NOVEL ANTIPSYCHOTICS AND MORE: THE NEAR FUTURE OF PSYCHOSIS TREATMENTS

FELICIA HANSELL, MD
MPS SPRING MEETING
MAY 3, 2025

1

I HAVE NO FINANCIAL DISCLOSURES.

I WILL DISCUSS NON-FDA-APPROVED TREATMENTS DURING THIS PRESENTATION (TREATMENTS CURRENTLY UNDER INVESTIGATION)

2

PRE-PRESENTATION POLL

How many of you have heard of Cobenfy?

- Prescribed it?
  - Seen benefit?

How many have heard of TAAR1 agonists?

Bonus trivia question: Which of the following molecules is a full agonist at the M1 receptor?

- Olanzapine
- Clozapine
- N-desmethylclozapine
- Donepezil

3

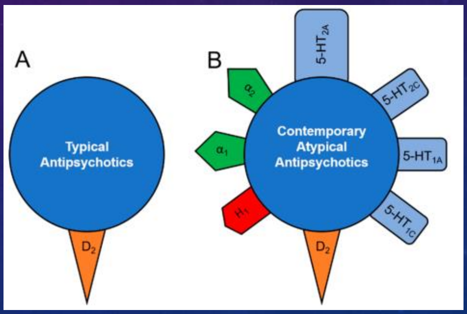
LEARNING OBJECTIVES

1	Describe the negative symptoms of schizophrenia
2	List the most common side effects of first- and second-generation antipsychotic medications
3	Name a receptor target for a novel antipsychotic medication
4	Name three neuromodulation techniques being investigated for psychosis

4

CURRENT EVIDENCE-BASED TREATMENTS FOR PSYCHOSIS

- First and second-generation antipsychotic medications
- ECT
- Medications for comorbid or underlying mood disorders, catatonia, etc
- Psychosocial interventions



5

BUT….

Side effects of antipsychotics:

Metabolic (5-HT2C, H1)

- Weight gain
- Hyperlipidemia
- Hypertension
- Type 2 Diabetes

Motor (D2)

- Dystonias
- Parkinsonism
- Tardive Dyskinesia

6

TABLE 1. Symptoms of schizophrenia

Positive psychotic symptoms	Positive disorganization symptoms	Negative symptoms
• Hallucinations • Delusions	• Disorganized speech, thought, language • Thought disorder characterization: thought blocking, loosening of associations, tangentiality • Disorganized behavior	• Alogia (poverty of speech) • Flat affect • Poor attention • Avolition (loss of motivation) • Anhedonia (lack of pleasure) • Loss of social interest • Attentional deficits

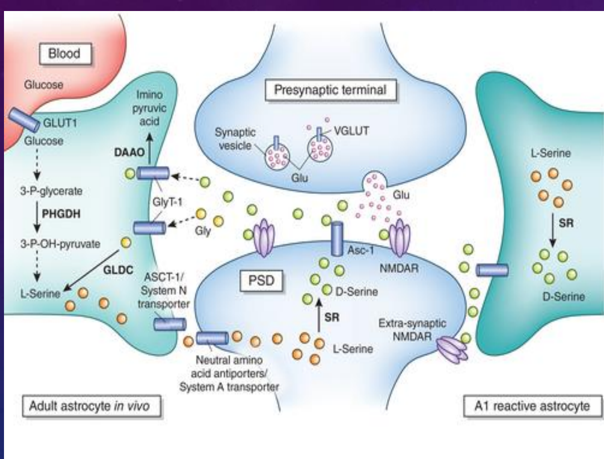
- Decreasing dopaminergic signaling throughout the brain can worsen negative symptoms
- Existing medications are highly effective at treating positive symptoms but not negative symptoms

1. Farinde A. Schizophrenia: a clinical overview. Clinical Advisor. Published March 3, 2017. Accessed April 29, 2025. https://www.clinicaladvisor.com/features/schizophrenia-a-clinical-overview/

