Emerging Therapeutic Targets for Schizophrenia:

A Focus on Muscarinic Acetylcholine Receptor Activation

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Disclosures

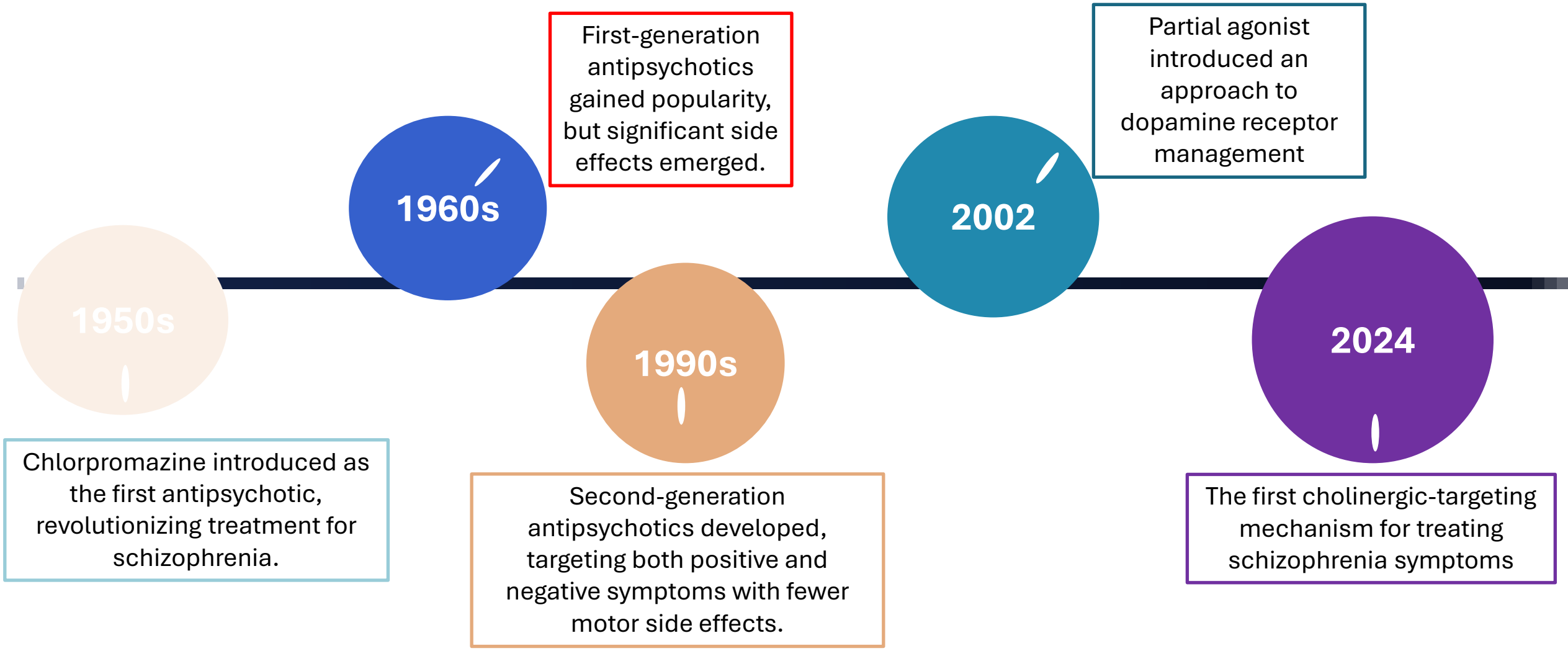
- The faculty have been informed of their responsibility to disclose to the audience if they will be discussing off-label or investigational use(s) of drugs, products, and/or devices (any use not approved by the US Food and Drug Administration).
- Applicable CME staff have no relationships to disclose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

Learning Objectives

- Describe the rationale supporting the role for muscarinic acetylcholine receptor activation in schizophrenia
- Evaluate the latest clinical data associated with emerging muscarinic acetylcholine receptor activators in schizophrenia
- Assess the management implications associated with muscarinic receptor activators, including their optimal placement in the treatment armamentarium and patient-centered care strategies

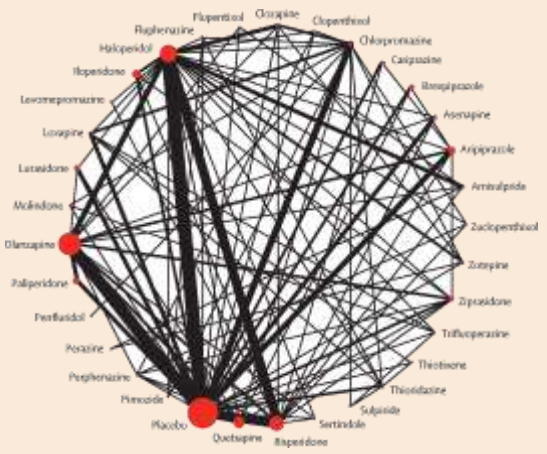
Overview of the Current Schizophrenia Treatment Landscape

Has Treatment for Schizophrenia Changed?



Menniti FS, et al. PDE10A Inhibitors-Clinical Failure or Window Into Antipsychotic Drug Action? *Front Neurosci*. 2021 Jan 20;14:600178. doi: 10.3389/fnins.2020.600178. PMID: 33551724; PMCID: PMC7855852.

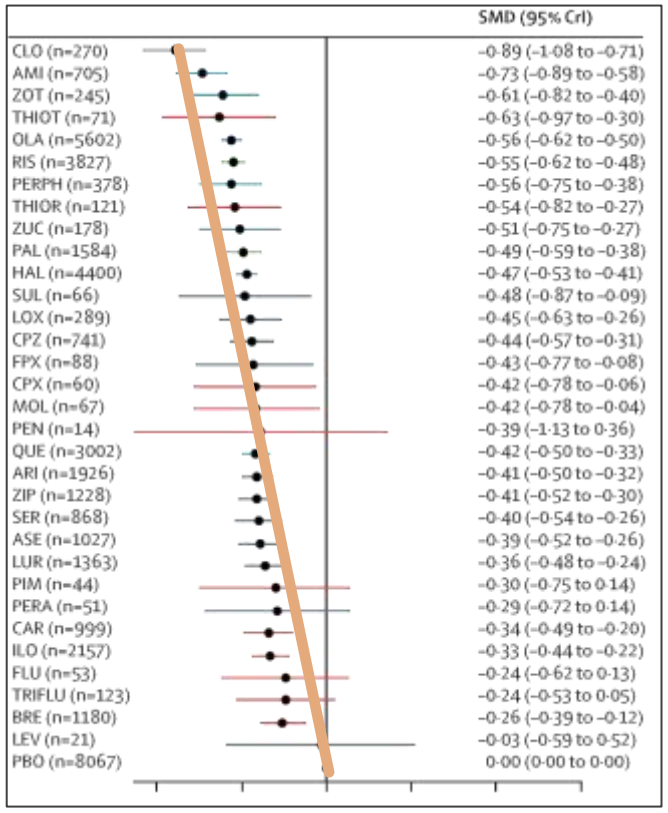
Little Variability of Efficacy in Current Treatments



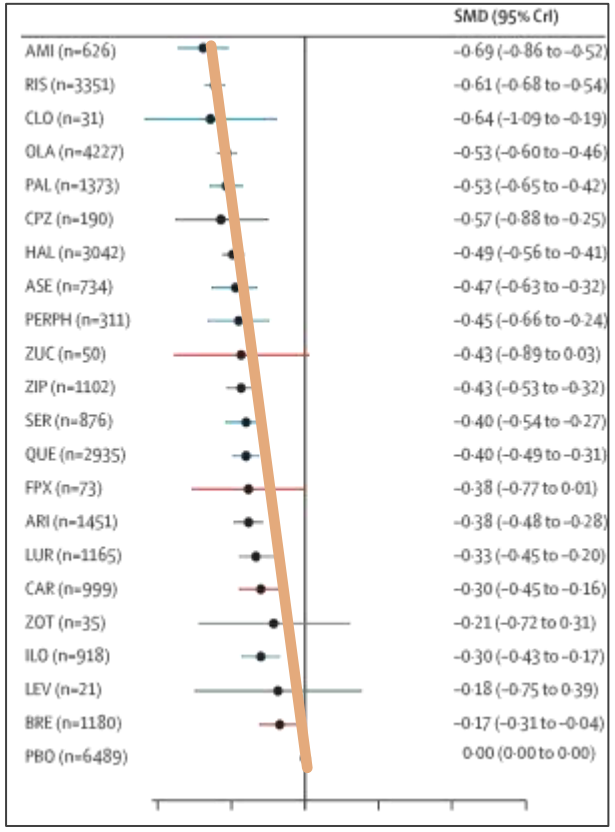
Network of Comparisons

A network meta-analysis of 402 trials, with **53,463 patients** assessed direct and indirect comparisons of the **efficacy and tolerability of 32 antipsychotics**

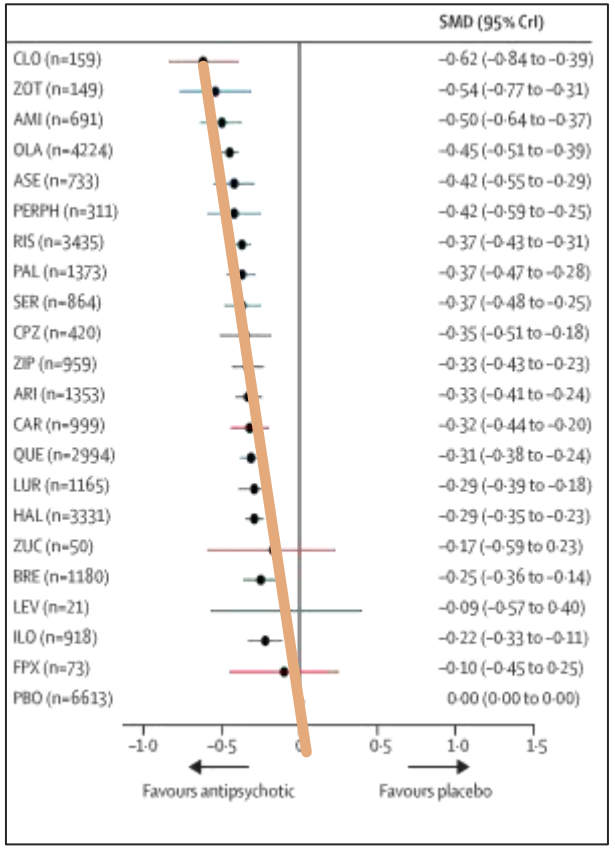
Overall Symptoms



Positive Symptoms



Negative Symptoms



Better efficacy

Level of Confidence in Evidence: High — Moderate — Low — Very low

Huhn M, et al. *Lancet*. 2019 Sep 14;394(10202):939-951. doi: 10.1016/S0140-6736(19)31135-3.

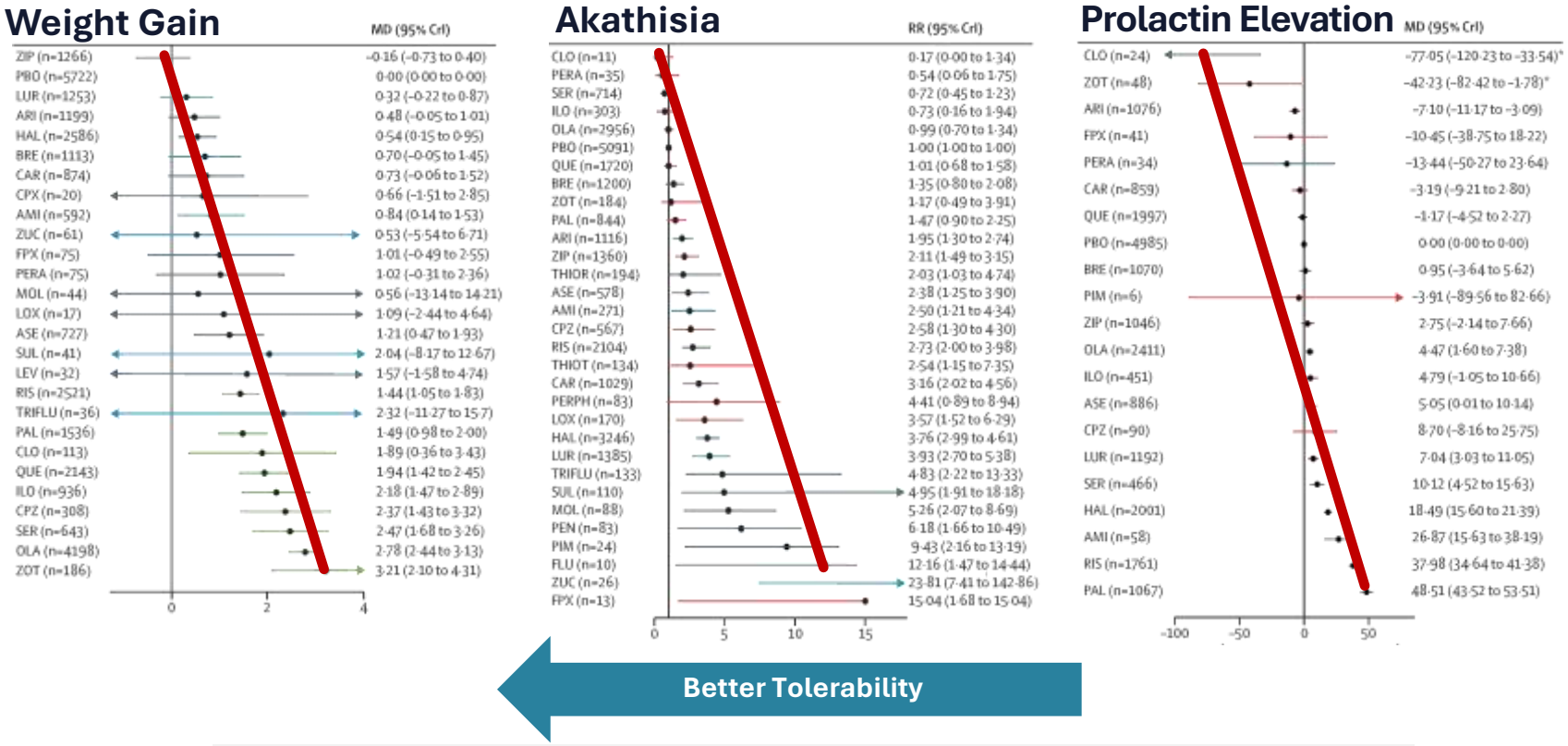
Trend lines include highest- and lowest-ranked agents available in the US

Antipsychotics Differ More in Their Side Effects than in Their Efficacy

Efficacy has not really improved at all. Treatment variability seems to be only in side effects, which are still problematic.

