

New treatments for schizophrenia

Oliver Freudenreich, MD, FACLP

Co-Director

MGH Psychosis Clinical and Research Program

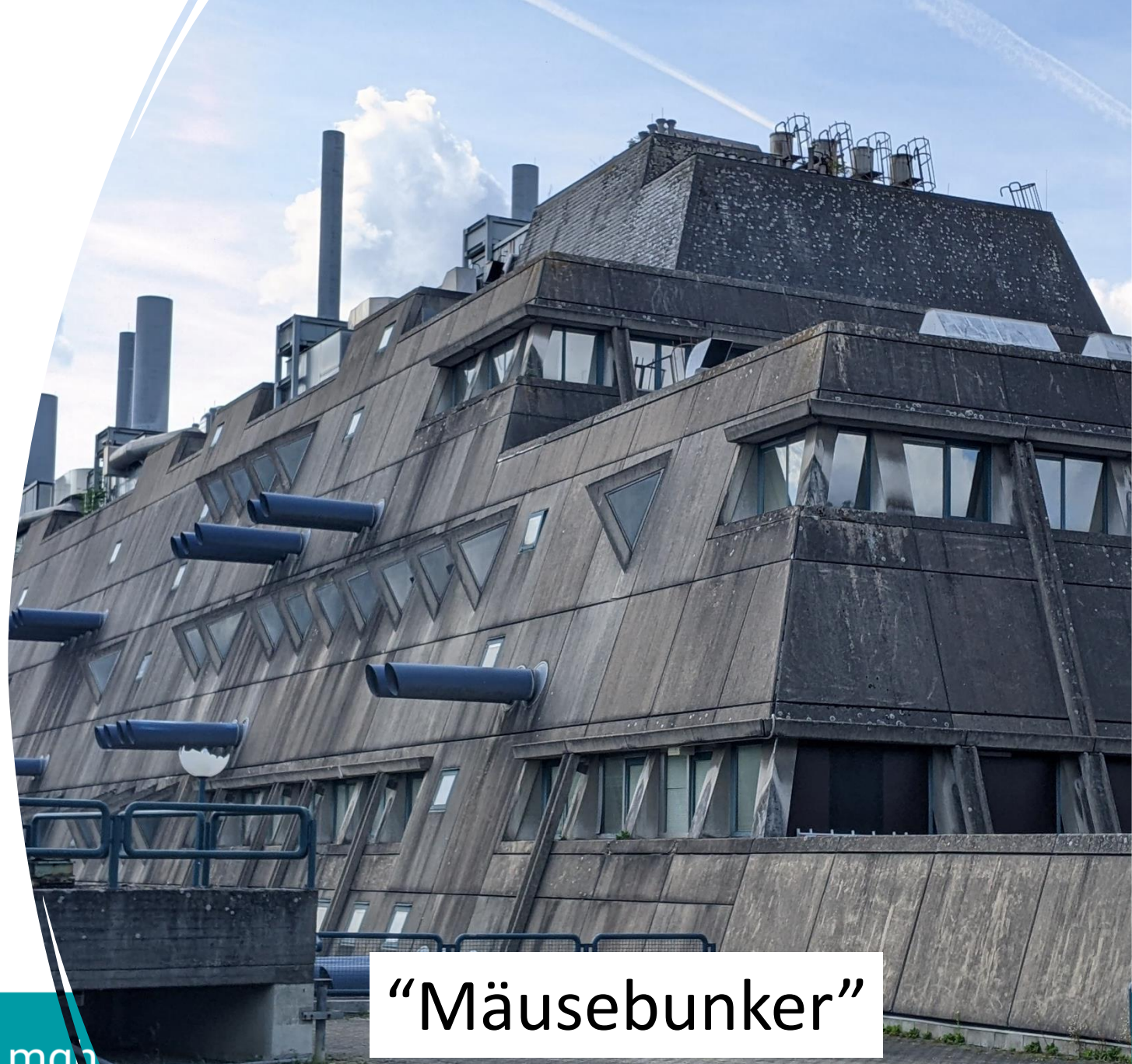
Disclosures

I have the following relevant financial relationship with a commercial interest to disclose:

- **Karuna** Research grant to institution (PI for MGH site)
- **Medscape** Speaker honorarium (medical peer education)
- **Psychopharmacology Institute** Speaker honorarium (medical peer education)
- **Wolters-Kluwer** Royalties for medical writing (medical peer education)

Concrete is the marble of the 20th century*

[https://www.sosbrutalism.org
/cms/15802395#about](https://www.sosbrutalism.org/cms/15802395#about)



“Mäusebunker”

*Arthur Erickson, Canadian architect, 1924-2009 mgh

Photo courtesy of Oliver Freudenreich

Outline

1. Unmet needs

A. **Symptom** clusters

- Refractory positive symptoms - TRS
- Prominent negative symptoms*
- Neurocognitive impairment*

