SCIENTIFIC OVERVIEW

Xanomeline-trospium chloride (XTC)
A Novel Paradigm in Schizophrenia

Andre R. Alexander, MD, MSHIA

TALK TRACK

Welcome. Today, we discuss XTC, a first-in-class muscarinic agonist and the first approved antipsychotic with a non-D2 mechanism in over 30 years

Context & Disclosures

Professional Intent

This presentation was developed independently as a professional medical writing sample to demonstrate data synthesis and visual design capabilities.

No Conflicts

The author has no financial affiliations, conflicts of interest, or sponsorships to disclose regarding the products discussed herein. Data is from peer-reviewed sources.

TALK TRACK

This deck is a self-directed clinical analysis. All data presented here is derived from public, peer-reviewed literature, primarily the EMERGENT clinical trial program.

Unmet Need in Schizophrenia

Current D2-Centric Antipsychotics Provide Limited Benefit for Cognitive and Negative Symptoms

Current SOC relies on D2 blockade. While effective for positive symptoms, unmet needs remain in cognitive and negative symptom domains.[1,2,3]

Side Effects

Metabolic syndrome, EPS, and sedation can cause significant disability.[4]

The Gap

There is a critical need for treatments targeting negative symptoms with improved tolerability profiles.

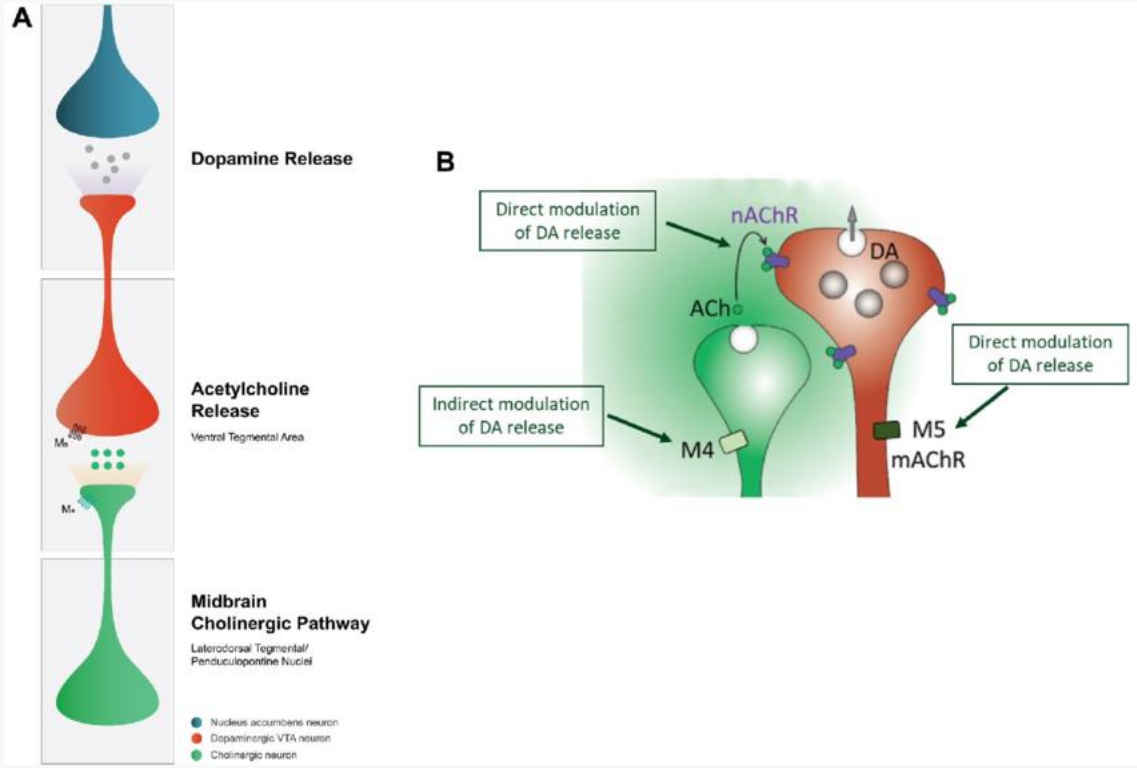
1. Huhn M, Nikolakopoulou A, Schneider-Thoma J, et al. Comparative efficacy and tolerability of 32 oral antipsychotics for the acute treatment of adults with multi-episode schizophrenia: a systematic review and network meta-analysis. *Lancet*. 2019;394(10202). doi:10.1016/s0140-6736(19)31135-3
2. Cerveri G, Gesi C, Mencacci C. Pharmacological treatment of negative symptoms in schizophrenia: update and proposal of a clinical algorithm. *Neuropsychiatr Dis Treat*. 2019;15:1525-1535. doi:10.2147/NDT.S201726
3. Feber L, Peter NL, Chiocchia V, et al. Antipsychotic drugs and cognitive function: a systematic review and network meta-analysis. *JAMA Psychiatry*. 2025;82(1):47–56. doi:10.1001/jamapsychiatry.2024.2890
4. Chow RTS, Whiting D, Favril L, Ostinelli E, Cipriani A, Fazel S. An umbrella review of adverse effects associated with antipsychotic medications: the need for complementary study designs. *Neurosci Biobehav Rev*. 2023;155:105454. doi:10.1016/j.neubiorev.2023.105454