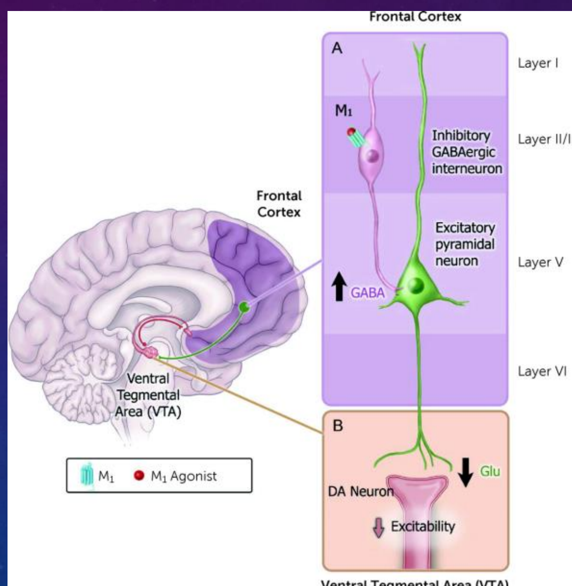
7

BEYOND DOPAMINE TO….

GLUTAMATE HYPOTHESIS[2]



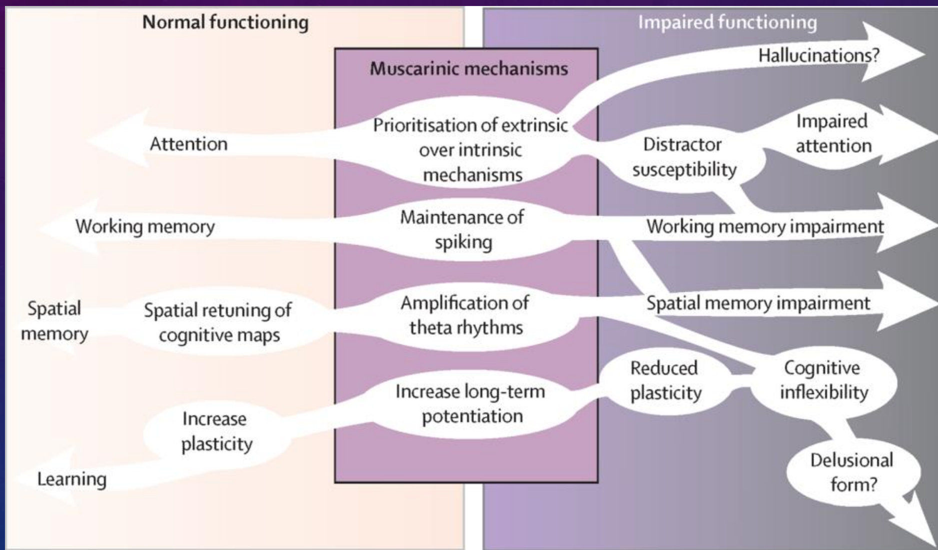
MUSCARINIC HYPOTHESIS[3]



8

MUSCARINIC FUNCTIONS IN NORMAL COGNITION

- Note the negative symptoms on the right-hand side
- If decreased muscarinic signaling is causing these impairments at baseline, what happens when we add anticholinergic medications?



9

COBENFY ™ (XANOMELINE AND TROSPIUM CHLORIDE)

- Systemic M1 and M4 agonist + anticholinergic that cannot cross blood-brain barrier

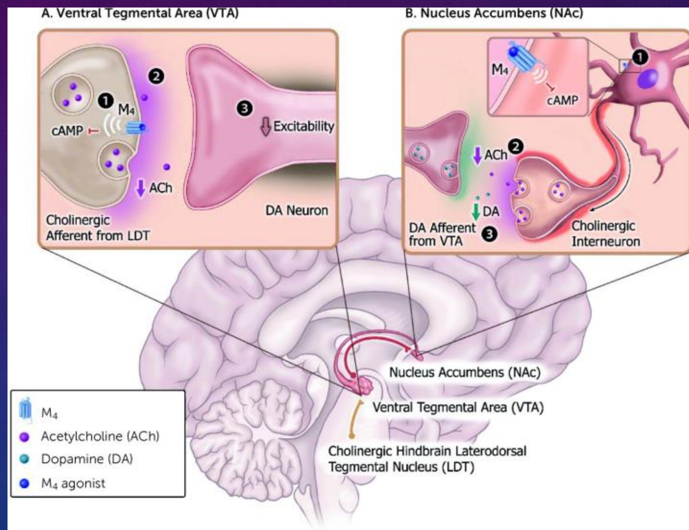
Xanomeline Trospium

- FDA Approved September 26, 2024 for schizophrenia
- The first novel antipsychotic mechanism in 70 years!
- Will this treat negative symptoms more effectively than existing medications?

