A New Frontier in Schizophrenia:
Muscarinic Modulators and Their Role in Treatment

Faculty

Brooke Kempf, PMHNP-BC

- *Indiana University Indianapolis*
- *Indianapolis, IN*

Greg Mattingly, MD

- *Associate Clinical Professor, Washington University*
- *CEO, Midwest Research Group*
- *President, American Professional Society for ADHD and Related Disorders*

Faculty Disclosures

- **Brooke Kempf, PMHNP-BC:** Advisory Board - Alkermes, Axsome, BMS Intracellular, Johnson & Johnson, Janssen, Teva; Speakers Bureau - Alkermes, Axsome, BMS, Intracellular, Johnson & Johnson, Janssen, Teva.

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

Disclosures

- The faculty have been informed of their responsibility to disclose to the audience if they will be discussing off-label or investigational use(s) of drugs, products, and/or devices (any use not approved by the US Food and Drug Administration).

- Applicable CME staff have no relationships to disclose relating to the subject matter of this activity.

- This activity has been independently reviewed for balance.

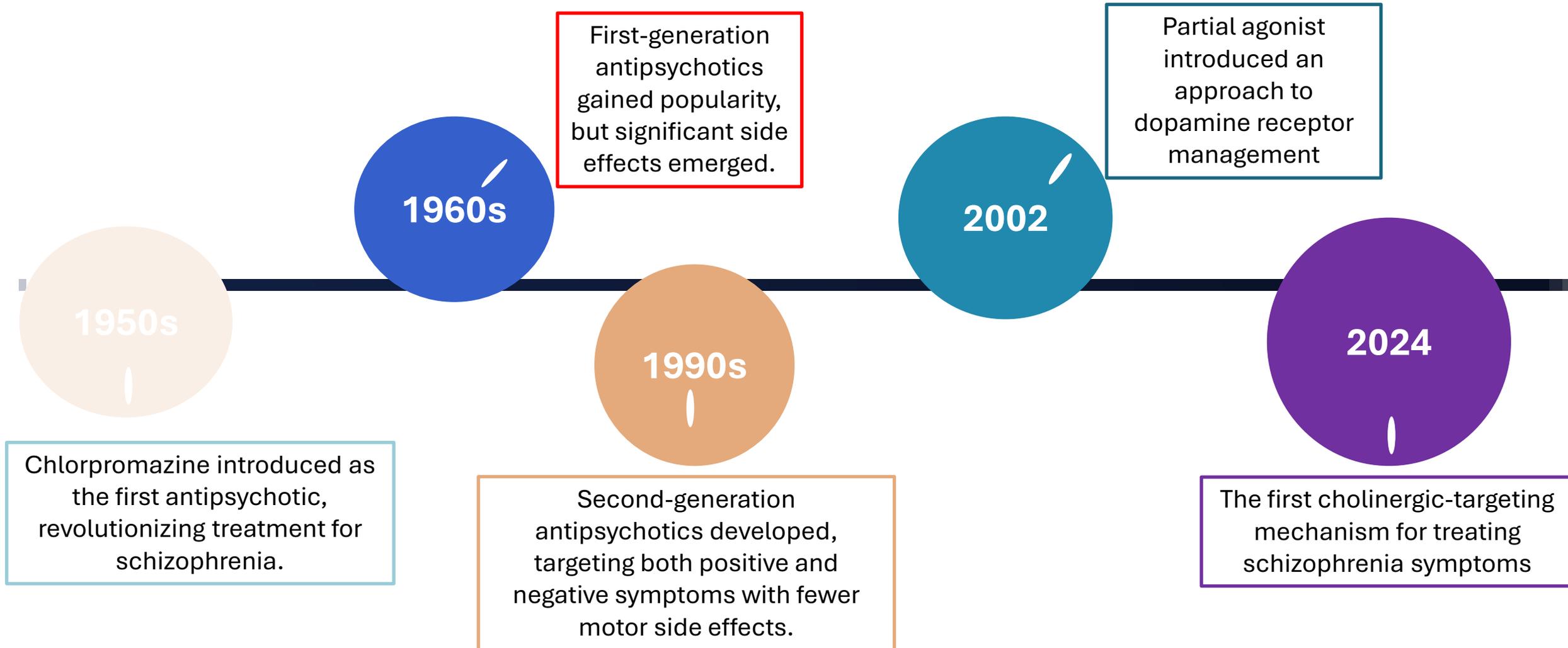References

Learning Objectives

- Describe the evidence supporting muscarinic acetylcholine receptor activation as a therapeutic approach in schizophrenia

- Evaluate the most up-to-date clinical trial data associated with both approved and investigational muscarinic acetylcholine receptor activators for schizophrenia

- Summarize the practical considerations for integrating muscarinic receptor activators into schizophrenia management, including treatment selection and sequencing and patient care optimization
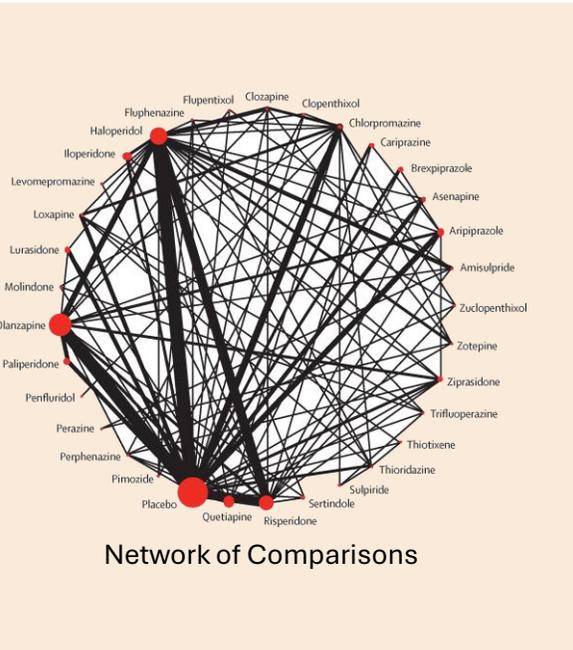
References

Overview of the Current Schizophrenia Treatment Landscape

Has Treatment for Schizophrenia Changed?

1950s

Chlorpromazine introduced as the first antipsychotic, revolutionizing treatment for schizophrenia.

1960s

First-generation antipsychotics gained popularity, but significant side effects emerged.

1990s

Second-generation antipsychotics developed, targeting both positive and negative symptoms with fewer motor side effects.

2002

Partial agonist introduced an approach to dopamine receptor management

2024

The first cholinergic-targeting mechanism for treating schizophrenia symptoms

Little Variability of Efficacy in Current Treatments

Network of Comparisons

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

Better efficacy

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

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

Overall Symptoms

	SMD (95% CrI)
CLO (n=270)	–0·89 (–1·08 to –0·71)
AMI (n=705)	–0·73 (–0·89 to –0·58)
ZOT (n=245)	–0·61 (–0·82 to –0·40)
THIOT (n=71)	–0·63 (–0·97 to –0·30)
OLA (n=5602)	–0·56 (–0·62 to –0·50)
RIS (n=3827)	–0·55 (–0·62 to –0·48)
PERPH (n=378)	–0·56 (–0·75 to –0·38)
THIOR (n=121)	–0·54 (–0·82 to –0·27)
ZUC (n=178)	–0·51 (–0·75 to –0·27)
PAL (n=1584)	–0·49 (–0·59 to –0·38)
HAL (n=4400)	–0·47 (–0·53 to –0·41)
SUL (n=66)	–0·48 (–0·87 to –0·09)
LOX (n=289)	–0·45 (–0·63 to –0·26)
CPZ (n=741)	–0·44 (–0·57 to –0·31)
FPX (n=88)	–0·43 (–0·77 to –0·08)
CPX (n=60)	–0·42 (–0·78 to –0·06)
MOL (n=67)	–0·42 (–0·78 to –0·04)
PEN (n=14)	–0·39 (–1·13 to 0·36)
QUE (n=3002)	–0·42 (–0·50 to –0·33)
ARI (n=1926)	–0·41 (–0·50 to –0·32)
ZIP (n=1228)	–0·41 (–0·52 to –0·30)
SER (n=868)	–0·40 (–0·54 to –0·26)
ASE (n=1027)	–0·39 (–0·52 to –0·26)
LUR (n=1363)	–0·36 (–0·48 to –0·24)
PIM (n=44)	–0·30 (–0·75 to 0·14)
PERA (n=51)	–0·29 (–0·72 to 0·14)
CAR (n=999)	–0·34 (–0·49 to –0·20)
ILO (n=2157)	–0·33 (–0·44 to –0·22)
FLU (n=53)	–0·24 (–0·62 to 0·13)
TRIFLU (n=123)	–0·24 (–0·53 to 0·05)
BRE (n=1180)	–0·26 (–0·39 to –0·12)
LEV (n=21)	–0·03 (–0·59 to 0·52)
PBO (n=8067)	0·00 (0·00 to 0·00)

Positive Symptoms

	SMD (95% CrI)
AMI (n=626)	–0·69 (–0·86 to –0·52)
RIS (n=3351)	–0·61 (–0·68 to –0·54)
CLO (n=31)	–0·64 (–1·09 to –0·19)
OLA (n=4227)	–0·53 (–0·60 to –0·46)
PAL (n=1373)	–0·53 (–0·65 to –0·42)
CPZ (n=190)	–0·57 (–0·88 to –0·25)
HAL (n=3042)	–0·49 (–0·56 to –0·41)
ASE (n=734)	–0·47 (–0·63 to –0·32)
PERPH (n=311)	–0·45 (–0·66 to –0·24)
ZUC (n=50)	–0·43 (–0·89 to 0·03)
ZIP (n=1102)	–0·43 (–0·53 to –0·32)
SER (n=876)	–0·40 (–0·54 to –0·27)
QUE (n=2935)	–0·40 (–0·49 to –0·31)
FPX (n=73)	–0·38 (–0·77 to 0·01)
ARI (n=1451)	–0·38 (–0·48 to –0·28)
LUR (n=1165)	–0·33 (–0·45 to –0·20)
CAR (n=999)	–0·30 (–0·45 to –0·16)
ZOT (n=35)	–0·21 (–0·72 to 0·31)
ILO (n=918)	–0·30 (–0·43 to –0·17)
LEV (n=21)	–0·18 (–0·75 to 0·39)
BRE (n=1180)	–0·17 (–0·31 to –0·04)
PBO (n=6489)	0·00 (0·00 to 0·00)

Negative Symptoms

	SMD (95% CrI)
CLO (n=159)	–0·62 (–0·84 to –0·39)
ZOT (n=149)	–0·54 (–0·77 to –0·31)
AMI (n=691)	–0·50 (–0·64 to –0·37)
OLA (n=4224)	–0·45 (–0·51 to –0·39)
ASE (n=733)	–0·42 (–0·55 to –0·29)
PERPH (n=311)	–0·42 (–0·59 to –0·25)
RIS (n=3435)	–0·37 (–0·43 to –0·31)
PAL (n=1373)	–0·37 (–0·47 to –0·28)
SER (n=864)	–0·37 (–0·48 to –0·25)
CPZ (n=420)	–0·35 (–0·51 to –0·18)
ZIP (n=959)	–0·33 (–0·43 to –0·23)
ARI (n=1353)	–0·33 (–0·41 to –0·24)
CAR (n=999)	–0·32 (–0·44 to –0·20)
QUE (n=2994)	–0·31 (–0·38 to –0·24)
LUR (n=1165)	–0·29 (–0·39 to –0·18)
HAL (n=3331)	–0·29 (–0·35 to –0·23)
ZUC (n=50)	–0·17 (–0·59 to 0·23)
BRE (n=1180)	–0·25 (–0·36 to –0·14)
LEV (n=21)	–0·09 (–0·57 to 0·40)
ILO (n=918)	–0·22 (–0·33 to –0·11)
FPX (n=73)	–0·10 (–0·45 to 0·25)
PBO (n=6663)	0·00 (0·00 to 0·00)

Favours antipsychotic ← → Favours placebo

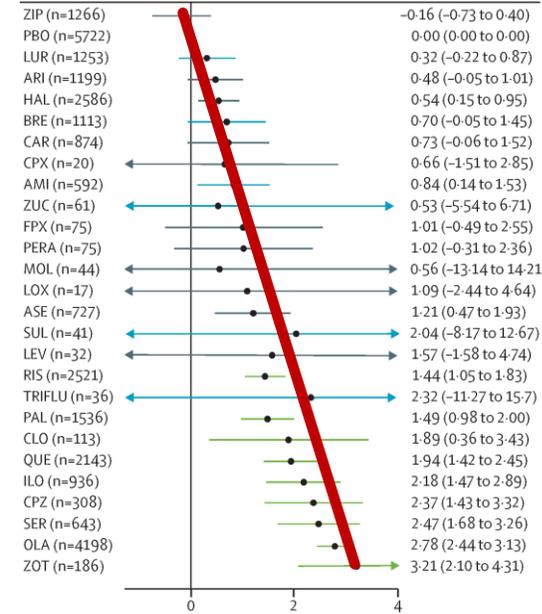# Antipsychotics Differ More in Their Side Effects than in Their Efficacy

Efficacy has not really improved at all. Treatment variability seems to be only in side effects, which are still problematic.
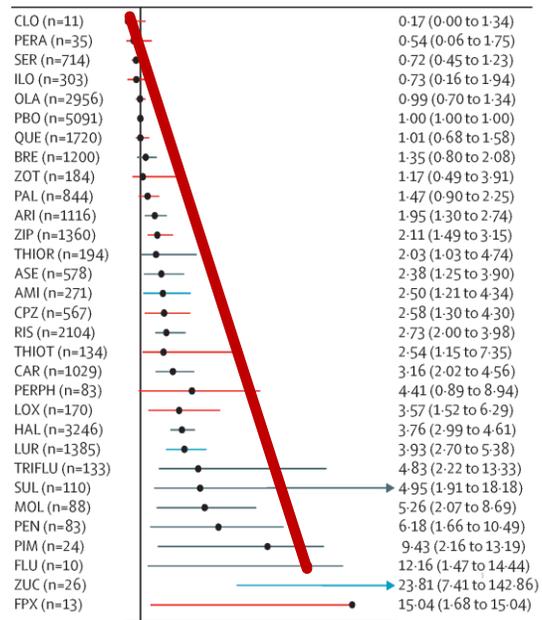
More patients dropped out due to inefficacy (40%) than due to adverse events (20%)

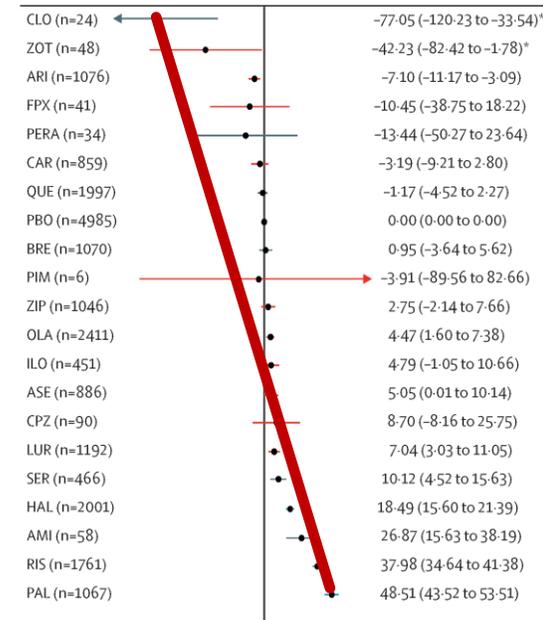**Trend lines include highest- and lowest-ranked agents available in the US**
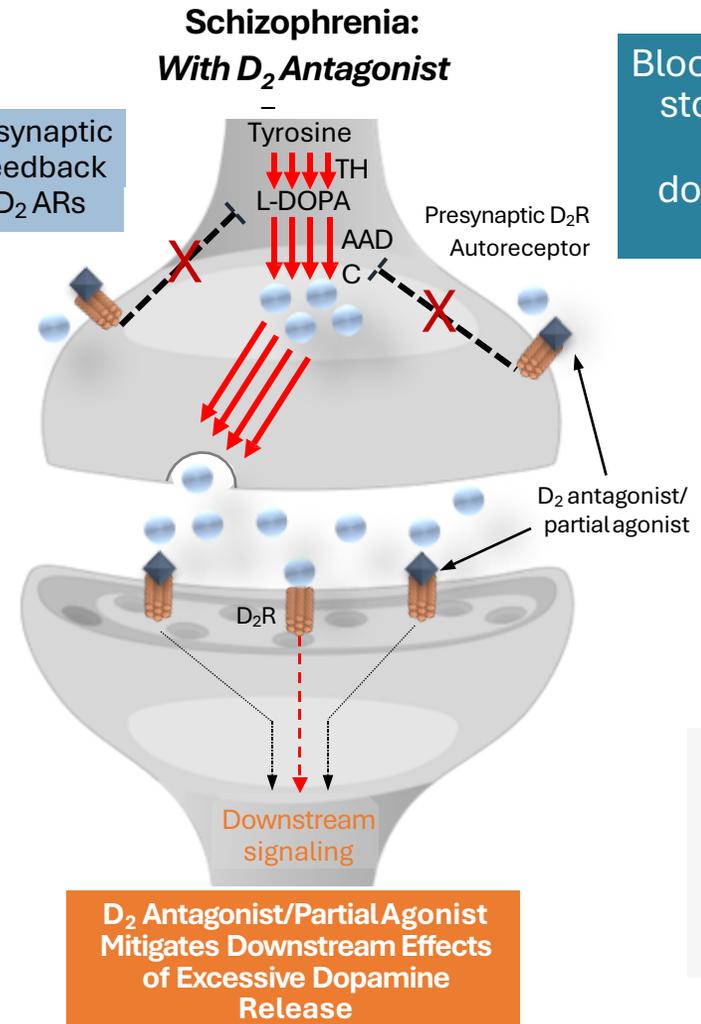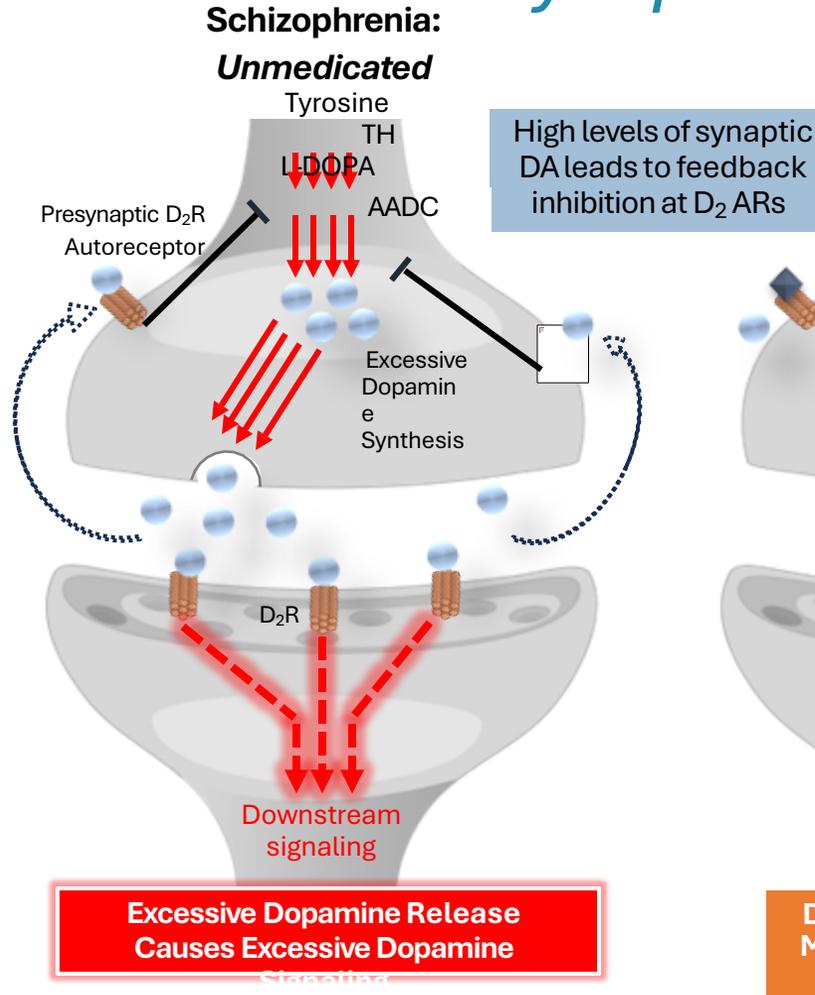
Weight Gain

