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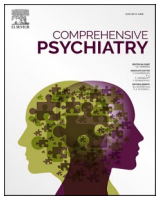

Navigating the challenges of substance use and psychopathology in depression, bipolar disorder, and schizophrenia☆

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ABSTRACT

Introduction: Dealing with Substance use disorders (SUDs) in conjunction with psychopathological conditions such as Major Depressive Disorder (MDD), bipolar disorder (BD), and schizophrenia - often referred to as *dual diagnosis* or *co-occurring disorders* - poses significant challenges for both patients and clinicians, requiring integrated treatment approaches that simultaneously tackle both substance use and psychopathology.

Aim and methods: The objective of this systematic review is to analyse and summarize the existing research on the various pharmacological treatments for dual diagnosis, providing a comprehensive understanding of their effectiveness and identifying areas requiring further exploration. The systematic review was structured in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and registered on the International Prospective Register of Systematic Reviews (PROSPERO) with the id number CRD 42024500114.

Results: The analysis of the available literature identified 66 articles, 29 related to SUDs & schizophrenia, 20 focused on SUDs & MDD, and 17 on SUDs & BD. Overall, most manuscripts recording SUDs concerned the following drugs: alcohol ($N = 26$), cannabis ($N = 19$), opioids ($N = 10$), cocaine (N = 10), and amphetamine ($N = 3$), while several studies described SUDs in general ($N = 12$). Findings were presented thematically based on the type of intervention for each of the main conditions recorded. In the case of psychotic symptoms and SUDs, aripiprazole appeared to be the most used medication in the maintenance therapy not only for its effectiveness but also for its safety profile. Alternatively, despite the side effects, clozapine showed a good efficacy in the management of symptoms and in terms of relapse prevention. Moreover, long-acting medications might be an effective option in the control of impulsivity and psychotic symptoms, but also in first-episode psychosis, reducing relapse and rehospitalization. With regard to the treatment of MDD/BD and SUDs, there are mixed findings regarding the best medication for symptom control; notably, different degrees of efficacy were recorded if added to psychological/behavioural interventions, or combined with specific SUD treatments, such as opioid receptor agonist/antagonist therapies or the anti-glutamatergic drugs acamprosate/memantine, etc.

Conclusion: The current body of evidence includes mixed findings in terms of which medication is superior in controlling symptoms, according to the specific psychopathology, the specific SUD involved, the treatment setting, and the primary objective of care. Overall, pharmacological treatments for dual diagnosis are complex and require personalized approaches considering the heterogeneity of the population. Future research should

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focus on developing individualized treatment plans and understanding the biological underpinnings of dual diagnosis to create more targeted, effective pharmacological interventions.

1. Introduction

1.1. Definitions available

Dual diagnosis, also referred to as co-occurring disorders, describes the condition in which an individual simultaneously experiences both a mental illness and a substance use disorder (SUD) [1,2]. The precise definition of dual diagnosis may vary depending on national guidelines or the diagnostic classification system employed (Table 1). Although the International Classification of Diseases (ICD) [3] provides diagnostic codes for mental and behavioural disorders and acknowledges the co-occurrence of mental disorders and SUDs, it does not explicitly use the term 'dual diagnosis.' Rather, it offers separate coding and criteria for each condition. Similarly, the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) [4], does not define 'dual diagnosis' as a distinct clinical entity. In practice, however, the term 'dual diagnosis' or 'co-occurring disorders' is widely used in clinical settings to refer to individuals who present with both a mental disorder and a SUD, regardless of the classification system applied.

1.2. Prevalence of dual diagnosis

Research consistently demonstrates a high rate of co-occurrence between SUDs and psychopathology, particularly major depressive disorder (MDD), bipolar disorder (BD), and schizophrenia [5]. For instance, individuals diagnosed with these disorders are significantly more likely to develop substance abuse problems and vice versa [6]. Moreover, patterns have emerged in terms of specific substance use associated with specific disorders [7]. Approximately 8 % of adults worldwide experience co-occurring SUD and mental health disorders, with prevalence rising to 15 % among young adults [8]. According to the World Mental Health Surveys coordinated by the World Health Organization, across 27 countries, about 33 % of individuals with a past-year SUD also had at least one other mental disorder, with higher comorbidity rates observed in high-income countries [9]. The rates of co-occurring SUDs vary across different psychiatric disorders, with MDD exhibiting a strong association with alcohol use disorder (AUD) and BD being linked to both alcohol and drug abuse [10], e.g., the prevalence of any SUDs in individuals with MDD is reported as 25 %, with 20.8 % for AUD, 11.8 % for cannabis use disorder (CUD) and 4 % for stimulant use disorder, and no significant differences in the subgroup analyses were found in terms of study settings (community, inpatient and outpatient), severity of the SUDs and current versus lifetime drug use disorders [11]. Among individuals with opioid use disorder (OUD), the prevalence of co-occurring mental health disorders is significant, with depression being reported in 36.1 %, anxiety in 29.1 % and BD in 8.7 % [12]. Schizophrenia has been associated with high rates of cannabis [13] and nicotine dependence [14]. Specifically, cannabis, especially high-potency cannabis, and synthetic cannabinoids use has been associated with an earlier onset of schizophrenia, dissociative symptoms, an increasing inpatient readmission risk

Table 1
Definitions of dual diagnosis.

DEFINITIONS	
World Health Organization (WHO)	The International Classification of Diseases (ICD) provides diagnostic criteria for both mental and behavioural disorders due to psychoactive substance use (e.g., F10–F19 in ICD-10) and other psychiatric disorders (e.g., schizophrenia, mood disorders, anxiety disorders, etc.); although the co-occurrence of these diagnoses is clinically acknowledged, 'dual diagnosis' is not a coded or formally defined term in the ICD
United Nations Office on Drugs and Crime (UNODC)	Double Diagnosis is a term used to describe a «subject diagnosed with a problem of alcohol or drug abuse in addition to other commonly-occurring psychiatric or depressive disorders or schizophrenia
European Monitoring centre for Drugs and Drug Addiction (EMCDDA)	Comorbidity/dual diagnosis is the temporal coexistence of two or more psychiatric disorders as defined by the International Classification of Diseases, one of which is problematic substance use
Centre for Addiction and Mental Health, Canada	'Concurrent disorders' is a term used to refer to co-occurring addiction and mental health problems. It covers a wide array of combinations of problems, such as: anxiety disorder and an alcohol problem, schizophrenia and cannabis dependence, borderline personality disorder and heroin dependence, and bipolar disorder and problem gambling
Substance Abuse and Mental Health Services Administration (SAMHSA)	The coexistence of both a mental illness and a substance use disorder is known as a co-occurring disorder. Co-occurring disorders may include any combination of two or more substance use disorders and mental disorders identified in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5-TR). No specific combinations of mental and substance use disorders are defined uniquely as co-occurring disorders. Some of the most common mental disorders seen in SUD treatment include: -Anxiety and mood disorders -Schizophrenia -Bipolar disorder -Major depressive disorder -Conduct disorders -Post-traumatic stress disorder -Attention deficit hyperactivity disorder
American Psychiatric Association (APA)	A formal definition of dual diagnosis is not provided. Rather, *substance-induced mental disorders* are described using the following criteria a. The disorder must have a significant clinical presentation of a considerable mental health disorder; b. There is evidence from anamnesis, target examination or laboratory data for both the following conditions: 1. the disorder developed during or within one month since the inoculation or abstinence or substance/drug intake; 2. the substance or medicament involved is able to produce the mental disorder in question; c. The disorder is not better specified by an independent mental health disorder. Such evidence may alternatively be: 1. the disorder precedes the onset of severe intoxication or abstinence or exposure to the substance/drug; 2. the disorder exhibits clinical relevance for more than one month since cessation of acute abstinence or severe intoxication or exposure to the substance/drug. (this criterion does not apply to possible persistent disorders, such as neurocognitive disorders); d. The disorder does not occur exclusively during the delirium; e. The disorder causes significant clinical distress, or significant difficulties in working-social function.
UK's National Institute for Health and Care Excellence (NICE)	The term 'dual diagnosis' is not used in official documents. Dual diagnosis is typically defined as: 'People who have both a mental health problem and misuse drugs or alcohol'.

and worse overall symptoms and course of psychosis [13–18]. On the other side, the overall prevalence of any SUDs among individuals with schizophrenia or first-episode psychosis was 41.7 % (46 % in non-clinical samples and 39 % in clinical settings), with different prevalence rates between lifetime and current SUDs (39 % and 27 %, respectively) [19].

Prevalence of dual diagnosis varies depending on the population studied and the definitions used. In the United States (US), the Substance Abuse and Mental Health Services Administration (SAMHSA) estimated that nearly half of young adults aged 18 to 25 in 2021 (45.8 % or 15.3 million people) accessing mental services had either a SUD or any mental illness in the past year. This percentage was higher than corresponding percentages among adults aged 26 to 49 (39.5 % or 40.4 million people) and adults aged 50 or older (22.6 % or 26.7 million people) [20]. Cannabis, tobacco, alcohol, and opioids were the most involved substances; moreover, the prevalence of comorbidity was found to be higher in populations with higher levels of instability and need (e.g., homelessness, criminal justice involvement, child welfare populations, crisis settings) [20]. According to the European Union Drugs Agency (EUDA) annual report, data on the prevalence of psychiatric comorbidity among drug users in Europe are more limited and heterogeneous with regard to the methodology of study and target populations [21], being the overall comorbidity of schizophrenia/depression/mood disorders and SUD prevalence varying between 12 and 80 % [22,23]. Also, in European drug treatment centres, studies have reported comorbidity rates ranging from 42 % in outpatient settings to 90 % in therapeutic communities, particularly for mood disorders [21]. Unfortunately, Italian data on dual diagnosis are limited. A recent study investigated the rate of dual diagnosis among people with SUD of a specific rural area in the Northern part of Italy, finding that out of 750 patients, patients with dual diagnosis were 24 %, and most of them (42.8 %) were dependent on central nervous system depressants, e.g. heroin, cannabis, benzodiazepines in the context of a polysubstance dependence (27.8 %); the remaining sample of patients included was affected by an AUD (18.3 %), cocaine dependence (8.3 %), and a behavioural addiction (gambling/shopping disorder; 2.8 %). Conversely, the most frequent mental illnesses identified were in order a mood disorder (40 %), a personality disorder (33.3 %), and schizophrenia or other psychotic disorder (13.3 %) [24].

1.3. Clinical pathways and features of dual diagnosis

Dual diagnosis presents significant challenges for clinicians due to the complex interaction between substance use and mental health symptoms [25–27] and increased difficulty in treatment. The co-occurrence of substance use and psychiatric disorders is thought to be influenced by shared causal pathways, involving common genetic vulnerabilities [28], neurobiological mechanisms [29,30], and environmental factors [31]. Research suggests that dysregulation of neurotransmitter systems, particularly dopamine, implicated in the rewarding effects of substances as well as the pathophysiology of depression, mania, and schizophrenia, plays a critical role in both conditions [32,33]. Substance use may serve as an ill-suited form of self-medication, potentially exacerbating psychiatric symptoms and impeding therapeutic efficacy. Moreover, differentiating substance-induced symptoms from inherent psychopathology presents a diagnostic challenge, particularly in the area of schizophrenia spectrum disorders [34]. Three main pathways can contribute to the development of dual diagnosis [6,35,36]: i)Common risk factors may underlie both mental illness and substance use and addiction; ii) Mental illness can contribute to the onset of substance use and addiction; iii) Conversely, substance use and addiction can lead to the development of mental illness. Additionally, the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) has proposed a fourth theory to explain the comorbidity observed in cases of dual diagnosis. This indicates that a transient psychiatric disorder, also referred to as a substance-induced disorder, develops as a result of intoxication or withdrawal from a particular substance [37] (Fig. 1).

Although both substance-induced disorders and dual diagnosis involve the co-occurrence of substance use and psychiatric symptoms, in the substance-induced disorder psychiatric symptoms (e.g., depression, anxiety, psychosis) are directly caused by substance use, intoxication, or withdrawal, thus, once the substance is removed, the symptoms often resolve or significantly improve. On the contrary, dual diagnosis refers to the presence of a separate, independent mental health disorder and a SUD. The psychiatric condition is not solely due to substance use and may persist even during sustained abstinence. Dual diagnosis is associated with poorer clinical outcomes, including heightened symptom severity, increased risk of suicide, poorer treatment response, increased health service utilization/hospitalisations, and early mortality [36].

1.4. Current clinical guidelines available

Despite very high co-prevalence, clinical guidelines for SUDs with severe mental illnesses tend to have limited considerations in diagnosis, treatment, and management of such conditions [25,38]. All guidelines available, in fact, show limited evidence base and address dual diagnosis using integrated interventions. Among them, both the British Association for Psychopharmacology (BAP) [39] and the National Institute for Health and Care Excellence (NICE) guidelines [40-,41]offer thorough details on every domain of the AGREE II tool (Appraisal of Guidelines for

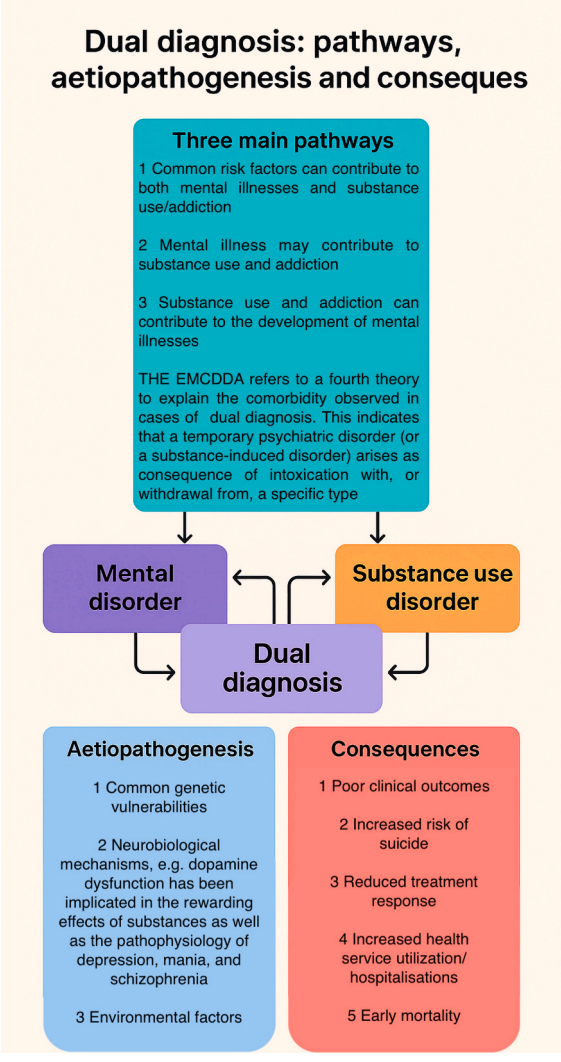

Fig. 1. Dual diagnosis: main pathways, aetiopathogenesis, and consequences.

Research and Evaluation) for standardized guidelines assessment [25,38]. Nonetheless, treating patients with dual diagnosis can be challenging for healthcare professionals due to unique psychiatric manifestations, as well as fragmented care—such as services that separately address mental health and substance use disorders—creating barriers to both accessing and delivering treatment. However, integrated treatment models, addressing both issues concurrently, eventually in the same setting, and encompassing psychotherapy, pharmacotherapy, psychoeducation, and preventive measures, have been associated with improved symptomatology and outcomes for this vulnerable population [36,40–42]. Nonetheless, more research is needed to identify tailored and personalized treatment strategies for specific psychiatric disorders-substance use combinations.

Aim of the study: The objective of this systematic review is to analyse and summarize the existing research on the various pharmacological treatments for dual diagnosis, providing a comprehensive understanding of their effectiveness and identifying areas requiring further exploration.

2. Materials and methods

2.1. Search strategy

A systematic electronic search was performed on 8 January 2024 on the following search engines: PubMed, Scopus, and Web of Science (WoS). The search strategy included a combination of keywords and MeSH terms such as (dual diagnosis OR co-occurring disorders) AND (mental health OR substance use) AND (treatment OR therapy OR intervention) AND "pharmacological treatment" OR non-pharmacological treatment). Other relevant papers not resulting from the described search were added from references of included articles.

The systematic review was structured in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [43,44] guidelines. Identified studies were assessed at title/abstract and full text screening against eligibility criteria. The systematic review protocol was registered on the International Prospective Register of Systematic Reviews (PROSPERO) with the id number CRD 42024500114.

2.2. Criteria for inclusion and exclusion

Inclusion Criteria:

- Studies that focus on pharmacological treatment approaches for dual diagnosis adult patients.
- Studies published in a peer-reviewed journal.
- Articles written in English.

Exclusion Criteria:

- Studies that do not explicitly focus on dual diagnosis treatment of adult patients.
- Studies focusing on non-pharmacological treatment approaches.

2.3. Screening process

Titles and abstracts were initially screened for relevance. After the initial screening, full-text articles were reviewed based on the inclusion and exclusion criteria. Two independent reviewers (A.M. and F.S.) conducted the screening process supervised by S.C. and M.P.; and discrepancies were resolved through discussion or consultation with a third reviewer (G.M.).

2.4. Data extraction

Relevant information were extracted from the selected studies, including the authors, year of publication, study design, sample size, type of co-occurring disorders, treatment interventions, outcome measures, and main findings. From a total of 294 articles (PubMed = 79; Scopus = 97; WoS = 110; other sources = 7), after deduplication (n = 123), 163 records were screened. Among the articles screened 24 were not considered original studies, 9 were not written in English, and 71 were not on dual diagnosis or were not pharmacotherapy. Of the 9 reports searched for retrieval, 2 were not dual diagnosis and 2 were not available. Finally, 66 articles were included in the systematic review and adequately analyse *(*Fig. 2*)*.

