combinations using the Boolean operator AND: "schizophrenia", "schizophre*", "dual diagnosis", "dual disorder", "substance use", "substance abuse", "substance use disorder", "drug abuse", "substance", "addiction", "dependence", "guidelines", "pharmacological interactions", "drug interactions", "substance interactions", "healthcare costs", "treatment acceptance", "treatment adherence", "share decision-making", "pharmacy", "partial agonists", "reward system", "dopamine receptor antagonists", "dopamine receptor agonists", "third-generation antipsychotics", "injectable antipsychotics", "clozapine", "risperidone", "olanzapine", "quetiapine", "amilsulpiride", "lurasidone", "ziprasidone", "asenapine", "paliperidone", "aripiprazole", "cariprazine", "brexpiprazole", "cannabis", "alcohol", "cocaine", "amphetamine", "LSD", and "MDMA". The search yield 2541 records; a total of 2465 publications were excluded due to duplication, ineligibility, and irrelevance to our topic, and nine were added by the authors No other specific or clinical inclusion/exclusion criteria were applied for article selection. Eighty-five articles were ultimately selected and included in the review (see the results of the search and the flow chart in the Additional file 2 and 3).

Results

Clinical features and burden of patients with schizophrenia and comorbid substance use disorder

Dual disorders are strongly associated with socioeconomic factors that can hinder recovery, such as poor family/social support, unemployment, homelessness and illegal behaviors/incarceration [18]. Although the profiles of patients with SCHZ/SUD are very heterogeneous, there is a predominance of males among this population, they experience an earlier onset of their mental disease, more severe (mostly positive and affective) symptoms and craving behavior, poorer premorbid functioning, and increased treatment resistance [5, 19–23]. Some reports have shown that tobacco (the first in prevalence), alcohol, cannabis, and cocaine are the most widely used

substances in individuals with schizophrenia, with frequent multiple drug use [22, 24, 25]. Moreover, comorbid SUD, particularly alcohol and multiple drug use, is associated with poor treatment adherence, which contributes to high rates of relapse, emergency visits, and hospitalizations in schizophrenia and an increase in healthcare resource use [13, 26–28]. People with SCHZ/SUD also experience a higher risk of self-injury, suicide, and all-cause mortality [29–32] and suffer from more physical comorbidities, such as cardiovascular, metabolic, and infectious diseases [1]. All of these aspects incur enormous emotional, economic, and social costs and increase the challenges of treating this population.

Costs and care management models for patients with schizophrenia and comorbid substance use disorder

The annual societal costs per person of schizophrenia in European countries range from US$13,000 in Italy to US$119,000 in Norway. These costs are firstly driven by productivity losses, followed by direct healthcare and nonhealthcare costs [33]. In Spain, healthcare costs associated with schizophrenia accounted for 2.7% of total public healthcare expenditure in 2002 [34]. To the best of our knowledge, no recent cost-of-illness studies have evaluated the economic burden of dual disorders, but they probably contribute to increasing the expenses of healthcare, social, justice, and educational systems [35]. In addition, allocations for mental health care in national budgets are usually disproportionate to the burden of mental illnesses in several countries, and there is a need to increase the efficiency of care delivery and avoid the misalignment of available management models and patients' needs [36].

The current models of care delivery for the management of SCHZ/SUD are the sequential, the parallel and the integrated models (Fig. 1). For both sequential and parallel models, the existence of two separate services to treat addiction and mental health independently usually results in insufficient and ineffective care due to coordination problems, favoring patient dropout, and poor clinical results [37]. As there is no clear line dividing the problems of SUD from the social and symptomatic problems associated with SCHZ, the management of the dual disorder needs to be integrated into a broader and collaborative approach, which is likely to reduce costs and improve outcomes [38]. This integrated model requires multidisciplinary follow-up to simultaneously address the psychological, medical, and social aspects of patients and their families, thus enhancing the continuity of support.

Since non-compliance or partial compliance could lead to an increased risk of relapse and (re)hospitalization, an additional cost-effective strategy in SCHZ/SUD may be to prescribe long half-life drugs with simplified dosages and routes of administration that facilitate treatment adherence [39, 40]. This is the case of long-acting injectable (LAI) antipsychotics, which have been shown to improve medication adherence and reduce healthcare resource utilization [41–43], with greater benefits in the early stages of schizophrenia [44, 45].