*Contributor to
functional impairment

B. **Tolerability**

- Weight gain

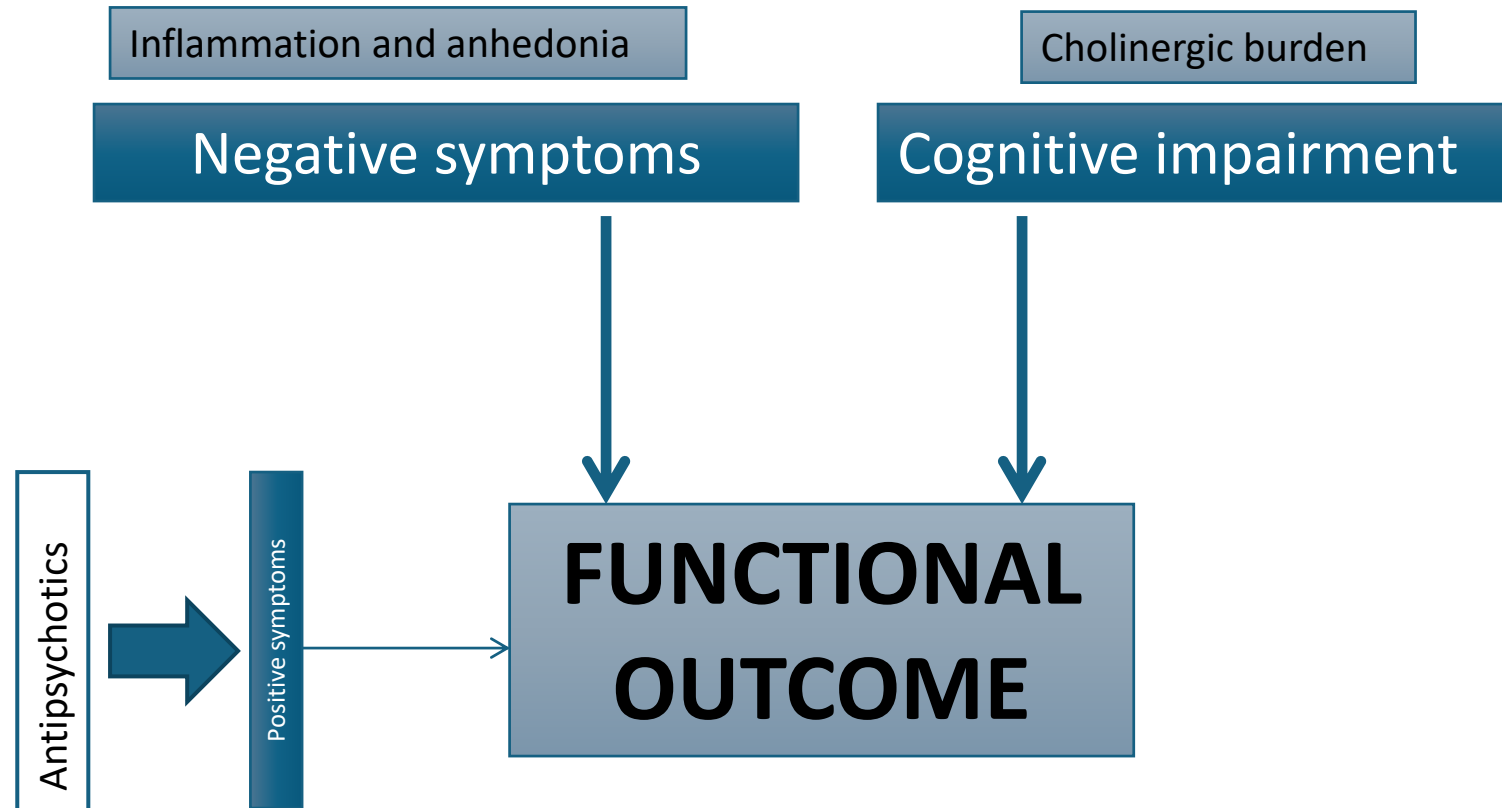
C. **Adherence**

2. Thinking outside the box

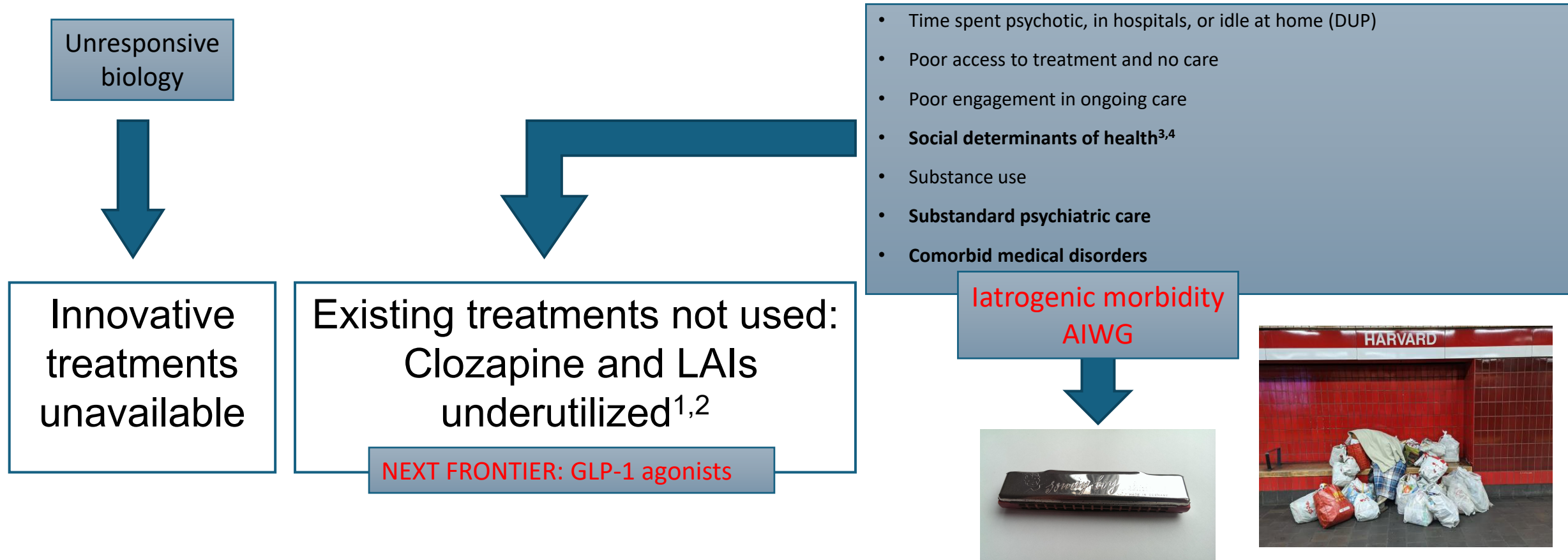
- Cholinergic system
- Other

3. The way forward

Symptom domains and functional outcome



Contributors to poor outcomes



Social (structural) interventions have greater impact on outcomes than molecular advances.⁵

¹Kelly DL et al. Psychiatr Serv. 2018;69(2):224-227. ²Torrey EF and Lieberman J. Psych Serv. 2025;76(1):90-92.

³Barry S et al. Psychiatr Serv. 2024;75(8):733-739. ⁴Wheatley MC. Premier J Public Health 2024;1:100008. ⁵Farmer PE et al. PLoS Med. 2006;3(10):e449.

A. SYMPTOMS

TRS as a biological subtype (?)

“The group of treatment-resistant schizophrenias”*

- Clinical differences
 - Earlier age of onset
 - Not more common in males
 - Worse outcome (circular reasoning)
- Biological differences
 - More familial and greater genetic loading
 - Possible specific cognitive deficits
 - Response to clozapine but not other antipsychotics
- Pathophysiology
 - Not dopamine-driven
 - Inflammation
 - Majority are resistant at presentation; minority develops resistance over time (related to relapse)

Pimavanserin for TRS

SSIA = Selective Serotonin Inverse Agonist

5-HT_{2A} inverse agonist

- Mechanism of action¹
 - Antagonist/inverse agonist at serotonin 5HT_{2A} receptors
 - Less potent antagonist/inverse agonist at 5HT_{2C} receptors
- 2016 FDA-approval for psychosis in Parkinson's disease (Nuplazid)^{2,3}
- Clinical case series (N=10) for TRS⁴
- Phase III 6-week add-on trial in (somewhat) TRS (Acadia's ENHANCE-1)⁵
 - Negative results for psychosis (PANSS total score)

¹Stahl SM. CNS Spectr. 2016;21:271-5. ²Cummings J et al. Lancet. 2014;383(9916):533-40.

³Mathis MV et al. J Clin Psychiatry. 2017; 78(6):e668-e673. ⁴Nasrallah HA et al. Schizophr Res. 2019;208:217-220.

⁵ClinicalTrials.gov Identifier: NCT02970292.

Evenamide for TRS

- Evanamide = NW-5309 (Newron)
- Mechanism: VGSC blocker (glutamate modulator)
 - Selective voltage-gated sodium channel (VGSC) blocker including (and not limited to) subtypes Nav1.3, Nav1.7, and Nav1.8
- Phase 2 study 014/015¹
 - Add-on for treatment-resistant schizophrenia (not on clozapine)
 - 6-week, randomized, rater-blinded, open-label, international, multi-site + 6-month extension
 - Encouraging efficacy
 - 12% reduction in PANSS score
 - CGI-S 0.7
 - High response rate of 77%
 - Too-good-to-be-true 1-year results: 25% remission
- Phase 2/3 study 008A²
 - 4-week, short term add-on trial
 - Effects size d=0.33
- ENIGMA phase 3 trials ongoing/initiated
 - ENIGMA TRS 1 and ENIGMA TRS 2 (NCT07184619)

¹Anand R et al. Neuropharmacology 2025; 266:110275.

²Anand R et al. Int J Neuropsychopharmacol 2025; 28: pyae061 [mghcme.org](https://www.mghcme.org)

Anand R et al. Ther Adv Psychopharmacol. 2026 Jan 26;16:20451253251414529.

The D3 story¹

- D3 has interesting brain distribution
 - Limbic system (ventral striatum) and thalamus
- D3 is of interest for several areas of psychiatry
 - Negative symptoms
 - Drug addiction
 - Mood disorders
 - Cognition
- Interesting observation that a pure D2/3 antagonist [amisulpride] does not cause EPS
 - Full D3 antagonists: antipsychotic without causing EPS?
 - D3-preferring antipsychotic candidate F17464 under development^{2,3}
- D3 agonist drugs [pramipexole, ropinirole; signal for aripiprazole] increased risk for pathological gambling, hypersexuality, compulsive shopping^{4,5}

¹Sokoloff P and Le Foll B. Eur J Neurosci. 2017;45:2-19. ²Slifstein M et al. Psychopharmacology. 2020;237(2):519-527.

³Bitter I et al. Neuropsychopharmacology. 2019;44(11):1917-1924 ⁴Seeman P. Synapse. 2015;69:183-9. ⁵Moore TJ et al. JAMA Intern Med. 2014;174:1930-3.

Cariprazine for negative symptoms

- Cariprazine is high-affinity D3 preferring D3/D2 partial agonist
- 26-week double-blind phase III RCT
 - Cariprazine 3 to 6 mg/d (N=227) versus risperidone 4 mg/d (N=229) as active reference antipsychotic
 - Stable schizophrenia patients with prominent negative symptoms but no prominent psychosis or depression
 - Minimum score of 24 on the PANSS-negative factor score (NFS)
- Outcome variables
 - Primary endpoint: PANSS-NFS
 - Secondary endpoint: Personal and Social Performance Scale (PSP)

D2/3 Partial Agonist Antipsychotics

	Indications	Typical dose range	Binding affinities (Ki)	Comments
Aripiprazole	Schizophrenia Bipolar disorder Adjunct depression Tourette Autism	10 to 30 mg/d	D2/3 0.21/0.93 D2/D3 = 0.22 5-HT1a 1.7 5-HT 2a 3.4	Half-life 94 h** CYP3A4 CYP2D6 High affinity for 5-HT 2c
Brexipiprazole	Schizophrenia Adjunct depression	2 to 4 mg/d 0.5 to 2mg/d	D2/3 0.30/1.1 D2/D3 = 0.27 5-HT1a 0.12 5-HT 2a 0.47	Half-life 91 h CYP3A4 CYP2D6
Cariprazine***	Schizophrenia Acute mania/mixed <i>Negative symptoms*</i>	1.5 to 6 mg/d 3 to 6 mg/d	D2/3 0.49/0.09 D2/D3 = 5.76 5-HT 1a 2.6 5-HT 2a 18.8	Longest half-life (1-3 weeks)** CYP3A4

*Not FDA-approved **Half-life including active metabolite

***Cariprazine metabolite has very high D3 selectivity D2/D3 = 24.87

Frankel JS and Schwartz TL. Ther Adv Psychopharmacol. 2017;7:29–41. Kiss B et al. J Pharmacol Exp Ther. 2010;333:328-40.

