Challenging Cases in Schizophrenia: Practical Considerations of Muscarinic Therapies in Practice

MasterClass

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Disclosure

- The faculty have been informed of their responsibility to disclose to the audience if they will be discussing off-label or investigational use(s) of drugs, products, and/or devices (any use not approved by the US Food and Drug Administration).

- Applicable CME staff have no relationships to disclose relating to the subject matter of this activity.

- This activity has been independently reviewed for balance.

Learning Objectives

- Differentiate muscarinic receptor-based mechanisms from traditional D2-targeting antipsychotic approaches in the treatment of schizophrenia
- Interpret clinical trial data for approved and investigational muscarinic therapies using appropriate efficacy endpoints and regulatory context
- Apply practical, patient-centered strategies for integrating muscarinic-based therapies into schizophrenia care, including considerations related to tolerability and concomitant medications

Case #1

Case 1

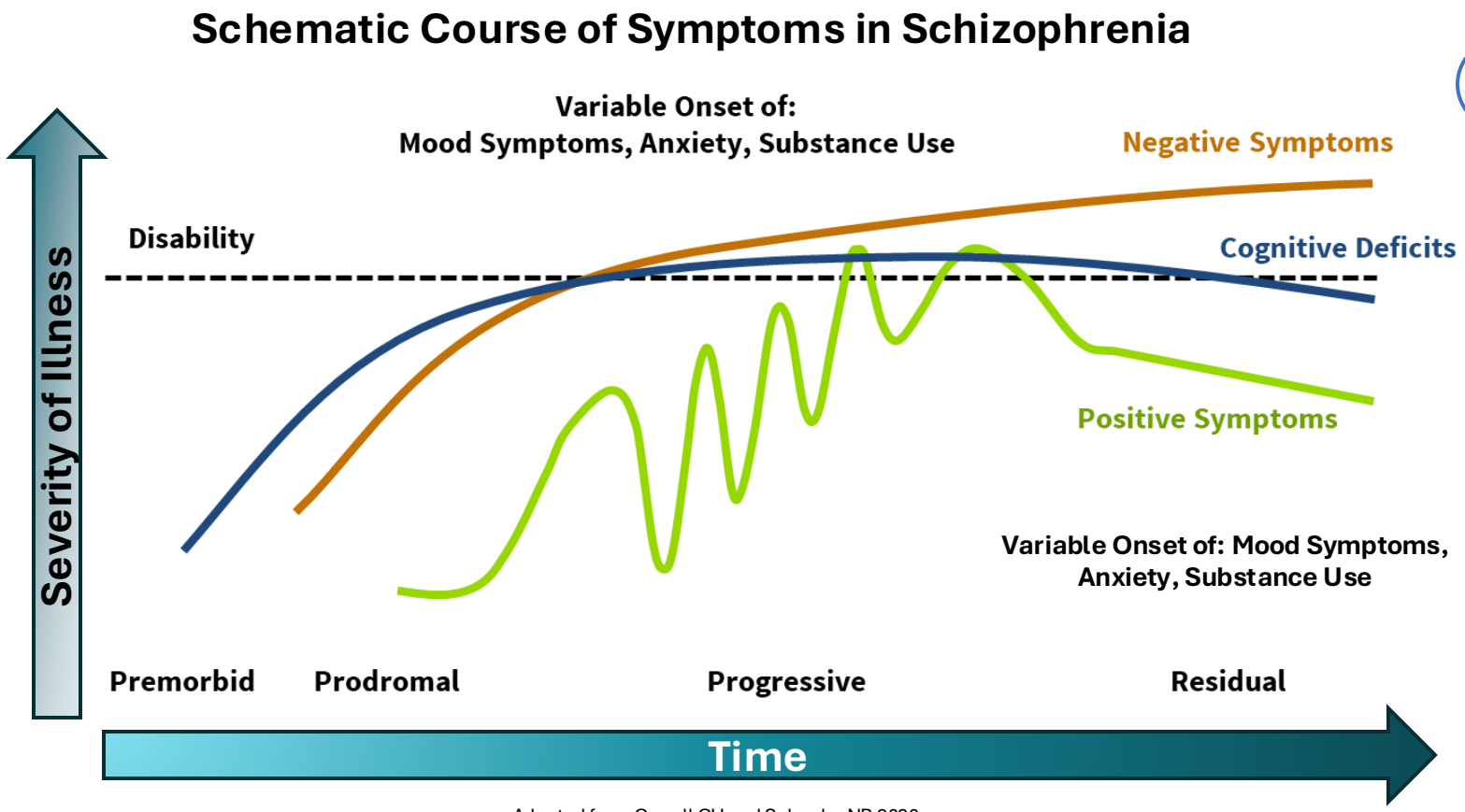
A 19-year-old male college student presents with a first episode of psychosis, along with several months of worsening social withdrawal, reduced motivation, diminished emotional expression, and cognitive decline affecting attention and academic performance.

His family notes that the behavioral and cognitive changes began before the onset of psychosis and continue to interfere with his ability to function day to day.

Concerns

- Can this patient be adherent with any oral medication?
- What is his attitude to treatment? What are his goals?
- Will access to newer branded medications be a problem without prior antipsychotic trials?

Course of Schizophrenia Symptoms Over Time



Adapted from Correll CU and Schooler NR 2020.

- Schizophrenia is chronic and requires lifelong treatment
- Careful consideration should be taken with respect to potential long-term consequences for drug of choice
- Goal is to minimize risk of relapse and reduce potential for treatment-related side effects (risk/benefit profile)

Correll CU. *J Clin Psychiatry*. 2013;74(2):e04. Correll CU, Schooler NR. *Neuropsychiatr Dis Treat*. 2020;16:519-534. Burchinski A, et al. *World Psychiatry*. 2023;22:116-128. Keepers GA, et al. *Am J Psychiatry*. 2020;177(9):868-872.

Schizophrenia Is a Complex Neuropsychiatric Disorder

Positive Symptoms

Some examples include:
Delusions
Hallucinations
Disorganized speech
Disorganized behavior

Negative Symptoms

Some examples include:
Blunted affect
Social withdrawal
Restricted speech
Lack of pleasure and/or motivation

Prevalence: On LAI treatment, persistent **primary** negative symptoms seen in 8%, and enduring negative symptoms (due to any cause) in 15%.

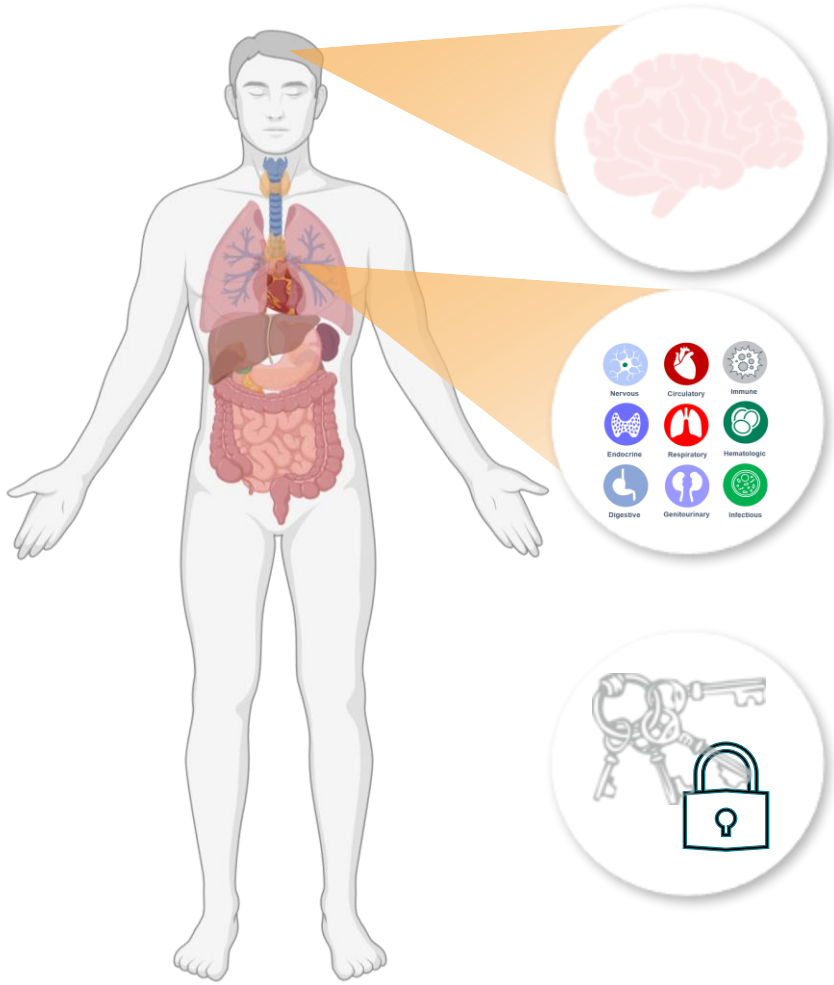
Cognitive Symptoms

Some examples include:
Impaired attention
Difficulty problem solving
Problems with maintaining goals
Impairments with serial learning

Prevalence: Seen in > 80% of patients with schizophrenia, and is a main determinant of functional disability and indirect costs of disease.

Meyer JM. Ch 19 - Pharmacotherapy of Psychosis and Mania. In: Brunton LL, ed. Goodman & Gilman's The Pharmacological Basis of Therapeutics, 14th Ed. Chicago, Illinois: McGraw-Hill; 2022:357-84. Giuliani L, et al. Persistent negative symptoms in the EULAST cohort: impact on functional outcome. Schizophr 2026; 12:36. Harvey PD et al. Schizophr Res Cogn 2022;29:100249; McCutcheon RA et al. Mol Psychiatry 2023;28(5):1902-18.

Schizophrenia Is A Heterogeneous Disorder Affecting the Brain and Body



Core Symptoms and Psychiatric Comorbidities

- Positive, negative, and cognitive symptoms
- Comorbidities: anxiety, depression, substance abuse

Abnormalities in Multiple Organ Systems

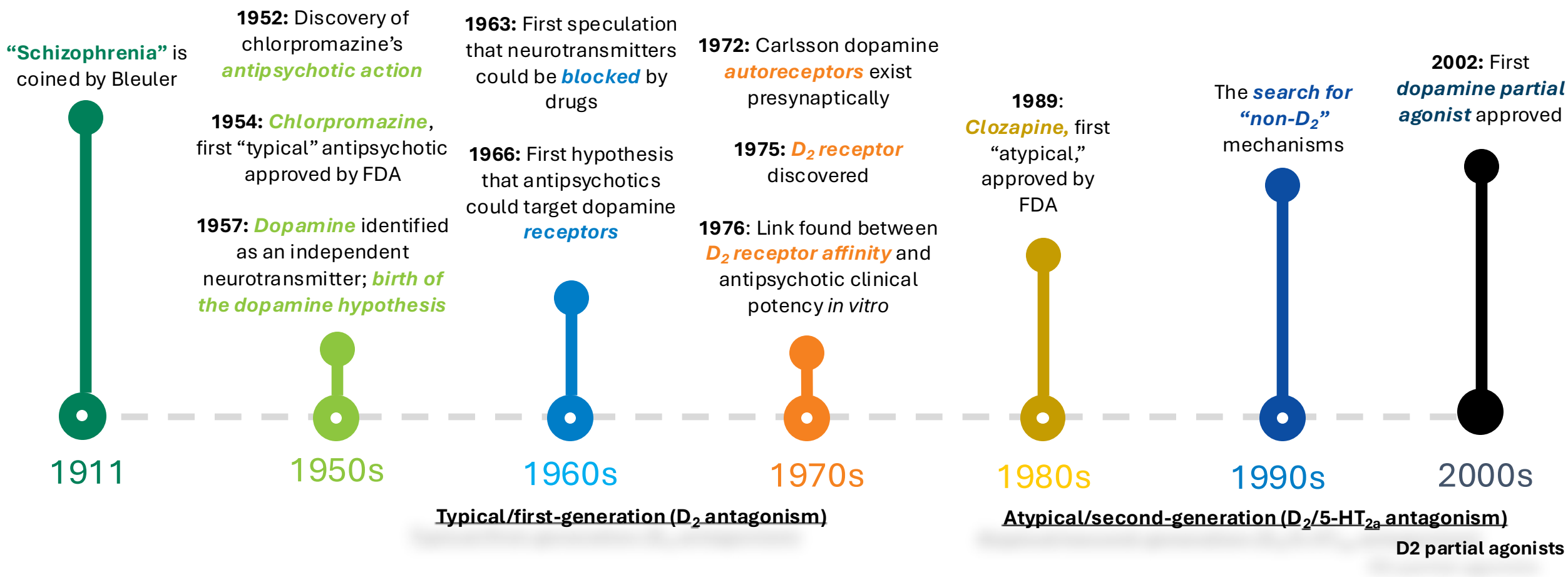
- >1.5 times the odds for comorbidities across several disease categories
- Excess and premature mortality
- >80% of individuals with schizophrenia experience disability
- Life expectancy shortened by >15 years

Highly Heterogeneous

- Patients are unique in brain structure and chemistry, leading to heterogeneous symptom presentation, clinical course, and treatment response
- Despite the need for more individualized approaches, pharmacologic treatment has remained fairly uniform

Keeley JW, Gaebel W. *Epidemiol Psychiatr Sci*. 2018;27:219-224. Arciniegas DB. *Continuum (Minneap Minn)*. 2015;21:715-736. Correll CU, Schooler NR. *Neuropsychiatr Dis Treat*. 2020;16:519-534. McCleery A, Nuechterlein KH. *Dialogues Clin Neurosci*. 2019;21:239-248. Buckley, PG et al. *Schiz Bull*. 2009; 35(2):383-402. Fakorede OO, et al. *Int J Soc Psych*. 2020;66(2):179-187. Hjorthoj C, et al. *Lancet Psychiatry*. 2017;4(4):295-301. Kane JM. *J Clin Psychopharmacol*. 2022;42 (5 Suppl):S1-S13. Ozomaro U, et al. *BMC Medicine*. 2013;11:132-142.Case M, et al. *Psychol Med*. 2011;41(6):1291-1300. Faden J, Citrome L. *Med Clin N Am*. 2023;107:61-72.

