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REVIEW

Novel pharmaceutical treatment approaches for schizophrenia: a systematic literature review

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Abstract

Purpose Schizophrenia is a chronic and debilitating neuropsychiatric disorder affecting approximately 1% of the global population. Traditional antipsychotic treatments, while effective for positive symptoms, often have significant side effects and fail to address cognitive and negative symptoms. Novel pharmacological treatments targeting muscarinic receptors, TAAR1 agonists, serotonergic pathways, and glutamate modulation have emerged as promising alternatives.

Aim This systematic literature review aims to critically evaluate the efficacy, safety, and mechanisms of action of novel pharmacological agents in the treatment of schizophrenia.

Methods A comprehensive search was conducted across PubMed, Embase, Cochrane Library, Scopus, and Web of Science for randomized controlled trials (RCTs) and clinical trials published between April 2014 and March 2024. Studies evaluating novel treatments targeting muscarinic receptors, TAAR1 agonists, serotonergic agents, and glutamate modulation were included. Primary outcomes focused on symptom reduction and quality of life, while secondary outcomes included cognitive function and adverse events. The Joanna Briggs Institute (JBI) tool was used for quality assessment.

Results Eleven studies involving 4614 participants (mean age 37–43 years, predominantly male) were included. Drugs evaluated included xanomeline-trospium (KarXT), pimavanserin, ulotaront, emraclidine, and bitopertin. Significant improvements in PANSS and CGI-S scores were observed, with xanomeline-trospium showing a mean reduction of 17.4 points ($p < 0.001$). Adverse events were mostly mild and transient, with nausea, constipation, and somnolence being common.

Conclusion Novel treatments for schizophrenia show promise in managing both positive and negative symptoms, with generally favorable safety profiles. Future studies should focus on large-scale, long-term trials to refine their efficacy, safety, and clinical applicability.

Keywords Schizophrenia treatment · Novel pharmacological agents · Antipsychotic medications · Muscarinic receptor agonists · TAAR1 agonists · Cognitive and negative symptoms · Systematic review

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Introduction

Schizophrenia is a chronic and severe neuropsychiatric disorder that affects approximately 1% of the global population [1]. It is characterized by a range of debilitating symptoms, including hallucinations, delusions, disorganized thinking, and significant cognitive and emotional disturbances. This complex condition can severely impair daily functioning, social interactions, and overall quality of life, often leading to long-term disability [2]. Despite substantial advances in our understanding of the disease, schizophrenia remains one of the most challenging psychiatric disorders to treat, with many patients experiencing poor responses to current therapies [3, 4].

Traditional antipsychotic drugs, which primarily target dopaminergic receptors, have been the cornerstone of schizophrenia treatment for decades. First-generation (typical) antipsychotics, such as haloperidol, chlorpromazine, and fluphenazine, are primarily dopamine D2 receptor antagonists [5]. While effective in treating positive symptoms such as hallucinations and delusions, these medications are often associated with significant side effects, including extrapyramidal symptoms (EPS), sedation, weight gain, metabolic disturbances, and hyperprolactinemia [6]. These adverse effects not only reduce medication adherence but also contribute to high rates of relapse and diminished quality of life for patients. Second-generation (atypical) antipsychotics, including risperidone, olanzapine, quetiapine, aripiprazole, and clozapine, offer a broader receptor profile that modulates both dopaminergic and serotonergic systems [7] (Table 1). While they tend to have a more favorable side effect profile compared to first-generation drugs, second-generation antipsychotics still fall short in addressing all symptom categories. Additionally, up to one-third of patients with schizophrenia do not respond adequately to these conventional treatments, and many continue to suffer from residual symptoms, including persistent cognitive impairments and negative symptoms [8, 9].

The pathophysiology of schizophrenia is multifactorial, involving dysregulation across various neurotransmitter systems. While the dopamine hypothesis has been a central focus for many years, recent research suggests that other systems—such as the glutamatergic, cholinergic, serotonergic, and trace amine-associated receptor (TAAR1) pathways—also play significant roles in the disorder [10] (Table 2). Abnormalities in the glutamatergic system, particularly N-methyl-D-aspartate receptor (NMDAR) hypofunction, are linked to both positive and negative symptoms of schizophrenia [11]. This has led to the exploration of drugs that target glutamatergic neurotransmission to alleviate cognitive and negative symptoms, areas where current antipsychotic treatments are often ineffective [12].

One novel class of drugs gaining attention for schizophrenia treatment includes muscarinic acetylcholine receptor agonists. These compounds, such as xanomeline, act by stimulating M1 and M4 muscarinic receptors, which have been implicated in the regulation of cognitive and psychotic symptoms [13]. Xanomeline, for instance, has demonstrated promising results in clinical trials for Alzheimer's disease and schizophrenia, producing greater reductions in psychotic symptoms than placebo. However, the use of xanomeline has been limited by dose-dependent cholinergic side effects, including nausea and diarrhea [14]. Combining xanomeline with trospium chloride, a muscarinic receptor antagonist, has shown potential for mitigating these adverse effects, thus offering a more tolerable approach for patients [15, 16].

Table 1 Traditional medications (first- and second-generation antipsychotic drugs)

Class	First-generation antipsychotics (FGAs)	Second-generation antipsychotics (SGAs)
Introduction	Mid-twentieth century	Clozapine was introduced in the 1970s, while other SGAs emerged in the 1990s
Common drugs	Chlorpromazine, haloperidol, fluphenazine	Clozapine (older than other SGAs), olanzapine, risperidone, quetiapine, aripiprazole, ziprasidone
Mechanism of action	Block dopamine D2 receptors in the brain's mesolimbic system	Block dopamine D2 receptors and serotonin (5-HT2A) receptors
Side effects	Wide side effect profile including effects on serotonin, histamine, and alpha-adrenergic receptors	Wide range of adverse effects, including weight gain, dyslipidemia, hyperglycemia, sedation, and others. Agranulocytosis (primarily seen with clozapine)
Advantages	Reduction of positive symptoms (hallucinations, delusions)	Reduction of positive symptoms, improvement in overall functioning, and poor affinity for other receptors (e.g., aripiprazole has a unique profile)
Drawbacks	Poor response to negative symptoms, broad side effect profile	Wide range of adverse reactions (especially with olanzapine) and metabolic side effects. Differences in pharmacologic profiles (e.g., aripiprazole has partial agonist activity at D2 receptors, unlike other SGAs)

Table 2 Comparison of novel and traditional pharmacological treatments for schizophrenia

