Psych Congress Network

Mastering Schizophrenia Treatment:

Optimal Use of Oral Antipsychotics Based on Neurobiological and Clinical Evidence

Psych Congress Network

Oral Antipsychotic Mechanisms of Action and Clinical Evidence in Schizophrenia

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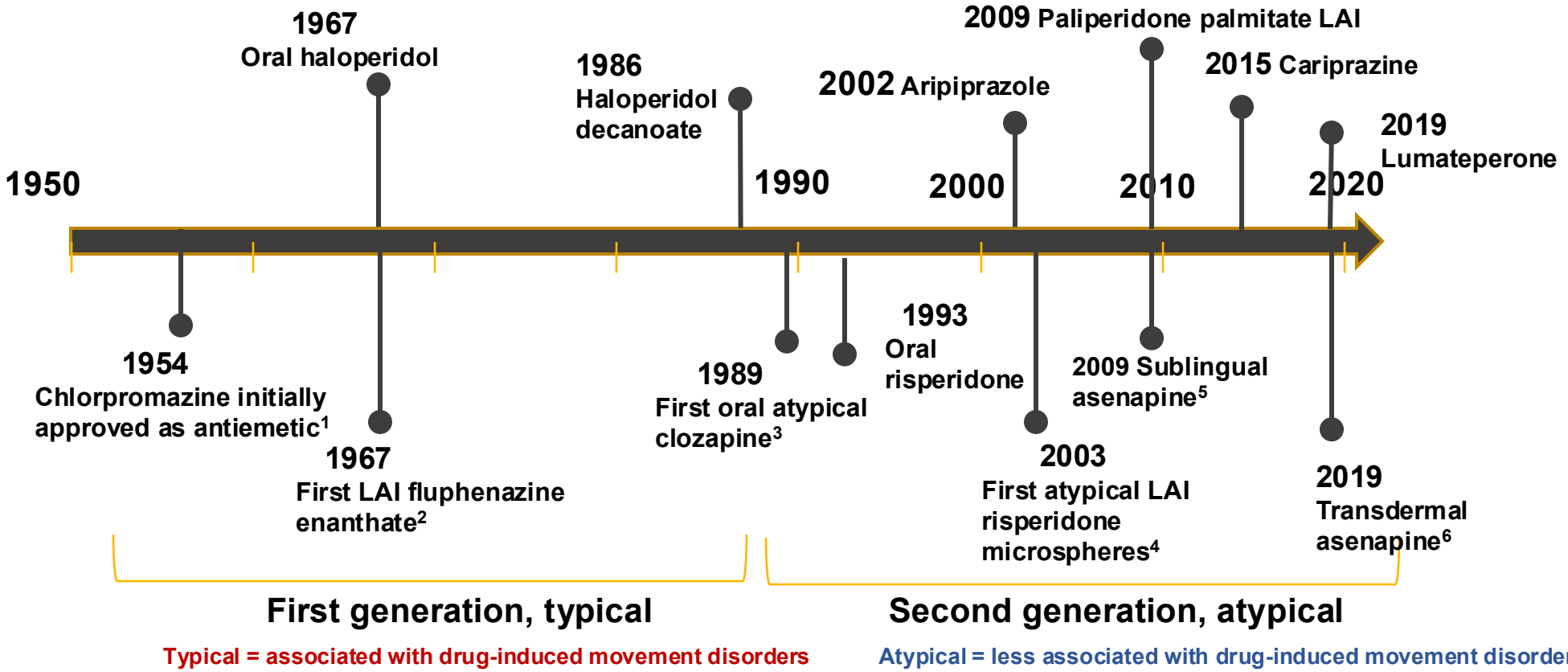
Learning Objectives

- Summarize the current utilization of OAPs for schizophrenia that target postsynaptic D2 receptors and the potential benefits and risks associated with this traditional approach

- Evaluate the latest clinical evidence and treatment implications associated with newer OAPs for schizophrenia that have presynaptic and multimodal mechanisms of action