A Brief History of Schizophrenia Treatment



5-HT2A = serotonin type 2A receptor; D_2 = dopamine D2 receptor.

Madras B. *J Hist Neurosci*. 2013;22:62-78. Correll CU, et al. *J Clin Psych*. 2022;1 (InfoPack 1):SU21024lp1. Creese I, et al. *Science*. 1976;192(4238):481-483. Seeman P, et al. *Nature*. 1976;261(5562):717-719.

What Did 5-HT_{2A} Antagonism Really Do For Us?

Reduced D_2-Related Motor AEs

- A 2019 meta-analysis of 32 oral antipsychotics confirmed lower rates of akathisia and need for antiparkinsonian medication among SGAs

Small Effect + Limited Clinical Significance for Neg/Cog Sx

- A 2023 review on negative symptoms found small benefits from 5-HT_{2A} antagonism, but the phase III ADVANCE-2 trial of adjunctive pimavanserin was negative (effect size 0.07) and it is no longer being studied
- A 2024 meta-analysis on antipsychotics and cognitive function (68 studies, n = 9525) concluded: "**Antipsychotics are not procognitive drugs**"

Huhn M et al. Lancet 2019;394:939; Romeo B et al. Psychiatry Research 2023;321:115104; Feber L et al. JAMA Psychiatry 2024;82(1):1-10.

Unmet Needs in Schizophrenia Treatment

Residual Symptoms and Inadequate Treatment Response

- 1 out of every 3 patients does not respond
- Negative and cognitive symptoms may persist

Varying levels of side effects and long-term risks may contribute to negative outcomes and poor adherence

- First generation APs: Generally associated with movement disorders and prolactin elevation
- Second generation APs: Typically associated with sedation, weight gain, and metabolic dysregulation

All APs work via essentially the same mechanism

AP = antipsychotic.

Correll CU, et al. *J Clin Psychiatry*. 2022;83(1):SU21024IP1. Faden J, Citrome L. *Med Clin N Am*. 2023;107:61-72. Howes OD, et al. *Am J Psychiatry*. 2017;174(3):216–29. DiBonaventura M, et al. *BMC Psychiatry*. 2012;12:20. Burschinski A, et al. *World Psychiatry*. 2023;22(1):116-128. Keepers GA, et al. *Am J Psychiatry*. 2020;177(9):868-872. Huhn M, et al. *Lancet*. 2019;394(10202):939-951. Kane, JM. *J Clin Psychopharmacology*. 2022;42(5 Suppl 1):S1-S13

In Schizophrenia, the Primary Dopamine Dysfunction Is Presynaptic

Presynaptic differences in schizophrenia

Elevated presynaptic striatal dopamine found in acutely psychotic individuals with

▶ **Effect sizes 0.63 to 1.25**

Doubled dopamine release after challenge in patients with schizophrenia vs healthy controls **in 5 of 5 studies** with moderate to large effect sizes

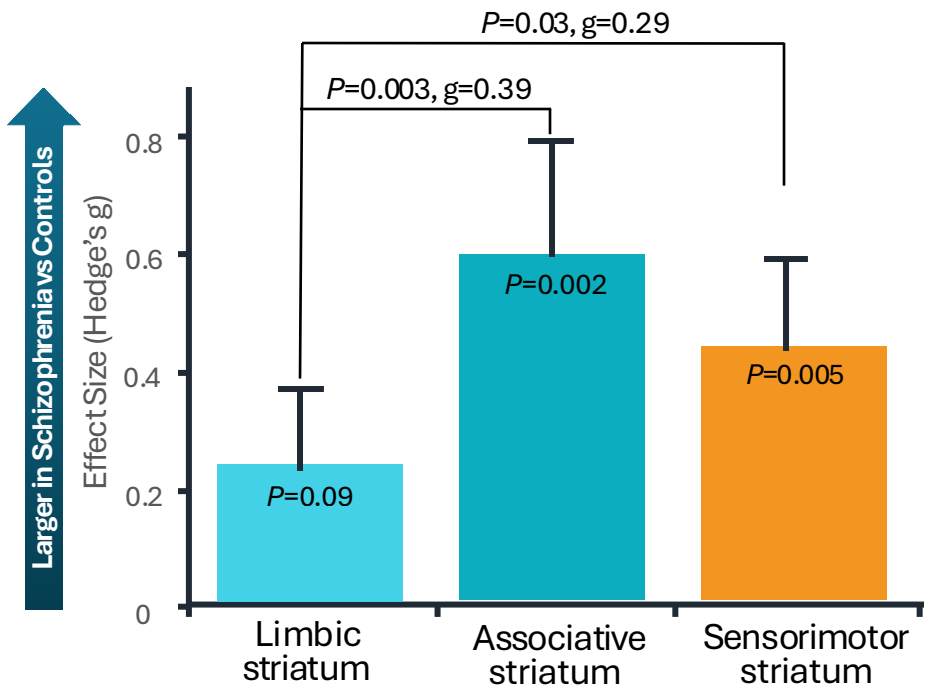
What About Nonresponders?

Imaging studies suggest that poor response to D_2 receptor modulation is associated with relatively normal striatal dopamine synthesis capacity but elevated anterior cingulate cortex (ACC) and striatal (caudate) glutamate levels.

▶ **different form of schizophrenia**

It's also not in the mesolimbic pathway!

Estimated Mean Difference in Presynaptic Dopamine Function in Patients vs Controls



Recent high-resolution imaging studies

Increased dopaminergic activity in associative and sensorimotor striatum, NOT in limbic striatum as seen in mouse models

Howes OD, S Kapur. Schizophr Bull. 2009;35(3):549-562. McCutcheon RA, et al. *Trends Neurosci. 2019;*42(3):205-220. McCutcheon RA, et al. *Schizophr Bull*. 2018;44(6):1301-1311. Merritt K, et al. JAMA Psychiatry. 2016;73(7):665-674. Egerton A, et al. Schizophr Bull. 2021;47(2):505-516. Stevens FL, et al. J Neuropsychiatry Clin Neurosci. 2011;23(2):120-125.

M1/M4 Receptors Selectively Regulate Presynaptic Striatal Dopamine Release via Two Circuits

GLU neuron

GABA neuron

LDT (Cholinergic neuron)

Cholinergic presynaptic terminal

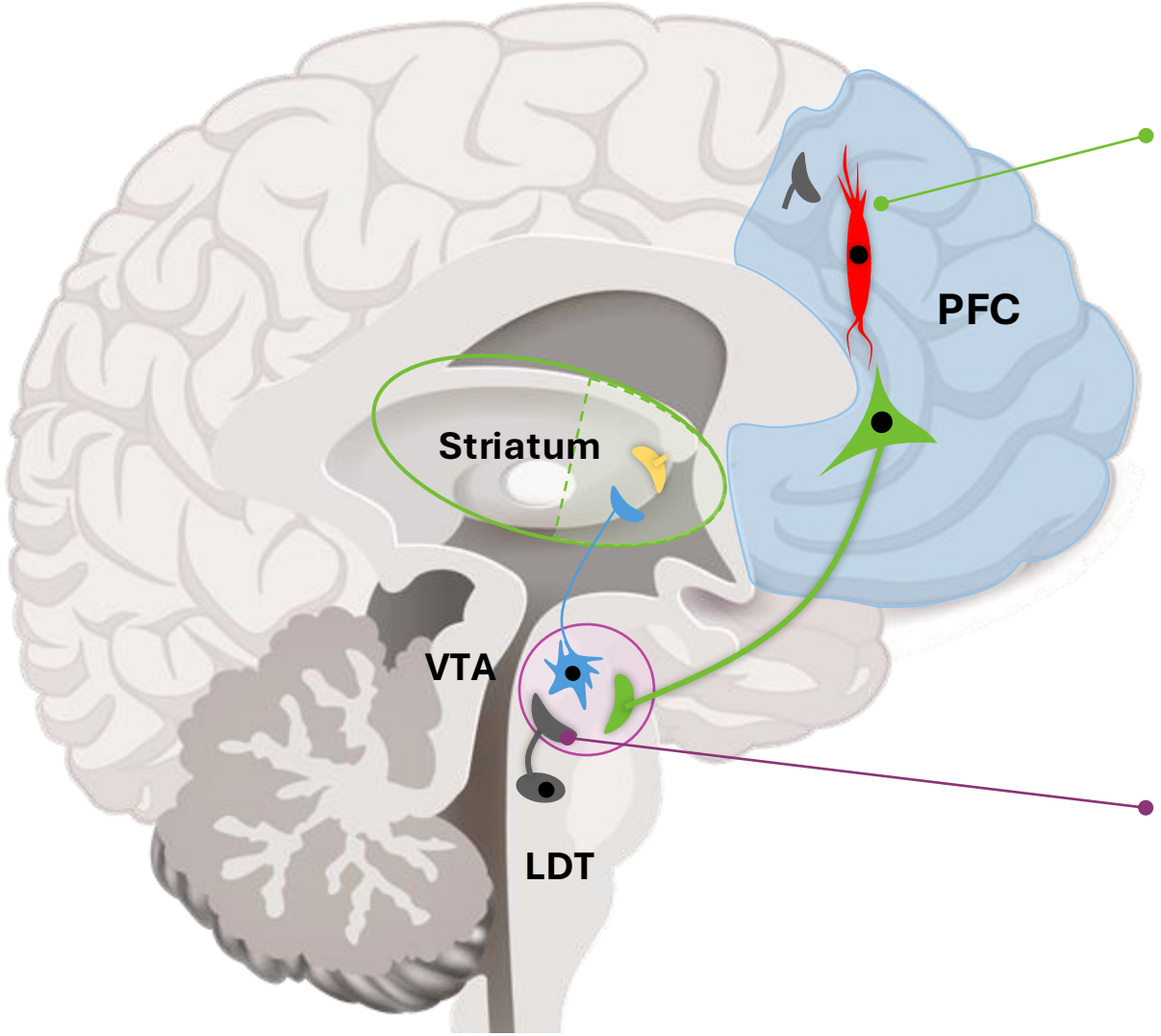
DA neuron

ACh

DA

D_2 receptor

Postsynaptic terminal



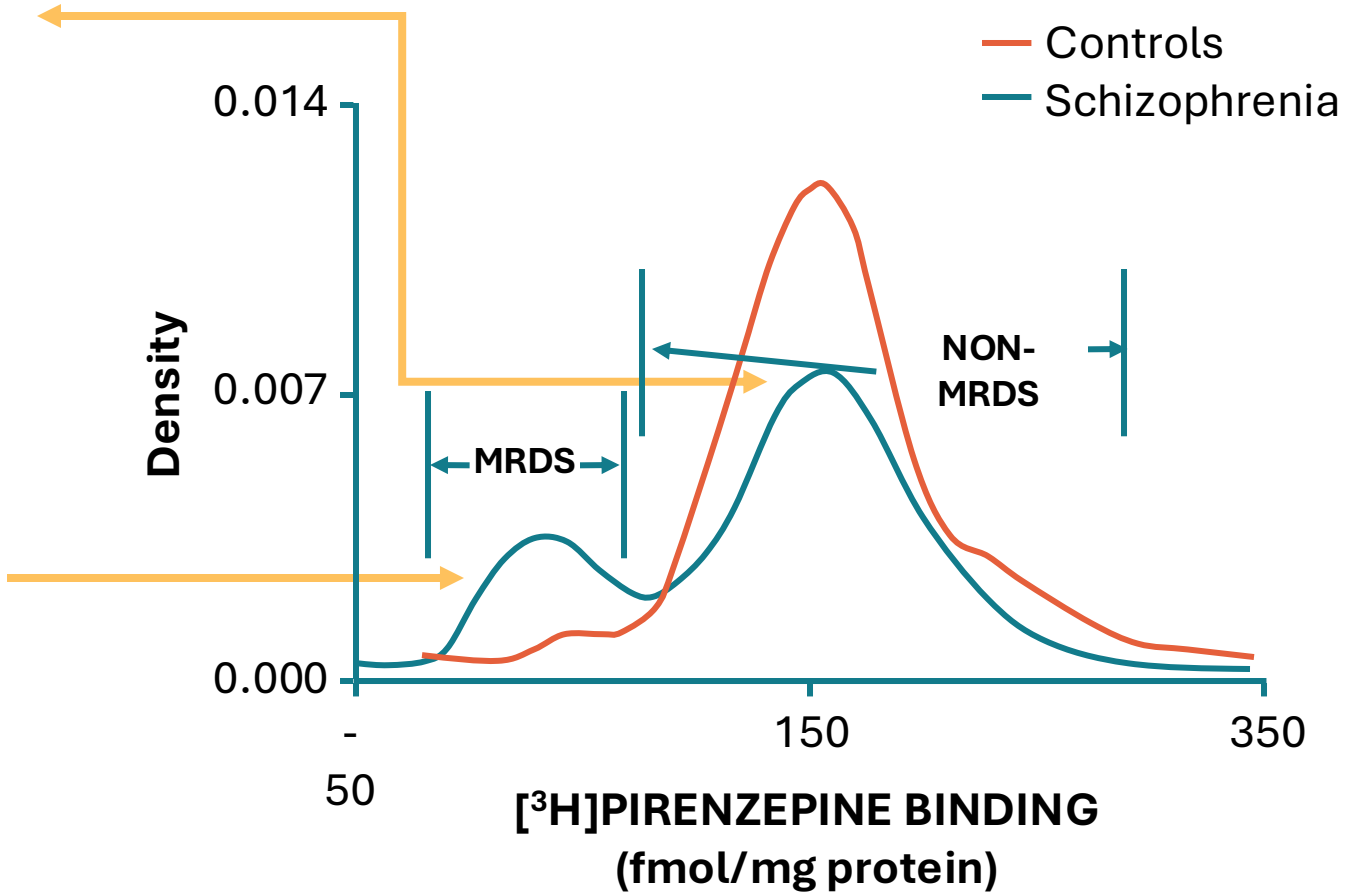
- **GABA-ergic interneurons:** Control glutamate pathways which themselves stimulate VTA dopamine release
- **The GABA-ergic interneuron expresses stimulatory M1 receptors on the cell body**[2]

- **LDT:** A cholinergic neuron that stimulates VTA dopamine release
- **The LDT has inhibitory M4 autoreceptors on axonal terminals**[3]

Paul SM, et al. Am J Psychiatry. 2022;179:611-627; Yohn SE, et al. Trends Pharmacol Sci. 2022;43:1098-1112; Ballinger EC, et al. Neuron. 2016;91:1199-1218.