More patients dropped out due to inefficacy (40%) than due to adverse events (20%)

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



Better Tolerability

Level of Confidence in Evidence: High — Moderate — Low — Very low

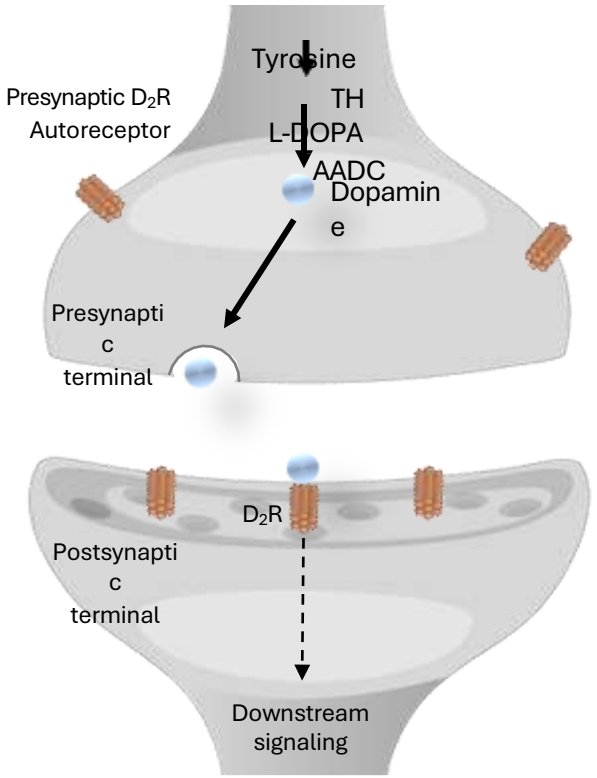
Taken as a whole, antipsychotics have a fairly wide range of tolerability profiles across multiple body systems, with a trend of improvement over time

Huhn M, et al. The Lancet. 394.10202 (2019): 939-951

D_2 Antagonists

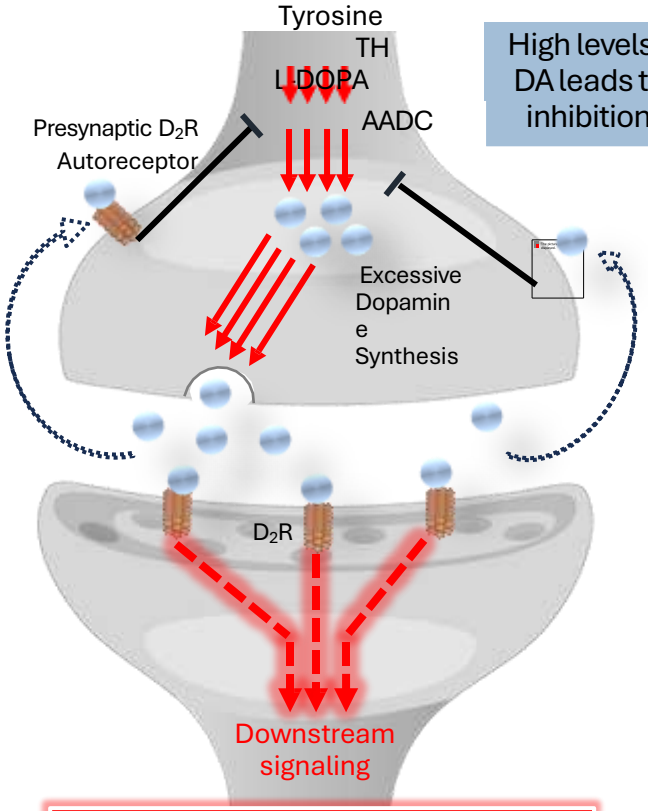
A Postsynaptic Treatment for a Presynaptic Problem

Healthy Controls



Normal Dopamine Release Normal Dopamine Signaling

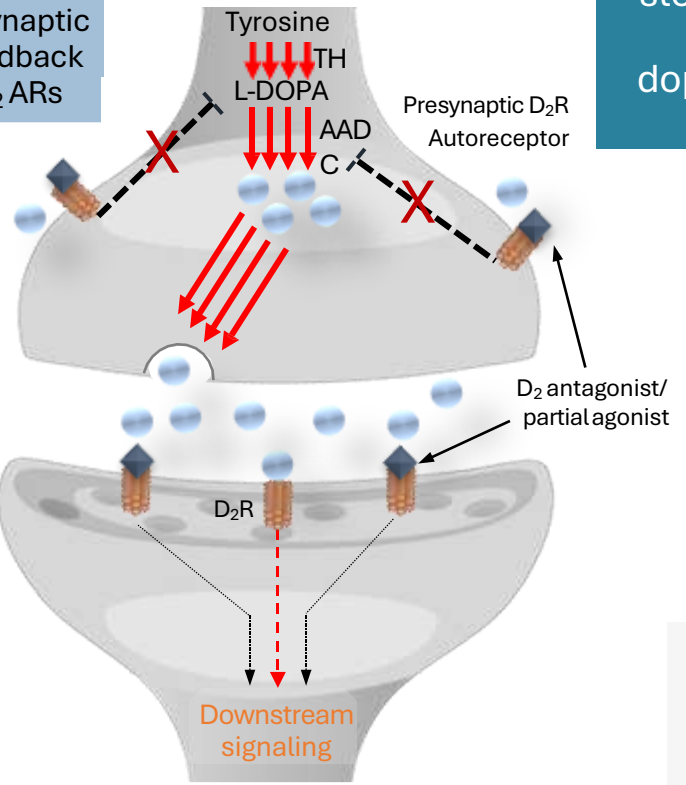
Schizophrenia: *Unmedicated*



Excessive Dopamine Release Causes Excessive Dopamine Signaling

High levels of synaptic DA leads to feedback inhibition at D_2 ARs

Schizophrenia: *With D_2 Antagonist*



D_2 Antagonist/Partial Agonist Mitigates Downstream Effects of Excessive Dopamine Release

Blocking the D_2 autoreceptor stops feedback inhibition, resulting in more dopamine production and release

D_2 antagonists or partial agonists can mitigate excessive postsynaptic dopamine transmission…

…but paradoxically may also compound the problem.

D_2R = dopamine D_2 receptors; AR=autoreceptor; DA = dopamine; TH = tyrosine hydroxylase; AADC = aromatic L-amino acid decarboxylase.

Halff EF, et al. *Trends in Neurosciences*. 2023;46 (1):60-74. Meyer JM. Ch 19 - *Pharmacotherapy of Psychosis and Mania*. In: Brunton LL, ed. *Goodman & Gilman's Pharmacological Basis of Therapeutics*. 14th Ed. Chicago, Illinois: McGraw-Hill; 2022: 357-84.

The Primary Dopamine Dysfunction in Schizophrenia is Not Post-Synaptic

4 of 4 PET scan studies have found elevated presynaptic striatal dopamine availability in acutely psychotic individuals with SCZ.

- Effect sizes 0.63 to 1.25

5 of 5 studies have found roughly <u>doubled</u> dopamine release following a challenge in SCZ vs. controls.

- Also with moderate to large effect sizes

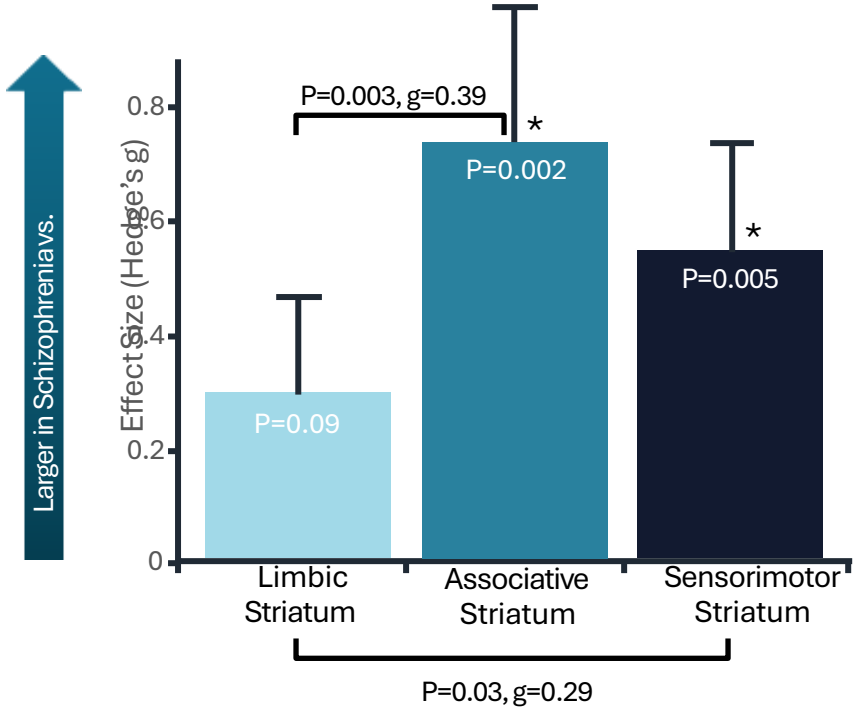
Whereas

A meta-analysis of 19 studies found at most a 10%-20% elevation in striatal <u>postsynaptic</u> D_2/D_3 receptor density in schizophrenia

- (Independent of the effects of antipsychotics)

It's also not in the mesolimbic pathway! SURPRISE!

Estimated Mean Difference in Presynaptic Dopamine Function in Patients vs Controls



Modern studies with higher resolution imaging find:

- Dopaminergic function in humans is significantly elevated in associative and sensorimotor striatum
- ...but <u>not</u> in the limbic striatum, as in mouse models

PET = Positron Emission Tomography; SCZ =schizophrenia.

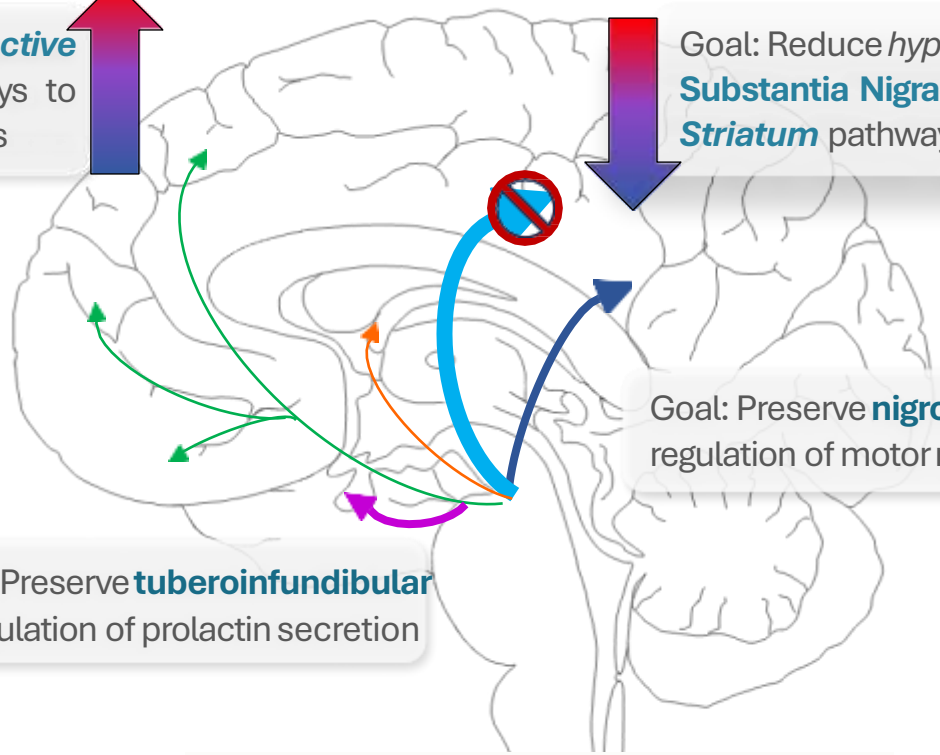
Howes OD, S Kapur. Schiz*ophr. Bull. 2009;*35(3):549-562. McCutcheon RA, et al. *Trends Neurosci. 2019;*42(3):205-220. McCutcheon RA, et al. *Schizophr. Bull*. 2018;44(6):1301-1311.

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 Feb 15;83(1):SU21204IP1. McCutcheon RA, et al. *Trends Neurosci*. 2019;42(3):205-220

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).

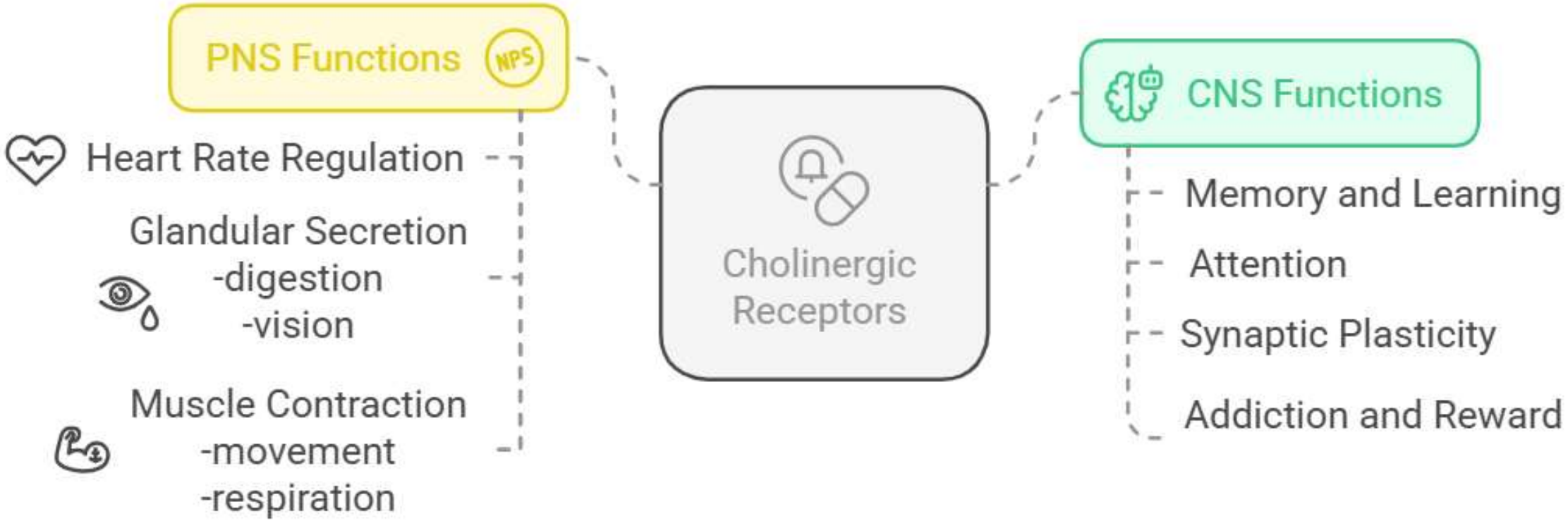
- ✓ Over the past 70 years, **antipsychotic efficacy has hardly improved while tolerability has only somewhat improved**, which may be the primary driver of adherence.

- ✓ 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

- Utilizes **acetylcholine (ACh)** as its primary neurotransmitter

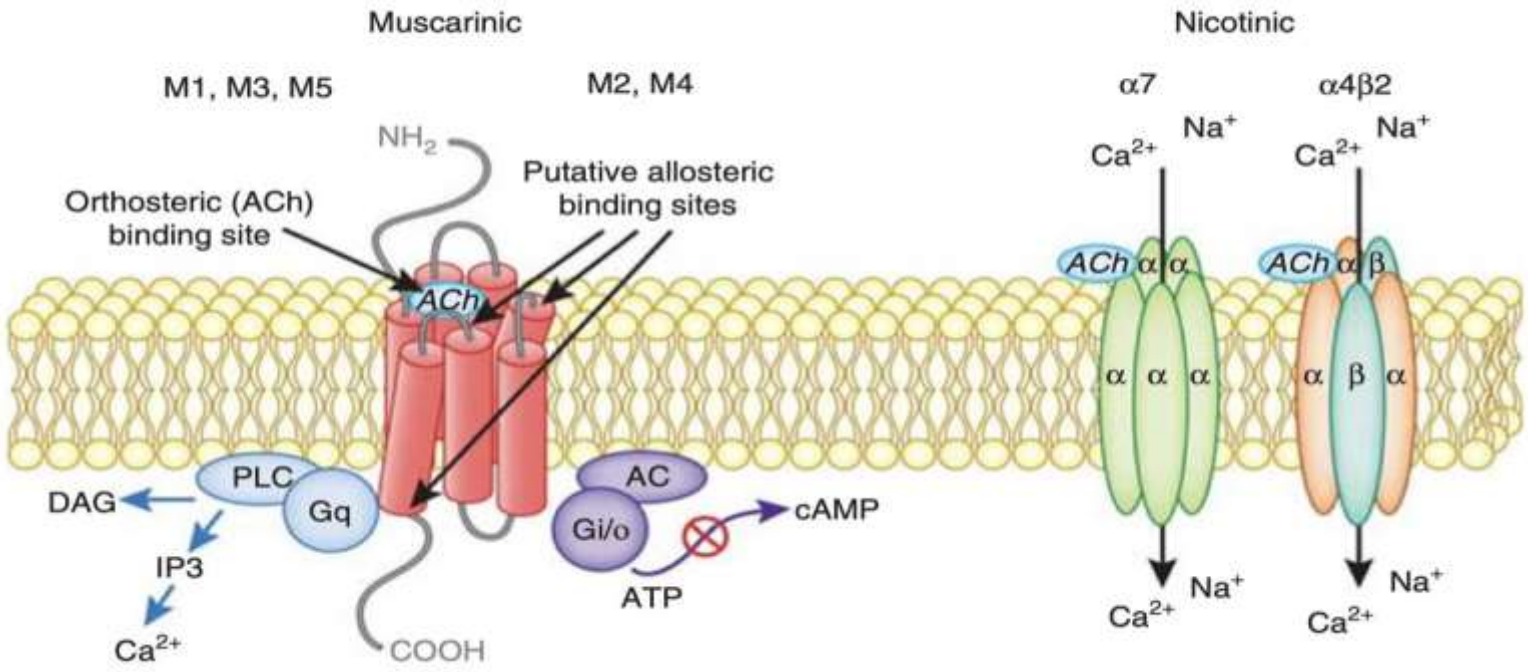


Carlson AB, Kraus GP. Physiology, Cholinergic Receptors. [Updated 2023 Aug 14]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: https://www.ncbi.nlm.nih.gov/sites/books/NBK526134/

The Cholinergic System: Nicotinic vs Muscarinic Cholinergic Receptors

Muscarinic Receptors

- **Type**: G-protein coupled receptors (GPCRs).
- **Location**: Found in the CNS and PNS, particularly in the heart, smooth muscles, and glands.
- **Subtypes**: **M1, M2, M3, M4, M5.**
- **Function**: Involved in modulating neurotransmission, influencing cognitive functions, and regulating autonomic responses.



