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BEYOND DOPAMINE BLOCKADE: MUSCARINIC RECEPTOR AGONISM AS A NOVEL THERAPEUTIC STRATEGY IN SCHIZOPHRENIA - A LITERATURE REVIEW OF XANOMELINE-TROSPIUM

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ABSTRACT

Background: Schizophrenia is a chronic mental illness affecting over 23 million people worldwide. Current pharmacotherapy, primarily based on dopamine D₂ receptor antagonism, is associated with significant adverse effects - including extrapyramidal symptoms, metabolic disturbances, and hyperprolactinemia - and up to 30% of patients show inadequate response.

Aim: This review aims to present and synthesize the available evidence on xanomeline-trospium (Cobenfy®) - the first approved antipsychotic with a predominantly muscarinic mechanism of action - as a novel therapeutic option for schizophrenia.

Methods: A narrative literature review was conducted in PubMed, Scopus, Web of Science, and Google Scholar databases up to June 2026, focusing on peer-reviewed articles, clinical trials, and systematic reviews on xanomeline-trospium in schizophrenia.

Results: Xanomeline-trospium demonstrated significant antipsychotic efficacy across the Phase 2 and Phase 3 EMERGENT trials, with moderate-to-large effect sizes (Cohen's $d = 0.60$). The safety profile is distinctly favorable: no extrapyramidal symptoms, weight gain, metabolic disturbances, or prolactin elevation were observed. Gastrointestinal adverse events (nausea, vomiting, constipation) were the most common but were generally mild, transient, and occurred early in treatment. Long-term open-label extension studies confirmed sustained efficacy and safety over 52 weeks, with ecological momentary assessment data indicating improvements in real-world social functioning and positive affect.

Conclusions: Xanomeline-trospium represents a promising alternative for schizophrenia treatment, particularly for patients intolerant to conventional antipsychotics or those with metabolic comorbidities. Its novel mechanism and favorable tolerability profile position it as a significant advancement in psychopharmacology. Further research is needed to clarify its role in treatment-resistant schizophrenia and to confirm long-term outcomes in diverse populations.

KEYWORDS

Xanomeline-trospium, Cobenfy, Schizophrenia, Muscarinic Receptor Agonist, Novel Antipsychotic, Treatment-resistant Schizophrenia

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1. Introduction

Schizophrenia is a chronic and severe mental illness affecting over 23 million people globally (GDB 2021 Schizophrenia Collaborators, 2026) in comparison to approximately 14.2 million in 1990 (Solmi et al., 2023), which highlights its growing public health burden. It is characterized by several symptom domains – positive (including hallucinations and delusions), negative (blunted affect, alogia, lack of motivation, asociality and anhedonia), cognitive impairment and mood disturbances. (Striebel, 2024) Schizophrenia is also associated with higher rates of death by suicide compared to the general population as well as increased mortality from natural causes. (Correll, Solmi, et al., 2022) A substantial body of evidence from pharmacological and neuroimaging studies indicates that abnormalities in dopaminergic neurotransmission underlie the development of psychotic symptoms, including hallucinations and delusions. (Owen et al., 2016) Since the introduction of chlorpromazine in the 1950s, antipsychotic pharmacotherapy has been based predominantly on modulation of dopaminergic neurotransmission. Most antipsychotic agents used in the treatment of schizophrenia exert their therapeutic effects primarily through antagonism of dopamine D₂ receptors (DRD2). Among currently available medications, clozapine demonstrates the greatest clinical efficacy, particularly in treatment-resistant schizophrenia. In addition to its high affinity for DRD2 receptors, clozapine and several other second-generation antipsychotics interact with multiple neurotransmitter systems, including serotonin 5-HT₂ receptors, which is thought to contribute to their distinct therapeutic and adverse effect profiles. (Owen et al., 2016; Correll & Howes, 2021) A common challenge in the treatment of

schizophrenia is an inadequate response to antipsychotic therapy. Treatment-resistant schizophrenia (TRS) is broadly defined as a failure to achieve an adequate clinical response despite at least two consecutive trials of antipsychotic medications administered at adequate doses and for an adequate duration, with confirmed treatment adherence. TRS affects up to 30% of individuals with schizophrenia. (Correll & Howes, 2021) Clozapine remains the gold-standard treatment for treatment-resistant schizophrenia (TRS); however, its use is associated with a broad spectrum of adverse effects. These range from relatively common symptoms that impair patients' quality of life, such as constipation, hypersalivation, and dizziness, to serious medical conditions, including metabolic syndrome and tachycardia, as well as potentially life-threatening complications such as agranulocytosis, seizures, cardiac arrhythmias, myocarditis, and pneumonia. (Falkai et al., 2025; Howes et al., 2022; Ying et al., 2023) However, the limitations of dopaminergic pharmacotherapy extend well beyond the safety concerns of clozapine. Hyperprolactinemia is a frequent adverse effect of antipsychotic treatment caused by dopamine D2 receptor blockade. It is associated with sexual and reproductive dysfunction, osteoporosis and endocrine disturbances, affecting up to 65% of women and 40–70 % of men treated with antipsychotics. (Lin et al., 2025) Extrapyramidal symptoms (EPS), including parkinsonism, dystonia, and akathisia, affect up to one-third of patients receiving antipsychotic treatment and may compromise treatment adherence. (Siafis et al., 2023) A particularly serious long-term form of EPS is tardive dyskinesia (TD), characterized by persistent involuntary movements, which affects approximately 22% of patients treated with antipsychotics in Europe. (Colosimo et al., 2026) Collectively, these limitations underscore the need for antipsychotic therapies that extend beyond dopamine D2 receptor antagonism. The development of compounds targeting alternative neurobiological pathways has therefore become a major focus of schizophrenia research. Among the most promising advances is the combination of xanomeline and trospium chloride, the first approved antipsychotic with a predominantly muscarinic mechanism of action and potential to treat positive, negative and cognitive symptoms of schizophrenia, while avoiding the long-term adverse effects associated with dopamine D2 receptor antagonism (Paul et al., 2022; Targum et al., 2026).