Amisulpride

- Pure, high-affinity D2/3 antagonist
 - Not available in US for schizophrenia (but for PONV as injection)
 - Low EPS and weight gain risk; prolactin elevation
- Excellent efficacy and effectiveness in clinical trials
 - EUFEST: first-episode patients
 - CUtLASS 1: quality of life
 - OPTiMiSE: first-episode patients
 - BeSt InTro: amisulpride vs. olanzapine vs. aripiprazole¹
- Best efficacy for positive symptoms after clozapine
- Effective clozapine augmentation
- Drug development (phase 2)
 - Methylated amisulpride (LB-102)²

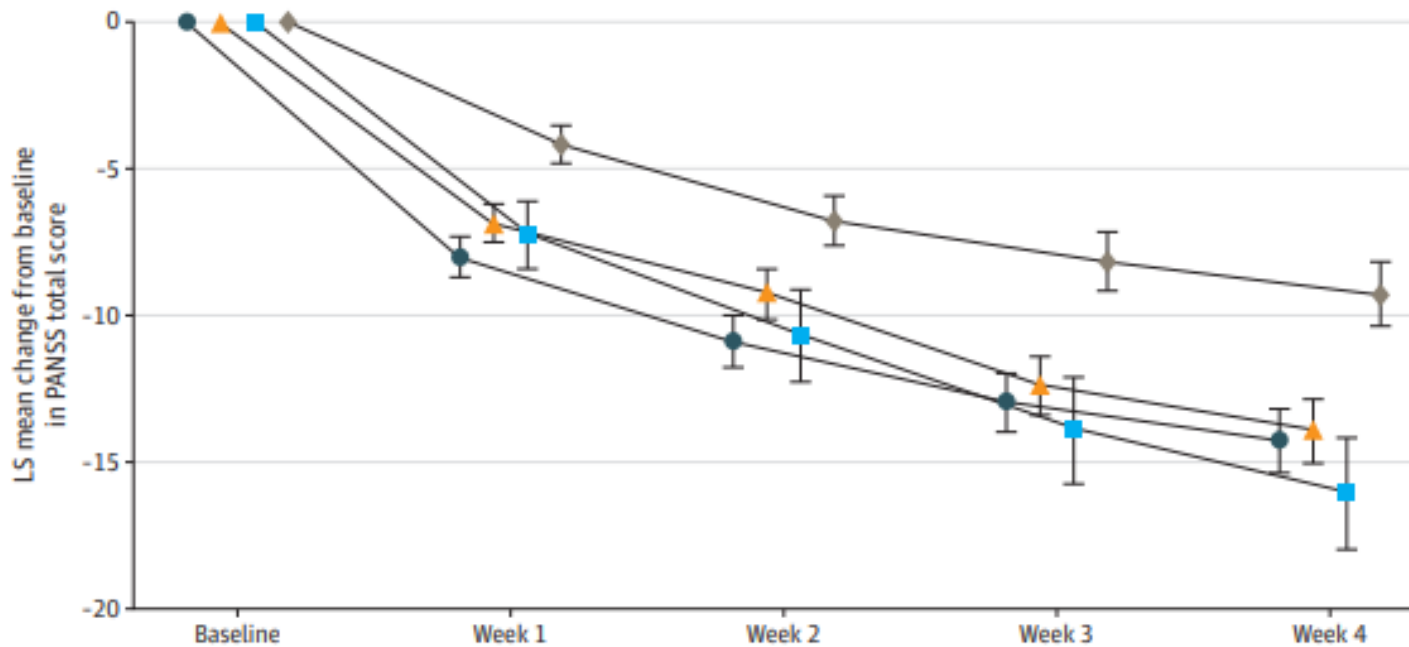
¹Johnsen E et al. Lancet Psychiatry. 2020;7(11):945-954. NCT01446328. ²Biernat L. Psychopharmacology. 2022;239(9):3009-3018.
<https://psychnews.psychiatryonline.org/doi/10.1176/appi.pn.2021.4.11> [Psychiatric News July 2021]

LB-102

N-methyl amisulpride

D2/D3/5-HT7 receptor antagonist

A Change from baseline in PANSS total score



Phase 2 RCT

- LB-102, 50 mg
(baseline = 93.9; n = 107)
LB-102, 50 mg vs placebo:
 $P < .001$ (multiplicity adjusted)
- ▲ LB-102, 75 mg
(baseline = 93.6; n = 108)
LB-102, 75 mg vs placebo:
 $P = .002$ (multiplicity adjusted)
- LB-102, 100 mg
(baseline = 93.9; n = 36)
LB-102, 100 mg vs placebo:
 $P = .002$
- ◆ Placebo
(baseline = 93.8; n = 108)

Pimavanserin

SSIA = Selective Serotonin Inverse Agonist

5-HT_{2A} inverse agonist

- Mechanism of action¹
 - Antagonist/inverse agonist at serotonin 5HT_{2A} receptors
 - Less potent antagonist/inverse agonist at 5HT_{2C} receptors
- 2016 FDA-approval for psychosis in Parkinson's disease (Nuplazid)^{2,3}
- Phase 2 add-on trial for depression⁴
- Clinical case series (N=10) for TRS⁵
- Phase 3 add-on trial in (somewhat) TRS (Acadia's ENHANCE-1)⁶
 - Negative results for psychosis (PANSS total score)
- Phase 2 add-on trial for negative symptoms (Acadia's ADVANCE)^{7,8}
 - Positive results, small effect size (ES = 0.2)
 - Better efficacy for higher dose (34 mg)⁹

¹Stahl SM. CNS Spectr. 2016;21:271-5. ²Cummings J et al. Lancet. 2014;383(9916):533-40. ³Mathis MV et al. J Clin Psychiatry. 2017; 78(6):e668-e673.

⁴Fava M et al. J Clin Psychiatry. 2019;80(6):19m12928.

⁵Nasrallah HA et al. Schizophr Res. 2019;208:217-220. ⁶ClinicalTrials.gov Identifier: NCT02970292. ⁷ClinicalTrials.gov Identifier: NCT02970305.

⁸Bugarski-Kirola D. Lancet Psychiatry. 2022;9(1):46-58. ⁹Darwish M et al. J Clin Psychopharmacol. 2022 Oct 3;42(6):544-551.

Pimavanserin for negative symptoms

- Phase 3 ADVANCE-2

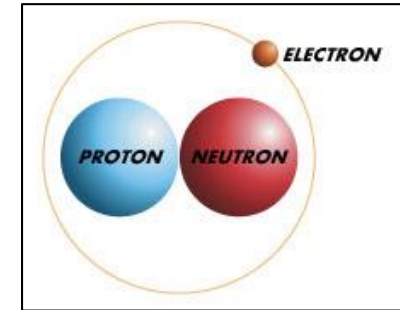
Fierce Pharma:
“Acadia to end Nuplazid testing
after schizophrenia trial flop and
years of failed expansion efforts”
By Zoey Becker
Mar 12, 2024

SAN DIEGO—(BUSINESS WIRE)—Mar. 11, 2024— Acadia Pharmaceuticals Inc. (Nasdaq: ACAD) today announced top-line results from the Phase 3 ADVANCE-2 trial evaluating pimavanserin for the treatment of negative symptoms of schizophrenia. **Pimavanserin did not demonstrate a statistically significant improvement over placebo on the study’s primary endpoint**, the change from baseline to week 26 on the Negative Symptom Assessment-16 (NSA-16) total score (-11.8 vs. -11.1; $p=0.4825$; effect size=0.07). The safety and tolerability profile of pimavanserin was consistent with previous clinical trials, showing a low rate of adverse events.

Dose tested: 34 mg

Deuterated medicines

- Hydrogen isotopes
 - Hydrogen (H); “heavy” H = deuterium (D); tritium (T)
 - D is stable (not radioactive!) and not toxic (1-2 gm)
 - (Remember “heavy water”)
- Deuteration of a molecule
 - Same 3-D structure!
 - Preserves pharmacodynamic properties
 - C-D bond 10x stronger than C-H bond
 - Changes pharmacokinetics: slows metabolism = longer half-life
- First FDA-approved deuterated product: Austedo
- AVP-786 = deuterated (d6)-dextromethorphan + ultra-low dose quinidine
 - Terminated after phase 3 failure for aggression in DAT
 - Terminated phase 2/3 for schizophrenia due to futility



Treatment for CIAS

CIAS = Cognitive Impairment Associated with Schizophrenia

- Avoid adding insult to injury
 - Reduce anticholinergic burden
 - Short-term and long-term risks (10% of dementia cases)¹
 - Quit smoking!²
 - Treat cardiovascular risk factors³
- Consider cognitive remediation, if available⁴
 - Active therapist, structured, integrated with rehab
- Psychopharmacology add-on strategies
 - Graveyard of drug development
 - CONNEX trial program for GlyT1 inhibitor iclepertin (BI 425809) once looked promising...⁵
 - Medication combined with computerized cognitive training⁶
- Kar-XT with benefit for subgroup (more severe impairment, with M1 downregulation)?^{7,8}

By age 66, 28% of patients with schizophrenia have dementia diagnosis (compared to 1.3%)!
- Stroup TS et al. JAMA Psychiatry. 2021;78(6):632-41.

Deprescription of unnecessary anticholinergic medications in schizophrenia must start now!
- Chengappa KNR et al. Am J Psychiatry. 2025;182(4):319-321.
- Mancini V et al. Am J Psychiatry. 2025;182(4):349-359.

¹Coupland CAC et al. JAMA Intern Med. 2019;179(8):1084-1093. ²Vermeulen JM et al. Am J Psychiatry. 2018;175(11):1121-8.

³Hagi K et al. JAMA Psychiatry. 2021;78(5):510-518 [Cardiovascular risks factors and cognitive impairment]

⁴Vita A et al. JAMA Psychiatry. 2021;78(8):848-858. ⁵Fleischhacker WW et al. Lancet Psychiatry. 2021;8(3):191-201. ⁶Harvey PD et al. Clin Drug Invest. 2020;40:377-85.

