The Future of Schizophrenia Care: A Closer Look at the Role of Muscarinic Acetylcholine Receptor Activation

Supported by an independent educational grant
from Bristol-Myers Squibb

Faculty

Craig Chepke, MD, DFAPA

Adjunct Associate Professor of Psychiatry
Atrium Health
Medical Director
Excel Psychiatric Associates

Huntersville, NC

Hara Oyedeji, APRN, PMHNP-BC, MSEd

Founder and Lead Clinician
Fortitude Behavioral Health, LLC

Baltimore, MD

Faculty Disclosures

Craig Chepke, MD

Advisory Board—AbbVie, Acadia, Alkermes, Axsome, Biogen, Bristol Myers Squibb, Corium, Idorsia, Intra-Cellular, Johnson & Johnson, Lundbeck, Moderna, Neurocrine, Noven, Otsuka, Sage, Sumitomo, Teva; Advisory Board (spouse): Bristol Myers Squibb, Otsuka; Consultant—AbbVie, Acadia, Alkermes, Axsome, Biogen, Boehringer Ingelheim, Bristol Myers Squibb, Corium, Intra-Cellular, Johnson & Johnson, Lundbeck, MedinCell, Moderna, Neurocrine, Noven, Otsuka, Sage, Sumitomo, Supernus, Teva; Research/Grant Support—Acadia, Axsome, Harmony, Neurocrine, Teva; Speaker's Bureau—AbbVie, Acadia, Alkermes, Axsome, Boehringer Ingelheim, Bristol Myers Squibb, Corium, Intra-Cellular, Johnson & Johnson, Lundbeck, Merck, Neurocrine, Noven, Otsuka, Sumitomo, Teva

Hara Oyedeji, APRN, PMHNP-BC, MSEd

Advisory Board - Alkermes PLC, BMS; Consultant - Alkermes PLC; Speaker's Bureau - Alkermes PLC, BMS, Intracellular, Neurocrine Biosciences Inc, Otsuka Pharmaceuticals, Teva Pharmaceuticals

Disclosures

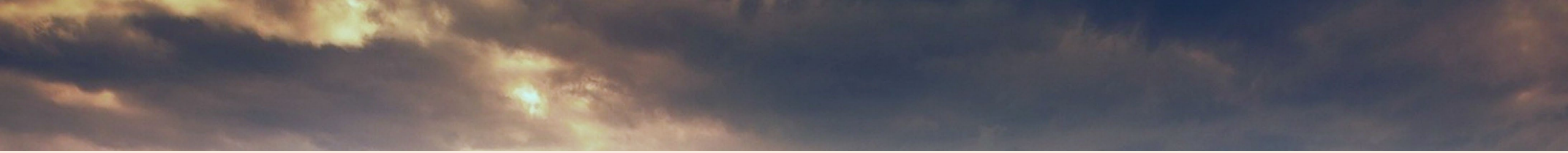
- The faculty have been informed of their responsibility to disclose to the audience if they will be discussing off-label or investigational use(s) of drugs, products, and/or devices (any use not approved by the US Food and Drug Administration).
- Applicable CME staff have no relationships to disclose relating to the subject matter of this activity.
- This activity has been independently reviewed for balance.

Learning Objectives

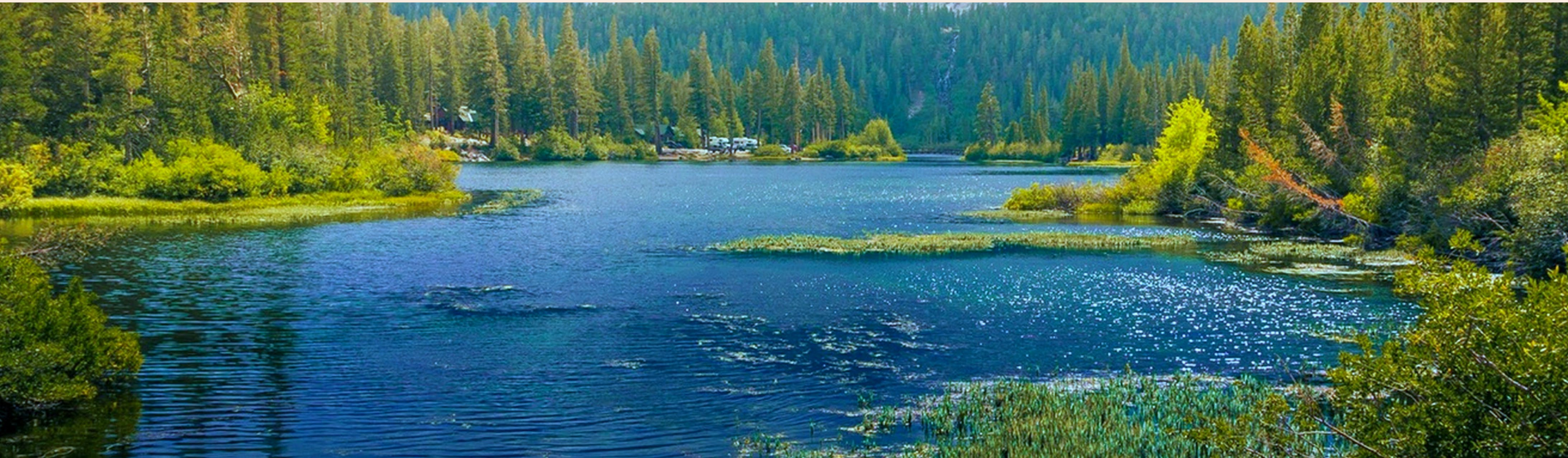
1. Explain the scientific basis for targeting muscarinic acetylcholine receptors in the treatment of schizophrenia

2. Describe recent clinical findings associated with approved and investigational muscarinic acetylcholine receptor activators for schizophrenia

3. Evaluate the clinical application of muscarinic receptor activators, including their role in treatment strategies and patient-centered care



Overview of the Current Schizophrenia Treatment Landscape



How Has Treatment for Schizophrenia Changed?

1950s

- Chlorpromazine introduced
- First antipsychotic
- Revolutionized schizophrenia treatment

1960s

- First-generation antipsychotics gain popularity
- Significant side effects emerge

1990s

- Second generation antipsychotics developed
- Target positive and negative symptoms
- Fewer side effects

2000s

- Partial agonist approach developed
- Dopamine receptor management now the focus

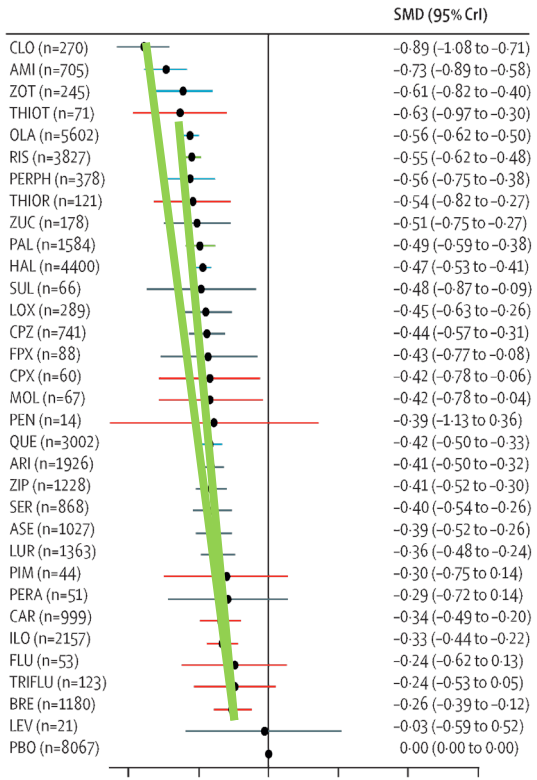
2024

- **First cholinergic-targeting medication**

Menniti FS, et al. *Front Neurosci*. 2021 Jan 20;14:600178. doi: 10.3389/fnins.2020.600178.

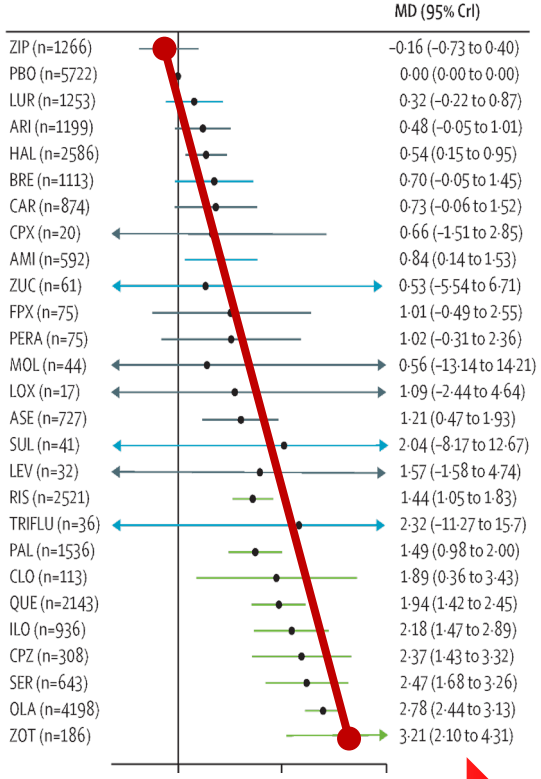
Little Variability of Efficacy, More Varied in Side Effects

Overall Symptom Change



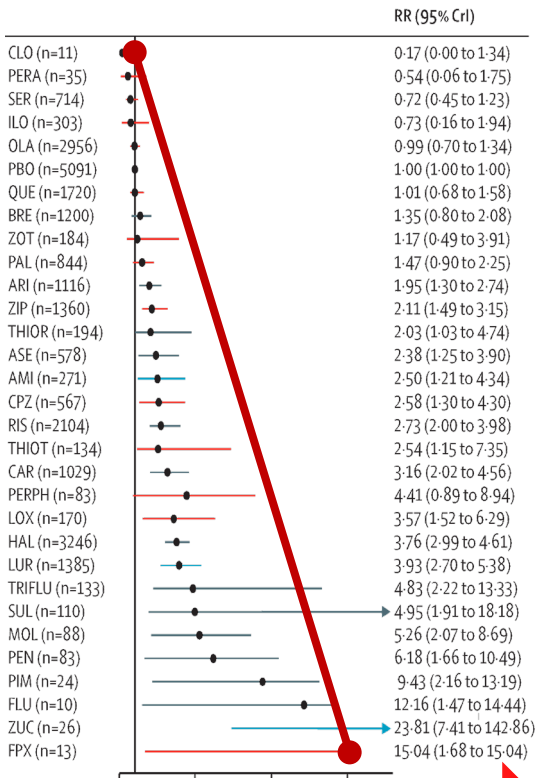
Better efficacy

Weight Gain



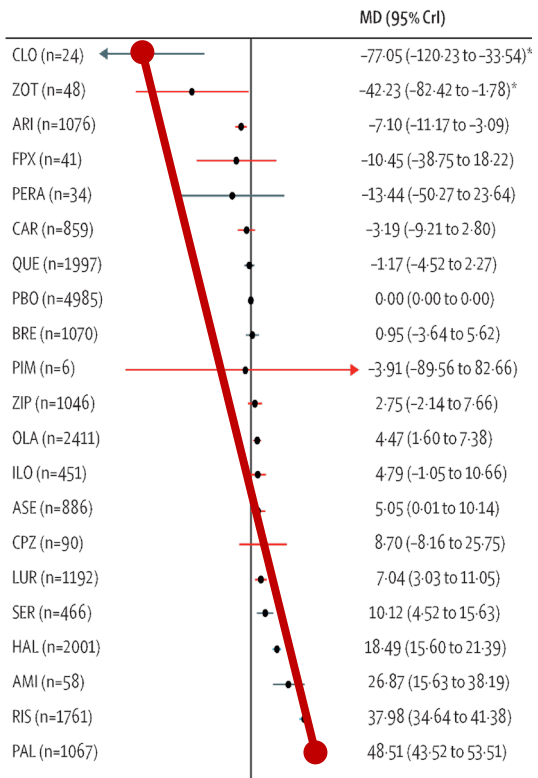
Worse tolerability

Akathisia



Worse tolerability

Prolactin Elevation



Worse tolerability

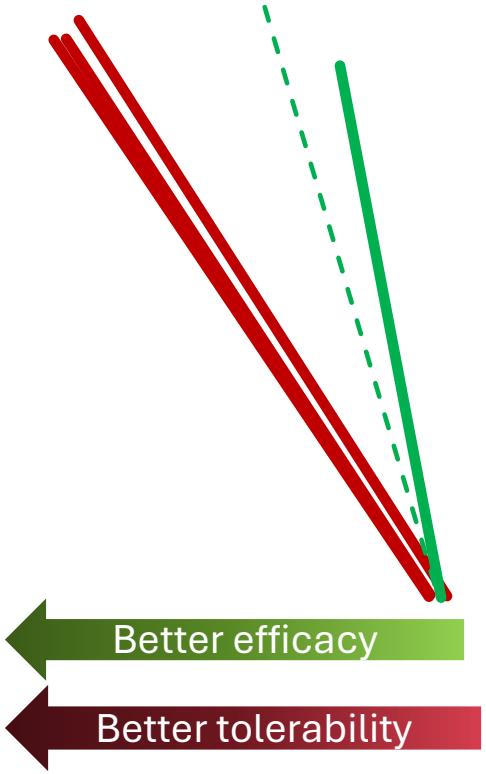
Level of Confidence in Evidence: High Moderate Low Very low

Trend lines include highest- and lowest-ranked agents available in the US in 2019