Nicotinic Receptors

- **Type**: Ionotropic receptors (ligand-gated ion channels).
- **Location**: Primarily found at the neuromuscular junction in the PNS and in various areas of the CNS.
- **Function**: Mediate fast synaptic transmission, muscle contraction, and play a role in cognitive functions and reward pathways.

CNS = central nervous system; PNS = peripheral nervous system.

Paul SM, et al. *Am J Psychiatry*. 2022;179(9):611-627. Brown DA. *Brain Neurosci Adv*. 2019;3:1-10. 3. Unwin N. *Q Rev Biophys*. 2013;46(4): 283-322..

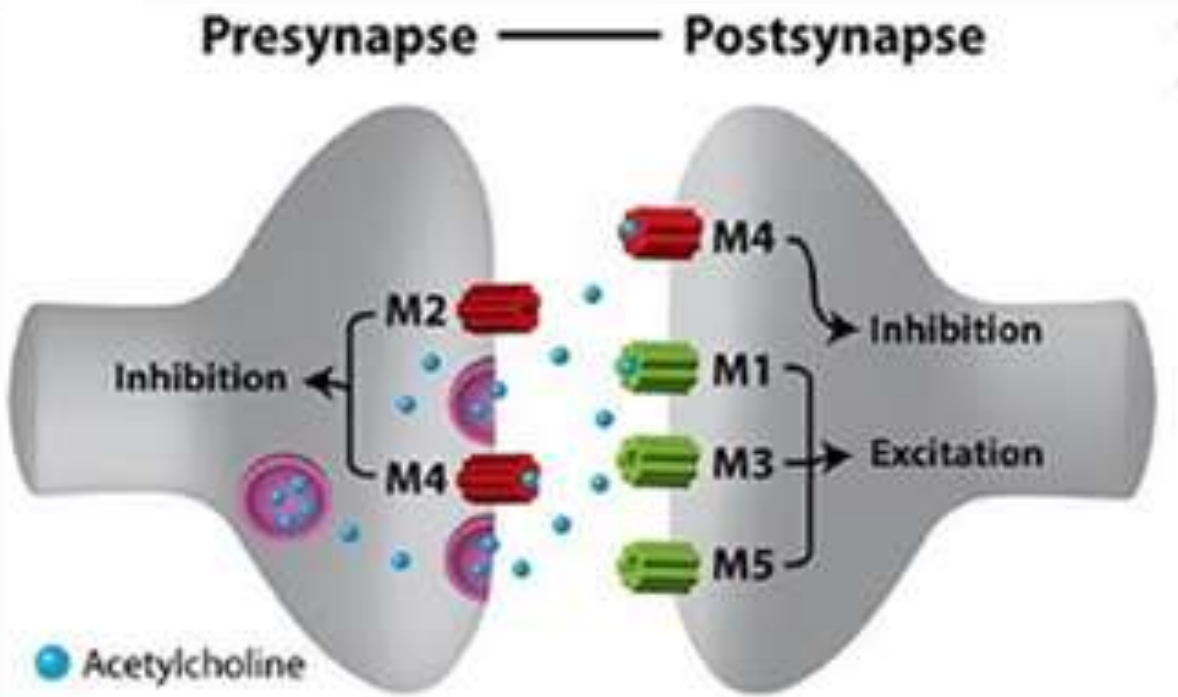
Signaling Selectivity among Muscarinic Acetylcholine M1-M5 Receptors

The muscarinic receptor family consists of five metabotropic receptors, M1–5; upon activation they trigger second messenger cascades within the neurons that express them

M2-like receptors

M2 M4

- Located pre- and post-synaptically
- Coupled with Gi/Go proteins which have predominantly **inhibitory effects**



M1-like receptors

M1 M2 M3

- Located postsynaptically
- Coupled with Gq/G11 proteins, which have **excitatory downstream effects**

Ryan AE, et al. Is there a role for antibodies targeting muscarinic acetylcholine receptors in the pathogenesis of schizophrenia? *Australian & New Zealand Journal of Psychiatry*. 2019;53(11):1059-1069. doi:10.1177/0004867419864438.

Location of M1 and M4 receptors: Where You Want, Not Where You Don't

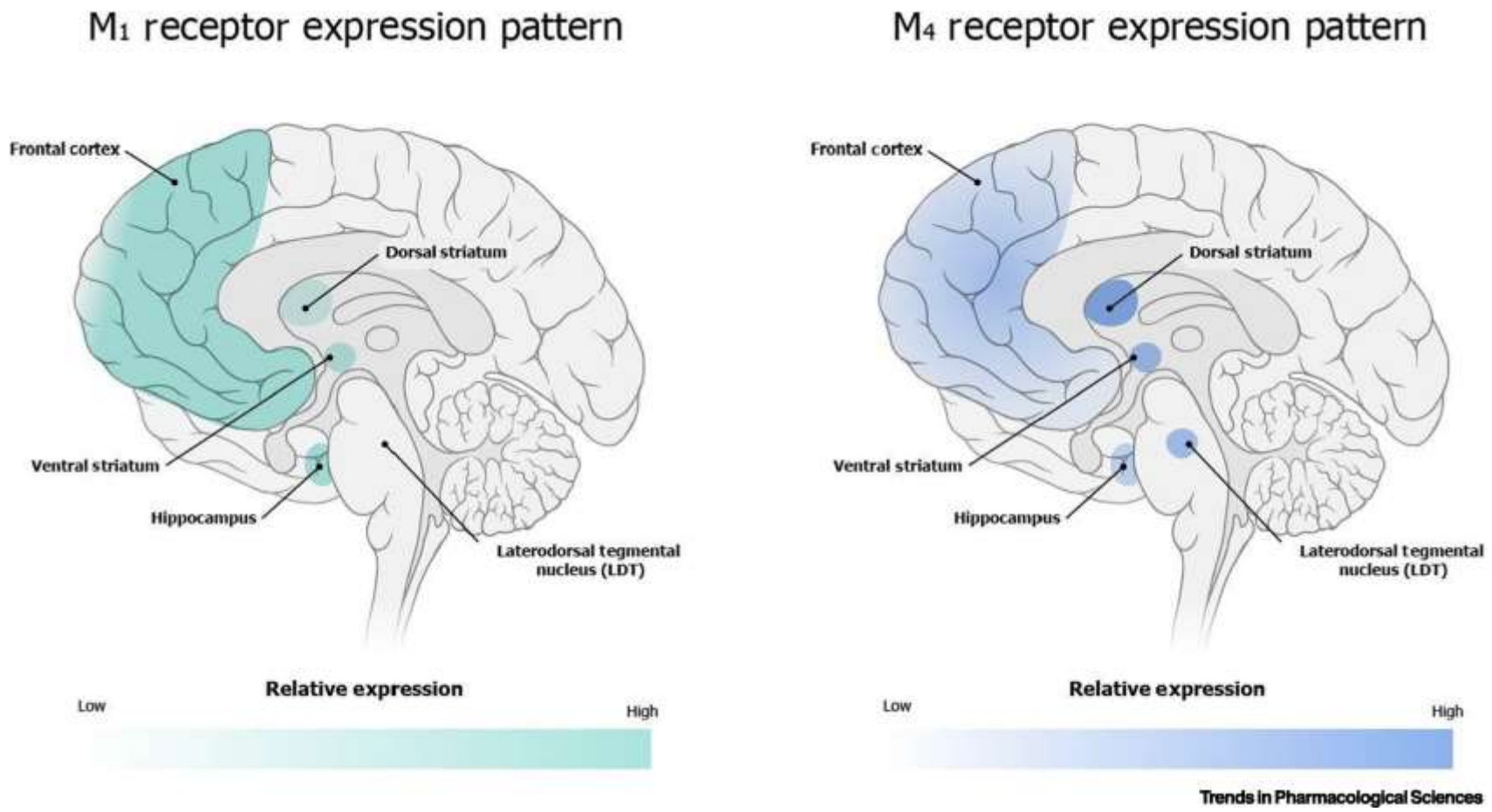
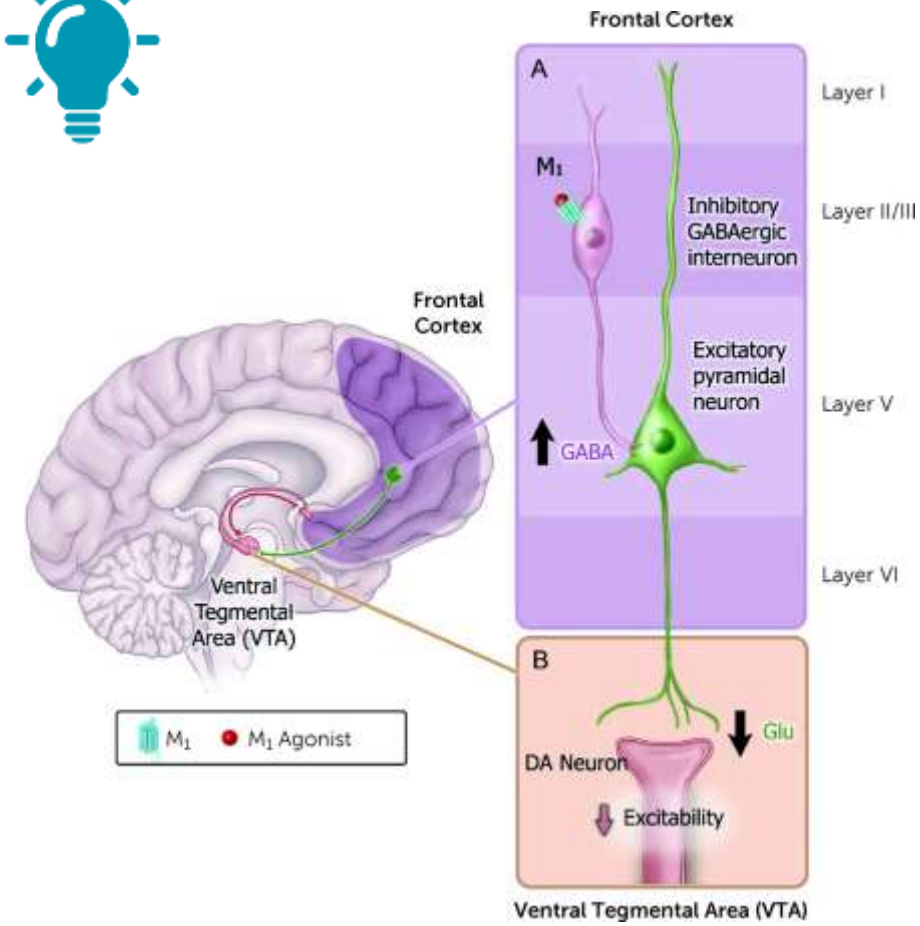


Image Credit and Reference: Yohn SE, et al. *Trends Pharmacol Sci*. 2022 Dec;43(12):1098-1112. Accessed March 10, 2025. https://www.sciencedirect.com/science/article/pii/S0165614722002024

Activation of M1 receptors in the Frontal Cortex Exerts *Top-Down* Control onto Midbrain Dopamine Circuits

1. Activation of M_1 receptors expressed inhibitory GABAergic interneurons (pink) **facilitates inhibitory drive onto excitatory output neurons**

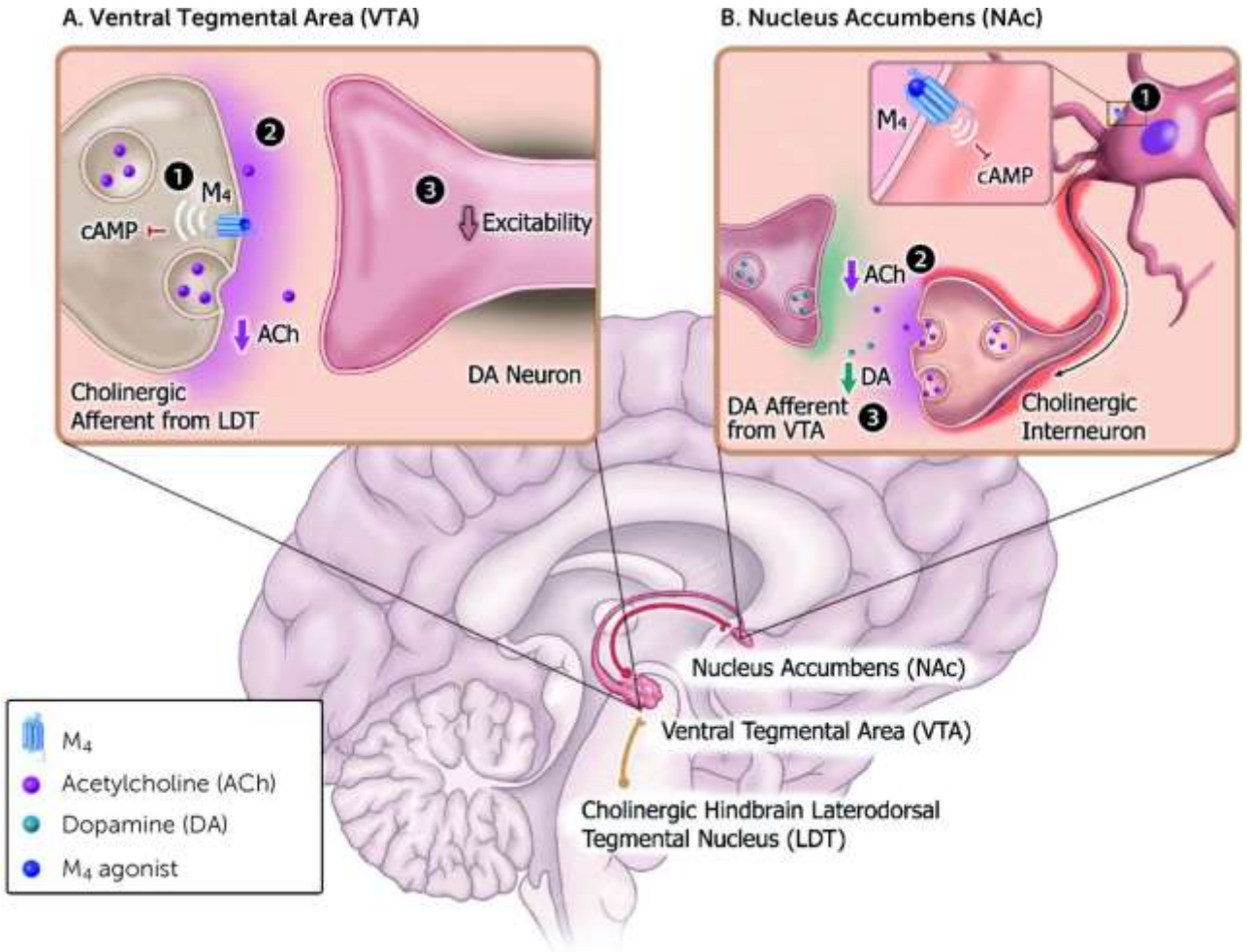
2. In panel B, enhanced inhibitory drive onto pyramidal neurons **decreases glutamatergic input to the ventral tegmental area (VTA).** A reduction of excitatory input **leads to a decrease in VTA dopamine** (DA; red) neuron activity and **reduced terminal DA release**.



Paul SM, et al. Muscarinic Acetylcholine Receptor Agonists as Novel Treatments for Schizophrenia. *American Journal of Psychiatry*. 2022;179(9): 611–627. https://doi.org/10.1176/appi.ajp.21101083.

Activation of M_4 Receptors for *Bottom-Up Regulation of Dopamine*

1. M4 receptor is an autoreceptor on cholinergic afferents that project into the ventral tegmental area (VTA).
2. Upon activation, M4 receptors **reduce acetylcholine (ACh) release onto VTA DA neurons**
3. **Decrease Dopamine neuron firing activity** due to reduced activation of ACh receptors



This leads to a downstream reduction of DA release within the nucleus accumbens (NAc).

1. Within the NAc, M4 receptors are located on cholinergic interneurons (ChIs).
2. Upon activation, M4 receptors decrease ChI spontaneous activity, and thus **decrease cholinergic release from these neurons**
3. **Reduced local cholinergic tone will also decrease stimulation (activation) of DA terminals**

Paul SM, et al. Muscarinic Acetylcholine Receptor Agonists as Novel Treatments for Schizophrenia. *American Journal of Psychiatry*. 2022;179(9): 611–627. https://doi.org/10.1176/appi.ajp.21101083.

