Psych Congress MasterClass

Advancing Schizophrenia Care:

Improving Outcomes with Muscarinic Modulators

Supported by an independent educational grant from Bristol-Myers Squibb

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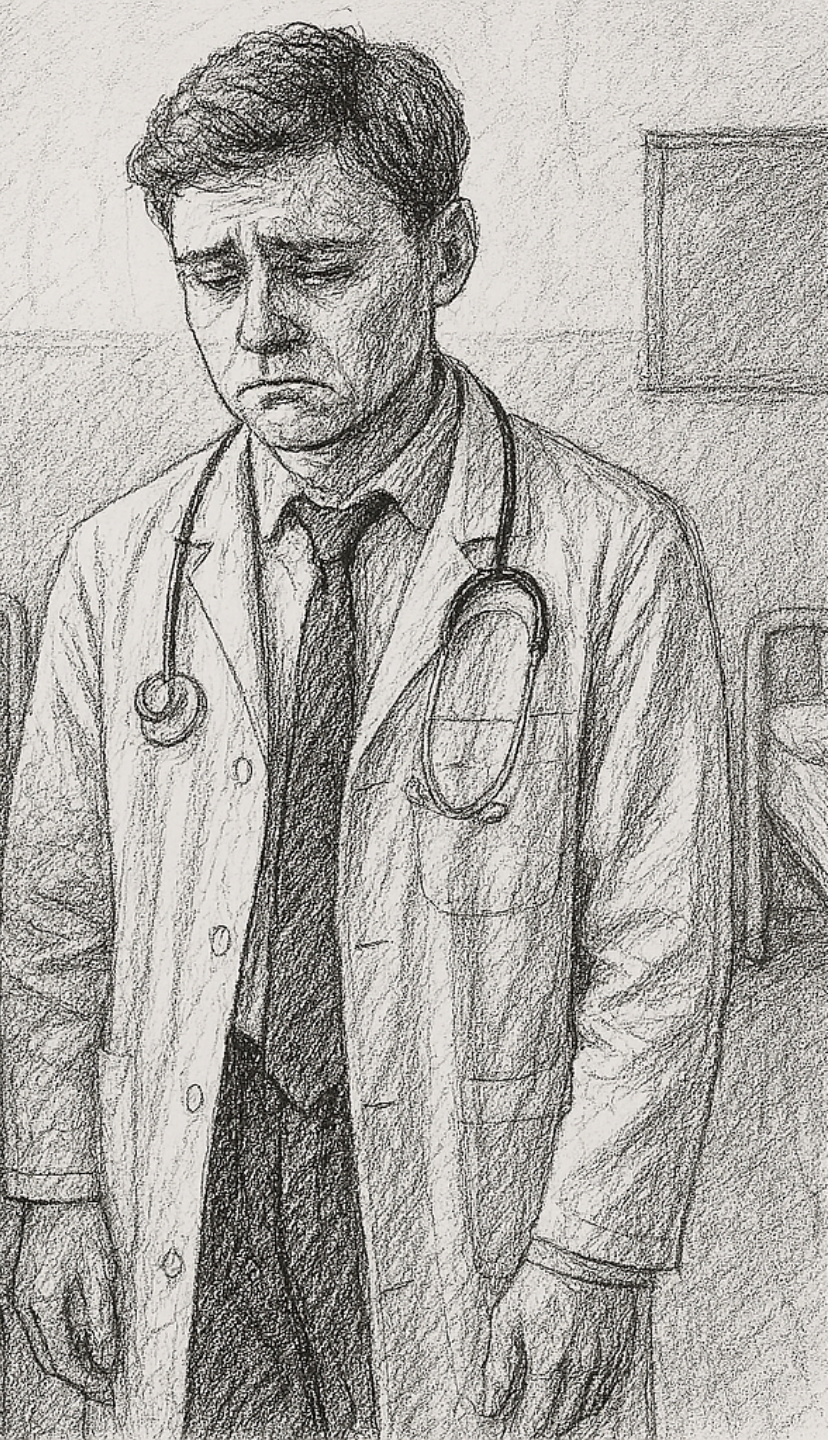
Learning Objectives

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

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

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

I have a story to share with you –

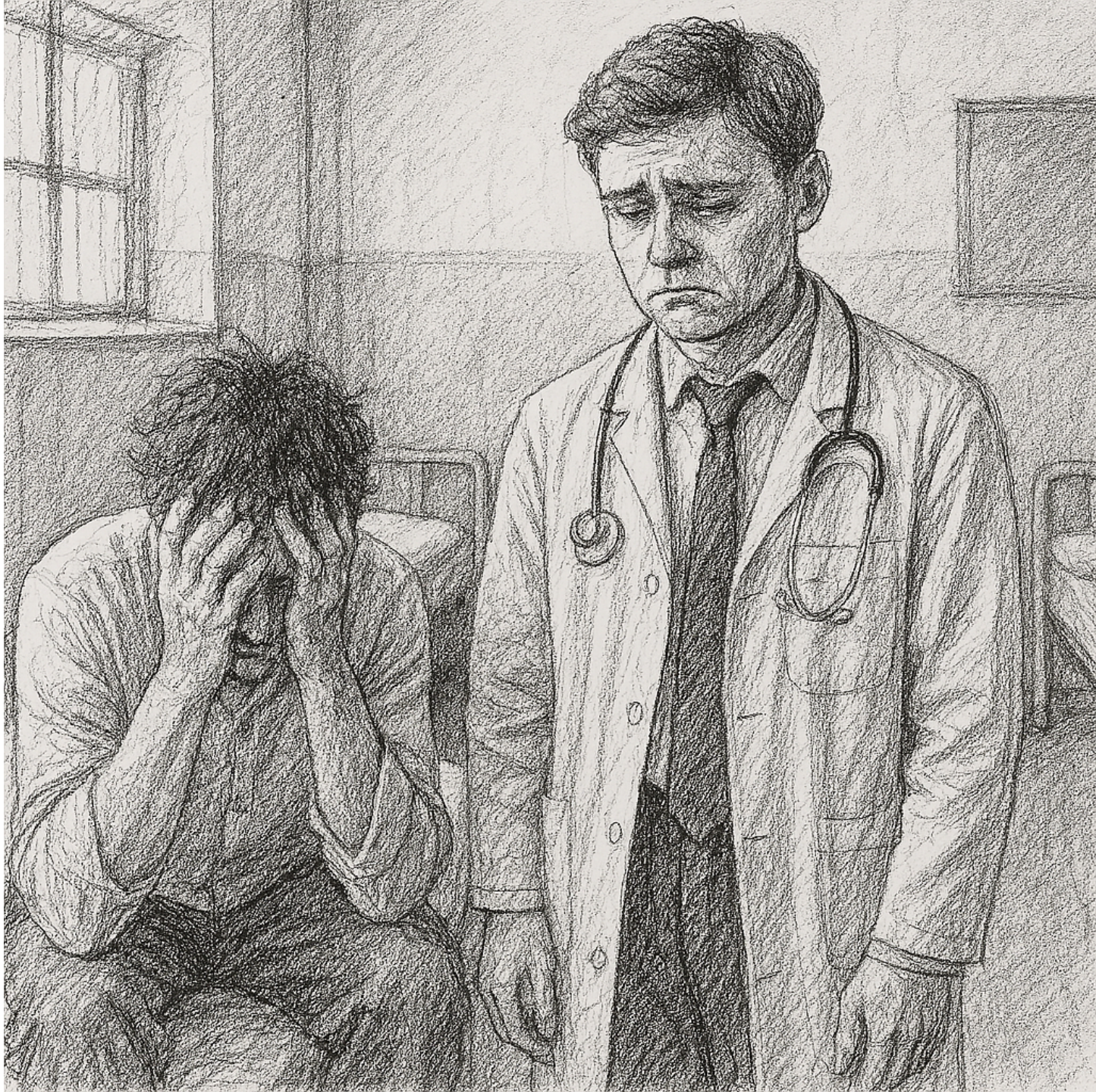


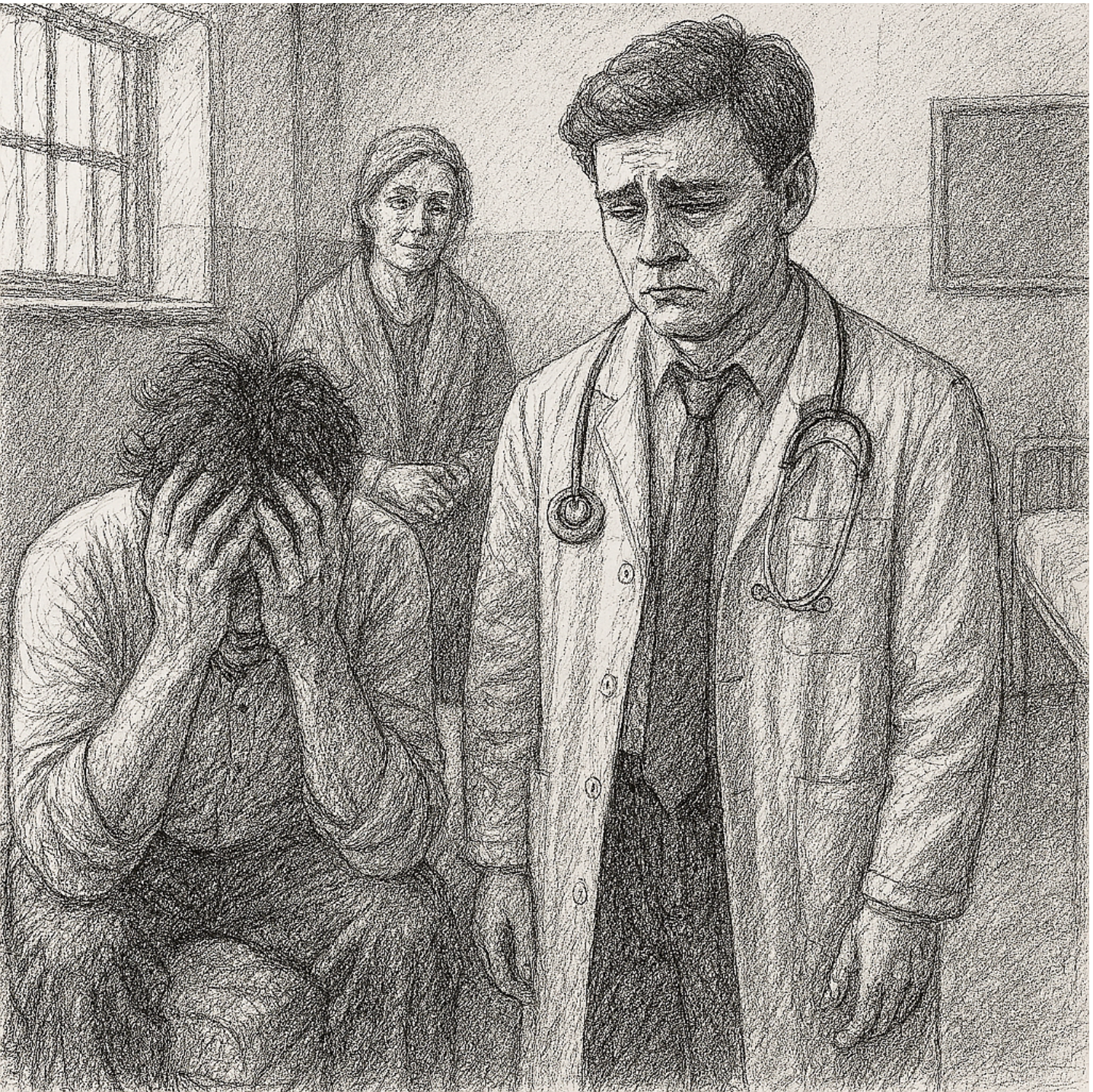
This Is My Story -

It's February 1, 1989, my first day of inpatient psychiatry rotation

My First Day as a Psychiatrist in Training – I meet my first patient afflicted with Schizophrenia

And Now… I Am "In Charge" of Helping Him Recover





I Met His Mother...

Her Agony, Her Helplessness, Her Pleading Eyes ...

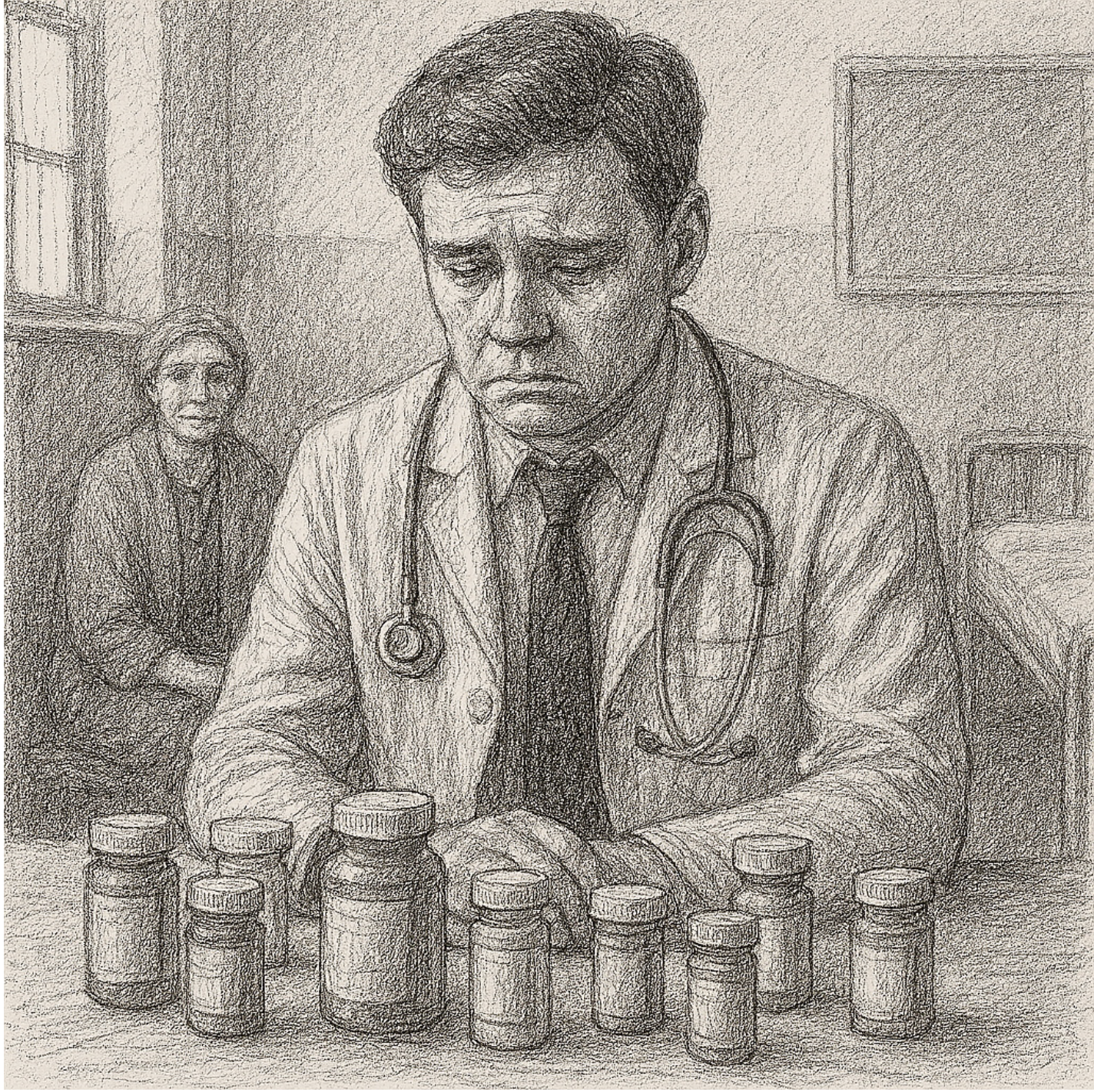
I Remember Them... Vividly

I tried one medication after another...

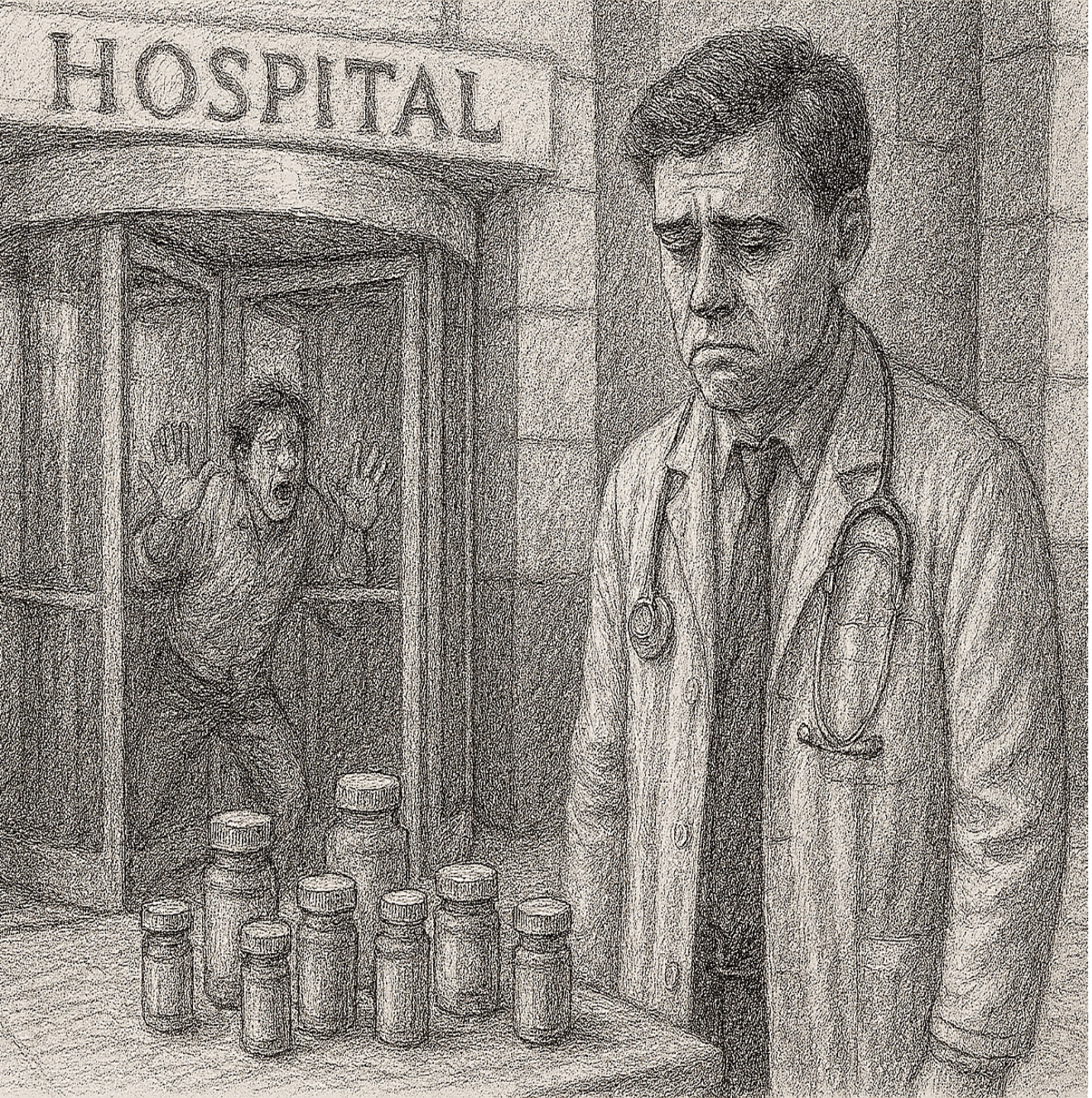
He Refused All LAIs...