10

IN THEORY…

- M1 agonism in cortex pyramidal cells decreased excitatory input to DA neurons in midbrain[4]
- M4 autoreceptor agonism in VTA decreased DA signaling in NAc[4]



11

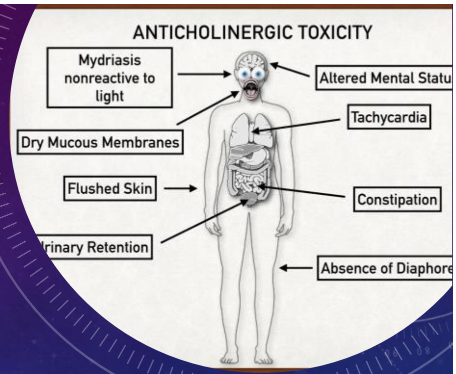
IN PRACTICE (SO FAR)

- 2021: 5 weeks, statistically outperformed placebo[5]
- 2025: 6 weeks, no significant benefit as adjunctive treatment to an SGA[6]
- As yet unknown: Head-to-head with an SGA; Head-to-head with clozapine

12

COBENFY: PRACTICAL ASPECTS

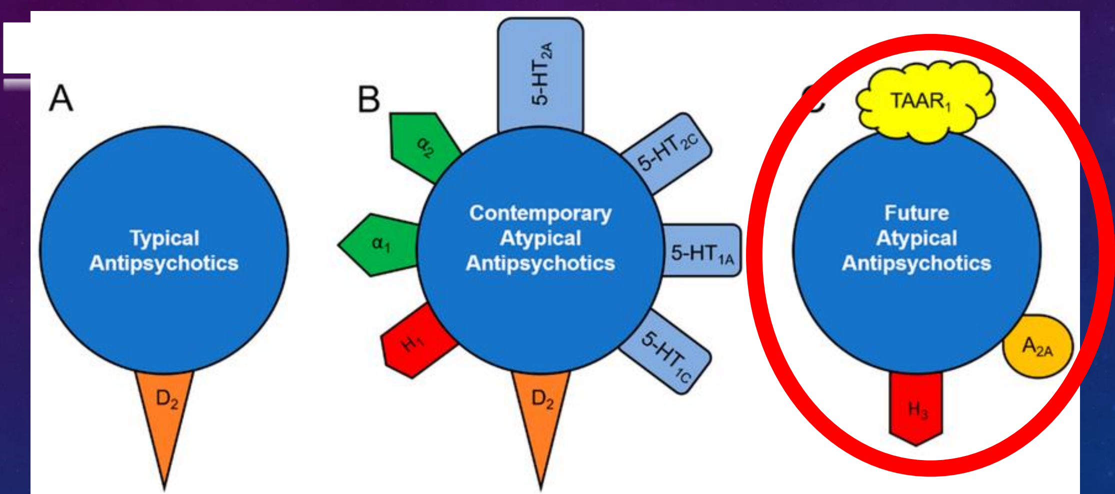
- Twice daily dosing
  - Standard dose: 100 mg / 20 mg BID
  - Max dose: 125 mg / 30 mg BID
- Side effects: both cholinergic and anticholinergic[5]
  - Most common: Nausea (19%) dyspepsia (18%), GERD (5%)
  - Anticholinergic: Constipation (17%), dry mouth (4%)
  - Cholinergic: Diarrhea (6%), sialorrhea (2%)
  - Other: Hypertension (11%)



Cholinergic Crisis. Accessed April 29, 2025. https://www.osmosis.org/answers/sludge-cholinergic-crisis-signs-and-symptoms-acronym
Anticholinergic Toxicity. Accessed April 28, 2025. https://www.ezmedlearning.com/blog/anticholinergic

