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COBCOBENFY (XANOMELINE–TROSPIUM) IN SCHIZOPHRENIA MANAGEMENT: A MUSCARINIC SHIFT FROM DOPAMINERGIC ANTIPSYCHOTICS

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ABSTRACT

Schizophrenia is a chronic, debilitating neurological condition that has a significant public health burden worldwide. Dopamine D2 receptor antagonists and partial agonists have long been considered effective in reducing positive symptoms and therefore are well known to treat negative symptoms, but they can hardly cope with negative and cognitive symptoms in addition to their large metabolic and neurological side effects. Cobenfy is a fixed-dose combination of xanomeline and trospium which is the first clinically approved non-dopaminergic antipsychotic. The combination of these two modulation for the M1/M4 receptor provides cholinergic equilibrium in key brain regions involved in psychosis. This review explores Cobenfy's mechanism of psychotherapy, clinical development, efficacy, safety and implications for reorienting schizophrenia management. Early-phase and pivotal Phase III studies show that Cobenfy does indeed improve clinically meaningful symptoms with rapid onset of action, a good safety profile and minimal risk for metabolic and extrapyramidal side effects. Cobenfy might be an indication of a shift from dopaminergic antagonism towards a more nuanced neurochemical modulation in the treatment of psychotic disorders.

1. INTRODUCTION

1.1 Schizophrenia and Current Treatment Challenges

Schizophrenia affects a whopping 20 million people around the world, mostly in late adolescence or early adulthood. Delusions, hallucinations, anhedonia, affective flattening, social withdrawal are all symptoms of delusions. They have cognitive deficits, including impaired memory and executive dysfunction. While antipsychotics remain the primary drug of choice, they are most commonly targeted in the dopaminergic system.

The first generation (typical) antipsychotics such as haloperidol are powerful D2 receptor antagonists and are serious in EPS and tardive dyskinesia. Second-generation (almost atypical) agents such as risperidone, olanzapine and clozapine combine dopamine and serotonin receptor blockade to reduce motor side effects but also introduce metabolic complications including weight gain, dyslipidemia, and diabetes. But, the treatment response can still be elusive and patients remain resistant to treatment in all instances and cognitive and negative symptoms persist over time, which demonstrates the need for mechanistically different remedies.

1.2 The Need for Non-Dopaminergic Alternatives

Recent research into schizophrenia revealed that the glutamatergic, GABAergic, and cholinergic systems are mutated in addition to dopaminergic dysfunction, due to the multifactorial nature of the neurobiology of schizophrenia. In particular, muscarinic cholinergic receptor deficits, particularly M1 and M4 subtypes, have been reported to have impaired cortical and hippocampal signaling associated with cognitive and psychotic symptoms. Special studies have demonstrated that cholinergic dysregulation is linked to illness in schizophrenia patients with low M1 receptor concentration, which suggests that there may be evidence for the role of cholinergic function in disease pathology.

1.3 Emergence of Cobenfy

The U.S. Food and Drug Administration approved Cobenfy, by Karuna Therapeutics, as the first non-dopaminergic antipsychotic for schizophrenia in 2024. Cobenfy incorporates xanomeline, the centrally acting muscarinic M1/M4 receptor agonist, with trospium, a peripherally inhibited muscarinic antagonist. The fixed-dose combination provides central cholinergic activation required to achieve antipsychotic efficacy and prevents peripheral cholinergic side effects, something that

overcomes the limitations of the earlier xanomeline monotherapy trials.

2. PHARMACOLOGICAL JUSTIFICATION AND MECHANISM OF ACTION

2.1 Xanomeline: A Muscarinic Receptor Agonist

Xanomeline is an agonist for the muscarinic receptors, specifically for the M_1/M_4 receptors, which are abundant in the hippocampus and prefrontal cortex and are believed to facilitate cognition and modulation of glutamatergic activity. The M_4 receptors are more localized in striatal and limbic areas and are thought to provide inhibitory control of dopaminergic neurotransmission and are in part, responsible for antipsychotic-like effects without direct D_2 receptor blockade.

Preclinical models provide strong evidence to suggest activation of M_1/M_4 receptors decreases dopaminergic hyperactivity in the mesolimbic pathway to increase cortical signaling; such effects are thought to be responsible for some of the antipsychotic benefits and pro-cognitive effects. Thus, xanomeline can indirectly modify dopaminergic tone via the cholinergic system.

2.2 Trospium: Peripheral Muscarinic Blockade

Trospium chloride, which is a quaternary ammonium compound is a peripherally restricted muscarinic antagonist that is FDA approved and used for and overactive bladder. Trospium does not cross the blood–brain barrier, thereby allowing for selective peripheral muscarinic antagonism while preserving central muscarinic receptor activation. In Cobenfy, trospium will address the most common cholinergic adverse events associated with the use of xanomeline including: bradycardia, nausea, sweating, salivation, and diarrhea which historically prevented the use of xanomeline as a therapeutic option.

