Muscarinic Myth Busters:

Addressing Misconceptions of Muscarinic Receptor Activation in Schizophrenia

MasterClass

Supported by an educational grant from Bristol-Myers-Squibb.

Faculty

Brooke Kempf, PMHNP-BC

Adjunct Faculty
Indiana University Indianapolis
Indianapolis, IN

Greg Mattingly, MD

Associate Clinical Professor,
Washington University
CEO, Midwest Research Group
Past-President, APSARD
St. Louis, MO

Faculty Disclosures

Brooke Kempf, PMHNP-BC: Advisory Board— Alkermes, Axsome, BMS, Indivior, Intracellular, Johnson and Johnson, Janssen, Neurocrine, Otsuka, Takeda, Teva; Speakers Bureau— AbbVie, Alkermes, Axsome, BMS, Intracellular, Johnson and Johnson, Janssen, Luye, Otsuka, Sage, Takeda, Teva

Greg Mattingly, MD: Consultant – AbbVie, Acadia, Akilli, Alkermes, Angelini, Axsome, Biogen, BMS, Boehringer Ingelheim, Cerevel, Colegium, Corium, Eisai, Intracellular, Johnson & Johnson, Liva Nova, Lumos Labs, Lundbeck, Neurocrine, Noven, Otsuka, Redax, Relmada, Revibe, Roche, Sage, Sirona, Sunovion, Supernus, Takeda, Teva, Tris Pharma; Research – AbbVie, Acadia, Alkermes, Akilli, Alto Therapeutics, Avanir, Axsome, BMS, Boehringer Ingelheim, Cingulate, Click Therapeutics, Corium, Emalex, Idorsia, Intracellular, Johnson & Johnson, Lumos Labs, Medgenics, Neurocrine, NLS Pharma, Redax, Relmada, Roche, Sage, Sirtsei, Sumitomo, Sunovion, Supernus, Takeda, Teva; Speakers Bureau – AbbVie, Alkermes, Angelini, Axsome, BMS, Corium, Intracellular, Ironshore, Johnson & Johnson, Lundbeck, Neurocrine, Noven, Otsuka, Sunovion, Supernus, Takeda, Teva, Tris Pharma

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

- This CME activity includes brand names for participant clarity purposes only. No product promotion or recommendation should be inferred

Learning Objectives

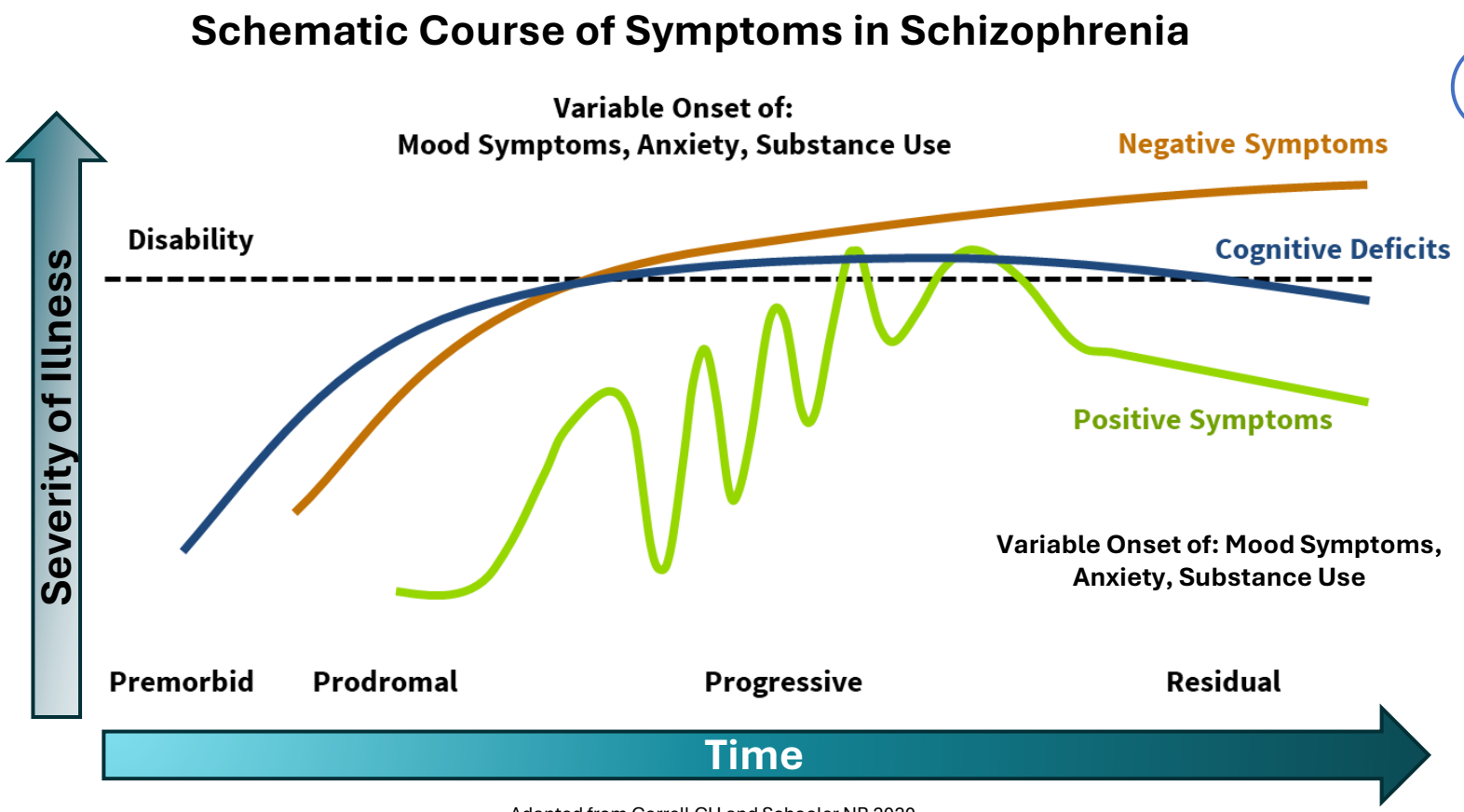
- Assess common myths regarding the role of dopamine receptor (D2) antagonism and partial agonism versus muscarinic receptor (M1/M4) activation in the treatment of schizophrenia.

- Evaluate the latest clinical efficacy, tolerability, and safety data associated with novel/investigational muscarinic receptor (M1/M4) activators the treatment of schizophrenia.

- Implement patient-centered strategies for optimal utilization of muscarinic receptor activators in the treatment of schizophrenia.

Schizophrenia:
A Brief Overview

Course of Schizophrenia Symptoms Over Time

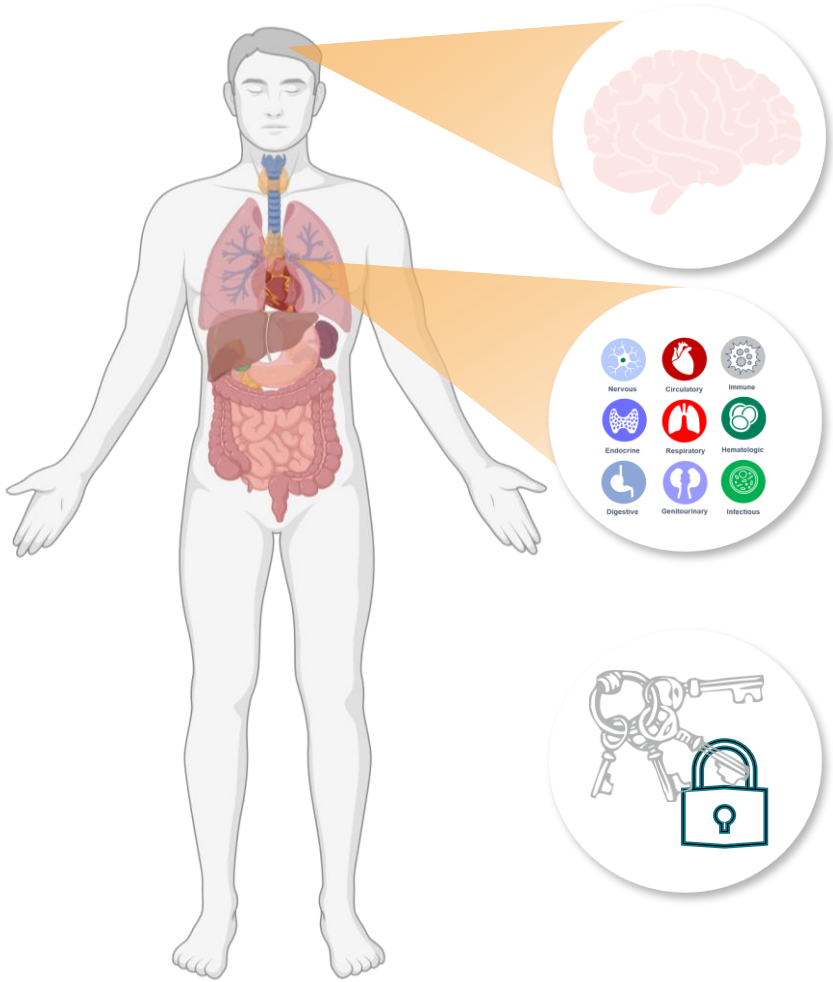


Adapted from Correll CU and Schooler NR 2020.

- 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 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

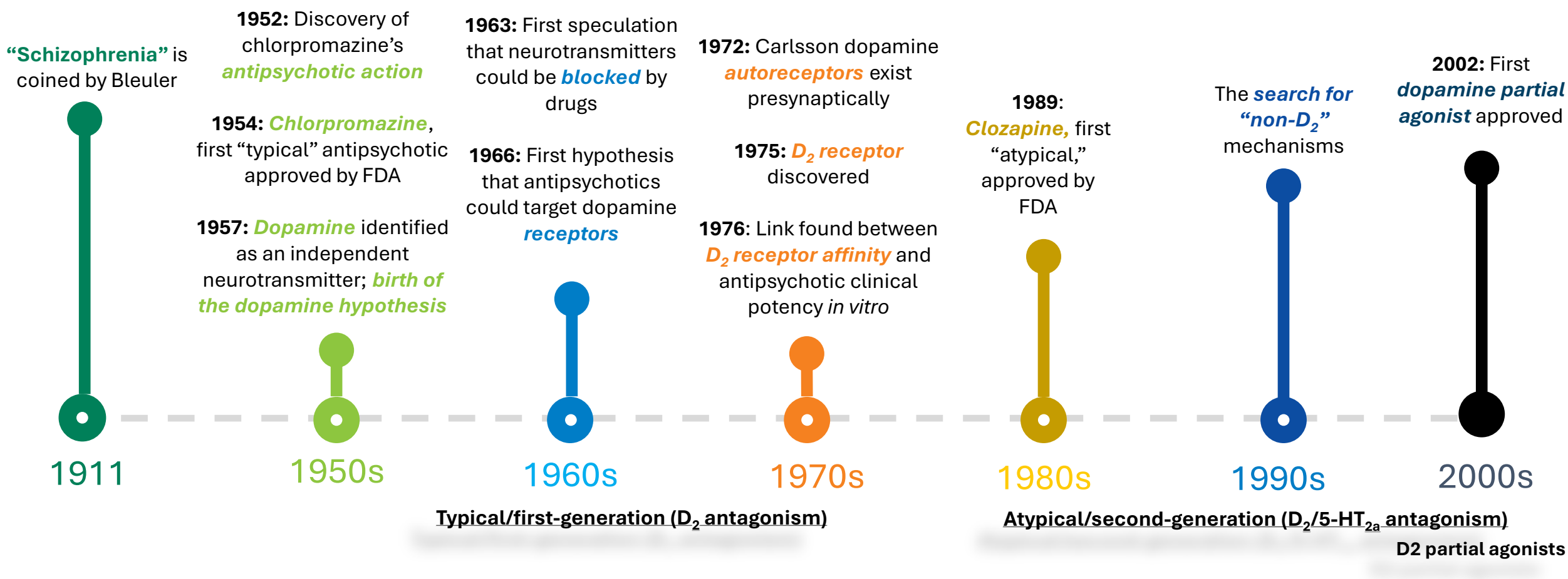
- >1.5 times the odds for comorbidities across several disease categories
- Excess and premature mortality
- >80% of individuals with schizophrenia experience disability
- Life expectancy shortened by >15 years

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.

Unmet Needs in Schizophrenia Treatment Remain

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.

