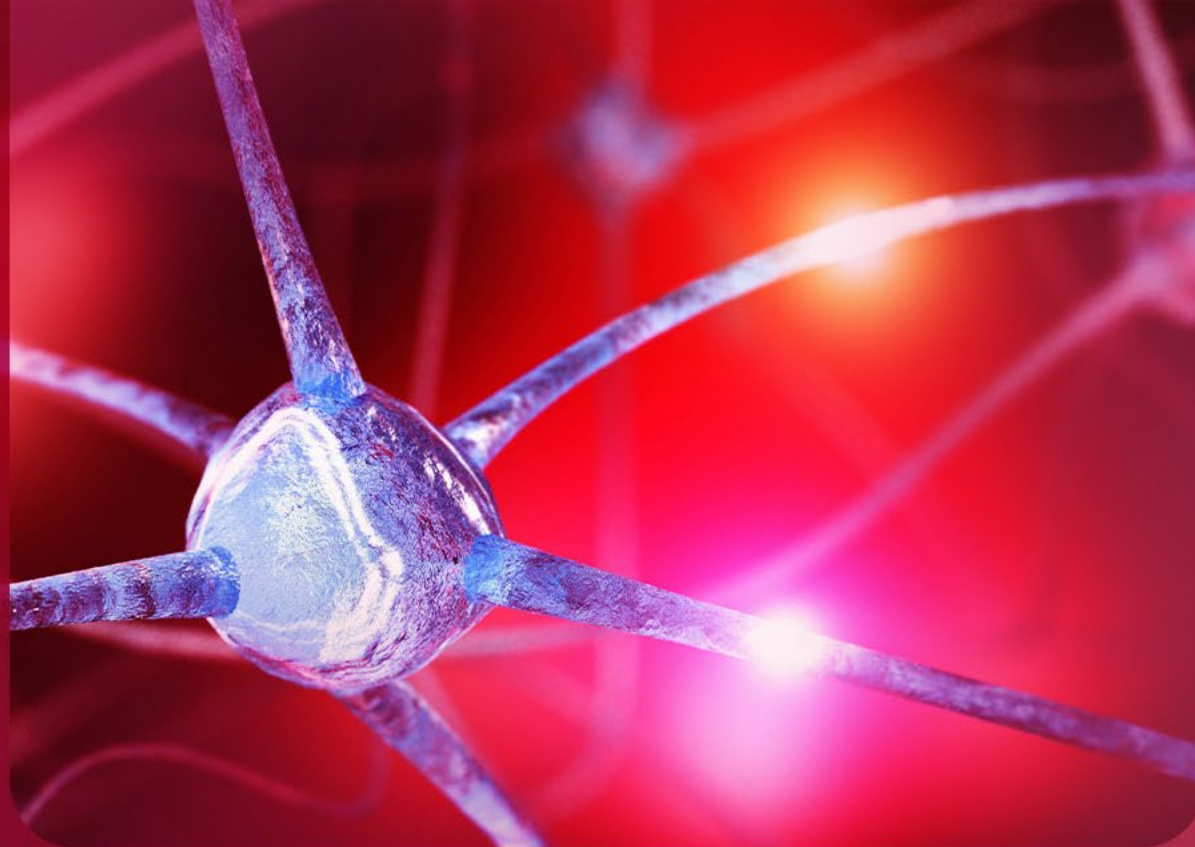




Presynaptic Possibilities: The Past, Present, and Future of ***Modulating Dopamine Release***

MasterClass

Supported by an educational grant from Bristol-Myers Squibb.

Faculty

Christoph U. Correll, MD

Clinical Professor of Psychiatry,
Zucker School of Medicine at
Hofstra/Northwell
New York, NY

Chelsie Monroe, MSN, APN, PMHNP-BC

Founder, Balanced Mental
Wellness
Littleton, CO

Faculty Disclosures

- **Christoph U. Correll, MD:** Advisory Board – AbbVie, Alkermes, Allergan, Angelini, Boehringer Ingelheim, Bristol Myers Squibb, Cerevel, Compass, Gedeon Richter, Janssen/J&J, Karuna, LB Pharmaceuticals, Lundbeck, Medincell, Merck, Neuraxpharm, Neurelis, Neurocrine Biosciences, Newron, Novo Nordisk, Otsuka, Recordati, Rovi, Sage, Seqirus, SK LifeScience, Sunovion, Supernus, Teva, Vertex, Viatris; Consultant – AbbVie, Alkermes, Allergan, Angelini, Autobahn, Boehringer Ingelheim, Bristol Myers Squibb, Cerevel, Compass, Denovo, Eli Lilly, Gedeon Richter, GH, Intra-Cellular Therapies, Janssen/J&J, Karuna, Kuleon Bioscience, LB Pharmaceuticals, Lundbeck, Medincell, Medlink, Merck, Mindpax, Neuraxpharm, Neurelis, Neurocrine Biosciences, Newron, Novo Nordisk, Otsuka, Recordati, Relmada, Reviva, Rovi, Sage, Seqirus, SK Life Science, Sunovion, Supernus, Teva, Vertex, Viatris; Grant/Research Support – Boehringer Ingelheim, Janssen, Takeda
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Learning Objectives

- Describe the evolution of presynaptic versus postsynaptic dopaminergic interventions in schizophrenia
- Compare the pathophysiologies of schizophrenia and BD-I mania based on neurobiological evidence and with a focus on dopaminergic dysregulation
- Assess the rationale for targeting presynaptic mechanisms that modulate dopamine release in schizophrenia and BD-I mania
- Evaluate clinical evidence and ongoing trials of selective muscarinic agents in schizophrenia and BD-I mania

**Dopaminergic Interventions
in Schizophrenia:**
*From Presynaptic to
Postsynaptic and Back Again*

In Schizophrenia, the Primary Dopamine Dysfunction Is Presynaptic

Presynaptic differences in schizophrenia

Elevated presynaptic striatal dopamine found in acutely psychotic individuals with

► **Effect sizes 0.63 to 1.25**

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

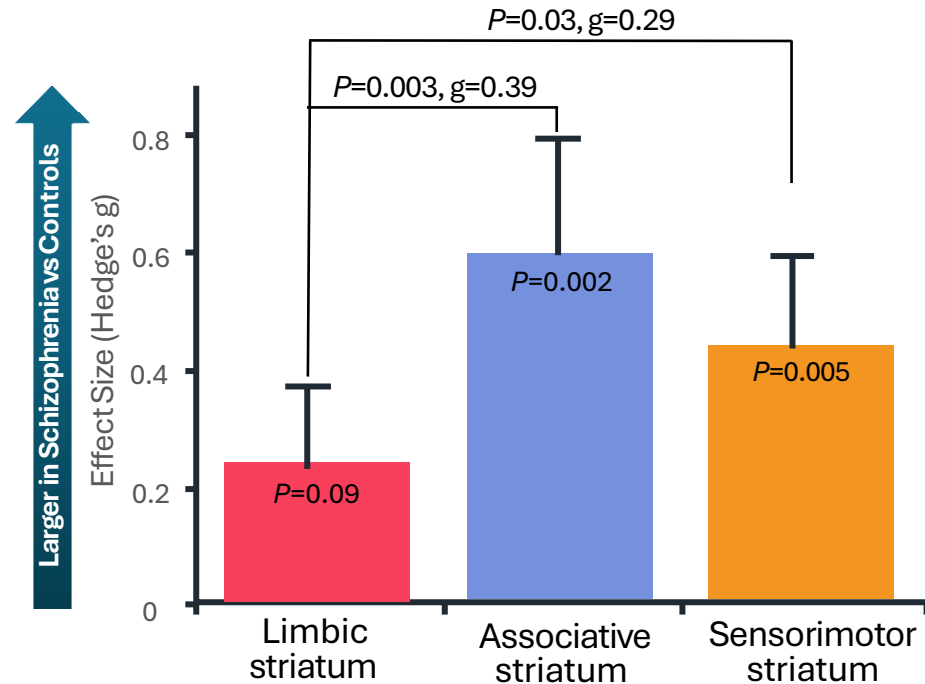
What About Nonresponders?

Imaging studies suggest that poor response to D₂ receptor modulation is associated with relatively normal striatal dopamine synthesis capacity but elevated anterior cingulate cortex (ACC) and striatal (caudate) glutamate levels.

► **different form of schizophrenia**

It's also not in the mesolimbic pathway!

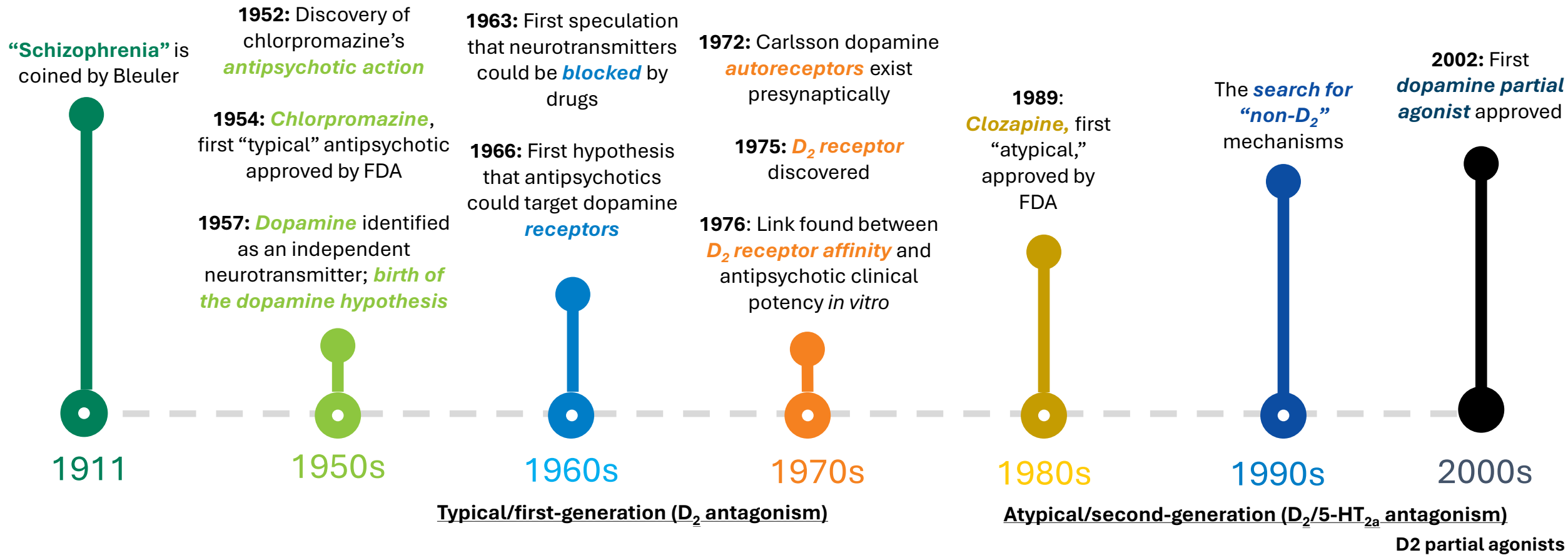
Estimated Mean Difference in Presynaptic Dopamine Function in Patients vs Controls



Recent high-resolution imaging studies

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

A Brief History of Schizophrenia Treatment

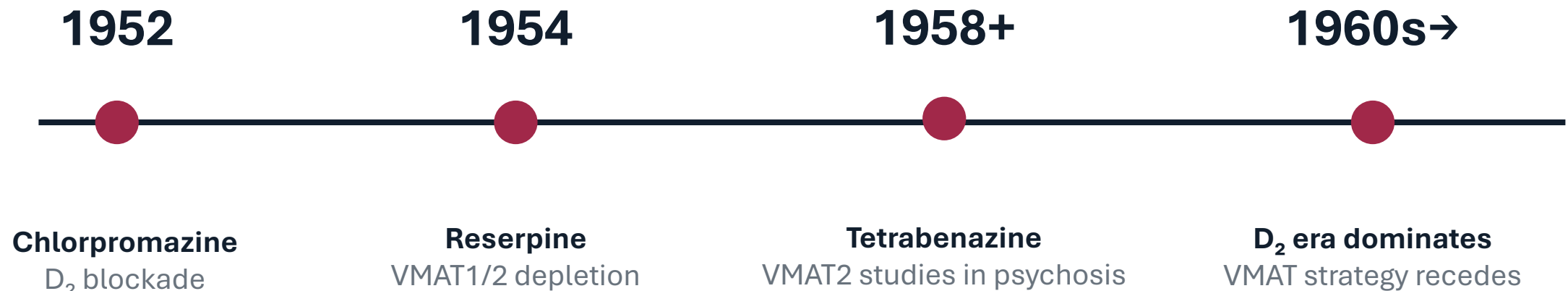


5-HT_{2A} = serotonin type 2A receptor; D₂ = dopamine D₂ receptor.

Madras B. *J Hist Neurosci*. 2013;22:62-78. Correll CU, et al. *J Clin Psych*. 2022;1 (InfoPack 1):SU21024Ip1. Creese I, et al. *Science*. 1976;192(4238):481-483. Seeman P, et al. *Nature*. 1976;261(5562):717-719.

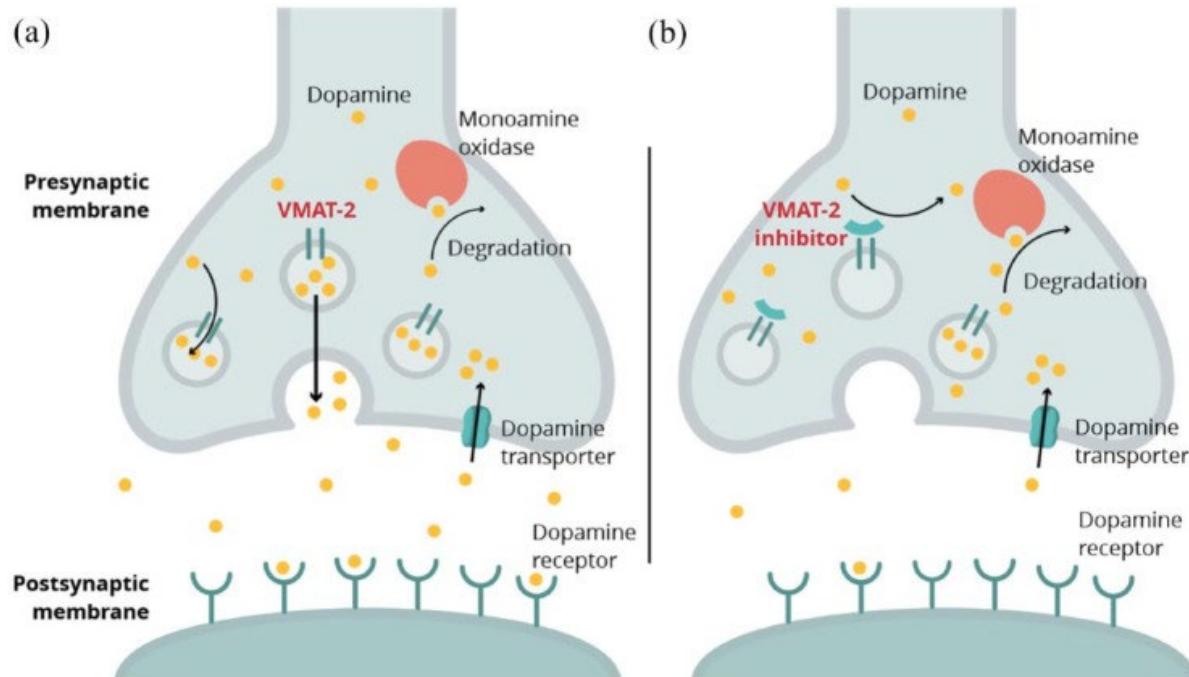
The Real History:

Presynaptic Monoamine Depletion and Postsynaptic Receptor Blockade Emerged Almost Simultaneously



The idea did not disappear because presynaptic dopamine was unsupported; early VMAT drugs were blunt, poorly tolerated tools.

