Psych Congress MasterClass

The Next Generation of Schizophrenia Treatment: Looking Beyond D2 and Exploring Novel Therapeutic Targets

Supported by an educational grant from Bristol-Myers Squibb

Faculty

Craig Chepke, MD, DFAPA

Adjunct Associate Professor of Psychiatry,
Sandra & Leon Levine Psychiatry
Residency Program at Atrium Health
Charlotte, NC

Medical Director,
Excel Psychiatric Associates
Huntersville, NC

Christoph U. Correll, MD

Professor of Psychiatry & Molecular Medicine,
The Donald and Barbara Zucker
School of Medicine at Hofstra/Northwell
New York, USA

Professor and Chair, Child and Adolescent Psychiatry
Charité – Universitätsmedizin
Berlin, Germany

Jonathan, Meyer, MD, DLFAPA

Voluntary Clinical Professor, Department of Psychiatry
University of California, San Diego
La Jolla, CA

Senior Academic Adviser
California Dept. of State Hospitals
Sacramento, CA

Faculty Disclosures

Craig Chepke, MD, DFAPA

Advisory Board– AbbVie, Acadia, Alkermes, Axsome, Biogen, Bristol-Myers Squibb, Corium, Idorsia, Intra-Cellular, Janssen, Lundbeck, Moderna, Neurocrine, Noven, Otsuka, Sage, Sumitomo, Teva; Advisory Board (spouse)– Bristol-Myers Squibb, Otsuka; Consultant– AbbVie, Acadia, Alkermes, Axsome, Biogen, Boehringer Ingelheim, Corium, Intra-Cellular, Janssen, Lundbeck, MedinCell, Moderna, Neurocrine, Noven, Otsuka, Sage, Sumitomo, Supernus, Teva; Research/Grant Support– Acadia, Axsome, Harmony, Neurocrine, Teva; Speaker's Bureau– AbbVie, Acadia, Alkermes, Axsome, Bristol-Myers Squibb, Corium, Intra-Cellular, Janssen, Lundbeck, Merck, Neurocrine, Noven, Otsuka, Sumitomo, Teva; Stocks/Ownership Interest– none.

Christoph U. Correll, MD

Consultant, honoraria and advisory boards: AbbVie, Acadia, Adock Ingram, Alkermes, Allergan, Angelini, Aristo, Biogen, Boehringer-Ingelheim, Bristol-Meyers Squibb, Cardio Diagnostics, Cerevel, CNX Therapeutics, Compass Pathways, Darnitsa, Delpor, Denovo, Eli Lilly, Gedeon Richter, Hikma, Holmusk, IntraCellular Therapies, Jamjoom Pharma, Janssen/J&J, Karuna, LB Pharma, Lundbeck, MedInCell, MedLink, Merck, Mindpax, Mitsubishi Tanabe Pharma, Maplight, Mylan, Neumora Therapeutics, Neurocrine, Neurelis, Newron, Noven, Novo Nordisk, Otsuka, PPD Biotech, Recordati, Relmada, Reviva, Rovi, Sage, Saladax, Sanofi, Seqirus, SK Life Science, Sumitomo Pharma America, Sunovion, Sun Pharma, Supernus, Tabuk, Takeda, Teva, Terran, Tolmar, Vertex, Viatris und Xenon; Grants: Boehringer Ingelheim, Einstein Foundation, Berlin, German Ministry of Health, German Research Foundation, Innovationsfond Germany, Janssen, National Institute of Mental Health (NIMH), Patient Centered Outcomes Research Institute (PCORI), Takeda, Thrasher Foundation; Shares (options): Cardio Diagnostics, Kuleon Biosciences, LB Pharma, Medlink, Mindpax, Quantic, Terran

Jonathan, Meyer, MD, DLFAPA

Reports having received advising fees in the prior 24 months from Alkermes, BioXcel, BMS, Cerevel, Delpor, ITCI, Neurocrine, Otsuka America, Inc., Relmada, Sumitomo, and Teva, and speaking fees in the prior 24 months from AbbVie, Alkermes, Axsome, BMS, ITCI, Neurocrine, Sumitomo, and Teva

Disclosures

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

Learning Objectives

LO#1 Describe the limitations of traditional D2-binding treatments for schizophrenia

LO#2 Assess the role of muscarinic acetylcholine receptor activation in schizophrenia, according to current neurobiological evidence

LO#3 Summarize the MOAs and latest efficacy, safety, and tolerability data associated with emerging muscarinic acetylcholine receptor activators for schizophrenia

LO#4 Evaluate the potential treatment implications of emerging muscarinic receptor activators for schizophrenia, including drug-drug interactions and risk/benefit discussions

Overview of the Current Schizophrenia Treatment Landscape

Craig Chepke, MD, DFAPA
Adjunct Associate Professor of Psychiatry,
Sandra & Leon Levine Psychiatry Residency Program
at Atrium Health
Charlotte, NC
Medical Director, Excel Psychiatric Associates
Huntersville, NC

A Historical Perspective on the Diagnostic Perception of Schizophrenia

1893

Emil Kraepelin:
Dementia Praecox
(chronic, progressive brain illness)

1911

Eugen Bleuler:
The Schizophrenias
(incoherence of cognition & affect)

1939

Kurt Schneider:
First-Rank Symptoms
(hallucinations & delusions)

1980

DSM-III
41 years later
Established primacy of First-Rank Symptoms

Perhaps because D_2 antagonists worked for them

2013

DSM-5
De-emphasized First-Rank Symptoms,
but most clinicians haven't followed suit.

Much of the field seems to perceive schizophrenia as an illness of positive symptoms with a "terminal" course.

Katschnig, H. *Journal of Evaluation in Clinical Practice.* 24.5 (2018):1093-1100. Andreasen, NC. *Schizophrenia Research*. 28.2-3 (1997): 105-109. Hoenig, J. *The British Journal of Psychiatry.* 142.6 (1983): 547-556. Tandon, R, et al. *Schizophrenia Research.* 150.1 (2013): 3-10.

Schizophrenia is a Multidimensional Illness...

- **Affective Symptoms**: Depression, Anxiety, Suicidality
- **Physical Comorbidities**: Cardiovascular diseases, Inflammation, Oxidative Stress
- **Cognitive Dysfunction**: Attention, Working Memory, Executive functioning, Processing speed
- **Negative Symptoms**: Affective flattening, Anhedonia, Amotivation, Asociality, Alogia
- **Positive Symptoms**: Hallucinations, Delusions, Thought disorder, Hostility, Excitability

...but we've had a mostly 2-dimensional view of it for 45 years, and a 1-dimensional treatment target for 70 years:

Postsynaptic D_2 receptors

Carbon et al. *CNS Spectr.* 2014;19:38. Millan et al. *Eur Neuropsychopharmacol.* 2014;24:645. Morrens et al. *Front Psychiatry*. 2014;5:145. Millan et al. *Nat Rev Drug Discov.* 2012;11:141. Ventriglio et al. *Front Psychiatry.* 2016;7:116. Pillinger et al. *Mol Psychiatry*. 2019;24:928.

The Landscape of Antipsychotics for Schizophrenia Has Expanded Markedly

Time of FDA Approval

Typical/First-Generation Antipsychotics

1950

1957
Chlorpromazine
Perphenazine

1959
Trifluoperazine

1960

1960
Fluphenazine

1962
Thioridazine

1967
Haloperidol
Thiothixene

1970

1975
Molindone
Loxapine

1980

1984
Pimozide

Atypical/Second-Generation Antipsychotics

1990

1989
Clozapine

1993
Risperidone

1996
Olanzapine

1997
Quetiapine

2000

2001
Ziprasidone

2006
Paliperidone

2009
Iloperidone
Asenapine

Dopamine partial agonists

2002
Aripiprazole

2010

2010
Lurasidone

2015
Brexpiprazole
Cariprazine

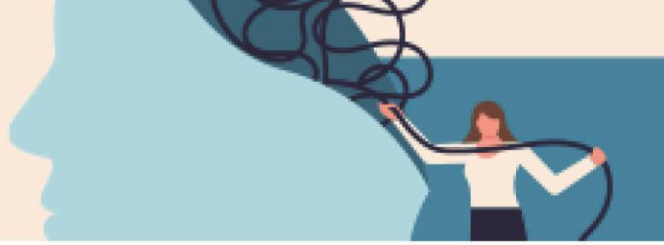
2020

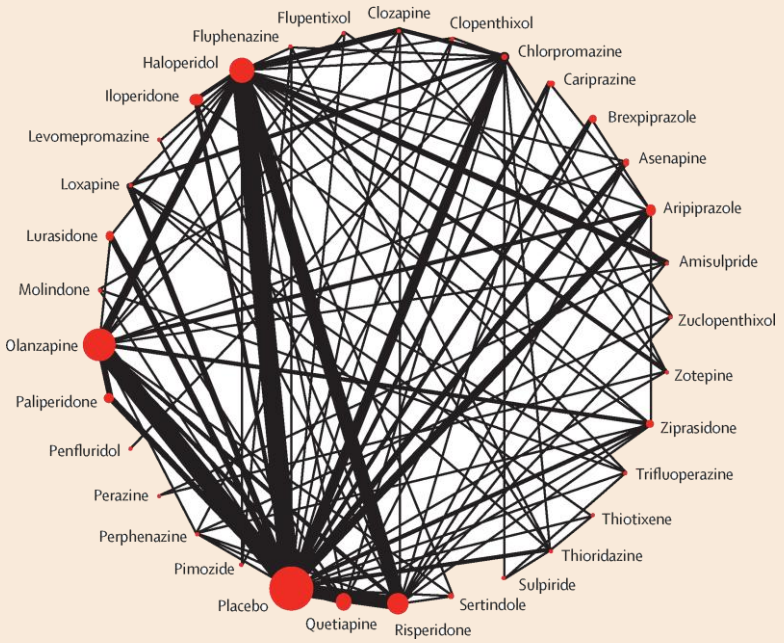
2019
Lumateperone

But how much change has there really been?

Huhn M, et al. *The Lancet*. 394.10202 (2019): 939-951. Schultz SH, et al. *Am Fam Physician*. 2007;75:1821-1829.

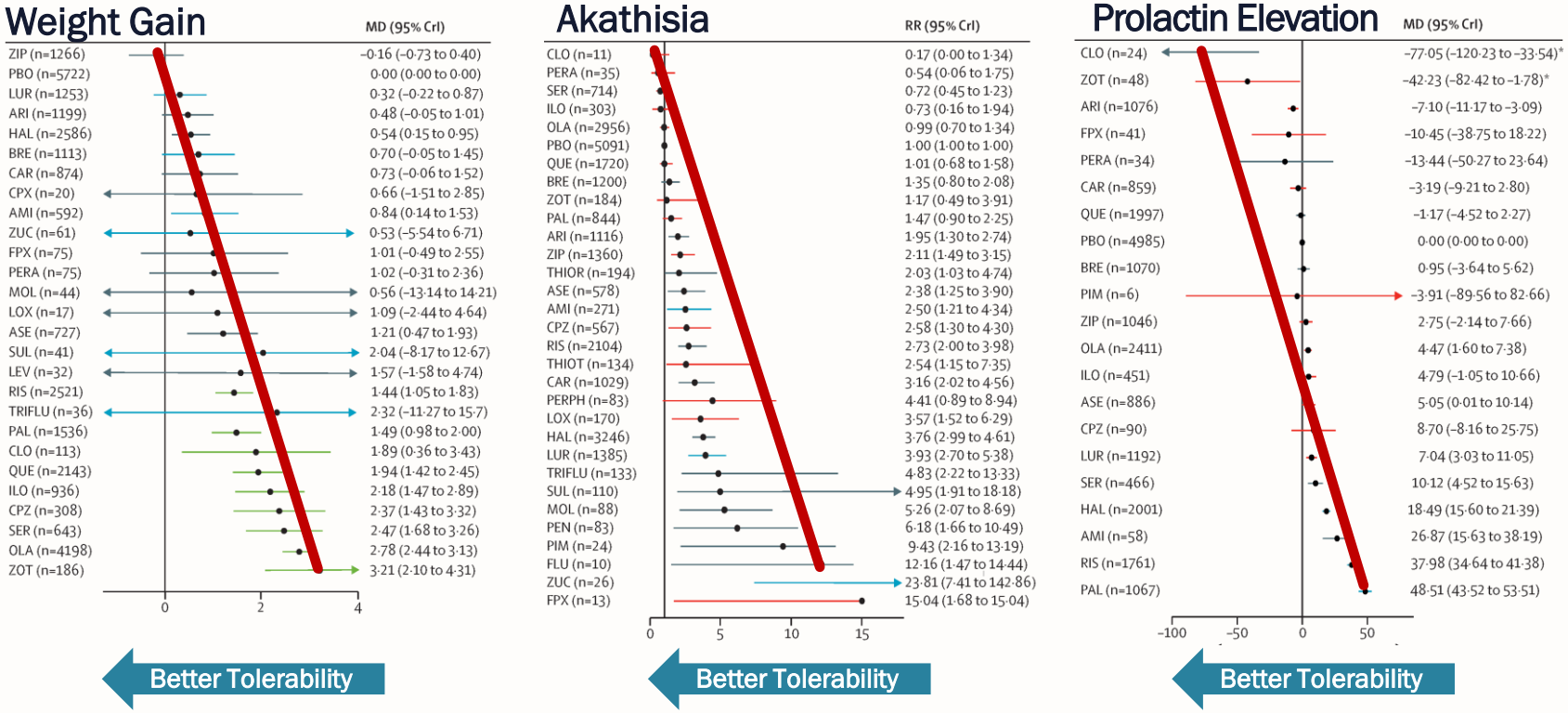
Antipsychotics Have a High Degree of Variability in Tolerability





Network of Comparisons

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



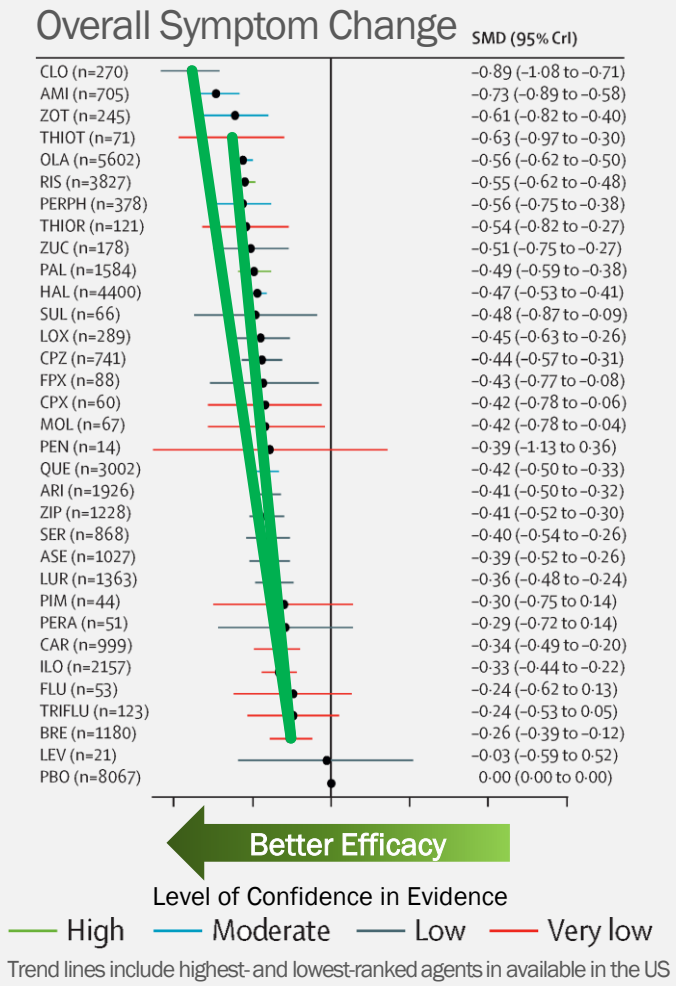
Level of Confidence in Evidence: High Moderate Low Very low

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

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

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

Despite Many Options, There is Little Variability of Efficacy in Historical Treatments



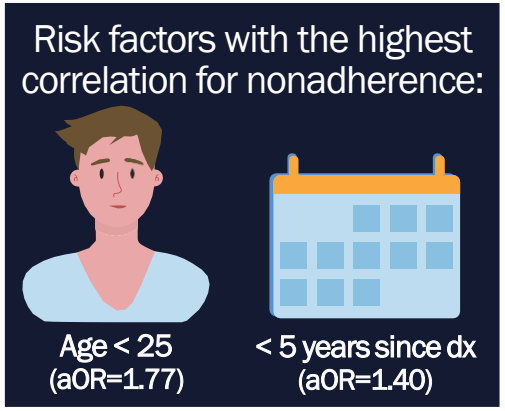
Trend lines include highest- and lowest-ranked agents in available in the US

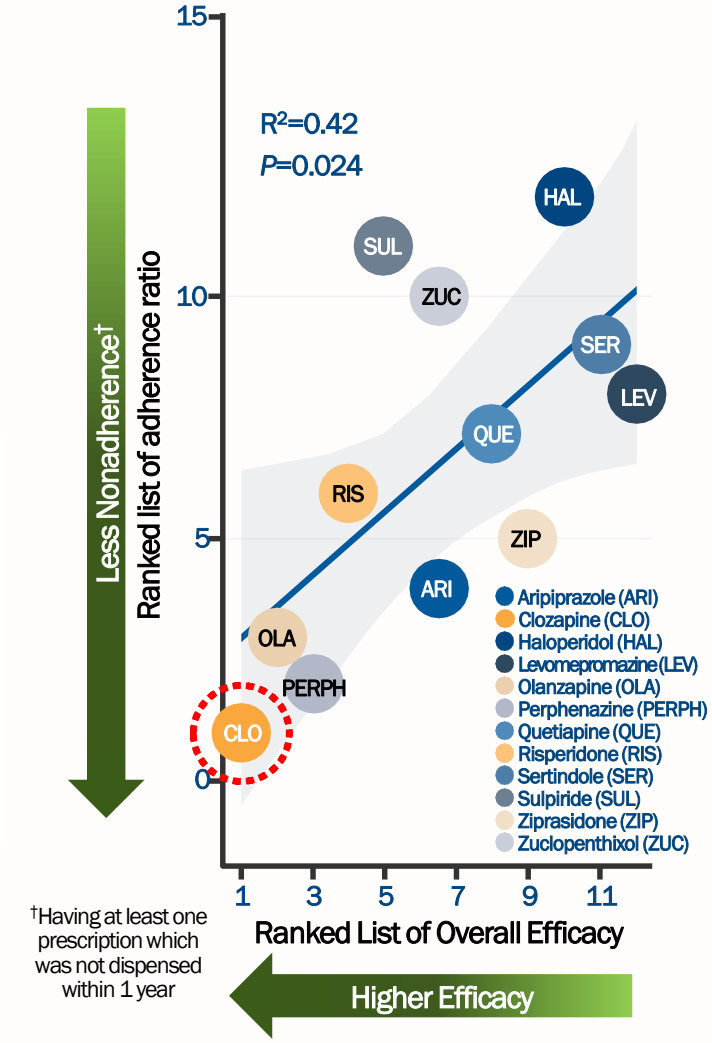
- Although there were many new antipsychotics introduced from 1957-2023, there was very little progress in overall efficacy
- Especially if one excludes the unrivaled (and thus far unduplicated) efficacy of clozapine

Researchers combined these data with a Finnish registry study and found that:

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

(n=29,956, 2015-2016)



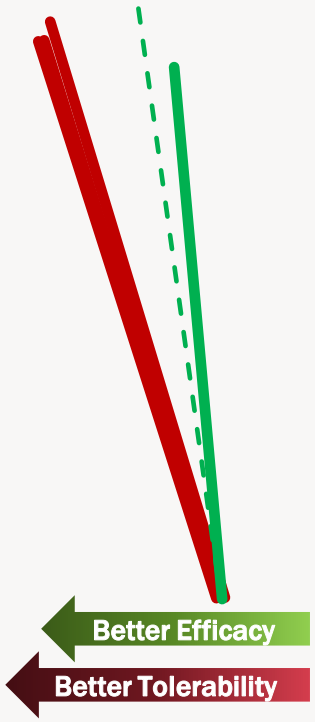


†Having at least one prescription which was not dispensed within 1 year

Huhn M, et al. *The Lancet.* 394.10202 (2019): 939-951. Lieslehto J, et al. *Schizophrenia Bulletin*. 48.3 (2022): 655-663.