2. Objective

Given the limitations of current antipsychotic pharmacotherapy, there is an ongoing need for novel treatment strategies in schizophrenia. The recent approval of xanomeline-trospium (Cobenfy®) – a first-in-class antipsychotic with a muscarinic receptor agonist mechanism of action – represents a significant advancement in this field. The aim of this review is to present and synthesize the available evidence from clinical trials and scientific literature on the efficacy, safety, and clinical applicability of xanomeline-trospium as a new therapeutic option for schizophrenia.

3. Methodology

Study Design This article is based on a narrative literature review, with the primary objective of synthesizing the available evidence on xanomeline–trospium as a novel therapeutic option for schizophrenia. To provide appropriate context for this novel agent, the review also incorporates information on the pharmacology, efficacy, and safety profiles of established antipsychotic drug classes, enabling a comparative evaluation.

Data Collection A literature search was conducted in PubMed, Scopus, Web of Science, and Google Scholar databases up to June 2026. Search terms included combinations of keywords such as "xanomeline", "trospium", "xanomeline–trospium", "muscarinic receptor agonist", "schizophrenia", "novel antipsychotic", "antipsychotic drugs", "schizophrenia treatment", "dopamine receptor antagonists", and "clozapine". The search was limited to peer-reviewed articles, randomized controlled trials, systematic reviews, and meta-analyses published between 2016 and 2026. Studies focusing on pediatric populations, non-English articles, and non-peer-reviewed sources were excluded. To provide a comprehensive comparative background, additional searches were conducted on the classification, mechanisms of action, and adverse effect profiles of first- and second-generation antipsychotics.

Analysis Techniques The selected studies were reviewed for relevance to the efficacy, safety, pharmacokinetics, and clinical applicability of xanomeline–trospium in the treatment of schizophrenia. Additional literature on conventional antipsychotics was examined to enable comparative analysis of safety profiles and therapeutic positioning. Due to the narrative nature of this review, no formal risk-of-bias assessment or statistical meta-analysis was performed. However, emphasis was placed on including up-to-date, high-quality sources, with priority given to randomized controlled trials (RCTs), systematic reviews, and meta-analyses published in peer-reviewed journals.

Table 1. summarizes the literature search parameters and inclusion criteria.

Table 1. Literature Search Parameters and Inclusion Criteria

Parameter	Description
Type of Review	Narrative literature review
Primary Focus	Xanomeline-trospium in schizophrenia
Comparative Context	Established antipsychotic drug classes (First and Second Generation Antipsychotics, Clozapine)
Databases Searched	PubMed, Scopus, Web of Science, Google Scholar
Search Time Frame	2016-2026
Keywords Used	"xanomeline", "trospium", "xanomeline–trospium", "muscarinic receptor agonist", "schizophrenia", "novel antipsychotic", "antipsychotic drugs", "schizophrenia treatment", "dopamine receptor antagonists", "clozapine"
Inclusion Criteria	Peer-reviewed articles, randomized controlled trials, systematic reviews, meta-analyses on xanomeline–trospium, muscarinic receptor agonists, and comparative antipsychotic literature
Exclusion Criteria	Non-English articles, non-peer-reviewed sources, studies on pediatric populations, preclinical studies
Number of Included Studies	32
Type of Studies	Randomized controlled trials (Phase 2 and 3), systematic reviews, meta-analyses, real-world evidence, pharmacological reviews