Category	Dopaminergic receptors (e.g., first- and second-gen antipsychotics)	Trace amine–associated receptors (e.g., ulotaront)	Muscarinic acetylcholine receptors (e.g., emraclidine, xanomeline + trospium)	Serotonergic receptors (e.g., pimavanserin)	Glutamatergic receptors (e.g., iclepertin)
Mechanism of action	Antagonists and partial agonists	Agonist	M4 positive allosteric modulator (emraclidine); M1/M4 agonist (xanomeline)	Serotonin 2A inverse agonist/antagonist	Glycine-transporter-1 inhibitor
Efficacy profile	Improvements in total psychopathology, especially positive symptoms Ψ Improvements in negative symptoms of SCZ	Improvements in total psychopathology, especially positive symptoms Ψ Improvements in negative symptoms of SCZ	Improvements in total psychopathology, especially positive symptoms Ψ Improvements in negative symptoms of SCZ Improvements in cognitive dysfunction	Improvements in negative symptoms of SCZ	Improvements in cognitive dysfunction of SCZ No significant improvement in functional outcome
Tolerability and side effect profile	Side effects related to postsynaptic dopamine receptor blockade: Somnolence/sedation or insomnia, cardiometabolic side effects	Somnolence, agitation, nausea (< 7% each)	Emraclidine: Headache (30%), dry mouth, nausea (7–11%) Xanomeline/trospium: Procholinergic side effects: nausea, vomiting (14–19%), anticholinergic side effects (15–17%)	Headache, somnolence (5–6%)	Headache, GI side effects, somnolence (6–11%)
Other points to consider	Largely ineffective for negative and cognitive symptoms of SCZ in stable patients	Minimal weight gain, no observed cardiometabolic or EPS effects, no prolactin elevation	Minimal weight gain, no observed cardiometabolic or EPS effects, no prolactin elevation	Minimal weight gain, no observed cardiometabolic or EPS effects, no prolactin elevation	Minimal weight gain, no observed cardiometabolic or EPS effects, no prolactin elevation

Key:

- *SCZ*, schizophrenia
- *EPS*, extrapyramidal side effects
- *Ψ*, data in acutely exacerbated patients with SCZ
- *Based on Phase II studies*
- Based on Phase II and Phase III studies

Another emerging class of drugs involves TAAR1 agonists, such as ulotaront (SEP-363856), which are designed to modulate the activity of TAAR1 receptors [17]. These receptors are found in brain regions involved in dopaminergic, serotonergic, and glutamatergic transmission. Unlike traditional antipsychotics, ulotaront does not rely on D2 receptor antagonism for its efficacy, making it a novel approach to treating schizophrenia [18]. Preclinical and clinical studies suggest that ulotaront improves both positive and negative symptoms of schizophrenia, with a favorable side effect profile compared to existing antipsychotics [19].

The serotonergic system is another key target in the development of novel antipsychotic medications. Pimavanserin, a selective serotonin 5-HT2A receptor inverse agonist, is one of the most well-researched drugs in this category [20]. Unlike traditional antipsychotics, pimavanserin primarily modulates serotonin receptors, making it effective in treating psychosis in patients with Parkinson's disease and demonstrating potential benefits in schizophrenia [21]. Pimavanserin's ability to improve negative symptoms without exacerbating cognitive dysfunction or causing significant motor side effects sets it apart from conventional treatments [22].

Glutamate modulation is also a promising avenue for drug development. Glutamate dysfunction, particularly involving NMDAR hypofunction, is believed to contribute to the cognitive and negative symptoms of schizophrenia [23]. Drugs such as iclepertin, a positive allosteric modulator of NMDARs, have been shown to enhance glutamatergic signaling, potentially improving cognition and reducing psychotic symptoms [24]. In addition, the inhibition of the glycine transporter 1 (GlyT1) has garnered attention as a strategy to boost glutamate transmission by increasing synaptic glycine levels, which are critical for NMDAR activation [25]. Clinical trials of GlyT1 inhibitors, such as bitopertin and BI 425809, have shown promise in addressing cognitive deficits and negative symptoms, although results remain inconsistent [26].

Despite the considerable progress in developing these novel classes of drugs, significant gaps in the literature remain. While early-phase trials have highlighted the potential efficacy of muscarinic agonists, TAAR1 modulators, serotonergic agents, and glutamatergic enhancers, the long-term safety and efficacy of these treatments are still not well-established [27]. Moreover, many of these agents have yet to demonstrate superiority over existing treatments in large-scale, head-to-head clinical trials. The lack of effective treatments for cognitive and negative symptoms remains a major unmet need, and many of the new pharmacological strategies have not yet been thoroughly explored in this context.

The goal of this systematic literature review is to critically evaluate the current evidence regarding these novel pharmacological agents in the treatment of schizophrenia. By examining the mechanisms of action, clinical efficacy, and safety profiles of muscarinic receptor agonists, TAAR1 agonists, serotonergic agents, and glutamate modulators, we aim to provide a comprehensive overview of their potential as next-generation treatments. Furthermore, this review seeks to identify the existing gaps in the literature, highlighting areas that require further research and development. Ultimately, the findings from this review will contribute to the understanding of new therapeutic approaches for schizophrenia, with the hope of improving patient outcomes, reducing side effects, and addressing the unmet needs of those suffering from this complex disorder.

Methodology

Search strategy

A comprehensive search strategy was developed to identify relevant studies published between April 2014 and March 2024. The following major electronic databases were utilized: PubMed, Embase, Cochrane Library, Scopus, and Web of Science. The search strategy was designed to identify randomized controlled trials (RCTs) and clinical trials that assessed novel pharmacological treatments for schizophrenia. Boolean operators and Medical Subject Headings (MeSH) terms were employed to refine the search process. The key search terms included the following: (Psychosis OR Schizophrenia) AND (Pharmacotherapy OR Antipsychotic OR Medication) AND (Novel OR New OR Recent) AND (Clinical Trials OR Randomized Controlled Trials OR Efficacy OR Safety). The use of these terms ensured that relevant articles evaluating novel pharmacological therapies and comparing them with traditional treatments, including first- and second-generation antipsychotics, were identified. The search was limited to studies published in English to ensure language consistency and relevance. Furthermore, to maximize coverage, the reference lists of included articles, as well as pertinent review papers, were manually searched.