Agent	MD (95% CrI)
ZIP (n=1266)	−0·16 (−0·73 to 0·40)
PBO (n=5722)	0·00 (0·00 to 0·00)
LUR (n=1253)	0·32 (−0·22 to 0·87)
ARI (n=1199)	0·48 (−0·05 to 1·01)
HAL (n=2586)	0·54 (0·15 to 0·95)
BRE (n=1113)	0·70 (−0·05 to 1·45)
CAR (n=874)	0·73 (−0·06 to 1·52)
CPX (n=20)	0·66 (−1·51 to 2·85)
AMI (n=592)	0·84 (0·14 to 1·53)
ZUC (n=61)	0·53 (−5·54 to 6·71)
FPX (n=75)	1·01 (−0·49 to 2·55)
PERA (n=75)	1·02 (−0·31 to 2·36)
MOL (n=44)	0·56 (−13·14 to 14·21)
LOX (n=17)	1·09 (−2·44 to 4·64)
ASE (n=727)	1·21 (0·47 to 1·93)
SUL (n=41)	2·04 (−8·17 to 12·67)
LEV (n=32)	1·57 (−1·58 to 4·74)
RIS (n=2521)	1·44 (1·05 to 1·83)
TRIFLU (n=36)	2·32 (−11·27 to 15·7)
PAL (n=1536)	1·49 (0·98 to 2·00)
CLO (n=113)	1·89 (0·36 to 3·43)
QUE (n=2143)	1·94 (1·42 to 2·45)
ILO (n=936)	2·18 (1·47 to 2·89)
CPZ (n=308)	2·37 (1·43 to 3·32)
SER (n=643)	2·47 (1·68 to 3·26)
OLA (n=4198)	2·78 (2·44 to 3·13)
ZOT (n=186)	3·21 (2·10 to 4·31)

Akathisia

Agent	RR (95% CrI)
CLO (n=11)	0·17 (0·00 to 1·34)
PERA (n=35)	0·54 (0·06 to 1·75)
SER (n=714)	0·72 (0·45 to 1·23)
ILO (n=303)	0·73 (0·16 to 1·94)
OLA (n=2956)	0·99 (0·70 to 1·34)
PBO (n=5091)	1·00 (1·00 to 1·00)
QUE (n=1720)	1·01 (0·68 to 1·58)
BRE (n=1200)	1·35 (0·80 to 2·08)
ZOT (n=184)	1·17 (0·49 to 3·91)
PAL (n=844)	1·47 (0·90 to 2·25)
ARI (n=1116)	1·95 (1·30 to 2·74)
ZIP (n=1360)	2·11 (1·49 to 3·15)
THIOR (n=194)	2·03 (1·03 to 4·74)
ASE (n=578)	2·38 (1·25 to 3·90)
AMI (n=271)	2·50 (1·21 to 4·34)
CPZ (n=567)	2·58 (1·30 to 4·30)
RIS (n=2104)	2·73 (2·00 to 3·98)
THIOT (n=134)	2·54 (1·15 to 7·35)
CAR (n=1029)	3·16 (2·02 to 4·56)
PERPH (n=83)	4·41 (0·89 to 8·94)
LOX (n=170)	3·57 (1·52 to 6·29)
HAL (n=3246)	3·76 (2·99 to 4·61)
LUR (n=1385)	3·93 (2·70 to 5·38)
TRIFLU (n=133)	4·83 (2·22 to 13·33)
SUL (n=110)	4·95 (1·91 to 18·18)
MOL (n=88)	5·26 (2·07 to 8·69)
PEN (n=83)	6·18 (1·66 to 10·49)
PIM (n=24)	9·43 (2·16 to 13·19)
FLU (n=10)	12·16 (1·47 to 14·44)
ZUC (n=26)	23·81 (7·41 to 142·86)
FPX (n=13)	15·04 (1·68 to 15·04)

Prolactin Elevation

Agent	MD (95% CrI)
CLO (n=24)	−77·05 (−120·23 to −33·54)*
ZOT (n=48)	−42·23 (−82·42 to −1·78)*
ARI (n=1076)	−7·10 (−11·17 to −3·09)
FPX (n=41)	−10·45 (−38·75 to 18·22)
PERA (n=34)	−13·44 (−50·27 to 23·64)
CAR (n=859)	−3·19 (−9·21 to 2·80)
QUE (n=1997)	−1·17 (−4·52 to 2·27)
PBO (n=4985)	0·00 (0·00 to 0·00)
BRE (n=1070)	0·95 (−3·64 to 5·62)
PIM (n=6)	−3·91 (−89·56 to 82·66)
ZIP (n=1046)	2·75 (−2·14 to 7·66)
OLA (n=2411)	4·47 (1·60 to 7·38)
ILO (n=451)	4·79 (−1·05 to 10·66)
ASE (n=886)	5·05 (0·01 to 10·14)
CPZ (n=90)	8·70 (−8·16 to 25·75)
LUR (n=1192)	7·04 (3·03 to 11·05)
SER (n=466)	10·12 (4·52 to 15·63)
HAL (n=2001)	18·49 (15·60 to 21·39)
AMI (n=58)	26·87 (15·63 to 38·19)
RIS (n=1761)	37·98 (34·64 to 41·38)
PAL (n=1067)	48·51 (43·52 to 53·51)

Better Tolerability

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

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

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

D$_2$ Antagonists
A Postsynaptic Treatment for a Presynaptic Problem

Healthy Controls

Tyrosine
TH
L-DOPA
AADC
Dopamine

Presynaptic D$_2$R Autoreceptor

Presynaptic terminal

D$_2$R

Postsynaptic terminal

Downstream signaling

Schizophrenia:
Unmedicated

Tyrosine
TH
L-DOPA
AADC

Presynaptic D$_2$R Autoreceptor

Excessive Dopamine Synthesis

High levels of synaptic DA leads to feedback inhibition at D$_2$ ARs

D$_2$R

Downstream signaling

Schizophrenia:
With D$_2$ Antagonist

Tyrosine
TH
L-DOPA
AADC

Presynaptic D$_2$R Autoreceptor

D$_2$ antagonist/ partial agonist

D$_2$R

Downstream signaling

Blocking the D$_2$ autoreceptor stops feedback inhibition, resulting in more dopamine production and release

D$_2$ antagonists or partial agonists can mitigate excessive postsynaptic dopamine transmission...

...but paradoxically may also compound the problem.

Dopamine

D$_2$ receptor

D$_2$ antagonist/partial agonist

Normal Dopamine Release Normal Dopamine Signaling

Excessive Dopamine Release Causes Excessive Dopamine Signaling

D$_2$ Antagonist/Partial Agonist Mitigates Downstream Effects of Excessive Dopamine Release

D$_2$R = dopamine D$_2$ receptors; AR=Autoreceptor; DA = dopamine; TH = Tyrosine Hydroxylase; AADC = aromatic L-amino acid decarboxylase.
Halff EF, et al. *Trends in Neurosciences*. 2023;46 (1):60-74. Meyer JM. Ch 19 - *Pharmacotherapy of Psychosis and Mania*. In: Brunton LL, ed. Goodman & Gilman's Pharmacological Basis of Therapeutics. 14th Ed. Chicago, Illinois: McGraw-Hill; 2022: 357-84.

The Primary Dopamine Dysfunction In Schizophrenia Is not Post-Synaptic

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

▶ Effect sizes 0.63 to 1.25

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

▶ Also with moderate to large effect sizes

Whereas

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

▶ (Independent of the effects of antipsychotics)

It's also not in the mesolimbic pathway!

Surpise!

Estimated Mean Difference in Presynaptic Dopamine Function in Patients vs Controls

Larger in Schizophrenia vs.

Effect Size (Hedge's g)

P=0.003, g=0.39

*

P=0.002

P=0.09

*

P=0.005

0.8

0.6

0.4

0.2

0

Limbic Striatum

Associative Striatum

Sensorimotor Striatum

P=0.03, g=0.29
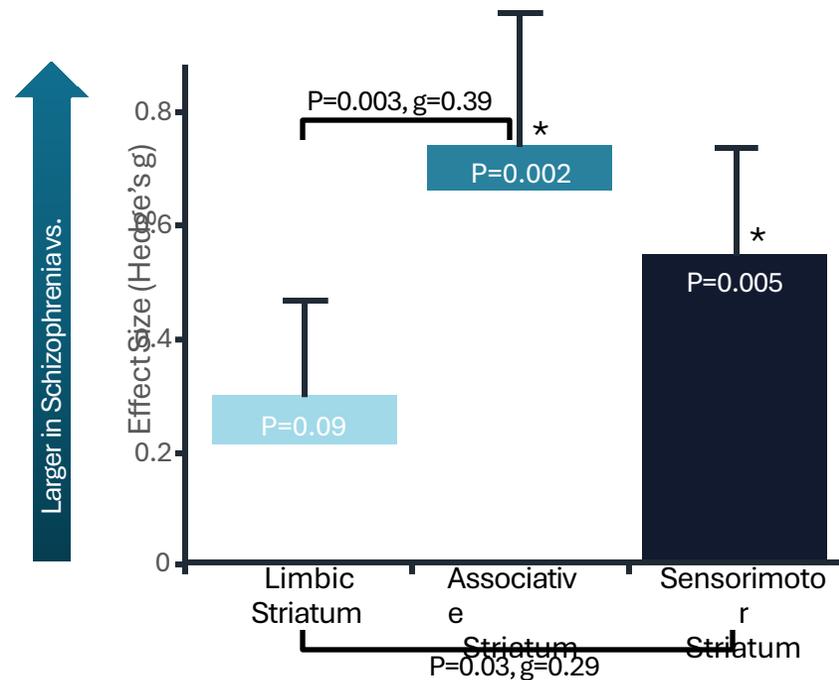
Modern studies with higher resolution imaging find:

• Dopaminergic function in humans is significantly elevated in associative and sensorimotor striatum

• ...but not in the limbic striatum, as in mouse models

Do D2-Binding Antipsychotics Help Reach Schizophrenia Treatment Goals?

Goal: Increase activity of *hypoactive* **mesolimbic** and **mesocortical** pathways to mediate negative and cognitive symptoms
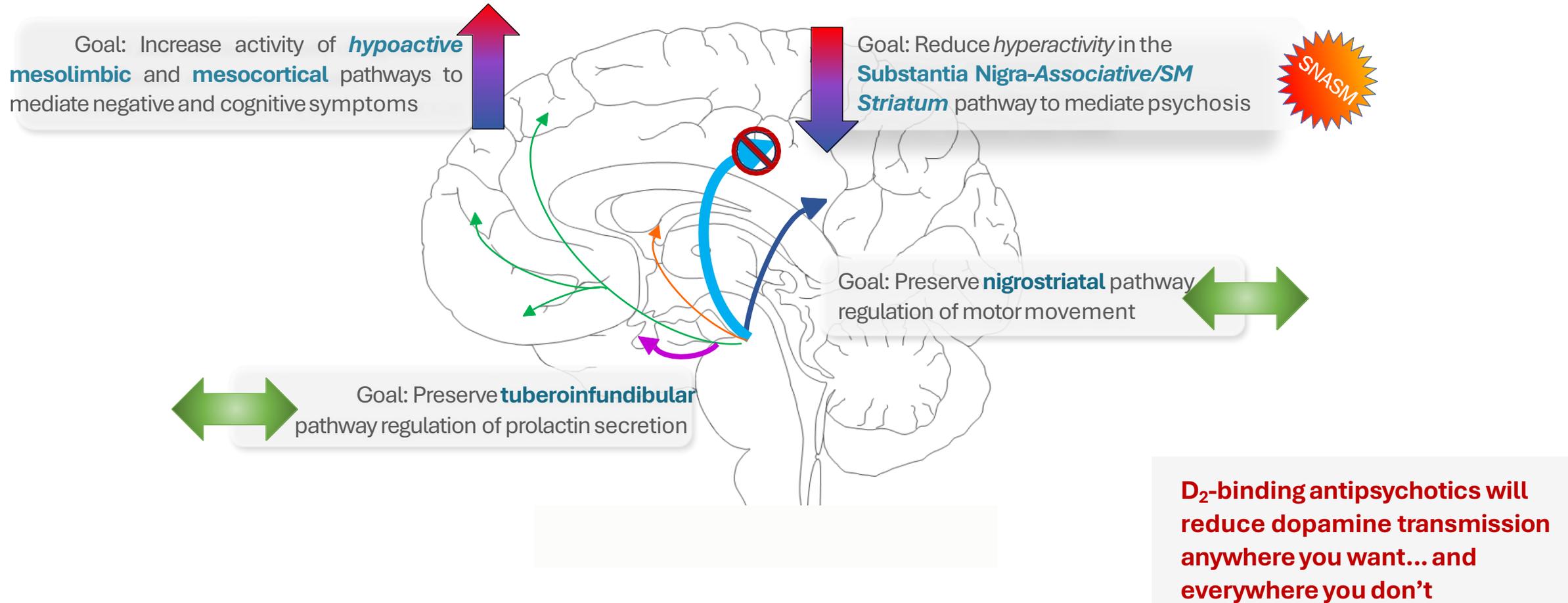
Goal: Reduce *hyperactivity* in the **Substantia Nigra-*Associative/SM Striatum*** pathway to mediate psychosis

SNASM

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

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

D$_2$-binding antipsychotics will reduce dopamine transmission anywhere you want… and everywhere you don't

What do we do when our bucket begins to overflow?

Maybe a presynaptic problem needs a presynaptic solution…?

Key Learning Points

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

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

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

References

There Was a Fork in the Road in the 1950s...

The antipsychotic action of chlorpromazine was discovered in 1952
However, another medication's antipsychotic efficacy was also noticed that year...

Reserpine

Reserpine is an irreversible inhibitor of VMAT 1 and 2.

- Inhibiting VMAT reduces the vesicular concentration of monoamines, e.g. dopamine.
- This results in less DA being released when the neuron fires.

▶ VMAT2 inhibition reduces DA release in the *CNS* which could cause substantial parkinsonism.
▶ VMAT1 inhibition reduces NE release in the *periphery* which could cause profound hypotension.

VMAT inhibitor
VMAT
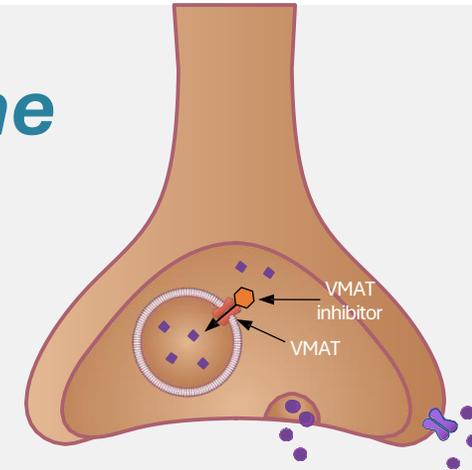
1954

- Tetrabenazine was created as a more tolerable alternative to reserpine, due to its *reversible* and *selective* VMAT2 inhibition.
- Review articles and trials comparing reserpine or tetrabenazine to chlorpromazine generally indicated comparable efficacy on average,
- but with a somewhat worse tolerability profile.

- But by the end of the decade, the field had largely chosen the path of creating successive iterations of chlorpromazine and its successors.

- Postsynaptic D_2 blockade has been the dominant paradigm ever since.

