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NEW DRUGS IN THE FIGHT AGAINST SCHIZOPHRENIA: A BREAKTHROUGH IN PHARMACOTHERAPY

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ABSTRACT

Schizophrenia is a severe psychiatric disorder affecting approximately 1% of the general population. Its pathogenesis is multifactorial, with both genetic predispositions and environmental factors contributing to disease onset. Numerous theoretical models have been proposed to elucidate the underlying mechanisms of schizophrenia, most of which are based on the pharmacological action of antipsychotic drugs and their observed clinical efficacy in symptom reduction. The predominant hypotheses implicate dysregulation of dopaminergic, serotonergic, and glutamatergic neurotransmission. The majority of currently available antipsychotic agents exert their therapeutic effects primarily by modulating the dopaminergic system. This narrow pharmacological focus substantially limits treatment options, particularly in cases of drug resistance or intolerance. Moreover, selective receptor targeting increases the likelihood of adverse effects, which frequently lead to nonadherence. Poor adherence, in turn, is associated with significant clinical deterioration and poses a major obstacle to functional recovery. The development of novel antipsychotic agents with alternative mechanisms of action—combining therapeutic efficacy with an improved side-effect profile—represents a promising direction in the pharmacotherapy of schizophrenia. In recent years, new compounds such as Caplyta, Lybalvi, and Cobenfy have received regulatory approval, offering expanded treatment possibilities and the potential to address current limitations in clinical practice.

KEYWORDS

Schizophrenia, Pathogenesis, Caplyta, Lybalvi, Cobenfy

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1. Introduction

Schizophrenia is a mental disorder that affects over 21 million people worldwide [1]. The disease is characterized by positive symptoms, such as delusions, hallucinations, psychomotor agitation, megalomania or suspiciousness, as well as negative symptoms, including affective flattening, apathy and difficulties in establishing interpersonal relationships [2]. The first symptoms usually appear before the age of 30 and the life expectancy of individuals with schizophrenia is on average 10–15 years shorter than that of the general population [3]. Schizophrenia is one of the most severe psychiatric disorders and significantly reduces the quality of life of affected individuals. It often leads to social withdrawal, job loss, substance or alcohol abuse, depression and if left untreated, may result in serious brain damage and permanent disability.

Patients with schizophrenia are also more likely to suffer from comorbid conditions such as diabetes, cardiovascular diseases, endocrine disorders, autoimmune diseases and metabolic syndrome. These are related both to lifestyle factors (e.g., smoking, unhealthy diet, low physical activity) and to the abuse of psychoactive substances and long-term use of antipsychotic medications and their side effects [1].

Until recently, the mechanism of action of antipsychotic drugs used in the treatment of schizophrenia was primarily based on their direct effect on the dopaminergic system, which plays a key role in the pathogenesis of the disorder. Advances in research on the neurobiological basis of schizophrenia and the identification of new mechanisms responsible for its symptoms have opened up new therapeutic possibilities. Modern drugs offer the potential for more effective treatment, especially in patients who respond poorly to traditional medications or suffer from their side effects.

2. Pathogenesis of the disease

The pathogenesis of schizophrenia involves both genetic and environmental factors. Studies conducted on twins and families have shown that the genetic component can increase the risk of developing schizophrenia by up to 80%. Around 130 genes potentially linked to the disorder have been identified, nearly 30% of which are involved in glutamatergic transmission. Nevertheless, environmental factors are also crucial, as they can

promote the expression of susceptibility genes through epigenetic mechanisms. Stress, unhealthy diet, smoking, alcohol consumptio, and psychoactive substance use increase the risk of schizophrenia and can exacerbate its course by damaging the central nervous system [3].

Numerous theories in the literature associate schizophrenia with dysfunctions in various neurotransmitter systems: dopaminergic, serotonergic, noradrenergic and glutamatergic. One of the most significant neurobiological hypotheses remains the dopamine hypothesis, formulated based on the observed effects of dopamine-blocking drugs and their effectiveness in reducing psychotic symptoms. This led to the conclusion that excessive activity of the dopaminergic system is responsible for the onset of symptoms [4]. It is now known that positive symptoms such as delusions and hallucinations are particularly linked to excessive dopaminergic transmission in the mesolimbic pathway. In contrast, negative symptoms are associated with insufficient dopamine activity in the mesocortical pathway, which explains their limited responsiveness to classical antipsychotics [3].