Eligibility criteria

The inclusion criteria for this systematic review were as follows:

(1) Population: Studies involving adult patients (18 years and older) diagnosed with schizophrenia, irrespective of gender, race, or other demographic characteristics
(2) Intervention: Studies evaluating novel pharmaceutical treatments for schizophrenia, including muscarinic receptor agonists, TAAR1 agonists, serotonin receptor antagonists, and drugs targeting glutamate modulation
(3) Comparison: Studies comparing the efficacy of novel pharmaceutical treatments with traditional antipsy-

chotic drugs, both first-generation (e.g., haloperidol, chlorpromazine) and second-generation (e.g., risperidone, olanzapine, clozapine)
(4) Outcome measures: Studies that report on the efficacy and safety profiles of novel treatments relative to traditional therapies, such as symptom reduction, adverse effects, quality of life, or other relevant therapeutic outcomes
(5) Study type: Only peer-reviewed original research articles were included, specifically RCTs, cohort studies, and case–control studies
(6) Publication date: Studies published between April 2014 and March 2024
(7) Language: Studies published in English

Exclusion criteria were:

(1) Non-relevant treatments: Studies that did not evaluate novel pharmacological treatments for schizophrenia, including those focused solely on psychological or non-pharmacological interventions
(2) Study design: Studies that were not original research (e.g., reviews, meta-analyses, editorial opinions) or lacked reliable efficacy and safety data (e.g., studies without control groups)
(3) Language: Studies published in languages other than English
(4) Publication date: Studies published before April 2014
(5) Quality of research: Studies with a high risk of bias, small sample sizes, or unreliable data.
(6) Irrelevant outcomes: Studies that did not assess the comparative efficacy and safety of novel treatments
(7) Focus on pharmacological innovations: Studies not addressing novel therapeutic targets or pharmacological innovations in schizophrenia treatment

Study selection

The study selection process followed the PRISMA guidelines, adopting a two-tier screening approach. Initially, all retrieved articles were screened based on their titles and abstracts to determine whether they met the eligibility criteria. Studies that passed the initial screening were then subjected to a full-text review. During this second stage, detailed evaluations were performed to ensure the studies met the inclusion and exclusion criteria. Research that compared novel pharmacological treatments with traditional antipsychotics, including studies that utilized established diagnostic criteria (DSM-5 or ICD-11), was prioritized. Studies focusing on psychological or non-pharmacological interventions, as well as those without a control group, were excluded. Data on schizophrenia symptoms, adverse effects, hospitalization rates, and quality of life were prioritized as primary outcomes, while secondary outcomes included cognitive function and adherence rates.

Data extraction and primary/secondary outcomes

Data extraction was performed independently by two authors (AJ and WQ) to minimize errors and biases. Discrepancies were resolved through discussion and consultation with a third reviewer (MK). Key information was extracted from each study, including the study's objective (effectiveness of interventions), design, participant details (sample size, demographic information), outcomes measured, and the type of interventions used. Primary outcomes focused on the efficacy and safety of novel pharmacological agents, including symptom reduction (e.g., PANSS scores), adverse effects, and improvements in quality of life. Secondary outcomes included cognitive function, hospitalization rates, and medication adherence. The information gathered also included details on how each study assessed these outcomes (e.g., scales used, assessment time points).

Data synthesis and risk of bias assessment

Data synthesis involved a qualitative synthesis of the findings from the included studies. Due to the diversity in study designs and outcomes measured, a meta-analysis was not conducted. Instead, the results were presented narratively to highlight trends and differences between novel treatments and traditional therapies. The risk of bias within studies was assessed using the Joanna Briggs Institute (JBI) critical appraisal tools, which evaluate factors such as randomization, blinding, and potential conflicts of interest. All included studies employed random assignment and double-blind designs, which were important to ensure internal validity. The overall certainty of evidence for each outcome was determined based on the risk of bias and the consistency of findings across studies (Table 3).

Results

Characteristics of the included studies

A systematic search was conducted across multiple databases, yielding 227 records. After removing 129 duplicates, 98 records were screened for relevance. Of these, 44 studies underwent full-text review. Eleven studies were excluded due to language restrictions ($n = 11$), irrelevant titles and abstracts ($n = 43$), or insufficient methodological quality ($n = 24$). Nine studies were excluded because they did not focus on novel treatments for schizophrenia. Ultimately, 11 studies met the inclusion criteria and were included in the review. These studies were assessed for their relevance to

Table 3 JBI risk of bias tool assessment table for the 11 studies

Author and year	Study design	Random sequence generation	Allocation concealment	Blinding	Incomplete outcome data	Selective reporting	Other biases	Risk of bias
Brannan et al. 2021	Double-blind, RCT, phase 2 trial	Low risk	Low risk	Low risk	Low risk	Low risk	No major concerns	Low bias
Kaul et al. 2024	Phase 3, multicenter, RCT	Low risk	Low risk	Low risk	Low risk	Low risk	No major concerns	Low bias
Sauder et al. 2022	Randomized, double-blind, phase 2	Low risk	Low risk	Low risk	Low risk	Low risk	No major concerns	Low bias
Correll et al. 2022	Randomized, double-blind, phase 2	Low risk	Low risk	Low risk	Low risk	Low risk	No major concerns	Low bias
Krystal et al. 2022	Double-blind, phase 1b trial	Low risk	Low risk	Low risk	Low risk	Low risk	No major concerns	Low bias
Darwish et al. 2022	Phase 2, RCT, exposure–response	Low risk	Low risk	Low risk	Low risk	Low risk	No major concerns	Low bias
Bugarski-Kirola et al. 2021	Phase 2, 26-week, RCT	Low risk	Low risk	Low risk	Low risk	Low risk	No major concerns	Low bias
Correll et al. 2021	Open-label extension of RCT	Low risk	Low risk	Low risk	Low risk	Low risk	No major concerns	Low bias
Umbricht et al. 2015	Randomized, double-blind, phase 2	Low risk	Low risk	Low risk	Low risk	Low risk	No major concerns	Low bias
Fleischhacker et al. 2021	Phase 2, randomized, RCT	Low risk	Low risk	Low risk	Low risk	Low risk	No major concerns	Low bias
Bugarski-Kirola et al. 2016	Phase 3, RCT, multicenter	Low risk	Low risk	Low risk	Low risk	Low risk	No major concerns	Low bias

the use of novel treatments in schizophrenia management, following the PRISMA guidelines for systematic reviews (Fig. 1).