4. Results

4.1 The development of xanomeline/trospium

Muscarinic acetylcholine receptor agonists were initially investigated as potential treatments for cognitive impairment in the course of Alzheimer's disease through direct activation of M1 receptors. Early compounds such as sabcomeline and cevimeline demonstrated modest improvements in cognition in preclinical and preliminary clinical studies. However, peripheral parasympathomimetic adverse effects, including gastrointestinal disturbances, hypersalivation and sweating, significantly limited their therapeutic utility and further clinical development. (Verma et al., 2018; Yohn et al., 2024) A pivotal observation emerged with xanomeline, which unexpectedly demonstrated antipsychotic benefits alongside its cognitive effects. This finding prompted investigation of this drug in schizophrenia treatment with clinical studies demonstrating significant reductions in psychotic symptoms and improvements in specific cognitive domains compared to placebo. These compelling results expanded the therapeutic scope of mAChR-targeted agents beyond neurodegenerative disorders. (Paul et al., 2022) However, a significant limitation to the clinical development of xanomeline emerged from its adverse effect profile. The therapeutic use of xanomeline was associated with adverse effects similar to those listed before for other muscarinic acetylcholine receptor agonists. These mAChR-mediated adverse events, resulting from xanomeline's activation of peripheral receptors, necessitated the development of strategies to reduce tolerability issues while maintaining the compound's centrally mediated therapeutic benefits. (Mazur et al., 2025; Yohn et al., 2024) To improve the tolerability of xanomeline, it was combined with trospium, a peripherally restricted, non-brain-penetrant pan-muscarinic acetylcholine receptor (mAChR) antagonist. Due to its inability to cross the blood–brain barrier, trospium selectively blocks peripheral mAChRs while leaving the centrally mediated activity of xanomeline intact. This combination, initially known as KarXT (later marketed as COBENFY™) was therefore designed to reduce peripheral cholinergic adverse effects while preserving the therapeutic effects of central mAChR activation. In a placebo-controlled phase 2 trial in patients with acute psychotic symptoms, xanomeline–trospium significantly reduced PANSS total scores and improved positive and negative symptoms as well as clinical global severity compared with placebo. Importantly, treatment was not associated with extrapyramidal symptoms, weight gain, or excessive sedation, while the observed cholinergic and anticholinergic adverse effects were generally mild to moderate and transient (Brannan et al., 2021; Paul et al., 2022; Yohn et al., 2024).

4.2 Clinical Pharmacology of the Xanomeline/Trospium

Xanomeline is thought to exert its therapeutic effects through preferential agonism of central M1 and M4 muscarinic acetylcholine receptors. Although xanomeline binds to all five muscarinic receptor subtypes (M1–M5) with comparable affinity, its agonist activity is greater at M1 and M4 receptors. In contrast, trospium chloride is a peripherally restricted muscarinic antagonist that primarily blocks muscarinic receptors in peripheral tissues, thereby reducing cholinergic adverse effects without interfering with the centrally mediated therapeutic activity of xanomeline (Meyer et al., 2025; Smith et al., 2025).

Following oral administration of COBENFY™, xanomeline reaches maximum plasma concentrations after approximately 2 hours, whereas trospium reaches peak concentrations after approximately 1 hour. Xanomeline exposure increases more than proportionally with increasing dose; following an increase in the COBENFY™ dose from 100 mg/20 mg twice daily to 125 mg/30 mg twice daily, xanomeline AUC_{0–12} and C_{max} increase by 50%. In contrast, trospium exposure increases proportionally across the same dosage range. Both components exhibit 2- to 3-fold accumulation at steady state, which is achieved within 3 to 5 days of twice-daily administration. Food intake substantially affects the absorption of COBENFY™. Following administration with a high-fat meal (800–1000 calories, 50% from fat), xanomeline C_{max} remains unchanged, whereas its AUC increases by 30%; in contrast, trospium C_{max} and AUC decrease by 70–75% and 85–90%, respectively. A low-fat meal (400–500 calories, 25% from fat) does not affect xanomeline C_{max} or AUC but reduces trospium C_{max} by 70–75% and AUC by 85–90%. Accordingly, COBENFY should be administered at least 1 hour before or at least 2 hours after a meal (Bristol-Myers Squibb Company, 2024).

The two components of COBENFY™ also exhibit distinct distribution profiles. The oral central volume of distribution is approximately 10,800 L for xanomeline and 531 L for trospium. Xanomeline is extensively bound to plasma proteins (approximately 95%), compared with approximately 80% for trospium. The elimination half-lives of xanomeline and trospium are approximately 5 and 6 hours, respectively. Apparent clearance is 1950 L/hour for xanomeline and 796 L/hour for trospium, while renal clearance is substantially higher for trospium (21 L/hour) than for xanomeline (0.085 L/hour). This difference is consistent with the predominant role of renal elimination in the clearance of trospium (Bristol-Myers Squibb Company, 2024).

Xanomeline undergoes extensive metabolism involving several cytochrome P450 (CYP) enzymes, primarily CYP2D6, with additional contributions from CYP2B6, CYP1A2, CYP2C9, and CYP2C19, as well as flavin monooxygenases FMO1 and FMO3. In contrast, trospium is unlikely to undergo metabolism mediated by CYP450 enzymes and is instead metabolized through ester hydrolysis and glucuronic acid conjugation, although these pathways have not been fully characterized. The elimination pathways of the two compounds also differ substantially. Approximately 78% of xanomeline is recovered in urine, although less than 0.01% is excreted unchanged, while approximately 12% is recovered in feces; the proportion of xanomeline excreted unchanged in feces is unknown. Trospium is predominantly excreted unchanged in urine, with approximately 85–90% of the dose eliminated through this route, and active tubular secretion contributes to its renal elimination. The extent of trospium excretion in feces is unknown (Bristol-Myers Squibb Company, 2024).

4.3 Dosage and Administration

Prior to initiating treatment, liver enzymes, bilirubin, and heart rate should be assessed, with continued monitoring as clinically indicated. The recommended starting dosage is 50 mg/20 mg (xanomeline/ trospium chloride) taken orally twice daily for at least two days. The dose should then be increased to 100 mg/20 mg twice daily for at least five days, and may be further titrated to a maximum of 125 mg/30 mg twice daily based on tolerability and response. The capsules should be administered at least one hour before or two hours after a meal and should not be opened. In geriatric patients, a lower starting dose of 50 mg/20 mg twice daily is recommended, with slower titration and a maximum dose of 100 mg/20 mg twice daily. COBENFY™ is available in three strengths: 50 mg/20 mg, 100 mg/20 mg, and 125 mg/30 mg capsules (Bristol-Myers Squibb Company, 2024).