First and Second-Generation OAPs for Schizophrenia

Selected FGA and SGA Approvals Over Time



1. López-Muñoz F et al. *Ann Clin Psychiatry*. 2005;17(3):113-15; 2. Citrome L. *Expert Rev Neurother*. 2013;13(7):767-83; 3. Clozaril® (clozapine) [prescribing information]. Drugs@FDA: FDA Approved Drugs. Accessed March 6, 2024. www.accessdata.fda.gov/scripts/cder/daf/; 4. US Food and Drug Administration (FDA). Drug approval package: Risperdal Consta® long-acting injection. Approval date: October 2003; 5. Saphris® (asenapine) [prescribing information]. Approved 2010. Drugs@FDA: FDA Approved Drugs. Accessed March 6, 2024. www.accessdata.fda.gov/scripts/cder/daf/; 6. SECUADO® (asenapine) [prescribing information]. Approved October 2019. Drugs@FDA: FDA Approved Drugs. Accessed March 6, 2024. www.accessdata.fda.gov/scripts/cder/daf

All Currently Available Antipsychotics Work by Blocking Postsynaptic Dopamine D2 Receptors

- The first commercially available antipsychotic, **chlorpromazine**, blocks postsynaptic dopamine D_2 receptors, reducing intensity and frequency of hallucinations and delusions

- All subsequent antipsychotics approved to date do this too

Stahl SM. CNS Spectr. 2018;23(3):187-91.

Collateral Damage from Blocking Postsynaptic Dopamine D2 Receptors

- Postsynaptic dopamine D_2 receptors are also blocked in the **dorsal striatum**, causing drug-induced "EPS" or **drug-induced movement disorders (DIMDs)**
  - Subsequent upregulation of these receptors in the dorsal striatum leads to **tardive dyskinesia**
- Postsynaptic dopamine D_2 receptors are also blocked in the hypothalamic-pituitary pathway, causing **hyperprolactinemia**
- The above can vary among antipsychotics

Volavka J, et al. *Expert Opin Pharmacother*. 2009;10(12):1917-28.

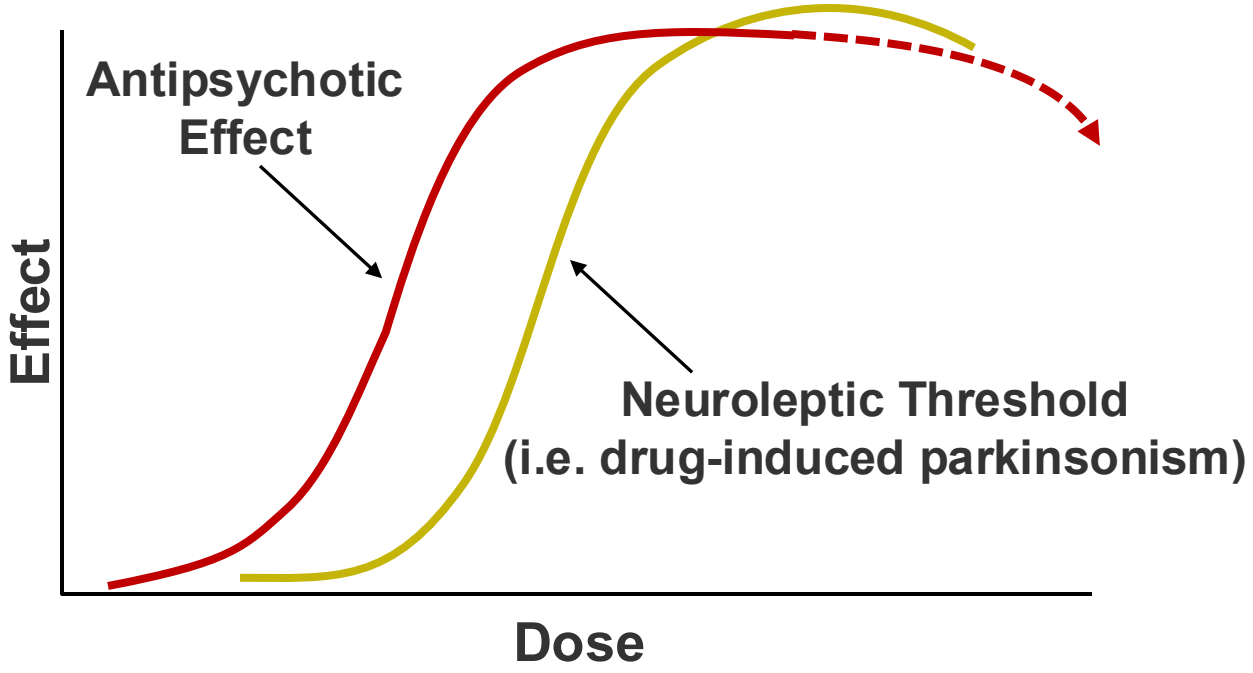
How Can We Avoid Drug-Induced Movement Disorders?