13

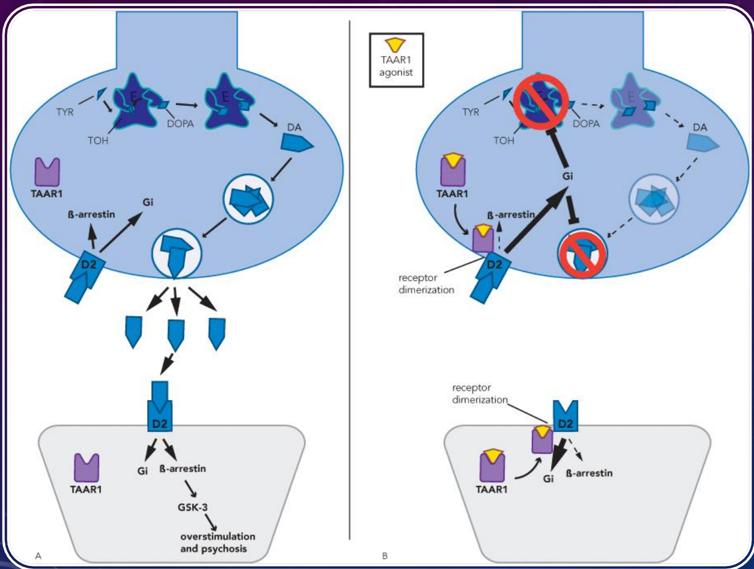
OTHER RECEPTORS



Grinchii D, Dremencov E. Mechanism of Action of Atypical Antipsychotic Drugs in Mood Disorders. *International Journal of Molecular Sciences*. 2020; 21(24):9532. https://doi.org/10.3390/ijms21249532

14

TRACE AMINO ACID RECEPTOR LIGANDS



- TAAR1 agonists: Reduce dopamine signaling without any activity at the D2 receptor[9]
- Ulotaront: Phase III trials
  - Also 5-HT1A agonist
  - Outperformed placebo in 4-week trial in acute schizophrenia[10]

Stephen M. Stahl, MD, PhD. 2021. Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Applications - 5th Ed. New York. Cambridge University Press. ISBN 978-1-108-83857-3. eISBN 978-1-108-98585-7. STAT!Ref Online Electronic Medical Library. https://online.statref.com/document/KIjMnFhK-cVTpu8Bu3qt_j. 4/28/2025 10:14:42 PM CDT (UTC -05:00).

15

STILL OTHERS!

- Roluperidone: Sigma-2 receptor agonist (also 5-HT2A antagonist and alpha-adrenergic antagonist)
  - Two RCTs supported use for negative symptoms[11]
  - FDA rejected roluperidone in 2024, citing need for more efficacy and safety data[12]
- D3 Antagonists
  - Cariprazine has this activity; others in development with no D2 activity

16

NEUROMODULATION IN PSYCHOSIS

ECT is highly effective

Response rates as high as 80%[13]

May be more effective than clozapine[14]

Undesirable to many patients: downtime, cognitive side effects

Magnetic seizure therapy

Depression studies: response similar to ECT with fewer cognitive side effects[15]