3. Results

The analysis of the available literature identified 66 articles, 29 related to SUDs & schizophrenia, 20 focused on SUDs & MDD, and 17 on SUDs & BD. Overall, the majority of manuscripts recording SUDs concerned the following substances/drugs: alcohol (N = 26), cannabis (N = 19), opioids (N = 10), cocaine (N = 10), and amphetamine (N = 3). A large group of articles described SUDs in general (N = 12).

Findings were presented thematically based on the type of intervention for each of the main conditions recorded (1. Substance Use Disorders & depression; 2. Substance Use Disorders & bipolar disorder; 3. Substance Use Disorders & schizophrenia). A narrative synthesis has been conducted to summarize and explain the findings of the selected studies (Tables 2–3). Where possible, we have organized each section into clearly defined subsections that separately present findings distinguishing the treatment outcomes related to SUD, the comorbid psychiatric condition (schizophrenia, BD, or MDD), and any potential interaction between the two.

3.1. Substance use disorders & schizophrenia

Overall, the relationship between substance use and psychosis is multifaceted and has been a topic of extensive research, especially concerning cannabis. Results were herein described according to the main classes of treatments used.

3.1.1. Oral antipsychotic medications

Early studies indicated that atypical antipsychotics like clozapine, risperidone, and olanzapine were effective in treating psychotic symptoms and reducing substance use in psychotic patients with dual diagnosis [45]. However, subsequent research has shown mixed results, suggesting that individual patient characteristics and the type of SUD can influence treatment efficacy [46–55].

With regard to SUD-related outcomes, Mesholam-Gately et al. (2014) examined the role of clozapine in an all-male cohort of 43 patients with schizophrenia and comorbid SUDs [46]. Clozapine has been linked to an enhanced hedonic response to rewards, which may lead to reduced substance use [46].; on the contrary,Comparing clozapine, olanzapine, and risperidone in cannabis-dependent patients, more severe craving for cannabis was recorded in patients treated with risperidone compared to those treated with clozapine or olanzapine [47]. Similarly, in a study of 31 patients with schizophrenia and cannabis dependence, clozapine was associated with reduced cannabis use, despite side effects such as somnolence and hypersalivation [48]. Supporting this, Brunette et al. (2006) found that clozapine was effective for patients with schizophrenia and comorbid SUD not only during active treatment but also throughout extended periods of remission from substance use [49]. Consistently, referring to the treatment outcomes related to both SUDs and the comorbid psychiatric conditions, in a sample of 67 all-male patients with schizophrenia and comorbid CUD, Machielsen et al. (2014) [50] suggested clozapine as potentially more effective in the resolution of positive symptoms than risperidone, highlighting the importance of D2 receptor occupancy and the D1/D2 receptor occupancy ratio. Comparing the effects of clozapine with ziprasidone in a sample of 30 patients with schizophrenia and comorbid cannabis abuse/dependence,

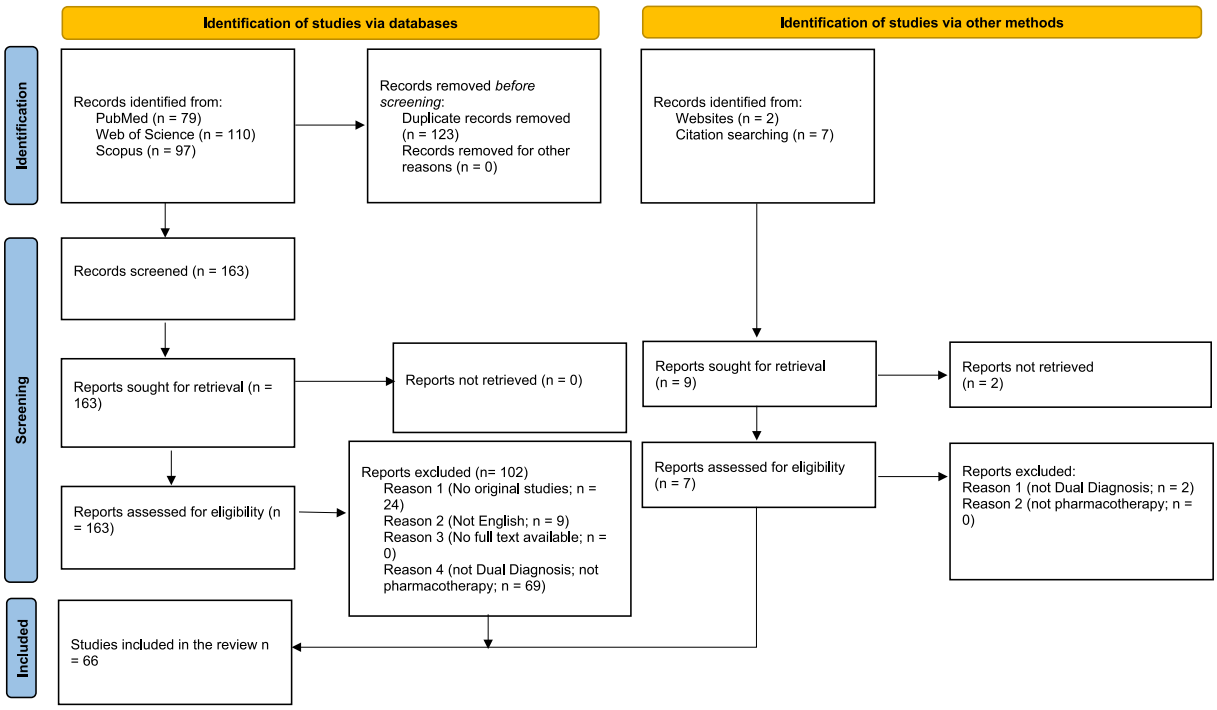

Fig. 2. PRISMA 2020 flow diagram for new systematic reviews which included searches of databases, registers, and other sources.

Schnell et al. (2014) [51] showed both drugs led to diminished cannabis use over 12 months, but a more pronounced decline in Positive and Negative Syndrome Scale (PANSS) positive scores was evident in the clozapine group. Finally, Kim et al. (2008) assessed clozapine against risperidone in 61 male adult patients with schizophrenia and AUD [52] finding a longer community survival exhibited by the clozapine-treated group, emphasizing the potential role of clozapine for symptom management and for reducing hospital readmissions. An overall comparison of substance use outcomes among antipsychotics was performed by Swartz et al. (2008), analyzing data from the Clinical Antipsychotic Trial of Intervention Effectiveness (CATIE) schizophrenia trial, which included 1432 patients formally diagnosed with schizophrenia randomized to one of four second-generation antipsychotic drugs (olanzapine, risperidone, quetiapine, and ziprasidone) or a first-generation antipsychotic (perphenazine), with an 18-month follow-up period [53]; although olanzapine led to less 'all cause discontinuation' in those not using illicit drugs, there was no difference in those abusing illicit drugs. Performing a further descriptive secondary analysis of the same data, Mohamed et al. (2015) reported significant effects of time, indicating a reduction in substance use over the 18 months (all $p < 0.0001$), with no evidence suggesting that any antipsychotic was markedly superior to the others in terms of substance use outcomes [54].

With regard to drug tolerability, a successful switch from olanzapine + escitalopram to aripiprazole in a 33-year-old male with schizophrenia and comorbid cannabis use was reported [56]. Similarly, Feeley et al. (2017) described a 71-year-old male with treatment-resistant schizophrenia and comorbid AUD who transitioned from clozapine to aripiprazole after clozapine-induced bowel obstruction. The patient showed prolonged improvement in positive symptoms and sustained sobriety for over two years [57]. Additionally, a study comparing aripiprazole, quetiapine, and haloperidol in 90 patients with schizophrenia and SUD found that aripiprazole and quetiapine led to better PANSS and BPRS scores than haloperidol, with aripiprazole showing superior efficacy for SUD-related symptoms. Beresford et al. (2017) compared aripiprazole to perphenazine in patients with schizophrenia and cocaine dependence, reporting reductions in both psychotic and SUD symptoms with reduced cocaine cravings over time [58]. Lastly, Rodriguez et al. (2021) presented the case of a 30-year-old male transitioning from haloperidol to the combination of cariprazine and quetiapine, resulting in enhanced cognitive function as well as reduced negative-positive symptoms and substance abuse [59]. Exploring the effectiveness of antipsychotics in the treatment of patients affected by schizophrenia, schizoaffective disorder, or schizophreniform disorder and CUD, Van Nimwegen-Campailla et al. (2008 a,b) compared olanzapine to risperidone during 6 weeks of treatment, finding similar improvements in subjective well-being in both groups [60,61]. Among the group with comorbid cannabis use ($n = 41$, 32 %), both treatment conditions resulted in a comparable reduction in cannabis cravings hypothesising a comparable dopamine D(2) occupancy [61]; moreover, olanzapine was associated with greater decreases in obsessive-compulsive symptoms scores [61]. Finally, a recent investigation presented data on lurasidone in four patients experiencing first cannabis-induced psychotic episode treated with lurasidone (74–128 mg/day), showing an overall improvement in the clinical symptomatology, with the remission of positive and negative symptoms and personal functioning [62].

In relation to pharmacotherapies specifically approved for the treatment of SUDs, recent research has identified acamprosate, an anti-craving medication widely approved for treating AUD, as a promising option for managing schizophrenia spectrum disorders with coexisting AUD. Tek et al. (2008) treated a 74-year-old woman with a 55-year history of schizophrenia and alcoholism using acamprosate (666 mg TID) [63]. This treatment reduced her alcohol intake by 50 % within six months, leading to complete abstinence after two years. Her overall medical condition, including diabetes, blood pressure, and glucose levels, also improved, with no reported side effects or withdrawal symptoms. Similarly, Ralevski et al. (2011) found significant reductions in both alcohol use and positive psychotic symptoms (measured by PANSS) in patients with schizophrenia and AUD, without adverse cognitive effects [64].

3.1.2. *Long-acting injectable antipsychotics*

A few studies were related to the use of long-acting injection (LAI) antipsychotics [65–72]-They have been investigated for their efficacy in addressing outcomes associated with both SUDs and schizophrenia. The

Table 2
Most important findings of studies retrieved.

Schizophrenia Spectrum and Substance Use Disorder								
Author and Year	Study design	Intervention (Pharmacotherapy according to NbN approach)	Sample of patients	Major indications	Treatment	Outcome	Adverse events	Remarks/Treatment recommendations
Beresford et al., 2017 [58]	Randomized Controlled Trial	Aripiprazole: Receptor partial agonism (D2, 5-HT1A)	N = 44 patients (N = 22 per group)	Schizophrenia disorder + CoUD	Cocaine-dependent schizophrenic subjects actively using cocaine received either Aripiprazole or Perphenazine in an 8-week trial	Reduced both psychotic and SUD scores; with regard to the second finding, the proportion of cocaine-free urine samples did not differ by medication group. Contrasting weeks 3 to 5 vs 6 to 8 revealed significant late reductions in craving with aripiprazole. On the respective 5-point subscales, craving intensity decreased by 1.53 ± 0.43 ($P < 0.0005$) points, craving frequency by 1.4 ± 0.40 ($P > 0.0004$) points, and craving duration by 1.76 ± 0.44 ($P > 0.0001$) points	Not reported	A drug effect of aripiprazole on craving items appeared at week 6 of treatment, on average, and was not seen before that length of drug exposure, suggesting that dopamine modulation reduces cocaine cravings but requires an acclimation period
Brunette et al., 2006 [49]	Open-label study	Clozapine: Receptor antagonism (D2, 5-HT2, NE alpha-2)	$N = 95$ adult community patients	Schizophrenia/ Schizoaffective disorder + AUD	$N = 25$ took clozapine $N = 62$ took FGA (16 in a decanoate form) $N = 8$ took other SGA (4 took risperidone and 4 took olanzapine)	Compared with patients taking other antipsychotic medications, patients taking clozapine were less likely to experience substance abuse relapse at 1 year following remission. Among patients taking first-generation antipsychotics, rates of relapse did not differ between those taking decanoates (long-acting injectables; $N = 16$) and those taking oral pills ($N = 46$). Additionally, the 8 patients taking risperidone or olanzapine experienced similar rates of substance abuse relapse as patients taking conventional antipsychotics. Patients who were prescribed clozapine also experienced better 1-year post remission outcomes on other measures of SUD than patients who were prescribed other antipsychotic medications	Not reported	Patients in 6-month remissions from their SUD who took clozapine had lower rates of relapse back into substance abuse compared with patients who took other antipsychotic medications, despite equivalent utilization of other treatment services. This advantage was maintained at 2 years after initial remission
Brunette et al., 2011 [48]	Randomized Controlled Trial	Clozapine: Receptor antagonism (D2, 5-HT2, NE alpha-2)	$N = 31$ patients (F/M: 7/24); Mean age: 36 (10.3) years	Schizophrenia + CUD	Clozapine group ($N = 15$, clozapine dosage: 400 mg by week 4). Group (N = 16) that has maintained the antipsychotic treatment as arrived in the scientific	Clozapine group: less frequent cannabis use. Both groups: no differences in symptoms or functioning	Somnolence: 11; Hypersalivation: 10; Weight gain: 8; Dizziness: 6; Vomiting: 6; Constipation: 4	The routine use of clozapine is a therapeutic option for outpatients with a co-occurring CUD

(*continued on next page*)

Table 2 (*continued*)

Schizophrenia Spectrum and Substance Use Disorder								
Author and Year	Study design	Intervention (Pharmacotherapy according to NbN approach)	Sample of patients	Major indications	Treatment	Outcome	Adverse events	Remarks/Treatment recommendations
					study (customized for each participant)			
Bruno et al., 2014 [109]	Open-label uncontrolled trial	Aripiprazole: Receptor partial agonism (D2, 5-HT1A); Methadone: Opioid agonism	*N* = 20 (F/M: 10/10), Age range: 18–40 years	Schizoaffective disorder + Opioid dependence	Aripiprazole: 10 mg/day until week 8. Topiramate was increased from 50 to 200 mg/day at week 4. Methadone: a dose reduction of 3 mg/day until suspension at week 4 was established	Aripiprazole plus topiramate showed a significant reduction in clinical symptoms, including PANSS domains, overall clinical symptomatology (BPRS, HRSD, and HRSA). Effective in promoting rapid methadone tapering-off	Common side effects: agitation (40 %), insomnia (50 %), sweating (40 %), nausea/vomiting (50 %), diarrhoea (10 %). Side effects were generally mild/moderate and transient	Combined treatment demonstrated safety and efficacy in treating schizoaffective symptoms while facilitating methadone tapering. Acknowledged limitations of small sample size, lack of control group, open design
Chen et al., 2019 [69]	Case Report	LAI-Aripiprazole: Receptor partial agonism (D2, 5-HT1A)	N = 1 male Age: not specified	Schizophrenia + Amphetamine use disorder	LAI-Aripiprazole (400 mg/4 weeks)	Significant reduction in psychotic symptoms and amphetamine cravings	Not reported	LAI Aripiprazole may be effective in stabilizing schizophrenic symptoms and reducing craving for amphetamines
Chiappini et al., 2023 [72]	Prospective, observational study	LAI-Aripiprazole: Receptor partial agonism (D2, 5-HT1A)	*N* = 24 Age: 18 and 35 years	Schizophrenia + AUD/SUD	LAI-Aripiprazole (400 mg/4 weeks)	During the study period, an improvement of both the clinical condition and general health from baseline was observed, as well as a reduction of craving for alcohol/substances, from the baseline (T0) to T1 and T2 (after 12 and 24 weeks). However, from T0, the number of patients who continued with this study decreased at T1 (*n* = 8) and then at T2 (*n* = 4)	No serious adverse events were reported, including changes in weight, lipid/glucose metabolism, electrocardiogram and extra-pyramidal side effects, except for the report of essential tremor after 24 weeks in a single patient, which did not require cancelation of medication or prescription of additional treatment	Although limited by the high number of drop outs, this observational real-world study provided insights into the use of aripiprazole once monthly among a sample of patients with schizophrenia and comorbid SUD/AUD
Cuomo et al., 2018 [70]	Randomized Trial	LAI-Aripiprazole Receptor partial agonism (D2, 5-HT1A); LAI-Paliperidone: Receptor antagonism (D2, 5-HT2, NE alpha-2)	*N* = 50 (F/M: 9/41, mean age: 32.92 years) assigned to LAI Aripiprazole 400 mg. *N* = 51 (F/M: 11/40, mean age: 36.92) assigned to 100 mg LAI Paliperidone	Schizophrenia/ Schizoaffettive disorder/ BD + SUD (AUD, CUD, CoUD, OUD)	LAI-Aripiprazole (400 mg/4 weeks) vs LAI-Paliperidone (100 mg/4 weeks)	Both groups showed significant reductions in clinical symptoms and substance-related cravings. LAI aripiprazole group maintained craving and quality of life improvements at 1-year follow-up	Minimal side effects: LAI aripiprazole group had akathisia (2 cases, dose lowered); LAI paliperidone group showed galactorrhoea (5 cases), hyperprolactinemia (4 cases), increased craving (2 cases), avolition (1 case), sexual dysfunction (1 case). No dropouts due to side effects	Both LAI aripiprazole and LAI paliperidone show effectiveness in enhancing clinical status, reducing craving, and improving quality of life. Given LAI aripiprazole superior impact on quality of life and craving, it could be preferred in the clinical practice
Desseilles et al., 2008 [56]	Case report	Aripiprazole: Receptor partial agonism (D2, 5-HT1A)	A 33-year-old man	Schizophrenia + CUD	Aripiprazole 15 mg/day for 12 months	Olanzapine 20 mg/day and escitalopram 10 mg/day were discontinued after aripiprazole was started; total stop from cannabis use	Not reported	Aripiprazole contributed to cannabis use diminution trough different mechanisms, such as aripiprazole's partial agonism at D2 receptors and a number of serotonergic actions that are not related to dopamine potentially modulating the response to cannabis. Secondly, a strong antagonist effect at the D2 receptors in the nucleus accumbens was involved in

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Table 2 (*continued*)