4.4 Clinical Trials

The efficacy and safety of xanomeline-trospium (formerly known as KarXT) have been extensively evaluated in the EMERGENT clinical trial program. This program comprised three 5-week, randomized, double-blind, placebo-controlled trials in patients with acute schizophrenia – EMERGENT-1 (Phase 2), EMERGENT-2 (Phase 3), and EMERGENT-3 (Phase 3) – as well as two 52-week, open-label extension studies, EMERGENT-4 and EMERGENT-5, designed to assess long-term safety and durability of response (Ramey & Silva Almodóvar, 2025; Żelabowski et al., 2026).

The EMERGENT-1 trial (NCT03697252) was a randomized, double-blind, placebo-controlled, phase 2 study evaluating the efficacy, safety, and tolerability of xanomeline-trospium (KarXT) in adults with schizophrenia experiencing an acute exacerbation of psychotic symptoms. The study enrolled 182 inpatients aged 18–60 years who had a primary diagnosis of schizophrenia, recent worsening of positive symptoms requiring hospitalization, a baseline PANSS total score of ≥ 80 , and a Clinical Global Impression–Severity (CGI-S) score of ≥ 4 . Patients with a history of treatment-resistant schizophrenia were excluded. Following a 7-day screening period, participants were randomized in a 1:1 ratio to receive KarXT or placebo twice daily for 5 weeks. KarXT dosing was flexible, beginning at 50 mg/20 mg of xanomeline/trospium twice daily and increasing to a maximum of 125 mg/30 mg twice daily. The study met its primary efficacy endpoint and several prespecified secondary endpoints, demonstrating a significantly greater reduction in PANSS total score compared with placebo. In addition, KarXT treatment was associated with improvements in measures of positive and negative symptoms and overall clinical severity. The safety population comprised 179 patients who received at least one dose of study treatment (KarXT, $n = 89$; placebo, $n = 90$). The most common adverse events associated with KarXT were nausea (16.9%), vomiting (9.0%), constipation (16.9%), and dry mouth (9.0%); however, most were mild, occurred predominantly during the first 1–2 weeks of treatment, and were transient. None of the procholinergic or anticholinergic adverse events led to treatment discontinuation. Somnolence and sedation occurred at low rates and were similar to placebo. Furthermore, KarXT was not associated with clinically meaningful changes in body weight, metabolic parameters, or vital signs over the 5-week treatment period. Overall, EMERGENT-1 provided evidence that xanomeline-trospium can produce antipsychotic efficacy while avoiding many adverse effects commonly associated with dopamine D2 receptor-blocking antipsychotics, although the short treatment duration limits conclusions regarding its long-term safety and tolerability (Correll, Angelov, et al., 2022).

The efficacy and safety of xanomeline-trospium were further evaluated in the EMERGENT-2 trial (NCT04659161), a 5-week, phase 3, multicenter, randomized, double-blind, placebo-controlled inpatient study conducted in adults hospitalized with an acute exacerbation of schizophrenia. The modified intention-to-treat population comprised 236 participants, with a mean age of 46 years; 75% were male and 75% were Black, and all 22 participating sites were located in the United States. Patients were randomized to receive xanomeline-trospium or placebo twice daily, with xanomeline-trospium administered using a flexible titration schedule from 50 mg/20 mg twice daily to a maximum of 125 mg/30 mg twice daily by the end of the first week, based on tolerability and investigator judgment. The primary outcome was the change in total PANSS score from baseline to week 5. By the end of treatment, xanomeline-trospium was associated with a 21.2-point mean reduction in total PANSS score, with a 9.6-point least-squares mean difference compared with placebo. The treatment group also showed greater improvements in negative symptoms, reflected by between-group differences of 3.4 points on the PANSS negative symptom subscale and 4.2 points on the Marder negative factor, corresponding to Cohen's d values of 0.40 and 0.44, respectively. Moreover, 55% of patients receiving xanomeline-trospium achieved at least a 30% reduction in total PANSS score, compared with 28% of those receiving placebo. From a safety perspective, treatment-emergent adverse events were reported in 75% of patients in the xanomeline-trospium group and 58% in the placebo group, while adverse events leading to treatment discontinuation occurred in 7% and 6% of patients, respectively. The most common adverse events associated with xanomeline-trospium included constipation (21%), dyspepsia (19%), nausea (19%), headache (14%), vomiting (14%), hypertension (10%), dizziness (9%), gastroesophageal reflux disease (6%), and diarrhea (6%). Four serious adverse events were reported among patients receiving xanomeline-trospium, none of which were considered treatment-related. Overall, the EMERGENT-2 findings demonstrated significant antipsychotic efficacy over the 5-week treatment period, including improvements in overall symptom severity and negative symptoms, with adverse events occurring predominantly in the gastrointestinal domain (Kaul et al., 2025; Ramey & Silva Almodóvar, 2025).