Potential for Antipsychotic Effect with Valbenazine

Valbenazine is a reversible VMAT2 inhibitor which has been approved for Tardive Dyskinesia since 2017. It is selectively converted to tetrabenazine's active [+]-α-HTBZ metabolite, its most potent and selective reversible of VMAT2
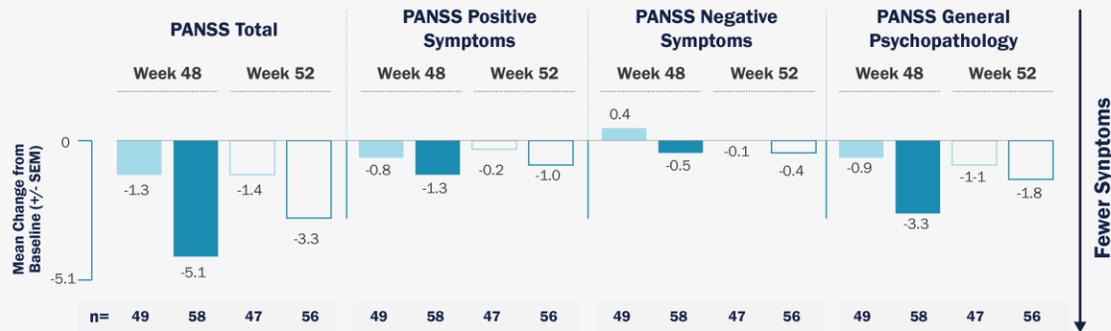
In Tardive Dyskinesia trials, a potential signal of symptom improvement was noted in participants with stable schizophrenia
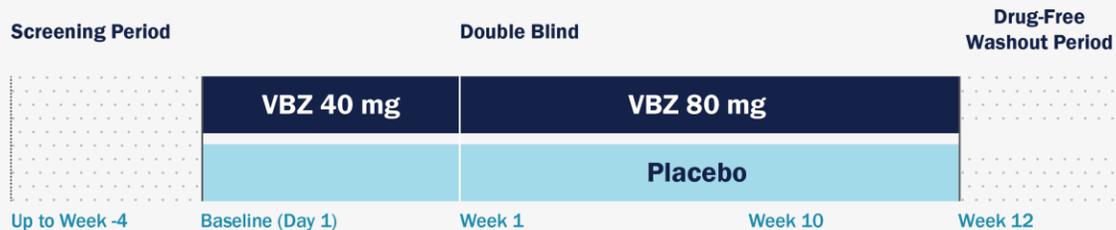
A phase 3 study of valbenazine for schizophrenia as an adjunct to standard of care antipsychotic treatments was recently completed, with results expected soon.
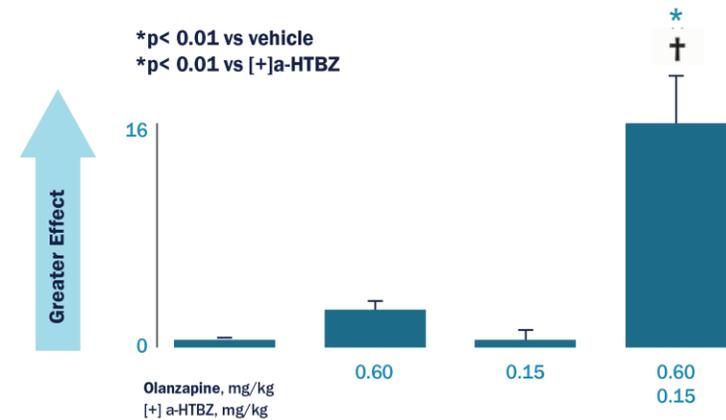
Animal models suggest that [+]-α-HTBZ could have synergistic effects with some common antipsychotics
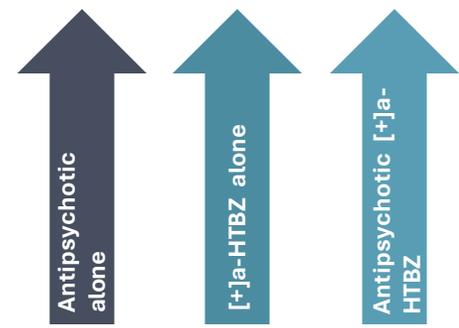
PANSS = Positive and Negative Syndrome Scale

Josiassen RC, et al. _Psychopharmacol Bull_. 2017;47(3):61-68. Grigoriadis, DE, et al. Poster Presented At The 56th Annual Meeting Of The American College Of Neuropsychopharmacology December 3-7, 2017. Palm Springs, CA. Accessed February 20, 2025. https://clinicaltrials.gov/study/NCT05110157.

There Was a Fork in the Road in the 1950s...

...and maybe the wrong one was taken?

Now it's time to take the road less traveled

Muscarinic Acetylcholine Receptor Activation
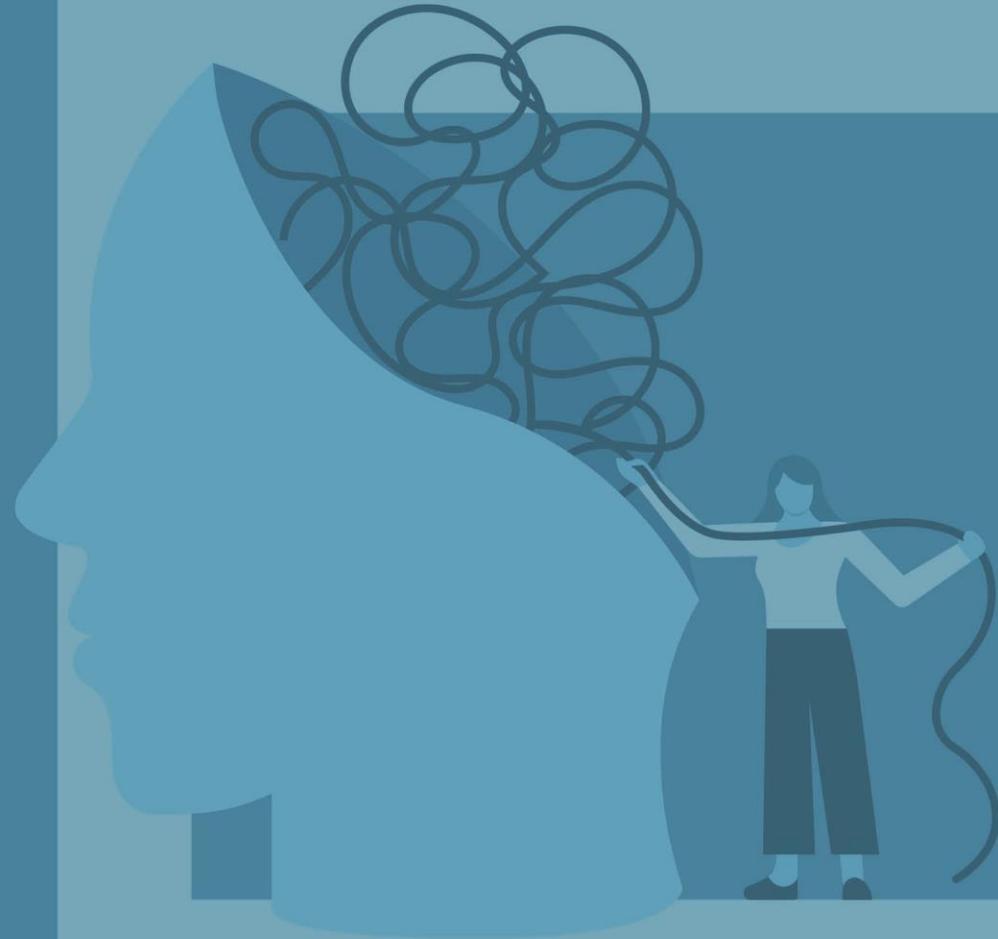
Relevance of Muscarinic Agonism in Schizophrenia

Clinical

1959
Arecoline derived from the betel nut reduced psychotic symptoms in patients with SZ

1986
Developments of mAChR PET tracers (i.e., $[^{11}C]$ scopolamine)

1996
First report of clinical trials with mAChR agonist (cevimline) in patients
....
Development of mAChR radioligand $[^{11}C]$ xanomeline

1997
In clinical trial in AD patients, the M_1/M_4 agonist xanomeline had unexpected AP-like effects

2001
In patients with SZ, decreased binding density of $[^3H]$-PRZ was reported in the strriatum, HPC and PFC

2002
In post-mortem tissue from patients with SZ, decreased M_1 and M_4 mRNA expression discovered in the HPC and PFC

2004
Post-mortem studies indicate a reduction in M_1 and M_4 in patients with SZ

2007
In a clinical trial in patients with SZ, xanomeline demonstrated a reduction in PANSS

2013
Post-mortem studies demonstrate CHRM1 and CHRM4 Polymorphisms in patients With SZ

2019
A phase 2 clinical trail showed efficacy of KarXT, dual M_1/M_4 agonist in patients with SZ

2022
Published report of M_4 PET-ligand
....
A Phase 1 clinical trial showed efficacy of emraclidine, M_4 PAM, in patients with SZ

Preclinical

Before 1960
Arecoline showed AP activity in preclinical models

1986
Cloning of mAChRs

Late 1995
Preclinical assessment of pan-mAChR agonists (pending observation of xanomeline clinical trails)

1998
Development of M_1 and M_4 KO mice

2001
Behavioral phenotype of M_1 KO mice recapitulates psychosis-phenotype
....
Development of the first M_1 PAM

2003
Behavioral phenotype of M_4 KO mice recapitulates psychosis-phenotype
....
Dual M_1/M_4 agonist modulated AP-like activity in NHP

2007
Assessment of AP activity of M_1 PAMs

2008
Development of first M_4 PAM
....
Assessment of AP activity of M_4 PAMs

2015
M_4 PAM effects on state-dependent alteration in sleep/wake ralated to AP-like effects

2021
Dual M_1/M_4 agonist modulates functional connectivity in preclinical models

AD = Alzheimer's disease; AP = antipsychotic; HPC = hippocampus; KO = knockout; NHP = nonhuman primate; PAM = positive allosteric modulator; PANSS = Positive and Negative Symptom Scale; PET = positron emission tomography; PFC = prefrontal cortex; PRZ = pirenzepine; SZ = schizophrenia.

The Cholinergic System: Nicotinic vs Muscarinic Cholinergic Receptors
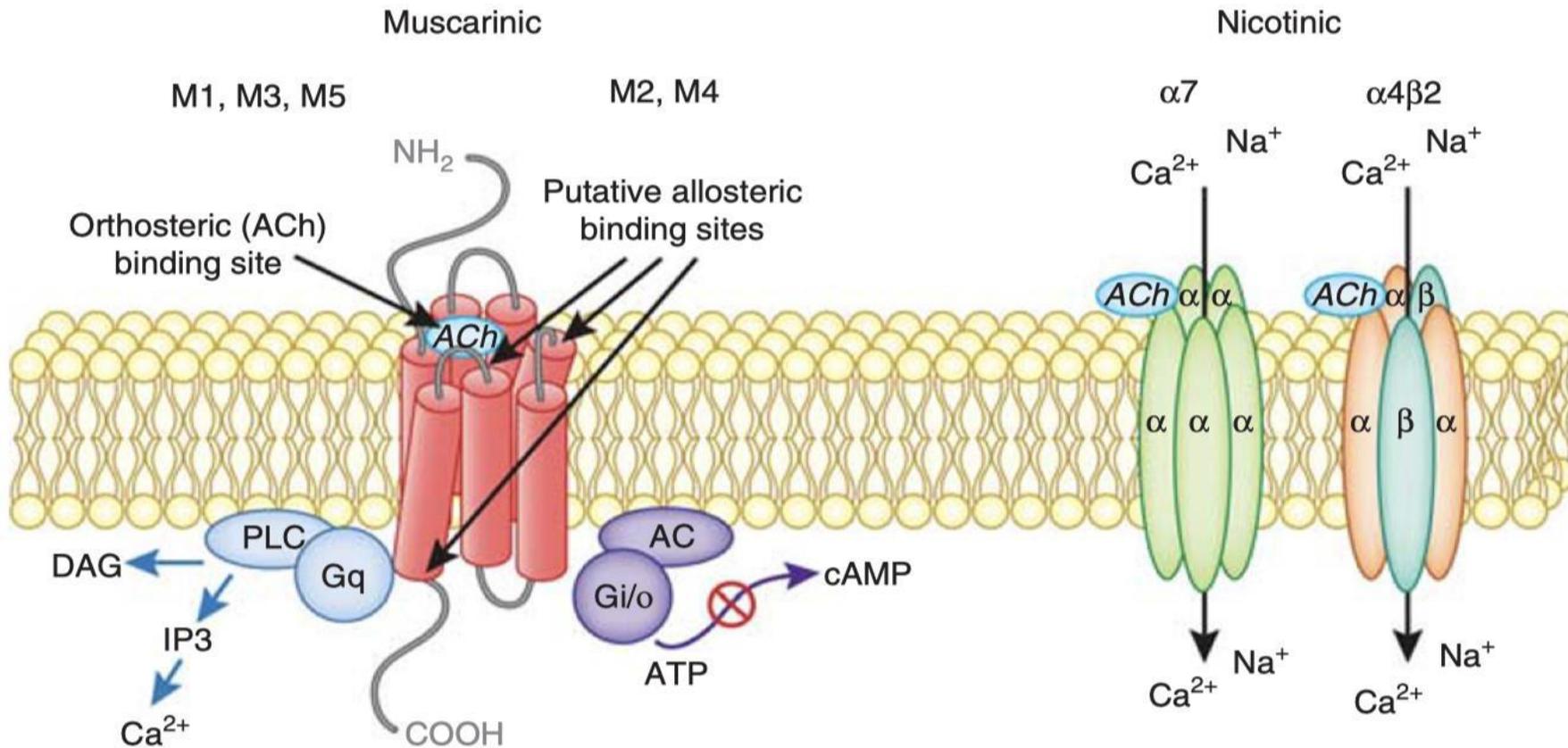
NICOTINIC RECEPTORS

- Ion-gated channel receptor
- Fast synaptic transmission
- CNS and neuromuscular junctions

MUSCARINIC RECEPTORS

- G-protein–coupled receptor
- Second messenger cascades
- CNS and PNS-mediating innervation to visceral organs

Signaling Selectivity among Muscarinic Acetylcholine M1-M5 Receptors

Postsynaptic Receptor

Presynaptic Autoreceptor

Stimulatory

Inhibitory
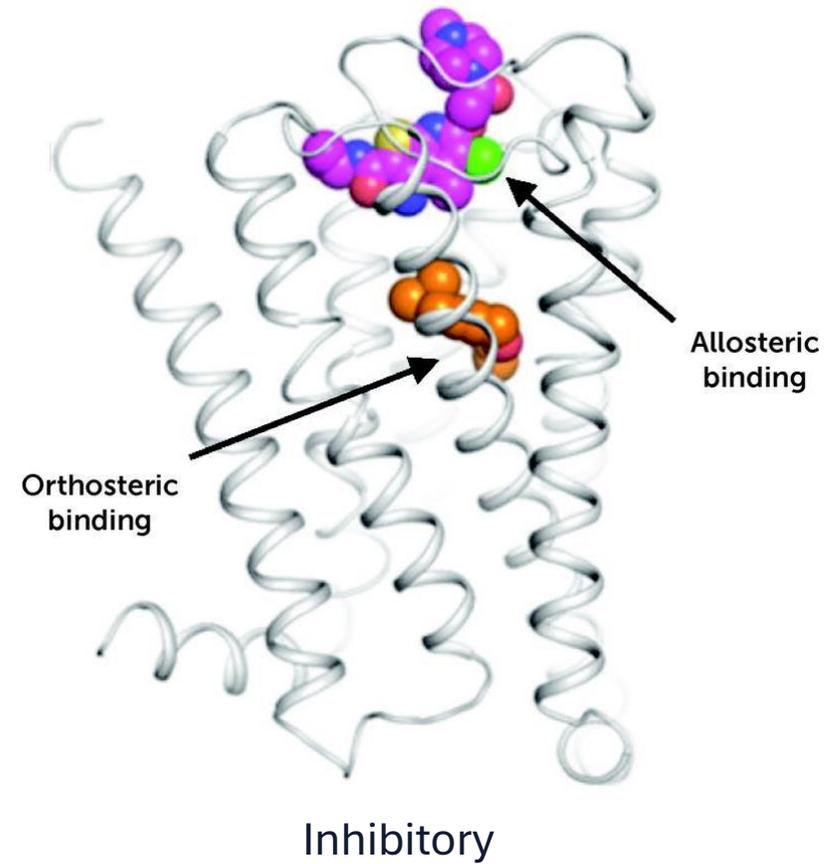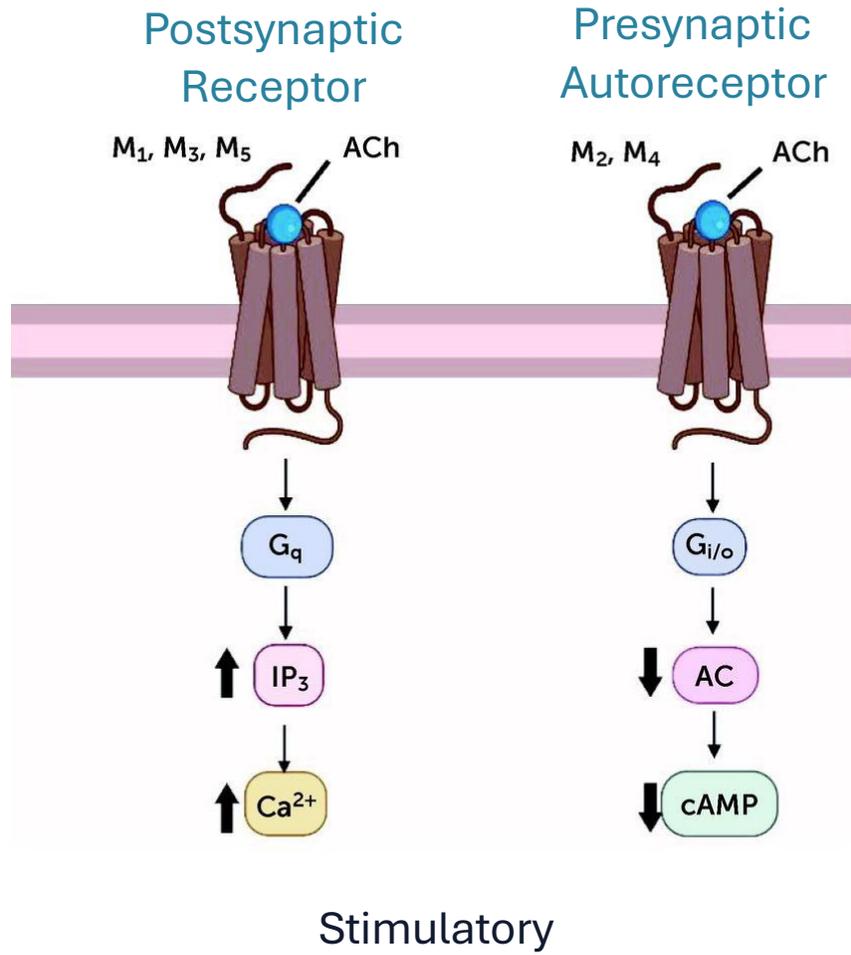
Quantification and Localization of Muscarinic Acetylcholine Receptor (mAChR) mRNAs In Central and Peripheral Human Tissues Using RNA Sequencing
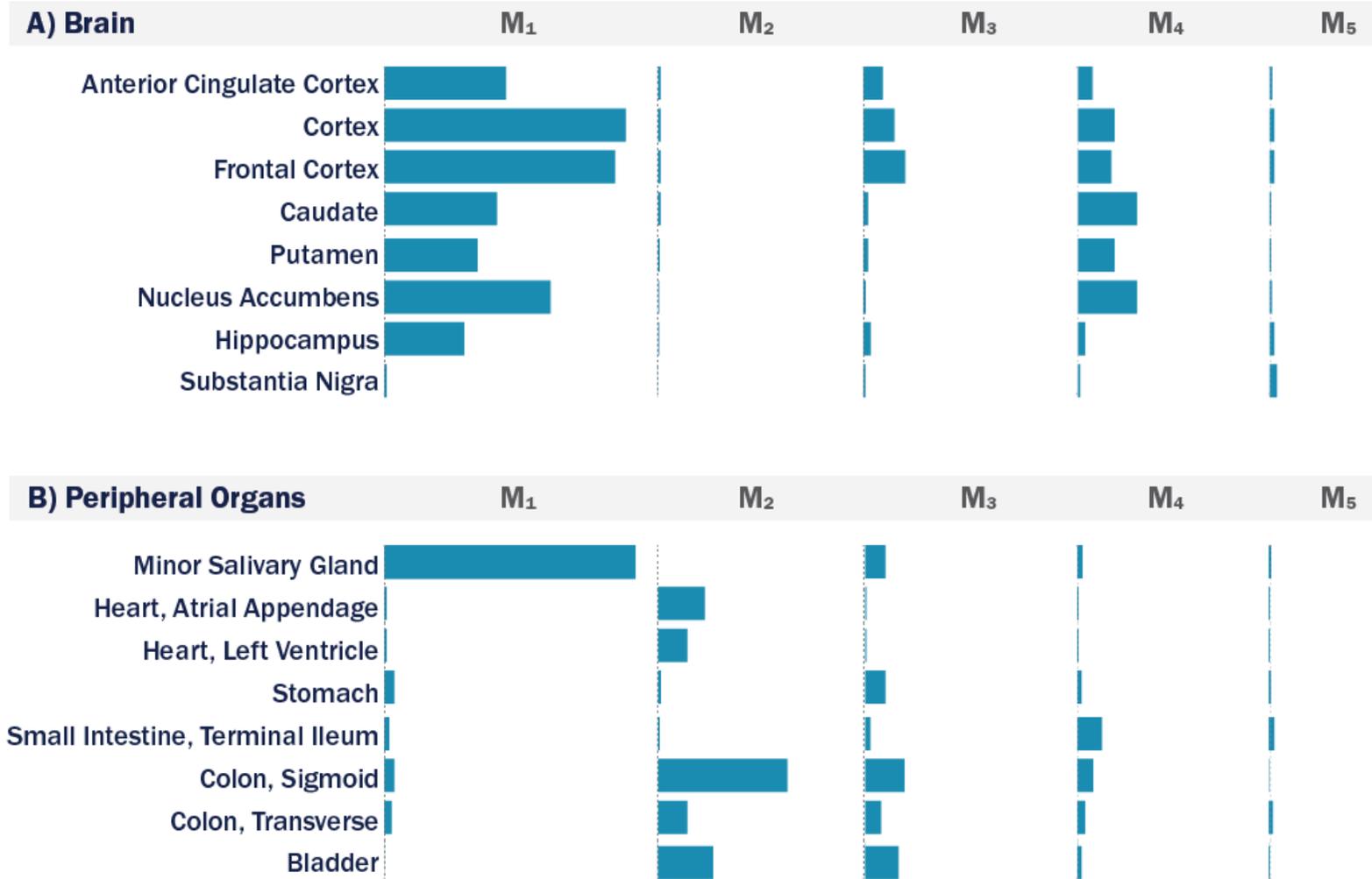
Relative expression of the five mAChR subtypes across key brain regions (panel A) and peripheral organs (panel B) associated efficacy and tolerability of mAChR agonists. (Data used for the relative expression analysis described in this figure were obtained from the Genotype-Tissue Expression [GTEx] Portal 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.)