Schizophrenia Spectrum and Substance Use Disorder								
Author and Year	Study design	Intervention (Pharmacotherapy according to NbN approach)	Sample of patients	Major indications	Treatment	Outcome	Adverse events	Remarks/Treatment recommendations
								concomitant increase in substance abuse with old antipsychotics. Moreover, unrelated to dopaminergic mechanisms, the use of certain antipsychotics with substantial side effects by schizophrenia patients may actually contribute to greater substance use in an effort to self-medicate the side effects. The reduction of cannabis use may have contributed to a reduction in eating together with the switch in the antipsychotic to aripiprazole, since aripiprazole is weight neutral and olanzapine is known to facilitate weight gain in patients
Erdogan et al., 2021 [71]	Case Report	LAI-Zuclopentixol: D2 Receptor antagonism; LAI-Aripiprazole: Receptor partial agonism (D2, 5-HT1A)	Case 1: a 31-year-old male patient Case 2: a 27-year-old male patient	Case 1: Schizophrenia with comorbid substance use (nicotine, alcohol, cannabinoids, and methamphetamine. Case 2: Psychotic disorder specified with past history of SUD (cannabis, synthetic cannabinoids, ecstasy)	Case 1: initially treated with Zuclopenthixol injection, Diazepam, Olanzapine, and Carbamazepine; later switched to LAI-Aripiprazole. Case 2: Firstly, Haloperidol, Olanzapine, Buspirone, Biperiden; then switched to LAI-Aripiprazole	Case 1: Partial remission, improvement in psychiatric symptoms; no substance use. Case 2: Recovery from psychotic symptoms and substance craving; overall improved functionality	Case 1: Transaminase enzyme increase. Poor compliance with oral medications Case 2: Not reported	Significant improvements in psychotic symptoms and substance use
Feeley et al., 2017 [57]	Case report	Aripiprazole: Receptor partial agonism (D2, 5-HT1A)	A 71-year-old	Treatment-Resistant Schizophrenia and comorbid AUD	Switched from Clozapine to Aripiprazole	Resolution of positive symptoms, depression, and anxiety. No relapses in alcohol use	Not reported	Aripiprazole was chosen given low propensity for extrapyramidal adverse effects, hyperprolactinemia, sedation, and weight gain
Green et al., 2015 [22]	Randomized Controlled Trial	Risperidone: Receptor antagonism (D2, 5-HT2, NE alpha-2)	N = 95 Mean age: 45.1 years	Schizophrenia + AUD	LAI-Risperidone (25 mg titrated to 37.5 mg/2 weeks) or Oral risperidone (4 mg/day)	No significant schizophrenia symptoms differences between groups. LAI risperidone group had fewer heavy drinking days	Not reported	LAI risperidone may be a better choice than the oral form for dual diagnosis patients
Lefebvre et al., 2017 [65]	Retrospective longitudinal study	LAI-Paliperidone: Receptor antagonism (D2, 5-HT2, NE alpha-2)	Of 6872 veterans in the study, 1684 (25 %) and 5188 (75 %) were treated with LAI-Paliperidone and other antipsychotics, respectively	Schizophrenia + SUD	LAI-Paliperidone	After adjustment, LAI-Paliperidone was associated with fewer all-cause inpatient, mental health-related inpatient, and long-term care stays, but more frequent mental health intensive case management visits compared with other antipsychotics. Similarly, LAI-Paliperidone was associated with significantly lower rates of SUD-related inpatient stays,	Not reported	LAI-Paliperidone was associated with significant total medical cost savings resulting from fewer hospitalizations and lower rates of SUD-related health care resource utilization compared with other antipsychotics in patients with schizophrenia and comorbid SUD

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Table 2 (*continued*)

Schizophrenia Spectrum and Substance Use Disorder								
Author and Year	Study design	Intervention (Pharmacotherapy according to NbN approach)	Sample of patients	Major indications	Treatment	Outcome	Adverse events	Remarks/Treatment recommendations
						mental health stays, long-term care stays, and outpatient visits than other antipsychotics (all $P < 0.001$). Relative to other antipsychotics, patients treated with LAI-Paliperidone also had lower mean annual all-cause and SUD-related medical costs		
Lynn et al., 2018 [66]	Randomized Controlled Trial	LAI-Paliperidone: Receptor antagonism (D2, 5-HT2, NE alpha-2)	SUD Cohort: $N = 130$, mean age 37.2 years, 84.6 % male; Non-SUD Cohort: $N = 96$, mean age 38.4 years, 86.5 % male	Schizophrenia patients with comorbid SUD	LAI-Paliperidone: 78–234 mg (flexible dosage) vs oral antipsychotics	LAI paliperidone was more effective than oral antipsychotics in delaying time to treatment failure in both substance abuse and non-abuse cohorts.	LAI paliperidone group: 87.7 % reported AE; Oral antipsychotics group: 83.6 % reported AE; no significant difference in serious AE or discontinuations due to them between the groups	Emphasize the importance of managing comorbid substance abuse in the schizophrenia population through multidisciplinary approaches, including counselling, residential treatment, recovery support services, and more
Machielsen et al., 2014 [50]	Randomized Controlled Trial	Risperidone: D2-Receptor antagonism; Clozapine: Receptor antagonism (D2, 5-HT2, NE alpha-2)	N tot = 36 patients (28 CUD and 8 non-CUD) and 19 HCs: 20 patients were randomized to risperidone (16 CUD) and 16 to clozapine (12 CUD)	Schizophrenia + SUD	Risperidone (mean dosage: 3.8 mg) vs Clozapine (mean dosage: 302 mg)	fMRI-study on brain response to cannabis-related, positive and neutral images. Clozapine group showed more pronounced reduction in craving and exhibited a greater decrease in amygdala activation when exposed to cannabis-related images, compared to those treated with risperidone. Clozapine in CUD patients showed greater reduction in desire and insula activation during the cannabis word Stroop. Risperidone group showed greater drop in activation of the right anterior cingulate cortex during the conventional Stroop. During the cannabis word Stroop, there was a strong correlation between decreases in perceived desire and decreases in insula activity	Not mentioned	Findings suggested that antipsychotics with a relatively low D2 occupancy rate, a relatively high dissociation rate, and a relatively high D1/D2 receptor occupancy ratio may be better for patients with schizophrenia and comorbid CUD. Clozapine may be a superior therapeutic option than risperidone in people with schizophrenia comorbid with CUD
Machielsen et al., 2012 [47]	Randomized Controlled Trial	Risperidone: D2-Receptor antagonism; Olanzapine: D2 and 5HT Receptors antagonists; Clozapine: Receptor antagonism (D2, 5-HT2, NE alpha-2)	N tot = 141 mean age 25.5 (5.9) years, 90.8 % male	Schizophrenia, Schizophreniform disorder, Schizoaffective disorder, Delusional disorder, Psychotic disorder NOS + Cannabis dependence	Clozapine $n = 23$, mean dosage 350 mg, Risperidone $n = 48$, mean dosage 3.46 mg, Olanzapine $n = 52$, mean dosage 13.78 mg	More severe craving for cannabis in cannabis-dependent patients treated with Risperidone compared with patients treated with Clozapine or Olanzapine.	Not mentioned	The better efficacy of Clozapine and Olanzapine as compared with Risperidone in treating substance abuse could be explained by the lower occupancy rate of the D2 receptor, the higher dissociation rate of the D2 receptor and the higher D1/ D2 receptor occupancy rate of

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Schizophrenia Spectrum and Substance Use Disorder								
Author and Year	Study design	Intervention (Pharmacotherapy according to NbN approach)	Sample of patients	Major indications	Treatment	Outcome	Adverse events	Remarks/Treatment recommendations
								these medications as compared with Risperidone
Mesholam-Gately et al., 2014 [46]	Pilot study	Clozapine: Receptor antagonism (D2, 5-HT2, NE alpha-2)	N tot = 43 male outpatients -HC group: mean age 40.1 years -Clozapine group: mean age 41.0 years -Typical antipsychotics group: mean age 39.5 years	Schizophrenia + SUD (*according to the SUD, subgroups assigned to specific pharmacological treatment were:* Alcohol abuse: 42 % clozapine, 69 % typical antipsychotics; Alcohol dependence: 25 % clozapine, 15 % typical antipsychotics; Cannabis abuse: 33 % clozapine, 46 % typical antipsychotics; Cannabis dependence: 25 % clozapine, 15 % typical antipsychotics; Polysubstance dependence: 25 % clozapine, 23 % typical antipsychotics; Cocaine abuse: 8 % clozapine, 15 % typical antipsychotics; Cocaine dependence: 8 % clozapine, 8 % typical antipsychotics; Heroin abuse: 8 % clozapine Hallucinogen abuse: 8 % typical antipsychotics; Inhalant abuse: 8 % typical antipsychotics)	Clozapine vs FGA (haloperidol or fluphenazine)	Clozapine limited alcohol/ substance use in patients diagnosed with schizophrenia and was associated with strengthening hedonic aspects of reward response potentially by ameliorating this brain reward circuit dysfunction, which could potentially translate to decreased substance use	Not mentioned	Further study with newer atypical antipsychotics recommended; potential use of fMRI response as a biomarker
Mohamed et al., 2015 [54]	Randomized Controlled Trial	SGAs: Olanzapine, Quetiapine, and Ziprasidone: D2 and 5HT Receptors antagonists; Risperidone: Receptor antagonism (D2, 5-HT2, NE alpha-2) versus FGA: Perphenazine: D2-Receptor antagonist	$N = 1430$ patients (mean age 40.6 years)	Schizophrenia + SUD	Olanzapine ($N = 328$) versus Perphenazine ($N = 256$) versus Quetiapine ($N = 326$) versus Risperidone ($N = 332$) versus Ziprasidone ($N = 182$)	There were significant effects of time showing reduction in substance use over the 18 months (all $p < 0.0001$), but no evidence was found that any antipsychotic was robustly superior to any other in a secondary analysis of data on substance use outcomes	Not mentioned	The clinical trial found no evidence that any SGA is superior to any other SGA or an FGA in reducing use of tobacco, alcohol, or drugs, and thus, impact on substance use ought not to be a consideration in selecting antipsychotic agents in the treatment of Schizophrenia
Ralevski et al., 2011 [64]	Randomized Controlled Trial	Acamprosate: NMDA receptor modulation, GABA-A modulation	$N = 23$ patients (M/F: 19/4), mean age (SD): 50.73 (7.311) years	Schizophrenia spectrum disorder + AUD	Acm (1998 mg/day) vs placebo	Both groups decreased alcohol consumption and decreased positive symptoms of psychosis (PANSS). No significant changes in negative symptoms	No adverse effects on cognitive function observed over the 12-week treatment period	Acm does not affect cognitive functioning in patients with alcohol dependence and schizophrenia spectrum disorders. Significant reduction

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Schizophrenia Spectrum and Substance Use Disorder								
Author and Year	Study design	Intervention (Pharmacotherapy according to NbN approach)	Sample of patients	Major indications	Treatment	Outcome	Adverse events	Remarks/Treatment recommendations
						of psychosis or general symptoms (PANSS). Cognitive functioning unchanged across memory, attention, and executive function domains for both groups		in alcohol consumption or psychotic symptoms does not lead to changes in cognitive function
Ricci et al., 2022 [62]	Case series	Lurasidone. Receptor antagonism (D2, 5-HT)7 and 5-HT2A)	N = 4 patients experiencing first cannabis-induced psychotic episode	Psychosis + cannabis	Lurasidone (74-148 mg/day)	In all patients, there was an improvement in the clinical picture of psychosis. The recovery was positive, not only with the remission of positive and negative symptoms, but also regarding disruptive behaviour, with the return of functioning.	No significant side effects were reported.	Lurasidone could be effective and tolerable in cannabis-induced psychotic symptoms
Rodriguez et al., 2021 [59]	Case Report	Haloperidol: Receptor antagonism (D2); receptor Quetiapine: antagonism (D2, 5-HT2) and reuptake inhibition (NET); Cariprazine: D3/D2 partial agonism	A 30-year-old male	Schizophrenia, cognitive dysfunction, history of cannabis, amphetamine, alcohol, opioids, LSD, and benzodiazepine use	Switched haloperidol to cariprazine + quetiapine	Improved cognitive and negative symptoms within 3 weeks of cariprazine switch. Alleviation of positive, negative, and cognitive symptoms. Reduced smoking, remained substance-free	Extrapyramidal symptoms and akathisia with cariprazine (dose reduced)	Cariprazine + Quetiapine combination effective in cognitive improvement, reducing substance abuse desire, and symptom management. Cariprazine D3 receptor agonism might reduce substance abuse
Rubio et al., 2006 [67]	Randomized Controlled Trial	LAI-Risperidone: Receptor antagonism (D2, 5-HT2, NE alpha-2) vs Zuclopenthixol Receptor antagonism (D2)	*N* = 115 patients including 56 inpatients and 59 outpatients	Schizophrenia + SUD	LAI Risperidone vs Zuclopenthixol decanoate	Reduction in drug use, significant improvement in psychopathology with risperidone microspheres	Minimal AE reported	Consider using SGA depot formulations for dual-diagnosis patients
Schnell et al., 2014 [51]	Randomized Controlled Trial	Ziprasidone: Receptor antagonism (D2, 5-HT2); Clozapine: receptor antagonist (D2, 5-HT2, NE alpha-2)	*N* = 30 patients (F/M: 4/26); Ziprasidone: mean age: 27.5 (5.0) years; Clozapine: 30.71 (10.5) years	Schizophrenia + CUD	Ziprasidone (N = 16): average daily dose was 200 mg (range: 80–400 mg). Clozapine (*N* = 14): average daily dose was 225 mg (range: 50–425 mg)	Reduction of cannabis use in both groups over 12 months. Decrease in PANSS positive scores in both, more pronounced in clozapine group. Ziprasidone group: more positive medication attitudes, higher attendance in group therapy	Clozapine: sedation; extreme hypersalivation, fever; Ziprasidone: agitation	There were 11 dropouts; in the clozapine group they were related to side effects. The authors recommend considering both clozapine and newer SGAs for treating dual-diagnosed patients. They emphasize individualized medication choices based on symptom profiles and side effect preferences
Skryabin et al., 2021 [110]	Randomized Comparative study	Aripiprazole: Receptor partial agonism (D2, 5-HT1A); Quetiapine: Receptor antagonism (D2, 5-HT2) and reuptake inhibition (NET); D2 antagonism	N = 90 male patients (Paranoid schizophrenia *N* = 22; schizotypal disorder *N* = 68; SUD: Opioids *N* = 52; Alcohol *N* = 21; Synthetic cathinones *N* = 17)	Schizophrenia patients with comorbid SUD	Patients were randomly randomized into three groups of 30 patients, each receiving for 21 days an antipsychotic: Aripiprazole at a dose of up to 20 mg daily, Quetiapine at a dose of up to 600 mg daily, or Haloperidol at a dose of up to 30 mg daily.	Aripiprazole and Quetiapine showed better results on the PANSS and BPRS scales than haloperidol and were equally effective for schizophrenic symptoms; Aripiprazole was more effective for SUDs than quetiapine	Aripiprazole: tremor, drowsiness, increase in anxiety level, headache; Quetiapine: drowsiness, blood pressure decrease, dizziness, xerostomia; Haloperidol: tremor, drowsiness headache	Atypical antipsychotics are more effective in both mental and SUDs

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Schizophrenia Spectrum and Substance Use Disorder								
Author and Year	Study design	Intervention (Pharmacotherapy according to NbN approach)	Sample of patients	Major indications	Treatment	Outcome	Adverse events	Remarks/Treatment recommendations
Swartz et al., 2008 [53]	Double-blind study	SGAs: Olanzapine, Quetiapine, and Ziprasidone: D2 and 5HT Receptors antagonists; Risperidone: Receptor antagonism (D2, 5-HT2, NE alpha-2) versus FGA: Perphenazine: D2-Receptor antagonist	N tot = 1432 patients (mean age 40.6 years) formally	Schizophrenia + SUD	Patients were randomized to four SGAs (Olanzapine, Risperidone Quetiapine, and Ziprasidone) and one FGA (Perphenazine), and followed them for up to 18 months	Although Olanzapine led to less 'all cause discontinuation' in those not using illicit drugs, there was no difference in those abusing illicit drugs. By contrast, alcohol use and abuse in the absence of illicit substance use had little effect on time to discontinuation, since these patients tended to be older and more stable	Not reported	Olanzapine was more effective than other antipsychotics as reflected by longer time to all-cause discontinuation, but illicit substance abuse attenuated this advantage, reinforcing the need for concurrent substance abuse treatment
Szerman et al., 2020 [68]	Multicentre, observational descriptive and retrospective study	LAI-Aripiprazole: Receptor partil agonism (D2, 5-HT1A)	N = 40 Gender: F/M: 9/31); Mean Age: 37.7 (9.9) years	Schizophrenia Spectrum Disorders + SUDs (alcohol, cannabis, opioids, cocaine)	LAI-Aripiprazole (variable dosages): 77.5 % was given 400 mg/4 weeks; 12.5 % was given 300 mg/4 weeks; 7.5 % was given 400 mg/3 weeks; and 2.5 % was given 400 mg/2 weeks	Overall, after 6 months of treatment with LAI-Aripiprazole at a dose of 400 mg/4 weeks in 77.5 % of the patients, a significant improvement was observed in the psychopathological symptoms, with a reduction of over 30 % in the scores of the five CGI-severity scales. The WHODAS-2.0 mean score was also significantly reduced from 57.6 (8.2) to 42.3 (4.3) points ($p < 0.001$). Regarding SUDs, after 6 months of treatment, substance use was stopped in 5 out of 9 patients with CoUD and in 3 of the 16 patients with AUD. A significant reduction in the severity of the dependence was observed only in the subgroups of participants with cocaine and alcohol use disorders	Limited data on AE	Promising results for managing psychotic symptoms; further randomized clinical trials needed for confirmation
Tek et al., 2008 [63]	Case report	Acm: NMDA receptor modulation, GABA-A modulation	N = one 74-year-old female patient	Schizophrenia + AUD	Acm (666 mg TID)	Immediate decrease in desire to drink; 50 % reduction in alcohol intake after 6 months; gradual decline in alcohol use over 2 years; complete abstinence achieved after 24 months; improved medical status, including control of diabetes, blood pressure, and blood glucose	No withdrawal symptoms or Acm side effects reported	Acm may be effective in comorbid alcoholism and schizophrenia; Acm reduces cravings in abstinent alcohol dependent patients
Thomas-Brown et al., 2018 [55]	Controlled Trial	Risperidone: Receptor antagonism (D2, 5-HT2, NE alpha-2); Haloperidol: Receptor antagonism (D2)	N = 50 adult male patients (Age > 18 years); Setting/status: first-time psychotic episode (60 %;	Schizophrenia/ Schizophreniform disorder/ Brief psychotic disorder + CUD	Oral Risperidone or Haloperidol as prescribed, with additional 2 mg/day benztropine: -Haloperidol varied based on clinical warrant within	Cannabis-exposed subjects showed shorter sleep time, more awakenings, and longer wakefulness after sleep; the sleep benefitted from haloperidol and risperidone.	Not mentioned	Risperidone may offer better sleep outcomes for schizophrenic patients who use cannabis, especially where cannabis use is high

