

Xanomeline-Tropium and Muscarinic Involvement in Schizophrenia

Neil Kidambi*, Omar H Elsayed*, Rif S El-Mallakh 

Mood Disorders Research Program, Depression Center, Department of Psychiatry and Behavioral Sciences, University of Louisville School of Medicine, Louisville, KY, 40202, USA

*These authors contributed equally to this work

Correspondence: Rif S El-Mallakh, Mood Disorders Research Program, Depression Center, Department of Psychiatry and Behavioral Sciences, University of Louisville School of Medicine, Louisville, KY, 40202, USA, Tel +1 502 588 4450, Fax +1 502 588 9539, Email rselma01@louisville.edu

Abstract: Schizophrenia is a severe mental illness that has its onset in late adolescence or early adulthood and is associated with significant dysfunction across multiple domains. The pathogenesis of schizophrenia remains unknown, but physiologic understanding of the illness has been driven by the dopamine hypothesis. However, acetylcholine (ACh) clearly plays a role with mixed results regarding effect on psychosis. Selective muscarinic M₁ and M₄ agonists, such as xanomeline, originally developed to aid in cognitive loss with Alzheimer's, showed promise in proof-of-concept study in 20 patients with schizophrenia. Unfortunately, tolerability problems made muscarinic agonists impractical in either condition. However, coadministration of tropium, a lipophobic, non-selective muscarinic antagonist previously used for the treatment of overactive bladder, with xanomeline resulted in a significant reduction of cholinergic adverse effects. A recent randomized, placebo-controlled study of the antipsychotic effects of this combination in 182 patients with acute psychosis revealed improved tolerability with 80% of subjects staying to the end of the 5 weeks study. At the end of the trial, the treatment group saw a -17.4 change in the positive and negative symptom scale (PANSS) score from baseline compared to a -5.9 change in the placebo arm ($P < 0.001$). Furthermore, the negative symptom subscore, was also superior in the active arm ($P < 0.001$). These early studies are exciting because they suggest that the cholinergic system may be recruited to treat a severe and disabling disorder with suboptimal treatment options. Xanomeline-tropium combination is currently in phase III studies.

Keywords: muscarinic agents, M₁ agonist, M₄ agonist, non-selective anticholinergic

Introduction

Schizophrenia is a severe mental illness that has its onset in late adolescence or early adulthood and is associated with significant dysfunction across multiple domains. It manifests as both positive symptoms – predominantly psychosis, and negative symptoms – predominantly flatness and amotivation; as well as cognitive dysfunction. The pathogenesis of schizophrenia remains unknown, but physiologic understanding of the illness has been driven by the dopamine hypothesis which has evolved over time. The most commonly cited iteration of the hypothesis is prefrontal dopaminergic hypoactivity and limbic system dopaminergic hyperactivity.^{1,2} The differential levels of activity have been explained by receptor distribution (D₁ versus D₂ receptors in the frontal and limbic areas),^{2,3} and dopaminergic circuits (mesocortical versus mesolimbic pathway integrity).¹ In the latter model, negative symptoms are related to dysfunction of either the frontal cortex or mesocortical dopaminergic pathways. This essentially eliminates frontal cortical function and is the reason patients with schizophrenia are unable to abstract. In this model, psychosis results when a patient with schizophrenia comes across a life situation requiring significant frontal cortical decision-making effort (labeled frontal cortical demand),⁴ the signal from the frontal cortex to the midbrain for additional dopamine to solve the problem⁵ results in dopamine transport from the midbrain. Frontal lobe or mesocortical dysfunction results in an ongoing need for dopamine, and a continuous signal to increase cortical dopamine, resulting in excessive limbic dopamine and psychosis.⁴

Alternatively, or additionally, glutamatergic dysfunction has also been reported in schizophrenia. Specifically, there is evidence of reduced glutamate dysfunction and schizophrenia can be worsened by glutamate antagonism.⁶

However, the “dual state theory” has several inconsistencies. For example, according to the theory of salience, D₂ is an autoreceptor which regulates dopaminergic inflow and filters out excess signaling,⁷ and in the case of schizophrenia, should be downregulated. However, several positron emission tomography (PET) and single-photon emission computerized tomography (SPECT) studies using radiolabeled L-dopamine demonstrated *elevations* of presynaptic dopaminergic synthesis rate in schizophrenic patients, and revealed an upregulation of D₂ striatal receptors in neuroleptic-free schizophrenics.⁸ Several lines of evidence suggest that the cholinergic system may be of particular interest in this condition.