2.3 Dual Mechanistic Synergy

Thus, the combination of xanomeline and trospium allows for central muscarinic receptor activation while mitigating peripheral events. The opposing peripheral muscarinic antagonism and central muscarinic modulation allows for restoration of neurotransmission within the cortex and hippocampus, also potentially improving psychotic symptoms and cognitive dimensions of schizophrenia.

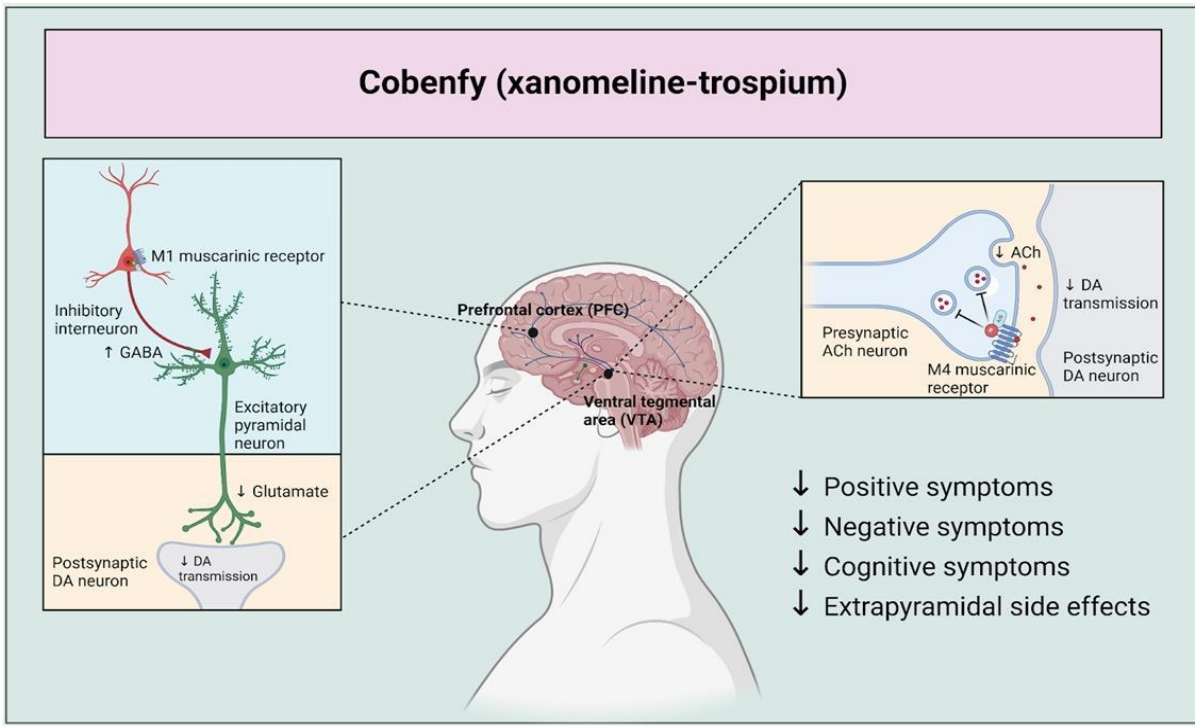

Figure 1: MOA of Cobenfy.

3. Clinical Development: The EMERGENT Trial Program

The efficacy and safety of Cobenfy were evaluated in the **EMERGENT program**, a series of Phase II and III clinical trials encompassing over 1,300 participants.

3.1 EMERGENT-1 (Phase II Proof-of-Concept)

A double-blind, randomized, placebo-controlled trial assessed xanomeline–trospium in 182 patients with acute exacerbations of schizophrenia. Cobenfy demonstrated **significant reductions in PANSS total scores** (–17.4 vs. –5.9 with placebo) over 5 weeks, with improvements observed as early as Week 2. Notably, discontinuation rates due to adverse events.

3.2 Comparative Analysis with Atypical Antipsychotics

Table 1: Comparative Analysis with Atypical Antipsychotics.

Drug name	Mechanism	PANSS Reduction	EPS risk	Metabolic risk
Cobenfy	Muscarinic M1/M4 agonist	High (~ 9.6 pts)	Low	Low
Aripiprazole	D2 partial agonist	Moderate (~7-8)	Moderate	Low
Risperidone	D2 antagonist + 5HT2A	High (~10-12)	High	Moderare
Olazapine	D2/5HT2A antagonist	High (~10-12)	Moderate	High
Lumateperone	D2 antagonist + serotonin mod	Low (~4-6)	Low	Low

4. Safety and Tolerability

Xanomeline-trospium (Cobenfy) has an improved safety profile compared to traditional antipsychotics. Throughout the EMERGENT clinical trial program, the tolerability of the combination was generally positive, as the majority of adverse events were low in severity, moderate in intensity, and self-resolving. The overall discontinuation due to adverse events was relatively low (approximately 5-8%), and there were no major safety signals.