The Price of Our Obsession with Post-Synaptic D_2 Receptors

Looking back, improvements in efficacy seem negligible...



...and not evenly applied

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

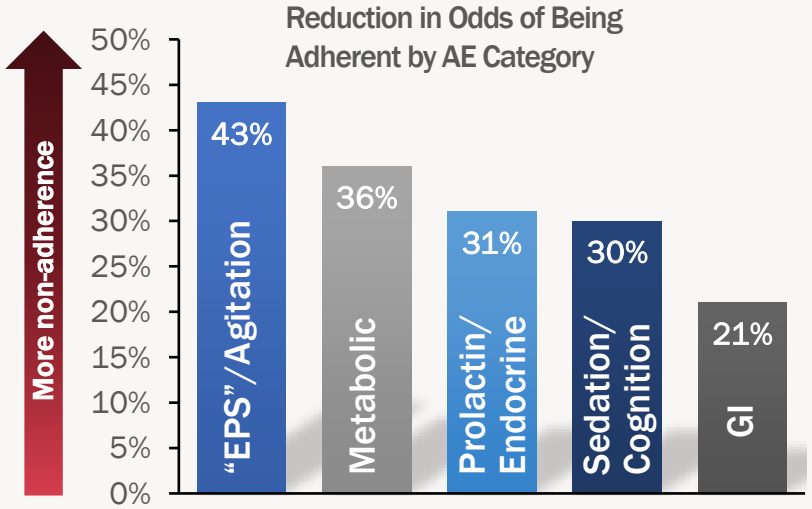
Overall, only ~14% achieve recovery

More excess CV deaths than from suicide

And far too many die far too young

Overall life expectancy reduced 10–20 years

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



EPS = Extrapyramidal Symptoms (but is a relatively meaningless term); GI = gastrointestinal; AE = Adverse Event

Huhn, M., et al. The Lancet 394.10202 (2019): 939-951. DiBonaventura M et al. BMC Psychiatry 2012;12:20. Velligan DI, et al. Schizophr Res. 1997;25(1):21-31 Mitchell AJ, et al. Schizophr Bull. 2013;39(2):306-318. Jääskeläinen, E, et al. Schizophrenia bulletin 39.6 (2013): 1296-1306.

ENOUGH!!!!!!

The Primary Dopamine Dysfunction In Schizophrenia Is Not Post-Synaptic

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

- Effect sizes 0.63 to 1.25

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

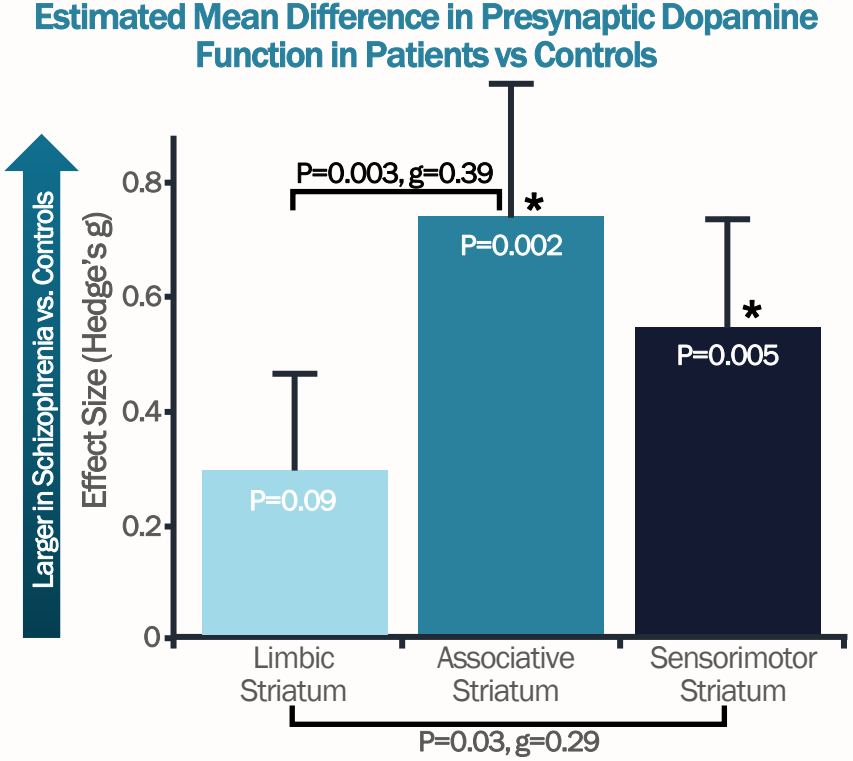
- Also with moderate to large effect sizes

Whereas

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

- (Independent of the effects of antipsychotics)

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



Modern studies with higher resolution imaging find:

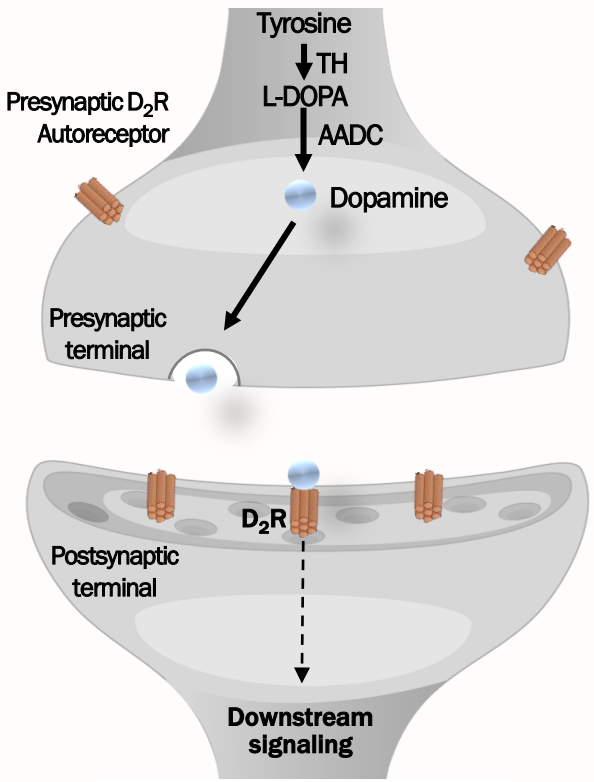
- Dopaminergic function **in humans** is significantly elevated in **associative** and **sensorimotor** striatum
- ...but <u>not</u> in the limbic striatum, as in mouse models

PET = Positron Emission Tomography; SCZ =schizophrenia

Howes OD, S Kapur. Schizo*phr. Bull.* 35.3 (2009): 549-562. McCutcheon RA, et al. *Trends Neurosci.* 42.3 (2019): 205-220. McCutcheon RA, et al. *Schizophr. Bull.* 44.6 (2018): 1301-1311.

How D_2 Antagonists Work in Schizophrenia

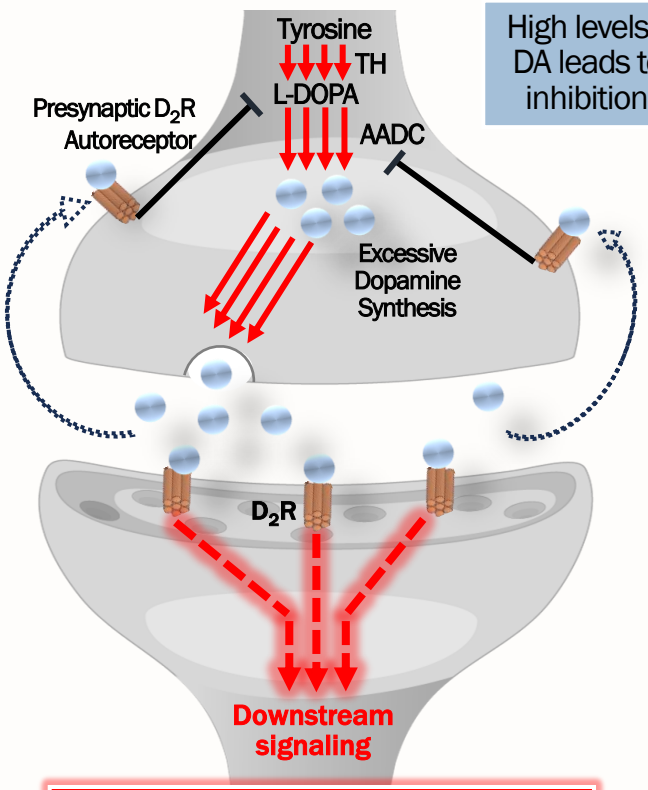
Healthy Controls



Normal Dopamine Release
Normal Dopamine Signaling

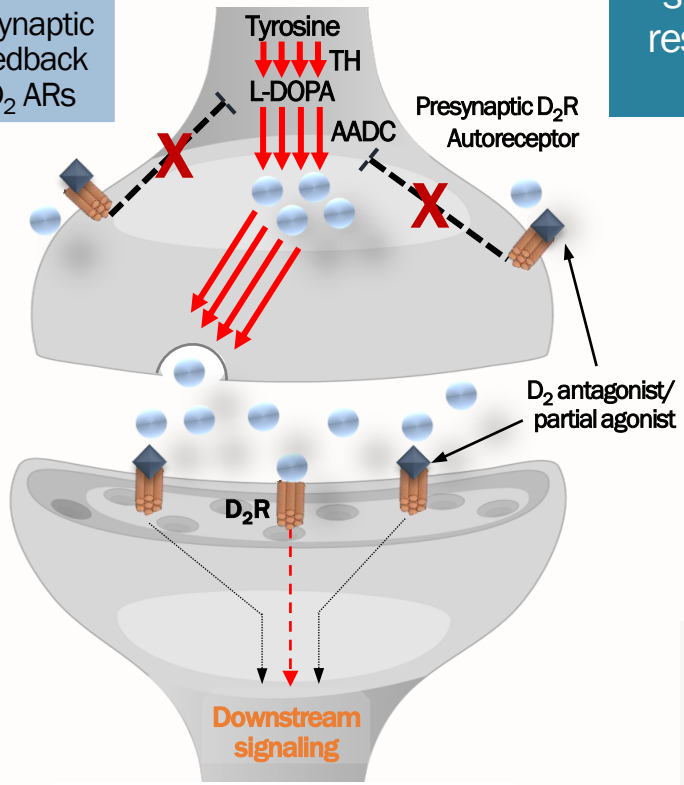
Schizophrenia: Unmedicated

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



Excessive Dopamine Release Causes Excessive Dopamine Signaling

Schizophrenia: with D_2 Antagonist



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

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

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

...but paradoxically may also compound the problem.

Dopamine

D_2 receptor

D_2 antagonist/partial agonist

D_2R = dopamine D_2 receptors; AR=Autoreceptor; DA = dopamine; TH = Tyrosine Hydroxylase; AADC = aromatic L-amino acid decarboxylase.

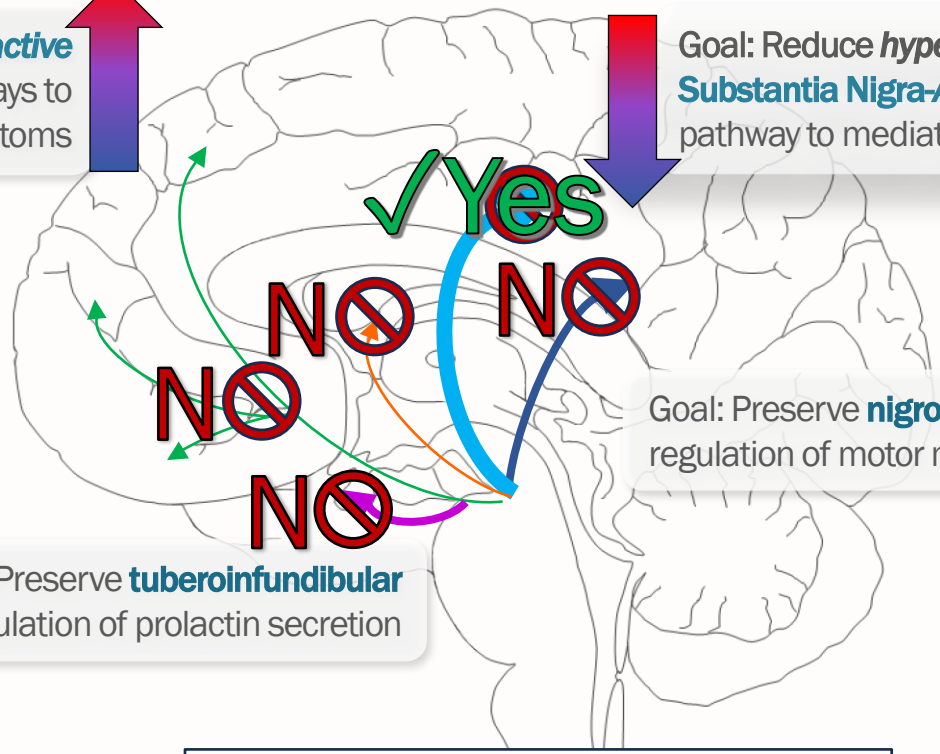
Halff EF, et al. *Trends in Neurosciences.* 2023; 46 (1): 60-74. Meyer JM. Ch 19 - *Pharmacotherapy of Psychosis and Mania*. In: Brunton LL, ed. Goodman & Gilman's Pharmacological Basis of Therapeutics. 14th Ed. Chicago, Illinois: McGraw-Hill; 2022: pp. 357-84.

Do D_2-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

Reduction of dopamine signaling by D_2 antagonist or partial agonist

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

DA = dopamine; SM = sensorimotor; SNASM = Substantia Nigra-Associative and Sensorimotor Cortex.

Correll CU, et al. *J Clin Psychiatry*. 2022 Feb 15;83(1):SU21204IP1. McCutcheon RA, et al. *Trends Neurosci.* 2019;42(3):205-220

We've Been Bailing Water Out of a Sinking Ship Instead of Fixing the Leak

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).
- While tolerability has somewhat improved over the past 70 years, there's been little to no improvement in efficacy, 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.

Next Generation Schizophrenia Treatments: Novel MOAs and Emerging Agents

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

The antipsychotic action of chlorpromazine was discovered in 1952

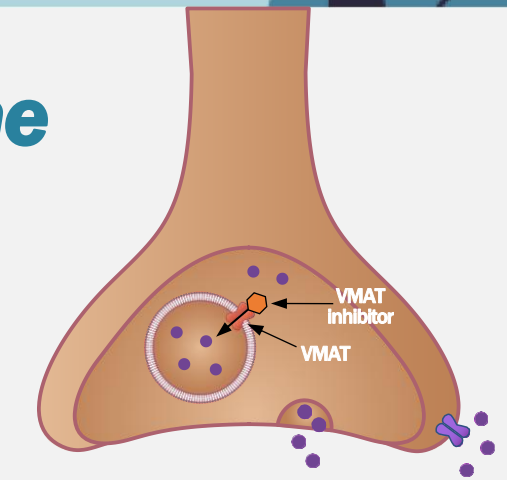
However, another medication's antipsychotic efficacy was also noticed that year...

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.



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.

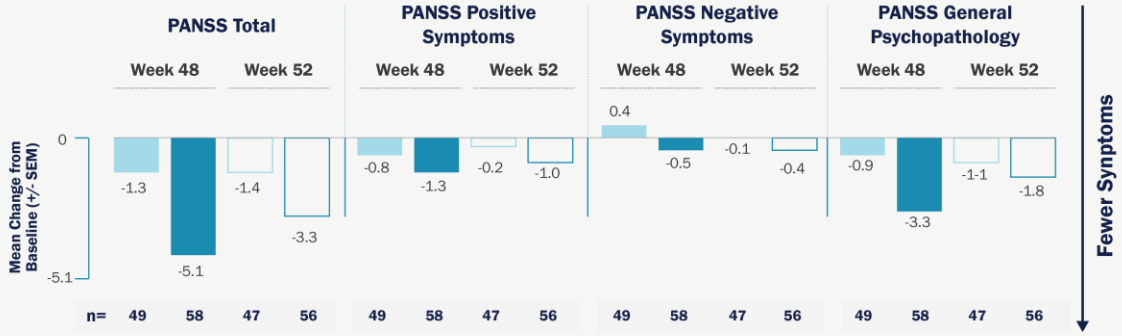
- **But by the end of the decade, the field had largely chosen the path of creating successive iterations of chlorpromazine and its successors.**
- **Postsynaptic D_2 blockade has been the dominant paradigm ever since.**

VMAT = Vesicular Monoamine Transporter; CNS = Central Nervous System; DA = dopamine; NE = norepinephrine

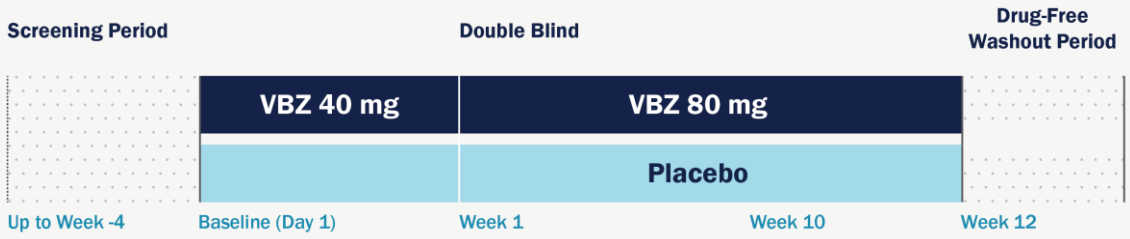
Bleuler M, et al. *Acad Sci*. 1955;61:167-73. Nur S, et al. *Cochrane Database Syst Rev*. 2016;4(4):CD012122. Published 2016 Apr 28. Ashcroft GW, et al. *J Ment Sci* .1961;107:287-93. Meyer, JM. *CNS Spectrums*. 2016;21(S1): 13-24.

Potential for Antipsychotic Effect with Valbenazine

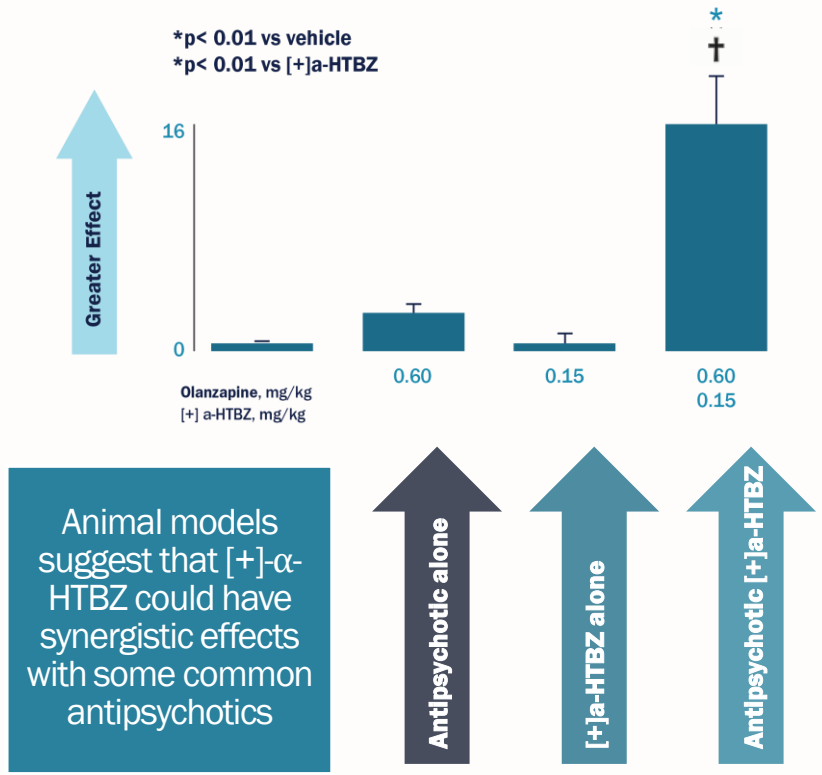
Valbenazine is a reversible VMAT2 inhibitor which has been approved for Tardive Dyskinesia since 2017. It is selectively converted to tetrabenazine's active [+]-α-HTBZ metabolite, its most potent and selective reversible of VMAT2



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.