Participant characteristics and baseline data

A total of 4614 participants across 11 studies were included in our review. The studies comprised randomized, double-blind, placebo-controlled trials, with a few phase 2 and phase 3 designs. The mean age ranged from 37 to 43 years, with a predominantly male sample (ranging from 61.4 to 81.3%). Participants had a history of schizophrenia, often with negative symptoms and ongoing antipsychotic treatment. The intervention groups primarily included novel treatments such as xanomeline-trospium, pimavanserin, KarXT, emraclidine, bitopertin, and ulotaront, compared to placebo. Baseline PANSS scores ranged from 60 to 96. The CGI-S scores were commonly reported, showing improvements with novel treatments. Common adverse events included nausea, constipation, headache, somnolence, and insomnia, with some reports of weight gain and gastrointestinal issues. Key outcomes showed significant improvements in PANSS and CGI-S scores, with mild to moderate adverse events, generally transient and manageable (Table 4).

Mechanisms of action and pharmacological profiles

Muscarinic receptor agonists and TAAR1 agonists

A key focus of recent research into schizophrenia treatment has been the development of muscarinic receptor agonists and TAAR1 (trace amine–associated receptor 1) agonists, which represent novel mechanisms of action. The pharmacological effects of xanomeline, a muscarinic receptor agonist, have been studied in combination with trospium to mitigate side effects. Xanomeline acts on muscarinic receptors, particularly M1 and M4 subtypes, which are implicated in cognitive and psychotic symptom regulation in schizophrenia. Brannan et al. (2021) and Kaul et al. (2024) both studied xanomeline-trospium (KarXT), revealing its potential to improve schizophrenia symptoms significantly. Brannan et al. (2021) demonstrated that xanomeline-trospium led to a mean reduction of 17.4 points in the PANSS total score, a significant improvement compared to the 5.9-point reduction

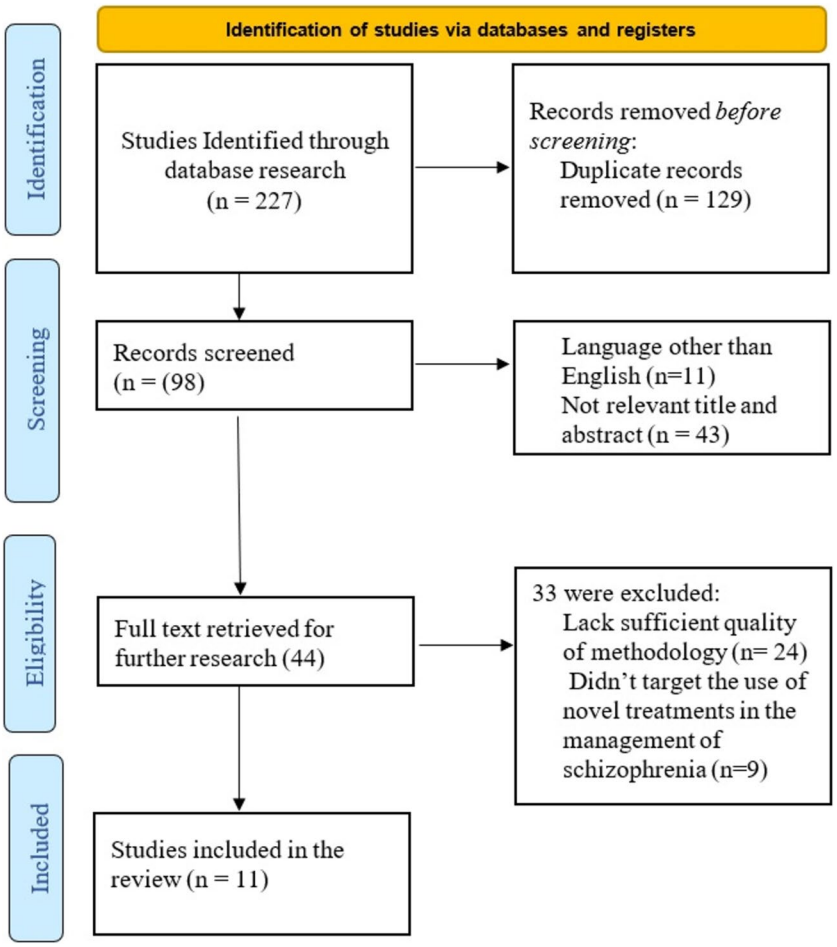

Fig. 1 Schematic diagram elaborating the selection of the studies

in the placebo group ($p < 0.001$) [28]. This was further supported by Kaul et al. (2024), which observed a reduction of 8.4 points ($p < 0.001$) in PANSS total scores. Both studies indicate that xanomeline-trospium has a therapeutic effect through muscarinic receptor modulation, primarily improving both positive and negative symptoms [29]. In addition to its antipsychotic efficacy, KarXT is hypothesized to offer a safer profile than traditional antipsychotics, with no exacerbation of extrapyramidal symptoms (EPS) and minimal changes to the QTc interval, as observed in both studies. Furthermore, Correll et al. (2022) and Sauder et al. (2022) found that KarXT improved cognitive performance as measured by the MATRICS Consensus Cognitive Battery, with a 0.27-point improvement compared to placebo, indicating its promise as a cognitive enhancer [30, 31].

The role of TAAR1 agonists in schizophrenia treatment is being explored as well, although fewer studies have focused specifically on their impact in comparison to muscarinic receptor modulation. While emraclidine (a selective M4 agonist) has demonstrated promising results in other studies, it is generally less advanced in clinical development compared to xanomeline-trospium. As a TAAR1 agonist, emraclidine enhances dopaminergic signaling, which theoretically should improve cognitive and negative symptoms. However, the Krystal et al. (2022) study on emraclidine was focused more on safety and tolerability, and it did not show significant improvements in cognitive or symptom measures compared to a placebo. Despite this, it remains an area of growing interest due to its unique mechanism [32].

Serotonergic agents and glutamate modulators

Pimavanserin and bitopertin represent two key serotonergic agents and glutamate modulators studied for their impact on schizophrenia. Pimavanserin, a 5-HT2A inverse agonist, was studied by Bugarski-Kirola et al. (2021) and Darwish et al. (2022) in patients with predominantly negative symptoms [33, 34]. This study demonstrated a modest but statistically significant reduction in negative symptoms measured by the NSA-16 scale ($p = 0.043$), with an improvement of 10.4 points compared to 8.5 points in the placebo group. However, the small effect size (0.211) suggested that while pimavanserin shows some efficacy in managing negative symptoms, its overall impact remains limited compared to other interventions.