Relevance of Muscarinic Agonism in Schizophrenia

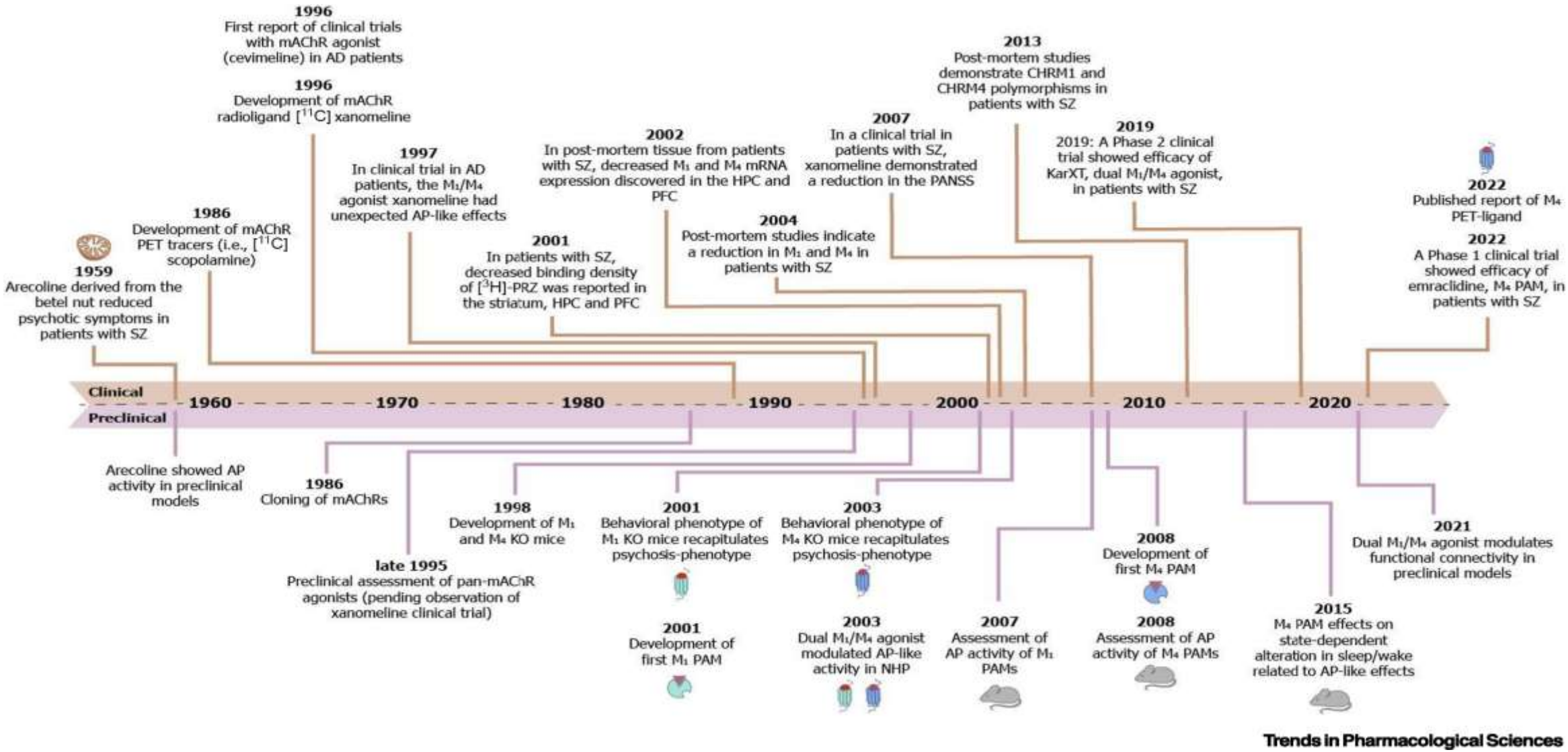


Image Credit and Reference: Yohn SE, et al. *Trends Pharmacol Sci*. 2022 Dec;43(12):1098-1112. Accessed March 10, 2025. https://www.sciencedirect.com/science/article/pii/S0165614722002024

ORIGINAL CONTRIBUTION

Effects of Xanomeline, a Selective Muscarinic Receptor Agonist, on Cognitive Function and Behavioral Symptoms in Alzheimer Disease

Neil C. Bodick, MD, PhD; Walter W. Offen, PhD; Allan I. Levey, MD, PhD; Neal R. Cutler, MD; Serge G. Gauthier, MD; Andrew Satlin, MD; Harlan E. Shannon, PhD; Gary D. Tollefson, MD, PhD; Kurt Rasmussen, PhD; Frank P. Bymaster, MS; Daniel J. Hurley, MD; William Z. Potter, MD, PhD; Steven M. Paul, MD

Objective: To evaluate the therapeutic effects of selective cholinergic replacement with xanomeline tartrate, an m1 and m4 selective muscarinic receptor (mAChR) agonist in patients with probable Alzheimer disease (AD).

Design: A 6-month, randomized, double-blind, placebo-controlled, parallel-group trial followed by a 1-month, single-blind, placebo washout.

Setting: Outpatients at 17 centers in the United States and Canada.

Participants: A total of 343 men and women at least 60 years of age with mild to moderate AD.

Interventions: Patients received 75, 150, or 225 mg (low, medium, and high doses) of xanomeline per day or placebo for 6 months.

Outcome Measures: Scores on the cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-Cog), the Clinician's Interview-Based Impression of Change (CIBIC+), the Alzheimer's Disease Symptomatology Scale (ADSS), and the Nurses' Observational Scale for Geriatric Patients (NOSGER).

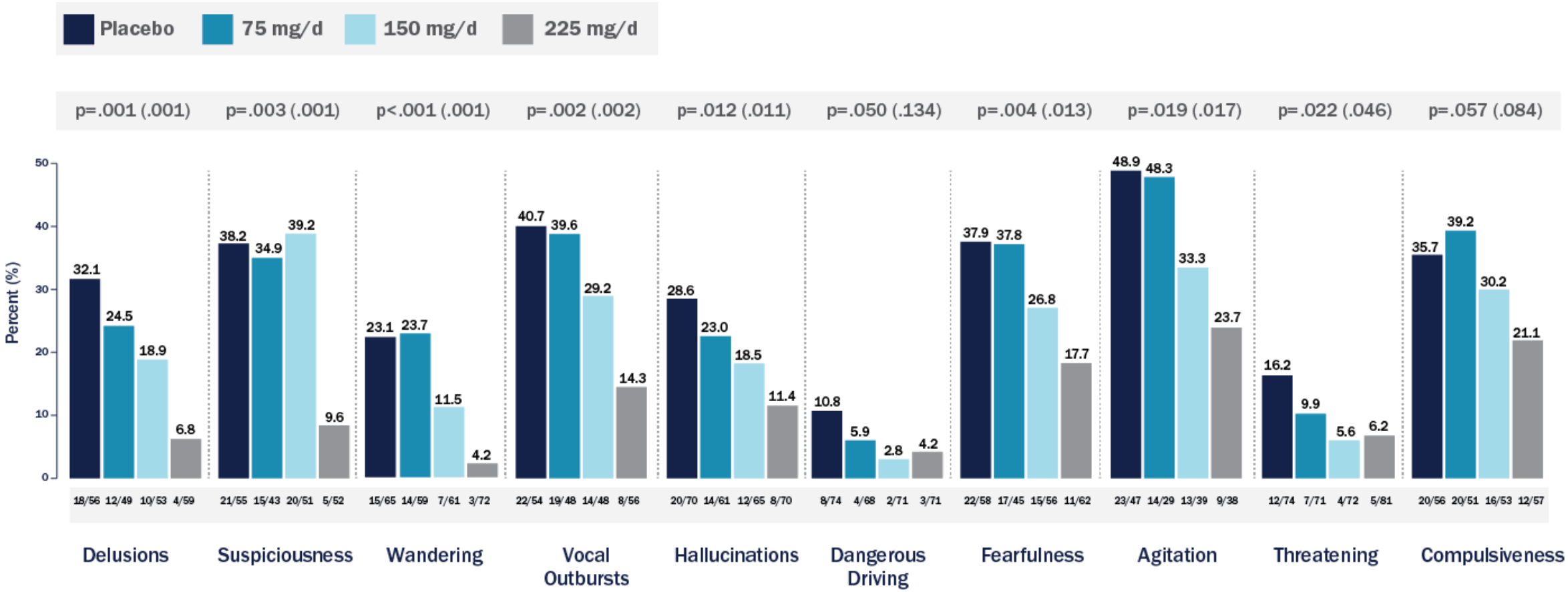
Results: A significant treatment effect existed for ADAS-Cog (high dose vs placebo; $P \leq .05$), and CIBIC+ (high dose vs placebo; $P \leq .02$). Treatment Emergent Signs and Symptoms analysis of the ADSS, which assesses behavioral symptoms in patients with AD, disclosed significant ($P \leq .002$) dose-dependent reductions in vocal outbursts, suspiciousness, delusions, agitation, and hallucinations. On end-point analysis, NOSGER, which assesses memory, instrumental activities of daily living, self-care, mood, social behavior, and disturbing behavior in the elderly, also showed a significant dose-response relationship ($P \leq .02$). In the high-dose arm, 52% of patients discontinued treatment because of adverse events; dose-dependent adverse events were predominantly gastrointestinal in nature. Syncope, defined as loss of consciousness and muscle tone, occurred in 12.6% of patients in the high-dose group.

Conclusions: The observed improvements in ADAS-Cog and CIBIC+ following treatment with xanomeline provide the first evidence, from a large-scale, placebo-controlled clinical trial, that a direct-acting muscarinic receptor agonist can improve cognitive function in patients with AD. Furthermore, the dramatic and favorable effects on disturbing behaviors in AD suggest a novel approach for treatment of noncognitive symptoms.

Arch Neurol. 1997;54:465-473

Alzheimer's Disease Symptomatology Scale:
Percentage of Patients *without* Symptoms at Baseline, Started While Receiving Treatment*

The values are for dose response and 225 mg/day of xanomeline tartrate vs placebo (in parentheses)

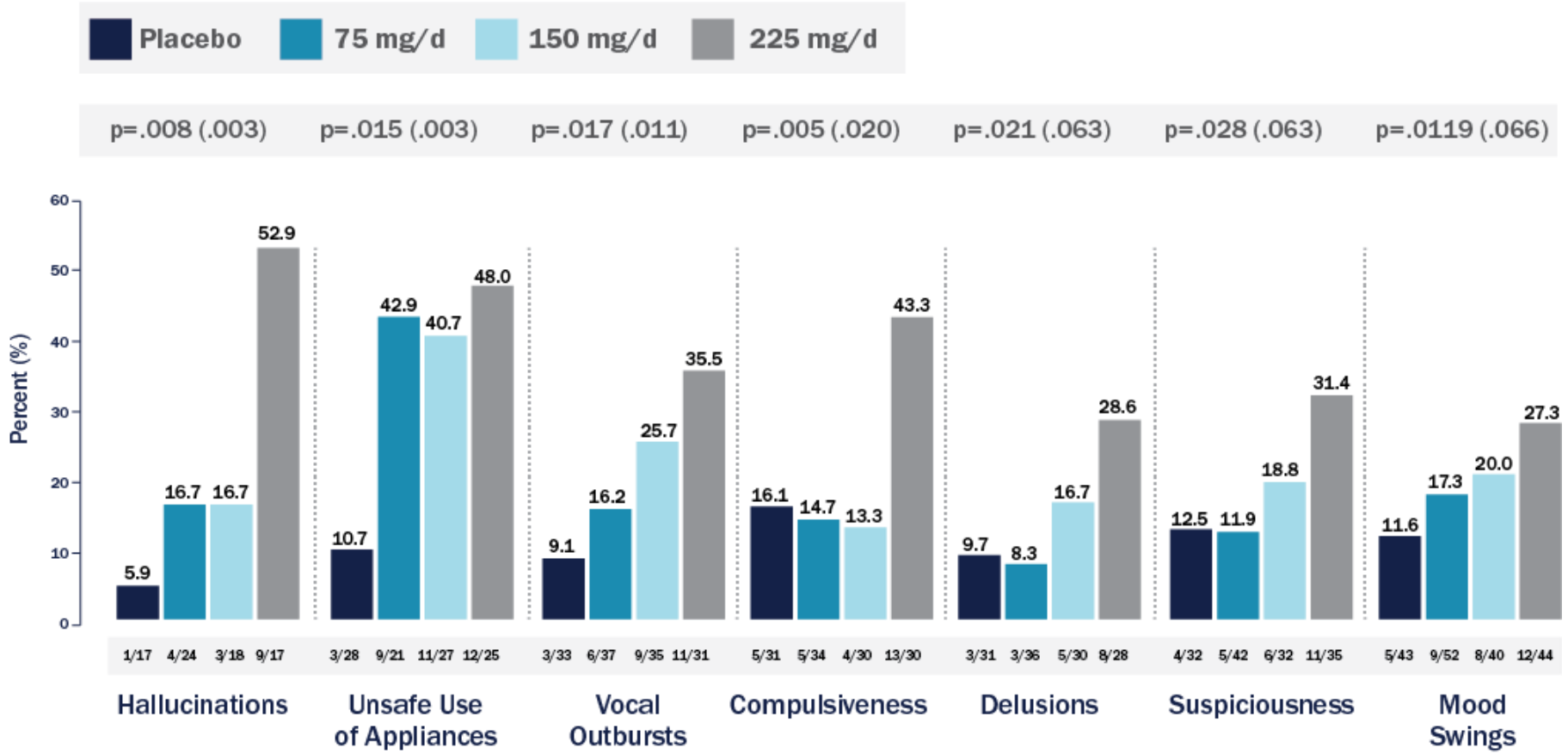


* Baseline lasted 2 weeks; treatment lasted up to 6 months.

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

Alzheimer's Disease Symptomatology Scale:
Percentage of Patients *with* Symptoms at Baseline, Stopped while Receiving Treatment*

The values are for dose response and 225 mg/day of xanomeline tartrate vs placebo (in parentheses)



*** Baseline lasted 2 weeks; treatment lasted up to 6 months.**
Bodick NC, et al. *Arch Neurol*. 1997 Apr;54(4):465-73.

Xanomeline for Alzheimer's Dementia: Adverse Effects

Event*	Dose†				
	Placebo (n=87)	Low (n=85)	Medium (n=83)	High (n=87)	Total (n=342)	P‡
Sweating	4 (4.6)	12 (14.1)	38 (45.8)	66 (75.9)	120 (35.1)	<.001
Nausea	17 (19.5)	24 (28.2)	29 (34.9)	45 (51.7)	115 (33.6)	<.001
Vomiting	8 (9.2)	11 (12.9)	33 (39.8)	37 (42.5)	89 (26.0)	<.001
Dyspepsia	7 (8.0)	20 (23.5)	23 (27.7)	21 (24.1)	71 (20.8)	.007
Chills	1 (1.1)	8 (9.4)	22 (26.5)	32 (36.8)	63 (18.4)	<.001
Chest Pain	1 (1.1)	5 (5.9)	13 (15.7)	10 (11.5)	29 (8.5)	.004
Increased Salivation	0 (0)	2 (2.4)	6 (7.2)	21 (24.1)	29 (8.5)	<.001
Syncope	4 (4.6)	3 (3.5)	11 (13.3)	11 (12.6)	29 (8.5)	.03
Fecal Incontinence	0 (0)	4 (4.7)	1 (1.2)	6 (6.9)	11 (3.2)	.04
Nausea and Vomiting	2 (2.3)	0 (0)	1 (1.2)	7 (8.0)	10 (2.9)	.009
Dysphagia	1 (1.1)	0 (0)	2 (2.4)	6 (6.9)	9 (2.6)	.03

*** Baseline lasted 2 weeks; treatment lasted up to 6 months. Only events statistically significant at P<.05 are given. Values are number (percentage) of patients unless otherwise indicated.**

† Low-dose group received 25 mg of xanomeline tartrate 3 times a day; medium, 50 mg 3 times a day; high, 75 mg 3 times a day. ‡Pearson $\chi 2$ test.

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

Article

Selective Muscarinic Receptor Agonist Xanomeline as a Novel Treatment Approach for Schizophrenia

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Christian C. Felder, Ph.D.

Objective: There are significant unmet needs in the treatment of schizophrenia, especially for the treatment of cognitive impairment, negative syndrome, and cognitive function. Preclinical data suggest that agonists with selective affinity for acetylcholine muscarinic receptors provide a potentially new mechanism to treat schizophrenia. The authors studied xanomeline, a relatively selective muscarinic type 1 and type 4 (M_1 and M_4) receptor agonist, to determine if this agent is effective in the treatment of schizophrenia.