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. https://clinicaltrials.gov/study/NCT05110157.

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

Muscarinic Acetylcholine Receptor Activation

Christoph U. Correll, MD
Professor of Psychiatry and Molecular Medicine
The Donald and Barbara Zucker School of Medicine at Hofstra/Northwell
New York, New York
Professor and Chair, Child and Adolescent Psychiatry
Charité – Universitätsmedizin
Berlin, Germany

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 [^{3}H]-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

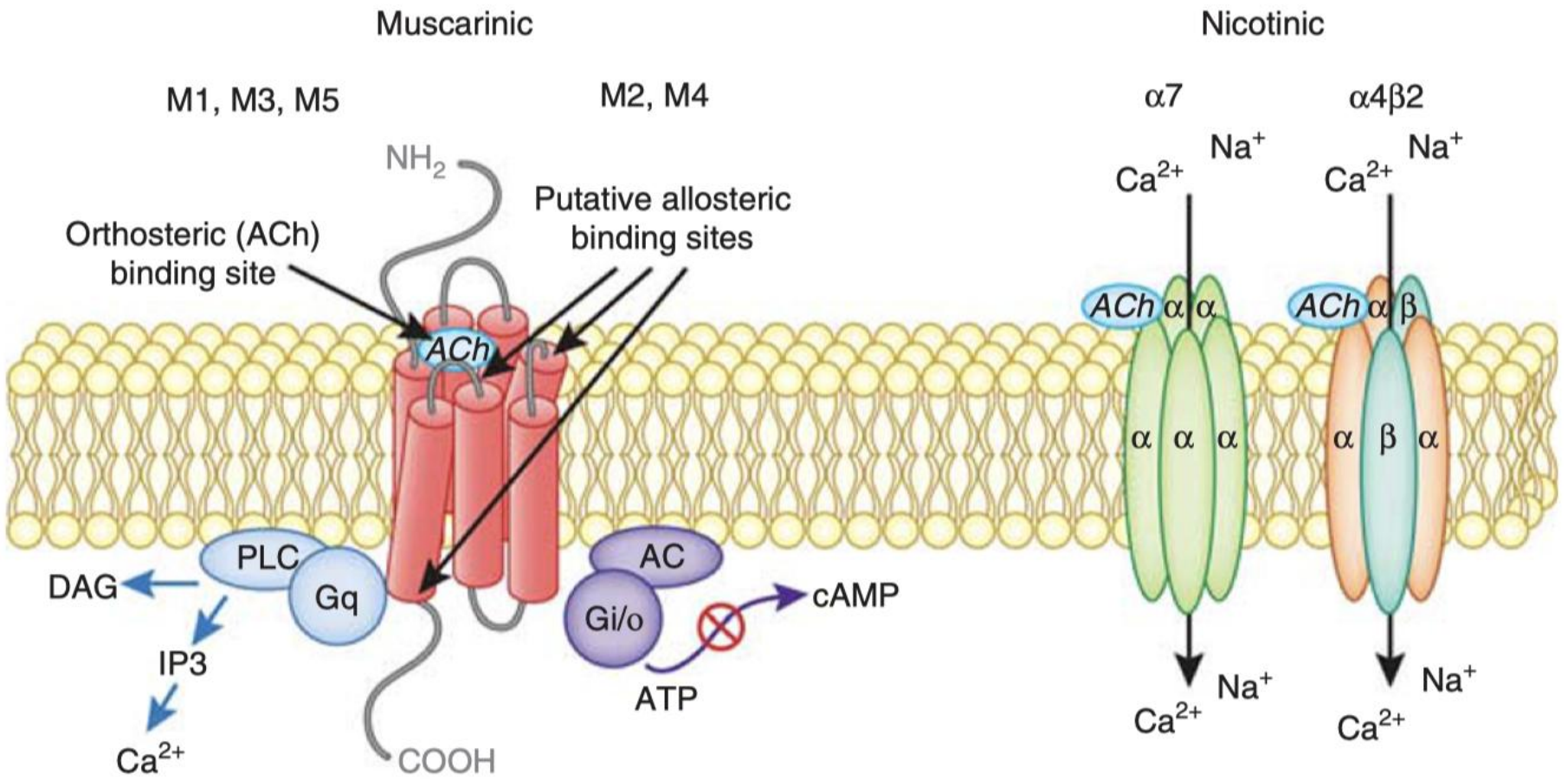
2015
M_4 PAM effects on state-dependent alteration in sleep/wake ralated to AP-like effects

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.

Yohn SE, et al. *Trends Pharmacol Sci.* 2022 Dec;43(12):1098-1112.

The Cholinergic System: Nicotinic vs Muscarinic Cholinergic Receptors



NICOTINIC RECEPTORS

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

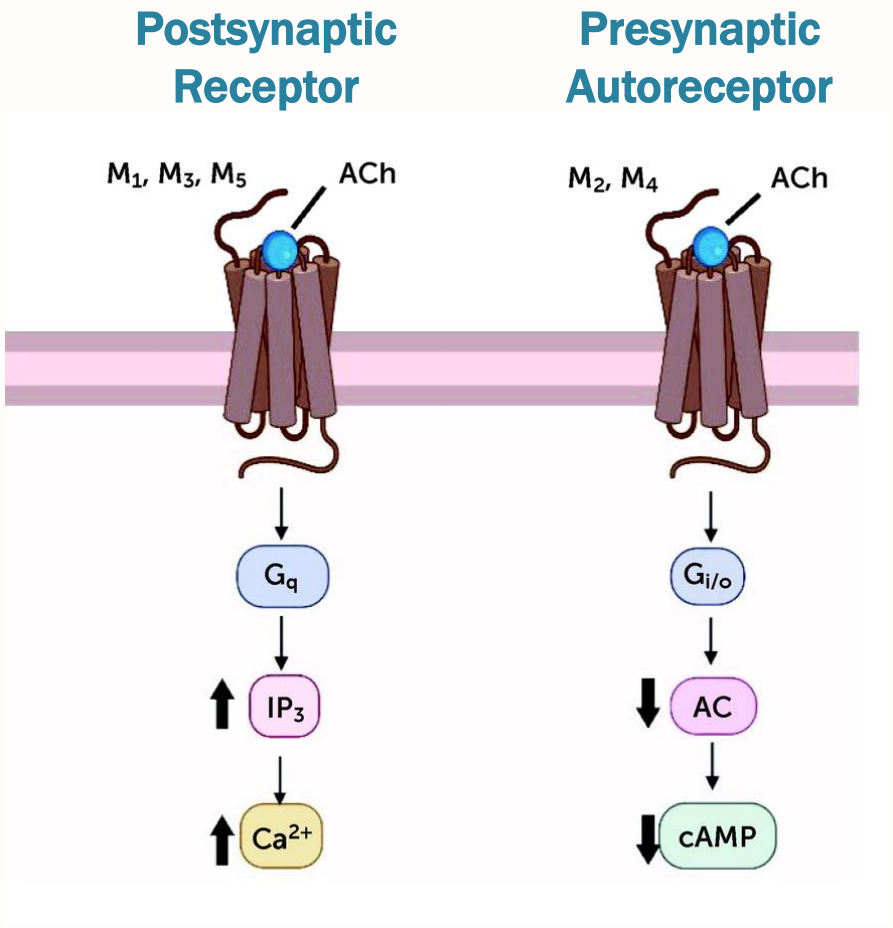
MUSCARINIC RECEPTORS

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

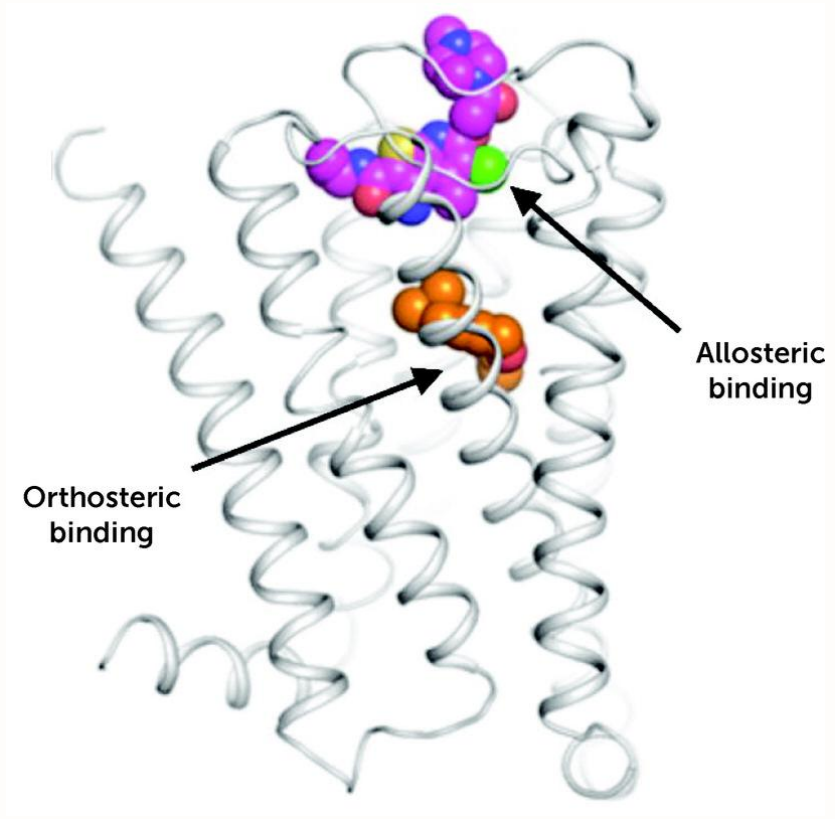
CNS = central nervous system; PNS = peripheral nervous system.

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

Signaling Selectivity Among Muscarinic Acetylcholine M1-M5 Receptors



Stimulatory



Inhibitory

Image Credit and Reference: Paul SM, et al. *Am J Psychiatry.* 2022 Sep;179(9):611-627. https://psychiatryonline.org/doi/10.1176/appi.ajp.21101083.

Quantification and Localization 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.)

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

Triple Mechanism of Action for Antipsychotic Activity of Muscarinic Agonism

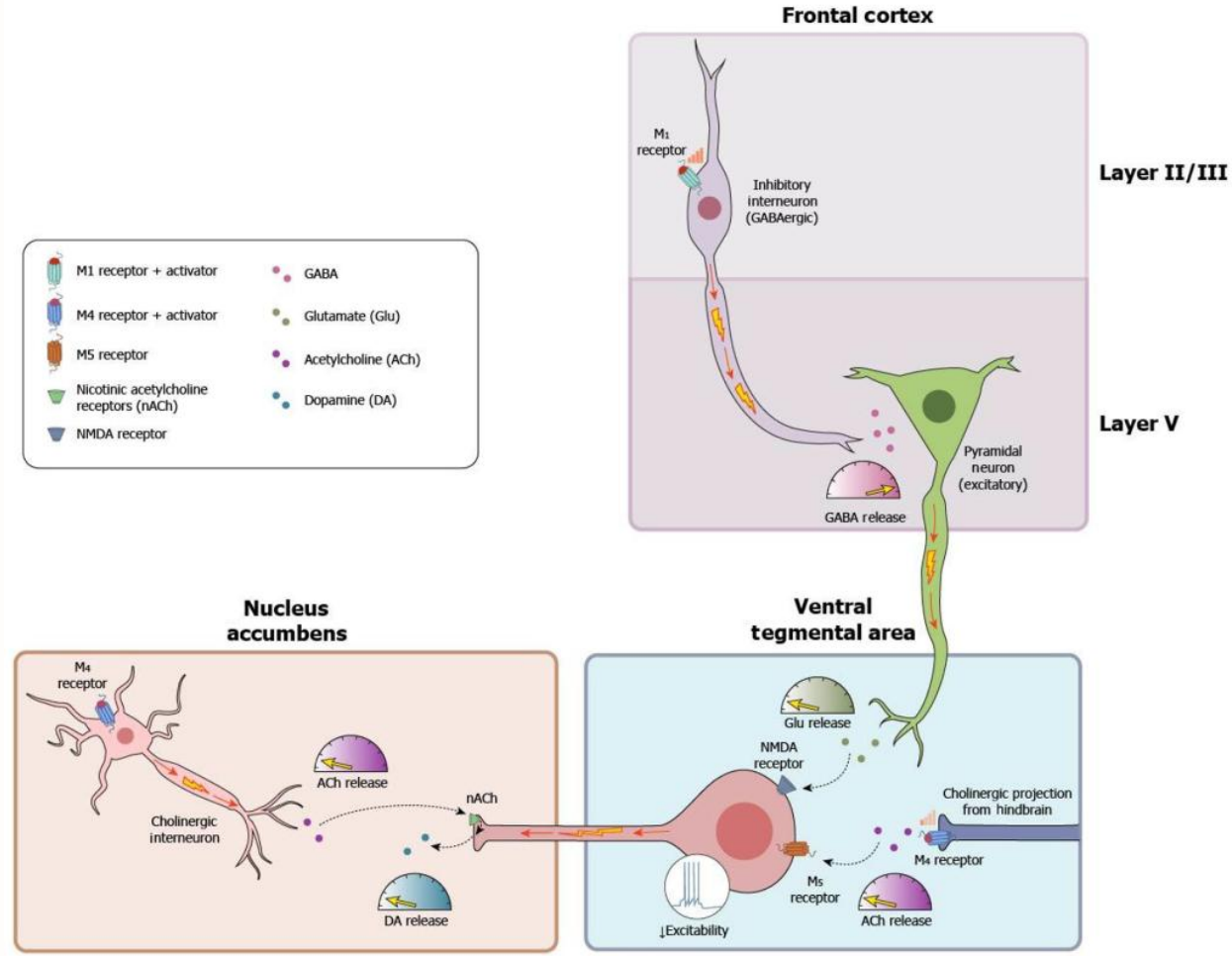
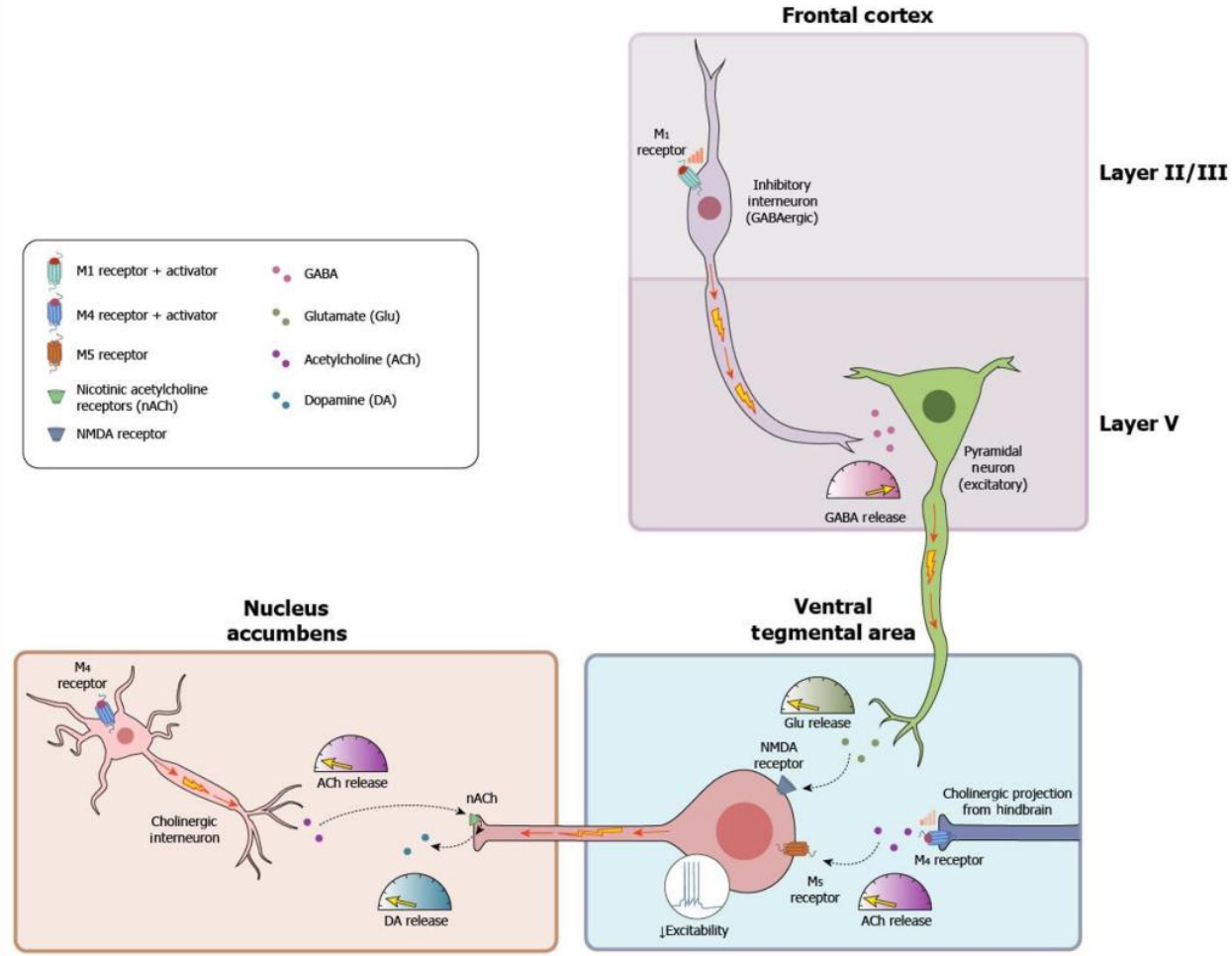


Image Credit and Reference: Yohn SE, et al. *Trends Pharmacol Sci*. 2022 Dec;43(12):1098-1112. Trends in Pharmacological Sciences, https://www.sciencedirect.com/science/article/pii/S0165614722002024 .

