October 03, 2024 3 min read

The inside story of Cobenfy

How a breakthrough drug languished for a quarter century before its resurrection

Obscured by the celebratory congratulations and profuse praise of the scientific advance marked by the FDA's approval of KarXT, now branded Cobenfy, is the revealing and instructive story of how this novel therapeutic agent came to fruition.

To give credit where due, the arrival of KarXT (xanomeline-trospium, Bristol Myers Squibb) is much more than just the approval of another antipsychotic. After nearly a century since the discovery of chlorpromazine and the unsuccessful expenditure of enormous efforts, obscene amounts of money and many careers, KarXT became the first therapeutically effective antipsychotic that does not target the dopamine 2 receptor and works through a novel mechanism of action. Even without knowing whether KarXT will prove to be superior in efficacy and/or safety to existing antipsychotic drugs and justifies Bristol Myers Squibb's astonishing $14 billion acquisition of Karuna and the rights to KarXT, its approval represents a significant milestone in the history of psychopharmacology.

The story of KarXT begins with **Alois Alzheimer's** historic observation of the histopathologic signature (amyloid plaques and neurofibrillary tangles) of the eponymous neurodegenerative disease. Flash forward 100 years, **Peter Davies, PhD,** a pathologist at Albert Einstein College of Medicine, discovered the loss of cholinergic neurons in the nucleus basalis of Meynert in postmortem brains of patients with AD. Following this**, Kenneth L. Davis, MD,** at Mount Sinai School of Medicine employed anticholinergic challenge tests to demonstrate clinical impairment of memory induced by antagonism of cholinergic neurotransmission. Thus was born the cholinergic hypothesis of AD, which inspired the Eisai's

development of Aricept (donepezil), a cholinesterase inhibitor. When comarketed with Pfizer, Aricept quickly became a multibillion-dollar drug and inspired numerous "me-too" pro-cholinergic drugs working through cholinesterase inhibition.

In the mid-1980s, Novo Nordisk had synthesized a compound, xanomeline, that worked by a pharmacodynamic mechanism stimulating muscarinic 1 and 4 receptors. Partnering with Eli Lilly, studies of xanomeline in patients with AD were carried out that showed signs of efficacy, particularly in psychotic symptoms, but the side effect burden in older patients proved to be a deterrent to the drug's viability. However, before discontinuing the drug's development, a study in schizophrenia was carried out by **Anantha Shekhar, MD, PhD,** and **William Potter, MD, PhD,** yielding robust results of antipsychotic efficacy. Moreover, the younger participants with schizophrenia tolerated xanomeline better than the older patients with AD, incurring fewer side effects. Despite this, Eli Lilly decided to shelve the drug in the mid 90s.

This would have been the end of xanomeline if not for **Steven M. Paul, MD.** Upon completion of his training at University of Chicago under the legendary **Daniel X. Freedman, MD,** Paul went to the National Institute of Mental Health's Intramural Research Program for more than a decade before joining Lilly as head of central nervous system (CNS) discovery in 1993. In 2003, he became head of Lilly Research Laboratories, responsible for all drug discovery and more than a billion-dollar research and development budget. During that time, he presided over Lilly's AD program and presumably participated in the decision to suspend xanomeline's development.

Paul retired from Lilly in 2010 and joined Karuna soon after, where he had the brainstorm of combining it with the peripheral anticholinergic trospium to preempt potential side effects. In 2012, Karuna licensed xanomeline from Lilly and the rest is history.

Several things are notable about this scenario. First, the success of xanomeline's reincarnation wasn't simply a case of Paul spotting a diamond in the rough, as he was more than familiar with the drug having presided over the drug's deactivation. This begs the question of why and how Lilly gave up on such a promising drug that Paul, armed with prior knowledge, was able to out-license and successfully develop. No one is feeling sorry for Lilly for having let xanomeline slip away, which currently is gushing profits from Mounjaro (tirzepatide), but in retrospect for a company that was then seen as having a strong CNS franchise —having launched Prozac (fluoxetine), Zyprexa (olanzapine), Strattera (atomoxetine) and duloxetine — it would seem to have been a glaring mistake.

The implications go beyond that of a wrong decision about the fate of a single drug. What does this say about the pharmaceutical industry and the drug development process overall that a major company retires a promising drug that is resurrected after remaining dormant for a quarter century, sold for $14 billion and poised to become a market leader?

While we don't want to look a gift horse in the mouth and are enthused and grateful for the arrival of xanomeline, one has to wonder about the apparent perspicacity or lack thereof, and unnecessary delays in bringing novel and potentially better treatments to patients in need.

For more information:

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Sources/Disclosures

Collapse —

Source: Expert Submission

Disclosures: Leiberman was an author on the phase 2 study of KarXT and a member of Karuna's scientific advisory board.

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September 27, 2024 3 min read

FDA approves first new class of schizophrenia treatment in more than 30 years

Key takeaways:

- Cobenfy is the first antipsychotic medication to treat schizophrenia by targeting cholinergic receptors.
- The approval is supported by data from the EMERGENT-2 and EMERGENT-3 trials.

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