Method: In this pilot study, the authors examined the efficacy of xanomeline on clinical outcomes in subjects with schizophrenia (N=20) utilizing a double-blind, placebo-controlled, 4-week treatment design. Outcome measures included the Positive and Negative Syndrome Scale (PANSS) for schizophrenia, the Brief Psychiatric Rating Scale (BPRS), the Clinical Global Impression (CGI) scale, and a test battery designed to measure cognitive function in patients with schizophrenia.

Results: Subjects treated with xanomeline did significantly better than subjects in the placebo group on total BPRS scores and total PANSS scores. In the cognitive test battery, subjects in the xanomeline group showed improvements most robustly in measures of verbal learning and short-term memory function.

Conclusions: These results support further investigation of xanomeline as a novel approach to treating schizophrenia.

(Am J Psychiatry 2008; 165:1033–1039)

Xanomeline for Schizophrenia: Patient Population, and Efficacy and Tolerability Outcomes

Characteristic	Placebo Group (N=10)		Xanomeline Group (N=10)	
	Mean	SD	Mean	SD
Age (years)	42.1	9.2	43.4	9.3
Education (years)	10.5	3.1	11.8	2.3
Duration of illness (years)	14.4	6.2	16.1	5.4
Baseline PANSS total score	85.2	10.22	81.3	5.1
Gender (male/female)	8/2		6/4	
Race (Caucasion/African American)	2/8		3/7	

Characteristic	Placebo Group	Xanomeline Group
	N	N
Nausea	4	7
Vomiting	1	6
Gastrointestinal distress	5	7
Salivation	1	2
Diarrhea	0	2
Constipation	1	2
Increase in liver function	1	2
Dizziness/lightheadedness	4	3
Sweating	1	3
Headache	2	1
Fatigue	1	1
Flushing	0	1
Insomnia	2	0
Flatulence	4	4

Clinical Outcome Total Scores	Difference Between Xanomeline and Placebo Groups		Analysis
	Mean	SD	p
Clinical Global Impression	1.1	1.5	0.94
PANSS	24.0	21.0	0.039*
PANSS positive symptom score	5.0	7.0	0.082*
PANSS negative symptom score	6.0	8.0	0.083*
Change in Simpson-Angus Rating	1.0	1.5	0.44*
Change in Abnormal Involuntary Movement Scale	-1.4	2.1	0.56*
Barnes Rating Scale for Drug Induced Akathisia	-1.1	1.4	0.18*

***Results (changes in clinical outcome from baseline to last visit for the two treatment groups) are on ANCOVA; last observations were carried forward.**
Shekhar A, et al. *Am J Psychiatry*. 2008 Aug;165(8):1033-9.

Xanomeline for Schizophrenia: Cognition

Cognative Measure	Placebo Groups			Xanomeline Groups		
	Pretreatment Score	Posttreatment Score	Change in Score	Pretreatment Score	Posttreatment Score	Change in Score
Speed of processing						
Trail Making Test, part A: time	43.5	50.4	6.9	59.1	51.7	-7.4
Trail Making Test, part B: time	133.5	144.3	10.8	160.8	151.6	-9.2
Attention/Vigilance						
Continuous Performance Test,						
Identical Pairs Version						
Total D prime	2.4	3.0	0.6	2.1	2.9	0.8
Mean reaction time	393.4	431.2	37.8	416.8	386.0	-30.8
Coding	29.0	29.7	0.7	27.3	28.2	0.9
Working memory						
Wechsler Adult Intelligence Scale, III:						
Digit span forward	7.7	7.2	-0.5	7.8	9.5	1.7
Digit span backward	3.8	4.3	0.5	4.7	4.3	-0.4
Wechsler Memory Scale:	7.8	8.2	0.4	7.7	10.4	2.7
Digit span[a]						
Story recall[a]	5.1	7.1	2.0	5.6	9.0	3.4
Verbal learning						
Hopkins Verbal Learning Test—Revised						
List recall	4.3	3.9	-0.4	4.1	4.4	0.3
List recognition total	18.5	16.5	-2.0	18.3	17.3	-1.0
List learning total[a]	20.0	21.9	1.9	22.2	26.5	4.3
Cooperative (Alzheimer's Disease Cooperative Society):						-1.1
List learning total	21.2	24.0	2.8	23.3	22.2	
Visual learning						
Brief Visuospacial Memory Test—Revised:						5.7
Immediate memory	69.3	76.0	6.7	70.4	76.1	9.2
Visuospacial/contructional	68.7	72.4	3.7	67.0	76.2	4.2
Language	78.1	84.1	6.0	76.5	80.7	8.4
Attention	61.6	65.8	4.2	61.0	69.4	8.8
Delayed memory[a]	68.5	54.7	-13.8	69.3	78.1	

[a] Significant differences between groups ($p<0.05$).

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

Key Learning Points

- ✓ **The muscarinic receptor family consists of five metabotropic receptors, M1–5**; upon activation they trigger second messenger cascades within the neurons that express them
- ✓ M_1 and M_4 receptor activation is associated with decreased presynaptic dopamine release in the associative striatum, which can reduce psychosis, and **decreased presynaptic dopamine release in the frontal lobe**, which can improve cognitive functioning.
- ✓ Xanomeline, given without a peripherally restricted anticholinergic agent, was **effective for psychosis and cognitive dysfunction in patients with Alzheimer's dementia and schizophrenia**, but development was halted due to limiting peripheral pro-cholinergic adverse effects.

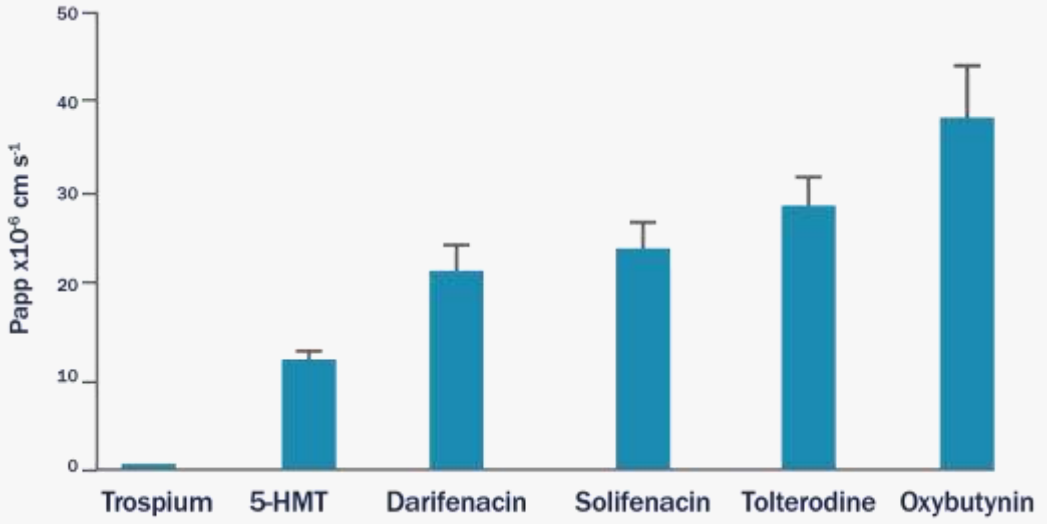
Managing the Peripheral Pro-Cholinergic Effects of Xanomeline

Issue: Xanomeline induces peripheral adverse effects, primarily related to muscarinic M_1 agonism

The answer: Find an anticholinergic with limited CNS penetration to mitigate xanomeline's peripheral effects

The winner: Trospium! Found after screening hundreds of compounds to look for anticholinergics with limited CNS penetration.

What is trospium? A nonselective muscarinic antagonist available since 1974 for overactive bladder (approved in 2004 in the US)



Trospium is a quaternary ammonium compound. The positively charged ammonium group makes trospium too polar to cross the BBB.

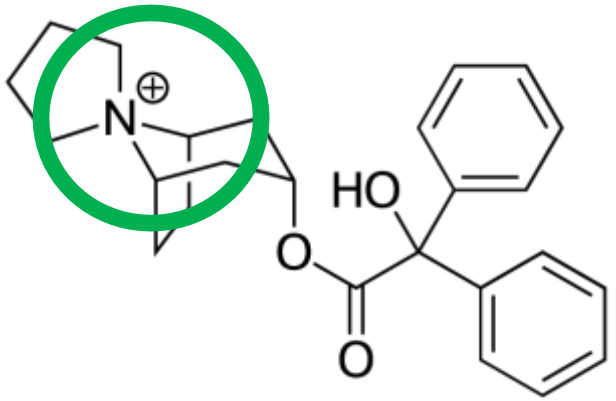


Figure: Passive diffusion across cloned kidney cells as a model for blood brain barrier penetration

Chancellor MB, et al. *Drugs Aging*. 2012;29(4):259-73. Duong V, et al. *Int Urogynecol J*. 2021;32(10):2693-702. Malcher MF, et al. *J Urol*. 2022: 208(4):863-71. Callegari E, et al. *Br J Clin Pharmacol*. 2011;72(2):235-46.

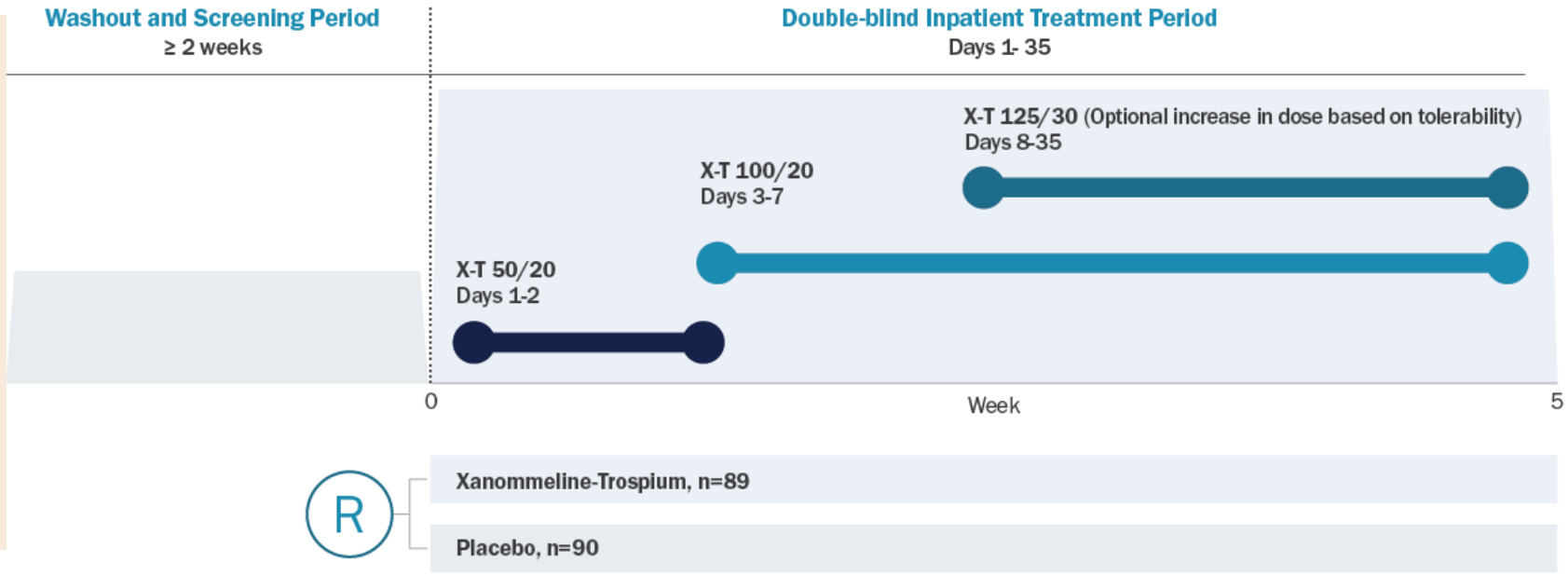
KarXT Clinical Development Program

OLE=open-label extension.
Clinical Trials.gov.
All following sites accessed February 19, 2025:

1. www.clinicaltrials.gov/study/NCT03697252.
2. EMERGENT-2. www.clinicaltrials.gov/study/NCT04659161.
3. EMERGENT-3. www.clinicaltrials.gov/study/NCT04738123.
4. EMERGENT-4. www.clinicaltrials.gov/study/NCT04659174.
5. EMERGENT-5. www.clinicaltrials.gov/study/NCT04820309.
6. ARISE. www.clinicaltrials.gov/study/NCT05145413.
7. ARISE OLE. www.clinicaltrials.gov/study/NCT05304767.
8. ADEPT-1. www.clinicaltrials.gov/study/NCT05511363.
9. ADEPT-2. www.clinicaltrials.gov/study/NCT06126224.
10. ADEPT-3. www.clinicaltrials.gov/study/NCT05980949.

Emergent 1: Phase 2 Clinical Trial Design

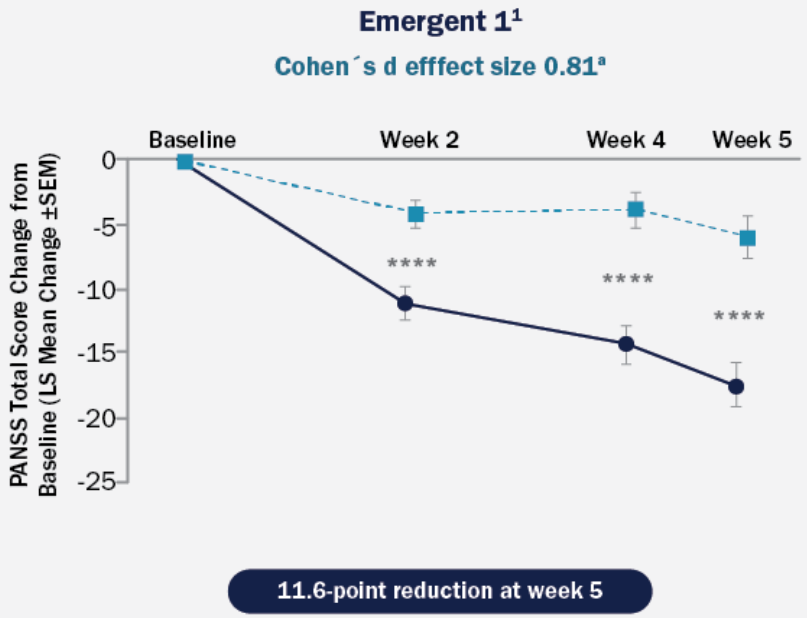
- 5-week double-blind, placebo- controlled inpatient trial
- Adults ages 18–60 with an acute exacerbation of schizophrenia (Emergent 2 & 3: Adults ages 18-65)
- Mean age 42.5 years, 70% male, 76% nonwhite, mean baseline PANSS 97.1

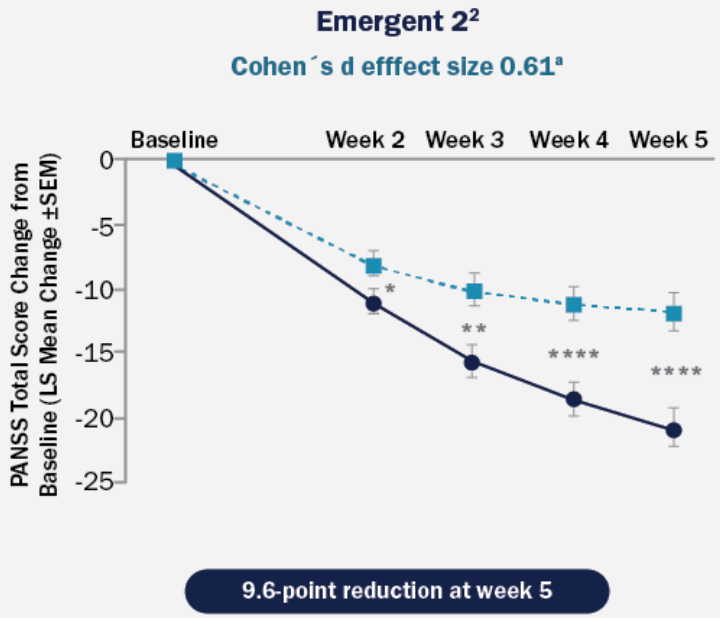


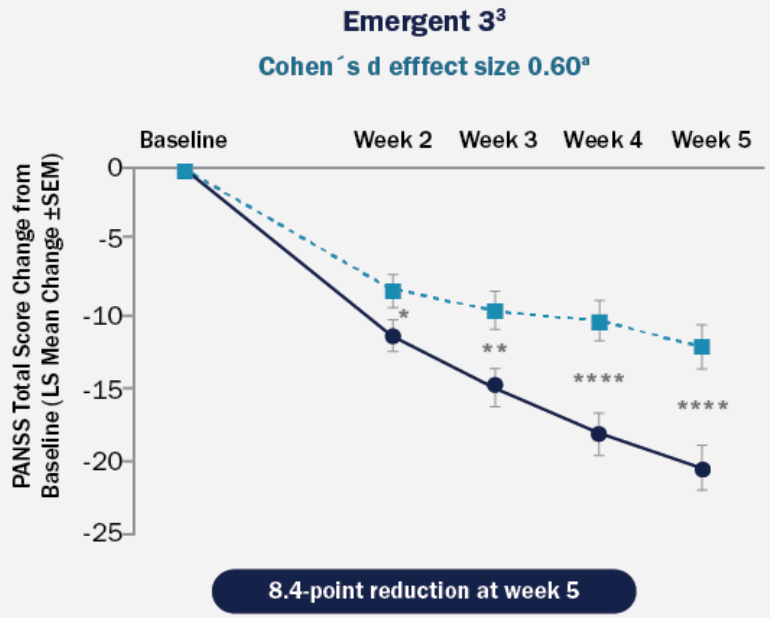
91% were able to tolerate titration at the highest dose of xanomeline-trospium

Brannan SK, et al. *N Engl J Med*. 2021;384(8):717-26.