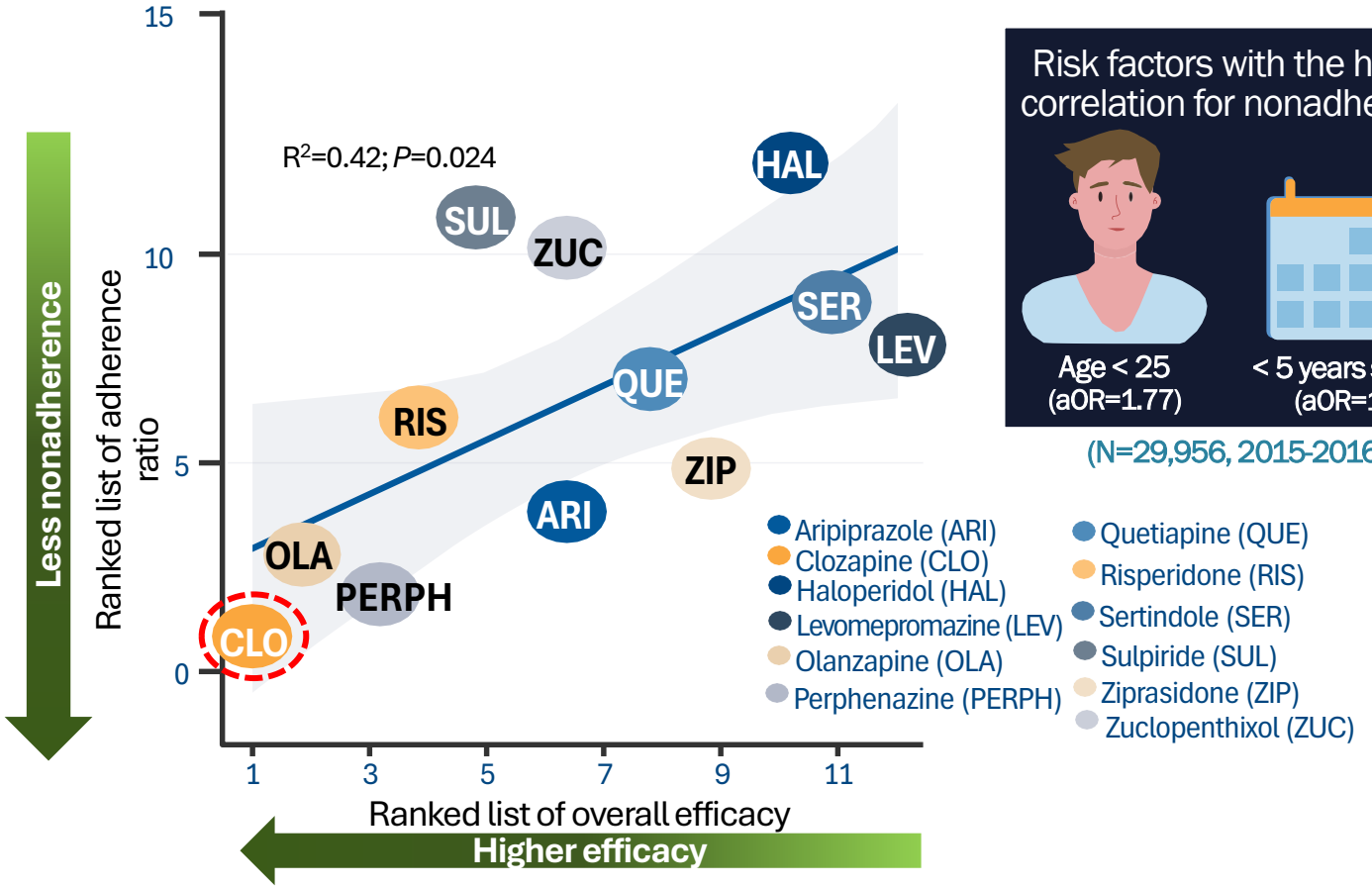
Huhn M, et al. *Lancet*. 2019;394(10202):939-51.

Gains in Tolerability May Not Drive Gains in Adherence

Among many antipsychotics introduced from 1957-2023 tolerability improved more than efficacy



In combination with Finnish registry study, these data showed



(N=29,956, 2015-2016)

Adherence correlated more highly with efficacy than tolerability when clozapine included.

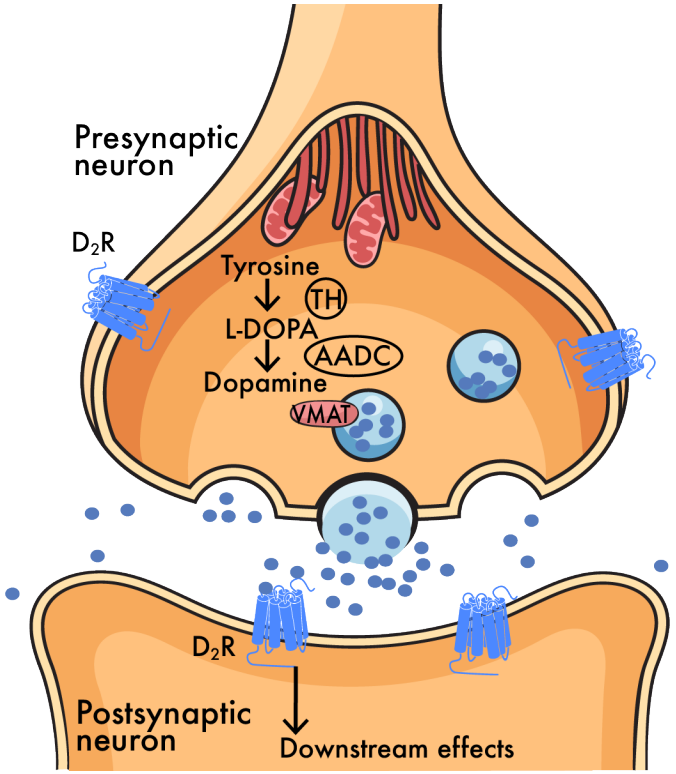
Nonadherence defined as have one or more unfilled prescriptions in 1 year

Huhn M, et al. *Lancet*. 2019 Sep 14;394(10202):939-51. Lieslehto J, et al. *Schizophrenia Bull*. 48.3 (2022): 655-63.

D_2 Antagonists and Partial Agonists

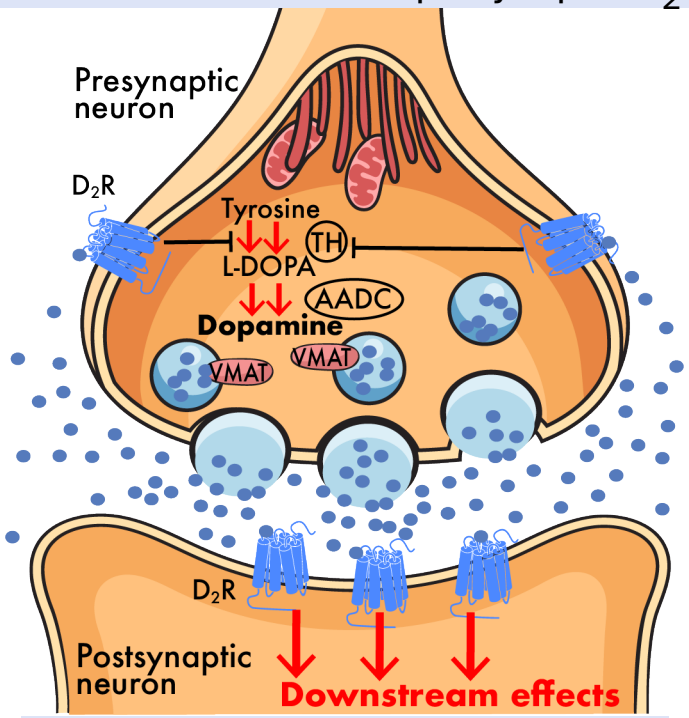
A Postsynaptic Treatment for a Presynaptic Problem

Healthy dopamine synapse



Schizophrenic dopamine synapse

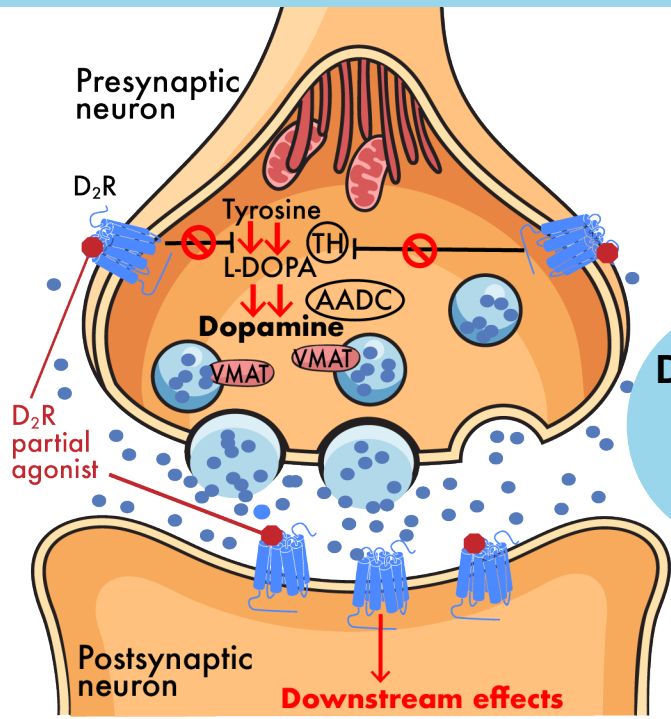
Excess dopamine in synapse leads to feedback inhibition at presynaptic D_2R



Excess dopamine release leads to increased downstream effects

with D_2R antagonist/partial agonist

Presynaptic D_2 autoreceptors blockade stops feedback inhibition of dopamine production



Dopamine release remains high

Paradoxically, may compound problem

D_2R = dopamine D_2 receptors; TH = tyrosine hydroxylase; AADC = aromatic L-amino acid decarboxylase. Meyer JM. Pharmacotherapy of Psychosis and Mania. In: Brunton LL, ed. *Goodman & Gilman's Pharmacological Basis of Therapeutics*. 14th Ed. McGraw-Hill; 2022: 357-84.

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

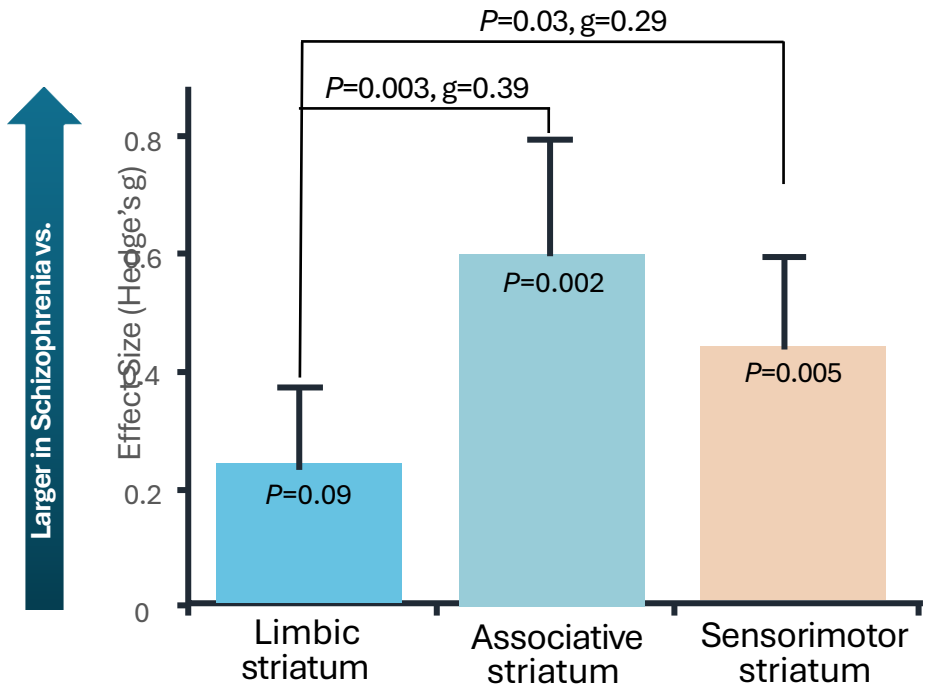
Meta-analysis of 19 studies found at most a 10%-20% elevation in striatal postsynaptic D_2/D_3 receptor density in schizophrenia

- (Independent of antipsychotic effects)

SURPRISE!

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

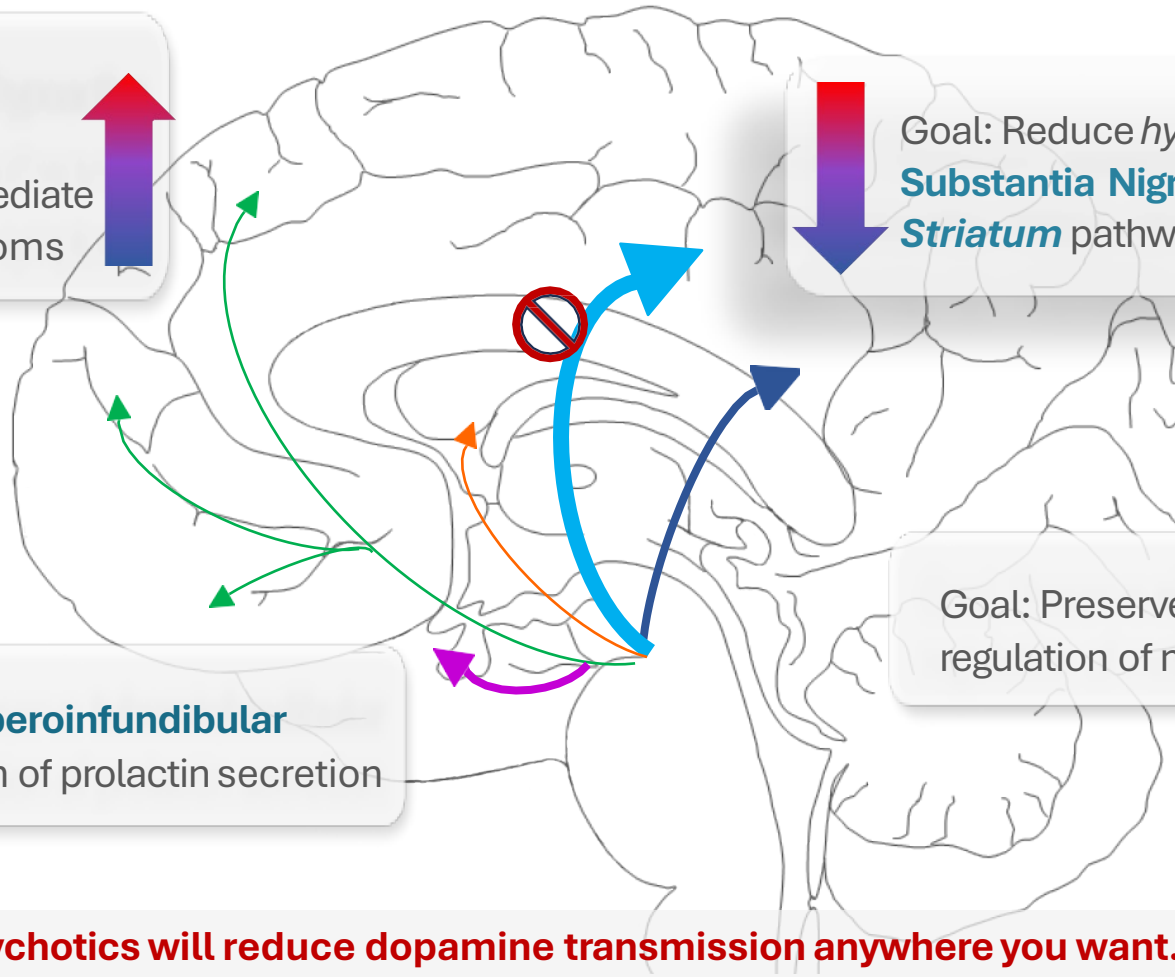
PET = Positron Emission Tomography. Howes OD, S Kapur. Schizo*phr. Bull. 2009;*35(3):549-62. McCutcheon RA, et al. *Trends Neurosci. 2019;*42(3):205-20. McCutcheon RA, et al. *Schizophr. Bull*. 2018;44(6):1301-11.