How Muscarinic Activation Might Improve Cognition

- Large study on muscarinic receptors revealed that 25% of patients have, on average, 75% lower M1 receptor levels; categorized as MRDS
- Same subgroup has slightly lower M1 mRNA levels and altered methylation vs controls
- Low levels of M1 associated with poorer performance in verbal learning and memory tasks and more severe negative symptoms in medication-free patients



MRDS, muscarinic receptor deficit sub-group.

Dean B, et al. Psychiatry Res. 2020;288:112989.

X/T Effect Size in Phase 2b/3 Trials

- Table on the right shows results from a meta-analysis of Positive and Negative Syndrome Scale (PANSS) outcomes from acute adult schizophrenia trials (212 trials; N = 43,049) [1]
- The pooled effect size across all three EMERGENT trials was 0.65 when calculated using the pooled variance from Mixed Model for Repeated Measures (MMRM) [2]
- A 2025 meta-analysis calculated the effect size at 0.56 across the 3 EMERGENT trials [3]
  - **This difference is likely due to the fact that in meta-analyses the pooled variance is calculated from the reported standard errors of the means or least squared means by treatment for a specific week;** this is a common approach and consistent with other published meta-analyses.

Drug	Effect Size (total PANSS)
Clozapine	0.88
Olanzapine	0.59
X/T[3]	**0.56**
Risperidone	0.56
Haloperidol	0.45
Quetiapine	0.44
Aripiprazole	0.43
Ziprasidone	0.39
Lurasidone	0.33

Leucht S et al. Lancet 2013;382:951-62; Kaul I et al. Schizophrenia (Heidelb) 2024;10(1):102; Fabiano N et al. Eur Neuropsychopharmacol 2025;92:62-73.

Pooled EMERGENT Trials: Safety During Phase 2b/3 Trials

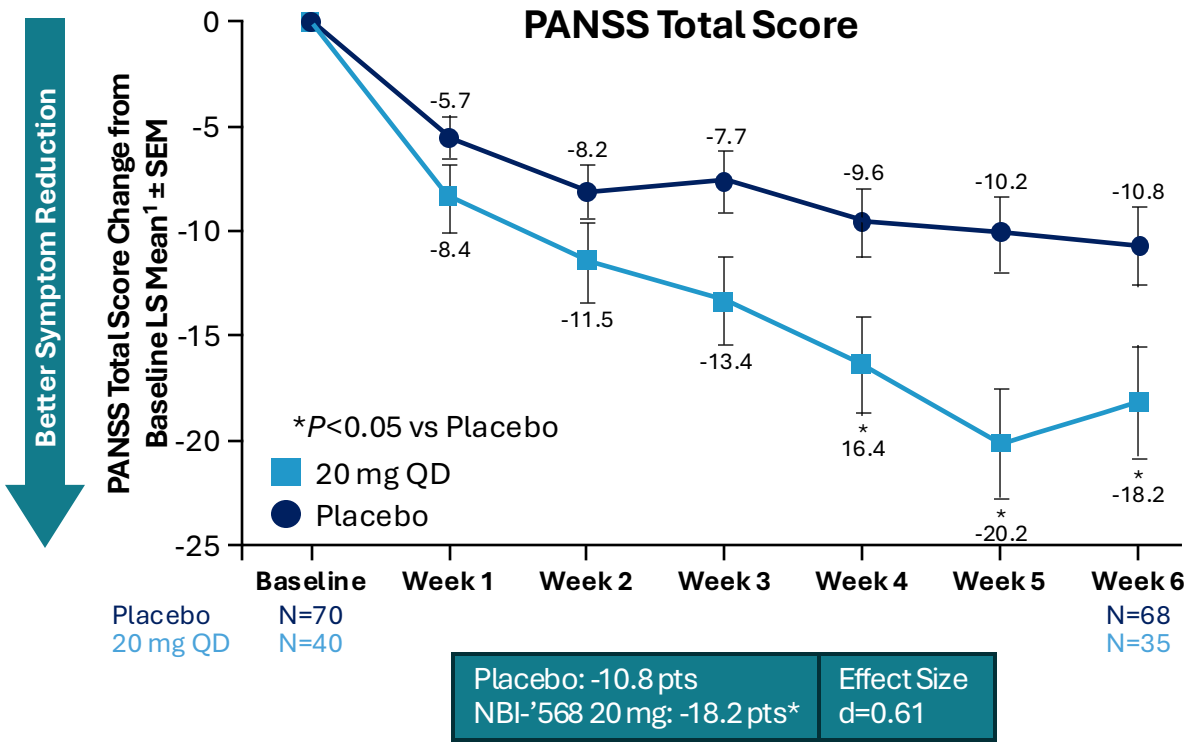
TEAE, %	Xanomeline + Trospium (n = 251)	Placebo (n = 253)
Nausea	19	4
Dyspepsia	18	5
Constipation	17	1
Vomiting	15	2
Hypertension	11	4
Abdominal pain	8	2
Diarrhea	6	2
Tachycardia	5	< 1
Dizziness	5	2
GERD	5	2
Dry mouth	4	0

- Mean changes in weight, metabolic measures, prolactin, and motor ratings with xanomeline + trospium were comparable to placebo
- Discontinuations due to AEs:
  - Emergent-1: 2% of patients in xanomeline + trospium and placebo arms
  - Emergent-2: 7% of patients in xanomeline + trospium arm vs 6% in placebo arm
  - Emergent-3: 6% of patients in xanomeline + trospium and placebo arms

Brannan SK et al. N Engl J Med 2021;384:717-26; Kaul I et al. Lancet 2024;403:160-70; Kaul I et al. JAMA Psychiatry 2024; 81:749-56.

Positive Phase 2a Results for Direclidine -M_4 Agonist with 500-fold Selectivity vs $M_{1/2/3/5}$

40 mg QD. 60 mg QD, and 30 mg BID doses were also studied, but did not separate from placebo



Placebo: -10.8 pts NBI-'568 20 mg: -18.2 pts*	Effect Size d=0.61

AEs Occurring in ≥ 5% of NBI111758620 Group	Placebo N=70	NBI-'568 20 mg N=40
Somnolence	3%	13%
Dizziness	1%	13%
Headache	20%	3%
Nausea	3%	5%
Constipation	3%	5%
Discontinuation due to AEs	5% across all dose arms vs 4.3% for placebo	

Few drug-induced movement disorders reported
Weight change was similar to placebo

Cardiovascular-related events were infrequent and deemed not clinically relevant at any tested dose

Two Phase 3 studies in schizophrenia are in progress and expected to complete Q4 2027

Nash A, et al. Once-Daily NBI-1117568, a Highly Selective Orthosteric M4 Muscarinic Receptor Agonist, Demonstrates Meaningful Improvements in PANSS Total Score and Is Well Tolerated in Adults With Schizophrenia: Phase 2 Study Results. Presented at: ASCP Annual Meeting; May 27-30, 2025; Scottsdale, AZ. ClinicalTrials.gov. Accessed August 20, 2025. https://clinicaltrials.gov/study/NCT06963034. ClinicalTrials.gov. Accessed August 20, 2025. https://clinicaltrials.gov/study/NCT07105098.

Ongoing Phase 2 trials -ML-007C-MA in Schizophrenia

ML-007C – novel M1/M4 agonist + peripherally acting muscarinic antagonist. Robust M1/M4 intrinsic activity. Potential for once daily dosing.

Insights from Phase 1:
270 healthy adults and elderly
BID Dosing

Healthy adults – generally well tolerated with low rates of anticholinergic AEs. No meaningful changes in BP, ECG or liver related findings. Mainly mild, transient Aes.

Elderly adults – generally well tolerated up to 210/3mg BID- highest dose was not well tolerated

Current: Phase 2 study design adults 18-64 dx schizophrenia.

5 week trial with follow up period
Three arms – Placebo BID, ML007C-MA 336/6mg QD
ML-007C-MA 210/3mg BID

Phase 2 topline data expected Q3 2026

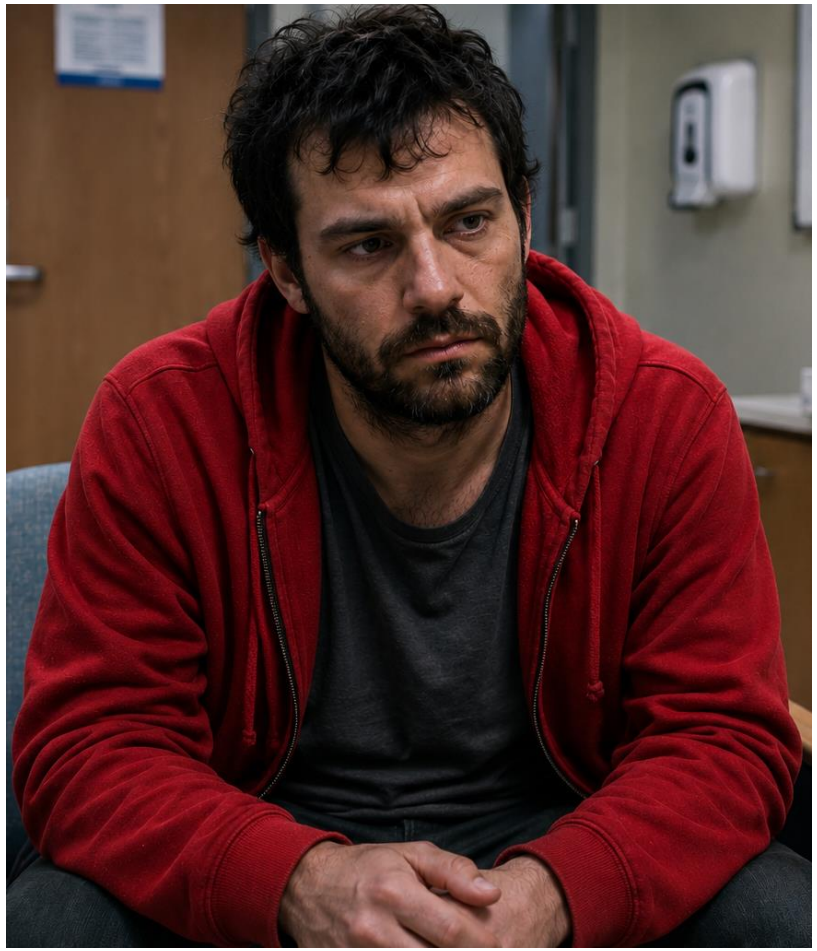
AEs – adverse events PAC = peripherally restricted cholinergic. Maplight. Accessed May 9th, 2026. https://ir.maplightrx.com/static-files/32aa3a07-5285-44a4-baee-c22f5c270147

Key Learning Points

- Positive symptoms of schizophrenia are believed to be a pre-synaptic hyper-dopaminergic state in the associated striatum in humans in responders
- XT reduces positive symptoms of schizophrenia by activating muscarinic M1 and M4 receptors that modulate dopamine release upstream of the D2 receptor, rather than through direct D2 receptor blockade

Case #2

Case 2



A 32-year-old male patient with schizophrenia was admitted for an acute exacerbation, (e.g. severe agitation, command auditory hallucinations, paranoid delusions, worsening social withdrawal/motivation, poor hygiene and grooming).

He was discharged on olanzapine 20 mg at bedtime after an inpatient stay of 4 days with modest improvement in his symptoms, but is not yet at his baseline. The patient notes that he did not do well on a partial agonist, and stopped his latest medication (risperidone) due to weight gain.

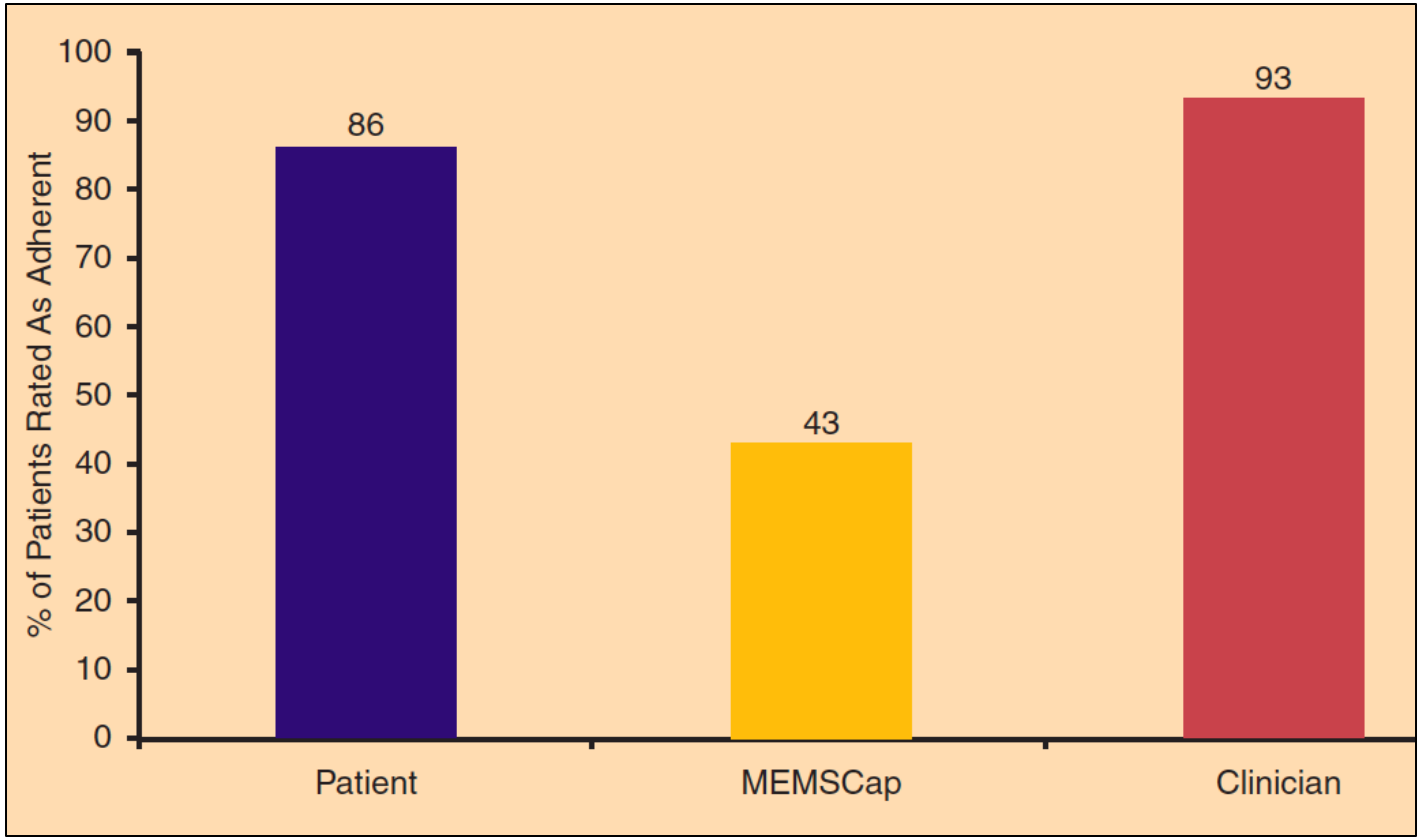
Concerns

- Is this patient treatment resistant? If not, why not?
- Will he take an oral medication reliably?
- How to transition from olanzapine if he wants to try a medication without weight gain risk?