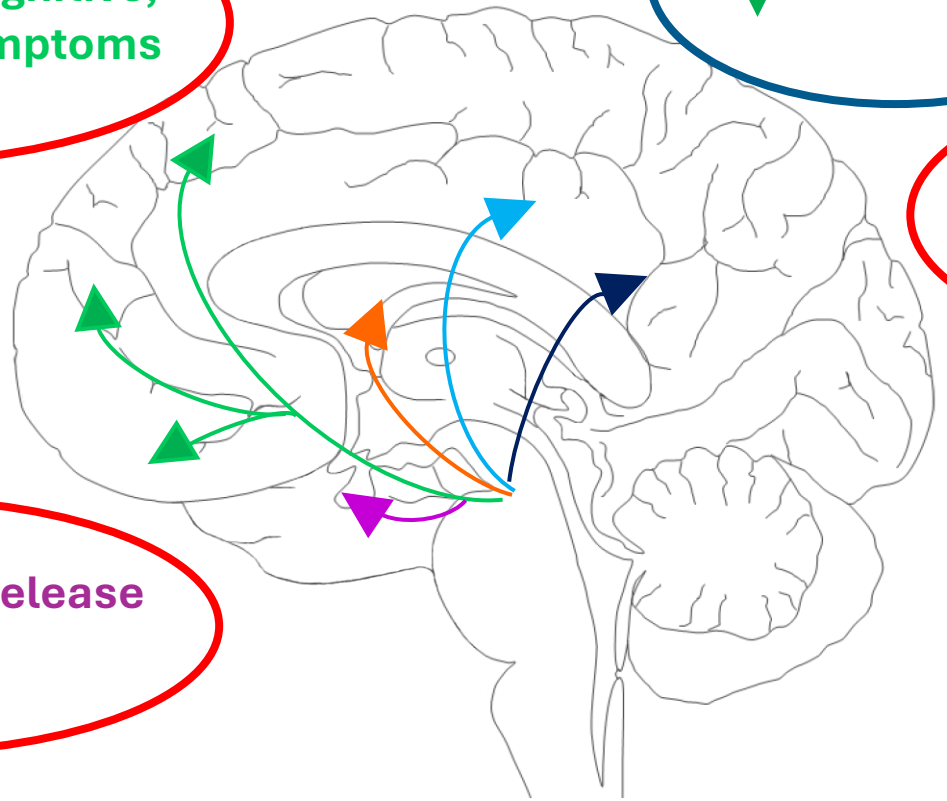
Correll CU, et al. *J Clin Psychiatry*. 2022;83(1):SU21024IP1. Faden J, Citrome L. *Med Clin N Am*. 2023;107:61-72. Howes OD, et al. *Am J Psychiatry*. 2017;174(3):216–29. DiBonaventura M, et al. *BMC Psychiatry*. 2012;12:20. Burschinski A, et al. *World Psychiatry*. 2023;22(1):116-128. Keepers GA, et 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.

Myth #1:
Muscarinics Aren't Going to Help Really "Sick" Patients with Schizophrenia Because They Don't Touch Dopamine Receptors

Dopamine D2 Receptor Antagonism Blocks Postsynaptic Effects of Hyperdopaminergia – with One Potential Positive Outcome, and Three Potential Negative Outcomes

↑ Negative, cognitive, affective symptoms

↓ Psychosis



↑ Movement disorders

↑ Prolactin release

*Advances in neuroimaging techniques found that DA dysfunction in schizophrenia is greatest within nigrostriatal pathways, implicating the dorsal striatum. DA overactivity in the circuit from the dorsomedial substantia nigra to the associative and adjacent sensorimotor striatum is linked to positive symptoms.

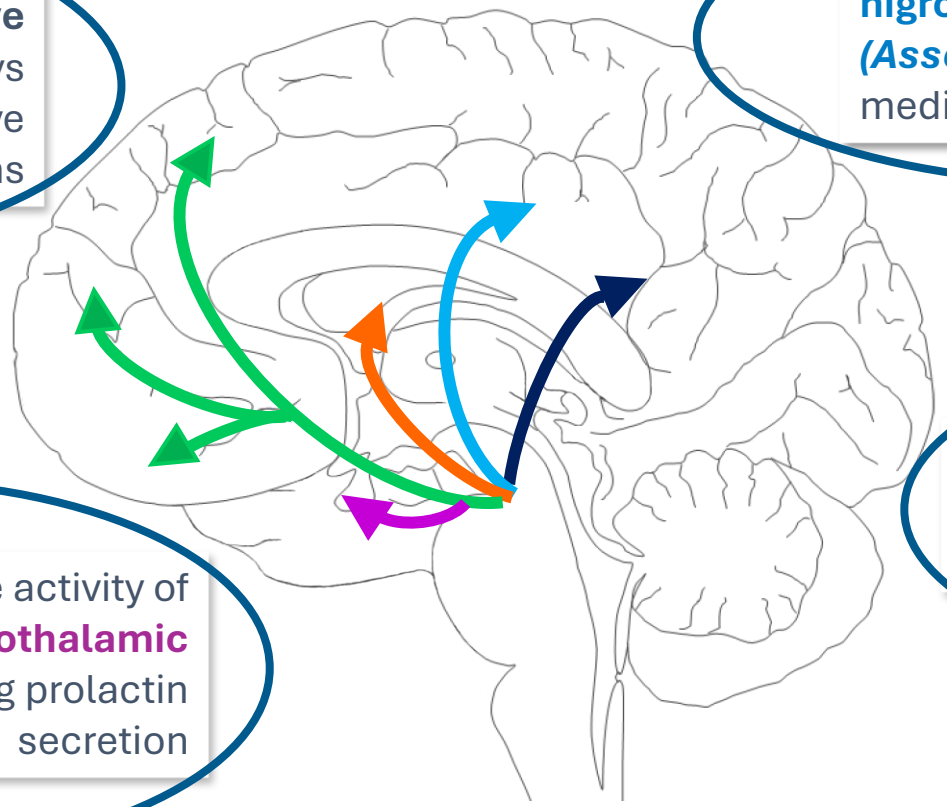
DA = dopamine.

Correll CU, et al. *J Clin Psychiatry*. 2022;83(1):SU21204IP1. McCutcheon RA, et al. *Trends Neurosci*. 2019;42(3):205-220.

The "Real" Goal for Schizophrenia Treatment: All 4 Below Are Desired and Needed Goals of Rx

Increase activity of hypoactive **mesolimbic** and **mesocortical** pathways to mediate negative and cognitive symptoms

Reduce hyperactivity in the **nigrostriatal pathway** ***(Associative Striatum)*** to mediate psychosis



Preserve activity of **tuberoinfundibular hypothalamic pathway** regulating prolactin secretion

Preserve activity of **nigrostriatal pathway** regulating motor movement

***Advances in neuroimaging techniques found that DA dysfunction in schizophrenia is greatest within nigrostriatal pathways, implicating the dorsal striatum. DA overactivity in the circuit from the dorsomedial substantia nigra to the associative and adjacent sensorimotor striatum is linked to positive symptoms.**

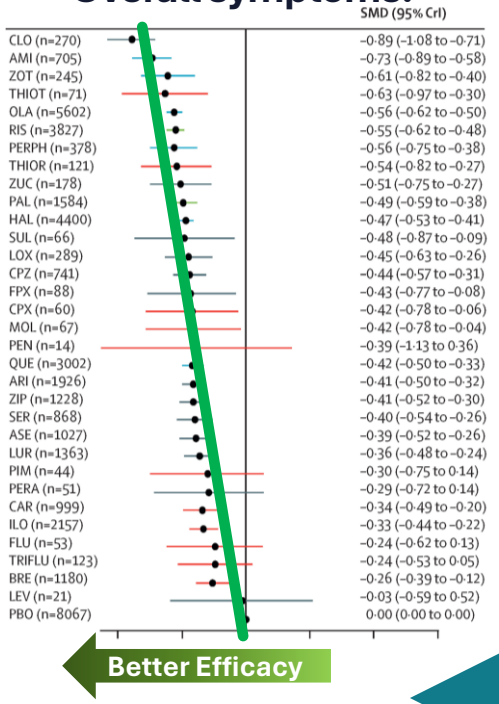
DA = dopamine; Rx = prescription.

Correll CU, et al. *J Clin Psychiatry*. 2022;83(1):SU21204IP1. McCutcheon RA, et al. *Trends Neurosci*. 2019;42(3):205-220.

The Price of Our Obsession with Post-Synaptic D_2 Receptors

Looking back, improvements in efficacy seem negligible…

Overall symptoms:



…and not evenly applied

Historically, antipsychotics have had lower efficacy for negative symptoms and cognitive dysfunction despite their higher burden

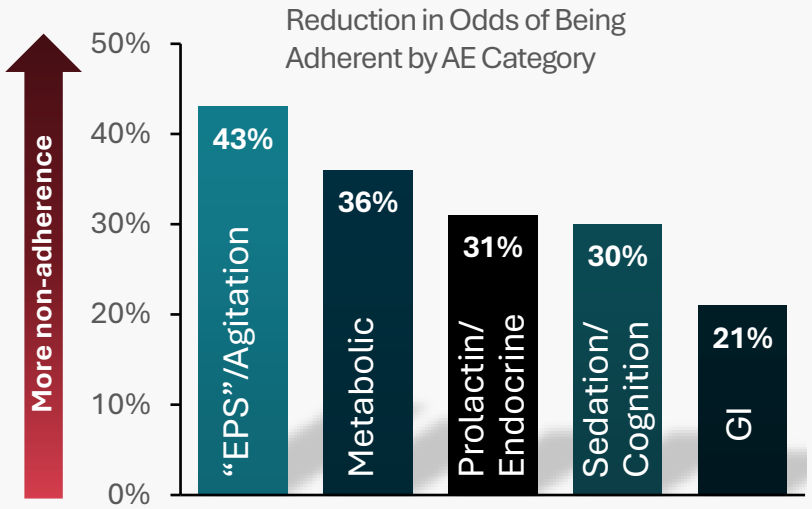
Overall, only ~14% achieve recovery

More excess CV deaths than from suicide

And far too many die far too young

Overall life expectancy reduced 10-20 years

Variability seems to be only in side effects, which are still problematic for most



EPS = extrapyramidal symptoms; GI = gastrointestinal; AE = adverse event; CV = cardiovascular.

Huhn M, et al. *Lancet*. 2019;394(10202):939-951. DiBonaventura M, et al. *BMC Psychiatry*. 2012;12:20. Velligan DI, et al. *Schizophr Res*. 1997;25(1):21-31. Mitchell AJ, et al. *Schizophr Bull*. 2013;39(2):306-318. Jääskeläinen E, et al. Schizophr Bull. 2013;39(6):1296-1306.

In Schizophrenia, the Primary Dopamine Dysfunction Is Pre-Synaptic

Pre-synaptic 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**

- Also with moderate to large effect sizes

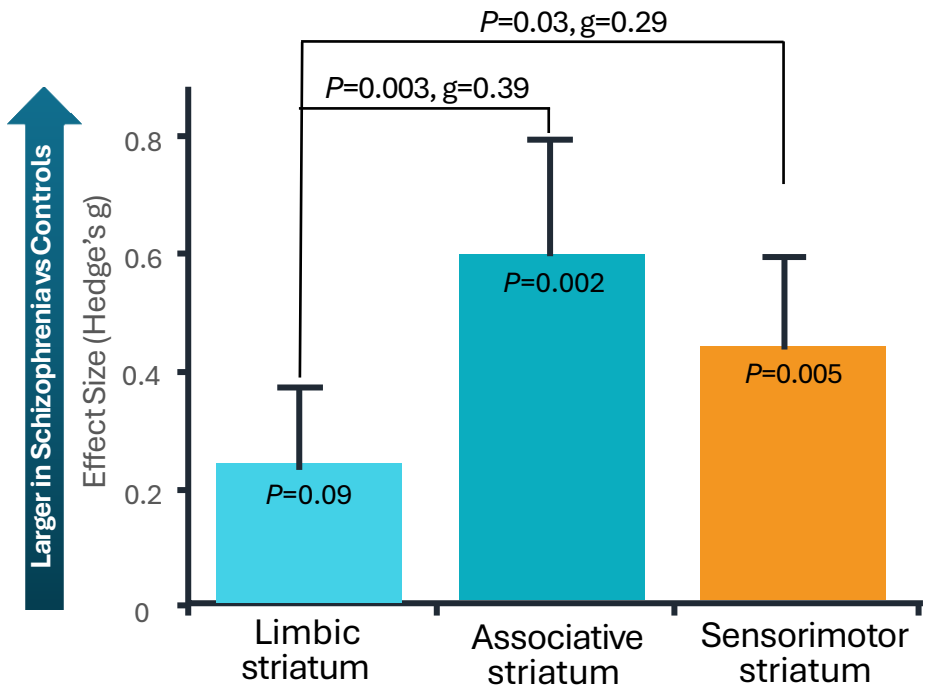
Post-synaptic differences appear to be smaller

Meta-analysis of 19 studies found at most a 10%-20% elevation in striatal postsynaptic D_2/D_3 receptor density in schizophrenia

- (Independent of antipsychotic effects)

It's also not in the mesolimbic pathway!

