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COBENFY - A NEW ANTIPSYCHOTIC DRUG

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ABSTRACT

Antipsychotic medications are the cornerstone of schizophrenia treatment and are traditionally classified into first-, second, and third-generation agents according to their pharmacological properties and mechanism of action. While these drugs effectively control psychotic symptoms through dopamine receptor antagonism or partial agonism, their clinical use is frequently limited by extrapyramidal symptoms, metabolic disturbances, hyperprolactinaemia, and inadequate efficacy against negative and cognitive symptoms. Cobenfy (xanomeline–trospium), approved by the U.S. Food and Drug Administration in 2024, represents the first antipsychotic with a non-dopaminergic mechanism of action. It combines xanomeline, a centrally acting muscarinic M1/M4 receptor agonist, with trospium chloride, a peripherally acting muscarinic antagonist that reduces cholinergic adverse effects without crossing the blood–brain barrier. This review summarizes the pharmacology, mechanism of action, pharmacokinetics, clinical efficacy, safety, and therapeutic role of Cobenfy based on available preclinical and clinical evidence. Phase II and III studies, including the EMERGENT clinical program, demonstrated significant improvements in Positive and Negative Syndrome Scale scores, sustained long-term efficacy, and a favourable metabolic profile with minimal effects on body weight and cardiometabolic parameters. Preliminary findings also suggest potential benefits for negative symptoms and cognitive impairment. Rather than replacing established antipsychotics, it expands current treatment options by introducing a novel cholinergic therapeutic strategy. Ongoing comparative, long-term, and real-world studies will further define its role in schizophrenia management and its potential application in other neuropsychiatric disorders, including Alzheimer's disease–related psychosis.

KEYWORDS

KarXT; Schizophrenia; Antipsychotic; Cobenfy; Muscarinic Receptors; Xanomeline-Trospium; Psychotic Disorders; Muscarinic Agonist, Cholinergic Agents

CITATION

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Abbreviations:

5-HT1A - serotonin 1A receptor
5-HT2A - serotonin 2A receptor
AD - Alzheimer's Disease
AE - Adverse Event
AIMS - Abnormal Involuntary Movement Scale
BARS - Barnes Akathisia Rating Scale
BMI - Body Mass Index
BPSD - behavioural and psychological symptoms of dementia
CANTAB - Cambridge Neuropsychological Test Automated Battery
CGI - Clinical Global Impression
CGI-I - Clinical Global Impression – Global Improvement
CGI-S- Clinical Global Impression - Severity
CMAI - Cohen-Mansfield Agitation Inventory
CMAI-IPA - Cohen-Mansfield Agitation Inventory - International Psychogeriatric Association
CNTB - Computerized Neuropsychological Test Battery
C-SSRS - Columbia Suicide Severity Rating Scale
CTP - Child-Turcotte-Pugh
DSM-5 - Diagnostic and Statistical Manual of Mental Disorders
eGFR - estimated glomerular filtration rate
ECG - ElectroCardioGram
FDA - Food and Drug Administration
FGAs - first-generation antipsychotics
HP - high potency
IAQ - Investigator Assessment Questionnaire
KarX-EC - Xanomelina Enteric-Coated
LP - low-potency
MART - multi-acting receptor targeted
MP - mid-potency
NMDA - N-methyl-D-aspartate
NNH - Number Need to Harm
NNT - Number Need to Treat
NPI-C - Neuropsychiatric Inventory–Clinician rating scale
NPI/NPI-NH - Neuropsychiatric Inventory – Nursing Home
NR - Not Reported
OTS - One Touch Stockings of Cambridge
PANSS - Positive And Negative Syndrome Scale
RVP - Rapid Visual Information Processing
SAS - Simpson-Angus Scale
SDA - serotonin-dopamine antagonists
SERT - serotonin transporter
SGAs - second-generation antipsychotics
SSP - Spatial Span

TEAE - Treatment-Emergent Adverse Event
TGAs - third-generation antipsychotics
VAS - Visual Analogue Scale
VRM - Verbal Recognition Memory

1. Conventional Antipsychotic Drugs and Their Mechanisms of Action

Antipsychotic medications are a crucial part of treating many psychiatric conditions, as they help manage psychosis and severe mood dysregulation that are common in various disorders **[1]**. These medications, also known as neuroleptics or major tranquilizers, have been a major shift in the field of psychiatry since their introduction in the 1950s. Before their discovery, people with mental illnesses were often institutionalized, but with the development of antipsychotic drugs, the focus shifted to targeted pharmacotherapy **[2]**. Over the next decades, the usage of these medications has evolved, and now the main goal is to improve their effectiveness in complex cases while minimizing the risk of neurological and metabolic side effects **[3]**.

1.1 Classes and Enumeration of Antipsychotic Drugs

Antipsychotics can be grouped into three main categories based on their chronological development, pharmacological profiles, and structural properties: FGAs, SGAs, and TGAs **[4,5]**.

1.1.1 First-Generation Antipsychotics

Also known as 'typical' antipsychotics, FGAs were introduced between the 1950s and 1970s. They are further divided by their chemical structure and clinical potency (as shown in Table 1) **[6]**. High-potency FGAs achieve therapeutic-level receptor blockade at lower doses but show a high risk of neurological side effects. Low-potency FGAs require higher doses for the same effect and show significant off-target receptor binding. Historically these agents revolutionized the treatment of acute psychosis but their clinical profile left a lot of patients struggling with side effects and unresolved symptoms **[7,8]**.

Table 1. FGAs divided by their chemical structure and their clinical potency. Abbreviations: FGA - First-Generation Antipsychotics; LP - low-potency; MP - mid-potency; HP - high potency.

Chemical Structure	FGA drugs and their potency
Phenothiazines (aliphatic)	Chlorpromazine (LP), trifluprомazine (LP), promazine (LP), levomepromazine (LP)
Phenothiazines (piperidine)	Thioridazine (LP), mesoridazine (LP), pericyazine (MP), pipotiazine (MP)
Phenothiazines (piperazine)	Fluphenazine (HP), perphenazine (MP), prochlorperazine (MP), trifluoperazine (HP), thioproperazine (HP)
Butyrophenones	Haloperidol (HP), droperidol (HP), benperidol (HP), trifluperidol (HP), melperone (MP), pipamperone (MP)
Thioxanthenes	Chlorprothixene (LP), thiothixene (HP), flupentixol (HP), zuclopenthixol (MP)
Diphenylbutylpiperidines	Pimozide (HP), fluspirilene (HP), penfluridol (HP)
Benzamides	Sulpiride (HP), sultopride (HP), tiapride (HP)
Other structures	Loxapine (a dibenzoxazepine, MP), molindone (an indole derivative, MP)

1.1.2 Second-Generation Antipsychotics

The introduction of clozapine in the late 1980s marked the beginning of a new era in the treatment of mental health disorders with the emergence of SGAs, also known as atypical antipsychotics. The important change they brought is their reduced risk of motor dysfunctions and broader receptor binding profiles **[9]**. SGA agents can be categorized into smaller groups including the MART-type, which includes clozapine, olanzapine, quetiapine, asenapine, zotepine. Another group is the SDA-type, which comprises risperidone, paliperidone (the primary active metabolite of risperidone), ziprasidone, iloperidone, lurasidone, sertindole, blonanserin, perospirone. Additionally, there are the atypical benzamides, such as amisulpride. These medications have been able to address symptoms more efficiently, thus ensuring better disease control. However, they have also created new challenges to deal with such as significant metabolic side effects, which can have a substantial impact on patients' overall health and well-being **[10,11]**.