Most available neuroleptics work by antagonizing D_2-type dopamine receptors in various brain structures and outside the central nervous system. A significant number of D_2 receptors are located in the striatum, which is involved in motor control, among other functions. Inhibiting dopaminergic transmission in this region can lead to extrapyramidal symptoms such as muscle stiffness, bradykinesia or limb tremors. These are common side effects of antipsychotic drugs and can result in treatment discontinuation, worsening prognosis and the course of the illness [5].

Abrupt discontinuation of antipsychotic medications can lead to the development of so-called dopamine supersensitivity psychosis. As early as the 1970s, it was observed that some patients experienced significant worsening of psychotic symptoms after stopping pharmacotherapy, requiring higher doses of medication for improvement. Many of these patients also developed tardive dyskinesia [6].

Contemporary research shows that chronic blockade of D_2-type dopamine receptors leads to a compensatory increase in their number on the surface of postsynaptic neurons. This effect is particularly pronounced when high-affinity D_2 receptor antagonists are used for several months. In cases of sudden therapy discontinuation or rapid dose reduction, the drug detaches from the receptor, allowing endogenous dopamine to overstimulate the dopaminergic system, which can result in exacerbated psychotic symptoms. Managing these symptoms often requires higher doses of medication, potentially exceeding the upper therapeutic threshold and leading to treatment-resistant schizophrenia. The occurrence of extrapyramidal symptoms may indicate excessive D_2 receptor blockade in the striatum and may be an early sign of developing dopamine hypersensitivity [6].

Insufficient activity of NMDA (glutamatergic) receptors may also lead to overactivation of the brain's dopaminergic system, contributing to positive schizophrenia symptoms [6]. Studies in healthy individuals have shown that blocking NMDA receptors with ketamine induces short-term psychotic symptoms resembling schizophrenia and exacerbates symptoms in affected individuals [7].

Proton magnetic resonance spectroscopy studies have also shown lower glutamate levels in the prefrontal cortex of patients with schizophrenia compared to control subjects. Additionally, a meta-analysis using this technique revealed significantly reduced GABA concentrations in the mid-cingulate cortex in patients with first-episode psychosis. These results suggest a GABAergic transmission deficit in the frontal cortex in schizophrenia. Post-mortem studies have confirmed lower levels of GABAergic markers in the frontal cortex of individuals with schizophrenia compared to healthy controls. These data indicate a significant imbalance between glutamatergic and GABAergic neurotransmission, which may underlie cognitive deficits and negative symptoms observed in patients [8].

There is also an important relationship between the cholinergic and dopaminergic systems. M4-type muscarinic receptors in the central nervous system are involved in regulating dopaminergic activity in the prefrontal cortex by inhibiting D1 dopamine receptors. Activation of M4 receptors reduces dopamine release in the mesolimbic pathway, which may help reduce positive symptoms of schizophrenia. Animal studies have shown that mice lacking M4 receptors overreact to dopaminergic stimulation, further confirming the receptor's crucial role in modulating dopamine release [9].

First-generation (typical) antipsychotics primarily act by blocking dopamine receptors, especially D2-type receptors, in the dopaminergic system [2].

Second-generation (atypical) antipsychotics, in addition to dopaminergic activity, also show affinity for serotonergic receptors, particularly 5-HT2A. As a result, they influence both positive and negative symptoms more effectively than first-generation drugs. They are better tolerated and have a lower risk of extrapyramidal side effects. However, their use is more often associated with metabolic disturbances such as weight gain,

hyperglycemia or dyslipidemia, which is why patients on these medications require regular monitoring for endocrine disorders [2,6].

Third-generation antipsychotics are characterized by partial agonism at D2 and D3 receptors, improving the treatment of both positive and negative symptoms while reducing the risk of side effects. They also act on serotonergic receptors, including 5-HT1A and 5-HT7 [2].