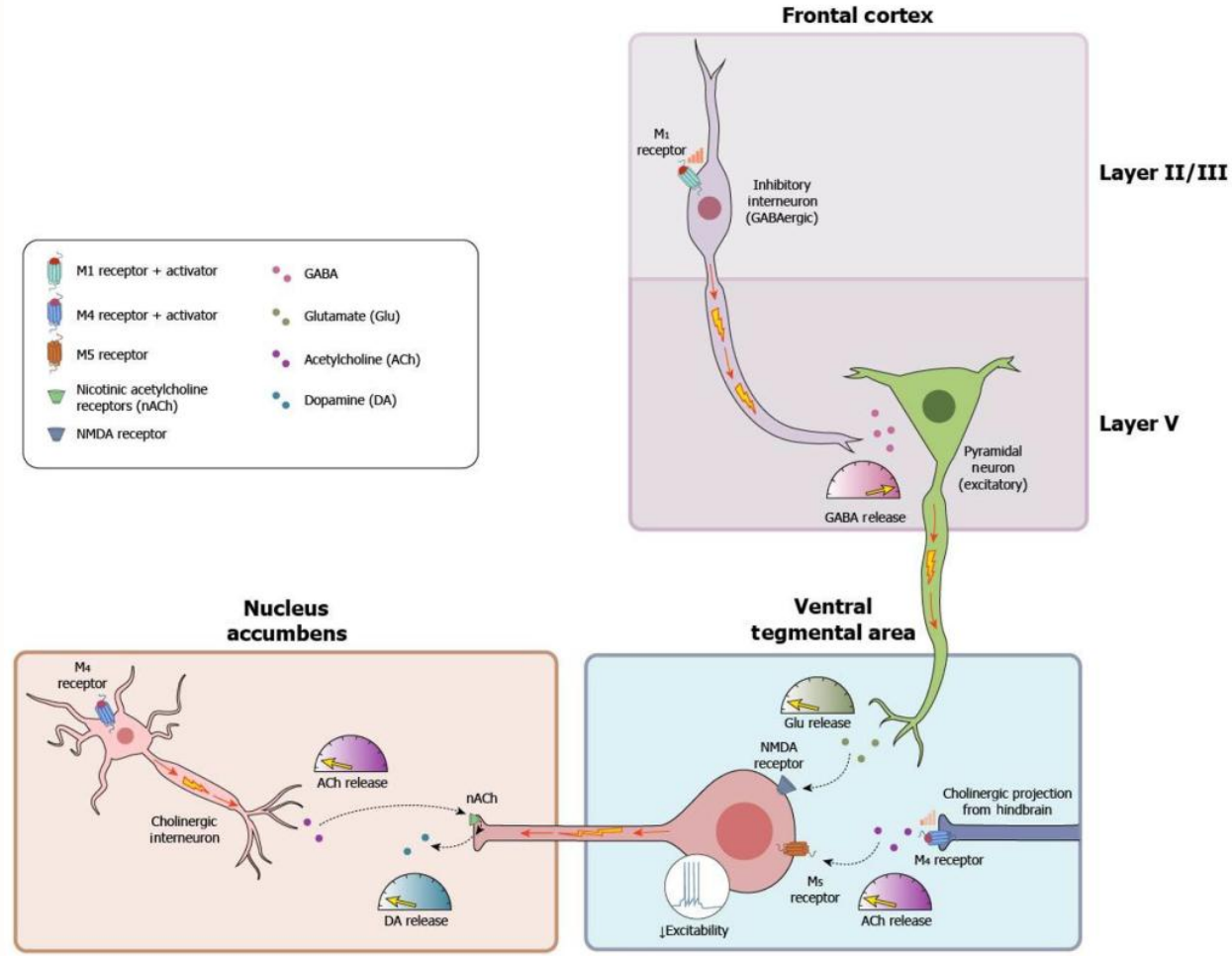
Triple Mechanism of Action for Antipsychotic Activity of Muscarinic Agonism



Activation of M4 receptors on cholinergic projections from the hindbrain results in decreased acetylcholine release to the ventral tegmental area (VTA), resulting in decreased dopamine release.

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

Triple Mechanism of Action for Antipsychotic Activity of Muscarinic Agonism



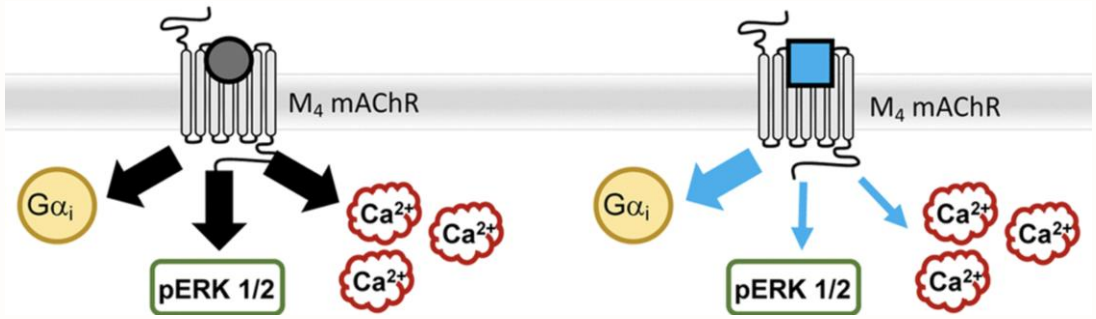
Activation of M4 receptors on cholinergic projections from the hindbrain results in decreased acetylcholine release to the ventral tegmental area (VTA), resulting in decreased dopamine release.

Activation of M1 receptors on GABAergic interneurons in the frontal cortex results decreased glutamate to the ventral tegmental area (VTA), resulting in decreased dopamine release.

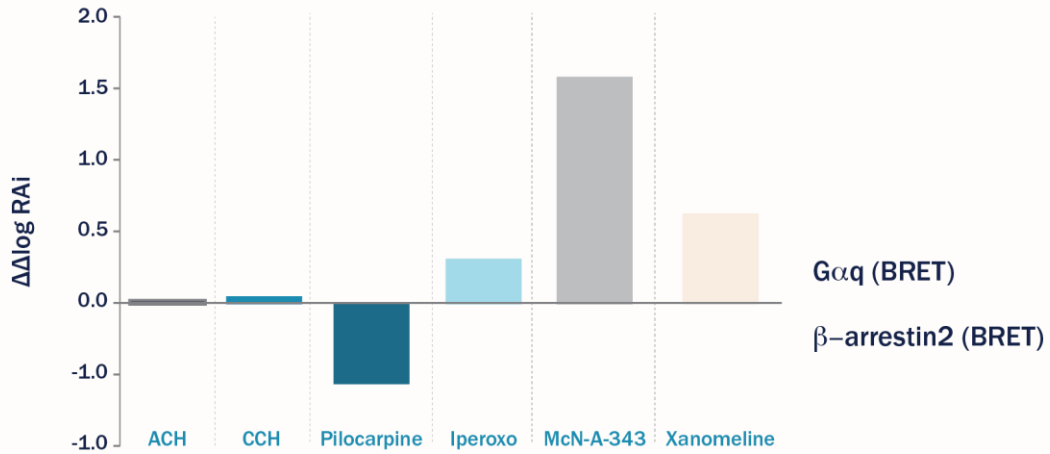
Image Credit and Reference: Yohn SE, et al. *Trends Pharmacol Sci*. 2022 Dec;43(12):1098-1112. Trends in Pharmacological Sciences, https://www.sciencedirect.com/science/article/pii/S0165614722002024 .

Xanomeline: “Biased Agonism” at M4 & M1 Receptors

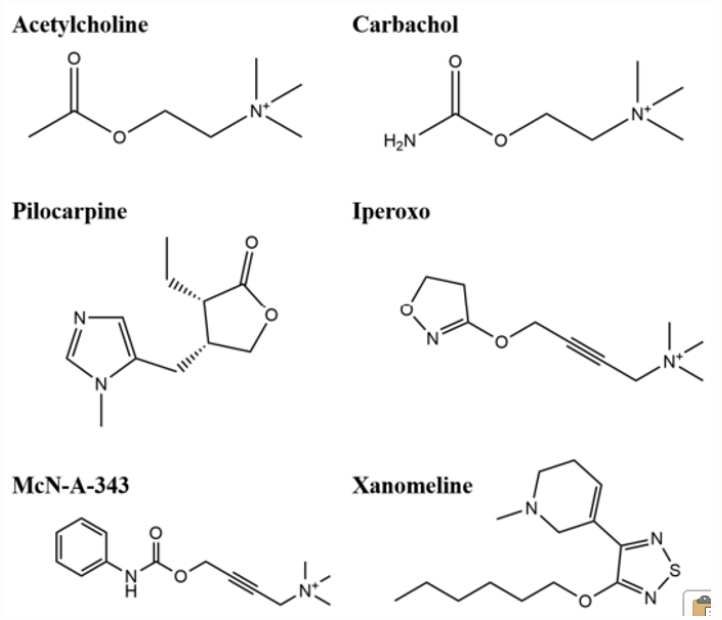
M4 Ach Receptor Activation: Differential Downstream Effects



M1 Ach Receptor Activation: Differential Downstream Effects



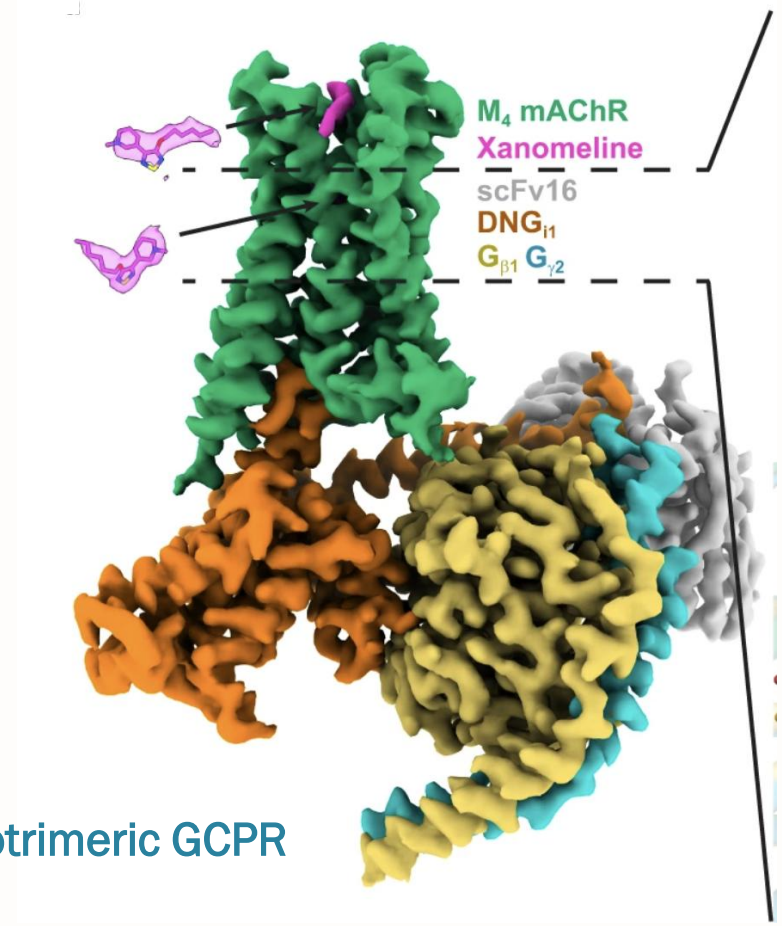
2D chemical structures of the six M1AChR Agonists

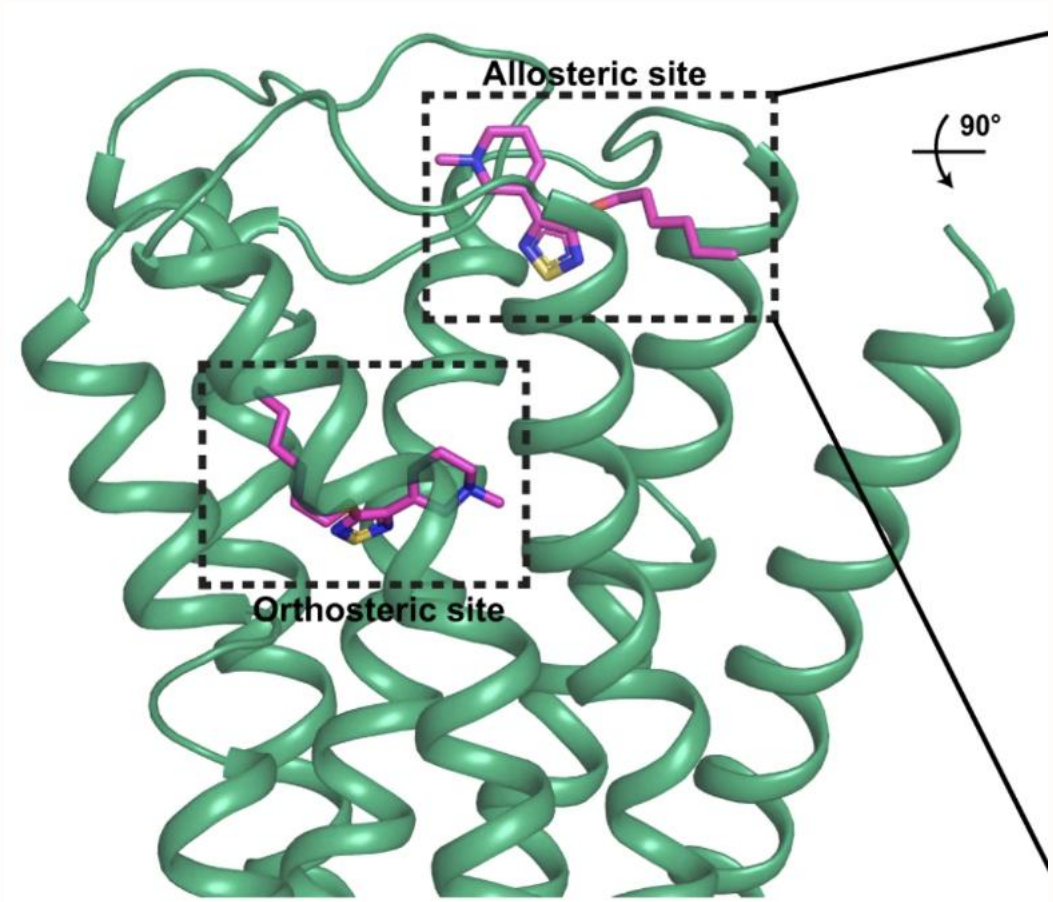


BRET = bioluminescent resonance energy transfer assay.
Image Credit:
www.sciencedirect.com/org/science/article/abs/pii/S1948719322001207
McDonald JK, et al. *ACS Chem. Neurosci.* 2022, 13, 8, 1206–1218.
Wang D, et al. Int J Mol Sci. 2023, Apr 16;24(8):7356.

Xanomeline: An M4 AChR "Dual Site, Single Target" (DSST) Concomitant Engaging Agent

Cryo Electron microscope M4 AChR





Burger WAC, et al. *Nat Commun.* 2023 Sep 6;14(1):5440.
Image Credit: https://www.nature.com/articles/s41467-023-41199-5.

ORIGINAL CONTRIBUTION

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

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

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

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

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

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

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

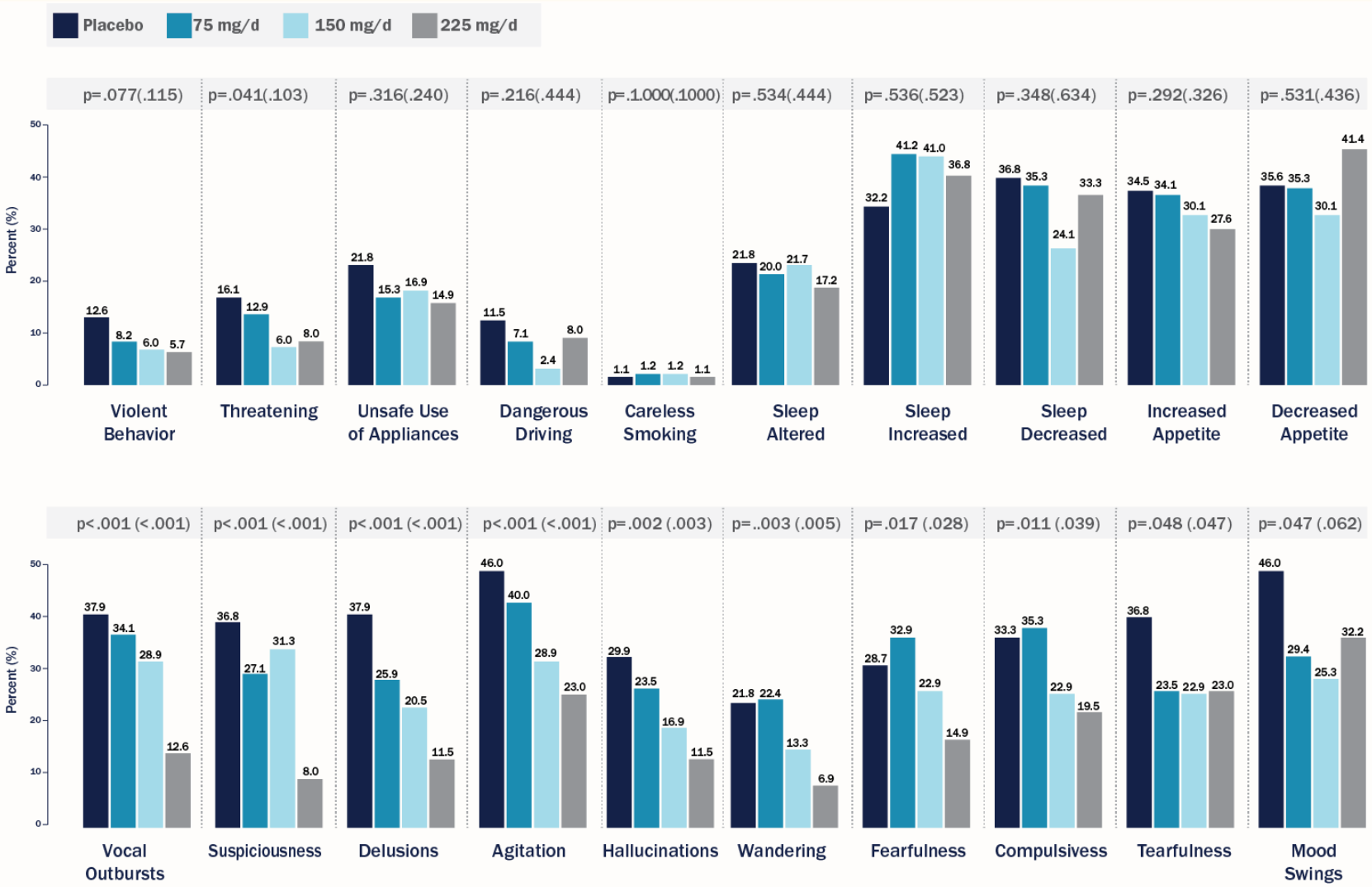
Outcome Measures: Scores on the cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-Cog), the Clinician's Interview-Based Impression of Change (CIBIC+), the Alzheimer's Disease Symptomatology Scale (ADSS), and the Nurses' Observational Scale for Geriatric Patients (NOSGER).

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

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

Arch Neurol. 1997;54:465-473

Alzheimer's Disease Symptomatology Scale: Percentage of Patients in Each Treatment Arm with Symptom Severity Increased Over Baseline*



P-values are for dose response and in parenthesis for xanomeline 225 mg/day vs placebo

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

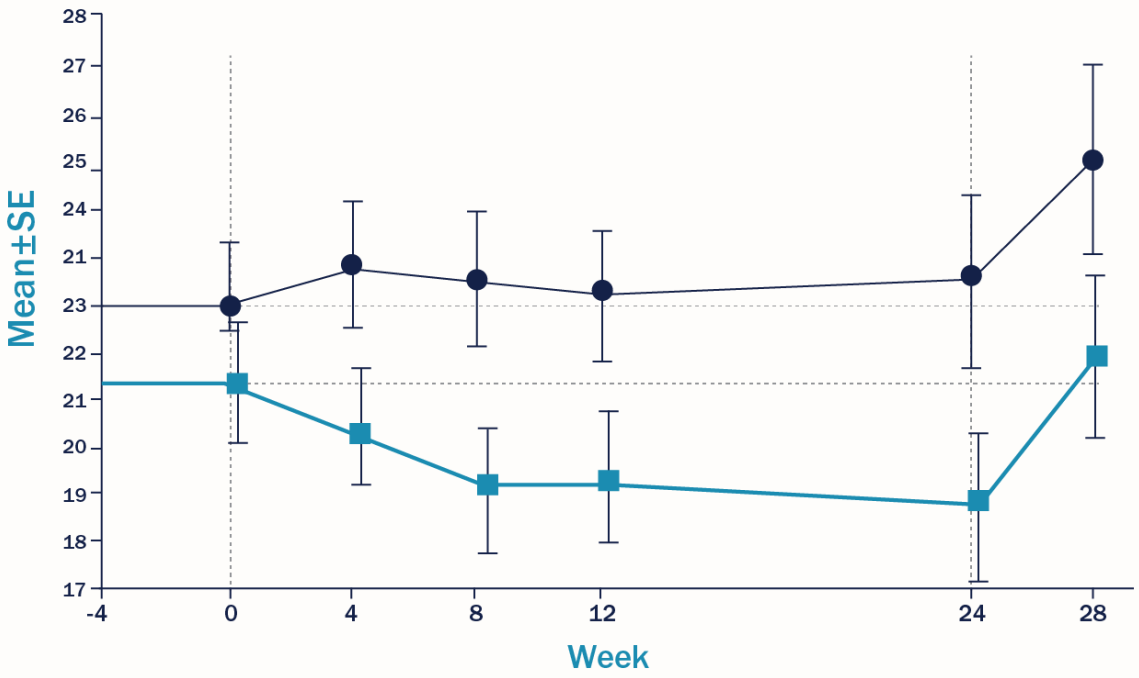
Bodick NC, et al. Arch Neurol. 1997 Apr;54(4):465-73.

