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Treatment of Schizophrenia with Cobenfy (KarXT): A Literature Review

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ABSTRACT

Introduction and purpose: In September 2024, the FDA approved a new drug for the treatment of schizophrenia in adults, Cobenfy, also known as KarXT. COBENFY combines xanomeline, a muscarinic agonist, and trospium chloride, a muscarinic antagonist. It is the first antipsychotic approved for the treatment of schizophrenia that targets cholinergic receptors rather than dopamine receptors, which could be a completely new standard of care. The purpose of this literature review is to introduce the new psychotropic drug, discuss the mechanism of action, and present the results of the EMERGENT-1, EMERGENT-2 and EMERGENT-3 clinical trials.

Materials and methods: The authors conducted an extensive review of articles available in PubMed and Google Scholar. Standard criteria were used to review the literature data. The search of articles in the database was carried out using the following keywords: schizophrenia, dopamine hypothesis, cholinergic hypothesis, xanomeline, trospium.

Conclusions: EMERGENT-2 and EMERGENT-3 trials have shown significant improvement in positive and negative symptoms of schizophrenia. Cobenfy may be a good alternative in the management of schizophrenia, especially in resistant cases to conventional therapy or intolerable side effects to conventional therapy. However, to evaluate the long-term safety, tolerability, and efficacy of KarXT there is a need to analyze longer studies whose ongoing research are unpublished yet.

Keywords: schizophrenia; dopamine hypothesis; cholinergic hypothesis; xanomeline; trospium

Introduction

Schizophrenia is a chronic, potentially devastating mental illness that affects about 3% of the general population [1]. Between 1990 and 2019, there was a 65% global increase in schizophrenia cases [2]. It usually begins in late adolescence or early adulthood and is characterized by a wide range of symptoms that have a significant impact on the lives of patients. These symptoms can be divided into three distinct groups: positive symptoms, which include delusions, hallucinations, and disorganized behavior; negative symptoms, such as reduced social drive and motivation; and cognitive symptoms, which include deficits in attention, memory, and learning [3]. Cognitive impairment in schizophrenia (CIAS) is one of the key symptoms of this mental disorder. Current antipsychotic drugs, including second-generation ones, have little benefit in improving cognitive functions [4]. Schizophrenia accounts for 1.1% of the DALYs and typically reduces life expectancy by approximately 10 years, with suicide contributing most of that reduction [5]. People with schizophrenia have a higher risk of developing cardiometabolic disorders such as obesity, type 2 diabetes and hypertension, which is due to various factors, including lifestyle, disease severity and side effects of psychotropic medications, especially antipsychotics [6].

Current psychiatric therapies typically focus on positive symptoms, which is understandable, since these symptoms are the most important in diagnosis and often lead to hospitalization. However, these symptoms account for only a fraction of the total functional impairment experienced by patients. Unmet negative symptoms and cognitive symptoms have a significant impact on patients' quality of life [7]. According to data, between 20 and 50 percent of patients do not react well to their current medications [3]. The exact cause of schizophrenia is still unclear, however, since the introduction of antipsychotics like chlorpromazine, for the last 60 years understanding of its biological basis has been shaped by the dopamine hypothesis. The dopamine hypothesis proposes that schizophrenia results from increased dopaminergic activity in the striatum and midbrain. Antipsychotic drugs are the mainstay for treating schizophrenia, they work primarily by antagonizing dopamine D2 receptors leading to reduction of the positive symptoms, but they have limited effectiveness against negative and cognitive symptoms [8,9]. First-generation antipsychotics such as chlorpromazine and haloperidol, also known as typical antipsychotics, function by blocking dopamine D2 receptors in the brain, significantly reducing positive symptoms of schizophrenia, such as hallucinations and delusions. Their action is widespread, affecting all major dopamine pathways, which can lead to both therapeutic effects and considerable adverse effects. Common side effects include extrapyramidal symptoms (EPS), such as tremors and rigidity, arising from decreased dopamine in the nigrostriatal