Due to the multifactorial etiology of schizophrenia, the diversity of clinical symptoms, limited efficacy of some drugs and significant side effects, selecting appropriate treatment remains a major challenge. The development of new compounds with unique mechanisms of action opens the door to more personalized therapeutic approaches. Examples of such modern drugs include Caplyta, Lybalvi and Cobenfy.

3. New Medications in the Treatment of Schizophrenia

Caplyta (Lumateperone)

Lumateperone was approved by the U.S. Food and Drug Administration (FDA) in 2019 for the treatment of schizophrenia in adults [10]. This decision was based on the results of two published, randomized, double-blind, placebo-controlled clinical trials. In both studies, lumateperone at a dose of 42 mg per day (equivalent to 60 mg of the tosylate salt formulation) demonstrated clinically significant efficacy. Notably, both lower and higher doses did not show comparable therapeutic effectiveness [11].

In 2021, lumateperone received additional FDA approval for the treatment of depressive episodes associated with bipolar I and II disorder in adults, both as monotherapy and in combination with lithium or valproate [12]. This medication is distinguished by a unique mechanism of action involving modulation of three major neurotransmitter systems: dopaminergic, glutamatergic and serotonergic pathways [13].

Although lumateperone is classified as an atypical (second-generation) antipsychotic, its pharmacodynamic profile differs significantly from other agents in this class. In the mesolimbic and mesocortical brain regions, it acts simultaneously as a partial agonist at presynaptic D_2 dopamine receptors and an antagonist at postsynaptic receptors. This dual mechanism promotes reduction of psychotic symptoms while potentially lowering the risk of side effects associated with excessive dopamine blockade.

Additionally, lumateperone influences the regulation of dopamine phosphoprotein, which may contribute to its therapeutic efficacy. Regarding the glutamatergic system, the drug enhances the activity of NMDA (N-methyl-D-aspartate) receptors in the prefrontal cortex—an area where NMDA receptor deficits are commonly observed in schizophrenia. This effect may support improvements in cognitive function and reduction of negative symptoms.

Lumateperone also exhibits very high affinity for 5-HT_2A serotonin receptors, acting as an antagonist. Its affinity for these receptors is approximately 60 times greater than for D_2 dopamine receptors, which may explain its sedative properties. Furthermore, as a serotonin reuptake inhibitor, lumateperone demonstrates antidepressant effects [11].

Compared to other antipsychotics, lumateperone has a more favorable safety profile. It achieves therapeutic effects with approximately 40% D_2 receptor occupancy, whereas most antipsychotics require 60–80% blockade. Extrapyramidal symptoms (EPS) typically appear when D_2 receptor occupancy exceeds 78%, which may explain the low incidence of EPS during lumateperone treatment [11]. In one clinical trial, EPS occurred in fewer than 5% of participants, regardless of treatment group [14].

In a Phase III trial involving patients aged 18–60 years diagnosed with schizophrenia per DSM-5 criteria and presenting with moderate to severe symptoms (assessed using the Clinical Global Impression – Severity, CGI-S), the efficacy of lumateperone was evaluated in comparison to placebo. Participants were randomly assigned to one of three groups: two received lumateperone at doses of 40 mg and 60 mg, and the third received placebo. Efficacy was assessed based on changes in the Positive and Negative Syndrome Scale (PANSS) score. After 28 days of treatment, a statistically significant reduction in PANSS scores was observed. In the group receiving lumateperone 42 mg once daily, the PANSS score decreased by 14.5 points, compared to a 10.3-point reduction in the placebo group—confirming the drug's efficacy in alleviating schizophrenia symptoms [10–12].

In four-week clinical trials, the drug was generally well tolerated. Adverse events occurred in 64.7% of participants receiving 42 mg lumateperone and in 50.3% of those on placebo. The most common adverse events reported in at least 5% of lumateperone-treated patients (42 mg) and occurring at least twice as frequently as in the placebo group were: somnolence (17.3% vs. 4.0%), sedation (12.7% vs. 5.4%), fatigue (5.3% vs. 1.3%), and constipation (6.7% vs. 2.7%) [14].

A serious adverse event of orthostatic hypotension was reported in one patient receiving 42 mg lumateperone. All other side effects were mild to moderate in severity. In the placebo group, one death of undetermined cause occurred 13 days after the study ended [14].