VMAT Inhibition Turns Down DA Upstream



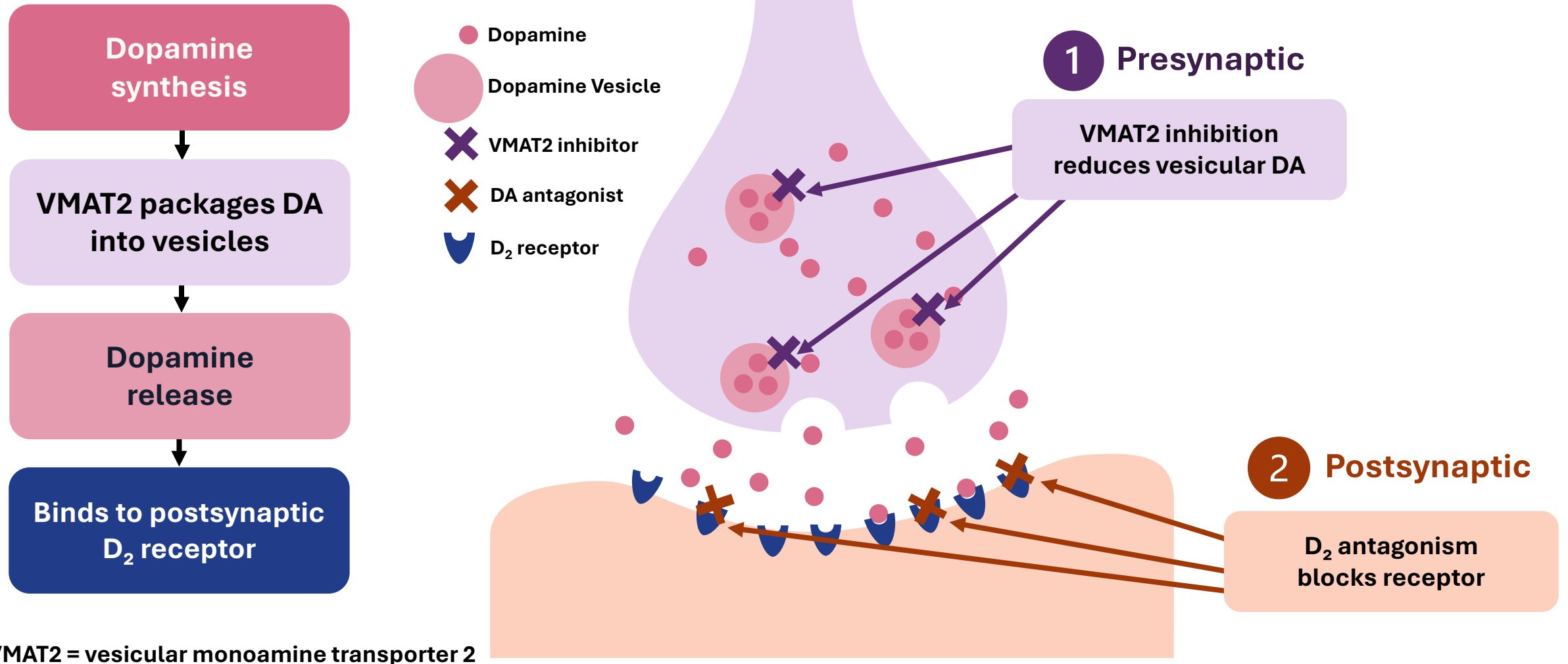
Reserpine
(VMAT1/VMAT2 inhibitor)
1954



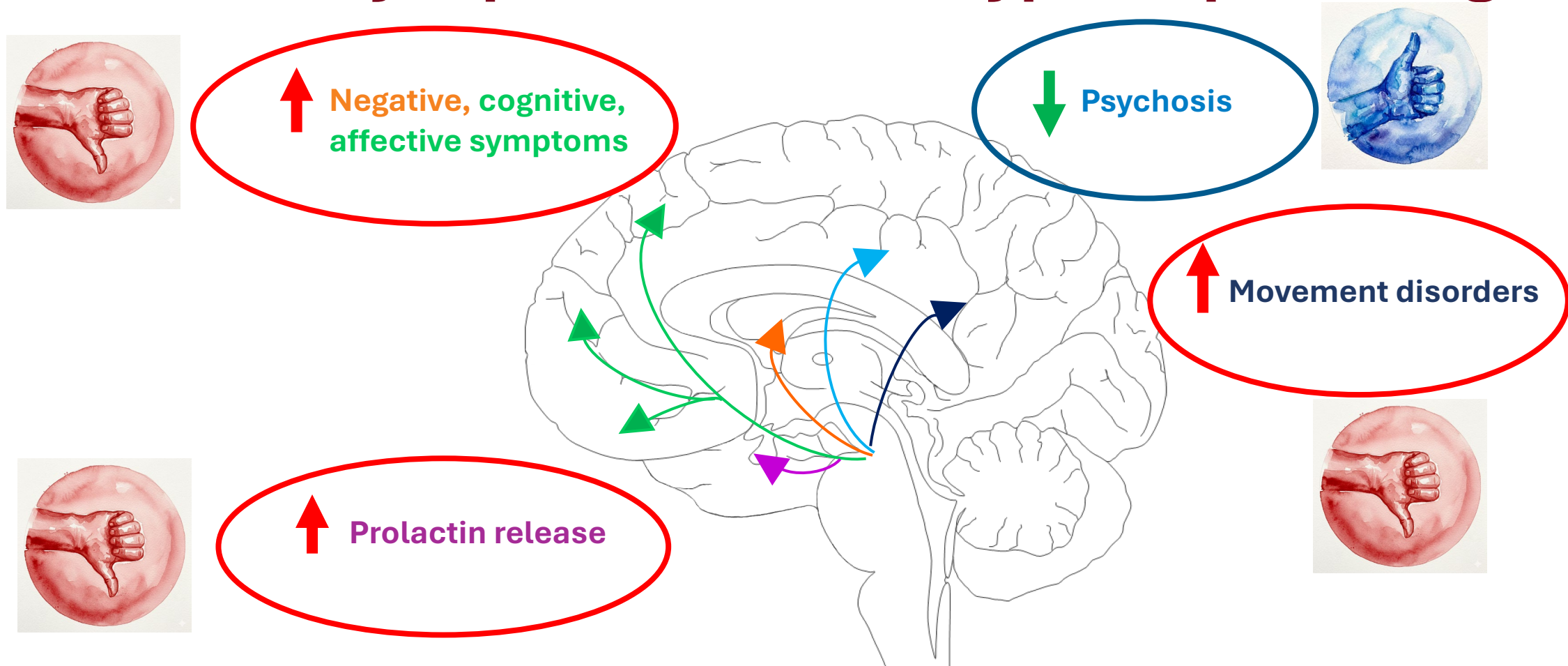
Tetrabenazine
(VMAT2) studied
in 1950's/1960's

↓ vesicular packaging = ↓ DA available for release → ↓ postsynaptic dopamine signaling

Two Ways to Turn Down Dopamine: Turn Down Release or Block DA Receptors



Dopamine D2 Receptor Antagonism Blocks Postsynaptic Effects of Hyperdopaminergia

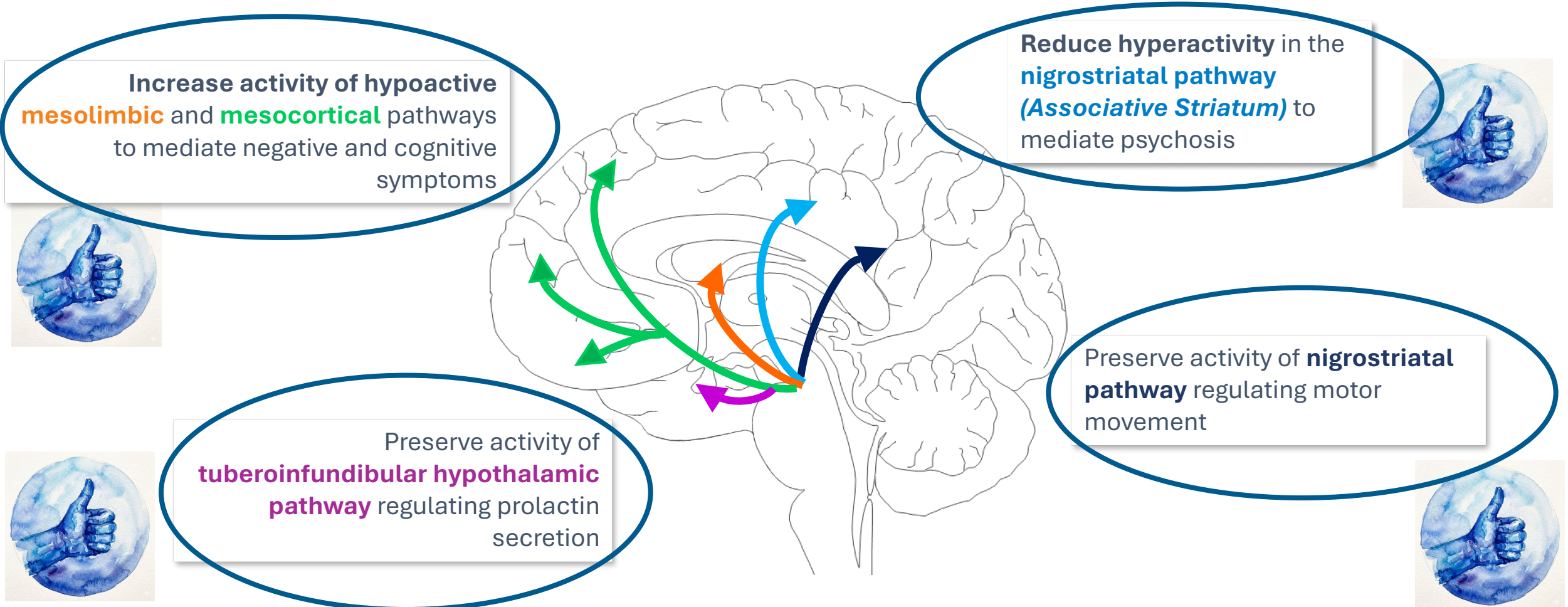


*Advances in neuroimaging techniques found that DA dysfunction in schizophrenia is greatest within nigrostriatal pathways, implicating the dorsal striatum. DA overactivity in the circuit from the dorsomedial substantia nigra to the associative and adjacent sensorimotor striatum is linked to positive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

DA = dopamine.

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

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



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

DA = dopamine; Rx = prescription.

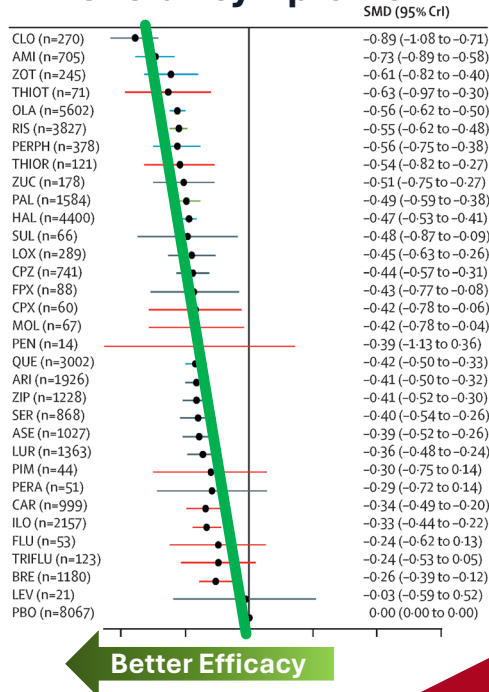
Correll CU, et al. *J Clin Psychiatry*. 2022;83(1):SU21204IP1. McCutcheon RA, et al. *Trends Neurosci*. 2019;42(3):205-220.

The Price of Our Obsession with Post-Synaptic D₂ Receptors

Looking back, improvements in efficacy seem negligible...

...and not evenly applied

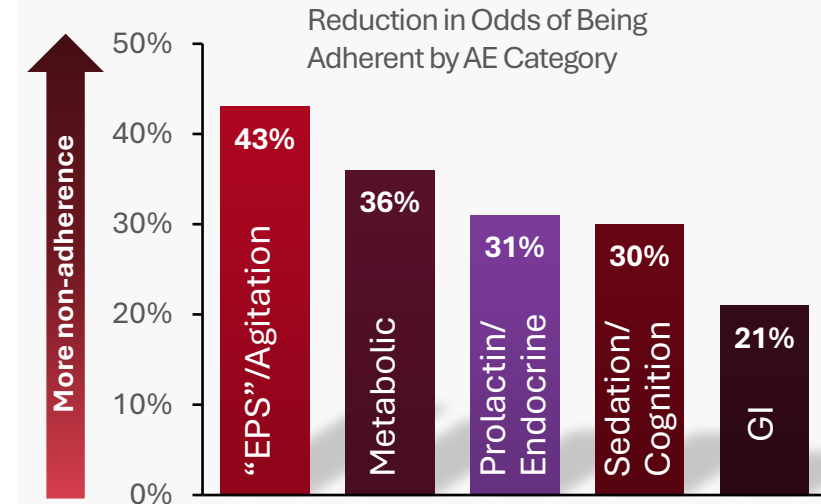
Overall symptoms:



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

Overall, only ~14% achieve recovery

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



More excess CV deaths than from suicide

And far too many die far too young

Overall life expectancy reduced 10-20 years

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

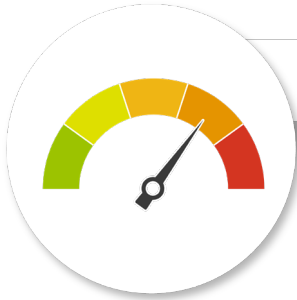
Huhn M, et al. *Lancet*. 2019;394(10202):939-951. DiBonaventura M, et al. *BMC Psychiatry*. 2012;12:20. Velligan DI, et al. *Schizophr Res*. 1997;25(1):21-31. Mitchell AJ, et al. *Schizophr Bull*. 2013;39(2):306-318. Jääskeläinen E, et al. *Schizophr Bull*. 2013;39(6):1296-1306.

Unmet Needs in Schizophrenia Treatment



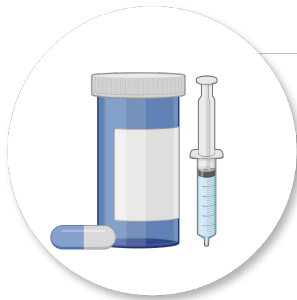
Residual Symptoms and Inadequate Treatment Response

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



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

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



All APs work via essentially the same mechanism

AP = antipsychotic.

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

Contemporary Investigation of VMAT2 Inhibition in SCZ: Negative Phase 3 Studies for Valbenazine

- Phase 3 (NBI-98854-ATS3019; NCT05110157):
 - 10-week Outpatient Schizophrenia adjunct trial of up to 80 mg/day Valbenazine
 - Criteria: PANSS ≥ 70 , CGI-S ≥ 4 , with positive symptom enriched criteria
 - Primary Endpoint: PANSS total change
 - Key Secondary: CGI-S and PSP
- Second Phase 3: same design, but study terminated after only 8 pts

Negative Phase 3 studies:
Valbenazine did not meet primary endpoints, but showed a positive effect on positive symptoms domain.

Insights will help inform further VMAT2 inhibitor development.

Another Presynaptic Approach to Modulate DA: TAAR-1 Agonism

- Ulotaront, a novel dual agonist of TAAR-1 and 5HT-1A receptor is thought to reduce the firing rate of dopaminergic neurons and modulate DA release in key areas associated with Schizophrenia (VTA)
- Activated by endogenous trace amines, which is believed to play an important role in dopaminergic, serotonergic, and glutamatergic activity
- Positive Phase 2 but Negative Phase 3:
- Ongoing Phase 3 trial SEP-363856 : study completion expected October, 2026
 - Ages 18-65, PANSS ≥ 80 , CGI-S ≥ 4 ,
 - 6 week trial, primary endpoint: change in baseline from PANSS total score

Key Learning Points



- The primary issue in schizophrenia is presynaptic DA dysfunction.
- Psychiatry explored both presynaptic and postsynaptic solutions:
 - Presynaptic DA-depleting agents, such as reserpine and tetrabenazine, caused intolerable adverse effects that limited their clinical use
 - Presynaptic options weren't selective enough, and ultimately D2 antagonism prevailed.
- There are significant consequences of postsynaptic D2 blockade, thus psychiatry has gone back to exploring presynaptic targeted options.

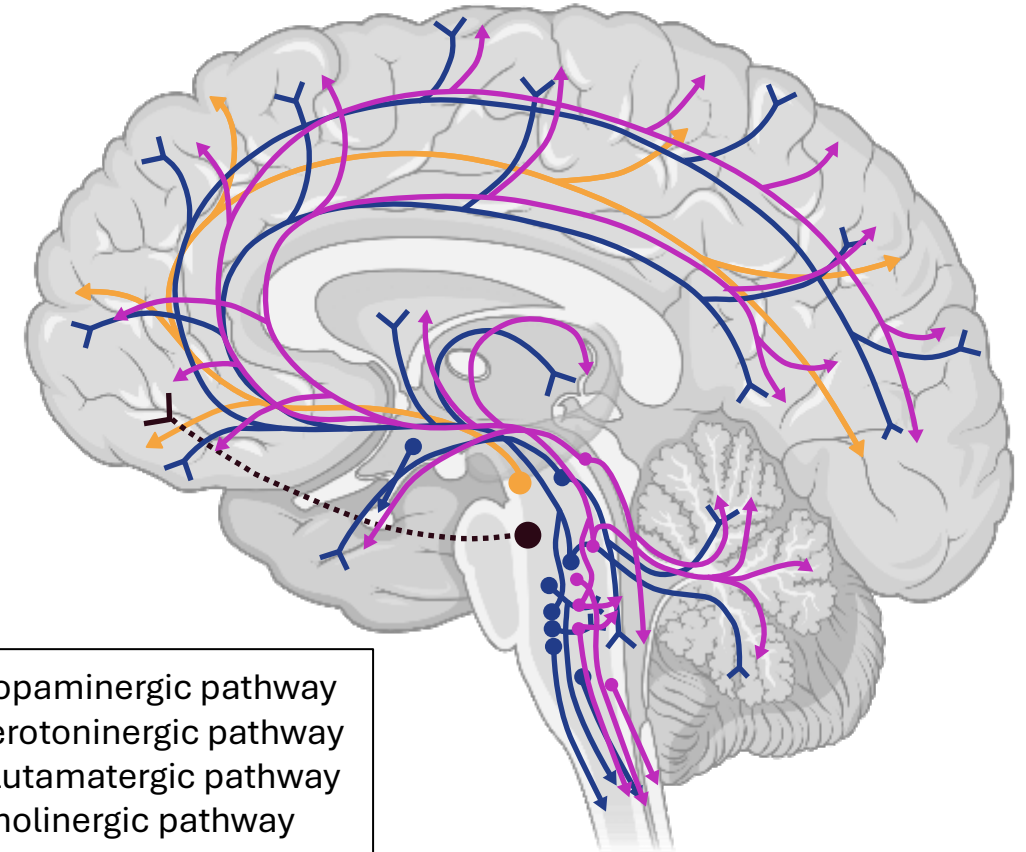
Selective Muscarinic Agents in Schizophrenia

The Cholinergic System Neuromodulates Multiple Neurotransmitter Systems

Dopaminergic, serotonergic, & glutamatergic pathways are all modulated by the cholinergic system

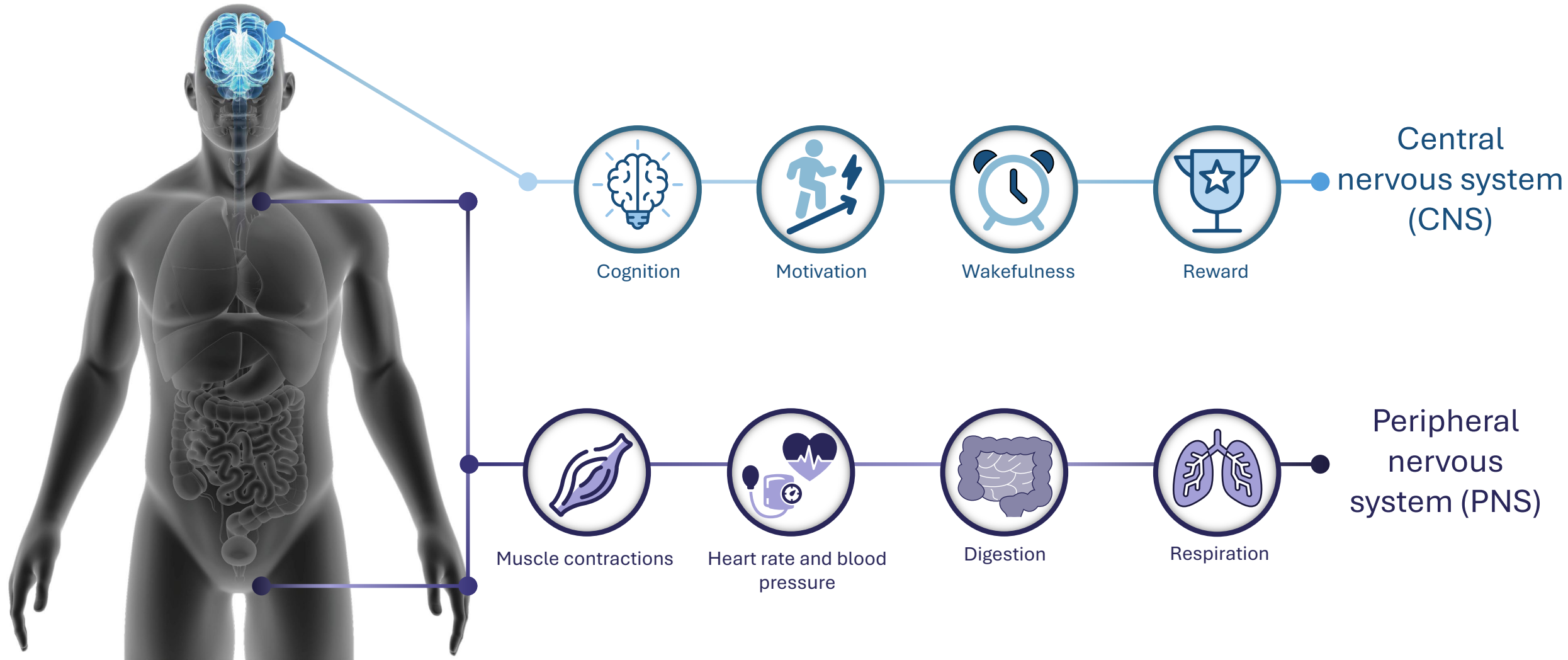
- In SCZ, AD, and BD, widespread cortical thinning occurs in areas of high connectivity between neurotransmitter systems
- Disease-related structural changes may propagate along interconnected neural circuits
- These macro-network disruptions support **a multi-system circuit disorder model** involving dopaminergic, glutamatergic, and cholinergic nodes

Targeting the cholinergic system may benefit multiple symptoms of SCZ and BD



Georgiadis F, et al. *Mol Psychiatry*. 2024;29(6):1869-1881; Zhang NK, et al. *Front Aging Neurosci*. 2024;16:1487875; Abé C, et al. *Mol Psychiatry*. 2023;28(7):2674-2682; McIntyre RS. *Expert Opin Investig Drugs*. 2025;34(6):519-526; Rajendran R, et al. *Adv Pharm Bull*. 2022;12(3):490-508; Glovac I, et al. *PLoS One*. 2015;10(7):e0131948.