1.1.3 Third-Generation Antipsychotics

The latest developments in psychopharmacology have led to the creation of a new generation of antipsychotics - TGAs. Some of the most significant drugs in this category include: aripiprazole, a prototype of this group, which displays D2 and 5-HT1A partial agonism alongside with 5-HT2A antagonism; brexpiprazole, a structural analogue of aripiprazole with lower intrinsic D2 activity and higher affinity for 5-HT1A and 5-HT2A receptors; cariprazine, unique for its stronger partial agonism at the dopamine D3 receptor rather than at D2 receptor, which results in benefits for motivation and reward pathways; lumateperone, a butyrophenone derivative with a unique mechanism combining presynaptic D2 modulation, SERT inhibition, and NMDA receptor enhancement. All of these drugs are able to act as dopamine receptor partial agonists rather than pure antagonists **[12]**. Thus, they aim to stabilize rather than silence dopaminergic transmission **[13,14]**.

1.2 Mechanisms of Action

The mechanism of action of antipsychotic drugs is linked to dopamine, serotonin, their metabolism and their networks across various brain pathways **[15]**.

1.2.1 Dopamine D2 Receptor Antagonism

All FGAs function primarily as pure antagonists at the dopamine D2 receptor **[16]**. Clinical effect is usually achieved when approximately 65% to 70% of D2 receptors in the striatum are saturated **[17]**. They block dopamine binding in the hyperactive mesolimbic pathway, thus inhibiting the neurochemical 'storm' that may take the form of a psychotic episode. However, pure D2 blockade is anatomically non-selective. Inhibition of the nigrostriatal pathway disrupts basal ganglia motor control, while suppression in the tuberoinfundibular pathway removes the inhibitory effect on the pituitary gland, leading to unregulated prolactin secretion **[18,19]**.

1.2.2 Serotonin-Dopamine Antagonism

SGAs are known for concurrent antagonism at both the dopamine D2 receptor and the serotonin 5-HT2A receptor [**20**] with the affinity for the 5-HT2A receptor being higher **[21]**. In general, serotonin has inhibiting properties on dopamine release in certain regions of the brain. Due to this, by blocking 5-HT2A receptors on presynaptic dopaminergic neurons in the nigrostriatal pathway, SGAs are able to allow local dopamine release. This causes the blockade in motor pathways to partially reverse, which leads to significantly lower risk of extrapyramidal side effects during therapy with SGAs **[22]**.

1.2.3 Dopamine Partial Agonism (Receptor Stabilization)

TGAs come with an even more subtle approach to neuroreceptor modulation **[23]**. As they are partial agonists at D2 and D3 receptors, their intrinsic activity is lower than endogenous dopamine but higher than that of a pure antagonist **[24]**. As partial agonists they manage psychosis in the mechanism that is based on suppressing the biological signal in the hyperdopaminergic mesolimbic pathway by competing with the local excess of endogenous dopamine. On the contrary, in the hypodopaminergic mesocortical pathway, the partial agonist provides just enough baseline stimulation to support cognitive and emotional functions, preventing the emotional blunting often observed during therapy with traditional antagonists **[25,26]**.

1.3 Therapeutic Effects: Symptom Resolution

Antipsychotic medications are not able to address the neurobiological root cause of psychiatric disorders; rather, they serve as powerful tools to reduce symptoms and improve quality of life. Their therapeutic effects can be categorized by their ability to resolve specific symptoms **[27]**. Their efficacy in managing different symptom clusters is shown in Table 2.

1.3.1 Resolution of Positive Symptoms

Positive symptoms are characterized by an excess or distortion of normal functioning. They are primarily caused by mesolimbic dopamine hyperactivity **[28]** and include hallucinations, delusions, disorganized thinking, agitation. Hallucinations are sensory perceptions that lack external stimuli. They can be auditory, visual, olfactory or tactile. Every generation of antipsychotics is highly effective in reducing the intensity and frequency of hallucinatory experiences, often as quickly as within the first two weeks of therapy. Delusions can be characterized as fixed, false beliefs. D2 antagonism helps detach the emotional intensity from these irrational beliefs. Disorganized thinking and speech can be expressed as derailment, tangentiality, or so called word salad. Antipsychotics are able to reconstruct logical thought processes by organizing the chaotic neural signaling. Acute psychomotor agitation can be quickly resolved by the sedative effect brought by D2-blocking properties of both FGAs and SGAs that enables the return of appropriate behavioral control.

1.3.2 Resolution of Negative Symptoms

Impairment or even loss of some brain functions is characteristic for negative symptoms. These are primarily caused by hypodopaminergia in the prefrontal cortex and mesocortical tracts **[29]**. FGAs tend to fail to improve or in some cases can even worsen these symptoms (referred to as secondary negative symptoms). However, SGAs and TGAs are specifically designed to address them. Negative symptoms include primarily avolition, alogia, anhedonia, affective flattening and asociality. Lack of drive or motivation to pursue goal-directed activities is defined as avolition. D3 partial agonism has been found efficient in restoring motivational drive. 5-HT2A antagonism helps increase prefrontal dopamine, slightly improving spontaneous speech and expression in patients suffering from alogia. As they avoid complete D2 blockade in reward pathways, TGAs and some SGAs help preserve the capacity for pleasure and reward anticipation in anhedonia patients. SGAs are helpful when dealing with affective flattening (unchanging facial expressions and reduced body language), often caused by high-potency typical antipsychotics. Severe social withdrawal is very common among patients presenting negative symptoms. Improvement in this domain often leads to mitigation of paranoia and subtle restoration of motivation provided by newer agents.

1.3.3 Resolution of Cognitive Symptoms

Cognitive deficits are one of the most frequent pathologies schizophrenia and severe affective disorders patients have to deal with and one that heavily impacts their functional recovery. They consist of impairment of working memory, executive functioning, sustained attention, and verbal fluency.

No antipsychotic completely restores regular cognition levels but SGAs and TGAs provide modest improvements. They help with the ‘brain fog’ and disorganization by modulating serotonin (5-HT1A, 5-HT6, 5-HT7) and muscarinic receptors. This allows them to increase prefrontal acetylcholine and dopamine release, which are critical neurotransmitters for attention and memory **[30]**.

1.3.4 Resolution of Affective (Mood) Symptoms

Antipsychotics are known for their significant mood-stabilizing and antidepressant properties. Acute manic symptoms such as grandiosity, flight of ideas, decreased need for sleep, impulsivity, can be addressed by the D2 antagonist properties of SGAs and FGAs. Their usage is also indicated in severe depressive symptoms such as feeling of hopelessness, profound sadness, psychomotor retardation. For example lurasidone, quetiapine, and brexpiprazole modulate 5-HT1A acting as partial agonists and block 5-HT2A, which resembles the downstream effects of traditional antidepressants but with a faster onset. They remain particularly impactful in treatment-resistant dysphoria as well as reducing suicidal ideation **[20]**.

Table 2. Efficacy of antipsychotic generations across symptom domains.

Symptom domain	Symptom examples	Efficacy of FGAs	Efficacy of SGAs	Efficacy of TGAs
Positive	Hallucinations, delusions, paranoia	High (gold standard)	High	High (fewer side effects)
Negative	Avolition, anhedonia, flat affect	Poor (may worsen)	Moderate	Moderate to high
Cognitive	Working memory, executive function	Poor	Mild improvement	Mild to moderate improvement
Affective	Depression, severe mania, lability	Moderate (mania only)	High (broad spectrum)	High (especially MDD adjunct)
Agitation	Acute severe psychomotor unrest	Very high (rapid acting)	High	Moderate (slower titration)

Abbreviations: FGAs - first-generation antipsychotics; SGAs -second-generation antipsychotics; TGAs - third-generation antipsychotics; MDD - major depressive disorder.

1.4 Adverse Effect Profiles

The clinical utility of all drugs is heavily constrained by adverse effects they might cause. Antipsychotics are no exception to this rule. Because they interact with dopamine, serotonin, histamine as well as muscarinic and alpha-adrenergic receptors, their side effect profile spans multiple physiological systems as shown in Table 3.

Table 3. Side effect profiles by antipsychotic class.