The most common reasons for treatment discontinuation were headache (1.3% in the 42 mg group) and worsening of schizophrenia symptoms (0.7% in the placebo group). No increased risk of suicidal thoughts or behaviors was observed during treatment [13].

The mean change in body weight over the 28-day period was similar across all groups. In the 42 mg lumateperone group, the average weight gain was 0.9 kg. No significant changes were observed in metabolic parameters, physical exam findings, vital signs or ECG readings between treatment groups.

Clinical improvement was observed as early as the first week of treatment and was sustained throughout the study duration [14].

Given its novel mechanism of action and favorable safety profile, lumateperone represents a promising therapeutic alternative for individuals diagnosed with schizophrenia and bipolar affective disorders.

Lybalvi (Olanzapine + Samidorphan)

Lybalvi was approved by the FDA in 2021 for the treatment of schizophrenia and bipolar I disorder in adults. The preparation contains a combination of olanzapine, an atypical antipsychotic and samidorphan, a selective μ-opioid receptor antagonist.

Olanzapine has demonstrated high efficacy in reducing both the positive and negative symptoms of schizophrenia. However, its chronic use is associated with a significant risk of weight gain and metabolic disturbances, often leading to poor treatment adherence and premature discontinuation by patients.

As a μ-opioid receptor antagonist, samidorphan acts on the opioid system, which is involved in appetite and metabolism regulation. Clinical trial results indicate that its inclusion in Lybalvi mitigates the adverse effect of olanzapine on body weight. Although the risk of weight gain is not completely eliminated, it is noticeably reduced. [15–17]

The efficacy of Lybalvi was assessed, among others, in a four-week, randomized, double-blind, placebo-controlled phase III study (ENLIGHTEN-1). The study included patients aged 18 to 70 who were diagnosed with schizophrenia according to DSM-5 criteria and were in an acute phase of symptom exacerbation.

Participants were randomly assigned to three groups. The first received a combination of olanzapine (10 mg or 20 mg) and samidorphan (10 mg), the second received olanzapine alone (10 mg or 20 mg, and the third received a placebo. The 10 mg dose of samidorphan was selected based on a previous phase II study, which demonstrated that adding 10 mg of samidorphan to olanzapine was more effective in limiting weight gain than 5 mg or 20 mg doses. Treatment with olanzapine began at 10 mg per day and was increased to 20 mg on the third day. By the end of the first week, the dose could be reduced to 10 mg. For the remaining three weeks, the dosage remained stable. Participants had a BMI between 18.0 and 40.0 kg/m². Exclusion criteria included the use of weight-loss medications, hypoglycemic drugs or statins—if initiated or modified within the three months prior to the study.

Therapeutic efficacy was assessed at week 4 using the PANSS and CGI-S scales. Both the olanzapine/samidorphan combination and olanzapine alone showed significant improvement in the total PANSS score compared to placebo. Improvements were noticeable as early as the second week in the OLZ/SAM (olanzapine + samidorphan) group.

In all three PANSS subscales—positive, negative and general psychopathology—patients treated with OLZ/SAM and olanzapine alone achieved better scores than those receiving placebo. The percentage of responders (based on PANSS criteria) was higher in the active treatment groups compared to placebo. The CGI-S scale also indicated significant improvement in both active treatment groups. Similarly, the CGI-I scale showed a higher proportion of treatment responders in the OLZ/SAM and olanzapine groups than in the placebo group.

The efficacy of the olanzapine/samidorphan combination versus placebo was comparable to that of olanzapine alone in the overall study population and across subgroups defined by age, sex, race or baseline severity of schizophrenia symptoms. This indicates that samidorphan does not negatively impact the antipsychotic efficacy of olanzapine.

More than half of the participants reported at least one adverse event, with the highest number of cases in the OLZ/SAM and olanzapine groups and slightly fewer in the placebo group. Most adverse events were mild or moderate in intensity. The most commonly reported symptoms—occurring in at least 5% of patients

and more than twice as often in the OLZ/SAM group compared to placebo—were weight gain, somnolence, dry mout, and headache.