Peripheral and CNS Acetylcholine Functions



Template Picciotto MR, et al. *Neuron*. 2012;76(1):116-129.

Sam C, et al. StatPearls Publishing; 2023. Updated April 10, 2023. Accessed June 6, 2023. <https://www.ncbi.nlm.nih.gov/books/NBK557825/>

Jones CK, et al. *Neuropsychopharmacology*. 2012;37(1):16-42.

Muscarinic Receptors

- Muscarinic receptors are located throughout central and peripheral nervous systems
 - Signal via G-protein cascades
 - Involved in a variety of bodily functions
- M_1 , M_3 , & M_5 are primarily postsynaptic and excitatory
 - Activation by agonists or positive allosteric modulators (PAM) increases intracellular 2nd messengers (e.g. IP3, calcium)
- M_2 and M_4 are primarily presynaptic and inhibitory
 - Activation by agonists or PAMs decreases intracellular cAMP

EXCITATORY

M_1 , M_3 , M_5

INHIBITORY

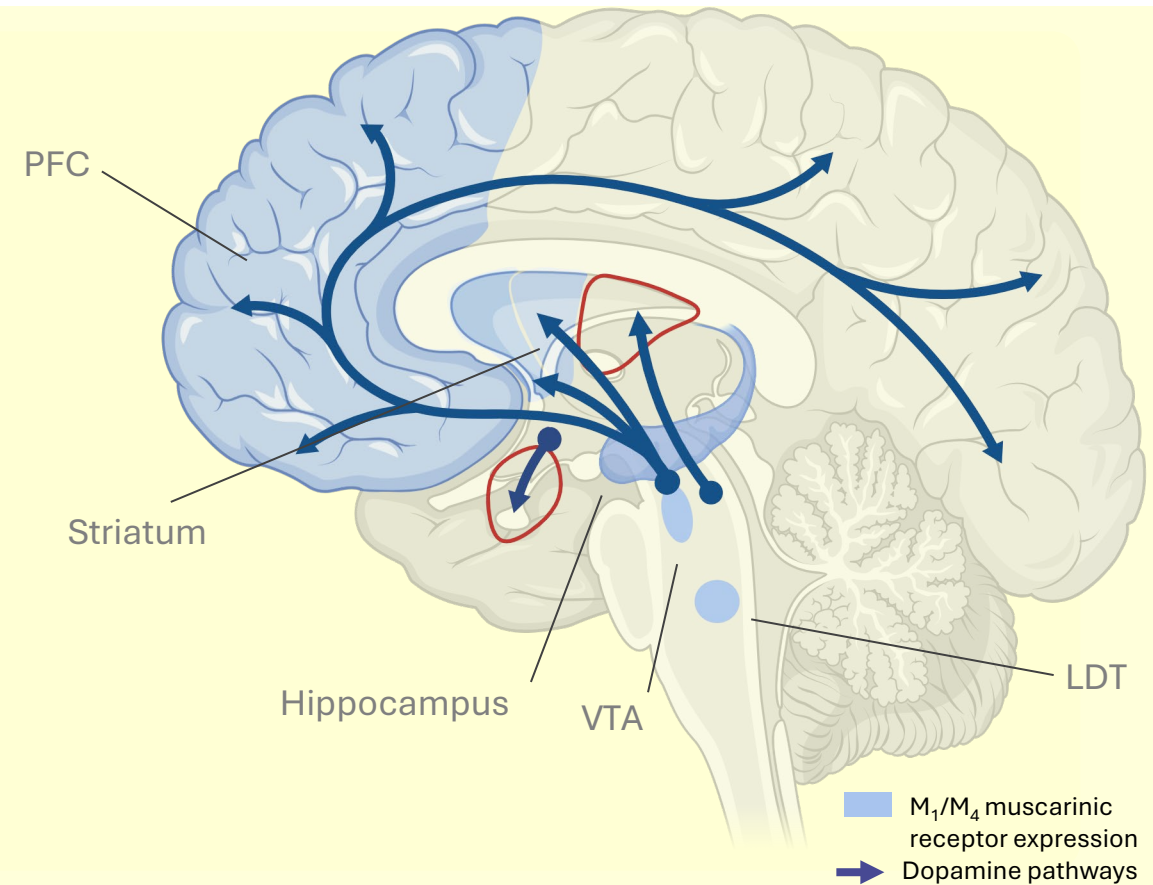
M_2 , M_4

MUSCARINIC RECEPTOR FUNCTIONS

- Neuronal excitability and neurotransmitter regulation
- Learning and memory
- Cardiac function
- Smooth muscle contraction
- Exocrine gland secretion (saliva, insulin)

M₁ and M₄ Receptor Stimulation As Therapeutic Targets in Schizophrenia

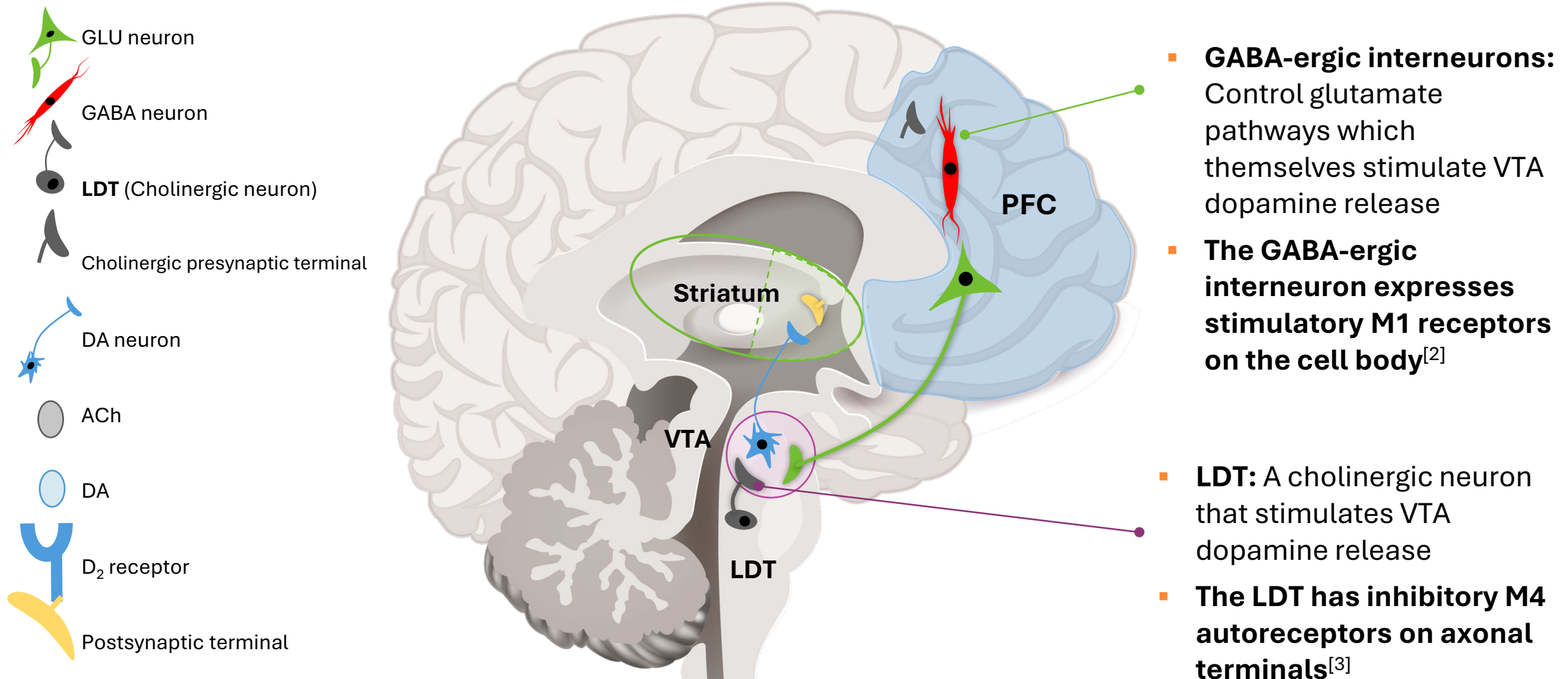
- M₁ or M₄ knockouts exhibit psychosis-like behaviors in animal models
- M₁ or M₄ receptor activating agents (agonists or positive allosteric modulators [PAMs]) improve these behaviors
- M₁ and M₄ receptors are highly expressed in areas related to symptoms, especially key dopamine circuits (e.g. VTA in animal models)
- The laterodorsal tegmentum (LDT) is a source of cholinergic stimulation to VTA dopamine release and is regulated by inhibitory M₄ autoreceptors.
- M₁ and M₄ receptors are not highly expressed in areas related to motor or endocrine adverse effects of D₂ blockade
- There is cholinergic modulation of motor dopamine circuits, but the effects of ligands on inhibitory autoreceptors in that cholinergic pathway (PPN) are dependent on M₂ receptor activation.



LDT, laterodorsal tegmentum; PFC, prefrontal cortex; PPN, pedunculopontine nucleus; VTA, ventral tegmental area.

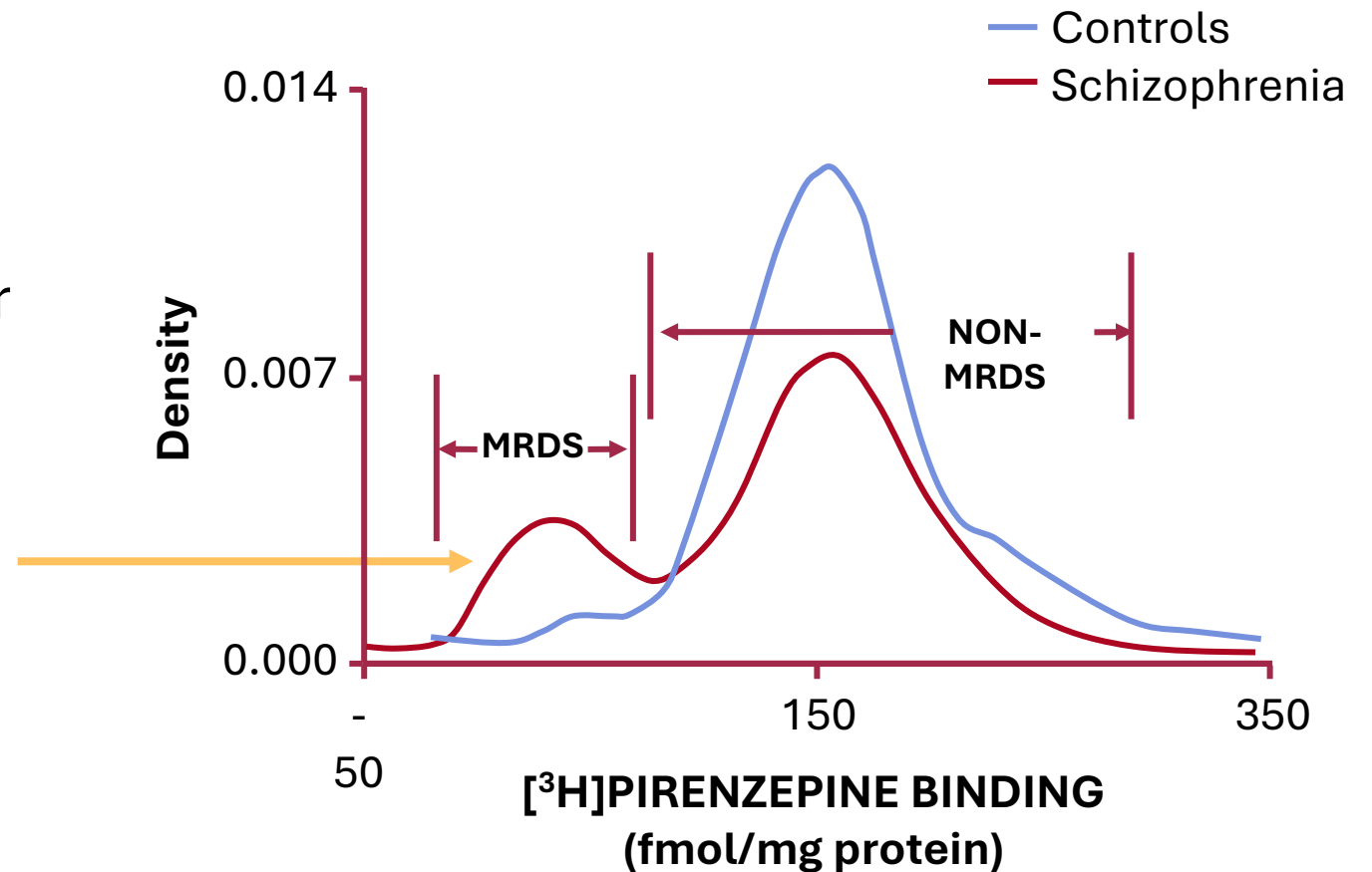
1. Paul SM, et al. Am J Psychiatry. 2022;179(9):611-627. 2. Correll CU, et al. J Clin Psychiatry. 2022;83(1):SU21024IP1. 3. Roh E, et al. Exp Mol Med. 2016;48(3):e216. 4. GTEx Portal. Accessed Jun 9, 2023. www.gtexportal.org/home/gene/CHRM1. 5. GTEx Portal. Accessed Jun 9, 2023. <https://www.gtexportal.org/home/gene/CHRM4>. 6. Stahl SM. Stahl's Essential Psychopharmacology. 5th ed. Cambridge University Press; 2021. 7. Weiden PJ, et al. Presented at: SIRS; Apr 6-10, 2022; Florence, Italy. Poster.

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



How Muscarinic Activation Might Improve Cognition

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



Muscarinic Agonism for Psychosis Rediscovered

- **1957:** Preclinical evidence that the **muscarinic agonist arecoline** inhibits conditioned response in rats in a manner comparable to reserpine and chlorpromazine
- **1957:** Clinical evidence that **arecoline** induces 'lucid intervals' in schizophrenia patients
- Limited interest in the cholinergic basis of schizophrenia or related meds through 1990:
 - **From 1960-1990:** 1299 papers in PubMed on dopamine/schizophrenia
 - **From 1960-1990:** Only 81 papers in PubMed on acetylcholine/schizophrenia
 - **From 1960-1990: Only 22 papers in PubMed with the keywords muscarinic and schizophrenia**
- Developments in the 1990s stimulated by the **xanomeline** findings:
 - Synthesis of muscarinic agonist ligands with antipsychotic effects in animals
 - Recognition that M₁ and M₄ knockout mice display behavior consistent with psychosis
 - Characterization of norclozapine:
 - Reverses amphetamine induced activity (**an effect dependent on M₄ agonism**)
 - **Stimulates M₁ receptors**, which may potentiate NMDA receptor activity and have procognitive effects

Pfeiffer CC, Jenney EH. Ann N Y Acad Sci 1957;66(3):753-64; Fulcher JH Jr et al. AMA Arch Neurol Psychiatry 1957;78(4):392-5; Bodick NC et al. Arch Neurol 1997;54(4):465-73; Sur C et al. Proc Natl Acad Sci U S A 2003;100(23):13674-9; Woolley ML et al. Eur J Pharmacol 2009;603(1-3):147-9; Watson J et al. Br J Pharmacol 1998;125(7):1413-20

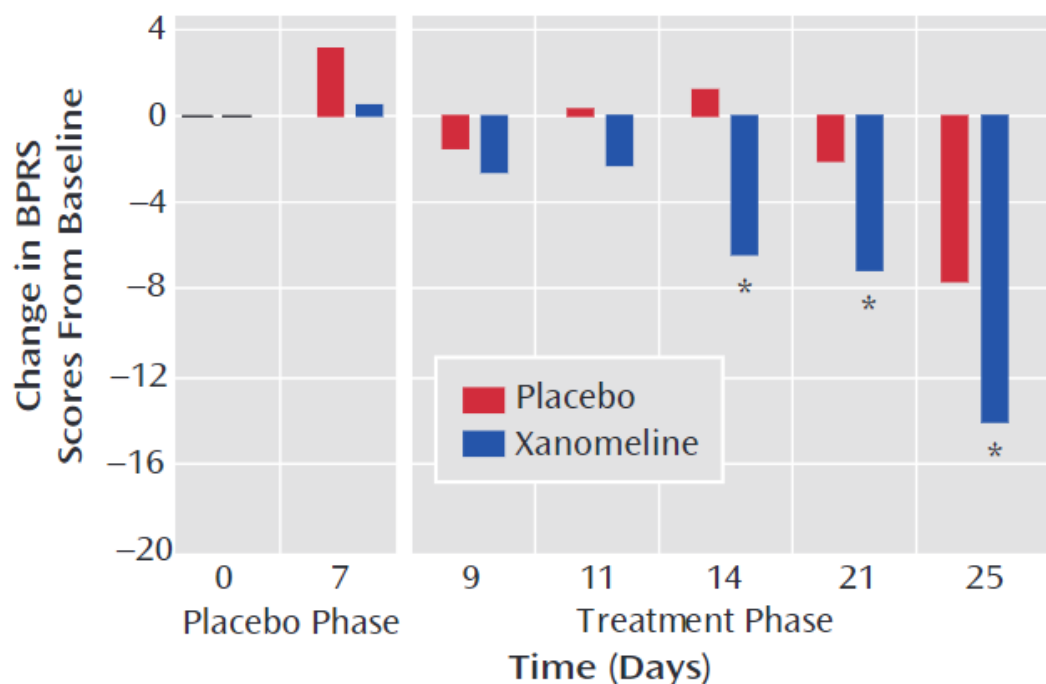
A Crack in the Postsynaptic Dopamine Edifice: The Unexpected Human Findings from LY246708

- **1992:** A novel compound LY246708 is synthesized by Eli Lilly and characterized initially as a selective M₁ agonist (M₄ and M₅ cloned receptors not yet being available). The intent was to develop a procognitive agent for dementia of the Alzheimer type. It had no D₂ binding.
- **1997:** Results of a large study (n=343) in mild-moderate Alzheimer's disease were published.
 - **Method:** Patients randomized in a double-blind manner to LY246708 (now called xanomeline) 75 mg/day, 150 mg/day or 225 mg/day or placebo and followed up to 6 months.
 - **Cognitive Results:** Patients in the high dose arm (225 mg/day) had superior endpoint scores on the ADAS-Cog vs placebo (p < 0.05).
 - **Behavioral Results:** Significant dose-dependent reductions in vocal outbursts, suspiciousness, delusions, agitation, and hallucinations.
 - **Tolerability:** 52% discontinued due to dose-dependent adverse events, mostly gastrointestinal. Syncope was seen in 12.6% in high-dose group.

