Evidence-Based Approaches to Integrating Emerging Schizophrenia Treatments into Clinical Practice

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Disclosures

Consultant:	Alkermes, Anavex, Boehringer-Ingelheim, Bristol Myers Squibb, Delpor, Karuna, Kuleon, Maplight Therapeutic
Speaker:	Alkermes, Bristol Myers Squibb, Neurocrine, Teva
Stock options:	Delpor, Kuleon

- The presentation will cover investigational antipsychotics “in the pipeline” for the indication of treatment of adults with schizophrenia.
- Not all of the pipeline medications are FDA approved at this time
- Efficacy and safety information presented are based on publicly available data from Clinical Development programs, including press releases, congress presentations and clinicaltrials.gov

When considering strategies for patients with schizophrenia who have partially responded to treatment, what is recommended for those who have shown a partial response and tolerated their current antipsychotic?

A. Optimize the current medication's dose
B. Immediately switch to a different antipsychotic
C. Augment with a nonpharmacological therapy
D. Add another agent with a different mechanism of action

Which combination represents the mechanism of action of xanomeline-trospium, a novel therapeutic agent for schizophrenia?

A. TAAR1 agonist and 5-HT1A agonist
B. M_1/M_4 agonist with peripheral muscarinic antagonist
C. Glycine transporter 1 inhibitor
D. 5-HT2A inverse agonist/antagonist

Which aspect of schizophrenia treatment is emphasized as an important goal beyond symptom control?

A. Engagement in life goals
B. Reduced risk of tardive dyskinesia
C. Complete symptom control
D. Improved adherence to medication

FDA recently approved xanomeline-trospium for adults with schizophrenia. how confident are you in knowing the differences between this treatment and the other approved antipsychotics?

A. Not Confident at All
B. Slightly Confident
C. Very Confident
D. Extremely Confident

How comfortable are you with prescribing new and novel therapeutics for the treatment of schizophrenia to your patients?

A. Not Comfortable at All
B. Slightly Comfortable
C. Very Comfortable
D. Extremely Comfortable

What are some treatment approaches for “real world” patients who continue to have symptoms or side effects?

Let’s start with a case……

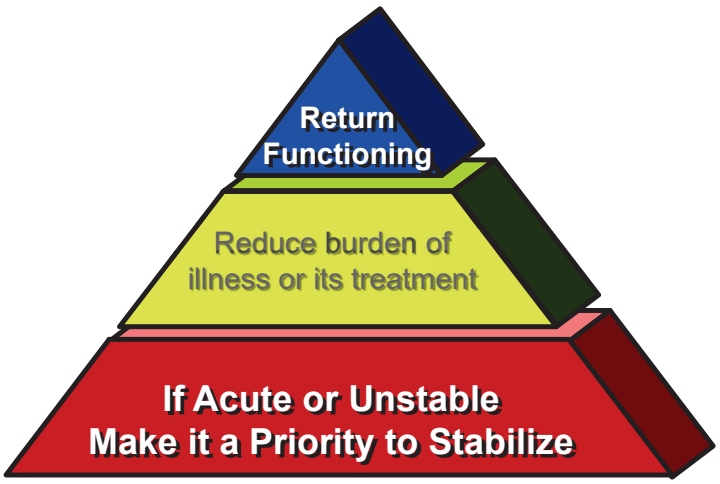
Meet Michael. You are asked to consult on this case.

- Michael is a 45-year-old man with schizophrenia
- He lives in a group home, and receives services from the local Assertive Community Treatment team
- In the prior 2 years, he has had 3 psychiatric hospitalizations because of exacerbations of hallucinations and delusions
- He is currently receiving risperidone 5 mg at bedtime
- The staff says he tolerates it well, but he complains of erectile difficulties
- The staff reports that since his last discharge, Michael is less interested in social activities, and has been having trouble keeping up with instructions and even following the plot of his favorite TV shows.
- What is the treatment plan? What do we do?

Helpful to Think of Hierarchal Goals

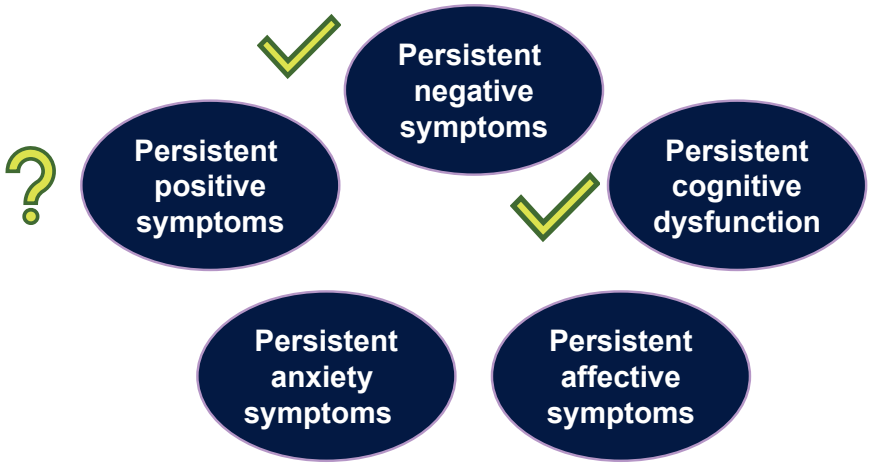
Focus on Specific Stages of Need and then Move to Next Level

- As in Michael's case, patients often have many problems at once
- Can be overwhelming
- Where to start?
- Is there a strategy to help with priorities?



Adapted from Weiden P et al: Atypical antipsychotic drugs and long-term outcome in schizophrenia. *J Clin Psychiatry*. 1996;57 Suppl 11:53-60.

Potential Symptom Targets for Psychopharmacology*



*All approved antipsychotics except clozapine are labeled in prescribing information as indicated for treatment of "schizophrenia" without identifying efficacy for specific domains. Clozapine is approved for treatment-resistant schizophrenia and for suicide risk as a second-line treatment. The FDA has signaled willingness to approve medications for cognitive or negative symptoms but to date no medication has been approved for either of these target symptoms.

Choice of Antipsychotic in Hierarchical Approach

How does this apply to Michael ?

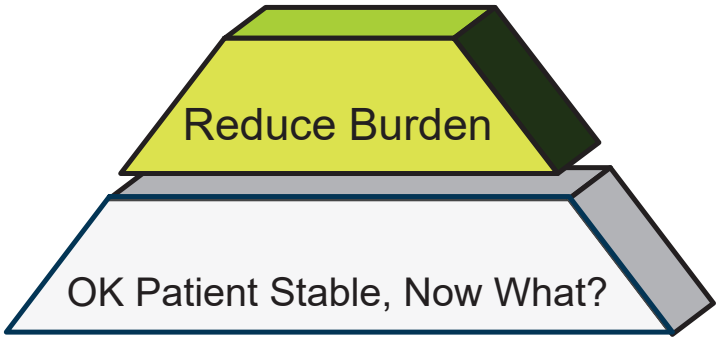
- When hospitalized, medication selection might prioritize:
  - Achieve therapeutic dosing quickly
  - Effective for acute symptoms
  - ***Short-term*** safety during course of hospitalization
- But consider after discharge ….
  - ***long-term*** safety, ***acceptability*** of expected side effects, ***LAI availability,*** effectiveness for ***relapse prevention***

Optimizing Acute Treatment Response

- Antipsychotic trial is not the first day taken first day at **therapeutic dose** [1]
- Some of the first-line antipsychotics may be more effective for acute positive symptoms [2]
  - All approved antipsychotics effective for acute treatment
  - But olanzapine and risperidone have better effect sizes (0.56 and 0.55) than many others
- What about inadequate response?
  - Plasma monitoring for unexpected nonresponse [4]
  - rule-out behavioral toxicity from medication (e.g. akathisia)
  - rule-out “cheeking”
  - Dosing high vs switching vs augmenting are used, no clear consensus [3]

ENR, early non-responder.
Hatta K, et al. Schizophr Res. 2014;158(1-3):213-22.
1 Weiden PJ. Iloperidone for the treatment of schizophrenia Clin Schizophr Relat Psychoses. 2012;6:34-44.
2 Huhn M et al: Comparative efficacy and tolerability of 32 oral antipsychotics for the acute treatment of adults with multi-episode schizophrenia…The Lancet. 2019;394:939-951. 3. hatta reference 4 Meyer JM, Stahl SM: The Clinical Use of Antipsychotic Plasma Levels: Stahl's Handbooks, Cambridge University Press; 2021.

Long-term Treatment Goals for Schizophrenia
Example of Michael’s Treatment Plan



When Symptoms or Side Effects Persist
Bird’s Eye View of Current Practice

Strategy	Definition
Watchful Waiting	Postpone decision
Adjust dose	Adjust dose of the current medication
Change route	Change route of drug delivery (eg LAI)
Add	Add a new medication
Substitute (“switching”)	Change medications within same class
Subtract (“deprescribing”)	Discontinue medication(s) from regimen

When Symptoms Persist

Bird's Eye View of Current Practice

Strategy	Pros	Cons
Waiting	• If more time needed for full response • Buys time to look for non-pharmacologic causes	• May seem too passive • Reach point of diminishing returns
Dose	Most likely to help when current antipsychotic has steep dose response curve [1]	• Unlikely to work when above high end of therapeutic • opportunity cost of not trying other options • Not realistic with dose-sensitive tolerability problems
Route	LAI is better than oral for long-term therapy	Not all antipsychotics have LAI options
Add	Within class: Relatively easy, don't have to stop current med	Within class: Controversial, may increase side effect burden.[2] not a substitute for clozapine
	Out of class: may be helpful for mood (SSRI) or anxiety (benzodiazepine)	Out of class: Mood stabilizers NOT helpful for persistent positive symptoms! Benzos not be as safe as once believed
Substitute	• Uses principle of differential efficacy • Only way to get to clozapine • May have additional benefits for problematic side effects	• Differential efficacy between first line aps is debated • Efficacy of any new medication is unknown • Switching process can be cumbersome • Risk of symptom exacerbation if switch goes awry
Subtract	Problems seem worsened by multiple medications	Hard to know where to start, needs to be done slowly

[1] Leucht S et al Dose-Response Meta-Analysis of Antipsychotic Drugs for Acute Schizophrenia. AJP 2020;177:342-353.
[2] Lähteenvuo M, Tiihonen J. Antipsychotic Polypharmacy for the Management of Schizophrenia: Evidence and Recommendations. Drugs. 2021;81:1273-1284.