Mean Scores Over time in the Cognitive Subscale of the Alzheimer's Disease Assessment Scale (ADAS-Cog) and Clinician's Interview-Based Impression of Change (CIBIC+)

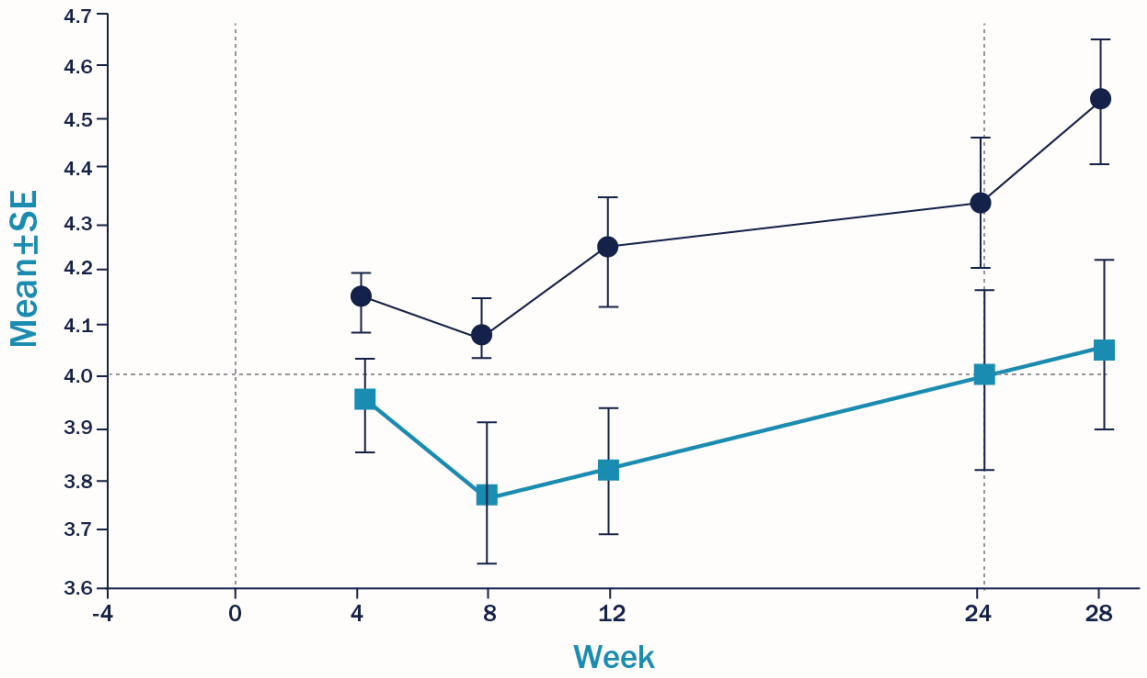
Placebo

225 mg/d Xanomeline Tartrate

ADAS-Cog Total



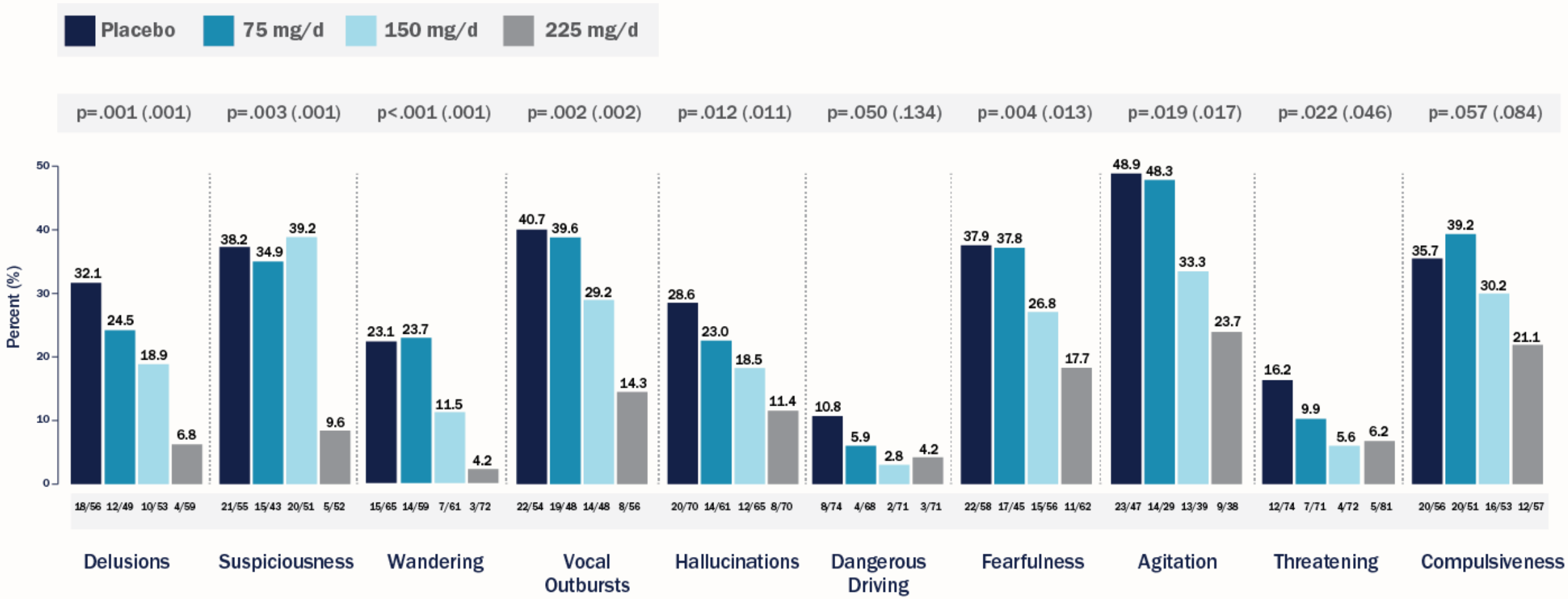
CIBIC+



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

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

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

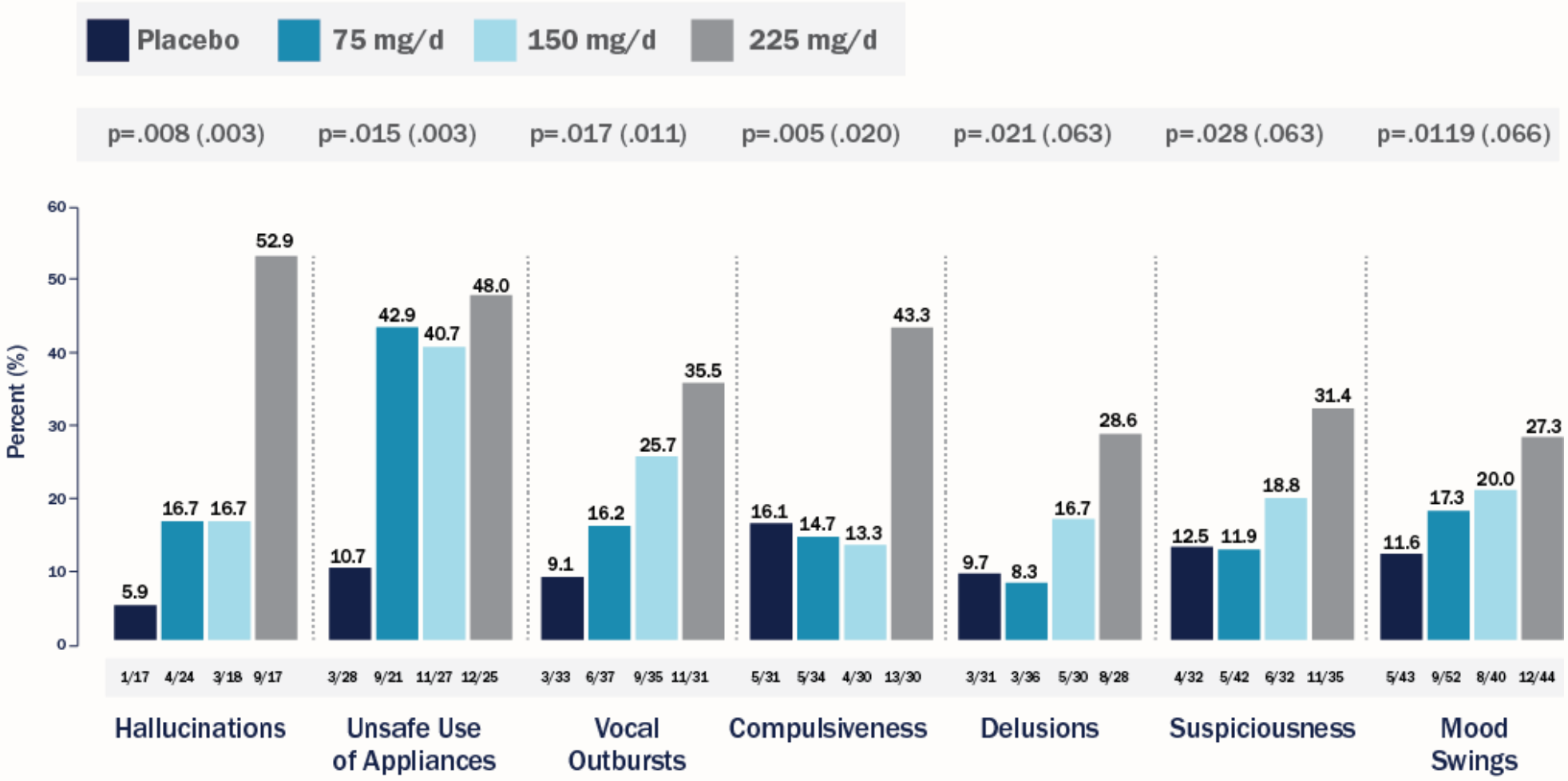


* Baseline lasted 2 weeks; treatment lasted up to 6 months.

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

Alzheimer's Disease Symptomatology Scale: Percentage of Patients with Symptom 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*	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 $\chi 2$ 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 function. Preclinical data suggest that agonists with selective affinity for acetylcholine muscarinic receptors provide a potentially new mechanism to treat schizophrenia. The authors studied xanomeline, a relatively selective muscarinic type 1 and type 4 (M_1 and M_4) receptor agonist, to determine if this agent is effective in the treatment of schizophrenia.

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

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

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

(Am J Psychiatry 2008; 165:1033–1039)

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

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

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

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

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

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

Xanomeline for Schizophrenia: Cognition

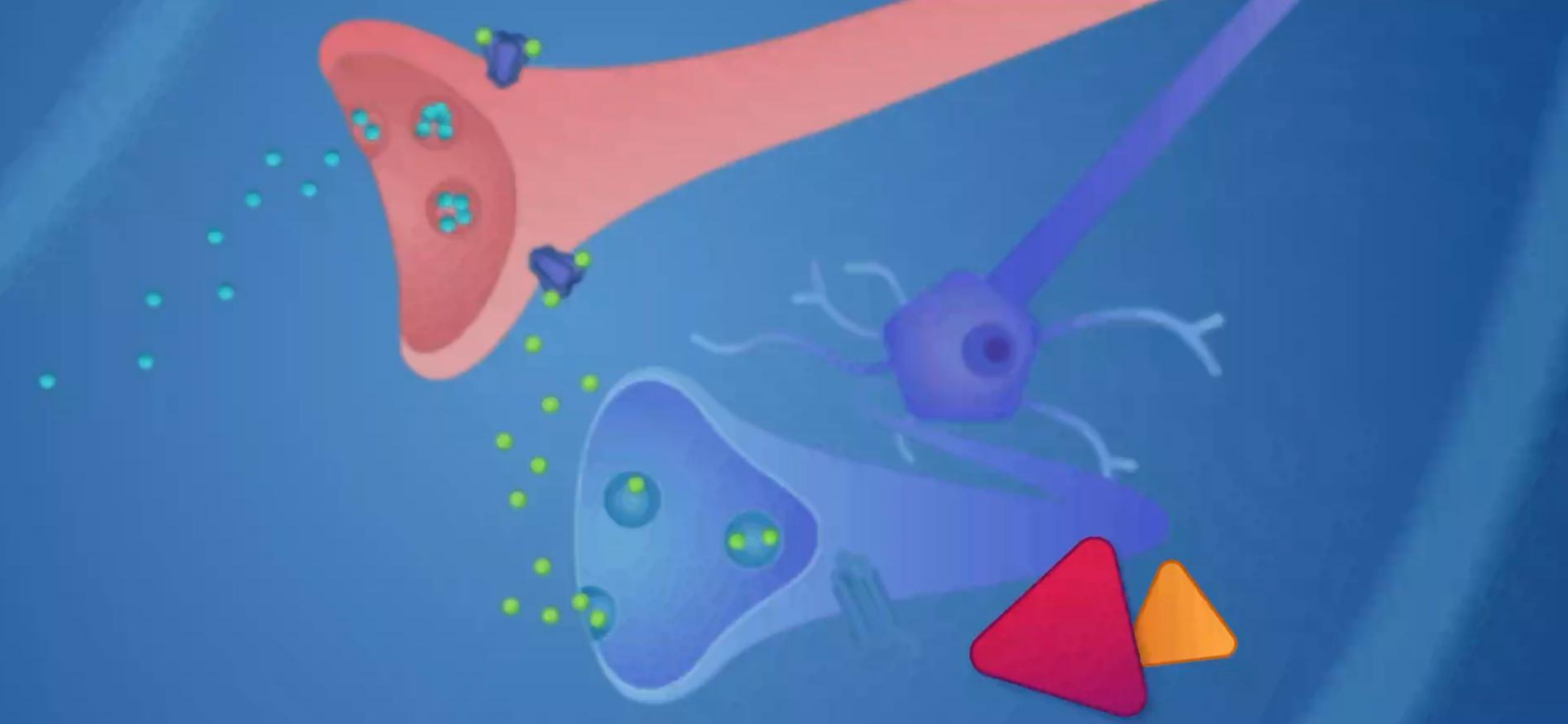
Cognative Measure	Placebo Groups			Xanomeline Groups		
	Pretreatment Score	Posttreatment Score	Change in Score	Pretreatment Score	Posttreatment Score	Change in Score
Speed of processing						
Trail Making Test, part A: time	43.5	50.4	6.9	59.1	51.7	-7.4
Trail Making Test, part B: time	133.5	144.3	10.8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

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

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

Key Learning Points

- 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

Xanomeline-Trospium Clinical Trials

Jonathan Meyer, MD, DLFAPA

Voluntary Clinical Professor,
Department of Psychiatry
University of California, San Diego
La Jolla, CA

Senior Academic Adviser
California Dept. of State Hospitals
Sacramento, CA

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)

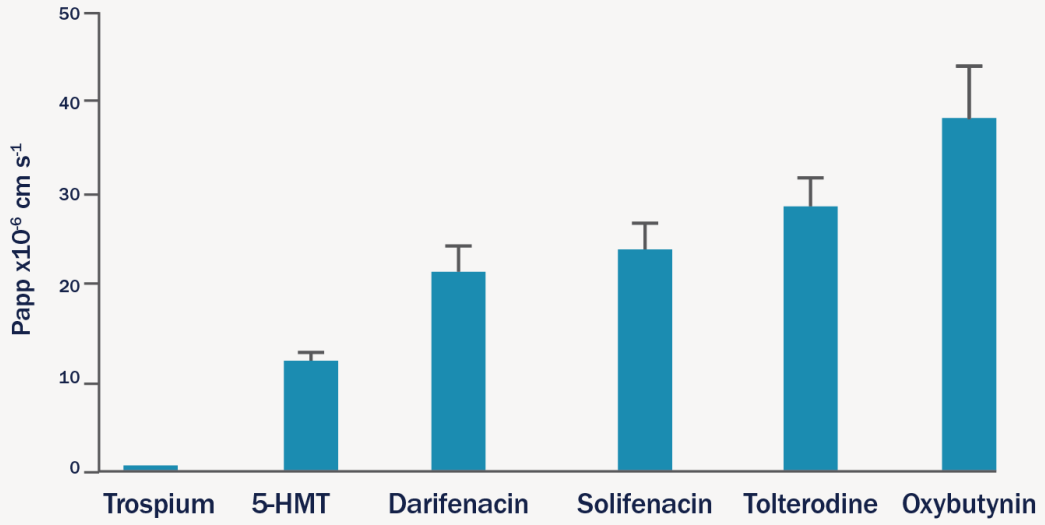
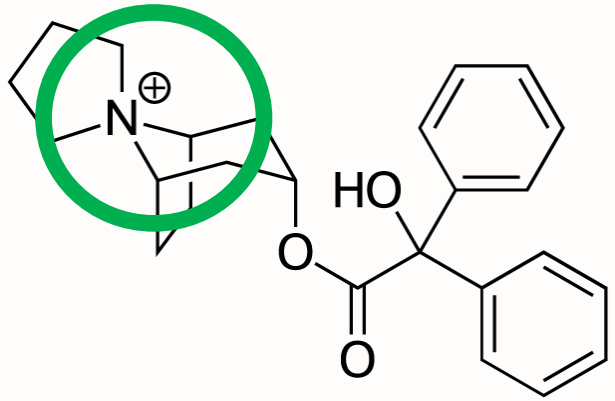


Figure: Passive diffusion across cloned kidney cells as a model for blood brain barrier penetration

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



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

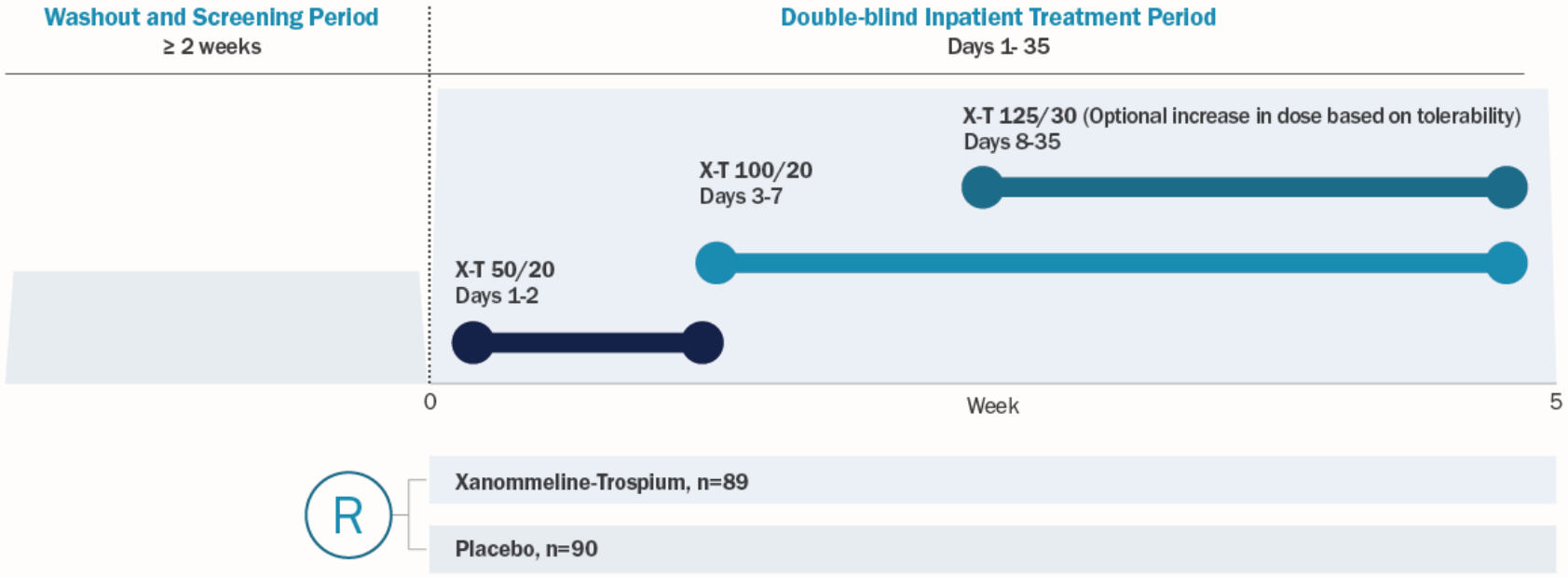
Program	Preclinical	Phase 1	Phase 2	Phase 3	Status
Schizophrenia	**Emergent 1**[1]				Complete
	Emergent 2[2]				Complete
	Emergent 3[3]				Complete
	Emergent 4 (open-label extension of EMERGENT 2 and EMERGENT 3)[4]				Complete
	Emergent 5 (long-term, open-label trail, newly enrolled participants)[5]				Active, not recruiting
Schizophrenia (adjunctive) Psychosis in people with inadaquately controlled symptoms of schizophrenia	**Arise**[6]				Enrolling
	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.