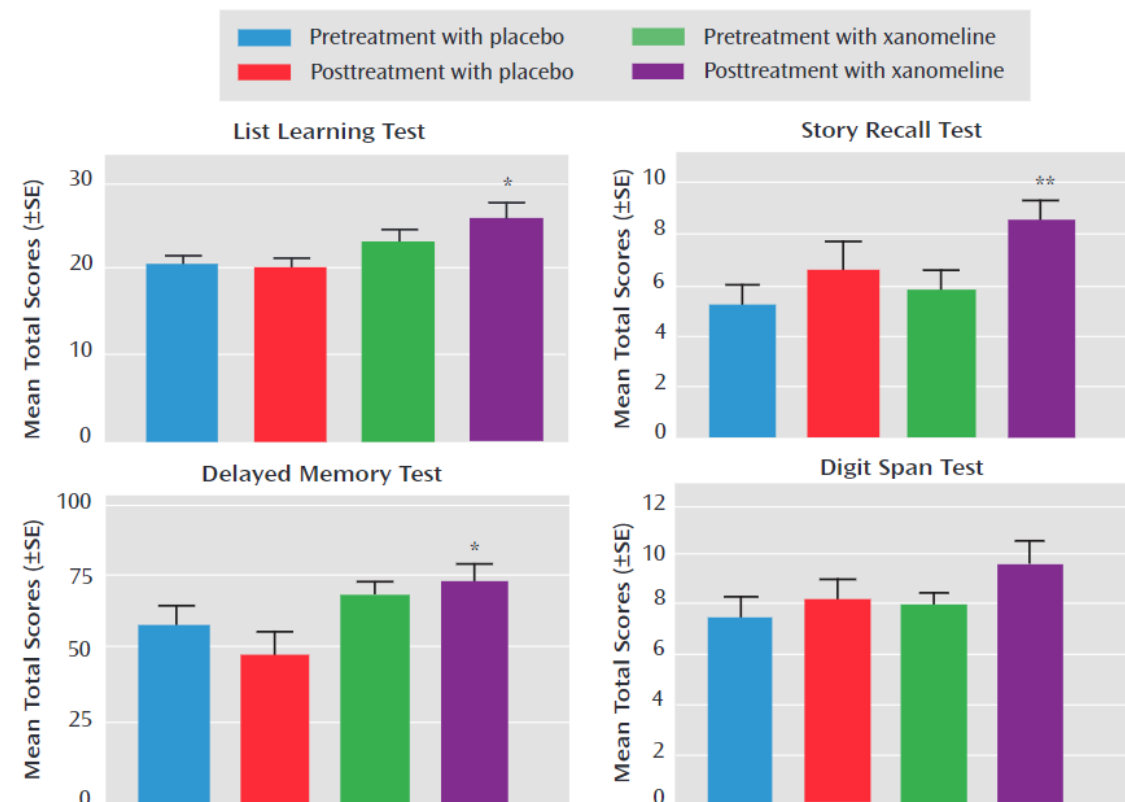
2008 Pilot Study: Xanomeline vs Placebo

- Method: double-blind, placebo-controlled, 4-week, inpatient trial of xanomeline
- Dosing: xanomeline started at 25 mg TID, increased every 2 days by 75 mg/day to 75 mg TID (if tolerated)
- Subjects: adults with an acute exacerbation of schizophrenia or schizoaffective disorder, PANSS > 60 with at least one positive item ≥ 4 or 2 items ≥ 3
- Completion: 8/10 xanomeline; 7/10 placebo; all drop-outs were due to lack of efficacy, none due to adverse events

Symptoms: Significant differences over last 2 weeks of the study on BPRS



Cognition: Significant differences on several tests



2008 Pilot Study: Xanomeline vs Placebo

Tolerability Notes:

1. Unlike the Alzheimer's study done a decade prior, these patients were much younger, and xanomeline was titrated over 6 days to the target dose of 225 mg/d (dosed as 75 mg TID)
2. None of the drop-outs were due to adverse events (AEs)
3. AEs: The pattern was consistent with known muscarinic M1 receptor agonist effects; although nausea was numerically more in the xanomeline group, only 10% of placebo patients experienced emesis vs 60% of xanomeline-treated patients

TABLE 4. Adverse Events Experienced by Subjects With Schizophrenia Randomly Assigned to Treatment With Either Placebo or Xanomeline

Adverse Event	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

Managing the Peripheral Pro-Cholinergic Effects of Xanomeline

- Issue: Xanomeline induces peripheral adverse effects, primarily related to M1 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
- 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.**

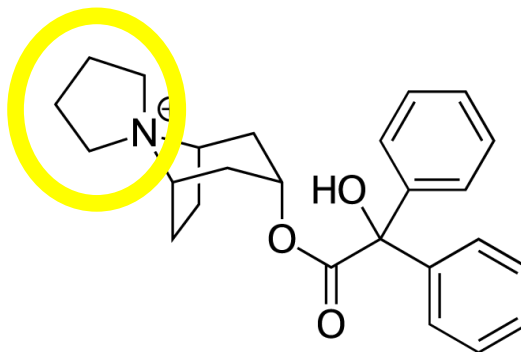
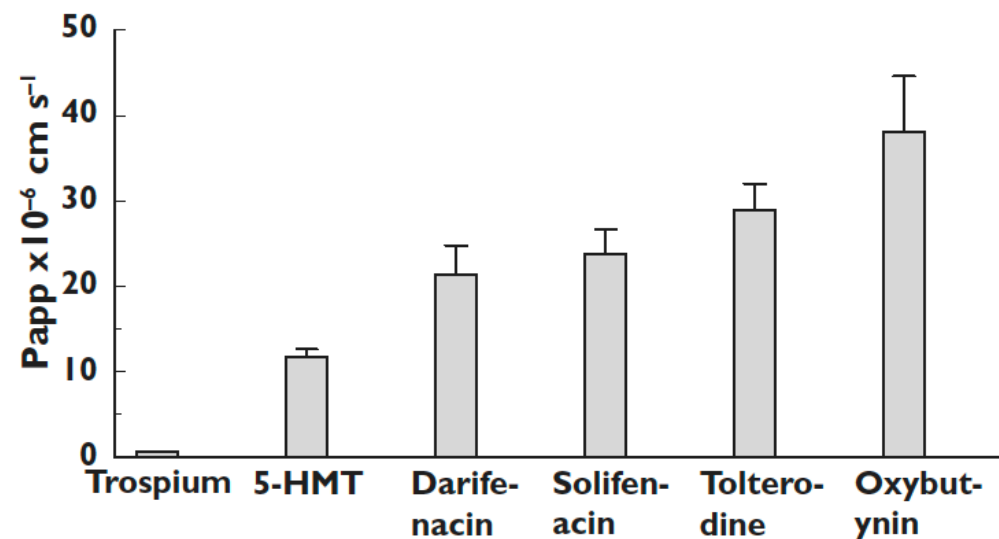
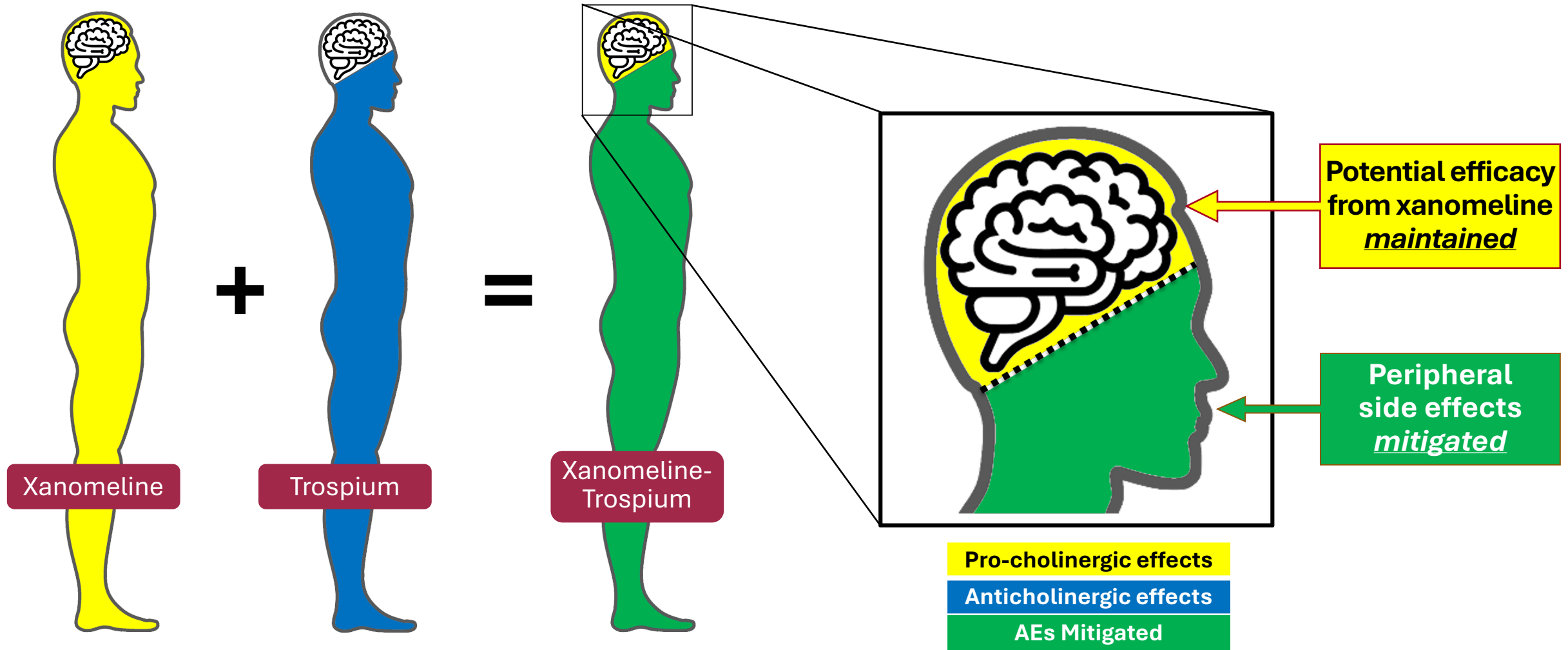


Figure: Passive diffusion across cloned kidney cells as a model for blood brain barrier penetration

Trospium Mitigates Peripheral Cholinergic AEs of Xanomeline While Preserving Central Efficacy

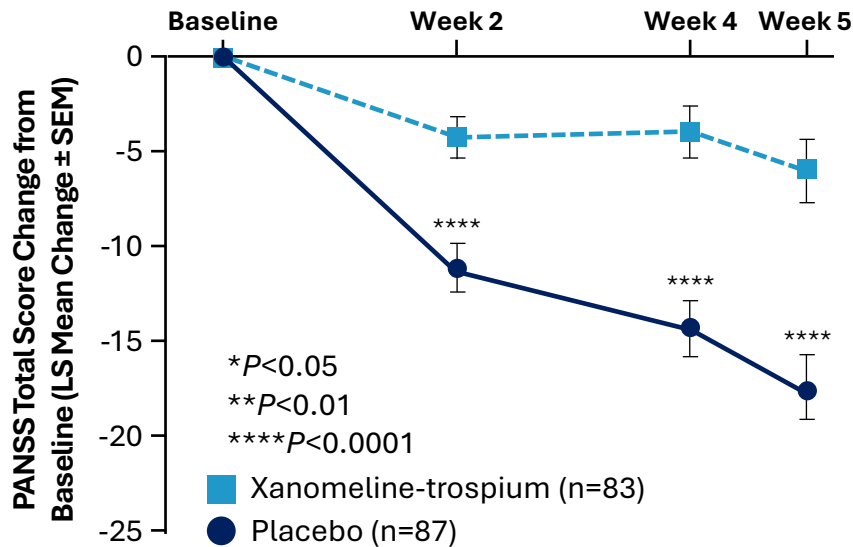


AE = adverse effects.

Brannan SK, et al. *N Engl J Med*. 2021;384(8):717-726.

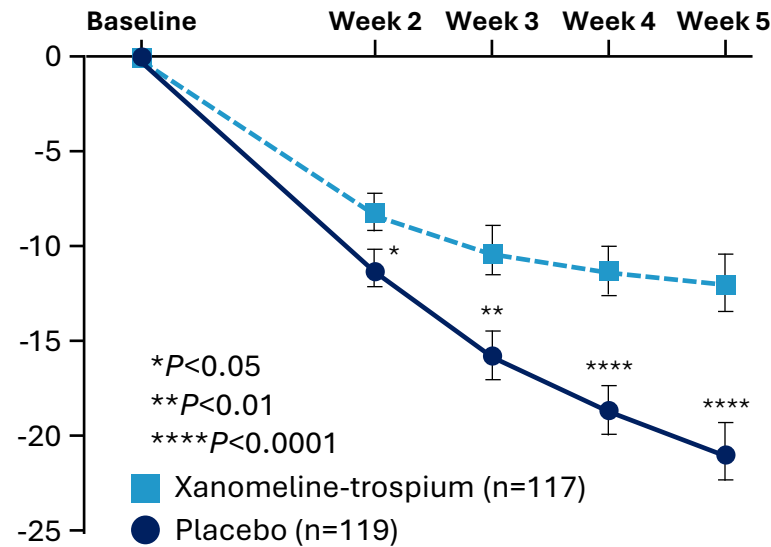
Xanomeline/Trospium Showed Consistent Efficacy in All Short-Term Phase 2 & 3 Trials

EMERGENT-1 (Phase 2)



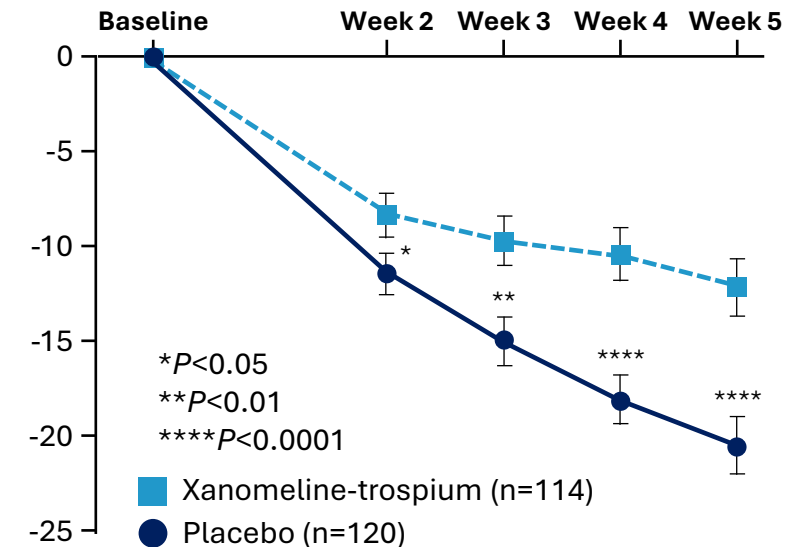
11.6-point reduction vs placebo at week 5
Effect size=0.81

EMERGENT-2 (Phase 3)



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

EMERGENT-3 (Phase 3)



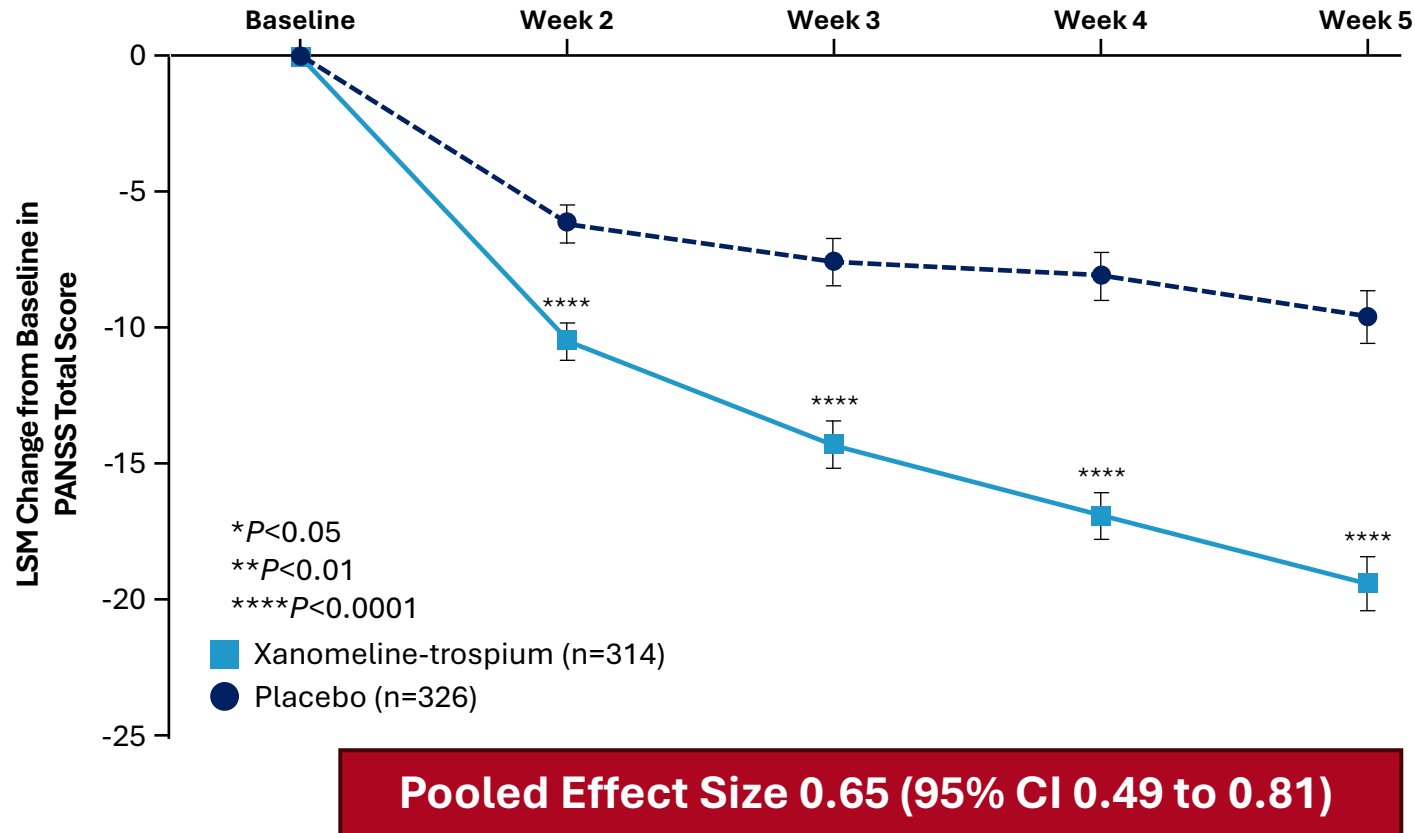
8.4-point reduction vs placebo at week 5
Effect size=0.60