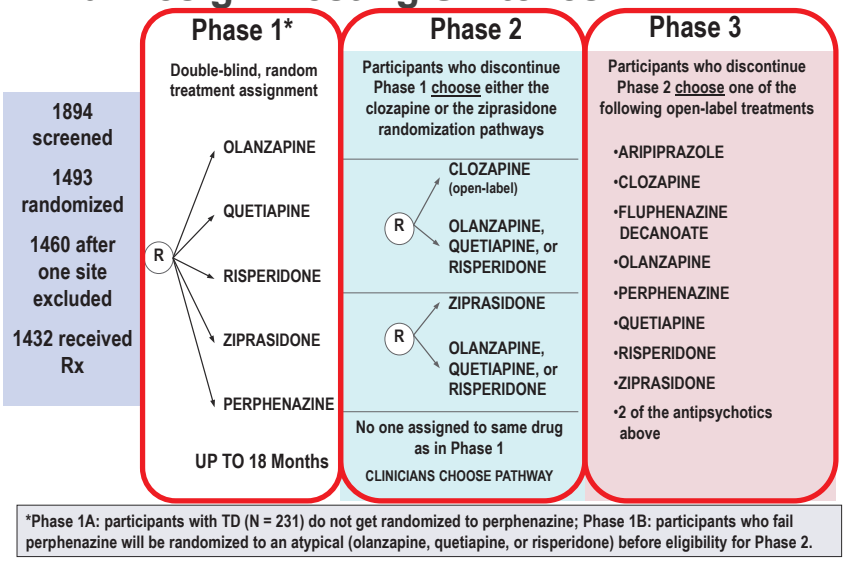
When Side Effects Persist

Common strategies for persistent side effects

Strategy	Pros	Cons
Waiting	• For early side effects likely to abate • For side effects that do not pose medical risk and are not distressing	• May be perceived by patient or family as insensitive or indifferent
Dose	• Lowering dose is very effective for dose-sensitive side effects	• Not helpful for side effects that are relatively dose-insensitive • May risk loss of efficacy by going lower than lowest effective dose
Route	• Side effects of newer LAI formulations not worse than their oral counterpart	• LAIs side effect profile is generally the same as the oral counterpart
Add	• Adding an adjunct to lower side effect is helpful when current medication needs to be continued or side effect is the same across the entire class of medication	• Additional burden and complexity of regimen • The adjunct will have other side effects that might be problematic
Substitute	• There are major differences in side effect liability for many of the common side effects of antipsychotics • The side effect changes from switching antipsychotics is predictable	• When switching for side effects there may be risk of efficacy differences between old and new medication • Even if side effect is better on new medication, there may be others that were not an issue with the prior medication that are associated with the new one
Subtract	• When there is a side effect that comes from > 1 of the medication, discontinuing the non-essential medication can be very effective	• Not always possible to use this approach

The CATIE SCHIZOPHRENIA STUDY
2005

CATIE Trial Design: Testing Switches



Rx, prescription; TD, tardive dyskinesia.
Stroup TS, et al. *Schizophr Bull*. 2003;29(1):15-31; www.nimh.nih.gov/funding/clinical-research/practical/catie/index.shtml.

Why Did Most Patients Change Medication?

Efficacy limitations, side effects, insight, all of above?

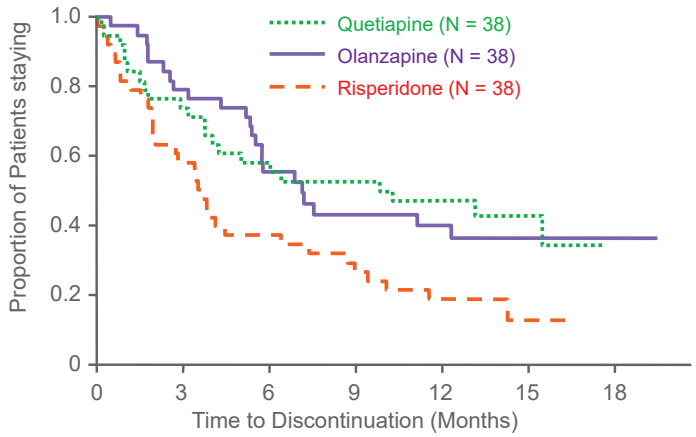
- CATIE was a large effectiveness study that tested switches; **time to all-cause discontinuation** was the primary outcome measure
  - Different outcomes were seen for the antipsychotics tested
    - Olanzapine had advantages in terms of all-cause discontinuation and efficacy
    - Quetiapine and olanzapine were better after failing perphenazine (phase 1b)
    - Clozapine was superior patients who discontinued an atypical antipsychotic
    - Ziprasidone had the lowest metabolic and weight burden and resulted in the most weight loss after prior weight gain

Citrome L. *Psychiatry (Edgmont)*. 2007;4(10):23-9.

Changing Antipsychotics CATIE Phase 2

Time on Next Antipsychotic after Switching from Perphenazine

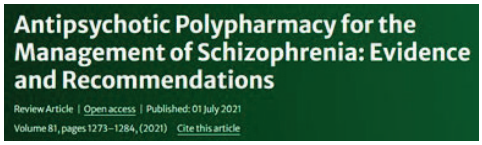
TAKE HOME MESSAGE
Better to switch to a low D_2 affinity antipsychotic (**quetiapine** or **olanzapine**) from the high D_2 antagonist perphenazine than to the high affinity D_2 antipsychotic **risperidone**



Stroup TS, et al. *Am J Psychiatry*. 2007;164(3):415-427.

Combining Antipsychotics for Persistent Symptoms

- In a meta-analysis, benefits of antipsychotic augmentation depended on study quality with higher quality studies not showing benefits
- At best, "home runs" not likely from combining antipsychotics with problem being similar Mechanism of Action across antipsychotics
- Exception might be for aripiprazole augmentation



Caveats

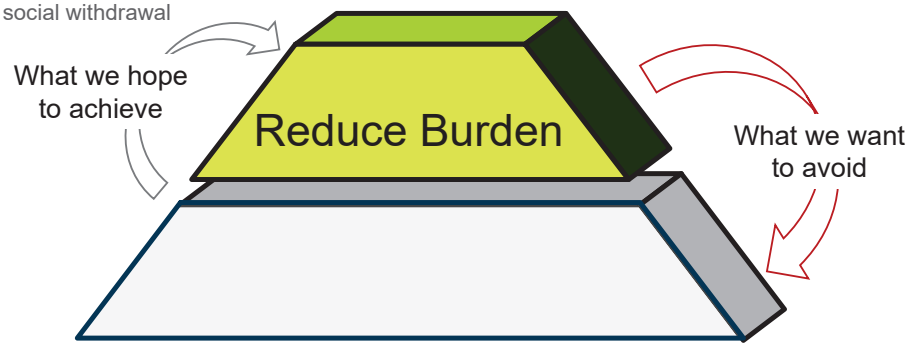
- One downside is polypharmacy associated with additional side effect burden
- Other downside is the opportunity cost of NOT using an LAI or clozapine
- There is a need for more research to optimize antipsychotic polypharmacy and treatment augmentation strategies in specific patient scenarios.

Galling B, et al. *World Psychiatry*. 2017;16(1):77-89. Lähteenvuo M, Tiihonen J.*Drugs*. 2021;81:1273-1284.

Michael's Treatment Plan

Dealing with Uncertainty and Gaps in Information

- Reduce risk of hospitalization
- Address side effect concerns (ED)
- Evaluate social withdrawal



What Does This Mean for Michael?

While no "right" answer, the wrong answer is to give up

- Complains of erectile difficulties. Can risperidone be saved?
  - If it is from hyperprolactinemia, adjunctive **aripiprazole** may be helpful
  - If it really is retrograde ejaculation, that is alpha antagonism not prolactin, and would resolve with an antipsychotic without alpha-1 antagonist properties
- What if there weren't any side effects? Is risperidone's efficacy good enough?
- If he had a full therapeutic trial of risperidone, CATIE results suggest **olanzapine** next
  - **BUT** CATIE study done before a partial agonist was available.
  - The partial agonism **aripiprazole** likely safer than olanzapine and available as an LAI
- If deemed treatment-resistant, then **clozapine** but needs more cooperation and support
- What if risperidone prescribed ≠ risperidone taken?
- Consider either serial plasma concentration assessments or an LAI trial to disentangle poor response from subtherapeutic concentrations (e.g. not taking medication)

LAI, long-acting injectable; TRIPP, Treatment Response and Resistance in Psychosis.
Howes OD, et al. *Am J Psychiatry*. 2017;174(3):216-29.

Prelude to the Future:
What if We Had Different Classes of Treatments?

- Problems with current risperidone
- Problems with adding aripiprazole
- Problems with olanzapine
- Problems with clozapine
- Problems with LAIs

All medications work in similar ways, which is bad news for those who don't respond to dopamine receptor antagonism)

Breakthrough positive symptoms is the rule even for "responders"

clozapine unique but has a lot of "baggage"

No approved pharmacologic treatment for cognitive or negative symptoms

"whack-a-mole" problem with side effects

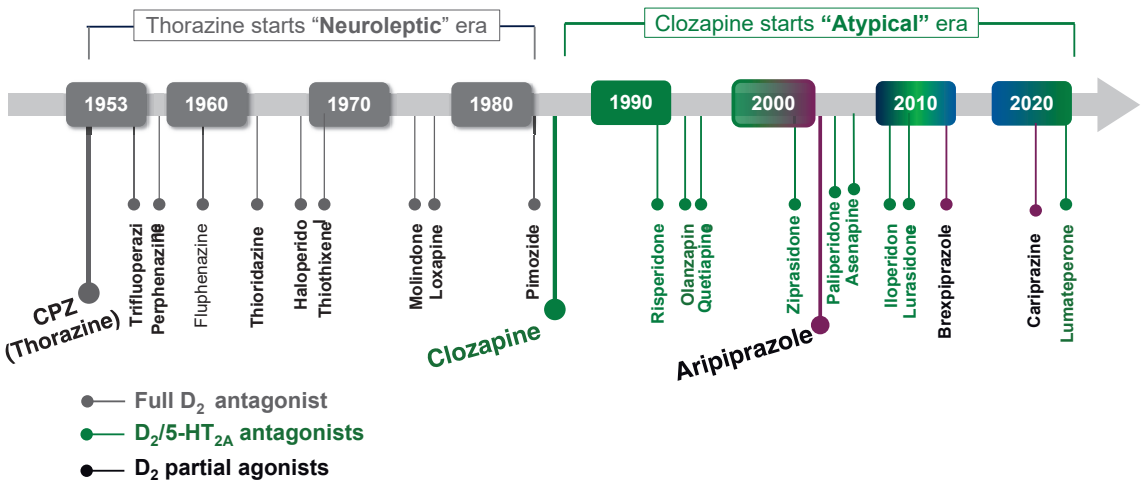
Not all options come in LAIs

LAI, long-acting injectable; TRIPP, Treatment Response and Resistance in Psychosis.
Howes OD, et al. *Am J Psychiatry*. 2017;174(3):216-29.

MedEd ON THE GO

D2 Antagonists Limitations and Challenges: A New Era in Schizophrenia Pathophysiology

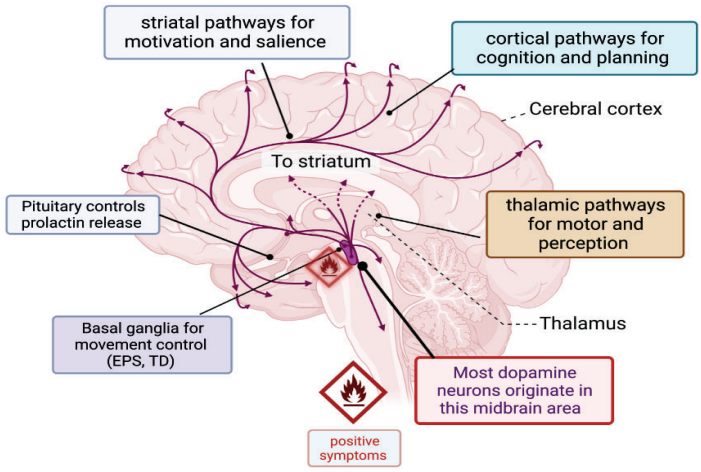
Progress Has Been Very Slow
Disruptive advances rare, most advances incremental



Stahl SM: Stahl's Essential Psychopharmacology 5th Edition ed, Cambridge 2023.