Emergent Trials:
PANSS Total Score Change from Baseline



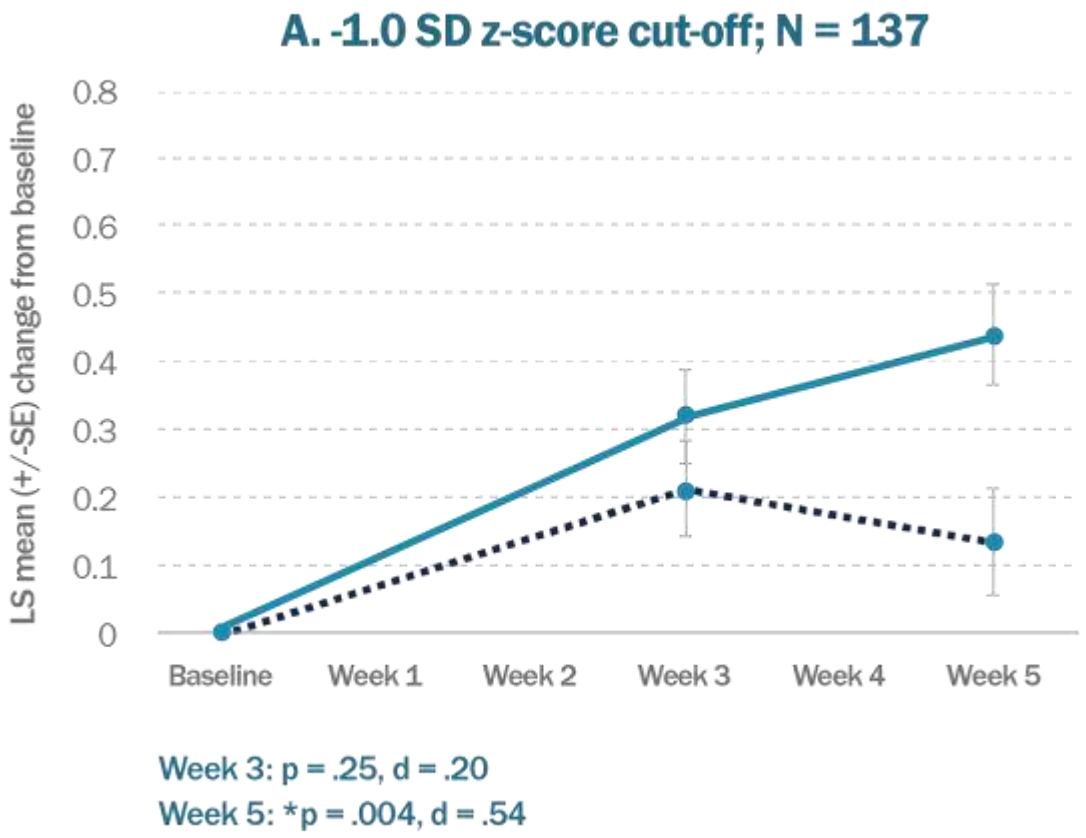


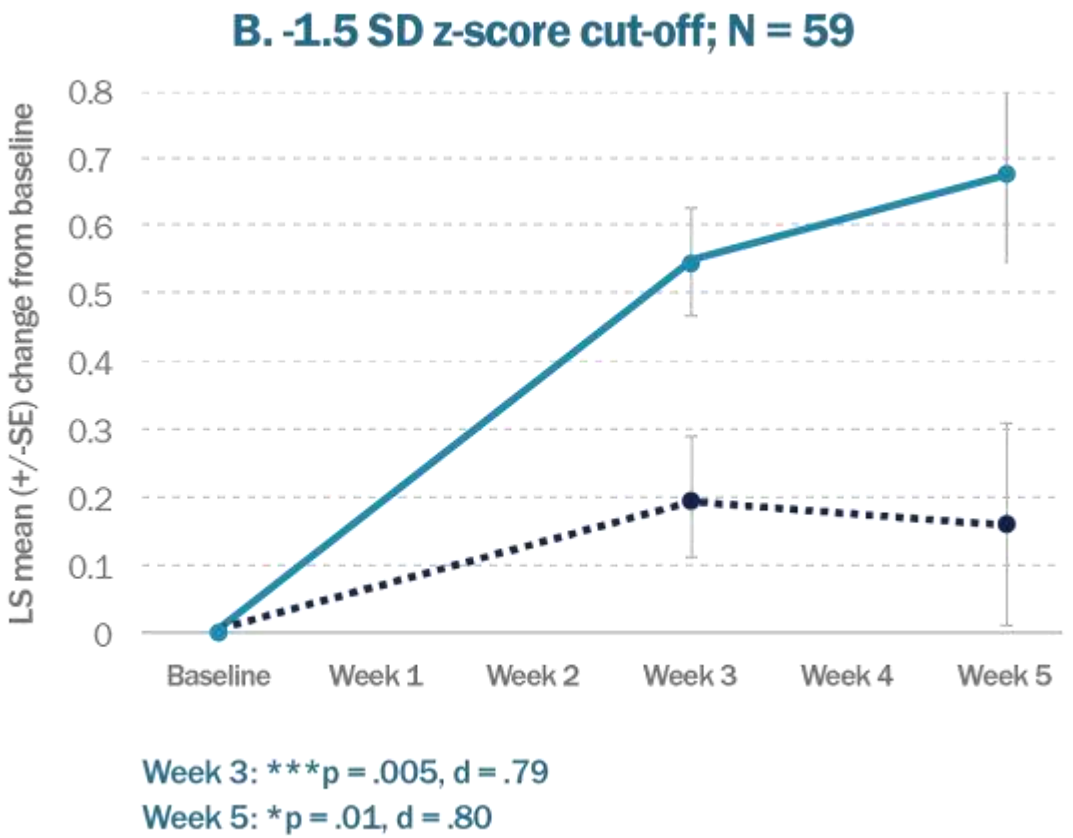


a. The updated effect size is calculated using LS means and pooled standard deviations and is consistent with calculations performed for KAR-007 (EMERGENT-2) and KAR-009 (EMERGENT-3). All efficacy analyses performed using the mITT analysis set, defined as all randomized individuals who received ≥1 dose of trial medication and ≥1 postbaseline PANSS assessment (EMERGENT-1: KarXT n=83, placebo n=87; EMERGENT-2: KarXT n=117, placebo n=119; EMERGENT-3: KarXT n=114, placebo n=120).1,3-5 LS, least squares; mITT, modified intent-to-treat; PANSS, Positive and Negative Syndrome Scale; SEM, standard error of the mean.

1. Brannan SK, et al. *N Engl J Med*. 2021;384(8):717-726; 2. Kaul I, et al. *Lancet*. 2024; 403(10422):160-170; 3. Kaul I, et al. *JAMA Psych*. 2024; 81(8):749-756.

Cognitive Benefit from M1 Stimulation? Pooled EMERGENT 1-3 Analysis





Horan W, et al. The Impact of KarXT on Cognitive Impairment in Acute Schizophrenia: Replication in Pooled Data From Phase 3 Trials. Poster Presented at 2024 SIRS Meeting, Florence, Italy, April 3-7, 2024.

Pooled EMERGENT Trials: Adverse Effects During the 5-Week Treatment Period

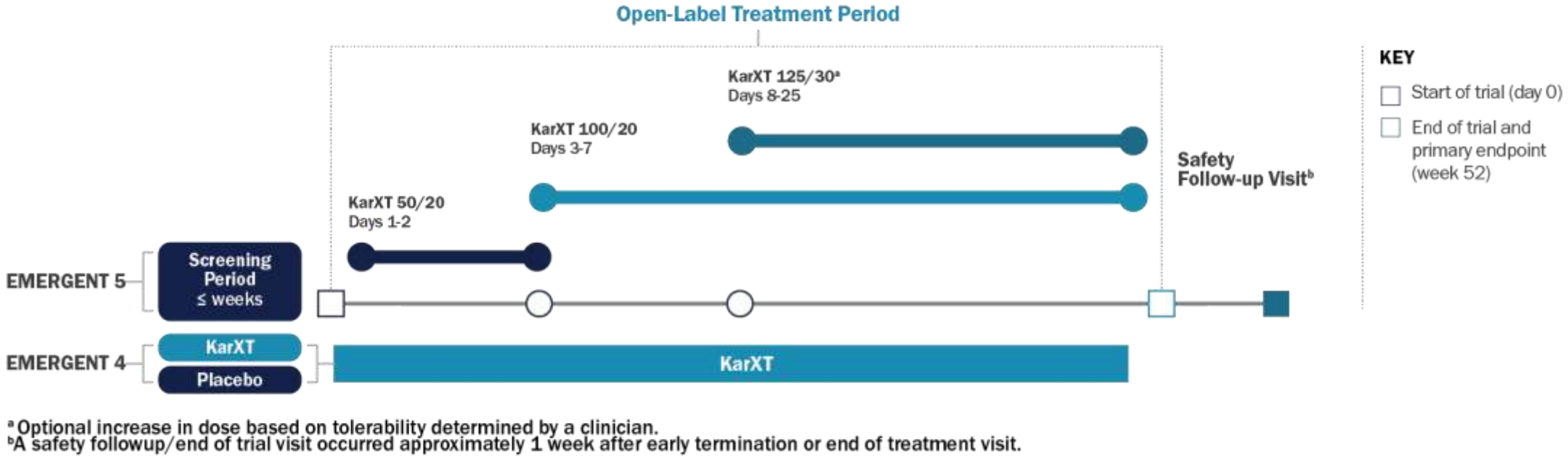
Safety Population

Variable	KarXT (n=340)	Placebo (n=343)
Any TEAE, n (%)	231 (67.9)	176 (51.3)
Serious TEAE, n (%)	4 (1.2)[a]	2 (0.6)[b]
TEAE leading to discontinuation, n (%)	19 (5.6)	16 (4.7)
TEAE occurring in ≥5% of people in the KarXT group, n (%)		
Nausea	63 (18.5)	13 (3.8)
Constipation	58 (17.1)	21 (6.1)
Dyspepsia	54 (15.9)	16 (4.7)
Vomiting	46 (13.5)	6 (1.7)
Headache	37 (10.9)	35 (10.2)
Hypertension[c]	29 (8.5)	6 (1.7)
Abdominal pain	20 (5.9)	10 (2.9)
Dry mouth	17 (5.0)	5 (1.5)
Tachycardia	17 (5.0)	8 (2.3)
Body weight (kg), mean change from baseline to week 5 ±SD	1.41±3.18	1.94±5.00
Body weight: ≥7% increase from baseline to week 5, n/N (%)	13/245 (5.3)	30/264 (11.4)
Simpson-Angus Scale score: mean change from baseline to week 5, ±SD	-0.1±0.62	-0.1±0.63
Barnes Akathisia Rating Scale score: mean change from baseline to week 5, ±SD	-0.1±0.90	-0.1±0.84
Abnormal Involuntary Movement Scale score, mean change from baseline to week 5 ±SD	0.0±0.66	0.0±0.15

Safety population defined as all participants who received ≥1 dose of trial medication.
a. Suicidal ideation (n=2), psychotic disorder (n=1), gastroesophageal reflux disease (n=1); b. Appendicitis (n=1), schizophrenia (n=1); c. Hypertension
Brannan SK, et al. Poster presented at the 2023 American Society of Clinical Psychopharmacology (ASCP) Annual Meeting, May 30-June 2, 2023, Miami, Florida.

Emergent 4, 5: Clinical Trial Design

Figure 1: Trial Designs



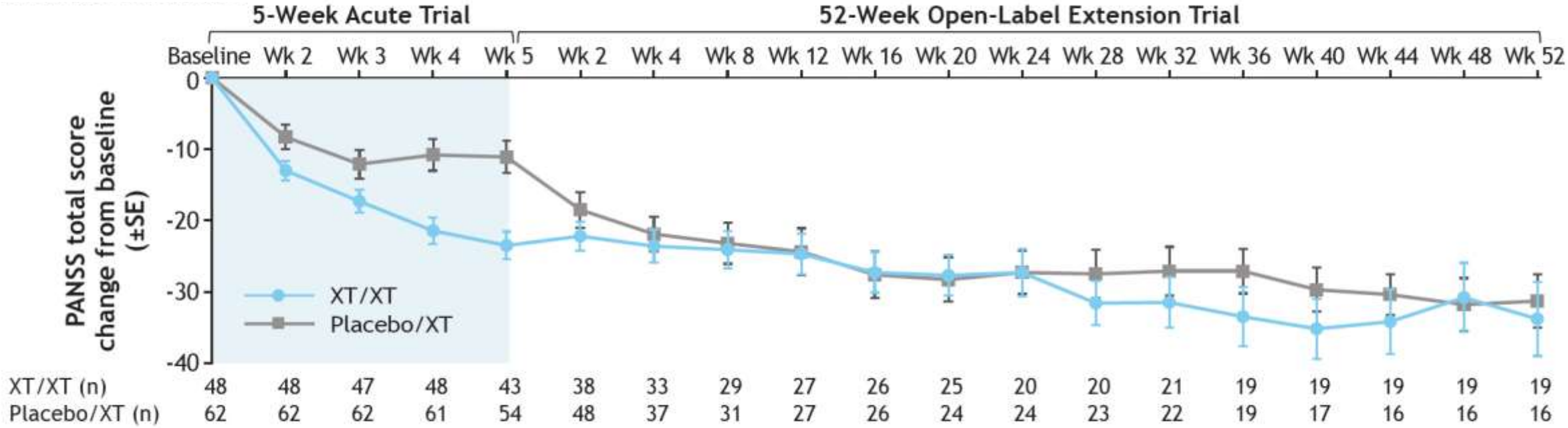
[a]Optional increase in dose based on tolerability determined by a clinician.
[b]A safety followup/end of trial visit occurred approximately 1 week after early termination or end of treatment visit.

EMERGENT-4 and EMERGENT-5 are phase 3, multicenter, outpatient, 52-week, open-label trials (Figure 1)

- EMERGENT-4 is an open-label extension that enrolled participants aged 18-65 years who previously completed the treatment period of EMERGENT-2 or EMERGENT-3
- EMERGENT-5 is an open-label trial in adults with a confirmed diagnosis of schizophrenia who have had no prior exposure to KarXT; participants with a Positive and Negative Syndrome Scale total score ≤80 and a Clinical Global Impression–Severity score ≤4 were eligible.
- All participants initiated KarXT at 50 mg/20 mg BID, titrated to a max dose of 125 mg/trospium 30 mg BID for 52 weeks
- Interim safety and tolerability data from the EMERGENT-4 and EMERGENT-5 trials were pooled; all analyses were conducted using the safety population, defined as all participants who received ≥1 dose of trial medication

Marcus R, et al. Poster F74 presented at 2024 Annual Conference of the Schizophrenia International Research Society (SIRS), April 3-7, 2024, Florence, Italy.