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. Accessed Nov 12, 2023. www.clinicaltrials.gov/study/NCT06126224. 10. ADEPT-3. www.clinicaltrials.gov/study/NCT05980949.

Emergent 1- Phase 2 Clinical Trial Design

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



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

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

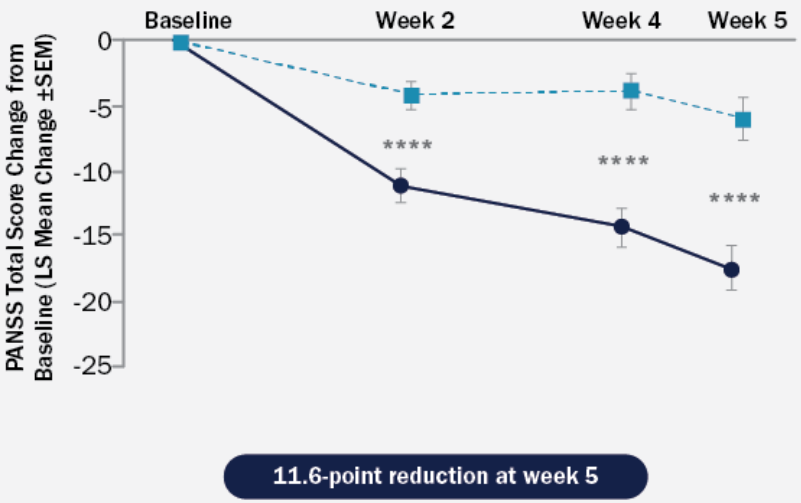
Emergent Trials: PANSS Total Score Change from Baseline

Placebo

*p<0.05 **p<0.01 ****p<0.0001

Emergent 1[1]

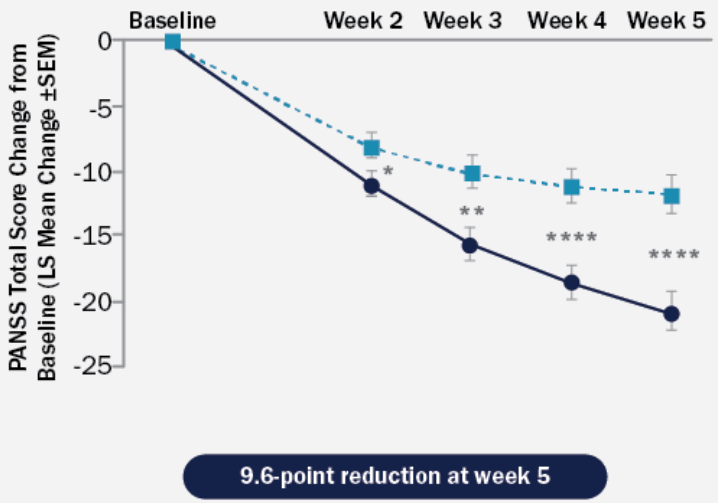
Cohen´s d efffect size 0.81[a]



11.6-point reduction at week 5

Emergent 2[2]

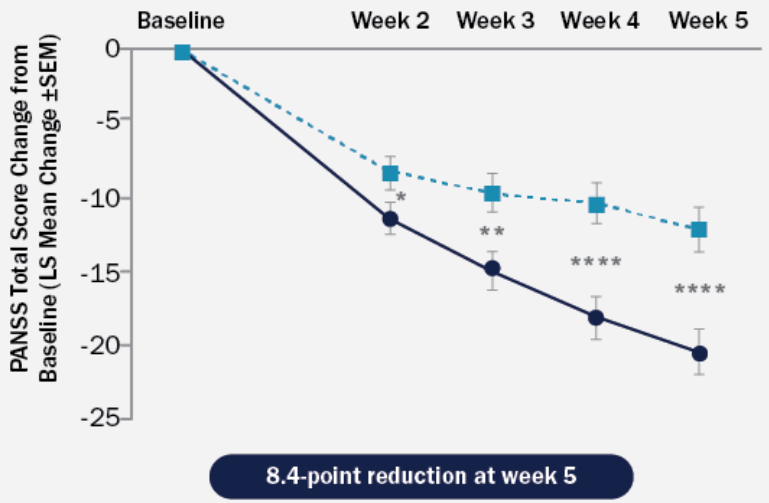
Cohen´s d efffect size 0.61[a]



9.6-point reduction at week 5

Emergent 3[3]

Cohen´s d efffect size 0.60[a]



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

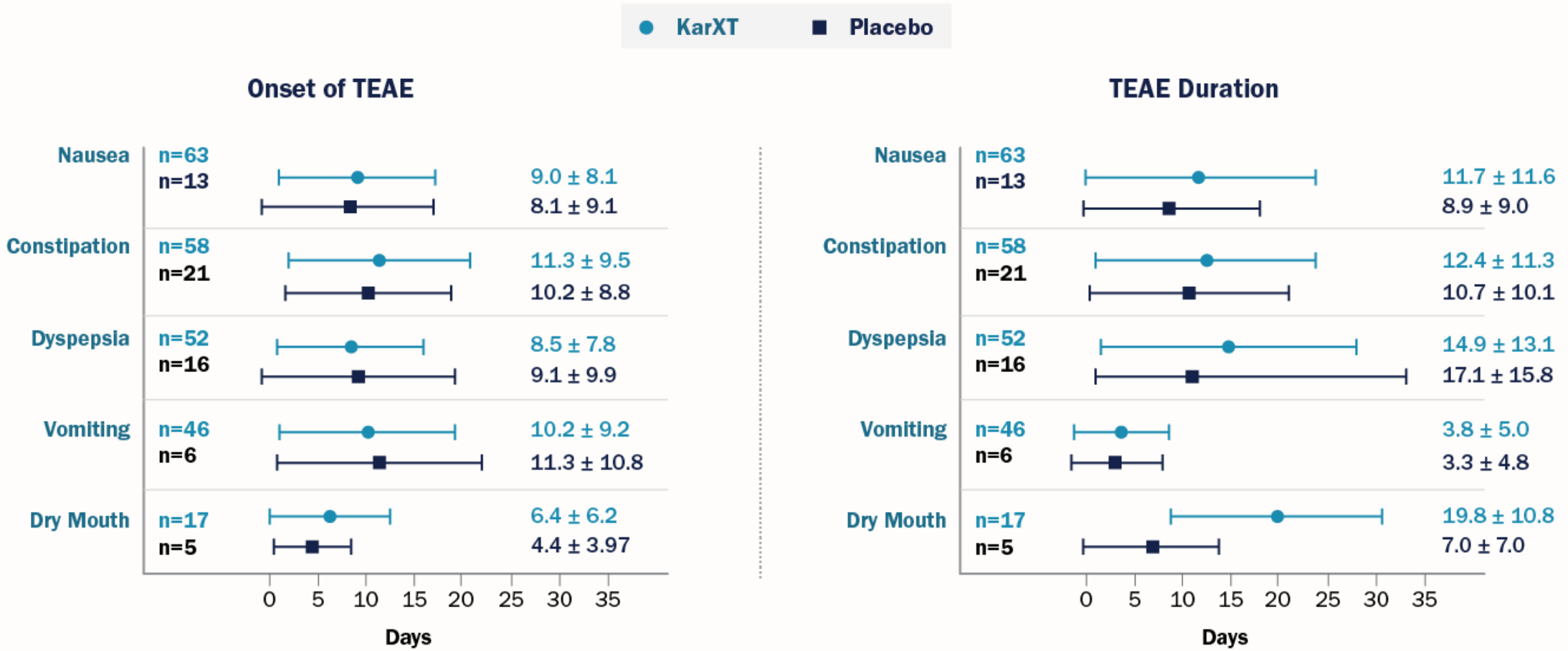
Safety Population

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

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

Pooled EMERGENT Safety Population



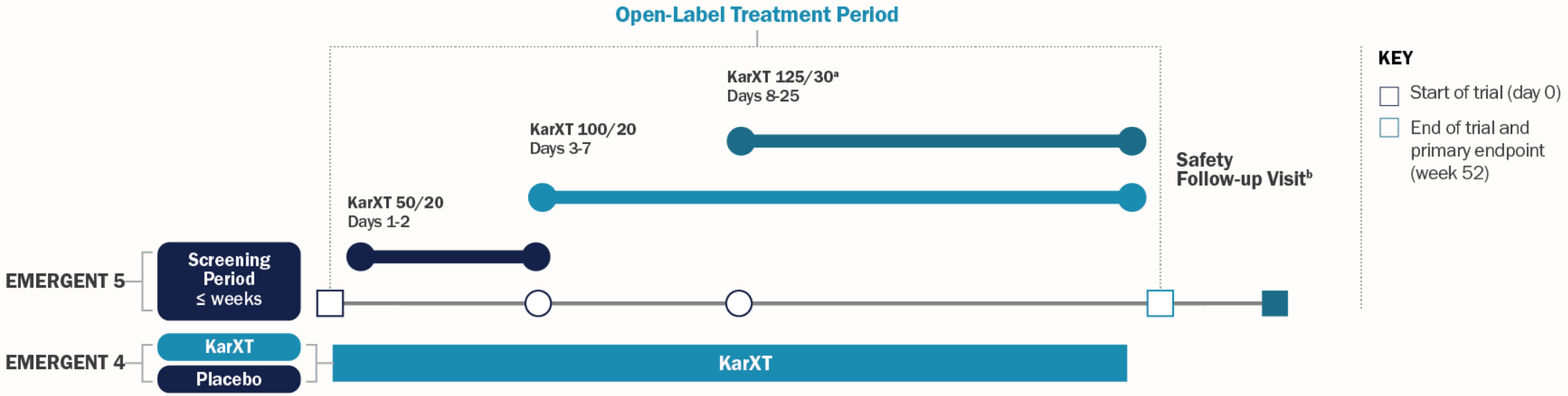
Safety population defined as all participants who received ≥1 dose of trial medication.

a. Suicidal ideation (n=2), psychotic disorder (n=1), gastroesophageal reflux disease (n=1); b. Appendicitis (n=1), schizophrenia (n=1); c. Hypertension .

Brannan SK, et al. Poster presented at the 2023 American Society of Clinical Psychopharmacology (ASCP) Annual Meeting, May 30-June 2, 2023, Miami, Florida.

Emergent 4, 5 - Clinical Trial Design

Figure 1: Trial Designs



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

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

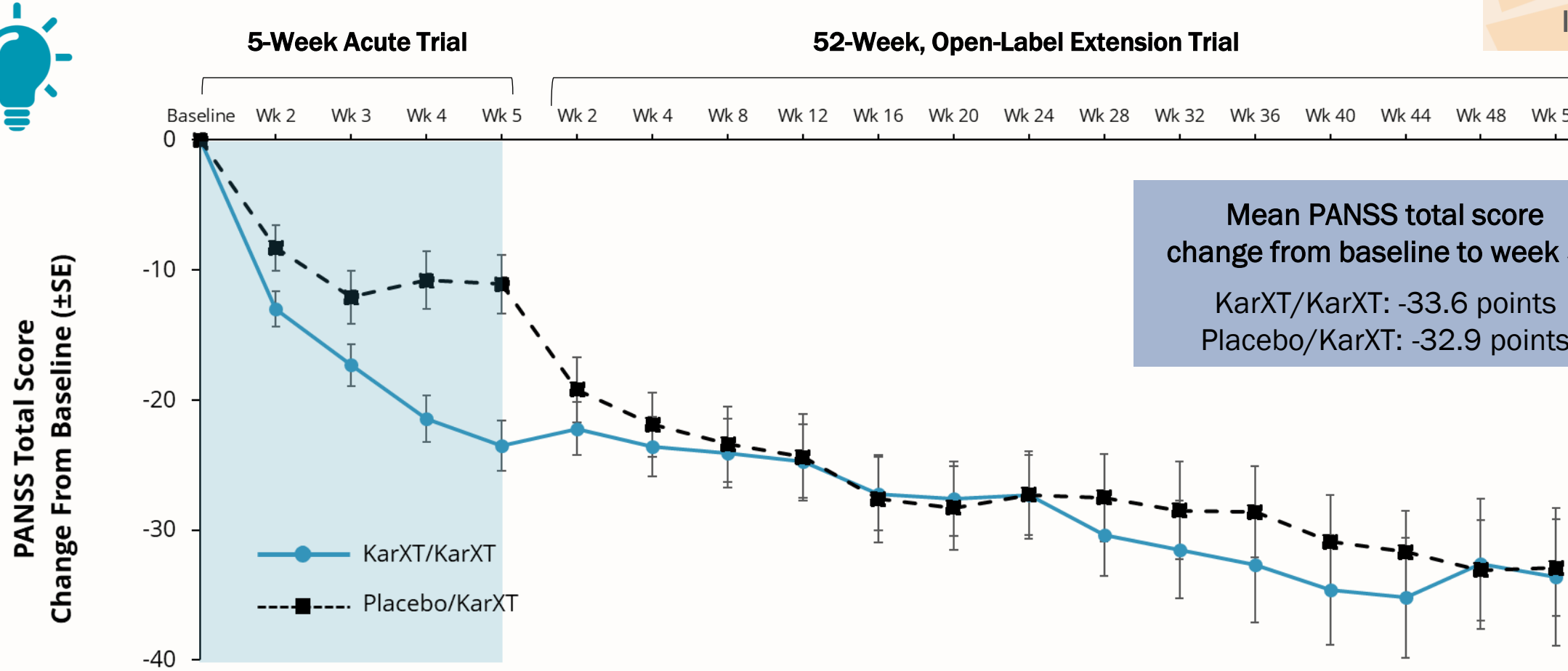
- EMERGENT-4 is an open-label extension that enrolled participants aged 18-65 years who previously completed the treatment period of EMERGENT-2 or EMERGENT-3
- EMERGENT-5 is an open-label trial in adults with a confirmed diagnosis of schizophrenia who have had no prior exposure to KarXT; participants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

Final data from Emergent 4 and Emergent 5 will be presented as posters in the Exhibit Hall!

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

Emergent 4 – Long Term Change in PANSS

Interim Data



KarXT/KarXT (n)	48	48	47	48	48	43	38	33	29	26	25	25	19	17	18	15	15	15	14
Placebo/KarXT (n)	62	62	62	61	62	54	48	36	31	27	26	24	24	21	20	18	16	15	15

Kaul I, et al. Poster F264 presented at 2024 Annual Conference of the Schizophrenia International Research Society (SIRS), April 3-7, 2024, Florence, Italy

Pooled Emergent 4, 5 Data: Safety and Tolerability

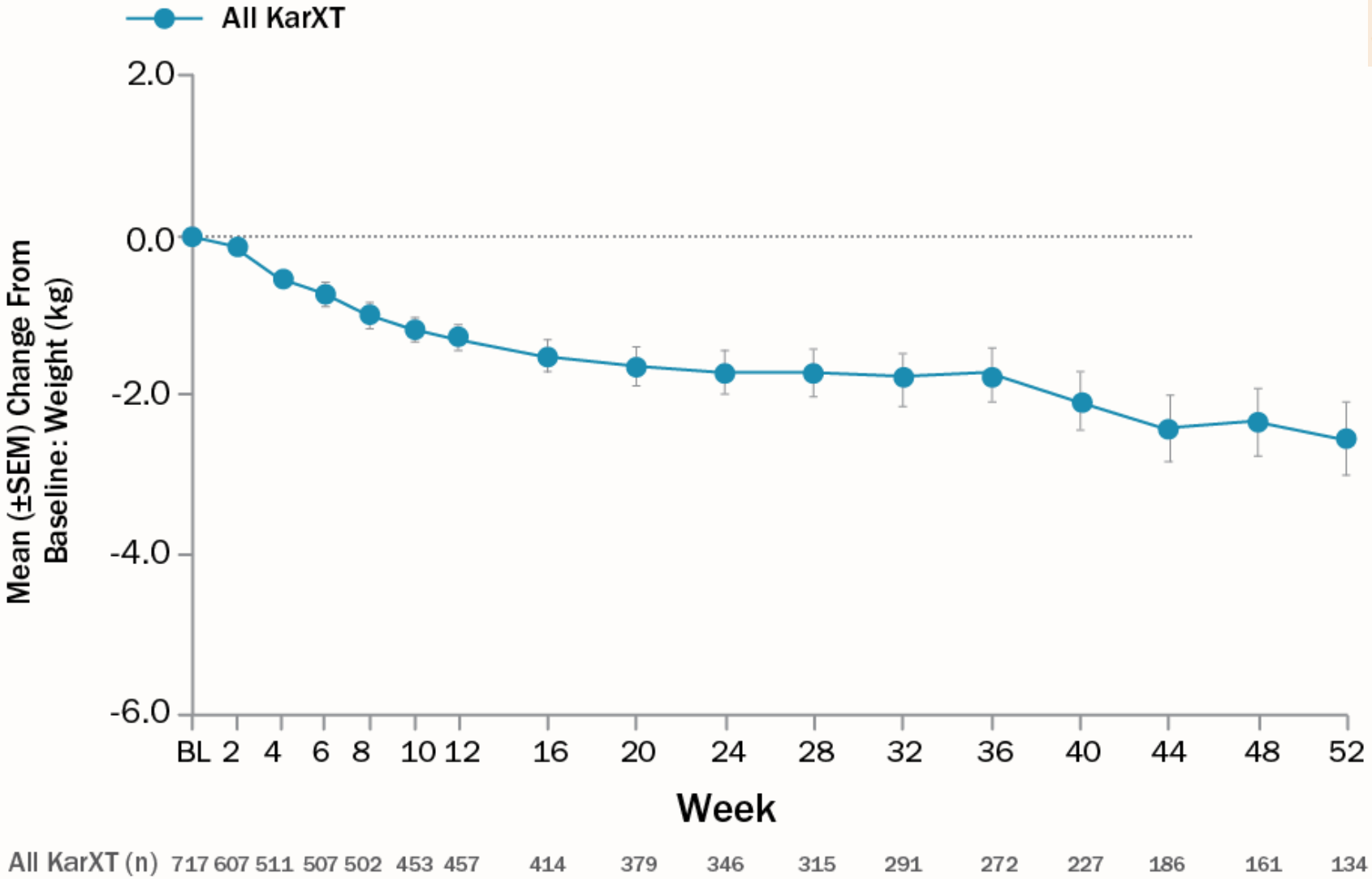
Interim Data

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

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

Pooled Emergent 4, 5 Data: 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: D_2 Related Adverse Effects