⁷Horan WP et al. Am J Psychiatry. 2025;182(3):297-306. ⁸Javitt DC. Am J Psychiatry. 2025;182(3):237-239. [Editorial]

GlyT-1 inhibitors for CIAS

glycine transporter 1

- Iclepertin = BI 425809
 - Glycine is co-agonist at NMDA receptor
 - Blockade of GlyT1 transporter enhances NMDA receptor-mediated glutamatergic neurotransmission and, consequently, cognitive function
- Boehringer Ingelheim
- Key published phase-2 trial (NCT02832037)
 - Typical add-on trial
 - Plus: add-on computerized cognitive training
 - Positive for primary outcome (MCBB)
- CONNEX trial program failed²
 - FDA Breakthrough Therapy Designation
 - Phase 3 CONNEX-1,2,3 and CONNEX-X extension trial

Welcome to the graveyard of drug development

ES around 0.3

¹Fleischhacker WW et al. Lancet Psychiatry. 2021 Mar;8(3):191-201.

²<https://www.boehringer-ingelheim.com/human-health/mental-health/schizophrenia/update-phase-iii-connex-clinical-program-schizophrenia>

Exercise for CIAS

- The challenge
 - Cardiovascular morbidity and mortality in SMI patients
 - Sedentary life-style associated with poor cognition¹
- The simple solution
 - Exercise is “neuroprotective”
 - Exercise has broad effects on well-being²
 - Improves global cognition³
 - Key pathways: inflammatory pathways, BDNF (hippocampus)⁴
- Challenges
 - Implementation: supported exercise
 - Maintaining gains: sustaining exercise
 - Need clinical trial with physical activity as end-point
 - Improving Cognition Via Exercise (ICE) in Schizophrenia⁵

COVID-19 adjustments⁶

¹Hamer M et al. Psychol Med. 2009;39:3-11. ²Noordsy DL et al. Am J Psychiatry. 2018;175(3):209-214.

³Firth J et al. Schizophr Bull. 2017;43:546-556. ⁴Kimhy D et al. Schizophr Bull. 2015;41(4):859-68.

⁵ClinicalTrials.gov Identifier: NCT03270098. [PI David Kimhy] ⁶Kimhy D et al. JMIR Ment Health. 2025;12:e68251.

B. TOLERABILITY

The day the music died



Samidorphan/olanzapine (ALKS 3831)

FDA approval Jun 1, 2021

- ALKS 3831 = samidorphan + olanzapine
 - Samidorphan¹
 - 3-carboxamido-4-hydroxynaltrexone
 - Potent mu-opioid receptor antagonist
- Alkermes development program
 - ENLIGHTEN phase 3 development program
 - Short-term (4 weeks) ENLIGHTEN-1 established efficacy²
 - Long-term (6 months) ENLIGHTEN-2 (completed)³
 - Lower percent weight gain and lower proportion 10% or more
 - ENLIGHTEN-Early showed less weight gain in early-course patients⁴
 - No benefit for schizophrenia and alcohol use disorder⁵
 - 4-year long-term study completed⁶

¹Turncliff R et al. Clin Ther. 2015;37(2):338-48. Silverman BL et al. Schizophr Res. 2018;195:245-251. [Phase I, PoC] ²Potkin SG et al. J Clin Psychiatry. 2020;81(2):61-9.

³ClinicalTrials.gov Identifier: NCT02694328. ⁴Brunette MF et al. J Clin Psychiatry. 2020;81(2):22-9. ⁵Kahn RS et al. J Clin Psychiatry. 2023;84(3):29-37.

⁶Pathak S et al. J Clin Psychiatry. 2020;81(2):19m12731. ⁶Ballon JS et al. J Clin Psychiatry 2025;86(1):24m15511

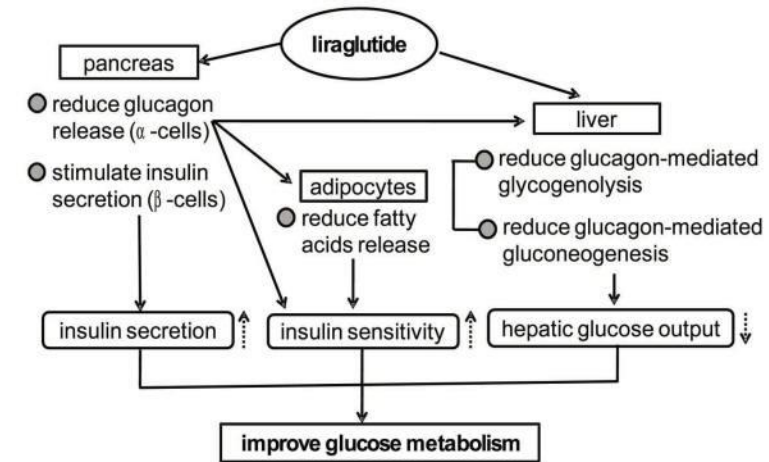
GLP-1 = glucagon-like peptide-1
GIP = glucose-dependent insulintropic polypeptide

Incretin mimetics

Weight loss + improved glucose control

- Antipsychotics increase glucagon¹
- Newer class (2010) of glucagon-like peptide-1 receptor agonist (GLP-1 receptor agonist)
 - Incretin hormone effect
 - Tirzepatide also agonizes a second hormone, GIP
 - Triagonists: GLP-1 + GIP + glucagon receptor
 - Low risk of hypoglycemia
 - Adding **bimagrumb** to prevent muscle loss²
- Medications
 - “Hot” new medication class for weight loss
 - Semaglutide³
 - 16% weight loss in 68-week trial with weekly injection
 - Liraglutide⁴
 - First GLP-1 agonist studied in schizophrenia
 - Loss of metabolic benefit once stopped⁵

Stimulate insulin release in response to meal
Decrease glucagon secretion
Decrease hepatic gluconeogenesis
Delay gastric emptying
Promote central satiety/reduce appetite



Yanai H et al. J Med Cases. 2011;2(2):76-80.

¹Aslanoglou D et al. Translational Psychiatry. 2021;11(1):59. ²Heymsfield SB et al. JAMA Netw Open. 2021;4(1):e2033457.

³Wadden TA et al. JAMA. 2021;325(14):1403-1413. [STEP-3 trial. NCT03611582] ⁴Larsen FR et al. JAMA Psychiatry. 2017;74(7):719-728.

⁵Svensson CK et al. Acta Psychiatr Scand. 2019;1139(1):26-36. [One-year follow-up] Jakubowska A et al. Endocrinol Metab. 2024;39:12-22.

Semaglutide for clozapine patients

COaST = Clozapine Obesity and Semaglutide Treatment trial

1. Methods

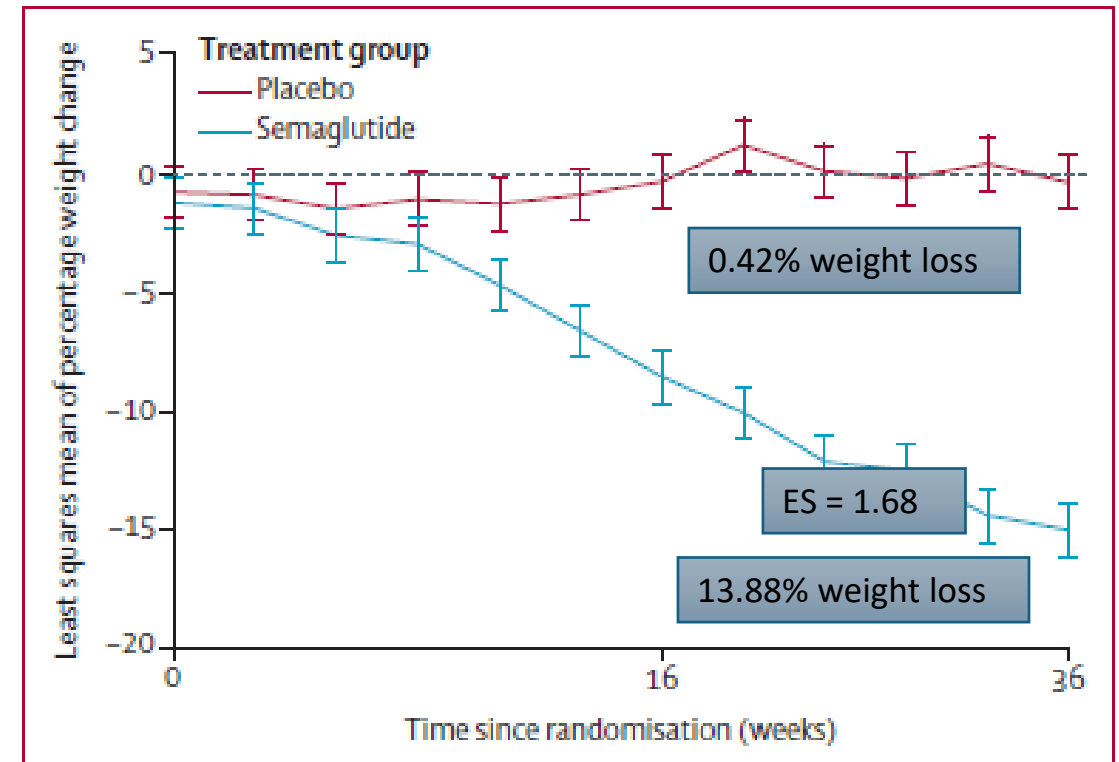
- Schizophrenia patients on clozapine from Queensland, Australia
- Obese and stable
- 36-week phase 2 RCT with blinding
- Semaglutide 2 mg SQ every week