TALK TRACK

Despite decades of progress, we still struggle with 'the revolving door' of schizophrenia. While positive symptoms are managed, the functional disability of negative symptoms remains a persistent unmet burden.

MOA: Selective Muscarinic Agonism

- **Xanomeline:** M1 and M4 mAChR-preferring agonist. Acts as both an orthosteric and allosteric agonis at the M4 receptor.[5]
- **Trospium:** Competitive antagonist at muscarinic cholinergic receptors.[6]
- **Blood-Brain Barrier:** Trospium does not cross the BBB, preserving central therapeutic effect.[7]



[8]**Fig. 3** **A** Midbrain muscarinic input increases dopamine release. **B** Modulation of dopamine release by acetylcholine via subtypes of nicotinic and muscarinic cholinergic receptors in the nucleus accumbens. Reproduced from Meyer JM, Correll CU. Increased metabolic potential, efficacy, and safety of emerging treatments in schizophrenia. *CNS Drugs*. 2023;37(7):545-570. doi:10.1007/s40263-023-01022-7 Licensed under CC BY-NC-ND 4.0. Unaltered image.

TALK TRACK

The co-formulation was designed to preserve central muscarinic receptor activity while reducing peripheral cholinergic adverse effects. Xanomeline provides central M1/M4 receptor agonism, whereas trospium limits peripheral muscarinic activation due to its minimal penetration of the blood-brain barrier.

5. Wessel, Pham V, Vuckovic Z, et al. Xanomeline displays concomitant orthosteric and allosteric binding modes at the M4 mAChR. *Nat Commun*. 2023;14(1). doi:10.1038/s41467-023-41199-5
6. Guay DR. Trospium chloride: an update on a quaternary anticholinergic for treatment of urge urinary incontinence. *Ther Clin Risk Manag*. 2005;1(2):157-167. doi:10.2147/tcrm.1.2.157.62912
7. Rovner ES. Trospium chloride in the management of overactive bladder. *Drugs*. 2004;64(21):2433-2446. doi:10.2165/00003495-200464210-00005

Study Design: EMERGENT-3[9]