Estimated Mean Difference in Presynaptic Dopamine Function in Patients vs Controls



Recent high-resolution imaging studies

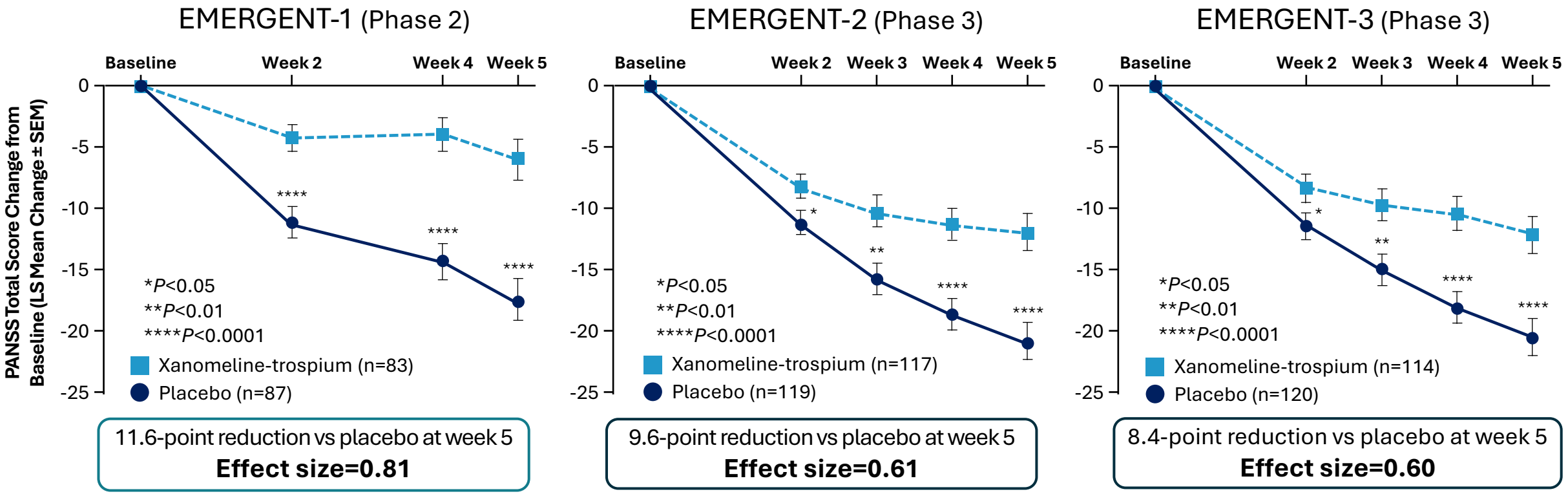
Increased dopaminergic activity in associative and sensorimotor striatum, NOT in limbic striatum as seen in mouse models

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.

Evidence for Efficacy with Muscarinic Medication

(Not “touching” the Postsynaptic D2 Receptor at all approach)

Xanomeline/Trospium Showed Consistent Efficacy in All Short-Term Phase 2 & 3 Trials



11.6-point reduction vs placebo at week 5
Effect size=0.81

9.6-point reduction vs placebo at week 5
Effect size=0.61

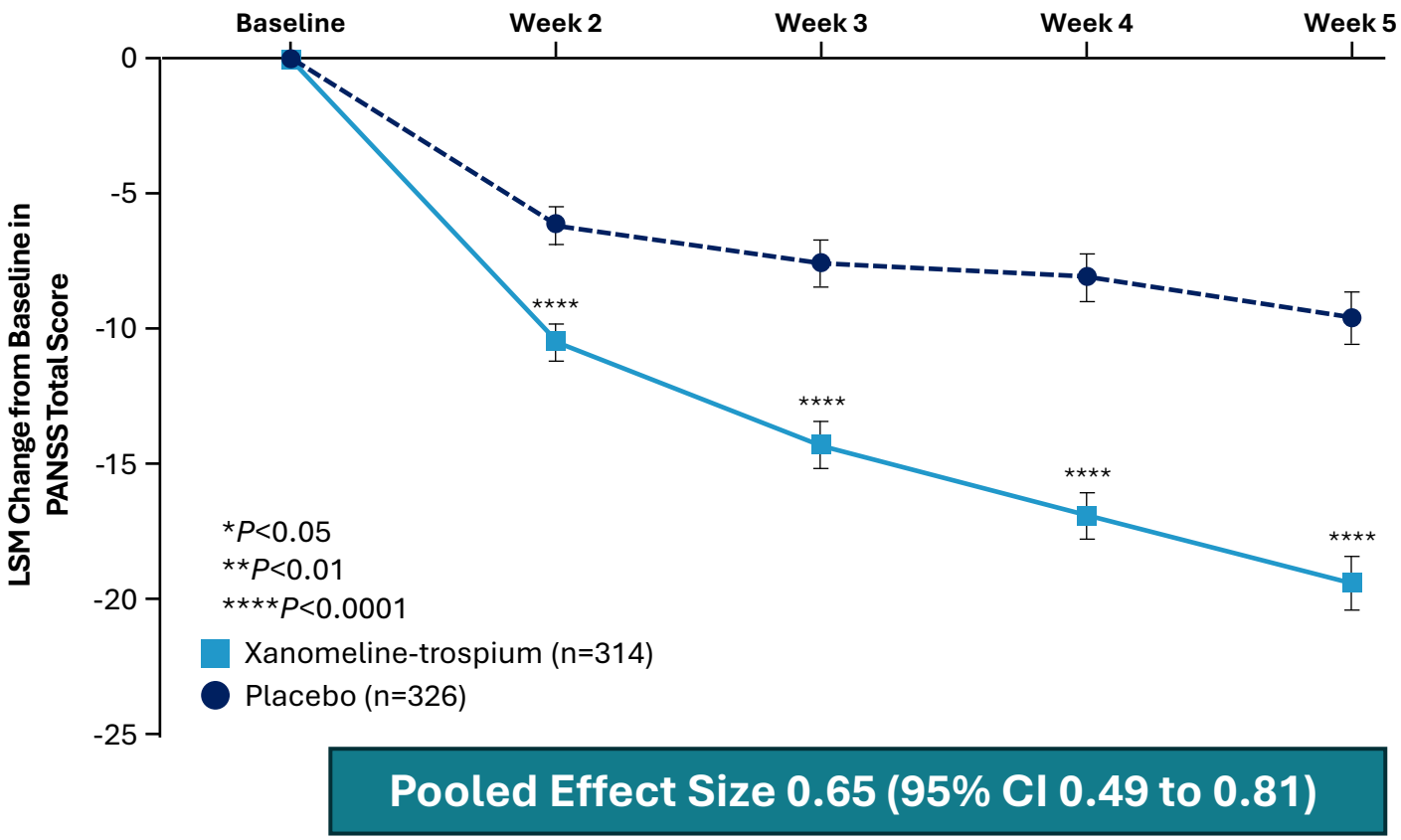
8.4-point reduction vs placebo at week 5
Effect size=0.60

Reductions in PANSS total with xanomeline-trospium were extremely similar across the three studies, but the placebo response was higher in phase 3 trials

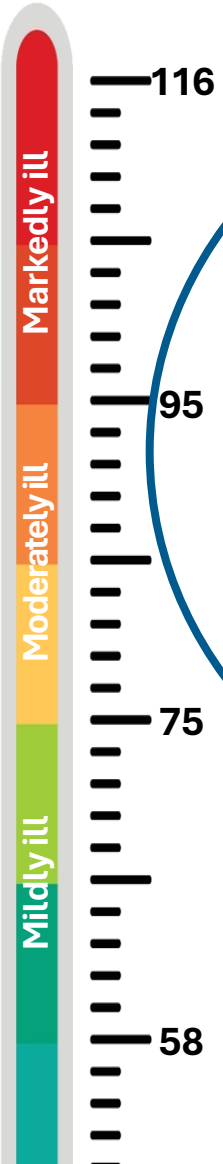
LS = least squares; SEM = standard error of the mean; PANSS = Positive and Negative Syndrome Scale.

Brannan SK, et al. *N Engl J Med*. 2021;384(8):717-726. Kaul I, et al. *Lancet*. 2024; 403(10422):160-170. Kaul I, et al. *JAMA Psych*. 2024; 81(8):749-756. Kaul I, et al. *Schizophrenia (Heidelb)*. 2024;10(1):102.

Post-Hoc Analysis of Xanomeline/Trospium Efficacy in 3 Pooled Short-Term Studies



Pooled Effect Size 0.65 (95% CI 0.49 to 0.81)



Comparative Efficacy by Network Meta-Analysis

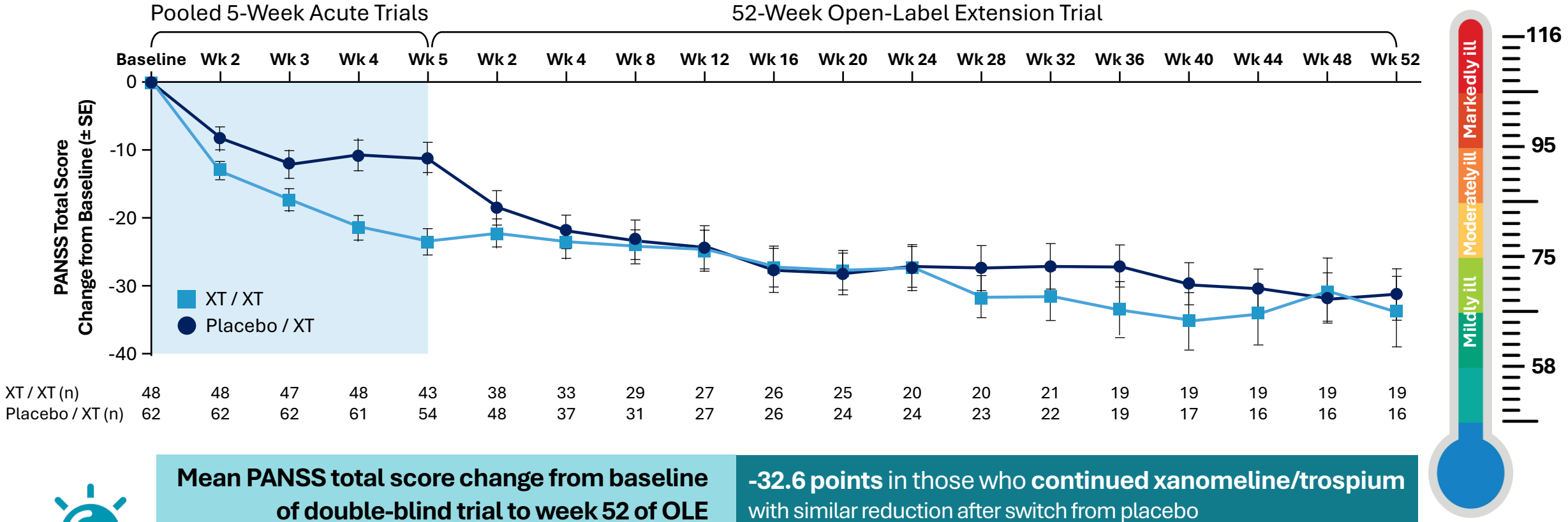
Agent	Overall Symptom Change Effect Size (95% CrI)
Clozapine	0.89 (0.71 to 1.08)
Olanzapine	0.56 (0.50 to 0.62)
Risperidone	0.55 (0.48 to 0.62)
Haloperidol	0.47 (0.41 to 0.53)
Aripiprazole	0.41 (0.32 to 0.50)

While Head-to-Head studies are necessary to make valid comparisons, xanomeline/trospium's consistent, robust efficacy stacks up well with historical antipsychotics

LSM = least squares mean; CI = confidence interval; CrI = credible interval.

Kaul I, et al. *Schizophrenia (Heidelb).* 2024;10(1):102. Huhn M, et al. *Lancet.* 2019;394(10202):939-951.

Long-Term Effect of Xanomeline/Trospium on PANSS in EMERGENT-4



Mean PANSS total score change from baseline of double-blind trial to week 52 of OLE

-32.6 points in those who **continued xanomeline/trospium** with similar reduction after switch from placebo

69% of patients achieved ≥30% reduction in PANSS total scores

Participants in both groups at the end of the study had a mean PANSS score firmly in the mildly ill range

SE = standard error; OLE = open-label extension.

Kaul I, et al. Poster presented at: 2025 Annual Congress of the Schizophrenia International Research Society (SIRS); March 29-April 2, 2025; Chicago, IL.

