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Review

Brexpiprazole in the Management of Schizophrenia and Comorbid Substance Use Disorders: A Narrative Review of Efficacy, Safety, and Real-World Evidence (2020–2026)

Miriam Olivola [1,2,3,*], Nicolaja Girone [2,3], Andrea Crippa [2,3], Monica Macellaro [2,3], Vassilis Martiadis [4], Fabiola Raffone [4], Tiziano Prodi [2,3], Natascia Brondino [1], Roberta Anniverno [2] and Bernardo Dell'Osso [2,3,5,6]

[1] Department of Brain and Behavioural Sciences, Universita di Pavia, 27100 Pavia, Italy
[2] Department of Mental Health and Addiction Services, Azienda Socio Sanitaria Territoriale Fatebenefratelli Sacco, 20131 Milan, Italy
[3] Department of Mental Health, Department of Biomedical and Clinical Sciences "Luigi Sacco", University of Milan, 20122 Milan, Italy
[4] Department of Mental Health, Azienda Sanitaria Locale Napoli 1 Centro, 80143 Naples, Italy
[5] "Aldo Ravelli" Center for Nanotechnology and Neurostimulation, University of Milan, 20122 Milan, Italy
[6] Department of Psychiatry and Behavioral Sciences, Stanford University, Stanford, CA 94305, USA
* Correspondence: miriam.olivola@asst-fbf-sacco.it; Tel.: +390-239-042-904

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Abstract: Background: Brexpiprazole, a third-generation antipsychotic with partial dopamine D2/D3 and serotonin 5-HT1A agonist properties, has emerged as a promising therapeutic option for patients with schizophrenia, including those with comorbid substance use disorders (SUDs). Managing psychosis in the presence of substance use represents a major clinical challenge, often associated with poorer outcomes, reduced adherence, and increased relapse risk. Methods: This narrative review(non-systematic) synthesizes evidence from randomized controlled trials, observational real-world studies, and expert consensus reports published between 2020 and 2026. The literature was examined to evaluate the pharmacological mechanisms, clinical efficacy, safety, and practical use of brexpiprazole in psychotic disorders, with particular attention to populations with comorbid substance use disorders. As a narrative review, this work does not employ systematic search protocols or quality appraisal tools; findings should be interpreted with this methodological limitation in mind. Results: Available evidence suggests that brexpiprazole can meaningfully reduce both positive and negative symptoms of psychosis, while also demonstrating beneficial effects on substance craving and functional outcomes in patients with dual diagnoses. Across randomized and real-world studies, brexpiprazole shows a favorable tolerability profile, characterized by minimal activation, low sedation, reduced risk of extrapyramidal symptoms, and limited cardiometabolic burden. These properties support its use in complex clinical populations requiring long-term treatment and polypharmacological management. Clinical Implications and Decision-Making: Based on the available evidence, brexpiprazole may be particularly suitable for: (1) patients with prominent negative symptoms requiring improvement in motivation and social functioning; (2) individuals with comorbid substance use disorders, particularly stimulant use, where dopaminergic modulation may address both psychotic symptoms and craving; (3)

patients who have experienced significant metabolic or motor side effects with other antipsychotics; (4) individuals requiring cognitive preservation or enhancement. However, clinicians should consider that most evidence derives from relatively short-term studies with selected populations, and long-term real-world effectiveness data remain limited. Treatment decisions should be individualized based on symptom profile, comorbidity burden, prior medication responses, and patient preferences. Conclusions: Brexpiprazole represents a clinically valuable option for the management of psychosis, particularly in patients with comorbid substance use disorders. Its balanced pharmacological profile, combined with consistent efficacy and good tolerability, supports its role in integrated, long-term treatment strategies for complex and dual-diagnosis populations.

Keywords: brexpiprazole; schizophrenia; substance use disorders; dual diagnosis; partial dopamine agonists; antipsychotic pharmacology

1. Introduction

Schizophrenia and other psychotic disorders are chronic and highly disabling mental health conditions, affecting approximately 1% of the global population and accounting for a substantial personal, familial, and societal burden [1,2]. Clinical management is often complex, but this complexity increases markedly when comorbid substance use disorders (SUDs) are present. Epidemiological data indicate that 40–60% of individuals with schizophrenia meet criteria for a lifetime SUD, a combination consistently associated with poorer outcomes, reduced treatment adherence, higher relapse and hospitalization rates, and increased mortality [3,4].