Accurate Assessment of Adherence is Difficult For Patients and Clinicians

Nonresponse May Not Mean Treatment Resistance

- In a dedicated study of adherence, both clinicians (93%) and patients (86%) overestimated oral antipsychotic adherence compared to the **MEMS cap data which indicated that only 43% took at least 70% of their medications.** [1]
- 35% of patients living with schizophrenia (n=99) at one academically affiliated site in London ***who were deemed treatment resistant*** had subtherapeutic plasma levels in one study. [2]



Byerly M, et al. Psychiatric Services 2007; 58:844–847; McCutcheon R., et al. Acta Psych Scandinav 2018; 137(1): 39-46; Meyer JM, Stahl SM. The Clinical Use of Antipsychotic Plasma Levels - Stahl's Handbooks. New York, NY: Cambridge University Press; 2021; 382 pp.

Clozapine Normalizes Caudate Glutamate in TRS Unresponsive to D2 Modulation

In TRS, Positive Symptoms Are a Glutamate Issue, ***Not*** a Presynaptic Dopamine Issue

Within 12 weeks of starting clozapine, patients with TRS exhibit:

- A longitudinal reduction in tissue-corrected glutamate concentration (Glu_{corr}) in the caudate (n=23, F = 7.61, *P*=.01) but not the ACC (n=24, F = 0.02, *P*=.59)
- The percent reduction in caudate Glu_{corr} positively correlates with percent improvement in symptoms as measured by PANSS total score (n=23, *r* = .42, *P*=.04)
- **Conclusion: Modulating glutamate signaling in the striatum is central to treating positive symptoms of psychosis in patients who respond inadequately to D_2 modulation.**
    - **Xanomeline,** the M_1/M_4 agonist, works by reducing presynaptic dopamine release. There is no data to indicate that it is effective for TRS, and it is designed to work on the same dopamine pathway that is overactive in non-TRS patients.

Merritt K, et al. JAMA Psychiatry. 2016;73:665-674; Egerton A, et al. Schizophr Bull. 2021;47:505-516; Stevens FL, et al. J Neuropsychiatry Clin Neurosci 2011;23:120-125; McQueen G, et al. Schizophr Bull. 2021;47:662-671.

Xanomeline for Treatment-Resistant Schizophrenia?

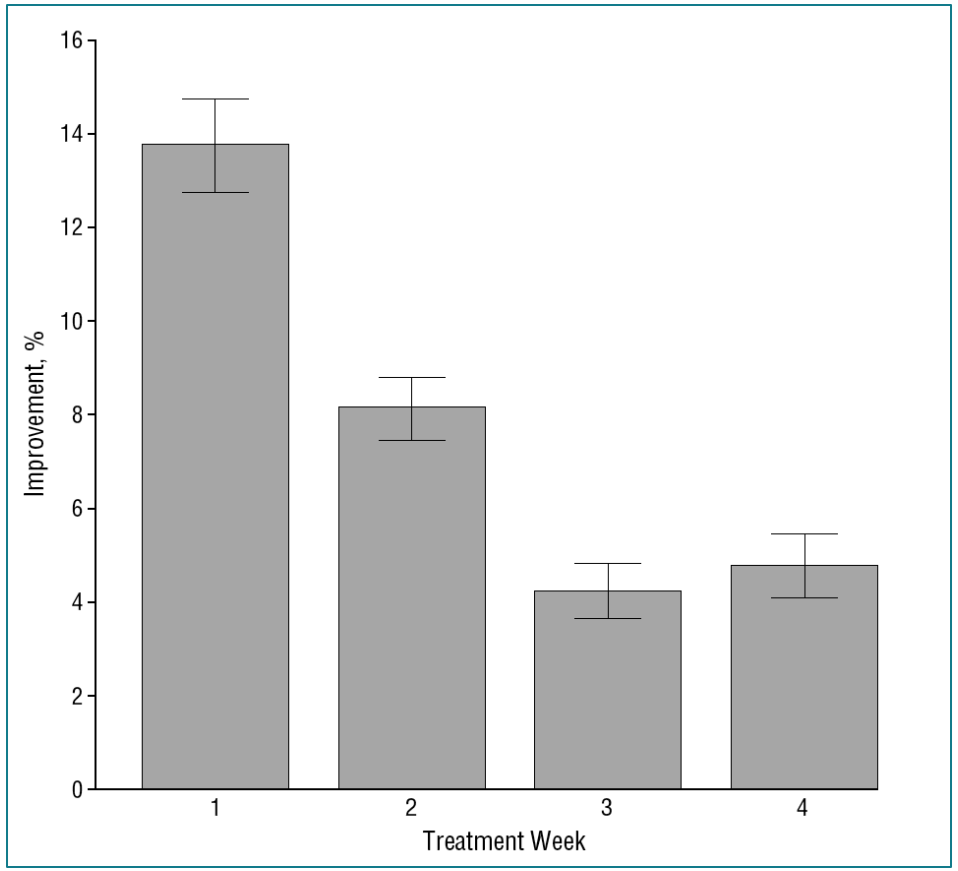
1. **Absence of clinical data:** There are no controlled clinical studies to suggest that xanomeline-trospium (XT) is effective in TRS patients
   - As of January 5, 2026 there is only one published case report of a patient who remained stable for 3.5 months on XT + olanzapine (15 mg) combination therapy after clozapine was stopped 18 months prior for VTE.
2. **The etiology argument:** Xanomeline's mechanism of action involves reduction of presynaptic dopamine release in the same pathway where D2 modulating antipsychotics act
   - Imaging studies of TRS patients do not indicate excessive presynaptic dopamine release/turnover in this striatal pathway (VTA in animal models, dorsomedial substantia nigra->associative striatum in humans)
3. **The ARISE trial adjunctive XT data:** Adjunctive XT did not improve PANSS total scores for patients with baseline scores ≥ 90.
4. **Is there a role for XT in inadequate responders to D2 binding antipsychotics?**
   - **Intolerant patients:** XT is devoid of D2 related movement or endocrine adverse effects (AEs), and lacks metabolic AEs that may limit adherence or preclude use of higher and potentially therapeutic doses of D2 binding agents.
   - **To definitively prove the need for clozapine:** For patients (or prescribers) reluctant to try clozapine, inadequate positive symptom response to max dose XT (monotherapy or combined with D2 blockade) for 2-4 weeks establishes that this form of schizophrenia does not improve with dopamine manipulation and demands a trial of clozapine.

Went NS, et al. Managing treatment-resistant schizophrenia following clozapine cessation: a case report of xanomeline-trospium and olanzapine combination therapy. Front Psychiatry 2025; 16: 1679678. Paul S et al. Am J Psychiatry. 2022;179:611. Brown D, et al. Poster 77 Presented at 2025 Psych Congress Annual Meeting, September 17-21, San Diego.

Using the 2-Week Rule to Assess Antipsychotic Response

1. Older sources state that 6 weeks is an adequate AP trial; however, the concept of delayed AP response in schizophrenia was disproven 23 years ago.[1] **The bulk of AP response occurs in the first 2 weeks.**
2. **Using the 2-week rule: <u>Nonresponse</u>** (i.e. less than minimally evident clinical response) at week 2 argues for a change in treatment direction. In the absence of dose limiting adverse effects, this usually will involve:
   - dose increase ***and***
   - verifying adherence (e.g. through plasma levels), especially if on oral medications and/or not manifesting adverse effects.

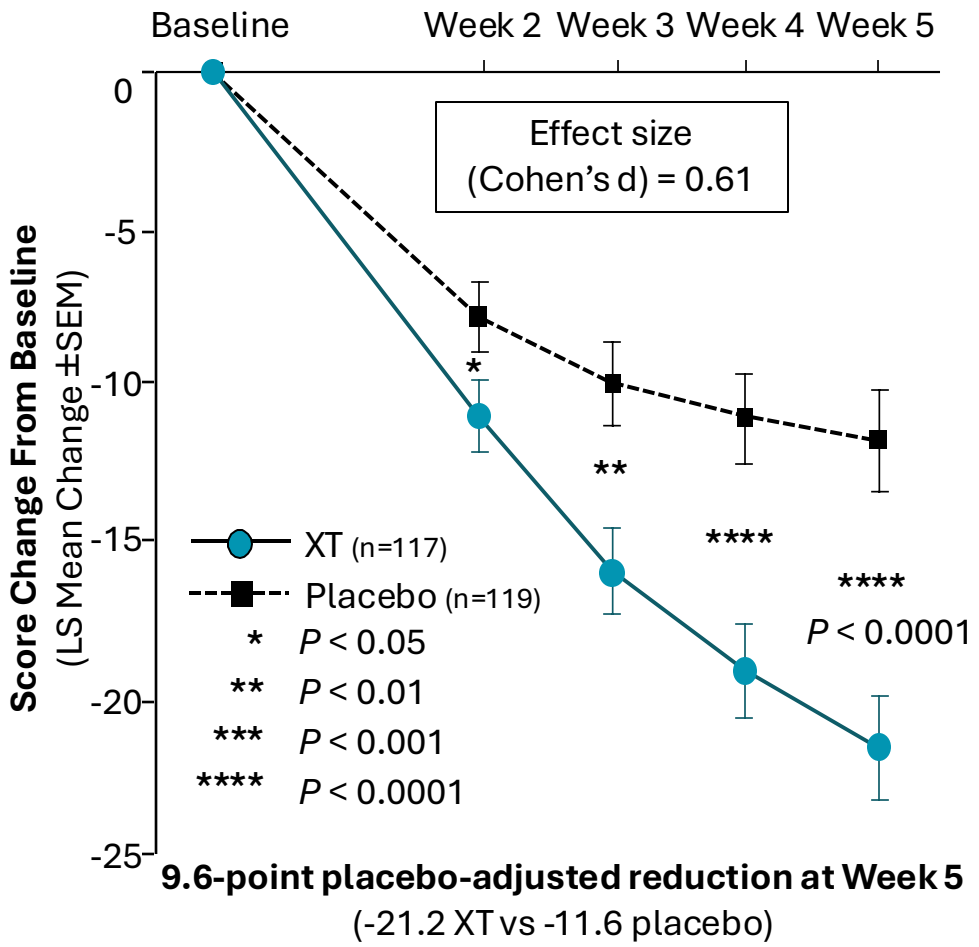
- **For our patient:** Day 5 is too early to tell – the fact that he is already noticeably better bodes well, but time will tell. If no minimal response after 2 weeks, then he is likely to be resistant.



Agid O, et al. Delayed-onset hypothesis of antipsychotic action: a hypothesis tested and rejected. Arch Gen Psychiatry. 2003;60:1228-35. Leucht S, et al. Early-onset hypothesis of antipsychotic drug action: a hypothesis tested, confirmed and extended. Biol Psychiatry. 2005;57:1543-9. Meyer JM, Stahl SM. The Clinical Use of Antipsychotic Plasma Levels (Stahl's Handbooks). Cambridge Univ. Press, 2021. Leucht S, Crippa A, Siafis S, et al. Dose-response meta-analysis of antipsychotic drugs for acute schizophrenia. American Journal of Psychiatry. 2020;177:342-53.