Homeostatic Role of Dopamine Circuits

DA Receptor Antagonists Disrupt Normal CNS Functioning



Created with BioRender.com by Peter J. Weiden

McCutcheon RA, et al. Schizophrenia, dopamine and the striatum: from biology to symptoms. *Trends in Neurosciences*. 2019;42:205-220.

Currently Available Antipsychotics Block Dopamine D2 Receptors: There Are Many Limitations to This Approach

Residual Symptoms and Inadequate Treatment Response

- 1 out of every 3 patients do not respond[1-3]
- Negative and cognitive symptoms may persist[1]

Varying levels of side effects and long-term risks[1] may contribute to negative outcomes and poor adherence[4]

- First generation APs: generally associated with movement disorders and prolactin elevation[5-7]
- Second generation APs: typically associated with sedation, weight gain, and metabolic dysregulation[5-7]

APs, antipsychotics.

1. Correll CU, et al Abi-Dargham A, Howes O. *JCP*. 2022; 2. Faden J, et al. and Citrome, L. *Med Clin North Am*. 2023;107: 61–72; 3. Howes OD, McCutcheon R, Agid O, et al. *Am J Psychiatry*. 2017;174(3):216–29; 4. DiBonaventura M, et al. *BMC Psychiatry*. 2012;12:20; 5. Burchinski et al. *World Psychiatry* 2023;22:116–128; 6. Keepers GA, et al. The APA Practice Guideline for the Treatment of Patients With Schizophrenia. Am J Psychiatry. 2020; 177(9):868-872; 7.Huhn, et al. *Lancet*. 2019; 394: 939–51; 8. Kane, JM. *JCP*. 2022; 42: S1-S13.

How Do We Get Back to the Future?


Hill Valley Telegraph

MONDAY, NOVEMBER 14, 1955

CLOCK TOWER STRUCK BY LIGHTNING

CLOCK STOPPED AT 10:04

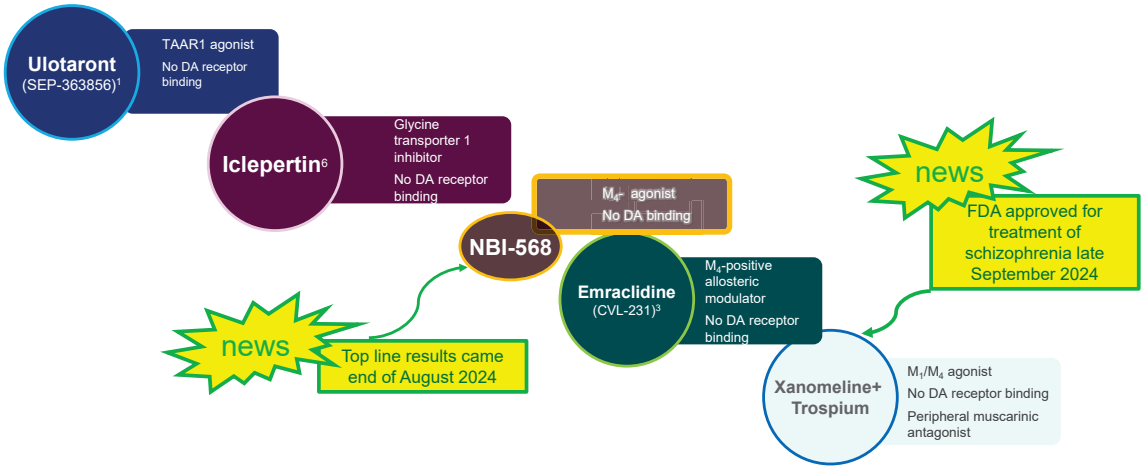
Plans To Launch Tests of New Toll System Here

The paper has an article on future of psych medications in 20 years but article not available for distribution!

Moving Away From D2 Antagonism: Emerging Agents with Novel Mechanisms of Action

Closer Look at Novel MOAs for Schizophrenia

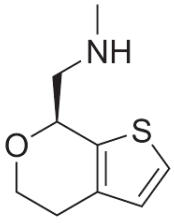
Examples of Investigational Treatments without any Direct Dopamine Receptor Activity in Development



MOA, mechanism of action; TAAR, trace amine-associated receptors; TAAR1, trace amine associated receptor 1.

1. Koblan KS, et al. *N Engl J Med*. 2020;382(16):1497-4506; 2. Brannan SK, et al. *N Engl J Med*. 2021;384(8):717-26; 3. Krystal JH, et al. *Lancet*. 2023 Dec 17;400(10369):2210-20; 4. Bugarski-Kirola D, et al. *Lancet Psychiatry*. 2022;9(1):46-58; 5. Davidson M, et al. *Am J Psychiatry*. 2017;174(12):1195-202; 6. Fleischhacker WW, et al. *Lancet Psychiatry*. 2021;8(3):191-201.

Background Story



- Example of a drug discovery process with “orphan receptor”
- Then the ligand was discovered which are these trace amino acids that are found in very low concentrations
- Next came testing TAAR ligands for drug development
- Several TAAR agonists developed and tested for schizophrenia
- No direct dopamine receptor
- Indirect at other parts of cell signaling pathways involving dopamine
- Initial studies showed promising safety and efficacy for schizophrenia

What Does an Agonist of TAAR1 Receptors Do?

Activation of TAAR1 Dampens Dopaminergic Activity

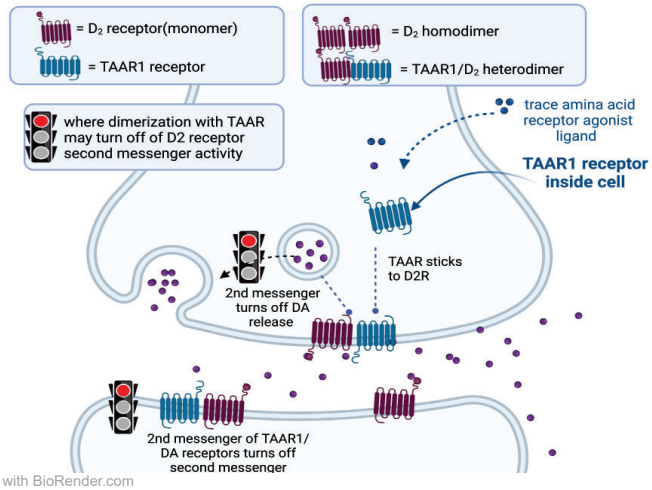
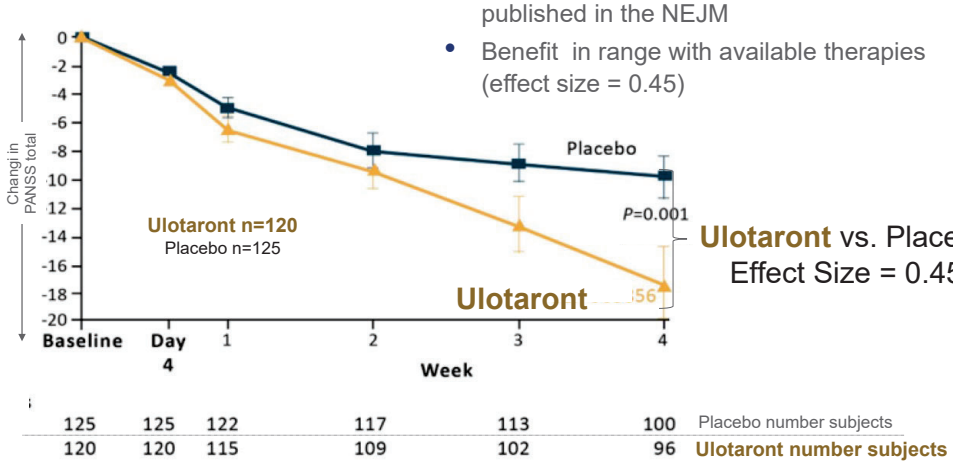


Image created by Peter Weiden with BioRender.com
Adapted from: Halff EF et al Trace amine-associated receptor 1 (TAAR1) agonism as a new treatment strategy for schizophrenia and related disorders. *Trends Neurosci*. 2023;46:60-74

Ulotaront (TAAR1 agonist) Shows Efficacy for Schizophrenia

- 1st non-dopamine receptor treatment published in the NEJM
- Benefit in range with available therapies (effect size = 0.45)



Ulotaront vs. Placebo
Effect Size = 0.45

Koblan KS, et al. *N Engl J Med*. 2020;382:1497-1506.

Ulotaront (TAAR1) Safety Profile Differs from Others

Adverse Events, n (%) over 4 -week inpatient treatment	Placebo N=125	Ulotaront (n=120)
	N (%)	N(%)
Any AE	63(50.4%)	55 (45.8%)
Most common AEs		
Somnolence	6 (4.8%)	8(6.7%)
Agitation	6 (4.8%)	6 (5%)
Nausea	4 (3.2%)	6 (5%)
Insomnia	13 (10.4%)	4 (3.3%)
Diarrhea	1 (0.8%)	3 (2.5%)
Dyspepsia	0	3 (2.5%)
Anxiety	9 (7.2%)	2 (1.7%)

- Most common side effect was somnolence
- No evidence of movement disorder side effects

Koblan KS, et al. A Non-D2-Receptor-Binding Drug for the Treatment of Schizophrenia. *N Engl J Med*. 2020;382:1497-1506.

Hope was Followed by Disappointment

Phase 3 Follow-up Studies Did Not Show Efficacy

Phase 3 Program (DIAMOND)

- Phase 3 short-term inpatient design
  - DIAMOND 1 compared 50 and 75mg/day to placebo
  - DIAMOND 2 compared 75 and 100mg/day vs placebo)
- Top line results
  - No difference between treatment and placebo for either study
  - Enrollment in pandemic and high placebo response
  - Ulotaront safety similar to earlier studies

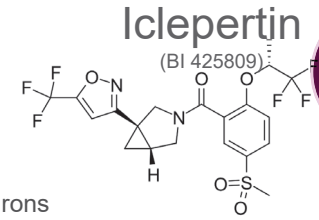
What next for TAAR1 ?

- Fate of schizophrenia program not clear
- TAAR likely to remain a valid drug development target in psychiatry
- Shows that clinical drug development is hard especially going from Phase 2 to Phase 3

Sumitomo. Press release: July 31 2023. Sumitomo Pharma and Otsuka Announce Topline Results from Phase 3 DIAMOND 1 and DIAMOND 2 Clinical Studies Evaluating Ulotaront in Schizophrenia. Accessed Aug 31st 2023. https://www.sumitomo-pharma.com/news/20230731-1.html

Going to Glycine

Iclepertin (BI 425809)



Iclepertin[6] — Glycine transporter 1 inhibitor

- Start with NMDA receptors
- Glutamate is the endogenous ligand
- Activation of NMDA receptors eventually tones down overexcited glutaminergic neurons associated with schizophrenia symptoms
- NMDA antagonists like PCP or ketamine cause symptoms resembling schizophrenia
- Direct NMDA agonists too excitotoxic; focus moved to indirect approaches

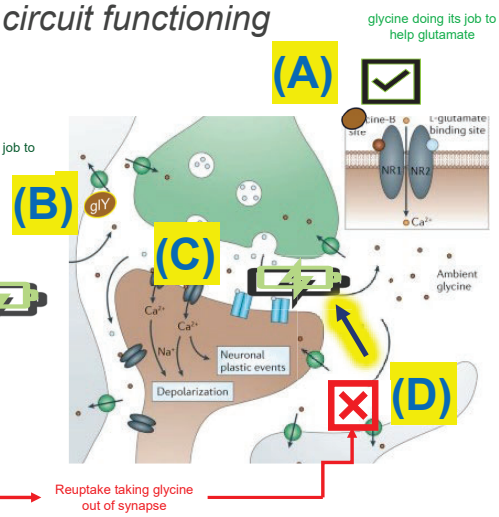
Why Glycine?