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Schizophrenia Spectrum and Substance Use Disorder								
Author and Year	Study design	Intervention (Pharmacotherapy according to NbN approach)	Sample of patients	Major indications	Treatment	Outcome	Adverse events	Remarks/Treatment recommendations
			previous outpatients and 40 % inpatients)		therapeutic range (10–20 mg/day); -Risperidone varied based on clinical warrant within therapeutic range (6–8 mg/day)	Risperidone showed better sleep outcomes with recent cannabis use		
Van Nimwegen-Campailla 2008a [60]	Double-blind Randomized Controlled Trial	Olanzapine: D2 and 5HT Receptors antagonists; Risperidone: Receptor antagonism (D2, 5-HT2, NE alpha-2)	*N* = 128 young adults with recent onset schizophrenia or related disorders	Schizophrenia, schizoaffective disorder, or schizophreniform disorder + CUD	Patients were randomized to groups of 6 weeks' treatment with Olanzapine (*N* = 59) or Risperidone (*N* = 63)	Similar improvements in subjective well-being were found in both groups. In the comorbid cannabis-using group (*n* = 41, 32 %), a similar decrease in craving for cannabis was found in both treatment conditions.	Not reported	Both Olanzapine and Risperidone were associated with improved subjective well-being. No evidence was found for a differential effect of Olanzapine or Risperidone on subjective experience or on craving for cannabis in dosages leading to comparable dopamine D(2) occupancy
Van Nimwegen-Campailla 2008b [61]	Double-blind Randomized Controlled Trial	Olanzapine: D2 and 5HT Receptors antagonists; Risperidone: Receptor antagonism (D2, 5-HT2, NE alpha-2)	N = 128 young adults with recent onset schizophrenia or related disorders	Schizophrenia, schizoaffective disorder, or schizophreniform disorder + CUD	Patients were randomized to groups of 6 weeks' treatment with Olanzapine (N = 59) or Risperidone (N = 63)	Treatment with Olanzapine was associated with greater decreases in obsessive-compulsive symptoms (OCS) scores	Not reported	A significant and clinically relevant difference in decreasing OCS scores favoured Olanzapine compared with Risperidone

Major Depressive Disorder or Depressive Symptoms and Substance Abuse Disorder								
Author and Year	Study design	Intervention (Pharmacotherapy according to NbN approach)	Sample of patients	Major indications	Treatment	Outcome	Adverse events	Remarks/Treatment recommendations
Afshar et al., 2012 [92]	Randomized Controlled Trial	Mirtazapine: Norepinephrine α2, 5-HT2, 5-HT3 receptor antagonism	*N* = 24 (M/F: 18/7): Mirtazapine Group *N* = 11 (mean age 43.8 ± 5.6 years); Placebo Group *N* = 13 (mean 47.2 ± 6.7 years)	MDD (or dysthymic disorder, or substance-induced mood disorder) + CoUD	12-week study with mirtazapine (target daily dose of 45 mg) or placebo	Reduction in cocaine urine concentrations, self-reported cocaine use, and strength of craving (CCS); Improvement in HAM-D and HAM-A scores; Increased sleep quality	Moderately severe AE: sleepiness, mood swings, agitation, fainting	Weekly relapse prevention counselling sessions
Altintoprak et al., 2008 [75]	Randomized double-blind study	Mirtazapine: Norepinephrine α2, 5-HT2, 5-HT3 receptor antagonism; Amitriptyline: Reuptake inhibition (SERT, NET)	*N* = 36 inpatients including N Mirtazapine group 20 (20 M), N Amitriptyline group 16 (M/F: 13/3)	MDD + AUD	Mirtazapine treatment group: started with 15 mg/day, increased to 30 mg/day, then to 45–60 mg/day as needed. Amitriptyline treatment group: started with 50 mg/day, increased to 100 mg/day, then to 125–150 mg/day as needed	The HDRS scores for mirtazapine/amitriptyline groups at baseline were 24.0 ± 4.4 vs 23.7 ± 4.8, with no significant difference between the groups. Alcohol craving scores showed a consistent reduction for both groups, with no significant difference between mirtazapine and amitriptyline groups at baseline or endpoint	Both group but considerably predominant in amitriptyline included tremor, constipation, diminished sexual desire, orthostatic dizziness	Mirtazapine, with its favourable side-effect profile, might have advantages over other antidepressants

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Table 2 (*continued*)

Major Depressive Disorder or Depressive Symptoms and Substance Abuse Disorder								
Author and Year	Study design	Intervention (Pharmacotherapy according to NbN approach)	Sample of patients	Major indications	Treatment	Outcome	Adverse events	Remarks/Treatment recommendations
Chiappini et al., 2023 [84]	Observational study	Esketamine: NMDA receptor antagonist	$N = 26$ adults (M/F: 11/15; mean age: 48.88 ± 11.82)	Treatment-Resistant Depression + SUD (AUD: 50 %; Benzodiazepine misuse:19 %; CUD: 15 %; CoUD:16 %)	The subjects enrolled completed the three different follow-up phases (T0: baseline, T1: 1 month, T2: three months). They were on treatment with: Serotonin-norepinephrine reuptake inhibitors 50 %; SSRI 46 %; Other Antidepressants 77 %; Mood Stabilizers 57 %; Antipsychotics 46 %.	A decrease in MADRS scores was recorded (MADRS decreased from T0 to T1, $t = 6.533$, $df = 23$, $p < 0.001$, and from T1 to T2, $t = 2.029$, $df = 20$, $p = 0.056$). No dropouts.	Considering tolerability and safety issues, one or more side effects were reported by 19/26 subjects (73 %) after treatment administration. All reported side effects were time-dependent and did not cause significant sequelae; among them, dissociative symptoms (38 %) and sedation (26 %) were the most frequently reported. Finally, no cases of abuse or misuse of ESK-NS were reported.	Despite study limitations related to the inherent nature of the study, a limited number of patients, and a short follow-up period, ESK-NS showed to be effective and safe in those patients
Cornelius et al., 2010 [91]	Double-blind Randomized Controlled Trial	Fluoxetine: Reuptake inhibition (SERT)	$N = 70$ outpatients (M/F: 43/37), age range: 14–25 (mean age 21.1 years)	MDD + CUD	Fluoxetine (10–20 mg) or placebo capsules + CBT and MET	Depressive Symptoms: both fluoxetine and placebo groups showed more than 50 % reduction reported depressive symptoms across the 12-week trial. Cannabis Use and Dependence: reduction of 39.5 % in DSM criteria for cannabis dependence observed across treatment groups. Reduction in number of days of cannabis use was not statistically significant in either group. No significant difference between treatment groups in terms of improvement in DSM criteria for cannabis dependence. Alcohol Use: males consumed more alcohol throughout the study. No significant main effects of gender on other depression-related or substance-use related variables	Rare and mild side effects; not specified	–
Cornelius et al., 2016 [64]	Double-blind placebo-controlled pilot trial	Mirtazapine: Norepinephrine α2, 5-HT2, 5-HT3 receptor antagonism + MET	N = 14 Mean age: 41.3 Males: 10	MDD + AUD	12-week pilot study with mirtazapine or placebo + MET	Within-group decrease in depressive symptoms by week 2 (mirtazapine), no significant decrease until week 8 (placebo). No significant decrease in alcohol consumption with mirtazapine.	Well tolerated; No significant AE reported	Mirtazapine showed limited efficacy for alcohol consumption reduction; Consider larger samples
Davis et al., 2012 [76]	Single-blind Randomized Trial	Escitalopram: Reuptake inhibition (SERT, NET, DAT) Bupropion:	$N = 664$ Substance group Mean age: 41.1 Male: 59.2 %	MDD + SUD/AUD	Escitalopram: Baseline 10 mg/day, Week 2 10 mg/day, Week 4 20 mg/day Bupropion-SR + Escitalopram:	Outcome Measures by Presence or Absence of SUD: Remission, response rates, and doses similar between SUD+	Not specified, but similar in all groups.	Single SSRI & combo antidepressants were equally effective.

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Major Depressive Disorder or Depressive Symptoms and Substance Abuse Disorder								
Author and Year	Study design	Intervention (Pharmacotherapy according to NbN approach)	Sample of patients	Major indications	Treatment	Outcome	Adverse events	Remarks/Treatment recommendations
		Norepinephrine α2, 5-HT2, 5-HT3 receptor antagonism	Non Substance group Mean age: 43.0 Male:28.9 % Setting: Similar primary clinical setting for both groups (47.1 % substance, 52.9 % non-substance). Depression Scores: Similar scores between groups - HRSD17: 23.5, IDS-C30: 38.0, QIDS-C16: 15.7, QIDS-SR16: 15.8		Baseline 150 mg/day, Week 1300 mg/day, Week 2 10 mg/day, Week 4400 mg/day, Week 6+ 400 mg/day Venlafaxine + Mirtazapine: Baseline 37.5 mg/day, Day 4 75 mg/day, Week 1150 mg/day, Week 2 15 mg/day, Week 4225 mg/day, Week 6 45 mg/day, Week 8300 mg/day	and SUD- groups at 12 and 28 weeks. SUD+ group attended fewer visits. SUD+ had more psychiatric SAEs at week 28 but low absolute numbers. No SAEs linked to suicidal ideation hospitalization. Outcome by Presence or Absence of SUD and Antidepressant Medication: Treatment effects similar for SUD+ and SUD- at weeks 12 and 28. At week 28, VEN + MIRT had higher SUD+ early termination ($p = 0.0138$). No major difference in side effects (FIBSER)		
Di Nicola et al., 2023 [77]	Retrospective study	Trazodone: Serotonin antagonist and reuptake inhibitor	$N = 100$ patients	MDD + AUD outpatients	Outpatients were retrospectively evaluated at 1, 3, and 6 months of treatment with extended-release trazodone (150–300 mg/day, flexibly dosed)	Trazodone reduced depressive symptoms ($p < 0.001$) with 54.5 % remission at the endpoint. Similar improvements were observed in all secondary outcomes, including anxiety, sleep alterations, and craving ($p < 0.001$)	Only mild side effects were reported and disappeared over time	Extended-release trazodone displayed good antidepressant properties in MDD + AUD patients, ameliorating overall symptomatology, functioning, and quality of life, with a good safety/ tolerability profile. Further, it significantly improved sleep disturbances and craving symptoms, which are associated with drinking relapse and worse outcomes
El Hage et al., 2018 [88]	Open-label pilot study	Desvenlafaxine: Reuptake inhibition (SERT and NET)	N = 18; Age range: 18–65 Male: 15	MDD + OUD	DESV was administered for 8 consecutive weeks Dosing: 50 mg daily during weeks 1 and 2, increased to 100 mg for weeks 3–8; participants who couldn't tolerate 100 mg continued with 50 mg Methadone treatment unchanged	MADRS, HAM-D 17, and CGI-S average total scores significantly decreased at week 8 compared with baseline. Anxiety decreased significantly at week 8 compared with baseline. Quality of Life assessed by the WHO Quality of Life questionnaire-BREF (domain 1) showed no significant improvement in psychological, social relationships, and environment facets domains. Suicidal Ideation: at baseline, five participants reported suicidal ideation within the past year. Four of them (80 %) stopped having suicidal	Headaches, nausea/vomiting dizziness/vertigo, constipation, fatigue 3 participants could not tolerate 100 mg dose of DESV (dose reduced to 50 mg)	Further trials with larger samples, explore different DESV doses, include buprenorphine/ naloxone patients

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Table 2 (*continued*)

Major Depressive Disorder or Depressive Symptoms and Substance Abuse Disorder								
Author and Year	Study design	Intervention (Pharmacotherapy according to NbN approach)	Sample of patients	Major indications	Treatment	Outcome	Adverse events	Remarks/Treatment recommendations
						thoughts by week 8 Drug Use and Craving Assessment: No significant changes were noted in the components of the Heroin Craving Questionnaire or in opioid urine drug tests during follow-up visits		
Friedmann et al., 2008 [78]	Double-blind randomized trial	Trazodone: Serotonin antagonist and reuptake inhibitors	$N = 173$ alcohol detoxification patients (trazodone: 88 versus placebo: 85)	MDD + AUD	Low dose trazodone (50–150 mg. at bedtime) versus placebo for 12 weeks	The trazodone group experienced less improvement in the proportion of days abstinent during administration of study medication (mean change between baseline and 3 months, −0.12; 95 % CI, −0.15 to −0.09), and an increase in the number of drinks per drinking day on cessation of the study medication (mean change between baseline and 6 months, 4.6; 95 % CI, 2.1 to 7.1). Trazodone was associated with improved sleep quality during its administration (mean change on the Pittsburgh Sleep Quality Index between baseline and 3 months, −3.02; 95 % CI, −3.38 to −2.67), but after it was stopped sleep quality equalized with placebo	Not reported	Trazodone (50-150 mg/day) showed a short-term benefit on sleep quality, but might require long-term use in the postdetoxification period (> 3 months)
Howland et al., 2009 [73]	Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial, which aimed to define the next best treatment steps for outpatients with non-psychotic MDD if initial treatment with citalopram did not produce an acceptable outcome (e.g., remission)	Citalopram: Reuptake inhibition (SERT, NET, DAT)	$N = 2838$ outpatients, 18–75 years	MDD + comorbid anxiety and/or SUD	Citalopram	Participants with non-psychotic MDD and comorbid anxiety and/or SUD showed several distinctive baseline sociodemographic and clinical features. They also showed greater depression severity; length of illness; likelihood of anxious, atypical or melancholic features; more intolerance/attrition; and worse remission/response outcomes with treatment	Participants with comorbid anxiety and SUD had a greater intensity and burden of side effects, more serious adverse events and psychiatric serious adverse events, and greater citalopram intolerance	Patients may benefit from multi-faceted treatment and psychosocial rehabilitation targeted at reducing their psychological comorbidity and functional impairment
Kotzalidis et al., 2021 [78]	Randomized Controlled Trial	Multimodal (Vortioxetine) vs. Other Antidepressants	$N = 226$ outpatients (M/F: 46 %/54 %), mean age: 48.95 ± 14.07 years	Major depressive episode in MDD, or SSOPDs with/without SUD	5–20 mg/day oral Vortioxetine vs other antidepressants (included Trazodone, Duloxetine, Sertraline, Paroxetine, Escitalopram, Venlafaxine, Bupropion,	Similar improvement in depression, psychopathology, anxiety, suicidal thinking, quality of life for vortioxetine and OADs, regardless of SUD. BD/SSOPDs patients on vortioxetine showed better	Observed in 53.97 % on vortioxetine and 62 % on other antidepressants, with vortioxetine showing milder side effects including nausea (15.08 %), gastrointestinal upset (9.52 %), and dizziness	Vortioxetine effective for major depressive episodes, especially in BD/SSOPDs patients. SUD impacts anxiety response.