Emergent 4 – Long Term Change in PANSS



Mean PANSS total score change from baseline to week 52

KarXT/KarXT: -33.6 points
Placebo/KarXT: -32.9 points

Kaul I, et al. Poster 65 presented at 2025 Psych Congress, October 29- November 1, Boston, MA

Pooled Emergent 4, 5 Data: Safety and Tolerability

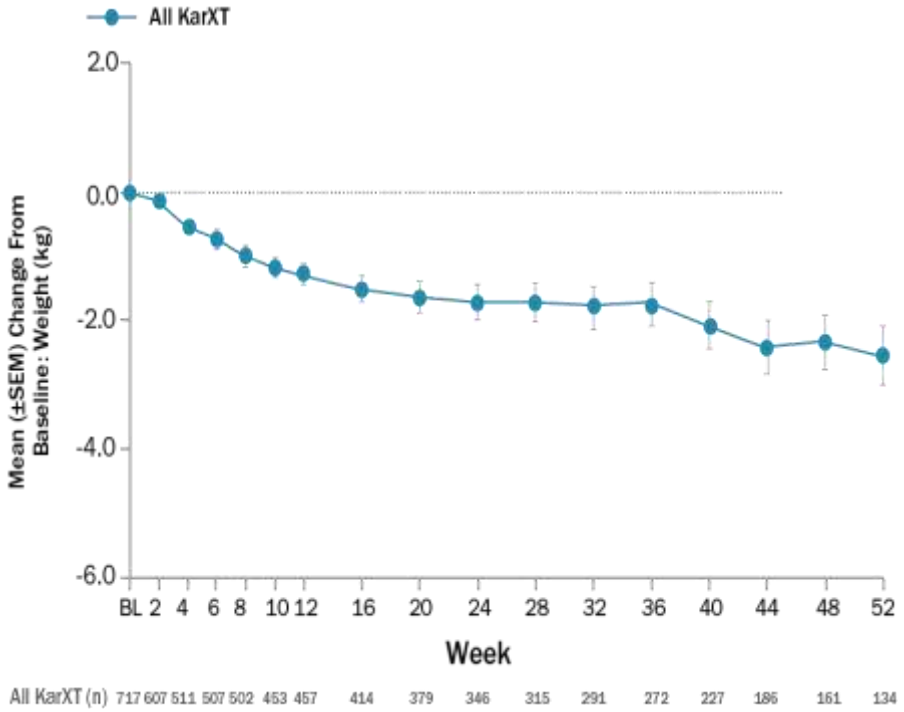
Interim Data

Variable	All KarXT (N=718)
Any TEAE, n (%)	558 (77.7)
Serious TEAE, n (%)	46 (6.4)
TEAEs leading to discontinuation, n (%)	107 (14.9)
TEAEs occurring in ≥5% of people in the KarXT group, n (%)	
Nausea	143 (19.9)
Vomiting	132 (18.4)
Constipation	119 (16.6)
Hypertension	72 (10.0)
Dry mouth	68 (9.5)
Dyspepsia	67 (9.3)
Diarrhea	61 (8.5)
Headache	57 (7.9)
Dizziness	56 (7.8)
Somnolence	52 (7.2)
Abdominal pain	50 (7.0)

Claxton A, et al. Oral presentation at 2024 Annual Conference of the Schizophrenia International Research Society (SIRS), April 3-7, 2024, Florence, Italy

Pooled Emergent 4, 5 Data: Adverse Events

Weight Change



Drug Induced Movement Disorders

Variable	All KarXT (N=340)		Placebo (N=343)	
	TEAE[1]	Treatment Related TEAE[2]	TEAE[1]	Treatment Related TEAE[2]
TEAE resembling EPS[a], n (%)	11 (3.2)	5 (1.5)	3 (0.9)	1 (0.3)
Akathisia	8 (2.4)	2 (0.6)	3 (0.9)	1 (0.3)
Dyskinesia	1 (0.3)	1 (0.3)	0	0
Dystonia	1 (0.3)	1 (0.3)	0	0
Extrapyramidal disorder	1 (0.3)	1 (0.3)	0	0

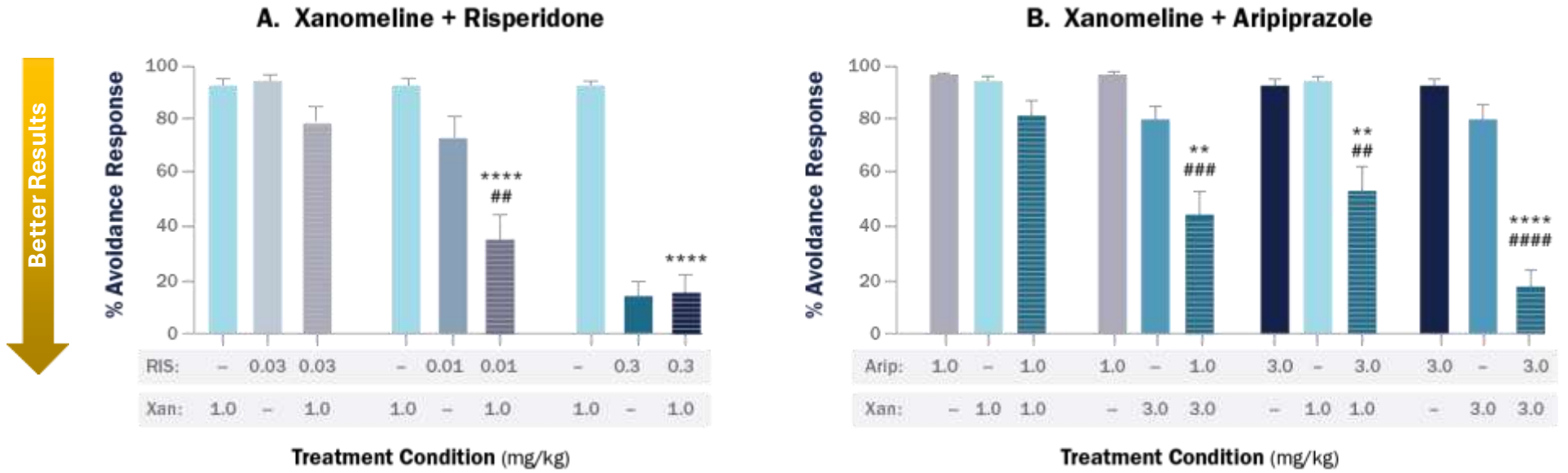
Movement Scale	All KarXT (N=340)	Placebo (N=343)
Simpson-Angus Scale total score[2], mean change from baseline to week 5 ±SD	-0.1±0.62	-0.1±0.63
Barnes Akathisia Rating Scale total score[2], mean change from baseline to week 5 ±SD	-0.1±0.90	-0.1±0.84
Abnormal Involuntary Movement Scale total score of items 1-7[2], mean change from baseline to week 5 ±SD	0.0±6.6	0.0±0.15

Safety population defined as all participants who received ≥1 dose of trial medication.
a. EPS TEAEs included any new onset dystonia, dyskinesia, akathisia, or extrapyramidal disorder reported any time after the first dose of trial medication.
EPS = extrapyramidal symptoms; SD = standard deviation; TEAE = treatment-emergent adverse event.
Weiden P, et al. Presented at: NEI; November 9-12, 2023; Colorado Springs, CO. Poster 85. Marcus R, et al. Poster F74 presented at 2024 Annual Conference of the Schizophrenia International Research Society (SIRS), April 3-7, 2024, Florence, Italy

Potential for Xanomeline-Trospium as Adjunctive Treatment in Schizophrenia

Xanomeline Augments Risperidone and Aripiprazole in Rodent Models of Psychosis

Post hoc analysis vs. xanomeline alone (*) and vs. comparator dose alone (#).
Values are mean ± SEM. ** p<0.01, **** p<0.0001; ## p<0.01, ### p<0.001, #### p<0.0001.

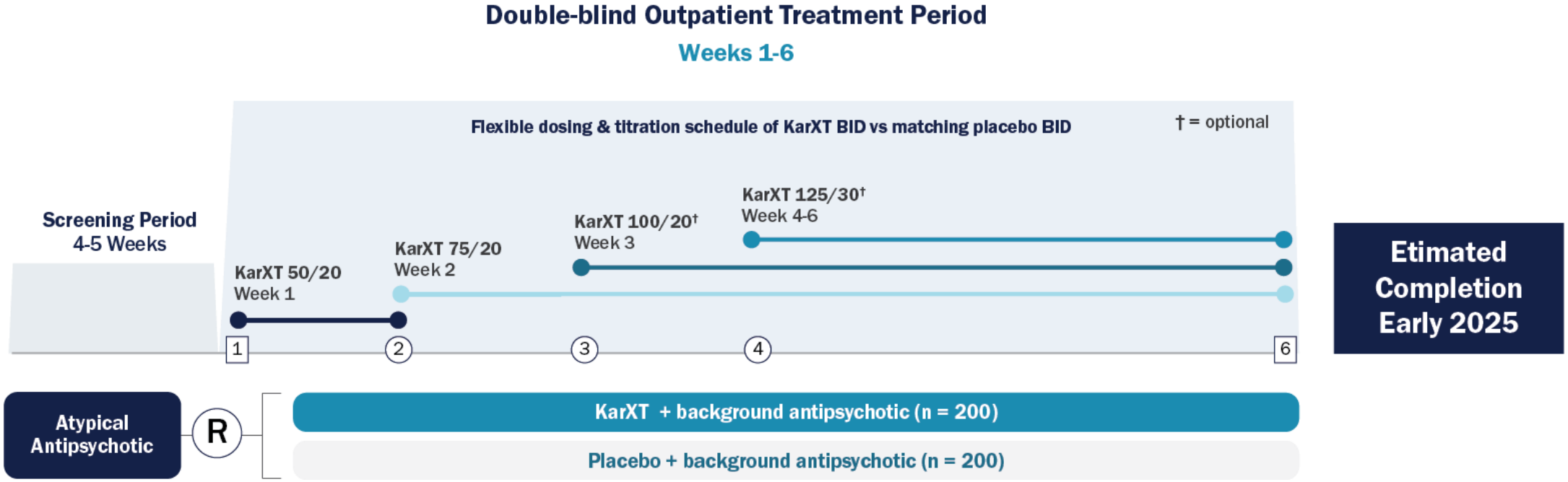


Combined low doses of [xanomeline + risperidone] or [xanomeline + aripiprazole] significantly augmented effects over those observed for each agent alone

Combination did not appear to incur greater rates of motor adverse effects

McKinzie, et al. Poster Presented at ACSP Annual Meeting. June 1-4, 2021.

Trial Design: KarXT as Adjunct Treatment of Inadequately Controlled Schizophrenia (ARISE)



- Must have at least 1 previous inadequate response to ≥ 6 weeks of an adequate monotherapy trial of:
- ziprasidone, lurasidone, cariprazine, or (oral or LAI) risperidone, paliperidone, or aripiprazole
- And must have a stable dose for ≥ 8 weeks as of Day 1 of the study, without changes throughout the study

Unlike the monotherapy studies:

1. Outpatients with entry PANSS ≥70
2. Uses a slower titration.
3. Flexible dose design.
4. 100/20 BID and 125/30 BID doses are optional based on tolerability and clinical response.

LAI = long-acting injectable

ClinicalTrials.gov. A Study to Assess Efficacy and Safety of Adjunctive KarXT in Subjects With Inadequately Controlled Symptoms of Schizophrenia (ARISE). Accessed September 10, 2024. https://clinicaltrials.gov/ct2/show/NCT05145413

Key Learning Points

- ✓ **Significant symptom reduction** (PANSS total score) seen in all EMERGENT 1-3 trials with effect sizes for ranging from 0.60-0.81

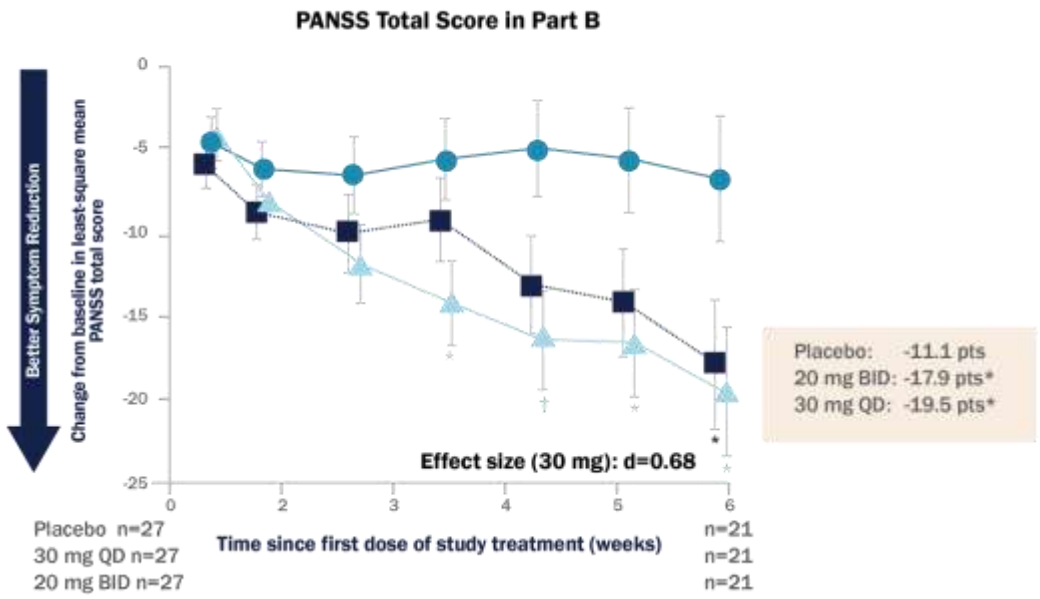
- ✓ **Trospium mitigated the procholinergic adverse effects**. Rates of AE related discontinuation in the 3 short term trials were 5.6% for XT vs. 4.7% for placebo. No evidence of significant D_2, metabolic or endocrine related adverse effects.

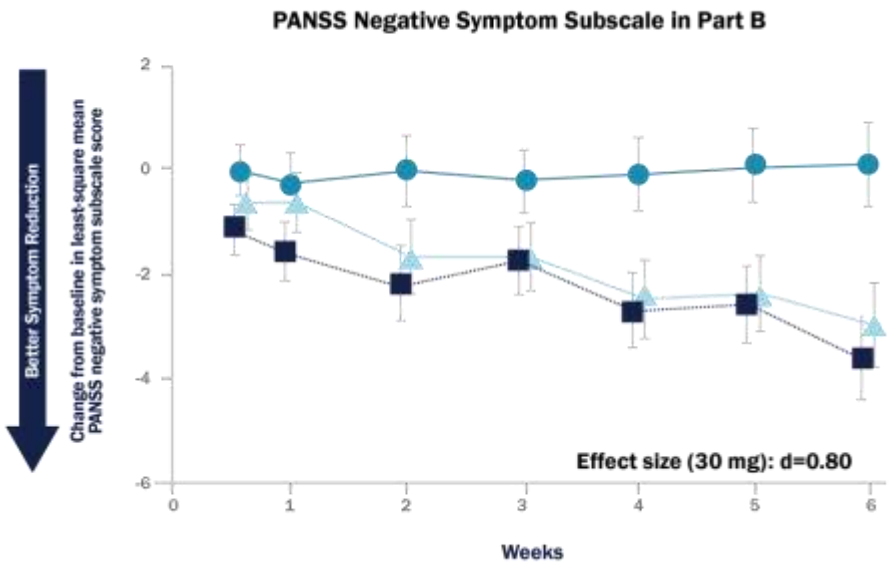
- ✓ There is a replicated signal across all phase 2b/3 studies of **improved cognitive functioning** in those with more significant baseline cognitive dysfunction.

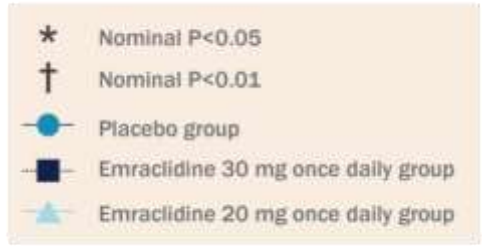
- ✓ The **EMERGENT-4** open-label extension study, which enrolled patients who completed either EMERGENT-2 or EMERGENT-3, **was associated with a mean PANSS total score change of -33.6 points from baseline to week 52 in those who received KarXT in the previous trial**

Other Activators of Muscarinic Receptors

Emraclidine M4 PAM Phase 1B Study Efficacy Results







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

- **Emraclidine has 390-fold selectivity as a PAM for M_4 relative to M_2, and no effect on other muscarinic receptors**
- **Part A of a Phase 1 study assessed the tolerability of emraclidine 5, 10, 20, and 30 mg QD and 20 mg BID**

QD = once daily; BID = twice daily; PANSS = Positive and Negative Syndrome Scale.

Krystal JH, et al. *The Lancet*. 2022;400(10369): 2210-2220. Butler CR., et al. *Journal of Medicinal Chemistry*. 2024;67(13): 10831-10847.