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

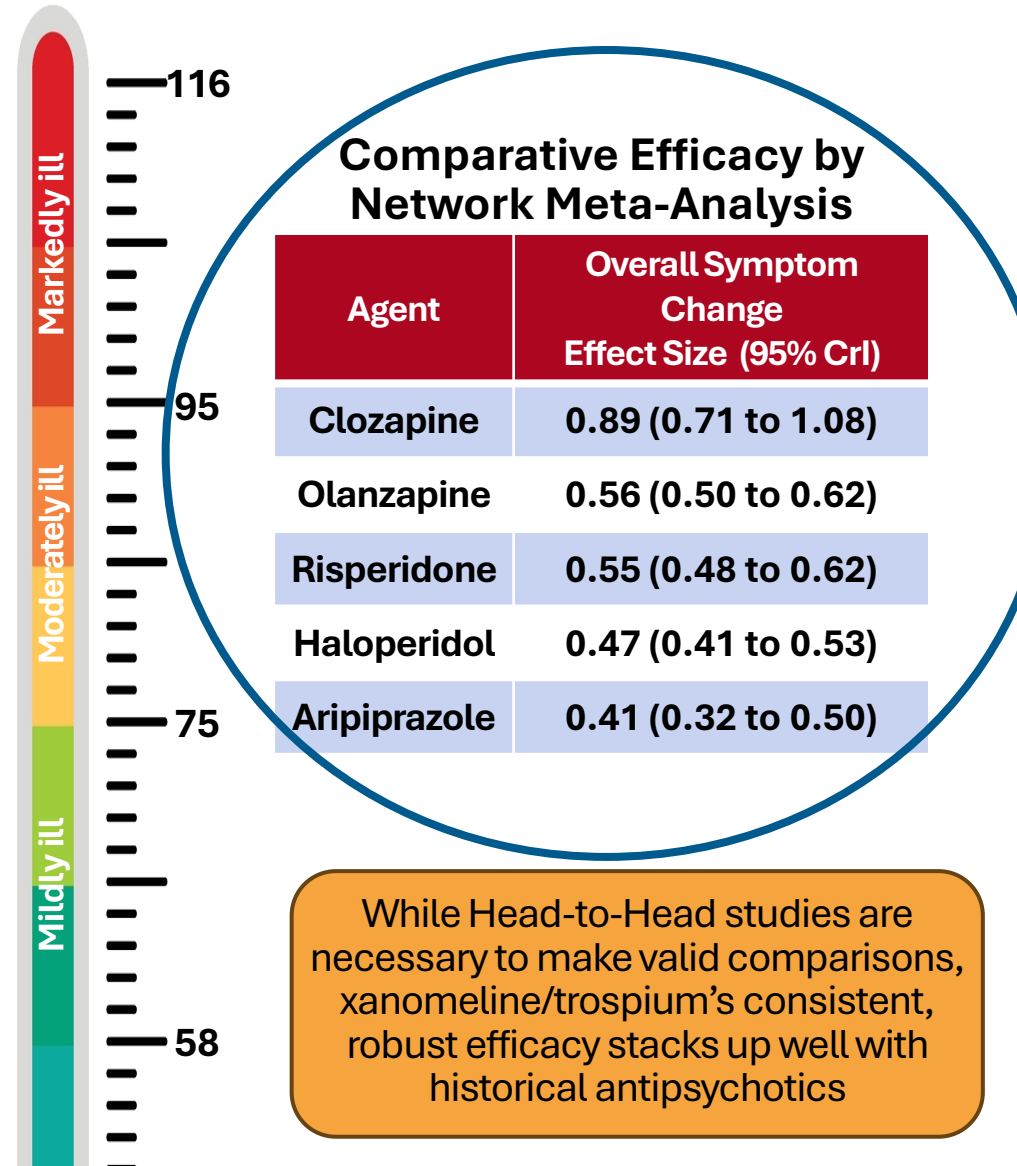
LS = least squares; SEM = standard error of the mean; PANSS = Positive and Negative Syndrome Scale.

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

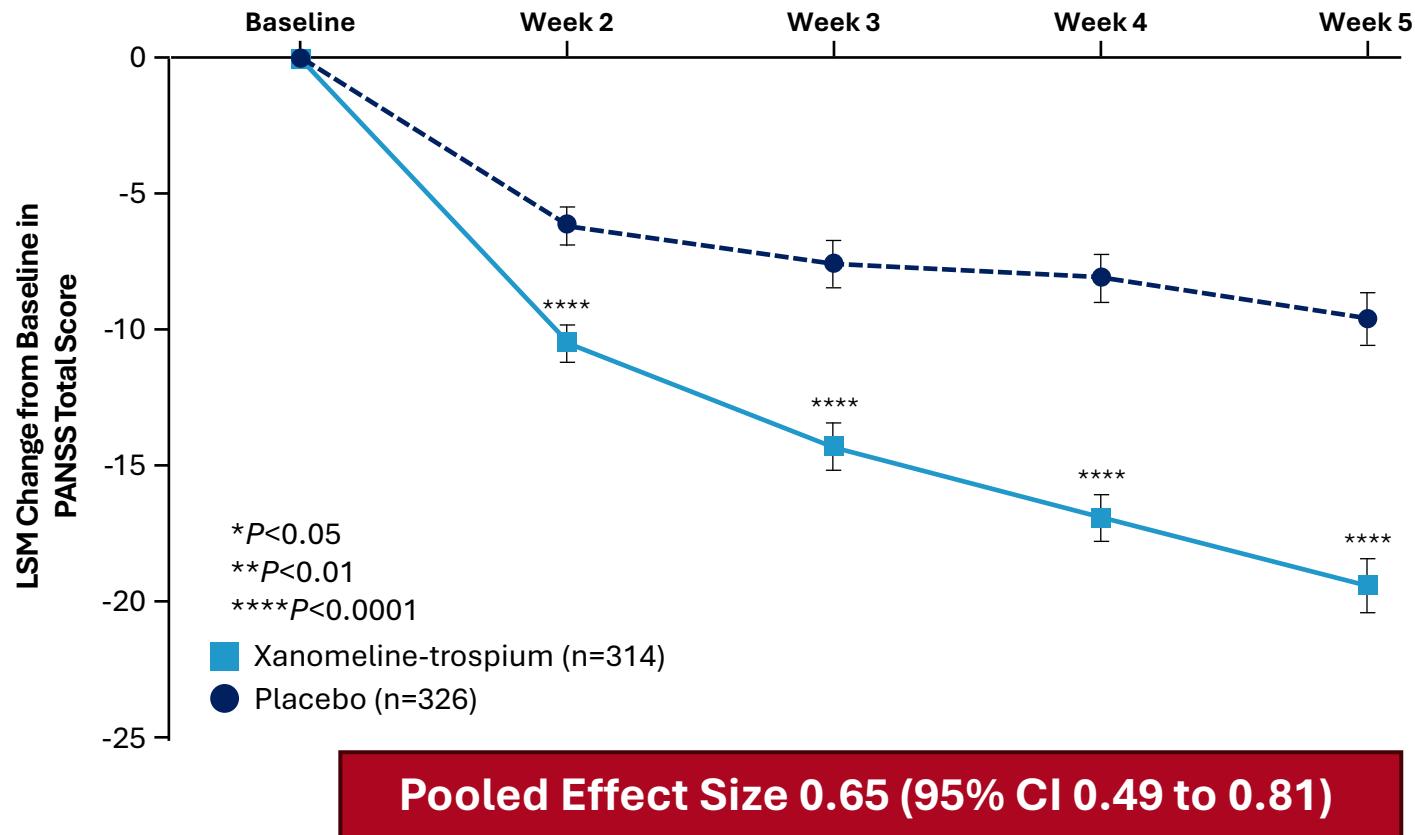
Post-Hoc Analysis of Xanomeline/Trospium Efficacy in 3 Pooled Short-Term Studies



LSM = least squares mean; CI = confidence interval; CrI = credible interval.
Kaul I, et al. *Schizophrenia (Heidelb)*. 2024;10(1):102. Huhn M, et al. *Lancet*. 2019;394(10202):939-951.



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



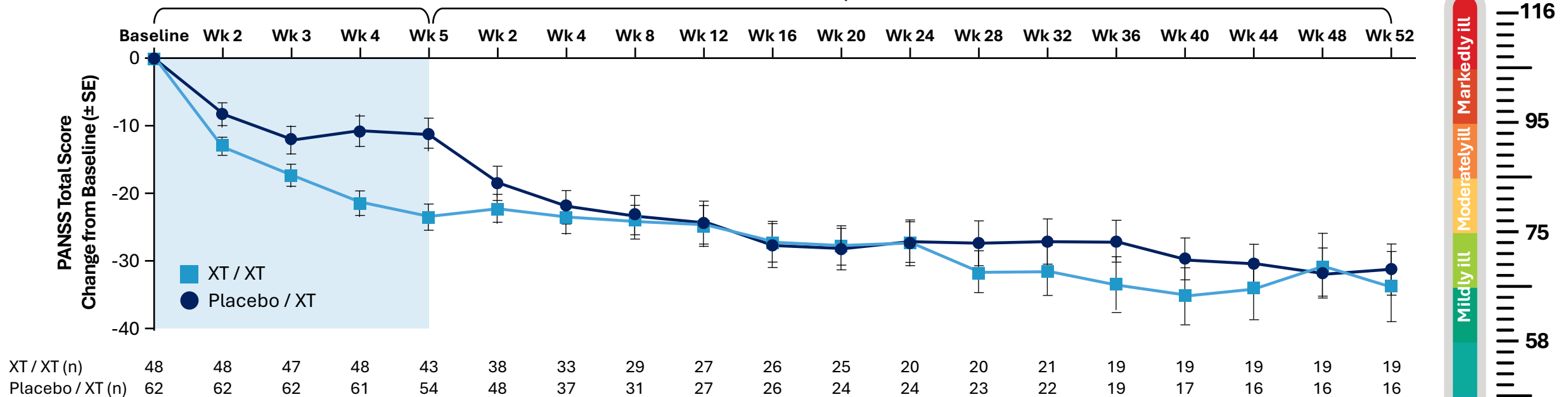
All three short-term studies revealed a reduction in not just the total PANSS, but in each of the three domains:

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

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

Pooled 5-Week Acute Trials

52-Week Open-Label Extension Trial

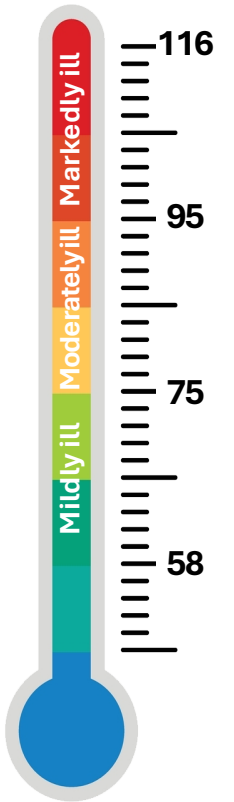


Mean PANSS total score change from baseline of double-blind trial to week 52 of OLE

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

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

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

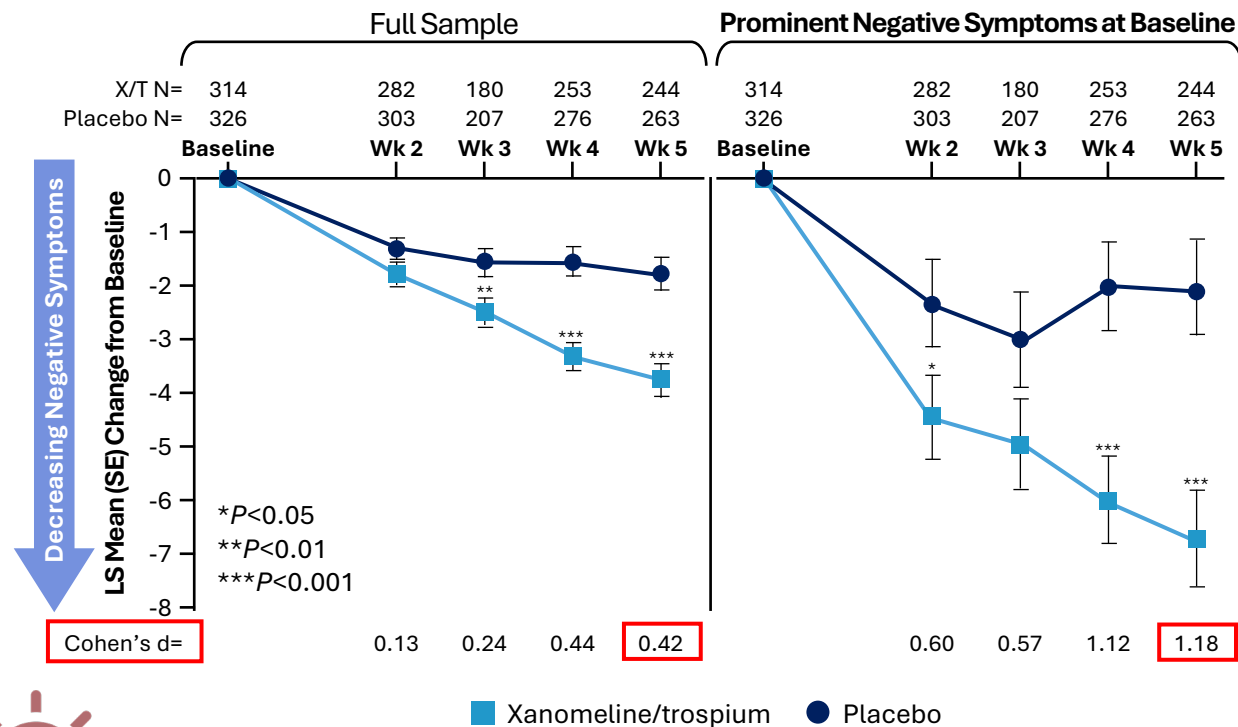


SE = standard error; OLE = open-label extension.

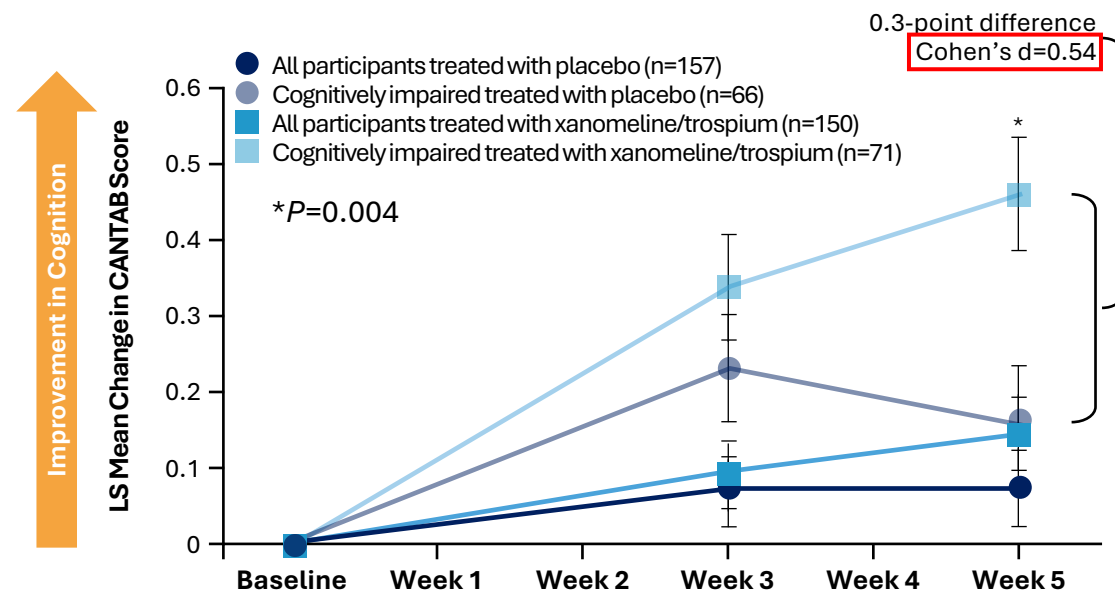
Kaul I, et al. Poster presented at: 2025 Annual Congress of the Schizophrenia International Research Society (SIRS); March 29-April 2, 2025; Chicago, IL.

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

Negative Symptoms



Cognitive Dysfunction



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

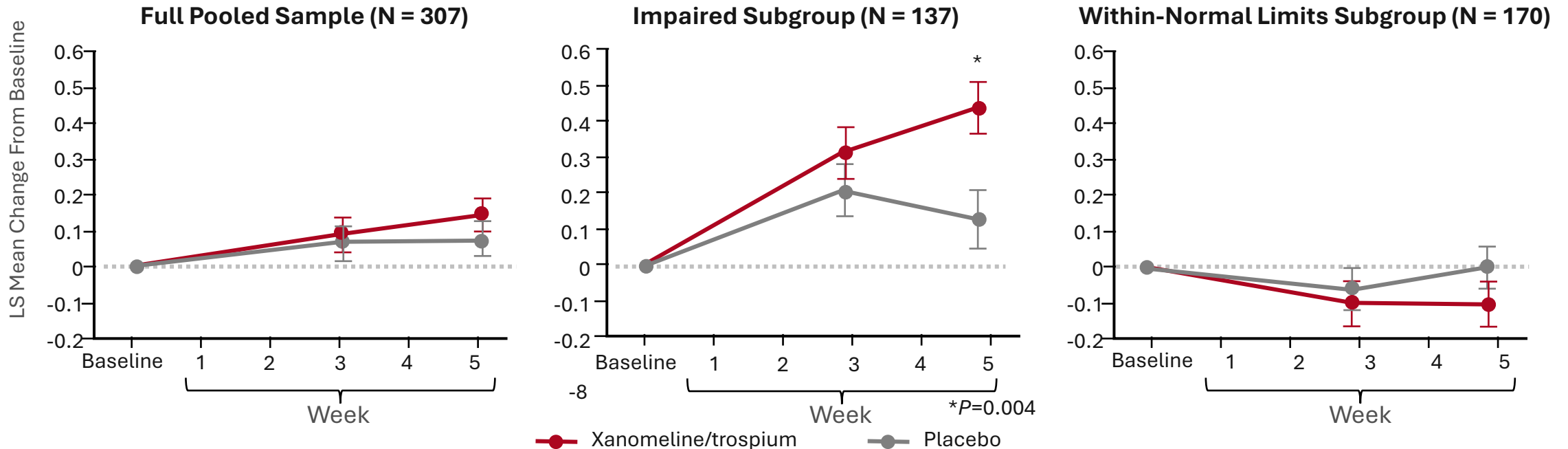
Pooled data from EMERGENT-2 and -3 suggest that xanomeline/trospium may have efficacy for negative and/or cognitive symptoms in those with more prominent symptoms of each

CANTAB = Cambridge Neuropsychological Test Automated Battery.