- **Avoid first-generation antipsychotics and avoid anticholinergic medications!**
  - FGAs are also referred to as "**typical**" antipsychotics because they typically are associated with drug-induced movement disorders
  - The "antidote" was thought to be co-administering an anticholinergic medication like benztropine; however, anticholinergic medications impair cognition, increase the risk of developing tardive dyskinesia, and can make existing tardive dyskinesia worse
- **Prescribe second-generation antipsychotics**
  - SGAs are also referred to as "**atypical**" antipsychotics because they are NOT typically associated with drug-induced movement disorders, particularly drug-induced parkinsonism or acute dystonia, however some SGAs are more likely to cause akathisia than others, and all dopamine receptor blocking agents can lead to tardive dyskinesia
  - When managing a DIMD, instead of using an anticholinergic, switch to a different SGA (there are many), lower the dose of the SGA, or if you must stay with the current antipsychotic at the current dose, prescribe amantadine

Ward KM, Citrome L. *Neurol Ther*. 2018 Dec;7(2):233-48.

Why It Is Hard to Avoid Drug-Induced Parkinsonism With First-generation Antipsychotics (FGAs)?

FGA Dose-Responsive Curve

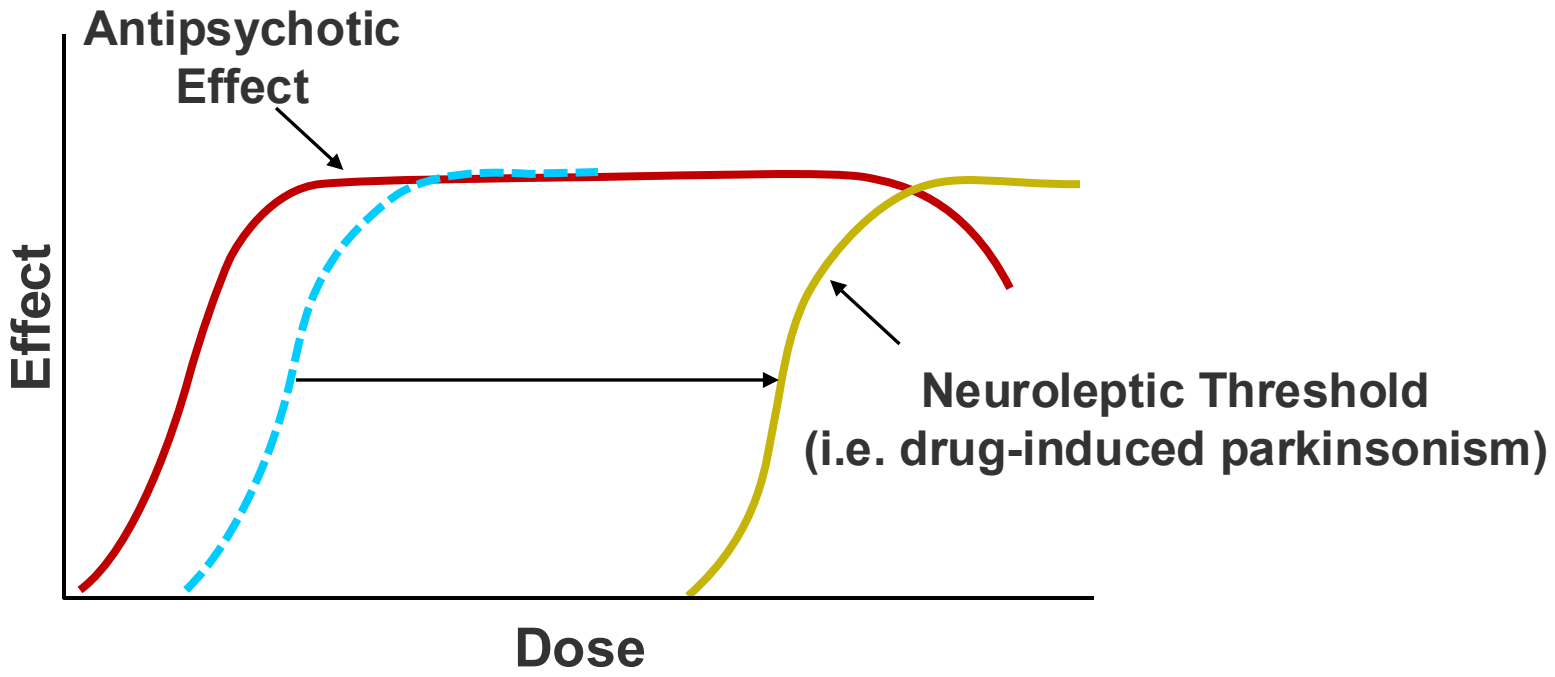


Narrow therapeutic window between antipsychotic effect and neuroleptic threshold. Dotted line indicates declining efficacy.

Pierre JM, et al. High-dose antipsychotics: Desperation or data-driven? *Current Psychiatry. 2004;*3(8):31-7. Accessed August 9, 2023. https://www.mdedge.com/psychiatry/article/59825/schizophrenia-other-psychotic-disorders/high-dose-antipsychotics

This Is Different for Second-generation Antipsychotics (SGAs)