- Glycine is needed for NMDA to function properly
- There are glycine reuptake pumps that recycle synaptic glycine.
- Inhibition of reuptake will increase synaptic glycine (analogous to SSRI's mechanism) with GLYT1 uptake as target
- The GLYT1 inhibitor iclepertin (BI 425809) has been developed and studied to be an adjunct for cognitive impairment associated with schizophrenia (CIAS)

NMDA Glutamate Hypothesis of Schizophrenia

Glycine is essential to normal circuit functioning

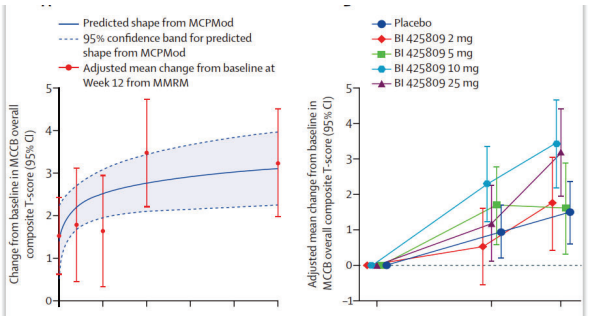
- the NMDA receptor needs glycine to permit glutamate to function properly **(A)** glycine doing its job to help glutamate
- Low glycine in synapse turns off post-synaptic NMDA receptor activity **(B)**
- Clinical trials adding adjunctive glycine or its analogues improve negative symptoms **(C)**
- Another way to raise glycine is to inhibit its clearance from the synapse **(D)** Reuptake



Harvey, R., Yee, B. Glycine transporters as novel therapeutic targets in schizophrenia, alcohol dependence and pain. Nat Rev Drug Discov 12, 866–885 (2013). https://doi.org/10.1038/nrd3893

Adjunctive GLY_1 Inhibitor Iclepertin Improved Cognitive Scores

Phase 2 study of four doses of iclepertin showed cognitive benefit with a middle dose



Better response associated with

- Antipsychotic monotherapy
- Higher negative symptoms at baseline
- No co-prescribed benzos

Better response to iclepertin 10 mg (middle dose) than lower or higher doses

Other predictors of response to iclepertin

- Relatively recent diagnosis (5-10 years since onset)
- aged 38 years or younger
- Female > Male

MCCB, MATRICS Consensus Cognitive Battery; MCPmod, multiple comparison procedure modeling; MMRM, mixed models for repeated models.
Fleischhacker WW, et al. *Lancet Psychiatry*. 2021;8(3):191-201.

Adjunctive Iclepertin for CIAS

Adverse Effects Appear Similar to placebo-arm

	BI 425809				Placebo (n=170)
	2 mg (n=85)	5 mg (n=84)	10 mg (n=85)	25 mg (n=85)	
Patients with adverse events	50 (59%)	44 (52%)	35 (41%)	36 (42%)	74 (44%)
Patients with severe adverse events	4 (5%)	2 (2%)	0	3 (4%)	0
Patients with drug-related* adverse events	18 (21%)	15 (18%)	14 (16%)	12 (14%)	29 (17%)
Patients with adverse events leading to discontinuation of trial medication	5 (6%)	4 (5%)	0	2 (2%)	4 (2%)
Patients with adverse events of special interest	0	1 (1%)	0	0	0
Patients with serious adverse events	2 (2%)	4 (5%)	2 (2%)	4 (5%)	4 (2%)
Fatal	0	0	0	0	0
Immediately life-threatening	0	0	0	1 (1%)	1 (1%)
Requiring or prolonging hospitalisation	2 (2%)	3 (4%)	2 (2%)	1 (1%)	2 (1%)
Other medically important serious event	0	1 (1%)	0	2 (2%)	1 (1%)
Patients with any other significant adverse events†	4 (5%)	4 (5%)	0	0	3 (2%)

Data are n (%). *As judged by the investigator. †According to International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use E3. All data are for the treated set.

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

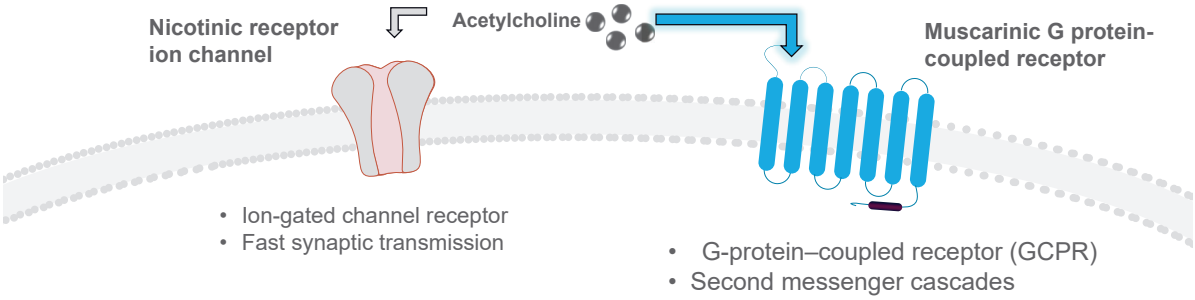
Future of Iclepertin and GLYT1 inhibitors

Phase 3 Results Pending and While We Wait

Clinical Development Program

- Iclepertin is now in active Phase 3 development and results pending
- Modified inclusion/exclusion criteria
  - Good news: May make success in Phase 3 more likely
  - Bad news: May make the patient profile more narrow
- If successful has potential to be 1st FDA approved treatment of cognitive symptoms of schizophrenia

Review of Acetylcholine (ACh) and its Receptors



- Ion-gated channel receptor
- Fast synaptic transmission

- G-protein–coupled receptor (GCPR)
- Second messenger cascades

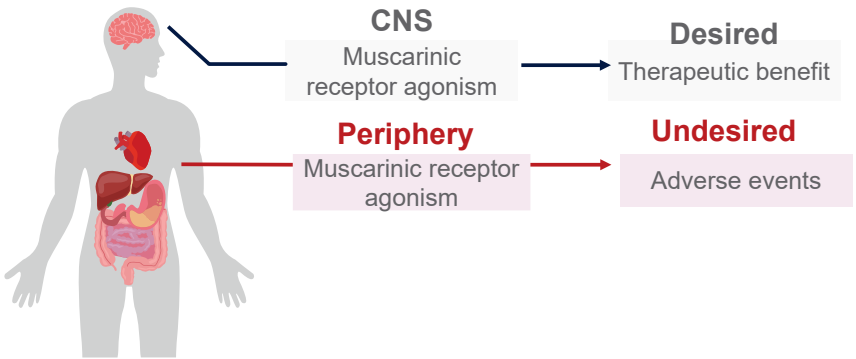
- Both receptor families are found throughout central and peripheral nervous system
- Any drug that raises ACh is relevant to both receptors (think AchE inhibitors)
- Drugs specific to one of these receptors will not bind to other receptor

GPCR, G protein-coupled receptor

1. McGehee DS, et al. *Curr Opin Neurobiol*. 1996;6(3):342-349. 2. Brown DA. *Brain Neurosci Adv*. 2019;3:1-10.

Activating Muscarinic Receptors for CNS Drug Development

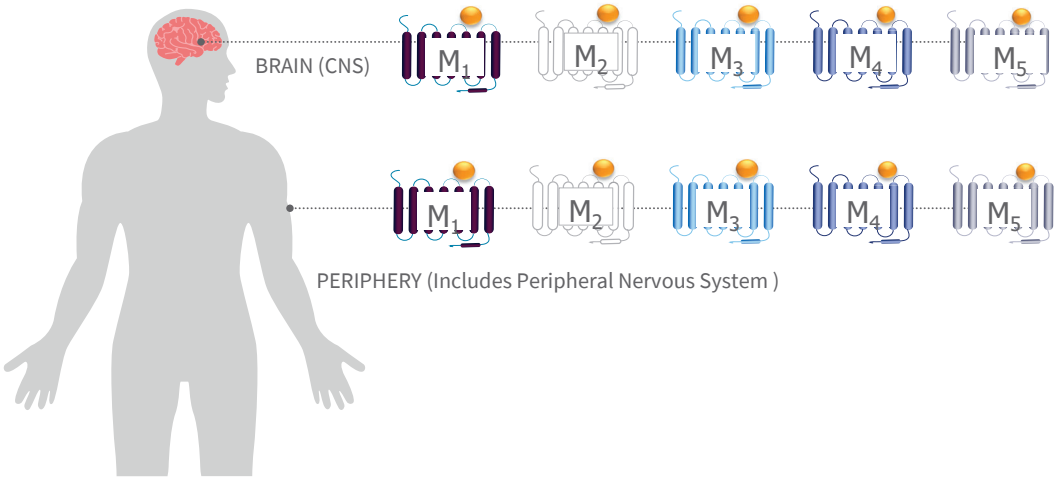
Brain is Desirable but Autonomic is a Problem



Yohn SE, et al. Muscarinic acetylcholine receptors for psychotic disorders: bench-side to clinic. Trends Pharmacol Sci. 2022;43:1098-1112.

Muscarinic Receptor Subtypes

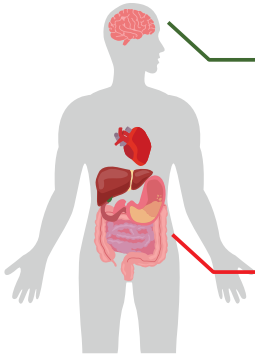
Muscarinic Receptors are Expressed in a Wide Variety of Tissues



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

What About Muscarinic Receptor Agonists?

This is true for ANY direct muscarinic agonist for CNS



Desired

All benefit from CNS activity include treating psychosis, improving cognition

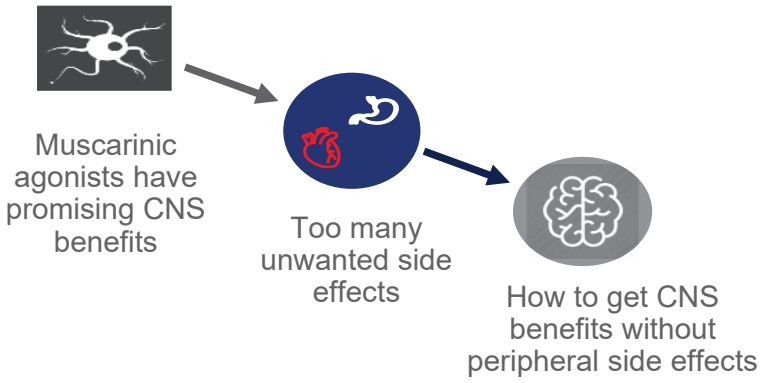
Undesired

Muscarinic receptors are found at end of parasympathetic neurons innervating smooth muscles in autonomic nervous system. Direct agonism can put ANS in overdrive and associated with nausea, vomiting, diarrea, sweating, salivation, tachycardia

Yohn SE, et al. Muscarinic acetylcholine receptors for psychotic disorders: bench-side to clinic. *Trends Pharmacol Sci*. 2022;43:1098-1112.