The Phase 2 Studies of Emraclidine Did Not Meet Their Primary Endpoints

Change from Baseline to Week 6 in PANSS Total Score

	EMPOWER-1			EMPOWER-2		
	Placebo N=127	Emraclidine 10 mg QD N=125	Emraclidine 30 mg QD N=127	Placebo N=128	Emraclidine 15 mg QD N=122	Emraclidine 30 mg QD N=125
Baseline (SD)	98.3 (8.16)	97.6 (7.65)	97.9 (7.89)	97.4 (8.22)	98.0 (8.49)	97.2 (7.75)
LS Mean (95% CI)	-13.5 (-17.0, -10.0)	-14.7 (-18.1, -11.2)	-16.5 (-20.0, -13.1)	-16.1 (-19.4, -12.8)	-18.5 (-22.0, -15.0)	-14.2 (-17.6, -10.8)

Efficacy
No significant improvement in PANSS scores

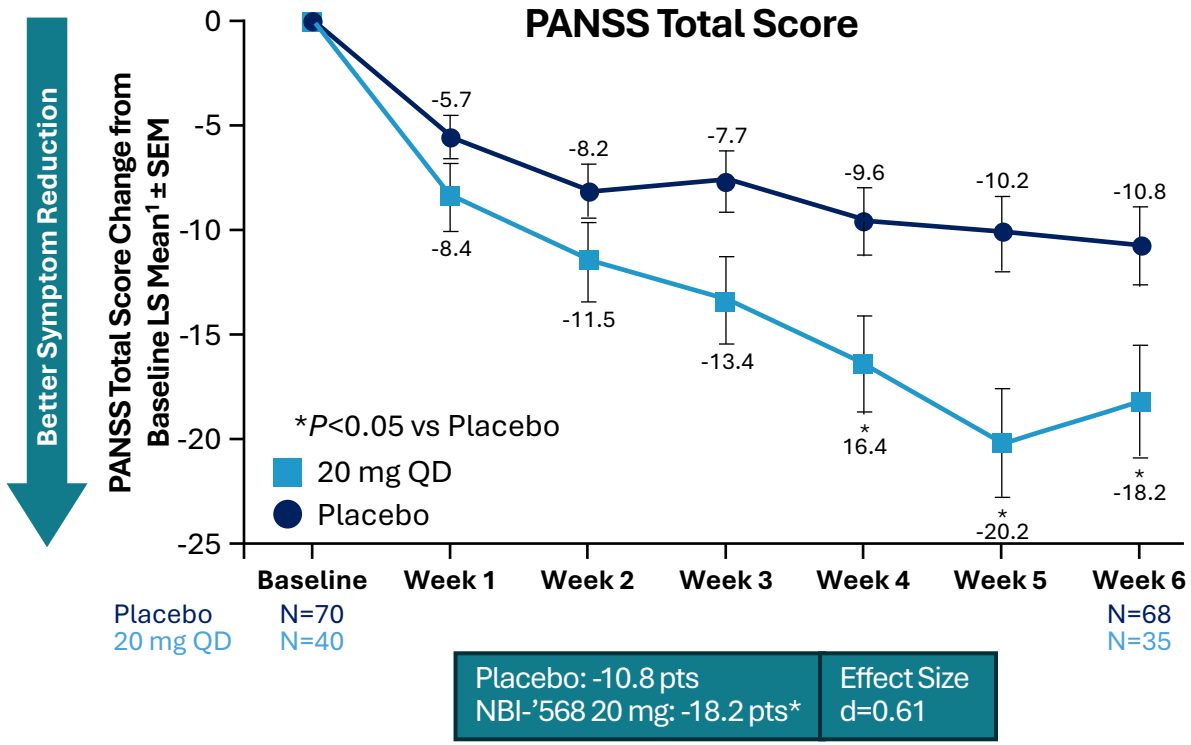
Tolerability
Well-tolerated with stable safety profile

SD = standard deviation.

AbbVie. Press release. November 11, 2024. Accessed March 6, 2025. https://news.abbvie.com/2024-11-11-AbbVie-Provides-Update-on-Phase-2-Results-for-Emraclidine-in-Schizophrenia.

Positive Phase 2a Results for NBI-1117568 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.

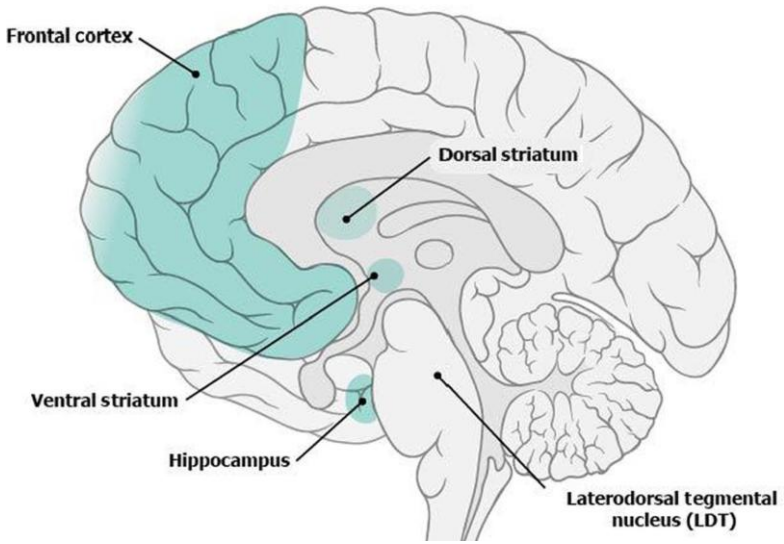
Key Learning Points

- Not “touching the Postsynaptic D2” receptor turns out to be a valid approach to treating all the symptoms of Schizophrenia
- The Postsynaptic D2 receptor is not the problem in Schizophrenia. It’s the excess presynaptic production of dopamine that is the challenge
- Muscarinic agonists (best evidence so far is from KarXT, and emerging from other sources) are a legitimate approach to reducing Presynaptic dopamine release
- The proof is, of course, in the pudding, and in the multiple KarXT short-term studies; and the long-term study convincingly reveals muscarinic agonists are a solid option in all types and phases of Schizophrenia

Myth #2:
Muscarinics Could Worsen Some Symptoms of Schizophrenia by Reducing Dopamine Release

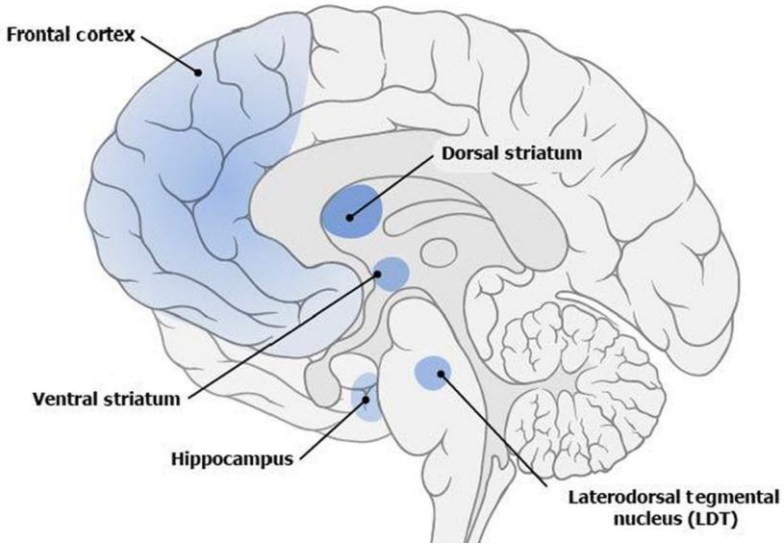
M_1 and M_4 Receptors Are Highly Enriched in Brain Areas Underlying Circuits Associated with Psychosis

Expression of M_1 Receptors



Increasing expression

Expression of M_4 Receptors



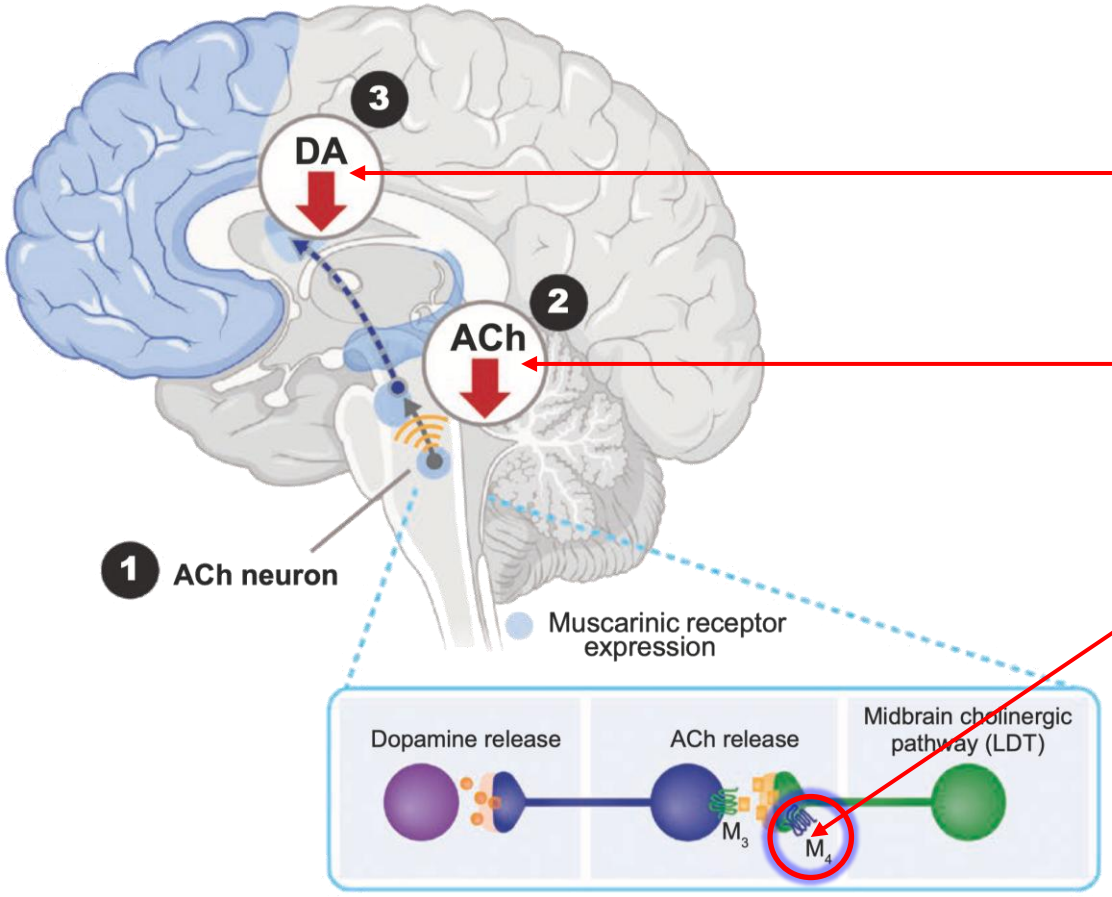
Increasing expression

…and have little expression in circuits associated with prolactin regulation or movement control

LDT = laterodorsal tegmentum.

Yohn SE, et al. *Trends Pharmacol Sci*. 2022;43(12):1098-1012.

M_4 Agonism Decreases Dopamine Release in Brain Circuits Related to Psychosis



3) Reduced ACh stimulation of VTA neurons <u>decreases</u> DA release in the striatum

2) Stimulating M_4 <u>inhibits</u> the LDT neuron, decreasing ACh release

1) M_4 is a presynaptic autoreceptor on LDT ACh neurons from the midbrain

<u>M_4 agonism reduces</u> dopamine signaling by reducing **<u>presynaptic dopamine release</u>** rather than blocking D_2 receptors postsynaptically

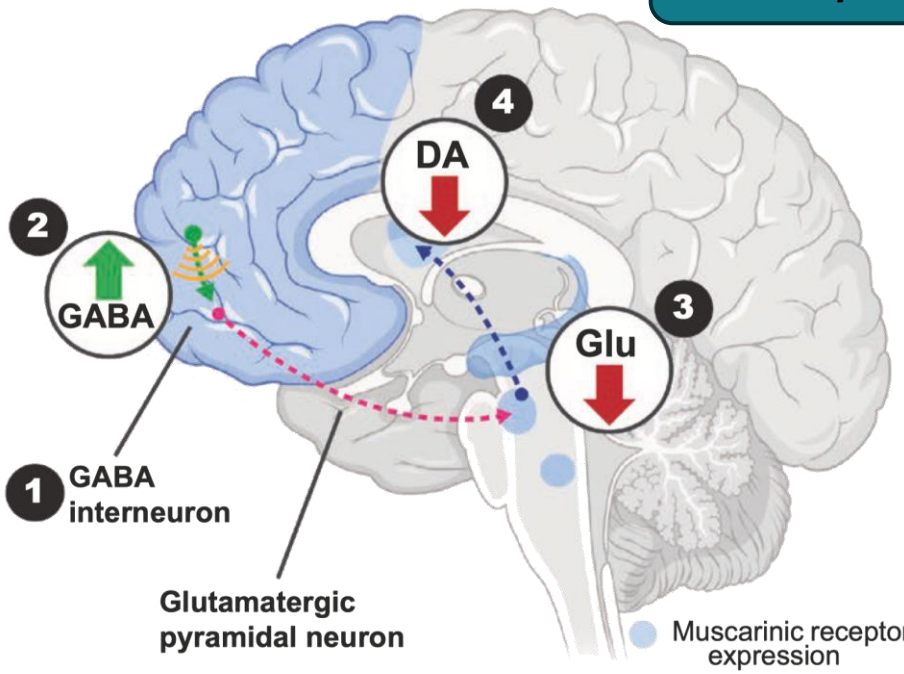
ACh = acetylcholine; VTA = ventral tegmental area.