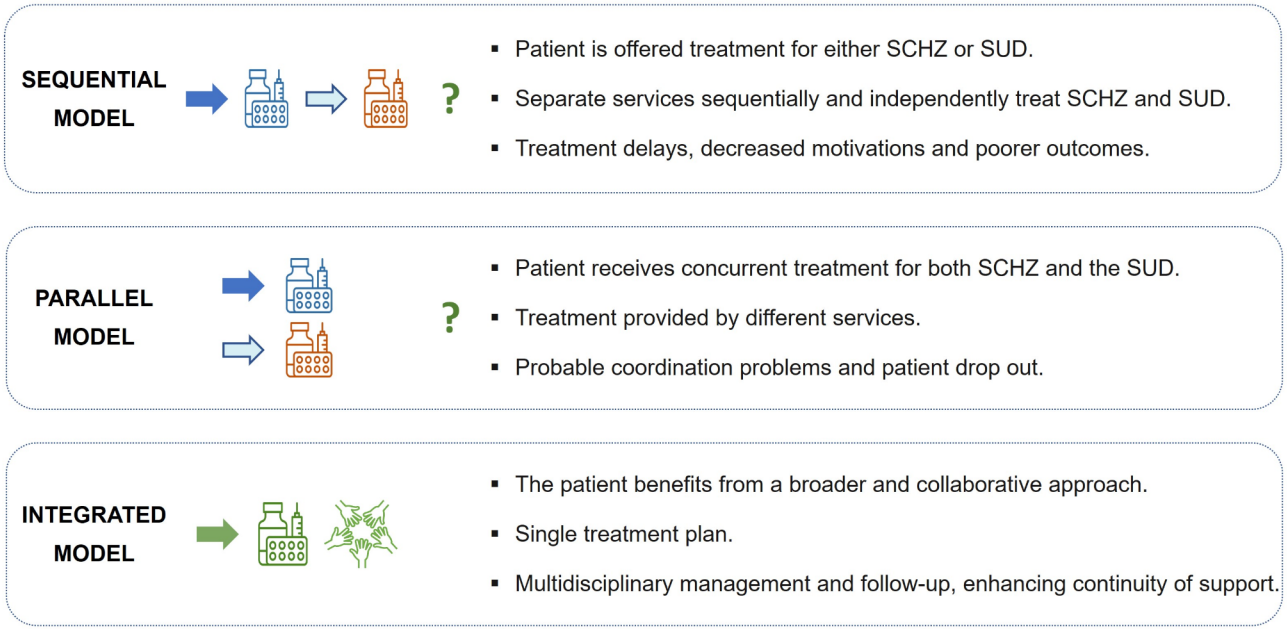

Fig. 1 Models of care delivery for comorbid schizophrenia (SCHZ) and substance use disorder (SUD)

Pharmacological treatment options for patients with schizophrenia and comorbid substance use disorder

Dopamine is a neurotransmitter that plays a crucial role in the pathology of schizophrenia and addiction. It is commonly associated with the pleasurable effects of recreational drugs and may be responsible for triggering neurobiological changes that lead to addiction, being involved in reward processing, motivation, and learning [46]. Despite differences in chemical structure and mechanism of action, all recreational drugs cause an increase in the release of dopamine, primarily in the nucleus accumbens. Chronic drug exposure triggers neuroadaptations in the dopaminergic striato-thalamo-cortical and limbic pathways (the amygdala and hippocampus). In parallel, changes in the expanded amygdala result in negative emotional states that perpetuate drug use in an attempt to alleviate them temporarily. However, actual drug use in addicted individuals is linked to reduced dopamine increases in the brain's reward regions, which perpetuates drug intake and the need for higher doses [46].

Schizophrenia is also associated with a dysregulation in dopaminergic transmission: on the one hand, a subcortical dopaminergic hyperfunction occurs in the mesolimbic projections, resulting in the hyperstimulation of D2 receptors and the development of positive symptoms. On the other hand, hypofunction in the mesocortical dopaminergic projections to the prefrontal cortex results in the hyperstimulation of D1 receptors, with consequent negative, affective, and cognitive symptomatology [47].

Antipsychotics are crucial components of both acute and maintenance pharmacotherapy in schizophrenia treatment. The first generation of antipsychotics, which antagonize the dopamine D2 receptor, supported the dopaminergic hypothesis and proved effective in reducing positive symptoms (e.g., delusions and hallucinations) but also resulted in undesirable effects, such as extrapyramidal side effects, tardive dyskinesia, hyperprolactinemia, and dopamine supersensitivity. Molecular imaging studies have demonstrated that achieving a dopamine D2 receptor occupancy rate higher than 65% with antipsychotic treatment is clinically effective; however, a D2 occupancy rate of >80% can provoke extrapyramidal effects and may be associated with depressive, cognitive, and/or negative symptoms [48, 49]. Second-generation antipsychotics (SGA) such as clozapine, risperidone, paliperidone, quetiapine, and olanzapine are dopamine D2/5-HT2A antagonists with better tolerability profiles [50]. Apart from antipsychotic action, the blockade of 5-HT2A receptors may reduce negative and cognitive symptoms in schizophrenia by increasing dopamine release in the prefrontal cortex. The main drawback of some SGA is that they can induce weight gain and metabolic dysfunction [51], and long- or high-dose exposures increase the risk of dopamine supersensitivity, although less than first-generation antipsychotics [49]. Supersensitization of the D2 receptor by potent antagonists has implications for comorbid SUD, which may negatively affect the clinical outcomes [52].

In patients with SCHZ/SUD, hypodopaminergy caused by continued substance use can worsen with potent D2 antagonists, leading to more side effects, anhedonia, reduced initiative, and the potential appearance of post-psychotic depressive episodes that hinder functional recovery and worsen prognosis [53]. Moreover, the potent D2 antagonism exerted by haloperidol, fluphenazine, chlorpromazine, risperidone, olanzapine, and paliperidone reduced the reward-enhancing effects of nicotine in smokers with schizophrenia, which would increase the consume and negatively affect the treatment of nicotine dependence in these patients [54]. In contrast, antipsychotics that are not potent dopaminergic antagonists have a particularly favorable profile in patients with dual schizophrenia. Accordingly, a recent systematic review and meta-analysis has suggested an association between clozapine treatment and significantly more abstinence from (time without consume of) substance use and lower rates of psychiatric hospitalization, compared with other first- and second-generation antipsychotic medications [55]. Clozapine has also been shown to reduce the risk of developing SUDs among patients with schizophrenia and the risk of relapse among patients with SCHZ/SUD [56]. When compared with first-generation antipsychotics, clozapine showed superiority in reducing self-reported measures of SUD among poly-substance users, and it was also superior to risperidone in poly-substance and cannabis users, but not superior to olanzapine or ziprasidone [57].