The findings from EMERGENT-2 were subsequently further evaluated in the similarly designed EMERGENT-3 trial (NCT04738123). The trial was designed to assess the efficacy and safety of xanomeline-

trospium in adults hospitalized due to an acute exacerbation of schizophrenia. This 5-week, phase 3, multicenter study used a randomized, double-blind, placebo-controlled inpatient design and included 256 participants in the mITT population. The mean participant age was 43 years, with males accounting for 74.6% of the sample; 60.9% of participants were Black and 38.3% were White. The study was conducted across 30 sites in the United States and Ukraine. Patients received xanomeline–trospium or placebo twice daily, with active treatment initiated at 50 mg/20 mg twice daily and titrated, depending on tolerability and investigator discretion, to a maximum dose of 125 mg/30 mg twice daily by the end of the first week. The primary outcome was the change in total PANSS score from baseline to week 5. Treatment with xanomeline–trospium resulted in a 20.6-point least-squares mean reduction in total PANSS score, corresponding to an 8.4-point difference relative to placebo and a moderate effect size (Cohen's $d = 0.60$). A significantly greater improvement in positive symptoms was also observed with xanomeline–trospium, whereas no significant between-group differences were found for the PANSS negative symptom subscale or the Marder negative factor. Furthermore, 50.6% of patients receiving xanomeline–trospium achieved a reduction of at least 30% in total PANSS score, compared with 25.3% of patients receiving placebo. Treatment-emergent adverse events were reported in 70.4 % of participants in the xanomeline–trospium group and 50% in the placebo group, while discontinuation due to adverse events occurred in 6.4% and 5.5% of participants, respectively. The adverse events most commonly reported with xanomeline–trospium were nausea (19.2%), dyspepsia (16%), vomiting (16%), constipation (12.8%), hypertension (6.4%), and diarrhea (5.6%). One serious treatment-emergent adverse event, gastroesophageal reflux disease, was reported in the xanomeline–trospium group. Overall, the findings from EMERGENT-3 provided further evidence of the efficacy of xanomeline–trospium in acute schizophrenia, particularly in reducing overall and positive symptom severity, while the safety profile was mainly characterized by gastrointestinal adverse events (Kaul et al., 2025; Ramey & Silva Almodóvar, 2025).

Long-term outcomes of xanomeline–trospium were assessed in EMERGENT-4, a 52-week open-label extension study enrolling participants who had previously completed one of the acute phase 3 EMERGENT-2 or EMERGENT-3 trials. Of the 366 patients who completed the preceding studies, 156 (42.6%) entered the extension phase, and 152 received at least one dose of study medication. Treatment was initiated with xanomeline 50 mg/trospium 20 mg administered twice daily, with subsequent dose escalation to a maximum of 125 mg/30 mg twice daily. Safety was primarily evaluated by monitoring treatment-emergent adverse events, while changes in psychopathology were assessed using the PANSS and CGI-S scales. During the year-long follow-up, 81 participants (53.3%) experienced at least one TEAE. The adverse-event profile was dominated by gastrointestinal complaints, including nausea, vomiting, dyspepsia, and dry mouth. These events were generally mild or moderate and typically subsided despite continued treatment. Importantly, prolonged exposure to xanomeline–trospium did not reveal new safety or tolerability concerns and was not associated with clinically meaningful motor abnormalities, hyperprolactinemia, weight gain, or unfavorable metabolic effects. Symptomatic benefits were also maintained throughout the extension period, with participants who had received xanomeline–trospium during the preceding acute trials showing a mean 33.8-point decrease in total PANSS score from the original acute-trial baseline to week 52. A comparable 31.3-point reduction was observed among participants who had initially received placebo. Improvements were likewise maintained across CGI-S and the positive and negative PANSS subscales. Taken together, these findings suggest that xanomeline–trospium can provide sustained symptomatic benefit over one year without the emergence of new major safety concerns (Kaul, Claxton, Sauder, et al., 2026; Ramey & Silva Almodóvar, 2025).

Long-term outcomes following treatment with xanomeline–trospium were investigated also in the EMERGENT-5 study (NCT04820309), which followed 566 psychiatrically stable adults with schizophrenia across 54 sites in the United States. The trial lasted 52 weeks and used an open-label phase 3 design, with participants receiving xanomeline–trospium twice daily at flexible doses of up to 125 mg/30 mg. The study population consisted of patients who had previously been stabilized on other antipsychotic medications. By the end of the observation period, 277 participants (48.9%) had completed all 52 weeks of treatment. Treatment-emergent adverse events were reported in 466 participants (82.3%), although most were mild or moderate in severity. The adverse events observed most frequently included nausea (23.1%), vomiting (20.3%), constipation (18.0%), hypertension (10.4%), diarrhea (9.4%), dry mouth (9.4%), and dizziness (8.8%). In terms of efficacy, more than three-quarters of participants achieved a reduction of at least 30% in total PANSS scores relative to baseline, with the mean PANSS score decreasing by 33.3 points. A mean improvement of 1.7 points was also observed on the CGI-S scale, corresponding to a clinically meaningful change in illness severity from the "significantly ill" category toward "moderately" or "mildly ill" status. Importantly, the one-year follow-up did not identify any new safety signals, and the overall tolerability profile remained consistent

with that observed in previous clinical trials. These findings further indicate that patients with stable schizophrenia can be transitioned from previous antipsychotic treatment to xanomeline–trospium while maintaining symptomatic improvement over a 52-week period (Kaul, Claxton, Chaturvedi, et al., 2026; Ramey & Silva Almodóvar, 2025; Żelabowski et al., 2026).

