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KarXT: Combination of Xanomeline and Trospium

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Current antipsychotic medications, which are frequently prescribed by doctors to treat a wide range of psychiatric conditions, including schizophrenia and bipolar disorder, share the same primary pathway and strategy of inhibiting D2 dopamine receptors and frequently 5-HT2A serotonin receptors. Despite the fact that these drugs have long been considered the gold standard of care, those who suffer from psychiatric disorders, especially schizophrenia, their doctors, and researchers have been looking for alternatives to improve treatment outcomes. Since the approval of chlorpromazine, which has significant anticholinergic side effects, the muscarinic cholinergic system has drawn attention in psychiatry. Nowadays, three approved drugs for the treatment of Alzheimer's disease target the acetylcholine system, as centrally active acetylcholinesterase inhibitors which raise acetylcholine levels in the brain [1].

There are 5 muscarinic cholinergic subtypes of receptors (M1 through M5), and all are metabotropic. They stand in stark contrast to the ion channels found in the nicotinic cholinergic receptor family. Research from preclinical studies and clinical trials has shown a correlation between the stimulation of muscarinic receptors in the central nervous system, specifically the stimulation of M1 and M4 receptors, and a reduction in psychotic symptoms with an increase in cognition. However, unfavourable side effects, which are thought to originate predominantly from stimulation of muscarinic receptors in peripheral tissues, have hindered the effective development of a therapeutic targeting muscarinic receptors [2].

KarXT is an oral, research-stage M1/M4-preferring muscarinic agonist that is being developed to treat psychiatric and neurological conditions, such as schizophrenia and Alzheimer's disease-related psychosis. It is a combination of the muscarinic agonist xanomeline and the muscarinic antagonist trospium. Idea behind this psychopharmaceutical is to preferentially stimulate muscarinic receptors in the central nervous system and to unlock the therapeutic potential of xanomeline, while minimizing adverse effects observed in prior studies. Positive results were reported by Karuna Therapeutics in the Phase III EMERGENT-2 trial (NCT04659161) of KarXT in acutely psychotic hospitalized adult patients with schizophrenia. KarXT could have a significant advantage over current atypical antipsychotics, including later-generation products, if it continues to demonstrate success in both the ongoing Arise trial (NCT05145413) as an adjunctive to traditional antipsychotics and the ongoing EMERGENT trial program as a monotherapy. KarXT was shown to reduce both positive and negative symptoms of schizophrenia after five weeks in the EMERGENT-2 trial, and it has also demonstrated a statistically significant almost 10-point reduction in Positive and Negative Syndrome Scale (PANSS) compared with placebo. Additionally, the trial revealed a statistically significant improvement measured by the positive and negative PANSS subscales. Thus, the primary and secondary endpoints of the study were successfully met. Furthermore, the course of treatment was generally well tolerated, and, importantly, the medication did not cause

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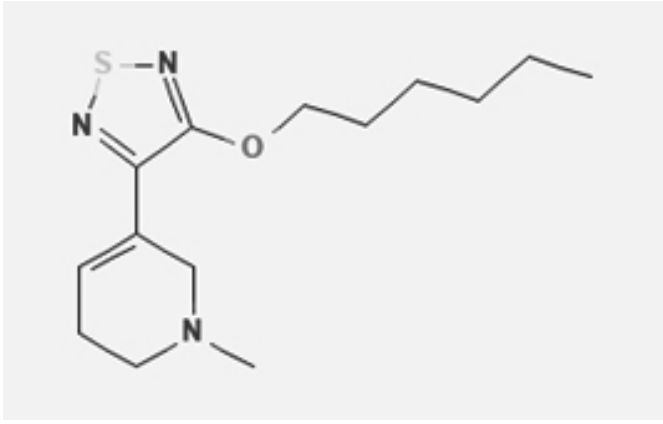

Figure 1. Chemical structure of xanomeline

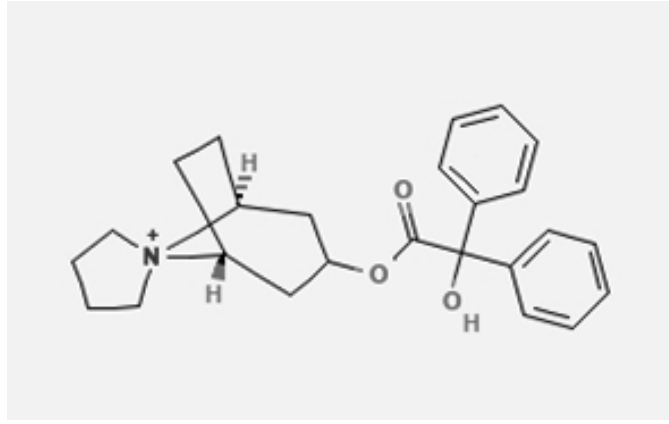

Figure 2. Chemical structure of trospium

the typical antipsychotic side effects such as weight gain, sedation, and movement disorders. Based on the promising Phase III results of KarXT, Karuna is planning to submit a New Drug Application by the middle of 2023. [3,4].

All in all, KarXT is the first potential medication of its kind with a genuinely distinctive dual mechanism that treats symptoms of severe mental illness without relying on the dopaminergic or serotonergic pathway. If approved, this strategy could offer people with serious mental illnesses a different kind of therapy and positively influence their lives.

Refrences

1. Karunatx. KarXT [Internet]. Boston (US): Karunatx; 2023 [updated 2022; cited 2023 Jan 31]. Available from: https: https://karunatx.com/pipeline-programs/karxt/
2. Stahl SM. Stahlovi temelji psihofarmakologije. Jastrebarsko (HR): Naklada Slap; 2017.
3. Clinical Trials Arena. Karuna's KarXT shows promise for schizophrenia treatment [Internet]. London (GB): Clinical Trials Arena; 2023 [updated 2022; cited 2023 Jan 31]. Available from:https://www.clinicaltrialsarena.com/comment/karxt-schizophrenia-treatment/
4. BioSpace. Karuna's KarXT Drug Could Signal New Hope for Schizophrenia - Updated [Internet]. Des Moines (US): Biospace; 2023 [updated 2022; cited 2023 Jan 31]. Available from: https://www.biospace.com/article/positive-phase-iii-results-could-give-karuna-an-entirely-new-class-of-drug-for-schizophrenia/