Treatment-Resistant Psychosis

Theoretical mechanisms aside, there is a significant problem with suboptimal response to available treatments for schizophrenia (TRS). Twenty to 50% of patients with schizophrenia do not respond adequately to current antipsychotic medications.⁹ As many as 70% of patients with TRS may have dopamine supersensitivity psychosis (previously known as tardive psychosis)¹⁰ However, a meta-analysis of 11,958 patients with first episode psychosis found that one-third of patients responded poorly or relapsed quickly after initial treatment, suggesting that TRS is not always caused by prior to treatment.¹¹ Clozapine is frequently considered the only evidence-based treatment available for TRS due to its perceived superiority,¹² but it does not maintain that superiority in multiple analyses.^{13,14} The current focus to address TRS is to develop medications that work with novel mechanisms such as inhibition of the vesicular monoamine transporter (VMAT2) (Hoare et al, 2023),¹⁵ trace amine receptor (TAAR1) agonists,^{16,17} or cholinergic stimulation.

Acetylcholine in Schizophrenia

Acetylcholine (ACh) is an ester of choline and acetic acid that is used as a neurotransmitter in the body and brain. In the periphery, it is the major mediator of the parasympathetic system. In the central nervous system, its main actions are in learning, memory, attention, arousal and motivation.

Attention to ACh in schizophrenia was brought about by understanding some of the neurochemical effects of clozapine. Clozapine attracted attention because it appears to be particularly effective in patients with treatment-resistant schizophrenia¹⁸ but has minimal blockade of the D₂ receptor¹⁹ but is a potent anticholinergic.

Cholinergic afferent neurons and interneurons are present in the basal forebrain and striatum, respectively. Cholinergic receptors mediate many important sensory, motor, and higher functions, such as those affected by schizophrenia, like reward, arousal, attention, and motivation.²⁰ There are two types of cholinergic receptors, nicotinic and muscarinic receptors. Differing in structure as well as pharmacodynamics, nicotinic receptors possess ligand-gated ion channels, which are immediate in onset and fast in action, whereas muscarinic receptors are G protein-coupled receptors that have multiple components and produce a longer lasting action.²¹ Muscarinic receptors, which are more abundant in the CNS when compared to nicotinic receptors, are of five types: M₁, M₂, M₃, M₄, and M₅. All the receptors appear to be region specific in the CNS, with the M₂ and M₄ receptors featuring predominantly on cholinergic interneurons within the neo-striatum (which includes the nucleus accumbens, an integral part of the mesolimbic pathway), while M₁ receptors are located on projection neurons in the neo-striatum and throughout the neo-cortex (which includes the prefrontal cortex).^{22,23} It also should be noted that M₅ receptors were the only muscarinic receptors present on dopaminergic neurons in the midbrain. In the context of schizophrenia, muscarinic receptors were found to be decreased in chronically medicated patients with schizophrenia and cholinergic cell bodies reduced in the nucleus basalis of Meynert.^{20,24} One neuroimaging study used SPECT with ¹²³I-quinuclidyl benzilate (IQNB), a radio-ligand with high affinity to all five receptor subtypes in patients suffering with schizophrenia for more than 12 years who had stopped antipsychotic and anticholinergic medications for 18 days prior to imaging. Receptor occupancy was reduced in these patients by 20–35% when compared to healthy controls.²⁰ Regarding specific receptors, radio-ligand binding studies using the procholinergic substance, pirenzepine, revealed that M₁ and M₄ receptors decreased in the frontal cortex in subjects with the disease compared to healthy controls.²⁵

Clozapine appeared to improve cognitive function in people with either responsive or treatment-resistant schizophrenia²⁶ despite strong antagonism at the muscarinic M₁ and M₄ receptors,²⁷ a process which is known to impair cognition in patients with psychosis.²⁸ It appears that clozapine metabolites are important in its action.

Despite the fact that metabolites of clozapine are efficiently excreted by the kidney while clozapine itself is reabsorbed, the free (non-protein bound) concentrations of clozapine are only 5.5% of total while the major active metabolite, *N*-desmethylclozapine, is 9.7%.²⁹ Thus, in 15 patients treated with clozapine monotherapy whose whole plasma levels were 387 and 227 ng/mL, respectively, the free levels were slightly lower for clozapine (21.3 ng/mL) versus *N*-desmethylclozapine (22.0 ng/mL).²⁹ These numbers suggest a major role for the *N*-desmethylclozapine metabolite.