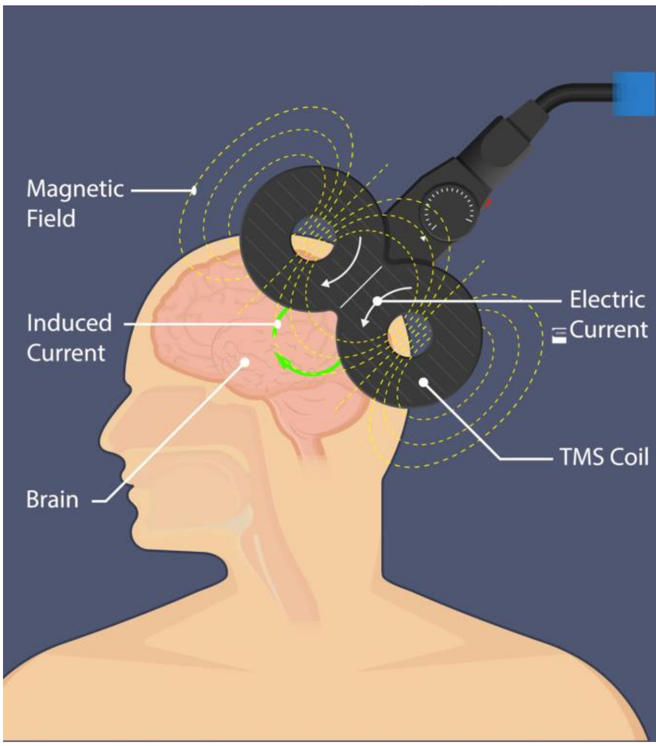
No RCTs for psychosis yet published

Deep Brain Stimulation

Pro: Effective in small non-blinded study (stimulating sgACC and NAcc)[15]

Con: Brain surgery

17



TRANSCRANIAL MAGNETIC STIMULATION

- Favorable tolerability/side effect profile compared to ECT
- Brain regions of interest, with mixed results:
  - Auditory hallucinations: Temporoparietal cortex (low frequency, inhibitory)[15]
  - Negative symptoms: Left DLPFC (high frequency rTMS)[15, 16, 17]
  - Cognitive symptoms: Left or bilateral PFC (high frequency rTMS)[15]

18

TRANSCRANIAL ELECTRIC STIMULATION

- tDCS: Frontotemporal region, evidence for reduction of auditory hallucinations[15] and improvement in insight[16]
- tACS: improvements in positive and negative symptoms, with varied placements and outcome measures[18]
- Transcranial random noise stimulation: improved negative symptoms when used over left DLPFC[17]

19

LEARNING OBJECTIVES

1	Describe the negative symptoms of schizophrenia
2	List the most common side effects of first- and second-generation antipsychotic medications
3	Name a receptor target for a novel antipsychotic medication
4	Name three neuromodulation techniques being investigated for psychosis

20

Bonus trivia question: Which of the following molecules is a full agonist at the M1 receptor?

A. Olanzapine
B. Clozapine
C. N-desmethylclozapine
D. Donepezil

AKA norclozapine!

21

THANK YOU FOR YOUR ATTENTION

QUESTIONS?

22

REFERENCES

1. Farinde A. Schizophrenia: a clinical overview. Clinical Advisor. Published March 3, 2017. Accessed April 29, 2025. https://www.clinicaladvisor.com/features/schizophrenia-a-clinical-overview/

2. Uno Y, Coyle JT. Glutamate hypothesis in schizophrenia. *Psychiatry and Clinical Neurosciences*. 2019;73(5):204-215. doi:https://doi.org/10.1111/pcn.12823

3. McCutcheon RA, Weber LAE, Nour MM, Cragg SJ, McGuire PM. Psychosis as a disorder of muscarinic signalling: psychopathology and pharmacology. *The Lancet Psychiatry*. 2024;11(7):554-565. doi:https://doi.org/10.1016/s2215-0366(24)00100-7

4. Paul SM, Yohn SE, Popiolek M, Miller AC, Felder CC. Muscarinic Acetylcholine Receptor Agonists as Novel Treatments for Schizophrenia. *The American Journal of Psychiatry*. 2022;179(9):appiajp21101083. doi:https://doi.org/10.1176/appi.ajp.21101083

5. *HIGHLIGHTS of PRESCRIBING INFORMATION*.; 2024. https://packageinserts.bms.com/pi/pi_cobenfy.pdf

6. Bristol Myers Squibb announces topline results from phase 3 ARISE trial evaluating Cobenfy (xanomeline and trospium chloride) as an adjunctive treatment to atypical antipsychotics in adults with schizophrenia. News release. April 22, 2025. https://news.bms.com/news/details/2025/Bristol-Myers-Squibb-Announces-Topline-Results-from-Phase-3-ARISE-Trial-Evaluating-Cobenfy-xanomeline-and-trospium-chloride-as-an-Adjunctive-Treatment-to-Atypical-Antipsychotics-in-Adults-with-Schizophrenia/default.aspx