Interim Data

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

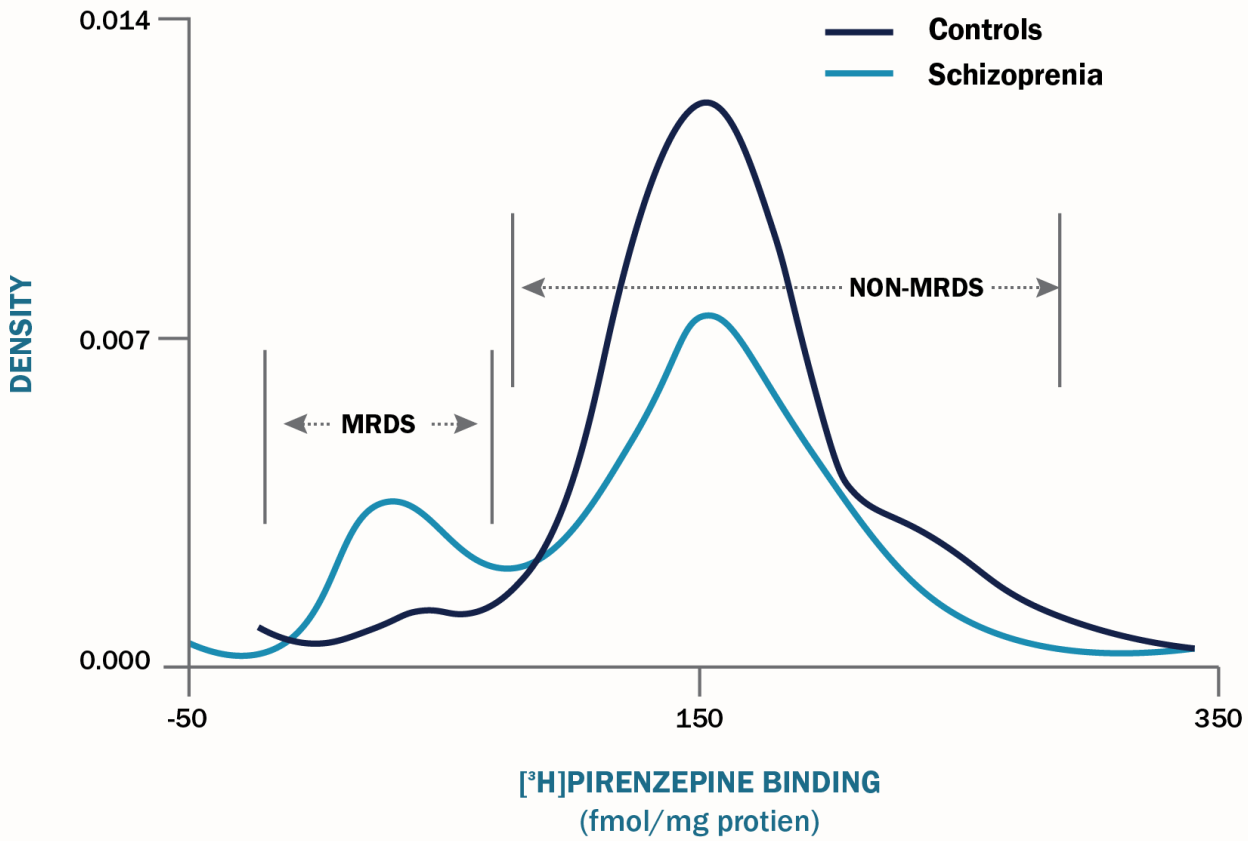
Why We Think Muscarinic Dysfunction Is Related to Schizophrenia: The M_1 Story

- **1996:** Using autopsy specimens, Dean and colleagues in Australia note 33% decreased M_1 receptor density in the caudate & putamen of 19 schizophrenia patients and 19 matched controls. Based on subsequent animal analyses, they hypothesize this is not the result of antemortem medications, as benztropine exposure in rats either has no effect or increases muscarinic receptor density.
- **2002: Crook**, Dean et al. document a decrease in M_1 receptor density in the dorsolateral PFC (Brodmann area 9) in postmortem schizophrenia specimens.
- **2003-2012:** Imaging studies demonstrate decreased M_1 receptor density in unmedicated antipsychotic naive schizophrenia patients. Moreover, 25% of schizophrenia patients have a 75% or more decrease in M_1 receptor density (referred to as the muscarinic receptor deficit subgroup - MRDS)

Dean B, et al. The density of muscarinic M1 receptors is decreased in the caudate-putamen of subjects with schizophrenia. *Mol Psychiatry.* 1996;1:54-8. Crook JM, et al. Low muscarinic receptor binding in prefrontal cortex from subjects with schizophrenia: a study of Brodmann's areas 8, 9, 10, and 46 and the effects of neuroleptic drug treatment. *Am J Psychiatry*. 2001;158:918-25. Bakker, G., et al. Relationship between muscarinic M1 receptor binding and cognition in medication-free subjects with psychosis. *Neuroimage Clin*. 2018; 18: 713–719

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 promotor 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. Muscarinic M1 and M4 receptors: hypothesis driven drug development for schizophrenia. *Psychiatry Res.* 2020;288:112989.

Cognitive Benefit from M_1 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.

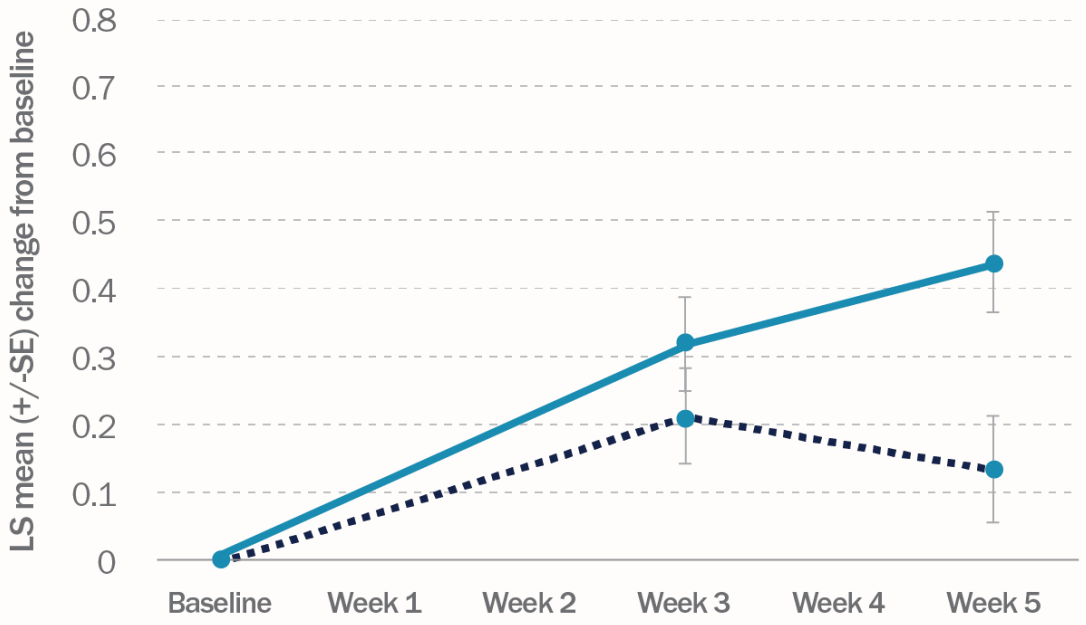
IIV outliers: The 1.5 interquartile range (IQR) rule was used to define outlier IIV assessments as individual test scores falling outside quartile 3 + 1.5 IQR. The approach of removing patients with highly variable assessment responses has been previously employed to examine treatment effects in schizophrenia.

ANCOVA=analysis of covariance, IIV: intraindividual variability, LS least squares.

Sauder C, et al. Effectiveness of KarXT (xanomeline-trospium) for cognitive impairment in schizophrenia- post hoc analyses from a randomised, double-blind, placebo-controlled phase 2 study. *Transl Psych.* 2022 Nov 21;12(1):491. doi: 10.1038/s41398-022-02254-9.

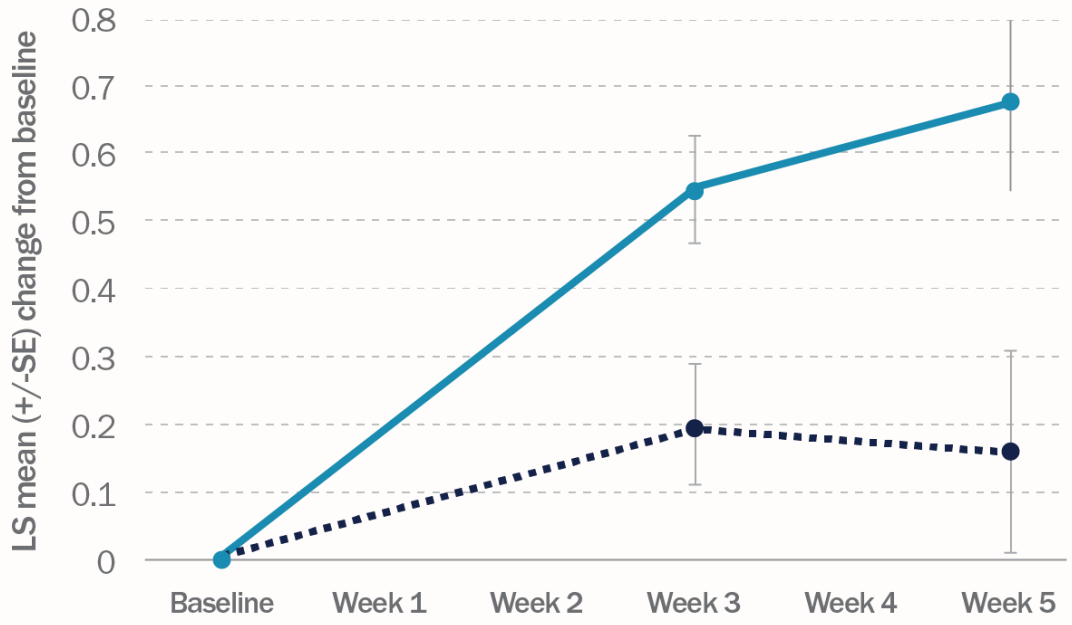
Cognitive Benefit from M_1 Stimulation? Pooled EMERGENT 1-3 Analysis

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

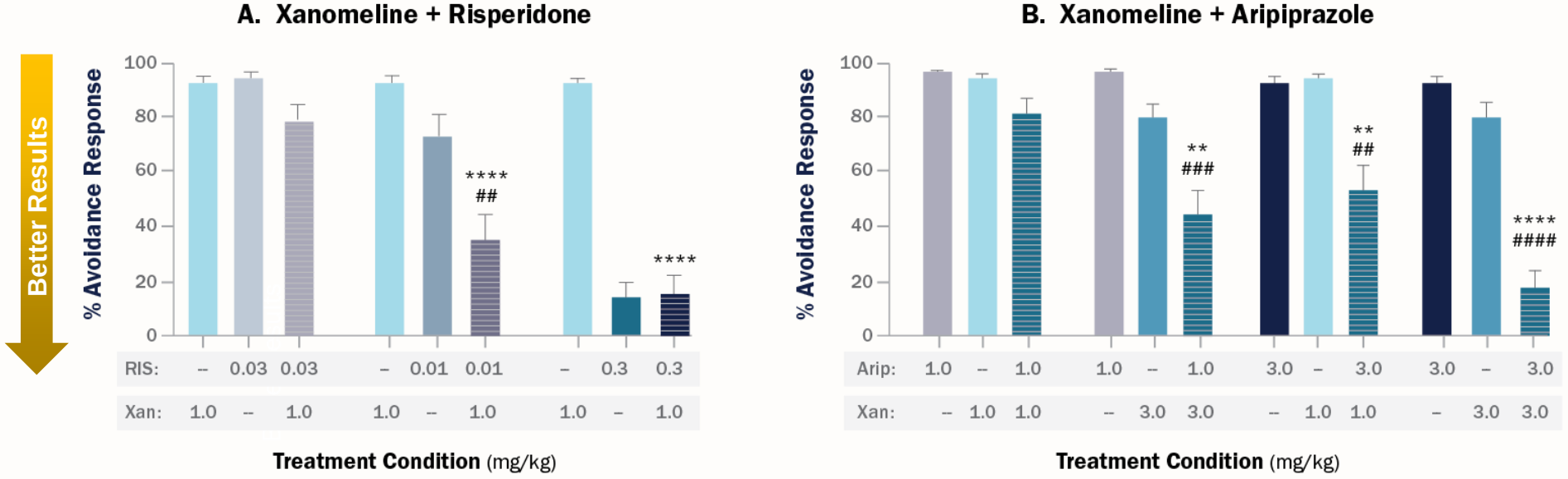


Week 3: ***p = .005, d = .79
Week 5: *p = .01, d = .80

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



- 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

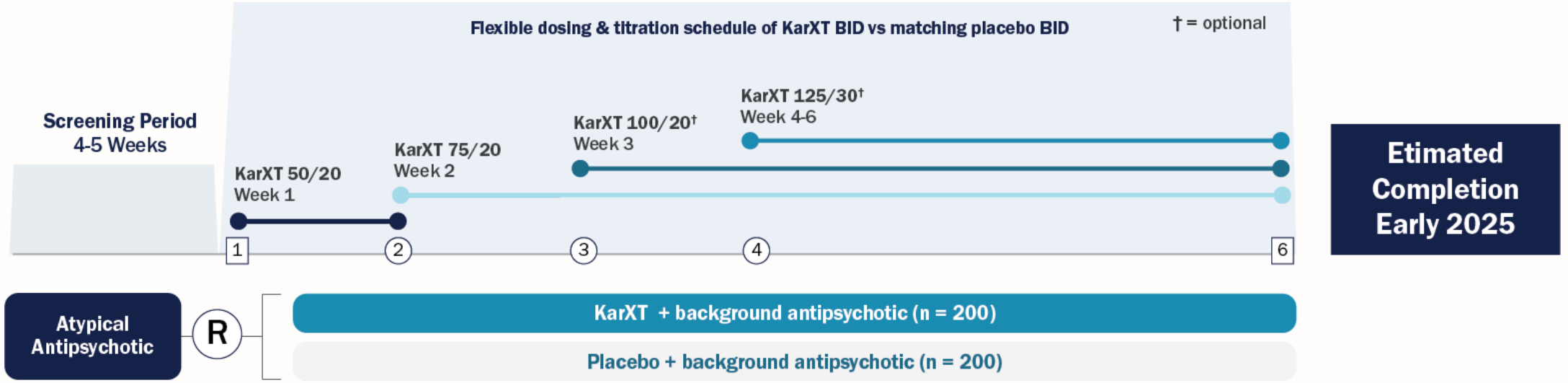
Post hoc analysis vs. xanomeline alone (*) and vs. comparator dose alone (#).
Values are mean ± SEM. ** p<0.01, **** p<0.0001; ## p<0.01, ### p<0.001, #### p<0.0001.

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

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

Double-blind Outpatient Treatment Period

Weeks 1-6



Etimated Completion Early 2025

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

Unlike the monotherapy studies:

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

LAI = long-acting injectable

ClinicalTrials.gov. A Study to Assess Efficacy and Safety of Adjunctive KarXT in Subjects With Inadequately Controlled Symptoms of Schizophrenia (ARISE). Accessed 9/10/2024. https://clinicaltrials.gov/ct2/show/NCT05145413

Key Learning Points

- Significant symptom reduction (PANSS total score) seen in all EMERGENT 1-3 trials with effect sizes for ranging from 0.60-0.81
- Trospium mitigated the procholinergic adverse effects. Rates of AE related discontinuation in the 3 short term trials were 5.6% for XT vs. 4.7% for placebo. No evidence of significant D_2, metabolic or endocrine related adverse effects.
- There is a replicated signal across all phase 2b/3 studies of **improved cognitive outcomes** in those with more significant baseline cognitive dysfunction.

Xanomeline-Trospium: How to Initiate

Titration issues: The PI allows for a slower titration than used in the clinical trials, presumably to help mitigate adverse effects. The wording states:

- The recommended starting dosage is one 50 mg/20 mg capsule (contains 50 mg of xanomeline and 20 mg of trospium chloride) orally twice daily *for at least two days.*
- Increase the dosage to one 100 mg/20 mg capsule (contains 100 mg of xanomeline and 20 mg of trospium chloride) orally twice daily *for at least five days.*
- The dosage may be increased to one 125 mg/30 mg capsule (contains 125 mg of xanomeline and 30 mg of trospium chloride) orally twice daily *based on patient tolerability.*

The food issue: The exposure to trospium is decreased 85%-90% if taken with food. Patients must take X-T 1 hour before or 2 hours after a meal.

- **Practical strategy:** dose X-T upon awakening or 1 hour before breakfast and then at bedtime (without food)

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

- **Practical strategy:** Use slower titration, taper off other anticholinergics, ask about urinary symptoms.

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

Xanomeline-Trospium: How to Initiate

Monitoring LFTs: Rate of ALT or AST elevation >3x ULN was 2.8% for X-T vs 0.4% for PBO. 1.6% had elevated LFTs at some point, but the majority occurred within the first month and resolved with continued X-T exposure.

- **Practical strategy:** PI states to obtain baseline LFTs including bilirubin and "and as clinically indicated during treatment." In the absence of clinical symptoms, consider repeating LFTs after 1 month to document lack of effect.

Monitoring Heart rate: In the phase 3 studies the endpoint difference from placebo was +5.9 BPM, and in a dedicated ambulatory study the endpoint difference was +9.8 BPM.

- **Practical strategy:** Baseline and periodically during treatment (as is often done when starting clozapine).

Drug interactions: CYP2D6 contributes to xanomeline metabolism, but the PI does not recommend dose adjustment, but to monitor for adverse reactions.

- **Practical strategy:** Consider a slower initial titration and lower maximal dose.

Hepatic and renal dysfunction: Cannot use with Child-Pugh B or C. Higher exposure in cirrhosis patients who are Child Pugh A. Approximately 2-fold higher xanomeline exposure with eGFR 30-89 ml/min

- **Practical strategy:** Consider a slower initial titration and lower maximal dose.