His Mother... Always There ...

Yet... with Each Trial the Light in Her Eyes Died A Little...



LAI = long-acting injectable.



Sadly, He Never Got Substantial Improvement...

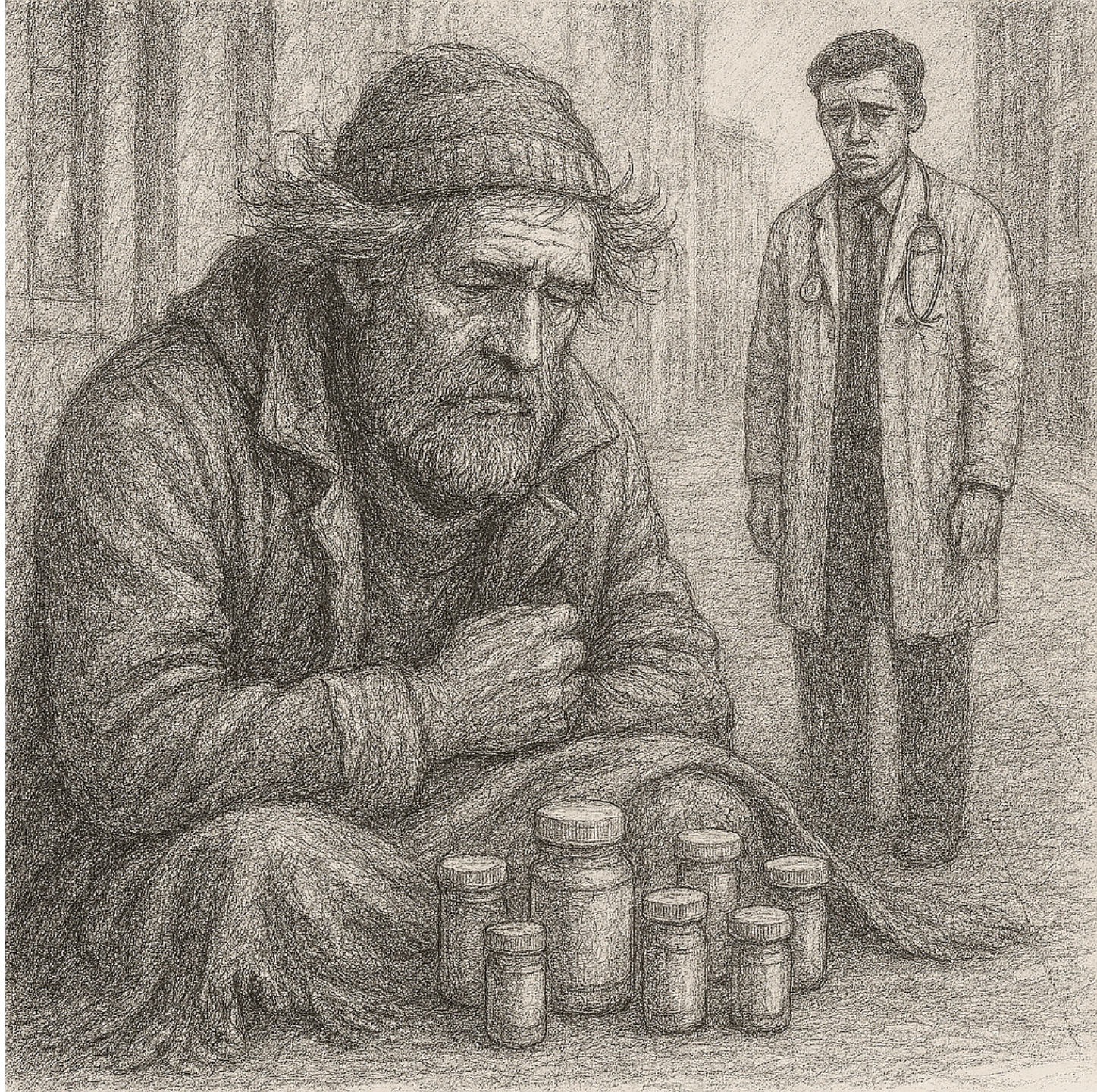
The "Revolving Door" of Multiple Hospitalizations Began...

He Kept Declining…

I Kept Offering Him Different Medication…

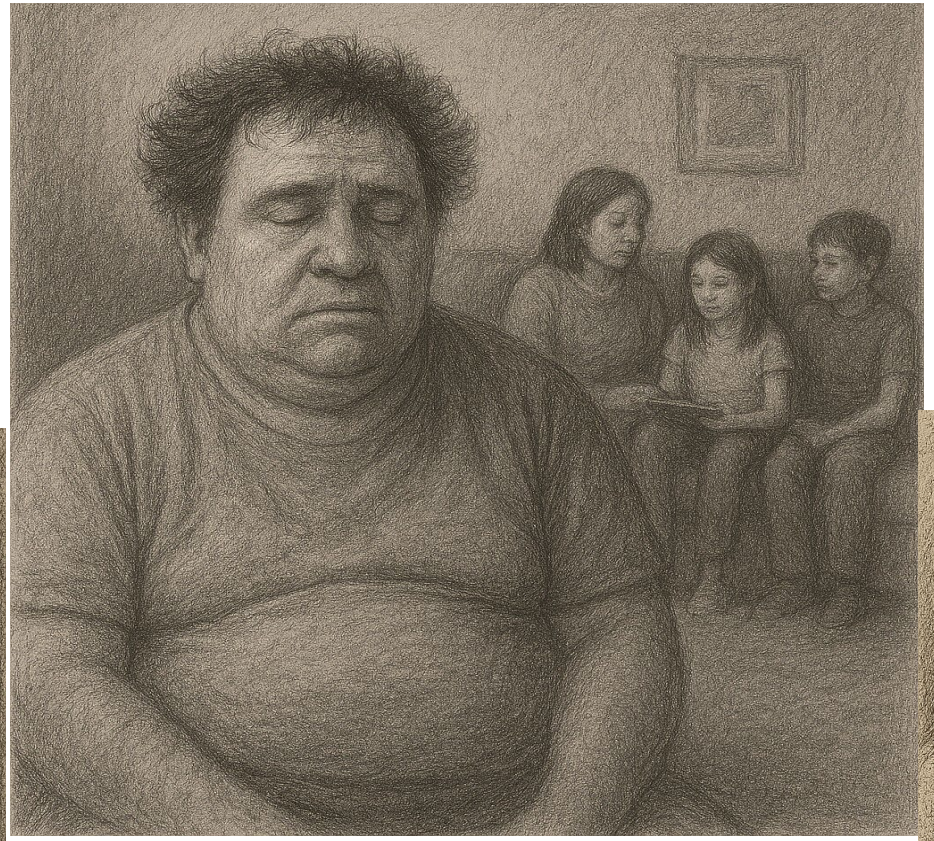
He Stopped Meds a Lot –

“They Don’t Help. And I Am Just Getting Fatter and Fatter.”

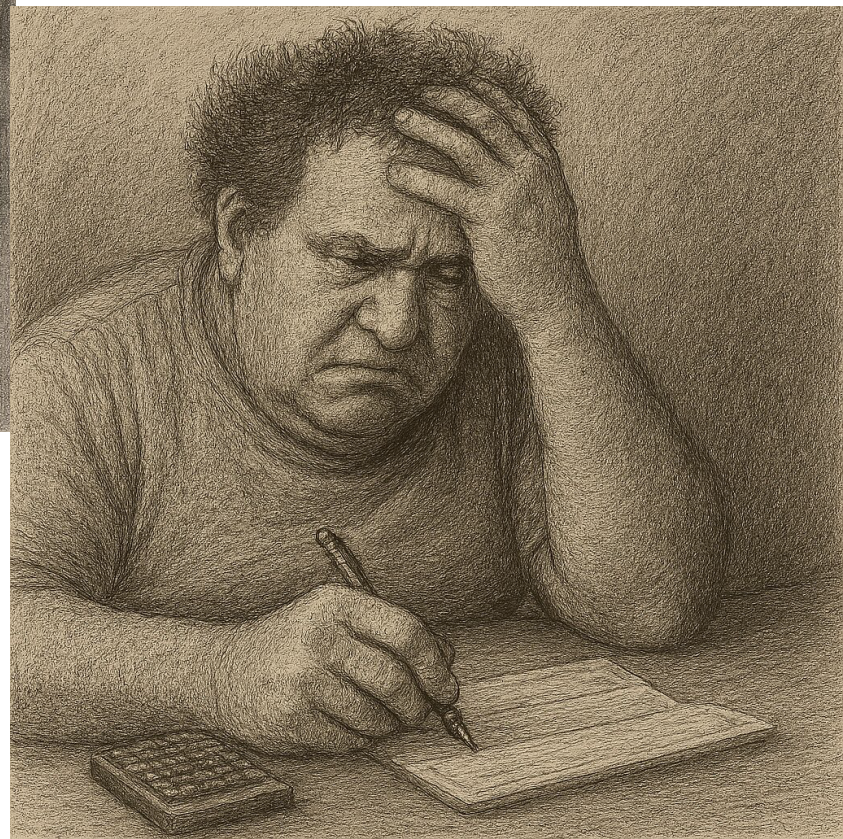


Positive Symptoms

Negative Symptoms



Cognitive Symptoms



His *Symptoms Prevailed*

Families Kept Pleading –

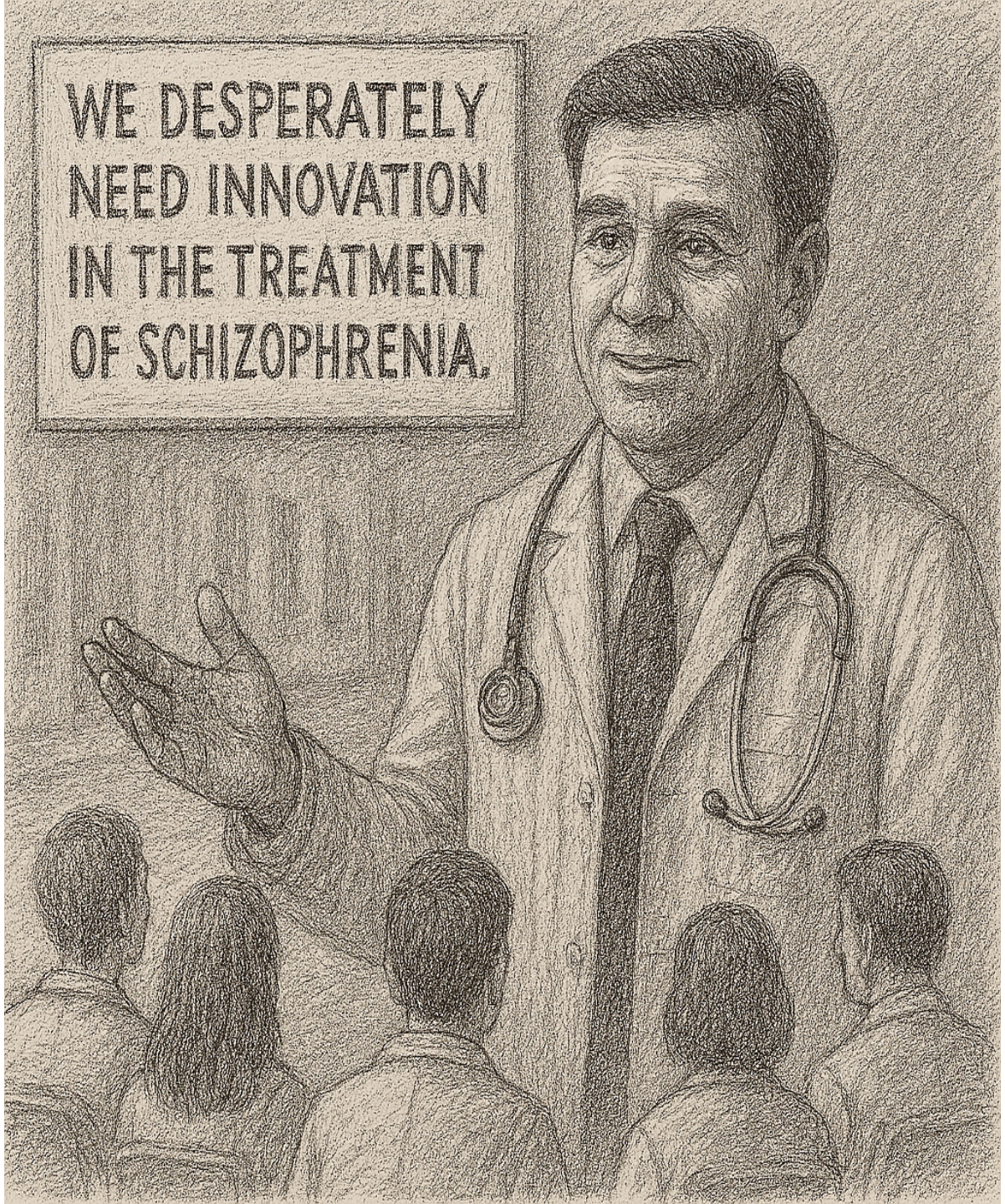
"…Help

Help

Help …"

I Felt So Helpless …

The Truth Is ➡



➡ Yes, We Need Innovation…

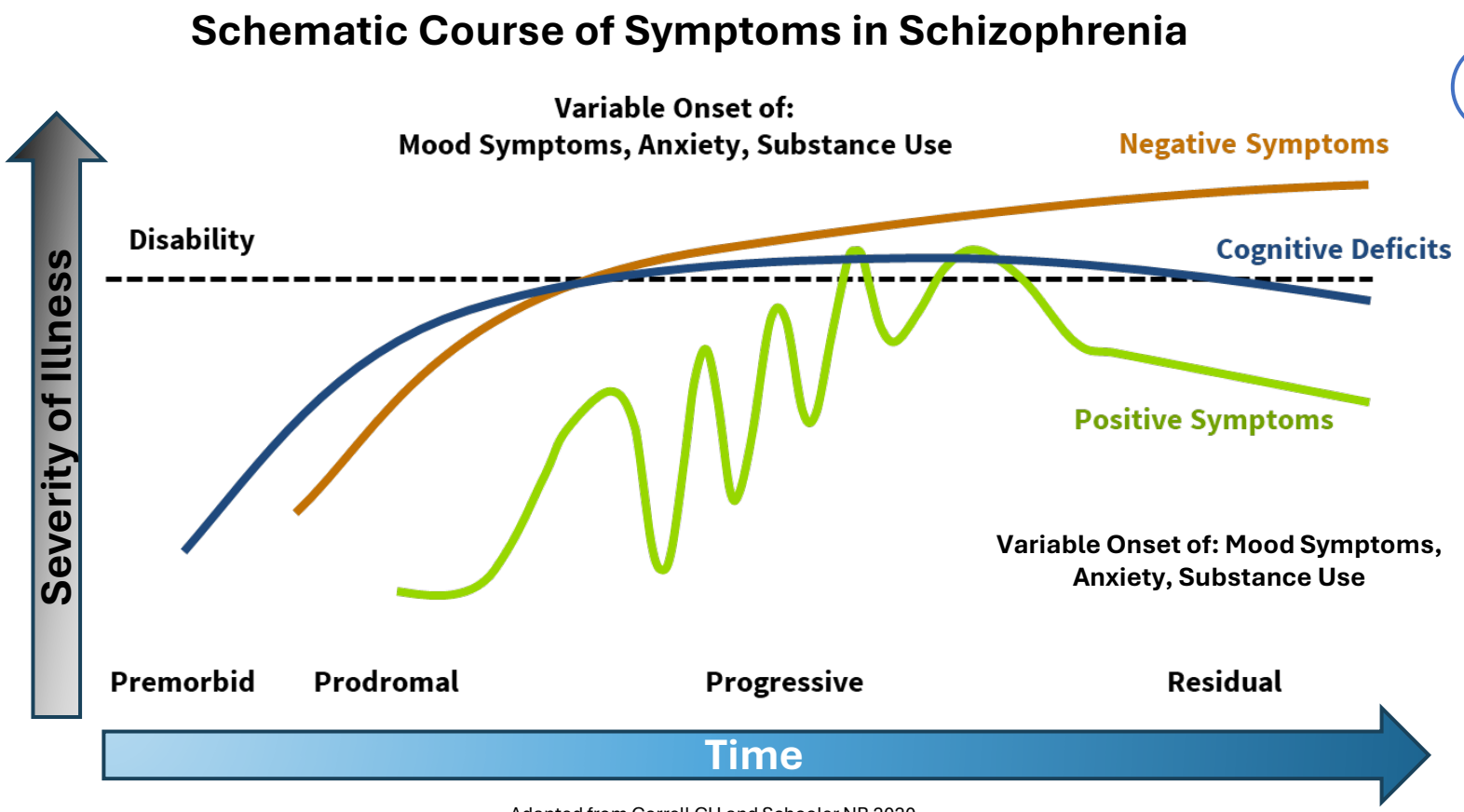
This Is Our Challenge for Today -

But...

Before We Think Boldly, Let's Take a Measure of Our Adversary –

Schizophrenia

Course of Schizophrenia Symptoms Over Time

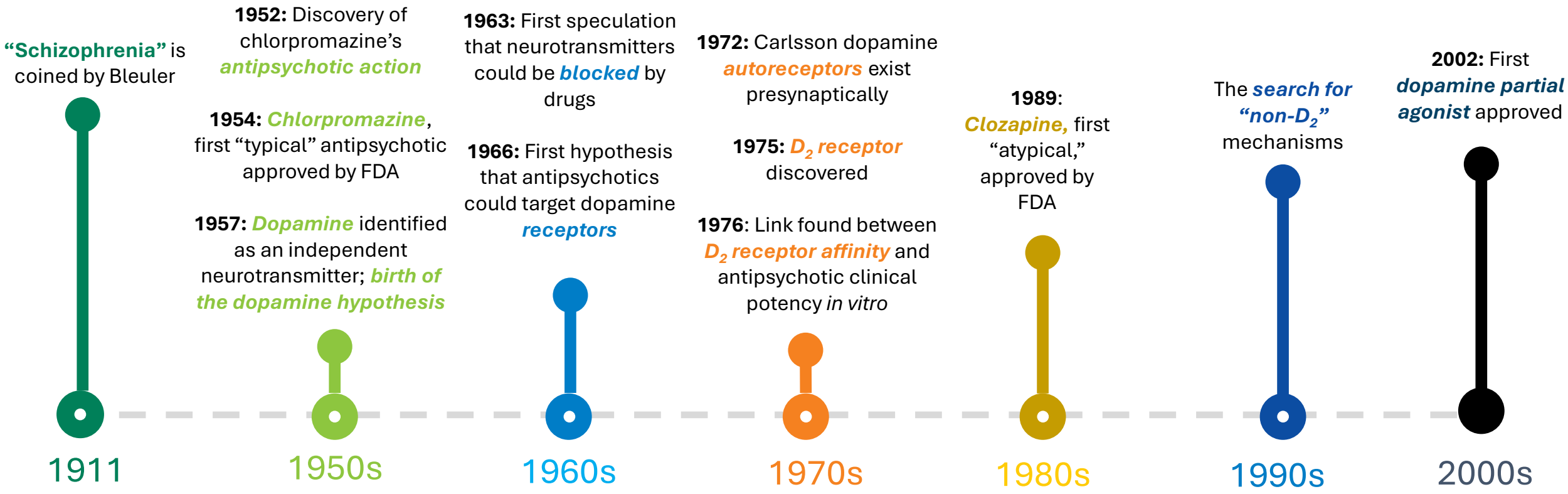


Adapted from Correll CU and Schooler NR 2020.