N-desmethylclozapine has been found to be a partial agonist (with intrinsic activity at $46 \pm 9\%$) at human M₁ receptors.³⁰ The high level of intrinsic activity and affinity³⁰ suggest that it may compete sufficiently with clozapine itself to significantly reduce the blockade of the M₁ receptor. Both clozapine and *N*-desmethylclozapine have over 500 times the affinity to muscarinic receptors as ACh itself.³¹

Regarding dopaminergic activity, muscarinic receptors may promote or depress dopamine transmission at the striatum. While M₁ stimulates the release of dopamine through dopaminergic afferents, the M₂ and M₄ receptors act as autoreceptors, putting a check on acetylcholine release through the cholinergic interneurons, and subsequent nicotinic acetylcholine receptor-dependent DA release at the striatum.²³ In a study done comparing M₄ receptor knockout (lacking the M₄ receptor) and wildtype mice, knockout animals were shown to have a considerable release of dopamine after amphetamine was administered.³² This not only suggests that M₄ has a regulatory influence of cholinergic output within the striatum, but also how the cholinergic and dopaminergic systems work in tandem.

History of ACh in Treatment of Schizophrenia

Use of ACh to treat schizophrenia was described predominantly in Europe in the early part of the twentieth century.^{33,34} Over the same time period, there was increasing recognition that procholinergic drugs with central nervous system access can cause psychosis.^{35–38} The mixed results suggested that some muscarinic stimulation is helpful in schizophrenia, but excessive stimulation may not be desirable. However, the initial successful introduction of the phenothiazines and the introduction of the dopamine hypothesis muted the interest in utilizing the ACh system to treat schizophrenia. Nonetheless, the introduction of cholinesterase inhibitors for the treatment of dementia served as an impetus for studies examining their use in cognitive benefits in schizophrenia. Open-label studies were generally positive, while randomized, placebo-controlled studies with cholinesterase inhibitors generally failed.³⁸ In a post hoc analysis of some of the data (falsely labelled meta-analysis but which included only 13 [instead of 28] double-blind studies of which four [out of 6] with rivastigmine, six with donepezil [out of 14], and three with galantamine [out of 8]) there was a small effect in improvement of memory and Trail Making Part A.³⁹

In addition to the work with cholinesterase inhibitors, there was an effort to develop selective muscarinic receptor agonists to aid with cognition in individuals with Alzheimer's disease. Eli Lilly and Novo Nordisk developed, xanomeline a selective M₁ and M₄ receptor agonist.⁴⁰ It was studied for Alzheimer's disease in a multicenter (17 sites; N = 343), double-blind, placebo-controlled study utilizing three doses of 25, 50, and 75 mg daily.⁴⁰ The treatment was administered for 6 months followed by a 1-month washout period. Xanomeline demonstrated a significant dose-dependent improvement in cognitive function as assessed by the Alzheimer's Disease Assessment Scale cognitive subscale. Maximal cognitive improvement occurred after 12 weeks of therapy. Additionally, dose-dependent improvements in coexisting psychotic symptoms of delusions, hallucinations, and suspiciousness were also observed.⁴⁰ Unfortunately, poor tolerability, particularly with gastrointestinal symptoms, precluded its introduction as a clinical treatment.^{40,41}

At the same time, ongoing research into the role of the muscarinic system in schizophrenia utilizing other techniques (such as animal models)⁴² and agents (such as the M₄ receptor agonist LY2033298)⁴³ continued to suggest an important role in modulation of the disease. Ultimately, a small proof of concept study done in 2008 showed a clear beneficial effect on positive symptoms.⁴⁴