Dopamine receptor partial agonists (aripiprazole, brexpiprazole, and cariprazine) differ from SGA owing to partial agonism at the dopamine D2 and D3 receptors. These drugs can act differently (either as antagonists or agonists) depending on the levels of endogenous dopamine: they act as antagonists in the mesolimbic pathway, where high concentrations of dopamine are present, or they can act as agonists in the prefrontal cortex, where dopamine levels are low. Thus, they are expected to reduce positive and negative symptoms with acceptable tolerability and safety profiles [51, 58]. Although these three drugs share a similar mechanism of action, each drug has particular pharmacodynamic and pharmacokinetic properties, forming a heterogeneous therapeutic class [59]. Currently, aripiprazole is the only dopamine partial agonist with available LAI formulation. The potential role of partial agonists in the treatment of SCHZ/SUD was first supported by a naturalistic trial that showed greater improvement in craving and quality of life among patients with comorbid psychosis and SUDs treated with

aripiprazole LAI than with paliperidone LAI, with similar clinical outcomes [60]. Later, a multicenter observational study also showed that aripiprazole LAI was efficacious in reducing psychotic symptoms and substance dependence, particularly alcohol and cocaine [61], and similarly effective in improving symptoms and global functioning in patients with schizophrenia with and without SUDs [62]. A post-hoc analysis of a head-to-head trial versus paliperidone LAI showed that the effectiveness of aripiprazole LAI on quality of life and functioning was not compromised by concomitant substance use [63]. Compared with haloperidol and quetiapine, aripiprazole was superior in terms of psychotic symptoms and craving among patients with dual disorders [64]. Recently, brexpiprazole has shown positive effects on psychopathology symptoms, quality of life, and craving in a cohort of real-world patients with SCHZ/SUD [65]. Another advantage of partial agonists is that they do not induce dopamine supersensitivity states, although switching from a potent D2 receptor antagonist to aripiprazole should be performed gradually over a long period of time, especially in patients with a history of previous dopamine supersensitivity psychosis, as it may exert more "agonism" and worsen symptoms [49].

Expert guidance on optimal management of schizophrenia and comorbid substance use disorder

Dual SCHZ/SUD is thought to be underdiagnosed and undertreated due to the lack of full diagnostic assessments and variations in clinical resources [66]. Adequate characterization of patients presenting with psychotic symptoms and SUD is essential for an effective treatment approach. Therefore, a thorough clinical evaluation is essential to make an accurate diagnosis and to be able to draw up an individualized treatment plan. A key aspect in optimizing patient management is to minimize the gaps between the need for SUD and schizophrenia treatment together with care delivery. This implies a more integrated patient-centered approach, planning a multidisciplinary follow-up from different perspectives and disciplines (psychiatric, medical, psychological, social, psychoeducational, etc.), and promoting a strong therapeutic alliance for better patient engagement [67]. The complexity of pharmacological treatment (polypharmacy, frequent dose changes, etc.), among other reasons, makes adherence to treatment difficult, especially in patients with dual SCHZ/SUD. It has been shown that patients' involvement in treatment decision-making can increase their satisfaction with antipsychotic therapy and improve treatment adherence [68]. Thus, clinicians should consider patient preferences and medication side-effect profiles, focusing on the early detection of possible antipsychotic undesirable effects that could interfere with patient compliance [69]. Special attention should be paid to the prevention of suicidal behaviors in higher-risk populations (e.g., adolescents) [70] and the management of female patients, who are particularly vulnerable to the effects of addictive substances [71, 72].

LAI antipsychotics are effective treatments for schizophrenia and are associated with improvements in medication adherence and reduced use of healthcare resources [41–43]. Within the shared decision-making process, education of patients (families and physicians) is needed to consider LAI antipsychotics not as drugs of last resort, but rather as a first step to facilitate continuity of treatment and clinical remission. The benefits of LAI formulations are not confined to non-adherent patients, and LAIs could also be offered during the initial stages of schizophrenia [73, 74]. Accordingly, a real-world observational study demonstrated that the early introduction of paliperidone LAI (three monthly injections) in patients with recently diagnosed schizophrenia was associated with relevant improvements in social functioning and a high degree of treatment satisfaction, while maintaining symptomatic stability [75]. Risperidone ISM provides a fast and sustained release of antipsychotic without need of oral supplementation or loading doses, and has shown a quick control of symptoms in patients with an acute SCHZ exacerbation [76]. In patients with first-episode schizophrenia, aripiprazole LAI was associated with a progressive improvement in positive and negative symptoms and a decrease in clinical global severity, together with an improvement in quality of life and social and personal functioning [77]. Although these studies were conducted with non-dual patients and should interpreted with caution [43], by eliminating daily oral antipsychotic dosing, LAIs could promote treatment acceptance, improve convenience, and enhance self-esteem, encouraging also dual patients to regain control of their lives [78]. Targeting substance use can also improve antipsychotic adherence, as shown among patients with opioid dependence receiving medications for schizophrenia, in which antipsychotic adherence increased by more than 50% in periods preceded by a period of methadone adherence [79].