M1, M4 or Both?
Antipsychotic Activity of Muscarinic Agonism

Top Down and Bottom Up Control of Dopamine Release
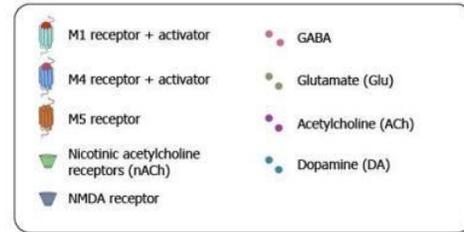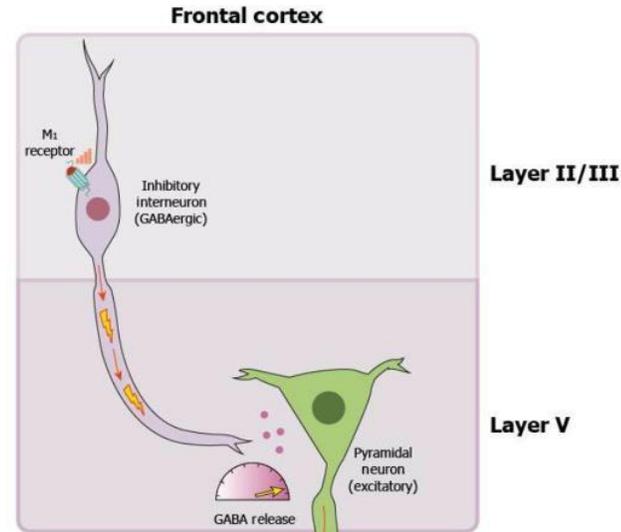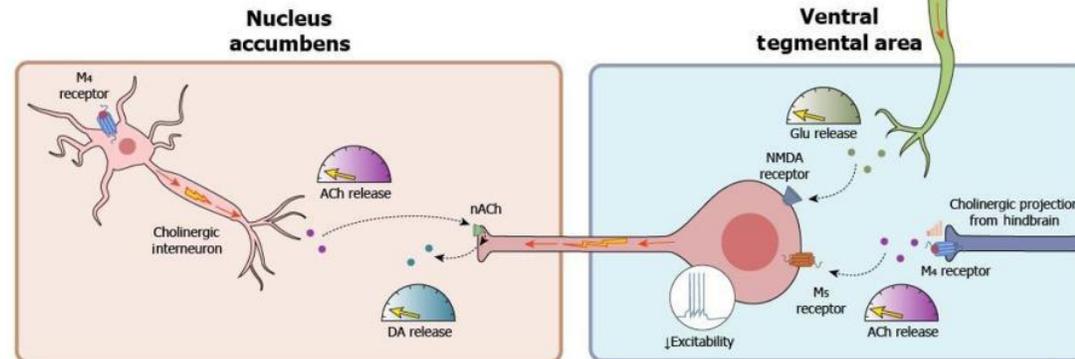
Effects of Xanomeline, a Selective Muscarinic Receptor Agonist, on Cognitive Function and Behavioral Symptoms in Alzheimer Disease

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

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

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

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

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

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

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

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

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

Arch Neurol. 1997;54:465-473
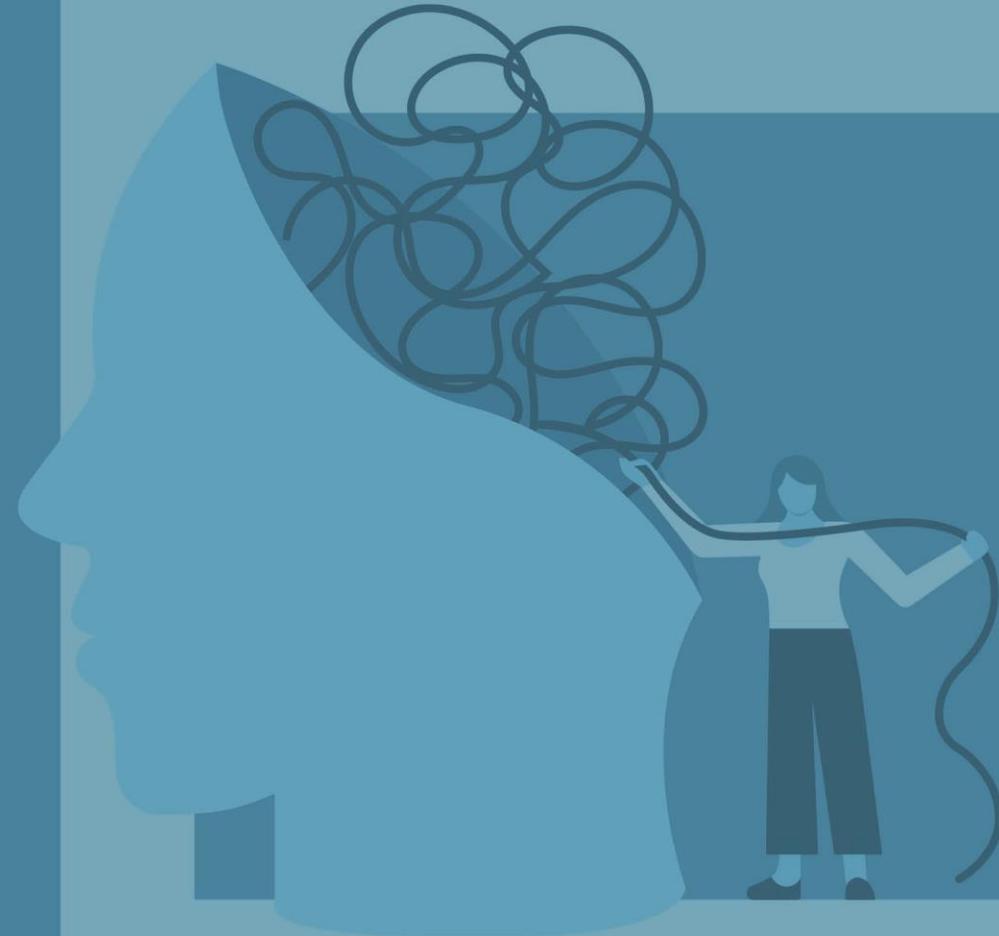
Alzheimer's Disease Symptomatology Scale: Percentage of Patients *Without* Symptoms at Baseline, Started While Receiving Treatment*

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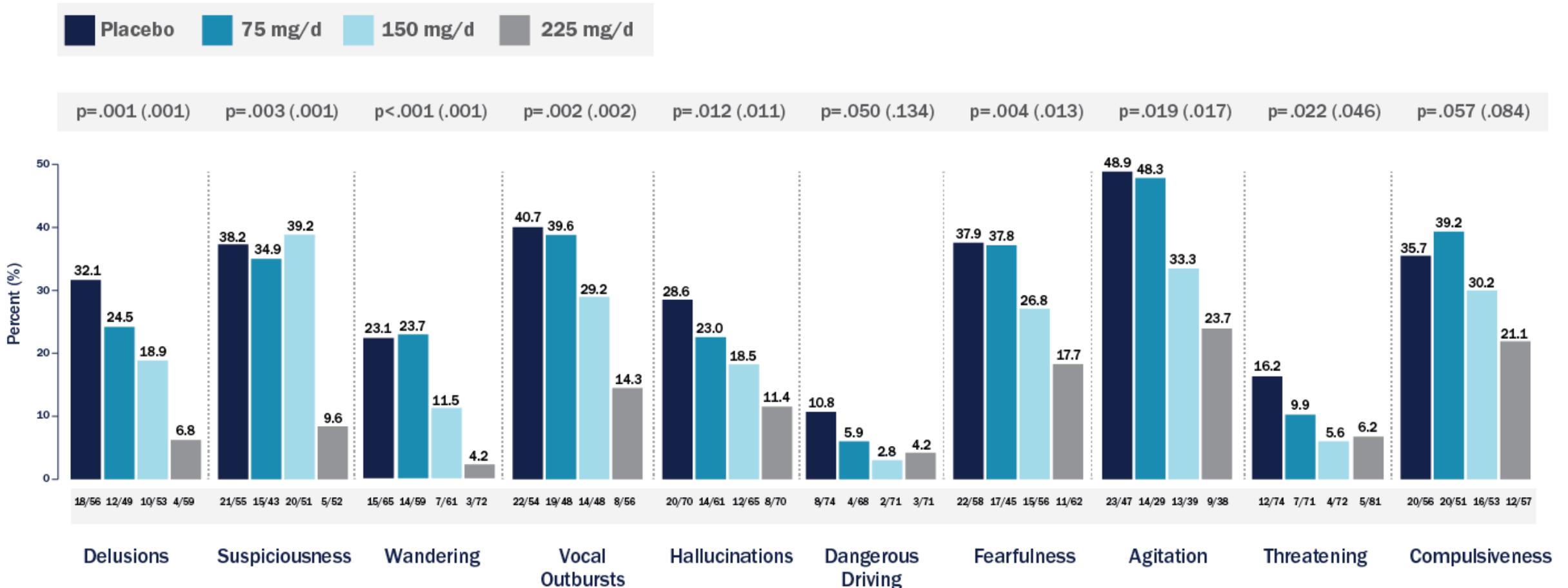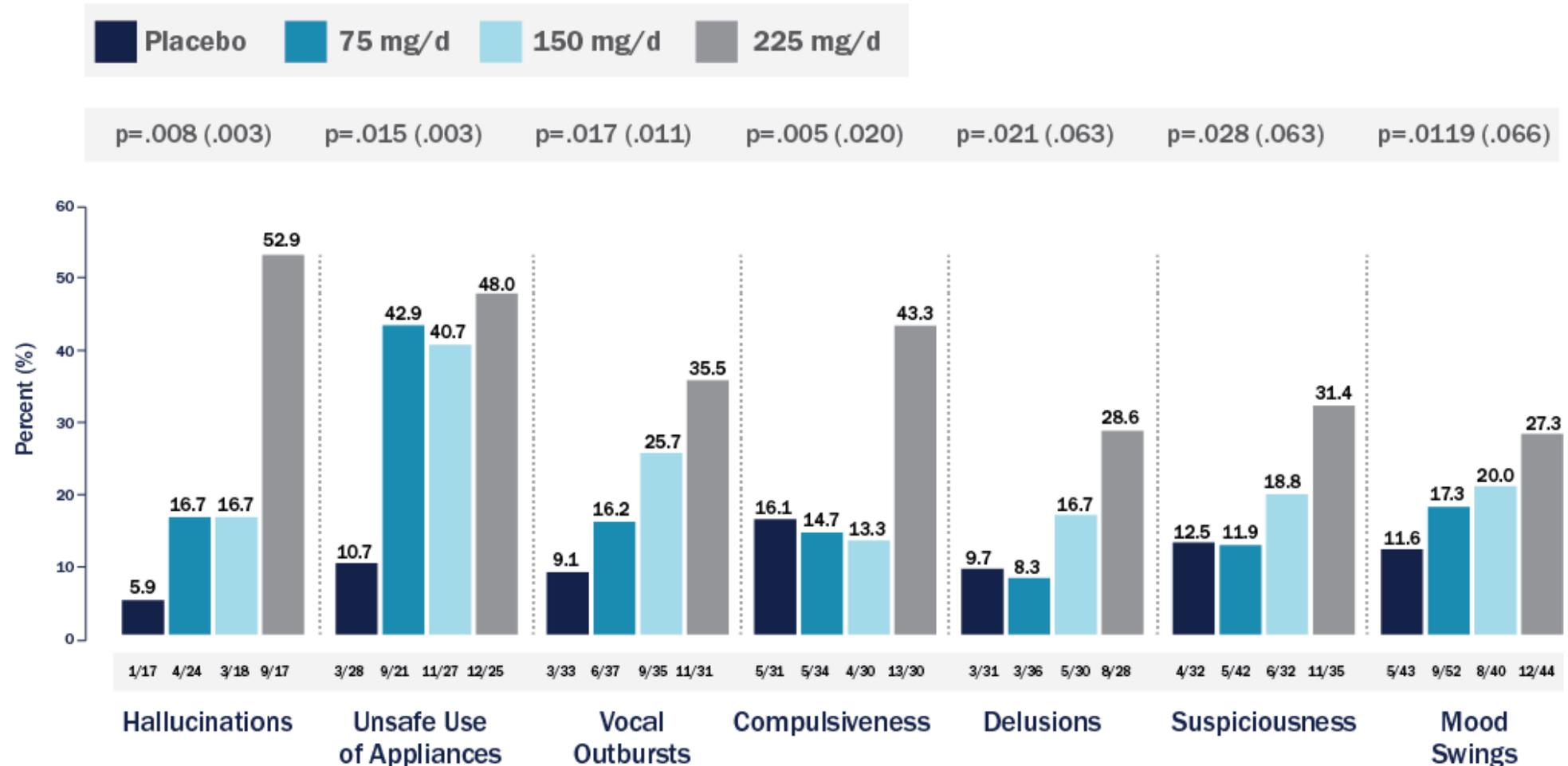

* Baseline lasted 2 weeks; treatment lasted up to 6 months.
Bodick NC, et al. *Arch Neurol*. 1997 Apr;54(4):465-73.

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

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

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

Xanomeline for Alzheimer's Dementia: Adverse Effects

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

*Baseline lasted 2 weeks; treatment lasted up to 6 months. Only events statistically significant at P<.05 are given. Values are number (percentage) of patients unless otherwise indicated.
†Low-dose group received 25 mg of xanomeline tartrate 3 times a day; medium, 50 mg 3 times a day; high, 75 mg 3 times a day. ‡Pearson χ2 test.
Bodick NC, et al. Arch Neurol. 1997 Apr;54(4):465-73.

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

Anantha Shekhar, M.D., Ph.D.

William Z. Potter, M.D., Ph.D.

Jeffrey Lightfoot, Ph.D.

John Lienemann, D.Pharm.

Sanjay Dubé, M.D.

Craig Mallinckrodt, Ph.D.

Frank P. Bymaster, M.Sc.

David L. McKinzie, Ph.D.

Christian C. Felder, Ph.D.

Objective: There are significant unmet needs in the treatment of schizophrenia, especially for the treatment of cognitive impairment, negative syndrome, and cognitive tu nction. Preclinical data sug gest that agonists with selective affinity for acetylcholine musca rinic receptors provide a potentially new mechanism to treat schizophrenia. The authors studied xanomeline, a relatively selective muscar inic type 1 and type 4 {M$_1$ and M$_4$) recep tor agonist, to determine if this agent is effective in the treatment of schizophre nia.

Method: In this pilot study, the authors examined the efficacy of xanomeline on clinical outcomes in subjects with schizo phrenia {N=20) utilizing a double-blind, placebo-controlled, 4-week treatment de-

sign. Outcome measures included the Positive and Negative Syndrome Scale (PANSS) for schizophrenia, the Brief Psy chiatric Rating Scale {BPRS), the Clinical Global Impression (CGI) scale, and a test battery designed to measure cognitive function in patients with schizophrenia.

Results: Subjects treated with xano meline did significantly better than sub jects in the placebo group on total BPRS scores and total PANSS scores. In the cog nitive test battery, subjects in the xanome line group showed improvements most robustly in measures of verbal learning and short-term memory function.

