

Lessons from the history of antipsychotic discovery: part 3 – muscarinic mechanisms

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Summary After more than seven decades in which antipsychotic drug development has been dominated by dopaminergic mechanisms, the recent emergence of a muscarinic receptor-based treatment represents a conceptual shift in the pharmacotherapy of psychosis. This article reviews the history and development of the first clinically effective non-dopaminergic antipsychotic, tracing its origins to unexpected behavioural effects observed during trials of muscarinic agonists developed for Alzheimer's disease. Early studies of the muscarinic agonist xanomeline demonstrated antipsychotic efficacy, but were limited by poor tolerability due to peripheral cholinergic adverse effects. Subsequent progress depended on the dissociation of central therapeutic effects from peripheral side-effects, through the combination of xanomeline with the peripherally restricted muscarinic antagonist trospium. The development of this treatment highlights several broader lessons for psychiatric drug discovery, including the value of revisiting previously abandoned compounds, the benefits of leveraging existing human safety data on the importance of early-phase translational research and the role of innovative companies.

Keywords History of psychiatry; psychopharmacology; psychotic disorders/schizophrenia; antipsychotics; clinical trials.

This third paper in the series explores the history of the recent identification and development of the first licensed muscarinic treatment for psychosis.^{1,2} From the 1950s to the early 2020s, the development of antipsychotic drugs was primarily based around modulation of dopamine signalling, particularly through D2 receptor antagonism. Although multiple new treatments based on dopaminergic mechanisms have been identified, these are primarily distinguished by differences in side-effect profile rather than efficacy; the side-effects associated with these drugs can have significant impacts on well-being and long-term health. Furthermore, dopaminergic antipsychotics, although often effective against positive symptoms of psychosis, do not improve negative and cognitive symptoms and may even worsen function in these domains. There has therefore been an urgent need for the identification of new mechanisms for the treatment of psychosis. Extensive research over the intervening decades has revealed many insights into the genomic and biological processes contributing to psychosis, but these studies have yet to lead to new treatments. However, a new treatment approach, based on muscarinic receptor agonism, has now been identified through clinical observation of drugs developed for a different indication, as was the case for many previous antipsychotics.¹ It is to be hoped that this

will pave the way for the development of a new generation of antipsychotic therapies.

Muscarinic mechanisms

Acetylcholine is a neurotransmitter that is broadly distributed in the central and peripheral nervous systems. Muscarinic acetylcholine receptors (of which there are five: M1–5) have long been considered a potential therapeutic target in Alzheimer's disease. This is because the loss of cholinergic neurons, particularly from the nucleus basalis of Meynert, is an early feature of Alzheimer's disease that is considered to contribute to the cognitive decline seen in this condition.

In the 1980s and 1990s, many major pharmaceutical companies had drug discovery programmes based around muscarinic receptors aimed at improving symptoms in Alzheimer's disease. Among those companies was Lilly, who developed a compound known as xanomeline with agonist activity at both M1 and M4 receptors, which they took to large-scale clinical trials in Alzheimer's disease. These trials were largely disappointing in terms of the primary end-point of cognitive function in Alzheimer's disease – showing only small improvements. However, they revealed a dramatic and unexpected effect on the secondary outcome measures of

behaviour and psychosis. Specifically, patients treated with xanomeline showed dramatic improvements in a range of positive psychotic symptoms, as well as in agitated and disturbed behaviours.³ These results were consistent with earlier theories positing that muscarinic agonism could be a beneficial therapeutic approach in agitated states such as mania.⁴

Unfortunately, xanomeline treatment was poorly tolerated due to significant side-effects, with many patients discontinuing the treatment.³ This is not surprising, because muscarinic receptors have a range of functions in the heart and gut, as well as in the central nervous system (CNS). Prominent side-effects included syncope, sweating, nausea, vomiting and diarrhoea, all of which limited tolerability.³

Despite the prominent side-effect profile, Lilly collaborated with the academic Anantha Shekhar to conduct a small trial of xanomeline in schizophrenia patients, based on the finding of reduced psychotic symptoms in patients with Alzheimer's disease. This trial included only 20 patients in total, but did show significant impact on positive psychotic symptoms over a 4-week period.⁵ However, once again, significant side-effects were a major problem in this group, limiting the potential use of xanomeline alone as a therapy in schizophrenia.⁵