An important point to maintain high satisfaction with the treatment and care received is to actively ask about possible adverse effects of the medication or potential interference in the patients' daily life. The pharmacological characteristics and pharmacokinetics/-dynamics of each antipsychotic should be considered, as well as patient backgrounds and preferences, to minimize drug interactions and side effects [80]. The patient should be warned about the possible interactions between the substance of addiction and the prescribed antipsychotic medication as well as the potential drug interactions with other medications or foods (Table 1). This is particularly relevant for commonly co-prescribed antiretrovirals (see

Table 1 Potential drug-drug interactions

Drug	Metabolizing mechanisms	Inducers	Inhibitors	Other interactions not mediated by CYP metabolism
Aripiprazole	CYP2D6 CYP3A4	Carbamazepine, rifampicin, efavirenz, nevirapine	Ketoconazole, grape juice, fluoxetine, erythromycin, HIV-protease inhibitors, bupropion, methadone	Selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs)
Cariprazine	CYP3A4	Carbamazepine, phenobarbital, efavirenz, etravirine	Azole antifungals, grape juice, boceprevir, macrolide antibiotics, cobicistat, HIV-inhibitors nefazodone, diltiazem, verapamil	P-glycoprotein substrates, such as dabigatran, digoxin
Clozapine	CYP1A2	Cigarette smoke, carbamazepine, phenytoin, rifampicin, omeprazole	Caffeine, perazine, fluvoxamine, oral contraceptives, ciprofloxacin	Bone marrow suppressants, benzodiazepines, anticholinergics, antihypertensives, warfarin, digoxin, lithium, disulfiram
Haloperidol	CYP3A4 CYP2D6	Carbamazepine, phenobarbital, phenytoin, rifampicin	Erythromycin, levofloxacin, buspirone, ritonavir, alprazolam, azole antifungals, nefazodone, fluoxetine, paroxetine, fluvoxamine	Class 1 A and class 3 antiarrhythmics, citalopram, methadone, ziprasidone, desipramine, imipramine
Olanzapine	CYP1A2	Carbamazepine, phenytoin, rifampicin, omeprazole	Fluvoxamine	Diazepam, charcoal, antihypertensive agents, levodopa
Paliperidone	-	-	-	Carbamazepine, valproate, levodopa
Quetiapine	CYP3A4	Carbamazepine, barbiturates, phenytoin, rifampicin, glucocorticoids	Azole antifungals, erythromycin, protease inhibitors	Levodopa, lorazepam, thioridazine
Risperidone	CYP2D6 CYP3A4	Carbamazepine, rifampicin, phenytoin, phenobarbital,	Paroxetine, fluoxetine, quinidine, azole antifungals, ritonavir and ritonavir-boosted protease inhibitors, verapamil	Levodopa, furosemide

https://hiv-druginteractions.org/checker for specific interactions) given the high prevalence of psychiatric illness in the HIV-infected population and the increased risk of HIV infection in patients with psychiatric illness [81]. Drug interactions of significant importance for psychiatrists, like those of antipsychotics with antidepressants, should be check on a one-by-one basis (see https://www.drugs.com/drug_interactions.html or https://www.webmd.com/interaction-checker/default.htm).

With regard to antipsychotic selection, the benefit on control of substance use [61, 64] and better tolerability profile of partial agonists [59] make these agents a good treatment option for dual SCHZ/SUD [60, 65, 82, 83]. Additionally, given the high rate of medical comorbidities in patients with SCHZ/SUD, regular health check-ups should be performed. Patients receiving SGA require exhaustive follow-up of their cardiometabolic health [84]. Early detection and prevention of organic diseases can improve the course and prognosis of psychotic disorders and SUD and allows timely referral to other medical specialties. Sharing electronic health records can simplify inter-professional communication, which is an essential component of integrated care [85].

Conclusions

Patients with SCHZ/SUD constitute a therapeutic challenge, as they often do not fit the usual treatment services and protocols. Care delivery for patients with dual schizophrenia requires adequate personnel training and adaptation of the therapeutic plan to the particular characteristics of each patient. Their management should include psychosocial and pharmacological therapy within an integrated and multidisciplinary mental health approach that focuses on maintaining patient engagement with the healthcare system and professionals. A strong therapeutic alliance, shared decision making, and minimizing the burden of side effects would lead to adequate treatment adherence and favorable outcomes.

Abbreviations

HIV	Human immunodeficiency virus
LAI	Long-acting injectable
LSD	Lysergic acid diethylamide
MDMA	3,4-methylenedioxymethamphetamine
SCHZ	Schizophrenia
SGA	Second-generation antipsychotics
SUD	Substance use disorder

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

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AN and MT had the idea for the article and coordinated the project. All authors performed the literature search and bibliographic review, drafted and/or critically revised the work. All authors read and approved the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
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References