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

EMERGENT Trials: CANTAB by Cognitive Subgroup

Pooled EMERGENT-2 and EMERGENT-3



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



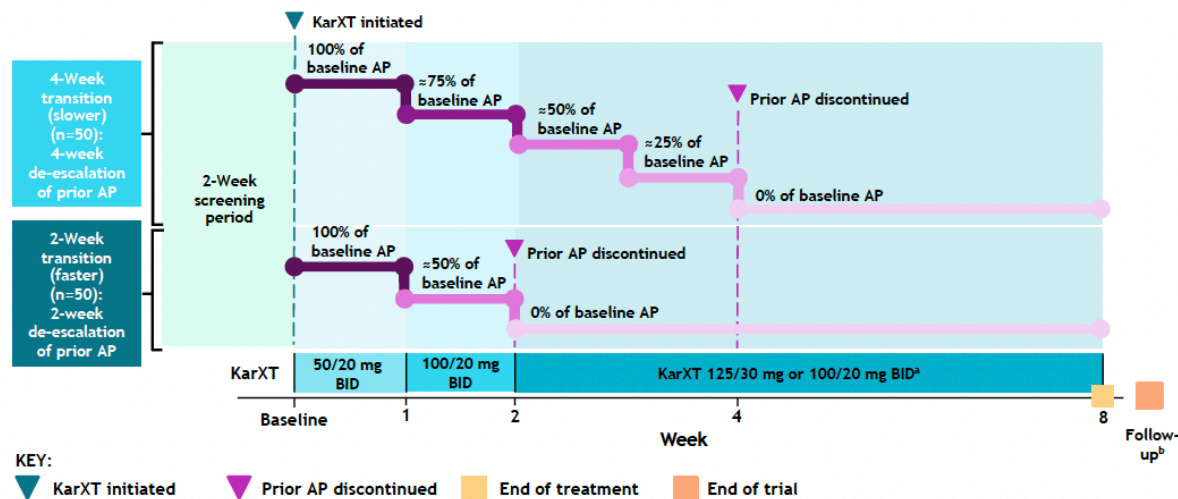
Pooled EMERGENT Trials: Safety During Phase 2b/3 Trials

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

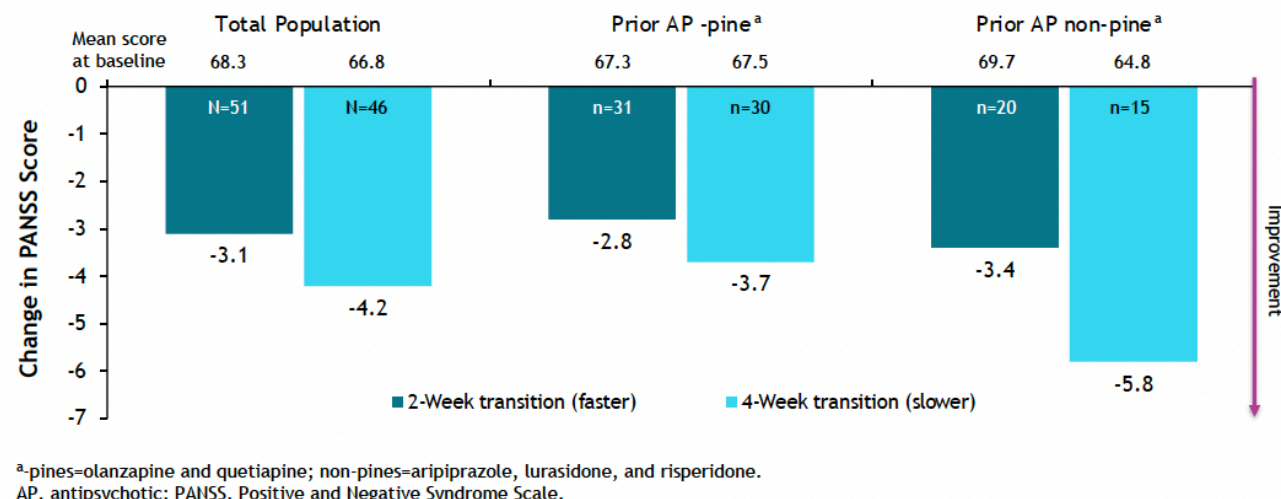
- Mean changes in weight, metabolic measures, prolactin, and motor ratings with xanomeline + trospium were comparable to placebo
- Discontinuations due to AEs:
 - Emergent-1: 2% of patients in xanomeline + trospium and placebo arms
 - Emergent-2: 7% of patients in xanomeline + trospium arm vs 6% in placebo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

Cross-Titration Study: Design and Symptom Outcome

Study design of an 8-week, multicenter, randomized, open-label, outpatient trial assessing the efficacy and safety of a switch from an atypical AP to KarXT monotherapy in adults with schizophrenia (NCT06924255)



Mean PANSS total scores improved from baseline to week 8 regardless of transition method or prior AP used



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

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

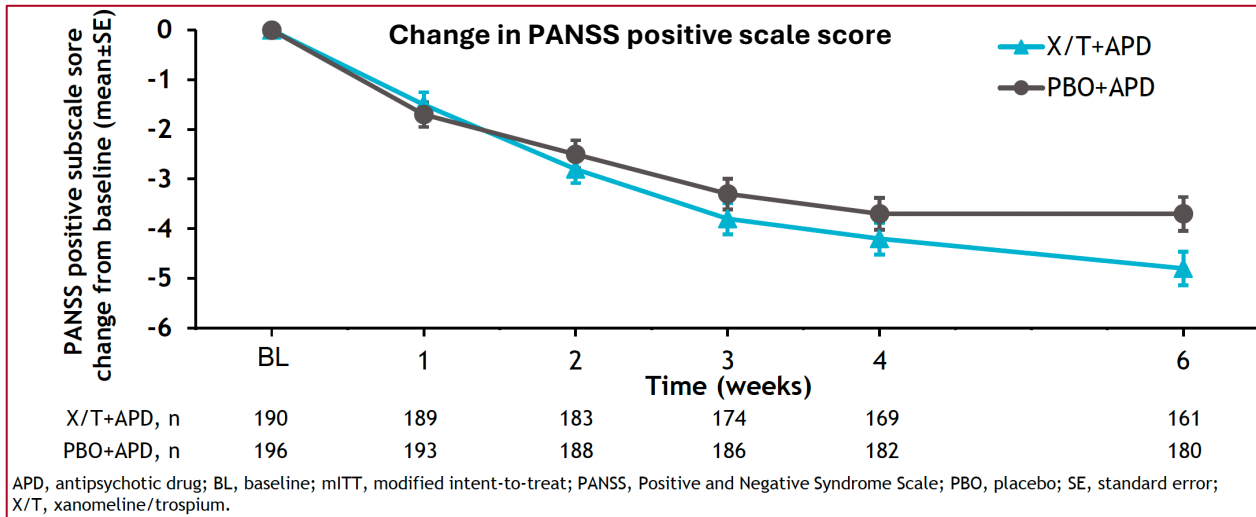
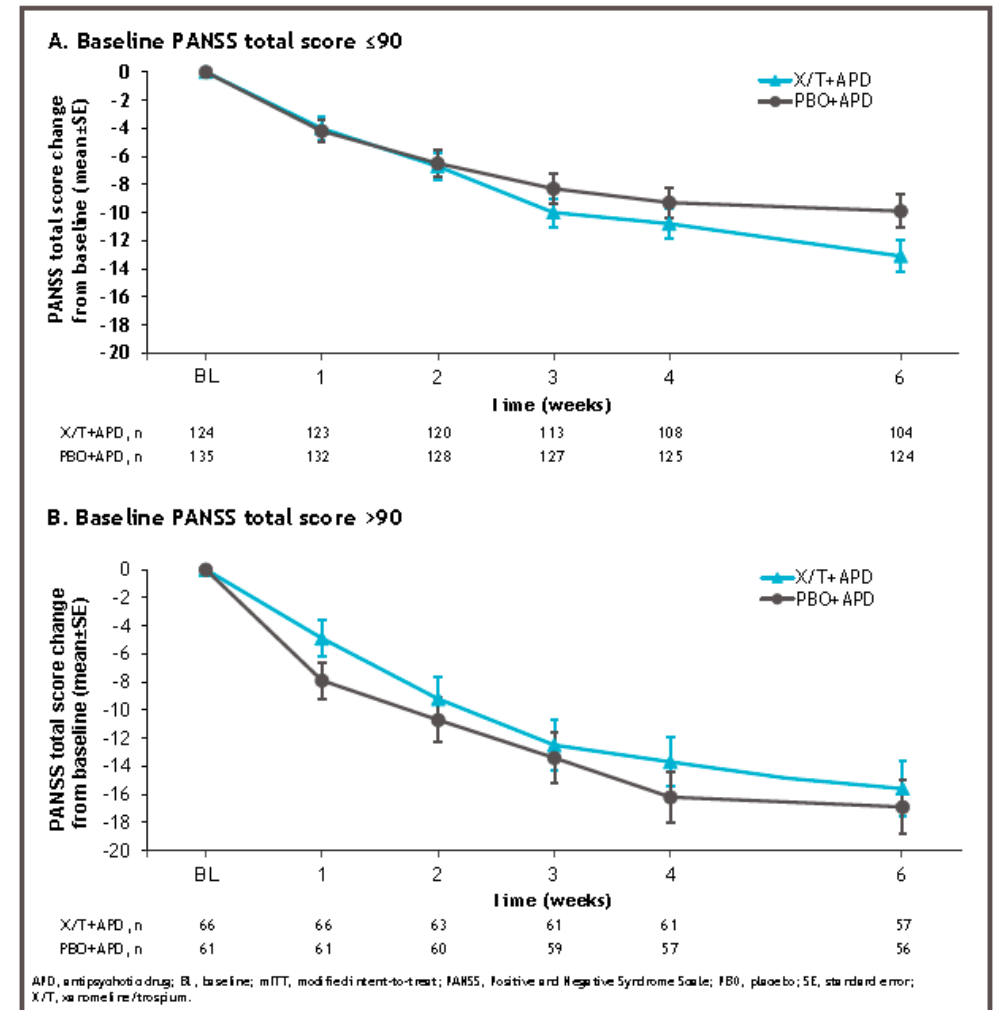


Figure 4. Post hoc change from baseline in PANSS total score by baseline PANSS total score ≤ 90 vs > 90 criteria (mITT population)



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

Legend: Favors X/T+APD (left), Favors PBO+APD (right)

Another Muscarinic Strategy: PAM

	Muscarinic agonist	Muscarinic PAM
What does it do?	Directly activates the receptor	Makes the receptor more responsive to ACh
Needs endogenous ACh?	No	Generally yes
Where does it bind?	Orthosteric site—the ACh binding site	Separate allosteric site
Effect	"Turns the receptor on"	"Turns up the volume" on ACh
Activity	Can drive signaling independent of normal ACh release	More dependent on when/where ACh is naturally released
Selectivity	Harder among M1–M5 because orthosteric sites are highly conserved	Greater subtype selectivity is possible because allosteric sites differ more

Agonist = provides the signal / PAM = amplifies the endogenous signal

PAM: Positive Allosteric Modulator

Conn PJ, Jones CK, Lindsley CW. "Subtype-selective allosteric modulators of muscarinic receptors for the treatment of CNS disorders." Trends Pharmacol Sci. 2009;30(3):148–155.

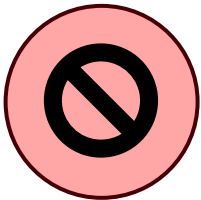
M4 PAM Showed a Promising Strategy

- **M4 receptors can function as a cholinergic “break” on dopaminergic circuitry, particularly through striatal circuitry involving cholinergic interneurons.**
- **Why use an M4 PAM?**
 - Selectivity to M4 to modulate striatal dopamine circuitry
 - PAM – “when acetylcholine activates M4, make that signal stronger.”
- **Emraclidine was studied as a novel, highly selective M4 receptor positive allosteric modulator in 2024**

Emraclidine: Phase 2 Studies Did Not Meet Their Primary Endpoints

Change from Baseline to Week 6 in PANSS Total Score

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



Efficacy
No significant improvement in PANSS scores



Tolerability
Well-tolerated with stable safety profile

SD = standard deviation.
ClinicalTrials.gov. NCT05227690; ClinicalTrials.gov. NCT05227703; AbbVie. AbbVie provides update on Phase 2 results for emraclidine in schizophrenia. Published November 11, 2024.

Positive Phase 2a Results for Direclidine -M₄ Agonist with 500-fold Selectivity vs M_{1/2/3/5}

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

AEs Occurring in ≥ 5% of NBI11758620 Group

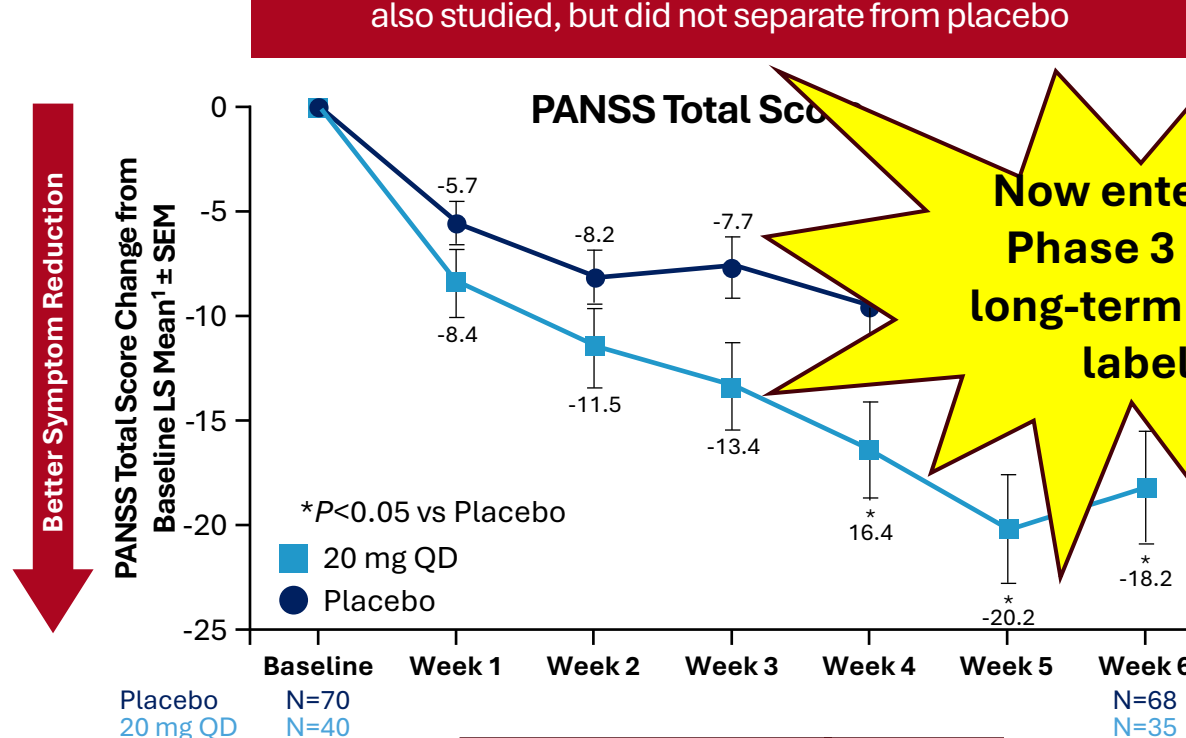
	Placebo N=70	NBI-'568 20 mg N=40
Somnolence	3%	13%
Dizziness	1%	13%
Headache	20%	3%
Nausea	3%	5%
Constipation	3%	5%

Discontinuation due to AEs 5% across all dose arms vs 4.3% for placebo

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

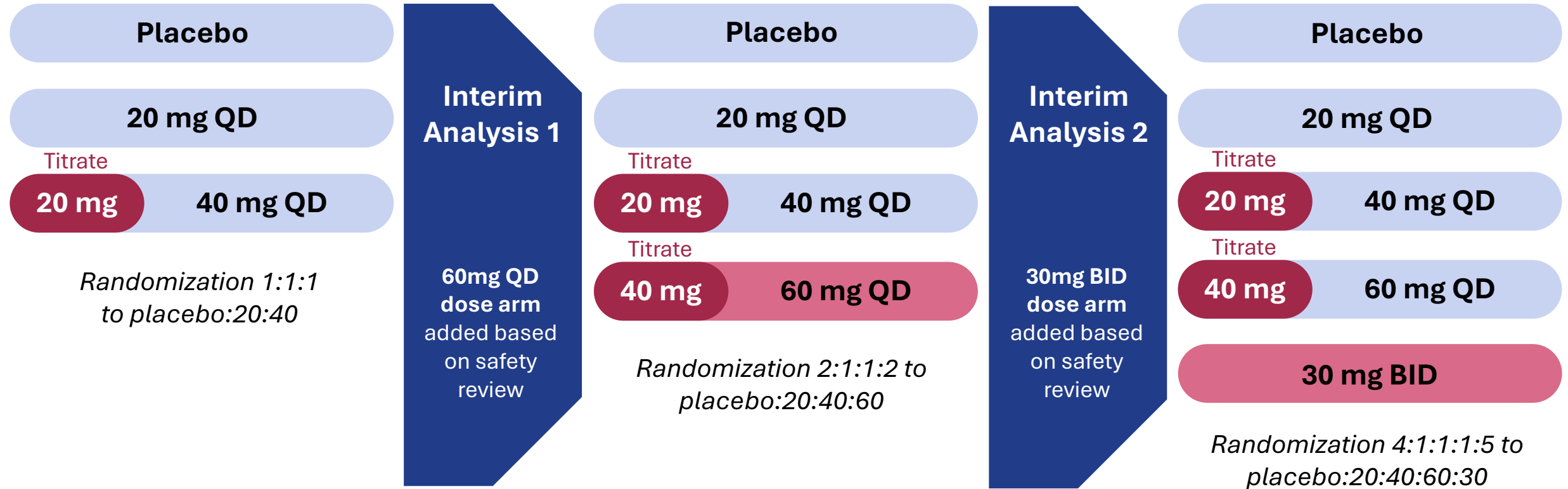
Cardiovascular-related events were infrequent and deemed not clinically relevant at any tested dose

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



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

NBI-'568 Phase 2 Study Design



Notes:

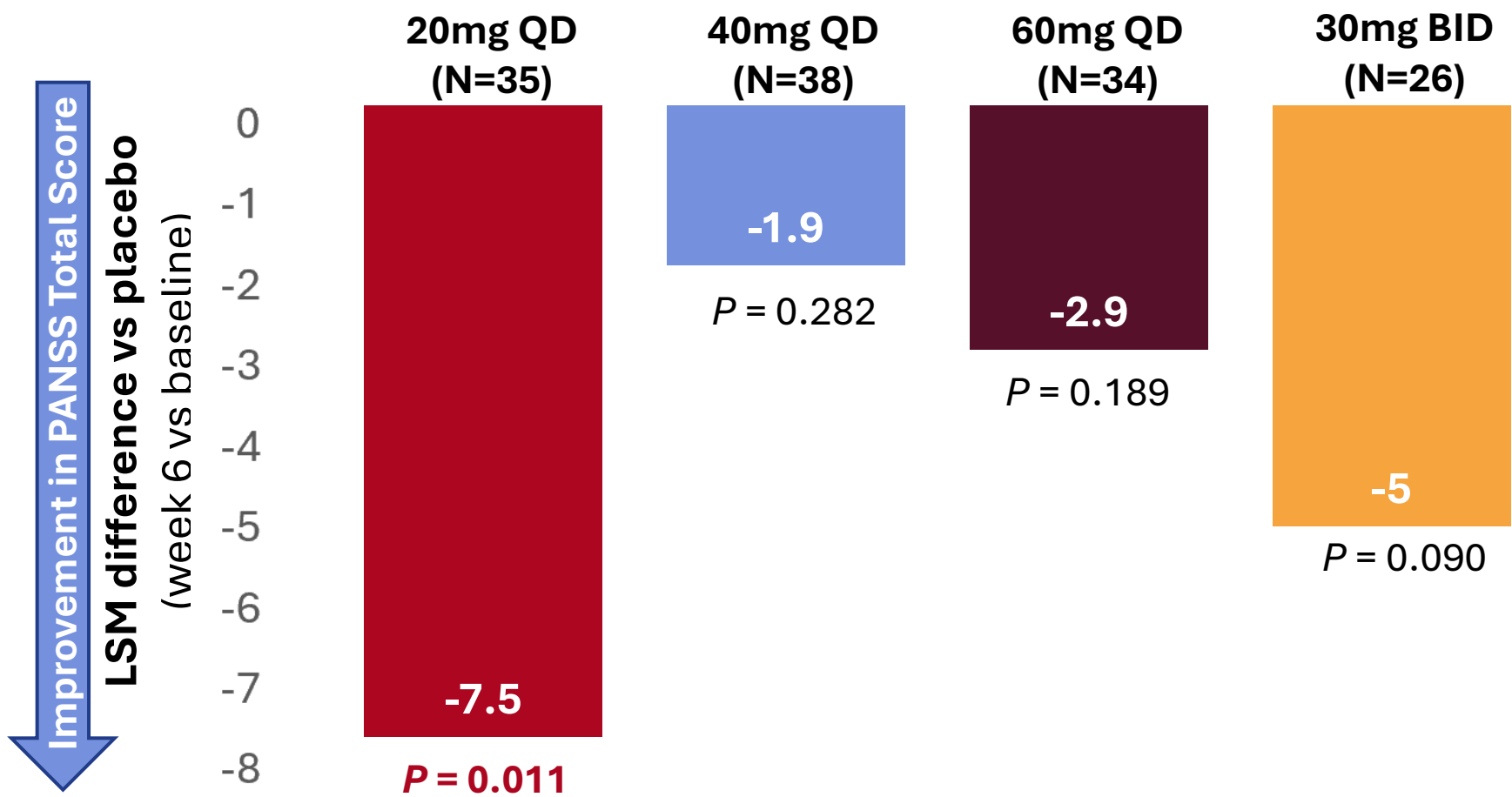
Adults with PANSS ≥ 80 ,
Ages 18-55 enrolled at
15 US sites (inpatient)

Primary Endpoint: Change in
PANSS total score from baseline at
Week 6

Doses of 60mg QD and 30mg BID were
added in a prespecified, blinded fashion
by an independent data review
committee based on safety and
tolerability of previous dose levels

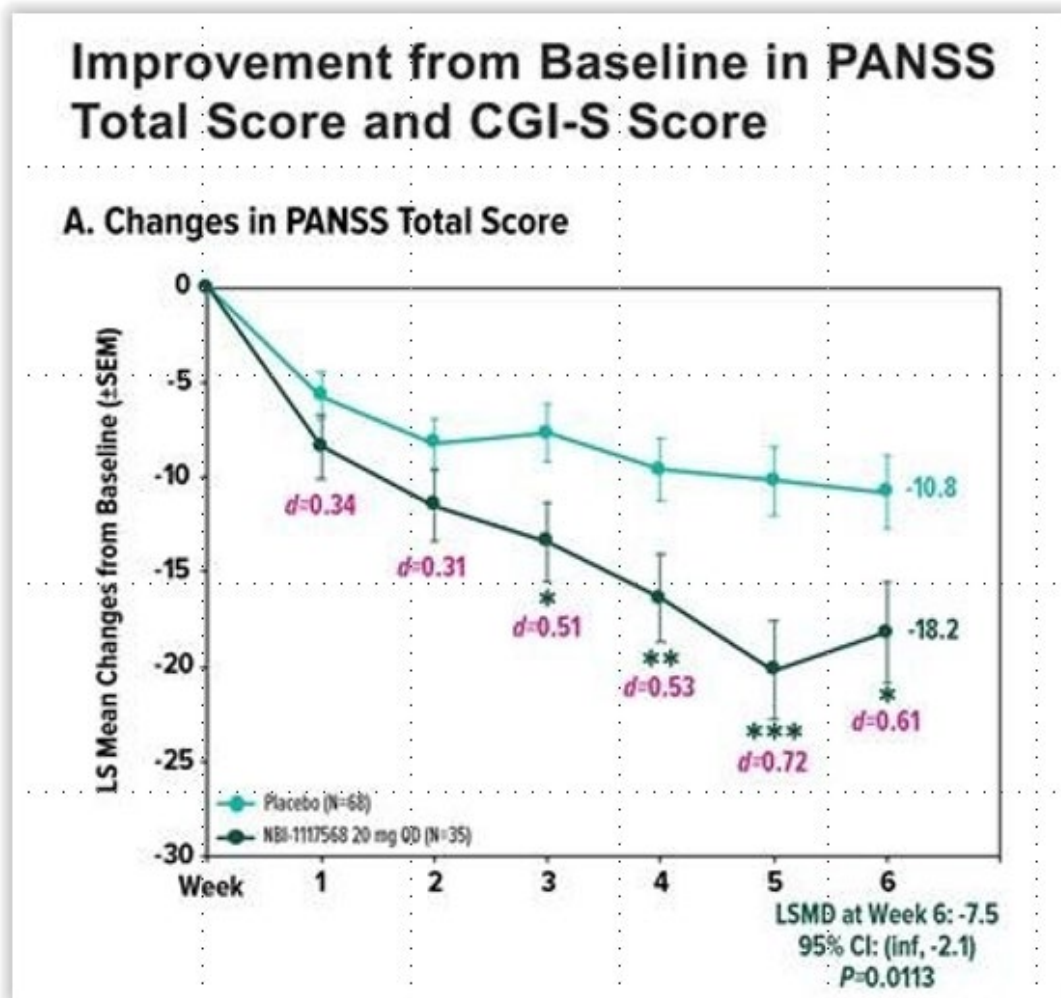
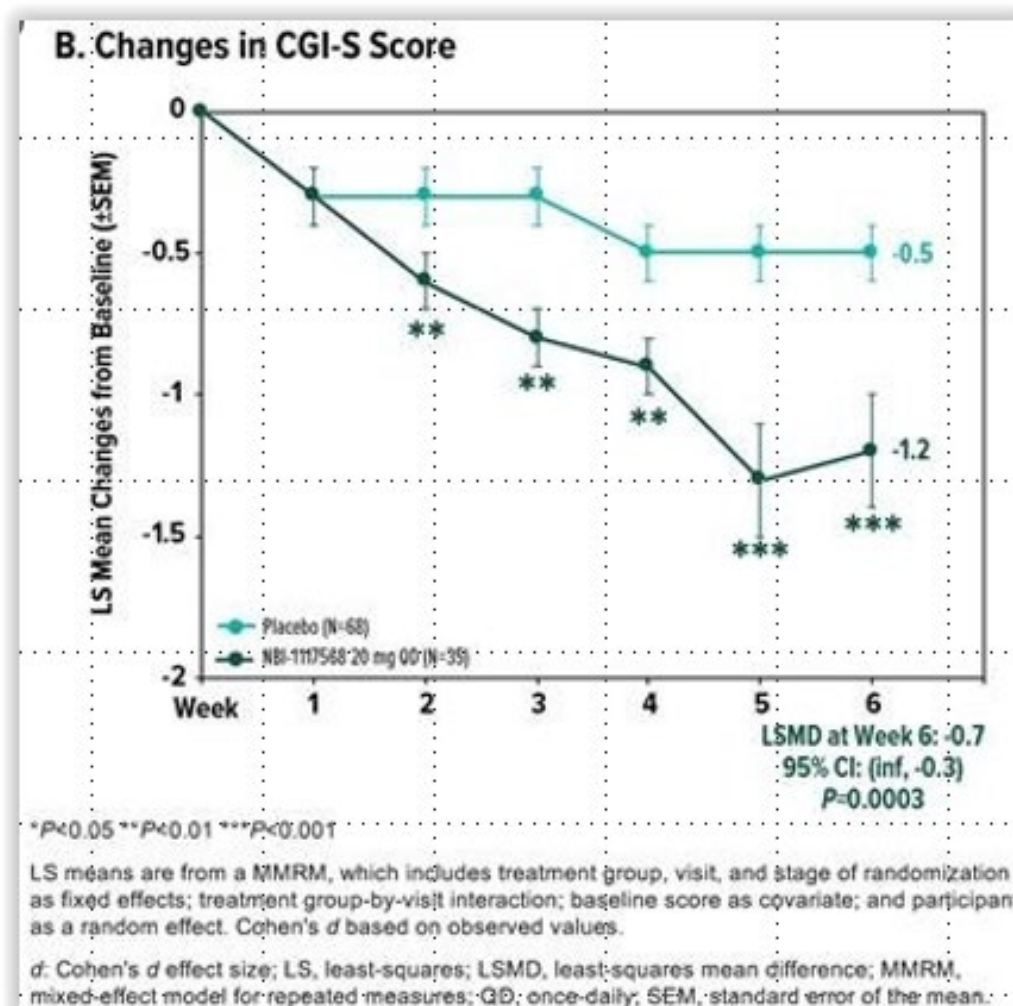
Maintained 2:1 randomization
ratio (all active doses: placebo)
in the study overall

Once-Daily 20mg Dose Met Primary Endpoint: Week 6



P-values reflect least square mean difference vs placebo
Neurocrine Biosciences, Inc. Neurocrine Biosciences reports positive Phase 2 data for NBI-1117568 in adults with schizophrenia. Published August 28, 2024.

Direclidine Orthosteric M4 Agonist: Phase 2A Results for 20 mg QD Arm



Nash A, et al. Once-daily NBI-1117568, a highly selective orthosteric M4 muscarinic receptor agonist, demonstrates meaningful improvements in PANSS total score and is well tolerated in adults with schizophrenia: Phase 2 study results. Presented at: ASCP Annual Meeting; May 27-30, 2025; Scottsdale, AZ.

Topline Results of Phase 2 ML-007C-MA in Schizophrenia

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

Phase 2 study design: adults 18-64 dx schizophrenia

5 week trial with follow up period

Three arms – Placebo BID, ML007C-MA 336/6mg QD

ML-007C-MA 210/3mg BID

Results: Dose 210/3 mg met primary endpoint showing statistically significant and clinically meaningful reduction in PANSS total score compared to placebo at week 5

BID arm achieved effect size of 0.37 (Cohen's d)

Notably, ML-007C-MA demonstrated a robust and clinically meaningful improvement in **cognitive performance** in the BID arm, based on the pre-specified secondary endpoint (effect size=0.51; 0.44 points versus placebo; p=0.041).

This cognitive benefit did not demonstrate correlation with the change in PANSS score, suggesting the effect was independent of, and not secondary to, improvement in psychotic symptoms

Summary of Muscarinic Approaches

Approach	Example	Mechanism	Current schizophrenia story
M1/M4 agonism	xanomeline/trospium	Direct orthosteric M1/M4 activation	Validated clinically/approved
M1/M4 agonism	ML-007C-MA	Direct orthosteric M1/M4 activation	Phase 2 complete
M4 PAM	emraclidine	Amplifies endogenous ACh signaling at M4	Promising Phase 1b → failed Phase 2
Selective M4 agonist	Direclidine	Direct, selective M4 activation	Positive Phase 2 → now Phase 3

Other Investigational Muscarinic Agents

	Mechanism	Development Stage
NMRA-266	M ₄ PAM	Placed on clinical hold by FDA 4/2024 due to pre-clinical data showing convulsions in rabbits
NMRA-898	M ₄ PAM	Phase 1 ongoing in healthy volunteers and patients with stable schizophrenia; data expected in H2 2026
NBI-1117569	M ₁ /M ₄ agonist	Phase 1 data expected in 2027
NBI-1117570	M ₁ /M ₄ agonist	Phase 2 ongoing for psychosis and cognition
NBI-1117567	M ₁ Preferring Agonist	Phase 1 data, Phase 2 planned in 2026 for Alzheimer's cognition

Other investigational muscarinic activators — both full agonists and PAMs—will explore a spectrum of M₄ and M₁ receptor activation in schizophrenia and various other neuropsychiatric disorders

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

Neumora Therapeutics, Inc. Press release. April 15, 2024. Neumora Therapeutics, Inc. Second-quarter 2026 business update. August 14, 2026. Nxera Pharma Co, Ltd. Corporate presentation. August 2026. Accessed September 8, 2026.

Key Learning Points



- Symptoms of schizophrenia are believed to be a pre-synaptic hyper-dopaminergic state in the associated striatum in humans in responders
- XT reduces positive, negative, and cognitive symptoms of schizophrenia by activating muscarinic M1 and M4 receptors that modulate dopamine release upstream of the D2 receptor, rather than through direct D2 receptor blockade
 - **EMERGENT trials showed XT had efficacy for patients with schizophrenia, with post-hoc analyses showing the greatest efficacy among those with more prominent negative or cognitive symptoms at baseline**
- Other investigational muscarinic activators — both full agonists and PAMs— will explore a spectrum of M₄ and M₁ receptor activation in schizophrenia and various other neuropsychiatric disorders

Selective Muscarinic Agents in BD-1 Mania

Dopaminergic Dysfunction: A Shared Mechanism Across Psychiatric Disorders

- DA neurons are mainly in the midbrain (retrosubstantia nigra, substantia nigra pars compacta) and ventral tegmental area
 - These neurons are structurally and metabolically vulnerable, with DA highly prone to oxidative stress
- DA modulates affective thinking, motor control, cognition, and behavior through multiple pathways/circuits



Neuropsychiatric illnesses: Dopaminergic and cholinergic systems maintain a functional balance; disruption of this interplay may exacerbate neuropsychiatric symptoms (NPS)

Schizophrenia



Excess subcortical DA in the associative striatum is strongly associated with positive symptoms



Reduced cortical DA is associated with negative symptoms and cognitive dysfunction

Bipolar disorder



Increased DA activity is hypothesized to contribute to mania



Reduced DA function is hypothesized to contribute to bipolar depression

Hypothesized Neurobiology of Mania

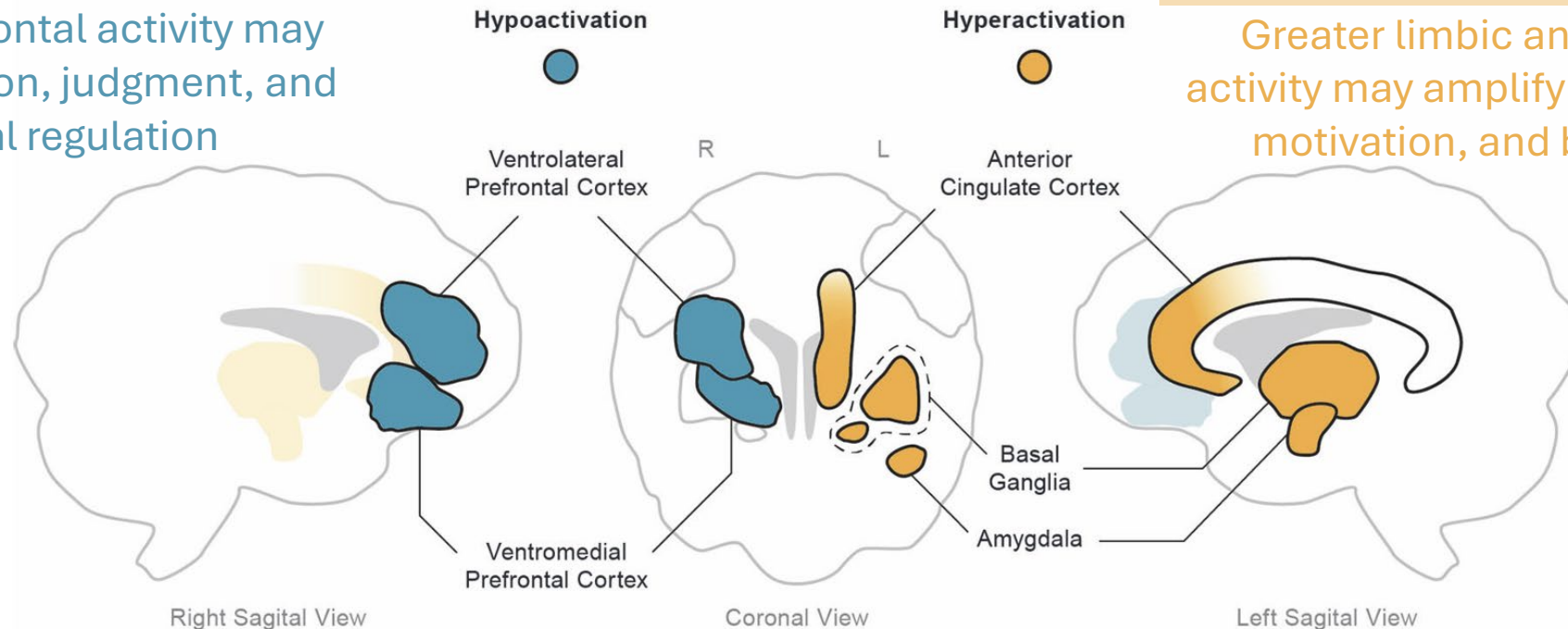


Reduced top-down regulation

Reduced prefrontal activity may weaken inhibition, judgment, and emotional regulation

Increased bottom-up activation

Greater limbic and reward-circuit activity may amplify emotion, salience, motivation, and behavioral drive



Mania emerges when heightened reward, salience, and emotional activation outpace the brain's capacity for inhibitory control

