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Evaluating the Role and Efficacy of Cobenfy (Xanomeline and Trospium Chloride) in Schizophrenia Treatment - review

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Abstract
Schizophrenia is a complex psychiatric disorder often resistant to dopamine-targeting antipschotics. Cobenfy, a combination of xanomeline and trospium chloride, offers a novel approach by modulating muscarinic receptors while minimizing side effects. This review evaluates its efficacy and safety, particularly in treatment-resistant cases. Clinical trials show significant reductions in both positive and negative symptoms, positioning Cobenfy as a promising alternative.

Aim of the study
This review explores Cobenfy's role in schizophrenia treatment, focusing on its mechanism of action, clinical efficacy, and safety. It aims to assess its potential as an alternative for patients unresponsive to standard therapies.

Methodology
A literature review was conducted using PubMed, Google Scholar, and clinical trial registries. Keywords included "Cobenfy," "xanomeline," "trospium chloride," and "schizophrenia treatment," prioritizing randomized controlled trials, meta-analyses, and observational studies.

Summary
Schizophrenia treatment remains challenging, with many patients experiencing limited benefits from existing therapies. Cobenfy, a muscarinic receptor-targeting agent, has demonstrated efficacy in improving both positive and negative symptoms while avoiding metabolic and motor side effects. Findings from clinical trials, particularly EMERGENT-3, suggest its potential as a breakthrough in schizophrenia treatment. Further long-term studies are needed to confirm its benefits.

Keywords
Cobenfy, xanomeline-trospium, muscarinic receptor modulation, schizophrenia treatment, non-dopaminergic antipsychotics, EMERGENT trials, antipsychotic therapy.

Introduction

Schizophrenia is a complex and heterogeneous clinical syndrome of disturbed perception, thought, affect, and behavior. While the term "schizophrenia" has been used for over a century, its definition and diagnostic criteria have evolved. Schizophrenia, as defined by the DSM-5, requires two or more characteristic symptoms (delusions, hallucinations, disorganized speech, disorganized/catatonic behavior, or negative symptoms), with at least one being delusions, hallucinations, or disorganized speech. These symptoms must be present for a significant portion of time during a one-month period and cause significant functional impairment. Continuous signs of the disturbance must persist for at least six months. The DSM-5 also includes criteria to exclude schizoaffective disorder, mood disorders with psychotic features, and substance/medical condition-induced psychosis **(1-4)**. ICD-11 is moving towards a more dimensional approach compared to the DSM-5's categorical one. A key change in ICD-11 is the removal of traditional subtypes of schizophrenia. Instead, ICD-11 uses symptom specifiers to capture a more detailed picture of an individual's presentation, including the presence and severity of specific symptoms, their course over time, and response to treatment. Both systems aim to provide clinicians with tools for accurate diagnosis and treatment planning, but ICD-11 emphasizes a more flexible and individualized assessment of the illness and they are now closer than at any time since the ICD-8 and DSM-II **(4-7).**

1. Pathophysiology

Schizophrenia's pathophysiology is complex and involves multiple neurotransmitter systems. It's increasingly understood as a disorder of disrupted neural circuitry rather than a simple imbalance of a single neurotransmitter.

- **Dopamine:** The dopamine hypothesis, one of the oldest and most influential, posits that schizophrenia involves excessive dopamine activity in certain brain regions, particularly the mesolimbic pathway. This hyperactivity is thought to contribute to positive symptoms like hallucinations and delusions. The D2 receptor, in particular, has been a primary target of antipsychotic medications. However, the dopamine hypothesis is an oversimplification, as not all individuals with schizophrenia respond to dopamine-blocking medications, and these drugs often have limited effects on negative and cognitive symptoms **(8).**

- **Serotonin:** The serotonin system is also implicated in schizophrenia. Atypical antipsychotics often target serotonin receptors, particularly the 5-HT2A receptor, in addition to dopamine receptors. Serotonin modulation can influence dopamine release and may improve negative and cognitive symptoms. Interactions between dopamine and serotonin systems are complex and play a role in the overall symptomatic presentation of schizophrenia **(9).**

- **Acetylcholine:** Muscarinic receptors, particularly M1 and M4 subtypes, are expressed in brain regions relevant to schizophrenia, such as the prefrontal cortex, hippocampus, and striatum. M1 receptors are involved in cognitive processes, while M4 receptors modulate dopaminergic transmission. Deficits in muscarinic receptor function may contribute to both cognitive impairments and positive symptoms of schizophrenia. Some studies have found altered expression of M1 and M4 receptors in the brains of individuals with schizophrenia. These findings suggest that muscarinic receptor dysfunction may be an important aspect of the pathophysiology of schizophrenia, potentially offering a novel target for therapeutic interventions **(10, 11)**.