1. Charlson FJ, Ferrari AJ, Santomauro DF, Diminic S, Stockings E, Scott JG, et al. Global Epidemiology and burden of Schizophrenia: findings from the global burden of Disease Study 2016. Schizophr Bull. 2018;44:1195–203.
2. Solmi M, Seitidis G, Mavridis D, Correll CU, Dragioti E, Guimond S, et al. Incidence, prevalence, and global burden of schizophrenia - data, with critical appraisal, from the global burden of Disease (GBD) 2019. Mol Psychiatry. 2023;28:5319–27.
3. McCutcheon RA, Reis Marques T, Howes OD. Schizophrenia-An Overview. JAMA Psychiatry United States. 2020;77:201–10.
4. Szerman N, Torrens M, Maldonado R, Balhara YPS, Salom C, Maremmani I, et al. Addictive and other mental disorders: a call for a standardized definition of dual disorders. Transl Psychiatry. 2022;12:446.
5. Hunt GE, Large MM, Cleary M, Lai HMX, Saunders JB. Prevalence of comorbid substance use in schizophrenia spectrum disorders in community and clinical settings, 1990–2017: systematic review and meta-analysis. Drug Alcohol Depend. 2018;191:234–58.
6. Temmingh H, Susser E, Mall S, Campbell M, Sibeko G, Stein DJ. Prevalence and clinical correlates of substance use disorders in South African xhosa patients with schizophrenia. Soc Psychiatry Psychiatr Epidemiol. 2021;56:695–706.
7. Hughes E, Bassi S, Gilbody S, Bland M, Martin F. Prevalence of HIV, Hepatitis B, and hepatitis C in people with severe mental illness: a systematic review and meta-analysis. Lancet Psychiatry. 2016;3:40–8.
8. Bouchard M, Lecomte T, Cloutier B, Herrera-Roberge J, Potvin S. Dropout rates in Psychosocial interventions for people with both severe Mental illness and substance misuse: a systematic review and Meta-analysis. Front Psychiatry. 2022;13:842329.
9. Lieslehto J, Tiihonen J, Lähteenvuo M, Tanskanen A, Taipale H. Primary non-adherence to antipsychotic treatment among persons with Schizophrenia. Schizophr Bull. 2022;48:655–63.
10. Schmidt LM, Hesse M, Lykke J. The impact of substance use disorders on the course of schizophrenia —a 15-year follow-up study: dual diagnosis over 15 years. Schizophr Res. 2011;130:228–33.
11. Alvarez-Jimenez M, Priede A, Hetrick SE, Bendall S, Killackey E, Parker AG, et al. Risk factors for relapse following treatment for first episode psychosis: a systematic review and meta-analysis of longitudinal studies. Schizophr Res. 2012;139:116–28.
12. Priester MA, Browne T, Iachini A, Clone S, DeHart D, Seay KD. Treatment Access barriers and disparities among individuals with Co-occurring Mental Health and Substance Use disorders: an integrative literature review. J Subst Abuse Treat. 2016;61:47–59.
13. Vadukapuram R, Zahid S, Lee HK, Patel RS. Region-wise distribution of Schizophrenia with Cannabis abuse and Medication Non-compliance in the United States: a nationwide analysis of 51,975 hospitalizations. Cureus. 2020;12:e7936.
14. Błachut M, Ścisło P, Jarząb M, Zając M, Piegza M, Badura-Brzoza K, et al. Impact of dual diagnosis in patients with schizophrenia and affective disorders during hospital treatment on the course of illness and outcomes of treatment - a preliminary report. Psychiatr Pol. 2019;53:1237–50.
15. Volkow ND, Torrens M, Poznyak V, Sáenz E, Busse A, Kashino W, et al. Managing dual disorders: a statement by the Informal Scientific Network, UN Commission on narcotic drugs. World Psychiatry. 2020;19:396–7.
16. Fantuzzi C, Mezzina R. Dual diagnosis: a systematic review of the organization of community health services. Int J Soc Psychiatry. 2020;66:300–10.
17. Arranz B, Garriga M, Bernardo M, Gonzalez-Pinto A, Arrojo M, Torrens M, et al. Guía De práctica clínica para El Tratamiento farmacológico Y psicológico De Los pacientes adultos con un trastorno del espectro esquizofrénico y un diagnóstico comórbido de trastorno por uso de sustancias. Adicciones. 2021;34:110.
18. Carrera I, Alfonzo L, Ferreira A. Patología Dual. Recomendaciones para la mejora de la calidad del proceso asistencial. Editorial Medica Panamericana; 2023.
19. Dondé C, Achim AM, Brunelin J, Poulet E, Mondino M, Haesebaert F. A meta-analysis of craving studies in schizophrenia spectrum disorders. Schizophr Res. 2020;222:49–57.
20. Chang S, Jeyagurunathan A, Lau JH, Shafie S, Samari E, Cetty L, et al. Problematic drug Use among outpatients with Schizophrenia and related psychoses. Front Psychiatry. 2021;12:762988.
21. Arsalan A, Iqbal Z, Tariq M, Ayonrinde O, Vincent JB, Ayub M. Association of smoked cannabis with treatment resistance in schizophrenia. Psychiatry Res Irel. 2019;278:242–7.
22. Arnau F, Benito A, Villar M, Ortega M, López-Peláez L, Haro G. Addressing Dual disorders in a medium-term admission unit. Brain Sci. 2021;12:24.
23. Prat G, Marquez-Arrico JE, Río-Martínez L, Navarro JF, Adan A. Premorbid functioning in schizophrenia spectrum disorders with comorbid substance use: a systematic review. Prog Neuropsychopharmacol Biol Psychiatry. 2021;110:110310.
24. Masroor A, Khorochkov A, Prieto J, Singh KB, Nnadozie MC, Abdal M, et al. Unraveling the Association between Schizophrenia and Substance Use Disorder-Predictors, mechanisms and treatment modifications: a systematic review. Cureus. 2021;13:e16722.
25. Tumenta T, Oladeji O, Gill M, Khan BA, Olayinka O, Ojimba C, et al. Substance use patterns and Schizophrenia Spectrum disorders: a retrospective study of inpatients at a community Teaching Hospital. J Clin Med Res. 2020;12:803–8.
26. Scheffler F, Phahladira L, Luckhoff H, Du Plessis S, Asmal L, Kilian S, et al. Cannabis use and clinical outcome in people with first-episode schizophrenia spectrum disorders over 24 months of treatment. Psychiatry Res. 2021;302:114022.
27. Kikkert M, Goudriaan A, de Waal M, Peen J, Dekker J. Effectiveness of Integrated Dual Diagnosis Treatment (IDDT) in severe mental illness outpatients with a co-occurring substance use disorder. J Subst Abuse Treat. 2018;95:35–42.
28. Lähteenvuo M, Batalla A, Luykx JJ, Mittendorfer-Rutz E, Tanskanen A, Tiihonen J, et al. Morbidity and mortality in schizophrenia with comorbid substance use disorders. Acta Psychiatr Scand. 2021;144:42–9.
29. Güney E, Alnıak İ, Erkıran M. Predicting factors for non-suicidal self-injury in patients with schizophrenia spectrum disorders and the role of substance use. Asian J Psychiatr. 2020;52:102068.
30. Olfson M, Stroup TS, Huang C, Wall MM, Crystal S, Gerhard T. Suicide risk in Medicare patients with Schizophrenia across the Life Span. JAMA Psychiatry. 2021;78:876–85.