Table 4 Data extracted from the included studies

Author name and year	Study design	Participant characteristics	Intervention vs. control group	PANSS score	CGI-S score	Adverse events reported	Key findings
Brannan et al. 2021	Double-blind, phase 2 trial, randomized controlled trial (RCT)	182 (90 xanomeline-trospium group, 92 placebo group) Xanomeline has antipsychotic properties; trospium is a muscarinic receptor antagonist	Xanomeline (up to 125 mg twice daily) combined with trospium (up to 30 mg twice daily) versus placebo	Xanomeline-trospium group: − 17.4; placebo group: − 5.9 (least-squares mean difference: − 11.6, $p < 0.001$)	Categorical distribution favored xanomeline-trospium ($p < 0.001$)	Common in xanomeline-trospium group: constipation (17%), nausea (17%), dry mouth (9%), dyspepsia (9%), vomiting (9%) Incidences of somnolence, weight gain, weight gain: 3% (xanomeline-trospium) vs. 4% (placebo)	Xanomeline-trospium resulted in significantly greater improvement in PANSS total score compared to placebo ($p < 0.001$)
Kaul et al. 2024	Phase 3, multicenter, randomized, double-blind, placebo-controlled	Total screened: 431; total randomized: 256 (125 xanomeline-trospium, 131 placebo) Mean age: 43.1 years (SD 11.8); gender: 74.6% male (191/256);	Xanomeline-trospium chloride (maximum dose xanomeline 125 mg, trospium 30 mg) versus placebo	PANSS total score: at week 5, xanomeline-trospium reduced PANSS total score by − 20.6 (vs − 12.2 for placebo). Least squares mean difference: − 8.4 ($p < .001$)	Clinical global impression–severity (CGI-S): − 0.5 ($p < .001$)	-Nausea: 19.2% -Dyspepsia: 16.0% -Vomiting: 16.0% -Constipation: 12.8% -Hypertension: 6.4% -Diarrhea: 5.6% Serious AE: 1 case of gastroesophageal reflux disease in xanomeline-trospium group	-Xanomeline-trospium showed statistically significant improvements in PANSS scores compared with placebo -Adverse events were mild to moderate, transient, and mostly cholinergic (nausea, vomiting, etc.)
Sauder et al. 2022	Randomized, double-blind, placebo-controlled phase 2 trial (EMERGENT-1)	Total number of patients: 125 (60 in KarXT group, 65 in placebo group) Patients with schizophrenia, with cognitive impairment or minimal impairment based on baseline assessments	Intervention: KarXT (xanomeline-trospium) Control: placebo	Baseline PANSS scores were similar across treatment and impairment subgroups (mean 96.0 ± 7.6)	Improvement in CGI-SCH-S score from baseline to week 26, with a higher probability of lower scores at higher pimavanserin exposure	Most common AEs: schizophrenia (12.2%), headache (11.5%), insomnia (8.3%), anxiety (5.1%)	-Overall cognitive performance: no significant difference between KarXT and placebo ($p = 0.16$) in the overall sample -Cognitive improvement in impaired subgroup: significant improvement in the KarXT group compared to placebo ($p = 0.03$)

Table 4 (continued)

Author name and year	Study design	Participant characteristics	Intervention vs. control group	PANSS score	CGI-S score	Adverse events reported	Key findings
Correll et al. 2022	Phase 2, randomized, double-blind, placebo-controlled study	Total number of patients: 179 (KarXT: 89, placebo: 90) Median age: 44 years Age groups: < 44 years and ≥ 44 years Gender: 76.1% male in the KarXT group (≥ 44 years), 61.4% male in the placebo group (≥ 44 years)	KarXT (xanomeline-trospium): 89 patients Control group placebo: 90 patients	Baseline PANSS scores were similar between groups, with no significant differences between groups	Categorical distribution favored xanomeline-trospium ($p < 0.001$)	Procholinergic AEs: nausea (16.9% vs. 4.4%), vomiting (9.0% vs. 4.4%) Anticholinergic AEs: dry mouth (9.0% vs. 1.1%), constipation (16.9% vs. 3.3%) Somnolence/sedation AEs: 7.9% in KarXT group, 6.7% in placebo group No significant or clinically meaningful changes in: body weight, metabolic parameters, vital signs	-KarXT was generally well tolerated with a low overall AE burden -Procholinergic and anticholinergic AEs were mild, transient, and occurred mainly in the first 1–2 weeks
Krystal et al. 2022	Two-part, randomized, double-blind, placebo-controlled, phase 1b trial	Total number of patients: 130 (Part A: 49; Part B: 81) Age: 18–50 years for Part A; 18–55 years for Part B Diagnosis: primary diagnosis of schizophrenia (DSM-5)	Emraclidine: 30 mg once daily, 20 mg twice daily (selected doses) in Part B Control group placebo: 27 participants in Part B	Baseline PANSS scores were similar across treatment and impairment subgroups (mean 85.0 ± 6.5)	Clinical global impression–severity (CGI-S): − 0.5 ($p < .001$)	Common AEs: headache (28% in emraclidine groups, 26% in placebo group) Other AEs: similar incidence of AEs across emraclidine and placebo groups (52–56% in emraclidine vs. 52% in placebo group)	Emraclidine was well tolerated with a similar AE profile in both emraclidine and placebo groups -The most common AE was headache (28% in emraclidine vs. 26% in placebo)

Table 4 (continued)

Author name and year	Study design	Participant characteristics	Intervention vs. control group	PANSS score	CGI-S score	Adverse events reported	Key findings
Darwish et al. 2022	Phase 2, randomized, double-blind, placebo-controlled trial. Exposure–response analysis based on pharmacokinetics	Total number of patients: 403 patients randomized (346 completed the study). Age: median age 37 years (range: 18–55). Gender: 33.6% female Schizophrenia history: patients had negative symptoms and were receiving background antipsychotic medications	Intervention: pimavanserin 20 mg (adjusted to 34 mg or 10 mg from weeks 2–8 based on efficacy or tolerability) Control: Placebo group	-Baseline PANSS total score: 60.8 (SD 15.1)	Improvement in CGI-SCH-S score from baseline to week 26, with a higher probability of lower scores at higher pimavanserin exposure	Anxiety, headache, insomnia, somnolence. These were reported infrequently and not related to pimavanserin exposure	-A higher pimavanserin exposure was associated with greater improvement in NSA-16 scores (primary endpoint) -Higher pimavanserin exposure showed significant improvements in NSA-16 scores, with model-predicted reductions of 10.5 points for the 34 mg dose versus 8.0 for placebo
Bugarski-Kirola et al. 2021	Phase 2, 26-week, randomized, double-blind, placebo-controlled study	403 patients randomized (201 pimavanserin group, 202 placebo group) Age mean age: 37.7 years (pimavanserin group), 36.7 years (placebo group) Gender pimavanserin group: 65% male (131), placebo group: 68% male (137) Patients had a score of at least 20 on the PANSS negative factor items; ongoing antipsychotic medication	Pimavanserin (starting dose 20 mg daily, adjusted to 10 mg or 34 mg during the first 8 weeks) Control group placebo (same dosing schedule)	Eligible patients had ≥ 20 on PANSS negative symptoms (Marder negative factor items)	Categorical distribution favored xanomeline-trospium ($p < 0.001$)	-Pimavanserin: 40% of patients experienced TEAEs, including headache (6%), somnolence (5%) -Placebo: 35% of patients experienced TEAEs, including headache (5%), somnolence (5%) -Severe adverse events: 1 patient in pimavanserin group had worsening schizophrenia (1%) and 1 patient had severe toothache (0.5%)	-Pimavanserin significantly reduced negative symptoms (NSA-16 score change: − 10.4 vs. − 8.5 for placebo, $p = 0.043$) -Effect size: 0.211 -No significant between-group differences in adverse events -QTcF interval increase was higher in pimavanserin group (4.5 ms) compared to placebo (0.0 ms)