Major Drug Development Challenge

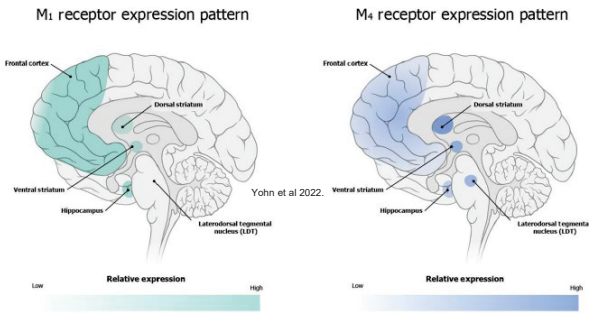
How to Get More CNS Benefit; Less Peripheral Side Effects



Yohn SE, Weiden PJ, Felder C & Stahl S: Muscarinic acetylcholine receptors for psychotic disorders: bench-side to clinic. *Trends in Pharmacological Sciences*. 2022;43(12):1098-1112.

Muscarinic Cholinergic Hypothesis of Schizophrenia

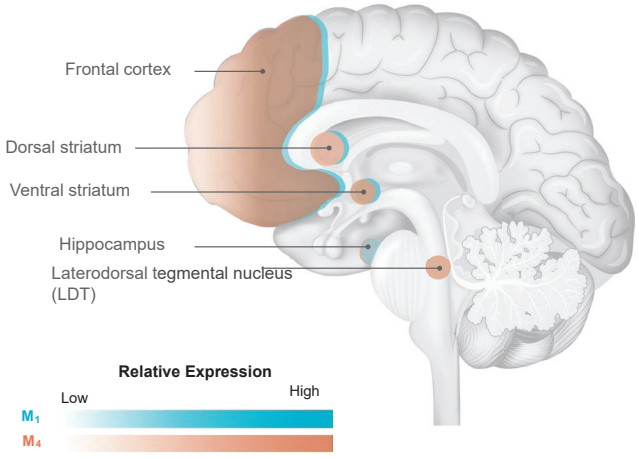
- In the 1950s, pro-cholinergic drugs were observed to increase "lucid intervals" in patients with psychosis,[1]
- M_1/M_4 receptor mouse knockout models replicate the phenotype of schizophrenia,[3] and muscarinic agonists, especially for M_4, improve positive and negative symptoms of schizophrenia in mice and humans[4]
- Postmortem studies[2,5,6] show reductions in M_1 receptor expression in brain regions implicated in schizophrenia, but this needs replication

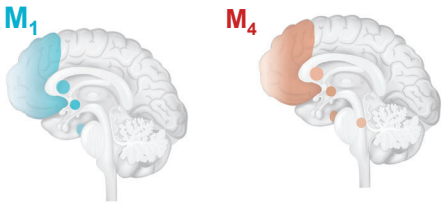


Glu, glutamate; M_1/M_4, acetylcholine muscarinic receptor M1 and M4 subtypes.
1. Pfeiffer CC, et al. *Ann N Y Acad Sci*. 1957;66(3):753-764. 2. Scarr E, et al. *Biol Psychiatry*. 2007; 15;61(10):1161-70; 3. Paul SM, et al. *Am J Psychiatry*. 2022;179(9):611-27; 4. Brannan SK, et al. *N Engl J Med*. 2021;384:717-26; 5. Scarr E, et al. *Transl Psychiatry*. 2013; 3:e230; 6. *Scarr E*, et al. *J Psychiatry Neurosci*. 2018; 43:338–46; 7. Yohn SE, et al. *Trends in Pharm Sci*. 2022; 43 (12):1098-112.

Muscarinic Receptors as Drug Development Targets

M_4 and M_1 Receptors are Found in CNS Regions Associated with Schizophrenia

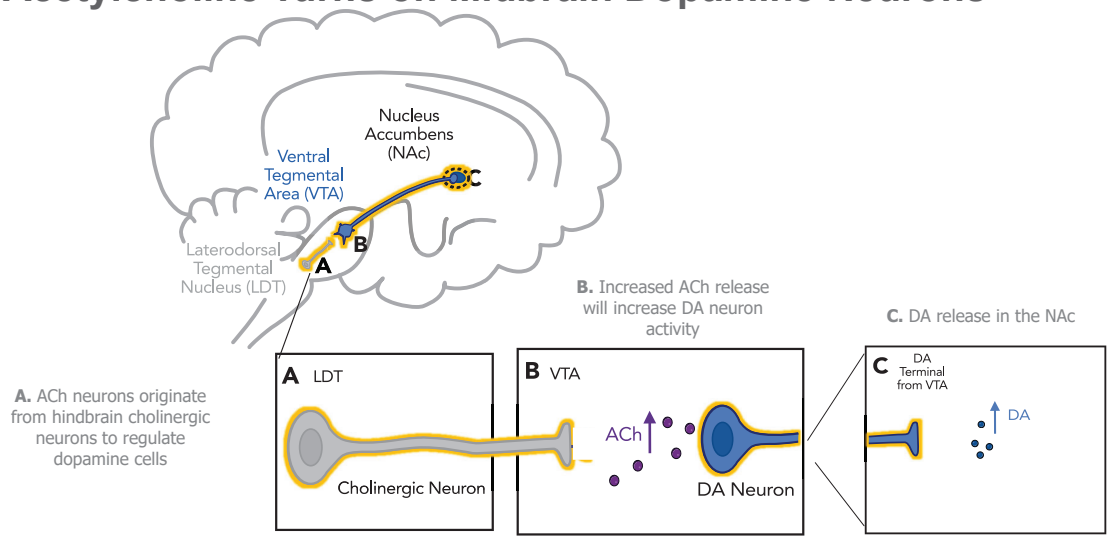




M_4 and M_1 receptors colocalize with dopamine circuits, but keep in mind these receptors are found in other areas

Yohn SE, Weiden P et al. Muscarinic acetylcholine receptors for psychotic disorders: bench-side to clinic. *Trends Pharmacol Sci*. 2022;43:1098-1112.

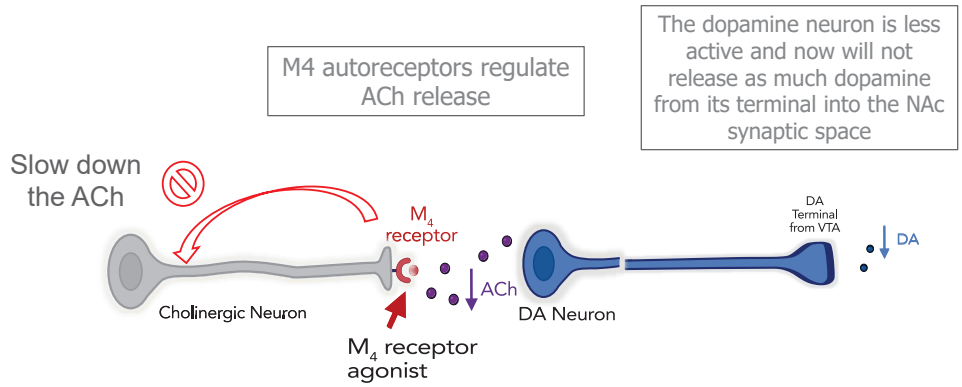
Acetylcholine Turns on Midbrain Dopamine Neurons



Adapted from Yohn SE, et al. Muscarinic acetylcholine receptors for psychotic disorders: bench-side to clinic. *Trends Pharmacol Sci*. 2022;43:1098-1112.

M_4 Receptor Activation Turns Off Acetylcholine

M_4 is part of feedback loop with ACh being natural ligand



Adapted from Yohn SE, et al. Muscarinic acetylcholine receptors for psychotic disorders: bench-side to clinic. *Trends Pharmacol Sci*. 2022;43:1098-1112.

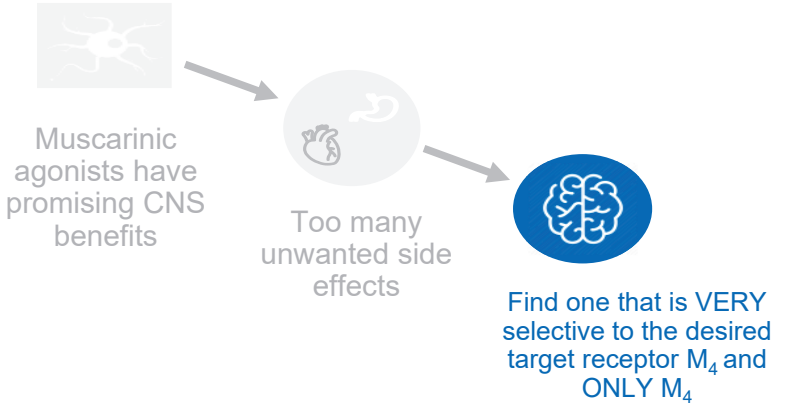
Investigational Muscarinic Receptor Activators

(updated September 2024)

Drug	Mechanism of Action	Company	Disorder(s)	Development Phase
KarXT (xanomeline-trospium)	M_1/M_4 preferring + peripheral antimuscarinic	BMS (Karuna)	Schizophrenia Alzheimer's (DRP)	Phase 3 schizophrenia completed
Emraclidine (CVL-231)	M_4 receptor Positive Allosteric activator (PAM)	Abbvie (Cerevel)	Schizophrenia	Phase 2 with favorable published Phase 1b
NBI-1117568 (HTL0016878)	M_4 receptor orthosteric agonist	Neurocrine (Heptares now Nxera)	Schizophrenia Alzheimer's (DRP)	Phase 2 (schizophrenia) with recently released favorable results
ML-007	M_1/M_4 preferring (dual) + peripheral anticholinergic	Maplight Therapeutics	Schizophrenia Autism	Autism ongoing Phase 2 schizophrenia starting
ANNOUNCED PRECLINICAL DEVELOPMENT PROGRAMS AS OF SEPTEMBER 2024				
Not disclosed	M_4 orthosteric receptor agonist	Sumitomo Dainippon	Schizophrenia Not disclosed	
NBI-11175684	M_1 orthosteric receptor agonist	Neurocrine (Heptares now Nxera)	Schizophrenia Alzheimer's (DRP)	Phase 1
NBI-1117570	M_1/M_4 preferring orthosteric agonist			Phase 1
Not disclosed	M_4 receptor Positive Allosteric activator (PAM)	Addex Therapeutics	Schizophrenia	

Major Drug Development Challenge

How to Get More CNS Benefit; Less Peripheral Side Effects



Yohn SE, Weiden PJ, Felder C & Stahl S: Muscarinic acetylcholine receptors for psychotic disorders: bench-side to clinic. *Trends in Pharmacological Sciences*. 2022;43(12):1098-1112.

Going For Subtype Specificity

Get to very selective binding on M_1 or M_4

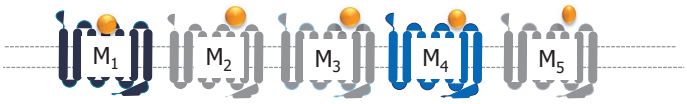


Figure by Peter J. Weiden created with Biorender.com
Yohn SE, et al. Muscarinic acetylcholine receptors for psychotic disorders: bench-side to clinic. *Trends in Pharmacological Sciences*. 2022;43 (12):1098-1112.

Going For Subtype Specificity

M_4 only avoids problems with $M_{1,2,3}$

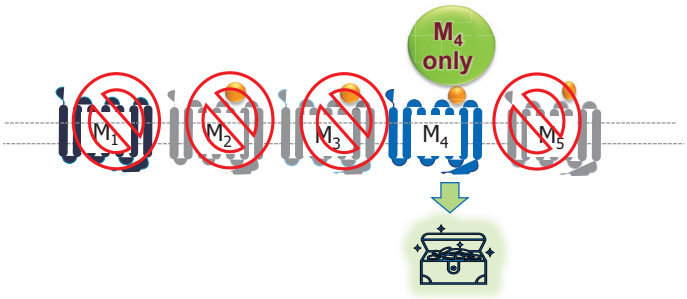


Figure by Peter J. Weiden created with Biorender.com
Yohn SE, et al. Muscarinic acetylcholine receptors for psychotic disorders: bench-side to clinic. *Trends in Pharmacological Sciences*. 2022;43 (12):1098-1112.