Adverse Effect Domain	Mechanism / Receptor Involvement	First-Generation (High Potency)	First-Generation (Low Potency)	Second-Generation	Third-Generation
Acute EPS (Dystonia, Parkinsonism)	Nigrostriatal D2 blockade >80%	Severe (requires anticholinergic prophylaxis)	Moderate	Low to moderate	Very low
Akathisia	D2/adrenergic mismatch	High	Moderate	Moderate (high in lurasidone)	High (especially aripiprazole)
Tardive Dyskinesia	D2 receptor up-regulation	High (cumulative lifetime risk)	Moderate to high	Low (clozapine virtually zero)	Very low
Metabolic Syndrome (Weight, Lipids)	5-HT2C and H1 antagonism	Low	Moderate	Severe (olanzapine /clozapine)	Low (metabolically neutral)
Glycemic Dysregulation	Muscarinic M3 blockade / insulin resistance	Low	Low to moderate	High (risk of DKA and type II DM)	Low
Hyperprolactinemia	Tuberoinfundibular D2 blockade	Severe (galactorrhea, amenorrhea, sexual dysfunction)	Moderate	High (risperidone /paliperidone only); low in others	Minimal (can actively reduce prolactin)
Cardiovascular (QTc Prolongation)	hERG potassium channel blockade	Moderate (high with haloperidol)	High (thioridazine)	Moderate (ziprasidone highest)	Low
Orthostatic Hypotension	Peripheral alpha-adrenergic blockade	Low	High (dizziness, falls)	Moderate (iloperidone, clozapine)	Low
Sedation / Somnolence	Central H1 histamine blockade	Low	Severe	High (quetiapine, olanzapine)	Low (can cause insomnia)
Anticholinergic Toxicity	Central and peripheral M1 blockade	Low	High (constipation, dry mouth, blurred vision)	High (clozapine, olanzapine)	Minimal

Abbreviations: EPS - extrapyramidal symptoms; DKA - diabetic ketoacidosis, DM - diabetes mellitus; hERG - voltage-gated inwardly rectifying potassium channel KCNH2; QTc - QT interval corrected for heart rate.

2. Cobenfy

2.1 Characterization of the drug

Cobenfy, also known as KarXT, is a recent antipsychotic medication that was approved by the FDA in 2024 **[31]**. Cobenfy is a rather innovative drug because its mechanism of action differs from that of typical antipsychotics, as it does not primarily rely on dopamine antagonism or partial agonism **[31,32]**. KarXT is a combination of two substances – xanomeline and trospium chloride **[31]**. Xanomeline is a muscarinic agonist agent selective towards M_1/M_4 muscarinic receptors **[33]**. It also exhibits lower binding affinity to serotonin $5\text{-}HT_{1a}$ and $5\text{-}HT_{2a}$ and $5\text{-}HT_{2c}$ receptors **[33].** Trospium chloride is a non-selective muscarinic receptor antagonist that does not cross the blood–brain barrier **[34]**.

2.2 Mechanism of action

Cholinergic signaling in the striatum is essential for regulating synaptic plasticity, neuronal excitability, and the formation of dendritic spines and synapses—processes that underlie many cognitive functions **[35]**. Activation of M_1 receptors, which are mostly post-synptic, enhances cholinergic tone, thus supporting glutamate transmission, which then increases cholinergic activity and thus strengthens cognitive network integrity **[36]**. In schizophrenia, M_1 receptors are dysfunctional, which results in reduced cholinergic tone, which impairs glutamate transmission **[37]**. This dysregulation leads to decreased dopamine levels in the prefrontal cortex and thus the development of negative and cognitive symptoms **[38]**. Moreover, impaired striatal dopaminergic signaling promotes the appearance of positive symptoms **[38]**.

M_4 receptors are predominantly pre-synaptic and behave as auto-receptors, decreasing the acetylcholine-mediated signaling through the Gi/o pathway **[39]**. The main role of M_4 receptors is regulating the excessive dopamine in the mesolimbic pathway by reducing acetylcholine release **[39]**. Therefore, M_4 receptors may contribute to the reduction of positive symptoms while limiting motor side effects associated with excessive cholinergic tone **[39]**. Moreover, the activation of M_4 receptors reduces glutamate signaling, thus supporting cognitive functions **[36]**.

Xanomeline, unlike typical antipsychotics, does not act via post-synaptic dopamine receptors **[36]**. In contrast to fully suppressing dopamine signalling, xanomeline acts via presynaptic modulation, which may offer a potentially superior approach **[36]**. Xanomeline acts via selective M_1 receptor activation to improve cognitive function **[40]**. M_1 receptors have been shown to be able to regulate brain functional connectivity, thereby improving cognitive and sensory processing networks **[40]**. Moreover, the activation of M_1 receptors has been associated with an enhanced gamma oscillation synchrony, which potentially may contribute to improving cognitive deficits in schizophrenia **[41]**. Furthermore, xanomeline has been found to influence gene expression **[42]**. It has been shown to activate immediate early genes like c-fos and upregulate genes linked to neuroplasticity and cell survival, including sirtuin-1 and haem oxygenase-1 **[42]**. Thus, xanomeline may promote long-term potentiation, synaptic strengthening, and cognitive resilience **[36]**.

Trospium chloride exerts peripheral antimuscarinic effects, primarily via antagonism of M_3 receptors **[43]**. Since trospium chloride does not cross the blood-brain barrier, it is able to mitigate peripheral cholinergic side effects while preserving xanomeline's central therapeutic actions **[43,44]**.

2.3 Pharmacokinetics

The half-life of xanomeline is 5 hours, and the half-life of trospium chloride is 6 hours **[43]**. Therefore, it should be taken twice a day **[43]**. Both xanomeline and trospium chloride are highly protein bound and have widespread distribution throughout the body tissues **[43]**. Xanomeline is metabolised through several cytochrome P450 pathways, including CYP2D6, CYP2B6, CYP1A2, CYP2C9, and CYP2C1 **[43]**. Strong CYP2D6 inhibitors have been found to elevate plasma concentrations of xanomeline **[43]**. Moreover, xanomeline is known to be able to suppress intestinal CYP3A4 and P-glycoprotein receptors without causing systemic inhibition **[43].** Therefore, it is possible for clinically relevant drug interactions to occur, and monitoring for side effects associated with concomitant administration of Cobenfy with CYP3A4-sensitive substrates and P-glycoprotein substrates is recommended **[43]**.

Trospium chloride is not metabolised by the cytochrome P450 enzymatic system **[43]**. Instead, it is broken down through ester hydrolysis and glucuronic acid conjugation **[43]**. However, trospium chloride may interact with other medications that rely on active tubular secretion for renal elimination, potentially resulting in elevated levels of trospium chloride or co-administered xanomeline **[43]**.

2.4 Safety of Cobenfy

Most common side effects of Cobenfy include nausea, vomiting, constipation, headache, dizziness, hypertension, and dry mouth **[45**].

Cobenfy is contraindicated in patients with coexisting urinary obstruction, gastric retention, active biliary disease, or known hypersensitivity to any of the medication's components **[43]**. Caution is advised if administering Cobenfy in patients with gastrointestinal obstructive disorders, ulcerative colitis, intestinal atony, or myasthenia gravis due to decreased gastrointestinal motility **[43].** It is recommended to monitor liver enzymes, bilirubin, and heart rate at baseline and periodically during treatment **[43]**.

Renal and hepatic impairment may alter the metabolism and elimination of Cobenfy **[43]**. It should not be administered in patients with an estimated glomerular filtration rate (eGFR) <60 mL/min or patients with Child-Turcotte-Pugh (CTP) class A, B, and C hepatic impairment **[43]**.

There is no data on the use of Cobenfy in pregnant or breastfeeding women **[43]**.

2.5 Clinical practice

Cobenfy is available in three dosage strengths: 50/20 mg, 100/20 mg, and 12/30 mg **[43]**. It should be administered twice daily, at least an hour before or 2 hours after a meal **[43]**.