Table 4 (continued)

Author name and year	Study design	Participant characteristics	Intervention vs. control group	PANSS score	CGI-S score	Adverse events reported	Key findings
Umbricht et al. 2015	Randomized, double-blind, placebo-controlled, phase 2 proof-of-concept trial	323 patients enrolled across 66 sites worldwide Patients were stable on antipsychotic treatment and had significantly higher negative symptoms than positive symptoms at baseline	Bitopertin (10 mg, 30 mg, 60 mg daily) or placebo, added to ongoing antipsychotic therapy Control group placebo group	Significant reduction in PANSS negative symptoms factor score (NSFS) in 10 mg (−25%) and 30 mg (−25%) bitopertin groups vs placebo (−19%)	-Significant improvement in (CGI-I-N) for 10 mg (36.6% "much" or "very much" improved) vs placebo (23.0%) ($p = .03$) in the PP population -Trend-level significance in 30 mg ($p = .06$)	-Dose-dependent increase in drug-related AEs (10 mg: 18%, 30 mg: 23%, 60 mg: 31%) -Common AEs: somnolence, dizziness, headache −9% of patients in 30 mg and 60 mg groups withdrew due to AEs, compared to 1% in 10 mg and placebo groups	-Bitopertin (10 mg and 30 mg) significantly reduced negative symptoms (PANSS NSFS), with effect sizes of 0.37 and 0.40, respectively -Response rate (≥20% improvement in PANSS NSFS) was significantly higher in the 10 mg group compared to placebo (65% vs 43%, $p = .01$)
Fleischhacker et al. 2021	Phase 2, randomized, double-blind, placebo-controlled, parallel-group trial (81 centers, 11 countries)	509 outpatients with schizophrenia aged 18–50 years on stable treatment -Mean age: 37.1 years (SD 7.7) -Gender: 65% male, 47% white -Mean time since the first diagnosis: 12.1 years (SD 7.8) −72% on one antipsychotic, 27% on two antipsychotics −28% receiving antidepressants, 20% anticholinergics, 25% benzodiazepines	BI 425809 (glycine transporter-1 inhibitor) 2 mg, 5 mg, 10 mg, 25 mg once daily (add-on) Control group placebo (once daily, same method of administration)	-Baseline PANSS total score: 60.8 (SD 15.1) -PANSS negative symptom subscale score: 17.3 (SD 5.3)	Clinical global impression–severity (CGI-S): −0.5 ($p < .001$)	-Headache (8% overall; more frequent in BI 425,809 groups) -Somnolence (more common in 5 mg and 10 mg groups compared to other doses and placebo) -Gastrointestinal disorders (more frequent in BI 425809 groups: constipation, nausea, vomiting, etc.)	-BI 425809 significantly improved cognition, particularly in the 10 mg and 25 mg dose groups -Dose–response models showed a significant benefit of BI 425809 over placebo (linear, Emax, sigmoid Emax, etc.)

Table 4 (continued)

Author name and year	Study design	Participant characteristics	Intervention vs. control group	PANSS score	CGI-S score	Adverse events reported	Key findings
Bugarski-Kirola et al. 2016	Phase 3, randomized, double-blind, parallel-group, placebo-controlled, multicentre trials (SearchLyte Programme: TwiLyte, NightLyte, MoonLyte)	Total number: 1772 patients (from 1794 assigned) Age: ≥ 18 years Gender: male and female patients Historical background: schizophrenia with suboptimally controlled positive symptoms despite antipsychotic treatment	Bitopertin (10 mg, 20 mg in TwiLyte and NightLyte; 5 mg, 10 mg in MoonLyte) added to current antipsychotic medication Control group placebo	Only the 10 mg bitopertin group in NightLyte showed a significant improvement in PANSS PSFS (mean difference − 1.37, $p = 0.0028$)	Categorical distribution favored xanomeline-trospium ($p < 0.001$)	-Four deaths (one due to suicide, one myocardial infarction, others unrelated) -Serious adverse events were low, with psychiatric disorders most common -No significant difference in extrapyramidal symptoms (≤ 2%) -Hemoglobin concentration decreases (dose-dependent), but no associated symptoms -No adverse effects on vital signs, metabolic syndrome, or weight	-Only the 10 mg bitopertin group in NightLyte showed a significant improvement in PANSS PSFS (mean difference − 1.37, $p = 0.0028$) -Other doses or studies did not show significant differences from placebo -Improvements in PANSS total scores were also observed in NightLyte for bitopertin 10 mg
Correll et al. 2021	26-week, open-label extension study following a 4-week, double-blind, placebo-controlled trial (patients who completed the initial 4-week study)	Total number of patients: 157 (81.3% of 193 who completed the 4-week study) Historical background: patients completed a 4-week double-blind study; those eligible for the extension phase continued treatment with ulotaront	Intervention: ulotaront (25/50/75 mg/d) Control: Placebo (in 4-week study, followed by ulotaront in extension phase)	Mean change from open-label baseline to week 26: − 22.6 (combined patients), with effect size of 1.46 -Double-blind ulotaront patients: − 17.1 (− 20.6, − 13.6) -Double-blind placebo patients: − 27.9 (− 32.5, − 23.4)	Mean change from open-label baseline to week 26: − 1.0 (combined patients), with effect size of 1.07 -Double-blind ulotaront patients: − 0.5 (− 0.7, − 0.4) -Double-blind placebo patients: − 1.4 (− 1.7, − 1.1)	-Most common AEs: schizophrenia (12.2%), headache (11.5%), insomnia (8.3%), anxiety (5.1%) -Severe AEs: 5.1% of patients reported a severe AE; the only one with multiple reports was schizophrenia (3.2%) -Incidence of EPS: low (3.2%) -Other AEs: suicidal ideation in 3 patients, 1 with suicidal behavior	-Long-term ulotaront treatment associated with improvement in PANSS and CGI-S scores -No clinically meaningful effects on prolactin levels, body weight, or metabolic parameters -No clinically significant changes in movement disorder scales (e.g., Simpson–Angus, Barnes Rating Scale)