Do D2-Binding Antipsychotics Help Reach Schizophrenia Treatment Goals?

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

Goal: Reduce *hyperactivity* in the **Substantia Nigra-*Associative/SM*** ***Striatum*** pathway to mediate psychosis

SNASM



Goal: Preserve **nigrostriatal** pathway regulation of motor movement

Goal: Preserve **tuberoinfundibular** pathway regulation of prolactin secretion

D_2 binding antipsychotics will reduce dopamine transmission anywhere you want… and everywhere you don't

DA = Dopamine; SM = sensorimotor; SNASM = Substantia nigra-associative and sensorimotor cortex. Correll CU, et al. *J Clin Psychiatry*. 2022;15;83(1):SU21204IP1. McCutcheon RA, et al. *Trends Neurosci*. 2019;42(3):205-20

What do we do when our bucket begins to overflow?

Maybe a Presynaptic Problem Needs a Presynaptic Solution…?

Key Learning Points

- ✓ Historical treatments for schizophrenia all involve direct D_2 (+/- 5-HT_{2A}) receptor modulation. **Antipsychotics may not address all symptoms, may worsen others**, and may cause side effects as well as long-term risks (eg, tardive dyskinesia)

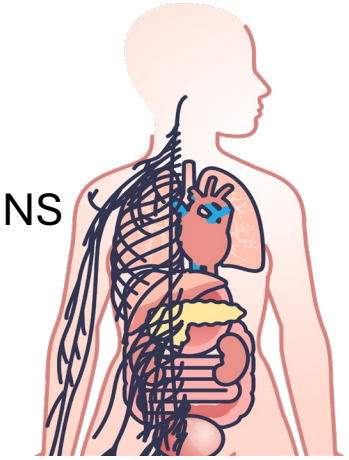
- ✓ Over the past 70 years, **antipsychotic efficacy has hardly improved while tolerability has only somewhat improved**, which may be the primary driver of adherence

- ✓ When treating schizophrenia, **we've been trying for >70 years to solve a presynaptic problem with a postsynaptic intervention**

Emerging Therapeutic Target in Schizophrenia: Muscarinic Acetylcholine Receptor Activation

Review of the Cholinergic System

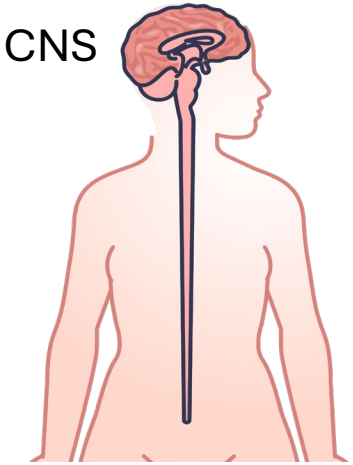
Acetylcholine subserves a wide variety of different functions in both the peripheral and central nervous systems



Glandular secretion (mucous membranes)

Heart rate regulation

Muscle contraction (movement, respiration)



Memory and learning

Attention

Synaptic plasticity

Reward processing

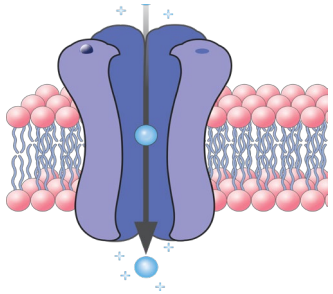
These functions are mediated by two families of acetylcholine receptors

Nicotinic Receptors

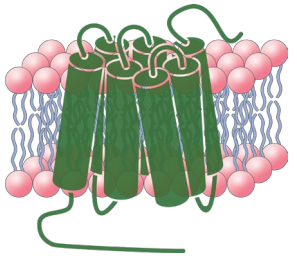
Ion-gated channel receptor

Fast synaptic transmission

Neuromuscular junctions and CNS



Muscarinic Receptors



G-protein–coupled receptor

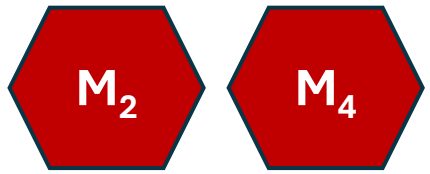
Second messenger cascades

CNS and PNS-mediating innervation to visceral organs

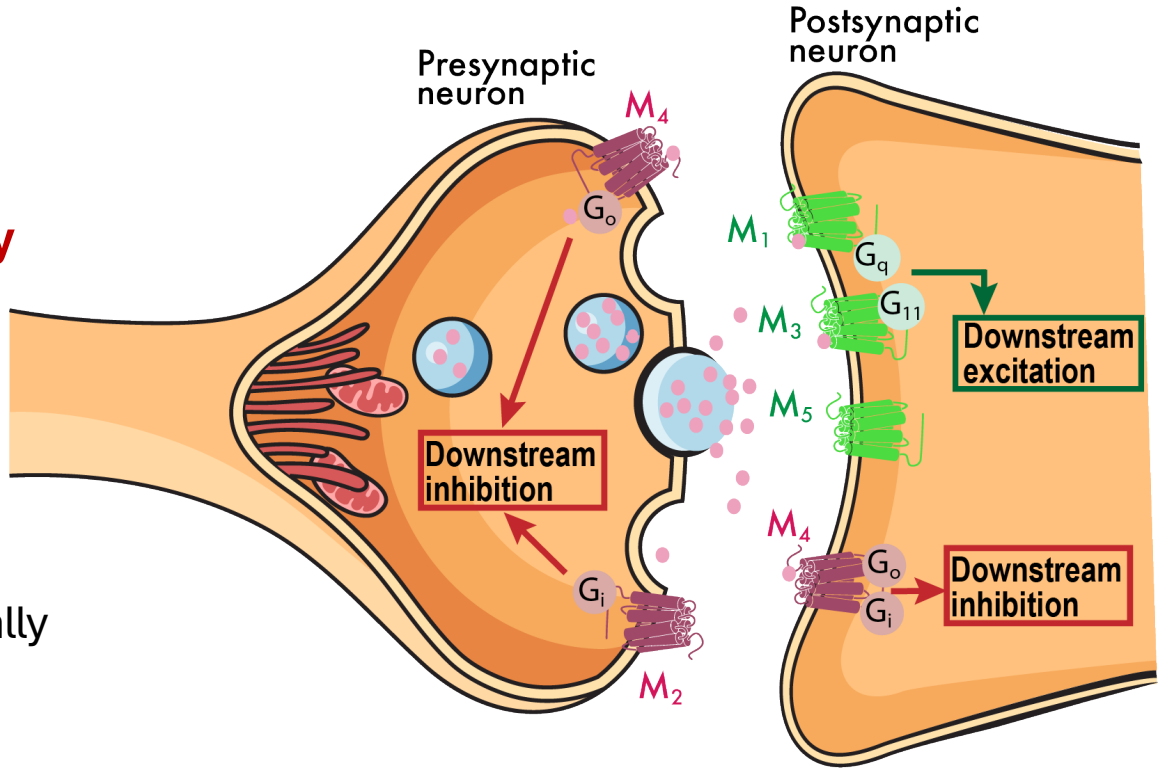
AChR = Acetylcholine receptor; CNS = Central nervous system; GPCR = G-protein coupled receptor; PNS = Peripheral nervous system. Paul SM, et al. *Am J Psychiatry*. 2022;179(9):611-27. Brown DA. *Brain Neurosci Adv*. 2019;3:1-10. 3. Unwin N. *Q Rev Biophys*. 2013;46(4): 283-22.

The Five Subtypes of Muscarinic Receptors Have Selective Effects

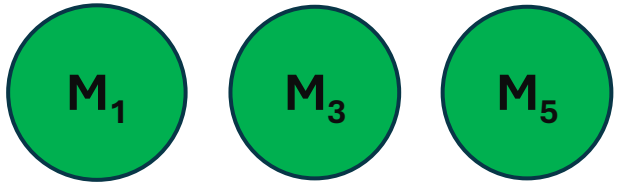
M_2 and M_4 are inhibitory



Found pre- and post-synaptically



M_1, M_3, M_5 are excitatory

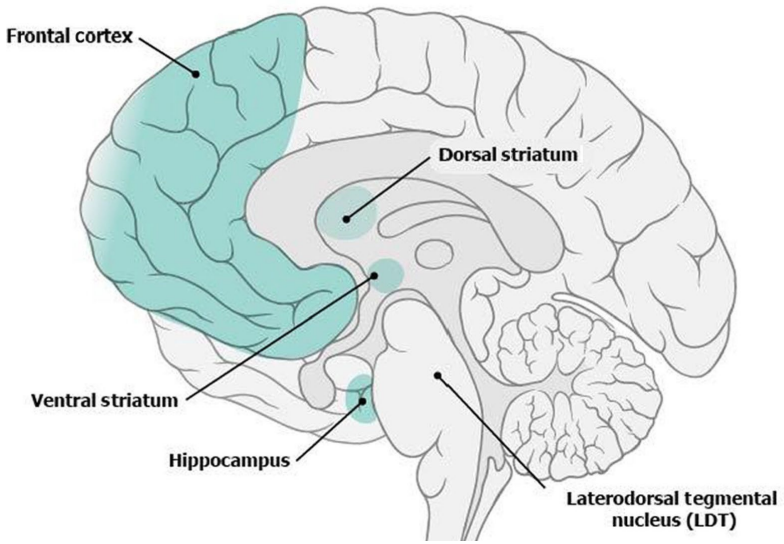


Found postsynaptically

Ryan AE, et al. *Aust New Zeal J Psychiatry*. 2019;53(11):1059-69. Paul SM, et al. *Am J Psychiatry*. 2022;179(9):611-27.

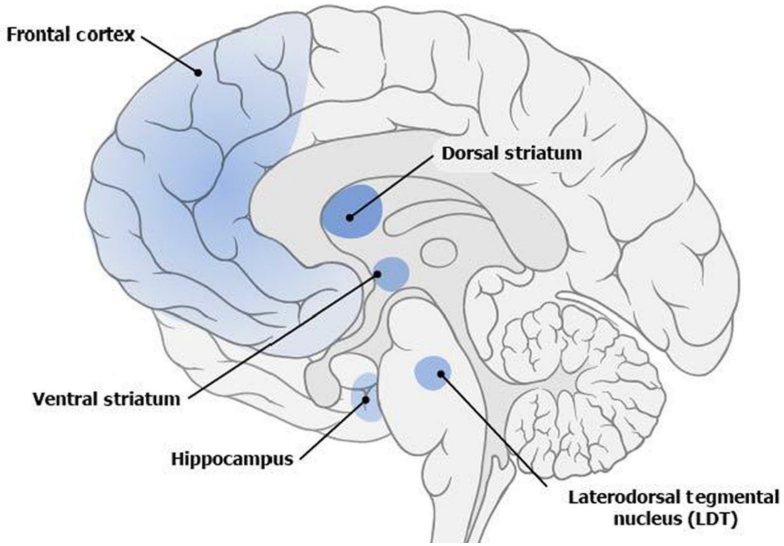
M_1 and M_4 Receptors are Highly Enriched in Brain Areas Underlying Circuits Associated with Psychosis

Expression of M_1 Receptors



Increasing expression

Expression of M_4 Receptors

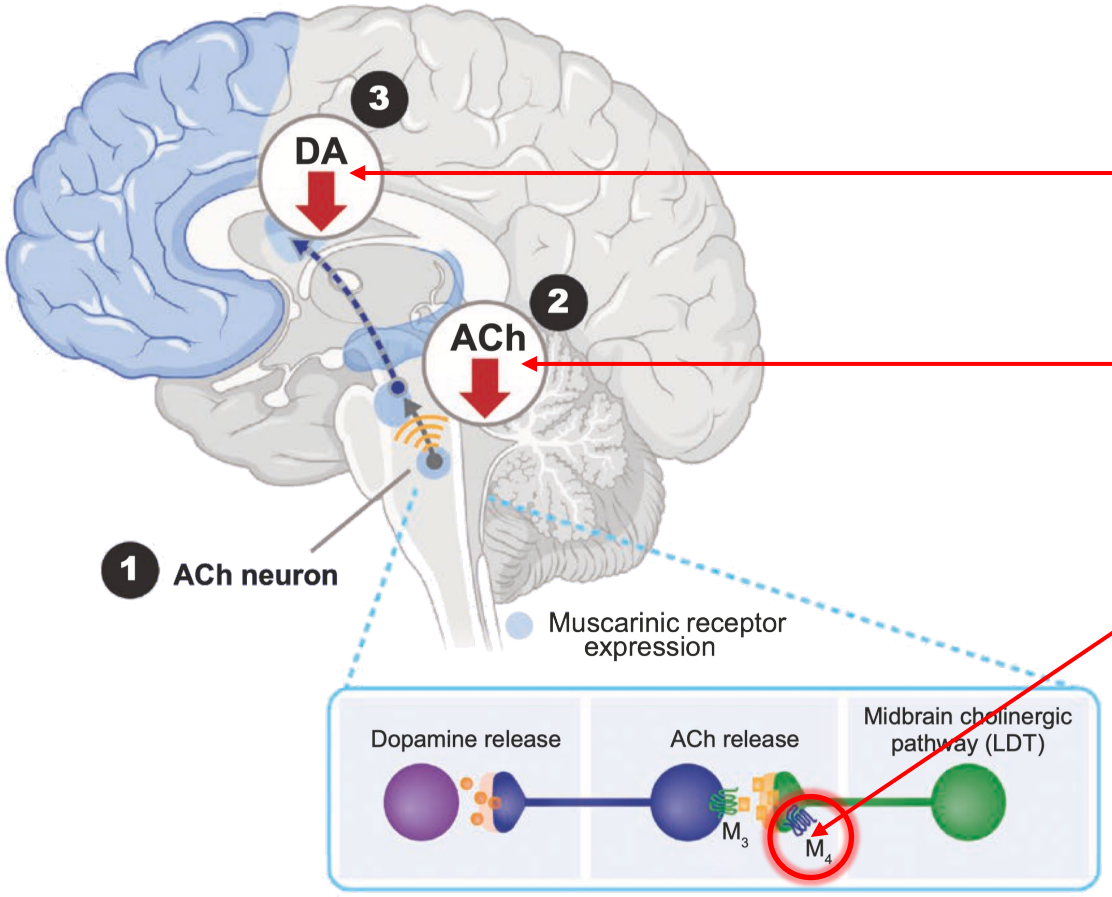


Increasing expression

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

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

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

Bottom Line

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

ACh = acetylcholine; LDT = Laterodorsal tegmental; VTA = Ventral tegmental area. Meyer, JM., et al. *Int J Neuropsychopharmacol*. 2025;28(4):pyaf015.