Meyer JM, et al. *Int J Neuropsychopharmacol*. 2025;28(4):pyaf015.

M_1 Agonism Selectively Decreases Striatal Dopamine Release by a Different Circuit

4) Less stimulation of VTA neurons leads to ***less dopamine*** *release* in the striatum

2) M_1 agonists cause an *increase* in GABA release



3) *Increased* GABA release *reduces* glutamate release in the medial VTA

1) GABA interneurons in the PFC express M_1 receptors

M_1 agonism also reduces dopamine signaling by reducing **presynaptic dopamine release** rather than blocking D_2 receptors postsynaptically

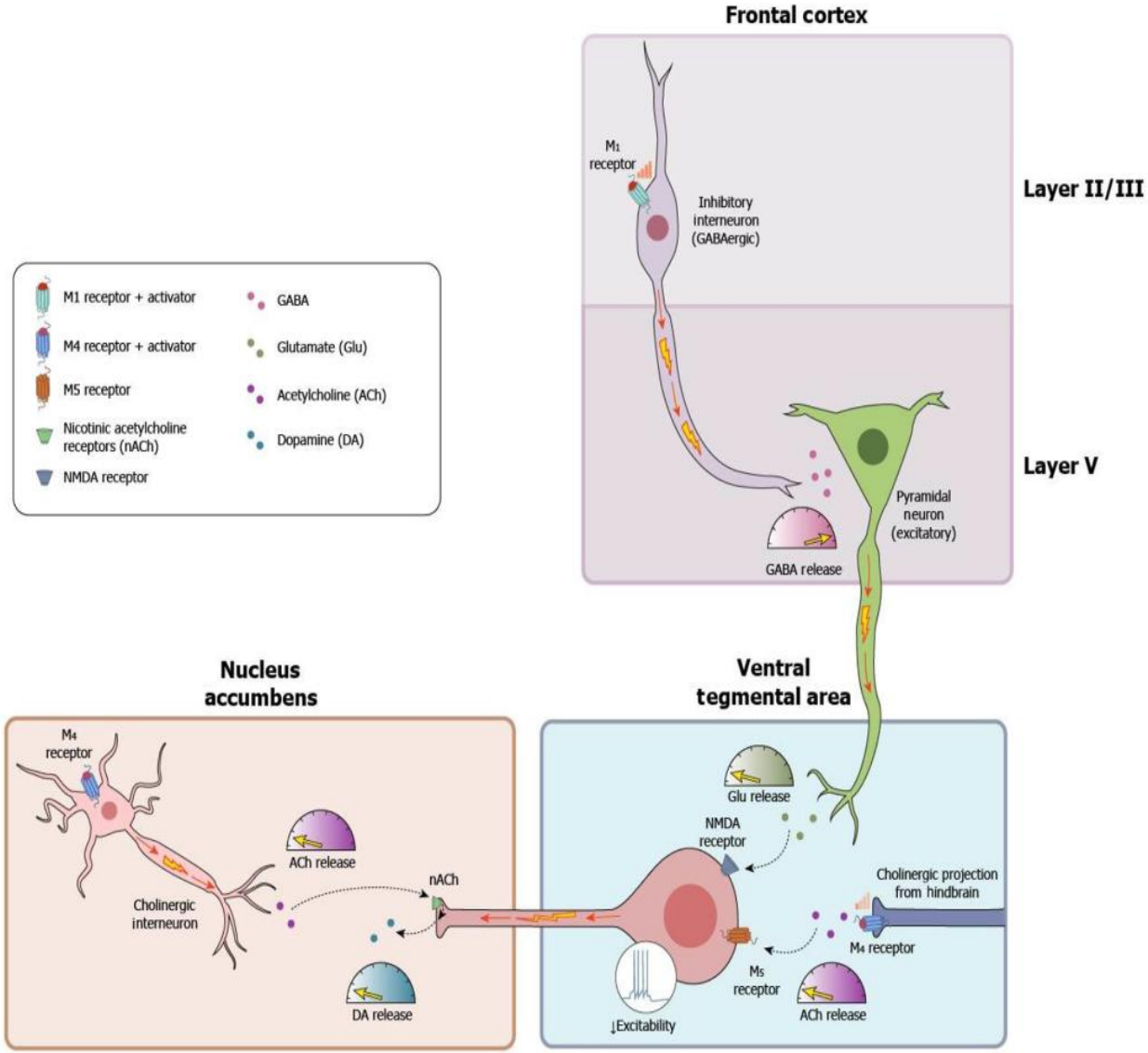
GABA = gamma-aminobutyric acid; PFC = prefrontal cortex.

Meyer JM, et al. *Int J Neuropsychopharmacol*. 2025;28(4):pyaf015. Paul SM, et al. *Am J Psychiatry*. 2022;179(9): 611-627.

Question: Why We Don't See Worsening of Cognitive and Negative Symptoms with Muscarinics (In Fact, We See Substantial Improvement)

Answer:

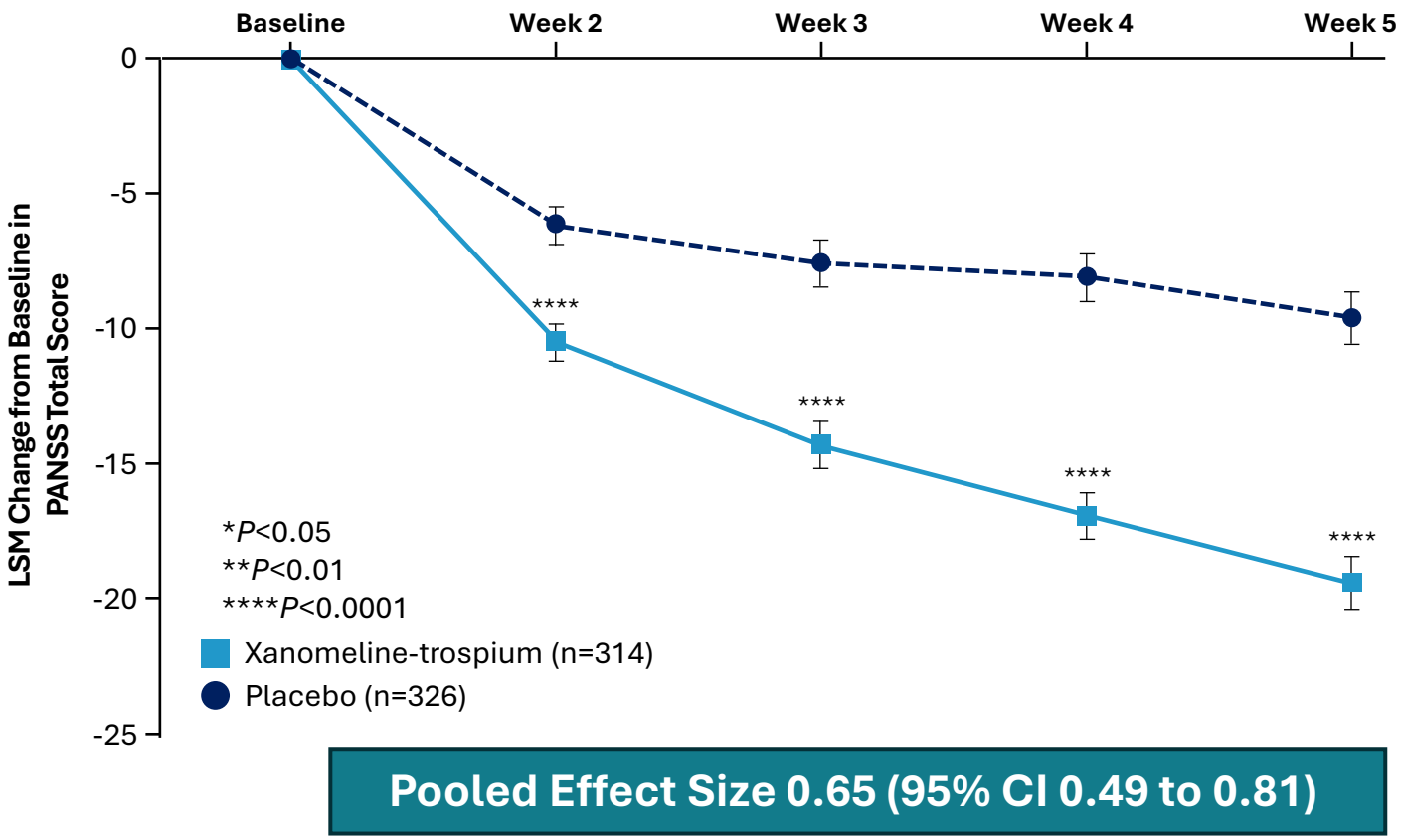
Location, Location, Location (M4 Is Striatal, M1 Is Cortical)



Yohn SE, et al. *Trends Pharmacol Sci*. 2022;43(12):1098-1112.

But.... Can WE Please Examine What the Data in Schizophrenia Actually Shows?

Post-Hoc Analysis of Xanomeline/Trospium Efficacy in 3 Pooled Short-Term Studies



Pooled Effect Size 0.65 (95% CI 0.49 to 0.81)

All three short-term studies revealed a reduction in not just the total PANSS, but in each of the three domains:

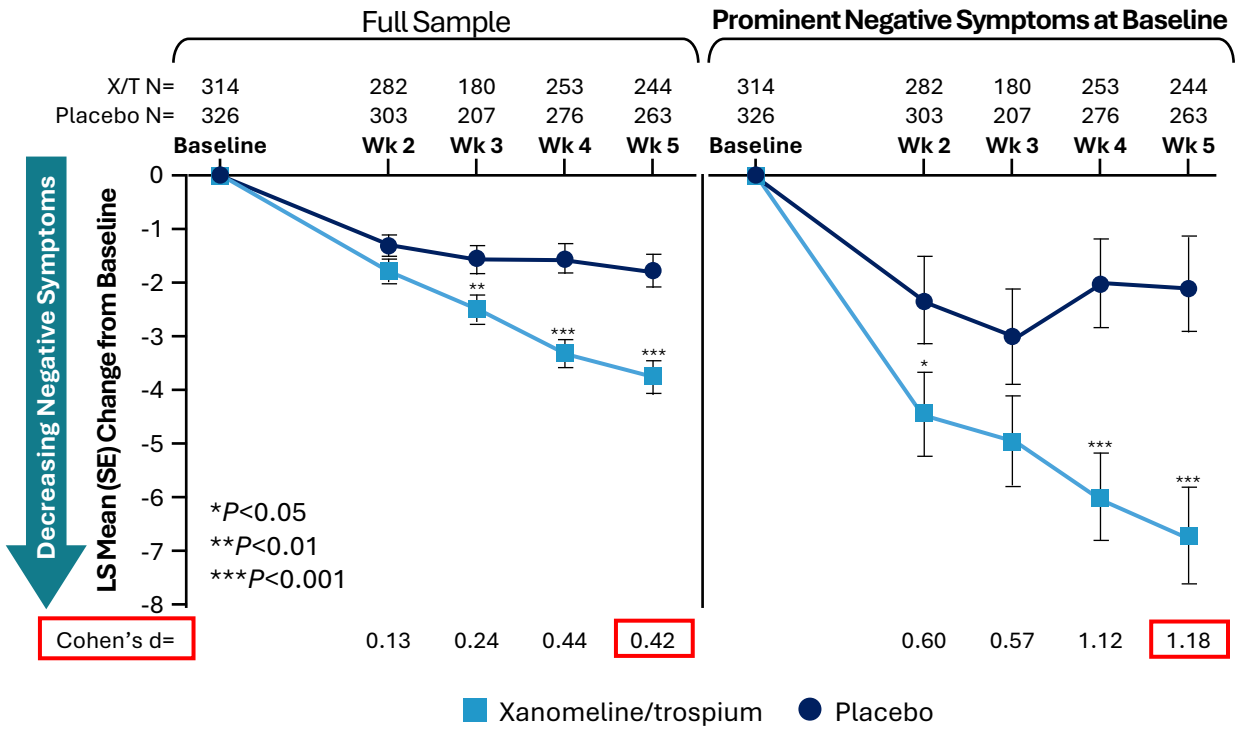
1. Positive Symptoms
2. Negative Symptoms
3. General Psychopathology

Brannan SK, et al. *N Engl J Med*. 2021;384(8):717-726. Kaul I, et al. *Lancet*. 2024; 403(10422):160-170. Kaul I, et al. *JAMA Psych*. 2024; 81(8):749-756. Kaul I, et al. *Schizophrenia (Heidelb)*. 2024;10(1):102.