7. Grinchii D, Dremencov E. Mechanism of Action of Atypical Antipsychotic Drugs in Mood Disorders. *International Journal of Molecular Sciences*. 2020; 21(24):9532. https://doi.org/10.3390/ijms21249532

8. Stephen M. Stahl, MD, PhD. 2021. Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Applications - 5th Ed. New York. Cambridge University Press. ISBN 978-1-108-83857-3. eISBN 978-1-108-98585-7. STAT!Ref Online Electronic Medical Library. https://online.statref.com/document/KIjMnFhK-cVTpu8Bu3qt_j. 4/28/2025 10:14:42 PM CDT (UTC -05:00).

9. Yang, S.M., Ghoshal, A., Hubbard, J.M. *et al.* TAAR1 agonist ulotaront modulates striatal and hippocampal glutamate function in a state-dependent manner. *Neuropsychopharmacol.* 49, 1091–1103 (2024). https://doi.org/10.1038/s41386-023-01779-x

10. Koblan KS, Kent J, Hopkins SC, Krystal JH, Cheng H, Goldman R, et al. A non–D2-receptor-binding drug for the treatment of schizophrenia. New England Journal of Medicine. 2020 Apr 16;382(16):1497–506. doi:10.1056/nejmoa1911772

23

REFERENCES

11. Davidson M, Saoud J, Staner C, Noel N, Werner S, Luthringer E, Walling D, Weiser M, Harvey PD, Strauss GP, Luthringer R. Efficacy and Safety of Roluperidone for the Treatment of Negative Symptoms of Schizophrenia. Schizophr Bull. 2022 May 7;48(3):609-619. doi: 10.1093/schbul/sbac013. PMID: 35211743; PMCID: PMC9077422

12. PharmD BP. FDA Denies Approval of Roluperidone for Negative Symptoms of Schizophrenia. Medical Professionals Reference. Published February 28, 2024. Accessed April 29, 2025. https://www.empr.com/home/news/drugs-in-the-pipeline/fda-denies-approval-of-roluperidone-for-negative-symptoms-of-schizophrenia/

13. Kaster TS, Daskalakis ZJ, Blumberger DM. Clinical Effectiveness and Cognitive Impact of Electroconvulsive Therapy for Schizophrenia: A Large Retrospective Study. *J Clin Psychiatry*. 2017;78(4):e383-e389. doi:10.4088/JCP.16m10686

14. Mishra BR, Agrawal K, Biswas T, Mohapatra D, Nath S, Maiti R. Comparison of Acute Followed by Maintenance ECT vs Clozapine on Psychopathology and Regional Cerebral Blood Flow in Treatment-Resistant Schizophrenia: A Randomized Trial. *Schizophr Bull*. 2022;48(4):814-825. doi:10.1093/schbul/sbac027

15. Neufeld NH, Blumberger DM. An Update on the Use of Neuromodulation Strategies in the Treatment of Schizophrenia. *Am J Psychiatry*. 2025;182(4):332-340. doi:10.1176/appi.ajp.20250068

16. Sabé M, Hyde J, Cramer C, et al. Transcranial Magnetic Stimulation and Transcranial Direct Current Stimulation Across Mental Disorders: A Systematic Review and Dose-Response Meta-Analysis [published correction appears in JAMA Netw Open. 2024 Jul 1;7(7):e2424292. doi: 10.1001/jamanetworkopen.2024.24292.]. *JAMA Netw Open*. 2024;7(5):e2412616. Published 2024 May 1. doi:10.1001/jamanetworkopen.2024.12616

17. Tseng PT, Zeng BS, Hung CM, et al. Assessment of Noninvasive Brain Stimulation Interventions for Negative Symptoms of Schizophrenia. *JAMA Psychiatry*. 2022;79(8):770. doi:https://doi.org/10.1001/jamapsychiatry.2022.1513

18. Elyamany O, Leicht G, Herrmann CS, Mulert C. Transcranial alternating current stimulation (tACS): from basic mechanisms towards first applications in psychiatry. *Eur Arch Psychiatry Clin Neurosci*. 2021;271(1):135-156. doi:10.1007/s00406-020-01209-9

24