SGA Dose-Responsive Curve



Wider therapeutic window with SGAs, compared with FGAs, as neuroleptic threshold (dotted line) moves right.

Pierre JM, et al. High-dose antipsychotics: Desperation or data-driven? *Current Psychiatry. 2004;*3(8):31-7. Accessed August 9, 2023. https://www.mdedge.com/psychiatry/article/59825/schizophrenia-other-psychotic-disorders/high-dose-antipsychotics.

All Currently Available Antipsychotics Are Dopamine Receptor Blocking Agents, However…

- Dopamine receptor **binding affinity in the striatum can vary** among the antipsychotics, and some are partial agonists rather than pure antagonists
  - This can mitigate against some dopamine blockade related adverse effects
- There is **heterogeneity** among the currently available antipsychotics regarding affinity to other receptors in other brain areas
  - Depending on the receptor, these effects may mitigate or trigger adverse effects
  - These effects may also contribute to efficacy

Volavka J, Citrome L. *Expert Opin Pharmacother.* 2009;10(12):1917-28.

Potential Association Between Receptor Blockade and Efficacy

Receptor	Potential Effects of blockade
D_2	**Antipsychotic, anti-manic, anti-aggression**
D_3	Improve negative symptoms and cognition
a_2 adrenergic	Antidepressant, increased alertness
H_1	Anxiolytic, sleep induction, anti-EPS/akathisia
M_1	Anti-EPS/akathisia
5-HT_{1A} (partial agonism)	Anxiolytic, antidepressant, improve negative symptoms and cognition, anti-EPS/akathisia
5-HT_{2A}	**Anti-EPS/akathisia, antipsychotic(?), improve cognition and mood**
5-HT_{2C}	Improve cognition/mood
5-HT_7	Antidepressant

Updated from Shayegan DK, et al. *CNS Spectr.* 2004;9(10 Suppl 11):6-14.