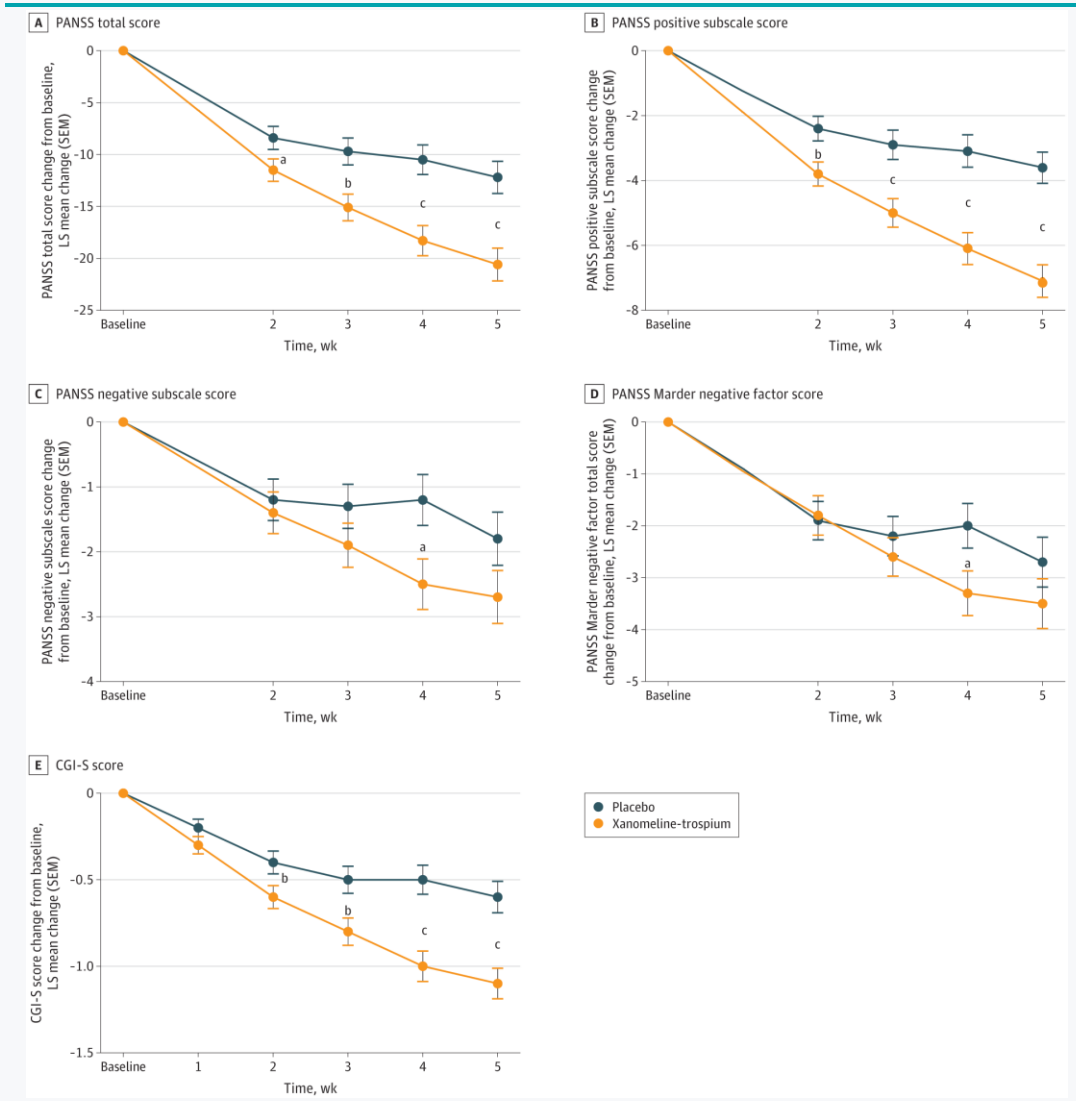
Feature	EMERGENT-3 Specifications
Study Type	Phase 3, Multicenter, Randomized, Double-Blind
Population	Adults (18-65) with Acute Schizophrenia Worsening
Primary Endpoint	Change in PANSS Total Score (Baseline to Week 5)
Sample Size	N = 256 Randomized (1:1 Ratio)
Dosing	Flexible titration up to 125mg Xanomeline / 30mg Trospium

TALK TRACK

EMERGENT-3 was an acute 5-week inpatient trial. We specifically looked at patients in acute relapse to see if XTC could manage severe positive symptoms without direct D2 intervention

9. Kaul I, Sawchak S, Walling DP, et al. Efficacy and safety of xanomeline-trospium chloride in schizophrenia: a randomized clinical trial. *JAMA Psychiatry*. 2024;81(8):749-756. doi:10.1001/jamapsychiatry.2024.0785

Primary Efficacy: PANSS Total Score[9]



Significant Reduction

-8.4 Point Difference vs Placebo (p<0.001)