pathway. Additionally, FGAs can cause hyperprolactinemia, resulting in hormonal side effects like gynecomastia and menstrual irregularities. They may even exacerbate negative symptoms, such as emotional flatness, highlighting the need for newer treatments that address these limitations [7]. Second-generation antipsychotics such as risperidone, olanzapine, quetiapine and aripiprazole cause fewer extrapyramidal side effects and tardive dyskinesia and are thus most widely prescribed category of antipsychotics. They primarily act as antagonists or partial agonists at dopamine D2 receptors, which is crucial for their antipsychotic effects. They also interact with various other neurotransmitter systems, such as serotonin and glutamate, thereby influencing multiple pathways that contribute to their effectiveness in treating schizophrenia. Despite their broader receptor profile, these second-generation drugs are not without limitations as their efficacy can be limited by the development of tolerance, adverse side effects such as a higher risk of metabolic side effects such as weight gain and diabetes, and inadequate control of negative and cognitive symptoms [10]. These side effects negatively impact drug compliance, leading to high hospitalization and relapse rates.Therefore, there is a growing need for schizophrenia drugs that work through different mechanisms of action.

Alterations in neuronal structure and functionality, such as reduced dendritic hairpin density and increased synaptic pruning, are now seen as key elements in the pathophysiology of schizophrenia, suggesting that traditional dopamine-based theories may not fully capture the complexity of this disorder and its response to treatment [11].

Particularly noteworthy for its effectiveness in treating treatment-resistant schizophrenia is the atypical antipsychotic clozapine, which has shown a superior response in 60–70% of patients who were previously unresponsive. In certain patient subgroups, clozapine also shows some promise in reducing cognitive symptoms [12].

Studies revealed that the therapeutic effects of clozapine can be linked to its effect on the muscarinic receptors, particularly the M1 and M4 subtypes, which are involved in cognitive function. This connection raised speculation that the modulation of the muscarinic system has the potential to reveal new perspectives for the development of antipsychotic treatment, justifying the hypothesis that cholinergic dysregulation is an etiology of schizophrenia pathophysiology [13].

Cholinergic theory

The cholinergic system is one of the most essential modulatory systems in the brain. It controls a wide range of brain activity, including cognitive functions. It is divided into two main

networks: brain stem complex - which is related to psychosis and forebrain complex - related to cognitive functions [14,15].

There are two main categories of cholinergic receptors responsible for these effects, nicotinic and muscarinic receptors. They differ not only structurally but also pharmacodynamically. Nicotinic receptors are ligand-gated ion channels that generate immediate, fleeting neural responses. Muscarinic receptors, on the other hand, are G protein-coupled receptors that involve more intricate signaling cascades and have longer durations of action. Muscarinic receptors are denser in the central nervous system than nicotinic receptors and occur in five subtypes: M1, M2, M3, M4, and M5. These receptors are variably localized in the brain, and M2 and M4 receptors are found predominantly on cholinergic interneurons in neo-striatum like nucleus accumbens, a critical component of the mesolimbic pathway, whereas M1 receptors are found on striatal projection neurons and neocortex as well as on prefrontal cortex. Notably, M5 receptors are alone found on dopaminergic neurons of the midbrain. These findings are particularly significant because the cognitive symptoms are usually seen before other psychotic symptoms and are great predictors of the illness course [1,16]. Postmortem studies in patients with schizophrenia show a decrease in the number of M1 receptors in the dorsolateral prefrontal cortex and a reduction in M4 receptors in the hippocampus. Studies have shown a correlation between the availability of these receptors and symptoms of schizophrenia, suggesting that their deficit may be related to the severity of psychotic symptoms [17]. Knockout mouse studies have provided key insights into the importance of muscarinic receptors in schizophrenia. Using genetic engineering techniques, it has become possible to create knockout mice in which specific receptor subtypes have been eliminated, allowing the study of their role in health and disease. Mice lacking the M1 receptor are deficient in cognitive functions such as learning and memory. This shows that the M1 receptor has a very crucial role in cognitive functions and could be employed as a target for therapy for increasing the cognitive deficits present in schizophrenia. Mice lacking the M4 receptor are hyperactive and more sensitive to psychostimulants, reflecting the psychopathology typical of schizophrenia. This confirms that M4 receptor activity is important for the regulation of dopaminergic activity. Mice lacking the M4 receptor show increased sensitivity to amphetamine, suggesting disturbances in dopaminergic signaling similar to those seen in patients with schizophrenia. M1-deficient mice also exhibit cognitive deficits, confirming the link between muscarinic receptor activity and cognitive function [18,19].