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

Xanomeline-Trospium: How to Initiate

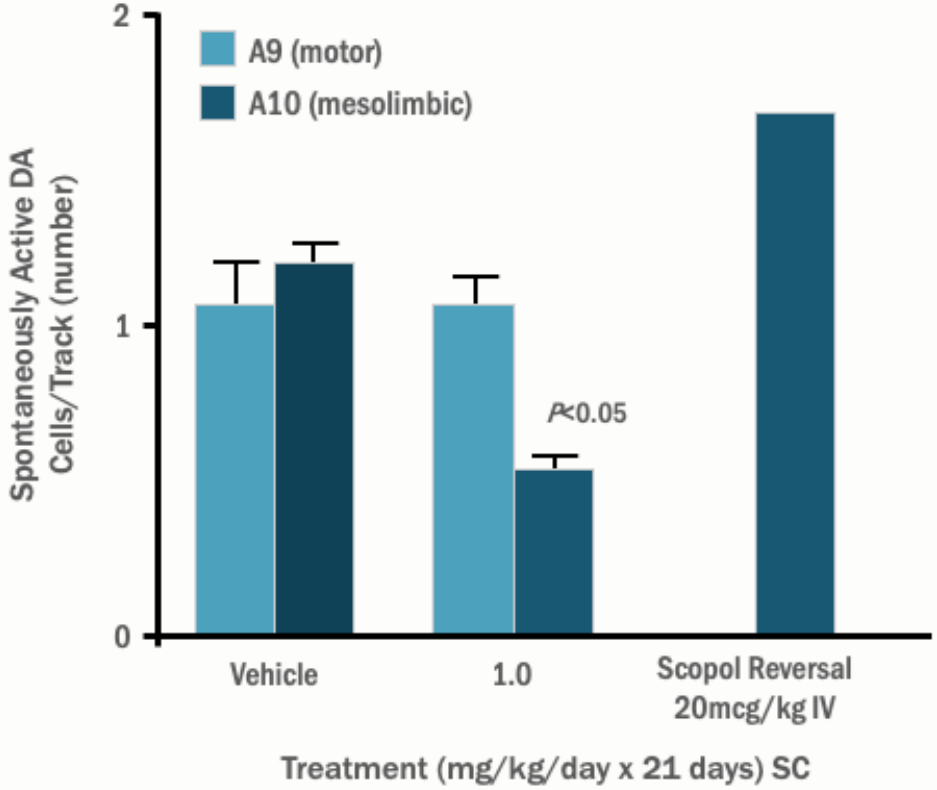
Implementation issues:

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

Anticholinergics impacting efficacy:

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

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



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

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 significance D_2, metabolic or endocrine related adverse effects.
- There is a replicated signal across all phase 2b/3 studies of improved cognitive outcomes in those with more significant baseline cognitive dysfunction.
- **This is the dawn of the muscarinic era for schizophrenia treatment**
  - Xanomeline/trospium (X-T), an M_1/M_4 agonist with no D_2 receptor binding is *now approved for schizophrenia* treatment in adults. **It does not have metabolic or D_2 related adverse effects (ie, movement disorders, hyperprolactinemia).**

Key Learning Points

This is the dawn of the muscarinic era for schizophrenia treatment

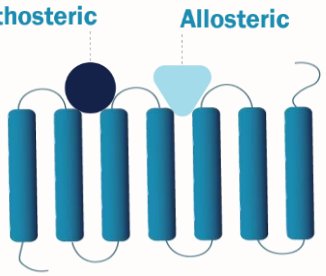
- Xanomeline/trospium (X-T), an M_1/M_4 agonist with no D_2 receptor binding is *now approved for schizophrenia* treatment in adults. **It does not have metabolic or D_2 related adverse effects (ie, movement disorders, hyperprolactinemia).**
- There is data noting improved cognition for X-T treated patients with higher levels of cognitive dysfunction.
- **NB:** Use of centrally acting anticholinergics poses a concern for their interference with the mechanism of action of any muscarinic activating medication.
- The M_4 positive allosteric modulator emraclidine has phase Ib data supporting efficacy, and the M_4 agonist NBI-1117568 has phase II data supporting efficacy

Other Activators of Muscarinic Receptors

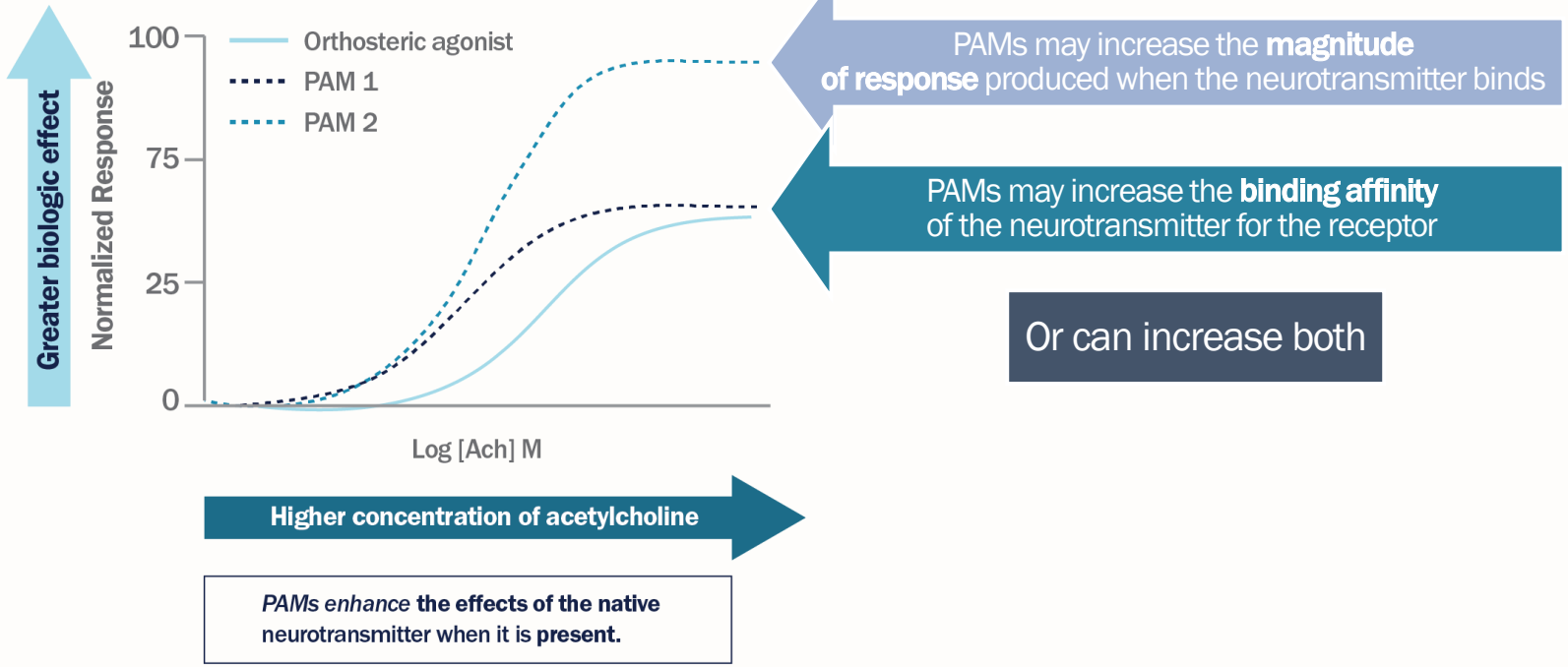
Craig Chepke, MD, DFAPA
Adjunct Associate Professor of Psychiatry,
Sandra & Leon Levine Psychiatry Residency Program at
Atrium Health
Charlotte, NC
Medical Director, Excel Psychiatric Associates
Huntersville, NC

What is Positive Allosteric Modulation?

Agonists bind to a receptor at the **orthosteric** site, where the native neurotransmitter binds, and increase its activity



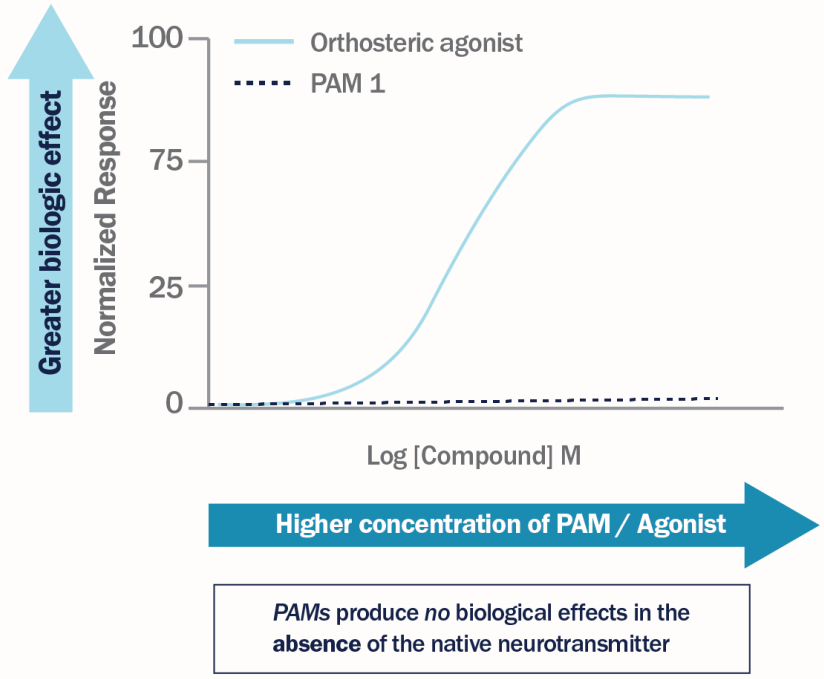
Allosteric Modulators bind to a receptor at a **different** site, and may increase or decrease the intracellular activity



PAMs may increase the **magnitude of response** produced when the neurotransmitter binds

PAMs may increase the **binding affinity** of the neurotransmitter for the receptor

Or can increase both



Higher concentration of acetylcholine

PAMs enhance **the effects of the native** neurotransmitter when it is **present.**

Higher concentration of PAM / Agonist

PAMs produce *no* biological effects in the **absence** of the native neurotransmitter

PAM = Positive Allosteric Modulator

Yohn SE., et al. *Trends in Pharmacological Sciences*. 2022;43(12): 1098-1112. Bubser M, et al. Muscarinic Receptor Pharmacology and Circuitry for the Modulation of Cognition. In: Fryer, A., Christopoulos, A., Nathanson, N. (eds) *Muscarinic Receptors. Handbook of Experimental Pharmacology, vol 208.* Springer, Berlin, Heidelberg; 2012.

Why is Positive Allosteric Modulation Relevant to Muscarinic Receptors?

M_1 M_2 M_3 M_4 M_5

- The **orthosteric** binding sites of the 5 muscarinic receptors are **highly similar** to each other.
- It's difficult to develop an agonist for one muscarinic receptor that does not bind to other muscarinic receptors, which can cause potential off-target effects

However…

M_1 M_2 M_3 M_4 M_5

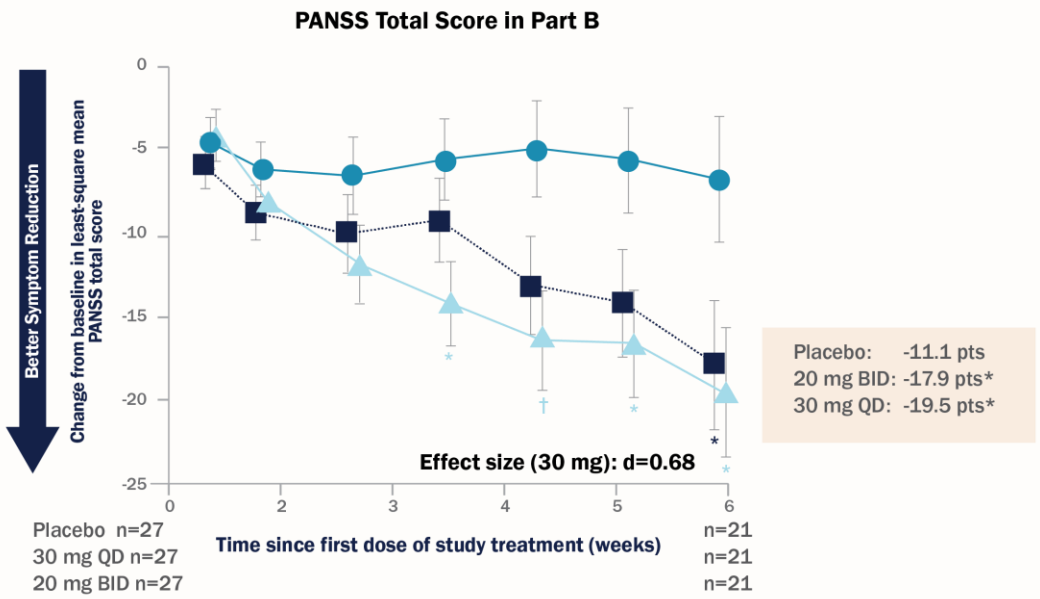
Each muscarinic receptor has an **allosteric** binding site which is much **more unique**, allowing a high degree of selectivity for a single receptor.

+	−
Theoretical Advantages of PAMs vs Agonists	**Theoretical Disadvantages of PAMs vs Agonists**
Often more selective for a single desired target than an agonist	Can only target one receptor at a time, even if multiple could be advantageous.
Enhancing the effects of neurotransmitter binding better preserves the geographical and temporal aspects of signaling	Endogenous neurotransmitter release may not be sufficient to produce the desired response

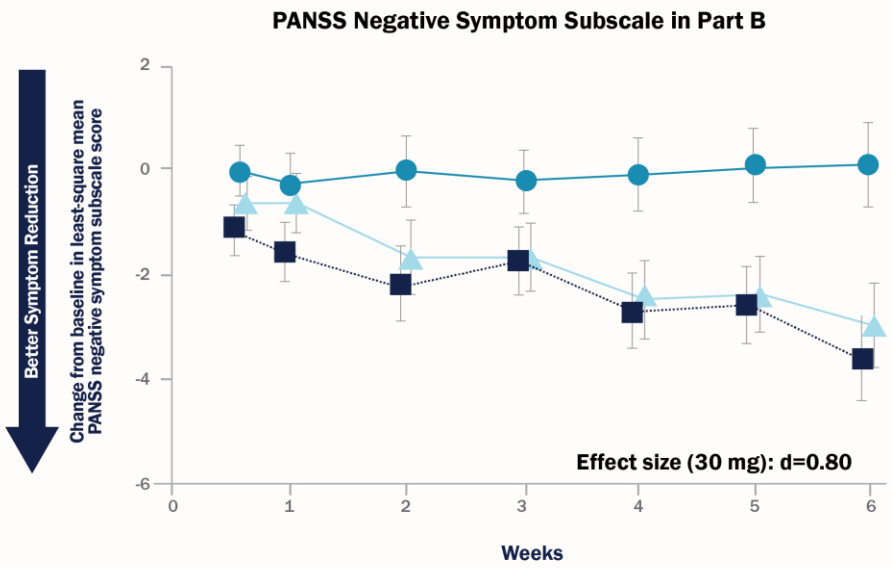
PAM = Positive Allosteric Modulator

Yohn SE., et al. *Trends in Pharmacological Sciences*. 2022;43(12): 1098-1112. Bubser M, et al. Muscarinic Receptor Pharmacology and Circuitry for the Modulation of Cognition. In: Fryer, A., Christopoulos, A., Nathanson, N. (eds) *Muscarinic Receptors. Handbook of Experimental Pharmacology, vol 208.* Springer, Berlin, Heidelberg; 2012.

Emraclidine M_4 PAM
Phase 1B Study Efficacy Results



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



* 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

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

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

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

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

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

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

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

They were asymptomatic, decreased over time, and not considered clinically 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

Emraclidine Phase 2 Trial 001 Design

Screening	Double-blind in Clinic Treatment Period (6 weeks)	Follow Up
R	n=124 → Emraclidine 10 mg QD n=124 → Emraclidine 30 mg QD n=124 → Placebo n=372	End of treatment Week 6-10

Screening | Baseline/Day 1 | Week 1 | Week 2 | Week 3 | Week 4 | Week 5 | Week 6 | Week 10

Emraclidine Phase 2 Trial 002 Design

Screening	Double-blind in Clinic Treatment Period (6 weeks)	Follow Up
R	n=124 → Emraclidine 15 mg QD n=124 → Emraclidine 30 mg QD n=124 → Placebo n=372	End of treatment Week 6-10

Screening | Baseline/Day 1 | Week 1 | Week 2 | Week 3 | Week 4 | Week 5 | Week 6 | Week 10

All doses of emraclidine in these studies are given once daily, without titration

A 52-week open-label safety study is also in progress (est. 2/26)

Open-label treatment period (52 weeks)

Rollover participants from EMPOWER-1 and EMPOWER-2	Emraclidine 30 mg QD
De novo participants	Dose can be reduced to 15 mg QD or further to 10 mg QD for tolerability reasons

De novo participants Screening period (1 to 15 days) | Baseline | Week 16 | Week 52

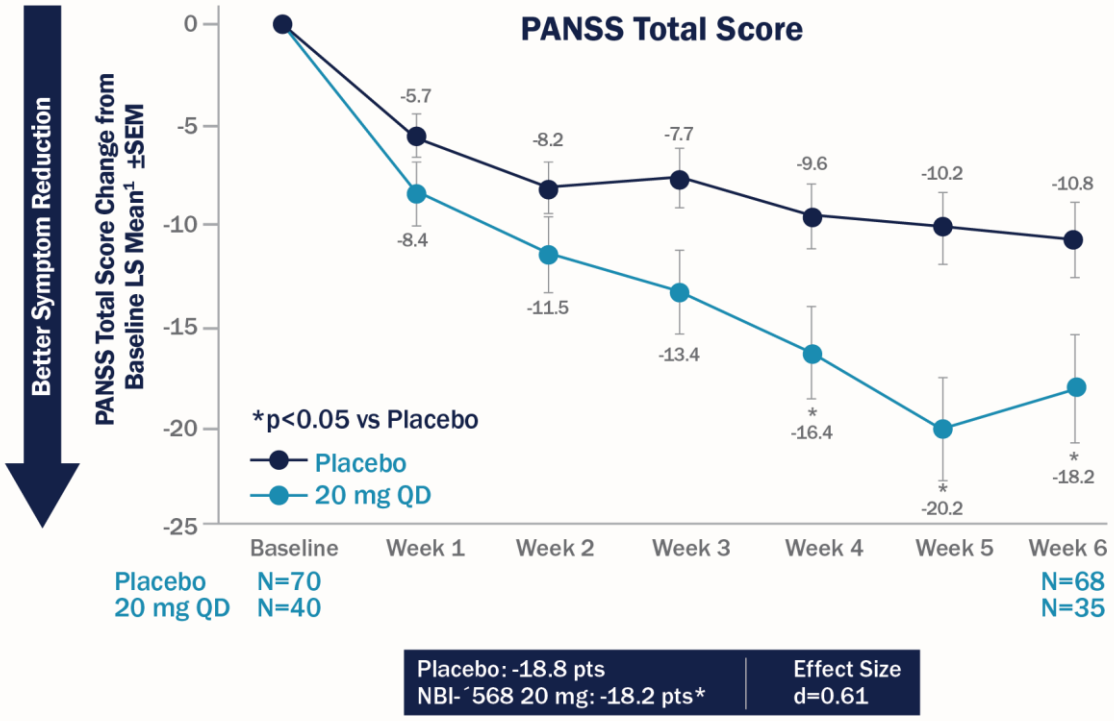
Two 6-Week Phase 2 Studies are expected to be completed by the end of 2024.

ClinincalTrials.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 .

NBI-1117568: Selective M_4 Agonist: Results from a Phase 2 Study

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

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



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

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

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

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

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

QD = once daily; BID = twice daily; LS = Least Squares; SEM = Standard Error of the Mean; TE = treatment-emergent; AE =a dverse event; D/C = discontinuations. Neurocrine Biosciences Reports Positive Phase 2 Data for NBI-1117568 in Adults with Schizophrenia. Accessed 9/10/24. https://neurocrine.gcs-web.com/news-releases/news-release-details/neurocrine-biosciences-reports-positive-phase-2-data-nbi-1117568 . Accessed 9/10/24.https://clinicaltrials.gov/study/NCT05545111.

Other Investigational Muscarinic Agents

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

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

Tobin AB. *Nat. Rev. Drug Discov.* 2024; 1-16. Neumora Therapeutics Announces Clinical Hold of Phase 1 NMRA-266 Study. Accessed 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-

Key Learning Points

- It's difficult to develop an orthosteric agonist for one muscarinic receptor that does not bind to other muscarinic receptors, which can cause potential off-target effects
- Positive Allosteric Modulation offers a different approach to activating M_4 receptors, and the selective M_4 PAM emraclidine will report results from two large scale phase 2 studies soon.
- Activation of specific muscarinic receptors offers the potential to improve positive symptoms, and other possible benefits, without the Metabolic, Endocrine, and Neurologic consequences of nonselective D_2 blockade.

Panel Discussion:
Implications for the Future Schizophrenia Treatment Landscape

Craig Chepke, MD, DFAPA

Adjunct Associate Professor of Psychiatry,
Sandra & Leon Levine Psychiatry
Residency Program at Atrium Health
Charlotte, NC

Medical Director,
Excel Psychiatric Associates
Huntersville, NC

Christoph U. Correll, MD

Professor of Psychiatry & Molecular Medicine,
The Donald and Barbara Zucker
School of Medicine at Hofstra/Northwell
New York, USA

Professor and Chair, Child and
Adolescent Psychiatry
Charité – Universitätsmedizin
Berlin, Germany

Jonathan, Meyer, MD, DLFAPA

Voluntary Clinical Professor,
Department of Psychiatry
University of California, San Diego
La Jolla, CA

Senior Academic Adviser
California Dept. of State Hospitals
Sacramento, CA

Visit the Newly Launched Schizophrenia Knowledge Base

- Expert insights
- Latest news
- Complimentary CME
- ...and more!

VISIT SCZKNOWLEDGEBASE.COM

Q&A