Conclusions: These results support fur ther investigation of xanomeline as a novel approach to treating schizophrenia.
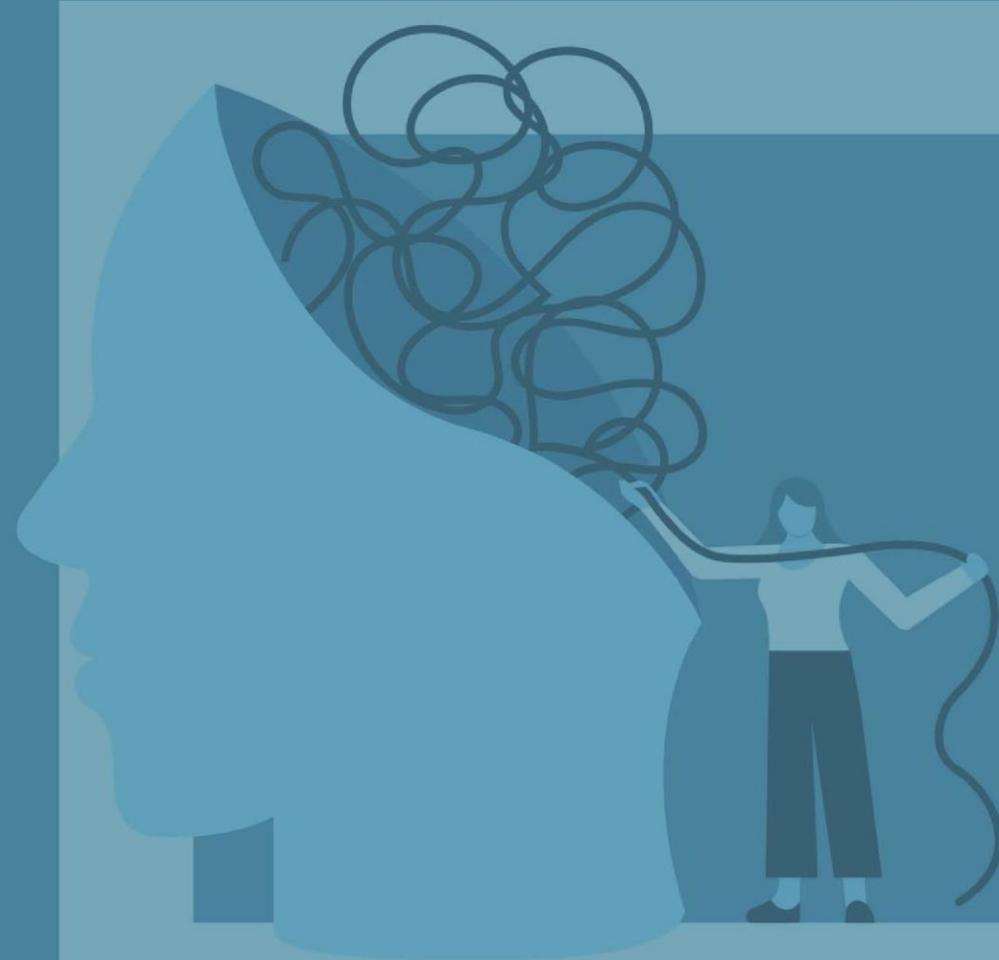
Xanomeline for Schizophrenia: Patient Population, and Efficacy and Tolerability Outcomes

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

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

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

*Results (changes in clinical outcome from baseline to last visit for the two treatment groups) are on ANCOVA; last observations were carried forward.

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

Xanomeline for Schizophrenia: Cognition

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

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

Key Learning Points

✓ Muscarinic receptor activation can occur both by orthosteric agonism at the acetylcholine binding site or by positive allosteric modulation at the allosteric binding site modulating physiologic acetylcholine activity.

✓ M_1 and M_4 receptor activation is associated with decreased presynaptic dopamine release in the associative striatum, which can reduce psychosis, and acetylcholine and dopamine release in the frontal lobe, which can improve cognitive functioning.

✓ Xanomeline, given without a peripherally restricted anticholinergic agent, was effective for psychosis and cognitive dysfunction in patients with Alzheimer's dementia and schizophrenia, but development was halted due to limiting peripheral procholinergic adverse effects.
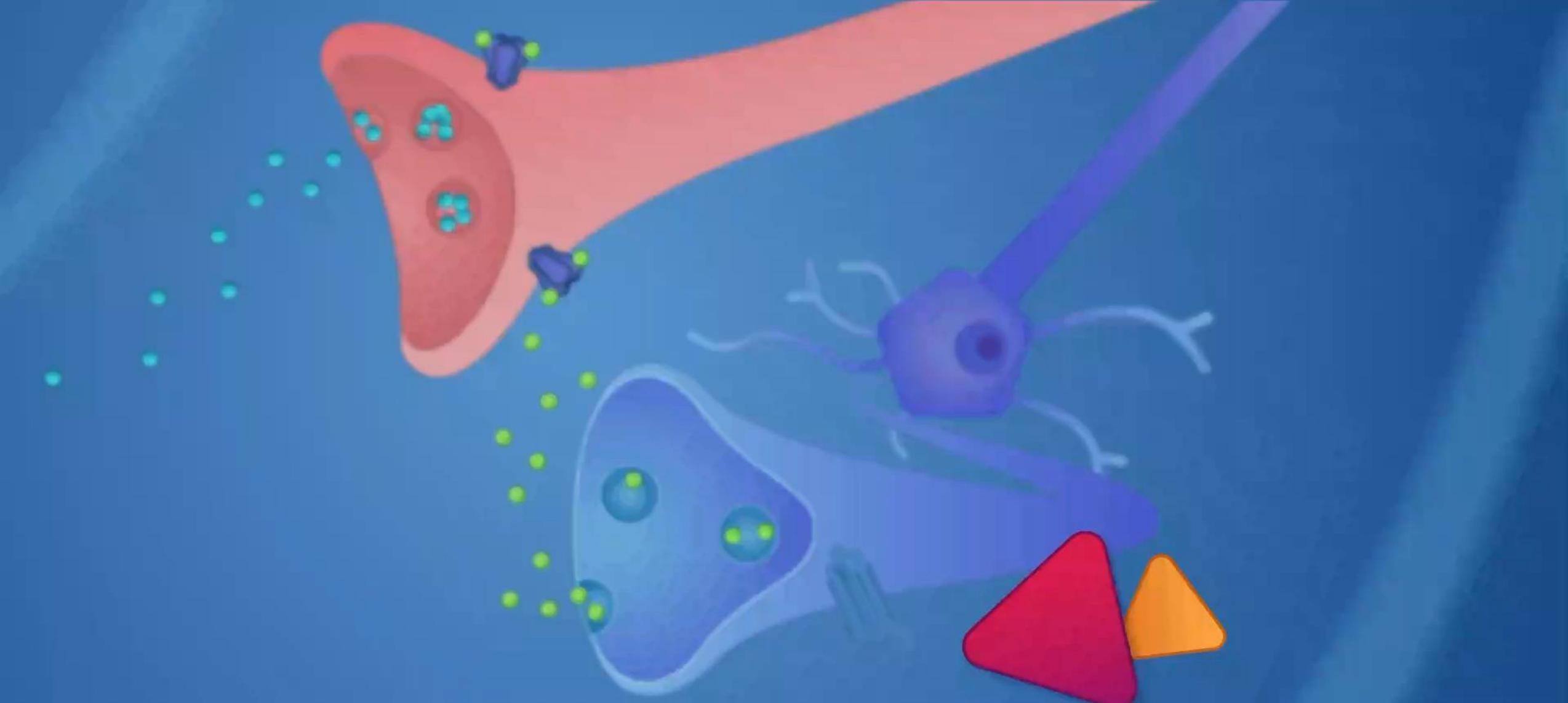
Understanding the Antipsychotic Potential of Muscarinic Agonists

Creative services provided by infograph-ed

Managing the Peripheral Pro-Cholinergic Effects of Xanomeline

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

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

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

What is trospium? A nonselective muscarinic antagonist available since 1974 for overactive bladder (approved in 2004 in the US)
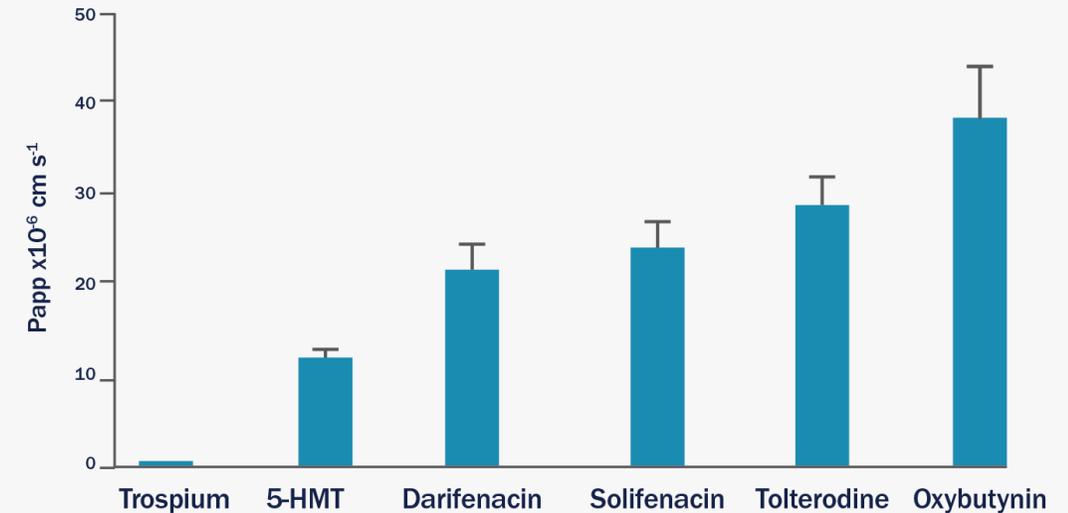
Trospium is a quaternary ammonium compound. The positively charged ammonium group makes trospium too polar to cross the BBB.
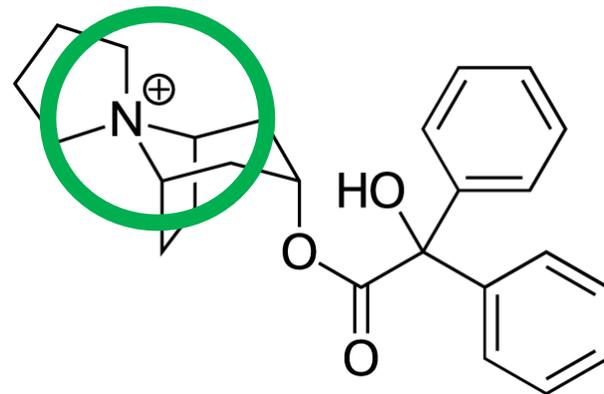
Figure: Passive diffusion across cloned kidney cells as a model for blood brain barrier penetration

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

KarXT Clinical Development Program

Program	Preclinical	Phase 1	Phase 2	Phase 3	Status
Schizophrenia	Emergent 1[-1]				Complete
	Emergent 2[2]				Complete
	Emergent 3[3]				Complete
	Emergent 4 (open-label extension of EMERGENT 2 and EMERGENT 3)[4]				Complete
	Emergent 5 (long-term, open-label trail, newly enrolled participants)[5]				Active, not recruiting
Schizophrenia (adjunctive)	Arise[6]				Enrolling
Psychosis in people with inadaquately controlled symptoms of schizophrenia	Arise 2[7]				Enrolling
Psychosis in Alzheimer´s Disease	Adept 1[8]				Enrolling
	Adept 2[9]				Enrolling
	Adept 3 (open–label extension)[10]				Enrolling

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

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

Emergent 1 - Phase 2 Clinical Trial Design

- 5-week double-blind, placebo- controlled inpatient trial

- Adults ages 18–60 with an acute exacerbation of schizophrenia (Emergent 2 & 3: Adults ages 18-65)

- Mean age 42.5 years, 70% male, 76% nonwhite, mean baseline PANSS 97.1

Washout and Screening Period
≥ 2 weeks

Double-blind Inpatient Treatment Period
Days 1- 35

X-T 125/30 (Optional increase in dose based on tolerability)
Days 8-35

X-T 100/20
Days 3-7

X-T 50/20
Days 1-2

0

Week

5

(R) ⎯ Xanommeline-Trospium, n=89

Placebo, n=90
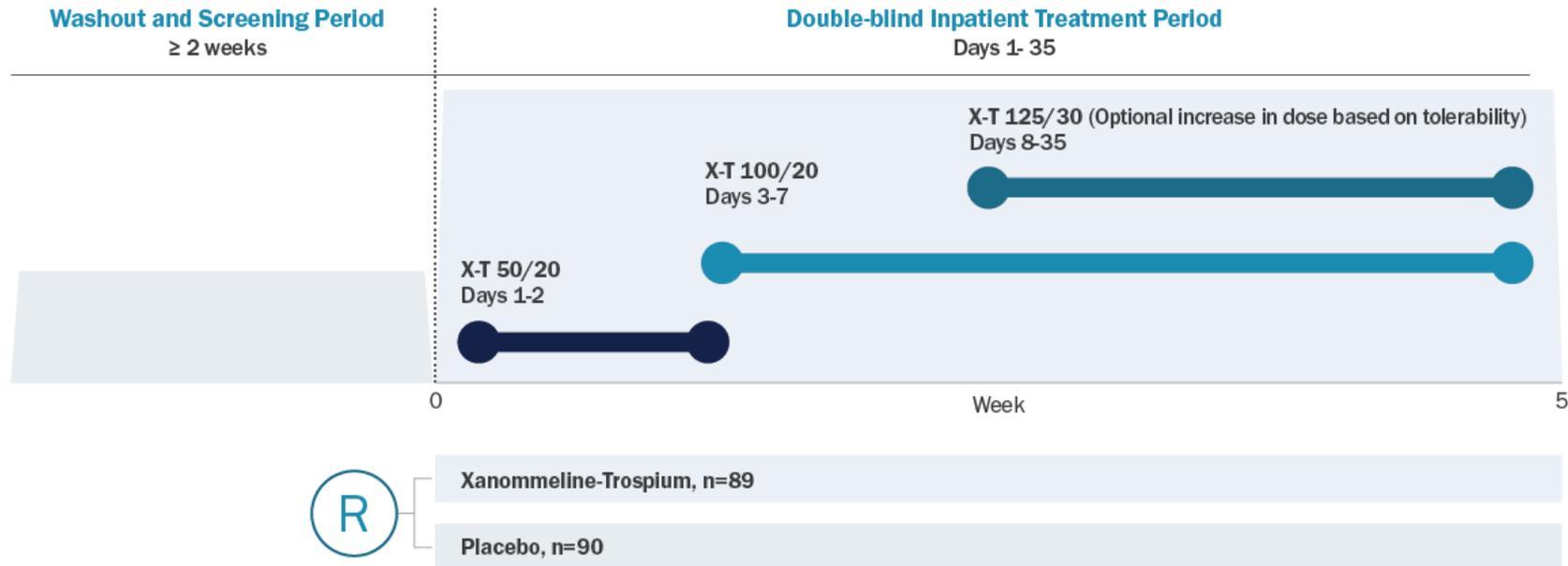
91% were able to tolerate titration at the highest dose of xanomeline-trospium

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

Emergent Trials:
PANSS Total Score Change from Baseline
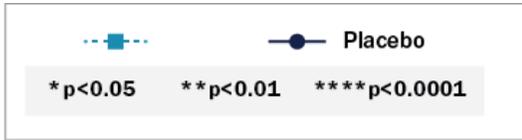
Emergent 1[1]
Cohen´s d efffect size 0.81[a]
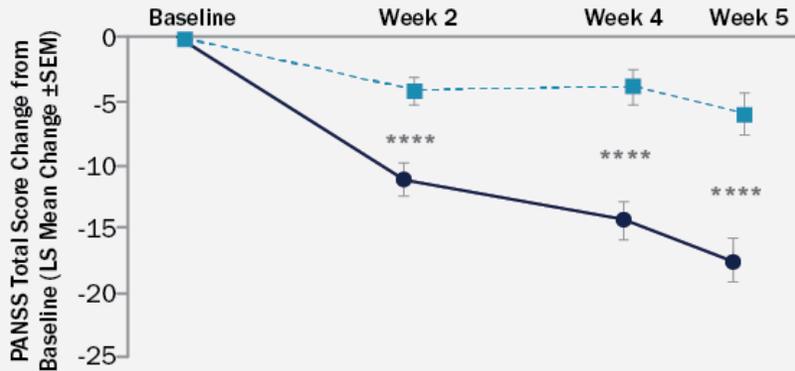
Emergent 2[2]
Cohen´s d efffect size 0.61[a]

Emergent 3[3]
Cohen´s d efffect size 0.60[a]
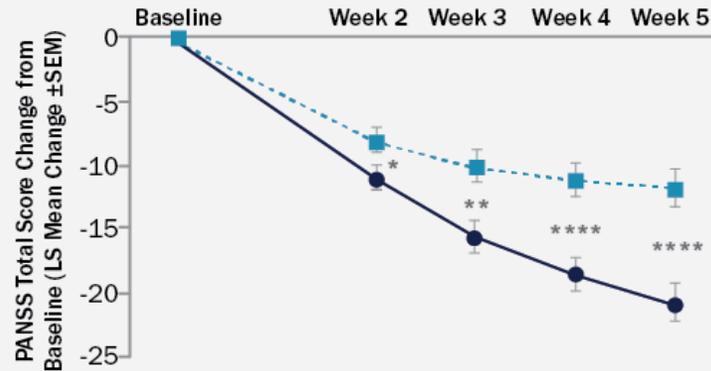
11.6-point reduction at week 5

9.6-point reduction at week 5
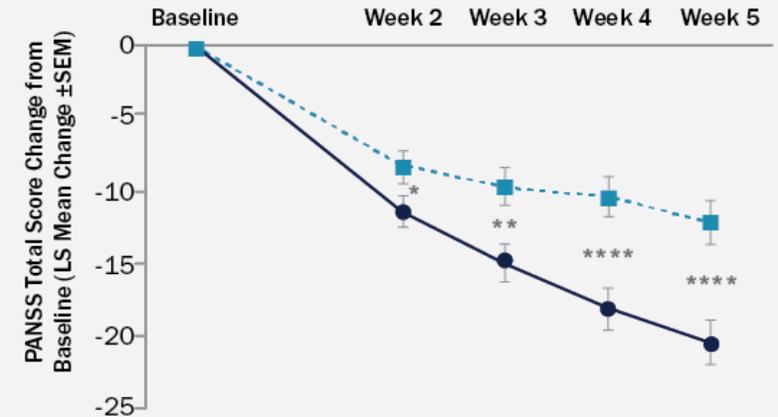
8.4-point reduction at week 5