Since the cholinergic system regulates learning, attention, and episodic memory, among other things, disturbances in cholinergic transmission affect cognitive functions. Another proof of the

importance of the cholinergic system in the pathophysiology of schizophrenia is the fact that the use of anticholinergic drugs can worsen cognitive functions [14,15]. Research has consistently indicated significant associations between polymorphisms in mAChR genes and the symptoms of schizophrenia. For example, studies have found that genetic variations can influence mAChR expression levels and function in critical brain regions implicated in the disorder (Bridges et al., 2010. The cholinergic hypothesis radically changes the way we think about schizophrenia, showing that it is a more complex disease that requires a holistic approach that takes into account different neurotransmitter systems. This change is crucial for the development of more effective therapeutic strategies that can better address the complexity of schizophrenic symptoms [21].

Xanomeline-Trospium

Xanomeline is an oral selective muscarinic cholinergic receptor agonist, in which it is a primary agonist of the M1 and M4 muscarinic receptors and an antagonist of the M5 receptors. It increases the release of dopamine in the prefrontal cortex, which is essential in schizophrenia [22]. The first reports of xanomeline's efficacy came from clinical trials of Alzheimer's disease in the 1990s. In a double-blind, proof-of- concept small study, patients with schizophrenia taking xanomeline showed significant improvement in cognitive symptoms, by increasing cholinergic modulation, which is crucial for memory and learning processes,as well as positive and negative symptoms. However, despite xanomeline's promising efficacy profile, the study was discontinued because of significant cholinergic side effects - nausea, vomiting, diarrhea, excessive sweating, and excessive salivation [23]. Trospium chloride, used for years in the treatment of overactive bladder, is a nonselective muscarinic antagonist. Due to its highly polarized tertiary amine structure, it does not enter the central nervous system [3]. Researchers anticipated that combining trospium chloride with xanomeline would reduce side effects of xanomeline and hypothesised this new therapy would reduce psychosis in people living with schizophrenia [24]. In a Phase 1 trial with healthy volunteers, adding trospium to xanomeline reduced the incidence of cholinergic adverse events by about 50% compared to xanomeline alone. These findings suggest that combining xanomeline with trospium may allow for the therapeutic stimulation of brain muscarinic receptors while minimizing peripheral side effects [3,13]**.**

The EMERGENT clinical program

The EMERGENT trial was designed to evaluate the efficacy of COBENFY, a novel antipsychotic medication consisting of a combination of xanomeline and trospium chloride in

the treatment of acute psychosis in DSM-5 candidacy for schizophrenia. The trial was formulated to evaluate a novel way of treating schizophrenia through muscarinic receptor agonism as opposed to the typical D2 dopamine receptor blockade. This research built on earlier work when xanomeline was discovered to show promise in psychosis symptom treatment but was limited by gastrointestinal side effects. To avoid such shortcomings, researchers mixed xanomeline with trospium chloride in an attempt to reduce gastrointestinal adverse effects without compromising therapeutic effects.

