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Review

XANOMELINE AND TROSPIUM

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Abstract

The cholinergic agonist xanomeline was first investigated for schizophrenia and Alzheimer's disease, but research was halted because of cholinergic adverse effects. Its usage in conjunction with trospium, a peripheral cholinergic antagonist, has recently been investigated in schizophrenia patients. Constipation, dry mouth, and nausea are examples of cholinergic side effects that may be lessened by this combination. Xanomeline has M1/M4 agonist activity and evidence from early studies is promising. The fixed-dose combination of xanomeline and trospium will be marketed as Cobenfy (KarXT) and results from phase III trials show xanomeline-trospium in phase III trials significantly reduce symptoms in schizophrenia with positive results backed by a strong efficacy profile and overall acceptable safety data.

Keywords: xanomeline, schizophrenia, Alzheimer's, trospium

INTRODUCTION

Xanomeline-Trospium chloride (XTC), marketed under the brand name Cobenfy, is a new medication for schizophrenia. It is an antipsychotic that acts as a muscarinic agonist and alleviates psychosis without the need for blocking the dopamine D2 receptor, similar to the action of standard antipsychotics [1]. The combination of xanomeline and the muscarinic antagonist trospium blocks peripheral cholinergic side effects while preserving central actions, hence improving therapeutic potential. Recently, in clinical studies, KarXT, the combination product, exhibited significant antipsychotic efficacy and increased tolerability compared to xanomeline alone, potentially heralding a new era in the treatment of schizophrenia [2].

HISTROY

Xanomeline was developed in the early 1990s by Eli Lilly and Novo Nordisk with the aim of creating a new drug for Alzheimer's Disease. Initial Phase II studies showed a statistically significant benefit in both cognition and behavior, and the program transitioned toward schizophrenia, where antipsychotic-like effects appeared [3]. However, in 1998 the program was stopped entirely due to the development of cholinergic side effects. A xanomeline formulation with trospium chloride was developed by Karuna Therapeutics in 2012 to address the cholinergic side effects. Trospium was originally developed in the 1960s and subsequently gained marketing approval in Europe and the United States (in 2007 as an extended-release formulation) [4]. The xanomeline-trospium formulation, Cobenfy, showed enhanced efficacy in Phase III trials and was FDA approved in September 2024, marking the first FDA approved antipsychotic through targeting cholinergic receptors, which is significant in the treatment of schizophrenia [5].

MECHANISM OF ACTION (PHARMACOLOGY)

XTC is believed to work by acting on muscarinic receptors, instead of the dopamine D2 receptor, which are modulating cognitive circuits while regulating dopamine levels in the CNS. Xanomeline is a selective agonist for M1 and M4 receptors [6]. Specifically, M1 receptors are believed to be activated in the prefrontal cortex and hippocampus, resulting in increased intracellular Ca++ and potentiating NMDA receptor function through a pathway of MAPK/CREB that helps facilitate cognitive processing [7]. Similarly, the M4 receptor has been implicated in modulating dopamine release in the striatum, which enables treatment of psychotic symptoms as a function of receptor activation without any unintended changes to motor functions, thus limiting the most common side effects associated with antagonism of D2 receptor-Dopamine [8]. Note, however, that non-selective activation of the muscarinic receptors can lead to unwanted peripheral side effects. Trospium is a peripherally acting antagonist that blocks M2 and M3 receptors, and it does not cross the blood-brain barrier [9]. The inclusion of trospium can therefore be considered as a means of providing some of the cognitive enhancement of XTC without the collateral side effects of activation of the peripheral receptors.