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

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

A Brief History of Schizophrenia Treatment



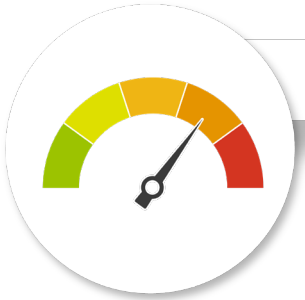
5-HT2A = serotonin type 2A receptor; D_2 = dopamine D2 receptor.

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

Unmet Needs in Schizophrenia Treatment Remain

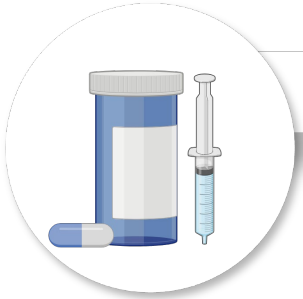
Residual Symptoms and Inadequate Treatment Response

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



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

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



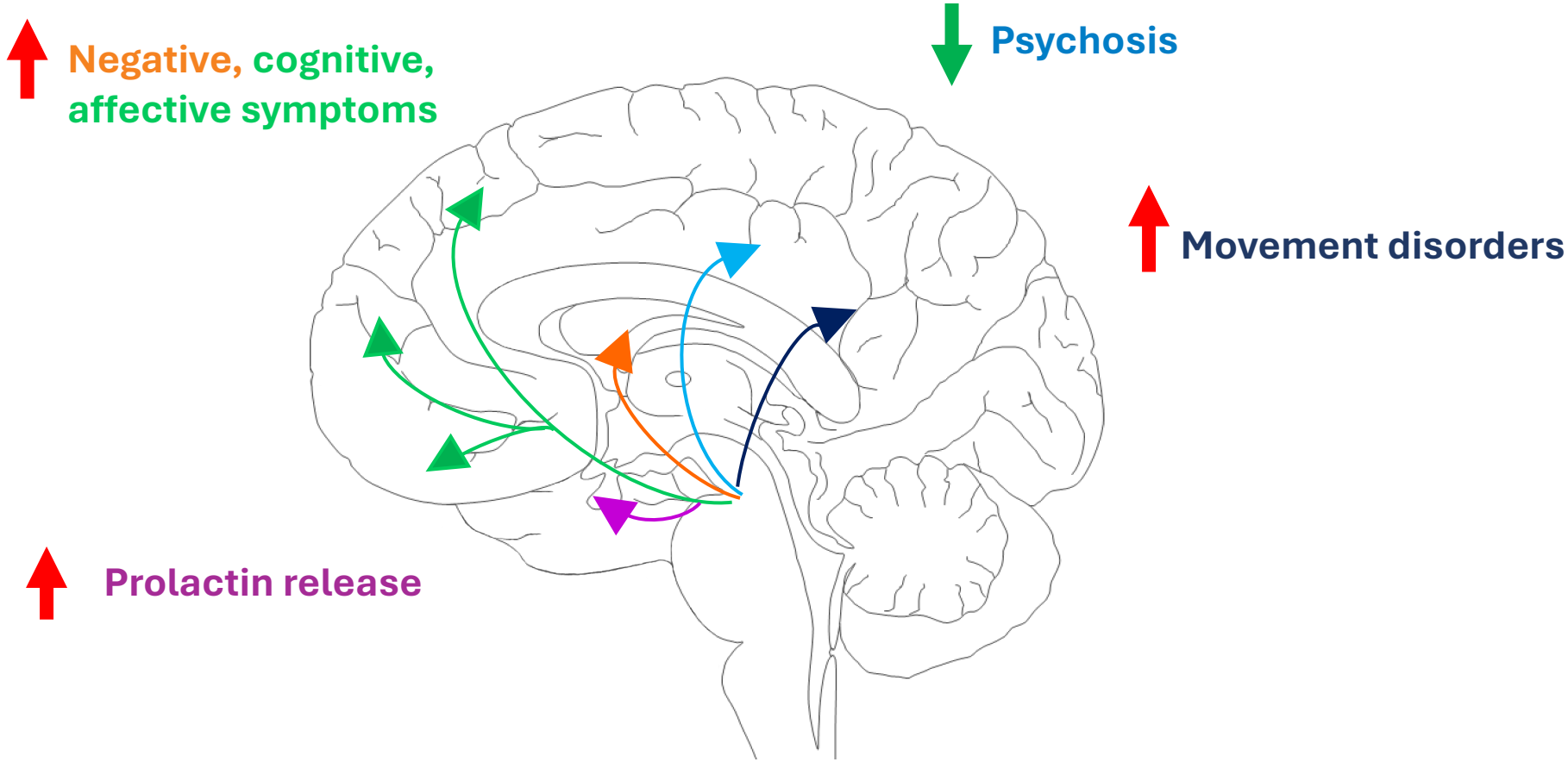
All APs work via essentially the same mechanism

AP = antipsychotic.

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

Evolving the Dopamine Hypothesis

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.

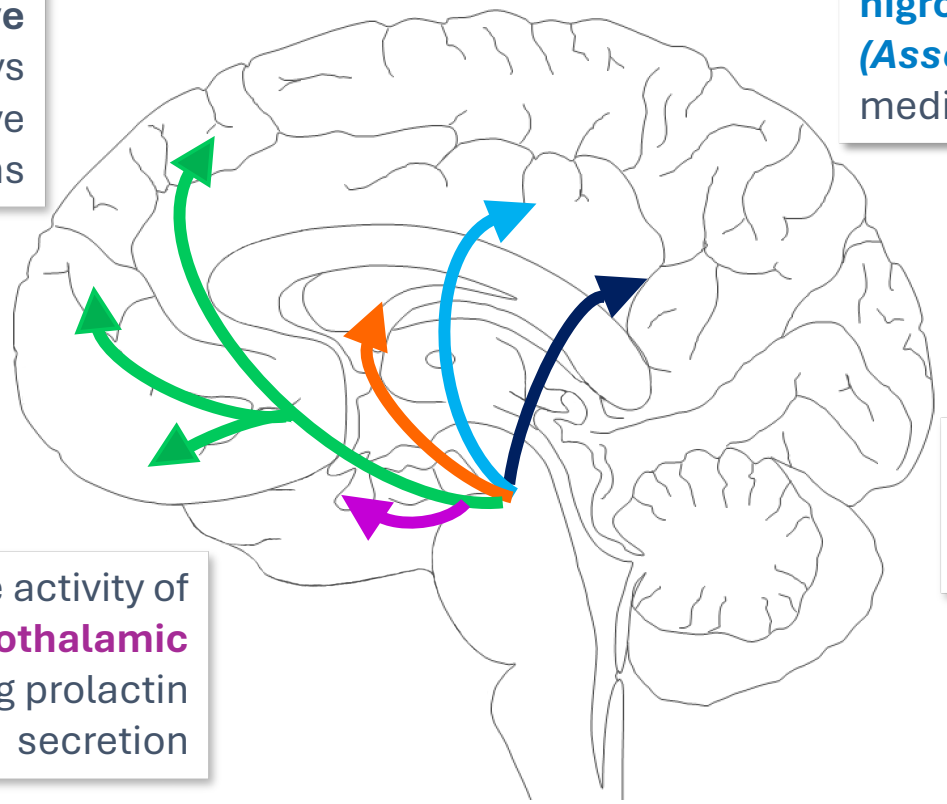
DA = dopamine; D_2R = dopamine D2 receptor.

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

Goal for Schizophrenia Treatment

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

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



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

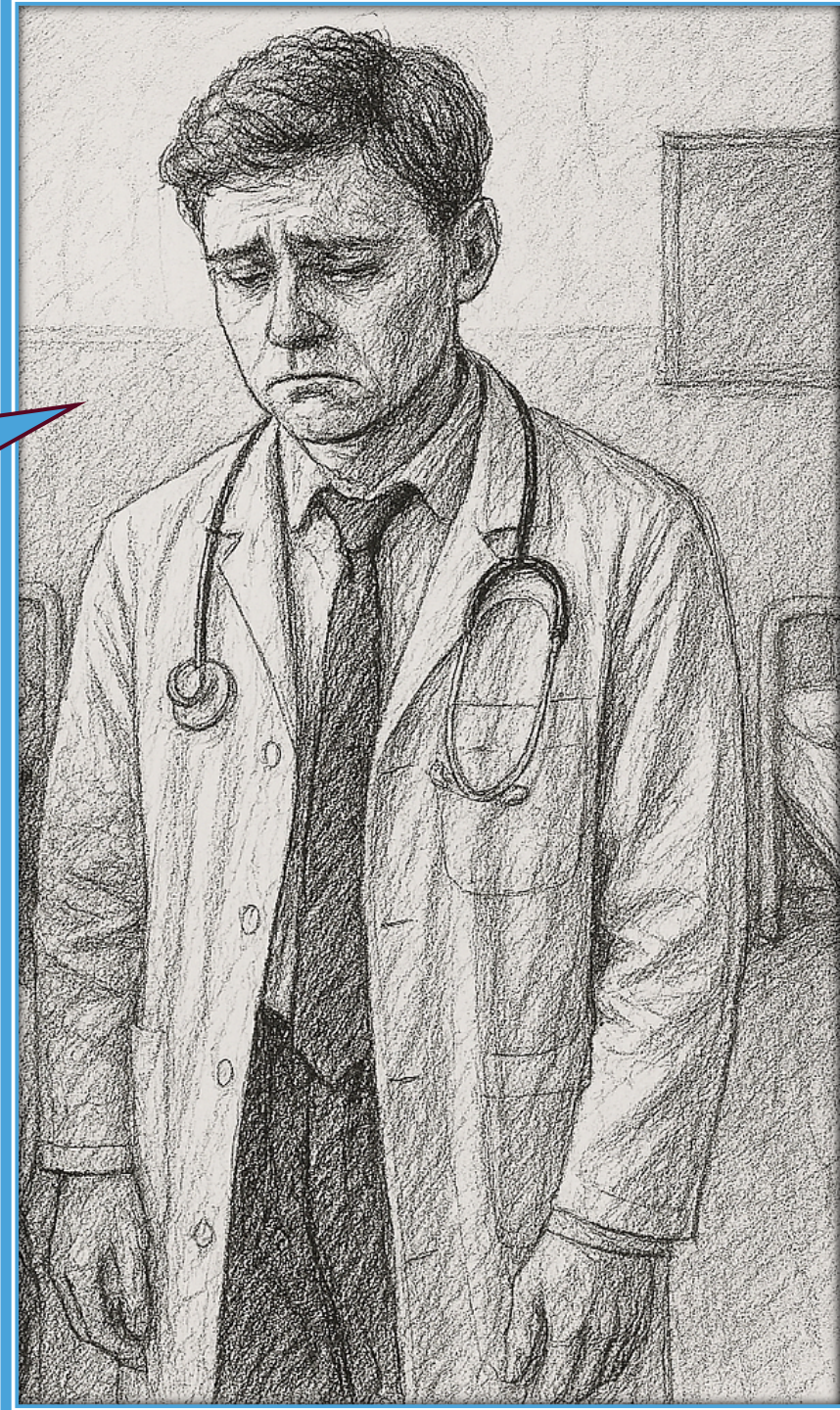
Preserve activity of **tuberoinfundibular hypothalamic pathway** regulating prolactin secretion

***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.[2]**

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

“The sad truth is – in the vast majority of patients, dopamine-based treatments prove sub-optimal.

We need to think differently in the treatment of Schizophrenia.”



Is It Time to Think Differently About Schizophrenia?

What Is The Evidence I Should Think Differently To Benefit My Patients?

Let's Start with Two Fundamental Mistakes We Made Decades Ago –

- One – We thought the main pathway of challenge in Schizophrenia was the Mesolimbic pathway. It's not! It is the Associative Striatum

- Two – We thought that the Dopamine problem was post-synaptic. It's not! It's presynaptic!

- These two findings have led to the emergence of the Muscarinic pathway to control the Positive, Negative, and Cognitive symptoms of Schizophrenia

In Schizophrenia, the Primary Dopamine Dysfunction Is Pre-Synaptic

Pre-synaptic differences in schizophrenia

Elevated presynaptic striatal dopamine found in acutely psychotic individuals with

- **Effect sizes 0.63 to 1.25**

Doubled dopamine release after challenge in patients with schizophrenia vs healthy controls **in 5 of 5 studies**

- Also with moderate to large effect sizes

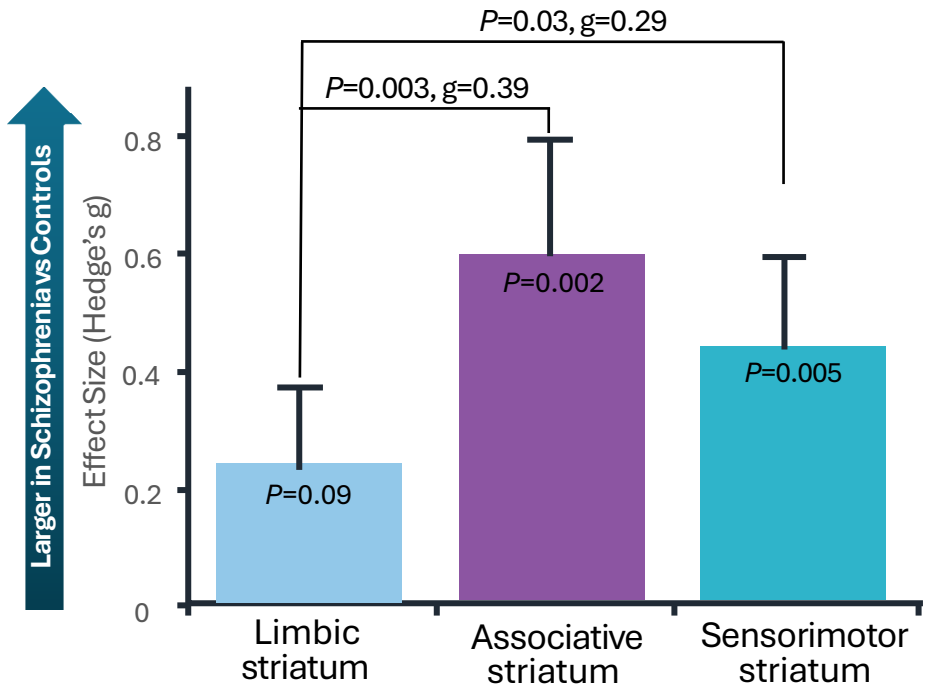
Post-synaptic differences appear to be smaller

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

- (Independent of antipsychotic effects)

It's also not in the mesolimbic pathway!

Estimated Mean Difference in Presynaptic Dopamine Function in Patients vs Controls



Recent high-resolution imaging studies	Increased dopaminergic activity in associative and sensorimotor striatum, NOT in limbic striatum as seen in mouse models

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

Here's an analogy:

If your kayak springs a hole and water is flooding in and threatening to sink you –

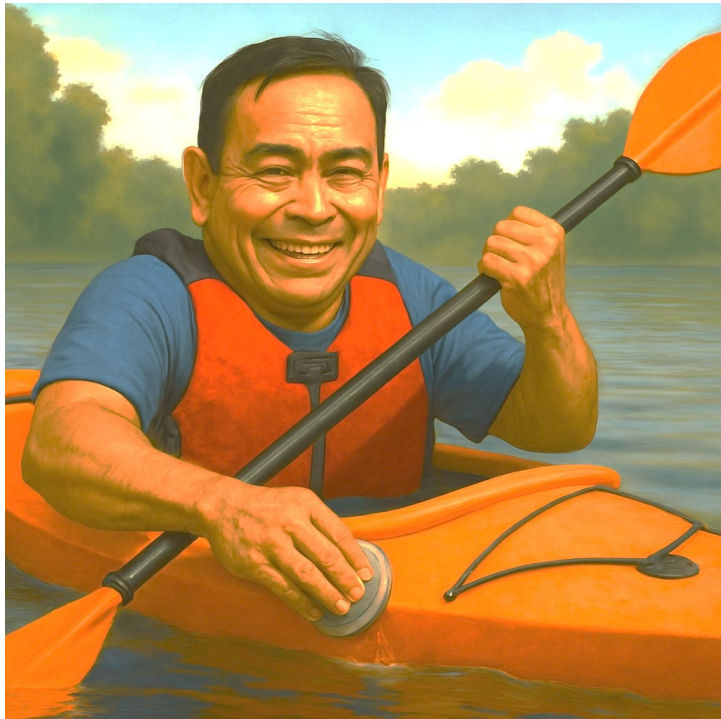
You have a "fork in the road" choice to make –

1. Do I keep bailing out the water?

Or

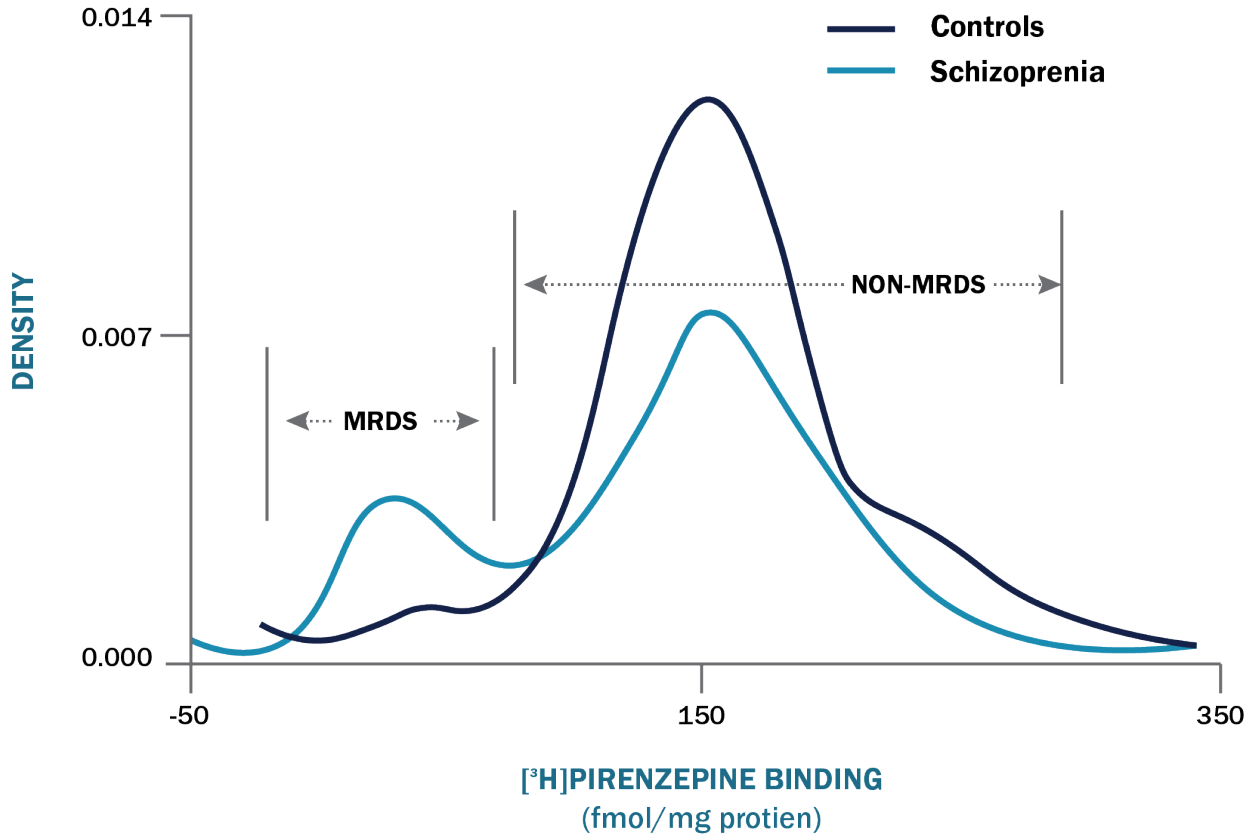
2. Do I plug the hole ?!