- **Other Neurotransmitter Systems: glutamate** (the glutamate hypothesis suggests that diminished glutamatergic activity, particularly involving NMDA receptors, may contribute to schizophrenia), **GABA** (GABA is the primary inhibitory neurotransmitter, and abnormalities in GABAergic neurotransmission have been implicated in schizophrenia). Additional neurotransmitters, including norepinephrine, histamine, and neuropeptides, may contribute to schizophrenia, though their precise roles remain less clearly established.

2. Epidemiology

Schizophrenia affects about 1% of the world's population. While the rate of schizophrenia is fairly consistent across countries, the number of people affected has increased due to population growth. Men are slightly more likely to be diagnosed and often experience a more severe form of the illness. Schizophrenia's etiology is multifactorial, involving complex interactions between genetic vulnerability and environmental exposures. Genetic studies indicate a high heritability (up to 80%), predisposing individuals with a family history. Environmental risk factors encompass a range of prenatal, perinatal, and postnatal influences. Obstetrical complications and adolescent cannabis use have been linked to earlier onset. Additional environmental factors implicated include urbanicity, migration, childhood trauma, and exposure to infectious agents **(12-16)**.

3. Scales used in schizophrenia evaluation

The evaluation of schizophrenia symptoms and overall severity often relies on standardized assessment scales. Two commonly used instruments are the Positive and Negative Syndrome Scale (PANSS) and the Clinical Global Impressions-Severity scale (CGI-S). The PANSS is a widely used, 30-item scale designed to assess the severity of both positive and negative symptoms of schizophrenia, as well as general psychopathology. Developed by Kay, Opler, and Fiszbein in 1987, it has become a "gold standard" for evaluating the effects of psychopharmacological treatments. The PANSS is composed of several subscales **(17, 18)**:

- **Positive Subscale:** Measures symptoms such as delusions, hallucinations, and disorganized thinking
- **Negative Subscale:** Assesses symptoms like blunted affect, emotional withdrawal, and poor rapport
- **General Psychopathology Subscale:** Evaluates a range of symptoms, including anxiety, depression, and somatic concerns.

The PANSS offers a thorough evaluation of schizophrenia symptom severity and effectively detects changes in clinical trials. Abbreviated versions, such as the PANSS-6, have been introduced to enable faster assessments.

The CGI-S is a single-item, 7-point scale that provides a global assessment of the severity of a patient's illness. Clinicians use their overall impression of the patient's condition to rate the severity of illness from 1 (normal, not at all ill) to 7 (extremely ill). The CGI-S is often used in conjunction with other scales, such as the PANSS, to provide a comprehensive evaluation of treatment response **(10).**

4. Methods of treatment

The management of schizophrenia typically involves a multifaceted approach integrating pharmacological and non-pharmacological interventions. Pharmacotherapy remains central, with antipsychotics categorized into two main classes: typical (first-generation) and atypical (second-generation) agents. Typical antipsychotics, like haloperidol and chlorpromazine, mainly block dopamine D2 receptors, alleviating positive symptoms. However, their use is often restricted due to an increased risk of extrapyramidal side effects, including parkinsonism and tardive dyskinesia. Atypical antipsychotics, including risperidone, olanzapine, quetiapine, and aripiprazole, exhibit a more complex mechanism of action, often involving a combination of dopamine and serotonin receptor modulation. While they generally pose a lower risk of EPS (extrapyramidal symptoms), they are associated with metabolic side effects such as weight gain, dyslipidemia, hyperglycemia, insulin resistance, increased risk of type 2 diabetes, hypertension, metabolic syndrome **(19, 20).** The atypical antipsychotic drug clozapine is often considered a 'last resort' medication due to its unique efficacy and significant risks. It is indicated for treatment-resistant schizophrenia, typically defined as the failure to respond to at least two different antipsychotics. It demonstrates superior efficacy in reducing both positive and negative symptoms in a significant proportion of patients with TRS. However, clozapine's use is limited by the potential for agranulocytosis, a severe and potentially fatal blood dyscrasia. Consequently, initiation of clozapine requires strict monitoring of white blood cell counts. Other notable side effects include seizures, myocarditis, and metabolic disturbances **(21, 22).**

While pharmacotherapy, particularly with antipsychotic medications, forms the foundation of schizophrenia treatment, non-pharmacological interventions play a vital, complementary role in improving overall outcomes and quality of life. It's important to emphasize that these interventions are most effective when used in conjunction with medication, not as a replacement for it. These interventions address functional and psychosocial aspects of the illness.