2. Results

- N=31 (premature end of enrollment)
- Effective
 - Primary: weight loss (15.2 kg, majority 5 to 10%)
 - Secondary: HBA1c improvement (5.4 → 5.0%)
- Safe (psychiatric and medical)
 - Stable psychopathology
 - Stable clozapine levels and low constipation rate

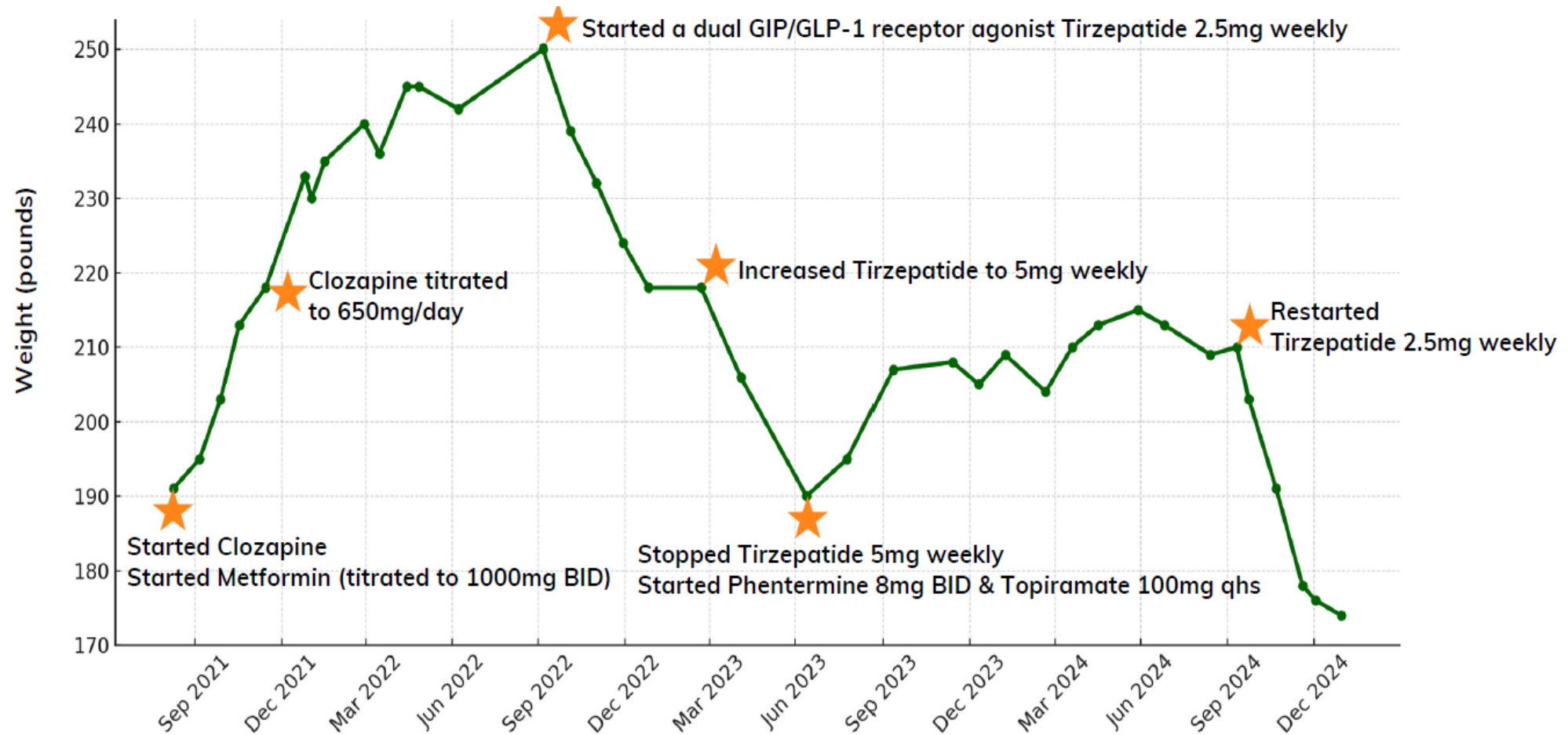
3. Significance

- First RCT of newer GLP-1 in metabolically high-risk psychiatric population
- As effective as in general population and psychiatrically safe



Percent weight change over 36 weeks

CASE: GLP-1 agonist in clozapine-treated patient



Lim C et al. MGB 13th Annual Public and Community Psychiatry Symposium 2025.

Lim C et al. Prim Care Companion CNS Disord. 2025;27(4):25cr03952.

C. ADHERENCE

Antipsychotic Therapeutic Drug Monitoring (TDM)

- Long history in psychiatry
 - Lithium
 - Tricyclic antidepressants
- Currently underutilized
- Renewed interest
 - First guideline for TDM published by TDM taskforce of AGNP in 2004 (update 2011 and 2017)
 - TDM best established for CLOZ, OLANZ, HAL, FLU, PER
 - International consensus statement 2020*
 - Development of new assays for antipsychotics**

Long-acting antipsychotic medications

- Broad selection with regards to dosing interval
 - How long is too long?¹
- New platform for extended release [SteadyTeq™, a copolymer technology proprietary to MedinCell]
 - Risperidone extended-release SC injectable FDA-approved April 2023
 - SOLARIS trial²
 - SOLARIS = Subcutaneous Olanzapine Extended-Release Injection Study
 - Positive phase 3 SC long-acting injectable olanzapine [, TEV-‘749], May 8, 2024
 - Pivotal phase 3 completed January 2025. No Post-Injection Delirium/Sedation Syndrome (PDSS), NDA Dec 2025
- Long-acting oral antipsychotics
 - Once-weekly risperidone capsule (LYN-005, Lyndra Therapeutics)
 - Phase 2 trial positive (NCT04567524)³
 - **STARLYNG-1 positive (NCT05779241)⁴**
 - Pivotal 6-month phase 3 safety study STARLYNG-2 did not happen⁵
 - Lyndra’s LYNX platform acquired by Nortiva⁶
 - Whatever happened to penfluridol?
 - T1/2 66 hours = “oral depot antipsychotic”
 - Once-a-week dosing

Long-acting olanzapine LAI without REMS

“Lyndra is the first company to demonstrate weekly oral therapy is possible. The board is grateful to all the employees, partners and vendors that developed the LYNX drug delivery platform and brought it to the point where it is ready for a phase 3 safety study,” a spokesperson told Fierce Biotech in an email. “In the current operating environment, the company was unable to secure the financing required to complete the phase 3 safety study. We look forward to the day when the safety study can be executed and, if successful, allow oral weekly therapies to reach physicians and patients who can benefit from their remarkable potential.”⁵

¹Dotson SM et al. J Clin Psychiatry. J Clin Psychiatry. 2023;84(4):23com14680. ³Results presented at SIRS 2021 Annual Meeting, April 18, 2021.

⁴Citrome L et al. Lancet Psychiatry. 2025;12(7):504-512.

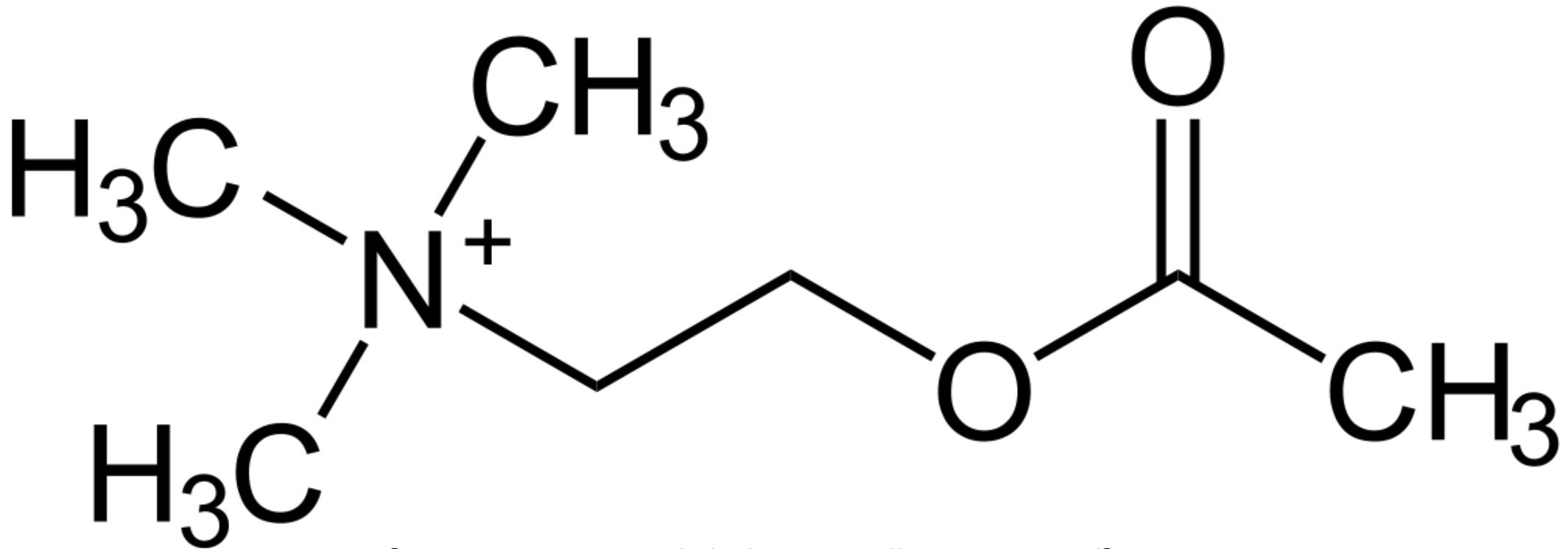
⁵<https://www.fiercebiotech.com/biotech/langer-spin-out-lyndra-therapeutics-begins-winding-down-operations-lays-staff> ⁶<https://nortivabio.com/platform/>

THINKING

OUTSIDE

THE BOX

Who am I?