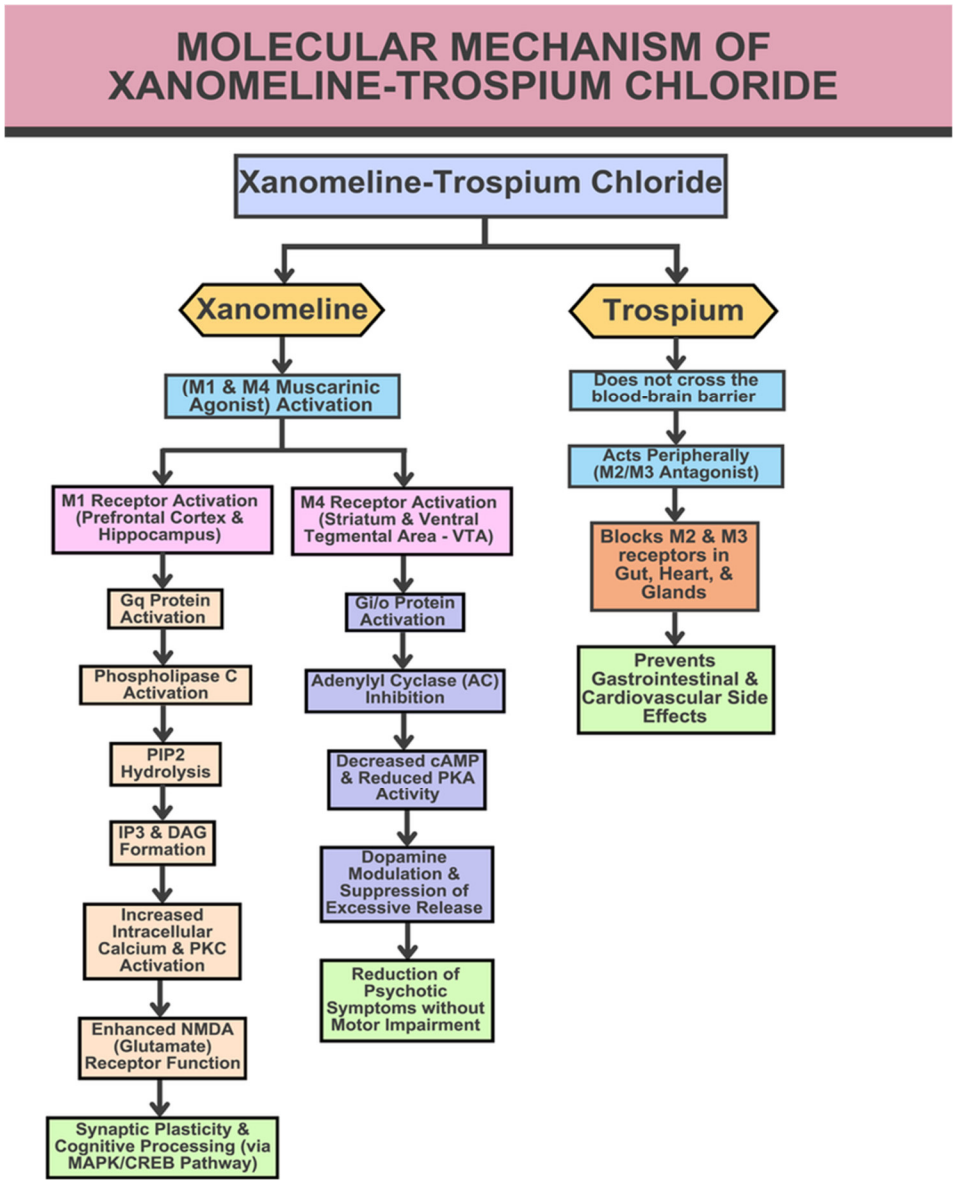

Fig-1

SIDE EFFECTS

Risk of Urinary Retention: Cobenfy has the potential to cause urinary retention, especially in elderly patients and patients with bladder outlet obstruction (e.g., benign prostatic hyperplasia [BPH]) [10]. It is contraindicated in patients with urinary retention and in patients with moderate to severe renal impairment.

Hepatic Impairment: Patients with hepatic impairment are more likely to experience increased systemic exposure to xanomeline and an increased risk of adverse effects [11]. Cobenfy is not recommended for these patients, and it is important to evaluate liver enzymes before and during treatment.

Biliary Disease: Cobenfy should not be used in patients with active biliary disease. Liver enzymes should be monitored, as well as the presence of symptoms of biliary disease [12].

Gastrointestinal Motility: Cobenfy may decrease gastrointestinal motility. It is advisable to use caution in patients with gastrointestinal obstructive disorders to avoid gastric retention [13].

Risk of Angioedema: Angioedema has been mentioned in the literature and may be life threatening [14]. If symptoms occur, discontinue use and ensure the airway is patent.

Narrow-angle Glaucoma: The agent can cause pupillary dilation, increasing the risk of acute angle closure in patients with narrow-angle glaucoma [15]. If the benefit of treatment outweighs the risk, use with caution and careful monitoring.

Increased Heart Rate: Cobenfy can increase heart rate, and patient heart rates should be assessed throughout treatment [16].

Renal Impairment: The active ingredient, trospium chloride is primarily eliminated from the body via the kidneys and adverse events may be increased in patients with renal impairment (eGFR <60 mL/min) [17].

CNS Effects: Trospium chloride should be avoided in patients with anticholinergic CNS effects including dizziness and confusion [18]. Patients should not drive or operate heavy machinery until they are aware of how the medication affects them, and should be monitored for these effects after starting treatment.