Emraclidine Safety and Tolerability in Part B of a Phase 1B Study

	Placebo (n = 27)	Emraclidine 30 mg QD (n = 27)	Emraclidine 20 mg BID (n = 27)
AEs in ≥5% of all Emraclidine			
Headache	7 (26%)	8 (30%)	7 (26%)
Nausea	1 (4%)	2 (7%)	2 (7%)
Weight increased	2 (7%)	1 (4%)	2 (7%)
Back pain	1 (4%)	1 (4%)	1 (4%)
CPK increased	0 (0)	1 (4%)	2 (7%)
Dizziness	0 (0)	1 (4%)	2 (7%)
Dry mouth	0 (0)	3 (11%)	0 (0)
Somnolence	0 (0)	1 (4%)	2 (7%)
Serious AEs	0 (0)	2 (7%)	1 (4%)
AEs leading to D/C	0 (0)	2 (7%)	1 (4%)

No clinically meaningful findings relative to placebo were observed in either part of the study in:

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

Transient, modest increases in heart rate and blood pressure were observed in both part A and part B.

They were asymptomatic, decreased over time, and not considered clinica ly meaningfulvs. placebo after 6 weeks.

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

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

Phase 2 Studies of Emraclidine *Did Not* Meet Their Primary Endpoint

EMPOWER-1 and EMPOWER-2 Phase 2 clinical trials did not meet their primary endpoint.

Change from Baseline to Week 6 in PANSS Total Score

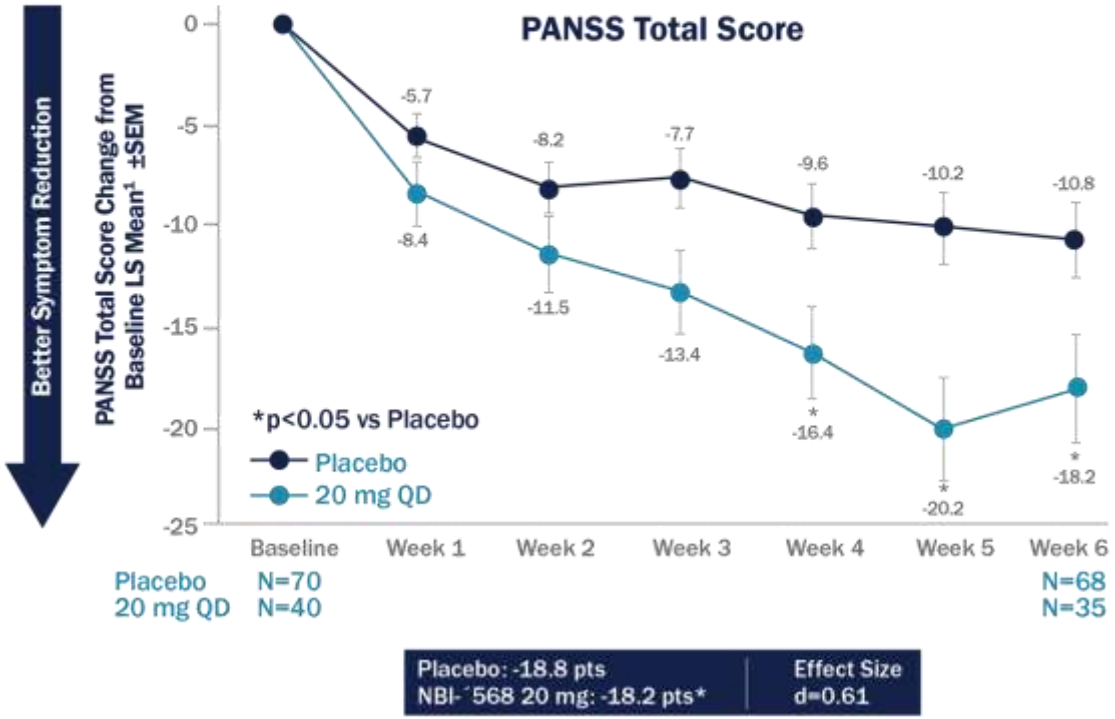
	EMPOWER-1			EMPOWER-2		
	Placebo (N= 127)	**Emraclidine 10mg QD (N = 125)**	**Emraclidine 30mg QD (N = 127)**	**Placebo (N = 128)**	**Emraclidine 15mg QD (N = 122)**	**Emraclidine 30mg QD (N = 123)**
Baseline (SD)	98.3 (8.16)	97.6 (7.65)	97.9 (7.89)	97.4 (8.22)	98.0 (8.49)	97.2 (7.75)
LS Mean (95% CI)	-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 News Center. November 11, 2024. *AbbVie provides update on Phase 2 results for Emraclidine in schizophrenia*. Accessed March 6, 2025. https://news.abbvie.com/2024-11-11-AbbVie-Provides-Update-on-Phase-2-Results-for-Emraclidine-in-Schizophrenia

NBI-1117568: Selective M4 Agonist: Results from a Phase 2 Study

>500-fold agonist selectivity for M_4 over other muscarinic receptors

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



Placebo: -18.8 pts NBI-´568 20 mg: -18.2 pts*	Effect Size d=0.61

TEAEs occurring in ≥ 5% of NBI-'568 All Treated Group

	Placebo N=70	NBI-'586 20mg QD N=40
Somnolence	2 (2.9%)	5 (12.5%)
Dizziness	1 (1.4%)	5 (12.5%)
Headache	14 (20.0%)	1 (2.5%)
Nausea	2 (2.9%)	2 (5.0%)
Constipation	2 (2.9%)	2 (5.0%)
D/C 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.**

NBI-'568 showed efficacy comparable to other muscarinic activators and a favorable tolerability profile

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.

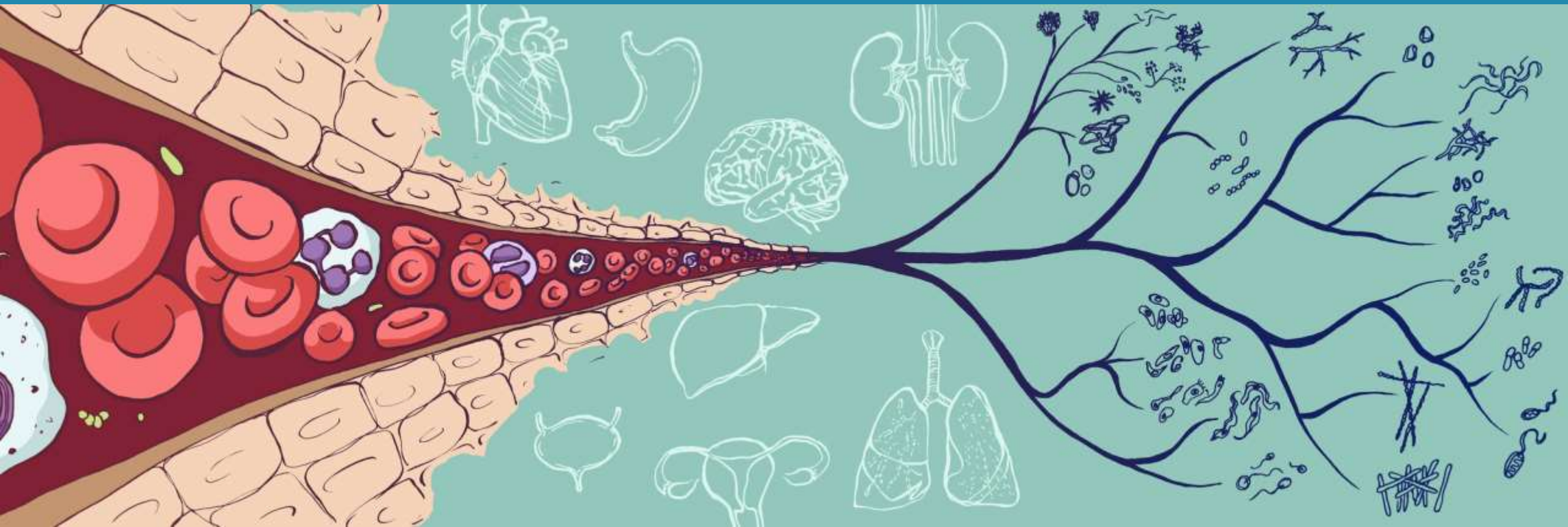
Other Investigational Muscarinic Agents

	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-

Implications for the Evolving Schizophrenia Treatment Landscape



Identify Patients that may Benefit from New Treatment Approach

- **Newly diagnosed** – have not been exposed to risks associated with D2 antagonism
- **Inadequate response** to existing antipsychotics, particularly those with prominent cognitive deficits or intolerance to metabolic/EPS side effects of current drugs.
- Emerging research may link **genetic variants** (eg, *CHRM1/CHRM4* polymorphisms) or **neuroimaging markers** (prefrontal connectivity) to muscarinic response.

- **Shared Decision-Making key communication points**:
  - **Mechanism**: Simplify to *"targets different brain pathways to improve thinking and motivation, not just hallucinations."*
  - **Benefits**: Highlight potential for symptom improvement and highlight side effects differences.
  - **Risks**: Transient **cholinergic effects** in muscarinic agents (nausea, diarrhea, sweating); rare risks (eg, syncope in trials).
  - **Realistic Expectations**: Emphasize gradual symptom improvement (weeks to months) and ongoing monitoring.

Aoki, Yumi et al. Shared decision-making interventions for people with mental health conditions. *The Cochrane Database of Systematic Reviews*. 11 Nov. 2022;11(11):CD007297. doi:10.1002/14651858. CD007297.pub3. Cobenfy (xanomeline-trospium) Prescribing Information. Drugs@FDA: FDA Approved Drugs. Accessed Feb. 11, 2025. www.accessdata.fda.gov/scripts/cder/daf/.

Overcoming Barriers to Our Newest FDA Approved Treatment

Xanomeline-Trospium: How to Initiate

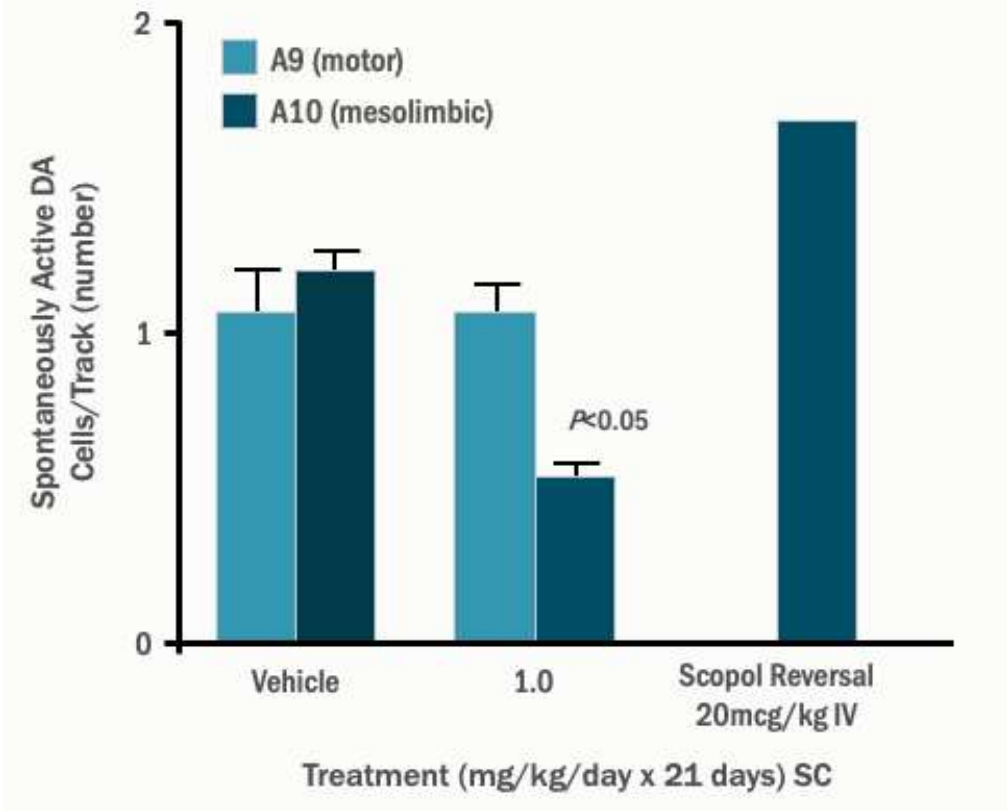
Implementation issues:

- Will certain patients selectively respond to the new muscarinic strategies?
- What about patients who are nonadherent with oral APs?
- What is the best method of cross-tapering existing antipsychotics?

Anticholinergics impacting efficacy:

- **How:** CNS acting anticholinergics will interfere with the mechanism of action of M1/M4 agonists or PAMs
- **Management:** Must taper off antiparkinsonian agents and other anticholinergics with high CNS penetration (eg, oxybutynin) when starting treatment with muscarinic activating antipsychotics
  - Unknown interactions with anticholinergic antipsychotics clozapine, olanzapine, quetiapine

Xanomeline selectively reduces dopamine cell firing in mesolimbic (A10) but not in striatal motor neurons (A9). Mesolimbic activity is blocked by the centrally acting anticholinergic scopolamine.



Shannon HE, et al. *Schizophrenia Research*. 2000;42(3):249-259.

Xanomeline-Trospium: How to Initiate

- Titration issues: The PI allows for a slower titration than used in the clinical trials, presumably to help mitigate adverse effects. The wording states:
  - The recommended starting dosage is one 50 mg/20 mg capsule (contains 50 mg of xanomeline and 20 mg of trospium chloride) orally twice daily *for at least two days*.
  - Increase the dosage to one 100 mg/20 mg capsule (contains 100 mg of xanomeline and 20 mg of trospium chloride) orally twice daily *for at least five days*.
  - The dosage may be increased to one 125 mg/30 mg capsule (contains 125 mg of xanomeline and 30 mg of trospium chloride) orally twice daily *based on patient tolerability*.
- The food issue: The exposure to trospium is decreased 85%-90% if taken with food. Patients must take X-T 1 hour before or 2 hours after a meal.
  - Practical strategy: dose X-T upon awakening or 1 hour before breakfast and then at bedtime (without food)
- Peripheral anticholinergic burden: Note use of other anticholinergics (e.g. overactive bladder meds) when initiating. Ask about LUTS in males when starting X-T. The max dose for geriatric patients is 100 mg/20 mg. Lastly, two contraindications are urinary or gastric retention.
  - Practical strategy: Use slower titration, taper off other anticholinergics, ask about urinary symptoms.

Cobenfy (xanomeline-trospium) Prescribing Information. Drugs@FDA: FDA Approved Drugs. Accessed January 10, 2023. www.accessdata.fda.gov/scripts/cder/daf/.

Xanomeline-Trospium: How to Initiate

- Monitoring LFTs: Rate of ALT or AST elevation >3x ULN was 2.8% for X-T vs 0.4% for PBO. 1.6% had elevated LFTs at some point, but the majority occurred within the first month and resolved with continued X-T exposure.
  - Practical strategy: PI states to obtain baseline LFTs including bilirubin and "and as clinically indicated during treatment." In the absence of clinical symptoms, consider repeating LFTs after 1 month to document lack of effect.
- Monitoring Heart rate: In the phase 3 studies the endpoint difference from placebo was +5.9 BPM, and in a dedicated ambulatory study the endpoint difference was +9.8 BPM.
  - Practical strategy: Baseline and periodically during treatment (as is often done when starting clozapine).
- Drug interactions: CYP2D6 contributes to xanomeline metabolism, but the PI does not recommend dose adjustment, but to monitor for adverse reactions.
  - Practical strategy: Consider a slower initial titration and lower maximal dose.
- Hepatic and renal dysfunction: Cannot use with Child-Pugh B or C. Higher exposure in cirrhosis patients who are Child Pugh A. Approximately 2-fold higher xanomeline exposure with eGFR 30-89 ml/min
  - Practical strategy: Consider a slower initial titration and lower maximal dose.

Cobenfy (xanomeline-trospium) Prescribing Information. Drugs@FDA: FDA Approved Drugs. Accessed January 10, 2023. www.accessdata.fda.gov/scripts/cder/daf/.

Key Learning Points

- ✓ **Initiate muscarinic agents gradually**, considering individual patient needs, tolerability, and potential interactions with other schizophrenia treatments and medical comorbidities to enhance adherence and minimize side effects.

- ✓ **Patient must be tapered off antiparkinsonian agents and other anticholinergics with high CNS penetration** (eg, oxybutynin) when starting treatment with muscarinic activating antipsychotics

- ✓ Incorporating **shared decision-making** and adherence strategies to support long-term success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Practical Take-Aways

- Traditional schizophrenia treatment often focus on postsynaptic D2-binding, but shifting to presynaptic mechanisms and muscarinic acetylcholine receptor activation offers new hope for improved efficacy and reduced side effects
- Emerging show potential as both monotherapy and adjunctive treatment options, targeting M1/M4 pathways with promising clinical trial data.
- By understanding the specific neurobiology of schizophrenia, clinicians can better identify which patients may benefit from muscarinic receptor activators, enabling more personalized and effective treatment approach.

Q&A