In this small pilot study, 20 patients with a diagnosis of schizophrenia or schizoaffective disorder, with a total positive and negative syndrome scale (PANSS) score of >60 and at least a 4 on one positive symptom item or a 3 on two positive items were

given placebo treatment for 7 days, after which they were randomized to xanomeline 25mg TID or placebo. Subjects were then titrated up to 75 mg TID according to tolerability. Patients were observed for 4 weeks. Total PANSS score was statistically significant across groups ($P = 0.039$) although the positive and negative symptoms scores separately did not separate ($P = 0.082$ and $P = 0.083$, respectively). Separation was observed in the brief psychiatric rating scale (BPRS) score by week 1 of treatment and was sustained. There was no difference in the CGI score ($P = 0.94$). Cognitive battery scores showed an improvement between groups across all categories, reaching clinical significance ($P < 0.05$) in Digit span memory scale, story recall memory scale, list learning total verbal learning scale, and delayed memory visual learning scale.⁴⁴ This study suggested an improvement in the schizophrenia symptoms, as well as in cognitive abilities, consistent with the previous Alzheimer's dementia study⁴⁰ but given the small size of the study, and lack of adjustments for multiplicity in the cognition, the value of the findings was limited. Regrettably, as with its use in Alzheimer's, the high incidence of gastrointestinal distress, including nausea vomiting, and indigestion across all doses, likely due to the peripheral muscarinic activity of xanomeline, ultimately resulted in discontinuing clinical development.⁴⁵

Xanomeline-Trospium

As previously noted, xanomeline is a muscarinic cholinergic agonist that has no dopaminergic effects.⁴⁶ It has a high affinity to the M_1 and M_4 muscarinic receptors (K_i in the low teen range nM⁴⁶ compared to M_2 , M_3 , and M_5 receptors (K_i in the 30s or higher nM⁴⁷) but still stimulates them at higher doses.⁴⁸ Xanomeline also exhibits an appreciable affinity to 5HT₁ and 5HT₂ receptors ($K_i > 120$ nM).⁴⁶ Despite not directly affecting dopamine receptors, M_1 and M_4 receptors, unlike the other muscarinic receptors, are primarily located in cortical and limbic regions of the brain that are commonly associated with a dopaminergic action involved in cognitive and affective functions.⁴⁹ Additionally, it seemed effective, just poorly tolerated.

Recently, a new co-formulation of xanomeline and trospium has been introduced as a clinical strategy to access clinical benefits with a tolerable level of adverse consequences.^{50,51} Karuna Therapeutics, a small pharmaceutical company established in Boston, Massachusetts, in 2009, added trospium chloride, a non-selective muscarinic antagonist that has been previously used for the treatment of overactive bladder for years,⁵² to xanomeline. Trospium has a highly polarized tertiary amine structure that prevents it from entering into the central nervous system.⁵³ Coadministration of trospium and xanomeline is believed to block the unwanted peripheral cholinergic side effects of xanomeline. Indeed, the combination appears to be associated with a 50% reduction of cholinergic side effects in healthy volunteers.^{54,55}

This was examined in a recently published 5-week multisite (12 sites), phase II trial; 182 patients with a diagnosis of schizophrenia confirmed with a Mini-International Neuropsychiatric Interview, and with a PANSS score exceeding 80 at baseline were randomized to receive either the combination medication (xanomeline-trospium) twice daily or placebo.⁵⁰ Dosing schedule was flexible, starting with 50mg/20mg combination (xanomeline/trospium) increased to a maximum of 125/30 and returning to 100/20 if higher doses were not tolerated. Most of the patients, 91% (72/90), in the active medication group reached the highest dose of the drug. Over 80% of the patients completed the study and the rates were not different (72/90 of active medication and 73/92 in the placebo group). At the end of the trial, the treatment group saw a -17.4 change in the PANSS score from baseline compared to a -5.9 change in the placebo arm ($P < 0.001$).⁵⁰ Secondary outcomes of PANSS positive symptom subscore, CGI-S scale, and negative symptom subscore, were also superior in the active arm ($P < 0.001$). Discontinuation rates due to adverse effects (AEs) were comparable in both groups (20% versus 21% in treatment and placebo groups, respectively). AE reports were also similar with AEs being reported in 54% vs 43% in treatment vs placebo groups ($P = 0.14$, $z = 1.5$). Most commonly reported AEs included constipation (17%), nausea (17%), with dry mouth, vomiting and dyspepsia being reported in 9% of the patients.⁵⁰ These findings suggest the promising efficacy of the medication combination, and the comparable discontinuation rates suggest tolerability of the cholinergic and anticholinergic side effects. Some of the limitations with the study include the short duration and the inpatient setting of the study.