Companies, including Lilly, continued to look at refining muscarinic drugs for the treatment of neuropsychiatric conditions, in particular seeking to parse out beneficial and adverse effects through the development of drugs selective for specific receptor subtypes. However, this approach proved challenging and interest in muscarinic receptors as a target in psychiatry gradually waned, despite some ongoing work highlighting the profound psychoactive effects of drugs modulating muscarinic receptors.⁶

Separating side-effects

In the early 2000s, the investment company PureTech Health began exploring options for the reinvigoration of therapeutic development in psychiatry. They had a particular interest in mechanisms that had shown potential for efficacy in humans but that had been constrained for other reasons, including side-effects. In 2009, PureTech Health set up Karuna Therapeutics under founding chief executive officer (CEO) Andrew Miller, to explore this mission in relation to psychiatric conditions, including schizophrenia. Miller came from an engineering background and had no formal training in psychiatry or neuroscience, but he brought an analytical approach to the task.

After considering a range of potential therapeutic targets for psychosis, Miller and his team at Karuna focused on muscarinic mechanisms, based on the findings of the Lilly studies with xanomeline. However, the key issue remained the concern over the significant side-effects associated with the drug. Miller and his team considered that it might be possible to separate out side-effects from therapeutic efficacy by attempting to block the peripheral effects of xanomeline (associated with side-effects) while retaining the CNS effects (associated with efficacy). This was a high-risk approach because there was a risk that certain side-effects, such as nausea, derive from both central and peripheral effects of xanomeline. Notwithstanding these concerns, Miller and his

team began to consider ways to block the peripheral side-effects associated with xanomeline.

The team at Karuna recognised that several peripheral antagonists of muscarinic receptors had been developed for other indications. Some of these had low brain penetrance and therefore could potentially be used to block the peripheral side-effects of muscarinic agonists such as xanomeline, without impeding the beneficial effects on psychosis in the CNS. The Karuna team identified 65 muscarinic agonists and 114 antagonists (making 7410 potential combinations), and developed an algorithm to assess their probable effectiveness in combination in supporting central effects while blocking peripheral effects. The combination with greatest support was xanomeline with trospium – a licensed drug used for bladder instability.⁷ One advantage was that both these compounds had already been tested and proven safe in humans, with extensive absorption, distribution, metabolism and excretion and safety data. Trospium was an approved medication in the USA and other territories, including Europe, and Lilly had conducted extensive testing and human trials with xanomeline. Karuna were subsequently able to license the safety data and residual intellectual property from Lilly for the relatively small sum of US\$100 000.

The trials of trials

Karuna were now in a position to test whether the drug combination (xanomeline + trospium) in people. However there remained a lot of scepticism about the potential of the combination, and Miller remembers being lectured at length at a scientific meeting by a senior professor about why such a combination drug would not succeed. Nevertheless, Phase 1 studies of xanomeline + trospium in healthy volunteers showed a significant reduction in side-effects with the combination treatment compared with xanomeline alone.⁸

Despite these encouraging results, it proved difficult to obtain financing for the company. Potential investors were concerned that Miller was a young CEO with no background in the field of neuropsychiatry. Furthermore, the development of new drugs for psychiatric disorders was notoriously difficult, and Karuna did not have a magical new chemical 'bullet' but, instead, a combination of two old drugs. In addition, there was still concern about the potential for side-effects driven by central muscarinic receptors.