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Table 2 (*continued*)

Major Depressive Disorder or Depressive Symptoms and Substance Abuse Disorder								
Author and Year	Study design	Intervention (Pharmacotherapy according to NbN approach)	Sample of patients	Major indications	Treatment	Outcome	Adverse events	Remarks/Treatment recommendations
					Amitriptyline, Clomipramine, Mianserine, and Mirtazapine)	improvement. SUD affected anxiety response. Men showed better depression improvement.	(2.38 %), while other antidepressants had weight gain (6 %) and sexual side effects (15 %)	
Mazza et al., 2022 [89]	Case series	Trazodone (serotonin receptor antagonists and reuptake inhibitor, SARI)	N = 3	CUD + depressive symptoms	Long-acting trazodone 150–300 mg/day was administered for the treatment of depressive/anxiety symptoms in patients diagnosed with CUD	150–300 mg prolonged-release trazodone dose once daily in the evening determined a prompt symptom resolution accompanied by abstinence from cannabis use; benefits were maintained in all cases for the entire follow-up period, which ranged from 27 to 32 weeks according to case	No side effects reported	Once-a-day formulation of trazodone showed a therapeutic role in patients with CUD, guaranteeing high tolerability
Muhonen et al., 2008 [80]	Randomized Controlled Trial	Reuptake inhibition (SERT) and NMDA receptor antagonism	*N* = 80 outpatients were randomized 1:1 in a double-blind manner to receive Memantine *N* = 40 (M/F: 23/17), mean age 47.5 years or Escitalopram N = 40 (M/F: 21/19), mean age 47.9 years	MDD + AUD	Orally administered 20 mg/day Memantine. Starting dose 5 mg/day, increased weekly by 5 mg/day to 20 mg/day. Weekly visits for medication checks and data collection. Orally administered 20 mg/day Escitalopram. Starting dose 5 mg/day, increased weekly by 5 mg/day to 20 mg/day. Weekly visits for medication checks and data collection. During the 26-week study period patients continued their routine treatment at the clinics. Abstinence was not required but encouraged	Reduced Alcohol Use Disorders Identification Test (AUDIT) scores from baseline in both groups and decreased alcohol consumption (drinking diary). Significant reduction in Obsessive Compulsive Drinking Scale (OCDS) scores indicating reduced alcohol craving	AE reported in a previous article. No significant difference in reporting AE between medication groups	Abstinent patients more likely to complete treatment. Age at onset of depression predicted different changes in OCDS in escitalopram group compared to memantine group. Age at onset of depression predicted less change in OCDS scores in escitalopram group. No differences in association between age at onset of depression/first alcohol intoxication and change in AUDIT/OCDS
Mysels et al., 2011 [87]	Open-label study	Naltrexone: opioid receptors antagonism	*N* = 34 opioid-dependent patients	MDD + OUD	Patients were treated with naltrexone maintenance and relapse prevention therapy	Patients demonstrated high baseline affective burden and significant improvement of depression scores over a 4-week period post-baseline. Somatic and cognitive-affective subscale scores significantly declined as well as the seven individual item scores. By contrast, the "late insomnia" item score significantly increased at 2 weeks post-baseline.	Late insomnia	Naltrexone induction and maintenance in newly abstinent opioid-dependent individuals does not appear to be associated with worsening of depression; however, it may be associated with sleep impairment early in treatment
Pettinati et al., 2010 [82]	Double-blind, placebo-controlled trial	Sertraline: Reuptake inhibition (SERT); Naltrexone: opioid receptors antagonism	*N* = 170 patients (M/F: 106/64), age range 21–75 years, were randomized to Naltrexone + Sertraline (*N* = 42); Naltrexone + placebo (*N* = 49);	MDD + AUD	Naltrexone was used up to 100 mg/day and Sertraline up to 200 mg/day. Pharmacological treatment was assisted by weekly individual CBT	Increased abstinence and decreased heavy drinking in sertraline + naltrexone group compared to other treatments; in 3 treatment weeks, the percentage of patients not depressed ranged from 71.4 % (sertraline + naltrexone) to 64.1	AE included anxiety, fatigue, decreased sexual desire, headache, nausea, orgasmic difficulty	Sertraline + Naltrexone patients showed longer time to return to heavy drinking, better depression outcomes

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Table 2 (*continued*)

Major Depressive Disorder or Depressive Symptoms and Substance Abuse Disorder								
Author and Year	Study design	Intervention (Pharmacotherapy according to NbN approach)	Sample of patients	Major indications	Treatment	Outcome	Adverse events	Remarks/Treatment recommendations
			Sertraline + placebo (N = 40); double placebo (*N* = 39)			% (placebo). HRSD scores varied from 64.3 % (sertraline + naltrexone) to 53.8 % (placebo). Higher abstinence rates and longer time to heavy drinking in sertraline + naltrexone group		
Raby et al., 2014 [93]	Randomized, double-blind, placebo-controlled Trial	Venlafaxine: Reuptake inhibition (SERT and NET)	*N* = 130 Male = 94 Placebo (*n* = 66) Mean Age: 38 (8) Venlafaxine (*n* = 64) Mean age: 37 (8) Setting: Outpatient	MDD or Dysthymia + CoUD	Venlafaxine up to 300 mg/day vs placebo	Mood Response: depression response criterion (50 % reduction in HAM-D score): 33 % on placebo; 41 % on venlafaxine. Global response rating: 48 % on placebo; 56 % on venlafaxine. Depression severity scores improved more rapidly on venlafaxine over the first 6 weeks, but placebo caught up between weeks 7 12. Cocaine Response: Around half of the patients rated as cocaine responders (42 % on placebo, 51 % on venlafaxine) based on reduction in cocaine use. Urine toxicology remained positive in both groups. Global measures of cocaine outcome did not significantly differ between treatment groups. Mood response (50 % drop in HAM-D score) was associated with better outcome on the clinicians' global rating of cocaine severity	Common side effects (>1 %) on venlafaxine/placebo: insomnia, headache, sexual dysfunction, nausea, lethargy, agitation, dizziness, chest pain, night sweats, diarrhoea, shortness of breath, sweating, decreased appetite. Venlafaxine-specific: diarrhoea, shortness of breath, sweating, weight loss, vivid dreams, high blood pressure	More focus on medication compliance and exploration of combination treatments is recommended for future trials.
Tomko et al., 2019 [90]	Randomized placebo-controlled clinical Trial	NAC: Glutamatergic pathway modulation -	NAC group *N* = 153 outpatients (M/F: 76.5 %/23.5 %), mean age: 29.8 years Placebo group *N* = 149 males, mean age: 30.8 years	Depressive symptoms + CUD	Patients were randomized to receive 2400 mg of NAC daily or matched placebo for 12 weeks. All participants received abstinence-based contingency management	Depressive symptoms did not differ between the NAC and placebo groups during treatment. There was no significant interaction between treatment and baseline depression predicting cannabis abstinence during treatment. Higher baseline depression was associated with decreased abstinence throughout treatment and a significant gender interaction suggested that this may be particularly true for females. Cross-lagged panel models suggested that depressive symptoms preceded increased cannabis use amounts	NAC and Placebo: no significant AE reported	Depression may be a risk factor for poor CUD treatment outcome and therefore should be addressed in the context of treatment. However, results do not support the use of NAC to concurrently treat co-occurring depressive symptoms and CUD in adults

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Major Depressive Disorder or Depressive Symptoms and Substance Abuse Disorder								
Author and Year	Study design	Intervention (Pharmacotherapy according to NbN approach)	Sample of patients	Major indications	Treatment	Outcome	Adverse events	Remarks/Treatment recommendations
						during the subsequent month. The reverse pathway was not significant (i.e., greater cannabis use preceding depressive symptoms)		
Witte et al., 2012 [80]	Double-blind, randomized placebo-controlled Trial	Escitalopram: Reuptake inhibition (SERT); Acm: NMDA receptor modulation, GABA-A modulation (Acm)	$N = 23$, mean age: 46 ± 14 years Acm group N: 12 (M/F: 8/4); placebo group N: 11 (M/F: 5/6)	MDD + AUD	Escitalopram (doses of 10 to 30 mg/d) combined with a behavioural intervention for AUD. Participants randomized to double-blind augmentation with either Acm at 2000 mg/d or an identical placebo for 12 weeks	Twelve subjects (acamprosate, $n = 7$; placebo, $n = 5$) completed the study. There was significant mean reduction in ratings of depressive symptoms from baseline in both treatment arms, with no significant difference between the groups. Those in the Acm group had a 50 % MDD response rate and a 42 % remission rate, whereas those in the placebo arm had a 36 % response and remission rate (not significant). Those assigned to Acm had significant reduction in number of drinks per week and drinks per month during the trial, whereas those assigned to placebo demonstrated no significant change in any alcohol use parameter, but the between-group difference was not significant. There were no significant associations between change in depressive symptoms and change in alcohol use	Escitalopram/Acm group: dry mouth, nausea, insomnia, gastrointestinal upset, diarrhoea, headache. Escitalopram/Placebo group: dry mouth, jaw tightening, nausea, headache, insomnia. Discontinuations ($N = 2$) were recorded with Escitalopram/Placebo due to AE (insomnia, anxiety, tension). No alcohol withdrawal symptoms reported	Acm added to escitalopram in adults with MDD and AUD was associated with reduction in the frequency of alcohol use, possibly hypothesising that a serotonergic drug might contribute to reducing alcohol use. Further study in a larger sample is warranted
Yoon et al., 2019 [83]	Open-label pilot study	Naltrexone: Opioid receptors antagonism and NMDA receptor antagonism	$N = 5$ (M/F:3/2); Setting: VA Connecticut Healthcare System	MDD + AUD	Injectable naltrexone (380 mg 2–6 days before first ketamine infusion) and repeated intravenous ketamine treatment (0.5 mg/kg once a week for 4 weeks)	Reduced depressive symptoms (57 % to 92 % improvement in MADRS scores); 60 % met response criteria after initial ketamine dose, 100 % by fourth dose	Safe and well tolerated; No serious adverse effects reported	Larger randomized trials needed; Preclinical research to understand opiate receptor role

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Major Depressive Disorder or Depressive Symptoms and Substance Abuse Disorder								
Author and Year	Study design	Intervention (Pharmacotherapy according to NbN approach)	Sample of patients	Major indications	Treatment	Outcome	Adverse events	Remarks/Treatment recommendations
Zhu et al., 2021 [86]	Clinical trial	Buprenorphine: Opioid Receptor Partial Agonism; Naloxone: Opioid receptor antagonism; Methadone: Opioid Receptor Agonism	N = 85 MDD (M/F: 50/35), mean age: 41.8 years Setting: mix of treatment centres	MDD + OUD	Buprenorphine-Naloxone and Methadone pharmacotherapy	MDD group had significantly more self-reported days using opioids and heroin compared to patients without comorbid mental disorders. MDD group spent more time engaged with OUD pharmacotherapy during the study period	Not reported	Assessment and treatment for MDD is important alongside pharmacotherapy for patients with OUD

Bipolar Disorder and Substance Abuse Disorder								
Author and Year	Study Design	Intervention (Pharmacotherapy according to NbN approach	Sample of patients	Major indications	Treatment	Outcome	Adverse events	Remarks/Treatment recommendations
Brown et al., 2009 [94]	Randomized, double-blind, placebo-controlled pilot study	Naltrexone: Opioid receptor antagonism	*N* = 43 outpatients (M/F: 21/22), mean age 41.1 years	BD (with current mood state of depressed or mixed mood) + AUD (use of at least 5 drinks in the past 7 days)	Naltrexone (50 mg/d) or identical appearing placebo, manual-driven CBT	Reduction in drinking days, heavy drinking days, and drinks per drinking day for naltrexone compared to placebo, decline in alcohol craving	Not reported	Results suggest the potential value and acceptable tolerability of naltrexone for alcohol dependence in BD
Brown et al., 2012 [104]	Randomized, double-blind, placebo-controlled, clinical Trial	Lamotrigine: Voltage-gated sodium channel block	*N* = 112 patients (M/F: 32/23), mean age: 45.1 (7.3)	BD (depressed or mixed phase) + CoUD	Lamotrigine therapy initiated at 25 mg/day and increased to 200 mg/day over 5 weeks, with additional increases to a maximum of 400 mg/day if criteria were met	Improvement in cocaine use observed, with lamotrigine group having no significantly higher probability of being cocaine-negative	Similar side effects in both groups, including somatic complaints, skin-related issues, and increased sweating	Lamotrigine efficacy observed in patients with baseline HRSD scores
Brown et al., 2015 [105]	Randomized, double-blind, placebo-controlled clinical Trial	Citicoline: Nootropic mechanisms	N = 130 outpatient, randomized to a Citicoline group: *N* = 61 (M/F: 45/16), mean age 41.1 (9.1) years and a Placebo group N = 61 (M/F: 37/24), mean age 43.6 (8.3) years	Dual diagnosis: BD + CoUD	Citicoline initiated at 500 mg/day, increased to 1000 mg/day at week 2, 1500 mg/day at week 4, and 2000 mg/day at week 6 vs placebo	Cocaine use was significantly reduced with citicoline initially, although treatment effects diminished over time suggesting the need for augmentation strategies to optimize long-term benefit	Citicoline was well tolerated for treatment of cocaine dependence in patients with BD.	Citicoline appears promising for treating cocaine use in BD patients, although its effects diminish over time. Adequately powered trials are warranted
Gao et al., 2017 [98]	Randomized, double-blind, placebo controlled clinical Trial	Quetiapine: Receptor antagonism (D2, 5-HT2) and reuptake inhibition (NET)	*N* = 90 (M/F: 47/33), divided into a Quetiapine-XR group *N* = 46 and a placebo group *N* = 44	BD + AUD	Quetiapine-XR (50 mg for days 1–2, 150 mg for days 3–4, then 300 mg/day from day 5 onwards) vs placebo	Quetiapine-XR group showed significant improvements in CGI-BD-S and QIDS-SR-16 scores for recent AUD/CUD patients compared to no recent AUD/CUD. Placebo group showed no significant differences. Among recent AUD/CUD patients, quetiapine-XR led to greater improvements in HAMD-17, HAMA, CGI-BD-S, and QIDS-SR-16 scores compared to placebo, with significance in QIDS-SR-16 scores	Quetiapine-XR group (AE = 137): dizziness (2.7 %), dry mouth (16.4 %), fatigue (15.1 %), and sedation (13.7 %). Similar rates were observed in the Placebo group (AE = 77)	Consider Quetiapine-XR for patients with BD, and recent alcohol abuse and/or CUD due to its effectiveness in reducing depressive symptoms

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Table 2 (*continued*)

Bipolar Disorder and Substance Abuse Disorder								
Author and Year	Study Design	Intervention (Pharmacotherapy according to NbN approach	Sample of patients	Major indications	Treatment	Outcome	Adverse events	Remarks/Treatment recommendations
Kemp et al., 2009 [97]	A 6-month, double-blind, parallel-group comparison	Lithium; Valproate: voltage-sensitive sodium channel modulator	Lithium +-Valproate	N = 149 patients who met DSM-IV criteria for BD I or II and SUD (alcohol, cannabis, or cocaine abuse within the last 3 months or dependence within the last 6 months)	Subjects were randomly assigned to remain on combination treatment or to discontinue Valproate and remain on Lithium monotherapy	Of 149 patients enrolled into the open-label acute stabilization phase, 79 % discontinued prematurely (poor adherence: 42 %, nonresponse: 25 %, intolerable side effects: 10 %). Of 31 patients (21 %) randomly assigned to double-blind maintenance treatment, 55 % (*N* = 17) relapsed (24 % [N = 4] into depression and 76 % [N = 13] into a manic/ hypomanic/mixed episode), 26 % (N = 8) completed the study, and 19 % (N = 6) were poorly adherent or exited prematurely. The combination Lithium + Vaproate was not superior in improving any of their chosen outcome measures including 'time to treatment' for a mood episode or time to discontinuation with medication. However, in those that entered the maintenance phase, substance use was reduced so that more than half were no longer abusing substances	Not reported	Patients stabilized after 6 months of treatment with Lithium plus Valproate. This combo might result in greater improvements in drinking outcomes, but not in improving mood
Khalili et al. 2019 [107]	Double blind Randomized Clinical Trial	Buprenorphine: Opioid Receptor Partial Agonism	N = 24	BD (with manic or depressive episodes and psychotic features) + OUD	Treatment: Buprenorphine (4 or 6 mg/d) + sodium valproate + risperidone	Both groups showed significant reduction in psychotic, depressive, and manic symptoms after 1 and 2 weeks. No significant difference between groups	Not specified	Buprenorphine did not add efficacy to usual treatment of psychotic episodes in BD.
Lee et al., 2018 [102]	Single arm clinical trial	Memantine: NMDA Receptor Antagonism	*N* = 45 outpatient and Inpatient	BD + AUD	Low-dose add-on Memantine (5 mg/day) + open-label VPA treatment	Outcome: Attenuated clinical severity, reduced alcohol use, lowered plasma cytokine levels, increased BDNF levels	Not reported	Further studies with larger samples and randomized double-blind design needed for confirmation
Martinotti et al., 2008 [97]	Open-label study	Quetiapine: D2 and 5HT Receptors antagonist	N = 28 subjects, after a detoxification period	BD/schizoaffective disorder/personality disorder + AUD	Orally treated with flexible doses of Quetiapine for 16 weeks	43 % percent of patients remained totally alcohol free, 32 % patients relapsed, with an average of 15.4 drinking days in the period of the study (112 days) and 25 % dropped out. Changes in alcohol craving correlated with psychiatric symptoms as to BPRS and HDRS, with the highest level of	Not reported	Quetiapine decreased alcohol consumption, craving for alcohol, and psychiatric symptoms intensity, maintaining a good level of tolerance

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Bipolar Disorder and Substance Abuse Disorder								
Author and Year	Study Design	Intervention (Pharmacotherapy according to NbN approach	Sample of patients	Major indications	Treatment	Outcome	Adverse events	Remarks/Treatment recommendations
						correlation evidenced for the HDRS items of insomnia		
Mazza et al., 2009 [89]	Observational study	Mood stabilizers anticonvulsants 52 (78.7 %) Antipsychotics Conventional 3 (4.5 %) Atypical Antidepressants 33 (50 %) Serotonin reuptake inhibitors 14 (21.2 %) Serotonin, norepinephrine reuptake inhibitors (TcA) 5 (7.5 %) Serotonin, norepinephrine reuptake inhibitors (SNRI) 4 (6 %) Trazodone: Serotonin multimodal 11 (16.6 %) Benzodiazepines 20 (30.3 %) Other 5 (7.5 %)	$N = 131$	BP-I $N = 65$ (49.2 %), BP-II $N = 29$ (22.3 %) CtD $N = 37$ (28.5 %)	Not reported	SUD patients received low medium overall treatment dosages and were more likely to be treated with unspecific antidepressants and less likely with NaSSA.	Drop-out was significantly associated with young age, low treatment dose, SUD diagnosis and BP-I diagnosis	Significantly higher comorbidity with substance abuse/dependence among BP-II and CtD patients. Treatment type did not influence drop-out in substance abuse/dependent patients, BP and BP with SUD were not different for primary outcome measure. BP patients with substance abuse/dependence were significantly more impaired in social functioning at any stage of the follow-up.
Prisciandaro et al., 2012 [95]	Randomized, double-blind, placebo-controlled Clinical Trial	Acm: NMDA receptor modulation, GABA-A modulation; Naltrexone: Opioid receptor antagonism	N = 30 participants (M/F: 19/11), mean age 42.33 years (SD = 9.41)	BD + AUD (with alcohol use in the past 90 days)	Acm (1998 mg daily) or matching placebo for 8 weeks	Naltrexone significantly predicted decreased Percent heavy drinking days ($p < 0.05$), and marginally predicted improved mental health quality of life via decreased Percent heavy drinking days ($p < 0.10$), and (ii) that the combinations of naltrexone and combined behavioural intervention, and acamprosate and combined behavioural intervention, each predicted significantly improved physical quality of life ($p < 0.05$), and marginally predicted decreased Percent heavy drinking days via improved physical quality of life ($p < 0.10$)	Skin reaction (Acm group)	Integrated treatment of BD and alcohol dependence may improve outcomes
Prisciandaro et al., 2022 [107]	Randomized, double-blind, placebo-controlled, crossover, multimodal-MRI pilot study	Gabapentin: Voltage-gated calcium channel block	$N = 22$ (M/F: 11/11), mean age 37.59 (11.91) years	BD (BD-I or BD-II) + CUD (moderate-to-severe)	Gabapentin administration: 1-week experimental conditions (gabapentin, placebo) in randomized order, titration to maximum dose (1200 mg/day), assessment and MRI	Increased dorsal anterior cingulate cortex (dACC) glutamate levels in Randomization Order #1 (RO#1), increased rostral basal ganglia (rBG) glutamate levels	Gabapentin was well-tolerated, fewer AEs reported compared to placebo (AEs not specified)	Gabapentin could be considered as an adjuvant medication to target disrupted brain GABA/glutamate homeostasis in individuals with BD + CUD, potentially reducing cannabis