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

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

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

Safety Population

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

EMERGENT Trials: Onset and Duration of Commonly Reported Adverse Effects During the 5-Week Treatment Period

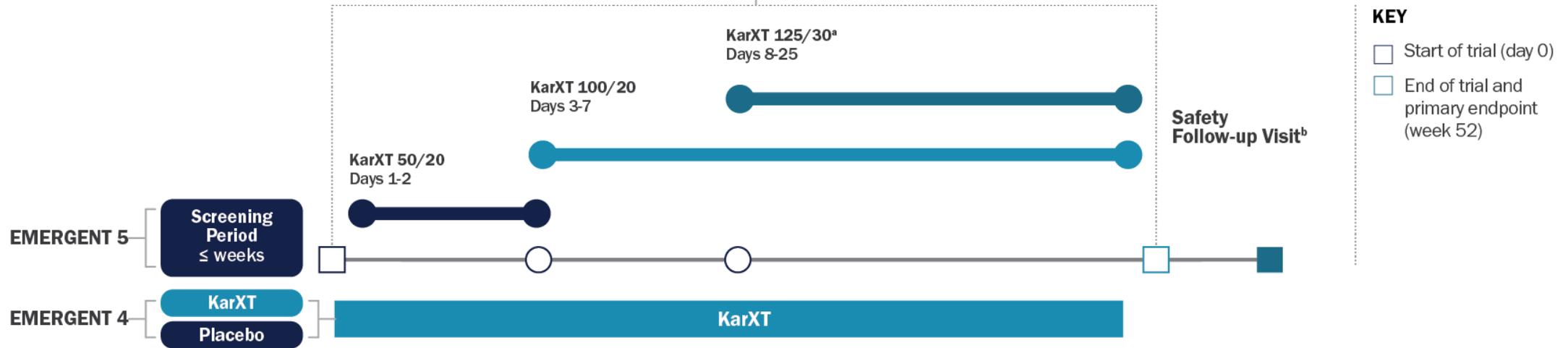## Pooled EMERGENT Safety Population

● KarXT   ■ Placebo

Onset of TEAE

Nausea	n=63	9.0 ± 8.1
	n=13	8.1 ± 9.1
Constipation	n=58	11.3 ± 9.5
	n=21	10.2 ± 8.8
Dyspepsia	n=52	8.5 ± 7.8
	n=16	9.1 ± 9.9
Vomiting	n=46	10.2 ± 9.2
	n=6	11.3 ± 10.8
Dry Mouth	n=17	6.4 ± 6.2
	n=5	4.4 ± 3.97

Days: 0 5 10 15 20 25 30 35

TEAE Duration

Nausea	n=63	11.7 ± 11.6
	n=13	8.9 ± 9.0
Constipation	n=58	12.4 ± 11.3
	n=21	10.7 ± 10.1
Dyspepsia	n=52	14.9 ± 13.1
	n=16	17.1 ± 15.8
Vomiting	n=46	3.8 ± 5.0
	n=6	3.3 ± 4.8
Dry Mouth	n=17	19.8 ± 10.8
	n=5	7.0 ± 7.0

Days: 0 5 10 15 20 25 30 35
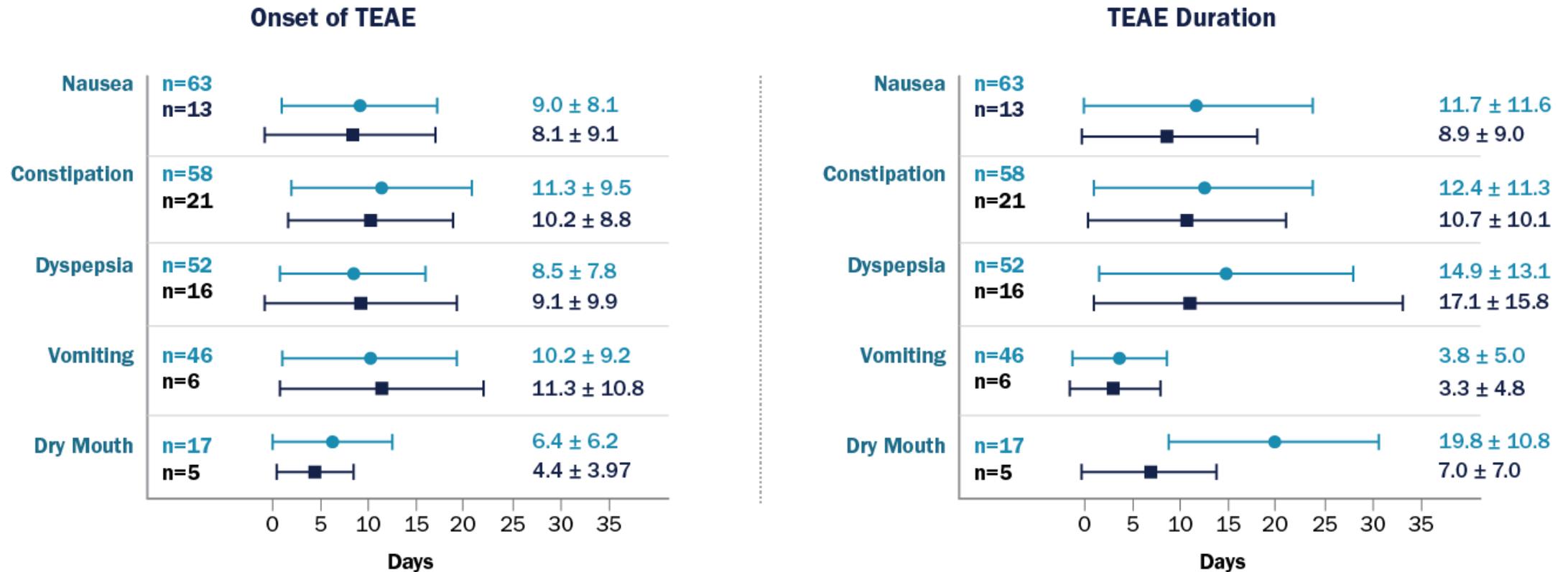
Safety population defined as all participants who received ≥1 dose of trial medication.
a. Suicidal ideation (n=2), psychotic disorder (n=1), gastroesophageal reflux disease (n=1); b. Appendicitis (n=1), schizophrenia (n=1); c. Hypertension
Brannan SK, et al. Poster presented at the 2023 American Society of Clinical Psychopharmacology (ASCP) Annual Meeting, May 30-June 2, 2023, Miami, Florida.

Emergent 4, 5 - Clinical Trial Design

**Figure 1: Trial Designs**

Open-Label Treatment Period

KarXT 125/30[a]
Days 8-25

KarXT 100/20
Days 3-7

KarXT 50/20
Days 1-2

Safety Follow-up Visit[b]

KEY
☐ Start of trial (day 0)
☐ End of trial and primary endpoint (week 52)

EMERGENT 5 — Screening Period ≤ weeks

EMERGENT 4 — KarXT / Placebo — KarXT

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

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

- EMERGENT-4 is an open-label extension that enrolled participants aged 18-65 years who previously completed the treatment period of EMERGENT-2 or EMERGENT-3

- EMERGENT-5 is an open-label trial in adults with a confirmed diagnosis of schizophrenia who have had no prior exposure to KarXT; participants with a Positive and Negative Syndrome Scale total score ≤80 and a Clinical Global Impression–Severity score ≤4 were eligible.

- All participants initiated KarXT at 50 mg/20 mg BID, titrated to a max dose of 125 mg/trospium 30 mg BID for 52 weeks

- Interim safety and tolerability data from the EMERGENT-4 and EMERGENT-5 trials were pooled; all analyses were conducted using the safety population, defined as all participants who received ≥1 dose of trial medication

Emergent 4 – Long Term Change in PANSS
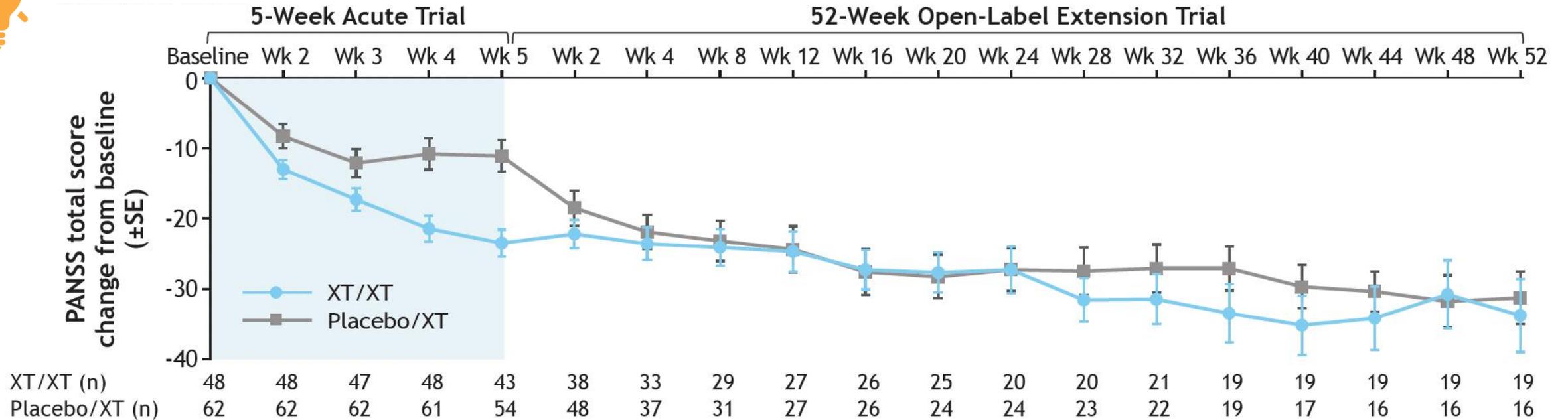
Mean PANSS total score change from baseline to week 52
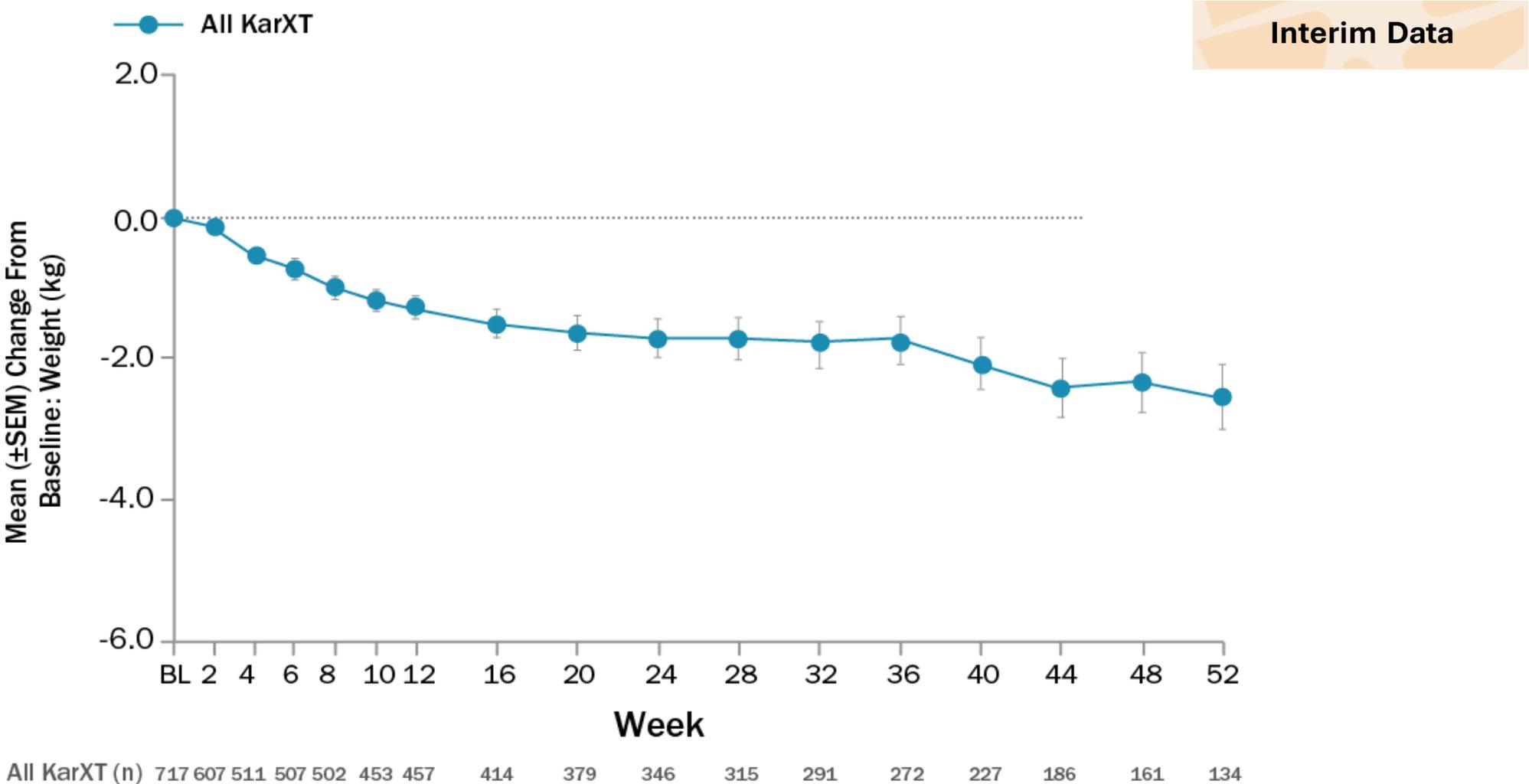
KarXT/KarXT: -33.6 points
Placebo/KarXT: -32.9 points

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

Pooled Emergent 4, 5 Data: Safety and Tolerability

Interim Data

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

Pooled Emergent 4, 5 Data: Weight Change

Interim Data

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

Pooled Emergent 4, 5 Data: D2 Related Adverse Effects

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

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

Safety population defined as all participants who received ≥1 dose of trial medication.
a. EPS TEAEs included any new onset dystonia, dyskinesia, akathisia, or extrapyramidal disorder reported any time after the first dose of trial medication.
EPS = extrapyramidal symptoms; SD = standard deviation; TEAE = treatment-emergent adverse event.
Weiden P, et al. Presented at: NEI; November 9-12, 2023; Colorado Springs, CO. Poster 85.

Xanomeline-Trospium and Cognitive Outcomes

Cognitive Benefit from M1 Stimulation? EMERGENT -1 Analysis

KarXT treatment effect on cognitive performance by baseline impairment subgroup, IIV outliers removed. *

Sample	LS means change from baseline at day 35		95% confidence interval			
	Treatment	**Estimate (SE)**	**Lower**	**Upper**	**_p_ value**	**Cohen´s _d_**
Minimally impaired	KarXT (n=34)	-0.017 (0.15)	-0.32	0.28	0.9	0.02
	Placebo (n=28)	-0.078 (0.15)	-0.38	0.22	0.6	0.09
	KarXT vs Placebo	0.06 (0.17)	-0.29	0.41	0.73	0.07
Impaired	KarXT (n=20)	0.66 (0.18)	0.28	1.00	0.001	0.53
	Placebo (n=35)	0.06 (0.12)	-0.19	0.30	0.65	0.08
	KarXT vs Placebo	0.6 (0.22)	0.16	1.10	0.009	0.79

LS means and p values are derived from post hoc ANCOVA models described earlier, with covariates of site, gender, age, and baseline performance. IIV outliers: The 1.5 interquartile range (IQR) rule was used to define outlier IIV assessments as individual test scores falling outside quartile 3 +1.5 IQR. The approach of removing patients with highly variable assessment responses has been previously employed to examine treatment effects in schizophrenia.

Cognitive Benefit from M1 Stimulation? Pooled EMERGENT 1-3 Analysis
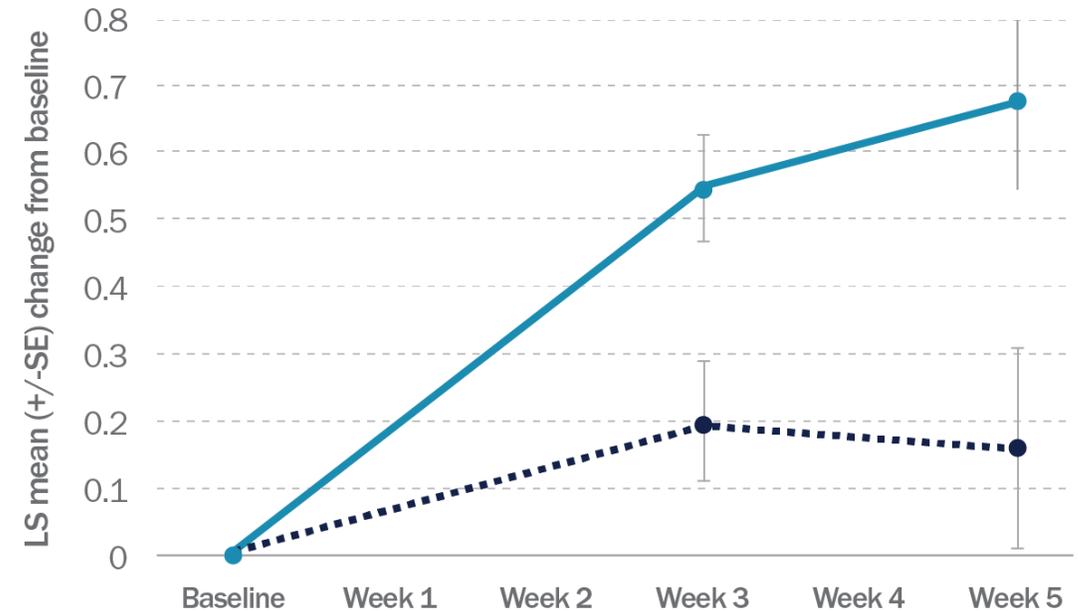
A. -1.0 SD z-score cut-off; N = 137
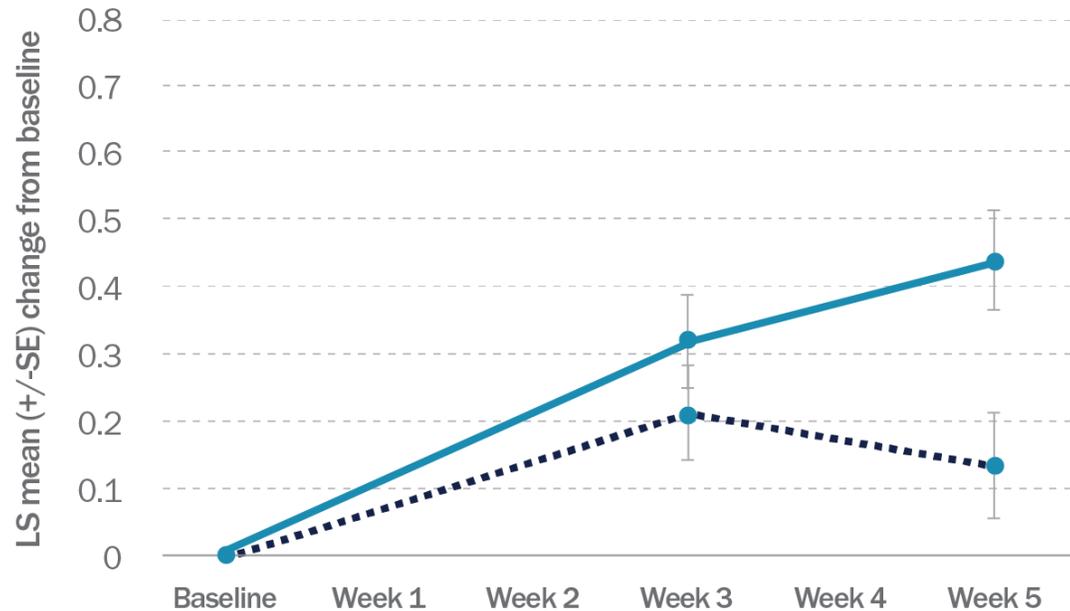
Week 3: p = .25, d = .20
Week 5: *p = .004, d = .54