3. Clinical Trials and Ongoing Research

3.1 Phase III Clinical Trials

3.1.1 EMERGENT-2

The EMERGENT-2 study (NCT04659161) was a 5-week, randomized, double-blind, phase III clinical trial that enrolled 252 patients diagnosed with schizophrenia according to DSM-5 criteria **[43, 45-54]**. Therapeutic response was assessed using the Positive and Negative Syndrome Scale (PANSS), with particular attention paid to symptom changes and response to the active treatment **[47]**. Eligibility criteria included, in addition to a confirmed diagnosis of schizophrenia, an age between 18 and 65 years, a history of symptom exacerbation and/or the need for hospitalization due to psychotic symptoms, a total PANSS score of 80–120 points, a score >4 on at least two of four symptom domains (disorganization, suspiciousness/persecution, hallucinations, and delusions), and a Clinical Global Impression–Severity (CGI-S) score of at least 4 points **[45, 47,50,53]**.

Individuals diagnosed with another psychiatric disorder within the previous year in addition to schizophrenia, patients with a history of treatment resistance to at least two antipsychotic medications, or those who experienced a >20% reduction in PANSS score relative to baseline were excluded from participation **[47,54,55]**. The primary endpoint was the change in PANSS total score from baseline to Week 5 of treatment **[43,47,48,56,57]**. Participants were randomly assigned in equal proportions to either a placebo control group or an investigational treatment group receiving the xanomeline–trospium combination therapy **[46,53]**. The study drug was initially administered at a dose of 50 mg xanomeline plus 20 mg trospium twice daily for the first two days. From Days 3–7, the dose was increased to 100 mg + 20 mg twice daily, followed by a maintenance dose of 125 mg + 30 mg twice daily beginning on Day 8 **[45, 47,49,52,53–55]**. Safety assessments were conducted similarly to those performed in the previous study (EMERGENT-1, described below), with the addition of the Abnormal Involuntary Movement Scale (AIMS) and a follow-up visit during Week 6 for participants who did not enroll in EMERGENT-4 (described below) **[47]**. Patients receiving Cobenfy demonstrated a statistically significant reduction in PANSS total score, with a 9.6-point greater improvement compared with participants receiving placebo [43, 45, 47,49,50,53]. The treatment group also showed significantly greater improvements across secondary efficacy endpoints, including the subscales of the primary assessment instruments **[47]**.

Regarding adverse events, the findings were comparable to those reported in the previous trial (EMERGENT-1, described below) **[45,47]**. Compared with placebo, the treatment group did not exhibit treatment-emergent adverse events (TEAEs) associated with weight gain, elevated blood pressure, electrocardiographic abnormalities, or adverse changes in metabolic parameters **[47]**. Several serious TEAEs were reported during the study, including suicidal ideation (n = 2) in patients receiving Cobenfy, appendicitis (n = 1), and worsening of schizophrenia symptoms (n = 1); however, none of these events were considered treatment-related by the investigators **[43, 47,52, 53]**.

3.1. 2. EMERGENT-3

The EMERGENT-3 study (NCT04738123) was a 5-week, randomized, double-blind, placebo-controlled phase III clinical trial involving 256 patients diagnosed with schizophrenia according to DSM-5 criteria **[43, 45, 47, 48, 52, 53,54,58]**. In addition to the diagnosis of schizophrenia, inclusion criteria comprised an age range of 18–65 years, a history of symptom exacerbation and/or hospitalization due to psychotic symptoms, a total PANSS score of 80–120 points, a score >4 on at least two of four symptom domains (disorganization, suspiciousness/persecution, hallucinations, and delusions), and a CGI-S score of at least 4 points **[47,50,51,54]**.Exclusion criteria included the diagnosis of another psychiatric disorder within the previous year, a history of resistance to at least two antipsychotic medications, or a >20% reduction in PANSS score relative to baseline **[47,54,56]**. The primary endpoint was the change in PANSS total score from baseline to Week 5 of treatment **[43, 47, 48,56,57]**. Participants were allocated to either the treatment group receiving xanomeline–trospium (n = 125) or the placebo group (n = 131) **[47,48]**. The dosing regimen consisted of 50 mg xanomeline plus 20 mg trospium twice daily for the first two days, escalation to 100 mg + 20 mg twice daily during Days 3–7, and maintenance therapy at 125 mg + 30 mg twice daily from Day 8 onward **[45, 47, 48, 55]**. Safety monitoring was conducted similarly to EMERGENT-2, as described above [47,51,55]. Baseline demographic and clinical characteristics were generally comparable between the two study groups, although the xanomeline–trospium group included a higher proportion of female participants compared with the placebo group **[47]**. Patients treated with Cobenfy achieved a substantial reduction in PANSS total score at Week 5, demonstrating a mean improvement of 20.6 points from baseline, whereas participants receiving placebo exhibited an improvement of only 12.2 points **[43, 45, 47, 50,51]**. As observed in EMERGENT-2, the treatment group did not demonstrate TEAEs associated with weight gain, increased blood pressure, electrocardiographic abnormalities, or unfavorable metabolic changes when compared with placebo [47]. During this trial, one serious TEAE was reported in the Cobenfy-treated group (n = 1), namely gastroesophageal reflux disease **[43, 47, 48, 51,52]**.

Subsequently, pooled analyses were conducted using data from the first three studies of the EMERGENT program to evaluate efficacy, tolerability, and safety outcomes **[43, 47]**. Kaul et al., Brannan et al., and Citrome et al. investigated different aspects of the pooled dataset, including primary and secondary efficacy outcomes, adverse event profiles in both treatment groups, and calculations of the Number Needed to Treat (NNT) and Number Needed to Harm (NNH) for Cobenfy **[36, 43,17,59-61]**.

Table 4 presents a comparison of adverse events reported across the EMERGENT-1, EMERGENT-2, and EMERGENT-3 trials in both the xanomeline–trospium and placebo groups **[17]**.

Table 4. Comparison of adverse events reported across the EMERGENT-1, EMERGENT-2, and EMERGENT-3 trials in both the xanomeline–trospium and placebo groups; AE – Adverse Event; NR – Not Reported

AE	EMERGENT-1	TRIAL	EMERGENT-2	TRIAL	EMERGENT-3	TRIAL
	Cobenfy (n=89)	Placebo (n=90)	Cobenfy (n=126)	Placebo (n=125)	Cobenfy (n=125)	Placebo (n=128)
Any AE	48	39	95	73	88	64
AE leading to discontinuation	2	2	9	7	8	7
Nausea	15	4	24	7	24	2
Dry mouth	8	1	NR	NR	NR	NR
Dyspepsia	8	4	24	10	20	2
Vomiting	8	4	18	1	20	1
Constipation	15	3	27	13	16	5
Headache	6	5	17	15	14	15
Somnolence	5	4	NR	NR	2	0
Hypertension	NR	NR	12	1	8	2
Insomnia	2	2	NR	NR	7	10
Diarrhea	2	4	7	4	7	1
Dizziness	3	3	11	4	NR	NR
Gastroesophageal reflux disease	NR	NR	8	0	1	0
Change in body weight from	1,5±2,8	1,1±3,5	1,4±3,3	2,5±6,9	1,4±3,4	2,0±3,1

Table 4 presents a comparison of adverse events reported across the EMERGENT-1, EMERGENT-2, and EMERGENT-3 trials in both the xanomeline–trospium and placebo groups **[47]**.