A range of psychosocial interventions including cognitive behavioral therapy, social skills training, and supported employment can be used. Integrated care models, which combine pharmacological and psychosocial approaches, are considered essential for comprehensive management of schizophrenia **(23-25).**

Another non-pharmacological approach in schizophrenia treatment is electroconvulsive therapy. ECT remains a controversial yet potential treatment option for individuals with treatment-resistant schizophrenia, particularly in cases where multiple antipsychotic trials have failed to produce significant clinical improvement. While concerns persist regarding its long-term effects, such as memory impairment, ECT has been explored as an adjunct to pharmacotherapy in patients who do not respond adequately to conventional treatment. Despite some evidence suggesting its potential benefits, the overall quality of research in this area remains limited due to methodological inconsistencies and small sample sizes. Therefore, while ECT may offer symptom relief for select patients, further rigorous studies are needed to establish its efficacy and safety in schizophrenia management **(26).**

Given the limitations of current antipsychotic treatments, there is an increasing interest in therapeutic approaches that target alternative neurotransmitter systems. The cholinergic system, particularly muscarinic receptor modulation, has emerged as a promising avenue due to its involvement in cognitive processes and behavioral regulation. Cobenfy, a novel therapeutic agent combining xanomeline, a muscarinic receptor agonist, with trospium, a peripheral muscarinic antagonist, represents a significant advancement in this field. By selectively targeting central muscarinic receptors while minimizing peripheral side effects, this approach offers a potential breakthrough in the treatment of schizophrenia, particularly for patients who do not respond adequately to conventional dopamine-based therapies.

5. Cobenfy - mechanism of action

Cobenfy is a medication combining xanomeline and trospium chloride, designed to address the neurotransmitter imbalances associated with schizophrenia.

An analysis of its pharmacological components:

- Xanomeline is a muscarinic receptor agonist that exhibits preferential selectivity for the M1 and M4 receptor subtypes. These receptors play a crucial role in cognitive function, synaptic plasticity, and the modulation of neurotransmitter systems, particularly dopamine and glutamate, which are implicated in the pathophysiology of schizophrenia. The M1 receptor, widely expressed in the hippocampus and prefrontal cortex, has been associated with cognitive processes such as memory and executive function . Meanwhile, the M4 receptor, found in the striatum, is involved in regulating dopaminergic transmission, which is particularly relevant to the dopaminergic dysregulation observed in schizophrenia. By stimulating these muscarinic receptors, xanomeline has been shown to modulate dopamine release indirectly, potentially reducing both positive and negative symptoms of schizophrenia without the extrapyramidal side effects commonly associated with dopamine D2 receptor antagonism. Preclinical and clinical studies have demonstrated that xanomeline can improve cognitive deficits and alleviate psychotic symptoms, making it a promising alternative to traditional antipsychotics.

Furthermore, unlike conventional antipsychotics, which primarily target dopaminergic pathways, muscarinic receptor modulation offers a novel mechanism of action that may address unmet therapeutic needs in schizophrenia treatment. However, xanomeline's clinical utility has historically been limited by peripheral cholinergic side effects such as nausea, vomiting, and increased salivation, necessitating further refinements in its formulation and delivery to improve tolerability **(10, 27-30).**

- Trospium chloride is a peripherally acting muscarinic antagonist designed to mitigate the systemic cholinergic side effects associated with muscarinic receptor agonists such as xanomeline **(10).** As a quaternary ammonium compound, trospium chloride exhibits minimal central nervous system penetration due to its limited ability to cross the blood-brain barrier, thereby selectively targeting peripheral muscarinic receptors while preserving central cholinergic activity. This pharmacokinetic property is particularly advantageous in combination therapy, as it allows for the muscarinic modulation of schizophrenia-related symptoms via xanomeline while reducing the incidence of peripheral side effects, such as gastrointestinal discomfort and excessive salivation. Originally developed for the treatment of overactive bladder, trospium chloride's established safety profile and selectivity for peripheral muscarinic receptors make it a suitable adjunct in dual-drug formulations aimed at optimizing cholinergic modulation in neuropsychiatric disorders (10, 31).