In routine clinical practice, dual diagnosis represents one of the most challenging scenarios for psychiatrists. Substance use may exacerbate psychotic symptoms, interfere with pharmacological response, and undermine therapeutic alliance. At the same time, psychotic symptoms themselves can contribute to maladaptive substance use as a form of self-medication or behavioral dysregulation. Despite this bidirectional relationship, patients with comorbid SUDs are frequently underrepresented or excluded from randomized clinical trials, resulting in a limited evidence base to guide treatment decisions in this population.

Conventional antipsychotics, while effective in controlling positive symptoms, often show limited efficacy on negative symptoms and functional impairment, which are key determinants of long-term outcome. Moreover, adverse effects such as extrapyramidal symptoms, metabolic disturbances, sedation, and dysphoria may further compromise adherence and quality of life, particularly in patients already vulnerable due to substance use [5–7]. These limitations highlight the need for antipsychotic agents that combine efficacy with a favorable tolerability profile and a pharmacological mechanism capable of stabilizing dopaminergic dysfunction without excessive blockade [8–11].

Brexpiprazole, approved by the U.S. Food and Drug Administration in 2015 for schizophrenia and as adjunctive treatment for major depressive disorder, belongs to the class of third-generation antipsychotics and is characterized by a distinctive pharmacological profile [12,13]. As a serotonin–dopamine activity modulator, brexpiprazole exhibits partial agonist activity at dopamine D2/D3 and serotonin 5-HT1A receptors, along with antagonist activity at 5-HT2A receptors and moderate affinity for noradrenergic α1B/2C receptors [2,14]. This balanced receptor activity has been hypothesized to translate into effective symptom control with reduced risk of activation, extrapyramidal symptoms, and metabolic burden.

Over the past decade, and particularly between 2020 and 2026, growing evidence from randomized controlled trials, real-world observational studies, and expert consensus reports has clarified the role of brexpiprazole in clinical practice, including in complex and under-studied populations. The present narrative review aims to synthesize this body of evidence, with a specific focus on the efficacy, safety, and practical application of brexpiprazole in patients with psychotic disorders, both with and without comorbid substance use disorders, in order to provide clinicians with pragmatic, evidence-informed guidance. To our knowledge, this is the first narrative review to systematically examine the evidence base for brexpiprazole in dual diagnosis populations published between 2020 and 2026, with a specific focus on real-world applicability.

2. Methods

This narrative review synthesizes evidence from randomized controlled trials, observational studies, real-world evidence, and expert clinical reports published between 2020 and 2026. A comprehensive literature search was conducted in PubMed, Scopus, Web of Science, and PsycINFO using combinations of the following search

terms: 'brexpiprazole', 'schizophrenia', 'psychosis', 'substance use disorder', 'addiction', 'dual diagnosis', 'comorbidity', 'efficacy', 'safety', 'real-world', and 'observational'. Reference lists of included studies were manually searched to identify additional relevant publications. As a narrative (non-systematic) review, this work does not employ formal systematic search protocols, pre-defined inclusion/exclusion criteria, or standardized quality appraisal tools; findings should be interpreted with this methodological limitation in mind. The review focuses on brexpiprazole's pharmacological profile, efficacy in acute and maintenance treatment of schizophrenia, safety and tolerability, real-world effectiveness, and its specific role in managing patients with comorbid substance use disorders. Particular emphasis is placed on studies investigating dual diagnosis populations, given the clinical relevance and complexity of managing psychosis in the context of active substance use.

3. Pharmacological Profile and Mechanism of Action

Brexpiprazole's therapeutic effects stem from its distinctive pharmacological profile, which differentiates it from other antipsychotics through its balanced receptor binding affinities and partial agonist properties [2,14]. Understanding these mechanisms is essential for appreciating its clinical advantages in managing psychosis and substance use comorbidity.

3.1. Dopaminergic Activity

Brexpiprazole functions as a partial agonist at dopamine D2 and D3 receptors with lower intrinsic activity compared to aripiprazole and cariprazine [15,16]. This partial agonism allows brexpiprazole to stabilize dopaminergic neurotransmission: in hyperdopaminergic states (as in acute psychosis), it acts as a functional antagonist, reducing excessive dopamine activity; in hypodopaminergic states (as in negative symptoms or prefrontal cortical dysfunction), it provides modest dopaminergic stimulation [2,14]. The D2/D3 stimulation-to-blocking ratio of brexpiprazole is lower than that of aripiprazole and cariprazine, potentially accounting for its reduced propensity to cause akathisia and activation [15].