Phase III studies have been completed but have not been published. One phase III study has been presented in poster form.⁵⁶ The study recruited 252 hospitalized patients with schizophrenia in 22 sites across the USA. The average age for

those randomized to xanomeline-trospium was 45.6 +/- SD 10.4 (75.4% male) compared to 46.2 +/- SD 10.8 (75.5% male) of those randomized to placebo. Baseline PANSS scores were similar at 98.3 +/- SD 8.9 and 97.9 +/- 9.7, respectively. Patients on xanomeline-trospium were statistically improved by week 2 ($P < 0.05$), and had a greater than 20 point reduction in total PANSS by study end at week 5 ($P < 0.0001$). Response rates, defined as a greater than 30% improvement, occurred in 35.7% of xanomeline-trospium-treated patients versus 17.9% of placebo-treated patients by week 3 ($P = 0.0027$) and 54.8% versus 28.3% ($P < 0.0001$) by week 5. Improvement in the negative symptom subscale was small (-4.2 points versus -2 points) but still statistically superior ($P = 0.002$) in the xanomeline-trospium group. There were 2 (1.6%) severe adverse events in each group. Any adverse events were more common in the active medication group (75.4% vs. 58.4), but few of those led to early study termination (7.1% vs. 5.6%). Simpson-Angus Scale Parkinsonian measures, Barnes Akathisia Scale, and prolactin measures were not different in the two groups. An additional phase III study was also completed with similar data and the results are available from Karuna Therapeutics.

Conclusion

Schizophrenia is a severe psychotic disorder that is associated with poor outcome and a high rate of treatment resistance and partial response. Furthermore, currently available treatments are associated with significant adverse consequences. The dopamine hypothesis has dominated the thinking about pathophysiology and treatment development for nearly half a century. While a potential role of cholinergic agents is not a product of new insight into disease process, clever merging of available agents may lead to new approaches to treatment. Specifically, combining an M1 and M4 agonist (xanomeline) with a peripheral nonselective anticholinergic (trospium) to reduce peripheral cholinergic AEs has produced a drug combination that appears to reduce antipsychotic symptoms, improve cognitive deficits, and is adequately tolerated. The xanomeline-trospium amalgam is currently in phase III study, and may eventually become a clinical tool. Proper utilization will require the development of predictive biomarkers that inform which approach might be preferred in a specific patient (dopamine blockade or muscarinic stimulation). Furthermore, there will be a need for head-to-head studies of different agents early in the course of illness, and augmentation studies that may inform the use of multiple mechanisms later in the illness or in treatment-resistant patients.

Acknowledgments

There was no extramural funding for this work.

Disclosure

Dr. El-Mallakh has grant funding from Sunovion and Roche. He is a speaker for Axsome, Idorsia, Intracellular Therapies, Janssen, Lundbeck, Myriad Neuroscience, Noven, Otsuka, and Teva. Neither of the other coauthors have potential conflicts to report.

References

1. Weinberger DR. Implications of normal brain development for the pathogenesis of schizophrenia. *Arch Gen Psychiatry*. 1987;44(7):660–669.
2. Toda M, Abi-Dargham A. Dopamine hypothesis of schizophrenia: making sense of it all. *Curr Psychiatry Rep*. 2007;9(4):329–336.
3. Davis KL, Kahn RS, Ko G, et al. Dopamine in schizophrenia: a review and reconceptualization. *Am J Psychiatry*. 1991;148(11):1474–1486.
4. El-Mallakh RS, Rhodes P, Dobbins K. The case for case management in schizophrenia. *Prof Case Manage*. 2019;24(5):273–276. doi:10.1097/NCM.0000000000000385
5. Westbrook A, Braver TS. Dopamine does double duty in motivating cognitive effort. *Neuron*. 2016;89(4):695–710. doi:10.1016/j.neuron.2015.12.029
6. McCutcheon RA, Krystal JH, Howes OD. Dopamine and glutamate in schizophrenia: biology, symptoms and treatment. *World Psychiatry*. 2020;19(1):15–33. doi:10.1002/wps.20693
7. Kapur S, Mizrahi R, Li M. From dopamine to salience to psychosis--linking biology, pharmacology and phenomenology of psychosis. *Schizophr Res*. 2005;79(1):59–68. doi:10.1016/j.schres.2005.01.003
8. Lau CI, Wang HC, Hsu JL, et al. Does the dopamine hypothesis explain schizophrenia? *Rev Neurosci*. 2013;24(4):389–400. doi:10.1515/revneuro-2013-0011
9. Nucifora FC, Woznica E, Lee BJ, et al. Treatment resistant schizophrenia: clinical, biological, and therapeutic perspectives. *Neurobiol Dis*. 2019;131:104257. doi:10.1016/j.nbd.2018.08.016
10. Chouinard G, Samaha AN, Chouinard VA, et al. Antipsychotic-induced dopamine supersensitivity psychosis: pharmacology, criteria, and therapy. *Psychother Psychosom*. 2017;86(4):189–219.