31. Correll CU, Solmi M, Croatto G, Schneider LK, Rohani-Montez SC, Fairley L, et al. Mortality in people with schizophrenia: a systematic review and meta-analysis of relative risk and aggravating or attenuating factors. World Psychiatry. 2022;21:248–71.
32. Heiberg IH, Jacobsen BK, Nesvåg R, Bramness JG, Reichborn-Kjennerud T, Næss Ø, et al. Total and cause-specific standardized mortality ratios in patients with schizophrenia and/or substance use disorder. PLoS ONE. 2018;13:e0202028.
33. Lin C, Zhang X, Jin H. The Societal cost of Schizophrenia: an updated systematic review of cost-of-illness studies. PharmacoEconomics. 2023;41:139–53.
34. Oliva-Moreno J, López-Bastida J, Osuna-Guerrero R, Montejo-González AL, Duque-González B. The costs of schizophrenia in Spain. Eur J Heal Econ. 2006;7:182–8.
35. Snow KJ, Petrie D, Young JT, Preen DB, Heffernan E, Kinner SA. Impact of dual diagnosis on healthcare and criminal justice costs after release from Queensland prisons: a prospective cohort study. Aust J Prim Health. 2022;28:264–70.
36. Ee C, Lake J, Firth J, Hargraves F, de Manincor M, Meade T, et al. An integrative collaborative care model for people with mental illness and physical comorbidities. Int J Ment Health Syst. 2020;14:83.
37. Mancheño JJ, Navas-León S, Fernández-Calderón F, Gutiérrez M, Sánchez-García M, Díaz-Batanero C, et al. Coordinated treatment between addiction and mental health services vs. uncoordinated treatment for patients with dual diagnosis: higher dropout rates but lower impairement of functional disability. Actas Esp Psiquiatr. 2021;49:71–80.
38. Rocks S, Berntson D, Gil-Salmerón A, Kadu M, Ehrenberg N, Stein V, et al. Cost and effects of integrated care: a systematic literature review and meta-analysis. Eur J Heal Econ. 2020;21:1211–21.
39. Gallastegui C, Fernández-Vega H, Piñeiro G, Rey-Gómez-Serranillos I, Olivares JM. Heras-Liñero E De Las. Assessment of adherence to treatment with injectable extended-release antipsychotics within a pharmacotherapeutic follow-up program. Farm Hosp. 2019;43:177–81.
40. Greene M, Burudpakdee C, Seetasith A, Behling M, Krasa H. Evaluation of patient support program and adherence to long-acting injectable aripiprazole for patients utilizing injection local care centers. Curr Med Res Opin. 2019;35:97–103.
41. Lin D, Thompson-Leduc P, Ghelerter I, Nguyen H, Lafeuille M-H, Benson C, et al. Real-world evidence of the clinical and economic impact of long-acting Injectable Versus oral antipsychotics among patients with Schizophrenia in the United States: a systematic review and Meta-analysis. CNS Drugs. 2021;35:469–81.
42. Wong KO, Klarenbach SW, Martins KJB, Chue P, Dursun SM, Snaterse M, et al. Health resource utilization and cost before versus after initiation of second-generation long-acting injectable antipsychotics among adults with schizophrenia in Alberta, Canada: a retrospective, observational single-arm study. BMC Psychiatry. 2022;22:444.
43. Coles AS, Knezevic D, George TP, Correll CU, Kane JM, Castle D. Long-acting Injectable Antipsychotic Treatment in Schizophrenia and Co-occurring Substance Use disorders: a systematic review. Front Psychiatry. 2021;12:808002.
44. Huang C-Y, Fang S-C, Shao Y-HJ. Comparison of long-acting injectable antipsychotics with oral antipsychotics and suicide and all-cause mortality in patients with newly diagnosed Schizophrenia. JAMA Netw open. 2021;4:e218810.
45. Corigliano V, Comparelli A, Mancinelli I, Montalbani B, Lamis DA, De Carolis A, et al. Long-acting Injectable Second-Generation antipsychotics improve negative symptoms and suicidal ideation in recent diagnosed Schizophrenia patients: a 1-Year follow-up pilot study. Schizophr Res Treat. 2018;2018:4834135.
46. Volkow ND, Michaelides M, Baler R. The neuroscience of drug reward and addiction. Physiol Rev. 2019;99:2115–40.
47. Howes OD, Bukala BR, Beck K. Schizophrenia: from neurochemistry to circuits, symptoms and treatments. Nat Rev Neurol. 2024;20:22–35.
48. Hart XM, Schmitz CN, Gründer G. Molecular Imaging of Dopamine Partial Agonists in Humans: Implications for Clinical Practice. Front psychiatry. Switzerland; 2022;13:832209.
49. Kimura H, Kanahara N, Iyo M. Rationale and neurobiological effects of treatment with antipsychotics in patients with chronic schizophrenia considering dopamine supersensitivity. Behav Brain Res. 2021;403:113126.
50. Huhn M, Nikolakopoulou A, Schneider-Thoma J, Krause M, Samara M, Peter N, et al. Comparative efficacy and tolerability of 32 oral antipsychotics for the acute treatment of adults with multi-episode schizophrenia: a systematic review and network meta-analysis. Lancet. 2019;394:939–51.
51. Orzelska-Górka J, Mikulska J, Wiszniewska A, Biała G. New atypical antipsychotics in the treatment of Schizophrenia and Depression. Int J Mol Sci. 2022;23.