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Table 2 (*continued*)

Bipolar Disorder and Substance Abuse Disorder								
Author and Year	Study Design	Intervention (Pharmacotherapy according to NbN approach	Sample of patients	Major indications	Treatment	Outcome	Adverse events	Remarks/Treatment recommendations
						in cigarette-smoking participants		use, mood symptoms, and anxiety
Sepede et al., 2014 [106]	Randomized Controlled Trial	Bupropion: Reuptake inhibition (SERT, NET, DAT)	N = 12 depressed BD-I inpatients, with a comorbid CoUD, treated with Valproate 1000 to 1500 mg/d and Aripiprazole 10 mg/d, were randomly assigned to receive Bupropion 150 mg/d as an open-label add-on therapy (N = 5) or to continue their previous treatment (*N* = 7)	BD + CoUD	Twelve depressed BD-I patients, with a comorbid CoUD, treated with Valproate 1000 to 1500 mg/d and Aripiprazole 10 mg/d, were randomly assigned to receive bupropion 150 mg/d as an open-label add-on therapy or to continue their previous treatment	After 4 weeks of observation, patients receiving add-on therapy with bupropion have improved in terms of HDRS scores and Drug Abuse Screening Test scores, with respect to those of the comparison group, whereas no significant increase of Young Mania Rating Scale scores over time was observed	ADD-ON group: Headache (40 %), insomnia (20 %), nausea (40 %); NO ADD-ON group: Nervousness (14.3 %), anxiety (14.3 %), nausea (28.6 %), fatigue (28.6 %)	Adding Bupropion to mood stabilizers may be promising for the short-term treatment of acute depression BD-I comorbid with CoUD
Sherwood Brown et al., 2021 [102]	Randomized Control Trial	Ondansetron: Serotonin 5-HT3 Antagonism	N = 70 outpatients (M/F: 42/28), age: 18–70 years (mean: 44.91)	BD, schizoaffective disorder, cyclothymic disorder, MDD with mixed features + AUD	Ondansetron (0.5 mg BID, dose increased based on response: 1.0 mg BID at week 4, 2.0 mg BID at week 8, 4.0 mg BID at week 10 if no response) vs placebo	Statistically significant positive effect on HRSD in favour of ondansetron. Ondansetron group had greater reduction in somatic complaints	Ondansetron group had greater reduction in somatic complaints; placebo group showed gastrointestinal issues (27 %), suicide attempt/ideation (13 %), hyperglycaemia (13 %), and auditory hallucinations (13 %)	No specific recommendations mentioned
Stedman et al., 2010 [99]	12-week, placebo-controlled study	Quetiapine: D2 and 5HT Receptors antagonist	*N* = 362 outpatients (mean 38.6 years)	BD I and AUD	Patients treated with Lithium or Valproate (ongoing or assigned at screening) were randomized to receive Quetiapine (dosed up to 400 mg/d over 7 days, followed by 300 to 800 mg/d flexible dosing until study end) or placebo	Of 362 enrolled patients, 176 were randomized to receive Quetiapine and 186 to placebo. The mean proportion of heavy drinking days at baseline was 0.66 in the quetiapine group and 0.67 in the placebo group. At Week 12, the mean change in the proportion of heavy drinking days was −0.36 with quetiapine and − 0.36 with placebo ($p = 0.93$). No statistically significant	The incidence of adverse events was consistent with the previously known tolerability profile of quetiapine	Quetiapine added to Lithium or Valproate did not result in significantly greater improvement compared with placebo in measures of alcohol use and dependence in patients with BD + AUD

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Bipolar Disorder and Substance Abuse Disorder								
Author and Year	Study Design	Intervention (Pharmacotherapy according to NbN approach	Sample of patients	Major indications	Treatment	Outcome	Adverse events	Remarks/Treatment recommendations
						differences in any of the secondary outcome measures (they included time to the first consecutive 2 weeks of abstinence, changes from baseline to Week 12 in the proportion of nondrinking days, mean number of standardized drinks per day, and CGI score) were noted between the quetiapine and placebo groups		
Sylvia et al., 2016 [100]	Randomized, placebo-Controlled Trial	Topiramate: Voltage-gated sodium channel modulation	N = 12 outpatients (M/F: 58 %/42 %), mean age 43.6 years (9.67)	BD + AUD	Randomized to Topiramate or placebo for 12 weeks	The Topiramate group, with two out of five participants (40 %) completing treatment, experienced less improvement in drinking patterns than the placebo group, with five out of seven participants (71 %) completing treatment	–	Topiramate did not improve drinking behaviour and was not well-tolerated. This study failed to recruit adequately. Problems surrounding high attrition, a small study sample, and missing data preclude interpretation of study findings
Xiao et al., 2015 [101]	Open label pilot study	Icariin: Inhibition of PI3K/AKT and Raf1/ERK1/2 signalling pathways	*N* = 11 outpatients (M/F: 6/5), mean age 51.4 (7.3) years	BD + AUD	Icariin dosages were titrated from 100 mg/day to 200 mg/day at week 3, and furtherly to a maximum of 300 mg/day at week 6	Depressive symptoms (measured by HAMD, QIDS), anxiety scores (HAMA), alcohol consumption, drinking days, and heavy drinking days all significantly decreased from baseline to exit	Vivid dreams, increased libido, slight constipation, diarrhoea, headache, hyperactivity, increased appetite, increased sleepiness, increased shedding of hair, indigestion, increased bowel movement, increased thirst, momentary calf cramps, nervousness, mild heartburn, and dry mouth	Further research with icariin needed in patients with mood and/or alcohol use disorders. Current findings do not warrant clinical use of icariin for treating BD and AUD
Zhu et al., 2021 [86]	Clinical Trial	Buprenorphine: Opioid receptor partial agonism	*N* = 593 outpatients, (M/F: 63.6 %/36.4 %), mean age 37.9 years	BD (N = 51) / MDD (*N* = 85)/ AXD (*N* = 121)/	BD - Buprenorphine (22.0 % of follow-up months) MDD - Methadone (60.0 % of	Groups with mental disorders had worse substance use outcomes and poorer	Not specified	Our results show that treatment outcomes in individuals with OUD vary by psychiatric

(*continued on next page*)

Table 2 (*continued*)

Bipolar Disorder and Substance Abuse Disorder								
Author and Year	Study Design	Intervention (Pharmacotherapy according to NbN approach	Sample of patients	Major indications	Treatment	Outcome	Adverse events	Remarks/Treatment recommendations
				No Mental Disorder (*N* = 336) + OUD	follow-up months) AXD - Methadone (45.2 % of follow-up months) NMD - Buprenorphine (10.5 % of follow-up months)	psychosocial functioning than the no mental disorder group. Participants with BD had significantly more self-reported days using opioids (Mean: 8.6 for BD vs. 3.4 days for no mental disorder group, $p <$ 0.01) and heroin (Mean: 6.4 for BD vs. 2.0 for MDD, 3.1 days for no mental disorder group, $p <$ 0.05) in the 30 days prior to the final interview. Compared to patients without mental disorders, patients with MDD spent more time engaged with OUD pharmacotherapy during the ~16-month period between MINI and final interview (mean: 71.6 % vs. 50.6 %; $p <$ 0.001).		comorbidity groups, which supports the need for mental health assessment and treatment for psychiatric conditions in the context of pharmacotherapy for patients with OUD. Improve screening and develop targeted treatment interventions for comorbid psychiatric disorders in patients with OUD

Abbreviations: 5-HT2: Serotonin 5-HT2 receptor; **5-HT3:** Serotonin 5-HT3 receptor; **AE:** Adverse Events; **Acm:** Acm; **AUD:** Alcohol Use Disorder; **AXD:** Anxiety Disorders; **BD:** Bipolar Disorder; **BDNF:** Brain-Derived Neurotrophic Factor; **BID:** bis in die (twice a day); **BPRS**: brief psychiatric rating scale; **CBT:** Cognitive Behavioural Therapy; **CtD:** Cyclothymic Disorder; **CGI-BP-S:** Clinical Global Impression for Bipolar Disorder-Severity; **CGI-S:** Clinical Global Impression - Severity; **CoUD**: Cocaine Use Disorder; **CUD:** Cannabis Use Disorder; **dACC:** Dorsal Anterior Cingulate Cortex; **DESV:** Desvenlafaxine; **DSM**: Diagnostic and Statistical Manual for mental Disorders; **fMRI:** Functional Magnetic Resonance Imaging; **GABA:** Gamma-Aminobutyric Acid; **GABA-A:** Gamma-Aminobutyric Acid A receptor; **HAMA:** Hamilton Anxiety Rating Scale; **HAMD-17:** Hamilton Depression Rating Scale-17; **HC**: healthy control; **HRSD:** Hamilton Rating Scale for Depression; **HRSA:** Hamilton Rating Scale for Anxiety; **IDS-C30:** Inventory of Depressive Symptomatology - Clinician-Rated; **ITT:** Intention-to-Treat; **LAI:** Long-Acting Injectable; **LSD**: Lysergic acid diethylamide; **MADRS:** Montgomery-Åsberg Depression Rating Scale; **MDD:** Major Depressive Disorder; **MET:** Motivation Enhancement Therapy; **MRI:** Magnetic Resonance Imaging; **N:** Number of participants; **NAC:** N-Acetylcysteine; **NbN:** Neuroscience-based nomenclature; **NE:** Norepinephrine; **NET:** Norepinephrine Transporter; **OUD:** Opioid Use Disorder; **PANSS**: Positive and Negative Syndrome Scale; **PI3K/AKT:** Phosphoinositide 3-kinase/protein kinase B pathway; **QIDS-SR:** Quick Inventory of Depressive Symptomatology - Self-Report; **Q-LES-Q:** Quality of Life Enjoyment and Satisfaction Questionnaire; **rBG:** Rostral Basal Ganglia; **SERT:** Serotonin Transporter; **SGA:** Second-Generation Antipsychotic; **SSOPDs:** Substance Use or Other Psychiatric Disorders; **SSRIs:** Selective Serotonin Reuptake Inhibitors; **SUD:** Substance Use Disorder; **VPA:** Valproic Acid; **WHODAS:** World Health Organization Disability Assessment Schedule; **XR:** Extended-Release.

utilization of LAI has emerged as an innovative strategy in the stabilization and treatment of patients affected with a dual diagnosis, underscoring the promising results for short and long-term management of psychotic symptoms [66–69], substance craving [22,69], and a substantial reduction in disability and improvement in quality of life [65]. Paliperidone palmitate was also associated with fewer all-cause and SUD-related inpatient admissions or long-term care stays and greater medical cost savings [64]. Comparing LAIs, Cuomo et al. (2018) highlighted aripiprazole's superior effectiveness compared to paliperidone in terms of clinical status, quality of life and craving [70]; these data were consistent with Erdogan et al. (2021) [71] and Chiappini et al. (2023) [72], both recording aripiprazole LAI- related clinical improvement without side effects, including changes in weight, lipid/glucose metabolism, electrocardiogram and extra-pyramidal side effects, except for the report of essential tremor.

3.2. Substance use disorders & depression

To enhance clarity for the reader and facilitate practical understanding, the results have been organized according to the specific SUD involved. A parallel structure was applied when reporting findings related to BD.

Focusing on symptoms of MDD, the first study included in this review broadly examined SUDs using data from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial. This study focused on patients with MDD comorbid with anxiety and/or an unspecified SUD [73], comparing their baseline clinical and sociodemographic characteristics and treatment outcomes to those without such comorbidities. Treatment with the selective serotonin reuptake inhibitor (SSRI) citalopram revealed that patients with comorbid MDD and anxiety and/or SUD exhibited greater baseline depression severity, longer illness duration, higher prevalence of anxious, atypical, or melancholic features, increased treatment intolerance and dropout rates, and poorer remission and response outcomes.

3.2.1. The treatment of alcohol use disorder comorbid with major depressive disorder or depressive symptoms

With regard to SUDs, according to the articles retrieved, the comorbidity of MDD and SUDs particularly involved alcohol as the primary substance. Herein, we closely evaluate each study, capturing nuances and intricacies of interventions, for a more profound understanding.

Among antidepressants, mirtazapine reduced depressive symptoms but did not significantly decrease alcohol consumption [74]. However, compared to amitriptyline, it showed reduced alcohol cravings in patients with MDD and alcohol dependence [75]. Adverse effects, mainly in the amitriptyline group, included tremor, constipation, reduced libido, and orthostatic dizziness. Davis et al. (2012) treated 665 outpatients with chronic or recurrent MDD, comparing those with comorbid SUD (13.1 %) to those without (86.9 %) using either escitalopram monotherapy or a combination of venlafaxine and mirtazapine, or escitalopram and bupropion. At 12 and 28 weeks, no significant differences were observed between MDD patients with or without SUD in terms of treatment response, remission rates, or time in treatment. Additionally, treatment outcomes did not differ based on SUD presence or treatment assignment [76]. Trazodone use in patients with MDD was reported in two studies. Di Nicola et al. (2023) retrospectively evaluated the effect of extended-release trazodone, flexibly dosed at 150–300 mg/day in 100 outpatients with MDD and comorbid AUD [77], finding after 6-months-treatment a significant improvement in depressive symptoms with 55 % of patients achieving remission. Similar improvements were observed in measures of anxiety, sleep quality, functioning, quality of life, clinical global severity, as well as alcohol craving. A previous randomized, double-blind, placebo-control trial from Friedmann et al. (2008), prescribing low dose trazodone (50–150 mg) for 12 weeks among 173 alcohol detoxification patients, showed that the trazodone group experienced less improvement in the proportion of days abstinent, but improved sleep quality during its administration [78]. Interestingly, in both studies no adverse effects were recorded neither dangerous drug interactions.

Kotzalidis et al. (2021) [79] assessed the superior efficacy and safety of vortioxetine compared to antidepressants like trazodone, duloxetine, and sertraline in treating unipolar depression and co-occurring SUD. Vortioxetine side effects were generally mild, including nausea (15.08 %), gastrointestinal upset (9.52 %), and dizziness (2.38 %).

With regard to pharmacological treatments specifically targeting AUD, in a randomized controlled trial the noncompetitive glutamate *N*-methyl-D-aspartate (NMDA)-receptor blocker memantine was compared to escitalopram, finding for both treatments a significant reduction of the baseline level of depression and anxiety, and an equally improved quality-of-life and substance -related outcomes [80]. Witte et al. (2012) in a double-blind randomized placebo-controlled study examined the efficacy and safety of acamprosate augmentation of escitalopram, demonstrating that acamprosate group experienced significant improvement in alcohol use parameters [81]. The synergy between opiate antagonist naltrexone and the antidepressant drug sertraline showed a promising 45 % symptom reduction in depressive outcomes but also notably delayed relapse into heavy drinking [82]. A pilot study on five subjects using injectable naltrexone with ketamine infusions showed a 60 % improvement in depressive symptoms over 8 weeks [83], suggesting that naltrexone pretreatment did not hinder ketamine's antidepressant effects and may enhance the treatment of comorbid AUD. This supports the hypothesis that opiate receptor stimulation mediates ketamine's antidepressant effects. Additionally, among new treatments available for MDD, Chiappini et al. (2023) retrospectively evaluated esketamine in 26 treatment-resistant depression patients with comorbid SUD, reporting reductions in several depression scores and substance-related outcomes, without any report of new-onset substance misuse, cravings, or esketamine misuse or diversion during the 3-month observation period [84].

3.2.2. The treatment of opioid use disorder comorbid with major depressive disorder or depressive symptoms

Among pharmacological interventions specifically used for the treatment of SUDs, two of the studies retrieved [85,86] examined the use of the buprenorphine+naloxone combination and methadone pharmacotherapy as treatment strategies for depressive symptoms and opioid craving. Bastien et al. (2022) described similar effectiveness in decreasing depressive symptoms comorbid with OUD [85].

This effect was partly attributed to a decrease in opioid use. Interestingly, only 36.8 % of these improvements could be directly linked to reduced opioid use, indicating that the interventions might have an independent therapeutic effect on depressive symptoms. Conversely, Zhu et al. (2021) found that patients with mental disorders (e.g., BD $N = 51$; MDD $N = 85$; anxiety disorder $N = 121$) and OUD who were treated with buprenorphine+naloxone and methadone exhibited worse substance use outcomes and poorer psychosocial functioning compared to those without mental disorders [86]. Additionally, Mysels et al. (2011) reported that newly abstinent opioid-dependent individuals with comorbid MDD treated with naltrexone showed significant improvement in depression scores over a 4-week period post-baseline, with marked reductions in somatic and cognitive-affective subscale scores [87]. Although naltrexone, as an opioid antagonist, influences endogenous opioids involved in mood regulation, it did not appear to worsen depression in this study.