M_4 Agonism Improves Psychosis by Reducing Striatal Dopamine Release in a Selective Fashion

D_2 antagonism/partial agonism will put the dopamine ball in the corner pocket

...but at a substantial price

M_4 agonism can get the same job done ***without*** the collateral damage.

Take Home

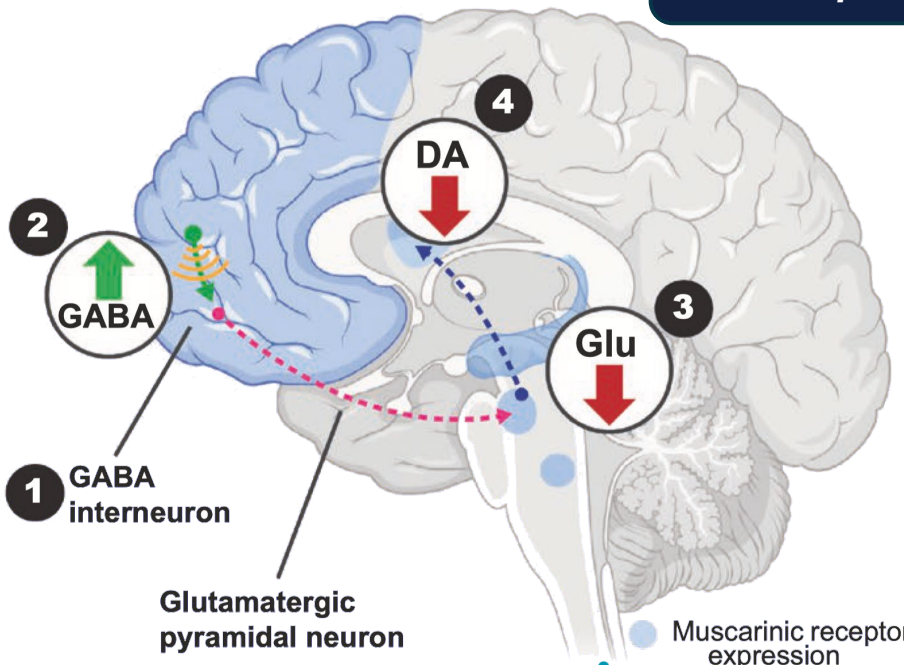
Because this circuit flows from the midbrain up to the VTA, we call it "bottom-up" regulation of dopamine

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

Bottom Line

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

Meyer, JM., et al. *Int J Neuropsychopharmacol*. 2025;28(4):pyaf015.Paul SM, et al. *Am J Psychiatry*. 2022;179(9): 611–27.

M_1 Agonism Improves Psychosis by Reducing Striatal Dopamine Release in a Selective Fashion

M_1 Agonism also clears the dopamine ball from the table ***without*** the collateral damage

...it's just a little fancier of a shot!

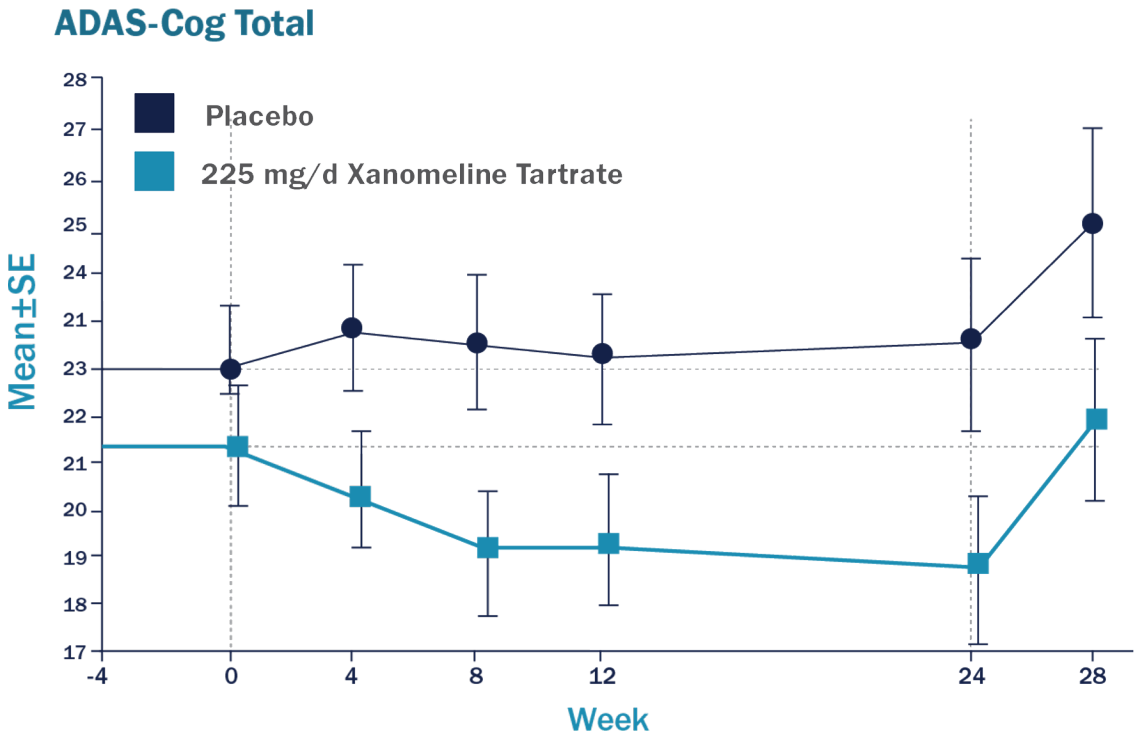
Take Home

Because this circuit flows from the PFC down to the VTA, we call it "top-down" regulation of dopamine

Meyer, JM., et al. *Int J Neuropsychopharmacol*. 2025;28(4):pyaf015.Paul SM, et al. *Am J Psychiatry*. 2022;179(9): 611–27.

The Origin Story of Xanomeline

Xanomeline is a Selective M_4 and M_1 Agonist Initially Studied in the 1990s for Alzheimer's Disease Cognition



Adverse Event	Placebo (n=87)	75 mg/d (n=85)	150 mg/d (n=83)	225 mg/d (n=87)	Xanomeline Pooled (n=342)
Sweating	5%	14%	46%	76%	35%
Nausea	20%	28%	35%	52%	34%
Vomiting	9%	13%	40%	43%	26%
Dyspepsia	8%	24%	28%	24%	21%
Chills	1%	9%	27%	37%	18%
Chest Pain	1%	6%	16%	12%	9%
Increased salivation	0%	2%	7%	24%	9%
Syncope	5%	4%	13%	13%	9%
Fecal incontinence	0%	5%	1%	7%	3%
Nausea / vomiting	2%	0%	1%	8%	3%
Dysphagia	1%	0%	2%	7%	3%
Discontinuation	35%	19%	48%	**59% (52% due to AE)**	

It was found to be efficacious…

But its tolerability profile was unacceptable

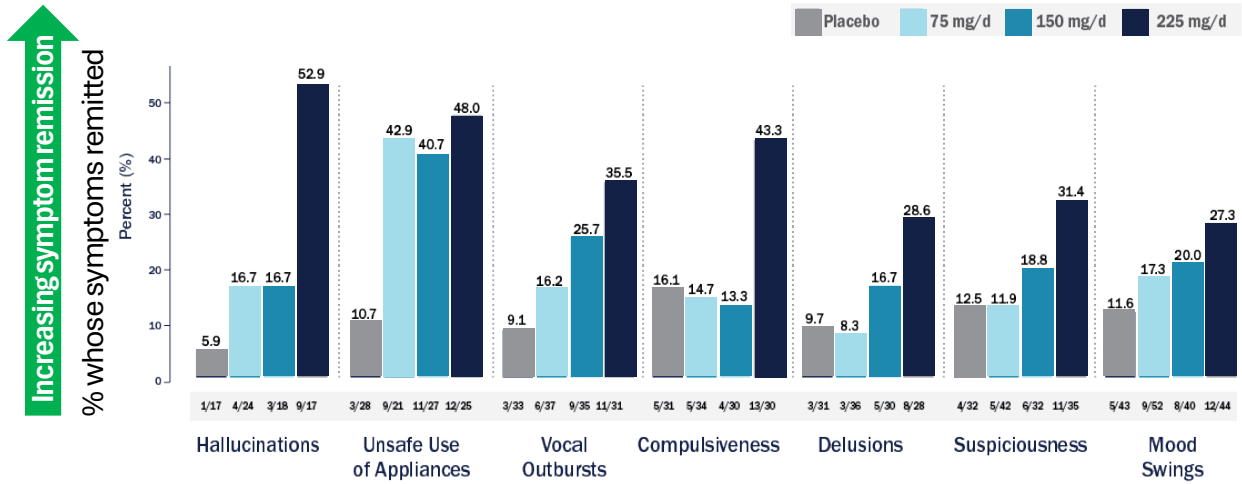
ADAS-Cog = Alzheimer's Disease Assessment Scale Cognitive Subscale; AE = Adverse event; CIBIC+ = Clinician's Interview-Based Impression of Change.

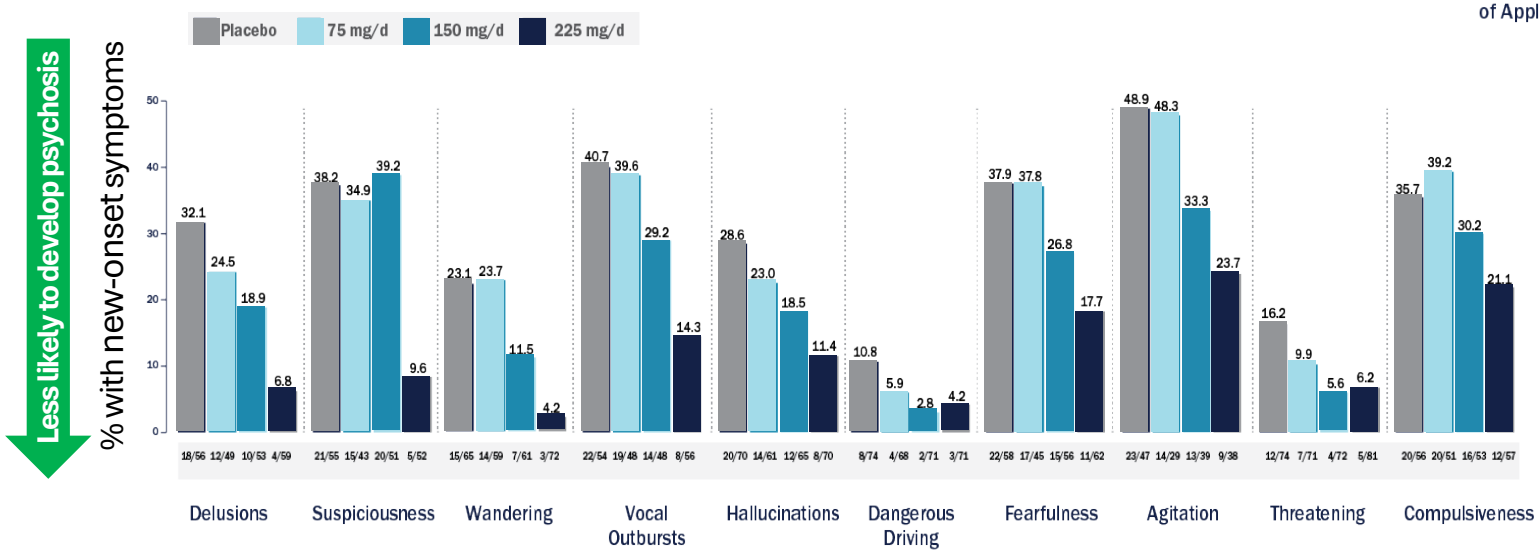
Bodick NC, et al. *Arch Neurol.* 1997;54(4):465-73.

Xanomeline is a Selective M_1 and M_4 Agonist Initially Studied For Cognition in Alzheimer's Disease

However, there were some interesting findings in the secondary outcomes…

Many who had psychosis when beginning the trial had a <u>resolution</u> of those symptoms with treatment