52. Peeters LD, Brown RW. Dopamine receptor supersensitivity and Schizophrenia. In: Kostrzewa RM, editor. Handb Neurotox. Cham: Springer International Publishing; 2021. pp. 1–15.
53. Khokhar JY, Henricks AM, Sullivan EDK, Green AI. Unique effects of Clozapine: a pharmacological perspective. Adv Pharmacol. 2018;82:137–62.
54. Whitton AE, Green AI, Pizzagalli DA, Roth RM, Williams JM, Brunette MF. Potent dopamine D2 antagonists Block the reward-enhancing effects of Nicotine in smokers with Schizophrenia. Schizophr Bull. 2019;45:1300–8.
55. Rafizadeh R, Danilewitz M, Bousman CA, Mathew N, White RF, Bahji A, et al. Effects of clozapine treatment on the improvement of substance use disorders other than nicotine in individuals with schizophrenia spectrum disorders: a systematic review and meta-analysis. J Psychopharmacol. 2023;37:135–43.
56. Lähteenvuo M, Luykx JJ, Taipale H, Mittendorfer-Rutz E, Tanskanen A, Batalla A, et al. Associations between antipsychotic use, substance use and relapse risk in patients with schizophrenia: real-world evidence from two national cohorts. Br J Psychiatry. 2022;221:758–65.
57. Arranz B, Garriga M, García-Rizo C, San L. Clozapine use in patients with schizophrenia and a comorbid substance use disorder: a systematic review. Eur Neuropsychopharmacol. 2018;28:227–42.
58. Osugo M, Whitehurst T, Shatalina E, Townsend L, O'Brien O, Mak TLA, et al. Dopamine partial agonists and prodopaminergic drugs for schizophrenia: systematic review and meta-analysis of randomized controlled trials. Neurosci Biobehav Rev. 2022;135:104568.
59. Keks N, Hope J, Schwartz D, McLennan H, Copolov D, Meadows G. Comparative tolerability of dopamine D2/3 receptor partial agonists for Schizophrenia. CNS Drugs. 2020;34:473–507.
60. Cuomo I, Kotzalidis GD, de Persis S, Piacentino D, Perrini F, Amici E, et al. Head-to-head comparison of 1-year aripiprazole long-acting injectable (LAI) versus paliperidone LAI in comorbid psychosis and substance use disorder: impact on clinical status, substance craving, and quality of life. Neuropsychiatr Dis Treat. 2018;14:1645–56.
61. Szerman N, Basurte-Villamor I, Vega P, Martinez-Raga J, Parro-Torres C, Cambra Almerge J, et al. Once-Monthly Long-Acting Injectable Aripiprazole for the treatment of patients with Schizophrenia and Co-occurring Substance Use disorders: a Multicentre, Observational Study. Drugs - Real World Outcomes. 2020;7:75–83.
62. Margolese HC, Boucher M, Therrien F, Clerzius G. Treatment with aripiprazole once-monthly injectable formulation is effective in improving symptoms and global functioning in schizophrenia with and without comorbid substance use - a post hoc analysis of the ReLiAM study. BMC Psychiatry. 2022;22:773.
63. Such P, Nylander A-G, Baker R, Schmidt S-N, Madera J. Effects of aripiprazole once-monthly and paliperidone palmitate in patients with schizophrenia and concomitant substance use: a post-hoc analysis of QUALIFY, a head-to-head study. Psych Congr. Netw. 2019 P118. https://www.hmpgloballearningnetwork.com/site/pcn/posters/effects-aripiprazole-once-monthly-and-paliperidone-palmitate-once-monthly-patients. Accessed 13 Jun 2023.
64. Skryabin VY, Vinnikova MA, Ezhkova EV, Titkov MS, Bulatova RA. Atypical antipsychotics in the treatment of patients with a dual diagnosis of schizophrenia spectrum disorders and substance use disorders: the results of a randomized comparative study. J Addict Dis. 2021;39:513–25.
65. Chiappini S, Cavallotto C, Mosca A, Di Carlo F, Piro T, Giovannetti G, et al. Investigating the effectiveness of Brexpiprazole in subjects with Schizophrenia Spectrum Illness and Co-occurring Substance Use Disorder: a prospective, multicentric, real-world study. Pharmaceuticals. 2024;17:535.
66. Carrà G, Johnson S, Bebbington P, Angermeyer MC, Heider D, Brugha T, et al. The lifetime and past-year prevalence of dual diagnosis in people with schizophrenia across Europe: findings from the European Schizophrenia Cohort (EuroSC). Eur Arch Psychiatry Clin Neurosci. 2012;262:607–16.
67. Browne J, Wright AC, Berry K, Mueser KT, Cather C, Penn DL, et al. The alliance-outcome relationship in individual psychosocial treatment for schizophrenia and early psychosis: a meta-analysis. Schizophr Res. 2021;231:154–63.
68. Torrecilla-Olavarrieta R, Pérez-Revuelta J, García-Spínola E, López Martín Á, Mongil-SanJuan JM, Rodríguez-Gómez C, et al. Satisfaction with antipsychotics as a medication: the role of therapeutic alliance and patient-perceived participation in decision making in patients with schizophrenia spectrum disorder. Int J Psychiatry Clin Pract. 2021;25:268–76.
69. Harvey PD, Kane JM. Addressing patients' unmet needs to improve outcomes in Schizophrenia. J Clin Psychiatry. 2021;82.