Beyond traditional rating-scale assessments, the long-term EMERGENT-5 trial incorporated ecological momentary assessment (EMA) to evaluate real-world behavioral changes. Among 500 participants who completed EMA surveys over 12 months, treatment with xanomeline–trospium was associated with significant reductions in time spent at home, time spent alone, and engagement in unproductive activities. Concurrently, significant increases were observed in productive activities, both at home and away from home, as well as in positive affect. These behavioral improvements emerged early, were sustained throughout the study period, and were multidimensional, encompassing various aspects of patients' social functioning, including greater social engagement, increased time spent outside the home, and more productive functioning (Harvey et al., 2025).

Table 2. summarizes the key efficacy and safety outcomes from the EMERGENT clinical trial program. Xanomeline-trospium consistently demonstrated significant antipsychotic efficacy across all short-term trials, with a favorable safety profile characterized by transient gastrointestinal adverse events and no metabolic, extrapyramidal, or endocrine complications. Long-term extension studies confirmed sustained efficacy and a consistent safety profile over 52 weeks.

Table 2. Summary of Key Efficacy and Safety Outcomes from the EMERGENT Clinical Trial Program

Trial	Phase	Design	Population (N)	PANSS Reduction (Active vs Placebo)	Most Common Adverse Events
EMERGENT-1	2	5-week, RCT, DB, PC	179 (mITT)	-17.5 vs -7.8	Nausea, Constipation, Vomiting, Dry mouth
EMERGENT-2	3	5-week, RCT, DB, PC, multicenter	236 (mITT)	-20.8 vs -10.3 (LS mean difference: -9.6)	Constipation, Dyspepsia, Nausea, Headache, Vomiting, Hypertension
EMERGENT-3	3	5-week, RCT, DB, PC, multicenter	256 (mITT)	-18.2 vs -8.4 (LS mean difference: -8.4, Cohen's d = 0.60)	Nausea, Dyspepsia, Vomiting, Constipation, Hypertension
EMERGENT-4	3	52-week, open-label extension	152 safety population	Mean decrease from acute-trial baseline: -33.8 (prior xanomeline-trospium) vs -31.3 (prior placebo)	Nausea, Vomiting, Dyspepsia, Dry mouth
EMERGENT-5	3	52-week, open-label	566 safety population	Mean PANSS decrease: -33.3; $\geq 30\%$ reduction: $>75\%$ of participants	Nausea, Vomiting, Constipation, Hypertension, Diarrhea, Dry mouth, Dizziness

Abbreviations: RCT – randomized controlled trial; DB – double-blind; PC – placebo-controlled; mITT – modified intention-to-treat; PANSS – Positive and Negative Syndrome Scale; LS – least-squares; GI – gastrointestinal

4.5 Safety and Tolerability

Evidence from the Phase 2 and Phase 3 EMERGENT program consistently demonstrates that xanomeline–trospium exhibits a safety profile that is markedly distinct from that of conventional antipsychotics targeting dopamine D₂ receptors. In trials, treatment-emergent adverse events were observed in 70–82% of patients receiving KarXT, the vast majority of which were mild to moderate in intensity. Gastrointestinal disorders - particularly nausea, vomiting, constipation, and dyspepsia - constituted the most common adverse events, generally presenting during the first two weeks of treatment and being transient in nature. Of particular clinical relevance, xanomeline–trospium was not associated with extrapyramidal symptoms, prolactin elevation, or metabolic derangements - adverse effects that are frequently encountered with D₂ receptor antagonists. The proportion of patients discontinuing treatment due to adverse events was low (6–7%), mirroring the rates observed in placebo groups. The 52-week extension studies, EMERGENT-4 and EMERGENT-5, further confirmed the absence of late-onset safety concerns, cumulative toxicity, or worsening tolerability, reinforcing the drug's favorable long-term risk-benefit profile. These findings collectively support the use of xanomeline–trospium as a well-tolerated therapeutic strategy, particularly for patients who are unable to tolerate conventional antipsychotics or who have pre-existing metabolic disorders (Kaul, Claxton, Chaturvedi, et al., 2026; Kaul, Claxton, Sauder, et al., 2026; Żelabowski et al., 2026).