The EMERGENT program consisted of three key 5-week, multisite, inpatient trials from September 2018 to December 2022 at 30 US sites and 12 sites in Ukraine. The trials were conducted in adults 18-60 years (EMERGENT-1) or 18-65 years (EMERGENT-2 and EMERGENT-3) with schizophrenia. Subjects were required to fulfill some inclusion criteria, including acute exacerbation requiring inpatient treatment within the last 2 months since screening, a range of baseline PANSS total scores of 80-120, and a CGI-S score ≥4. Every trial adhered to the principles of the Declaration of Helsinki and Good Clinical Practice guidelines and had centralized institutional review board approval. The trials utilized a flexible-dose design using the same dose level used across all three trials. Statistical analysis used a modified intention-to-treat population [25,26].

Efficacy Measures

The CGI-S and PANSS were assessed at screening, baseline, and weekly during the 5-week treatment period. The CGI-S (Clinical Global Impressions-Severity) evaluates the current severity of a patient's condition during the assessment. The CGI-S categorizes the severity of the illness as: 1 = Normal, not at all ill; 2 = Borderline mentally ill; 3 = Mildly ill; 4 = Moderately ill; 5 = Markedly ill; 6 = Severely ill; and 7 = Among the most extremely ill patients. The PANSS is a medical scale used for measuring symptom severity of participants with schizophrenia. The PANSS rating form contains 7 positive symptom scales, 7 negative system scales, and 16 general psychopathology symptom scales. Participants are rated from 1 to 7 on each symptom scale. The total score is the sum of all scales with a minimum score of 30 and a maximum score of 210. A decrease in PANSS total score correlates with an improvement in schizophrenia symptoms [27]. Participants needed a baseline PANSS total score between 80 and 120, with scores of 4 or higher on at least two of the following positive scale items: delusions (P1), conceptual disorganization (P2), hallucinatory behavior (P3), and suspiciousness/persecution (P6). A CGI-S score of at least 4 was also required at both screening and baseline.

The mean PANSS total score at baseline for patients receiving Cobenfy was 97.5. The dosing regimen was the same in all 3 EMERGENT trials. KarXT was taken twice daily according to the following schedule:

1. Days 1-2: 50 mg xanomeline and 20 mg trospium twice a day.
2. Days 3-7: 100 mg xanomeline and 20 mg trospium twice a day.
3. Day 8 onward: The dose could be increased to 125 mg xanomeline and 30 mg trospium twice daily, based on how well the patient tolerated the medication, except for the last 2 weeks, when no dose changes were permitted. This flexible approach allowed for dose adjustments to ensure better tolerability while maximizing the potential benefit of the treatment.

EMERGENT 1

The EMERGENT 1 trial involved 182 adult patients aged 18 to 60 years with schizophrenia. They had severe positive symptoms necessitating hospitalization. In the study group, 90 patients were given KarXT and 92 were given placebo. The trial was conducted for 5 weeks, following a 7-day screening period. Patients were assigned to the experimental or control group 1:1. Vital signs, metabolic effects, and adverse events were monitored. Two categories of adverse events were found: procholinergic (e.g. nausea, vomiting) and anticholinergic (e.g. dry mouth, constipation) [6,28]. At baseline, the xanomeline–trospium group's PANSS total score was 97.7, while the placebo group was 96.6. The xanomeline-trospium group experienced a significantly larger change from baseline to week five, with a reduction of -17.4 points compared to −5.9 points with a placebo. The xanomeline-trospium group experienced a significant improvement in symptoms when compared to the placebo group, as evidenced by the statistically significant ($P<0.001$) difference in the two groups' least-squares means of −11.6 points with a 95% CI of −16.1 to −7.1. Though symptom reduction was apparent, the percentage of patients with a CGI-S response did not reach statistical significance between the groups, suggesting that overall clinical improvement may have been less noticeable from the clinician's point of view. Constipation (17%), nausea (17%), dry mouth (9%), dyspepsia (9%), and vomiting (9%), were the most frequent adverse events in the xanomeline-trospium group. It's interesting to note that none of these events resulted in treatment discontinuation and were all classified as mild to moderate in intensity. Constipation stayed constant throughout the trial, but the frequency of dry mouth, nausea, and vomiting declined. The two treatments were found

to be equally tolerable, with a 20% discontinuation rate in the xanomeline-trospium group and a 21% discontinuation rate in the placebo group [14,29].