Common adverse events included nausea, constipation, dizziness, dry mouth, and slight increased blood pressure. These events commonly occurred early in treatment and resolved over time or by conservative therapeutic intervention. Nausea was the most frequent complaint, while constipation and dizziness were less common. No laboratory or ECG findings were observed to be clinically significant.

A significant advantage of Cobenfy is the reduced risk of extrapyramidal symptoms (EPS) since it does not block dopamine receptors. Rates of Parkinsonism, akathisia, or dystonia were comparable to placebo and no instances of tardive dyskinesia were reported. Sedation is uncommon, and Cobenify does not diminish the patients' awareness or cognitive capacity, making it competent to use for chronic dosing and for those patients that may be more susceptible to dopaminergic side-effects.

Cobenfy also demonstrates a metabolic neutral profile and does not cause weight gain, dyslipidemia, or glucose abnormalities like the atypical antipsychotics olanzapine and risperidone. In trials of Cobenfy lasting up to 12 weeks, patients showed little change in body weight, with no clinically meaningful changes in glucose or lipid values. Prolactin levels remained stable, further supporting that Cobenfy's pharmacology was not associated with clinically meaningful dopamine blockade.

Trospium is a peripherally acting muscarinic antagonist that limits peripheral cholinergic side-effects, which hampered the earlier development of xanomeline. By selectively blocking muscarinic receptors peripherally and outside of the central nervous system, trospium may decrease cholinergic side effects, such as sweat, excessive salivation, and bradycardia, when used as an adjunct to xanomeline, while allowing xanomeline to exert central therapeutic effects.

Overall, Cobenfy's safety profile is characterized by a low risk of neurologic and metabolic side effects, tolerable gastrointestinal side effects, and good tolerability, indicating promise for acute and maintenance therapy of schizophrenia, particularly for patients who experience intolerability from conventional dopaminergic antipsychotics.

5. Mechanistic Innovation

Cobenfy employs a new treatment method within schizophrenia focused on muscarinic M_1 and M_4 receptor engagement, rather than dopamine D_2 receptor blockade. This muscarinic modulation signifies a significant change in management of psychotic symptoms. Agonism of the M_1 receptors, located in the prefrontal cortex and hippocampus, potentiates cholinergic and glutamatergic signaling, which serve cognitive processing, attention and memory. The M_4 receptors are located to indirectly regulate dopaminergic release in striatal and limbic circuits, and maintain stabilization of mesolimbic hyperactivity that contributes to positive psychotic symptoms.

Cobenfy, by working through these pathways, holds promise to improve negative symptomatology and cognitive deficit—where other conventional dopamine antagonists work minimally. A key aspect of Cobenfy is that by not blocking dopamine receptors Cobenfy is able to largely avoid the translation to extrapyramidal symptoms, tardive dyskinesia, and hyperprolactinemia that occurs with long-term treatment, resulting in increased neurological burden over time.

The combination of centrally acting muscarinic agonism and peripherally acting cholinergic blockade from trospium may be a mechanistic innovation which will redefine neurochemical targets within antipsychotic treatment. Additionally, it suggests that returning relative balance to M_1/M_4 and dopamine systems may allow for symptom relief, cognitive enhancement, and stripping away some of the side effects of dopamine receptor blockade.

6. CONCLUSION

Cobenfy offers a promising alternative to traditional antipsychotics, particularly for patients who are unresponsive or intolerant to dopamine receptor antagonists. By selectively activating central muscarinic M_1 and M_4 receptors, it achieves effective control of psychotic symptoms without the neurological and metabolic drawbacks associated with dopaminergic

blockade. This unique mechanism may also address cognitive and negative symptoms that remain unmet needs in schizophrenia care. The addition of trospium enhances tolerability by reducing peripheral cholinergic effects, making long-term use more feasible. As the first approved non-dopaminergic antipsychotic, Cobenfy represents a pivotal step toward broader neurochemical targeting in psychosis, meriting continued research, real-world evaluation, and wider clinical integration.

The study on drug cobenfy demonstrates that the combination of xanomeline and trospium (Cobenfy) produces clinically meaningful, rapid, and sustained antipsychotic efficacy in patients with acute schizophrenia exacerbations, as evidenced by a substantial reduction in PANSS total scores compared with placebo. Although treatment was associated with a modest increase in discontinuations due to adverse events, the overall benefit–risk profile supports Cobenfy as a promising new therapeutic option for this challenging condition.

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