A presynaptic problem needs a presynaptic solution!



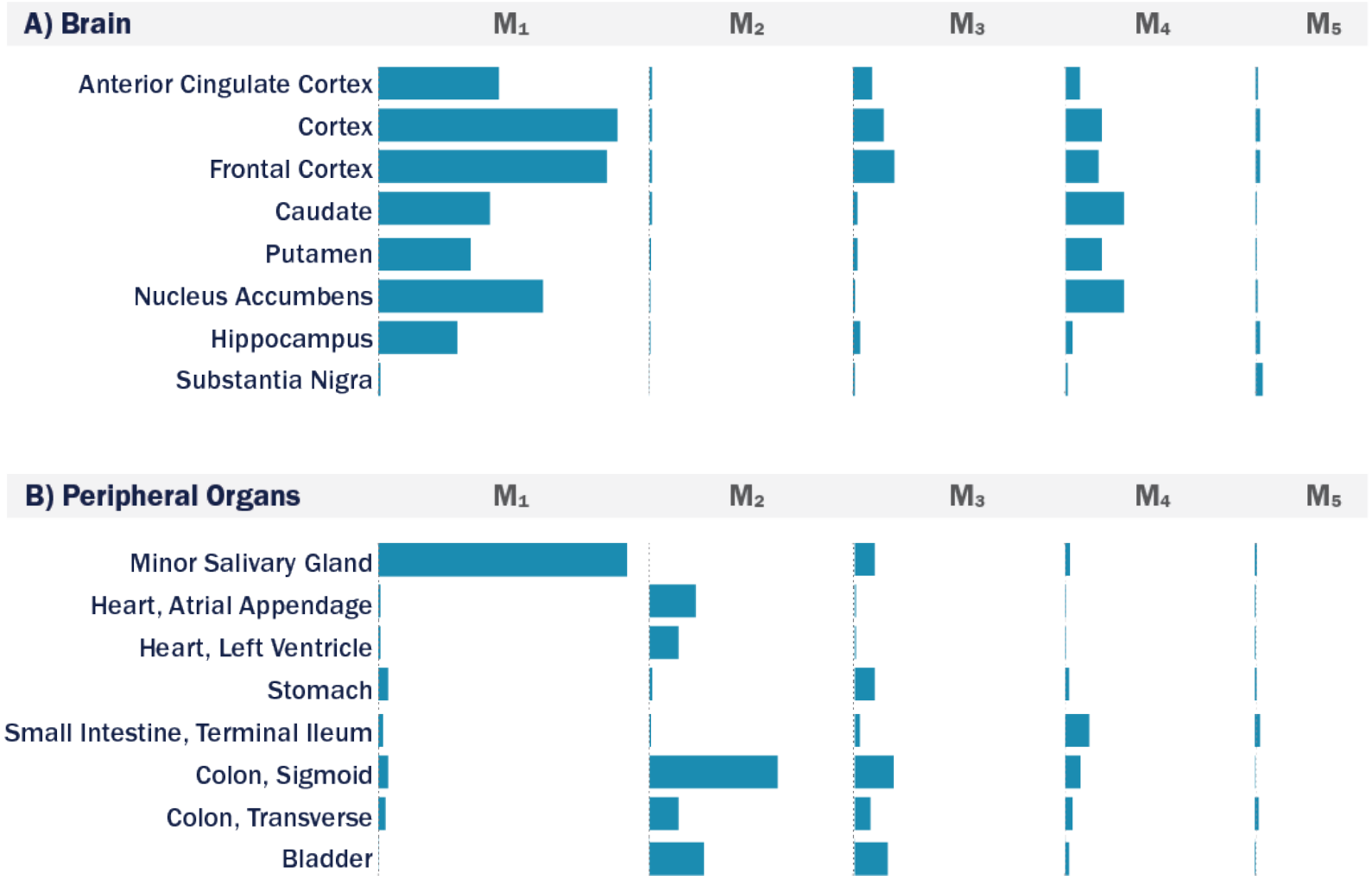
Severe Muscarinic Receptor Deficits Exist in 25% of Patients with Schizophrenia

- **2013:** Studies in muscarinic receptor deficit subgroup (MRDS) schizophrenia patients show widespread decreases in cortical M_1 receptors, altered patterns of M_1 receptor gene promoter methylation, and lower levels of muscarinic M_1 receptor mRNA compared to controls. **Notably, non-MRDS do not differ in these measures from controls**
- **2018:** Lower levels of muscarinic M_1 receptors associated with poorer performance in verbal learning and memory and more severe negative symptoms in medication-free patients with a psychotic disorder



Dean B, Scarr E. *Psychiatry Res*. 2020;288:112989.

Quantification and Localization of Muscarinic Acetylcholine Receptor (mAChR) mRNAs in Central and Peripheral Human Tissues Using RNA Sequencing

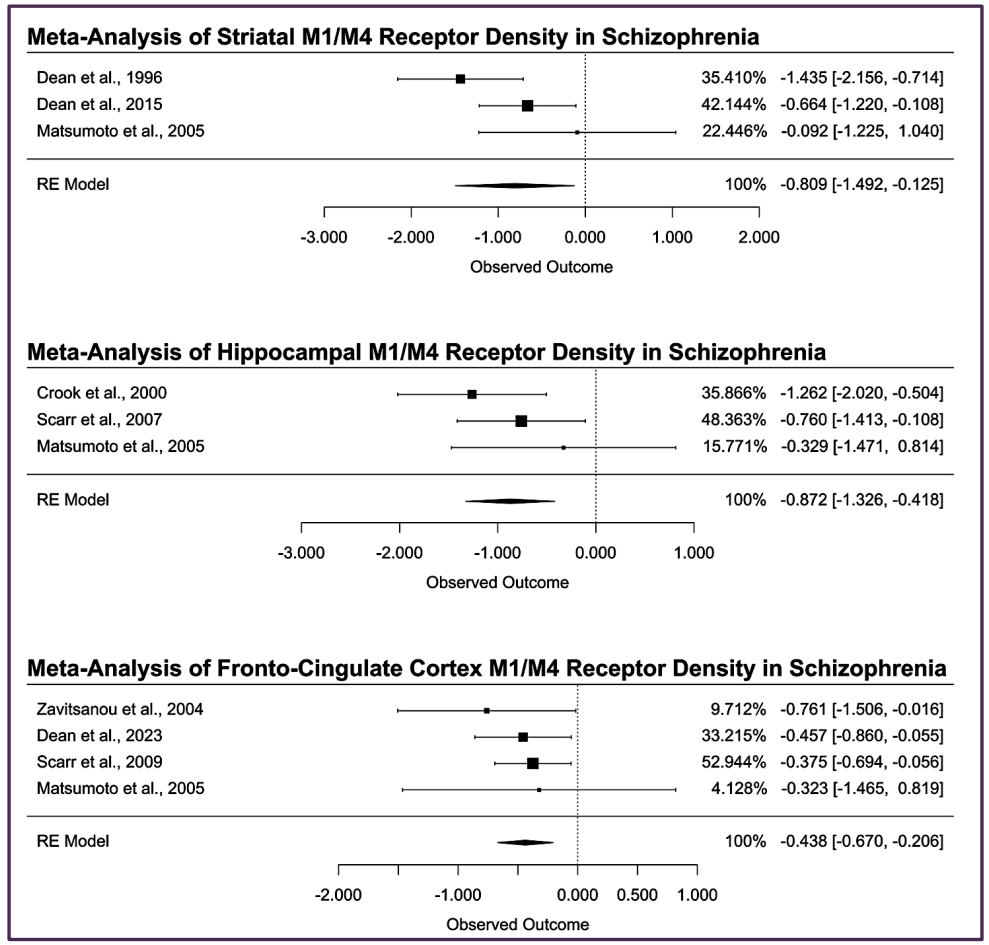


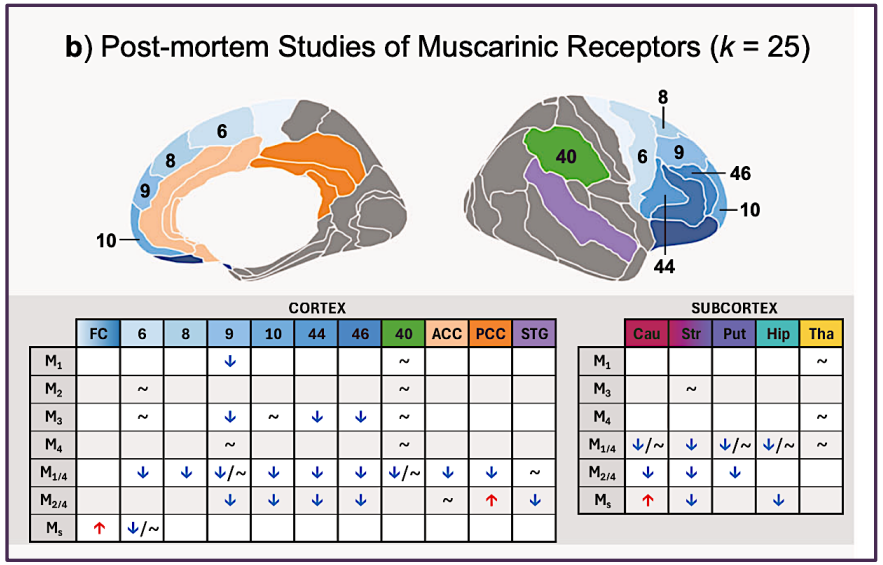
Relative expression of the five mAChR subtypes across key brain regions (panel A) and peripheral organs (panel B) is associated with efficacy and tolerability of mAChR agonists. (Data used for the relative expression analysis described in this figure were obtained from the Genotype-Tissue Expression [GTEx] Portal on March 29, 2021. The GTEx Project was supported by the Common Fund of the Office of the Director of the National Institute of Health and by the National Cancer Institute, the National Human Genome Research Institute, the National Heart, Lung, and Blood Institute, the National Institute on Drug Abuse, the National Institute on Mental Health, and the National Institute of Neurological Disorders and Strokes.)

GTEx = Genotype-Tissue Expression.

Paul SM, et al. *Am J Psychiatry*. 2022;179(9):611-627.

There Is Substantial Evidence M4 and M1 Is Implicated in Schizophrenia





"Review demonstrates a widespread decrease in muscarinic and nicotinic receptor levels in schizophrenia, evident in both neuroimaging and post-mortem studies. Our meta-analyses show large to moderate effects for the reductions in M1/M4 muscarinic receptors in the striatum, hippocampus, and fronto-cingulate cortex."

Saint-Georges Z, et al. Mol Psychiatry. 2025;30(7):3301-3315.

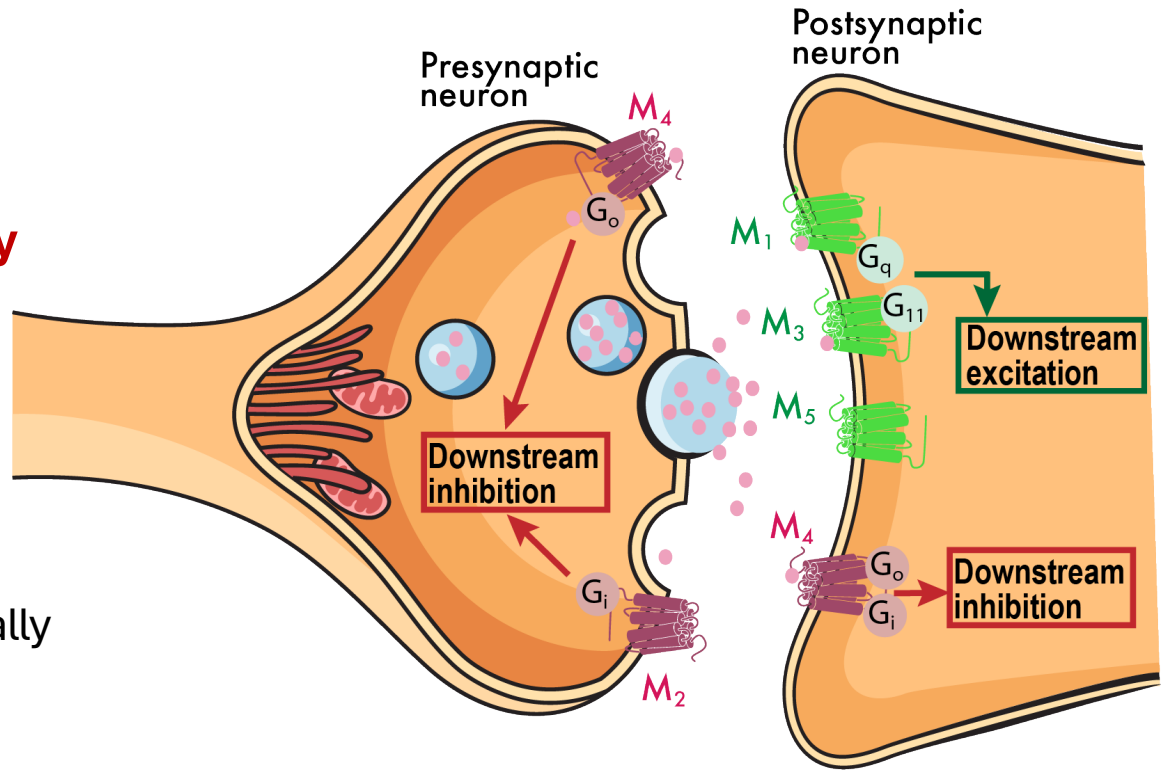
Emerging Therapeutic Target in Schizophrenia: Muscarinic Acetylcholine Receptor Activation

The Five Subtypes of Muscarinic Receptors Have Selective Effects

M_2 and M_4 are inhibitory

M_2 M_4

Found pre- and post-synaptically



M_1, M_3, M_5 are excitatory

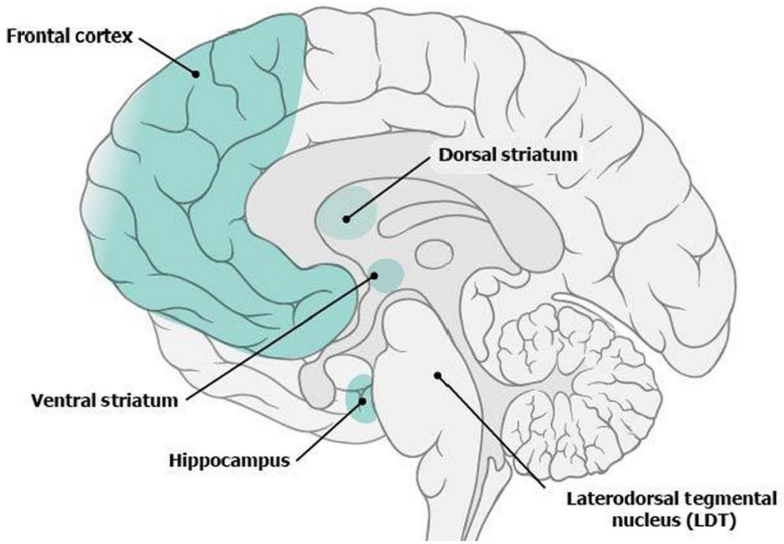
M_1 M_3 M_5

Found postsynaptically

Ryan AE, et al. *Aust New Zeal J Psychiatry*. 2019;53(11):1059-1069. Paul SM, et al. *Am J Psychiatry*. 2022;179(9):611-627.

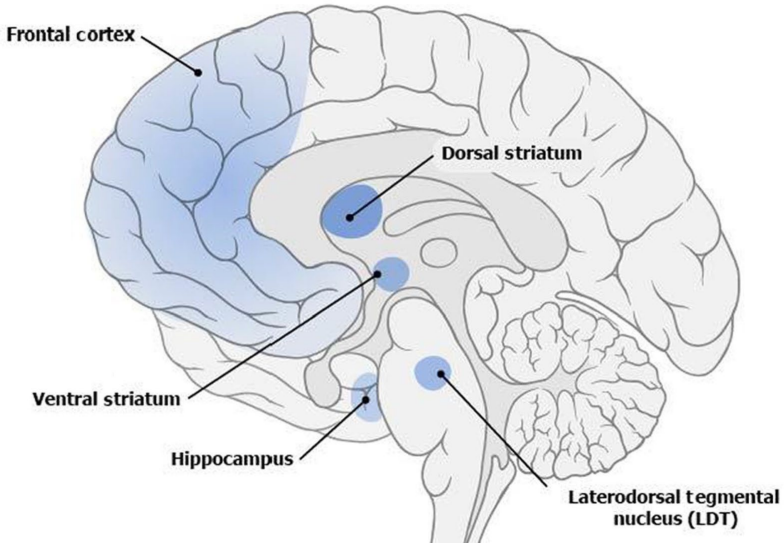
M_1 and M_4 Receptors Are Highly Enriched in Brain Areas Underlying Circuits Associated with Psychosis

Expression of M_1 Receptors



Increasing expression

Expression of M_4 Receptors



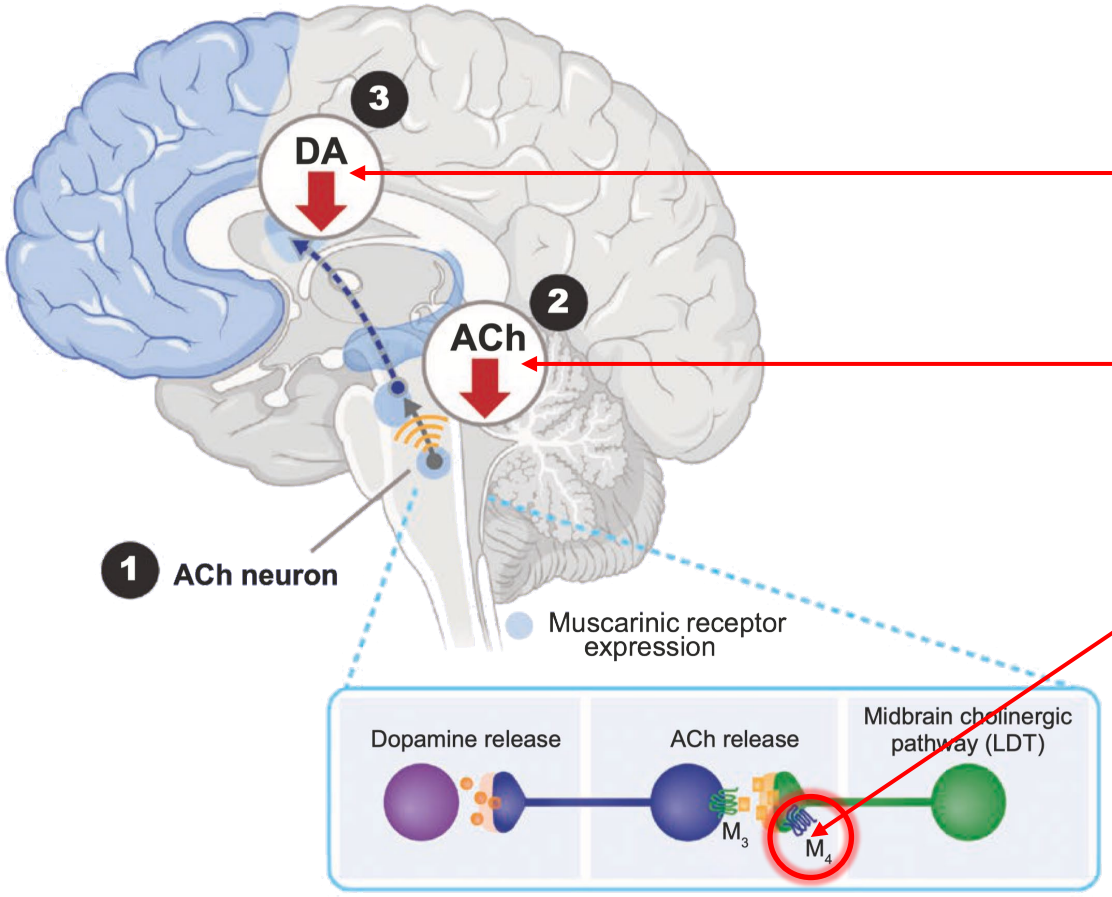
Increasing expression

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

LDT = laterodorsal tegmentum.