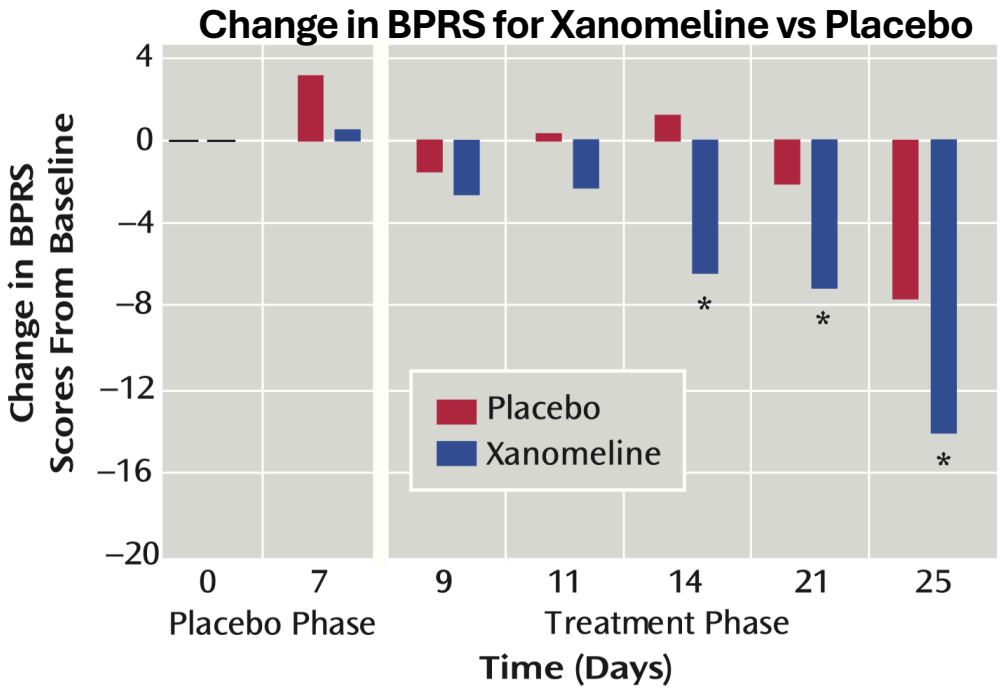




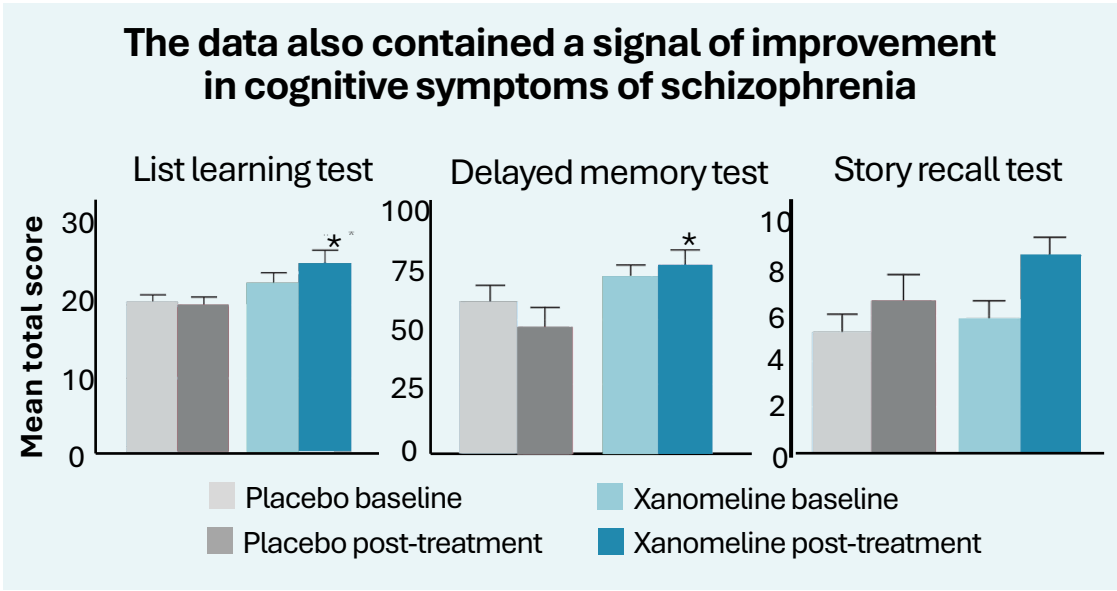
And of those without psychosis at baseline, <u>fewer</u> who received xanomeline developed new-onset psychosis

Bodick NC, et al. *Arch Neurol*. 1997;54(4):465-73.

A Pilot Study Showed Xanomeline Also Had Potential in Schizophrenia



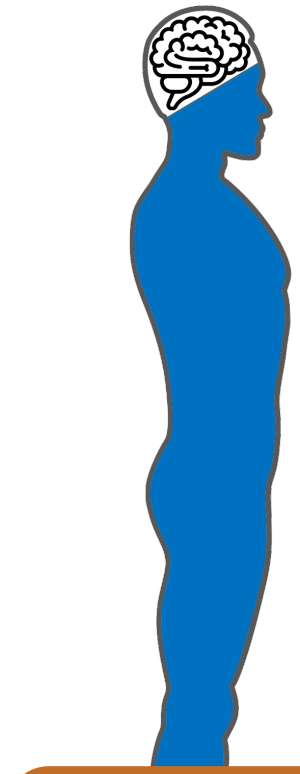
Key Adverse Events	Placebo (n=10)	Xanomeline (n=10)
Nausea	40%	70%
Vomiting	10%	60%
GI Distress	50%	70%



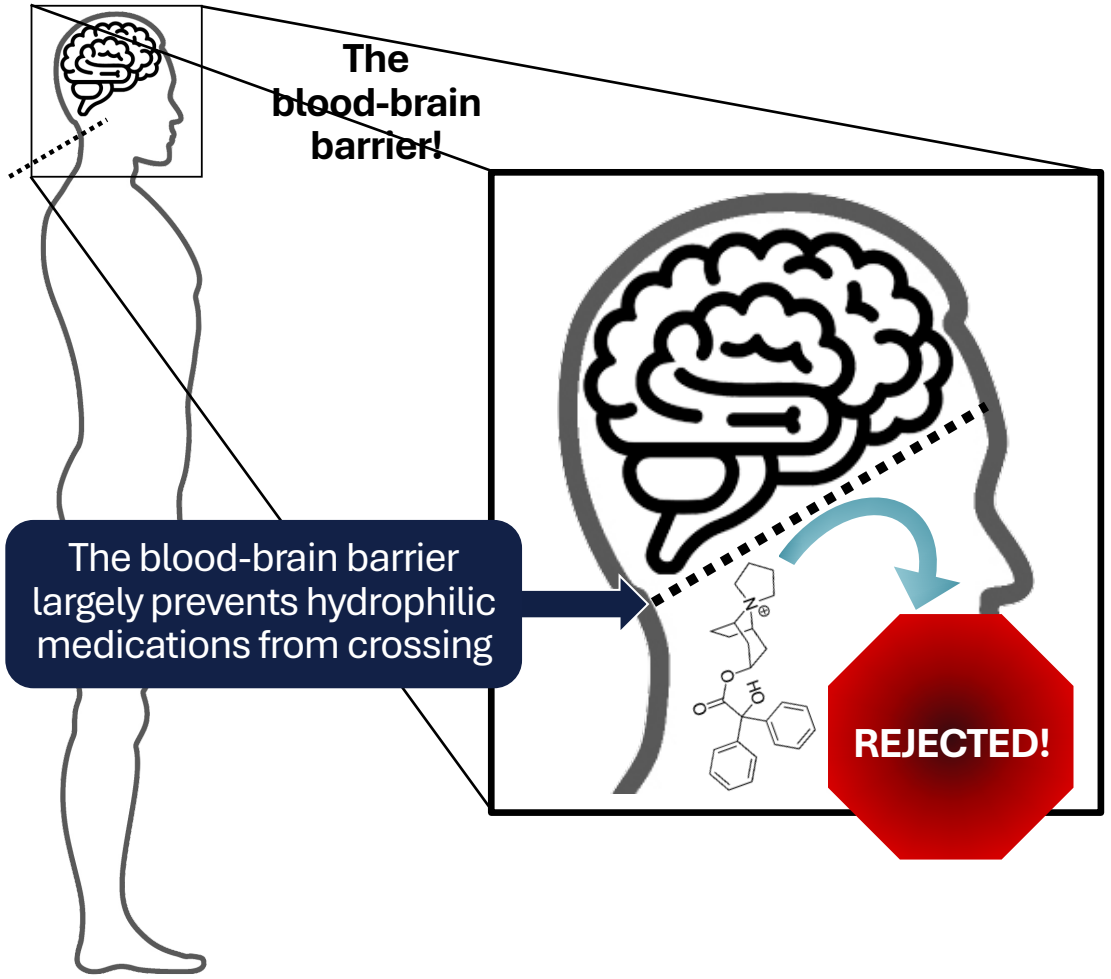
Xanomeline was also effective for treating the symptoms of schizophrenia, but was still too poorly tolerated to pursue

Shekhar A, et al. *Am J Psychiatry*. 2008 Aug;165(8):1033-9.

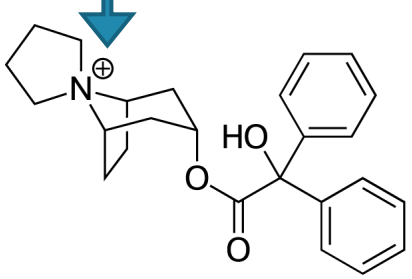
Selectively Neutralizing Peripheral Cholinergic Effects



An anticholinergic with only peripheral effects would be ideal to add to trospium



A strong positive charge makes trospium too hydrophilic to meaningfully cross the blood-brain barrier



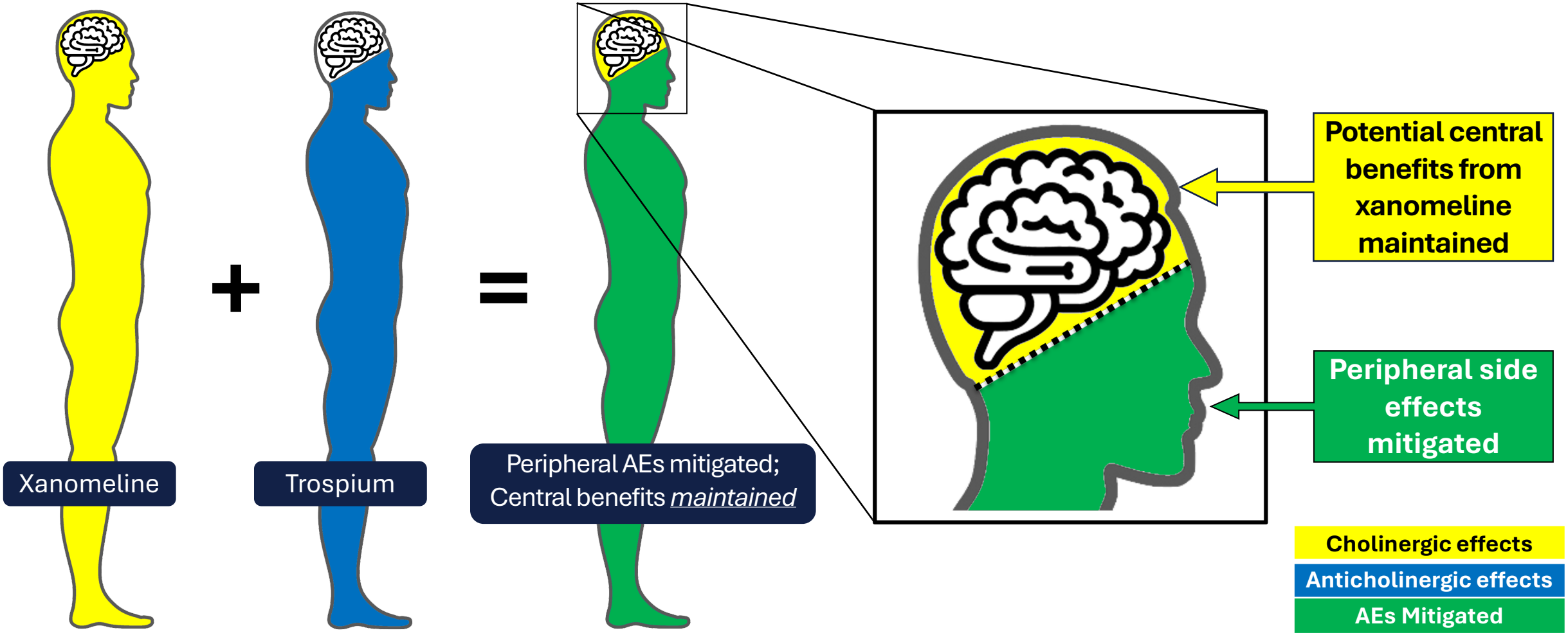
After screening hundreds of compounds, trospium was identified as a candidate

Trospium is a pan-muscarinic antagonist approved for overactive bladder in 2004 in the US and in 1974 internationally

Little to no impact on cognition or other central effects and not associated with increased dementia risk

Callegari, E, et al. Br J Clin Phamacol. 2011;72.2: 235-46. Chancellor MB, et al.. *Drugs Aging* 2012;29:259-73. Duong V, et al. *Int Urogynecol J.* 2021;32:2693-702. Malcher MF, et al. *J Urol* 2022:101097.

Trospium Neutralizes Primarily the Peripheral Cholinergic Effects when Added to Xanomeline



Brannan SK, et al. *N Engl J Med*. 2021;384(8):717-76

Key Learning Points

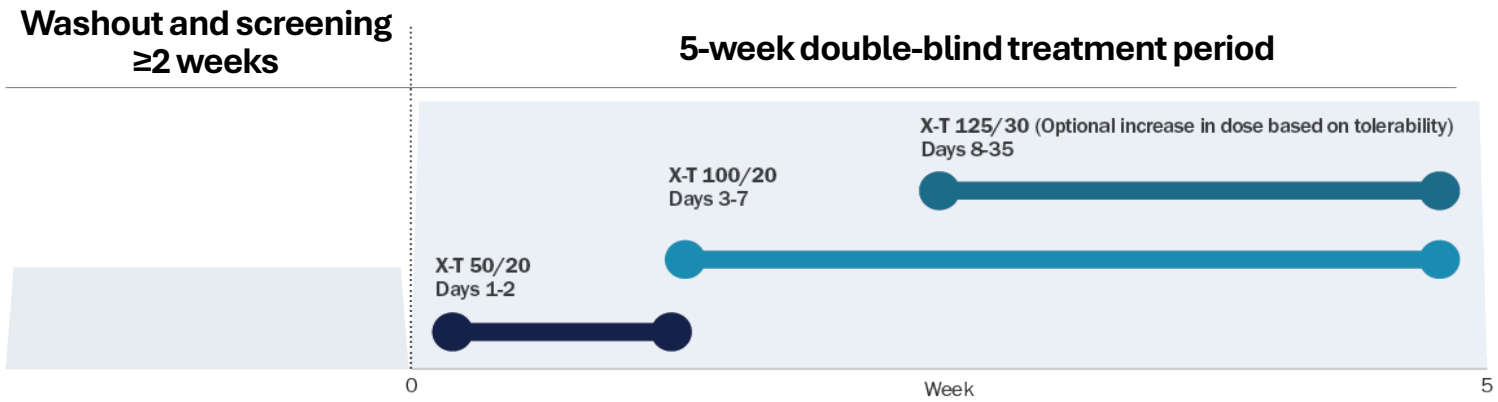
- ✓ **Stimulation** of **M_4** receptors **decreases dopamine release** in the **VTA,** which **reduces** symptoms of **psychosis**

- ✓ **Stimulation** of **M_1 receptors** in the PFC also **decreases dopamine release** in the **VTA**, which may also **reduce** symptoms of **psychosis**

- ✓ Xanomeline was **effective for psychosis and cognition in Alzheimer's disease and schizophrenia**, but development was halted due to peripheral cholinergic adverse effects

Clinical Evidence for Xanomeline-Trospium in Schizophrenia

Overview of Short-Term Xanomeline/Trospium Trials



The clinical trial program consists of 3 nearly identically designed 5-week inpatient studies of acutely exacerbated schizophrenia

In the phase 2 EMERGENT-1 trial, patients were aged 18 to 60 years; and 18 to 65 years in phase 3 EMERGENT-2 and -3

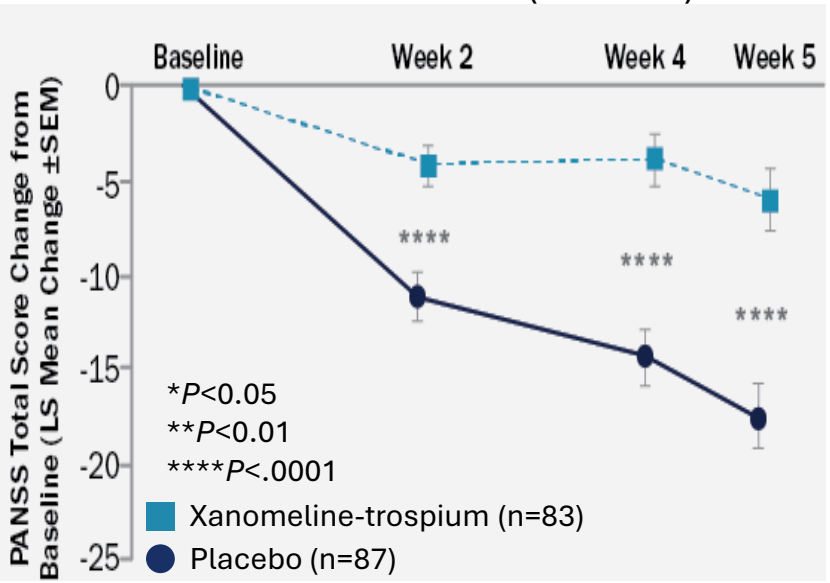
Pooled Demographics

	X-T (n = 314)	Placebo (n=326)
Age (years), mean ±SD	44.6 ± 10.7	43.7 ± 11.3
Male	74.2%	76.7%
Female	25.8%	23.3%
Black	71.7%	67.8%
White	26.4%	30.1%
Weight (kg), mean ±SD	88.9 ± 18.5	87.3 ± 18.6
BMI (kg/m^2), mean ±SD	29.2 ± 5.5	28.9 ± 5.4
PANSS total mean ± SD	97.5 ± 9.0	97.0 ± 8.9

Kaul I, et al. Schizophrenia 10.1 (2024): 102.