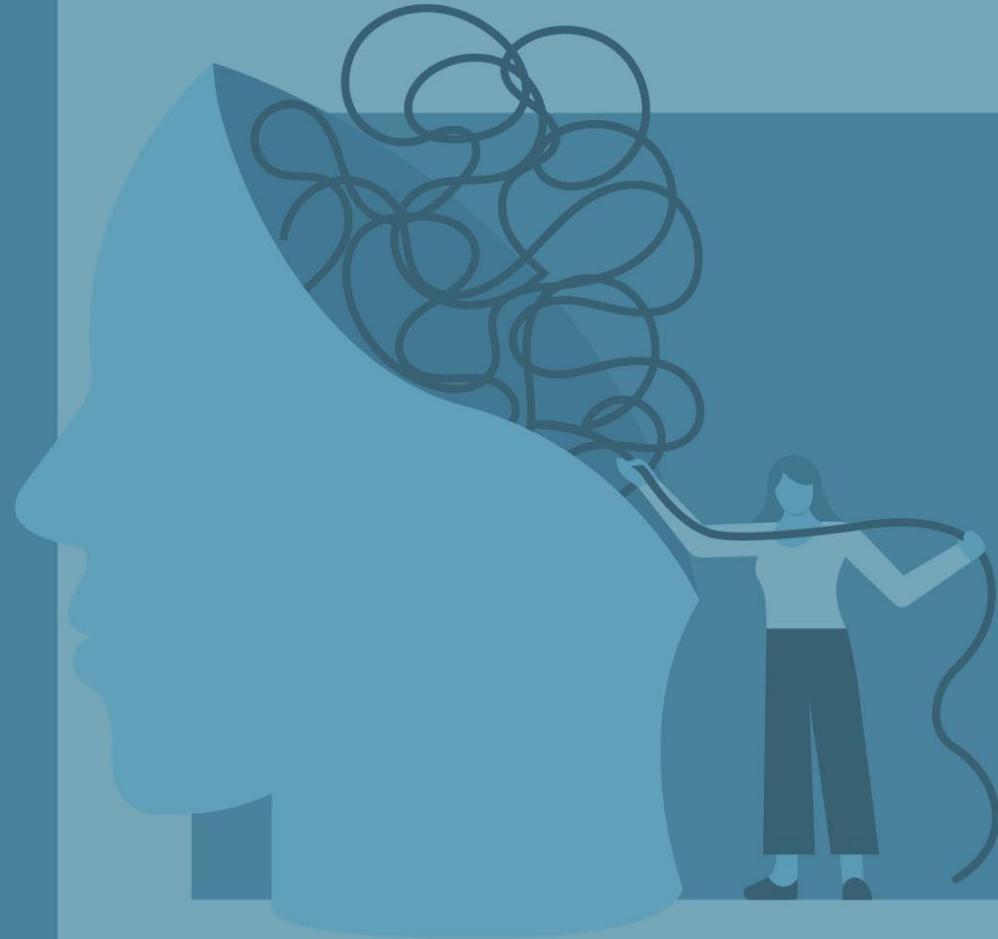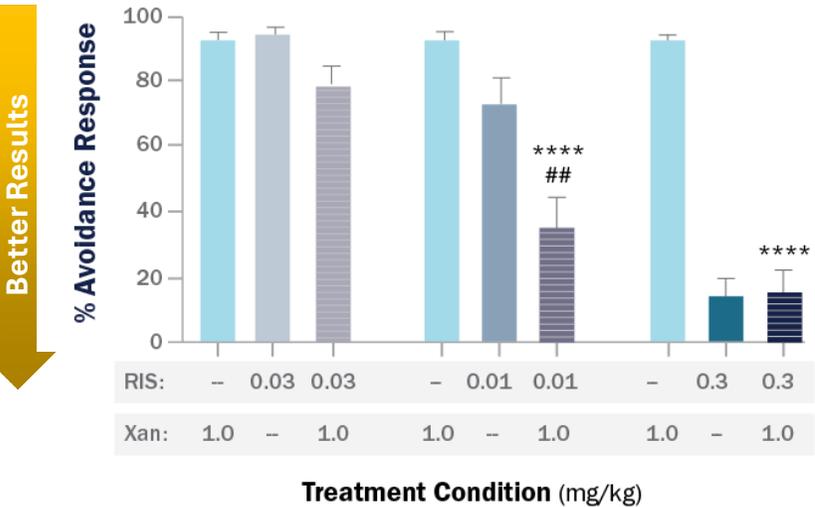B. -1.5 SD z-score cut-off; N = 59

Week 3: ***p = .005, d = .79
Week 5: *p = .01, d = .80

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

Potential for Xanomeline-Trospium as Adjunctive Treatment in Schizophrenia

Xanomeline Augments Risperidone and Aripiprazole in Rodent Models of Psychosis

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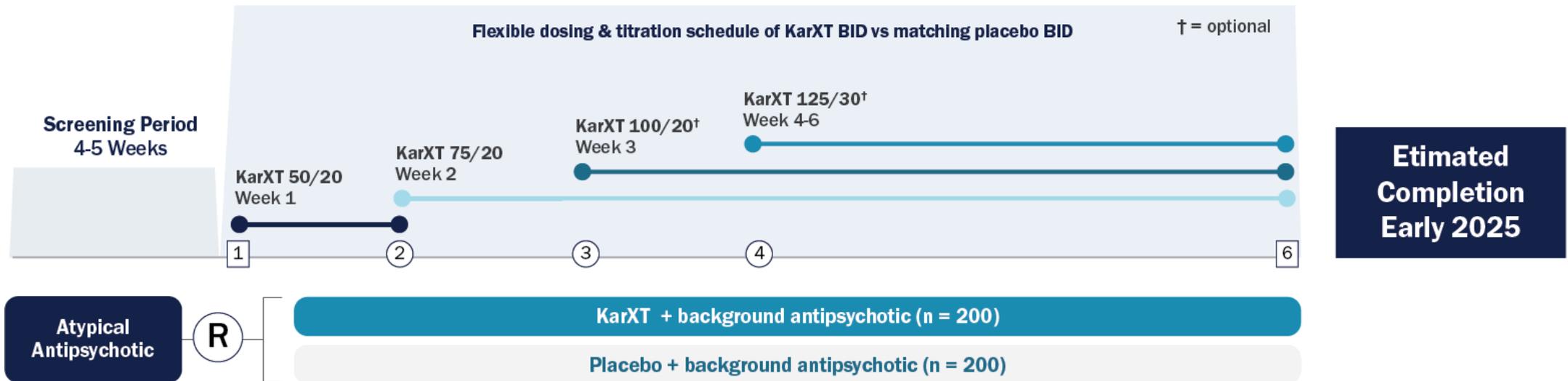Values are mean ± SEM. ** $p<0.01$, **** $p<0.0001$; ## $p<0.01$, ### $p<0.001$, #### $p<0.0001$.

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

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

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

Double-blind Outpatient Treatment Period

Weeks 1-6

Flexible dosing & titration schedule of KarXT BID vs matching placebo BID

† = optional

Screening Period 4-5 Weeks

KarXT 50/20 Week 1

KarXT 75/20 Week 2

KarXT 100/20† Week 3

KarXT 125/30† Week 4-6

Etimated Completion Early 2025

Atypical Antipsychotic — R

KarXT + background antipsychotic (n = 200)

Placebo + background antipsychotic (n = 200)

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

Unlike the monotherapy studies:

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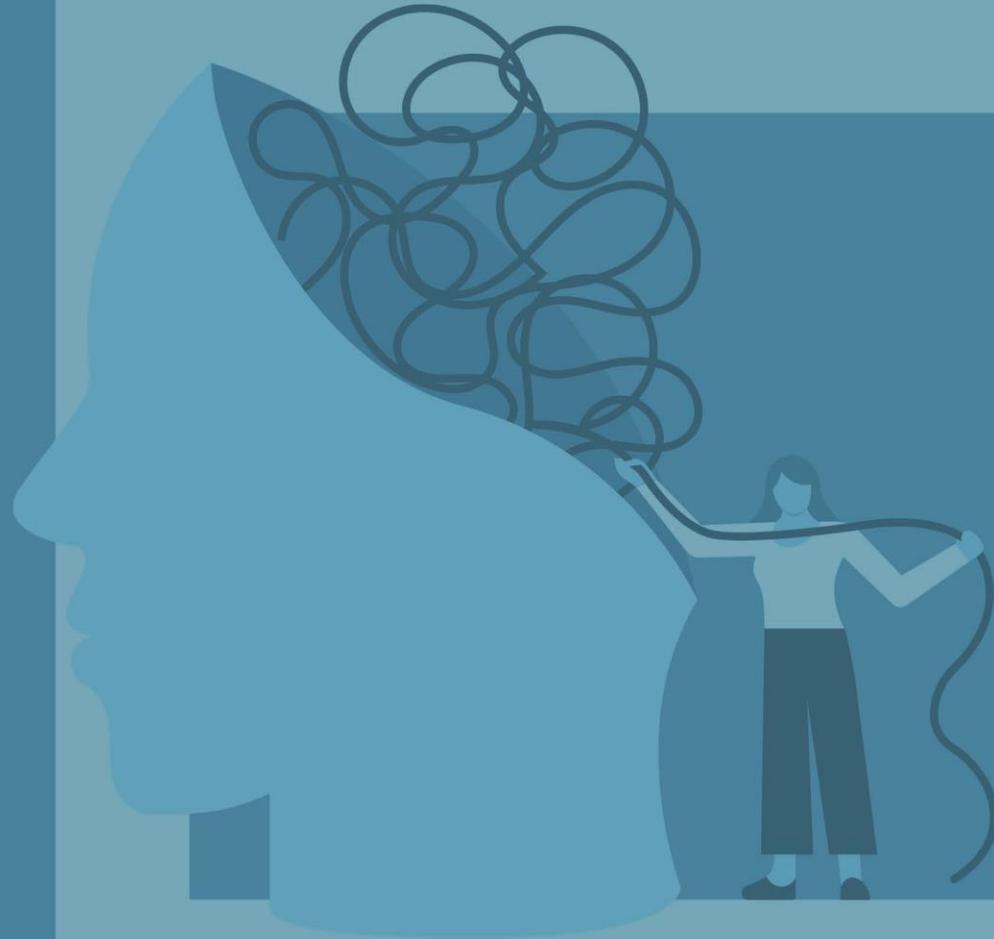
Key Learning Points

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

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

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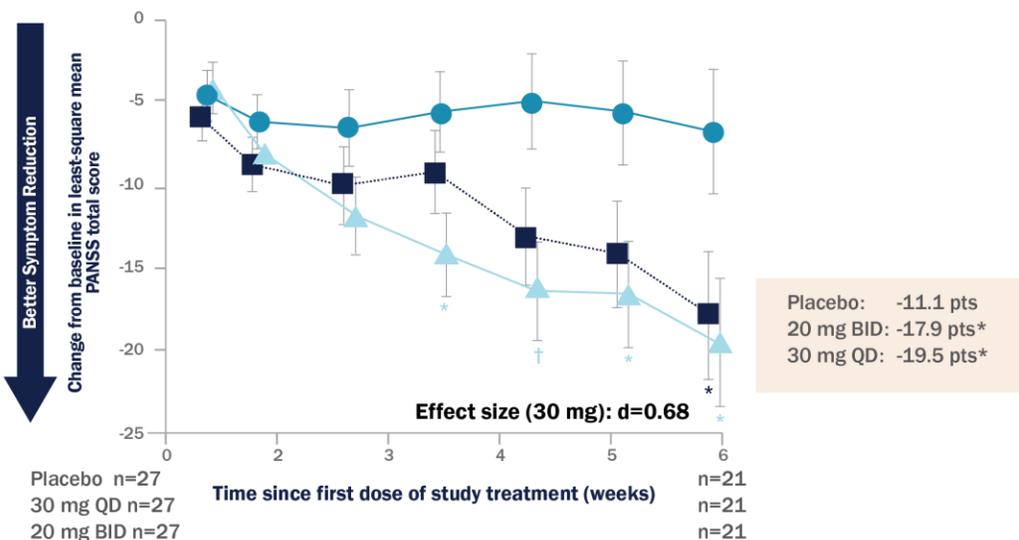
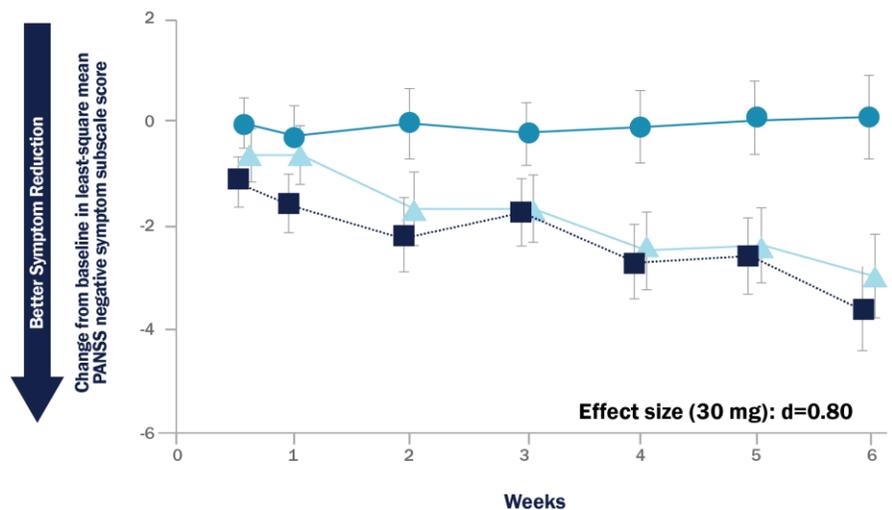# Other Activators of Muscarinic Receptors

Emraclidine M4 PAM
Phase 1B Study Efficacy Results

PANSS Total Score in Part B

Better Symptom Reduction

Change from baseline in least-square mean PANSS total score

Placebo: -11.1 pts
20 mg BID: -17.9 pts*
30 mg QD: -19.5 pts*

Effect size (30 mg): d=0.68

Time since first dose of study treatment (weeks)

Placebo n=27 — n=21
30 mg QD n=27 — n=21
20 mg BID n=27 — n=21

PANSS Negative Symptom Subscale in Part B

Better Symptom Reduction

Change from baseline in least-square mean PANSS negative symptom subscale score

Effect size (30 mg): d=0.80

Weeks

* Nominal P<0.05
† Nominal P<0.01
● Placebo group
■ Emraclidine 30 mg once daily group
▲ Emraclidine 20 mg once daily group

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

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

- **Part A of a Phase 1 study** assessed the tolerability of emraclidine 5, 10, 20, and 30 mg QD and 20 mg BID

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

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

No clinically meaningful findings relative to placebo were observed in either part of the study in:
- Clinical laboratory assessments
- Changes in weight
- Drug-induced movements
- ECG parameters