Miller describes things getting so bad that he became the only full-time employee, working with four part-time consultants. At this stage, Miller took what he calls a 'Hail Mary' approach by approaching the Wellcome Trust in the UK. Wellcome were impressed by the potential of xanomeline + trospium and provided funds for a Phase 2 clinical trial testing the safety and efficacy in adults with schizophrenia experiencing acute psychosis (EMERGENT-1). Critically, this study demonstrated a positive result in terms of its primary end-point of a reduction in positive psychotic symptoms, with a good safety profile.⁹

Following the success of EMERGENT-1, Karuna were able to raise capital to conduct further Phase 2/3 studies of xanomeline + trospium in schizophrenia. These have consistently shown positive results in patients with schizophrenia,

with reduced side-effects compared with xanomeline alone, although some side-effects remain. Most notably, three large Phase 2/3 clinical trials in schizophrenia xanomeline + trospium have shown not only robust antipsychotic effects but also significant improvement in negative symptoms of schizophrenia.^{9–11} There is also emerging evidence that xanomeline + trospium may have beneficial effects on cognition in individuals with schizophrenia and cognitive impairment, although further trials are required to confirm this effect.¹²

Across trials of xanomeline + trospium in schizophrenia the side-effect profile has been relatively favourable, and certainly superior to that seen in trials of xanomeline alone.^{9–11} Whereas symptoms of constipation, nausea and vomiting, dyspepsia and dry mouth were more common in patients treated with xanomeline + trospium than in those treated with placebo, these effects were generally relatively mild, often self-limiting and were not associated with higher rates of medication discontinuation.^{9–11} Transient increases in heart rate and blood pressure were also reported in some studies, but did not produce clinically significant symptoms.^{9–11} Notably, xanomeline + trospium produced no impacts on extrapyramidal symptoms, akathisia, weight gain or sedation – side-effects commonly seen with existing antipsychotics.^{9–11} These results suggest that the combination of xanomeline with trospium is effective in reducing the peripheral muscarinic side-effects seen with xanomeline alone, and that xanomeline + trospium does not have the same side-effect profile as that seen with existing antipsychotics. It remains to be seen how significant the residual side-effects of xanomeline + trospium are in long-term naturalistic studies. However, results from an initial open-label, 52-week study suggest good overall safety and efficacy, but WITH some residual cholinergic side-effects (especially nausea and vomiting), and higher rates of discontinuation than those seen in the shorter Phase 2/3 clinical trials.¹³ It is nevertheless clear that xanomeline + trospium is a new effective antipsychotic treatment that has a distinct mechanism of action and side-effect profile compared with all previous licensed antipsychotic medications.

Bringing the new treatment to market

On the basis of the Phase 2/3 trials, in September 2023 Karuna submitted an application to the Food and Drug Administration (FDA) in the USA for the approval of xanomeline + trospium as a medical product. Karuna by this time had a market capitalisation of US\$1.4 billion and were developing trials of xanomeline + trospium in Alzheimer's disease and were considering moving into autism and paediatric indications, as well as further studies in schizophrenia. Karuna was even beginning to assemble a sales team to take xanomeline + trospium to the market. However, the results of the EMERGENT trials of xanomeline + trospium in schizophrenia had gained broader attention. A number of major companies looking for a major new product began to take an interest in acquiring Karuna which, as a publicly listed company, was open to acquisition.

In September 2024, Bristol Meyers Squib (BMS) acquired Karuna for US\$14 billion, just prior to xanomeline + trospium being approved by the FDA. For Miller and the

team at Karuna it was a time of mixed feelings – they had been working on xanomeline + trospium for nearly 15 years and had been preparing to market the combination drug themselves. Now their product would be taken forward by another company, albeit one making the largest ever single pharmaceutical investment in psychiatry. For BMS, the investment in xanomeline + trospium represented a major move to acquire a potential blockbuster treatment in an area of huge clinical need. However, it was not without risks, given the remaining uncertainties about the real-world impacts of xanomeline + trospium and the potential for unanticipated side-effects or the emergence of competitor compounds. Many of these questions will now be answered because xanomeline + trospium, now branded as Cobenfy, is available on the market in the USA and is likely to be approved as a safe treatment in other territories in the near future.

Lessons and future perspectives for psychiatric drug development

The discovery of the antipsychotic effects of xanomeline was based, like the discovery of chlorpromazine, on serendipity combined with informed clinical observations and subsequent skilful clinical development. The general antipsychotic effects of xanomeline + trospium suggest that, like dopaminergic therapies, muscarinic treatments can benefit a wide range of patients (although probably not all) with psychosis. It is to be hoped that the successful development of xanomeline + trospium will stimulate further innovation and mechanistic insight in relation to muscarinic drugs in psychiatry.