3.2. Serotonergic Modulation

Brexpiprazole exhibits potent partial agonist activity at serotonin 5-HT1A receptors, which contributes to its efficacy against negative symptoms, cognitive deficits, anxiety, and depressive symptoms commonly observed in schizophrenia [2,14]. Simultaneously, it acts as an antagonist at 5-HT2A receptors, a property shared with most second-generation antipsychotics that enhances antipsychotic efficacy while reducing EPS risk [14]. The balanced 5-HT1A agonism and 5-HT2A antagonism may also contribute to improved mood regulation and reduced impulsivity, factors relevant to substance use behaviors [14].

3.3. Noradrenergic and Histaminergic Effects

Brexpiprazole demonstrates moderate affinity for noradrenergic α1B and α2C receptors, which may contribute to its effects on cognition, attention, and mood [2,14]. Additionally, its antihistaminergic (H1) properties, while stronger than aripiprazole, remain relatively modest compared to agents like quetiapine or olanzapine [15]. This antihistaminergic activity may contribute to reduced akathisia, agitation, and insomnia, while potentially causing mild sedation in some patients [15].

3.4. Relevance to Substance Use Disorders

The pharmacological profile of brexpiprazole offers several theoretical advantages for managing comorbid substance use disorders. The balanced dopaminergic modulation may reduce substance cravings by normalizing mesolimbic reward circuitry dysfunction without inducing the dysphoria or anhedonia that can drive compensatory substance use [3,17]. The 5-HT1A partial agonism may reduce impulsivity and improve executive function, addressing cognitive vulnerabilities associated with substance use [12]. Furthermore, the favorable side effect profile may enhance medication adherence, a critical factor in dual diagnosis populations [3,18] (Table 1).

Table 1. Safety profile summary of brexpiprazole in dual diagnosis populations.

Adverse Effect Category	Frequency/Severity	Clinical Considerations
Weight gain	Low to moderate (1–3 kg mean)	Less than olanzapine, quetiapine; monitor BMI
Metabolic effects	Minimal impact on glucose/lipids	Baseline and periodic monitoring recommended
Akathisia	Most common EPS (5–14%)	Dose-dependent; consider dose reduction
Sedation	Mild to moderate (dose-related)	May improve with continued use; bedtime dosing
Cardiovascular	Minimal QTc prolongation	ECG monitoring in high-risk patients
Prolactin elevation	Minimal or absent	Advantage over first-generation agents
Sexual dysfunction	Low incidence	May be preferred in patients with prior issues

4. Efficacy in Schizophrenia and Psychotic Disorders

4.1. Acute Phase Treatment

Multiple randomized controlled trials have established brexpiprazole's efficacy in acute schizophrenia. A meta-analysis by Qin et al. examining four RCTs with 2178 patients demonstrated that standard-dose brexpiprazole (2–4 mg/day) significantly reduced Positive and Negative Syndrome Scale (PANSS) total scores compared to placebo. Importantly, this meta-analysis found that low-dose brexpiprazole (<2 mg/day) was not superior to placebo and was significantly inferior to standard doses, establishing 2–4 mg/day as the optimal therapeutic range [19].

However, it is important to note that many of these trials involved relatively short follow-up periods (6–8 weeks) and modest sample sizes; longer-term effectiveness and generalizability to diverse clinical populations require further investigation.

Watanabe et al. reviewed pooled analyses of randomized, double-blind, placebo-controlled trials demonstrating that brexpiprazole significantly reduced PANSS total scores and improved Clinical Global Impression-Severity (CGI-S) scores and Personal and Social Performance (PSP) scale scores, indicating benefits across symptom domains and functional outcomes [12]. The therapeutic effects were evident within the first weeks of treatment and were maintained throughout acute treatment phases.

A post hoc analysis by Correll et al. specifically examined early-episode schizophrenia patients (≤5 years illness duration) from four Phase 3 trials, including both adults and adolescents. Brexpiprazole 2–4 mg/day produced a mean PANSS total score reduction of −21.4 compared to −17.8 with placebo ($p = 0.042$) at Week 6, demonstrating significant efficacy in this critical early treatment window [20]. This finding is particularly important given the prognostic significance of early intervention in schizophrenia.

4.2. Maintenance and Long-Term Management

Long-term efficacy and safety are essential considerations in schizophrenia management, given the chronic nature of the illness and the need for sustained treatment to prevent relapse [21,22]. Inada et al. conducted a 56-week open-label study in Japanese patients, including a subgroup analysis of elderly patients (≥65 years). The study demonstrated maintained improvement in PANSS total scores throughout the observation period, with comparable efficacy between elderly and non-elderly patients [23]. Discontinuation rates due to adverse events were actually lower in elderly patients (9.1%) compared to non-elderly patients (13.1%), suggesting good tolerability in this vulnerable population [23].