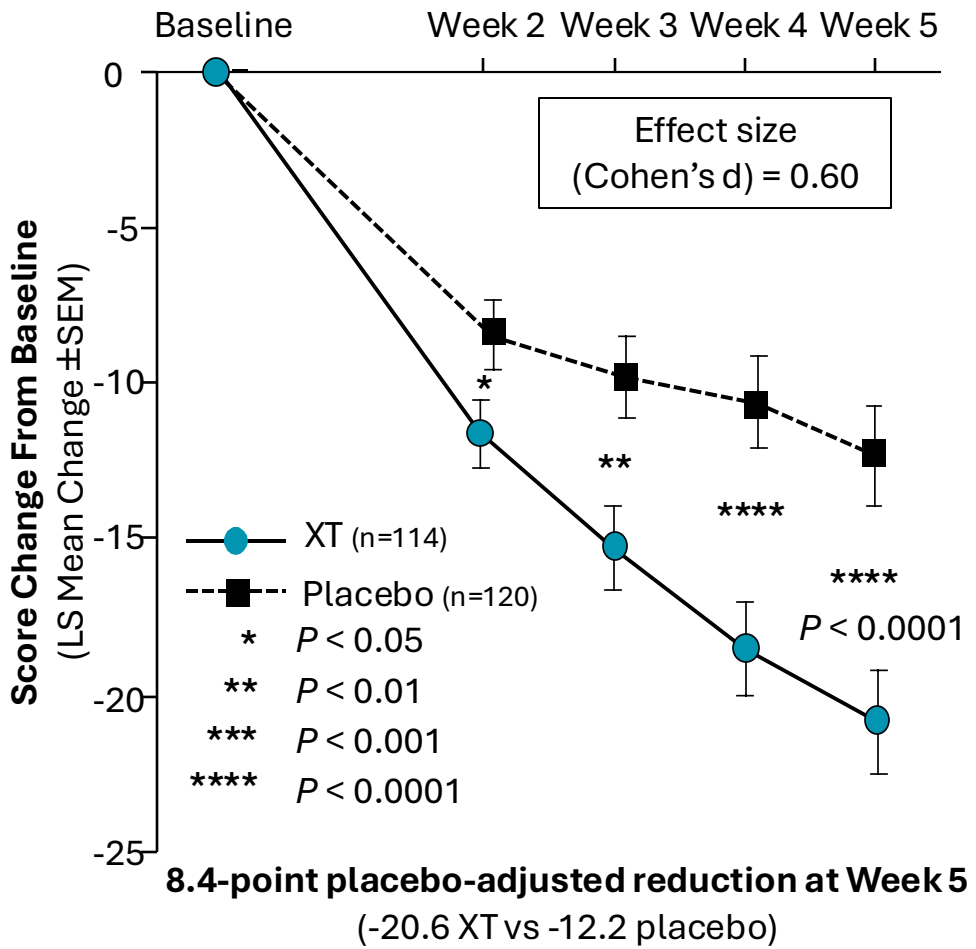
Main Result of EMERGENT Phase 3 Trials

EMERGENT-2[1]



9.6-point placebo-adjusted reduction at Week 5
(-21.2 XT vs -11.6 placebo)

EMERGENT-3[2]

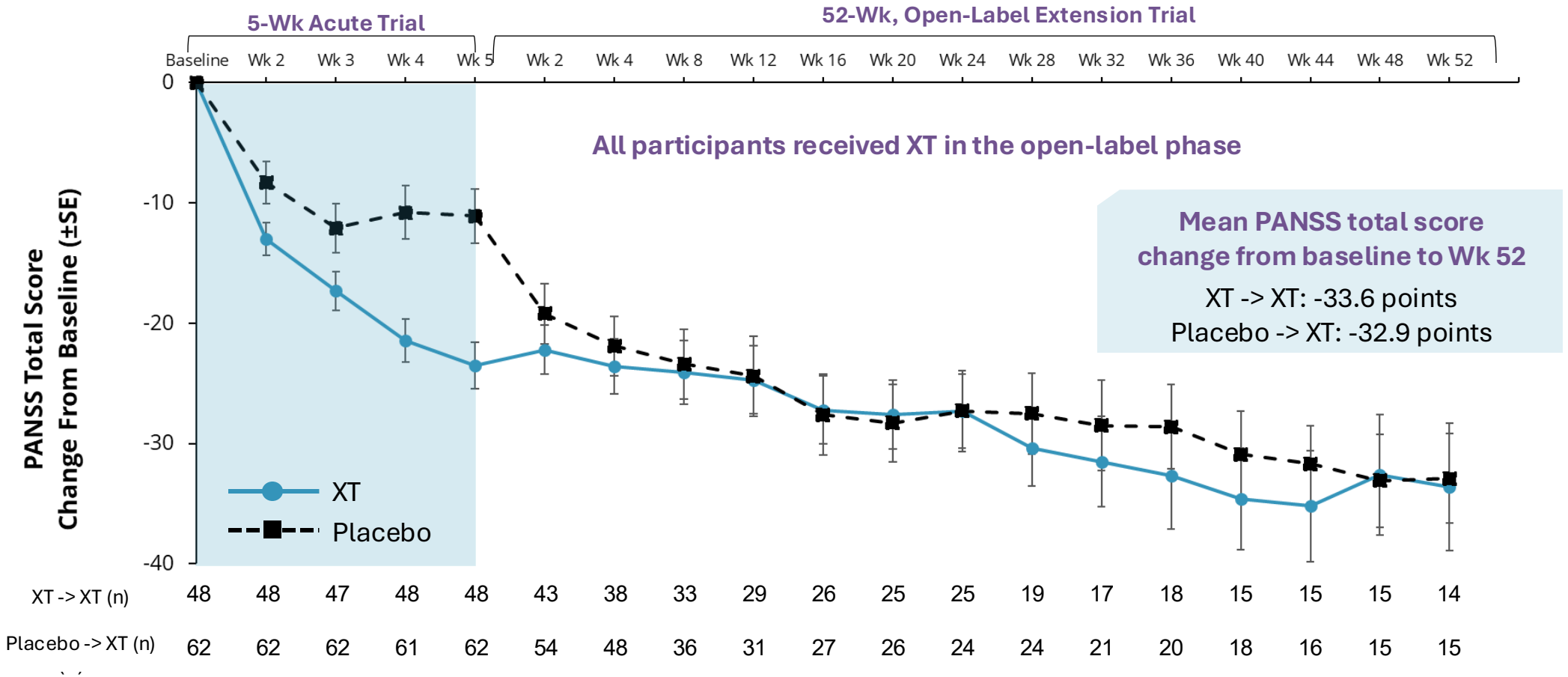


8.4-point placebo-adjusted reduction at Week 5
(-20.6 XT vs -12.2 placebo)

Kaul I, et al. *Lancet*. 2024;403(10422):160-170. Brannan SK, et al. *N Engl J Med*. 2021;384:717-726.

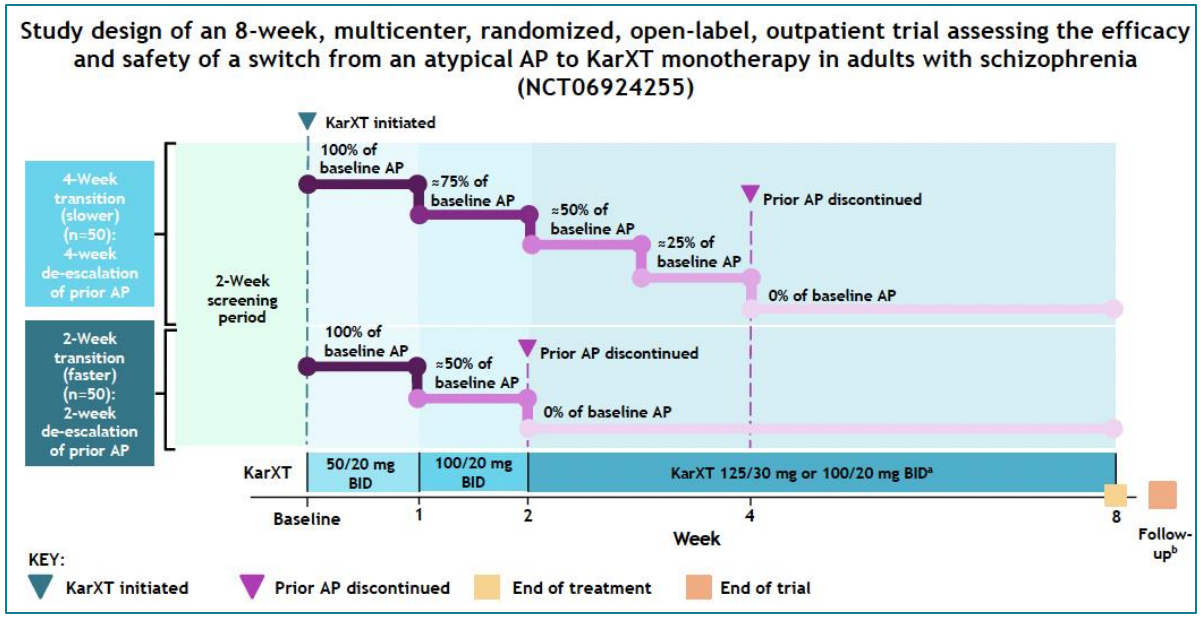
Long-Term Change in PANSS Total Score

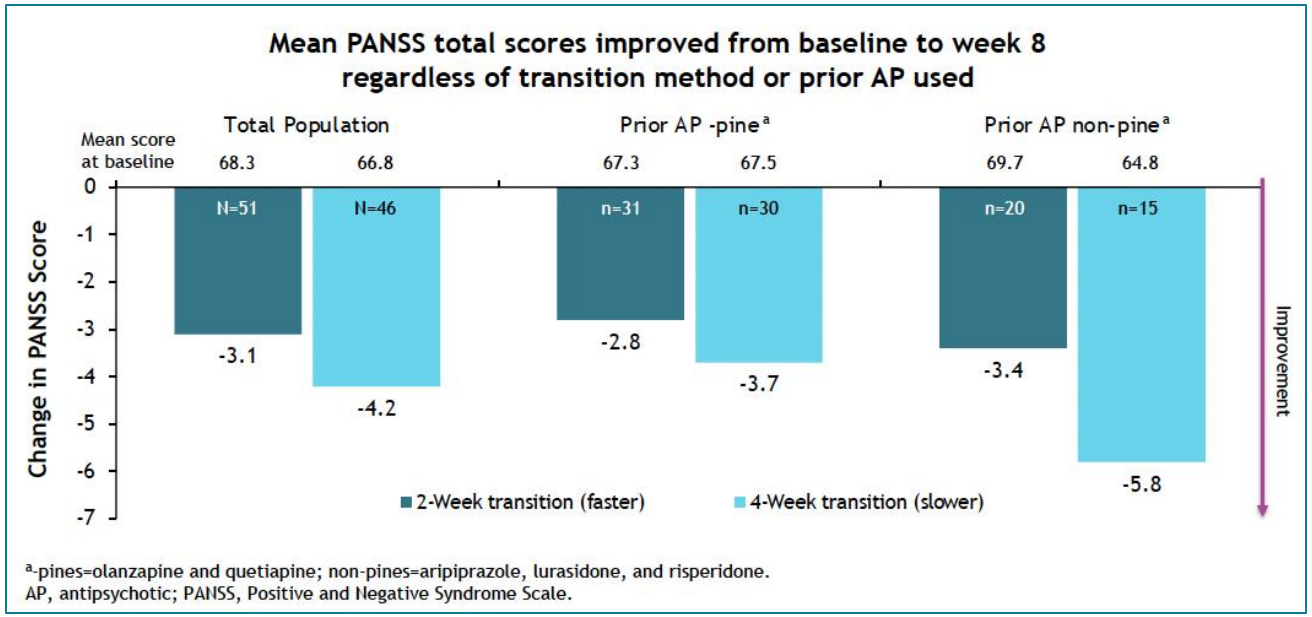
EMERGENT-4: Subjects were rolled over from EMERGENT 1, 2 and 3, *and* retitrated during the first week



Kaul I, et al. Maintenance of efficacy of KarXT (xanomeline and trospium) in schizophrenia. Abstract presented at: Annual Congress of the Schizophrenia International Research Society (SIRS); Florence, Italy; April 3-7, 2024.

Cross-Titration Study: Design and Symptom Outcome





Patients were successfully switched from prior atypical antipsychotics to KarXT using either a 2- or 4-week cross-titration approach, with PANSS symptom improvement observed by Week 8 **regardless of transition speed or prior antipsychotic**

Walling D, et al. SIRS 2026.

Speed of Taper in Cross-Titration Makes a Difference

Comments:

1. Regardless of prior medication (non-pine vs -pine) those patients tapered over 2 weeks had > 2-fold higher rates of moderate AEs
2. For those on –pines, rates of AEs leading to discontinuation strongly favored using a 4 week titration (as opposed to a 2 week titration)

	Overall (N=105)	Total Population		Prior AP -pine[a]		Prior AP non-pine[a]	
		2-Week Transition (faster) (n=52)	4-Week Transition (slower) (n=53)	2-Week Transition (faster) (n=31)	4-Week Transition (slower) (n=35)	2-Week Transition (faster) (n=21)	4-Week Transition (slower) (n=17)
Participants with ≥1 TEAE	51 (48.6)	26 (50.0)	25 (47.2)	14 (45.2)	19 (54.3)	12 (57.1)	6 (35.3)
TEAEs by severity							
Mild	41 (39.0)	19 (36.5)	22 (41.5)	8 (25.8)	17 (48.6)	11 (52.4)	5 (29.4)
Moderate	10 (9.5)	7 (13.5)	3 (5.7)	6 (19.4)	2 (5.7)	1 (4.8)	1 (5.9)
Severe	0	0	0	0	0	0	0
≥1 TEAE leading to study drug discontinuation	3 (2.9)	2 (3.8)	1 (1.9)	2 (6.5)	1 (2.9)	0	0
≥1 TEAE leading to study discontinuation	2 (1.9)	2 (3.8)	0	2 (6.5)	0	0	0
≥1 serious TEAE	0	0	0	0	0	0	0

Walling D, et al. SIRS 2026.

Key Learning Points

- Non-response to treatment in schizophrenia may represent ‘Pseudo-resistance’ and
- TRS positive symptoms are a glutamate issue not a presynaptic dopamine Issue
- Cross titration from SGAs to XT had higher rates of AE’s tapering SGA in 2 weeks. Tapering –Pines may benefit from 4 week taper.

Case #3

Case 3

A 25-year-old female outpatient diagnosed 4 years ago with schizophrenia presents with ongoing breakthrough symptoms, including intermittent paranoia, low motivation, and cognitive slowing, despite prior treatment with multiple antipsychotics.

She has a history of frequent nonadherence and multiple prior treatment discontinuations due to poor tolerability, including weight gain and sedation.

Concerns

- Will she take any oral medication reliably even if it does not have the adverse effects which have been problematic (e.g. sedation, weight gain)?
- If an LAI must be used, what's a good option for a female patient?
- Is there any data on use of XT adjunctively with other antipsychotics?

Applying Motivational Interviewing to Discussions About Meds

Motivational Interviewing-Guided Discussion

- Basic premise of **MOTIVATIONAL INTERVIEWING**: A patient's ambivalence to change is normal and that all patients vary in their readiness to change
- Use open-ended questions and reflective listening
- Remember **RULE**
  - ***Resist*** making too many suggestions
  - ***Understand*** the patient's motivation **(what are their goals)**
  - ***Listen*** with a patient-centered empathic approach
  - ***Empower*** the patient

- **What are your goals (e.g. job, school, relationships, etc.)?**
- What are some of the good things about not taking your medications?
- I can understand that those things would be difficult to deal with
- Are there any not-so-good effects when you don't take your meds?
- Are there any good things about taking your meds?
- How do the not-so-good things compare with the good things about taking your meds?