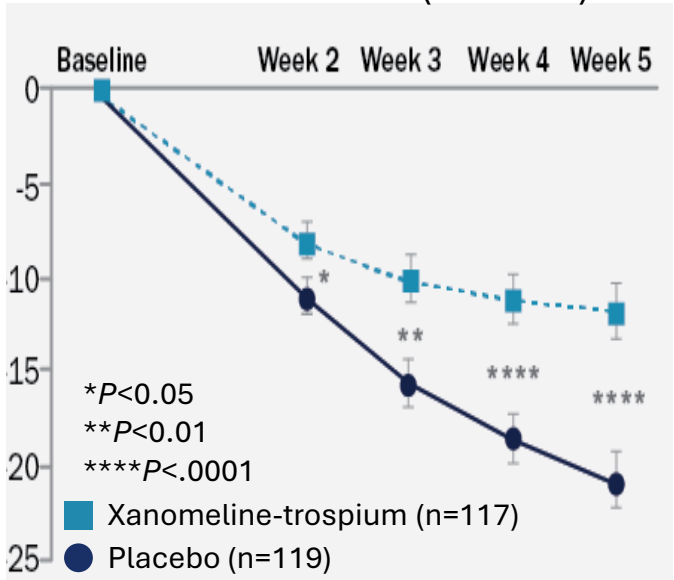
Xanomeline/Trospium Showed Consistent Efficacy in All Short-Term Phase 2 & 3 Trials

EMERGENT-1 (Phase 2)



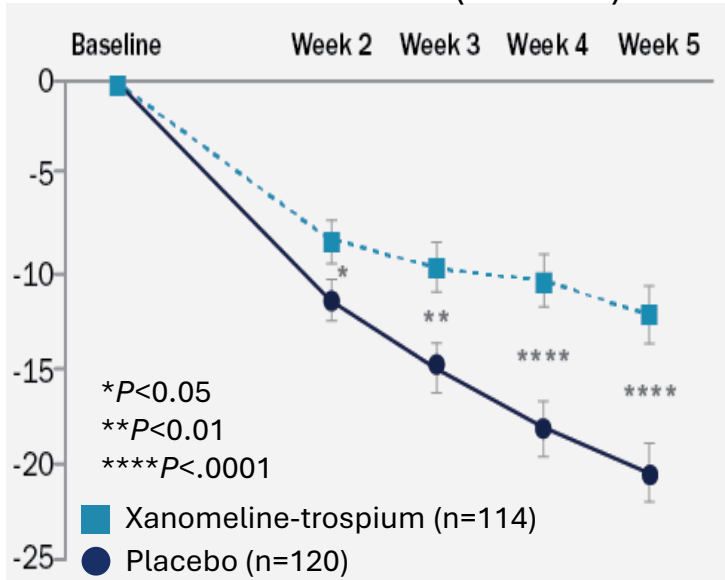
11.6-point reduction vs placebo at week 5
Effect size=0.81

EMERGENT-2 (Phase 3)



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

EMERGENT-3 (Phase 3)

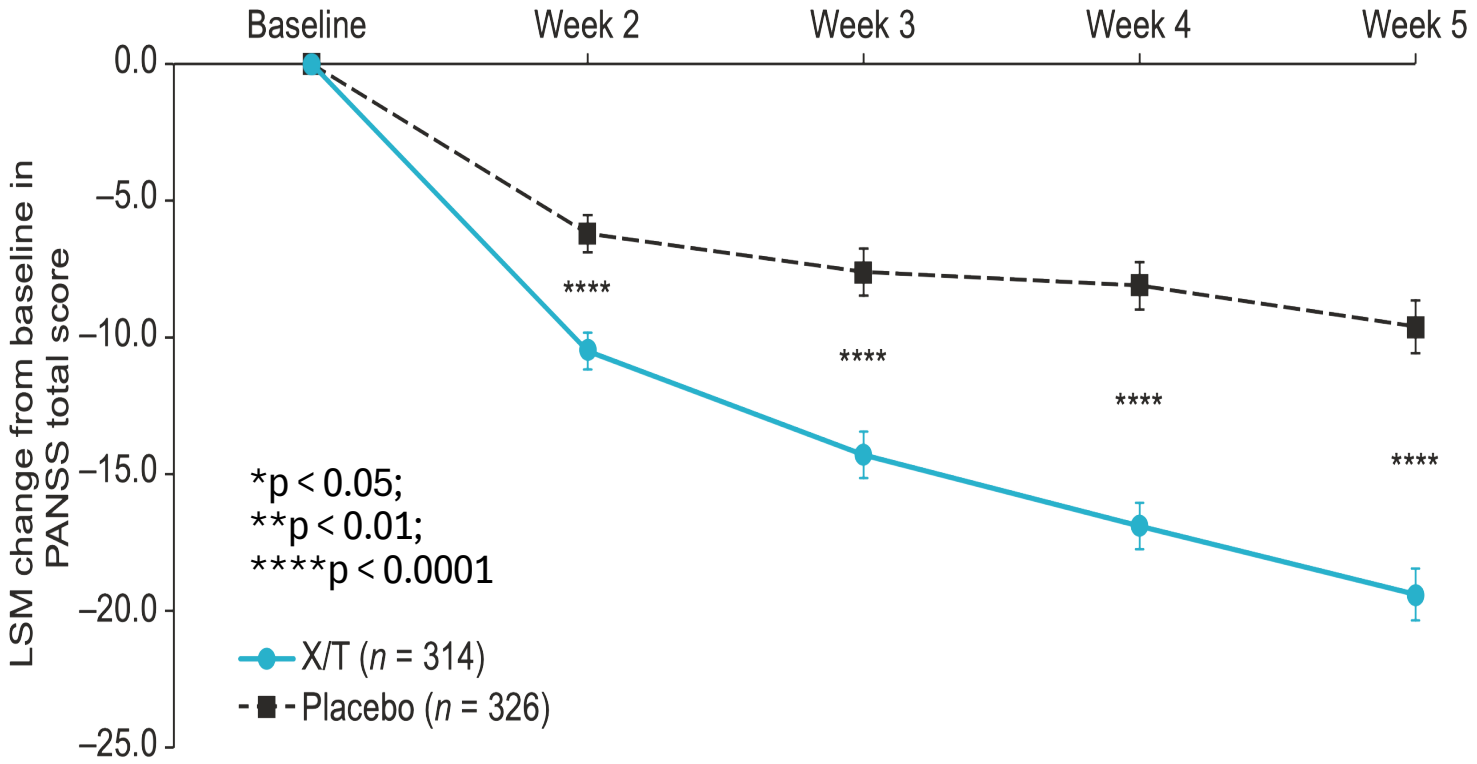


8.4-point reduction vs placebo at week 5
Effect size=0.60

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

Brannan SK, et al. *N Engl J Med*. 2021;384(8):717-26. Kaul I, et al. *Lancet*. 2024; 403(10422):160-70;3. Kaul I, et al. *JAMA Psych*. 2024; 81(8):749-56. Kaul I, et al. Schizophrenia 10.1 (2024): 102.

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



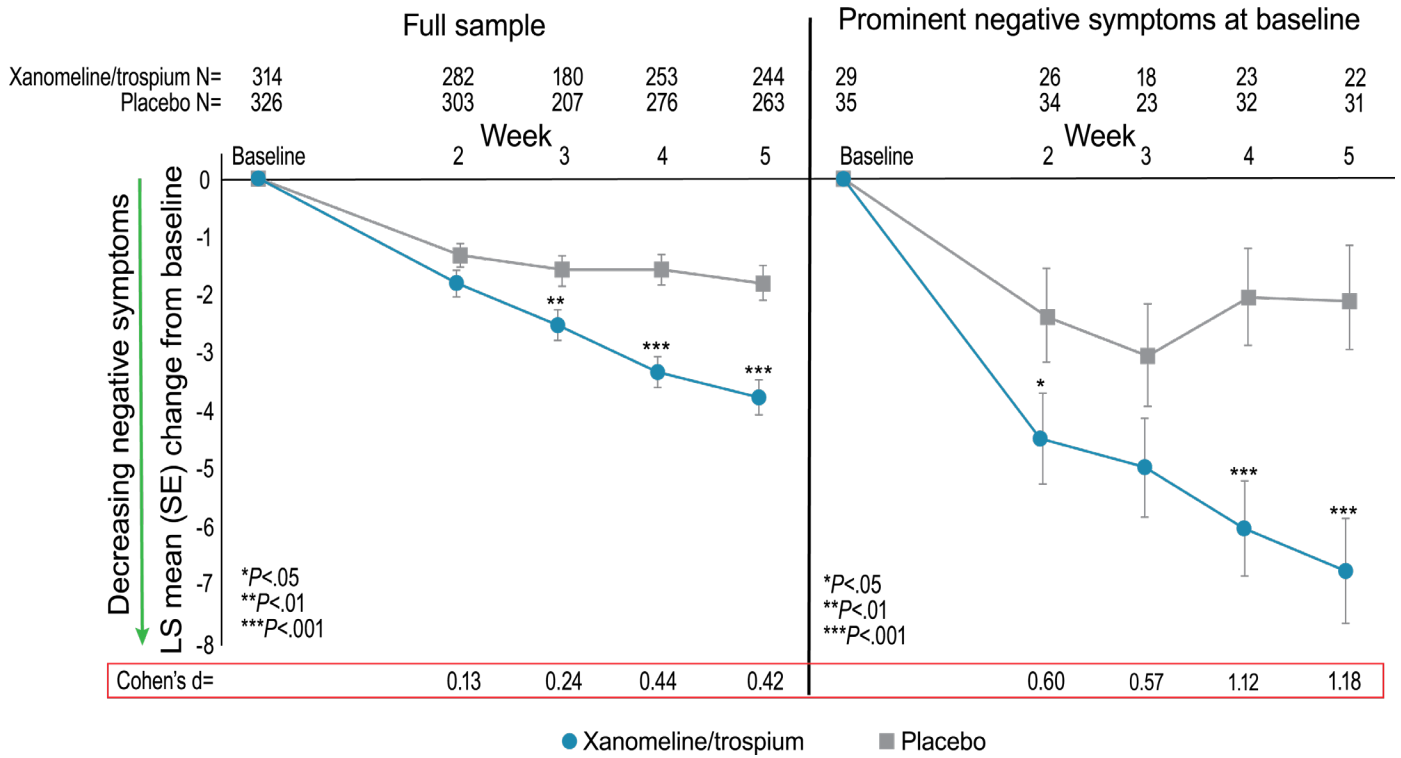
Pooled Effect Size 0.65 (95% CI ≈0.49 to 0.81)

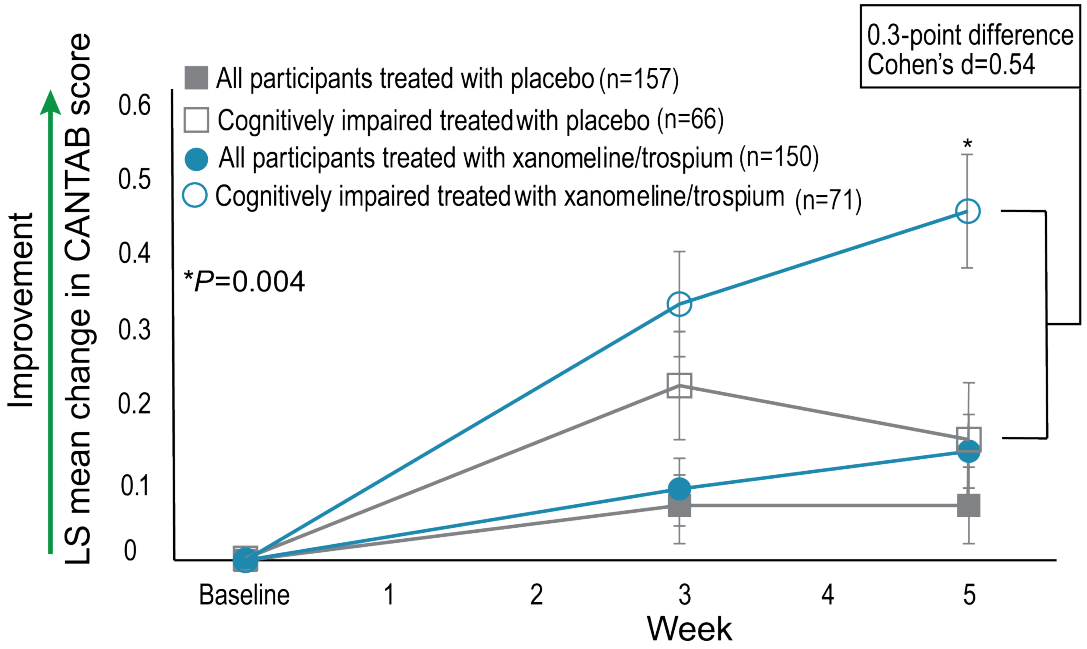
Comparative Efficacy by Network Meta-Analysis

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)

CI=Confidence interval; CrI=Credible interval. Kaul I, et al. Schizophrenia 10.1 (2024): 102. Huhn M, et al. *Lancet*. 2019; 394(10202):939-51.