Potential Association Between Receptor Blockade and Tolerability

Receptor	Effects of blockade
D_2	EPS/akathisia, tardive dyskinesia, increased prolactin
a_1 adrenergic	Postural hypotension, dizziness, syncope, akathisia (protective)
a_2 adrenergic	Increased blood pressure
H_1	Sedation, weight gain
M_1	Memory, cognition, dry mouth
M_{2-4}	Blurred vision, constipation, urinary retention
5-HT_{2C}	Increased appetite

Shayegan DK, et al. *CNS Spectr*. 2004;9(10 Suppl 11):6-14.

Examples of How Antipsychotics Vary in Receptor Binding Affinities in Vitro

Binding affinity (K_i, nM), indicating partial agonist (pink) or antagonist (blue) activity

Receptor	Aripiprazole	Brexpiprazole	Cariprazine	Lurasidone	Quetiapine	Risperidone
D_2	0.34	0.30	0.49 (D_{2L}), 0.69 (D_{2S})	1	626	2.2
α_{1A}	25.7	3.8	155	NR	22	0.60
α_{1B}	34.8	0.17	NR	NR	14.6	9.0
α_{1D}	NR	2.6	208.9	NR	NR	NR
α_{2C}	37.9	0.59	NR	10.8	28.7	9.1
H_1	61	19	23.2	≥ 1000 (IC_{50})	4.41	19
M_1	6780	67% inhibition at 10 μM	> 1000 (IC_{50})	> 1000 (IC_{50})	1086	2800

Data are from different experiments and are not intended for direct comparison; alternate sources may report different values, and there may be discrepancies due to species differences; partial agonist/antagonist activity from Stahl (2013), Maeda et al. (2014), and Kiss et al. (2010); brexpiprazole data are mean values calculated by nonlinear regression analysis using data from 3 assays performed in duplicate or triplicate; norquetiapine (active metabolite of quetiapine) has similar activity at D_2 receptors, but greater activity at 5-HT_{2A} receptors, compared to quetiapine; in addition, norquetiapine has a high affinity for muscarinic M_1 receptors (K_i=38.3 nM); IC_{50} = half-maximal inhibitory concentration; NR = not reported.

Prescribing information data used where available, otherwise published data. US Food and Drug Administration. Drugs@FDA: FDA Approved Drug Products. www.accessdata.fda.gov/scripts/cder/daf/. Stahl SM. Stahl's Essential Psychopharmacology. Fourth Edition. Cambridge University Press; 2013. Shapiro DA, et al. *Neuropsychopharmacology*. 2003;28(8):1400-11. Kiss B, et al. *J Pharmacol Exp Ther.* 2010;333(1):328-40. Ishibashi T, et al. *J Pharmacol Exp Ther.* 2010;334(1):171-81. Duncan GE, et al. *Mol Psychiatry*. 1999;4(5):418-28. Kroeze WK, et al. *Neuropsychopharmacology*. 2003;28(3):519-26. Maeda K, et al. Presented at: 2014 American Psychiatric Association Annual Meeting. PDSP 2014. Schotte A, et al. *Psychopharmacology.* 1996;124(1-2):57-73.

Selected FGAs and All Available SGAs

Generic Name	Brand Name and Availability in Other Formulations	Year 1st Approved	Oral Target Dose in Current Label (Schizophrenia)
Chlorpromazine	Thorazine	1954	75-300, up to 2000 mg/d
Perphenazine	Trilafon	1957	12-64 mg/d
Fluphenazine	Prolixin (also available as LAI)	1959	2.5-10 up to 40 mg/d
Haloperidol	Haldol (also available as LAI)	1967	Moderate Symptomatology – 1-6 mg/d Severe Symptomatology – 6-15, up to 100 mg/d
Clozapine	Clozaril	1989	300-450, up to 900 mg/d
Risperidone	Risperdal (also available as LAI)	1993	4-8, up to 16 mg/d
Olanzapine	Zyprexa (also available as LAI)	1996	10, up to 20 mg/d
Quetiapine	Seroquel (also XR)	1997	150-750 mg/d (IR), 400-800 mg/d (XR)
Ziprasidone	Geodon	2001	40-160, up to 200 mg/d
Aripiprazole	Abilify (also available as LAI)	2002	10-15, up to 30 mg/d
Paliperidone	Invega (also available as LAI)	2006	3-12 mg/d
Asenapine	Saphris SL (also transdermal Secuado)	2009	10-20 mg/d
Iloperidone*	**Fanapt**	**2009**	**12-24 mg/d**
Lurasidone	Latuda	2010	40-160 mg/d
Cariprazine*	**Vraylar**	**2015**	**1.5-6 mg/d**
Brexpiprazole*	**Rexulti**	**2015**	**2-4 mg/d**
Lumateperone*	**Caplyta**	**2019**	**42 mg/d**
Olanzapine-Samidorphan*	**Lybalvi**	**2021**	**10/10-20/10 mg/d**