Finally, studying the effectiveness of pharmacological interventions in addressing psychiatric symptomatology, a study from El Hage et al. (2018) analysed the use of the antidepressant desvenlafaxine in 18 dual diagnosis patients under treatment with methadone, suggesting substantial improvements in depressive symptoms and quality of life, but no effects on heroin craving [88].

3.2.3. The treatment of cannabis use disorder comorbid with major depressive disorder or depressive symptoms

Evaluating treatment-related changes in psychiatric symptoms in individuals with MDD and CUD, three studies, differing in their pharmacotherapeutic approaches, provide different insights. The first study [89] examined the use of long-acting trazodone at doses of 150–300 mg/day for treating depressive and anxiety symptoms in three patients with CUD. It reported prompt depression and anxiety symptom resolution alongside abstinence from cannabis, with benefits maintained throughout the follow-up period of 27 to 32 weeks and no significant side effects. The second study was a randomized placebo-controlled trial assessing the efficacy of the glutamatergic drug *N*-acetylcysteine in 153 outpatients [90]. After 12 weeks of treatment with 1200 mg/day, no direct reduction in depressive symptoms was observed, nor was it more effective in promoting cannabis cessation among participants with higher baseline depression, which correlated with lower cessation rates regardless of treatment. Although no bidirectional associations between cannabis use and depressive symptoms were found, elevated depressive symptoms were linked to increased cannabis use. In contrast, Cornelius et al. (2010) combined fluoxetine (10–20 mg) or placebo with cognitive behavioural treatment (CBT) and motivational enhancement therapy (MET), achieving over a 50 % reduction in depressive symptoms and a 39.5 % reduction in DSM criteria for cannabis dependence, though the reduction in cannabis use days did not reach statistical significance [91].

3.2.4. The treatment of cocaine use disorder comorbid with major depressive disorder or depressive symptoms

In terms of treating coexisting depressive symptoms and cocaine use disorder, the antidepressant mirtazapine showed positive results, producing a reduced cocaine use and craving, along with improvements in both depression and anxiety scores [92]. In Raby et al. (2014), depression symptoms improved more rapidly on venlafaxine than placebo, but these differences disappeared by weeks 6–8 [93]; moreover, cocaine outcomes did not differ between treatment groups (venlafaxine versus placebo), and the proportion of patients achieving three or more consecutive weeks of urine-confirmed abstinence was low (venlafaxine: 16 %; placebo: 15 %); interestingly, reduction in cocaine use was associated with mood response.

3.3. Substance use disorders & bipolar disorder

The majority of the research findings primarily centred on AUD, with a smaller proportion of cases addressing cannabis, cocaine, and opioids. Consequently, the presentation of results followed this hierarchical sequence.

3.3.1. The treatment of alcohol use disorder comorbid with bipolar disorder

Among pharmacological interventions for SUDs, Brown et al. (2009) provided insights via their randomized, double-blind, placebo-controlled pilot study including a sample size of 43 outpatients (average age of 41.1 years) affected by BD (either I or II) and manifesting recent alcohol consumption [94]. Naltrexone at 50 mg/day combined with CBT determined a tangible reduction in drinking days, heavy drinking days, and a decrease in alcohol craving. No changes in BD symptoms were recorded [94]. Similarly, integrating treatment of BD with acamprosate daily for eight weeks, Prisciandaro et al. (2012) reported improvements in outcomes related to alcohol dependence alone, e.g. management of alcohol cravings and drinking patterns [95]. Great improvements in drinking outcomes, but not for mood improvement, were described by Kemp et al. (2009) in the combination of two mood stabilizers - valproate and lithium [96].

Considering both AUD-related and BD outcomes, Martinotti et al. (2008) demonstrated quetiapine might improve psychiatric symptoms and drinking use in patients diagnosed with BD/schizoaffective disorder/personality disorder and AUD [97]. Consistently, Gao et al. (2017) demonstrated significant improvements in alcohol/cannabis users concomitantly diagnosed with a BD administered with quetiapine-extended release (XR) at increasing dosages (50–300 mg/day) [98]: patients had larger decreases in depressive symptoms and in both the number of drinking days/week and number of cannabis joints/week compared to those who received placebo. However, Stedman et al. (2010) reported that adding quetiapine to lithium or valproate did not result in significantly improved outcomes for alcohol use and dependence compared to placebo in patients with BD-I and AUD [99].

Among mood stabilizers, the antiepileptic topiramate was studied as a specific intervention for AUD symptoms, showing an antagonism on alcohol's rewarding effects by inhibiting mesocorticolimbic dopamine release via the contemporaneous facilitation of gamma-amino-butyric acid activity and inhibition of glutamate function. However, its use in clinical practice requires a careful consideration of the potential benefits and side effects. Indeed, in the study from Sylvia et al. (2016) [100] the topiramate group (with a 40 % completion rate) had inferior improvement in drinking patterns compared to the placebo group (71 % completion); moreover, the topiramate group experienced a more significant side effect burden, i.e. dizziness, tingling sensations in the hands and feet, weight loss, cognitive-related issues.

With regard to new therapeutic approaches, Xiao et al. (2016) embarked on a unique path in an open-label pilot study with 11 adult outpatients [101]. Targeting BD and AUD, the study employed the flavonoid icariin, titrated from 100 mg/day to 300 mg/day. Salient outcomes revealed significant reductions in depressive symptoms, anxiety scores, alcohol consumption, and heavy drinking days from baseline to exit. Nevertheless, a plethora of side effects, ranging from vivid dreams to mild heartburn, were reported. Lee et al. (2018) undertook a single-arm clinical trial with 45 both outpatient and inpatient participants, using a low-dose add-on of memantine (5 mg/day) combined with open-label valproic acid treatment [102]. Outcomes suggested attenuated clinical severity in psychiatric symptoms, reduced alcohol use, and variations in plasma cytokine and brain-derived neurotrophic factor (BDNF) levels. Finally, more recently, Sherwood Brown et al. (2021), treated 70 outpatients ranging from 18 to 70 years using the serotonin 5-HT3 receptor antagonist ondasentron, with dosages escalating based on responsiveness, demonstrating a statistically significant positive effect on mood symptoms and somatic complaints for the ondansetron group [103].

3.3.2. The treatment of bipolar disorder in comorbidity with cocaine use disorder

In recent years, pivotal studies have striven to elucidate potential therapeutic interventions for both BD and cocaine use disorder symptoms. The mood stabilizer lamotrigine (from 25 mg/day to 400 mg/day) was used for the treatment of 112 patients in the depressed or mixed phase of BD with concurrent cocaine use [104], finding it effective in preventing depression symptoms than as an acute treatment of them, with a high profile of tolerability. The same group was studied for the nootropic citicoline, which offered only initial therapeutic advantages, but no long-term benefits [105]. Finally, the antidepressant bupropion emerged as a potentially promising adjunctive therapy in a randomized-controlled trial involving 12 patients [106]. The sharp contrast in responses, with 80 % of the ADD-ON group showing at least an antidepressant partial response as opposed to the complete lack of response in the NON ADD-ON group, presents a tantalizing glimpse into the potential of reuptake inhibitors in this complex clinical puzzle.

3.3.3. The treatment of bipolar disorder in comorbidity with cannabis use disorder

To the date of this review, evidence remains limited, with only one study reporting effects on BD and CUD symptoms. Prisciandaro et al. (2022) reported the results of a randomized, double-blind, placebo-controlled, crossover, multimodal-magnetic resonance imaging (MRI) pilot study, involving a cohort of 22 participants diagnosed with BD comorbid moderate-to-severe CUD [107] administered with gabapentin,

an antiepileptic drug mainly operating via a voltage-gated calcium channel block mechanism. The MRI assessments therein yielded intriguing neurochemical insights: an uptick in the glutamate levels of the dorsal anterior cingulate cortex (dACC) was evident in the first randomized order, while cigarette-smoking participants exhibited increased glutamate concentrations in the rostral basal ganglia (rBG), possibly explaining lower manic/mixed and depressive symptoms. Gabapentin, moreover, increased activation to visual cannabis cues in the posterior midcingulate cortex (pMCC, a region involved in response inhibition to rewarding stimuli), reducing cannabis use. Overall, gabapentin showed to be an effective adjuvant medication to target disrupted brain GABA/glutamate homeostasis in individuals with BD + CUD, potentially reducing cannabis use, mood symptoms, and anxiety.

3.3.4. The treatment of bipolar disorder in comorbidity with opioid use disorder

Specifically, in relation to studies that have reported on the treatment of BD and OUD symptoms, Khalili et al. (2019) described the use of the combination buprenorphine (dosed at either 4 or 6 mg/day), sodium valproate, and risperidone in 24 patients diagnosed with BD, manifesting either manic or depressive episodes coupled with psychotic features, and comorbid with an OUD [108]. While the outcomes revealed a marked reduction in psychotic, depressive, and manic symptoms after 1 and 2 weeks of treatment in both groups, the comparative efficacy analysis between them revealed no significant divergence, showing that buprenorphine did not accentuate the treatment outcome. In a sample of patients with BD/MDD and OUD, Zhu et al. (2021) [84] reported significantly more days of opioid use (mean: 8.6 days) compared to those without medical disorders (mean: 3.4 days) and a higher heroin use among patients with BD (mean: 6.4 days) compared to those with MDD (mean: 2.0 days) and those without medical disorders (mean: 3.1 days) in the 30 days leading up to the final interview. Moreover, they exhibited a notable inclination to maintain buprenorphine treatment, resorting to its use in 22.0 % of follow-up months; this propensity was in significant contrast when compared to participants without any mental disorder, who reported buprenorphine usage in just 10.5 % of their follow-up period.

4. Discussion

Reviewed studies collectively described a clinical scenario laden with pharmacological, psychological, and physiological complexity. Addressing the co-occurrence of schizophrenia/BD/MDD and SUDs represents a complex therapeutic challenge that has prompted investigations into innovative psychotherapeutic approaches.

The review showed that no clear indications emerged, considering the setting, the specific SUD, and the specific mental illness or individual patient characteristics. Indeed, literature contains a wide variety of studies and outcomes, but few randomized controlled trials, with most of them case series. Most have small samples and short duration, and the majority differentiates among primary and secondary outcomes, some focusing on psychiatric symptoms, and others on substance-use related symptoms.

Both SUDs and comorbid psychiatric conditions involve dysregulation in shared neurocircuits—particularly the mesolimbic dopamine system, prefrontal cortex, and amygdala, which govern reward, impulse control, and emotional regulation. Key neurotransmitters implicated include dopamine, glutamate, gamma-aminobutyric acid, and serotonin. For instance, dopaminergic dysregulation contributes to both addiction and psychosis, while glutamate imbalances are linked to mood instability and craving. Treatments such as atypical antipsychotics and mood stabilizers may modulate these pathways, offering benefit across comorbid presentations.

In the case of psychotic symptoms and SUDs, aripiprazole appeared to be the most used medication in the maintenance therapy not only for its effectiveness but also for its safety profile [56–58,68,109,110]. This is consistent with an Italian survey recording prescribing practices for the treatment of patients affected by psychotic symptoms and SUDs, showing haloperidol and aripiprazole were the most common first-line drugs respectively in the acute and maintenance settings [111]. As an alternative treatment option, clozapine showed a good efficacy in the management of psychotic symptoms and in terms of relapse prevention, due to its relatively low affinity for and rapid dissociation from D2 dopamine receptors [112]; however, side effects were recorded in most studies involving clozapine [49–51].

Surprisingly, although its favourable pharmacological characteristics, the atypical antipsychotic lurasidone is mentioned in only one study showing a great efficacy in four cases reporting cannabis induced psychotic symptoms with a very high tolerability and safety [62]. Indeed, it exhibits a distinct receptor profile, showing: i) a high affinity for serotonin 5HT-2 A and dopamine D2 receptors, deemed responsible for antipsychotic effects; ii) a strong affinity for 5HT-7 receptors which should yield favourable effects on mood, cognitive functions, sleep regulation, and negative symptoms; and iii) low affinity for H1 and M1 receptors, which translates to a decreased risk of weight gain, metabolic changes, sedation, anticholinergic side effects like dry mouth and constipation as well as a minimal risk of QTc prolongation [113]. Moreover, consistently with this, a recent study documented the beneficial effects of lurasidone in a 14-year-old patient with a history of alcohol, cannabis, and LSD abuse, along with behavioural issues (self-injurious behaviours) and psychotic symptoms, such as auditory hallucinations [114].

Long-acting medications demonstrated significant potential in addressing the unique complexities of schizophrenia comorbid with SUDs and might be an effective option in the control of impulsivity and psychotic symptoms, but also in first-episode psychosis with comorbid SUD, reducing the risk of relapse and rehospitalization [45,66,69–71]. In the set of studies related to the comorbidity of psychotic symptoms and SUD-related symptoms, cannabis appeared among the most consumed substance. This is of relevance considering psychopathological risks related to cannabis use: although the exact mechanism by which cannabis contributes to psychosis is still under investigation, with some hypotheses including its effect on dopamine transmission, neurodevelopmental disruptions, and its impact on the endocannabinoid system, a risk of psychosis related to cannabis use both in the short- and long-term has been documented. Specifically, in the short-term, tetrahydrocannabinol (THC), the primary psychoactive compound in cannabis, can produce transient psychotic symptoms in some users. This might include hallucinations, delusions, and disorganized thoughts. Such symptoms are more common in naive users, in those with a large consumption, or when potent strains of cannabis are consumed [115–118]. In the long-term, numerous studies, including longitudinal research, suggest that cannabis use, especially if initiated during adolescence, is associated with an increased risk of developing a psychotic disorder later in life. This relationship seems to be dose-dependent and heavier use is linked with a higher risk [116,119,120]. In this context, an increasing rates of high potency synthetic cannabinoids entering the market [120–122], providing new clinical and psychopathological features (classical vs chemical/synthetic psychoses), has been presenting various challenges in clinical settings [123,124].

With regard to the treatment of MDD/BD and SUD, the current body of evidence includes mixed findings in terms of which medication is superior in controlling symptoms, according to the specific mental disorder, SUD involved, and the treatment setting. Individuals with co-occurring MDD and SUD tend to exhibit more severe symptoms—such as heightened anhedonia, emotional blunting, and cognitive impairment—compared to those with MDD alone. These may often undermine craving regulation, increase substance use, elevate relapse risk, and reduce adherence to treatment, perpetuating a cycle of deepening depressive symptoms, functional decline, chronicity, and increased rates of morbidity, mortality, and healthcare use [125]. The effectiveness of antidepressant treatments in this population remains uncertain and inconsistent, largely due to methodological limitations in clinical trials

Table 3
Treatments for dual diagnosis recorded by studies reviewed.

Category	Drug/Treatment	Key Points/Findings	Reference
Substance Use Disorders & Schizophrenia			
	Clozapine	Heightened hedonic aspect of reward response, which could potentially translate to decreased substance use; a more pronounced decline in Positive and Negative Syndrome Scale (PANSS) positive scores, highlighting its potential for managing positive symptoms; clozapine as a potentially superior therapy over risperidone and ziprasidone. Better efficacy in treating craving in cannabis- dependent patients than Risperidone	Brunette et al., 2011; Machielsen et al., 2014; Mesholam-Gately et al., 2014; Schnell et al., 2014 Machielsen et al., 2012
	Olanzapine	Better efficacy in treating craving than Risperidone in cannabis-dependent patients	Machielsen et al., 2012
	Risperidone	Compared to clozapine in efficacy, clozapine demonstrated its efficacy in symptom management and in reducing hospital readmissions. Compared to clozapine and olanzapine risperidone is less efficacy in treating craving in cannabis- dependent patients	Kim et al., 2008; Machielsen et al., 2014; Machielsen et al., 2012
	Ziprasidone	Comparable to clozapine for reducing cannabis use	Schnell et al., 2014
	Aripiprazole	Transitioning from clozapine to aripiprazole, improved positive symptoms and sobriety, but several relapses were recorded	Desseilles et al., 2008; Feeley et al., 2017
	Cariprazine and Quetiapine	Transitioning from haloperidol to the combination of cariprazine and quetiapine resulted in enhanced cognitive function, a reduction in negative and positive symptoms, and minimized substance abuse	Rodriguez et al., 2021
Oral Antipsychotic	Lurasidone	It showed improvements in positive and negative symptoms and in the overall functioning. Lurasidone was well tolerated, with no significant side effects reported.	Ricci et al., 2022
Long-Acting Injectable (LAI) antipsychotic	Aripiprazole	Promising results for short and long-term management of psychotic symptoms, substance craving, and a substantial reduction in disability. Comparing LAIs, highlighted aripiprazole's superior impact on quality of life and craving, and reduced side effects in terms of minimal weight gain or sedation and cardiac parameters, e.g. QTc alteration, frequently altered in subjects with AUD and UD	Chen et al., 2019; Chiappini et al., 2023; Cuomo et al., 2018; Erdogan et al., 2021; Green et al., 2015; Rubio et al., 2009; Starr et al., 2017; Szerman et al., 2020
NMDA receptor transmission and GABAA transmission modulator	Acamprosate	Despite the robust decrease in both alcohol consumption and positive symptoms of psychosis, there were no significant changes in negative or general symptoms or in the cognitive functioning across memory, attention, and executive function domains	Ralevski et al. (2011); Tek et al. (2008)
Substance Use Disorders & Depression			
Alcohol Use Disorder			
	Mirtazapine	Decreased depressive symptoms; no significant decrease in alcohol consumption. Conversely, comparing in a randomized double-blind study the efficacy of mirtazapine and amitriptyline, reduced alcohol craving was demonstrated. Drug-related adverse effects, which were predominantly observed in the amitriptyline group, included tremor, constipation, diminished sexual desire, and orthostatic dizziness	Altintoprak et al. (2008); Cornelius et al. (2015)
	Citalopram, Escitalopram, Venlafaxine, Mirtazapine, Bupropion	No significant differences in treatment responses between MDD with or without SUD. Conversely, in Howland et al. (2009), participants with non-psychotic MDD and comorbid anxiety and/or SUD are clinically identifiable, showing several distinctive baseline sociodemographic and clinical features. They also showed greater depression severity; length of illness; likelihood of anxious, atypical or melancholic features; more intolerance/attrition; and worse pharmacological treatment outcomes. They may benefit from multi-faceted treatment and psychosocial rehabilitation targeted at reducing their psychological comorbidity and functional impairment	Davis et al. (2012), Howland et al. (2009)
	Trazodone	Extended-release trazodone (150-300 mg/day) displayed good antidepressant properties in MDD + AUD patients, ameliorating overall symptomatology, functioning, and quality of life, with a good safety/ tolerability profile. Further, it significantly improved sleep disturbances and craving symptoms, which are associated with drinking relapse and worse outcomes Trazodone (50-150 mg/day) showed a short-term benefit on sleep quality, but might require long-term use in the postdetoxification period (> 3 months)	Di Nicola et al. (2023) Friedmann et al. (2008)
Antidepressant	Vortioxetine	Similar improvements as other antidepressants; milder side effects	Kotzalidis et al. (2021)
NMDA-blocker	Memantine (+ Escitalopram)	Reduced depression and anxiety; improved quality-of-life outcomes	Muhonen et al. (2008)
NMDA receptor transmission and GABAA transmission modulator	Acamprosate (+ Escitalopram)	Acamprosate added to escitalopram significantly improved alcohol use parameters	Witte et al., 2012