Phase 3 Trials of Xanomeline/Trospium Suggest an Efficacy Signal for Negative and Cognitive Symptoms





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 Dec:274:57-65.

Xanomeline/Trospium Had a Very Different AE Profile From That of Antipsychotics in Phase 3 Studies

AEs Occurring in ≥5% Treated with Xanomeline/Trospium in Phase 3 Studies

	X-T (n=340)	Placebo (n=343)
Nausea	19%	4%
Dyspepsia	18%	5%
Constipation	17%	7%
Vomiting	15%	1%
Hypertension	11%	2%
Abdominal pain	8%	4%
Diarrhea	6%	2%
Tachycardia	5%	<1%
GERD	5%	2%

Mean weight gain	Placebo 1.4 lbs	Xanomeline-trospium 2.0 lbs
Proportion with weight gain ≥7%	Placebo 11%	Xanomeline-trospium 5%

Other AEs of Interest in Phase 3 Studies

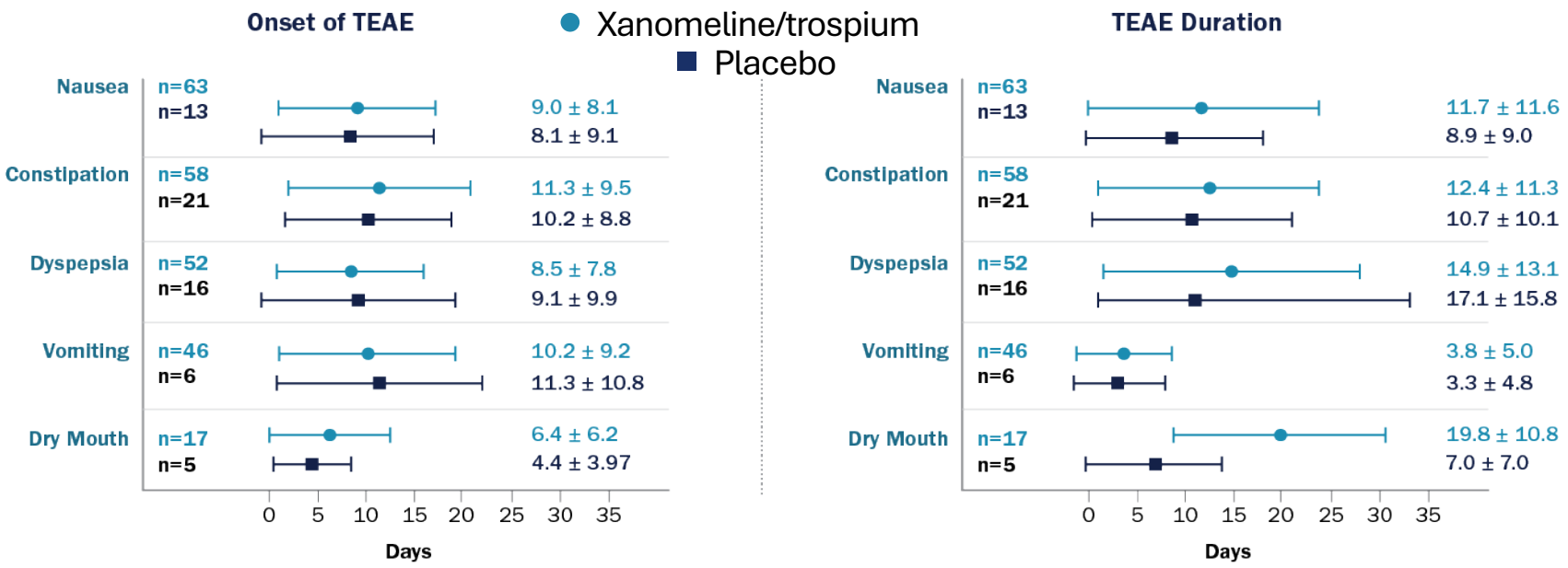
	X-T	Placebo
HR Change, Day 8	+13.5 bpm	+4.0 bpm
HR Change, Day 35	+11.4 bpm	+5.5 bpm
ALT or AST ≥ 3x ULN	2.8%	0.4%
Urinary Retention	0.8%	0.4%

No differences between groups in akathisia, parkinsonism, or tardive dyskinesia

Discontinuations due to AEs
Xanomeline/trospium 6% vs. placebo 4%

X-T=Xanomeline-Trospium. Cobenfy (xanomeline-trospium) Prescribing Information. Drugs@FDA: FDA Approved Drugs. Accessed May 23, 2025. www.accessdata.fda.gov/scripts/cder/daf/.

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

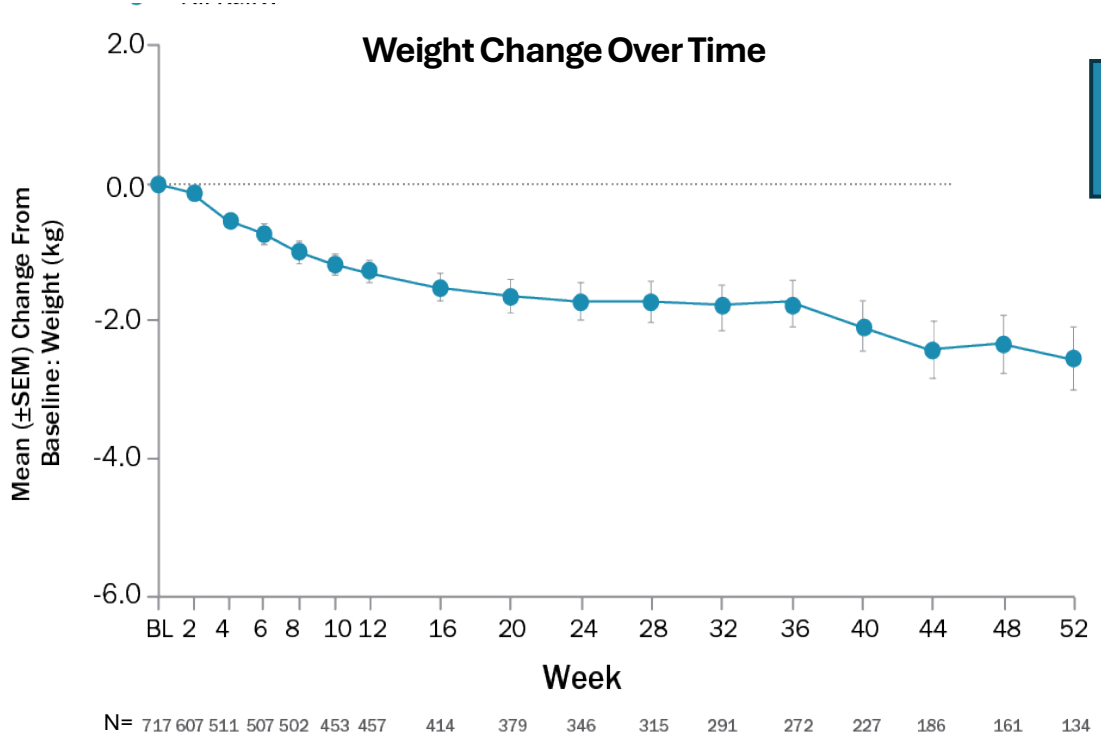
TEAE=Treatment-emergent adverse event. Kaul I, et al. *J Clin Psychiatry* 86.1 (2025): 24m15497.

Safety and Tolerability in Pooled Interim EMERGENT-4 and -5 Data

EMERGENT-4 is the 52-week open-label extension of EMERGENT-2 or -3
EMERGENT-5 is an open-label safety study for those not previously exposed to xanomeline/trospium

AEs Occurring in ≥5% (N=718)	
Nausea	19%
Vomiting	16%
Constipation	15%
Dry mouth	9%
Dyspepsia	7%
Dizziness	7%
Hypertension	6%
Any AE	62%
Serious	2%
Schizophrenia	1%
Other	0.5%

Discontinuation due to TEAEs was 14.9%



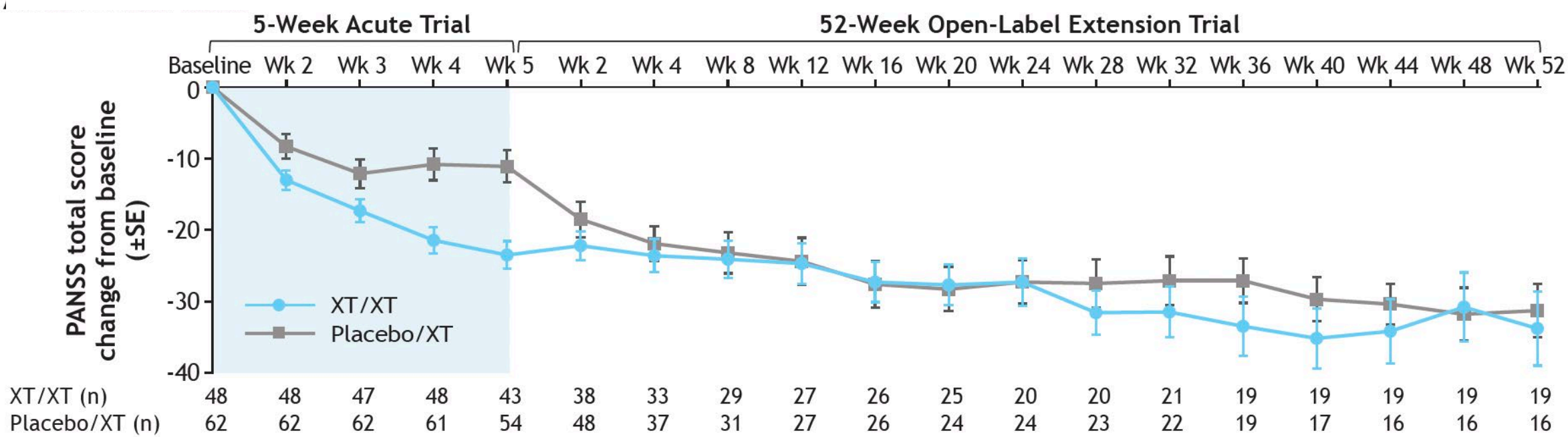
After 52 Weeks

Mean body weight change:	- 5.6 lbs
Body weight increase of ≥7%:	4.1%
Body weight decrease of ≥7%:	17.6%

Not associated with clinically meaningful changes in **prolactin** or **movement disorder** scale scores over 52 weeks

Marcus R, et al. Poster F74 presented at 2024 Annual Conference of the Schizophrenia International Research Society (SIRS), 2024.

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

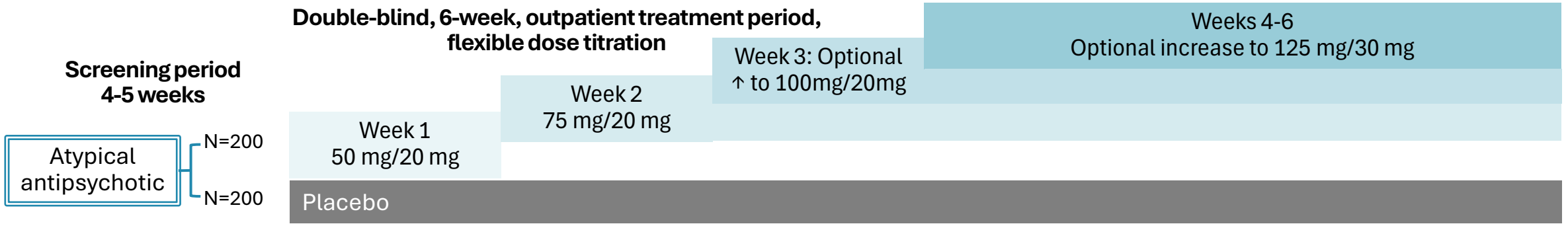


Mean PANSS total score change from baseline of double-blind trial to week 52 of OLE

-33.6 points in those who **continued xanomeline/trospium** with similar reduction after switch from placebo

Kaul I, et al. Poster Presented at the 2025 Annual Congress of the Schizophrenia International Research Society (SIRS).