Kisely S et al. *Australas Psychiatry*. 2012;20(2):138-142. Lewis-Fernández R, Coombs AA, Balán IC, Interian A. Motivational Interviewing: Overcoming Disparities in Pharmacotherapy Engagement. J Clin Psychiatry. 2018;79(3):18ac12150. doi:10.4088/JCP.18ac12150. Haque SF, D'Souza A. Motivational interviewing: The RULES, PACE, and OARS. Curr Psychiatry 2019;18(1):27-8;

Applying Motivational Interviewing to Discussions About Meds

Motivational Interviewing-Guided Discussion

- **What are your goals (e.g. job, school, relationships, etc.)?**
- What are some of the good things about not taking your medications?
- I can understand that those things would be difficult to deal with
- Are there any not-so-good effects when you don't take your meds?
- Are there any good things about taking your meds?
- How do the not-so-good things compare with the good things about taking your meds?

Kisely S et al. *Australas Psychiatry*. 2012;20(2):138-142.

What's An Optimal Initial Antipsychotic Choice For Females Experiencing Their First Episode of Psychosis?

1. **Adverse effects guide initial AP choice in FEP:** Clinical practice guidelines (CPGs) for FEP suggest minimal efficacy differences between APs but marked differences in adverse effects (AEs).
2. **Limitations of current CPGs:** Due to historical under-representation of females in preclinical and clinical trials, existing CPGs are primarily based on studies conducted in predominantly male populations and do not provide sex-specific recommendations. These CPGs remain limited in their ability to account for how females experience side effects and what they consider most important in the decision-making process.
3. **An FEP CPG for Females (March 7, 2026):** Avoiding prolactin-elevation and cardiometabolic AEs were prioritized in AP selection for females. Medicines with higher risks (FGAs, olanzapine, quetiapine, risperidone, paliperidone, and amisulpride) are not recommended first-line.
   - Due to widespread international availability, aripiprazole as recommended as the preferred first-choice due to its consistently favorable prolactin and cardiometabolic profile; **however…**
   - Xanomeline-trospium, lumateperone and cariprazine were discussed and might be incorporated into a future revision, but due to their availability only in the US, were excluded from the current guideline algorithm.

Comment: If this patient needs an LAI, aripiprazole seems appropriate. Is there any value for an adjunctive muscarinic agonist in the event of inadequate positive symptom response?

AP = antipsychotic; FEP = first episode of psychosis

Hynes-Ryan C, Keating D, Carolan A, et al. Clinical practice guideline on the choice of first antipsychotic medicine for females experiencing a first-episode of psychosis. Schizophr Bull. 2026;52.

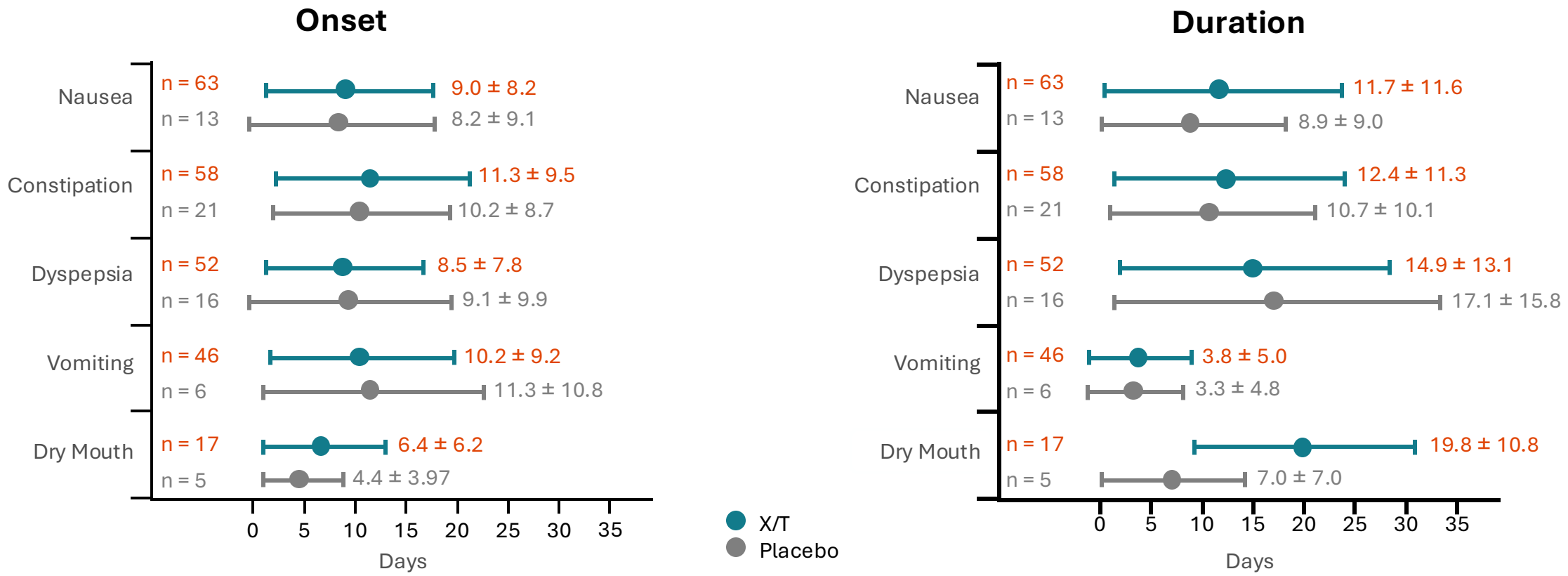
Xanomeline/Trospium: How to Initiate

- **Titration PI allows a slower titration and lower maximum dosage**
  - Starting dosage: 50 mg/20 mg PO BID for ≥ 2 days (can be longer, but not forever)
  - Increase to 100 mg/20 mg PO BID for ≥ 5 days (**NB:** the xanomeline dose has doubled, but not the trospium dose)
  - Can be increased to 125 mg/20 mg PO BID based on patient tolerability/response (**NB:** this dose increases xanomeline exposure by only 25% ***but doubles the trospium exposure***)
- **Food issue: Exposure to trospium is decreased 85% to 90% if taken with food**
  - Must take XT 1 hr before or 2 hr after a meal. Practical strategy: dose upon awakening or 1 hr before breakfast and then in the evening ≥ 2 hours after dinner. **Note: do not give with food to treat nausea.**
  - **Nausea/vomiting:** If it occurs, may be transient. Nonetheless, consider prophylactic use of ondansetron. If ondansetron is not sufficient (e.g. 8 mg BID), *and the patient is taking XT correctly without food,* may consider extra trospium 20 mg PO qam if on ≤ 100 mg/20 mg BID.
- **Anticholinergic adverse reactions:** Note use of other anticholinergics (e.g., overactive bladder meds) when initiating; ask about LUTS in males when starting; max dose for geriatric patients is 100 mg/20 mg; contraindications urinary/gastric retention
  - Practical strategy: Use slower titration while tapering off other anticholinergics, ask about urinary symptoms

COBENFY™ (xanomeline and trospium chloride) capsules [prescribing information]. Princeton, NJ: Bristol-Myers Squibb Company; 2026

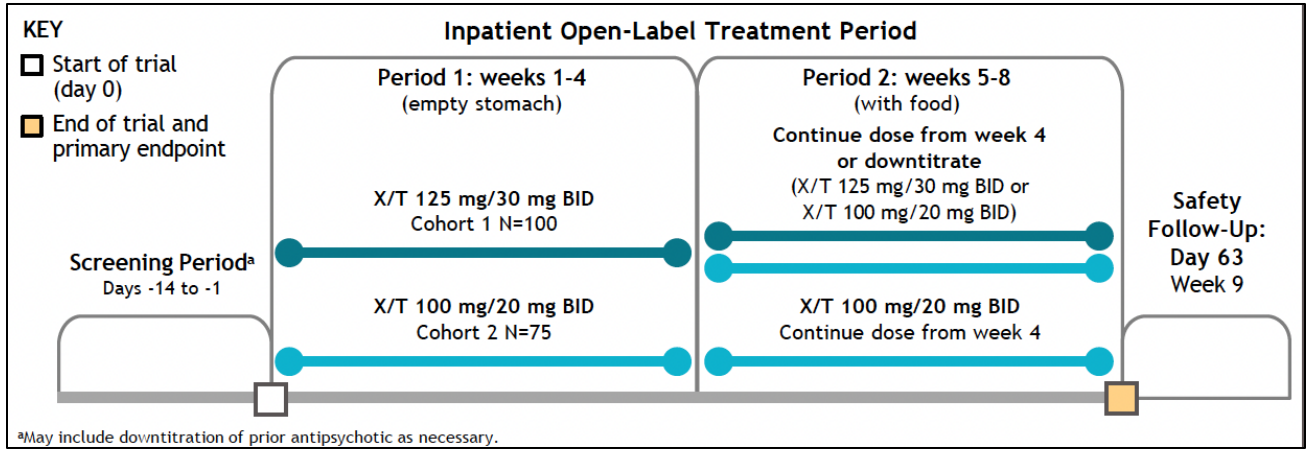
EMERGENT Trials:
Onset and Duration of Pro- or Anticholinergic AEs

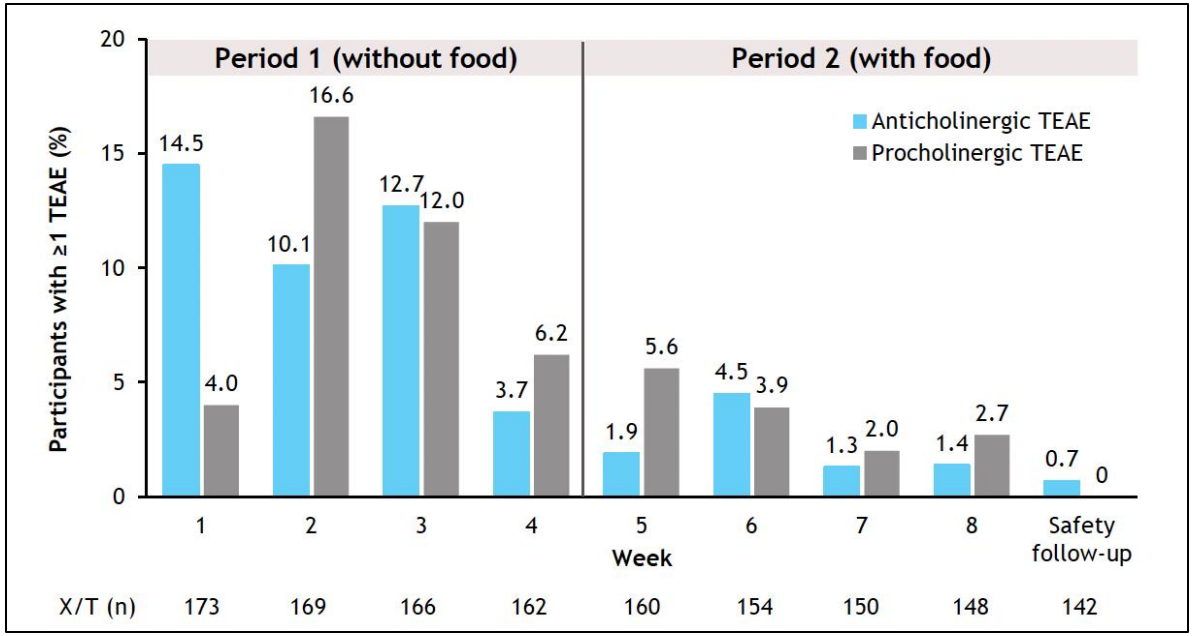
Pooled EMERGENT-1, EMERGENT-2, and EMERGENT-3



Kaul. J Clin Psychiatry. 2025;86:24m15497.

Patients in Stable Therapeutic XT Doses for ≥ 4 Weeks Might Be Able to Take It With Food

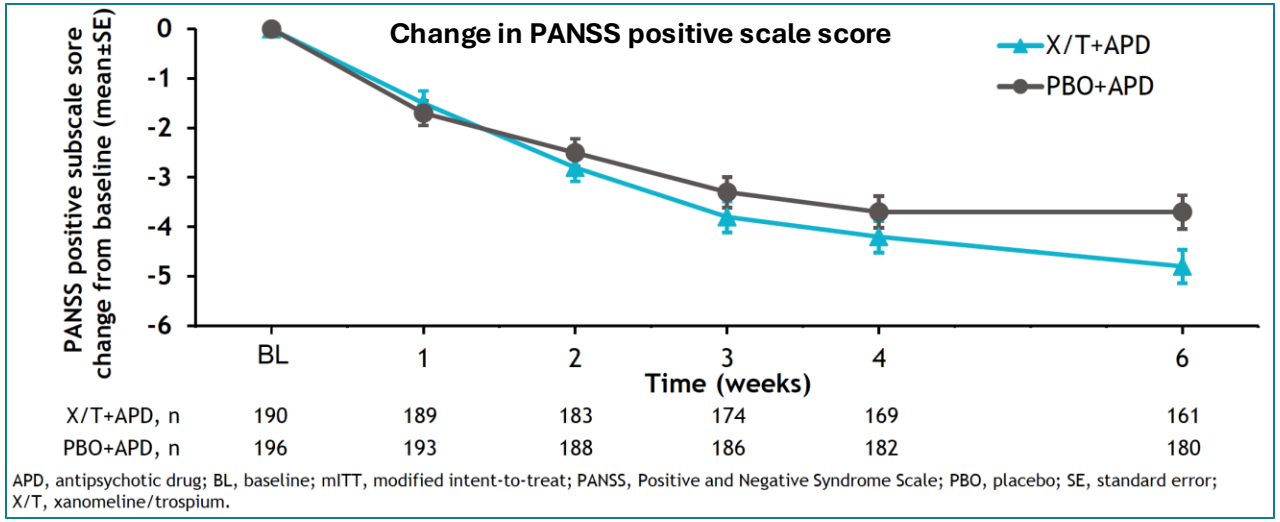




After 4 weeks of stabilization on XT, switching from fasting administration to dosing with food did not increase cholinergic or anticholinergic adverse events,
suggesting that taking XT with food may be a tolerable option for some stable patients

Hoogerheyde J, et al. Psych Congress 2025.

What Can We Learn From the ARISE: Adjunctive Trial Findings?