CLINICAL STUDIES

Xanomeline (both by mouth and transdermally) was discontinued for Alzheimer's disease in 1998 due to side effects. This was also true for xanomeline in schizophrenia since peripheral cholinergic side effects (like diarrhea and sweating) were generally greater than its effects. However, there was renewed interest in supporting its effects with trospium, a nonselective antimuscarinic, which does not have any effect on the central nervous system [19]. This combination purportedly improved bioavailability of xanomeline and decreased cholinergic adverse effects, demonstrated in a Phase I trial comparing xanomeline-trospium with xanomeline alone [20].

This study randomly assigned 70 participants to xanomeline plus trospium or xanomeline plus placebo, and did evaluate adverse events on a Visual Analogue Scale [21]. Somewhat surprisingly, although the researchers concluded that there was not an overall significant reduction in cholinergic adverse effects, there were significant reductions in adverse effects when directly comparing 'active' to placebo [22]. The specific adverse effects, of nausea, vomiting, diarrhea, sweatiness and salivation were also noted to be significantly less in the xanomeline-trospium group.

A recent Phase I study with 69 healthy volunteers evaluated multiple doses of xanomeline and trospium. Most dose combinations (100 /20mg and 125/40mg) caused mild cholinergic side effects that were well tolerated. We are still awaiting information regarding higher doses (150mg) [23].

Additionally, a recent Phase II study investigated the effects of xanomeline with trospium in adults with schizophrenia. Patients aged 18-60 were studied, while individuals with treatment resistant illness were excluded. The primary outcome of this study was the change from baseline in PANSS total score over 5 weeks [24]. Notably, there was a significant decrease in PANSS scores indicating a reduction in both positive and negative symptoms, although the reduction in PANSS was more pronounced for positive symptoms. It should be noted that adverse events occurred more frequently in the combination treatment condition, as compared to placebo, with constipation, nausea, dry mouth and dyspepsia most commonly reported [25].

ADVERSE DRUG REACTIONS

Gastrointestinal Adverse Effects:

-Constipation
- Nausea
- Vomiting
- Dyspepsia
- Abdominal cramps

Anticholinergic Effects (from trospium):
- Dry mouth
- Urinary retention
- Blurred eyesight
- Reduced sweating (anhidrosis), increasing heat intolerance
- Dry eyes

Cardiovascular Effects:
- Fast heart rate
- Postural hypotension
- High blood pressure (less common)

Central Nervous System Effects:
- Headaches
- Light-headedness
- Trouble sleeping
- Drowsiness
- Rare reduction in cognitive function compared to standard anticholinergics

Less Common Adverse Effects:
- Urinary hesitancy/obstruction (anticholinergic effect)
- Rare confusional states (trospium typically has low CNS penetration)
- Severe constipation requiring medical intervention
- Rare hypersensitivity reactions (rash, pruritus)
- Increased risk of heat stroke from low sweating capacity

Serious but Rare Adverse Effects:
- Severe gastrointestinal ileus
- Urinary retention worsened by acute constipation
- Possible cardiac events (tachyarrhythmias) in susceptible patients
- Increased risk of worsening narrow-angle glaucoma

CONTRAINDICATIONS

Xanomeline–Trospium (KarXT) has several contraindications based on the pharmacologic profiles of each compound, particularly trospium, which is a peripherally acting anticholinergic. The contraindications include:

1. Uncontrolled Narrow-Angle Glaucoma: Tropism's anticholinergic effects are known to raise intraocular pressure, and KarXT is contraindicated in individuals with untreated or uncontrolled angle-closure glaucoma [15].

2. Urinary Retention: Trospium can inhibit detrusor muscle contraction in the bladder, worsening urinary retention, and is contraindicated in patients with bladder outlet obstruction or urinary retention [10].

3. Gastric Retention / Significant GI Motility Disorders: Anticholinergic effects may slow GI motility even further, and KarXT is contraindicated in individuals affected by gastric retention, severe gastroparesis, or who are at high risk of GI obstruction [13].

4. Hypersensitivity Reactions: Any history of a hypersensitivity reaction to xanomeline, trospium, or ingredients contained in the formulation is a contraindication for use [16].

5. Severe Renal Impairment: Trospium is renally eliminated, and thus KarXT is contraindicated in patients with severe renal impairment (eGFR <30 mL/min/1.73m²) and at risk for drug accumulation and enhanced anticholinergic toxicity [17].

6. Myasthenia Gravis: In individuals with myasthenia gravis, anticholinergic medications like trospium can increase feelings of muscle weakness and impede neuromuscular transmission.

7. Toxic Megacolon Risk or Severe Ulcerative Colitis: Anticholinergics significantly reduce motility, which can exacerbate toxic megacolon and cause consequences including paralytic ileus [32]. The advice against usage is justified by the high level of risk.

8. Severe Heart Conditions: The cholinergic effects of xanomeline and the anticholinergic actions of trospium can cause orthostatic hypotension and tachycardia. Therefore, individuals with unstable coronary artery disease, uncontrolled arrhythmia, or a recent myocardial infarction should not utilize KarXT [16].