3.1. 3. EMERGENT-4 and EMERGENT-5

EMERGENT-4 and EMERGENT-5 (NCT04659174, NCT04820309) were 52-week Phase III clinical trials designed to evaluate the long-term safety, tolerability, and efficacy of xanomeline–trospium therapy compared with placebo **[36,43,45,47,48,52,62,63]**. EMERGENT-5 enrolled adults diagnosed with schizophrenia according to DSM-5 criteria who had previously been treated with conventional antipsychotic therapies, including quetiapine, aripiprazole, olanzapine, and risperidone **[47]**. The EMERGENT-4 population consisted of participants from the previous EMERGENT-2 and EMERGENT-3 studies (48 from the active treatment groups and 62 from the placebo groups), all of whom were subsequently assigned to receive Cobenfy **[43,47]**. All participants received the study medication at an initial dose of 50 mg xanomeline plus 20 mg trospium twice daily for the first two days. The dose was increased to 100 mg + 20 mg twice daily from Days 3–7 and subsequently to 125 mg + 30 mg twice daily from Day 8 until study completion **[45, 47, 52]**. Analysis of the 52-week outcomes demonstrated that more than 75% of patients achieved a greater than 30% improvement in PANSS scores, with a mean reduction of 33.3 points from baseline **[47]**. Furthermore, participants who had previously received placebo in EMERGENT-2 and EMERGENT-3 exhibited substantial clinical improvement following initiation of Cobenfy treatment **[43, 47]**. Claxton et al. conducted an analysis of metabolic outcomes and safety data from all 718 participants enrolled in EMERGENT-4 and EMERGENT-5 **[47, 64]**. At study completion, approximately 65% of participants experienced weight reduction, with a mean decrease of 2.6 kg; the greatest effect was observed among patients with elevated baseline body mass index (BMI) values [47]. No clinically meaningful changes were observed in lipid metabolism or glycemic parameters **[47]**. Although all EMERGENT trials (EMERGENT-1 through EMERGENT-5) demonstrated significant reductions in PANSS scores compared with placebo, suggesting robust efficacy, direct comparative studies evaluating the safety profile of Cobenfy against other atypical antipsychotics, such as cariprazine or the olanzapine/samidorphan combination, remain unavailable **[49]**.

3.1.4. ARISE

The ARISE study (NCT05145413), sponsored by Bristol Myers Squibb, was conducted in two parallel groups: a placebo group and a xanomeline/trospium treatment group **[36, 45, 65]**. The study enrolled outpatients aged 18–65 years who had demonstrated an inadequate therapeutic response to their current treatment regimen and who had a stable baseline PANSS score of at least 70 points **[45]**. The dosing regimen in the Cobenfy group was comparable to that used in previous studies, beginning with 50 mg + 20 mg twice daily and gradually escalating the xanomeline dose through 75 mg and 100 mg until the target dose of 125 mg + 30 mg twice daily was achieved **[45]**. Although the treatment group demonstrated a 2.0-point greater reduction in PANSS score than the placebo group, this difference did not reach statistical significance **[36]**. A post hoc analysis revealed that patients previously treated with conventional antipsychotic agents, including ziprasidone, lurasidone, cariprazine, and aripiprazole, experienced greater PANSS improvements when receiving Cobenfy compared with placebo (15.1 versus 11.7 points, respectively) [36]. In contrast, no significant treatment benefit was observed among patients previously receiving risperidone [36]. This finding may be attributable to risperidone's potent dopaminergic effects or to differences in disease characteristics, including symptom profile and severity, which could influence the overall therapeutic response to Cobenfy **[36]**. Despite failing to meet its primary endpoint, the ARISE study provided an important foundation for future investigations aimed at identifying patient subgroups most likely to benefit from xanomeline–trospium therapy **[36]**.

3.1.5. ADAGIO-1 and ADAGIO-2

ADAGIO-1 (NCT07011732) and ADAGIO-2 (NCT07011745) are randomized, double-blind, Phase III clinical trials designed to evaluate the efficacy, tolerability, and safety of Cobenfy utilizing an enteric-coated xanomeline formulation (KarX-EC) **[45, 52, 66,67]**. Each study plans to enroll approximately 350 participants aged 55–90 years who meet the 2024 Alzheimer's Association diagnostic criteria for Alzheimer's disease (AD), confirmed by amyloid positron emission tomography or cerebrospinal fluid biomarkers **[45, 52]**.

Eligible participants were required to exhibit clinically significant agitation, confirmed by the following criteria: (1) a documented history of agitation for at least two weeks before screening; (2) a Neuropsychiatric Inventory/Neuropsychiatric Inventory–Nursing Home (NPI/NPI-NH) agitation/aggression score of at least 4 at both screening and baseline; (3) a CGI-S score of at least 4 at screening and baseline; and (4) weekly aggressive behavior documented using the Cohen-Mansfield Agitation Inventory–International Psychogeriatric Association (CMAI-IPA) instrument **[45, 52]**.In both trials, participants were randomized to receive either placebo or Cobenfy with KarX-EC. The primary endpoint is the change in CMAI-IPA score at Week 14 **[45,52]**.

3.1.6. ADAGIO-3

ADAGIO-3 (NCT06937229) is an extension study designed to evaluate the long-term safety and tolerability of treatment in participants who have completed ADAGIO-1 or ADAGIO-2. Follow-up is planned for up to 30 weeks after enrollment into the extension phase **[45, 52, 68**].

3.1. 7. ADEPT-1

ADEPT-1 (NCT05511363) was a 38-week study designed to assess the potential of Cobenfy to prevent relapse of psychosis in patients with Alzheimer's disease compared with placebo **[52, 69]**. The study enrolled 380 participants aged 55–90 years who met the diagnostic criteria for possible or probable mild Alzheimer's disease **[45, 52]**.Participants were required to meet the following criteria: (1) a documented history of psychotic symptoms; (2) moderate-to-severe delusions and/or hallucinations as assessed by the Neuropsychiatric Inventory–Clinician Rating Scale (NPI-C); and (3) a CGI-S score of at least 4 points **[52]**.

During the initial 12-week open-label phase, all participants received Cobenfy at the maximum dose of 66.7 mg + 6.67 mg three times daily. Participants were subsequently randomized to either placebo or continued Cobenfy treatment for an additional 26-week double-blind phase **[45, 52]**.

3.1. 8. ADEPT-2

ADEPT-2 (NCT06126224) was a 14-week study designed to evaluate the efficacy and safety of Cobenfy in the treatment of psychosis associated with Alzheimer's disease **[45, 52, 70]**. Approximately 400 participants were enrolled using eligibility criteria identical to those applied in ADEPT-1 **[45, 52]**. A notable difference from ADEPT-1 was the dosing regimen, which ranged from 60 mg + 6 mg to a final target dose of 200 mg + 20 mg [58]. The primary endpoint was the change from baseline in NPI-C score **[45,52]**. Secondary outcomes included changes from baseline in the Cohen-Mansfield Agitation Inventory (CMAI) and CGI-S scores **[45]**.

3.1. 9. ADEPT-3

ADEPT-3 (NCT05980949) is an open-label extension study that will enroll participants from ADEPT-1, ADEPT-2, and ADEPT-4 (approximately 600 participants) to assess the long-term safety and tolerability of Cobenfy treatment **[45, 52, 71]**. Participants will be monitored from study initiation until two weeks after administration of the final dose, with the overall study duration extending up to 54 weeks **[68]**. The primary objective is to evaluate the incidence and characteristics of treatment-emergent adverse events associated with Cobenfy therapy **[45, 52]**.

3.1. 10. ADEPT-4

ADEPT-4 (NCT06585787) is a 14-week study with a design similar to ADEPT-2, evaluating the efficacy and safety of Cobenfy in patients with Alzheimer's disease–related psychosis **[45,52,72]**. Approximately 400 participants were recruited. However, the eligibility criteria differed slightly from previous ADEPT studies and included: age 55–90 years, fulfillment of the 2024 National Institute on Aging–Alzheimer's Association diagnostic criteria for Alzheimer's disease with biomarker confirmation, and a documented history of psychotic symptoms for at least two months before enrollment **[52]**. The primary endpoint was the change from baseline in NPI-C score **[45,52]**.