Breaking News on a 3rd Muscarinic Agonist

Neurocrine is sponsor and MOA is M_4 selective orthosteric agonism

- Neurocrine has an active muscarinic program with four different investigational muscarinic receptor agents
- The one furthest along is muscarinic agonist NBI-1007568 (M_4 orthosteric selective agonist)
- Phase 2 study design looking at escalating doses of NBI-568 (M4 agonist) vs placebo
  - 20,40, and 60mg day, with 60mg groups divided into 1 x day and 30mg BID
- Results reported by recent press release
- This makes it the 3rd muscarinic activator to show antipsychotic efficacy in schizophrenia

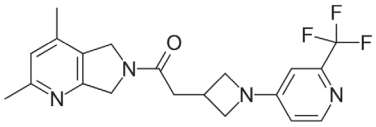
NBI-568 (M_4 orthosteric agonist)

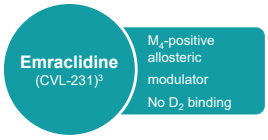
Efficacy shown in lowest dose arm (20mg)

	← Randomized groups →				
DOSE	placebo	20mg 1xd	40mg 1xd	60mg 1xd	60mg (30 bid)
# randomized	N=68	N=35	N=38	N=34	N=26
Change in PANSS total (within group) baseline to Week 6	-10.8	-18.2	-12.6	-13.7	-15.8
Difference in PANSS total Placebo vs 20mg group at week 6		**-7.5***	**-1.9**	**-2.9**	**-5.0**
statistical significance p value (placebo – 20mg group scores)		*p=0.01	P=0.28	P=0.19	P=0.09

Adapted from press release August 28 2024 https://www.neurocrine.com//assets/2024/08/NBI-568-Phase-2-Results-Presentation-FINAL.pdf accessed Sept 6 2024

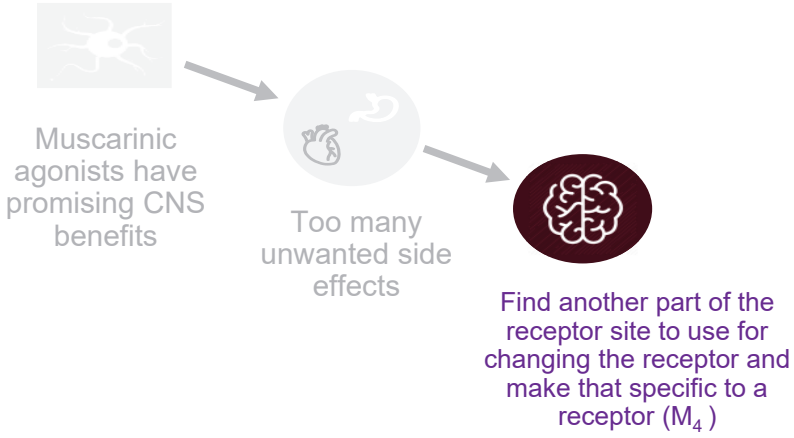
Emraclidine





Major Drug Development Challenge

How to Get More CNS Benefit; Less Peripheral Side Effects



Yohn SE, Weiden PJ, Felder C & Stahl S: Muscarinic acetylcholine receptors for psychotic disorders: bench-side to clinic. *Trends in Pharmacological Sciences*. 2022;43(12):1098-1112.

Going For Subtype Specificity

Get to very selective binding on M_1 or M_4

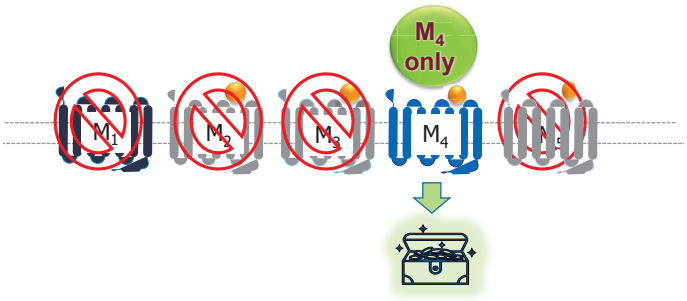


Figure by Peter J. Weiden created with Biorender.com
Yohn SE, et al. Muscarinic acetylcholine receptors for psychotic disorders: bench-side to clinic. *Trends in Pharmacological Sciences*. 2022;43 (12):1098-1112.

Emraclidine Getting Selective

Finding Other Landing Fields Unique to a Subtype Receptor

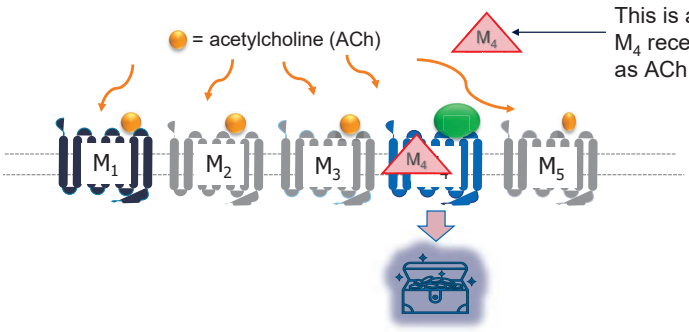


Figure by Peter J. Weiden created with Biorender.com
Yohn SE, et al. Muscarinic acetylcholine receptors for psychotic disorders: bench-side to clinic. *Trends in Pharmacological Sciences*. 2022;43 (12):1098-1112.

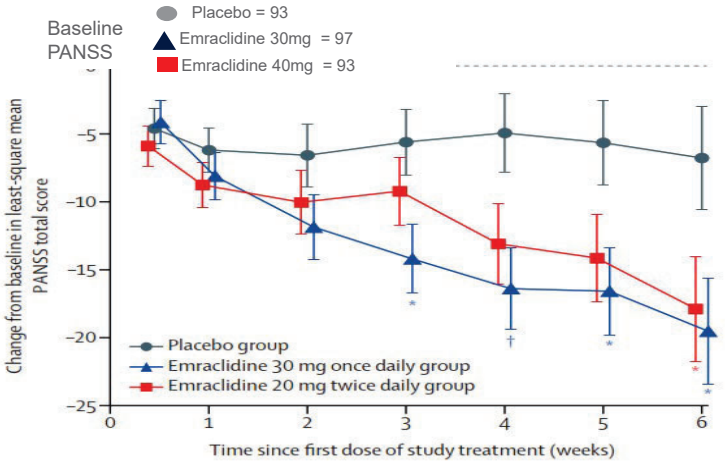
Overview of the Published Emraclidine Efficacy Study*

- Emraclidine is selective to the M_4 muscarinic receptor
- Was tested in a Phase 1b study with results published
- For efficacy component, 81 patients randomly assigned to:
  - Placebo
  - Emraclidine 30mg/day given once daily
  - Emraclidine 40mg/day given as 20 BID
- Once randomized, followed as inpatients for 6 weeks

Krystal JH, et al. Emraclidine, a novel positive allosteric modulator of cholinergic M4 receptors, for the treatment of schizophrenia: a two-part, randomised, double-blind, placebo-controlled, phase 1b trial. *The Lancet*. 2022;400(10369):2210-2220.

This Study Showed a Strong Efficacy Signal for Emraclidine

(But Phase Still 1 Needs Replication)



- 30mg group had 12.7 point improvement in PANSS vs placebo at week 4; 40mg (20 BID) was 11.1 (p<.05)
- Effect size (Cohen's d) = 0.68 for 30mg and 0.59 for 40mg groups
- But limited by being a single Phase 1b with small N and needs replication
- Phase 2 program underway

Krystal JH, et al. Emraclidine, a novel positive allosteric modulator of cholinergic M4 receptors, for the treatment of schizophrenia: a two-part, randomised, double-blind, placebo-controlled, phase 1b trial. *The Lancet*. 2022;400(10369):2210-2220.

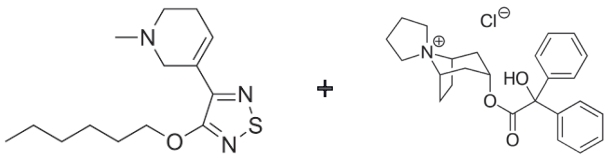
Safety of Emraclidine Consistent with M_4 Receptor Selectivity

Adverse Events, n (%)	Placebo (n=27)	Emraclidine 30mg/day (n=27)	Emraclidine 40mg/day (n=27)
Any AE	14 (52%)	14 (52%)	15 (56%)
AE related to study medication	10 (37%)	7 (26%)	12 (44%)
AE of special interest	3 (11%)	2 (7%)	4 (15%)
Serious AE	0	2 (7%)	1 (4%)
AE leading to study medication discontinuation	0	2 (7%)	1 (4%)
Most common AEs (≥5% for emraclidine)			
Headache	7 (26%)	8 (30%)	7 (26%)
Nausea	1 (4%)	2 (7%)	2 (7%)
Back pain	1 (4%)	2 (7%)	1 (4%)
Elevated CPK	0	1 (4%)	2 (7%)
Dizziness	0	1 (4%)	2 (7%)
Dry mouth	0	3 (11%)	0
Somnolence	0	1 (4%)	2 (7%)

- No side effects associated with dopamine receptor antagonism
- Consistent with concept of M_4 relative selectivity lowering pro-cholinergic burden
- Some changes in heart rate and BP observed but no medically significant effect in follow up safety study [1]

[1] Press release dated December 19 2022. Accessed July 13 2023. https://investors.cerevel.com/node/8841/pdf
Krystal JH, et al. Emraclidine, a novel positive allosteric modulator of cholinergic M4 receptors, for the treatment of schizophrenia: a two-part, randomized, double-blind, placebo-controlled, phase 1b trial. *The Lancet*. 2022;400(10369): 2210-2220.

Xanomeline-trospium chloride



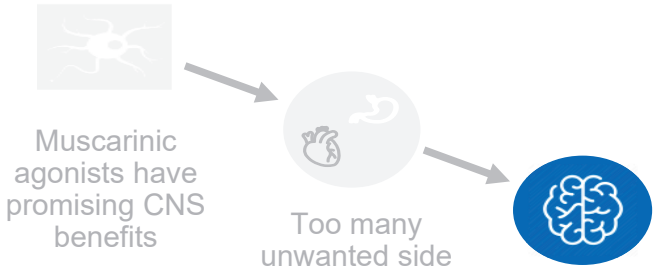
Xanomeline + Trospium chloride

Xanomeline+ Trospium[2]

M_1 and M_4 agonist (Xanomeline)
No D_2 binding
Peripheral muscarinic antagonist (Trospium)

Major Drug Development Challenge

How to Get More CNS Benefit; Less Peripheral Side Effects



Find another medication that is antimuscarinic in the PNS only that counteracts the **peripheral** muscarinic agonist **without affecting central benefits**

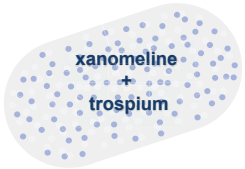
Yohn SE, Weiden PJ, Felder C & Stahl S: Muscarinic acetylcholine receptors for psychotic disorders: bench-side to clinic. *Trends in Pharmacological Sciences.* 2022;43(12):1098-1112.