Evaluation of Xanomeline/Trospium for Adjunctive Treatment of Schizophrenia



- ≥1 prior inadequate response to ≥6 weeks monotherapy of ziprasidone, lurasidone, cariprazine, risperidone, paliperidone, or aripiprazole
- Were on a stable dose of an atypical antipsychotic for ≥8 weeks on day 1 of treatment

Xanomeline/trospium reduced PANSS by 2 points more than placebo, but did not reach statistical significance (*P*=0.11)

Safety and tolerability was consistent with prior clinical trials of xanomeline/trospium as monotherapy for schizophrenia

In a post-hoc analysis, adjunct use with non-risperidone antipsychotics (~2/3 of total patients) reduced PANSS by 3.4 points more than placebo (nominal p=0.03)

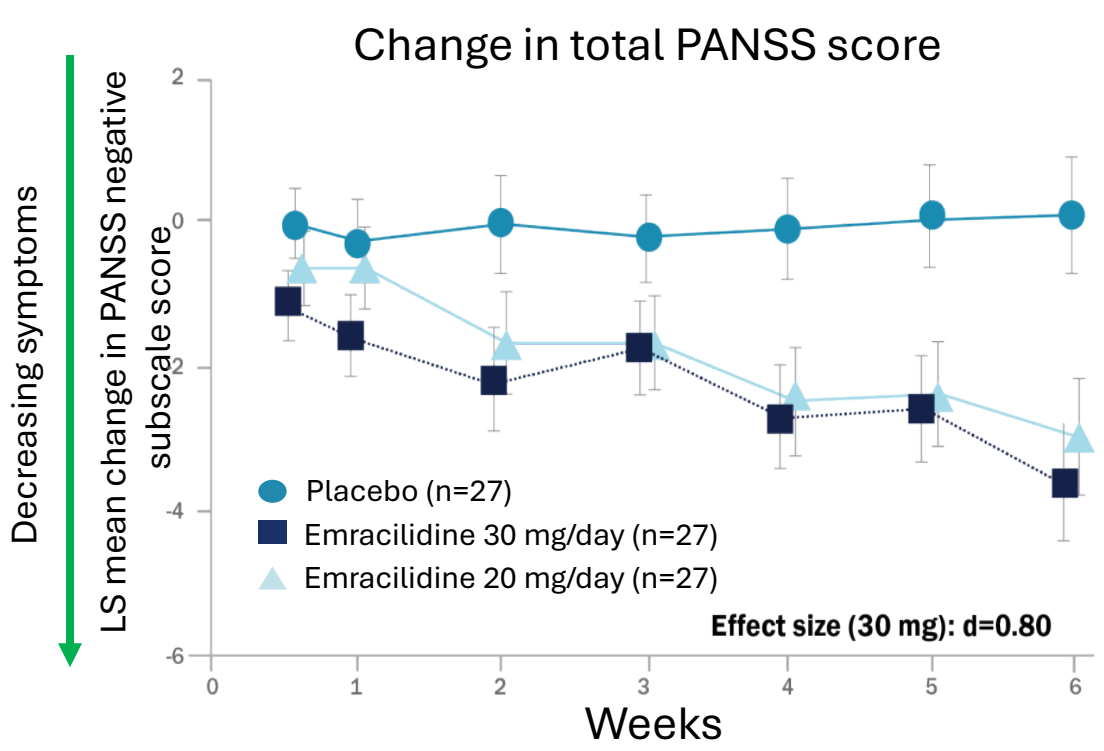
https://clinicaltrials.gov/ct2/show/NCT05145413. Bristol Myers Squibb [press release], April 22, 2025. Accessed May 22, 2025. https://news.bms.com/news/details/2025/Bristol-Myers-Squibb-Announces-Topline-Results-from-Phase-3-ARISE-Trial-Evaluating-Cobenfy-xanomeline-and-trospium-chloride-as-an-Adjunctive-Treatment-to-Atypical-Antipsychotics-in-Adults-with-Schizophrenia/default.aspx

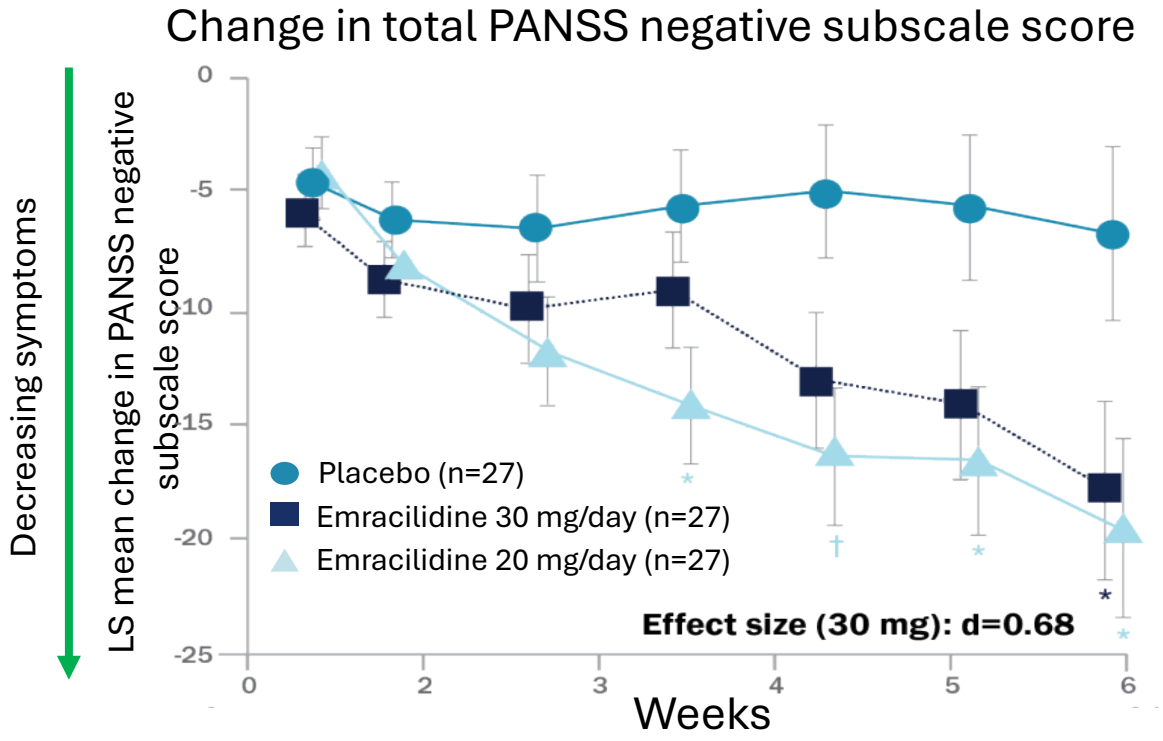
Key Learning Points

- ✓ **Trospium largely mitigated the procholinergic adverse effects of xanomeline**. AE-related discontinuation was 6% with xanomeline/trospium vs 4% with placebo.
- ✓ There is a replicated signal across all phase 2b/3 studies of **improved cognitive functioning** in those with more significant baseline cognitive dysfunction.
- ✓ In the **EMERGENT-4 open-label extension** study of patients with schizophrenia who completed either the EMERGENT-2 or EMERGENT-3 clinical trial, treatment with **xanomeline-trospium was associated with a mean PANSS total score change of -33.6**.

Other Activators of Muscarinic Receptors

Phase 1B Study of Positive Allosteric M4 Modulator Emraclidine





Emraclidine has 390-fold selectivity as a PAM for M_4 relative to M_2, and no effect on other muscarinic receptors

This small study showed a strong signal of efficacy, consistent with that of an orthosteric agonist

Discontinuation rate was 22% in each arm.

Krystal JH, et al. *The Lancet*. 2022;400(10369): 2210-20. Butler CR., et al. *J Medicinal Chem*. 2024;67(13): 10831-47.

Safety and Tolerability of Emraclidine in Phase 1B Study

	Placebo (n = 27)	Emraclidine 30 mg (n = 27)	Emraclidine 20 mg (n = 27)
AEs in ≥5% of all patients taking emraclidine			
Headache	26%	30%	26%
Nausea	4%	7%	7%
Weight increased	7%	4%	7%
Back pain	4%	4%	4%
CPK increased	0%	4%	7%
Dizziness	0%	4%	7%
Dry mouth	0%	11%	0%
Somnolence	0%	4%	7%
Serious AEs	0%	7%	4%
AEs leading to discontinuation	0%	7%	4%

Emraclidine's tolerability profile in this small study was very favorable

No clinically meaningful findings relative to placebo were observed, including

- Clinical laboratory assessments
- Changes in weight
- Drug-induced movements
- ECG parameters

- Transient, modest increases in heart rate and blood pressure occurred
  - Asymptomatic
  - Decreased over time,
  - Not considered clinically meaningful vs placebo at 6 weeks

Krystal JH, et al. *The Lancet*. 2022;400(10369): 2210-2220.

Phase 2 Studies of Emraclidine Did Not Meet Primary Endpoints

Efficacy

No significant improvement in PANSS scores

Tolerability

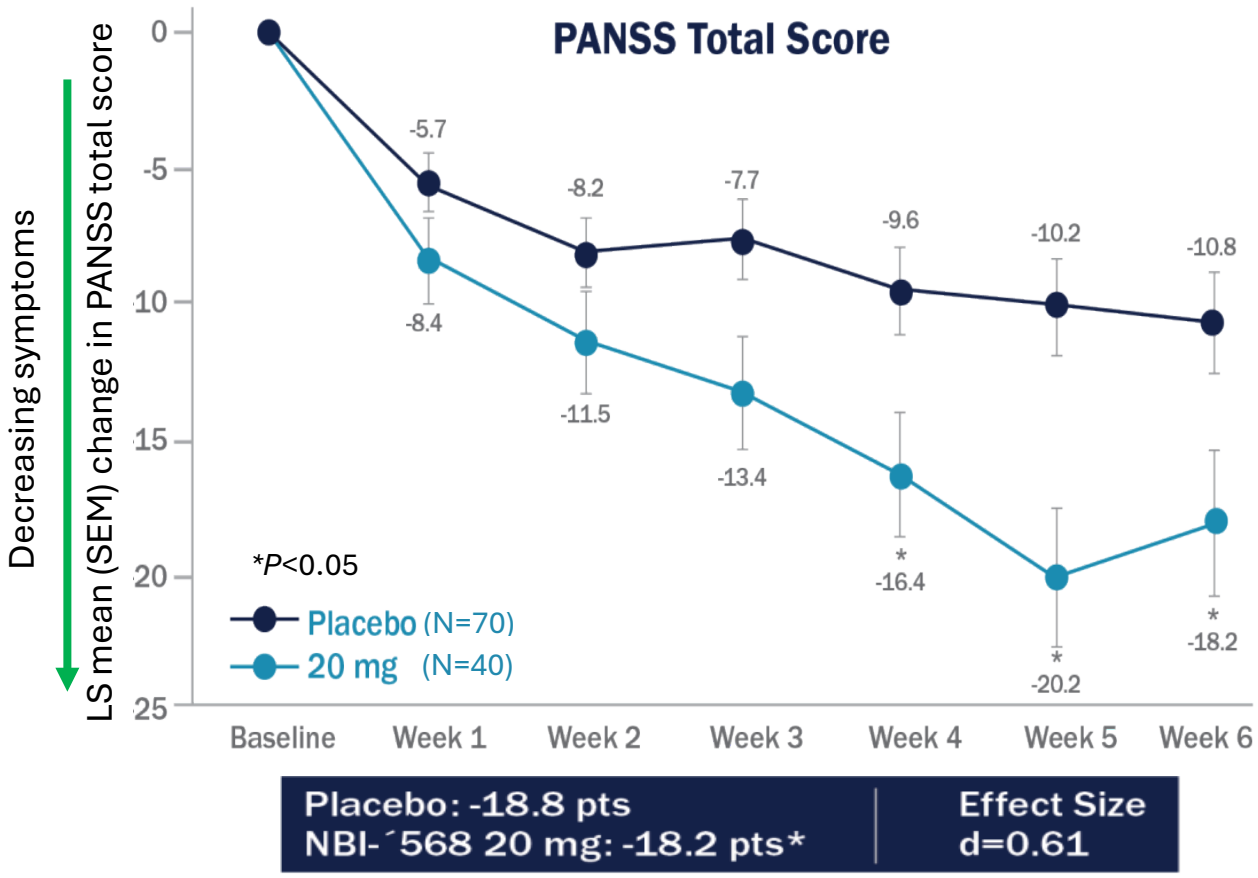
Well-tolerated with stable safety profile

Change from Baseline to Week 6 in PANSS Total Score

	EMPOWER-1			EMPOWER-2		
	Placebo (N= 127)	Emraclidine 10mg QD (N = 125)	Emraclidine 30mg QD (N = 127)	Placebo (N = 128)	Emraclidine 15mg QD (N = 122)	Emraclidine 30mg QD (N = 123)
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)

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

NBI-1117568 Is a M_4 Agonist with 500-fold More Selectivity for M_4 vs Other Muscarinic Receptors



Adverse Events Occurring in ≥ 5% of NBI111758620 –treated Group		
Adverse event	**Placebo N=70**	**NBI111758620 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	

- **Gastrointestinal AEs were infrequent and similar to placebo. Few drug-induced movement disorders were reported. Weight change is similar to placebo.**
- **Cardiovascular-related events were infrequent and deemed not clinically relevant at any tested dose.**

QD = once daily; BID = twice daily; LS = Least Squares; SEM = Standard Error of the Mean; TE = treatment-emergent; AE =adverse event; D/C = discontinuations.

Neurocrine Biosciences Reports Positive Phase 2 Data for NBI-1117568 in Adults with Schizophrenia. Accessed September 10, 2024. https://neurocrine.gcs-web.com/news-releases/news-release-details/neurocrine-biosciences-reports-positive- phase-2-data-nbi-1117568 . September 10, 2024.https://clinicaltrials.gov/study/NCT05545111.

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
ML-007/PAC	M_4/M_1 Agonist + Peripherally Acting Anticholinergic	3 completed phase 1 trials without PAC complete. Phase 1 trial with PAC began 3/2024.
NBI-1117570	M_4/M_1 Agonist	Phase 1
NBI-1117569	M_4 Preferring Agonist	Phase 1
NBI-1117567	M_1 Preferring Agonist	Phase 1

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

Tobin AB. *Nat. Rev. Drug Discov.* 2024; 1-16. Neumora Therapeutics Announces Clinical Hold of Phase 1 NMRA-266 Study. Accessed September 10, 2024. https://ir.neumoratx.com/news-releases/news- release-details/neumora-therapeutics-announces-clinical-hold-phase-1-nmra-266. MapLight Therapeutics Announces Initiation of Phase 1 Clinical Trial for ML-007/PAC, Under Development for Schizophrenia and Alzheimer's Disease Psychosis. Accessed September 10, 2024. https://maplightrx.com/maplight-therapeutics-an-nounces-initiation-of-phase-1-clinical-trial-for-ml-007-pac-under-development-

Panel Discussion

Implications for the Evolving Schizophrenia Treatment Landscape

Integrating Muscarinic Agonists into Clinical Practice

Identifying Patients that May (or May Not) Benefit

- Are certain patients more likely to respond?
- Address adherence to oral medications
- Assess ability to adhere to food restrictions

Key Points to Communicate in Shared Decision Making

- Mechanism
- Benefits
- Risks
- Realistic expectations

Starting Patients on Muscarinic Agonists

- If on anticholinergics (or antipsychotics)?
- Titration (and Cross-Titration)

Monitoring: Obtain baseline HR and LFTs (including bilirubin) and "as clinically indicated during treatment."

How to Position Muscarinic Agonists in Your Treatment Algorithm

- Use as Monotherapy or Adjunctive Therapy?
- First-Line vs Later Lines of Treatment?

Aoki, Yumi et al. *Cochrane Database Syst Rev*. 2022;11(11):CD007297. Cobenfy (xanomeline-trospium) Prescribing Information. Drugs@FDA: FDA Approved Drugs. Accessed Feb. 11, 2025. www.accessdata.fda.gov/scripts/cder/daf/.

Practical Take-Aways

- Historically, schizophrenia treatment has focused on the D_2 receptor and the development of agents that act upstream of dopamine release at muscarinic receptors may offer new hope for improved efficacy and reduced side effects.
- Emerging treatments show potential as both monotherapy and adjunctive treatment options, targeting M_1/M_4 pathways with promising clinical trial data.
- Understanding the neurobiology of schizophrenia may help clinicians better identify which patients may benefit from muscarinic receptor activators, enabling a more personalized and effective treatment approach.

Questions?