Adapted from: Groenendaal E, et al. *J Psychiatr Res*. 2023;158:273-80. Respective Drug Prescribing Information: Drugs@FDA: FDA-Approved Drugs. Accessed March 6, 2024. www.accessdata.fda.gov/scripts/cder/daf/.

Classifying SGAs Into Groups: Easier to Remember

- **"Pines"**
  - Clozapine, olanzapine, quetiapine, asenapine
  - Generally, more sedating and with a higher risk of adverse metabolic outcomes (weight gain, lipid and glucose dysregulation), but with a lower risk of drug-induced movement disorders; need to taper off slowly
- **"Dones" and a "Rone"**
  - Risperidone, paliperidone, ziprasidone, iloperidone, lurasidone, lumateperone
  - Generally, a lower risk of adverse metabolic outcomes but a higher risk of dose-related drug-induced movement disorders (iloperidone and lumateperone being the exceptions)
- **"Pips" and a "Rip"**
  - Aripiprazole, brexpiprazole, cariprazine
  - These are dopamine receptor partial agonists and can be associated with akathisia (aripiprazole and cariprazine in particular), but they are not all the same – for example, cariprazine has a higher binding affinity to dopamine D3 receptors than to D2 receptors, and has a very long half-life (1-3 weeks)

Stahl SM. *Essential Psychopharmacology, 5th Edition.* Cambridge University Press 2021; Citrome L. *Int J Clin Pract.* 2015;69(11):1211-20.

Each SGA Has Its Own "Tolerability Personality"