How Xanomeline/trospium Mitigates the Pro-cholinergic Side Effects

Trospium is added to counteract peripheral muscarinic side effects

- Xanomeline is an M_1/M_4 muscarinic agonist that had been studied for Alzheimer's disease in the 1990s and found to have antipsychotic properties in Dementia-Related Psychosis
- Also shown in a small study in schizophrenia
- However xanomeline was not developed due to the pro-cholinergic peripheral side effects
- Karuna studied a peripheral anticholinergic that does not cross the blood-brain barrier, and chose Trospium (brand name Sanctura) used for Overactive Bladder and met this criteria
- Co-formulation well tolerated at therapeutic dose levels of xanomeline and cut the pro-cholinergic side effects by about 2/3rds

KarXT co-formulation

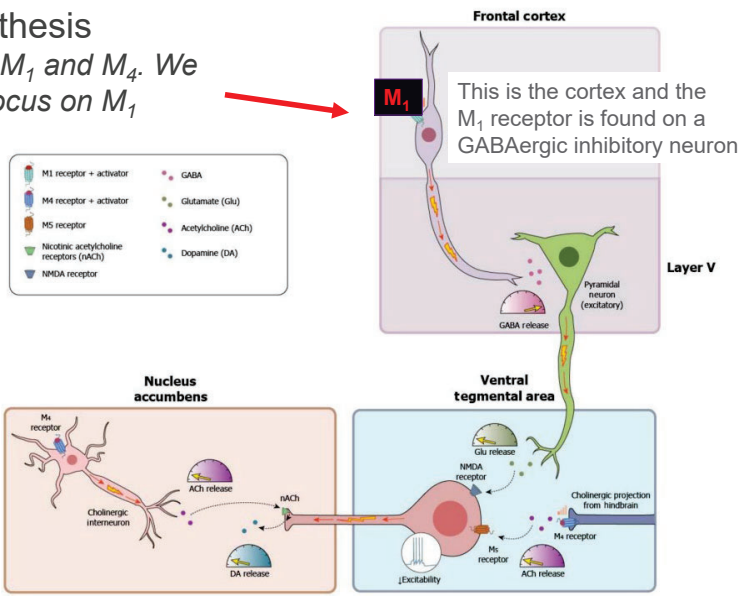


- Variable xanomeline/trospium ratios
- Ones used in Phase 3 schizophrenia studies
  - 50mg/20mg (starting dose BID)
  - 100mg/20mg (BID target dose)
  - 125mg/30mg (BID target dose)

1. Breier A, Brannan SK, Paul SM, Miller AC. Evidence of trospium's ability to mitigate cholinergic adverse events related to xanomeline: phase 1 study results. *Psychopharmacology (Berl).* 2023;240:1191-1198.

Introducing M_1 Hypothesis

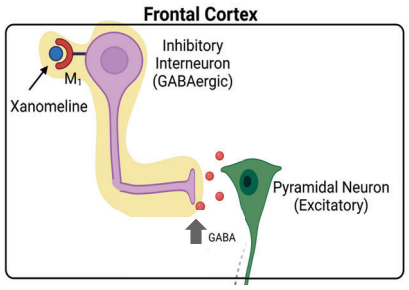
Xanomeline is active on M_1 and M_4. We covered M_4 already so focus on M_1



ACh, acetylcholine; DA, dopamine; GABA, gamma-aminobutyric acid; Glu, glutamate; nACh, nicotinic acetylcholine receptors; NMDA, N-methyl-D-aspartate.
Yohn SE et al. Trends Pharmacol Sci. 2022;43(12):1098-112.

Activation of Inhibitory GABA Interneurons

Activation of M_1 receptors expressed on inhibitory GABAergic interneurons

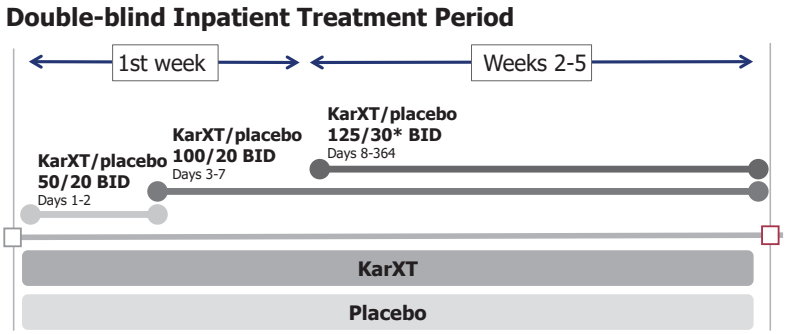


Decreased excitatory glutamatergic input onto dopaminergic neurons associated with psychosis

GABA = gamma aminobutyric acid; Glu = glutamine; DA = dopamine.
Adapted from Yohn SE, et al. Muscarinic acetylcholine receptors for psychotic disorders: bench-side to clinic. *Trends Pharmacol Sci*. 2022;43:1098-1112.

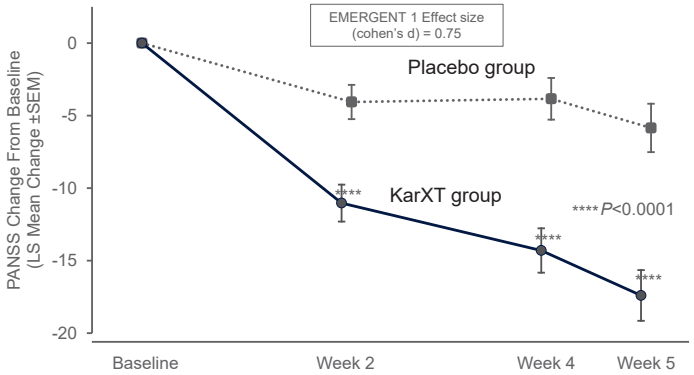
Overview of the Pivotal Efficacy Studies for KarXT

- There are 3 short-term pivotal studies of KarXT (EMERGENT 1, 2 and 3)
- EMERGENT 1 was Phase 2; EMERGENT 2 and 3 were Phase 3
- All shared key design and primary outcomes



EMERGENT-1 Showed Strong Efficacy Signal

Primary Endpoint Was KarXT * vs Placebo in Reducing PANSS Total Scores



Clinically meaningful and statistically significant improvement in total PANSS vs placebo

- 11.6-point improvement in PANSS total score vs placebo at week 5 (effect size 0.75)
- *P*<0.0001 (-17.4 KarXT vs -5.9 placebo)
- This is at least as good as the effect size of current antipsychotics
- Formed basis for Phase 3 Clinical Development

* KarXT was name during Phase 3 clinical program

All efficacy analyses performed using the mITT analysis set, defined as all randomized individuals who received ≥1 dose of study medication at baseline and ≥1 postbaseline PANSS assessment.(KarXT n=90, placebo n=92).
LS = least squares; mITT = modified intent-to-treat; PANSS = Positive and Negative Syndrome Scale; SEM = standard error of the mean.
Brannan SK, et al. *N Engl J Med*. 2021;384(8):717-726.

Safety Profile of KarXT Consistent with Muscarinic Receptor Activity

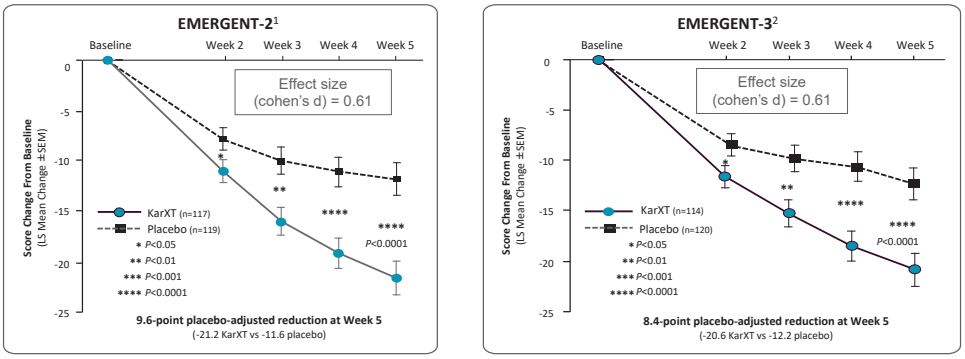
Adverse Events, n (%)	KarXT (n=89)	Placebo (n=90)
Any TEAE	48 (53.9%)	39 (43.3%)
Serious TEAE	1 (1.1%)[a]	0 (0%)
Severe TEAE	1 (1.1%)[a]	1 (1.1%)[b]
TEAE leading to study discontinuation	2 (2.2%)[c]	2 (2.2%)[d]
Most common AEs (≥5% KarXT arm)		
Constipation	15 (16.9%)	3 (3.3%)
Nausea	15 (16.9%)	4 (4.4%)
Dry mouth	8 (9.0%)	1 (1.1%)
Dyspepsia	8 (9.0%)	4 (4.4%)
Vomiting	8 (9.0%)	4 (4.4%)
Headache	6 (6.7%)	5 (5.6%)
Somnolence	5 (5.6%)	4 (4.4%)

- No side effects associated with dopamine receptor antagonism
- Most AEs are pro-cholinergic (from xanomeline) like nausea or peripheral anticholinergic (from trospium) like constipation
- None of these were "deal breakers" for subjects in the study; no AE related discontinuation
- Because general effects of muscarinic agonists on heart rate and BP, a separate study will be done.

- Safety population included all participants who received ≥1 dose of study medication.
- [a]A serious, severe TEAE of increased psychosis was reported in 1 patient in the KarXT group, which led to study Withdrawal; [b]A severe TEAE of worsening schizophrenia was reported in 1 patient in the placebo group, which led to study withdrawal; [c]The second TEAE leading to withdrawal in the KarXT group was elevated GGT; [d]The second TEAE leading to withdrawal in the placebo group was worsening schizophrenia.
- AE = adverse event; GGT = gamma-glutamyl transferase; TEAE = treatment-emergent adverse event.
- Brannan SK, et al. *N Engl J Med*. 2021;384(8):717-726.

The Two Phase 3 Efficacy Studies Also Successful

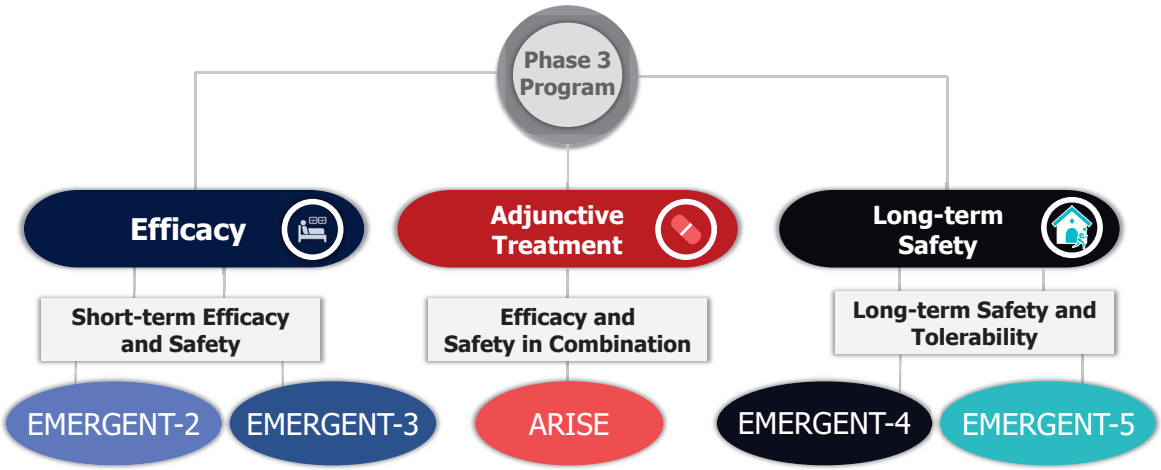
EMERGENT 2 and 3 Met Primary Endpoints



These 3 studies were part of a New Drug Application (NDA) submitted Sept 28 2023; long-term safety studies underway and results pending. [3]

Kaul I et al: 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. Lancet. 2024 Jan 13;403(10422):160-170.
Kaul, Inder, et al. "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." The Lancet 403.10422 (2024): 160-170.