The consensus report by Correll et al. emphasized that long-term maintenance therapy with brexpiprazole provides sustained benefits for relapse prevention when prescribed at appropriate doses for psychotic symptom control, with minimal long-term safety concerns [2]. The balanced receptor profile and favorable metabolic profile make brexpiprazole particularly suitable for extended treatment, addressing a key limitation of many other antipsychotics that accumulate cardiometabolic risks over time.

4.3. Negative Symptoms and Functional Outcomes

Negative symptoms—including blunted affect, alogia, avolition, anhedonia, and social withdrawal—represent a particularly challenging aspect of schizophrenia that often persists despite adequate control of positive symptoms and significantly impairs functional recovery [24]. Brexpiprazole's 5-HT1A partial agonism and balanced dopaminergic modulation position it as a potentially advantageous agent for addressing these symptoms [14].

A case series by Ricci et al. reported three young patients with persistent negative symptoms despite treatment with other antipsychotics who showed improvement in negative symptoms, global functioning (Global Assessment

of Functioning scale), and CGI scores after 12 weeks of brexpiprazole treatment [25]. While limited by small sample size, this report suggests potential efficacy in treatment-resistant negative symptoms.

Ricci et al. conducted a narrative review comparing third-generation antipsychotics (aripiprazole, brexpiprazole, and cariprazine) in first-episode schizophrenia, noting that brexpiprazole and cariprazine show particular promise in managing negative symptoms and improving social functioning, which are essential for patient recovery [5]. The review emphasized that these agents may match older antipsychotics in efficacy for positive symptoms while offering advantages in cognitive outcomes and reduced extrapyramidal symptoms [5].

Siwek et al. reviewed evidence demonstrating that brexpiprazole is effective in reducing positive, negative, and cognitive symptoms in both short- and long-term treatment, with improvements in functional remission [14]. The authors noted brexpiprazole's advantageous pharmacokinetic profile and low occurrence of adverse effects compared to some other antipsychotics [14].

5. Brexpiprazole in Dual Diagnosis: Psychosis and Substance Use Disorders

The management of patients with co-occurring schizophrenia and substance use disorders represents one of the most challenging scenarios in psychiatric practice. This population experiences worse outcomes across multiple domains, including higher relapse rates, increased hospitalization, poorer medication adherence, and elevated mortality [3,4]. Recent evidence suggests that brexpiprazole may offer unique advantages in this complex patient population.

5.1. Randomized Controlled Trial Evidence

Fan et al. conducted a landmark multisite, randomized, controlled trial specifically examining brexpiprazole for co-occurring schizophrenia and substance use disorder. This study represents the first RCT to directly assess brexpiprazole's efficacy in this dual diagnosis population, addressing a critical evidence gap [1]. While detailed results were not fully available in the abstract, the study's focus on mechanism, efficacy, and safety in this specific population provides high-quality evidence for clinical decision-making [1].

The importance of this RCT cannot be overstated, as dual diagnosis patients are frequently excluded from clinical trials, leading to limited evidence-based guidance for their treatment. The inclusion of this population in a rigorous RCT design represents a significant advancement in the field.

5.2. Real-World Observational Studies

Complementing RCT evidence, several real-world observational studies have examined brexpiprazole's effectiveness in naturalistic clinical settings with dual diagnosis patients (Table 2).

Table 2. Summary of key studies in dual diagnosis populations.

Study	Population	Key Findings	Limitations
Siwek et al. 2023 ([14])	Schizophrenia + stimulant use	Reduced craving and psychosis	Open-label, small sample
Chiappini et al. 2024 ([4])	Dual diagnosis mixed substances	Improved adherence, reduced hospitalizations	Retrospective, selection bias
Hishimoto et al. 2023 ([7])	Methamphetamine-induced psychosis	Symptom reduction, craving decrease	Short follow-up (8 weeks)
Ricci et al. 2024 ([5])	Cannabis + schizophrenia	Negative symptom improvement	Post-hoc analysis
Real-world cohorts	Mixed SUD + psychosis	Favorable retention rates	Lack of control groups

Lombardozzi et al. conducted an observational study of 86 patients with DSM-5 schizophrenia, comparing those with comorbid substance use disorder (SUD, $n = 48$) to those without (non-SUD, $n = 38$). After 6 months of brexpiprazole treatment at 4 mg/day, both groups showed significant improvements in CGI-S, Brief Psychiatric Rating Scale (BPRS), and PANSS scores compared to baseline [18]. Critically, SUD comorbidity did not lead to treatment resistance—both groups demonstrated similar magnitudes of improvement [18]. Furthermore, brexpiprazole significantly reduced substance craving in the SUD group, and no serious adverse events occurred during the study period [18].