9. Untreated Hyperthyroidism: Increased sympathetic tone may increase the risk of tachycardia and potentially induce arrhythmias. Reasonably speaking, the use of KarXT should be avoided in patients with untreated hyperthyroidism.

10. Severe Hepatic Impairment: Although this serves as precautionary, indications of severe liver failure do not include any safety data for use and carry a risk of drug accumulation, making this a functional contraindication [11].

LIMITATIONS

Xanomeline-trospium (Cobenfy) is approved by the FDA for schizophrenia, but has multiple limitations.

- **Cardiovascular Limitations:** The approved medication also significantly increases heart rate (~10.4 bpm) and blood pressure; this could be dangerous in patients with hypertension or cardiovascular disease [26].
- **Urinary Retention:** The medication is contraindicated in people with urinary retention, which presents its own set of risks particularly in the elderly and those with bladder issues.
- **Pregnancy and Breastfeeding:** Use is limited due to risk for the mother and fetus; there is no data on safety during breastfeeding [27].
- **Limited Long Term Safety Data:** The clinical studies were not long--only five weeks--in order to assess longer term effects such as tardive dyskinesia [28].
- **Pediatric Limitations:** The safety and efficacy have not been determined for use in children; it is indication for use only in adults [29].
- **Administration of the Medication:** The drug needs to be taken at specific times (1 hour before/2 hours after meals), which prohibits convenience [30].
- **Cholinergic and Anticholinergic Effects:** The balance of these effects causes symptoms like dry mouth and urinary retention [31].
- **Not for Use for Acute Agitation:** The drug is not indicated for acute control because of its slower onset of action compared to traditional antipsychotics.
- **Renal Impairment:** The medication requires adjustment for moderate-to- severe renal impairment.
- **Cost and Availability:** The drug is expensive, has limited access, and insurance may not cover it.

PRECAUTIONS

• Speak to your physician about beginning xanomeline and trospium if you are allergic to anything they contain or to these medications.

• Notify your physician of any medications you are currently taking or plan to take to prevent adverse interactions between medications being taken and to consider dose or monitoring changes [32].

• Let your doctor know if you have ever had a urinary problem, kidney or liver disease, gastrointestinal problems, glaucoma, or if you are pregnant or breastfeeding.

• Elderly patients could experience a greater risk of side effects; consult a doctor to begin taking a lower dose and closely monitor if you are elderly [33].

• These medications may cause drowsiness; avoid driving or operating machinery until you know how each medication will affect you.

• Alcohol may increase side effects; ask your doctor about safe alcohol use while taking these medications [34].

• Urinary retention is a potential side effect, especially in elderly patients; monitor for urinary retention and call your provider to report symptoms.

• Hepatic and biliary impairment can increase risk; evaluate liver function prior to treatment and follow up for liver monitoring needs during treatment [35].

• Caution is warranted in patients with any gastrointestinal mobility problems and or a history of angioedema or angle closure glaucoma [36].

• Monitor heart rate, especially for patients with renal impairment and those taking an anticholinergic drug (e.g. confusion, dizziness) because CNS effects may occur [37].

CONCLUSION

Xanomeline-trospium chloride (XTC), known as Cobenfy, is an exciting new antipsychotic for schizophrenia that acts on muscarinic receptors instead of the dopamine D2 receptors and minimizes many of the effects of D2 blockade. The compound was originally investigated as a treatment for schizophrenia as well as Alzheimer's disease, but credibility trials faced challenges with adverse effects related to the cholinergic system. The pairing

of xanomeline with trospium helps enhance tolerability and effectiveness, along with improved safety leading to an FDA approval for schizophrenia in September 2024. Cobenfy acts on the M1 and M4 receptors to improve cognition and treat psychotic symptoms while minimizing the screen of side effects that D2 antagonism can commonly generate. However, the drug does carry some risk for urinary retention, especially for patients over 65 years of age. There are also precautions that need to be taken with patients who have hepatic impairment; however, the clinical trials demonstrated efficacy across the symptom and severity spectrum showing significant benefits. While Cobenfy does have some side effects, they were not more prevalent than the control groups, meaning that Cobenfy requires continuous monitoring. Cobenfy has gastrointestinal, cardiac, and central nervous system side effects, with less serious adverse effects being immediate termination of medication, delirium, and severe renal impairment. While clinical trials did not evaluate Cobenfy in pediatric patients, the FDA has not approved it for pediatric use. Cobenfy will be dosed and monitored at lower doses, for example, in individuals aged 65 and older. All health issues and complaints should be monitored continuously while on the medication.

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Fig-1
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