3.1. 11. ADEPT-5

ADEPT-5 (NCT06947941) is a 12-week study evaluating the efficacy and safety of Cobenfy utilizing the KarX-EC formulation for the treatment of psychosis in patients with Alzheimer's disease **[45,52,73].** The study commenced in July 2025; however, recruitment had not yet begun at the time of reporting. It has been speculated that more than 1,000 participants meeting criteria similar to those used in ADEPT-4 will ultimately be enrolled **[45,52]**.

The primary endpoint is the change from baseline in NPI-C score **[45,52]**.

3. 1. 12. PENNANT

The PENNANT study (NCT05643170) was a three-year Phase IIIb clinical trial designed to evaluate the efficacy, safety, tolerability, and overall clinical impact of Cobenfy treatment **[45,74]**. Eligibility criteria included: (1) a diagnosis of schizophrenia according to DSM-5 criteria and (2) inadequate tolerability or insufficient efficacy of currently prescribed antipsychotic medications **[45]**.

Ultimately, only four participants were enrolled. They received 50 mg xanomeline plus 20 mg trospium twice daily for two days, followed by 100 mg + 20 mg twice daily from Days 3–7, and subsequently 125 mg + 30 mg twice daily for the remainder of the study **[45]**.

Clinical outcomes were assessed using several validated instruments, including the Investigator Assessment Questionnaire (IAQ), Clinical Global Impression (CGI), Clinical Global Impression–Severity of Illness (CGI-S), and Clinical Global Impression–Improvement (CGI-I) scales **[45]**.

The study was completed in March 2023; however, no results have been made publicly available **[45]**.

3.1. 13. UNITE-001

The UNITE-001 study (NCT05919823) was designed to evaluate both the short-term and long-term safety and efficacy of Cobenfy in patients with schizophrenia experiencing acute psychosis **[45,75]**. A total of 202 Chinese participants aged 18–65 years were ultimately enrolled **[45]**. Inclusion criteria were generally comparable to those employed in the EMERGENT clinical program (EMERGENT-1 through EMERGENT-5) **[45]**. The study consisted of two phases: an initial 5-week randomized, double-blind phase in which the investigational treatment was administered in parallel with placebo, followed by a 12-week open-label extension phase **[45]**. In both phases, the dosing regimen consisted of 50 mg + 20 mg twice daily during the first two days, escalation to 100 mg + 20 mg twice daily through Day 7, and maintenance therapy at 125 mg + 30 mg twice daily from Day 8 until study completion **[45]**. Although the study was completed in May 2025, the full dataset and final study results have not yet been published **[45]**.

3.2. Phase II Clinical Trials

3.2.1. EMERGENT-1

The EMERGENT-1 study (NCT03697252) was a 5-week, randomized, double-blind, placebo-controlled Phase II clinical trial involving 182 participants, designed to evaluate differences in treatment outcomes measured using the Positive and Negative Syndrome Scale (PANSS) and the Clinical Global Impression–Severity (CGI-S) scale following administration of Cobenfy compared with placebo **[43,45, 47, 54, 76-80]**. Eligibility criteria included age between 18 and 60 years, a diagnosis of schizophrenia according to DSM-5 criteria, and a baseline CGI-S score of at least 4 points [47, 50, 79, 80]. Additionally, participants were required to have a baseline PANSS score of at least 80 points, with at least one positive symptom rated ≥5 or at least two positive symptoms rated ≥4, as well as a documented history of psychotic exacerbation or relapse requiring hospitalization **[47]**.

The primary endpoint was the change in PANSS total score at Week 5 relative to baseline **[47, 56, 78, 80]**.

All antipsychotic medications were required to be discontinued for two weeks prior to study initiation. Patients with a history of treatment resistance to at least two antipsychotic agents or those who demonstrated a >20% reduction in PANSS score between screening and baseline assessments were excluded from participation **[47]**.

Participants were randomized to either a placebo control group (n = 92) or an investigational treatment group receiving the xanomeline–trospium combination (n = 90) **[43, 47,79]**. Treatment in the active group was initiated at a dose of 50 mg xanomeline plus 20 mg trospium twice daily, with gradual dose escalation to 125 mg + 30 mg twice daily **[43, 45, 47, 50, 54, 78,79]**.

Clinical efficacy was assessed using the PANSS and CGI-S scales at baseline and at Week 5 of treatment **[47]**. In addition, study visits—including Visit 1 (Day 2) and Visit 9 (Day 35)—included assessments of vital signs, body weight, laboratory parameters, and electrocardiographic monitoring **[47].** During these visits, the Columbia Suicide Severity Rating Scale (C-SSRS), Simpson–Angus Scale (SAS), and Barnes Akathisia Rating Scale (BARS) were also administered to evaluate suicidal ideation, parkinsonian symptoms, and akathisia among study participants **[43,47]**.

Treatment with the xanomeline–trospium combination resulted in a statistically significant reduction in PANSS total score at the study endpoint, with a least-squares mean change of –17.4 points compared with –5.9 points in the placebo group **[45,47,50,78,79].**

Participants receiving Cobenfy also demonstrated significant improvements across secondary efficacy endpoints, including subscales derived from the primary outcome measures used in the study **[47]**.Regarding adverse events, treatment-emergent adverse events (TEAEs) were reported in 50% of participants receiving Cobenfy compared with 43% of participants receiving placebo **[47]**. The most frequently reported TEAEs included nausea (17%), constipation (17%), dry mouth (9%), vomiting (9%), and dyspepsia (9%) **[45,47,77,78]**.

Following study completion, several post hoc analyses were conducted by Correll et al., Weiden et al., and Sauder et al. These investigations evaluated, among other outcomes, the effects of treatment on metabolic parameters (including lipid profiles and glycemic control), cholinergic adverse events, changes in vital signs (heart rate and systolic/diastolic blood pressure), and cognitive dysfunction associated with schizophrenia **[43,47,77-80]**.

3.3. Phase I Clinical Trials

The Phase I clinical trial (NCT02831231), conducted by Bristol Myers Squibb and lasting nine weeks, initiated the development program investigating combined xanomeline–trospium therapy **[45,77,81]**. To evaluate the potential benefits of adding trospium to xanomeline treatment in order to mitigate the adverse effects associated with xanomeline monotherapy, a randomized, double-blind study design was employed **[45]**.

One study group received xanomeline in combination with placebo (n = 33), whereas the second group received xanomeline together with trospium (n = 35). Healthy volunteers aged 18–60 years were recruited for participation **[45]**.

Participants in the active treatment group received xanomeline at a dose of 75 mg three times daily and trospium at a dose of 20 mg twice daily [45]. During the first two days, participants received either trospium or placebo alone. Xanomeline was subsequently added and maintained for the following seven days **[45]**.

Throughout the study, a broad range of parameters was monitored, including cardiovascular function, visual analogue scale (VAS) assessments, and laboratory measures **[45]**. The results demonstrated that the addition of trospium reduced the incidence of five common adverse effects associated with xanomeline monotherapy—hyperhidrosis, salivation, nausea, diarrhea, and vomiting—by an average of 46%. No significant differences were observed with respect to electrocardiographic findings, renal or hepatic function, or routine laboratory parameters **[45]**.