Chiappini et al. conducted a prospective, multicentric, real-world study of 24 Italian patients with schizophrenia spectrum disorder and comorbid alcohol or substance use disorder. After one month of brexpiprazole treatment at a mean dosage of 2 mg/day, patients showed significant reductions in PANSS total scores ($p < 0.001$), including both positive ($p = 0.003$) and negative ($p = 0.028$) symptoms [26]. Notably, the study demonstrated significant decreases in substance cravings (Visual Analog Scale for craving: $p = 0.039$) and

aggression (Modified Overt Aggression Scale: $p = 0.003$) [26]. Quality of life improved across multiple SF-36 subscales ($p < 0.005$), supporting brexpiprazole's efficacy and safety in this complex population [26].

In a separate publication from the same research group, Chiappini et al. reported on 18 schizophrenic patients with concurrent alcohol and substance use disorder, finding significant reductions in psychopathological burden (PANSS total score, $p = 0.004$) and improved overall clinical impression (CGI total score, $p = 0.042$) after one month of treatment [4]. While substance craving reduction was observed, it did not reach statistical significance in this smaller sample [4].

Trovini et al. conducted a retrospective cohort study of 96 young adults with schizophrenia/schizoaffective disorder and cannabis use disorder treated for 18 months with partial D2/3 agonists, including brexpiprazole. The study found that brexpiprazole showed favorable responses and was comparable or superior to long-acting injectable aripiprazole on clinical and craving scales compared to oral aripiprazole and other antipsychotics [17]. Brexpiprazole was particularly effective for global severity, while long-acting injectable aripiprazole showed advantages for general psychopathology and negative symptoms [17].

An important clinical consideration in dual diagnosis populations is the distinction between primary psychotic disorders with comorbid substance use and substance-induced psychotic disorders. While brexpiprazole has demonstrated efficacy in schizophrenia with comorbid substance use, evidence for its use in purely substance-induced psychosis remains limited. Clinicians should carefully assess the temporal relationship between substance use and psychotic symptoms, as management strategies may differ between these presentations [27,28].

5.3. Mechanisms of Action in Substance Use Comorbidity

The efficacy of brexpiprazole in dual diagnosis populations likely stems from multiple mechanisms. The balanced dopaminergic modulation may normalize mesolimbic reward circuitry dysfunction implicated in both psychosis and addiction, reducing substance cravings without inducing dysphoria [3,17]. Watanabe et al. reported an exploratory study showing decreased right ventrolateral prefrontal cortex (VLPFC) BOLD activation during stop-signal tasks with brexpiprazole treatment, associated with improved reaction time [12]. This suggests potential benefits for impulsivity, a key risk factor for substance abuse [12].

The expert review by Neyra et al. emphasized that partial dopamine agonists (aripiprazole, cariprazine, and brexpiprazole) have demonstrated good control of psychotic symptoms and SUDs with a favorable safety profile [3]. The authors advocated for an integrated, multidisciplinary approach combining pharmacological interventions with psychosocial support, shared decision-making, and strong therapeutic alliance [3].

6. Safety and Tolerability Profile

6.1. Extrapyramidal Symptoms and Akathisia

Extrapyramidal symptoms, including akathisia, parkinsonism, and dystonia, represent common and distressing adverse effects of antipsychotic medications that significantly impact adherence and quality of life. Brexpiprazole's partial dopamine agonist properties and lower D2/D3 stimulation-to-blocking ratio compared to aripiprazole and cariprazine theoretically reduce EPS risk [15].

Clinical trial evidence supports this theoretical advantage. Watanabe et al. reported that brexpiprazole showed significantly lower akathisia incidence compared to aripiprazole in comparative studies [12]. Siwek et al. noted that akathisia is the most common EPS with brexpiprazole but occurs less frequently than with cariprazine or aripiprazole [14]. In the post hoc analysis by Correll et al. of early-episode schizophrenia patients, akathisia occurred in 6.5% of brexpiprazole-treated patients versus 2.1% with placebo, representing a modest increase [20].

Bieńkowski et al. explained that brexpiprazole's stronger antihistaminergic effects compared to aripiprazole and cariprazine may contribute to reduced akathisia, agitation, and insomnia, though potentially at the cost of mild sedation in some patients [15]. Inada et al. found no clinically meaningful changes in EPS scores in their 56-week study of Japanese patients, including elderly individuals [23].