11. Siskind D, Orr S, Sinha S, et al. Rates of treatment-resistant schizophrenia from first-episode cohorts: systematic review and meta-analysis. *Br J Psychiatry*. 2022;220(3):115–120.
12. Siskind D, McCartney L, Goldschlager R, et al. Clozapine v. first- and second-generation antipsychotics in treatment-refractory schizophrenia: systematic review and meta-analysis. *Br J Psychiatry*. 2016;209(5):385–392. doi:10.1192/bjp.bp.115.177261
13. Cipriani A, Boso M, Barbui C. Clozapine combined with different antipsychotic drugs for treatment resistant schizophrenia. *Cochrane Database Syst Rev*. 2009;3:CD006324.
14. Samara MT, Dold M, Gianatsi M, et al. Efficacy, acceptability, and tolerability of antipsychotics in treatment-resistant schizophrenia: a network meta-analysis. *JAMA Psychiatry*. 2016;73(3):199–210.
15. Hoare SRJ, Kudwa AE, Luo R, et al. Efficacy of VMAT2 inhibition and synergy with antipsychotics in animal models of schizophrenia. *J Pharmacol Exp Ther*. 2023;384(2):79–95.
16. Koblan KS, Kent J, Hopkins SC, et al. A non-D2-receptor-binding drug for the treatment of schizophrenia. *N Engl J Med*. 2020;382(16):1497–1506.
17. Dedic N, Dworak H, Zeni C, et al. Therapeutic potential of TAAR1 agonists in schizophrenia: evidence from preclinical models and clinical studies. *Int J Mol Sci*. 2021;22(24):13185. doi:10.3390/ijms222413185
18. Conley RR, Tamminga CA, Kelly DL, et al. Treatment-resistant schizophrenic patients respond to clozapine after olanzapine non-response. *Biol Psychiatry*. 1999;46(1):73–77.
19. Seeman P. Clozapine, a fast-off-D2 antipsychotic. *ACS Chem Neurosci*. 2014;5(1):24–29. doi:10.1021/cn400189s
20. Raedler TJ, Bymaster FP, Tandon R, et al. Towards a muscarinic hypothesis of schizophrenia. *Mol Psychiatry*. 2007;12(3):232–246. doi:10.1038/sj.mp.4001924
21. Foster DJ, Bryant ZK, Conn PJ. Targeting muscarinic receptors to treat schizophrenia. *Behav Brain Res*. 2021;405:113201. doi:10.1016/j.bbr.2021.113201
22. Abrams P, Andersson KE, Buccafusco JJ, et al. Muscarinic receptors: their distribution and function in body systems, and the implications for treating overactive bladder. *Br J Pharmacol*. 2006;148(5):565–578. doi:10.1038/sj.bjp.0706780
23. Shin JH, Adrover MF, Wess J, et al. Muscarinic regulation of dopamine and glutamate transmission in the nucleus accumbens. *Proc Natl Acad Sci U S A*. 2015;112(26):8124–8129. doi:10.1073/pnas.1508846112
24. El-Mallakh RS, Kirch DG, Shelton R, et al. The nucleus basalis of Meynert, senile plaques, and intellectual impairment in schizophrenia. *J Neuropsychiatry Clin Neurosci*. 1991;35:3383–3386.
25. Dean B, McLeod M, Keriakous D, et al. Decreased muscarinic1 receptors in the dorsolateral prefrontal cortex of subjects with schizophrenia. *Mol Psychiatry*. 2002;7(10):1083–1091. doi:10.1038/sj.mp.4001199
26. Lee MA, Thompson PA, Meltzer HY. Effects of clozapine on cognitive function in schizophrenia. *J Clin Psychiatry*. 1994;55(Suppl B):82–87.
27. Zorn SH, Jones SB, Ward KM, et al. Clozapine is a potent and selective muscarinic M4 receptor agonist. *Eur J Pharmacol*. 1994;269(3):R1–R2. doi:10.1016/0922-4106(94)90047-7
28. Bakker G, Vingerhoets C, Boucherie D, et al. Relationship between muscarinic M₁ receptor binding and cognition in medication-free subjects with psychosis. *Neuroimage Clin*. 2018;18:713–719. doi:10.1016/j.nicl.2018.02.030