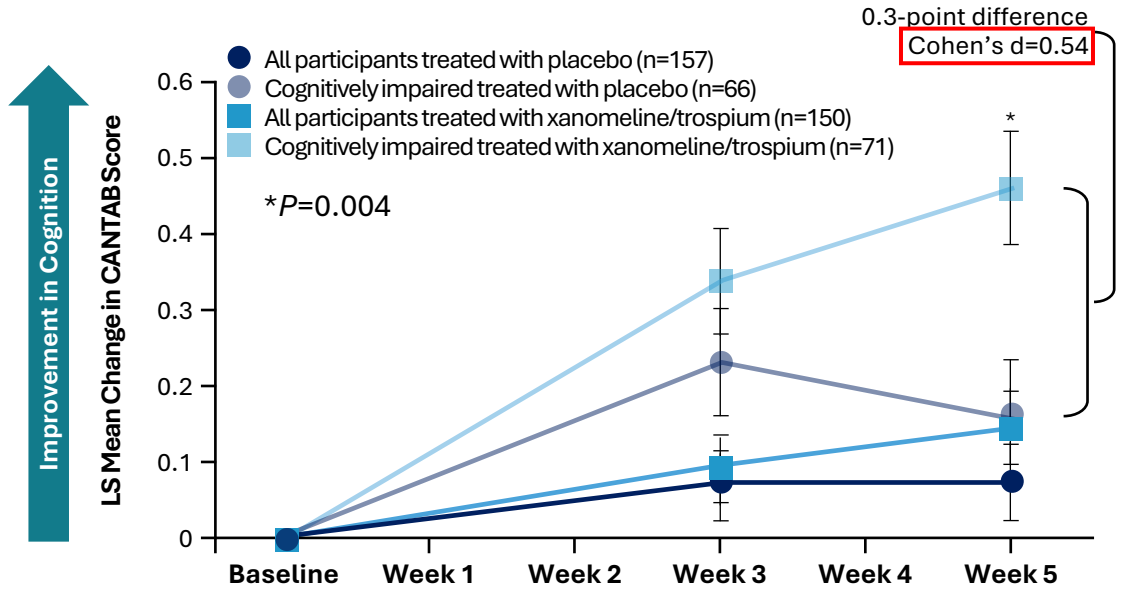
And a Deeper Analysis of Both Negative and Cognitive Symptoms Change with Muscarinic Treatment Reveals...

Post-Hoc Analyses of Ph 3 Xanomeline/Trospium Trials Suggest an Efficacy Signal for Negative & Cognitive Symptoms

Negative Symptoms



Cognitive Dysfunction



Pooled data from EMERGENT-2 and -3 suggest that xanomeline/trospium may have efficacy for negative and/or cognitive symptoms in those with more prominent symptoms of each

Prospective studies designed to test for changes in negative symptoms or cognitive dysfunction are necessary to confirm a potential benefit

CANTAB = Cambridge Neuropsychological Test Automated Battery.

Horan W, et al. *Am J Psychiatry*. 2025;182(3):297-306. Horan WP, et al. Schizophr Res. 2024:274:57-65.

Key Learning Points

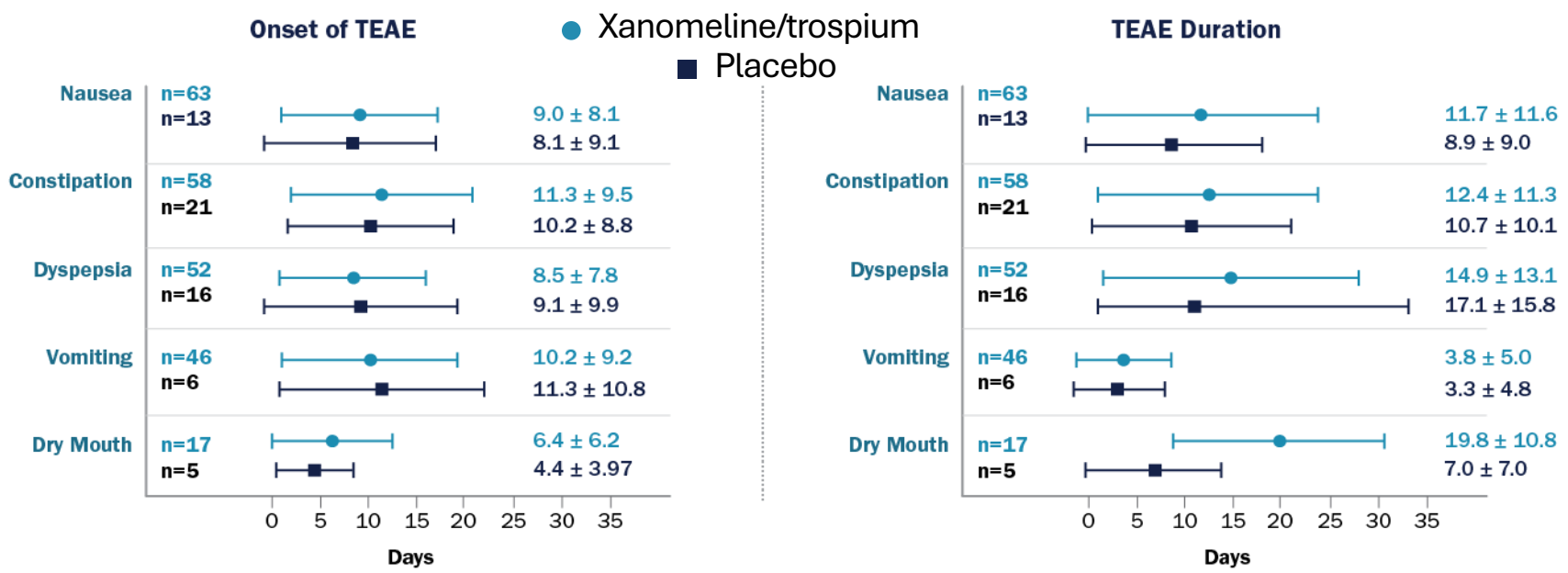
- Muscarinics appear to have a broad and beneficial impact on the symptoms of Schizophrenia
- The Striatal location of M4 receptors (which are inhibitory) and the cortical location of M1 receptors (which are excitatory) seem to explain this broad range of effects
- Careful analysis of the data does not reveal an adverse impact on Cognitive or Negative symptoms
- While we need further studies, the myth that “reducing dopamine” will adversely impact Negative and Cognitive symptoms is simply false, and needs to be put to rest

Myth #3:
“Start Low, Go Slow” is the Best Approach to Avoid Nausea and Vomiting with Muscarinics for Schizophrenia

Onset, Duration, and Severity of Common Adverse Events in Pooled Xanomeline/Trospium Short-Term Studies

Proportion of Commonly Reported TEAEs in X-T Group (n=340) by Intensity Level

	Mild	Moderate
Nausea	76%	24%
Constipation	82%	19%
Dyspepsia	70%	30%
Vomiting	67%	33%
Dry Mouth	71%	29%



Most of the common TEAEs in short-term studies were transient, had their onset in the titration period, and were predominantly mild-to-moderate

TEAE = treatment-emergent adverse event.

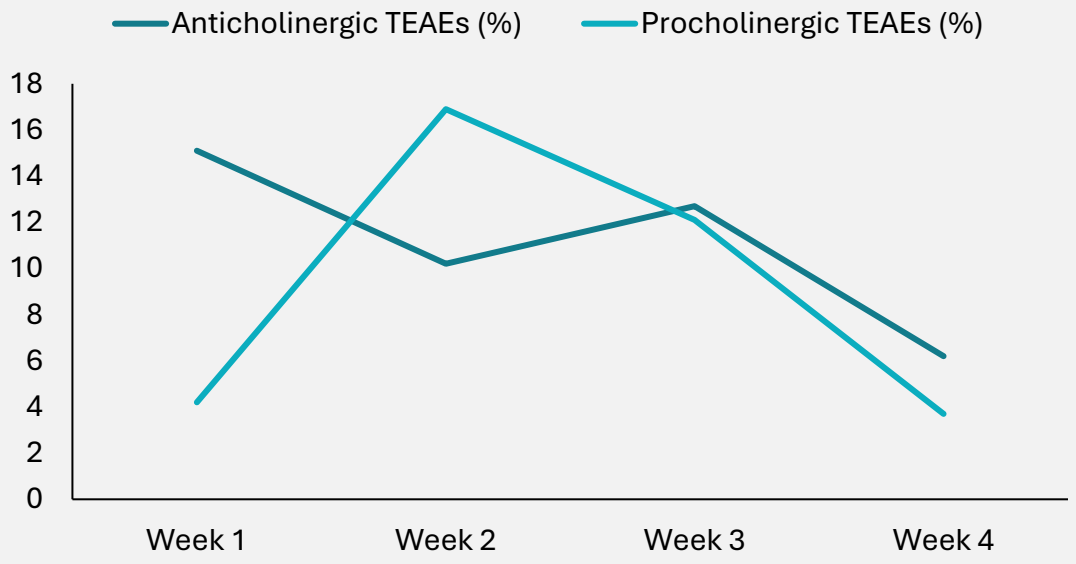
Kaul I, et al. *J Clin Psychiatry*. 2025;86(1):24m15497.

Incidence of Cholinergic Adverse Events Over Time

The incidence of both anticholinergic and procholinergic **TEAEs peaked early during titration at the X/T 100 mg/20 mg dose across Phase 4 and pooled acute EMERGENT trials.** After this peak, TEAE rates plateaued or decreased over time regardless of dose, suggesting adaptation or tolerance development.

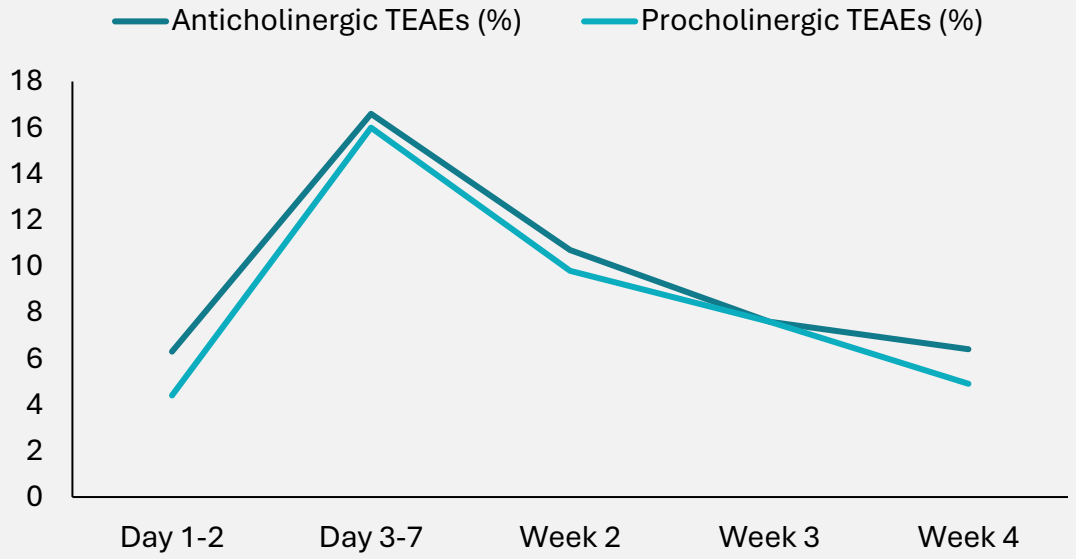
Weekly Incidence of Cholinergic TEAEs in Phase 4

Procholinergic TEAEs peaked at 16.9% in week 2; anticholinergic TEAEs peaked at 15.1% in week 1.



Cholinergic TEAEs in Pooled EMERGENT Trials

Both anticholinergic and procholinergic TEAEs peaked around days 3-7 at 100 mg/20 mg dose, rates near 16%.



Kaul I, et al. *J Clin Psychiatry*. 2025;86(1):24m15497.