KarXT Phase 3 Schizophrenia Clinical Program

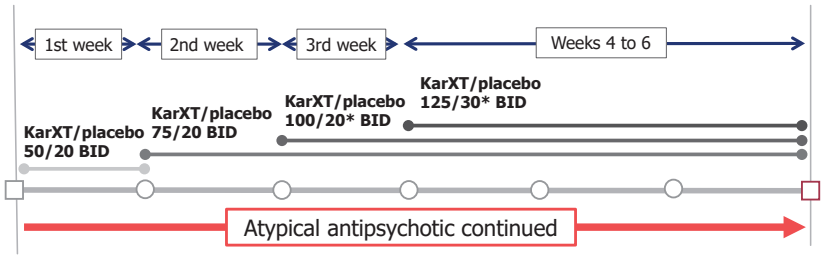


Adjunctive KarXT for Persistent Symptoms: ARISE Study

Rationale: Are combining two different MOAs more likely to succeed ?

- Phase 3 trial evaluating KarXT + ongoing antipsychotic
  - Targets patients with persistent symptoms despite ongoing antipsychotic
  - Provides safety information for combining KarXT with atypical antipsychotics
  - Will assess whether different MOA can improve persistent symptoms

Double-blind Outpatient Treatment Period



KarXT Clinical Development Summary

- Phase 3 Efficacy studies (EMERGENT 2 and 3) showed similar pattern of efficacy and safety to the EMERGENT 1 study[1]
- Safety primarily those consistent with muscarinic agonists (e.g. nausea or vomiting) or peripheral antimuscarinic effects (e.g. dry mouth or constipation)
- No evidence of side effects related to dopamine receptor antagonism
  - No antipsychotic-induced parkinsonism, prolactin elevation, or sedation
  - No evidence of weight gain over and above placebo
- A phase 1b blood pressure/heart rate safety study completed and no underway and no clinically significant blood pressure noted
- NDA submitted late September 2023 for FDA review
- FDA review is due end of September 2024 approval[2]

* KarXT is still investigational and not approved so final prescribing information if FDA approved will await final prescribing information
# personal opinion Peter J. Weiden, M.D. as of May 16 2024 based on published information and does not reflect opinion of Karuna / BMS or FDA

FDA approved on September 28th 2024 for Treatment of Adults with Schizophrenia

- Xanomeline-trospium (brand name COBENFY) is approved for schizophrenia but is NOT classified as an antipsychotic
  - Adverse Events do NOT list antipsychotic-induced parkinsonism or tardive dyskinesia!
  - No “black box” on using in elderly with dementia
- It is a fixed combination capsule available as 50mg/20mg (xanomeline/trospium) to be given BID x 2 days and up-titration to 100mg/20mg BID x 5 days and then 125mg/30mg BID as high target dose
  - Suggest taking BID seriously
  - Trospium not absorbed when taken with meal so take 1 hour before or 2 hours after meals
- “The most common adverse reactions (≥5% and at least twice placebo) were nausea, dyspepsia, constipation, vomiting, hypertension, abdominal pain, diarrhea, tachycardia, dizziness, and gastroesophageal reflux disease”
  - Contraindicated or caution when patient has liver or biliary disease, urinary retention, reduced GI motility
- Prescribing information suggests minimizing anticholinergic exposure as much as possible

Please add link to prescribing information for xanomeline-trospium chloride

From Trial to Treatment: Translating Emerging Clinical Data into Meaningful Schizophrenia Clinical Care

Where and How Would Novel Agents Fit?

1. Minimize adverse effects due to current mechanism medications
2. Expand efficacy for unaddressed domains, like negative and cognitive symptoms
3. Achieve efficacy on partial non-responders or even refractory illness
4. Augment efficacy of current agents in partial responders
5. Improve subjective well-being, quality of life and functionality in individuals with schizophrenia

Correll CU, et al. *JAMA Psychiatry*. 2024;81(2):118-20.

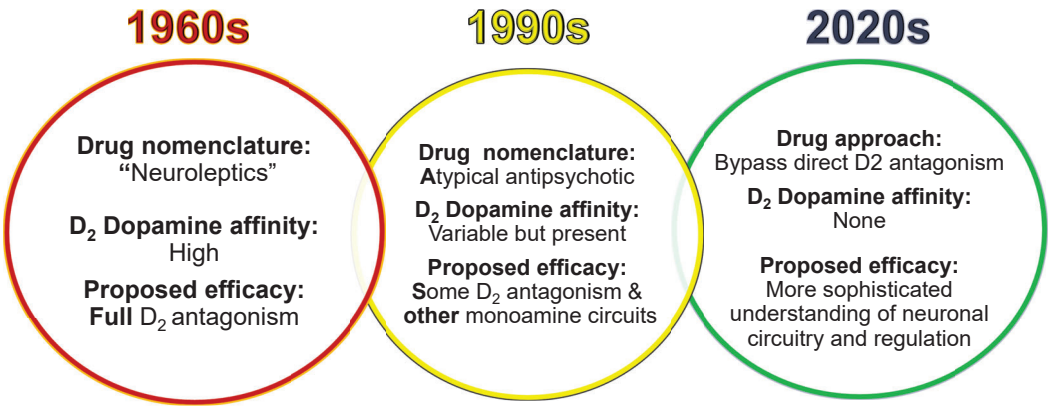
New Medication Approved, Now What?*

Assume FDA approval of iclepertin or one or two muscarinic agonists

Strategy	Possible approach
Waiting	Applies to muscarinic agonists and GLYT1: Issue here will be when to start a new MOA – wait until more experience or go sooner for patients or families who are frustrated
Adjust dose	Applies to both muscarinic agonists: Dose-response of muscarinic agonists unknown but may be narrower than current therapies
Change route	Applies to muscarinic agonists and GLYT1: None of these will be available as an LAI anytime soon so will not be suitable as primary treatment for muscarinic agents. if any new agents used most likely will be as an adjunct
Add	Applies to muscarinic agonists and GLYT1: Add a new medication to the regimen is the approach to iclepertin. Will be very complicated about combining muscarinic agonists with current medications and likely debated but based on experience will likely be common after FDA approval. Rationale for muscarinic agonists combination over within class combination is the different MOA may have pharmacodynamic benefits. Likely would not be advisable to add to highly antimuscarinic antipsychotics such as clozapine
Substitute (“switching”)	Applies to muscarinic agonists: unlikely that these agents will be used for patients without any prior treatment history at least until more is known so issue will be whether switching Standard-of-Care for antipsychotics will generalize to a dopamine antagonist → muscarinic agonist switch, which may have different considerations. Managing any medication that is anticholinergic may be a big issue given theoretical possibility of central antimuscarinic counteracting efficacy from central muscarinic agonism
Subtract (“deprescribing”)	Applies to muscarinic agonists and GLYT1: it is likely that the GLYT1 will not work with some medications (e.g. anticholinergics; multiple antipsychotics) so question is on what can be deprescribed before adding iclepertin. This will also become a major question for patients on anticholinergic agents for movement disorders (e.g. benztropine) or instinsic to psychiatric indication (e.g. clozapine, olanzapine, paroxentine) or for medical reasons (e.g. asthma)

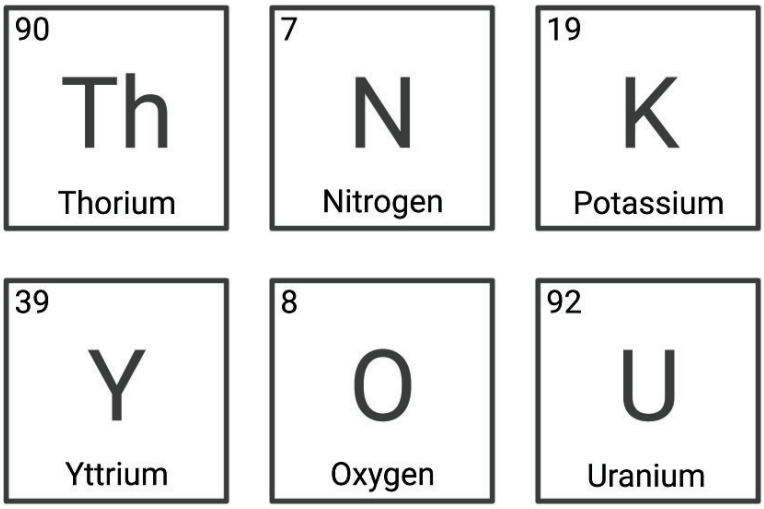
* All are speculative and personal opinion Peter J. Weiden, M.D. as of May 2024.
Intended to provide basis for discussion in preparing for possible non-dopaminergic medications

Summary of Past, Present, and Future



Summary and Conclusions

- After 7 decades of the primacy of dopamine receptor blockade, the field is finally seeing alternative treatment options for schizophrenia emerge
- Encouraging Phase 1b, 2, 3 results for:
  - M_1/M_4 agonist KarXT xanomeline + trospium chloride for total psychotic symptoms (3 positive trials) and cognition
  - M_4 positive allosteric modulator emraclidine for total psychotic symptoms (1 positive phase 1B trial, 2 ongoing phase 2 trials)
  - M_4 orthosteric agonist NBI 508
  - TAAR1 agonist ulotaront for total psychotic symptoms (1 positive phase 2 trial, 2 negative phase 3 trials)
  - Adjunctive iclepertin for cognitive dysfunction (1 positive phase 2 trial, 2 ongoing phase 3 trials)
- Novel mechanism action drugs for schizophrenia and its different domains remain an urgent needed
- The transferability of clinical trial data into the real world and potential superiority of novel mechanisms of action agents for specific subtypes of patients require further study



When considering strategies for patients with schizophrenia who have partially responded to treatment, what is recommended for those who have shown a partial response and tolerated their current antipsychotic?

A. Optimize the current medication's dose
B. Immediately switch to a different antipsychotic
C. Augment with a nonpharmacological therapy
D. Add another agent with a different mechanism of action

Which combination represents the mechanism of action of xanomeline-trospium, a novel therapeutic agent for schizophrenia?

A. TAAR1 agonist and 5-HT1A agonist
B. M_1/M_4 agonist with peripheral muscarinic antagonist
C. Glycine transporter 1 inhibitor
D. 5-HT2A inverse agonist/antagonist

Which aspect of schizophrenia treatment is emphasized as an important goal beyond symptom control?

A. Engagement in life goals
B. Reduced risk of tardive dyskinesia
C. Complete symptom control
D. Improved adherence to medication

FDA recently approved xanomeline-trospium for adults with schizophrenia. how confident are you in knowing the differences between this treatment and the other approved antipsychotics?

A. Not Confident at All
B. Slightly Confident
C. Very Confident
D. Extremely Confident

How comfortable are you with prescribing new and novel therapeutics for the treatment of schizophrenia to your patients?

A. Not Comfortable at All
B. Slightly Comfortable
C. Very Comfortable
D. Extremely Comfortable