29. Schaber G, Stevens I, Gaertner HJ, et al. Pharmacokinetics of clozapine and its metabolites in psychiatric patients: plasma protein binding and renal clearance. *Br J Clin Pharmacol*. 1998;46(5):453–459. doi:10.1046/j.1365-2125.1998.00822.x
30. Thomas DR, Dada A, Jones GA, et al. N-desmethylozapine (NDMC) is an antagonist at the human native muscarinic M₁ receptor. *Neuropharmacology*. 2010;58(8):1206–1214. doi:10.1016/j.neuropharm.2010.02.017
31. Sur C, Mallorga PJ, Wittmann M, et al. N-desmethylozapine, an allosteric agonist at muscarinic 1 receptor, potentiates N-methyl-D-aspartate receptor activity. *Proc Natl Acad Sci U S A*. 2003;100(23):13674–13679. doi:10.1073/pnas.1835612100
32. Tzavara ET, Bymaster FP, Davis RJ, et al. M4 muscarinic receptors regulate the dynamics of cholinergic and dopaminergic neurotransmission: relevance to the pathophysiology and treatment of related CNS pathologies. *FASEB J*. 2004;18(12):1410–1412. doi:10.1096/fj.04-1575fje
33. Cohen LH, Thale T, Tissenbaum MJ. Acetylcholine treatment of schizophrenia. *Arch Neuropsych*. 1944;51(2):171–175. doi:10.1001/archneurpsyc.1944.02290260061006
34. Armocida G, Licata M, Gorini I, et al. The acetylcholine therapy in the treatment of schizophrenia – the experience of Mario Fiamberti in the Hospital of Varese (1937). *Acta Med Hist Adriat*. 2019;17(1):91–102. doi:10.31952/amha.17.1.5
35. Barak S, Weiner I. Scopolamine induces disruption of latent inhibition which is prevented by antipsychotic drugs and an acetylcholinesterase inhibitor. *Neuropsychopharmacol*. 2007;32:989–999. doi:10.1038/sj.npp.1301208
36. Tom NR, Varghese GH, Alexander H, et al. A case report on atropine induced psychosis. *Int J Pharmaceutical Sci Res*. 2016;7(1):387–391.
37. Basha SA, Sathiswara B. Atropine induced psychosis: a report of two cases. *Int Health Sci Res*. 2017;12:325–327.
38. Pae CU. Role of the cholinesterase inhibitors in the treatment of schizophrenia. *Expert Opin Investig Drugs*. 2013;22(3):293–298. doi:10.1517/13543784.2013.762355
39. Ribeiz SRI, Bassitt DP, Arrais JA, et al. Cholinesterase inhibitors as adjunctive therapy in patients with schizophrenia and schizoaffective disorder. *CNS Drugs*. 2010;24:303–317. doi:10.2165/11530260-000000000-00000
40. Bodick NC, Offen WW, Shannon HE, et al. The selective muscarinic agonist xanomeline improves both the cognitive deficits and behavioral symptoms of Alzheimer disease. *Alzheimer Dis Assoc Disord*. 1997;11(Suppl 4):S16–S22.
41. Sramek JJ, Hurley DJ, Wardle TS, et al. The safety and tolerance of xanomeline tartrate in patients with Alzheimer's disease. *J Clin Pharmacol*. 1995;35(8):800–806. doi:10.1002/j.1552-4604.1995.tb04123.x
42. Shannon HE, Hart JC, Bymaster FP, et al. Muscarinic receptor agonists, like dopamine receptor antagonist antipsychotics, inhibit conditioned avoidance response in rats. *J Pharmacol Exp Ther*. 1999;290(2):901–907.
43. Chan WY, McKinzie DL, Bose S, et al. Allosteric modulation of the muscarinic M4 receptor as an approach to treating schizophrenia. *Proc Natl Acad Sci U S A*. 2008;105(31):10978–10983. doi:10.1073/pnas.0800567105
44. Shekhar A, Potter WZ, Lightfoot J, et al. Selective muscarinic receptor agonist xanomeline as a novel treatment approach for schizophrenia. *Am J Psychiatry*. 2008;165(8):1033–1039. doi:10.1176/appi.ajp.2008.06091591