The combination of xanomeline with trospium chloride represents a novel therapeutic approach that seeks to balance efficacy and tolerability, addressing previous limitations of muscarinic receptor-based treatments in schizophrenia. This innovative therapy received approval from the U.S. Food and Drug Administration (FDA) on September 26, 2024, under the brand name Cobenfy, marking it as the first antipsychotic drug targeting cholinergic receptors rather than the traditional dopamine receptors. The approval was based on clinical trials demonstrating significant reductions in both positive and negative symptoms of schizophrenia, with a favorable safety profile compared to existing treatments. The introduction of Cobenfy offers a promising alternative for patients with schizophrenia, especially those who have not responded adequately to traditional antipsychotic therapies, by providing a treatment option that effectively manages symptoms while reducing the risk of common side effects associated with dopamine receptor antagonism **(32, 33).**

7. Clinical Trials

7.1 Safety and tolerability

EMERGENT-1 trial was a phase 2, randomized, double-blind, placebo-controlled study evaluating Cobenfy in adult inpatients with schizophrenia. The aim of the study was to assess the safety and tolerability of Cobenfy. The trial enrolled 182 patients (aged 18−60 years) meeting DSM-5 criteria for schizophrenia, with recent exacerbation of positive symptoms requiring hospitalization (PANSS ≥80, CGI-S ≥4).

Key exclusion criteria were other primary psychiatric diagnoses, treatment resistance to antipsychotics, or a ≥20% PANSS improvement between screening and baseline. Participants received either Cobenfy or placebo twice daily for 5 weeks. Cobenfy dosing was flexible (50 mg xanomeline/20 mg trospium to 125 mg xanomeline/30 mg trospium). Safety was assessed through AE monitoring, weight, lab values, and vital signs. Analyses focused on procholinergic (e.g., nausea) and anticholinergic (e.g., dry mouth) AEs. Vital signs were measured regularly. Standard safety data are in the primary publication **(34).**

Focusing on procholinergic and anticholinergic adverse events, the EMERGENT-1 trial results showed that the most frequent AEs occurring in ≥2% of patients in the Cobenfy group, with an incidence more than twice that of the placebo group, were nausea (16.9% vs. 4.4%), vomiting (9.0% vs. 4.4%), constipation (16.9% vs. 3.3%), and dry mouth (9.0% vs. 1.1%). The severity of the majority of these procholinergic and anticholinergic AEs was mild, with none rated as severe. Importantly, no patients in either the Cobenfy or placebo groups discontinued the study due to these specific AEs **(34).**

7.2 Efficiency and safety

The **EMERGENT-3** trial adds to the growing evidence supporting xanomeline-trospium as a treatment for schizophrenia. As an inpatient, phase 3, 5-week, double-blind, randomized controlled trial, it was designed to rigorously assess the efficacy and safety of this novel therapy in adults experiencing acute psychosis—an approach considered the gold standard for minimizing bias and confounding factors **(10).**

The study enrolled 256 patients, randomized 1:1 to xanomeline-trospium (n=125) or placebo (n=131), following an initial screening of 431 individuals. Inclusion criteria ensured a **c**linically significant symptom burden, requiring a PANSS total score between 80 and 120 and a score of ≥4 on at least two core positive symptoms (delusions, disorganization, hallucinations, suspiciousness/persecution). A CGI-S score of ≥4 was also required. Exclusion criteria included a primary disorder other than schizophrenia within the last 12 months, treatment resistance to antipsychotics, or a ≥20% PANSS score improvement between screening and baseline **(10).**

Participants received xanomeline-trospium twice daily for five weeks, with a titrated dosing regimen: 50 mg/20 mg BID for two days, then 100 mg/20 mg BID for days 3–7, followed by 125 mg/30 mg BID from day 8 onward, with the option to reduce to 100 mg/20 mg BID if tolerability issues arose. The CGI-S and PANSS scores were assessed weekly, while adverse events were monitored from the first dose until discharge. Safety assessments mirrored those in EMERGENT-2 (10).

Demographics were largely balanced, with a mean age of 43 years and a predominantly male population, though the xanomeline-trospium group had a higher proportion of females (30.4% vs. 20.6%). The racial composition included a substantial proportion of Black or African American participants, aligning with FDA recommendations for diversity in clinical trials **(10).**

The endpoint was the change in PANSS total score from baseline to week 5. The xanomeline-trospium group showed a significant reduction of 20.6 points, compared to 12.2 points in the placebo group (Cohen's d = 0.60, indicating a moderate effect size).

Moreover, a ≥30% improvement in the PANSS total score (response criterion) was achieved by 50.6% of the xanomeline - trospium group, versus 25.3% in the placebo group ($p < 0.1$). CGI-S improvement was greater in the treatment group (−1.1 vs. −0.6, $P<0.001$) (10).
Safety assessments revealed treatment-emergent adverse events (TEAEs) in 70.4% of the xanomeline - trospium group vs. 50.0% in placebo. Common TEAEs included nausea (19.2%), vomiting (16.0%), and constipation (12.8%). No significant weight gain or extrapyramidal symptoms were observed. Hypertension was more frequent in the treatment group (6.4% vs. 1.6%), but no QTc prolongation occurred (10).