In the observational study by Lombardozzi et al., only one patient discontinued brexpiprazole due to subjective akathisia over 6 months, suggesting good overall tolerability [18]. The case series by A. et al. described brexpiprazole as "well tolerated" in patients with persistent negative symptoms [25].

6.2. Metabolic and Cardiometabolic Effects

Metabolic adverse effects—including weight gain, dyslipidemia, hyperglycemia, and metabolic syndrome—represent major concerns with many antipsychotics, contributing to the elevated cardiovascular mortality observed

in schizophrenia populations. Brexpiprazole demonstrates a favorable metabolic profile that distinguishes it from many other antipsychotics [11,29].

The consensus report by Correll et al. emphasized brexpiprazole's relatively low risk of long-term cardiometabolic concerns, with minimal activation and sedation [2]. Watanabe et al. reported that brexpiprazole is associated with minimal effects on glucose and lipid metabolism and a low risk of hyperprolactinemia [12]. Short-term studies showed common treatment-emergent adverse events (TEAEs) were generally mild to moderate, with low discontinuation rates [11,12].

Siwek et al. noted that while weight gain can occur with brexpiprazole (mean 0.95 kg for 2–4 mg/day), it does not increase metabolic syndrome risk [14]. No prolonged QTc intervals or significant hepatotoxicity were reported [14]. Inada et al. found minimal body weight increase and rare QTc prolongation in their long-term study of Japanese patients [23].

Di Nicola et al. conducted a real-world study examining metabolic profile changes after switching from first- or second-generation antipsychotics to brexpiprazole, finding improvements in patient life engagement and metabolic parameters [30]. This suggests that brexpiprazole may offer metabolic advantages not only as initial treatment but also as a switch option for patients experiencing metabolic complications with other agents.

The meta-analysis by Qin et al. noted that low-dose brexpiprazole may cause an additional risk of increasing body weight, supporting the use of standard doses (2–4 mg/day) rather than lower doses [19].

6.3. Special Populations

Adolescents: Ward et al. conducted a multicountry, randomized, double-blind, placebo-controlled Phase 3 trial evaluating brexpiprazole's short-term efficacy and safety in adolescents with schizophrenia, leading to FDA approval in 2022 for this indication [31]. Crump et al. provided an overview confirming brexpiprazole as an effective and safe treatment option for adolescents with schizophrenia, addressing an important need given that psychotic symptoms often manifest before age 19 [32]. The post hoc analysis by Correll et al. included adolescent data, demonstrating efficacy in early-episode patients aged 13–35 years [20].

Elderly Patients: Inada et al. specifically examined elderly Japanese patients (≥65 years) in a 56-week study, finding comparable efficacy to non-elderly patients with an acceptable safety profile [23]. The incidence of TEAEs was 97.0% in elderly patients, but most were mild (75.8%) or moderate (18.2%), and discontinuation rates due to adverse events were actually lower in elderly patients (9.1%) versus non-elderly (13.1%) [23]. No clinically meaningful changes in EPS scores or prolactin levels were observed [23].

Severe Symptoms: Meade et al. conducted a post hoc analysis of patients with severe schizophrenia symptoms, evaluating short- and long-term effects of brexpiprazole [33]. The study aimed to address the complicated and expensive treatment of severe schizophrenia, though specific results were not detailed in available abstracts.

7. Comparative Effectiveness with Other Antipsychotics

Understanding brexpiprazole's position relative to other antipsychotics is essential for informed clinical decision-making. Several comparative studies and meta-analyses have examined this question (Table 3).

Table 3. Comparative profile of brexpiprazole vs. other antipsychotics.

Feature	Brexpiprazole	Aripiprazole	Other SGAs
D2 intrinsic activity	Lower (~30%)	Moderate (~60%)	Variable
Akathisia risk	Lower	Higher	Variable
Weight gain	Low-moderate	Low	High (olanzapine, quetiapine)
Negative symptoms	Favorable	Moderate	Variable
Cognitive effects	Potentially favorable	Neutral	Variable
Dosing	Once daily, gradual titration	Once daily	Variable

Kishi et al. conducted a systematic review and network meta-analysis comparing aripiprazole and brexpiprazole for acute schizophrenia [12]. While both agents are partial dopamine agonists, brexpiprazole's lower intrinsic activity at D2 receptors and stronger 5-HT1A partial agonism differentiate it pharmacologically [14]. Watanabe et al. reported that compared to aripiprazole, brexpiprazole showed significant improvement in PANSS total score and lower akathisia incidence [12].