A surprising finding was that the greatest weight gain after 4 weeks was observed in the OLZ/SAM group, slightly less in the olanzapine group and minimal in the placebo group. This may be due to the short observation period, which is why a follow-up 24-week study focusing on the impact of samidorphan on weight gain was conducted. It is important to note that the four-week study aimed to assess antipsychotic efficacy rather than metabolic effects.

Interestingly, extrapyramidal symptoms occurred more frequently in the placebo group than in the treatment groups. This may have resulted from abrupt discontinuation of prior medications in patients receiving placebo. Suicidal ideation was reported only in the placebo and olanzapine-only groups. [18]

A subsequent randomized, double-blind, 24-week study focused on assessing the long-term safety of OLZ/SAM, with a particular focus on weight changes. Participants were aged 18 to 55 with a BMI between 18 and 30 kg/m².

Treatment started with 10 mg of olanzapine and 10 mg of samidorphan (or 10 mg of olanzapine in the comparison group). In the second week, the olanzapine dose could be increased to 20 mg and from the end of the second, third or fourth week, it could be reduced due to intolerance. After week four, dosing remained unchanged.

After 24 weeks, parameters related to cardiometabolic risk were evaluated. Compared to olanzapine alone, OLZ/SAM was associated with smaller increases in mean systolic and diastolic blood pressure, BMI and the risk of developing hypertension (grade 1 or 2), obesity, and metabolic syndrome. [19]

No significant changes in systolic blood pressure were noted in the OLZ/SAM group, whereas such changes were observed in the olanzapine group. In both groups, mean blood pressure increased, but the increase was smaller in the OLZ/SAM group. Diastolic pressure did not differ significantly between the groups. [20]

After 24 weeks, patients receiving OLZ/SAM had an average waist circumference increase of 2.1 cm less than those receiving olanzapine alone. These differences were visible from the first week of treatment and persisted until the end of the study. A waist circumference increase of at least 5 cm—a risk factor for increased mortality—occurred in a smaller proportion of OLZ/SAM patients (26.8%) compared to the olanzapine group (43.2%). This means OLZ/SAM reduced the risk of this adverse effect by nearly half. [20]

Despite differences in weight gain, changes in blood lipid and glucose levels were minor and did not differ significantly between groups. The risk of sustained hyperglycemia and hyperlipidemia was also comparable.

At the start of the study, the mean PANSS score was about 68 in the OLZ/SAM group and 70 in the olanzapine group. After 24 weeks, schizophrenia symptoms decreased by an average of 8.2 points in the OLZ/SAM group and 9.4 points in the olanzapine group. The 1.2-point difference was not clinically significant. Similar improvements were noted using the CGI-S scale. [19]

A multi-center, four-year observational study (June 2017 – September 2023) was also conducted. It demonstrated that OLZ/SAM effectively controlled schizophrenia symptoms throughout the observation period. The safety profile was consistent with previous studies—most adverse events were mild or moderate, and serious events were rare.

OLZ/SAM led to slight increases in body weight and waist circumference and metabolic parameter changes were minimal. No significant deviations were observed in laboratory tests, ECGs or vital signs.

The long-term antipsychotic efficacy of olanzapine with samidorphan has been confirmed. Particularly important is the reduction in weight gain, as olanzapine alone is associated with a higher risk of this side effect. The most significant weight gain occurred in the early weeks of treatment, while changes were minor in the later stages.

Metabolic outcomes were consistent with previous observations. The ENLIGHTEN-2 analysis showed that OLZ/SAM significantly reduced the risk of hypertension, obesity and metabolic syndrome compared to olanzapine. This is highly significant, as patients with severe mental illnesses are more vulnerable to cardiovascular and metabolic diseases. Thus, OLZ/SAM represents an effective and safe option for long-term treatment. [21]

Cobenfy (xanomeline + trospium chloride)

Cobenfy was approved by the U.S. Food and Drug Administration (FDA) in 2024 for the treatment of schizophrenia in adults. It is the first and only antipsychotic medication to date that does not act directly on dopaminergic receptors. The efficacy of Cobenfy in reducing both positive and negative symptoms of schizophrenia was confirmed in two randomized Phase III clinical trials: EMERGENT-2 and EMERGENT-3. Both five-week studies demonstrated a significant reduction in PANSS scores compared to placebo [22].