70. Ati NAL, Paraswati MD, Windarwati HD. What are the risk factors and protective factors of suicidal behavior in adolescents? A systematic review. J Child Adolesc Psychiatr Nurs. 2021;34:7–18.
71. McPherson KL, Tomasi DG, Wang G-J, Manza P, Volkow ND. Cannabis affects cerebellar volume and sleep differently in men and women. Front Psychiatry. 2021;12:643193.
72. Cornish JL, Prasad AA. Sex differences in Substance Use disorders: a neurobiological perspective. Front Glob Women's Heal. 2021;2:778514.
73. Fiorillo A, Barlati S, Bellomo A, Corrivetti G, Nicolò G, Sampogna G, et al. The role of shared decision-making in improving adherence to pharmacological treatments in patients with schizophrenia: a clinical review. Ann Gen Psychiatry. 2020;19:43.
74. Kane JM, Schooler NR, Marcy P, Achtyes ED, Correll CU, Robinson DG. Patients with early-phase Schizophrenia will accept treatment with sustained-release medication (Long-Acting Injectable antipsychotics). J Clin Psychiatry. 2019;80.
75. Garcia-Portilla MP, Benito Ruiz A, Gómez Robina F, García Dorado M, López Rengel PM. Impact on functionality of the paliperidone palmitate three-month formulation in patients with a recent diagnosis of schizophrenia: a real-world observational prospective study. Expert Opin Pharmacother. 2022;23:629–38.
76. Vita A, Fagiolini A, Maina G, Mencacci C, Spina E, Galderisi S. Achieving long-term goals through early personalized management of schizophrenia: expert opinion on the role of a new fast-onset long-acting injectable antipsychotic. Ann Gen Psychiatry. 2023;22:1.
77. Giordano G, Tomassini L, Cuomo I, Amici E, Perrini F, Callovini G, et al. Aripiprazole Long-Acting Injection during First Episode Schizophrenia—An exploratory analysis. Front Psychiatry. 2020;10:935.
78. Milz R, Benson C, Knight K, Antunes J, Najarian D, Lopez Rengel P-M, et al. The effect of longer Dosing intervals for Long-Acting Injectable antipsychotics on outcomes in Schizophrenia. Neuropsychiatr Dis Treat. 2023;19:531–45.
79. Rezansoff SN, Moniruzzaman A, Somers JM. Temporal associations between medication adherence for patients with schizophrenia and opioid dependence: a 17-year Canadian cohort study. Schizophr Res. 2019;210:157–63.
80. Kamei H. Polypharmacy Management of antipsychotics in patients with Schizophrenia. Medicina. 2022;58.
81. Goodlet KJ, Zmarlicka MT, Peckham AM. Drug-drug interactions and clinical considerations with co-administration of antiretrovirals and psychotropic drugs. CNS Spectr. 2019;24:287–312.
82. Peris L, Szerman N. Partial agonists and Dual disorders: Focus on Dual Schizophrenia. Front Psychiatry. 2021;12:769623.
83. Lombardozzi G, Trovini G, Amici E, Kotzalidis GD, Perrini F, Giovanetti V, et al. Brexpiprazole in patients with schizophrenia with or without substance use disorder: an observational study. Front Psychiatry. 2023;14:1321233.
84. Ali RA, Jalal Z, Paudyal V. Barriers to monitoring and management of cardiovascular and metabolic health of patients prescribed antipsychotic drugs: a systematic review. BMC Psychiatry. 2020;20:581.
85. Gowda GS, Isaac MK. Models of care of Schizophrenia in the Community-An International Perspective. Curr Psychiatry Rep. 2022;24:195–202.

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