45. Bymaster FP, Carter PA, Yamada M, et al. Role of specific muscarinic receptor subtypes in cholinergic parasympathomimetic responses, in vivo phosphoinositide hydrolysis, and pilocarpine-induced seizure activity. *Eur J Neurosci.* **2003**;17(7):1403–1410. doi:10.1046/j.1460-9568.2003.02588.x
46. Shannon HE, Bymaster FP, Calligaro DO, et al. Xanomeline: a novel muscarinic receptor agonist with functional selectivity for M1 receptors. *J Pharmacol Exp Ther.* **1994**;269(1):271–281.
47. Jakubik J, El-Fakahany EE, Doležal V. Differences in kinetics of xanomeline binding and selectivity of activation of G proteins at M₁ and M₂ muscarinic acetylcholine receptors. *Mol Pharmacol.* **2006**;70:656–666. doi:10.1124/mol.106.023762
48. Thorn CA, Moon J, Bourbonnais CA, et al. Striatal, hippocampal, and cortical networks are differentially responsive to the M₄- and M₁-muscarinic acetylcholine receptor mediated effects of xanomeline. *ACS Chem Neurosci.* **2019**;10(3):1753–1764. doi:10.1021/acchemneuro.8b00625
49. Heinrich JN, Butera JA, Carrick T, et al. Pharmacological comparison of muscarinic ligands: historical versus more recent muscarinic M1-preferring receptor agonists. *Eur J Pharmacol.* **2009**;605(1–3):53–56. doi:10.1016/j.ejphar.2008.12.044
50. Brannan SK, Sawchak S, Miller AC, et al. Muscarinic cholinergic receptor agonist and peripheral antagonist for schizophrenia. *N Engl J Med.* **2021**;384(8):717–726. doi:10.1056/NEJMoa2017015
51. Weiden PJ, Breier A, Kavanagh S, et al. Antipsychotic efficacy of KarXT (xanomeline-trospium): post hoc analysis of positive and negative syndrome scale categorical response rates, time course of response, and symptom domains of response in a Phase 2 study. *J Clin Psychiatry.* **2022**;83(3):21m14316. doi:10.4088/JCP.21m14316
52. Halaska M, Ralph G, Wiedemann A, et al. Controlled, double-blind, multicentre clinical trial to investigate long-term tolerability and efficacy of trospium chloride in patients with detrusor instability. *World J Urol.* **2003**;20(6):392–399. doi:10.1007/s00345-003-0321-8
53. Staskin D, Kay G, Tannenbaum C, et al. Trospium chloride has no effect on memory testing and is assay undetectable in the central nervous system of older patients with overactive bladder. *Int J Clin Pract.* **2010**;64(9):1294–1300. doi:10.1111/j.1742-1241.2010.02433.x
54. Brannan SK, Miller AC, Paul SM, et al. KarXT, a combination of the M₁/M₄ cholinergic receptor agonist xanomeline and trospium for the treatment of psychosis and cognitive impairment in schizophrenia: Phase I studies; Presented at poster session I of the American College of Neuropsychopharmacology 57th Annual Meeting; Hollywood, FL. *Neuropsychopharmacol.* **2018**;43(Suppl 1):77–227.
55. Singh A. Xanomeline and trospium: a potential fixed drug combination (FDC) for schizophrenia – a brief review of current data. *Innov Clin Neurosci.* **2022**;19(10–12):43–47.
56. Correll CU, Miller AC, Sawchak S, Kaul I, Paul SM, Brannan SK. Safety and efficacy of KarXT (xanomeline-trospium) in schizophrenia in the phase 3 randomized, double-blind, placebo-controlled EMERGENT-2 trial. Presented at the 28th Annual National Psychopharmacology Update of the Nevada Psychiatric Association (NPA); February 15-18; 2023; Las Vegas, Nevada, USA.

Neuropsychiatric Disease and Treatment

Dovepress

Publish your work in this journal

Neuropsychiatric Disease and Treatment is an international, peer-reviewed journal of clinical therapeutics and pharmacology focusing on concise rapid reporting of clinical or pre-clinical studies on a range of neuropsychiatric and neurological disorders. This journal is indexed on PubMed Central, the 'PsycINFO' database and CAS, and is the official journal of The International Neuropsychiatric Association (INA). The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Submit your manuscript here: <https://www.dovepress.com/neuropsychiatric-disease-and-treatment-journal>