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

M_4 Agonism Decreases Dopamine Release in Brain Circuits Related to Psychosis



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

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

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

Bottom Line

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

ACh = acetylcholine; VTA = ventral tegmental area.

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

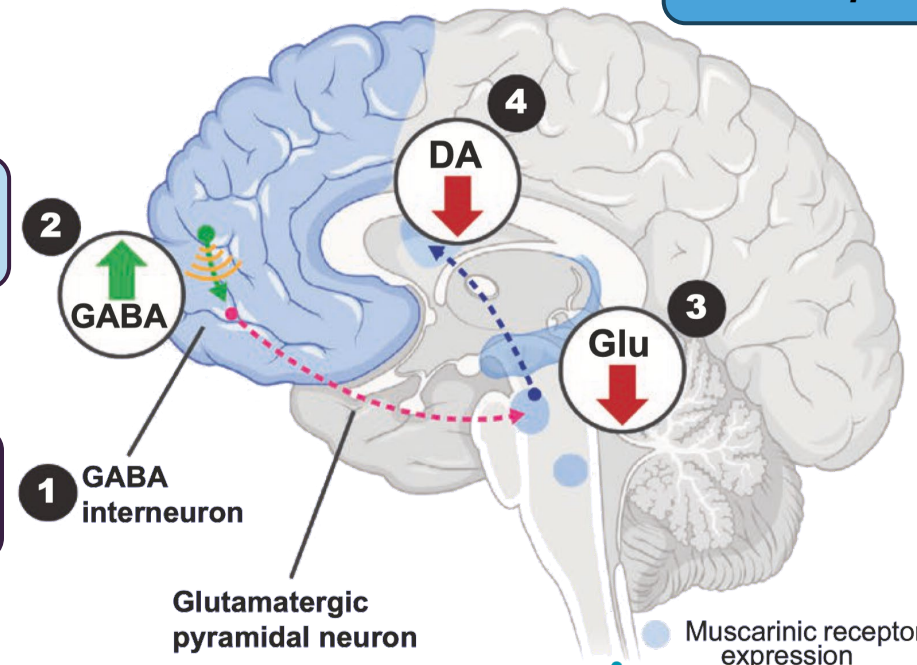
M_1 Agonism Selectively Decreases Striatal Dopamine Release by a Different Circuit

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

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

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

1) GABA interneurons in the PFC express M_1 receptors



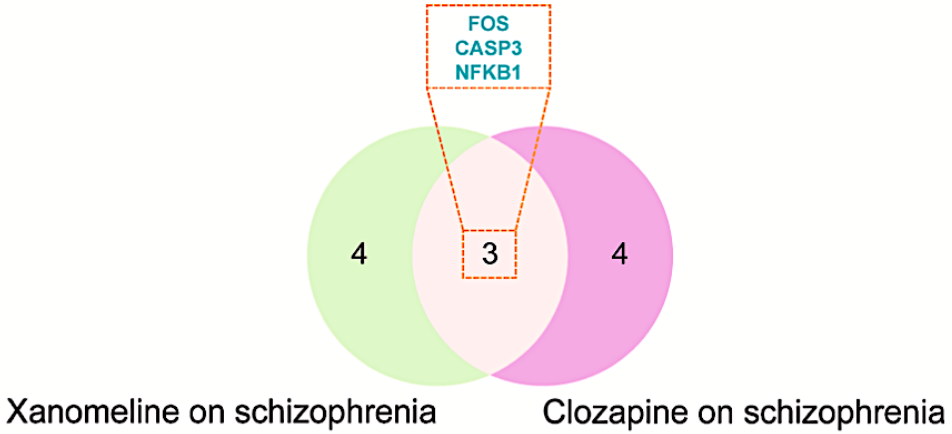
Bottom Line

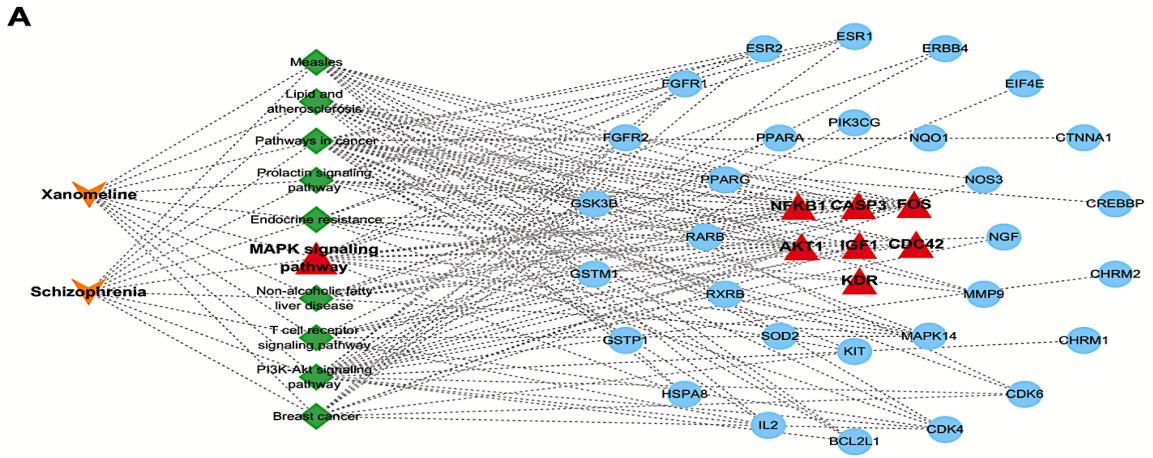
M_1 agonism also reduces dopamine signaling by reducing **presynaptic dopamine release** rather than blocking D_2 receptors postsynaptically

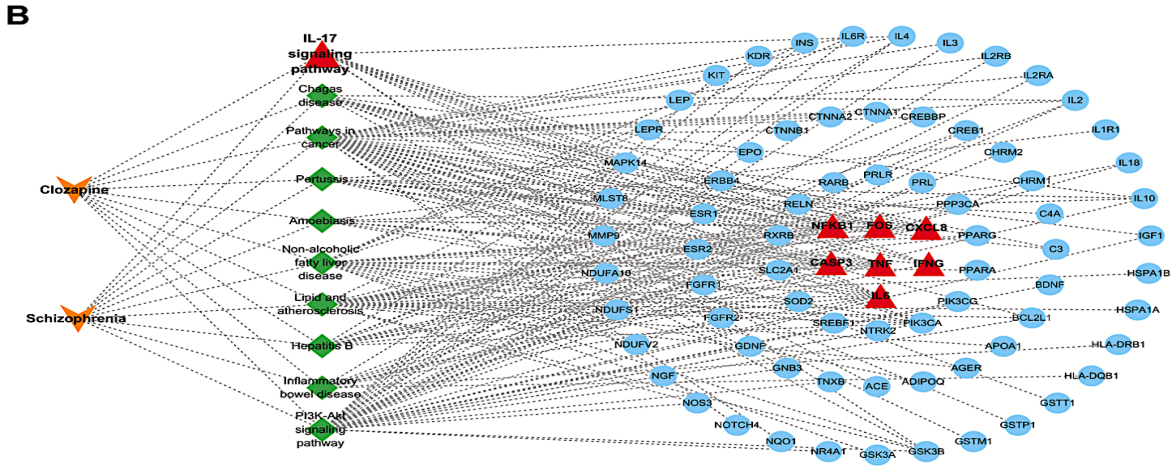
GABA = gamma-aminobutyric acid.

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

There Are Therapeutic Implications to Broadening Our Understanding of Schizophrenia







Take Home Message:

There are Distinct overlapping and non-overlapping molecular targets from Dopaminergic and Muscarinic Interventions

Zhuo C, et al. *Neurotherapeutics*. 2025:e00714.

Key Learning Points

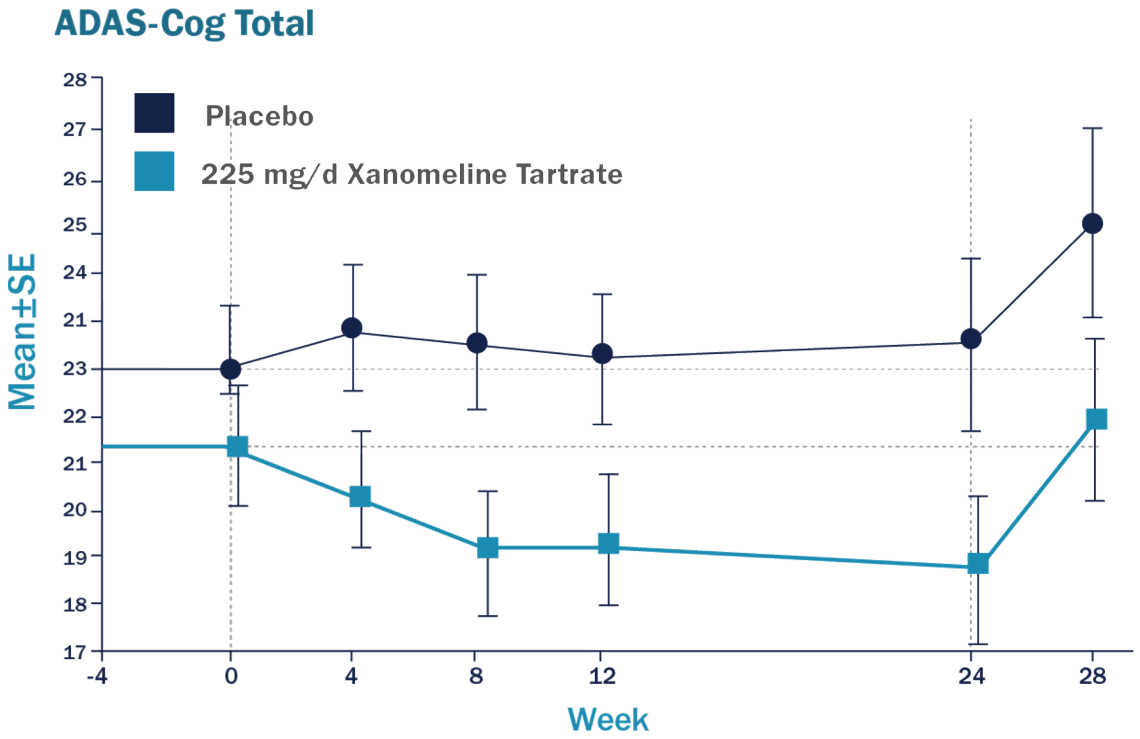
- ✓Schizophrenia remains a **complex, mostly inadequately treated disorder** and it extracts a profound price from human life via its set of positive, negative and cognitive symptoms

- ✓Emerging neurobiology of schizophrenia reveals one can target its dopamine dysregulation without directly impacting the dopamine 2 receptor

- ✓The latest pharmacogenomic studies reveal **muscarinic drugs have both an overlapping, and a distinct non-overlapping patterns of gene and receptor activity profile on nuclear and cellular proteins**

The Origin Story of Xanomeline

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



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

It was found to be efficacious…

But its tolerability profile was unacceptable

ADAS-Cog = Alzheimer's Disease Assessment Scale Cognitive Subscale; CIBIC+ = Clinician's Interview-Based Impression of Change; SE = standard error.

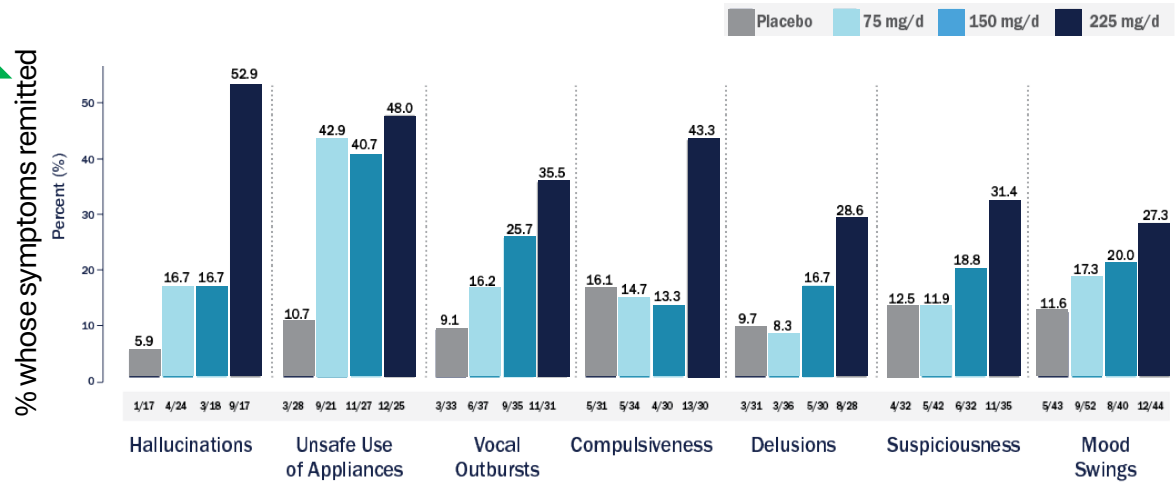
Bodick NC, et al. *Arch Neurol*. 1997;54(4):465-473.

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

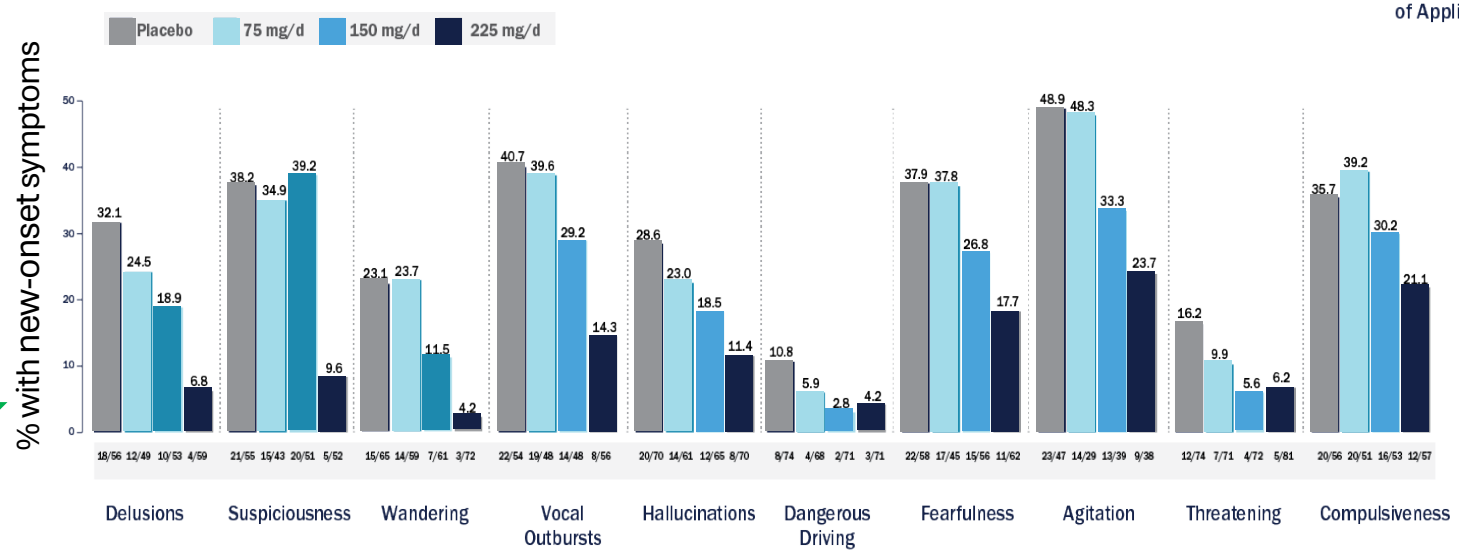
However, there were some interesting findings in the secondary outcomes…