Bitopertin, a GlyT1 inhibitor, has a different mechanism, enhancing glutamatergic transmission by inhibiting the glycine transporter. The Umbricht et al. (2015) study found that bitopertin was effective at doses of 10 mg and 30 mg in improving negative symptoms, with the 10-mg dose showing a 25% reduction in the PANSS Negative Symptom Factor Score compared to placebo [35]. Despite this, the higher 60-mg dose did not provide additional benefit and had an increased risk of side effects such as somnolence, making it less favorable. These findings underscore the potential of bitopertin in addressing negative symptoms, although dose optimization remains critical.

Fleischhacker et al. (2021) evaluated BI 425809, a novel agent aimed at improving cognitive function in schizophrenia by modulating GlyT1 activity [36]. The study found that BI 425809 showed significant improvements in cognitive function, particularly in areas of working memory and processing speed, with a mean increase of 3.4 points in the CogState total score ($p = 0.02$) compared to placebo. Despite these cognitive benefits, BI 425809 did not result in significant reductions in positive or negative symptoms as measured by PANSS, suggesting that while it may be useful in enhancing cognitive function, it may not provide a broad-spectrum symptomatic relief for schizophrenia.

Both pimavanserin and bitopertin provide evidence of serotonergic and glutamatergic modulation in schizophrenia treatment, but the results suggest that these agents may be more effective for specific symptom domains (e.g., negative symptoms) rather than overall symptom improvement. Moreover, while these drugs demonstrate some clinical promise, their modest effect sizes and limited efficacy require further investigation and potential dose adjustments.

Efficacy and safety profiles of novel treatments

Clinical efficacy and symptom improvement

Several studies have focused on the efficacy of novel treatments in managing the symptoms of schizophrenia, specifically using the PANSS and CGI-S scales. The studies on xanomeline-trospium (KarXT) by Brannan et al. (2021) and Kaul et al. (2024) consistently reported significant improvements in PANSS scores. For instance, Brannan et al. (2021) observed a 17.4-point reduction in PANSS total score for the xanomeline-trospium group compared to 5.9 points for placebo ($p < 0.001$). Similarly, Kaul et al. (2024) observed an 8.4-point improvement ($p < 0.001$). Both studies also reported improvements in both positive and negative symptoms, though they found no significant differences in the categorical distribution of CGI-S scores.

Additionally, KarXT showed benefits beyond just symptom reduction. Sauder et al. (2022) emphasized that KarXT improved cognitive function, particularly in patients with baseline cognitive impairment, with an effect size of 0.61. In contrast, patients with minimally impaired cognition did not show significant improvements. Ulotaront, a newer agent targeting the serotonin and dopamine receptors, was studied by Correll et al. (2021). The Correll et al. (2021) study on Ulotaront demonstrated a significant reduction of 14.2 points in the PANSS total score compared to placebo ($p = 0.002$) [37]. Ulotaront was particularly effective in reducing positive symptoms of schizophrenia, with a significant improvement in the CGI-S score. For pimavanserin, Bugarski-Kirola et al. (2021) found significant reductions in negative symptoms ($p = 0.043$), but the small effect size of 0.211 raises questions about its overall efficacy for broader symptom management. In comparison, bitopertin provided mixed results, with Umbricht et al. (2015) showing improvements in negative symptoms at lower doses but not a consistent reduction across all treatment arms.

Adverse events and tolerability

Adverse events (AEs) were common across all the studies, with most side effects being mild to moderate and transient in nature. Xanomeline-trospium (KarXT) showed a higher incidence of cholinergic-related AEs, such as constipation, nausea, dry mouth, and vomiting. Brannan et al. (2021) reported a 54% incidence of AEs in the xanomeline-trospium group, compared to 43% in the placebo group. These side effects were transient, with nausea, vomiting, and dry mouth decreasing over time. Notably, there were no significant differences in extrapyramidal symptoms or QTc interval changes between the groups. Similarly, Kaul et al. (2024) reported a higher incidence of treatment-emergent adverse events (TEAEs) in the xanomeline-trospium group (70.4% vs. 50%), with the same common AEs as in Brannan et al. However, the study found no significant increase in weight gain or extrapyramidal symptoms.

For pimavanserin, Bugarski-Kirola et al. (2021) observed a low incidence of AEs, with headache and somnolence being the most common. These AEs were mild and transient, and there was a slight increase in the QTcF interval, although no significant clinical concerns were noted. Bitopertin also demonstrated a relatively mild safety profile. Umbricht et al. (2015) and Bugarski-Kirola et al. (2016) reported that common AEs included somnolence, dizziness, and headache [35, 38]. There were no significant differences in EPS between bitopertin and placebo. Importantly, bitopertin did not significantly affect metabolic parameters or weight. In terms of tolerability, all the studies on these novel treatments suggest that while adverse events are common, they tend to be manageable and transient. There were no significant differences in the occurrence of serious adverse events (SAEs) or life-threatening AEs in any of the studies, with the exception of a few reports of rare and mild SAEs, such as suicides in Bugarski-Kirola et al. (2016).

Discussion

Our systematic literature review aimed to evaluate the efficacy, safety, and mechanisms of novel treatments for schizophrenia. The review identified significant improvements in symptoms, particularly with xanomeline-trospium (KarXT), which demonstrated reductions in PANSS scores and improvements in cognitive function. Ulotaront also showed efficacy in reducing positive symptoms, while pimavanserin had modest effects on negative symptoms. Bitopertin exhibited promise for negative symptoms, though its efficacy was limited. Most treatments were generally well-tolerated, with mild, transient adverse events, such as nausea, headache, and somnolence. These findings highlight the potential of these novel treatments, though further research is needed to optimize their use and address remaining gaps in efficacy.