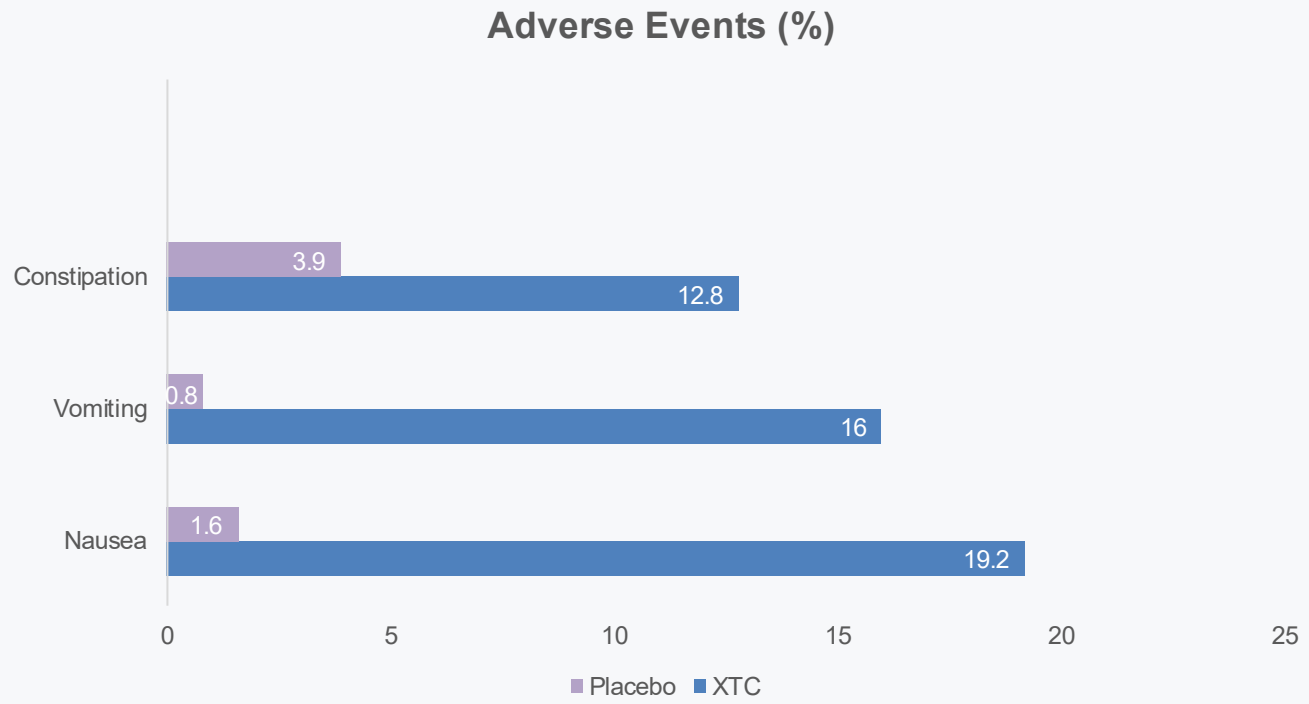
Effect size (Cohen's d) of **0.60** was observed at Week 5.

TALK TRACK

Note the separation by Week 2. XTC achieved a significant PANSS reduction that was enhanced through the end of the trial (Week 5), demonstrating a clinically meaningful treatment effect.

[9]**Figure 2. Positive and Negative Syndrome Scale (PANSS) and Clinical Global Improvement-Severity (CGI-S) End Points (Modified Intent-To-Treat [mITT] Population)** Reproduced from Kaul I, Sawchak S, Walling DP, et al. Efficacy and safety of xanomeline-trospium chloride in schizophrenia: a randomized clinical trial. *JAMA Psychiatry*. 2024;81(8):749-756. doi:10.1001/jamapsychiatry.2024.0785. Licensed under CC BY-NC-ND 4.0. Unaltered image.

Most Common Adverse Events



Majority of GI events were **mild-to-moderate** and **transient**, occurring in the titration phase

TALK TRACK

Tolerability is key. While GI effects are higher than placebo, they rarely led to discontinuation. Most patients habituate to these effects within the first two weeks.

Differentiating the Safety Profile

Limited Metabolic and EPS Burden

- **Metabolic:** No significant weight gain compared to baseline.
- **EPS:** No clinically significant akathisia or drug-induced parkinsonism.