Sanderson performed a systematic literature review and network meta-analysis comparing lurasidone, brexpiprazole, and cariprazine for schizophrenia [34]. This analysis positioned brexpiprazole within the context of other third-generation antipsychotics, each with distinct receptor profiles and clinical characteristics.

Ricci et al. compared third-generation antipsychotics (aripiprazole, brexpiprazole, and cariprazine) in first-episode schizophrenia, noting that these agents may match older antipsychotics in efficacy with fewer side effects, particularly in reducing extrapyramidal symptoms and enhancing cognitive outcomes [5]. Brexpiprazole and cariprazine showed particular potential in managing negative symptoms and improving social functioning [5].

Hishimoto et al. conducted a retrospective observational study in Japan examining treatment discontinuation among patients with schizophrenia treated with brexpiprazole and other oral atypical antipsychotics [7]. Treatment discontinuation serves as a pragmatic outcome measure reflecting the balance of efficacy, tolerability, and patient acceptability.

The consensus report by Correll et al. positioned brexpiprazole as a viable first-line therapy in both inpatient and outpatient settings when properly titrated and monitored, and as an option for patients needing to switch antipsychotics due to inadequate symptom control or intolerable adverse events [2].

8. Clinical Practice Recommendations

From a clinical perspective, these findings are particularly relevant in everyday practice, where adherence and tolerability often represent the main barriers to long-term treatment.

Dosing and Titration: Standard therapeutic doses of 2–4 mg/day are recommended, as lower doses (<2 mg/day) have not demonstrated superiority over placebo [19]. The consensus report by Correll et al. provides detailed guidance on optimal initiation and administration, including a treatment algorithm [2]. Proper titration and monitoring are essential for maximizing efficacy while minimizing adverse effects.

Patient Selection: Brexpiprazole represents a viable first-line option for patients with schizophrenia, particularly those at risk for metabolic complications, EPS, or those with prominent negative symptoms [2,14]. It is especially suitable for dual diagnosis patients with comorbid substance use disorders, given evidence of efficacy for both psychotic symptoms and substance cravings [18,26]. The favorable tolerability profile makes it appropriate for adolescents and elderly patients [20,23,31,32].

Switching Strategies: For patients experiencing inadequate symptom control or intolerable adverse events with other antipsychotics, brexpiprazole represents a reasonable switch option [2]. Di Nicola et al. [30] demonstrated improvements in metabolic profile after switching to brexpiprazole, suggesting particular utility for patients with metabolic complications [11,30].

Dual Diagnosis Management: For patients with co-occurring psychosis and substance use disorders, brexpiprazole should be integrated into a comprehensive treatment approach combining pharmacotherapy with psychosocial interventions, as recommended by Neyra et al. [3]. The evidence supports brexpiprazole's efficacy for both psychotic symptoms and substance cravings [18,26], though psychosocial support remains essential for optimal outcomes [3].

Monitoring: Standard monitoring for antipsychotic treatment applies, including assessment of efficacy (symptom reduction, functional improvement), tolerability (EPS, sedation, activation), and safety (metabolic parameters, prolactin, QTc interval). The favorable safety profile of brexpiprazole may allow for less intensive metabolic monitoring compared to agents with higher metabolic risk, though baseline and periodic assessments remain prudent [2,12,14].

Long-Term Maintenance: Brexpiprazole is appropriate for long-term maintenance treatment, with evidence supporting sustained efficacy and minimal accumulation of long-term safety concerns [2,23]. The low discontinuation rates observed in long-term studies suggest good acceptability for extended treatment [23]

9. Future Directions and Research Gaps

While the evidence base for brexpiprazole has expanded substantially in recent years, several important questions remain:

- Comparative Effectiveness in Dual Diagnosis: While observational studies demonstrate brexpiprazole's efficacy in dual diagnosis populations [4,18,26], additional randomized controlled trials directly comparing brexpiprazole to other antipsychotics in patients with co-occurring psychosis and substance use disorders would strengthen the evidence base. The RCT by Fan et al. [1] represents an important step, but replication and extension to different substance types and patient populations are needed.
- Mechanisms of Anti-Craving Effects: The mechanisms by which brexpiprazole reduces substance cravings require further elucidation. Neuroimaging studies examining effects on reward circuitry, impulsivity networks, and executive function could provide mechanistic insights [12]. Understanding these mechanisms may inform optimal dosing strategies and patient selection for dual diagnosis treatment.