The exact mechanisms through which agonism of M1 and M4 receptors by xanomeline produces antipsychotic effects are not fully understood; however, preclinical studies have shown that agonism of M4 receptors in the midbrain and basal ganglia can exert a specific suppressive effect on dopaminergic signalling. This suggests that at least part of the antipsychotic effects of xanomeline may derive from modulation of the dopaminergic system, but in a manner that is more specific than current antipsychotic treatments. M1 receptor agonism can also modulate cortical interneuron firing, which may contribute to improvements in negative and cognitive symptom domains as well as positive psychotic symptoms.¹

There are already moves to develop and test drugs with greater receptor subtype specificity, as well as partial agonists (and potentially antagonists). Not all of these will meet with success given the inherent complexity of the underlying biology, and the promising M4 selective agonist emraclidine recently failed in Phase 2 clinical trials for schizophrenia.^{14,15} However, it remains highly likely that further, more selective, treatments for schizophrenia and related disorders based on muscarinic mechanisms will be developed.

Xanomeline + trospium was developed by revisiting a drug that had previously been trialled in an alternative indication for which there was existing safety data in humans.² Notably, there are several other such drugs available for further experimental medicine and trial approaches.¹⁶ There are also a number of mechanisms that have shown considerable potential, only to 'fail' in late-

stage trials, but which may remain effective in subgroups of patients,^{17,18} and opportunities may exist to develop other drug combinations in psychiatry. Findings from large-scale molecular genetic studies also highlight a number of promising new druggable targets in the pathology of major psychosis, including voltage-gated calcium channels and glutamate receptors (although notably not muscarinic receptors).¹⁹ It is to be hoped that the success of xanomeline + trospium/Cobenfy will stimulate renewed interest in this range of additional targets for drug development in psychiatry.

It is worth noting the role of entrepreneurship in the development of xanomeline + trospium. Large pharmaceutical companies have significantly disinvested from psychiatry due to the complexity of developing new drugs, leaving a space for innovative smaller companies to develop products to the stage when they can attract major investment. This is reminiscent of the approach adopted in a previous era by pioneers such as Janssen.²⁰ A critical challenge in developing confidence and value in new assets is completion of Phase 1 and early Phase 2 testing. The Wellcome Trust have supported early-phase clinical testing for Karuna and for other psychiatry spin-outs, including Draig Therapeutics.⁹ Broader provision of funding for Phase 1/2 testing of promising therapeutics is likely to be key to unlocking further potential value and investment in psychiatric therapeutics.

Overall, it is to be hoped that the development and commercialisation of xanomeline + trospium/Cobenfy will stimulate renewed commercial and academic interest in psychiatric drug discovery. The investment by BMS in obtaining xanomeline + trospium/Cobenfy does, however, impose a financial challenge in making the drug broadly available while still ensuring a return on investment. Real-world challenges remain in establishing xanomeline + trospium/Cobenfy in new territories, and establishing its place as a recognised treatment in the armamentarium of therapies for psychosis. However, after 70 years, it is an exciting time to have a new and distinctive treatment mechanism available to both clinicians and patients with psychosis.