TALK TRACK

This represents an important point of differentiation. In addition to efficacy, the safety profile is notable for the absence of clinically meaningful weight gain and low rates of extrapyramidal symptoms during the study period.

Clinical Response at Week 5

50.6%

Responder Rate (XTC)

Significant Patient Response

Defined as ≥30% improvement in floor-adjusted PANSS scores.

Compared to only **25.3%** in the placebo group, XTC doubled the likelihood of a clinically meaningful response within 5 weeks.

TALK TRACK

Beyond the primary endpoint, the responder analysis provides additional clinical context. Approximately one-half of patients receiving XTC achieved a clinically meaningful improvement in symptoms by Week 5, compared with one-quarter of patients receiving placebo.

Conclusion & Future Outlook

- **First-in-Class:** XTC is the first muscarinic agonist to show Phase 3 efficacy in schizophrenia.
- **Broad Efficacy:** Improvements were observed across positive and negative symptom subscales (PANSS subscales).
- **Tolerability:** Associated with minimal weight gain and low rates of EPS during the study period.
- **Strategic Value:** Represents a shift toward non-dopaminergic treatment pathways.

TALK TRACK

In summary, XTC offers a novel treatment approach that demonstrated efficacy while maintaining a differentiated metabolic and EPS profile in the Phase 3 program.

Questions & Discussion

Andre R. Alexander, MD, MSHIA

Medical Communications & Scientific Strategy

Psychiatry & CNS Therapeutics

TALK TRACK

Thank you for your attention. I am happy to address any question regarding the EMERGENT program.

References

1. Huhn M, Nikolakopoulou A, Schneider-Thoma J, et al. Comparative efficacy and tolerability of 32 oral antipsychotics for the acute treatment of adults with multi-episode schizophrenia: a systematic review and network meta-analysis. *Lancet.* 2019;394(10202):1165-1176. doi:10.1016/S0140-6736(19)31135-3.
2. Cerveri G, Gesi C, Mencacci C. Pharmacological treatment of negative symptoms in schizophrenia: update and proposal of a clinical algorithm. *Neuropsychiatr Dis Treat.* 2019;15:1525-1535. doi:10.2147/NDT.S201726.
3. Feber L, Peter NL, Chiocchia V, et al. Antipsychotic drugs and cognitive function: a systematic review and network meta-analysis. *JAMA Psychiatry.* 2025;82(1):47-56. doi:10.1001/jamapsychiatry.2024.2890.
4. Chow RTS, Whiting D, Favril L, Ostinelli E, Cipriani A, Fazel S. An umbrella review of adverse effects associated with antipsychotic medications: the need for complementary study designs. *Neurosci Biobehav Rev.* 2023;155:105454. doi:10.1016/j.neubiorev.2023.105454.
5. Burger W, Pham V, Vuckovic Z, et al. Xanomeline displays concomitant orthosteric and allosteric binding modes at the M4 mAChR. *Nat Commun.* 2023;14(1):5446. doi:10.1038/s41467-023-41199-5.
6. Guay DR. Trospium chloride: an update on a quaternary anticholinergic for treatment of urge urinary incontinence. *Ther Clin Risk Manag.* 2005;1(2):157-167. doi:10.2147/TCRM.1.2.157.62912.
7. Rovner ES. Trospium chloride in the management of overactive bladder. *Drugs.* 2004;64(21):2433-2446. doi:10.2165/00003495-200464210-00005.
8. Meyer JM, Correll CU. Increased metabolic potential, efficacy, and safety of emerging treatments in schizophrenia. *CNS Drugs.* 2023;37(7):545-570. doi:10.1007/s40263-023-01022-7.
9. Kaul I, Sawchak S, Walling DP, et al. Efficacy and safety of xanomeline-trospium chloride in schizophrenia: a randomized clinical trial. *JAMA Psychiatry.* 2024;81(8):749-756. doi:10.1001/jamapsychiatry.2024.0785.

TALK TRACK

For those interested in the deep dive, I recommend starting with the Kaul 2024 primary paper which covers the full Phase 3 results in detail.