[Hint: note ester and choline as well as acetic acid]

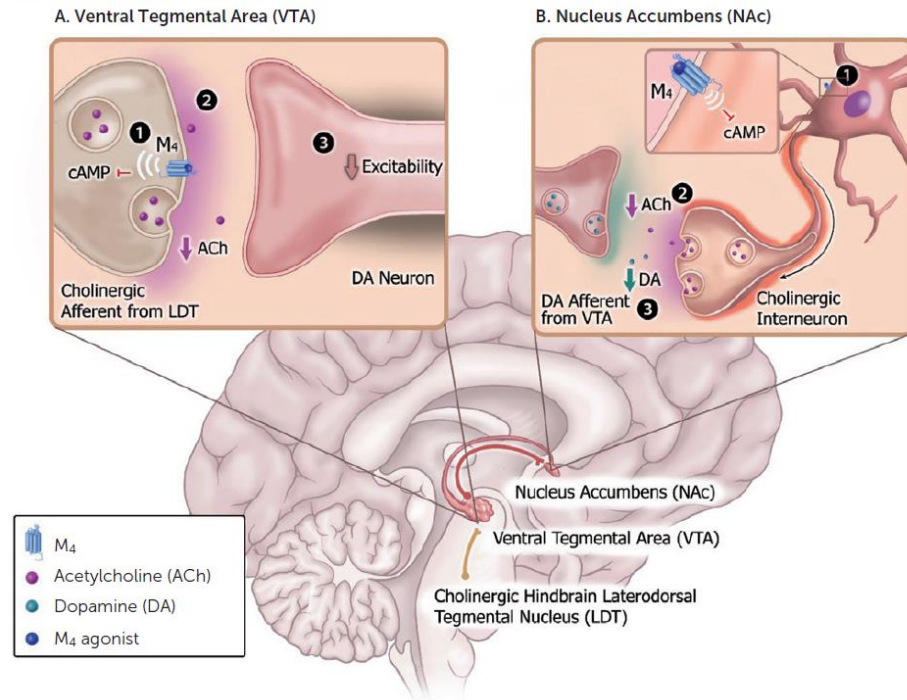
Cholinergic system

“The cholinergic system has been described as a widely distributed neuromodulatory system whose sources include **local interneurons** that are present in multiple brain regions, and **cholinergic projection neurons** that produce and release acetylcholine from two distinct clusters: basal forebrain nuclei* which innervate cortical, hippocampal, and thalamic areas; and the brainstem nuclei which innervate midbrain, hindbrain, thalamic, and cerebellar areas.”

*Nucleus basalis of Meynert

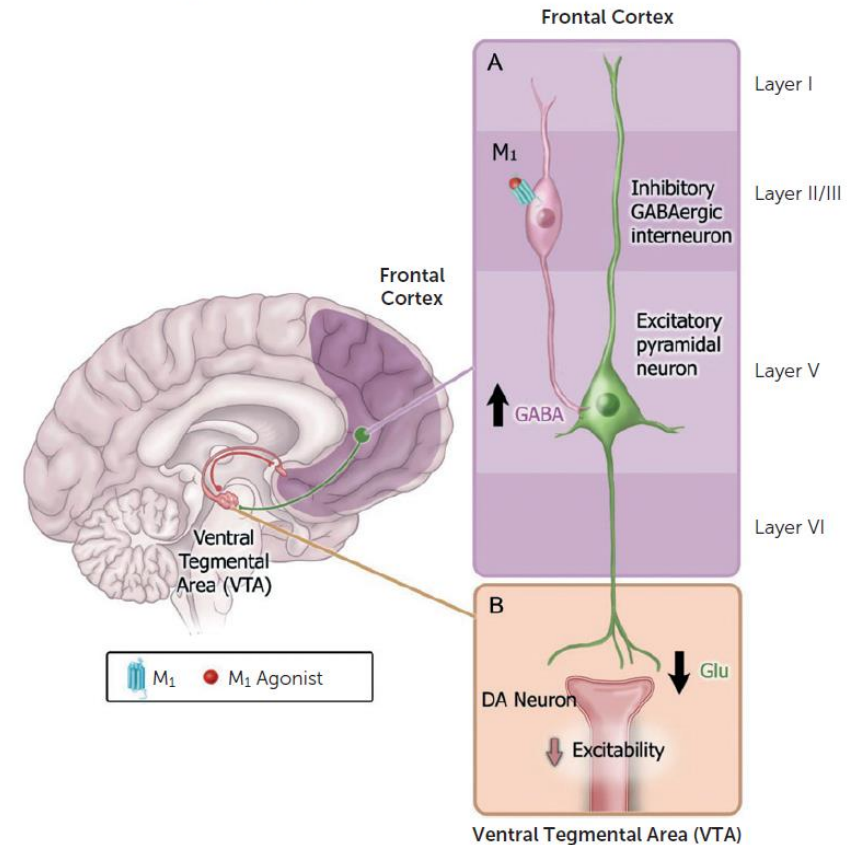
Neuroanatomy

FIGURE 5. Activation of M_4 receptors modulates cholinergic tone within midbrain dopamine (DA) centers to regulate terminal DA release^a



^aThe M_4 receptor is an autoreceptor on cholinergic afferents (point 1 in panel A) that project into the ventral tegmental area (VTA). Upon activation, M_4 receptors reduce acetylcholine (ACh) release onto VTA DA neurons (point 2 in panel A) and subsequently decrease neuron firing activity due to reduced activation of ACh receptors located on DA cell bodies (point 3 in panel A). This leads to a downstream reduction of DA release within the nucleus accumbens (NAc). Locally, within the NAc, M_4 receptors are located on cholinergic interneurons (ChIs) (point 1 in panel B). Upon activation, M_4 receptors decrease ChI spontaneous activity, and thus decrease cholinergic release from these neurons (point 2 in panel B). Reduced local cholinergic tone will also decrease stimulation (i.e., activation) of DA terminals (point 3 in panel B).

FIGURE 6. Activation of M_1 receptors in the frontal cortex exerts top-down control onto midbrain dopamine (DA) circuits^a



^aAs illustrated in panel A, activation of M_1 receptors expressed on layer II/III inhibitory GABAergic interneurons (pink) facilitates inhibitory drive onto excitatory output neurons (i.e., pyramidal neurons; green). In panel B, enhanced inhibitory drive onto pyramidal neurons decreases glutamatergic input to the ventral tegmental area (VTA). A reduction of excitatory input leads to a decrease in VTA dopamine (DA; red) neuron activity and reduced terminal DA release.

Cholinergic pharmacology – muscarinic side

- Central and peripheral
- Muscarinic receptors
 - G protein-coupled receptors
 - Subtypes M1 to M5
- Available cholinergic drugs
 - Cholinesterase inhibitors for Dementia of the Alzheimer type (DAT)
 - Donepezil, galantamine
 - Directly-acting post-synaptic M1 agonists for DAT: xanomeline
 - Anticholinergics
 - Muscarinic antagonist: trospium
 - Clozapine and its metabolite
- Sarin explains side effects of overstimulation

Cholinergic system and schizophrenia

- Dopaminergic and cholinergic system
 - Seesaw theory in neurology for Parkinson's disease
 - Clozapine is only mildly antidopaminergic but very anticholinergic
- Muscarinic hypothesis of schizophrenia
 - Cholinergic interneuron deficit^{1,2}
 - Schizophrenia subtype: low cortical M1 receptor density^{3,4}
 - KarXT with cognitive benefit for this subgroup?^{5,6}

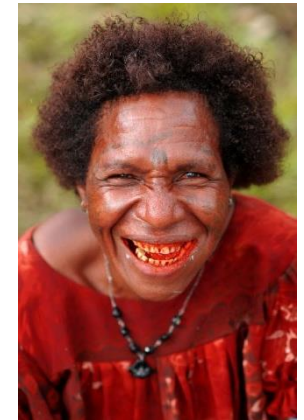
¹Holt DJ et al. Neuroscience. 1999;94(1):21-31. ²Holt DJ et al. Biol Psychiatry. 2005 Sep 1;58(5):408-16.

³Raedler TJ et al. Mol Psychiatry. 2007;12(3):232-246. ⁴Dean B et al. Schizophr Bull. 2018 Apr; 44(Suppl 1): S70–S71.