APD, antipsychotic drug; BL, baseline; mITT, modified intent-to-treat; PANSS, Positive and Negative Syndrome Scale; PBO, placebo; SE, standard error; X/T, xanomeline/trospium.

	X/T+APD LSM±SE	PBO+APD LSM±SE	LSM Difference (95% CI)
Overall	-14.3±1.01	-12.2±0.98	-2.0 (-4.5 to 0.5)
Aripiprazole (36.2%)	-14.8±1.5	-11.2±1.5	-3.6 (-7.2 to 0.0)
Risperidone (32.9%)	-11.3±1.9	-12.3±1.7	1.1 (-3.7 to 5.9)
Paliperidone (18.4%)	-15.2±2.3	-12.1±2.0	-3.1 (-8.7 to 2.8)
Others (11.0%)	-11.7±4.0	-7.1±4.6	-4.6 (-13.7 to 4.5)

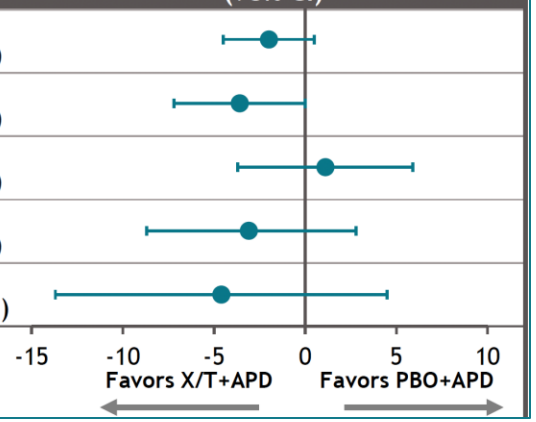
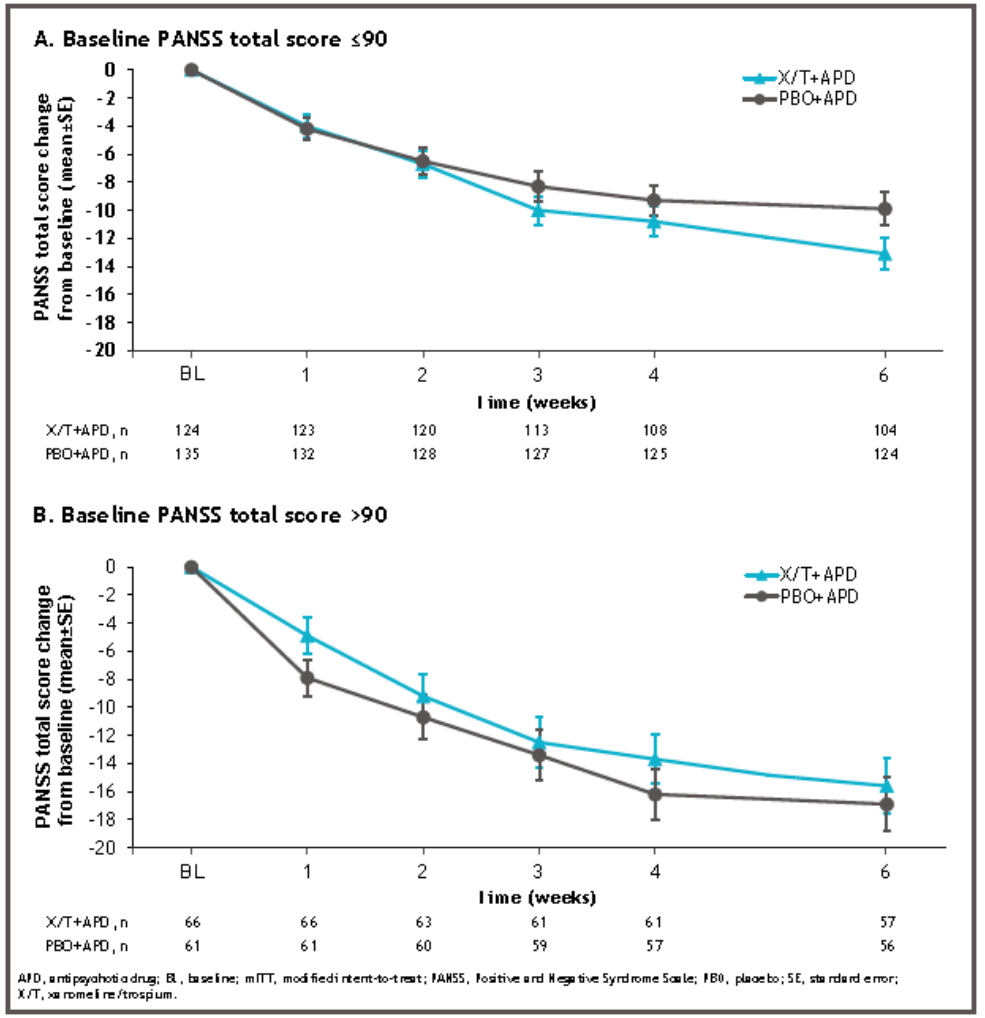


Figure 4. Post hoc change from baseline in PANSS total score by baseline PANSS total score ≤90 vs >90 criteria (mITT population)



APD, antipsychotic drug; BL, baseline; mITT, modified intent-to-treat; PANSS, Positive and Negative Syndrome Scale; PBO, placebo; SE, standard error; X/T, xanomeline/trospium.

Brown D, et al. Poster 77 Presented at 2025 Psychiatric Congress Annual Meeting, September 17-21, San Diego.

Key Learning Points

- Initial assessment must extend beyond psychiatric symptoms to include the patient's treatment goals and preferences, substance use, trauma, physical health, psychosocial functioning, and suicide/violence risk—as these factors profoundly impact treatment selection, adherence, and long-term outcomes
- N/V with XT is typically early-onset and self-limiting, resolving with continued treatment rather than requiring dose reduction.
- Standard titration to therapeutic doses (100/20 mg or 125/30 mg) is well-tolerated with discontinuation rates similar to placebo.
- XT should be taken at least 1 hour before or 2 hours after a meal because food reduces trospium exposure by 85–90%
- Food timing does not significantly impact N/V, though it may affect overall tolerability

Case #4

Case 4

A 35-year-old male patient with schizophrenia is stable on treatment with risperidone 5 mg qhs and benztropine 1 mg PO BID after failing aripiprazole and cariprazine.

He has good control of positive symptoms and no recent hospitalizations. He lives with his parents, who help manage his care and daily needs because he continues to complain of cognitive impairment and low motivation that limit progress toward full independence.

His initial goal is to start a volunteer job at the local animal shelter and hopefully have more social interaction because of this.

Concerns

- Can any antipsychotic improve his cognition?
- Why would any human being be on benztropine chronically in 2026? How to taper it off?

Tapering Anticholinergics Is Possible: Data from 1999-Present

1. **Ungvari (1999):** Among 28 schizophrenia patients on FGAs, **90.5%** were able to gradually taper off trihexyphenidyl 1 mg/2 wks over **2-6 months**
2. **Mori (2002):** Among 21 inpatients on FGA or SGA, **66.7%** were able to gradually taper off anticholinergics over **4 weeks**
3. **Drimer (2004):** Among 27 inpatients over age 60, **100%** were able to gradually taper off biperiden over **3 days**
4. **Ogino (2011):** Among 24 Japanese outpatients on SGAs, **96%** were able to gradually taper off biperiden (mean dose 2.2 ± 0.8 mg/d) at the rate of **1 mg every 2-4 weeks. The benefits of discontinuation were seen as:**
   - Significant improvement in: attention, processing speed, and composite cognitive score
   - Significant improvement in: quality of life (using the Schizophrenia Quality of Life Scale), and in the general psychopathology score on the PANSS
5. **Desmarais (2014):** 20 outpatients in Montréal were gradually tapered off over 4 weeks (mean dose 7.3 mg/d benztropine equivalent) as follows: wk 1: 75%; wk 2% 50%; wk 3: 25%; wk 4: 12.5%. **90% were able to successfully complete the taper.**

Desmarais JE, et al. Anticholinergics in the era of atypical antipsychotics: short-term or long-term treatment? J Psychopharmacol 2012;26:1167-74. Ogino S, et al. Effects of discontinuation of long-term biperiden use on cognitive function and quality of life in schizophrenia. Prog Neuro psychopharmacol Biol Psychiatry 2011;35:78-83. Desmarais JE, et al. Effects of discontinuing anticholinergic treatment on movement disorders, cognition and psychopathology in patients with schizophrenia. Ther Adv Psychopharmacol 2014; 4(6) 257–267.

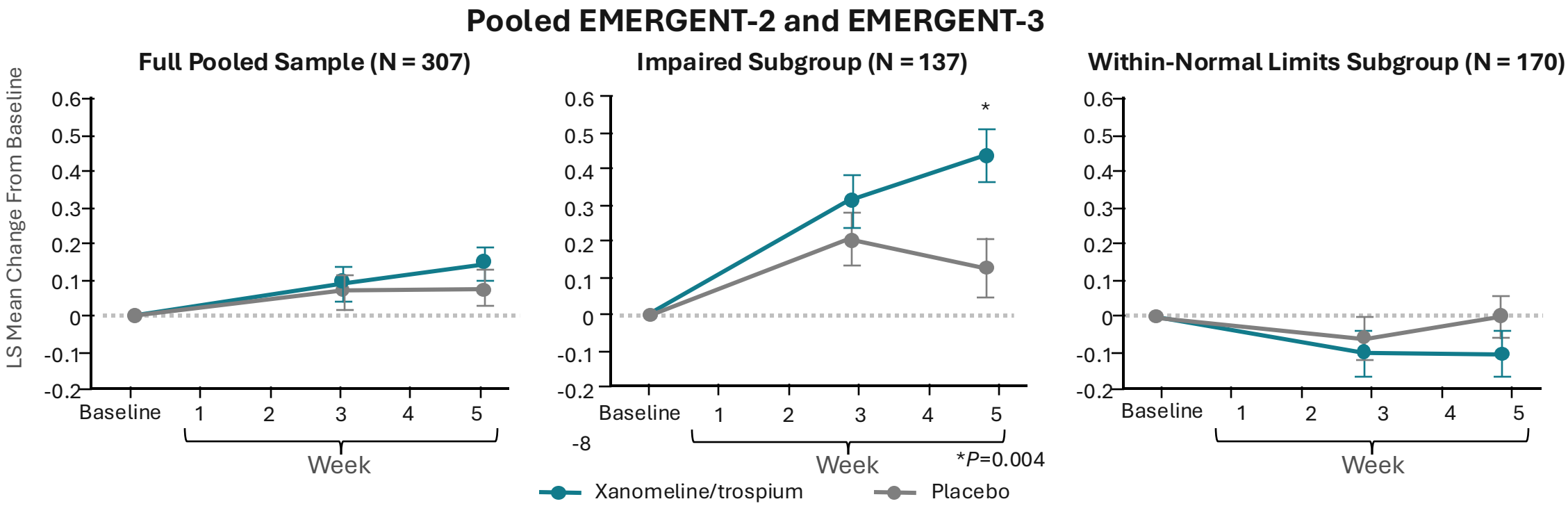
What is a Reasonable Tapering Schedule?

Equivalence: 1 mg benztropine = 2.5 mg trihexyphenidyl = 25 mg diphenhydramine

- **Titration:** 0.5 mg benztropine (or the equivalent) per week. If rebound symptoms develop (vivid dreams/nightmares) then the titration should be slowed to 0.5 mg every 2 weeks.
- **If parkinsonism** develops, consider a cross-taper to amantadine.
  - In a double-blind cross-over study, 26 schizophrenia inpatients were placed on 2 weeks each of amantadine (200 mg/day) or biperiden (4 mg/day). Biperiden treatment was associated with significantly lower scores on multiple memory and attention scales.

Van Putten T, Gelenberg AJ, Lavori PW, et al. Anticholinergic effects on memory: benztropine vs. amantadine. Psychopharmacol Bull 1987;23:26-9.
Silver H, Geraisy N. Effects of biperiden and amantadine on memory in medicated chronic schizophrenic patients. A Double-blind cross-over study. Br J Psychiatry 1995;166:241-3.

EMERGENT Trials: CANTAB by Cognitive Subgroup



- Xanomeline/trospium demonstrates significant cognitive improvement in the impaired subgroup (p=0.004) with increasing benefits through week 5, while showing minimal effect in the full sample and no benefit in cognitively normal patients
- Treatment effect is most pronounced in patients with baseline cognitive impairment, suggesting targeted efficacy for addressing cognitive symptoms in schizophrenia

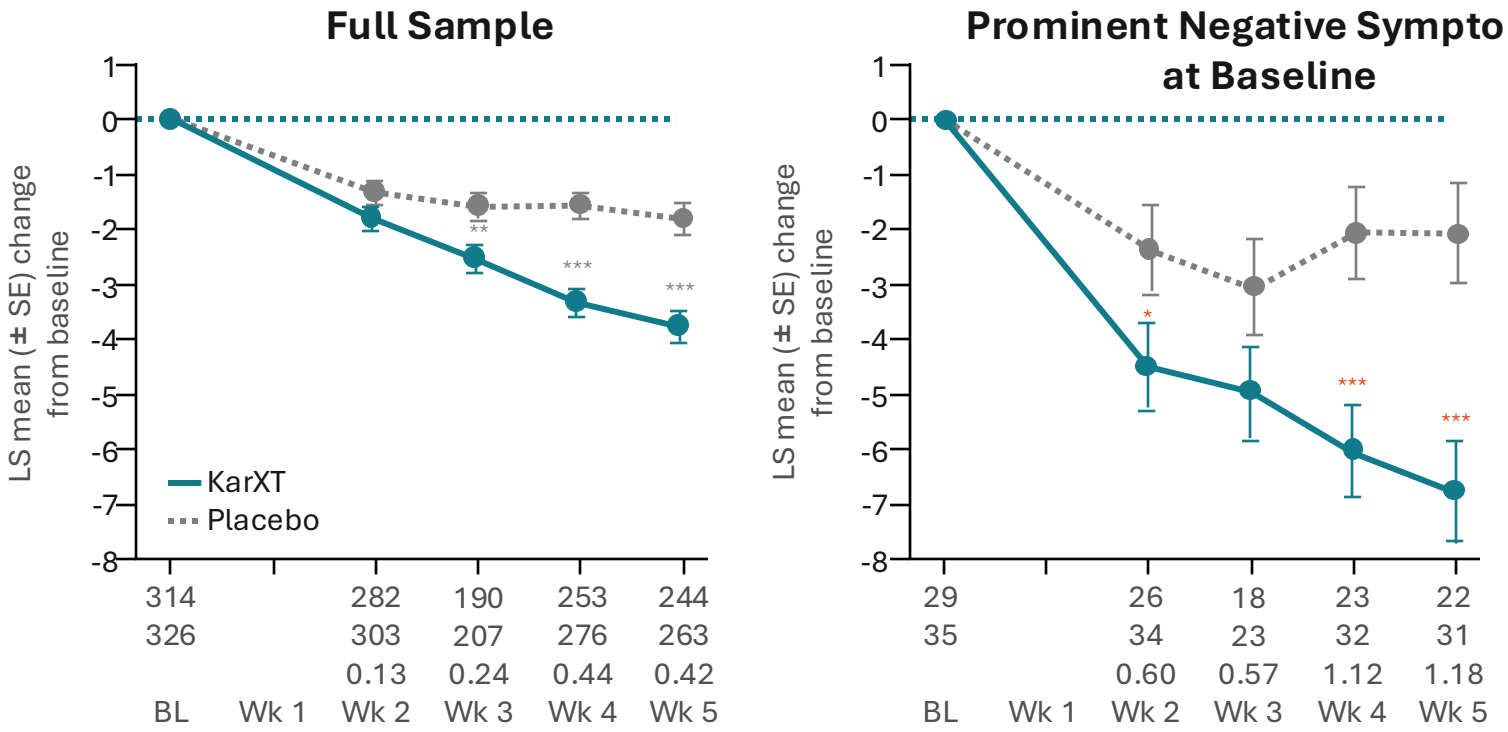
Horan. Am J Psychiatry. 2025;182(3):297-306.