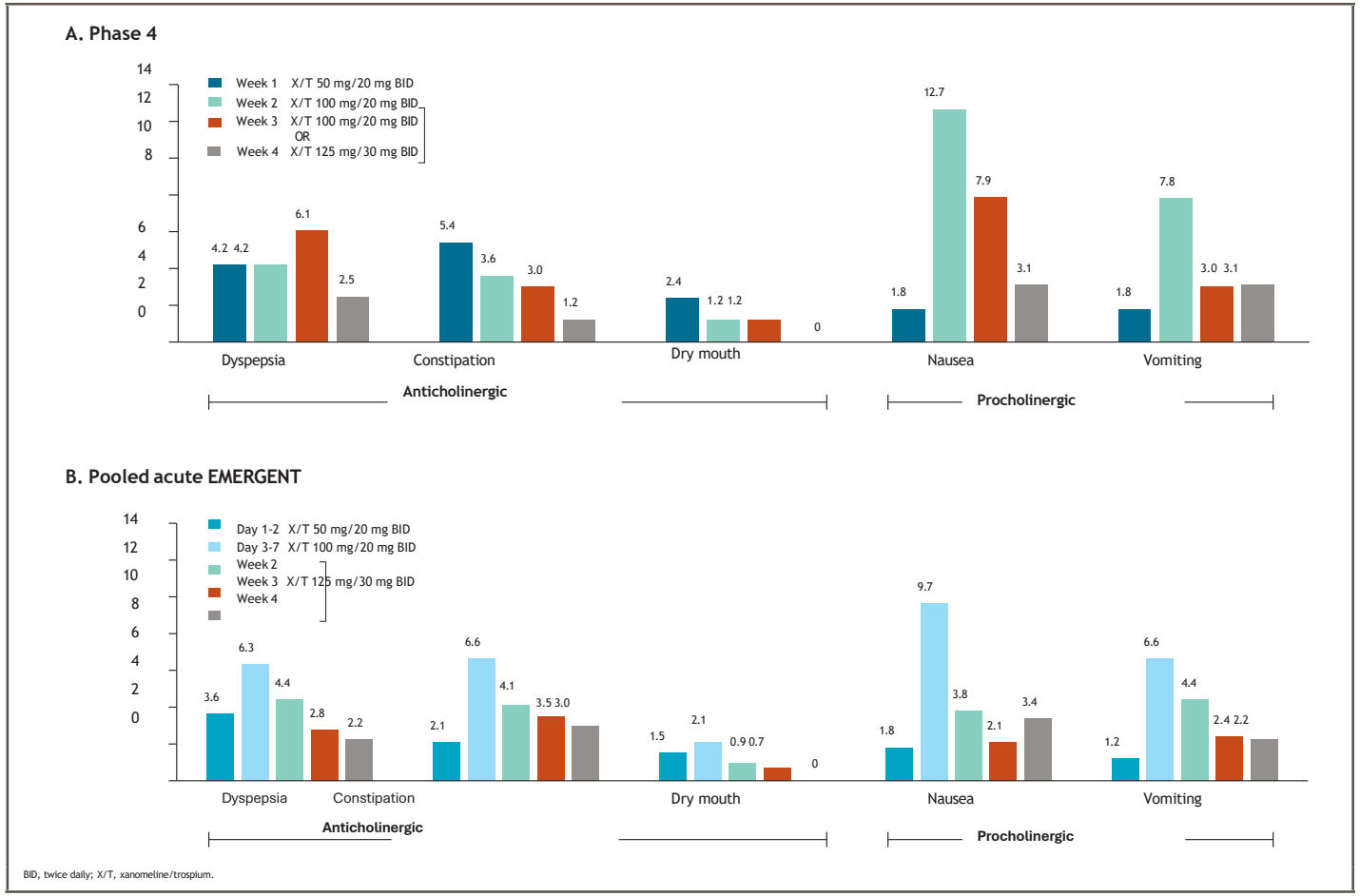
Myth Perpetuating Misconceptions

Common Misunderstandings about Titration and Nausea/Vomiting

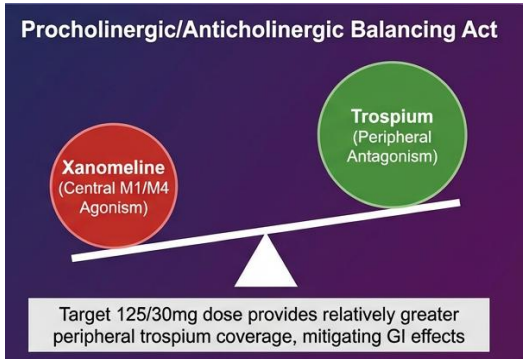
Many practitioners believe that ***slower titration*** and ***lower doses*** can effectively prevent nausea and vomiting (N/V). However, these misconceptions overlook the complexities of drug mechanisms and patient responses.

N/V = nausea and vomiting.

Dose Impact on Events



BID, twice daily; X/T, xanomeline/trospium.



Key Findings

- In contrast with other psychotropic medications, slower titration does not appear to avoid or mitigate procholinergic TEAEs
- The evidence suggests slower titration may increase the risk of incidence and prolong the duration
- The longer duration of certain TEAEs in subjects who remain at X/T 100 mg/20 mg BID may be due to the higher ratio of xanomeline to trospium of 5:1 vs 4.1:1
- In some circumstances, potential improvements in tolerability may be seen with a more rapid titration and/or uptitration to X/T 125 mg/30 mg BID

Dyme R, et al. Onset, Duration, and Incidence of Adverse Events by Dose and Titration Schedule of Xanomeline and Trospium Chloride. Presented at: Neuroscience Education Institute Fall Congress; November 6, 2025; Colorado Springs, CO. Bristol Myers Squibb. Accessed February 2026. www.globalbmsmedinfo.com.

Understand Your Combo: Xanomeline & Trospium

Xanomeline: Muscarinic Agonist & Procholinergic

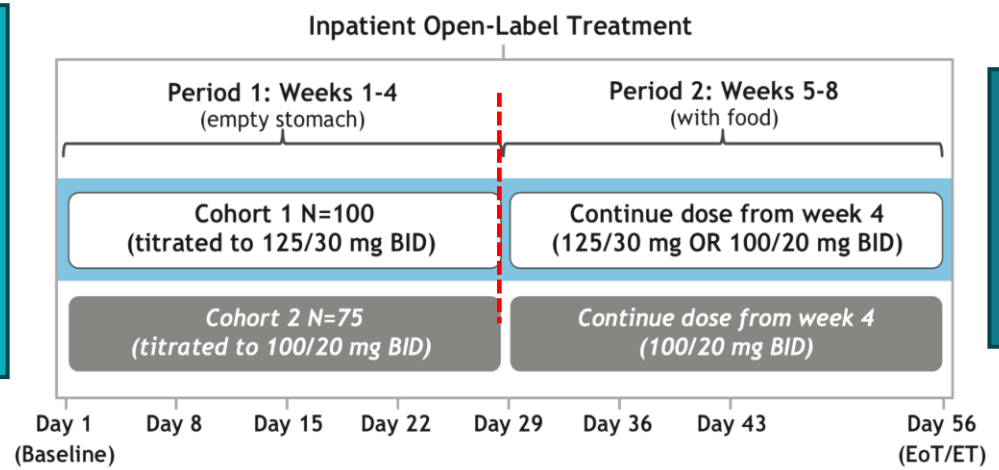
Promotes cholinergic activity, leading to 'wet' side effects such as increased salivation, nausea, and diarrhea.

Trospium: Antagonist & Anticholinergic

Blocks peripheral muscarinic receptors, reducing unwanted cholinergic side effects like constipation, dry mouth, and blurred vision.

If My Patient Has Nausea, Should I Recommend Taking with Food?

The study enrolled individuals with stable symptoms, (baseline PANSS of 65.1±10.6)

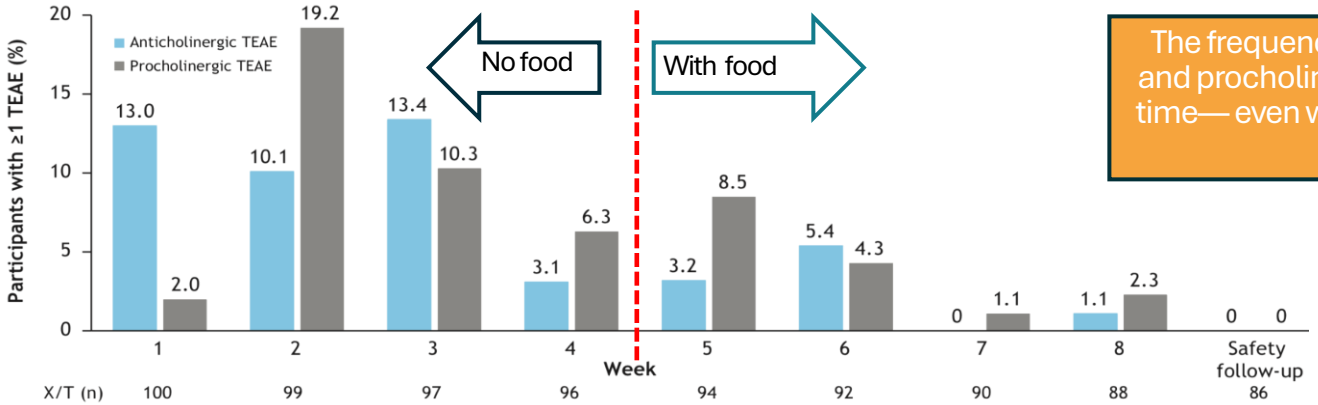


And Utilized a slower titration:

50mg/20mg x1 wk

100mg/20/mg x1 wk

Prevalence of anticholinergic or procholinergic TEAE by week



The frequency of both anticholinergic and procholinergic AEs decreased over time— even with administration of food after week 4

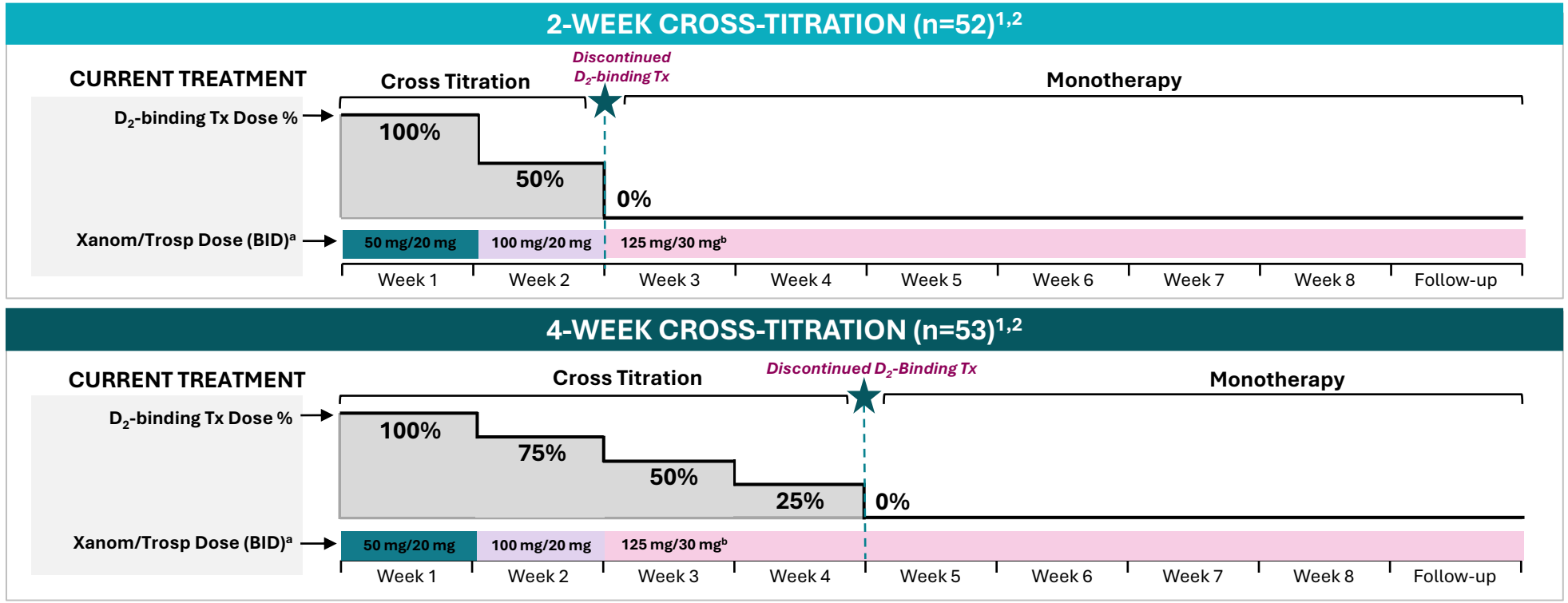
Potential Practice Implications

In general, no notable increase was seen in the incidence or intensity of AEs when switched to dosing with food

This suggests that after the first month of treatment, adhering to food restrictions may not be necessary for some

Hoogerheyde J, et al. A Phase 4, Open-Label, Multicenter, Two-Cohort, Two-Period, Slow-Titration and Food Effect Trial to Assess the Safety and Efficacy of Xanomeline and Trospium Chloride in Participants With Schizophrenia. Presented at: 2025 Annual Meeting of the American Society of Clinical Psychopharmacology (ASCP); May 27-May 30, 2025; Scottsdale, AZ.