⁷Horan WP et al. Am J Psychiatry. 2025;182(3):297-306. ⁸Javitt DC. Am J Psychiatry. 2025;182(3):237-239. [Editorial]

Betel nut chewing

- Betel nut
 - Chewing common in Asian and Pacific cultures¹
 - Natural, active ingredient, arecoline is pan-muscarinic agonist
- Interesting epidemiological observation
 - Palau, Micronesia
 - Betel chewers with schizophrenia scored significantly lower on the positive ($P = 0.001$) and negative ($P = 0.002$) sub-scales of the PANSS than did non-chewers²
 - Male high-consumption betel chewers significantly milder positive symptoms than low-consumption chewers over 1 year³

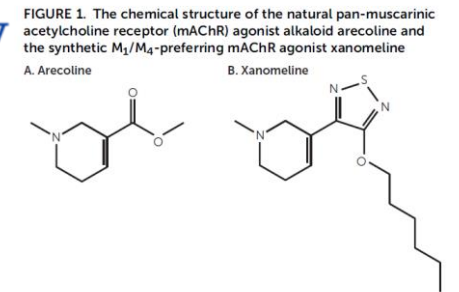


¹Ye Jin Joo et al. Subst Use Misuse. 2020;55(9):1422-1442.

²Sullivan RJ et al. Br J Psychiatry. 2000;177:174-8. ³Sullivan RJ et al. Am J Psychiatry. 2007;164(4):670-3.

Photos: <https://blog.twmuseums.org.uk/an-unusual-addiction/>.

Xanomeline for schizophrenia



- Early interest in procholinergic drugs for schizophrenia
- Work in Alzheimer's disease with cholinesterase inhibitors
 - Mostly failed drug development with AChE inhibitors for schizophrenia¹
- Synthetic dual M1/M4-preferring direct agonist xanomeline
- Xanomeline is effective for psychosis
 - Serendipity: Bodick xanomeline trial in DAT²
 - Proof-of-concept: Shekhar xanomeline trial in schizophrenia³
- Potential for further cholinergic drug development⁴
 - Emraclidine: M4-selective positive allosteric modulator (PAM) (AbbVie)
 - However: phase 2 EMPOWER-1 and -2 emraclidine failed⁴
 - NBI-1117568: M4-selective orthosteric agonist in phase 3 after positive phase 2 (Neurocrine)⁵

¹Freudenreich O et al. Psychopharmacology (Berl). 2005;181(2):358-63. ²Bodick NC et al. Arch Neurol 1997; 54:465-473.

³Shekhar A et al. Am J Psychiatry 2008; 165:1033-1039.

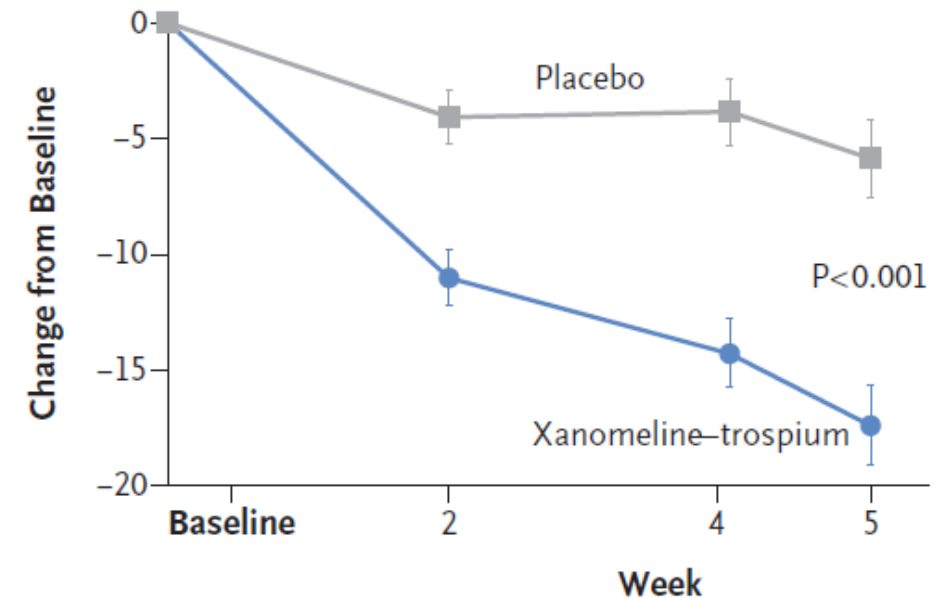
⁴<https://news.abbvie.com/2024-11-11-AbbVie-Provides-Update-on-Phase-2-Results-for-Emraclidine-in-Schizophrenia>

⁵<https://neurocrine.gcs-web.com/news-releases/news-release-details/neurocrine-biosciences-reports-positive-phase-2-data-nbi-1117568>

Xanomeline + trospium = KarXT

- Xanomeline = mAChR M1/M4 agonist
 - Poor oral tolerability (cholinergic syndrome)
- Tolerability improved by co-formulating with trospium as KarXT (Karuna)
 - Trospium (brand name Sanctura) = FDA-approved peripheral muscarinic antagonist for overactive bladder
- EMERGENT clinical trials program
 - Positive phase 2 trial published¹
 - Two positive phase 3 trial published^{2,3}

A PANSS Total Score



ES = 0.75

Side effects: GI, cardiac (?)

¹Brannan SK et al. NEJM. 2021;384(8):717-726. Neary J et al. NEJM. 2021;384(25):e105. [Editorial]

²Kaul I et al. Lancet. 2024;403(10422):160-170. ³Kaul I et al. JAMA Psychiatry. 2024; 81(8):749-756.

For anatomy see: Paul SM et al. Am J Psychiatry 2022; 179:611-627.

KarXT Clinical Trials Program



Massachusetts General Hospital
Founding Member, Mass General Brigham

Psychiatry Academy

Feb 2021

NEW ENGLAND JOURNAL of MEDICINE

Monotherapy: EMERGENT

ORIGINAL ARTICLE

Muscarinic Cholinergic Receptor Agonist and Peripheral Antagonist for Schizophrenia

Stephen K. Brannan, M.D., Sharon Sawchak, R.N., Andrew C. Miller, Ph.D.,

Efficacy and safety of the muscarinic receptor agonist KarXT (xanomeline-trospium) in schizophrenia (EMERGENT-2) in the USA: results from a randomised, double-blind, placebo-controlled, flexible-dose phase 3 trial

Inder Kaul, Sharon Sawchak, Christoph U Correll, Rishi Kakar, Alan Breier, Haiyuan Zhu, Andrew C Miller, Steven M Paul, Stephen K Brannan

Summary

Background New treatments with new mechanisms are urgently needed for people with schizophrenia. Xanomeline is a dual M₁ and M₄-preferring muscarinic receptor agonist that does not block D₂ dopamine receptors, unlike all currently approved treatments for schizophrenia. Xanomeline-trospium (KarXT) combines xanomeline with the peripherally restricted muscarinic receptor antagonist trospium chloride with the goal of ameliorating xanomeline-related adverse events associated with peripheral muscarinic receptors. The EMERGENT-2 trial aimed to assess the efficacy and safety of KarXT in people with schizophrenia experiencing acute psychosis.

Methods EMERGENT-2 was a randomised, double-blind, placebo-controlled, flexible-dose, 5-week, inpatient, phase 3 trial in people with schizophrenia. Participants were adults aged 18–65 years with a diagnosis of schizophrenia who

Lancet 2024; 403: 160–70
Published Online
December 14, 2023
[https://doi.org/10.1016/S0140-6736\(23\)02190-6](https://doi.org/10.1016/S0140-6736(23)02190-6)
See Comment page 120
Karuna Therapeutics, Boston, MA, USA (I Kaul MD, S Sawchak RN, H Zhu PhD, et al.)

JAMA Psychiatry | Original Investigation

Efficacy and Safety of Xanomeline-Trospium Chloride in Schizophrenia: A Randomized Clinical Trial

Inder Kaul, MPH; Sharon Sawchak, RN; David P. Walling, PhD; Carol A. Tamminga, MD; Alan Breier, MD; Haiyuan Zhu, PhD; Andrew C. Miller, PhD; Steven M. Paul, MD; Stephen K. Brannan, MD

May 2024

Short term Efficacy & safety of KarXT vs. placebo in inpatients experiencing acute psychosis	Phase 2	EMERGENT 1 (5 weeks)
	Phase 3	EMERGENT 2 (5 weeks)
		EMERGENT 3 (5 weeks)
Long term Safety & tolerability of KarXT	Phase 3	EMERGENT 4 (5 weeks) Open-label extension of EMERGENT 2 & 3
		EMERGENT 5 (56 weeks) Open label new patients

New Drug Application Submitted

FDA Approval September 26, 2024

mghome.org

Xanomeline update

Long-term trials^{1,2}

- EMERGENT-4 and EMERGENT-5
- Durable improvement
- Good tolerability
 - Nausea and vomiting
 - No prolactin elevation
 - No weight gain
 - No tardive dyskinesia

Number needed to treat (NNT)³

- Data from the three 5-week, randomized, double blind, placebo controlled EMERGENT-1, EMERGENT-2, and EMERGENT-3⁴
- NNT=5 [95% CI, 4–8]
 - For response = at least 30% PANSS reduction
- NNH over 10 except for N/V

¹Kaul I et al. Am J Psychiatry. 2026;183(3):183-192. Goff DC. Am J Psychiatry. 2026;183(3):152-153. [Editorial] ²Kaul I et al. Schizophr Res. 2026;288:86-94.