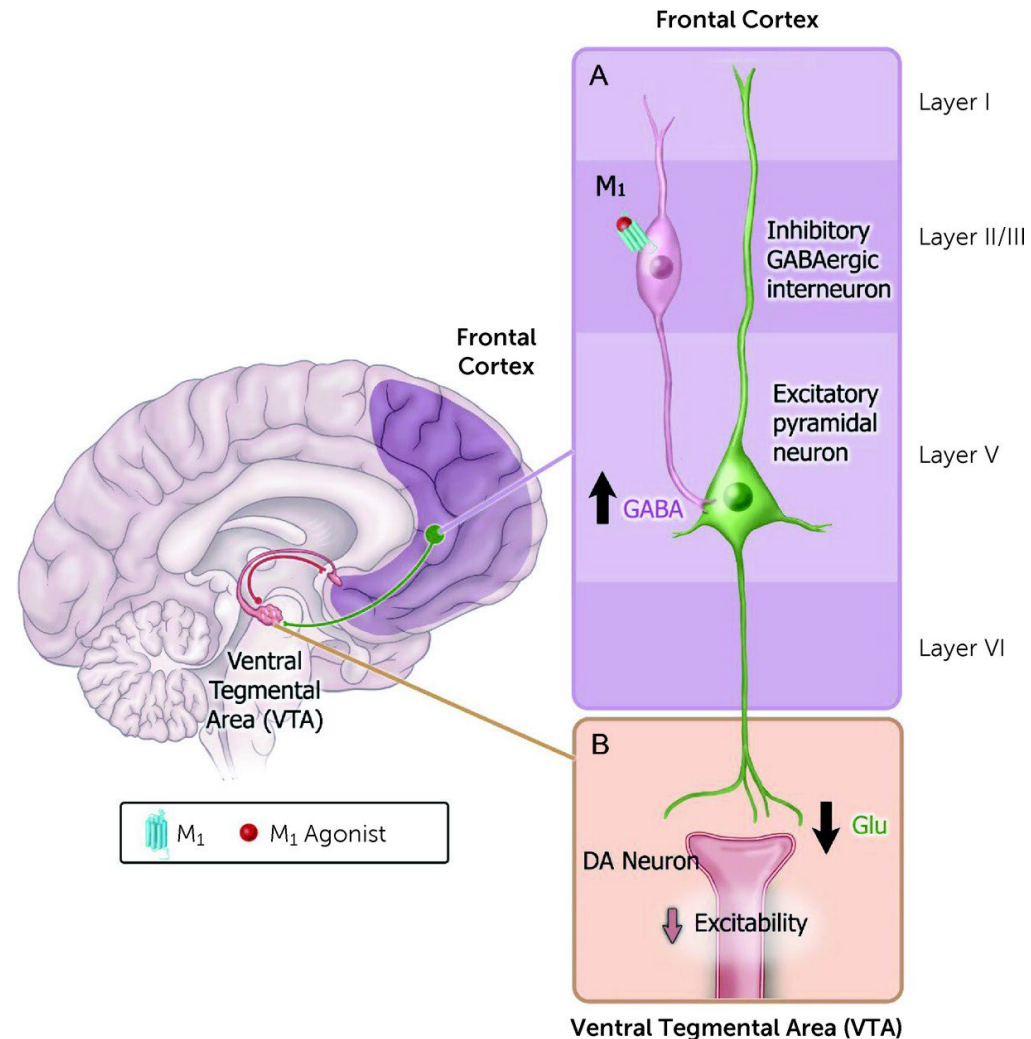
Cholinergic Modulation of Mania Is an Old Hypothesis With New Therapeutic Relevance



Janowsky DS, et al. *Lancet*. 1972;2:632-635. Janowsky DS, et al. *Arch Gen Psychiatry*. 1973;28:542-547. Shopsin B, et al. *Neuropsychobiology*. 1975;1:180-187. Davis KL, et al. *Arch Gen Psychiatry*. 1978;35:119-122. McIntyre RS, et al. ASCP Annual Meeting; 2026. Poster W92. ClinicalTrials.gov: NCT06951698; NCT06951711.

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

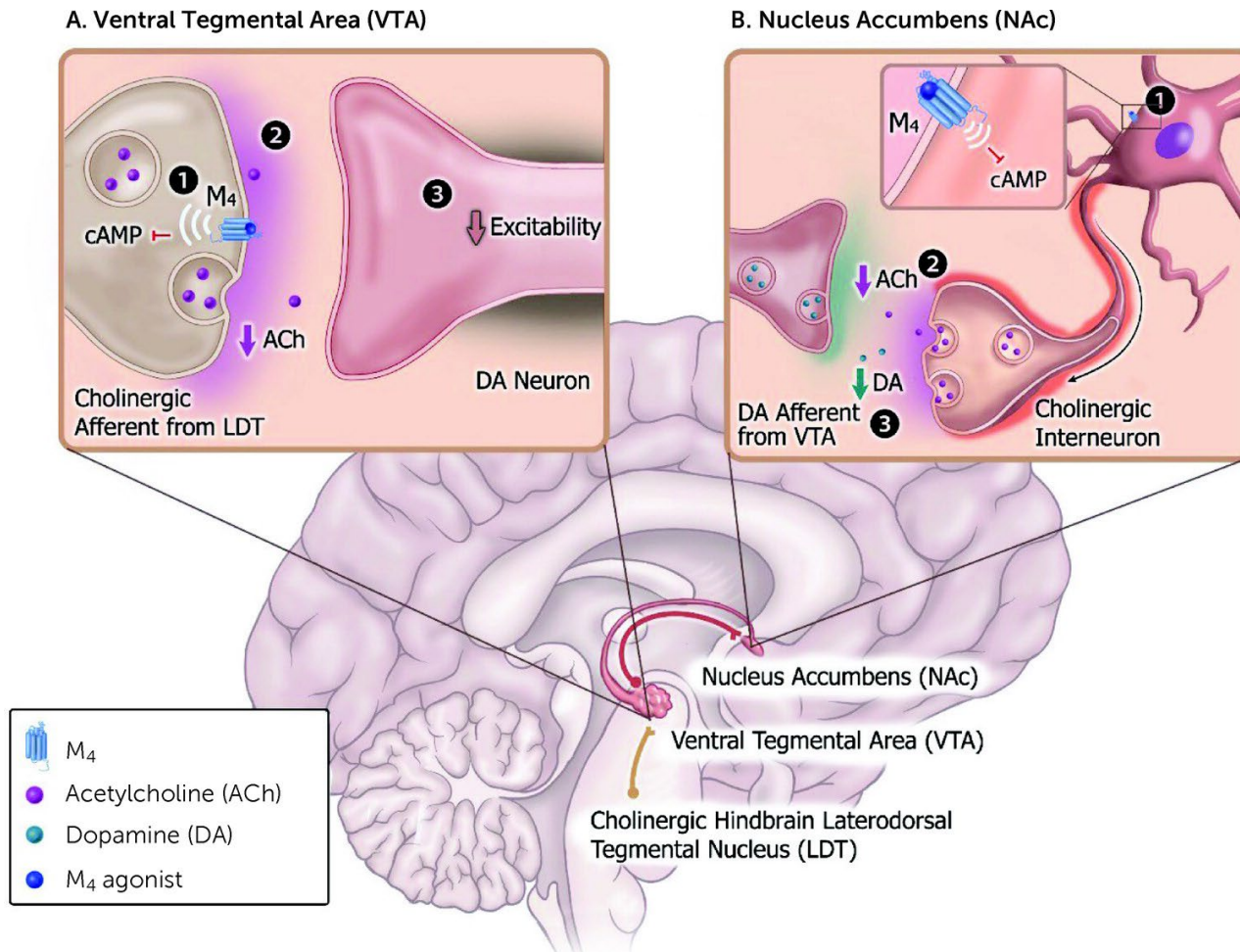
1. Activation of M₁ receptors expressed inhibitory GABAergic interneurons (pink) **facilitates inhibitory drive onto excitatory output neurons**
2. In panel B, enhanced inhibitory drive onto pyramidal neurons **decreases glutamatergic input to the ventral tegmental area (VTA)**. A reduction of excitatory input **leads to a decrease in VTA dopamine (DA; red) neuron activity and reduced terminal DA release**.



M4 Activation May Indirectly Reduce Excessive Dopamine Signaling



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 in 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**

The Potential Efficacy of KarXT in Bipolar Disorder

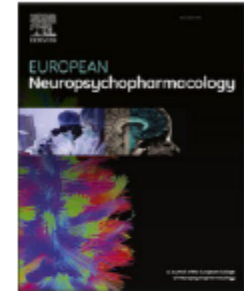
European Neuropsychopharmacology 95 (2025) 4–5



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Muscarinic acetylcholine receptor agonists in bipolar disorder

Meritxell González-Campos^{a,b,c,d}, Eduard Vieta^{a,b,c,d,e,*} 

^a Departament de Medicina, Facultat de Medicina i Ciències de la Salut, Universitat de Barcelona (UB), c. Casanova, 143, 08036, Barcelona, Spain

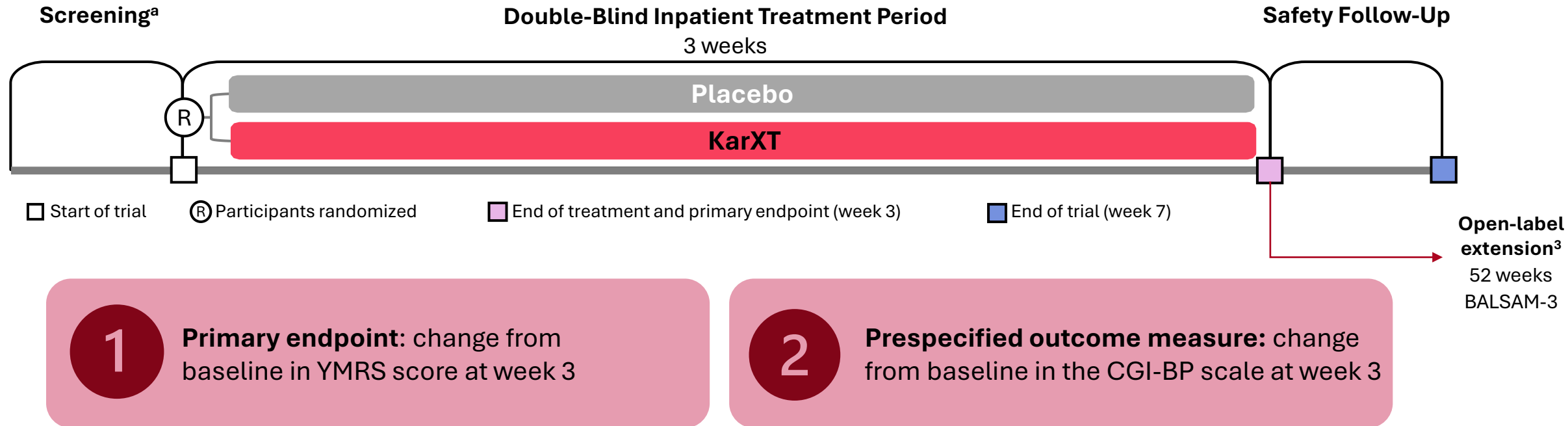
^b Institut de Neurociències (UBNeuro), Spain

^c Bipolar and Depressive Disorders Unit, Hospital Clínic de Barcelona, c. Villarroel, 170, 08036, Barcelona, Spain

^d Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), c. Villarroel, 170, 08036, Barcelona, Spain

^e Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Instituto de Salud Carlos III, Madrid, Spain

Phase 3 Studies Are Ongoing: BALSAM-1 and BALSAM-2 Trial Design



N≈274 estimated enrollment. **Topline results readout currently forecasted for Q4 2026**

^aWashout of prior psychotropic medications. ^bFlexible dosing trial; participants can down-titrate, if needed. ^cThe YMRS comprised of 11 items that assess the severity of manic symptoms. All items are given a severity rating, with 4 items graded from 0 to 8 (irritability, speech, thought content, and disruptive/aggressive behavior), and the remaining 7 items are graded from 0 to 4 points. The highest score obtainable on the YMRS is 60 and the higher the number the greater the number of symptoms and/or the greater their severity.

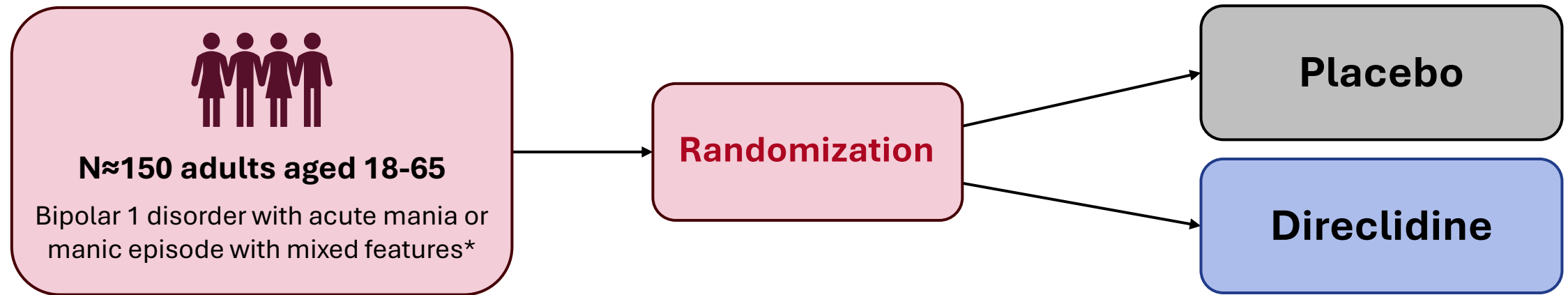
CGI-BP, Clinical Global Impressions-Bipolar; KarXT, xanomeline/trospium; Q4, fourth quarter; YMRS, Young Mania Rating Scale. 1. NIH. Updated Oct 21, 2025. Accessed Nov 19, 2025.

<https://clinicaltrials.gov/study/NCT06951698>. 2. NIH. Updated Nov 19, 2025. Accessed Nov 19, 2025. <https://clinicaltrials.gov/study/NCT06951711>.

3. NIH. Updated Nov 12, 2025. Accessed Nov 19, 2025. <https://clinicaltrials.gov/study/NCT06929273>.

Phase 2 Study Ongoing for Direclidine (NBI-1117568) for Bipolar Mania

M4-selective receptor agonist • Phase 2 • Recruiting • Primary completion anticipated February 2028



1

Primary endpoint:
Change from baseline in
YMRS total score at day 21

2

Secondary endpoint:
Change from baseline in
CGI-S score at day 21



Also assessed:
safety, tolerability, and
pharmacokinetics

*at least 1 prior documented manic episode that required treatment; current episode may occur with or without psychotic symptoms
YMRS = Young Mania Rating Scale; CGI-S = Clinical Global Impression–Severity scale. [ClinicalTrials.gov. An Assessment of Efficacy, Safety, and Pharmacokinetics of NBI-1117568 in Adults With Bipolar I Disorder With Current Mania. NCT07288320.](https://clinicaltrials.gov/ct2/show/study/NCT07288320)

First-in-Human Study of ABBV-1042 Is Ongoing

- ABBV-1042 is an oral **M4 receptor agonist** being investigated for the treatment of **bipolar mania**
- **Double-blind, placebo-controlled phase 1 study in healthy adults (18-55 yo)**
 - Began in October 2025 with expected completion in 2026
 - Evaluating safety, tolerability, and pharmacokinetics
 - No results available yet

Potential Other Indications for Muscarinic Agents

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



Key Learning Points

- Bipolar mania is likely related to a mismatch between brain excitation and inhibition
 - **Reduced top-down regulation and increased bottom-up activation result in midbrain hyperdopaminergia, specifically in frontolimbic circuitry**
- Pro-cholinergic studies in the 1970s had mixed results
- Now resurgence of several procholinergic approaches via muscarinic M4 and M1/M4 activation are being investigated for BD-I mania
 - The downstream effects of M4 activation reduce striatal dopaminergic release by reducing acetylcholine release onto dopaminergic neurons in the VTA

Faculty Panel Discussion

**Reinvestigation of Old Presynaptic Hypotheses to Develop New
Pharmacotherapies in Psychiatry**

**Modulation of Dopamine Release in Schizophrenia and BD-1 Mania
(Distinctive Factors to Consider in Each Condition)**

What is the Potential Role for Muscarinics in the Future?

How to Titrate/Apply Principles of KarXT for Patients with Schizophrenia

Practical Take-Aways



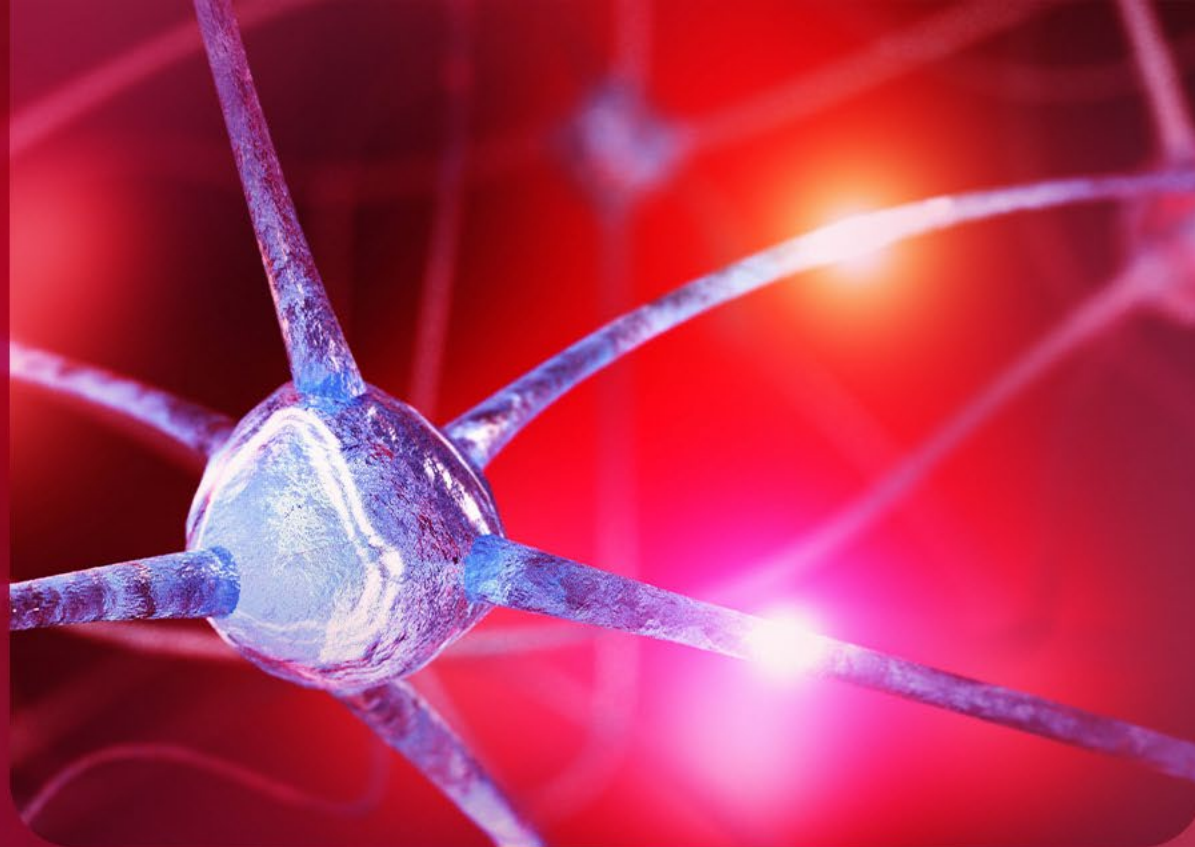
Muscarinics are perhaps one of the greatest advances in decades in the treatment of schizophrenia. Presynaptic strategies were initially targeted but forgotten as D2 antagonism grew. With its recent resurgence, the myth about its efficacy can be laid to rest based on high-quality, multiple, double-blind studies



The impact of muscarinics is not limited to positive symptoms, negative symptoms, cognitive symptoms, or general psychopathology. Data shows it impacts all domains of the Schizophrenia disorder.



The potential for other disease state targets bring excitement as most phase 2 and phase 3 trials are underway.



Q&A