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

Increasing symptom remission



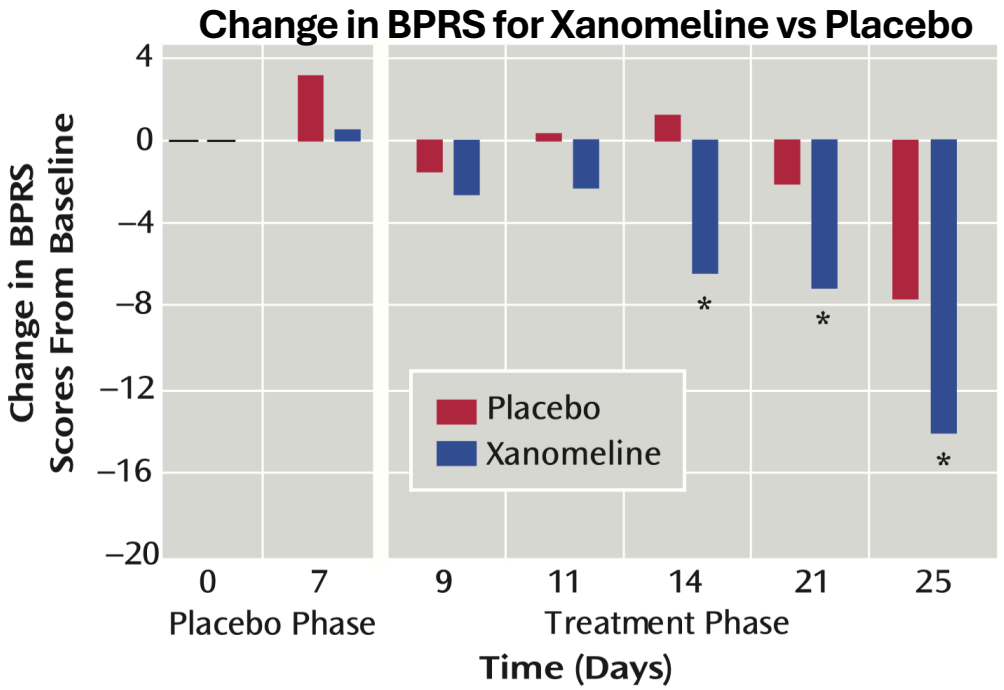
Less likely to develop psychosis

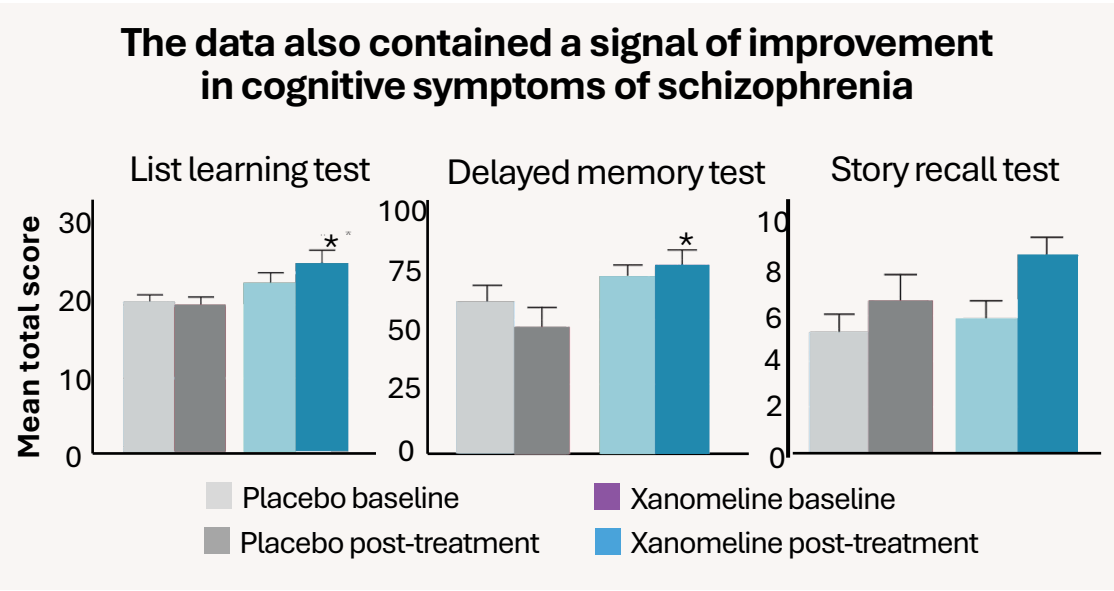


And of those without psychosis at baseline, <u>fewer</u> who received xanomeline developed new-onset psychosis

Bodick NC, et al. *Arch Neurol*. 1997;54(4):465-473.

A Pilot Study Showed Xanomeline Also Had Potential in Schizophrenia





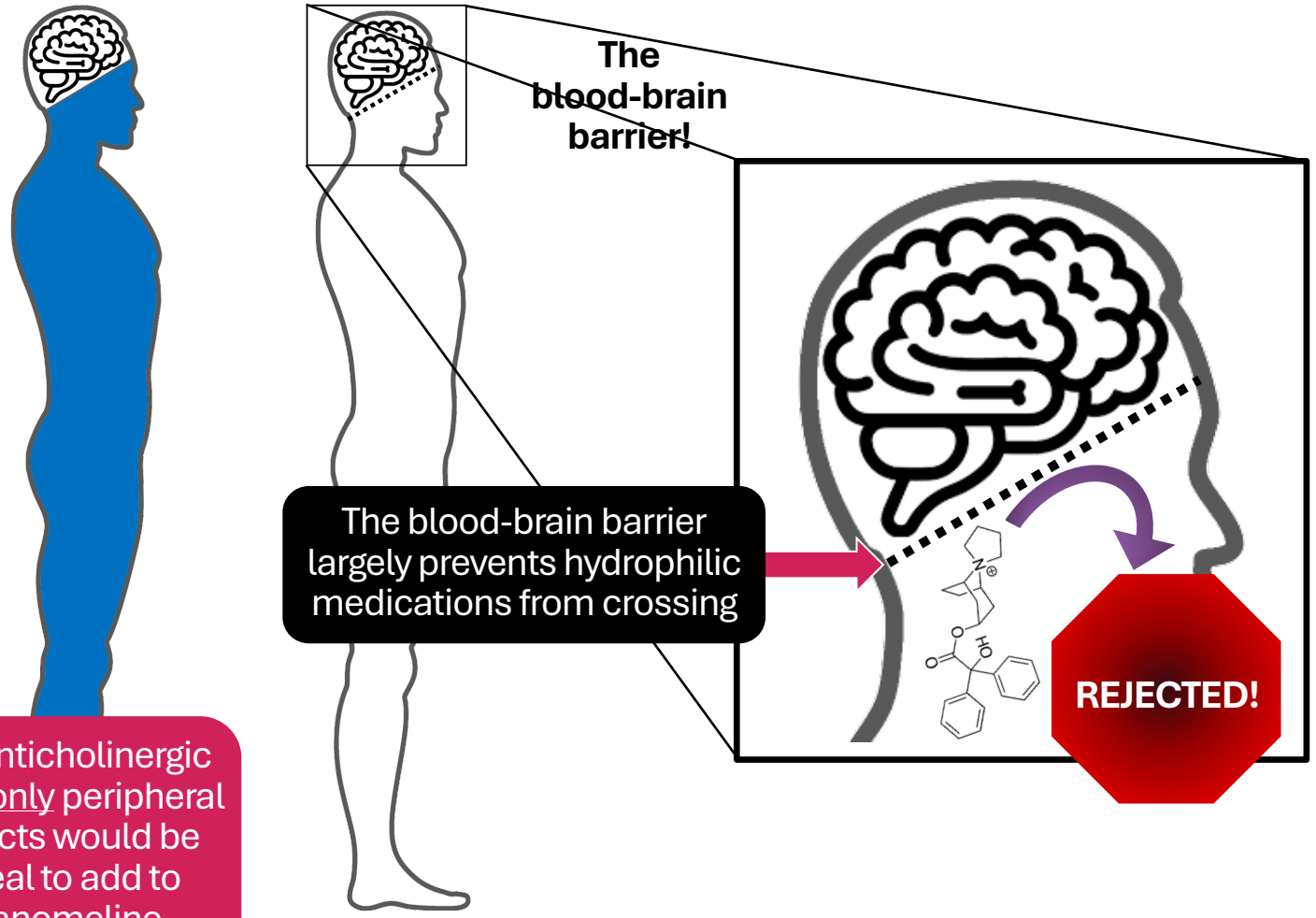
Key Adverse Events	Placebo (n=10)	Xanomeline (n=10)
Nausea	40%	70%
Vomiting	10%	60%
GI Distress	50%	70%

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

BPRS = Brief Psychiatric Rating Scale.

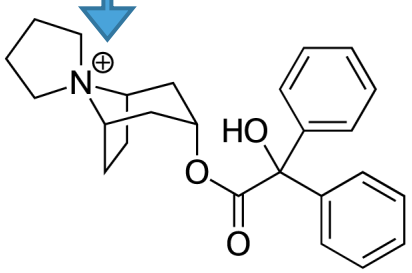
Shekhar A, et al. *Am J Psychiatry*. 2008;165(8):1033-1039.

Selectively Neutralizing Peripheral Cholinergic Effects



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

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



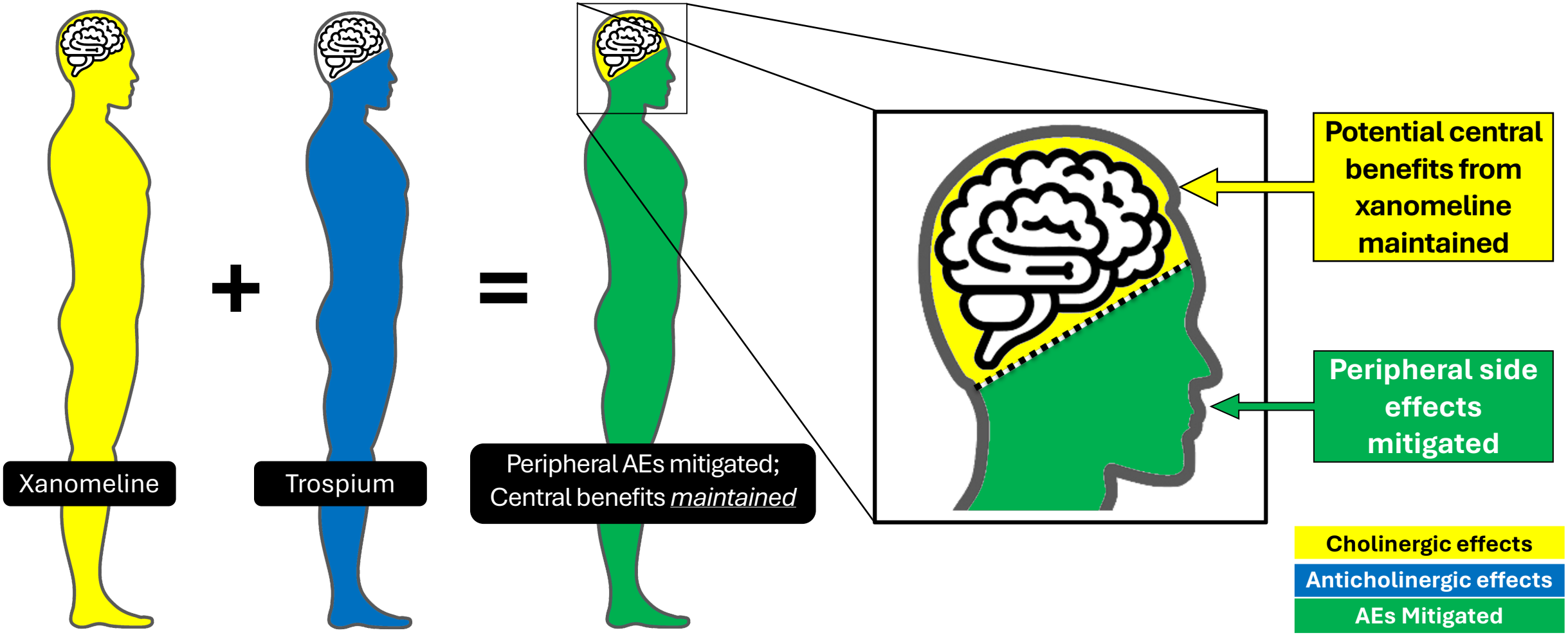
After screening hundreds of compounds, trospium was identified as a candidate

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

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

Callegari E, et al. *Br J Clin Phamacol*. 2011;72(2):235-246. Chancellor MB, et al. *Drugs Aging*. 2012;29:259-273. Duong V, et al. *Int Urogynecol J*. 2021;32:2693-2702. Malcher MF, et al. *J Urol*. 2022:101097.

Trospium Neutralizes Primarily the Peripheral Cholinergic Effects When Added to Xanomeline



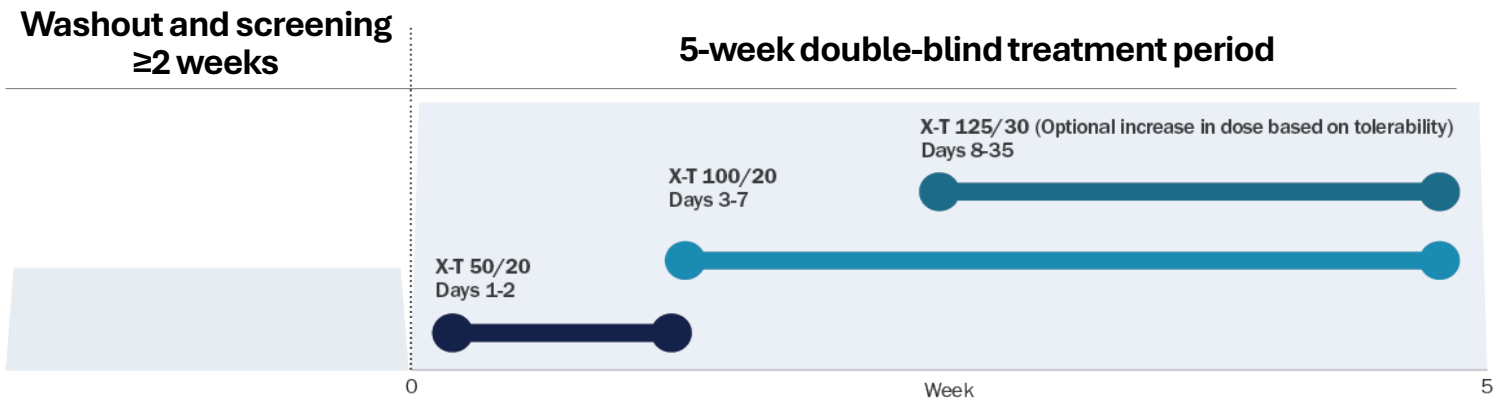
Brannan SK, et al. *N Engl J Med*. 2021;384(8):717-776.

Key Learning Points

- ✓ **Stimulation** of **M_4** receptors **decreases dopamine release** in the **VTA,** which **reduces** symptoms of **psychosis**
- ✓ **Stimulation** of **M_1 receptors** in the PFC also **decreases dopamine release** in the **VTA**, which may also **reduce** symptoms of **psychosis**
- ✓ Xanomeline was **effective for psychosis and cognition in Alzheimer's disease and schizophrenia**, but development was halted due to peripheral cholinergic adverse effects

Clinical Evidence for Xanomeline-Trospium in Schizophrenia

Overview of Short-Term Xanomeline/Trospium Trials



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

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

Pooled Demographics

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

SD = standard deviation; BMI = body mass index.

Kaul I, et al. *Schizophrenia (Heidelb)*. 2024;10(1):102.

Understanding the PANSS: Symptom Domains and Total Score Severity

The PANSS is a clinician-rated measure of schizophrenia symptoms with 30 items (scored 1-7) across three domains:

Positive Symptoms

- P1. Delusions
- P2. Conceptual disorganization
- P3. Hallucinatory behavior
- P4. Excitement
- P5. Grandiosity
- P6. Suspiciousness/ persecution
- P7. Hostility

Negative Symptoms

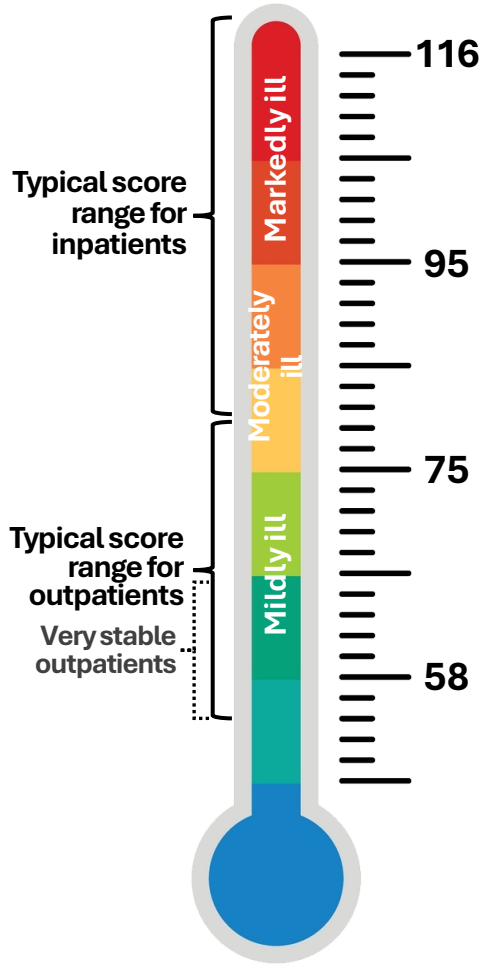
- N1. Blunted affect
- N2. Emotional withdrawal
- N3. Poor rapport
- N4. Passive/apathetic and social withdrawal
- N5. Difficulty in abstract thinking
- N6. Lack of spontaneity and flow of conversation
- N7. Stereotyped thinking

General Psychopathology Symptoms

G1. Somatic concern	G6. Depression	G11. Poor attention
G2. Anxiety	G7. Motor retardation	G12. Lack of judgment & insight
G3. Guilt feelings	G8. Uncooperativeness	G13. Disturbing of volition
G4. Tension	G9. Unusual thought content	G14. Poor impulse control
G5. Mannerism and posturing	G10. Disorientation	G15. Preoccupation
		G16. Active social avoidance

The General Psychopathology domain makes up **>50%** of the total PANSS score!

An analogy to understand what the **PANSS total score** means is to think of it like the **temperature in Fahrenheit**

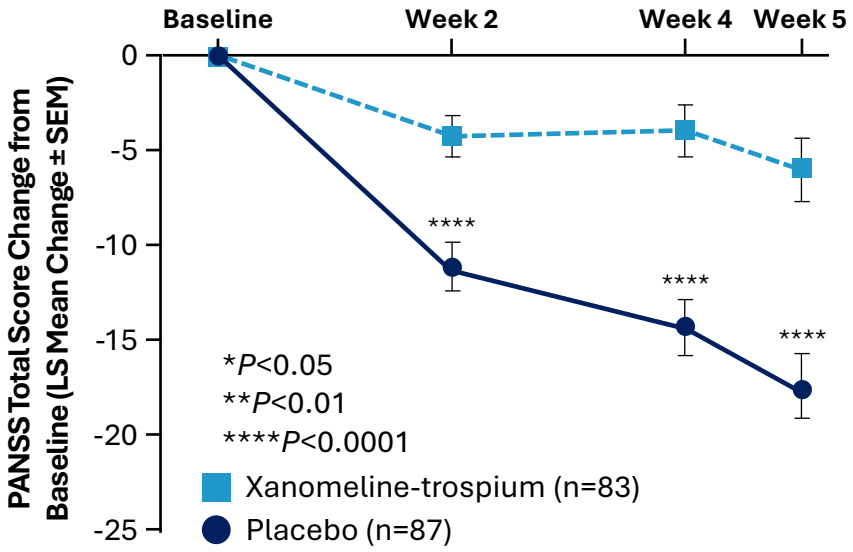


CATIE = Clinical Antipsychotic Trials of Intervention Effectiveness.

Kay SR, et al. *Schizophr Bull*. 1987;13(2):261-276. Leucht S, et al. *Schizophr Res*. 2005;79(2-3):231-238. Chwastiak LA, et al. *Psychiatr Serv*. 2006;57(8):1102-1109. Hermes ED, et al. *J Clin Psychiatry*. 2012;73(4):526-532. Berwaerts J, et al. *JAMA Psychiatry*. 2015;72(8):830-839.