³Citrome L. Acta Psychiatr Scand 2008; 117: 412–419. ⁴Citrome L et al. Neuropsychiatr Dis Treat. 2025;21:761–773.

Adjunctive treatment with xanomeline

RATIONAL

- Biological heterogeneity
 - Partial response to antipsychotics
 - Treatment-resistance to antidopaminergic antipsychotics
- Combining agents with differing mechanisms of action can bring additive, synergistic effect
- Preclinical animal trials
 - M1 positive allosteric modulator adjunct---enhanced procognitive effect
 - Clozapine metabolite (norclozapine) acts on M1
 - M4 positive allosteric modulator adjunct---augmented conditioned avoidance
 - M4 receptors are also present on cortical glutamatergic afferent terminals in the striatum and post-synaptically on dopamine D1-expressing spiny projection neurons
 - Xanomeline adjunct-- attenuated hyperactivity induced by NMDAR antagonist

ARISE

- Target population
 - Outpatients with some treatment resistance
- ARISE-1 (KAR-12): 6-week safety and efficacy study
- ARISE-2 (KAR-13): 52-week open-label extension
- Preliminary results ARISE-1
 - Failed to reach significance for primary end-point
 - Perhaps differential benefit depending on antipsychotic it was added to

Scientific progress is not linear

Editorial in the American Journal of Psychiatry

Cholinergic agonists as
novel treatments for
schizophrenia: the promise
of rational drug
development for
psychiatry

Lieberman JA et al. Am J Psychiatry. 2008;165(8):931-935.

Ulotaront

- Ulotaront: SEP-363856 [Sunovion]
- “First in class”
 - Non-D2-receptor-binding antipsychotic
 - MOA: TAAR1 + 5-HT1A
- Phase II trial [NCT02969382]¹
 - 4-week RCT (drug versus placebo)
 - Efficacy for PANSS total score
 - ES 0.45
 - Safety and tolerability
 - One death in treatment group (patient had heart disease)
 - 26-week extension results [NCT02970929]²
- Two negative phase 3 trials (DIAMOND 1 and 2) [NCT04072354, NCT04092686]
 - High placebo response

Monoamine receptor activator

TAAR-1 = Trace amine-associated receptor 1
DAAO = D-amino acid oxidase

TAAR1 agonists = -taront

Ulo-taront (Sunovion) – phase 3 [DIAMOND]
Ralmi-taront (Roche) – phase 2

Nedic N et al. Int J Mol Sci. 2021;22:13185.

Targeting neurocircuits

- Lesion-based module disruption
 - Critical lesion takes out brain module
 - Classical neurology
- Distributed yet delineated circuit dysfunction
 - Alexander's parallel, segregated circuits¹
 - Neuropsychiatry
- Large-scale network disruption
 - The search for specific cellular pathology (e.g., chandelier interneurons and GABA²)
- Magnetic and electric stimulation

¹Alexander GE et al. Annu Rev Neurosci 1986;9:357. ²Lewis DA. Dev Neurobiol 2011;71:118. ³Dougall N et al. Cochrane Database Syst Rev. 2015 Aug 20;(8):CD006081. ⁴Brady RO et al. Am J Psychiatry 2019;176(7):512–520. ⁵Gupta T et al. Front Behav Neurosci. 2018 May 28;12:94. Tseng PT. JAMA Psychiatry. 2022; JAMA Psychiatry. 2022;79(8):770-779.

Diets – food and fasting as treatment

- Nutritional psychiatry¹
- Types of dietary interventions²
 - Adding something (vitamins, micronutrients)
 - Removing something (toxins, allergens)
 - Combination in the form of “healthy diets”
 - Gut microbiome
 - Fasting and ketogenic diet
- Ketogenic diet³
 - Well-established in treatment-resistant epilepsy
 - Mechanism: restoration of normal energy metabolism; anti-inflammatory
 - Possible broad benefits beyond symptoms⁴
 - Controlled trial results pending
- Clozapine, TRS and gut microbiome⁵

¹Adan RAH et al. *European Neuropsychopharmacology*. 2019;29(12):1321-1332. [Review]

²Palmer CM. *J Clin Psychiatry*. 2020;81(1):62-63. ³Palmer CM et al. *Schizophr Res*. 2019;208:439-440.

⁴Murray SL et al. *Front Psychiatry*. 2025;16:1710785. ⁵Vasileva S et al. *JAMA Psychiatry*. 2024;81(3):292-302.

The way forward

- Heterogeneity as opportunity¹
 - Focus on biology of treatment-resistance
 - Focus on other sources of treatment resistance
 - Focus on circuits underlying specific symptoms clusters
- Improve clinical trials methodology²
 - Increasing placebo response and decreasing effect size in schizophrenia trials²
 - Precision Clinical Trials (PCTs)³
 - Treatment-targeted enrichment, adaptive treatment, precision measurement
 - Take into account effects of dopamine blockade (!)
 - Problem of add-on trials⁴
- Harness disruptive psychopharmacology⁵
- Repurpose psychiatric drugs⁶
- Move towards precision medicine^{7,8}

Lost in translation.
The value of psychiatric clinical trials.⁹

Beyond dopamine – towards a pluralistic model.¹⁰

¹McCutcheon RA et al. JAMA Psychiatry. 2020;77(2):201-10. ²Gopalakrishnan M et al. J Clin Psychiatry. 2020;81(2):38-44. Editorial: Laughren TP. J Clin Psychiatry. 2020;81(2):19com13110.
³Lenze EJ et al. JAMA Psychiatry. 2020;77(7):663-664. ⁴Grace AA and Uliana D. Biol Psychiatry. 2026 (in press). ⁵Heifets BD and Malenka RC. JAMA Psychiatry. 2020;76(8):775-776. [Viewpoint]
⁶Lenze EJ et al. J Clin Psychiatry. 2023;84(3):38-45. ⁷Hill MD et al. Molecular Psychiatry. 2024;29:1528-1549. ⁸Kas MJH et al. Mol Psychiatry. 2025;30:3846-3855;
⁹Markowitz JC and Milrod BL. J Clin Psychiatry. 2022;83(6):76-79. ¹⁰Keshavan MS et al. JAMA Psychiatry. 2026 (in press).

Promising pipeline for CNS drugs

Compound	Mechanism of action	Target symptom	Company	Phase	NCT number
spg302	Synaptic regeneration (glutamate)	General	Spinogenix	2	06442462
CPL500036	PDA10A inhibitor	General	Celon	2	05278156 Positive phase 2
Evanamide	VGSC blocker	TRS	Newron	3	07184619
Brilaroxazine (Oxaripiprazole)	Partial D2/D3 agonist	General	Reviva	3	05184335 2nd phase 3 needed for FDA
Milsaperidone (BYSANTI)	Dopamine antagonist (iloperidone metabolite)	General	Vanda	N/A	Approved February 20, 2026
TAK-831 Luvadaxistat	DAAO inhibitor	Negative Cognition	Takeda	2	03382639, 05182476 Pos (INTERACT), neg (ERUDITE)
SEP-363856 Ulotaront	TAAR-1 5-HT1A agonist	General (Negative)	Sunovion	3	04072354 Two negative trials
BI 425809 Iclepertin	Glycine transporter-1 inhibitor	Cognition	Boeringer Ingelheim	3	04860830 CANCELLED
ALTO-101T	(Transdermal) PDE4 inhibitor	Cognition	Alto Neuroscience	2	NCT06502964 Negative proof-of-concept trial
NBI-1117568 Direclidine	M4 agonist	General	Neurocrine	2/3	06963034 Positive phase 2

What is treatment resistance in psychiatry?

- Failed concept
 - Focus on acute illness mode and symptom remission
 - Focus on psychopharmacology and symptoms
 - Often used as endpoint¹
 - Built-in pessimism
 - Devoid of empathy
 - Erodes care quality
- Difficult-to-treat schizophrenia²
 - Emphasis on collaborative, multi-modal treatment
 - Better fit for chronic illness where a cure is illusive
 - Focus on quality of life
- Palliative psychiatry³
 - Better approach to (pharmacological) futility

¹Putman HP. Psych Res Clin Pract. 2024;6:112–114. ²Demyttenaere K. World Psychiatry. 2019;18(3):354-355.

³Trachsel M et al. BMC Psychiatry. 2016;16:260.

MGH Treatment-resistant schizophrenia (TRS) Service MGH TRS ACCESS

<https://mghaccess.org/>

- **Director**
 - Oliver Freudenreich, MD, FACLP
- **Mission**
 - To improve the care of patients with treatment-resistant schizophrenia
- **Goals**
 - **Innovate:** More effective and safer treatments
 - **Integrate:** Fewer silos and more partners
 - **Instruct:** Easier access to consultation
 - **Influence:** Disseminate knowledge



Lim C, Donovan AL, Freudenreich S, Cather C, MacLaurin S, Freudenreich O. Second opinions for diagnoses of psychotic disorders: delivering stage-specific recommendations. *Psychiatr Serv.* 2024;75(10):1035-1038.

Molly McCarthy