EMERGENT 2

In double-blind phase 3 EMERGENT-2 trial 126 patients were assigned to receive xanomeline–trospium and 126 to receive placebo. The PANSS total score at baseline was 98.3 in the xanomeline-trospium group and 97.9 in the placebo group. The change from baseline to week 5 was significantly greater in the xanomeline-trospium group: a reduction of −21.2 points and −11.6 points with placebo. The least squares mean difference between KarXT and placebo was −9.6 points, with a 95% confidence interval of −13.9 to −5.2, and a p-value of <0.0001, indicating a highly statistically significant improvement with KarXT. COBENFY showed significantly better outcomes than placebo on PANSS, as well as global assessments of illness severity (CGI-S) [30]. The trial showed low discontinuation rates due to adverse events, 6.2% for the xanomeline/trospium group and 4.3% for the placebo group. The predominant side effects observed were gastrointestinal in nature, including nausea, vomiting, constipation, and dyspepsia, which were largely mild to moderate and self-limiting. The outcomes of the trial show that xanomeline/trospium is therapeutic in its effect and has an acceptable safety profile, and it is a candidate for the quest for improved therapy for schizophrenia [31].

EMERGENT 3

In double-blind, phase 3 EMERGENT-3 trial 125 patients were assigned to receive xanomeline–trospium and 131 to receive placebo. The PANSS total score at baseline was 97.3 in the xanomeline–trospium group and 96.7 in the placebo group. The change from baseline to week 5 was significantly greater in the xanomeline-trospium group: a reduction of −20.6 points and −12.2 points with placebo.The least squares mean difference between KarXT and placebo was −8.4, with a 95% confidence interval of −12.4 to −4.3, and a P-value of <0.001, indicating a highly statistically significant result.

70.4% of participants in the xanomeline-trospium group and 50% in the placebo group developed side effects.The most frequent were nausea (19.2%), dyspepsia (16.0%), vomiting (16.0%), and constipation (12.8%), which is indicative of a prevalence of gastrointestinal effects. Discontinuation rates between both groups were similar (6.4% for xanomeline-trospium and 5.5% for placebo). Most significantly, there were no appreciable increases in weight gain, somnolence, or extrapyramidal symptoms, all of which are problems that are commonly associated with conventional antipsychotics. The study concluded that in patients with acute

psychosis and schizophrenia, xanomeline-trospium was both effective and well tolerated.Its ability to decrease PANSS scores significantly further supports that it holds promise as a new medicine option that is distinct from traditional antipsychotic medications that act on D2 dopamine receptors.

The findings are similar to the results of previous tests (EMERGENT-1 and EMERGENT-2) and align with the hypothesis that xanomeline-trospium may be the first of a new class of antipsychotic medications that target muscarinic receptors without having the significant side effects typically associated with existing treatments [25]. Findings across three EMERGENT trials consistently pointed towards a Cohen's d of approximately 0.60, highlighting robust efficacy.

Tolerability and Safety

The study used specific exclusion criteria to protect participants from the potential risk of including people with other psychiatric conditions that could affect treatment outcomes or cause additional complications. Patients with a primary disorder other than schizophrenia in the previous 12 months, a history of treatment resistance to antipsychotics, minimal symptoms, and participants who showed at least a 20% improvement in the PANSS between the study and screening were excluded. This allows the study of xanomeline-trospium to provide more reliable data on its safety and efficacy in the treatment of schizophrenia, which is crucial for the future development of this drug [25].