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Declaration of interest

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References

- 1 Paul SM, Yohn SE, Brannan SK, Neugebauer NM, Breier A. Muscarinic receptor activators as novel treatments for schizophrenia. *Biol Psychiatry* 2024; **96**: 627–37.
- 2 Hall J. Schizophrenia – new treatments soon. *Br J Psychiatry* 2025; **226**: 127–8.
- 3 Bodick NC, Offen WW, Levey AI, Cutler NR, Gauthier SG, Satlin A, et al. Effects of xanomeline, a selective muscarinic receptor agonist, on cognitive function and behavioral symptoms in Alzheimer disease. *Arch Neurol* 1997; **54**: 465–73.
- 4 Janowsky DS, el-Yousef MK, Davis JM, Sekerke HJ. A cholinergic-adrenergic hypothesis of mania and depression. *Lancet* 1972; **2**: 632–5.
- 5 Shekhar A, Potter WZ, Lightfoot J, Lienemann J, Dube S, Mallinckrodt C, et al. Selective muscarinic receptor agonist xanomeline as a novel treatment approach for schizophrenia. *Am J Psychiatry* 2008; **165**: 1033–9.
- 6 Drevets WC, Zarate CA, Furey ML. Antidepressant effects of the muscarinic cholinergic receptor antagonist scopolamine: a review. *Biol Psychiatry* 2013; **73**: 1156–63.
- 7 Betancourt A, Rehlaender B, Thibert R. *Composition Comprising Xanomeline and Trospium for Treating Disorders Ameliorated by Muscarinic Receptor Activation*. Karuna Therapeutics Inc., 2020.
- 8 Breier A, Brannan SK, Paul SM, Miller AC. Evidence of trospium's ability to mitigate cholinergic adverse events related to xanomeline: phase 1 study results. *Psychopharmacology* 2023; **240**: 1191–8.
- 9 Brannan SK, Sawchak S, Miller AC, Lieberman JA, Paul SM, Breier A. Muscarinic cholinergic receptor agonist and peripheral antagonist for schizophrenia. *N Engl J Med* 2021; **384**: 717–26.
- 10 Kaul I, Sawchak S, Correll CU, Kakar R, Breier A, Zhu H, et al. Efficacy and safety of the muscarinic receptor agonist KarXT (xanomeline-trospium) in schizophrenia (EMERGENT-2) in the USA: results from a randomised, double-blind, placebo-controlled, flexible-dose phase 3 trial. *Lancet* 2024; **403**: 160–70.
- 11 Kaul I, Sawchak S, Walling DP, Tamminga CA, Breier A, Zhu H, et al. Efficacy and safety of xanomeline-trospium chloride in schizophrenia: a randomized clinical trial. *JAMA Psychiatry* 2024; **81**: 749–56.
- 12 Sauder C, Allen LA, Baker E, Miller AC, Paul SM, Brannan SK. Effectiveness of KarXT (xanomeline-trospium) for cognitive impairment in schizophrenia: post hoc analyses from a randomised, double-blind, placebo-controlled phase 2 study. *Transl Psychiatry* 2022; **12**: 491.
- 13 Kaul I, Claxton A, Chaturvedi S, Patel T, Wu H, Sawchak S, et al. Long-term efficacy, safety, and tolerability of xanomeline and trospium chloride in schizophrenia: a 52-week, open-label trial (EMERGENT-5). *Schizophr Res* 2026; **288**: 86–94.
- 14 Kuntz L. *Emracridine for Schizophrenia Fails to Meet Primary Endpoints in Phase 2 EMPOWER Trials*. Psychiatric Times, 2024 (<https://www.psychiatrictimes.com/view/emracridine-for-schizophrenia-fails-to-meet-primary-endpoints-in-phase-2-empower-trials>).
- 15 Krystal JH, Kane JM, Correll CU, Walling DP, Leoni M, Duvvuri S, et al. Emracridine, a novel positive allosteric modulator of cholinergic M4 receptors, for the treatment of schizophrenia: a two-part, randomised, double-blind, placebo-controlled, phase 1b trial. *Lancet* 2022; **400**: 2210–20.
- 16 Nutt DJ. Drug development in psychiatry: 50 years of failure and how to resuscitate it. *Lancet Psychiatry* 2025; **12**: 228–38.
- 17 Patil ST, Zhang L, Martenyi F, Lowe SL, Jackson KA, Andreev BV, et al. Activation of mGlu2/3 receptors as a new approach to treat schizophrenia: a randomized Phase 2 clinical trial. *Nat Med* 2007; **13**: 1102–7.
- 18 Kinon BJ, Millen BA, Zhang L, McKinzie DL. Exploratory analysis for a targeted patient population responsive to the metabotropic glutamate 2/3 receptor agonist pomaglumetad methionil in schizophrenia. *Biol Psychiatry* 2015; **78**: 754–62.
- 19 Coyle JT, Paul SM. *Nat Rev Drug Discov* 2026; **25**: 310–30.
- 20 Janssen PAJ. The butyrophenone story. In *Discoveries in Biological Psychiatry* (eds FJ Ayd, B Blackwell): 165–79. Lippincott, 1970.