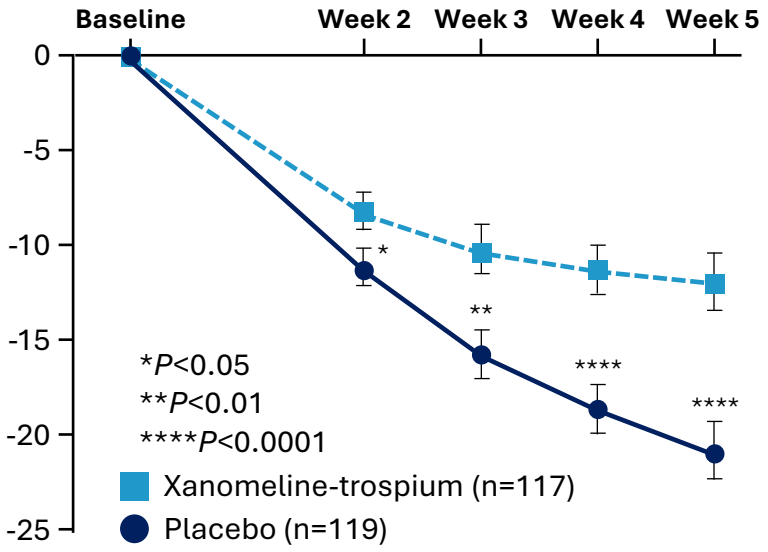
Xanomeline/Trospium Showed Consistent Efficacy in All Short-Term Phase 2 & 3 Trials

EMERGENT-1 (Phase 2)



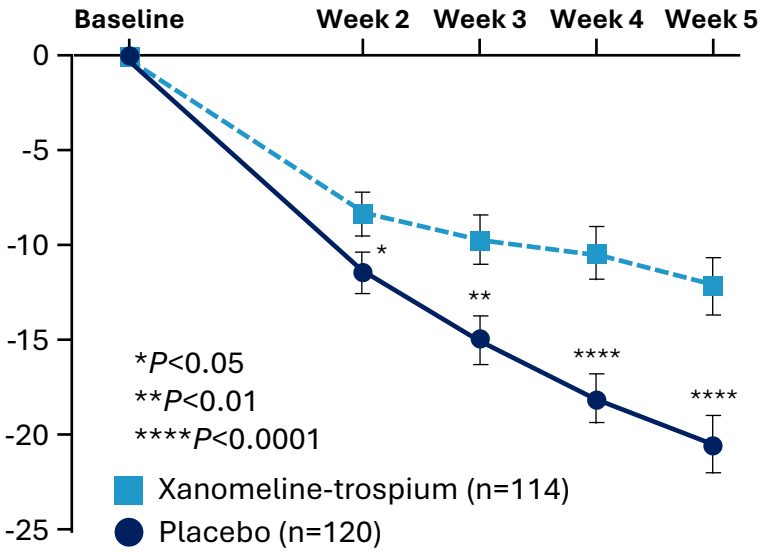
11.6-point reduction vs placebo at week 5
Effect size=0.81

EMERGENT-2 (Phase 3)



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

EMERGENT-3 (Phase 3)



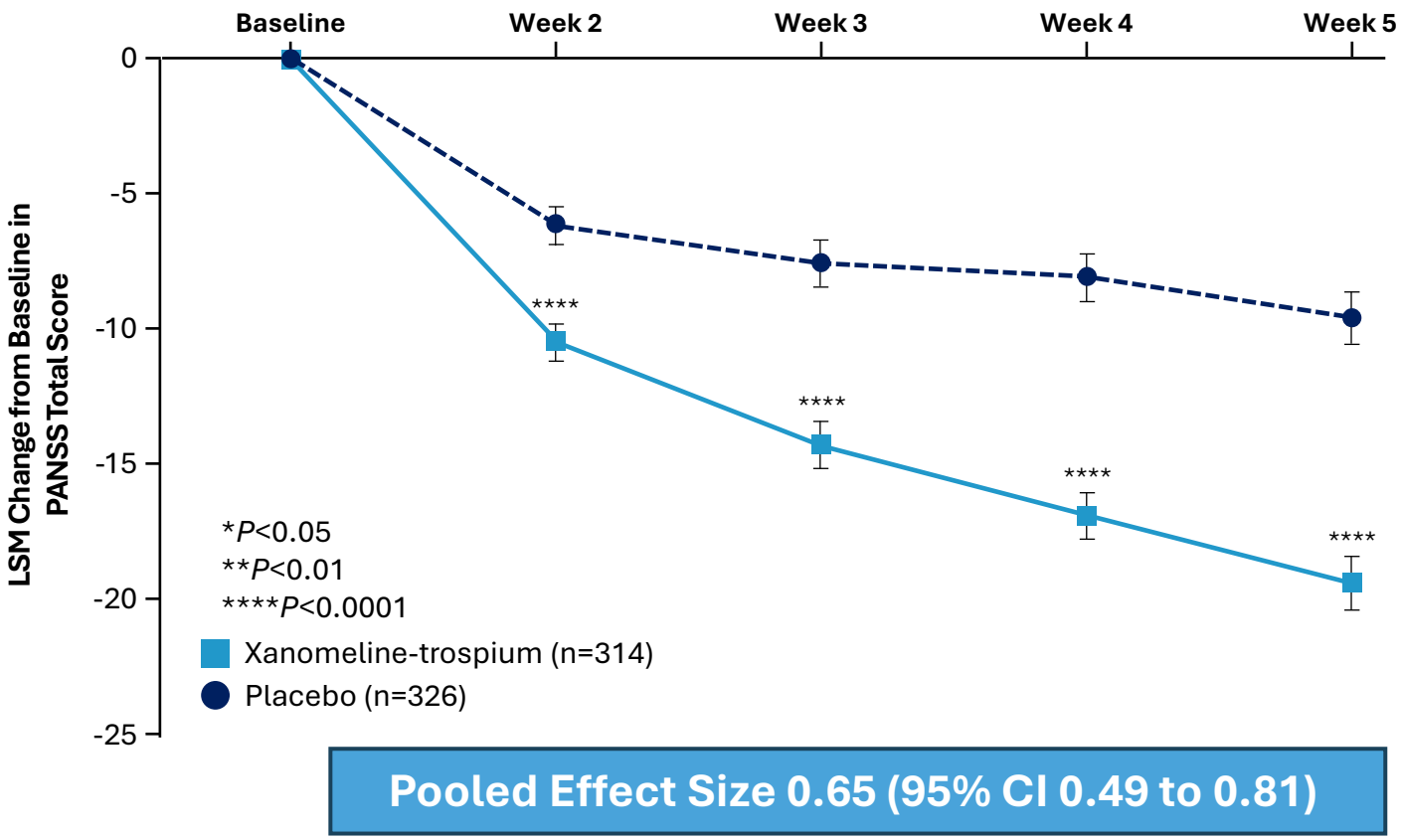
8.4-point reduction vs placebo at week 5
Effect size=0.60

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.

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

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



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

Comparative Efficacy by Network Meta-Analysis

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

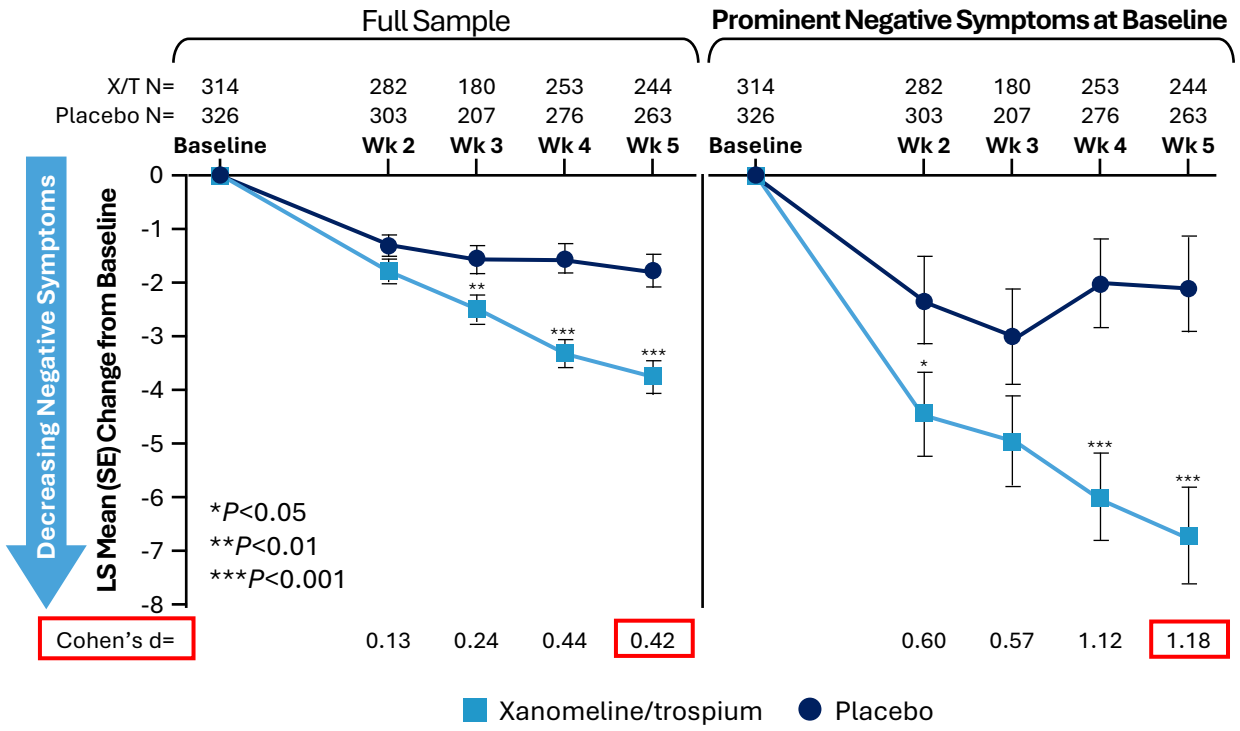
While Head-to-Head studies are necessary to make valid comparisons, xanomeline/trospium's consistent, robust efficacy stacks up well with historical antipsychotics

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

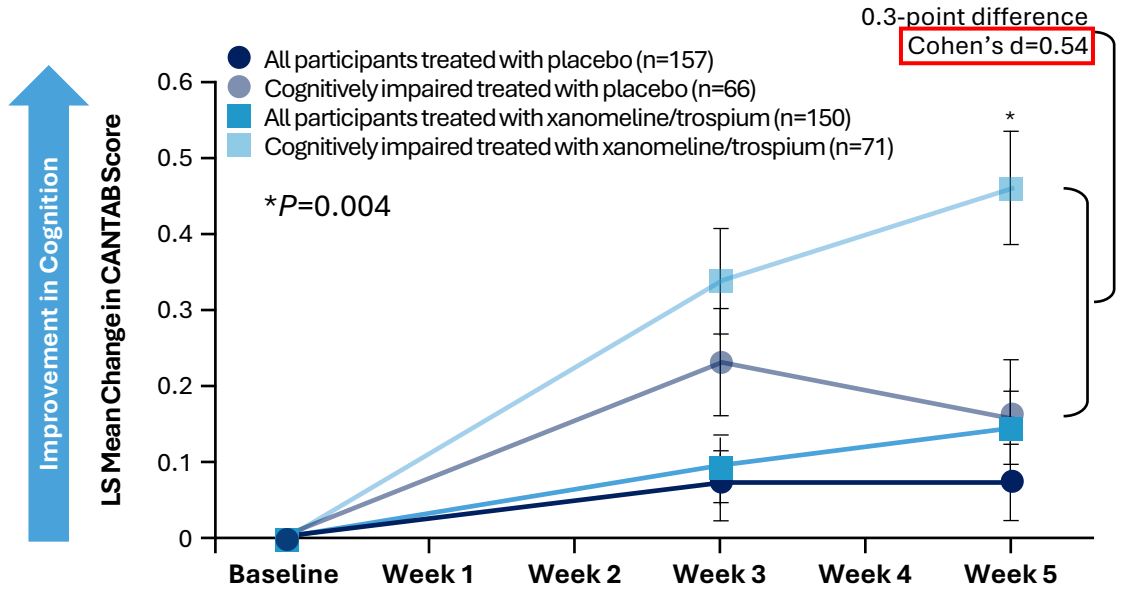
Kaul I, et al. *Schizophrenia (Heidelb).* 2024;10(1):102. Huhn M, et al. *Lancet.* 2019;394(10202):939-951.

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

Negative Symptoms



Cognitive Dysfunction



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

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

CANTAB = Cambridge Neuropsychological Test Automated Battery.

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

Xanomeline/Trospium Has a Very Different AE Profile from That of Any Antipsychotic

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

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

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

Other AEs of Interest in Phase 3 Studies

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

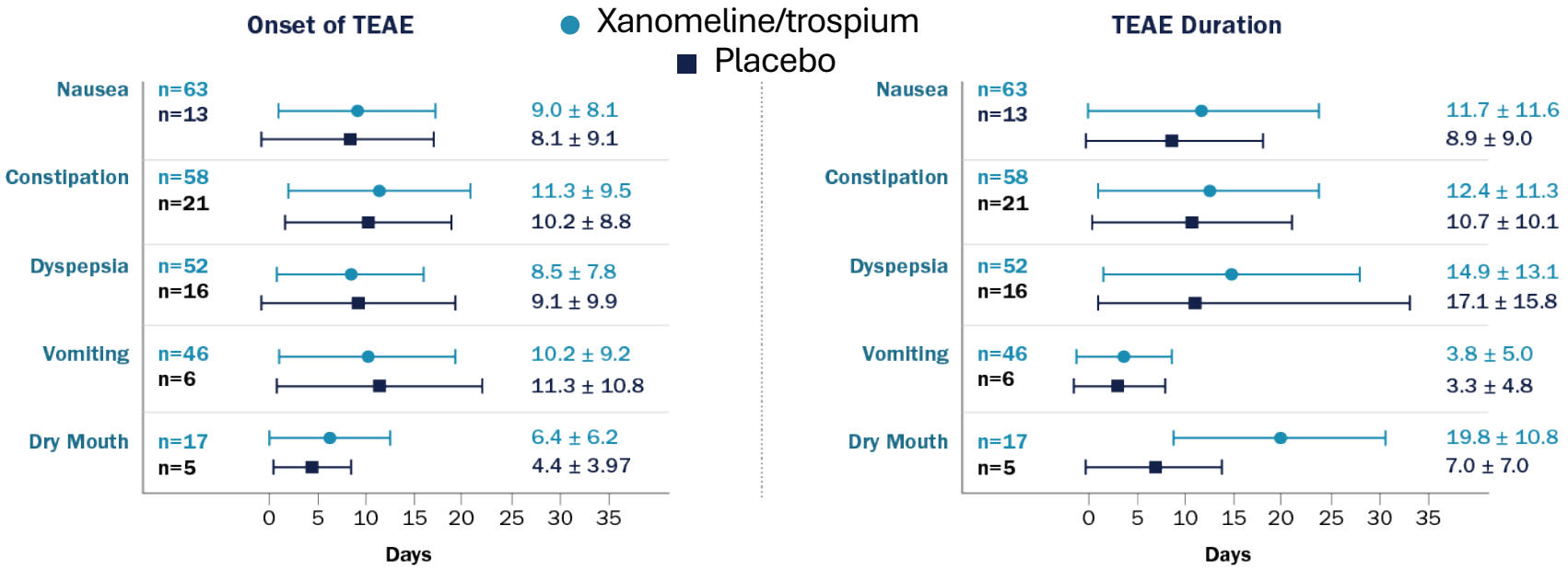
No differences between groups in akathisia, parkinsonism, or tardive dyskinesia

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

X-T = xanomeline-trospium; ALT = alanine transaminase; AST = aspartate aminotransferase; ULN = upper limit of normal.

Cobenfy™ (xanomeline and trospium chloride) Prescribing Information. Drugs@FDA: FDA Approved Drugs. Accessed August 20, 2025. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/216158s000lbl.pdf.

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



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

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

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

TEAE = treatment-emergent adverse event.

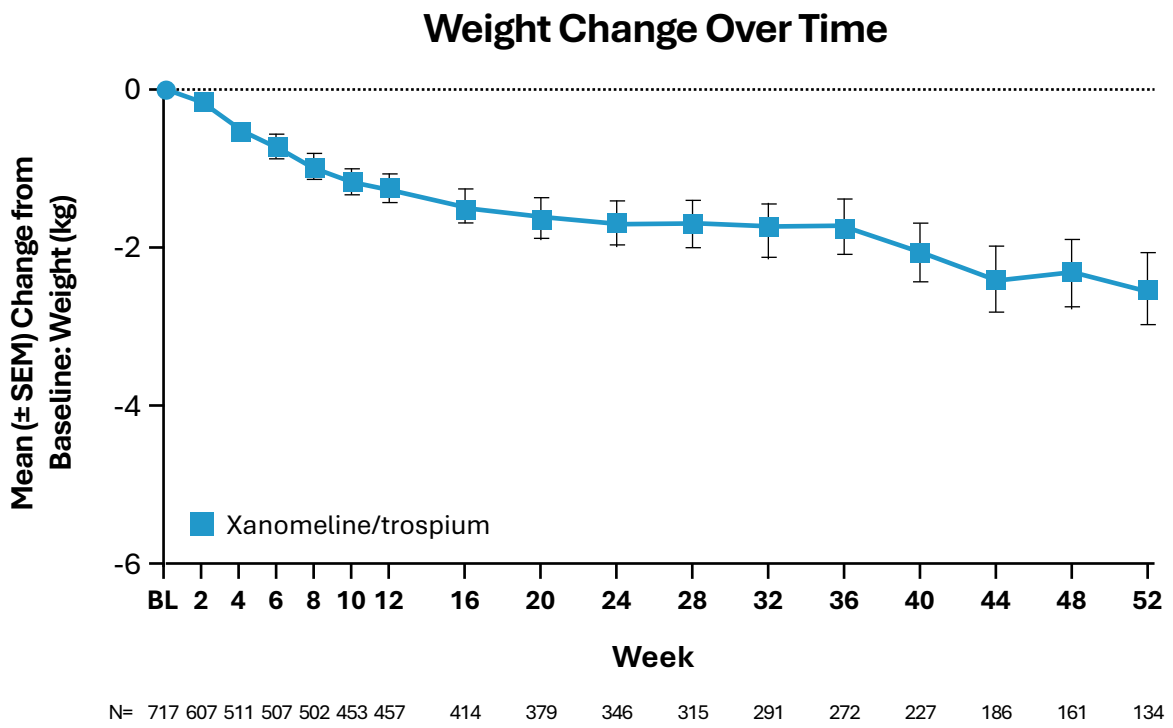
Kaul I, et al. *J Clin Psychiatry*. 2025;86(1):24m15497.