4. Possibilities of using the Cobenfy

The approval of xanomeline-trospium (Cobenfy) represents a major milestone in psychopharmacology, introducing the first medication approved by the FDA for the treatment of schizophrenia that exerts its therapeutic effects without directly antagonizing dopamine receptors **[36,47]**. Approved by the FDA in September 2024, Cobenfy combines xanomeline, a centrally acting muscarinic M1/M4 receptor agonist, with trospium chloride, a peripherally acting muscarinic antagonist that limits cholinergic adverse effects outside the central nervous system **[36]**. This combination establishes a novel pharmacological class for schizophrenia treatment by targeting the cholinergic rather than the dopaminergic system **[36,47]**. Xanomeline was originally developed in the 1990s as a potential treatment for AD **[36,83,85]**. During early clinical development, xanomeline demonstrated dose-dependent improvements in cognitive performance together with reductions in neuropsychiatric symptoms, including hallucinations, delusions, agitation, and other behavioural disturbances in patients with AD **[36,80,83-85]**. No significant improvements in affective symptoms were observed **[80,84,85]**. Furthermore, xanomeline tartrate was associated with significant improvements in simple reaction time and delayed verbal recall, as assessed using the CNTB **[84,86]**. These unexpected antipsychotic effects observed in patients with dementia ultimately led to the investigation of xanomeline in schizophrenia **[36]**. Unlike conventional antipsychotics, whose efficacy primarily depends on dopamine D2 receptor blockade, xanomeline-trospium acts through central muscarinic receptor activation **[36,47]**. Although modulation of cholinergic neurotransmission may secondarily influence dopaminergic signalling, its effects on dopamine pathways appear substantially more selective and indirect than those of traditional antipsychotic agents **[36,47]**. Consequently, Cobenfy occupies a unique position among currently available antipsychotic treatments and may provide a valuable therapeutic alternative for patients who are unable to tolerate dopamine receptor antagonists because of extrapyramidal symptoms, tardive dyskinesia, hyperprolactinaemia, or metabolic adverse effects **[36,47]**. Some authors have proposed that xanomeline-trospium could be considered a first-line treatment option, particularly for individuals at increased risk of developing extrapyramidal or metabolic complications associated with dopamine-blocking antipsychotics **[47].** However, further clinical experience and long-term comparative studies are required before its role in treatment algorithms can be fully established **[36,47]**. The patient populations most likely to benefit from Cobenfy have not yet been fully established; however, available evidence suggests that several clinical subgroups may represent particularly appropriate candidates for this treatment, as shown in the Table X **[36]**.

Patients who are intolerant to dopamine receptor antagonist antipsychotics or who have previously experienced clinically significant extrapyramidal side effects, tardive dyskinesia, or antipsychotic-induced hyperprolactinaemia. Individuals with metabolic syndrome, pre-existing obesity or weight-related concerns, or those at increased risk of developing antipsychotic-induced metabolic adverse effects. Patients with prominent cognitive impairment and/or persistent negative symptoms that remain insufficiently responsive to conventional antipsychotic therapy. Emerging evidence suggests that improvements in cognitive functioning may reduce vulnerability to psychosis, enhance treatment responsiveness, and promote functional recovery. Patients requiring an alternative mechanism of action, including those with an inadequate response to standard

antipsychotic treatment or those receiving adjunctive therapy. Although the current evidence is insufficient to support the use of Cobenfy as monotherapy for treatment-resistant schizophrenia, it may represent a promising adjunctive treatment option in carefully selected patients, with individualized assessment of the potential benefits and risks.

Table 5. Groups of patients who can benefit most from using Cobenfy.

Patients who are intolerant to dopamine receptor antagonist antipsychotics or who have previously experienced clinically significant extrapyramidal side effects, tardive dyskinesia, or antipsychotic-induced hyperprolactinaemia.
Individuals with metabolic syndrome, pre-existing obesity or weight-related concerns, or those at increased risk of developing antipsychotic-induced metabolic adverse effects.
Patients with prominent cognitive impairment and/or persistent negative symptoms that remain insufficiently responsive to conventional antipsychotic therapy. Emerging evidence suggests that improvements in cognitive functioning may reduce vulnerability to psychosis, enhance treatment responsiveness, and promote functional recovery.
Patients requiring an alternative mechanism of action, including those with an inadequate response to standard antipsychotic treatment or those receiving adjunctive therapy. Although the current evidence is insufficient to support the use of Cobenfy as monotherapy for treatment-resistant schizophrenia, it may represent a promising adjunctive treatment option in carefully selected patients, with individualized assessment of the potential benefits and risks.

The cholinergic neurotransmitter system plays a fundamental role in learning, memory, attention, and executive functioning **[36,47, 78,82]**. Accordingly, there is increasing interest in the potential pro-cognitive effects of xanomeline-trospium **[36,47,78,82]**. Preliminary clinical data suggest that, in addition to reducing positive psychotic symptoms, xanomeline-trospium may improve negative symptoms and cognitive deficits, domains that remain inadequately addressed by currently available antipsychotic medications **[36,47,78,82]**. Although these findings are encouraging, additional randomized controlled trials are needed to confirm the magnitude and durability of these benefits **[36,47]**.

Evidence supporting the cognitive effects of xanomeline-trospium has been obtained using several standardized neuropsychological assessment tools **[84,87]**. In patients with schizophrenia, an enriched post hoc analysis demonstrated significantly greater cognitive improvement with xanomeline-trospium than with placebo across multiple domains evaluated using the CANTAB, including executive functioning assessed by the OTS, short-term visuospatial memory measured by the SSP, sustained attention and processing speed evaluated using the RVP task, and verbal learning and memory assessed by the VRM test **[84,87]**. Together with earlier findings from Alzheimer's disease studies, these data support the hypothesis that xanomeline-trospium exerts direct pro-cognitive effects and may have therapeutic potential across several neuropsychiatric disorders characterized by cognitive dysfunction **[84].**

Beyond schizophrenia, growing evidence suggests that cholinergic modulation may have broader transdiagnostic applications **[88]**. Xanomeline-trospium chloride has been proposed as a potentially effective treatment not only for schizophrenia but also for mania, mixed affective states, and cognitive impairment associated with bipolar disorder **[88]**. Available evidence indicates that the combination is generally safe and well tolerated and has not been associated with depressogenic effects or increased suicidality in adults with schizophrenia **[88]**. Future studies should also evaluate whether other investigational muscarinic receptor modulators, including M4-positive allosteric modulators and selective orthosteric agonists, demonstrate efficacy for mood symptoms and cognitive impairment in bipolar disorder **[88]**.

Mechanistically, there is also a compelling neurobiological rationale for investigating xanomeline-trospium in BPSD [**52**]. Alzheimer's disease is characterized by degeneration of cholinergic neurons within the nucleus basalis of Meynert and reduced acetylcholine availability in the hippocampus and cerebral cortex **[52,89]**. Current symptomatic treatments, including acetylcholinesterase inhibitors such as donepezil, rivastigmine, and galantamine, aim to enhance cholinergic neurotransmission by preventing acetylcholine degradation **[22,90]**. In contrast, xanomeline directly stimulates postsynaptic muscarinic receptors, principally M1 receptors within the cerebral cortex and hippocampus and M4 receptors located in the cortex, hippocampus, and striatum **[52,85,91]**. Activation of M1 receptors is believed to improve cognition through enhanced cortical network synchrony and synaptic plasticity, whereas M4 receptor activation may reduce excessive excitatory

neurotransmission within hippocampal circuits, thereby contributing to more stable neuronal network function **[52,92]**. Collectively, these mechanisms are hypothesized to reduce psychosis and behavioural disturbances through downstream modulation of dopaminergic neurotransmission while simultaneously improving cognitive performance via enhanced central cholinergic signalling **[52,92]**.

Although Cobenfy has been approved exclusively for schizophrenia, its unique mechanism of action has generated considerable interest regarding its potential use in AD and BPSD **[52]**. The increasing global prevalence of dementia underscores the urgent need for safer and more effective therapeutic options, particularly because currently available antipsychotics provide limited efficacy and are associated with substantial safety concerns in older adults **[52]**. At present, no completed clinical trials have evaluated Cobenfy in BPSD; however, several ongoing studies are investigating its efficacy in psychosis and agitation associated with AD **[52]**. The results of these studies will be critical in determining the efficacy, safety, and potential clinical role of xanomeline-trospium in older adults with dementia **[52]**.

Overall, the currently available evidence indicates that xanomeline-trospium is a safe and effective treatment for adults with schizophrenia and represents the only approved antipsychotic therapy that achieves antipsychotic efficacy without directly targeting dopamine receptors **[36,47]**. Clinical trials demonstrate clinically meaningful reductions in psychotic symptoms together with promising, although still preliminary, improvements in negative symptoms and cognition **[47]**. Nevertheless, further long-term studies are required to clarify its optimal positioning within schizophrenia treatment algorithms, identify patient populations most likely to benefit, and establish its therapeutic potential across other neuropsychiatric disorders **[36,47]**.