4.6 Comparison with Other Antipsychotics

Currently available antipsychotics, with the exception of xanomeline–trospium, primarily act through the dopaminergic system, either as dopamine D₂ receptor antagonists or as partial dopamine agonists. Traditional classifications into first-generation (typical) and second-generation (atypical) antipsychotics have been criticized as neither valid nor useful, and the Neuroscience-based Nomenclature (NbN) has been proposed as an alternative framework, categorizing drugs primarily by their mechanism of action (Leucht et al., 2024). First-generation antipsychotics, such as haloperidol and fluphenazine, are potent D₂ receptor antagonists associated with a high risk of extrapyramidal symptoms (EPS) and tardive dyskinesia. Second-generation antipsychotics, including olanzapine, risperidone, and quetiapine, combine D₂ antagonism with serotonin receptor blockade and offer a lower risk of EPS, but are associated with significant weight gain and metabolic disturbances. Clozapine, while uniquely effective in treatment-resistant schizophrenia, requires regular hematological monitoring due to the risk of agranulocytosis and is associated with substantial metabolic and cardiovascular side effects (Leucht et al., 2024; Crawford & Go, 2022). In contrast to these dopaminergic agents, xanomeline–trospium offers a fundamentally different mechanism - dual M₁/M₄ muscarinic receptor agonism - and a distinct safety profile. It is not associated with EPS, tardive dyskinesia, hyperprolactinemia, or metabolic abnormalities, which are common with dopamine D₂ receptor antagonists. Although gastrointestinal adverse events are more frequent than with conventional antipsychotics, they are typically transient and mild to moderate in severity (Bristol-Myers Squibb Company, 2024; Kaul et al., 2024; Kaul, Claxton, Chaturvedi, et al., 2026).

Table 3. provides a comparative overview of the key characteristics of the main antipsychotic drug classes including their mechanisms of action, clinical applications, and associated adverse effects.

Table 3. Comparative Overview of the Main Antipsychotic Drug Classes

Drug Class	Mechanism of Action	Example Agents	Common Adverse Effects
First-Generation Antipsychotics	D ₂ receptor antagonism	Haloperidol, Chlorpromazine, Fluphenazine	EPS, Tardive Dyskinesia, Hyperprolactinemia
Second-Generation Antipsychotics	D ₂ and receptor antagonism/partial agonism	Olanzapine, Risperidone, Quetiapine, Aripiprazole, Clozapine ¹	Weight gain, metabolic syndrome, sedation; variable EPS and prolactin risk ²
Muscarinic Receptor Agonists	M ₁ /M ₄ receptor agonism	Xanomeline-Trospium	Nausea, vomiting, dyspepsia, constipation

Abbreviations: EPS – Extrapyramidal symptoms

¹ Clozapine is occasionally listed as a separate category due to its unique efficacy in TRS and its specific safety profile. Its detailed pharmacology is beyond the scope of this review, which focuses on xanomeline–trospium. ² EPS risk is highest for risperidone and lowest for olanzapine and quetiapine. Prolactin elevation is most pronounced with risperidone and least with aripiprazole. Weight gain and metabolic effects are most pronounced with olanzapine and clozapine.

Sources: (Bristol-Myers Squibb Company, 2024; Crawford & Go, 2022; Leucht et al., 2024; Morrison et al., 2025).

4.7 Use in Special Populations

Data regarding the use of xanomeline–trospium during pregnancy are lacking, and no conclusions can be drawn about its potential to cause major birth defects, miscarriage, or other adverse outcomes. Nevertheless, untreated schizophrenia carries its own significant risks for pregnant women, including a higher likelihood of relapse, hospitalization, suicidal behavior, and adverse perinatal events such as preterm delivery. In animal studies, administration of xanomeline alone or in combination with trospium chloride during pregnancy and lactation produced maternal toxicity (manifested as clinical signs, reduced weight gain, decreased food intake, and mortality) along with embryofetal and developmental effects, including lower fetal and neonatal weight, stillbirths, and neonatal deaths. No structural malformations were observed in animal offspring, and the no-observed-adverse-effect level for maternal and developmental toxicity was comparable to or exceeded the maximum recommended human dose (Bristol-Myers Squibb Company, 2024).

Information on the presence of xanomeline or trospium in human milk and their effects on breastfed infants or milk production is unavailable. However, as both compounds are detectable in animal milk, their transfer into human milk is considered probable; thus, breastfeeding decisions should balance the benefits of nursing against the mother's clinical need and potential risks to the infant. The safety and effectiveness of COBENFY™ in pediatric patients have not been established (Bristol-Myers Squibb Company, 2024).

In geriatric patients, controlled clinical trials did not include sufficient numbers of individuals aged 65 years and older to determine whether they respond differently from younger adults. Given the elevated risk of urinary retention - particularly in older men with benign prostatic hyperplasia - a reduced maximum dose and more gradual titration are advised (Bristol-Myers Squibb Company, 2024).

Renal impairment affects the pharmacokinetics of both components. Although patients with mild renal impairment (eGFR 60 to <90 mL/min) exhibit higher systemic exposures to xanomeline and trospium, the safety profile observed in clinical studies was comparable to that in patients with normal renal function; therefore, no dose adjustment is required in this group. In moderate or severe renal impairment (eGFR <60 mL/min), however, use is not recommended (Bristol-Myers Squibb Company, 2024).

Hepatic dysfunction also increases xanomeline exposure. In patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment, xanomeline concentrations are substantially elevated. Consequently, COBENFY™ is contraindicated in moderate or severe hepatic impairment and is not recommended even in mild hepatic impairment; its pharmacokinetics in severe (Child-Pugh Class C) hepatic impairment have not been evaluated (Bristol-Myers Squibb Company, 2024).