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

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

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

D/C due to TEAEs was 14.9%



After 52 Weeks

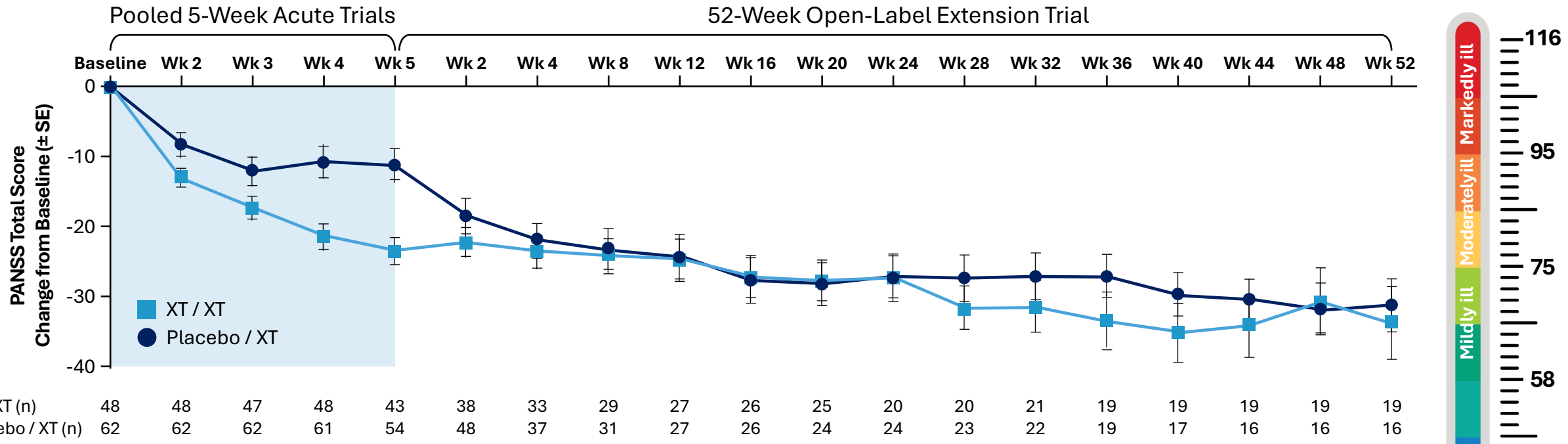
Mean body weight change:	- 5.6 lbs
Body weight increase of ≥7%:	4.1%
Body weight **decrease** of ≥7%:	17.6%

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

TE=treatment Emergent; AE=Adverse Event; D/C=Discontinuation

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

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



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

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

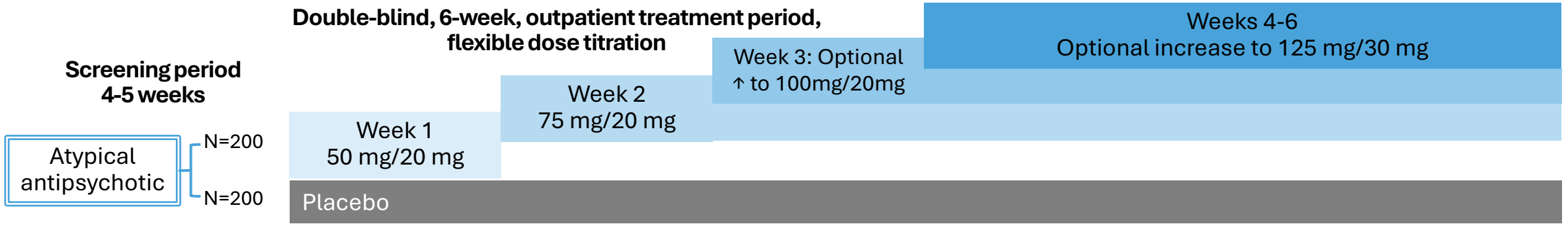
69% of patients achieved ≥30% reduction in PANSS total scores

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

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.

Evaluation of Xanomeline/Trospium for Adjunctive Treatment of Schizophrenia



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

Xanomeline/trospium reduced PANSS by 2 points more than placebo, but did not reach statistical significance (*P*=0.1 1)

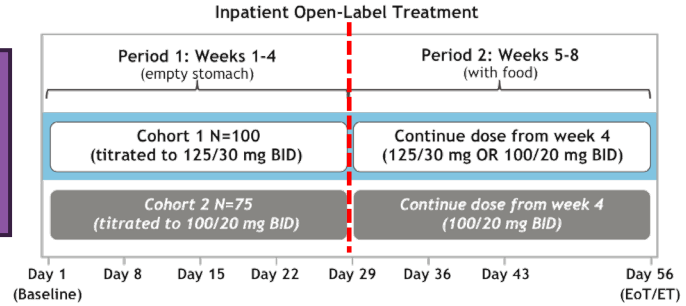
Safety and tolerability was consistent with prior clinical trials of xanomeline/trospium as monotherapy for schizophrenia

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

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

New Interim Clinical Data on the Effects of Food on Xanomeline-Trospium May Inform Treatment

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

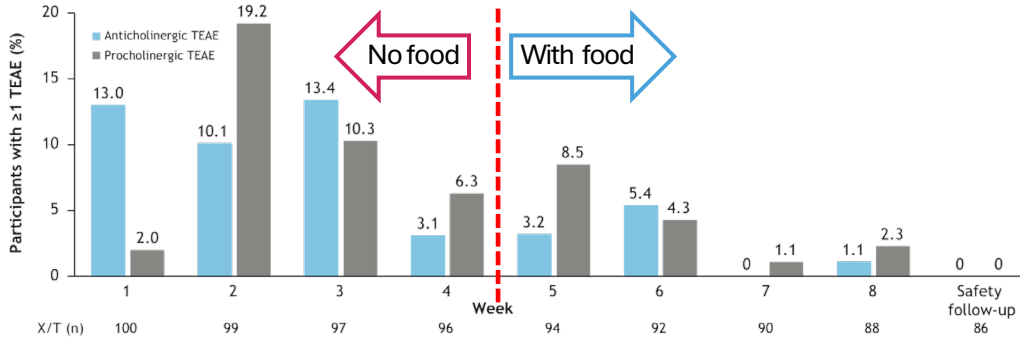


And utilized a slower titration:

50mg/20mg x1 wk

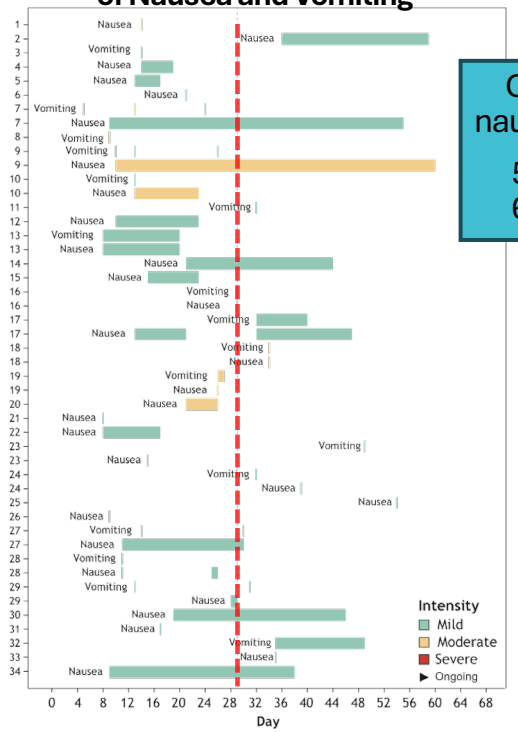
100mg/20/mg x1 wk

Prevalence of anticholinergic or procholinergic TEAE by week



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

Per Patient Incidence and Duration of Nausea and Vomiting



Of those who did not have nausea or vomiting in period 1:

5 had nausea in period 2,
6 had vomiting in period 2

Potential Practice Implications

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

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

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

Key Learning Points

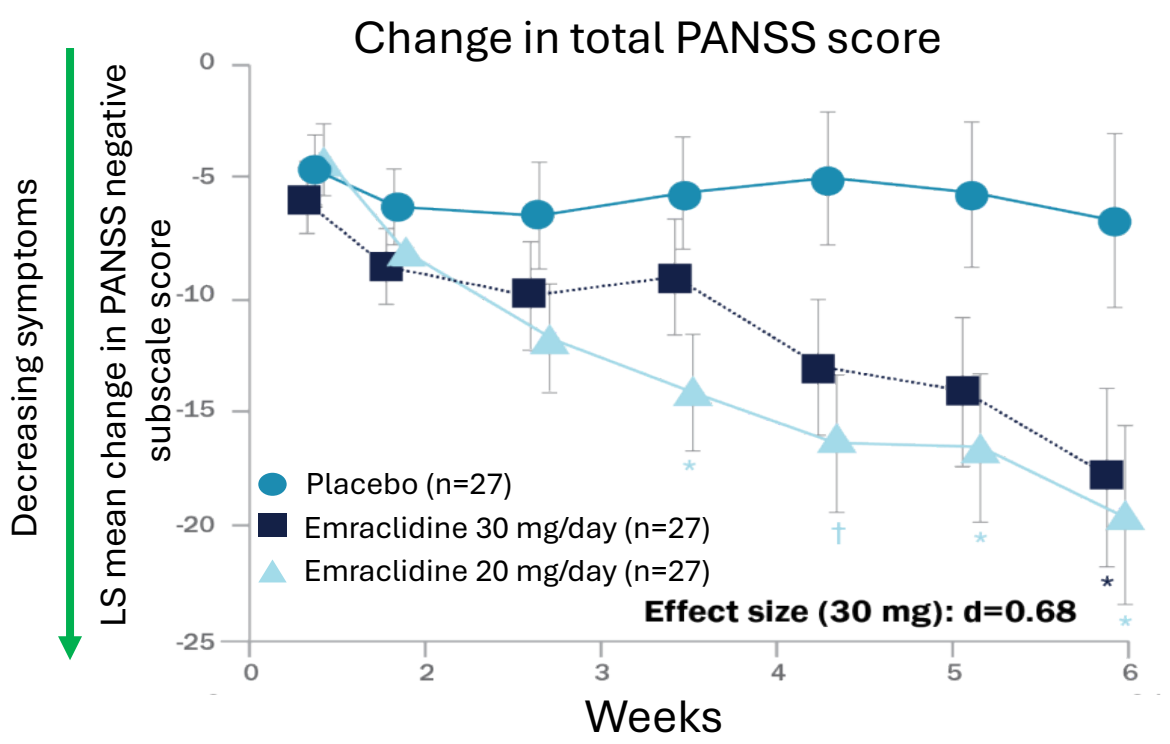
- ✓ **Trospium largely mitigated the procholinergic adverse effects of xanomeline**. AE-related discontinuation was 6% with xanomeline/trospium vs 4% with placebo

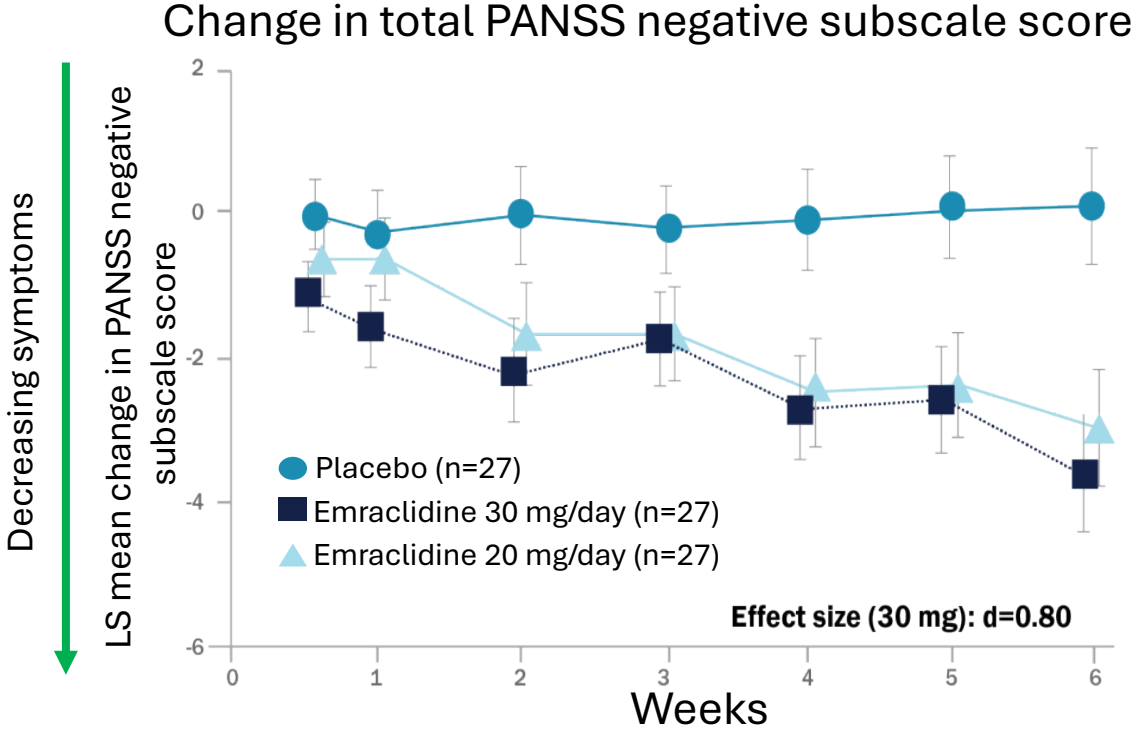
- ✓ There is a replicated signal across all phase 2b/3 studies of **improved cognitive functioning** in those with more significant baseline cognitive dysfunction

- ✓ In the **EMERGENT-4 open-label extension** study of patients with schizophrenia who completed the two phase 3 clinical trials, treatment with xanomeline-trospium was associated with a mean PANSS total score change of -32.6
  - ✓ **69% of patients achieved ≥30% reduction in PANSS total scores**

Other Activators of Muscarinic Receptors

Phase 1B Study of M_4 Positive Allosteric Modulator Emraclidine





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

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

Discontinuation rate was 22% in each arm.

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

Safety and Tolerability of Emraclidine in Phase 1B Study

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

No clinically meaningful findings relative to placebo were observed, including

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

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

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

CPK = creatine phosphokinase; ECG = electrocardiogram.

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

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

Change from Baseline to Week 6 in PANSS Total Score

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

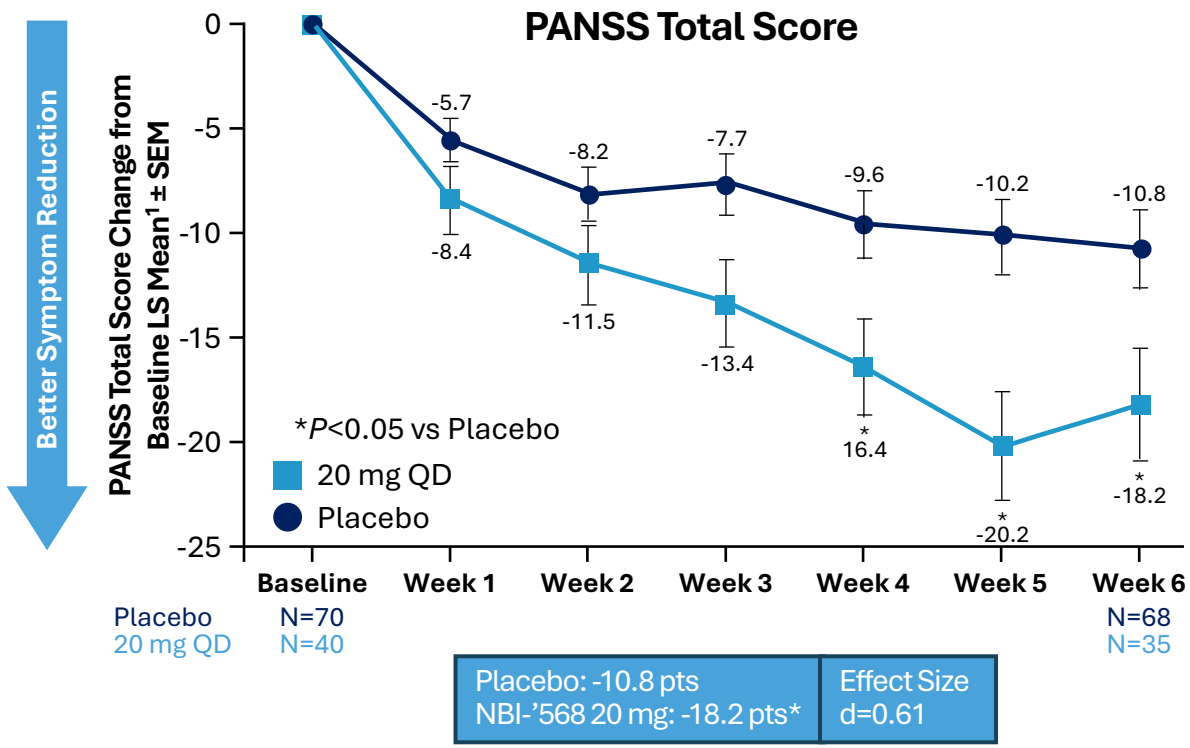
Efficacy
No significant improvement in PANSS scores

Tolerability
Well-tolerated with stable safety profile

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

Positive Phase 2a Results for NBI-1117568 M_4 Agonist with 500-fold Selectivity vs $M_{1/2/3/5}$

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



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

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

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

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

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

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

Nash A, et al. Once-Daily NBI-1117568, a Highly Selective Orthosteric M 4 Muscarinic Receptor Agonist, Demonstrates Meaningful Improvements in PANSS Total Score and Is Well Tolerated in Adults With Schizophrenia: Phase 2 Study Results. Presented at the ASCP Annual Meeting May 27-30, 2025; Scottsdale, AZ. https://clinicaltrials.gov/study/NCT06963034. Accessed 8-20–25. https://clinicaltrials.gov/study/NCT07105098. Accessed 8-20-25.

Other Investigational Muscarinic Agents

	Mechanism	Development Stage
NMRA-266	M_4 PAM	Placed on clinical hold by FDA 4/2024 due to pre-clinical data showing convulsions in rabbits
NMRA-861	M_4 PAM	Phase 1 initiated 7/2025, explicitly noted no rabbit convulsions in preclinical work
ML-007C-MA	M_4/M_1 Agonist + PAC	3 phase 1 trials without PAC completed. Most AEs in phase 1 trial with PAC were mild and transient
NBI-1117569	M_4 Preferring Agonist	Phase 1 data expected this year
NBI-1117570	M_4/M_1 Agonist	Phase 1 data and Phase 2 initiation expected 2025
NBI-1117567	M_1 Preferring Agonist	Phase 1 data expected 2025
NBI-???????	M_1 Selective Agonist	Preclinical

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

PAC = peripherally-acting anticholinergic.

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

Panel Discussion

Implications for the Evolving Schizophrenia Treatment Landscape

6 Practical Issues in the Use of Muscarinics in Everyday Clinical Practice

1.

2.

3.

4.

5.

6.

1

How do I overcome nausea with muscarinics?

2

Are muscarinics a monotherapy or a combination intervention?

3

Are muscarinics for “early” schizophrenia treatment or for “late” schizophrenia treatment?

4

What about the use of muscarinics with anticholinergics, or anticholinergic antipsychotics?

5

How do we identify the “right” patient for muscarinic treatment? And who are the “wrong” patients for such treatment?

6

How do we use Motivational Interviewing techniques when we are recommending muscarinic medication to a patient for the first time?

Practical Take-Aways

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

Questions?