5. Place in therapy

Cobenfy adds a new option to the treatment of schizophrenia because it targets the disorder through a pharmacological pathway distinct from most currently used antipsychotics. Instead of relying mainly on dopamine D_2 receptor blockade, xanomeline/trospium is based on muscarinic cholinergic modulation, with xanomeline acting as a muscarinic receptor agonist and trospium added to reduce peripheral cholinergic adverse effects **[47,78]**. This gives the drug a potentially important place in therapy, particularly for patients in whom standard antipsychotics are difficult to continue because of adverse effects or poor tolerability.

The patients most likely to benefit from Cobenfy are those for whom avoiding dopamine-related adverse effects is an important treatment goal. This may include individuals who have previously had poor acceptance of antipsychotic therapy because of extrapyramidal symptoms, akathisia, hyperprolactinaemia, sedation, weight gain, or metabolic deterioration **[93-95].** For these patients, Cobenfy may make long-term treatment more feasible by offering a mechanism and tolerability profile that differ from those of many established antipsychotics **[47,95]**. It may also be valuable in shared decision-making, especially when a patient is reluctant to restart or continue a medication from the traditional dopamine-blocking class **[47]**.

At the same time, Cobenfy is not an ideal choice for every patient. Its use may be less appropriate when gastrointestinal, urinary, cardiovascular, or anticholinergic risks are already clinically important **[47,95].** The adverse effects most often reported in trials and pooled analyses were gastrointestinal and muscarinic-related, including nausea, vomiting, dyspepsia, constipation, dry mouth, and increases in blood pressure **[95,96]**. Therefore, treatment requires caution in patients with significant constipation, gastrointestinal hypomotility, urinary retention, urinary outflow obstruction, tachycardia, or a high cumulative anticholinergic burden **[47,95]**. Particular care is also needed when patients are already taking clozapine, anticholinergic drugs for extrapyramidal symptoms, sedating antihistamines, tricyclic antidepressants, or medications for urinary symptoms **[47,95]**.

Compared with conventional antipsychotics, Cobenfy is best understood as a complementary option rather than a universal replacement **[47,93]**. Established antipsychotics still offer important advantages, including extensive clinical experience, multiple formulations and the availability of long-acting injectable preparations **[93,97]**. Cobenfy's main comparative strength is its differentiated mechanism and relatively favourable profile regarding motor symptoms, prolactin-related effects, weight gain, sedation, and metabolic outcomes in available studies **[95,96]**. Its main practical limitations are gastrointestinal tolerability, the need to monitor anticholinergic burden, twice-daily oral administration, and the current lack of a long-acting injectable formulation **[47,95,97]**.

The possible relevance of Cobenfy for negative symptoms is one of the more clinically interesting aspects of the current evidence base **[54,96].** In pooled EMERGENT data, xanomeline/trospium improved PANSS total score and showed benefits on PANSS subscales, including negative symptoms, compared with placebo **[54]**. A systematic review and meta-analysis also reported improvement in PANSS negative symptom

scores and Marder negative factor scores, suggesting that the drug's effects may extend beyond positive symptom control **[96]**. These findings should still be interpreted carefully, because they come mainly from acute trials and do not yet establish efficacy in patients with predominant primary negative symptoms **[54,96]**.

The cognitive findings are also encouraging, although still preliminary **[87]**. In pooled phase 3 analyses, xanomeline/trospium did not significantly improve cognition in the overall study population, but it was associated with significant benefit in patients who had clinically relevant cognitive impairment at baseline **[87]**. This points to patients with more pronounced cognitive deficits as a potentially important subgroup for future research **[87]**. For now, Cobenfy should not be described as a proven cognitive-enhancing treatment, but the available data justify continued investigation of its cognitive effects **[87]**.

The role of Cobenfy in combination with other antipsychotics is still not clearly established **[47,98]**. Combining it with a dopamine-based antipsychotic is pharmacologically reasonable because the mechanisms are different, but routine long-term augmentation is not yet supported by strong clinical evidence. In practice, the most defensible use of temporary combination therapy is cross-titration, such as when switching from risperidone, olanzapine, quetiapine, aripiprazole, or another antipsychotic to Cobenfy **[47,98]**. This approach may help maintain antipsychotic coverage during the transition while reducing exposure to dopamine-related adverse effects over time **[47,93]**.

Combination with clozapine requires particular caution because both treatments may contribute to constipation, tachycardia, sedation, and cumulative anticholinergic burden **[47,95]**. Cobenfy should not be considered a substitute for clozapine in treatment-resistant schizophrenia **[99]**. Clozapine remains the reference treatment when a patient has failed to respond adequately to at least two appropriate antipsychotic trials, with adherence, dose, duration, and symptom severity properly assessed **[99]**. Cobenfy may be considered before clozapine when previous treatment failure was driven mainly by intolerance rather than true pharmacological resistance, but it should not delay clozapine when criteria for treatment-resistant schizophrenia are met **[47,99]**.

Long-term findings suggest that Cobenfy may have a role beyond short-term symptom control **[100,101]**. In a 52-week open-label extension study, xanomeline/trospium was generally well tolerated, showed no new safety concerns, and was associated with durable symptom improvement **[100]**. EMERGENT-5 further supports the feasibility of longer-term use and switching from prior antipsychotics to xanomeline/trospium in clinically stable adults with schizophrenia **[101]**. These findings are encouraging, although controlled relapse-prevention studies and real-world data are still needed to define its long-term position more precisely **[47,100,101]**.

Overall, Cobenfy appears most appropriate for patients who need effective antipsychotic treatment but are poorly suited to continued direct D_2 receptor blockade. It is especially relevant for patients with previous extrapyramidal symptoms, akathisia, prolactin-related adverse effects, metabolic concerns, or poor subjective tolerability of conventional antipsychotics **[93-96]**. It is less appropriate for patients with substantial gastrointestinal, urinary, cardiovascular, or anticholinergic risk factors **[47,95]**. Its place in therapy is therefore best defined as a mechanistically novel and clinically valuable alternative that expands treatment options for patients for whom standard antipsychotics may be effective, but difficult to use in everyday practice **[47,98]**.

6. Conclusions

Cobenfy (xanomeline–trospium) is the first FDA-approved antipsychotic for schizophrenia that exerts its therapeutic effects without direct dopamine receptor antagonism, representing a novel cholinergic approach to the treatment of psychosis. It combines xanomeline, a selective M1/M4 muscarinic receptor agonist that modulates brain functional connectivity and may improve cognitive and sensory processing, with trospium chloride, a peripherally acting muscarinic antagonist that reduces the peripheral cholinergic adverse effects of xanomeline. Clinical trials have consistently demonstrated significant improvements in psychotic symptoms, reflected by reductions in PANSS scores, while long-term studies indicate sustained efficacy and a favourable metabolic profile with minimal effects on body weight and cardiometabolic parameters. Preliminary evidence also suggests potential benefits for negative symptoms and cognitive impairment, although these findings require further confirmation. Owing to its distinct mechanism of action and favourable tolerability profile, Cobenfy may be particularly valuable for patients who cannot tolerate conventional dopamine-based antipsychotics because of extrapyramidal symptoms, hyperprolactinaemia, metabolic adverse effects, or poor treatment acceptance. The most commonly reported adverse events include gastrointestinal symptoms, headache, dizziness, hypertension, and dry mouth, and the drug is administered twice daily; however, data regarding its use during pregnancy and breastfeeding remain unavailable. Overall, Cobenfy represents a promising alternative to traditional antipsychotic therapies, while ongoing comparative, long-term, real-world, and neuropsychiatric studies, including in Alzheimer's disease, will further define its clinical role and therapeutic potential.

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