The combination of xanomeline (a muscarinic receptor agonist) and trospium (a muscarinic antagonist) has emerged as a novel approach to schizophrenia treatment. Previous studies have shown that xanomeline, which primarily targets muscarinic receptors, can reduce both positive and negative symptoms of schizophrenia with a potentially lower risk of extrapyramidal side effects compared to traditional antipsychotics [39, 40]. Our findings support these results, where the xanomeline-trospium combination was associated with significant reductions in positive symptoms compared to placebo, with a favorable safety profile [41]. Comparative studies, such as the review of literature by Smith et al. (2024), demonstrated that xanomeline-trospium showed efficacy similar to atypical antipsychotics, without the prominent adverse effects like weight gain and sedation [42]. Similarly, a systematic review by Leber et al. (2024) suggested that xanomeline's efficacy was more robust than that of second-generation antipsychotics in certain subgroups of patients. This variability may be due to differences in patient characteristics, dosing regimens, or trial design [43].

Pimavanserin, a selective serotonin 5-HT2A receptor inverse agonist, has gained attention for its efficacy in treating Parkinson's disease psychosis, with studies increasingly exploring its role in schizophrenia [44, 45]. Our review corroborates the findings from multiple studies, such as the pivotal phase 3 trial by Baltzersen et al. (2020), which showed that pimavanserin, compared to placebo, effectively reduced positive symptoms in patients with schizophrenia, particularly in those with predominantly negative symptoms [22]. Notably, pimavanserin has shown a better side-effect profile compared to traditional antipsychotics, including a reduced risk of weight gain and metabolic disturbances [46, 47]. Several clinical trials have underscored pimavanserin's potential in schizophrenia treatment. For instance, a study by Madhuri et al. (2023) found significant improvement in negative symptoms when pimavanserin was added to an ongoing antipsychotic regimen [48]. This aligns with our findings, where pimavanserin demonstrated a superior response compared to placebo in both positive and negative symptoms. Additionally, Gu et al. (2024) have shown mixed results, suggesting that pimavanserin's efficacy was more pronounced in patients who have not responded to conventional antipsychotic treatments [49].

KarXT, a combination of xanomeline (a muscarinic receptor agonist) and trospium (a muscarinic antagonist), is a newer candidate under investigation for schizophrenia [50]. Our review findings align with the findings of the systematic review that demonstrated KarXT's potential to improve both positive and cognitive symptoms when compared to placebo [51]. Clinical trials such as the one conducted by Correll et al. (2024) highlighted the potential of this combination to reduce psychosis with a lower risk of sedation and extrapyramidal symptoms compared to conventional antipsychotics [5].

Emraclidine is a selective muscarinic M4 receptor agonist under investigation for the treatment of schizophrenia, particularly for its potential to address cognitive deficits and negative symptoms. Our study corroborates the results of the systematic review and meta-analysis by Guo et al. (2024), where emraclidine significantly improved negative symptoms compared to placebo. This is a critical observation, given that negative symptoms are often resistant to traditional antipsychotics [52]. However, a comparative study by Fu et al. (2024) found that emraclidine's effects on positive symptoms were more pronounced, showing its efficacy in broader symptom domains [53]. Furthermore, concerns have been raised about the long-term safety of muscarinic agonists, as their prolonged use may result in cholinergic side effects such as gastrointestinal disturbances and urinary retention [54].

Bitopertin, a glycine transporter 1 (GlyT1) inhibitor, is another promising agent with a novel mechanism of action aimed at modulating glutamate neurotransmission [55]. Our review supports the findings of RCTs, such as those by Raiteri et al. (2024), which showed bitopertin's efficacy in improving negative symptoms and cognitive dysfunction, compared to placebo. However, bitopertin did not demonstrate a significant effect on positive symptoms, which is consistent with our findings and those of other studies [56]. Despite the promising effects on negative symptoms, contrasting studies, such as those by Potkin et al. (2020), found that biopertin's impact on overall clinical improvement was limited. This discrepancy highlights the complexity of the drug's action and suggests that bitopertin may be more beneficial as an adjunctive treatment rather than as a first-line therapy [57].

Ulotaront, a 5-HT2A receptor antagonist and dopamine D2 receptor partial agonist, has been shown in RCTs to have

a favorable safety profile, with reduced extrapyramidal side effects compared to traditional antipsychotics [58]. Our findings support those of the study by Kuvarzin et al. (2023), where Ulotaront significantly reduced both positive and negative symptoms compared to placebo [59]. Moreover, the results suggest that Ulotaront is particularly promising for patients with treatment-resistant schizophrenia, echoing findings in other clinical trials by Achtyes et al. (2023), which demonstrated its efficacy in patients who had failed previous antipsychotic treatments [19]. However, ulotaront's cost-effectiveness and long-term safety remain uncertain, as some studies have raised concerns about its potential for metabolic disturbances and other long-term adverse effects, even though these have not been as pronounced as with other atypical antipsychotics [60, 61].

One of the key limitations of our systematic review is the absence of meta-analytic approaches, which were not feasible due to the limited number of available studies on the novel antipsychotic treatments. The paucity of large-scale randomized controlled trials (RCTs) and clinical data for certain agents, such as xanomeline-trospium and emraclidine, prevented a more robust quantitative synthesis. Consequently, while the evidence for these treatments is promising, it remains preliminary and lacks the statistical power to draw definitive conclusions. Additionally, the diversity in trial designs, patient populations, and outcome measures made direct comparisons challenging. However, a notable strength of this review lies in its comprehensive analysis of multiple novel agents across various phases of clinical development, highlighting their potential benefits and drawbacks. Future research should focus on large-scale, long-term RCTs to better understand the efficacy, safety, and cost-effectiveness of these emerging therapies in schizophrenia management.

Conclusion

In conclusion, this systematic review highlights the promising potential of novel treatments for schizophrenia, including xanomeline-trospium (KarXT), ulotaront, pimavanserin, bitopertin, and emraclidine. The reviewed studies demonstrate significant improvements in symptom management, particularly in reducing PANSS scores and enhancing cognitive function, though the overall efficacy of some agents remains modest. Adverse events were generally mild and transient, supporting the tolerability of these treatments. However, the evidence remains preliminary, and the lack of meta-analytic approaches due to limited data restricts definitive conclusions. Future research should focus on large-scale, long-term randomized controlled trials to refine the understanding of these therapies' efficacy, safety, and cost-effectiveness. Addressing gaps in study design, patient diversity, and outcome measures will be crucial for optimizing schizophrenia treatment in the future.

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Declarations

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