The Art of Switching: Go Slow or Get it Done?
2-week vs 4-week Cross Taper From Other Atypicals



Allowed on oral D_2-binding Tx (N=105)

- Olanzapine
- Quetiapine

63%

- Aripiprazole
- Brexpiprazole
- Lumateperone
- Lurasidone
- Paliperidone
- Risperidone
- Ziprasidone

36%

Primary Endpoint[1]

- All-cause discontinuations

Select Prespecified Secondary Endpoints[1]

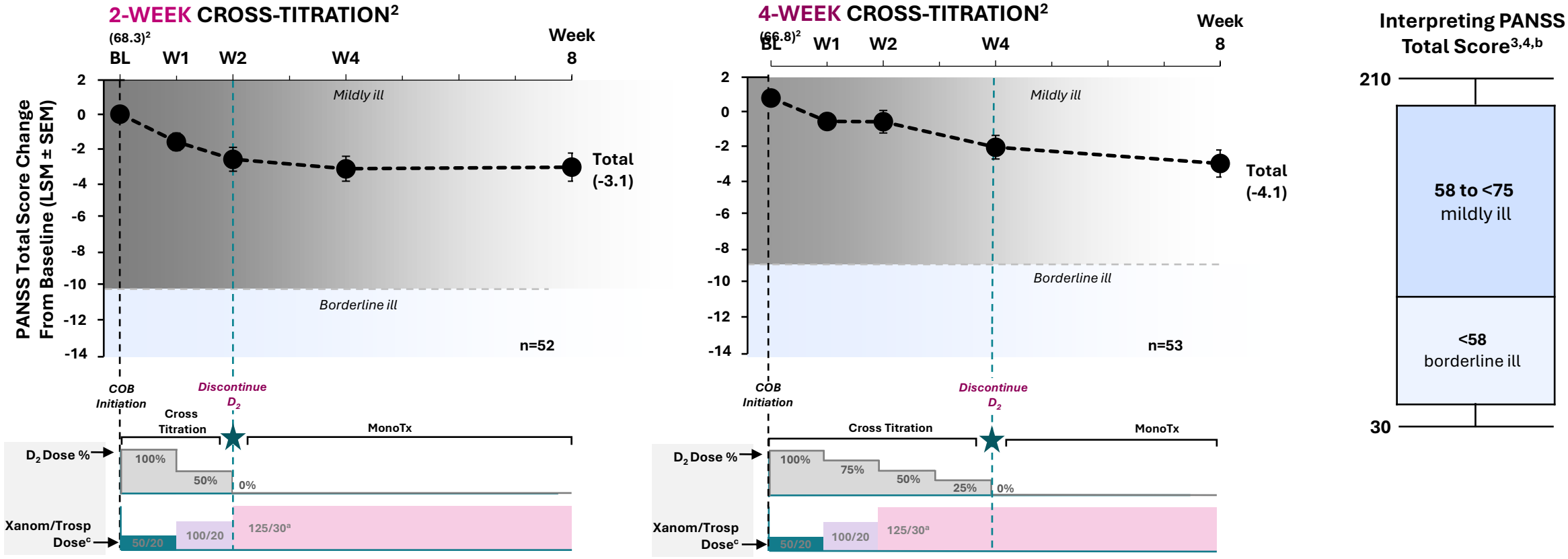
- Discontinuation due to lack of efficacy, AEs
- Change from baseline to Week 8 in PANSS total score
- Incidence of AEs

Select Eligibility Criteria[1]

- 18-65 y, confirmed schizophrenia diagnosis, and PANSS ≤80, CGI-S ≤4 at baseline
- No required increased care due to symptom exacerbation w/in 12 weeks of screening
- Stable treatment regimen of oral APs for ≥6 weeks at time of screening

Walling DP, et al. Presented at: Psych Congress; September 17-21, 2025; San Diego, CA. .

Change in PANSS Total Score When Cross-Titrating From D_2-Binding Medicines



No participants discontinued treatment due to lack of efficacy (secondary endpoint

Walling DP, et al. Presented at: Psych Congress; September 17-21, 2025; San Diego, CA. .

Switch Study Side Effects

Select TEAEs occurring in ≥5% of patients in Switch Study

Adverse Reactions		Total (N=105)	2-Week Cross-titration (n=52)	4-Week Cross-titration (n=53)
Procholinergic	Nausea[b]	**14** (13.3%)	**10** (19.2%)	**4** (7.5%)
	Vomiting[c]	**12** (11.4%)	**6** (11.5%)	**6** (11.3%)
Anticholinergic	Dry mouth	**9** (8.6%)	**3** (5.8%)	**6** (11.3%)
	Constipation	**7** (6.7%)	**4** (7.7%)	**3** (5.7%)

2.9% of participants discontinued treatment due to adverse events (secondary endpoint)

Walling DP, et al. Presented at: Psych Congress; September 17-21, 2025; San Diego, CA. .

Key Learning Points

- 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
- The xanomeline/trospium ratio is optimized at higher doses, making dose reduction potentially counterproductive to the procholinergic/anticholinergic balance
- Supportive management rather than dose reduction should be the primary strategy for managing transient N/V
- Food timing does not significantly impact N/V, though it may affect overall tolerability

Myth #4:
Muscarinic Agents for Schizophrenia Cannot Be Used with Concomitant Anticholinergics

Managing Anticholinergic Use

- Xanomeline Trospium combines xanomeline (muscarinic agonist) and trospium chloride (muscarinic antagonist), affecting muscarinic receptors
- Concurrent use with other anticholinergic drugs may increase peripheral side effects, like dry mouth and constipation, and central nervous system effects
- Clinical trials excluded patients on anticholinergics, but concomitant use is not contraindicated; clinical judgment is essential
- Common anticholinergic medications in schizophrenia include treatments for extrapyramidal symptoms (eg, benztropine) and OTC drugs (eg, diphenhydramine)
- Regular patient communication about all medications taken is critical to identify and manage additive anticholinergic effects

OTC = over-the-counter.

Xanomeline and Trospium Chloride Prescribing Information. Drugs@FDA: FDA-Approved Drugs. Accessed February 2026. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/216158s000lbl.pdf.

Dual Anticholinergic Effects and Constipation Management

↗ Pros

- Trospium selectively reduces xanomeline's peripheral cholinergic side effects such as salivation, nausea, and diarrhea
- Concomitant anticholinergics may add further peripheral symptom control without impacting central efficacy
- Clinical trials show constipation rates of 18%-21% with KarXT, but symptoms are generally manageable
- Trospium's limited ability to cross the blood-brain barrier avoids central anticholinergic adverse effects
- Use of peripheral anticholinergics does not negate xanomeline's central therapeutic benefits

↘ Cons

- Constipation remains a common adverse event in 18%-21% of patients using KarXT
- Theoretical risk that additional anticholinergic agents could exacerbate constipation symptoms
- Some patients may require careful monitoring and management of gastrointestinal side effects
- Potential for dry mouth and other peripheral anticholinergic effects when combining agents
- Concomitant use requires clinical judgment to balance benefits and gastrointestinal tolerability

Kaul I, et al. *JAMA Psychiatry*. 2024;81(8):749-756.

Real-World Implementation Insights

Emerging Clinical Experience (2025)

- Cross-titration strategies with traditional antipsychotics showing promise
- Individualized approaches to concomitant medication management supported

Case Reports

- Early outpatient experience (40 patients) demonstrates feasibility of polypharmacy approaches
- Tracking cholinergic vs anticholinergic side effects guides dose adjustments

Clinical Flexibility

- Real-world practice often requires managing comorbidities and complex regimens
- Monitoring strategy more important than absolute prohibition

Melnick I, et al. *J Clin Psychiatry*. 2025;86(4):hxtachi2509. Price MZ, Price RL. *Front Psychiatry*. 2025;16:1630574.

Key Learning Points

- Trospium's peripheral restriction allows central muscarinic activation by xanomeline without CNS anticholinergic interference
- Higher XT doses optimize the procholinergic/anticholinergic ratio, potentially outcompeting central effects of concomitant anticholinergics
- The combination of peripheral anticholinergics may require monitoring for additive effects (eg, constipation), but is not contraindicated
- 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

CNS = central nervous system.

Faculty Discussion: Practical Strategies to Optimize Treatment of Schizophrenia

Case Presentation # 1

28-Year-Old Former State Champion Soccer Player

- Won 2 state championships with winning goals in each
- Playing soccer at D1 University
- By Jr Year was “depressed and didn’t fit in”
- Transferred to smaller D3 university for “less stress”
- By Sr year had quit the team and got treated for “depression” but
- Graduated college but 6 months later had his first psychotic break
- Initially diagnosed with bipolar disorder but had uncle with schizophrenia
- Placed on aripiprazole and SSRI in hospital
- Hospitalized again after skipping meds and smoking MJ
- Placed on LAI aripiprazole and diagnosed as possibly having schizophrenia
- Things looking up and Got a job in a leadership training program for a car rental company

Continued

- Gradually got psychotic again, was sleeping in his car on the driveway because he was frightened to come in the house
- Got into an altercation with his family and was hospitalized again
- Placed on olanzapine 20 mg qd in hospital
- Less psychotic but poorly engaged, disorganized thinking and gained 30 pounds with family now applying for Social Security
- Agreed to trying a different treatment when offered a new type of medicine with little weight gain and potential benefits for social engagement and thinking
- Mom called not sure he would take something twice a day
- Cross tapered over 4 weeks to Xanomeline/Trospium monotherapy and …….

Case Presentation # 2

Mr. Jason

Patient Profile:

A 42-year-old male with schizophrenia experiencing acute psychotic symptoms, including auditory hallucinations and paranoid delusions, requiring hospitalization. Previous antipsychotic trials resulted in significant weight gain (25 lbs over 6 months) and akathisia.

Treatment Initiation:

Started on xanomeline-trospium **50 mg/20 mg twice daily** for the first 2 days, taken at least 1 hour before meals. On Day 3, increased to **100 mg/20 mg twice daily** as per the standard titration protocol.

Week 1 Challenges:

- Day 4: Patient reported **moderate nausea and dyspepsia**
- Day 6: Experienced one episode of vomiting
- **Management**:
  - **Prescribed ondansetron 8 mg orally PRN** for nausea/vomiting (maximum 16 mg daily)
  - Patient instructed to take ondansetron at first sign of nausea
  - Provided reassurance that gastrointestinal symptoms are typically **transient and resolve with continued treatment**
  - Emphasized importance of proper meal timing (dosing at least 1 hour before or 2 hours after meals)
  - Patient used ondansetron twice on Day 6 and once on Day 7 with good effect

Continued

Week 2 Progress:

- Nausea decreased from moderate to mild intensity with ondansetron support
- Patient required ondansetron only 2-3 times during Week 2 (decreasing frequency)
- Tolerated 100 mg/20 mg twice daily dosing well
- **Psychotic symptoms began improving**
- Developed mild constipation, managed with increased fluid intake, dietary fiber, and stool softener

Week 2 (Day 8) Titration Decision:

- Given adequate tolerability with ondansetron support, increased to target dose of **125 mg/30 mg twice daily**. Patient experienced brief recurrence of mild nausea for 2 days, managed with ondansetron 8 mg once daily.

Week 5 Outcome:

- **Gastrointestinal symptoms largely resolved**, consistent with the pattern that most adverse events occur within the first 2-3 weeks and improve thereafter
- **Ondansetron discontinued** as no longer needed (patient had not required it for 10 days)
- Significant reduction in positive symptoms
- **No extrapyramidal symptoms, weight gain, or metabolic changes**

Holistic Assessment of Patients with Schizophrenia

Key Assessment Domains

Clinical Symptoms: Understanding comprehensive patient experiences

Assess positive, negative, and cognitive symptoms effectively.

Functional Assessment: Evaluating daily living capabilities

Analyze cognitive deficits and social interaction skills.

Physical Health Screening: Prioritizing overall wellness

Screen for metabolic syndrome and infectious diseases.

Psychosocial Factors: Exploring environmental influences

Examine housing stability and social support networks.

Psychiatric Comorbidities: Addressing mental health complexities

Identify trauma history and related psychiatric conditions.

American Psychiatric Association (APA). 2020. Accessed February 2026. https://psychiatryonline.org/doi/book/10.1176/appi.books.9780890424841. Tandon R, et al. *J Clin Psychiatry*. 2025;86(4):hfrecachi2505.

Patient-Centered Approach

Shared Decision-Making

Encourages collaboration between patient and provider

Motivational Interviewing

Supports patient engagement in their own care

Measurement-Based Care

Tracks symptoms and quality of life consistently

Correll CU. *J Clin Psychiatry*. 2020;81(3):MS19053BR2C.

Looking Ahead: Ongoing Clinical Trials of Muscarinic Agents

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
ML-007C-MA	M_4/M_1 Agonist + PAC	3 phase 1 trials without PAC completed. Most AEs in phase 1 trial with PAC were mild and transient
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
NBI-???????	M_1 Selective Agonist	Preclinical

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	Not Yet Recruiting
Schizophrenia in Adolescents	Recruiting
Long-Acting Injectable	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

Q&A