Discussion

The clinical significance of xanomeline–trospium lies not only in its efficacy but also in its potential to address long-standing unmet needs in schizophrenia treatment. For patients who are intolerant to conventional antipsychotics due to EPS, metabolic complications, or hyperprolactinemia, this new agent offers a therapeutic alternative with a fundamentally different tolerability profile. Its lack of weight gain and metabolic effects may be particularly advantageous for patients with pre-existing metabolic conditions, such as diabetes or obesity. Furthermore, the preliminary evidence of improvement in negative symptoms and cognitive function - domains poorly addressed by dopaminergic agents - suggests broader clinical utility beyond positive symptom control (Correll, Angelov, et al., 2022; Kaul, Claxton, Chaturvedi, et al., 2026; Yohn et al., 2024).

In the context of existing treatment options, xanomeline–trospium fills an important gap. While clozapine remains the gold standard for treatment-resistant schizophrenia, its use is limited by its complex safety profile and the need for intensive monitoring. Xanomeline–trospium, by contrast, offers a novel mechanism with a favorable risk-benefit ratio that may make it a viable option for a broader range of patients, including those who are unable to tolerate clozapine. However, head-to-head studies comparing xanomeline–

trospium with clozapine in treatment-resistant populations are lacking, and its exact place in the therapeutic algorithm remains to be defined (Correll & Howes, 2021; Ramey & Silva Almodóvar, 2025).

In contrast to conventional symptom rating scales, the long-term EMERGENT-5 trial incorporated ecological momentary assessment (EMA) to provide an ecologically valid perspective on patients' daily lives. The EMA data indicated that treatment with xanomeline–trospium was accompanied by marked reductions in time spent at home and in solitude, alongside increased engagement in productive tasks and sustained improvements in positive affect. These changes were evident from the early weeks of therapy and persisted throughout follow-up. Their multidimensional character underscores clinically meaningful progress in social connectedness and everyday functioning - outcome domains that are essential for recovery yet frequently underappreciated in standard trial designs (Harvey et al., 2025).

Several limitations of the available evidence should be acknowledged. The short-term EMERGENT trials were limited to 5 weeks of double-blind, placebo-controlled observation, which, while sufficient to establish acute efficacy, provides limited insight into long-term outcomes. The 52-week open-label extension studies, EMERGENT-4 and EMERGENT-5, offer reassuring data on sustained efficacy and tolerability; however, their open-label design lacks a placebo comparator, limiting the strength of causal inferences regarding long-term benefits relative to no treatment. The exclusion of patients with treatment-resistant schizophrenia from the short-term trials represents a significant evidence gap, as does the absence of head-to-head comparisons with clozapine or any other antipsychotic agent. Furthermore, the short-term trial populations were relatively homogeneous (predominantly male and Black), raising questions about generalizability to broader demographic groups. Finally, data on the use of xanomeline–trospium in specific vulnerable populations - including pregnant women, breastfeeding mothers, pediatric patients, and elderly individuals (aged 65 years and older) - remain absent or limited, as discussed in the special populations section above (Bristol-Myers Squibb Company, 2024; Kaul, Claxton, Chaturvedi, et al., 2026; Kaul, Claxton, Sauder, et al., 2026; Kaul et al., 2025).

Looking ahead, several research directions warrant pursuit. Long-term comparative effectiveness studies against established antipsychotics, particularly clozapine, are needed to clarify the role of xanomeline–trospium in treatment-resistant schizophrenia, as no head-to-head trials have been conducted to date and current evidence is limited to indirect comparisons. Studies in more diverse populations, including elderly patients (excluded from the EMERGENT trials) and those with comorbid conditions, will be essential to confirm its safety and efficacy in routine clinical practice. The promising EMA data on functional outcomes should be replicated in larger, controlled studies. Additionally, as other muscarinic agonists and glutamatergic agents progress through clinical development, future research should investigate optimal treatment sequencing and the potential for augmentation strategies in patients with partial response. The distinct mechanism of xanomeline–trospium also raises questions about its role in early intervention and its applicability to other neuropsychiatric disorders characterized by cholinergic dysfunction.

Conclusions

Xanomeline–trospium represents a significant advancement in the pharmacotherapy of schizophrenia, offering the first approved antipsychotic with a predominantly muscarinic mechanism of action. The EMERGENT clinical trial program has established its efficacy across both short-term and long-term treatment, with consistently favorable safety and tolerability profiles. Unlike dopamine D₂ receptor antagonists, xanomeline–trospium is not associated with extrapyramidal symptoms, weight gain, metabolic disturbances, or hyperprolactinemia, addressing several long-standing unmet needs in schizophrenia care. Gastrointestinal adverse events, while common, are generally mild, transient, and manageable. For clinical practice, xanomeline–trospium may be particularly advantageous for patients who are intolerant to conventional antipsychotics or who have pre-existing metabolic conditions. Its distinct mechanism also raises the possibility of use in patients with partial response to dopaminergic agents, though head-to-head comparative studies are lacking. Future research should focus on long-term comparative effectiveness studies against established antipsychotics, particularly clozapine, to define its place in the therapeutic algorithm. Studies in more diverse populations including elderly patients, those with comorbid conditions, and treatment-resistant individuals are essential to confirm its safety and efficacy in routine clinical practice. As other muscarinic agonists and glutamatergic agents advance through clinical development, investigations into combination strategies and optimal treatment sequencing will be important next steps in realizing the full potential of this novel therapeutic class.

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