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

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

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

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

Emraclidine Phase 2 Clinical Trial Program
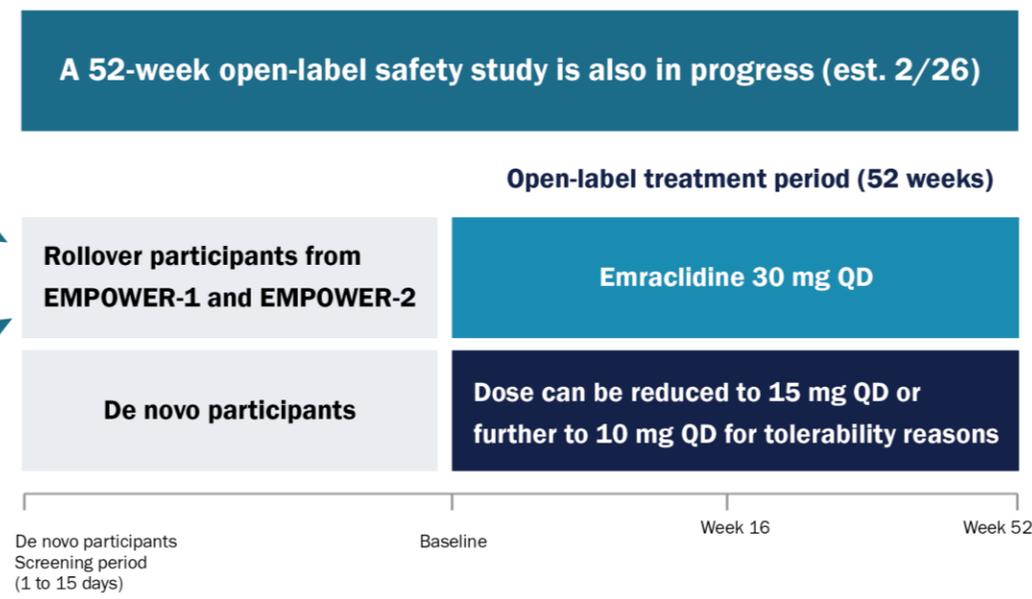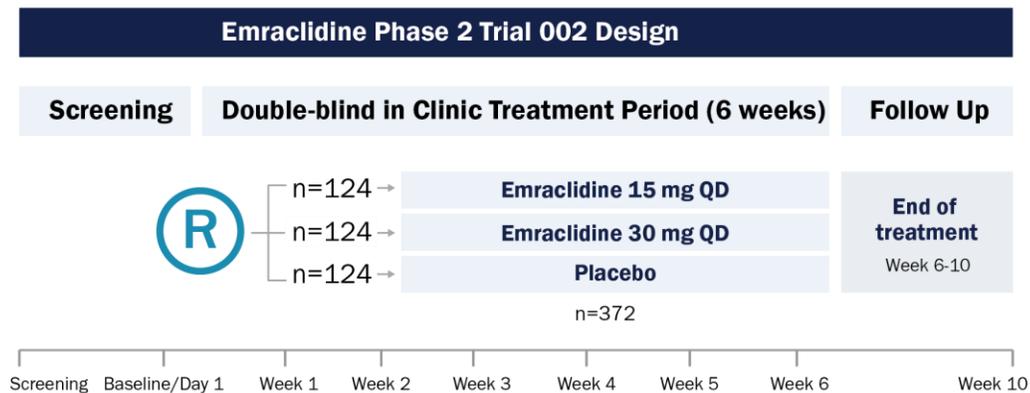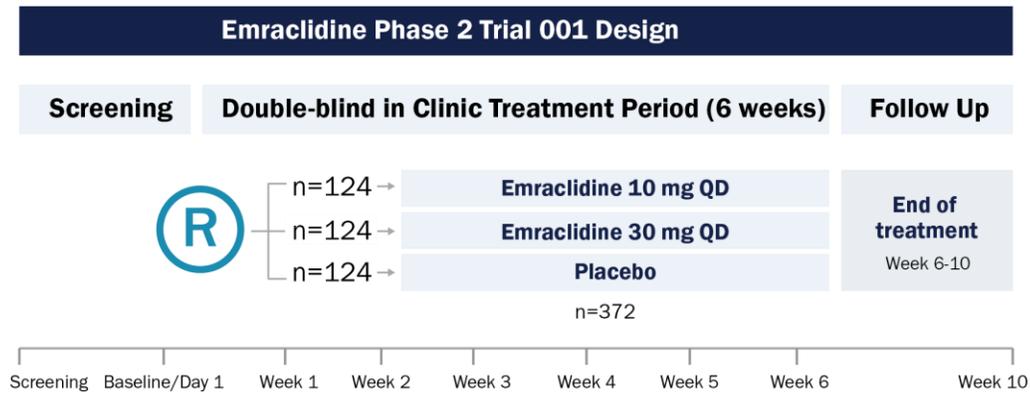
All doses of emraclidine in these studies are given once daily, without titration

ClinicalTrials.gov: A Trial of 15 and 30 mg Doses of CVL-231 (Emraclidine) in Participants With Schizophrenia. Accessed September. 15, 2024. https://clinicaltrials.gov/study/NCT05227703;   A Trial of 10 and 30 mg Doses of CVL-231 (Emraclidine) in Participants With Schizophrenia. Accessed September. 15, 2024. https://clinicaltrials.gov/study/NCT05227690 .   A Study to Evaluate Safety and Tolerability of CVL-231 (Emraclidine) in Adult Participants With Schizophrenia. Accessed September 15, 2024. https://clinicaltrials.gov/study/NCT05443724.

EMPOWER-1 and EMPOWER-2 Did *Not* Meet Their Primary Endpoint

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

- Emraclidine was well-tolerated with an adverse event profile consistent with Phase 1b trial

Change from Baseline to Week 6 in PANSS Total Score

	EMPOWER-1			EMPOWER-2		
	Placebo (N= 127)	Emraclidine 10mg QD (N = 125)	Emraclidine 30mg QD (N = 127)	Placebo (N = 128)	Emraclidine 15mg QD (N = 122)	Emraclidine 30mg QD (N = 123)
Baseline (SD)	98.3 (8.16)	97.6 (7.65)	97.9 (7.89)	97.4 (8.22)	98.0 (8.49)	97.2 (7.75)
LS Mean (95% CI)	-13.5 (-17.0, -10.0)	-14.7 (-18.1, -11.2)	-16.5 (-20.0, -13.1)	-16.1 (-19.4, -12.8)	-18.5 (-22.0, -15.0)	-14.2 (-17.6, -10.8)

Efficacy
No significant improvement in PANSS scores

Tolerability
Well-tolerated with stable safety profile

AbbVie. (2024, November 11). *AbbVie provides update on Phase 2 results for Emraclidine in schizophrenia*. Accessed March 6, 2025. .
https://news.abbvie.com/2024-11-11-AbbVie-Provides-Update-on-Phase-2-Results-for-Emraclidine-in-Schizophrenia

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

>500-fold agonist selectivity for M₄ over other muscarinic receptors

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

PANSS Total Score

Better Symptom Reduction

PANSS Total Score Change from Baseline LS Mean[1] ±SEM

*p<0.05 vs Placebo
— Placebo
— 20 mg QD

Placebo: -5.7, -8.2, -7.7, -9.6, -10.2, -10.8
20 mg QD: -8.4, -11.5, -13.4, -16.4*, -20.2*, -18.2*

Baseline, Week 1, Week 2, Week 3, Week 4, Week 5, Week 6

Placebo N=70 → N=68
20 mg QD N=40 → N=35
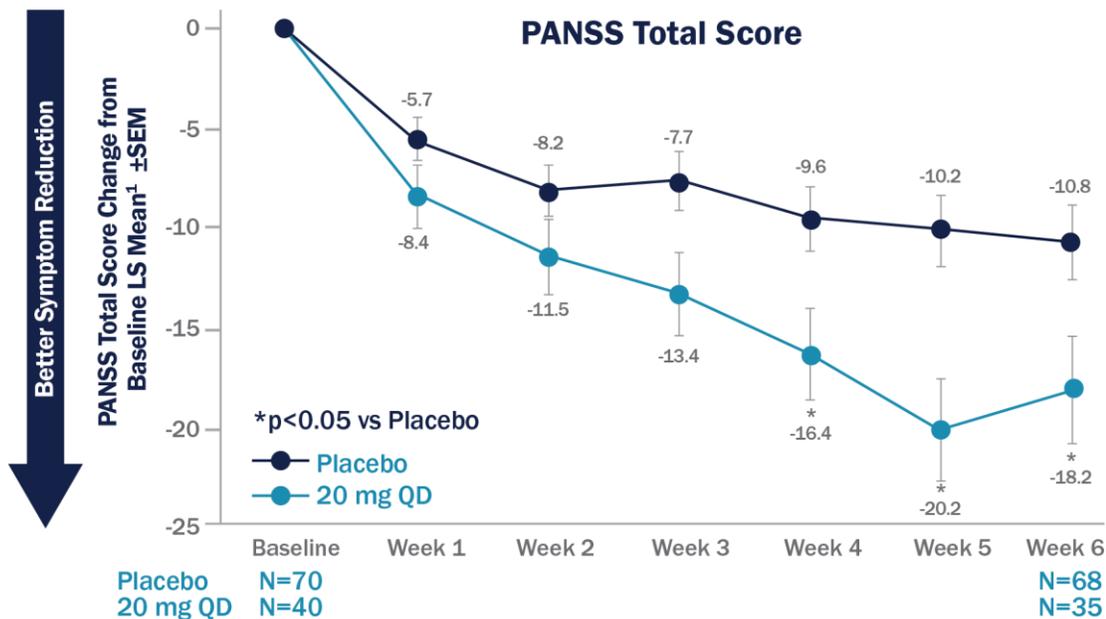
| Placebo: -18.8 pts | Effect Size |
| NBI-´568 20 mg: -18.2 pts* | d=0.61 |

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

	Placebo N=70	NBI-'586 20mg QD N=40
Somnolence	2 (2.9%)	5 (12.5%)
Dizziness	1 (1.4%)	5 (12.5%)
Headache	14 (20.0%)	1 (2.5%)
Nausea	2 (2.9%)	2 (5.0%)
Constipation	2 (2.9%)	2 (5.0%)
D/C due to AEs	5% across all dose arms vs. 4.3% for placebo	

- Gastrointestinal AEs were infrequent and similar to placebo. Few drug-induced movement disorders were reported. Weight change is similar to placebo.

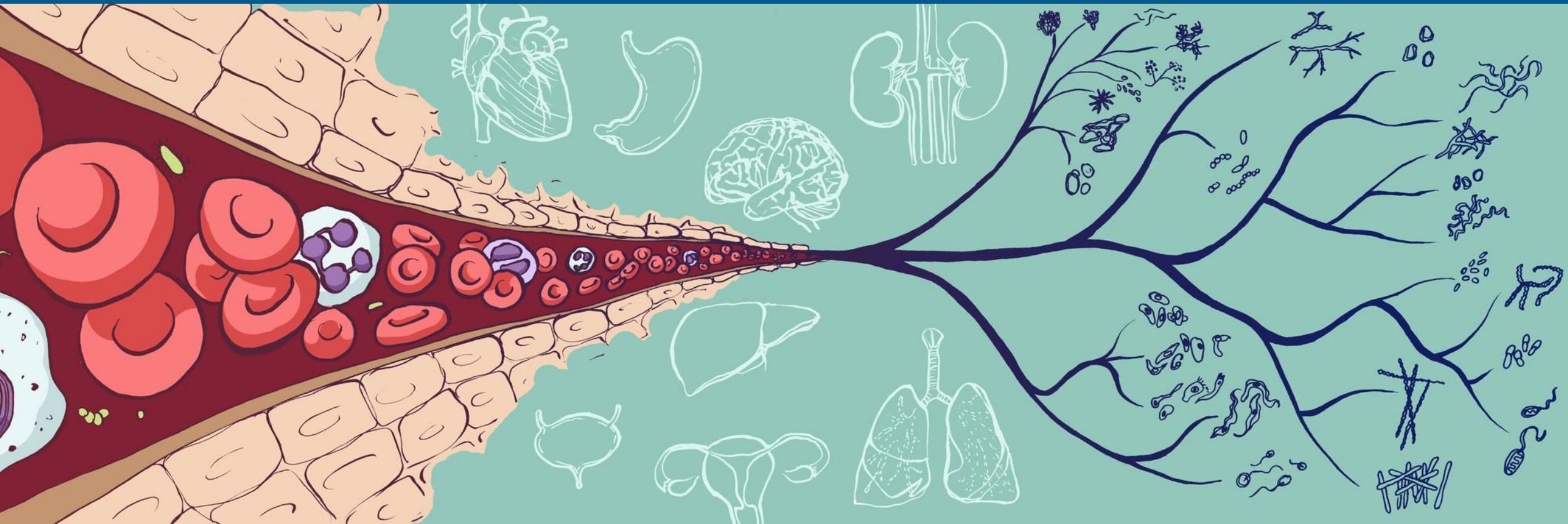- Cardiovascular-related events were infrequent and deemed not clinically relevant at any tested dose.

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

Other Investigational Muscarinic Agents

	Mechanism	Development Stage
NMRA-266	M_4 PAM	Placed on clinical hold by FDA 4/2024 due to pre-clinical data showing convulsions in rabbits
ML-007/PAC	M_4/M_1 Agonist + Peripherally Acting Anticholinergic	3 completed phase 1 trials without PAC complete. Phase 1 trial with PAC began 3/2024.
NBI-1117570	M_4/M_1 Agonist	Phase 1
NBI-1117569	M_4 Preferring Agonist	Phase 1
NBI-1117567	M_1 Preferring Agonist	Phase 1

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

Tobin AB. *Nat. Rev. Drug Discov.* 2024; 1-16. Neumora Therapeutics Announces Clinical Hold of Phase 1 NMRA-266 Study. Accessed 9-10-2024. https://ir.neumoratx.com/news-releases/news- release-details/neumora-therapeutics-announces-clinical-hold-phase-1-nmra-266. MapLight Therapeutics Announces Initiation of Phase 1 Clinical Trial for ML-007/PAC, Under Development for Schizophrenia and Alzheimer's Disease Psychosis. Accessed 9-10-2024. https://maplightrx.com/maplight-therapeutics-an-nounces-initiation-of-phase-1-clinical-trial-for-ml-007-pac-under-development-

Implications for the Evolving Schizophrenia Treatment Landscape

Identify Patients that May Benefit from New Treatment Approach

- **Newly diagnosed** – have not been exposed to risks associated with D2 antagonism

- **Inadequate response** to existing antipsychotics, particularly those with prominent cognitive deficits or intolerance to metabolic/EPS side effects of current drugs.

- Emerging research may link **genetic variants** (eg, *CHRM1/CHRM4* polymorphisms) or **neuroimaging markers** (prefrontal connectivity) to muscarinic response.

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

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

Overcoming Barriers to Our Newest FDA Approved Treatment

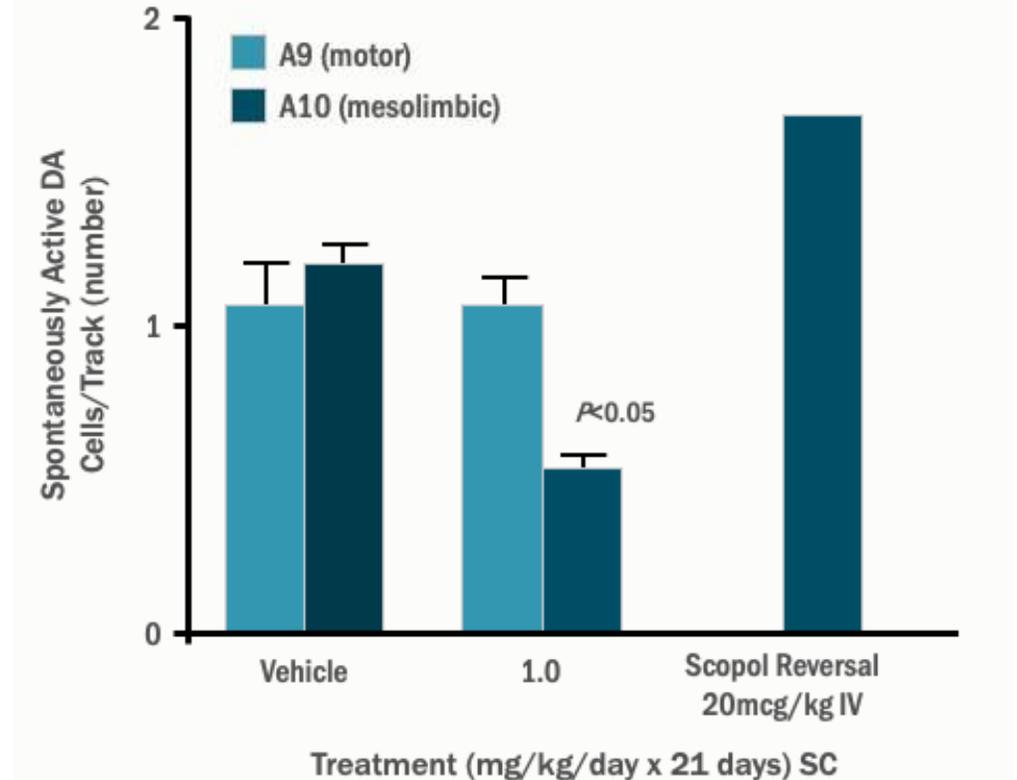# Xanomeline-Trospium: How to Initiate

Implementation issues:

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

Anticholinergics impacting efficacy:

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

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

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

Xanomeline-Trospium: How to Initiate

- **Titration issues:** The PI allows for a slower titration than used in the clinical trials, presumably to help mitigate adverse effects. The wording states:
  - The recommended starting dosage is one 50 mg/20 mg capsule (contains 50 mg of xanomeline and 20 mg of trospium chloride) orally twice daily *for at least two days*.

  - Increase the dosage to one 100 mg/20 mg capsule (contains 100 mg of xanomeline and 20 mg of trospium chloride) orally twice daily *for at least five days*.

  - The dosage may be increased to one 125 mg/30 mg capsule (contains 125 mg of xanomeline and 30 mg of trospium chloride) orally twice daily *based on patient tolerability*.

- **The food issue:** The exposure to trospium is decreased 85%-90% if taken with food. Patients must take X-T 1 hour before or 2 hours after a meal.
  - **Practical strategy:** dose X-T upon awakening or 1 hour before breakfast and then at bedtime (without food)

- **Peripheral anticholinergic burden:** Note use of other anticholinergics (e.g. overactive bladder meds) when initiating. Ask about LUTS in males when starting X-T. The max dose for geriatric patients is 100 mg/20 mg. Lastly, two contraindications are urinary or gastric retention.
  - **Practical strategy:** Use slower titration, taper off other anticholinergics, ask about urinary symptoms.

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

Xanomeline-Trospium: How to Initiate

- Monitoring LFTs: Rate of ALT or AST elevation >3x ULN was 2.8% for X-T vs 0.4% for PBO. 1.6% had elevated LFTs at some point, but the majority occurred within the first month and resolved with continued X-T exposure.
  - Practical strategy: PI states to obtain baseline LFTs including bilirubin and "and as clinically indicated during treatment." In the absence of clinical symptoms, consider repeating LFTs after 1 month to document lack of effect.

- Monitoring Heart rate: In the phase 3 studies the endpoint difference from placebo was +5.9 BPM, and in a dedicated ambulatory study the endpoint difference was +9.8 BPM.
  - Practical strategy: Baseline and periodically during treatment (as is often done when starting clozapine).

- Drug interactions: CYP2D6 contributes to xanomeline metabolism, but the PI does not recommend dose adjustment, but to monitor for adverse reactions.
  - Practical strategy: Consider a slower initial titration and lower maximal dose.

- Hepatic and renal dysfunction: Cannot use with Child-Pugh B or C. Higher exposure in cirrhosis patients who are Child Pugh A. Approximately 2-fold higher xanomeline exposure with eGFR 30-89 ml/min
  - Practical strategy: Consider a slower initial titration and lower maximal dose.

Key Learning Points

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

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

✓ Incorporating shared decision-making and adherence strategies to support long-term success

References

Embrace emerging treatments –

-Elevate care-

-Transform lives

Bernat Casero - www.bernatcasero.com

Practical Take-Aways

- Traditional schizophrenia treatment often focus on postsynaptic D2-binding, but shifting to presynaptic mechanisms and muscarinic acetylcholine receptor activation offers new hope for improved efficacy and reduced side effects.

- Emerging show potential as both monotherapy and adjunctive treatment options, targeting M1/M4 pathways with promising clinical trial data.

- By understanding the specific neurobiology of schizophrenia, clinicians can better identify which patients may benefit from muscarinic receptor activators, enabling more personalized and effective treatment approach.

References

Q&A