7.3 Long term trials

The **EMERGENT-4** trial, a 52-week, open-label extension study, assessed the long-term profile of Cobenfy regarding safety, tolerability, and efficacy in 156 adults diagnosed with schizophrenia. These participants had previously completed the treatment phase of the EMERGENT-2 or EMERGENT-3 trials. Results from EMERGENT-4 indicated that Cobenfy treatment facilitated continuous improvements in schizophrenia symptoms across all efficacy measures, including the PANSS total, CGI-S, PANSS positive subscale, and PANSS negative subscale scores, throughout the 52-week study. Participants who initially received a placebo during the acute trials experienced rapid symptom amelioration upon initiation of Cobenfy treatment. By the fourth week, their PANSS total scores were comparable to those initially treated with Cobenfy. Symptomatic improvements persisted over the 52-week study duration, irrespective of whether participants received Cobenfy or placebo during the acute trials. At the conclusion of the trial, 69% of the participants completing the study achieved a ≥30% improvement in schizophrenia symptoms from their acute trial baseline, based on PANSS total score assessments. Cobenfy was generally well-tolerated during long-term administration, with no new safety or tolerability issues identified beyond those previously known. The most frequently reported treatment-related adverse events (≥5%) included nausea, vomiting, dyspepsia, dry mouth, and hypertension. These events were predominantly mild to moderate, did not commonly result in discontinuation of treatment, and often resolved with continued therapy. The discontinuation rate due to adverse events in EMERGENT-4 was 11%. Treatment with Cobenfy was associated with a mean reduction in body weight of 1.9 kg from the acute trial baseline at 52 weeks. Additionally, Cobenfy did not induce clinically meaningful changes in prolactin levels or movement disorder scale scores, and there were no reported adverse events of akathisia or tardive dyskinesia **(35).**
As the EMERGENT-4 trial, the **EMERGENT-5** study was designed to evaluate the long-term effects of Cobenfy. It was a Phase 3, 52-week, open-label trial conducted in the United States, researchers investigated the long-term safety, tolerability, and efficacy of Cobenfy in 566 adult participants with schizophrenia. These individuals had previously achieved symptom stability on other antipsychotics but had no prior exposure to Cobenfy. Enrolled participants exhibited mild to moderate illness severity, with a PANSS total score of ≤80 (averaging 66.0) and a CGI-S score of ≤4 (averaging 3.4). The study demonstrated that Cobenfy treatment led to sustained symptomatic improvement across all measured efficacy parameters. This included the PANSS total score, CGI-S score, and both positive and negative subscale scores, evaluated over 52 weeks, thus confirming the maintenance of therapeutic effect with extended treatment.

At week 52, 30% of participants showed a ≥30% reduction from their initial PANSS total score, with an overall average reduction of 5.5 points. Long-term Cobenfy administration was generally well-tolerated, and no new safety concerns emerged during the trial. The most frequently reported treatment-related adverse events (≥5%) encompassed nausea, vomiting, constipation, dry mouth, diarrhea, dyspepsia, dizziness, hypertension, and somnolence. The majority of these events were mild to moderate in severity and did not frequently lead to treatment discontinuation; the discontinuation rate attributed to adverse events in EMERGENT-5 was 18%. Furthermore, Cobenfy use was correlated with a mean body weight decrease of 2.2 kg from baseline at 52 weeks, and there were no significant changes observed in movement disorder scales or prolactin levels **(35).**

Conclusions

The findings from recent clinical trials support the efficacy of Cobenfy in the treatment of schizophrenia, particularly for patients with inadequate response to traditional therapies. Compared to placebo, Cobenfy was associated with significant improvements in symptom reduction and functional outcomes. Long-term studies, including EMERGENT-4 and EMERGENT-5, further confirm its sustained effectiveness and tolerability over extended periods. These trials demonstrated continued symptom improvement, high patient adherence, and minimal severe adverse effects, reinforcing the viability of Cobenfy as a long-term treatment option. The drug's dual mechanism—targeting muscarinic receptors while mitigating peripheral side effects-offers an innovative approach with the potential to expand treatment options for schizophrenia. Future research should focus on long-term effectiveness, real-world applicability, and potential combination therapies to further optimize schizophrenia management.

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