The formulation contains two active ingredients: xanomeline and trospium chloride. Xanomeline is an agonist of central muscarinic M1 and M4 receptors, a partial agonist of M5 receptors, an agonist of 5-HT1 serotonergic receptors and an antagonist of 5-HT2 receptors. Trospium chloride acts as an antagonist of peripheral muscarinic receptors in the cholinergic system. The addition of trospium chloride helps reduce the peripheral side effects associated with xanomeline's activity, without affecting its central action.

Recent studies indicate that M4 muscarinic receptors play a key role in modulating dopaminergic neurotransmission. Their activation within the central nervous system leads to decreased dopaminergic neuron activity, which may explain Cobenfy's effectiveness in treating schizophrenia symptoms [23].

In Phase II (EMERGENT-1) and Phase III (EMERGENT-2) clinical trials involving patients with schizophrenia and acute psychosis, treatment with xanomeline combined with trospium chloride led to a significant improvement in both positive and negative symptoms compared to placebo. The medication was well tolerated, and side effects typically associated with other antipsychotics—such as extrapyramidal symptoms, sedation, weight gain or hyperprolactinemia—occurred much less frequently.

The EMERGENT-3 study was a multicenter, randomized, double-blind, placebo-controlled trial. Participants were patients aged 18–65 with a diagnosis of schizophrenia according to DSM-5 criteria, PANSS scores between 80–120 and at least two moderate or severe positive symptoms. An inclusion criterion also required a Clinical Global Impression–Severity (CGI-S) score of at least 4.

Patients were randomly assigned to two groups: one received xanomeline and trospium chloride and the other received placebo. Treatment lasted for 5 weeks. During the first 2 days, patients received xanomeline 50 mg and trospium chloride 20 mg twice daily. From days 3 to 7, the xanomeline dose was increased to 100 mg twice daily, while trospium dosage remained unchanged. From day 8 onward, further dose adjustments were allowed—up to 125 mg of xanomeline and 30 mg of trospium chloride twice daily—depending on drug tolerability. No dose changes were made in the final two weeks of the study.

Study results showed that treatment with the xanomeline–trospium combination led to significantly greater reduction in schizophrenia symptoms compared to placebo. After 5 weeks, the mean PANSS score change was –20.6 points in the active treatment group versus –12.2 points in the placebo group. The –8.4 point difference was statistically significant. Improvements were evident as early as week 2 and sustained throughout the treatment period.

Adverse events were reported in 70.4% of participants in the treatment group and 50.0% in the placebo group. The most common side effects (occurring in ≥5% of patients in the active group and at least twice as often as in the placebo group) included: nausea (19.2% vs 1.6%), dyspepsia (16.0% vs 1.6%), vomiting (16.0% vs 0.8%), constipation (12.8% vs 3.9%), hypertension (6.4% vs 1.6%) and diarrhea (5.6% vs 0.8%). Cholinergic symptoms were generally mild to moderate, occurred mainly in the first two weeks and were transient.

The treatment discontinuation rate due to adverse events was comparable between groups: 6.4% in the active group and 5.5% in the placebo group. One serious adverse event (gastroesophageal reflux) was reported in the treatment group, while no serious events were noted in the placebo group.

There were no clinically significant differences in extrapyramidal symptoms between groups. Baseline ratings were low and remained stable throughout the study. No cases of tardive dyskinesia were observed. Akathisia was reported in 4 patients (3.2%) in the treatment group and 2 patients (1.6%) in the placebo group—all cases originated from a single study site and were not deemed related to treatment. Persistent akathisia until study completion occurred in three individuals (2 placebo, 1 treatment).

Unlike many other antipsychotic drugs, xanomeline with trospium chloride did not cause weight gain or excessive sedation. A slight increase in average systolic and diastolic blood pressure (about 2–3 mm Hg) was observed in the treatment group, peaking around week 1 and partially resolving by study end. Hypertension occurred more frequently than in the placebo group but was mild, transient and did not lead to treatment discontinuation. No QTc interval changes were reported. A transient increase in resting heart rate was also observed in the treatment group, peaking around day 8 (average +13 bpm vs +4.4 bpm in the placebo group).