From 1,088 screened individuals, 690 participants were randomized across the EMERGENT trials, with 341 assigned to xanomeline/trospium (X/T) and 349 to placebo. Of these, 339 and 344 participants received treatment in the X/T and placebo groups, respectively. The most common reason for discontinuation in both groups was withdrawal of consent (X/T: 18.2%, placebo: 13.8%), followed by adverse events (X/T: 6.2%, placebo: 4.3%). The modified intent-to-treat (mITT) population, used for efficacy analyses, included 314 participants in the X/T group and 326 in the placebo group. The safety analysis included 340 participants from the X/T group and 343 from the placebo group. 690 patients were randomized overall: 82 in EMERGENT-1, 252 in EMERGENT-2 and 256 in EMERGENT-3.

Although the drug has a favorable safety profile, with a lower incidence of extrapyramidal symptoms and weight gain than traditional antipsychotics, Cobenfy carries a risk of rare but serious side effects, such as urinary retention and liver damage.The safety of the drug in clinical practice has not yet been fully established, and the requirements for its use may change as new data are gained about its effects on patients over the longer term [32].

Discussion

EMERGENT-2 was a multicenter, double-blind trial with a large sample size, which made it more robust in terms of validity. However, the entire subjects of the study were United States citizens, and so making a generalization to the rest of the world was weak. EMERGENT-3 was also weak in representativeness, considering that less than 20% of the sample was from Ukraine. It is necessary that grouping was blinded to participants so that bias is minimized. In EMERGENT, outcome assessors were blinded, but the success of these processes was not measured. Moreover, KarXT vs. placebo study comparisons do not state how the medication performs compared to available treatments. Active comparison studies and network analyses must be undertaken to gain a better understanding of the drug's efficacy compared to existing therapies.The studies focused on clinician-reported symptom scores, which is considered the standard. However, patient-reported outcomes are also important because they impact patients' overall quality of life. Including these results may better illustrate the drug’s impact and cost-benefit ratio.

Finally, all studies conducted on KarXT are sponsored by the company manufacturing the drug. Sponsored research can be more beneficial to the manufacturers, and independent trials are therefore crucial.

Conclusions

Schizophrenia carries severe health repercussions, such as reduced life expectancy. It also has an impact on social functioning, resulting in loss of work capacity, social isolation and self-esteem issues. Stigmatization often faces the patients, which degrades their self-esteem and is a cause of social isolation. Negative patient attitudes exacerbate the condition, and discrimination and limitations in receiving suitable medical treatment are the results. Complications such as stigmatization and the expense of treatment require new strategies and social interventions for the delivery of improved quality of life to those affected by this disorder. The rise in the incidence and prevalence of schizophrenia suggests a need to rethink and adapt treatment strategies. Traditional antipsychotic drugs that block dopamine receptors are not always effective, because they focus mainly on treating positive symptoms and can cause serious side effects, such as weight gain and extrapyramidal symptoms. The results of the EMERGENT study represent a breakthrough in the treatment of treatment-resistant patients. Xanomeline-trospium was efficacious and well tolerated in people with schizophrenia experiencing acute psychosis. Clinical studies have shown that Cobenfy significantly alleviates both positive and negative symptoms of schizophrenia and improves cognitive functions.

KarXT may offer an alternative for those who experience intolerable side effects of traditional therapies, as well as for those for whom previous therapies have proven ineffective. Therefore, drugs such as Cobenfy can contribute to improving the quality of life of patients struggling with difficulties in treating their disease. The modern approach based on cholinergic receptors opens the door to further development of therapy, providing hope for many patients who struggle with this serious mental disorder.

Schizophrenia is a lifelong disease, however the study duration of these trials was only 5 weeks. It will be necessary to continue monitoring the long-term safety and efficacy of Cobenfy in different patient populations. The results of the ongoing EMERGENT-4 and EMERGENT-5 studies may provide new data that will help systematize reports on KarXT.

Disclosure

Author's contribution Statement

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