EMERGENT- 1-3: Impact of Baseline Negative Impairment on Improvement in Marder Negative Symptom Factor

Those with prominent negative symptoms at baseline were defined by:

- Score ≥ 24 on Marder Negative Factor Score: blunted affect (N1), emotional withdrawal (N2), poor rapport (N3), passive/apathetic social withdrawal (N4), lack of spontaneity (N6), motor retardation (G7), and active social avoidance (G16).
- Score ≥ 4 on at least 2 of the following PANSS core negative symptom items: blunted affect (N1), passive/apathetic social withdrawal (N4), or lack of spontaneity and flow of conversation (N6).
- While meeting PANSS total entry criteria, scored ≤ 19 PANSS Mohr positive Sx subscore: delusions (P1), hallucinatory behavior (P3), grandiosity (P5), suspiciousness/persecution (P6), and unusual thought content (G9). This is to help define a subgroup without prominent positive symptoms.

Horan. Schizophr Res 2024; 274:57.



Analysis intended to separate out a specific negative symptom effect that was not pseudospecific, meaning it was related to total symptom improvement.

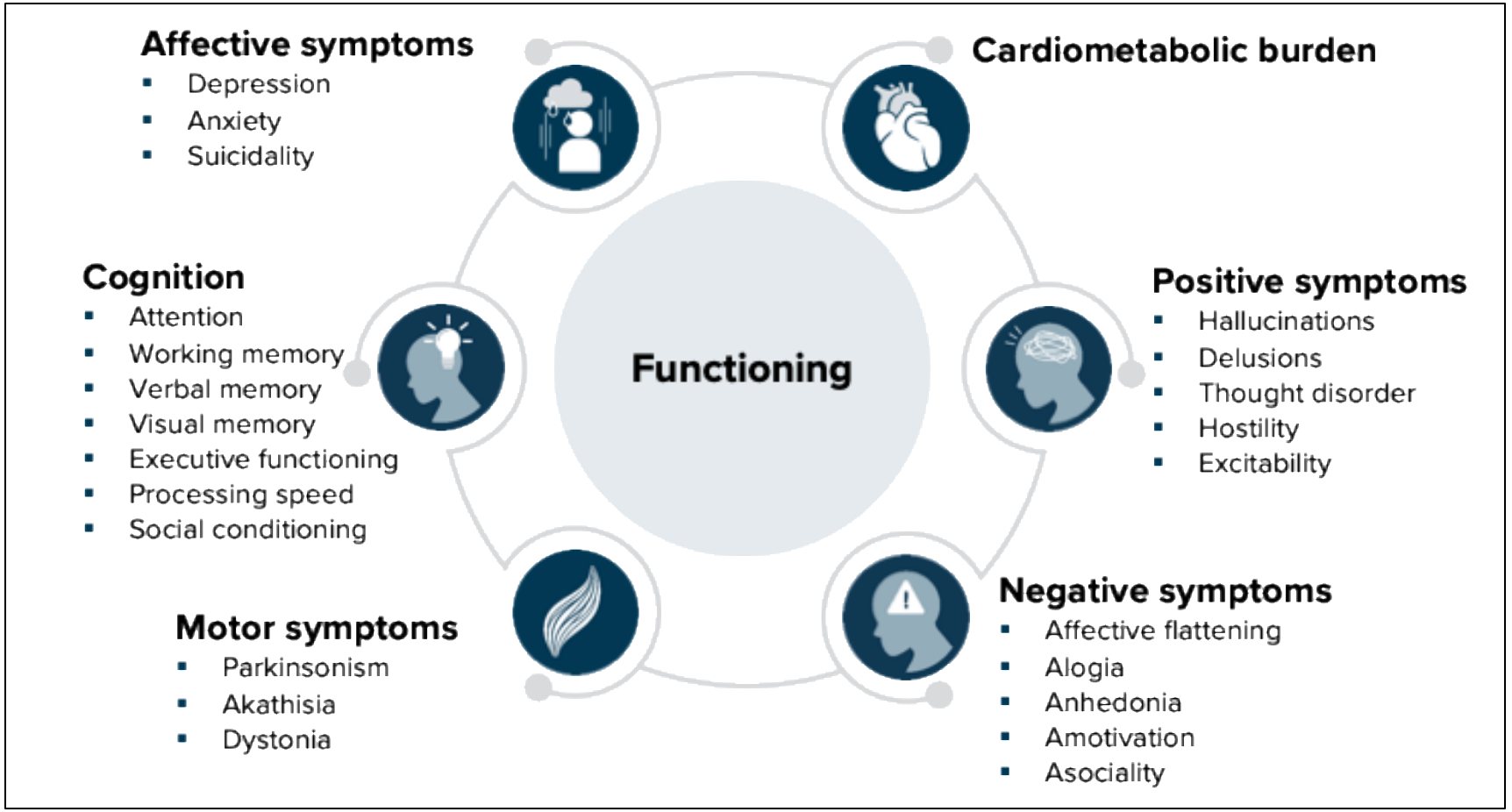
- Full sample neg Sx effect size: **Cohen's d 0.42**
- Prominent neg Sx subgroup effect size: **Cohen's d 1.18**

Key Learning Points

- Tapering and discontinuation of anticholinergics may improve cognition, quality of life and improvements on general psychopathology.
- Xanomeline/trospium demonstrates significant cognitive improvement **in patients with schizophrenia with baseline cognitive impairment**, but not in patients without baseline cognitive impairment
- Concurrent anticholinergic use with XT requires monitoring for additive effects, but is not contraindicated

Practical Strategies to Optimize Schizophrenia Treatment

There Are Many Clinical Domains of Schizophrenia: Which Of These Bother the Patient?



Carbon M, et al. CNS Spectr. 2014;19 Suppl 1:38-52; Millan MJ, et al. Eur Neuropsychopharmacol. 2014;24:645-692; Morrens M, et al. Front Psychiatry. 2014;5:145; Millan MJ, et al. Nat Rev Drug Discov. 2012;11:141-168; Ventriglio A, et al. Front Psychiatry. 2016;7:116.

Assess Antipsychotic Drug Side Effects

Table 1. Potential side effects of antipsychotics addressed by questions in the SMARTS checklist.

SMARTS checklist questions (Are you troubled by...)	Potential side effect addressed
1. Difficulties in your movement such as shaking, stiffness or muscle aches?	Parkinsonism, tremor
2. Changes in your weight or appetite?	Weight and appetite change
3. Problems with your sex life?	Sexual dysfunction (may reflect raised prolactin and/or other pharmacological mechanisms)
4. Changes in your periods or changes in your breasts?	Hyperprolactinaemia
5. Dizziness or light-headedness?	Postural hypotension
6. Tiredness or sleepiness?	Sedation
7. Restlessness or feeling fidgety?	Akathisia
8. Constipation, diarrhoea, nausea, stomach problems or dry mouth?	Gastrointestinal side effects (e.g. antimuscarinic side effects)
9. Difficulty passing water or passing water very frequently?	Urinary symptoms (e.g. antimuscarinic action may cause urinary retention; type 2 diabetes may cause polyuria)
10. Problems with your concentration or memory?	Sedation
11. Feeling anxious or depressed?	Affective side effects
12. Any other problems that you think may be related to your medication? Please state	Miscellaneous side effects

Haddad PM et al. Ther Adv Psychopharmacol 2014; 4(1)15-21.

Xanomeline/Trospium: Thoughts on Initiation

First episode patients:

- Obvious advantages if the patient can be adherent with oral medication.
- Access may be a problem without prior AP trials

Cross-tapering: primarily an issue if the current antipsychotic is anticholinergic (e.g., olanzapine, quetiapine)

- Practical strategy for olanzapine/quetiapine: cross-taper slowly over first month as X/T is titrated.
  - If patient is on higher doses of quetiapine (e.g., > 300 mg QHS), may need 2 mo or longer to completely taper off
- Practical strategy for other APs (egg, aripiprazole, risperidone/paliperidone, cariprazine.): There are no pharmacodynamic interactions with APs that are not anticholinergic; may decide to taper the primary AP after X/T has reached the maximum tolerated dose

Combination: if patient is on oral or LAI and has inadequate response to current AP

- Evidence: Preclinical data suggest synergistic activity with postsynaptic D2 receptor modulating APs. The adjunctive study (ARISE) did not show benefit for APs other than aripiprazole and only for those who are not markedly ill

Xanomeline and trospium chloride PI. Brown. 2025 Psychiatric Congress Annual Meeting. Poster 77.

Xanomeline/Trospium: Drug–Drug Interactions and Monitoring

Monitoring LFTs: Rate of ALT/AST elevation >3x ULN was 2.8% for X/T vs 0.4% for placebo; 1.6% had elevated LFTs at some point, but most occurred within 1 mo and resolved with continued treatment

- Practical strategy: Obtain baseline LFTs (egg, bilirubin) and “as clinically indicated during treatment”; in the absence of clinical symptoms, consider repeating LFTs after 1 mo to document lack of effect

Monitoring HR: In 2 placebo-controlled studies, the endpoint difference from placebo was +5.9 beats/min; in a dedicated ambulatory study, the difference was +9.8 beats/min

- Practical strategy: Monitor at baseline and periodically during treatment (as is often done when starting clozapine)

Drug interactions: CYP2D6 contributes to xanomeline metabolism, but PI does not recommend dose adjustment; instead, monitor for adverse reactions

- Practical strategy: Consider a slower initial titration and lower maximal dose

Hepatic and renal dysfunction: Contraindicated in Child-Pugh B/C; patients with Child-Pugh A/B have higher xanomeline exposure

- Practical strategy: Consider a slower initial titration and lower maximal dose

COBENFY™ (xanomeline and trospium chloride) capsules [prescribing information]. Princeton, NJ: Bristol-Myers Squibb Company; 2026

Other Investigational Muscarinic Agents

	Mechanism	Development Stage
NMRA-266	M_4 PAM	Placed on clinical hold by FDA 4/2024 due to pre-clinical data showing convulsions in rabbits
NMRA-861	M_4 PAM	Phase 1 initiated 7/2025, explicitly noted no rabbit convulsions in preclinical work
NBI-1117569	M_4 Preferring Agonist	Phase 1 data expected this year
NBI-1117570	M_4/M_1 Agonist	Phase 1 data and Phase 2 initiation
NBI-1117567	M_1 Preferring Agonist	Phase 1 data
Emraclidine	M_4 PAM	Phase 2 – trial enrolling

Other investigational muscarinic activators — both full agonists and PAMs — will explore a spectrum of M_4 and M_1 receptor activation in schizophrenia and various other neuropsychiatric disorders

PAC = peripherally-acting anticholinergic; PAM = positive allosteric modulators.

Tobin AB. *Nat Rev Drug Discov*. 2024;23(10):743-758. Neumora™. Accessed August 20, 2025. https://ir.neumoratx.com/news-releases/news-release-details/neumora-therapeutics-announces-initiation-phase-1-clinical-study. MapLight. Accessed August 20, 2025. https://maplightrx.com/maplight-therapeutics-announces-results-from-phase-1-trial. Neurocrine Biosciences®. Accessed August 20, 2025. https://www.neurocrine.com/documents/101/NBIX_Q2_2025_Earnings_Presentation_07.30.25_Final.pdf.

Potential Other Indications for Muscarinic Agents

Indication	Development
Alzheimer’s Psychosis	Recruiting
Bipolar Mania	Recruiting
Autism Irritability	Recruiting
Schizophrenia in Adolescents	Recruiting
Alzheimer’s Agitation	Recruiting
Cognitive Impairment In Alzheimer's	Recruiting
Cognitive Impairment In Schizophrenia	Recruiting

Source: ClinicalTrials.Gov

Practical Take-Aways

- Muscarinics are perhaps one of the greatest advances in decades in the treatment of schizophrenia. The myth about its efficacy can be laid to rest based on high-quality, multiple, double-blind studies
- The impact of muscarinics is not limited to positive symptoms, negative symptoms, cognitive symptoms, or general psychopathology. Data shows it impacts all domains of the disorder.
- Transient cholinergic side effects with Xanomeline Trospium are driven by dose rather than titration speed, and standard titration—including use with concomitant anticholinergics—is both effective and well-tolerated
- Treatment planning using motivational interviewing and shared decision making to include consideration on treatment options to best match patients needs on adherence, side effects, and preferences for treatment.