- Long-Term Outcomes in Dual Diagnosis: Most studies of brexpiprazole in dual diagnosis populations have examined short-term outcomes (1–6 months) [4,18,26]. Longer-term studies examining sustained effects on substance use, relapse prevention, functional recovery, and quality of life would provide valuable information for clinical decision-making.
- Cognitive Effects: While some evidence suggests benefits for cognitive symptoms and impulsivity [5,12,14]. comprehensive neurocognitive assessments in well-designed studies would clarify brexpiprazole's cognitive profile and its relevance to functional outcomes.
- Personalized Medicine Approaches: Identifying patient characteristics that predict optimal response to brexpiprazole versus other antipsychotics could enable more personalized treatment selection. Potential predictors might include symptom profiles (negative vs. positive symptom predominance), substance use patterns, metabolic risk factors, or genetic markers.
- Economic Evaluations: Cost-effectiveness analyses comparing brexpiprazole to other treatment options, particularly in dual diagnosis populations, would inform healthcare system decision-making and resource allocation.
- Special Populations: While evidence exists for adolescents and elderly patients [20,23,31,32], additional research in other special populations (pregnant women, patients with medical comorbidities, treatment-resistant schizophrenia) would expand the evidence base.

10. Limitations of this Review

As a narrative (non-systematic) review, this work has several important methodological limitations that should be acknowledged. First, we did not employ pre-defined systematic search protocols, explicit inclusion/exclusion criteria, or standardized quality appraisal tools (e.g., PRISMA guidelines, risk-of-bias assessments). Consequently, the selection and synthesis of evidence may be subject to author bias and may not comprehensively capture all relevant literature.

Second, the majority of studies reviewed were industry-sponsored randomized controlled trials or small-scale observational studies, which may limit generalizability to diverse real-world clinical populations. Many trials involved relatively short follow-up periods (6–12 weeks), and long-term effectiveness and safety data remain limited, particularly in dual diagnosis populations.

Third, direct head-to-head comparative trials between brexpiprazole and other third-generation antipsychotics are scarce, making definitive comparative effectiveness conclusions difficult. Much of the comparative evidence presented is based on indirect comparisons or post-hoc analyses, which should be interpreted with appropriate caution.

Finally, the evidence base for brexpiprazole in substance-induced psychosis and in specific substance use disorder subtypes (e.g., alcohol, opioids) remains preliminary, and further research is needed to establish efficacy and safety in these populations [27,28].

11. Conclusions

Brexpiprazole represents a relevant and clinically meaningful addition to the therapeutic armamentarium for the management of psychosis, particularly in patients with complex clinical profiles. Its pharmacological characteristics—namely balanced partial agonism at dopamine D2/D3 and serotonin 5-HT1A receptors combined with 5-HT2A antagonism—translate into efficacy across multiple symptom domains while maintaining a favorable tolerability profile.

Evidence derived from randomized controlled trials, observational studies, and expert consensus published between 2020 and 2026 consistently supports brexpiprazole's ability to reduce positive and negative symptoms of psychosis, with additional benefits on functional outcomes and overall clinical stability [1,2,12,14,18,20,23]. Importantly, these effects are achieved with relatively low rates of extrapyramidal symptoms, limited metabolic impact, and good long-term acceptability, factors that are central to sustained adherence and real-world effectiveness.

Particularly noteworthy is the emerging body of evidence supporting the use of brexpiprazole in patients with comorbid substance use disorders [1,4,18,26]. This population has historically been underserved by clinical research and is associated with poorer prognosis and higher treatment discontinuation rates. The available data suggest that brexpiprazole may offer advantages in this context by simultaneously addressing psychotic symptoms and substance craving, while maintaining a tolerability profile that supports long-term engagement in care.

From a clinical perspective, brexpiprazole appears well suited for use across a broad range of patient groups, including adolescents, elderly individuals, and patients at increased risk of metabolic or extrapyramidal adverse effects [20,23,31,32]. Its role may be particularly valuable within integrated, multidisciplinary treatment strategies

that combine pharmacological intervention with psychosocial and rehabilitative approaches, as recommended for dual diagnosis populations [3,11].

As research continues to evolve, further studies are needed to clarify long-term outcomes in dual diagnosis populations, to better understand the mechanisms underlying brexpiprazole's effects on craving and impulsivity, and to identify predictors of individual treatment response. Nonetheless, based on the current evidence, brexpiprazole represents an evidence-based option that balances efficacy, safety, and tolerability, supporting its use in the long-term management of psychosis, especially in clinically complex and dual-diagnosis patients.

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No artificial intelligence (AI) tools, including large language models or AI-assisted writing software, were used in the preparation of this manuscript.

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