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Table 3 (*continued*)

Category	Drug/Treatment	Key Points/Findings	Reference
		The synergy between opiate antagonist naltrexone and the antidepressant drug sertraline showed a promising 45 % symptom reduction in depressive outcomes but also notably delayed relapse into heavy drinking	
	Naltrexone (+ Sertraline)	Injectable naltrexone coupled with ketamine infusions demonstrated a 60 % improvement in depressive symptoms over just 8 weeks), suggesting that naltrexone pretreatment did not interfere with the antidepressant effects of ketamine and might enhance the treatment of comorbid alcohol use disorder, supporting the hypothesis that opiate receptor stimulation	Pettinati et al. (2010)
Opioid antagonist	Naltrexone (+ Ketamine)	mediates the antidepressant effects of ketamine	Yoon et al. (2019)
Opioid Use Disorder			
Opioid agonist/antagonist	Buprenorphine + Naloxone	Buprenorphine+Naloxone and methadone showed similar effectiveness in decreasing depressive symptoms comorbid with opioid use disorder. Worse substance use outcomes and poorer psychosocial functioning were reported in double diagnoses patients, compared to patients affected with a SUD, but not a mental disorder	Bastien et al. (2022); Zhu et al. (2021)
Antidepressant	Desvenlafaxine (+ methadone)	Substantial improvements in depressive symptoms and quality of life, but no effects on heroin craving	El Hage et al. (2018)
Cannabis Use Disorder			
Glutamatergic drug	*N*-acetylcysteine	After administering 1200 mg/day of n-Acetylcysteine for 12 weeks, the results did not delineate a direct reduction in depressive symptoms; interestingly the severity of baseline depressive symptoms correlated with lower rates of cannabis cessation	Tomko et al., 2019
	Fluoxetine with CBT/MET	A reduction of over 50 % in depressive symptoms across the 12-week trial, and a 39.5 % reduction in cannabis dependence across treatment groups, albeit the reduction in the number of cannabis use days didn't reach statistical significance High efficacy in the treatment of depressive symptoms and	Cornelius et al. (2010)
Antidepressant	Trazodone	craving, but also a good profile of safety and tolerability	Mazza et al., 2022
Cocaine Use Disorder			
Antidepressant	Mirtazapine	Reduction in cocaine use and craving, along with improvements in both depression and anxiety scores	Afshar et al. (2012)
Antidepressant	Venlafaxine	Depressive symptoms improved more rapidly on than placebo, but these differences disappeared by weeks 6–8. Cocaine outcomes did not differ between treatment groups (venlafaxine versus placebo), and the proportion of patients achieving three or more consecutive weeks of urine-confirmed abstinence was low; moreover, reduction in cocaine use was associated with mood response	Raby et al. (2014)
Repetitive Transcranial Magnetic Stimulation (rTMS)		Administered over a four-week period, the rTMS treatment yielded significant reductions in cocaine use (56.25 %) and craving, as well as depressive symptoms. Suicidal ideation remained unaffected	Pettorruso et al. (2019)
Substance Use Disorders & Bipolar Disorder			
Alcohol Use Disorder			
Opioid antagonist	Naltrexone + CBT	Reduction in drinking days, heavy drinking days, and alcohol craving	Brown et al. (2008)
NMDA receptor transmission and GABAA transmission modulator	Acamprosate	integrated treatment of BD using acamprosate daily for eight weeks, improving outcomes related to alcohol dependence	Prisciandaro et al. (2012)
Antipsychotic	Quetiapine-XR	Improvements in various symptom scales (QIDS-SR-16 and CGI-BP-S). Patients who received quetiapine-XR had larger decreases in the number of drinking days/week and number of cannabis joints/week compared to those who received placebo	Gao et al. (2017)
Prenylated flavanol glycoside	Icariin	Significant reductions in depressive symptoms, anxiety scores, alcohol consumption, and heavy drinking days	Xiao et al. (2015)
Mood stabilizer	Topiramate	No significant improvement in drinking patterns compared to placebo	Sylvia et al. (2016)
NMDA antagonist	Memantine (+ Valproic Acid)	Reduced clinical severity and alcohol use and variations in plasma cytokine and brain-derived neurotrophic factor (BDNF) levels	Lee et al. (2018)
Serotonin 5-HT3 receptor antagonist	Ondansetron	Positive effect on mood symptoms and somatic complaints	Sherwood Brown et al. (2021)
Cocaine Use Disorder			
Mood stabilizer	Lamotrigine	Improved likelihood of cocaine-negative results, and efficacy of lamotrigine among patients with baseline depression scores, suggesting a potential subgroup where the treatment might be especially beneficial	Brown et al. (2012)
Nootropic	Citicoline	Citicoline might offer initial therapeutic advantages, its long-term benefits might be constrained	Brown et al. (2015)
Antidepressant	Bupropion	80 % of ADD-ON group showed response as opposed to the complete lack of response in the NON ADD-ON group	Sepede et al. (2014)

(*continued on next page*)

Table 3 (*continued*)

Category	Drug/Treatment	Key Points/Findings	Reference
Cannabis Use Disorder			
Mood stabilizer	Gabapentin	The MRI assessments therein yielded intriguing neurochemical insights: an uptick in the glutamate levels of the dorsal anterior cingulate cortex (dACC) was evident in the first randomized order, while cigarette-smoking participants exhibited increased glutamate concentrations in the rostral basal ganglia (rBG). Thus, gabapentin could be considered as an adjuvant medication to target disrupted brain GABA/glutamate homeostasis potentially reducing cannabis use, mood symptoms, and anxiety	Prisciandaro et al. (2022)
Opioid Use Disorder			
Opioid agonist	Buprenorphine + Sodium Valproate + Risperidone	While the outcomes revealed a marked reduction in psychotic, depressive, and manic symptoms post 1 and 2 weeks of treatment in both groups, the comparative efficacy analysis between them revealed no significant divergence, showing that buprenorphine did not accentuate the treatment outcome of psychotic episodes inherent to BD	Khalili et al. (2019)
	Buprenorphine	Patients with BD exhibited a notable inclination to maintain buprenorphine treatment, resorting to its use in 22.0 % of follow-up months. This propensity was in significant contrast when compared to those participants without any mental disorder, who reported buprenorphine usage in just 10.5 % of their follow-up period	Zhu et al. (2021)

Abbreviations: AUD: Alcohol Use Disorder; **BD:** Bipolar Disorder; **CBT**: Cognitive Behavioural Therapy; **CoUD**: Cocaine Use Disorder; **CUD:** Cannabis Use Disorder; **GABA**: gamma-amino-butyric acid; **MDD**: Major Depressive Disorder; **MRI:**_ magnetic resonance imaging; **NMDA:** *N*-methyl-D-aspartate; **QIDS-SR-16**: the 16-item Quick Inventory of Depressive Symptomatology-Self-Report; **CGI-BP-S:** Clinical Global Impression for Bipolar Disorder-Severity; **SUD:** Substance Use Disorder.

and the difficulty of isolating medication effects from those of psychological interventions in real-world practice. With regard to antidepressants, several pharmacological options were considered, ranging from SSRI antidepressants, such as escitalopram or fluoxetine, to the tricyclic amitriptyline, to other recently marketed molecules, including trazodone, vortioxetine and desvenlafaxine. Specifically, trazodone not only showed a high efficacy in the treatment of depressive symptoms and craving, but also a good profile of safety and tolerability [89], the latter being one of the points to be considered in the treatment of young patients affected with a SUD. Previously, consistently with this, in a study focusing on $N = 25$ alcohol-dependent patients, trazodone showed a positive effect on depressive and anxious symptoms maintaining abstinence and reducing craving for alcohol in a detoxification phase [126].

Notably, varied degrees of efficacy were recorded if added to CBT/MET/behavioural interventions, or combined with specific SUD treatments, such as opioid receptor agonist/antagonist therapies or the anti-glutamatergic drugs acamprosate/memantine, etc. This strongly suggests that the interplay between mental illnesses and SUDs remains intricate and these conditions are associated with several neurobiological impairments, e.g., abnormalities in the circuitry of the frontal-limbic regions of the brain, particularly the nucleus accumbens, implicated in the loss of reward responsiveness, or in the ventrolateral prefrontal cortex function, contributing to emotional regulation and decision-making; and a dysregulation of the endogenous opioid system implicated in emotion and stress regulation, and impulsive-like behaviour [42]. In this regard, several studies investigated mood improvements using depression-related scores/scales. Of note, besides depressed mood, anhedonia is one of the two core symptoms of depression, and it is also present in SUDs as part of the abstinence symptomatology, involved in craving and protracted withdrawal [127,128]. Novel therapeutic approaches, such as NMDA receptor antagonists like ketamine [83] and esketamine [84], along with non-invasive brain stimulation techniques like repetitive transcranial magnetic stimulation (rTMS) [129], have demonstrated favourable safety and tolerability profiles, warranting investigation in large-scale trials. Given the varying response trajectories and extensive side-effect profiles, individualized therapeutic strategies grounded in a deeper understanding of the underlying neurobiological pathways may be crucial for managing this specific comorbidity. Regarding BD, several mood stabilizers [99,100,104,106,107] have been evaluated. Valproate is currently the preferred treatment for individuals with BD and SUDs, while evidence suggests that lithium monotherapy lacks efficacy. Quetiapine appears to be a viable treatment option for patients with BD and recent alcohol abuse or CUD, effectively reducing depressive symptoms and decreasing alcohol consumption and cravings [97,98].

Interesting findings emerged from the study by Mysels et al. (2011), showing depression was not worsened by naltrexone treatment [87]. We might hypothesise that, in individuals with alcohol dependence, naltrexone' primary action to reduce alcohol craving and consumption counteracts in the long-term the effects of alcohol itself, which is a depressant and can exacerbate depressive symptoms. Thus, naltrexone overall impact on mood in this context can be neutral to positive, as reduced alcohol consumption can often lead to improved mood and overall well-being. Interestingly, several trials have found that naltrexone can effectively reduce alcohol consumption in individuals with schizophrenia as well [112,130]. Similarly, in the context of opioid addiction, naltrexone helps maintain abstinence and prevents relapse, which can improve overall life quality and, subsequently, mood. These considerations might take into account the following mechanistic points: naltrexone selectively blocks opioid receptors, but it does not block all the pathways involved in mood regulation. Brain's reward and mood systems are multifaceted and involve multiple neurotransmitters, including dopamine, serotonin, and norepinephrine. Moreover, by blocking opioid receptors, naltrexone might lead to compensatory changes in the levels of endogenous opioids or their release patterns. Such changes could potentially counterbalance some of the direct blocking effects on mood. Consistently with this hypothesis, Latif et al. (2019) recorded no change in psychiatric distress reported as symptoms of anxiety, depression, or insomnia in adults with opioid dependence, who were randomized to short-term treatment with either naltrexone or combined buprenorphine-naloxone followed by a longer-term treatment [131]. On the contrary, the antidepressant effects of buprenorphine align with existing pharmacological evidence suggesting that μ-opioid receptor agonism is associated with increased dopamine release, improved hedonic tone, and enhanced feelings of well-being—factors that collectively contribute to its antidepressant properties. Additionally, buprenorphine may exert antidepressant effects through its ability to inhibit monoamine reuptake. It also antagonizes kappa-opioid receptors, and this functional antagonism—demonstrated in preclinical models—has been proposed as a key mechanism for its antidepressant

action. This mechanism is also believed to underlie the therapeutic potential of buprenorphine in combination with naltrexone for treating opioid dependence [132].

Complexity in dual diagnosis is not only seen in the clinical presentation of patients [133], but also in the broad spectrum of treatment outcomes, the diversity of settings in which these individuals are attended [39], and the unique challenges posed by special populations [39]. Indeed, dual diagnosis outcomes can range from full recovery in both disorders to chronic relapses in one and both conditions. Additionally, the influence of one disorder on another can be unpredictable. Moreover, the intertwining of SUDs with other psychiatric disorders can complicate the trajectory of treatment and prognosis. For instance, patient's depressive symptoms may be alleviated, but their substance use might continue or even escalate, affecting the overall wellbeing. In the treatment choice, clinicians should define if the primary goal is detoxification, relapse prevention and maintenance of abstinence, craving management, psychiatric symptom reduction, improved social functioning, or a combination of them [39]. In this regard, treatment settings may offer several but different opportunities, e.g., dual diagnosis patients frequently present in crisis, necessitating specialized training for emergency personnel in handling and referring such cases. Inpatient care might become essential for acute cases, especially when there is a risk of harm to oneself or others. Community-based programs play a pivotal role in early identification, intervention, and long-term support: peer support groups and community health workers offer grassroots-level care; finally, in primary care, providers require adequate training to identify dual diagnosis and facilitate appropriate referrals. Drug and alcohol services provide specialized care targeting SUDs, but need to be equipped to address concurrent psychiatric disorders, including psychoeducation sessions and psychotherapy (e.g., CBT, social skill training, dialectical behavioural therapy, psychodynamic therapies, etc.). Indeed, motivational and CBT have been associated with decreased substance use in several trials involving the treatment of SUDs in patients with schizophrenia. These interventions focus on enhancing motivation to change, developing coping strategies, and preventing relapse [112,130].

Real-world studies, such as observational studies, might play a crucial role in understanding the effectiveness, safety, and tolerability of medications, and factors influencing treatment response in diverse patient populations outside of controlled clinical trial settings, including specific patient populations, such as adolescents, offenders, pregnant women, homeless population, all demanding specialized intervention strategies. Finally, there might be cultural and ethnic issues conditioning treatment approaches, which must be culturally sensitive, acknowledging the unique challenges faced by different ethnic groups, including barriers to access, stigma, and differing substance use patterns.

Overall, an integrated model of treatment [25,38–41,134,135] addressing dual diagnosis and combining pharmacotherapy, psychotherapy, and socio-rehabilitative measures should be developed.

This is crucial for several reasons: i) Complex interactions between SUDs and other mental disorders which can exacerbate symptoms, complicate treatment, and worsen outcomes; ii) Treating both disorders concurrently can lead to better outcomes, such as reduced substance use, improved psychiatric symptoms, and decreased hospitalizations; iii) The avoidance of sequential treatment, a practice frequently observed in non-integrated approaches, often proves ineffective because the untreated condition can persist and worsen the treated condition; iv) Better patient engagement; v) Cost-Effectiveness; vi) Holistic understanding of patients' needs and challenges; vii) Reduction of stigma; viii) Enhanced treatment retention.

4.1. Limitations of the study

Despite providing a comprehensive overview of the existing research on the topic, our study potentially shows some specific limitations. In fact, reviewed studies were characterised by a high heterogeneity in design, populations, interventions, duration, and outcomes. Studies might possibly be limited in the number, considering patients with SUD are often excluded from various types of research studies for several reasons, including confounding variables, compliance concerns, health and safety concerns, stability of living conditions, determining limited evidence on their treatment and reduced generalizability. Lastly, this review only included studies published in English.

5. Conclusion

Overall, pharmacological treatments of dual diagnosis are complex and require personalized and integrated approaches considering the heterogeneity of the population. The literature supports the use of several medication classes, but the effectiveness varies depending not only on the specific symptomatology, but also on the specific comorbidity patterns, the type of populations, and study outcomes. Moreover, since many individuals in the general population suffer from SUD, and considering SUD are common in the real-world setting, excluding them from studies can lead to results that are not generalizable. Future research including this category of patients is needed, in order to obtain comorbidity insights, understand potential drug-drug interactions or how substance use might impact on the effectiveness and safety of a specific treatment and the biological underpinnings of dual diagnosis, and reach better treatment outcomes developing effective treatment plans and public health strategies.

CRediT authorship contribution statement

Stefania Chiappini: Writing – original draft, Methodology, Data curation, Conceptualization. **Mosca Alessio:** Writing – original draft, Data curation. **Francesco Semeraro:** Writing – original draft, Data curation. **Andrea Amerio:** Supervision, Conceptualization. **Isabella Berardelli:** Supervision, Data curation. **Laura Cremaschi:** Supervision, Resources. **Ilaria Di Bernardo:** Methodology, Data curation. **Mauro Pettorruso:** Writing – review & editing, Supervision, Methodology. **Gianluca Serafini:** Writing – review & editing, Supervision, Conceptualization. **Bernardo Dell'Osso:** Writing – review & editing, Supervision, Conceptualization. **Giovanni Martinotti:** Writing – review & editing, Supervision, Methodology, Conceptualization.

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