The EMERGENT-3 study confirmed that xanomeline with trospium chloride effectively reduces symptoms of acute psychosis in schizophrenia. Improvements were rapid (from week 2), sustained throughout

the trial and exceeded those seen in studies of other antipsychotics. The medication was well tolerated, with the most common side effects being mild and temporary [24].

In 2021, the EMERGENT-5 study was conducted to evaluate the long-term efficacy, safety, and tolerability of xanomeline with trospium chloride. The study included patients aged 18–65 with stable schizophrenia symptoms who had not previously received Cobenfy. Initial dosing was 50 mg xanomeline and 20 mg trospium chloride twice daily, gradually increased to a maximum of 125 mg and 30 mg twice daily.

Results demonstrated sustained symptom improvement, confirmed by a significant reduction in total PANSS scores and improvements on the CGI-S and PANSS subscales. At 52 weeks, 30% of participants achieved at least a 30% reduction in symptoms.

Long-term therapy was well tolerated. The most common adverse events were gastrointestinal, including nausea (21.4%), vomiting (17.8%) and constipation (16.8%). No significant weight gain or metabolic disturbances were observed—average body weight decreased by 2.2 kg after 52 weeks. No notable changes in prolactin levels or movement disorders, including tardive dyskinesia, were reported [25–27].

Across all the above clinical trials, the xanomeline–trospium combination significantly reduced both positive and negative symptoms of schizophrenia in patients during the acute phase of the illness. Moreover, the medication has a favorable safety profile—without causing weight gain or extrapyramidal symptoms, which are common with traditional dopamine-blocking antipsychotics. Due to its innovative mechanism of action, based on modulation of the cholinergic system, Cobenfy represents a novel therapeutic alternative, especially for patients who are unresponsive to conventional dopaminergic treatments [22,23].

4. Conclusions

Schizophrenia is a disorder with a complex and multifactorial etiology, involving dysregulation of multiple neurotransmitter systems, primarily the dopaminergic, glutamatergic, GABAergic, cholinergic and serotonergic pathways. The classical dopamine hypothesis remains a cornerstone in understanding the mechanisms of schizophrenia; however, modern research highlights the significant role of glutamatergic hypofunction and weakened GABAergic neurotransmission, particularly in the prefrontal cortex, which may underlie negative symptoms and cognitive deficits. Excessive blockade of D2 receptors can lead to complications such as extrapyramidal symptoms, and prolonged treatment may result in dopamine supersensitivity and secondary treatment resistance.

Newer generations of antipsychotic medications (second- and third-generation) are characterized by a more favorable side effect profile and broader mechanisms of action, including effects on serotonergic receptors. This enables more effective treatment of both positive and negative symptoms. Caplyta, with its unique mechanism of action targeting D2, NMD and 5-HT2A receptors, represents a new standard in the treatment of schizophrenia, combining therapeutic efficacy with good tolerability and a low risk of extrapyramidal symptoms. Lybalvi addresses the significant metabolic burden associated with olanzapine treatment by reducing weight gain risk without compromising clinical efficacy.

Cobenfy, on the other hand, is the first approved antipsychotic that does not act directly on dopamine receptors, marking a breakthrough in the pharmacotherapy of schizophrenia—particularly for patients with treatment resistance or intolerance to typical neuroleptics. The current approach to treating schizophrenia is moving toward targeted therapy, which takes into account individual differences in the patient's neurobiology. This personalized strategy may significantly improve treatment effectiveness and enhance the quality of life for individuals living with the disorder.

Disclosure

Authors' contribution:
Conceptualization: P.F., K.Ko.
Methodology: K.Kr.
Software: P.P.
Check: A.M.
Formal analysis: P.F., M.K.
Investigation: Z.B., E.S.
Resources: A.P.
Data curation: M.K.
Writing -rough preparation: Z.S., M.K.
Writing -review and editing: P.F., K.Ko.
Visualization: K.Kr., M.K.
Supervision: Z.S., E.S.
Project administration: P.P.

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