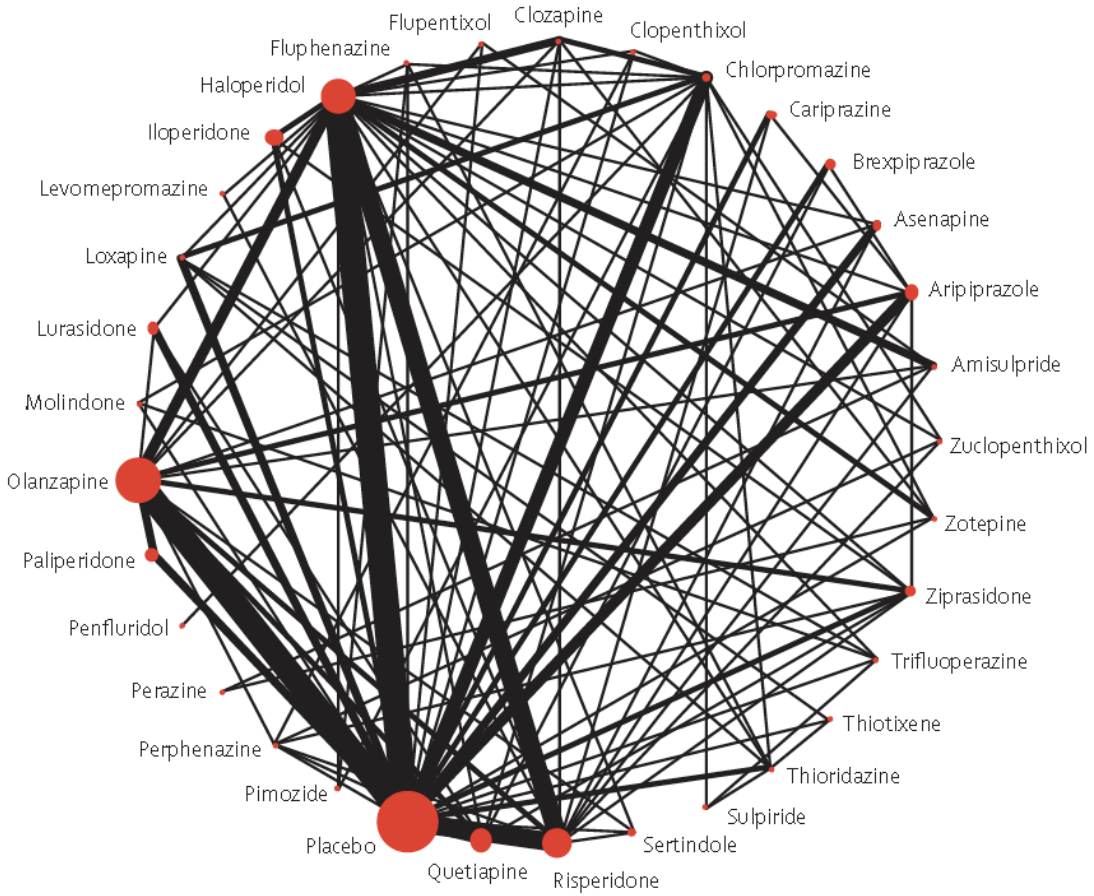
Meta-Analysis

- 32 antipsychotics for schizophrenia
- Direct and indirect comparisons for efficacy and adverse events

Data set

- 402 RCTs in acute schizophrenia (adults), n= 53,463

Key finding: "There are some efficacy differences between antipsychotics, but most of them are gradual rather than discrete. *Differences in side-effects are more marked*."

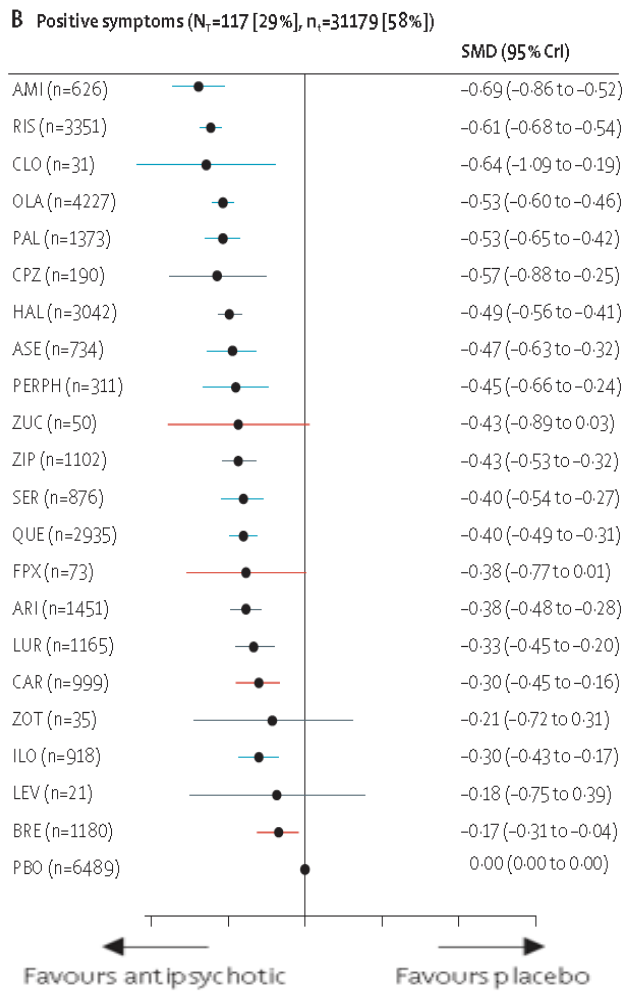


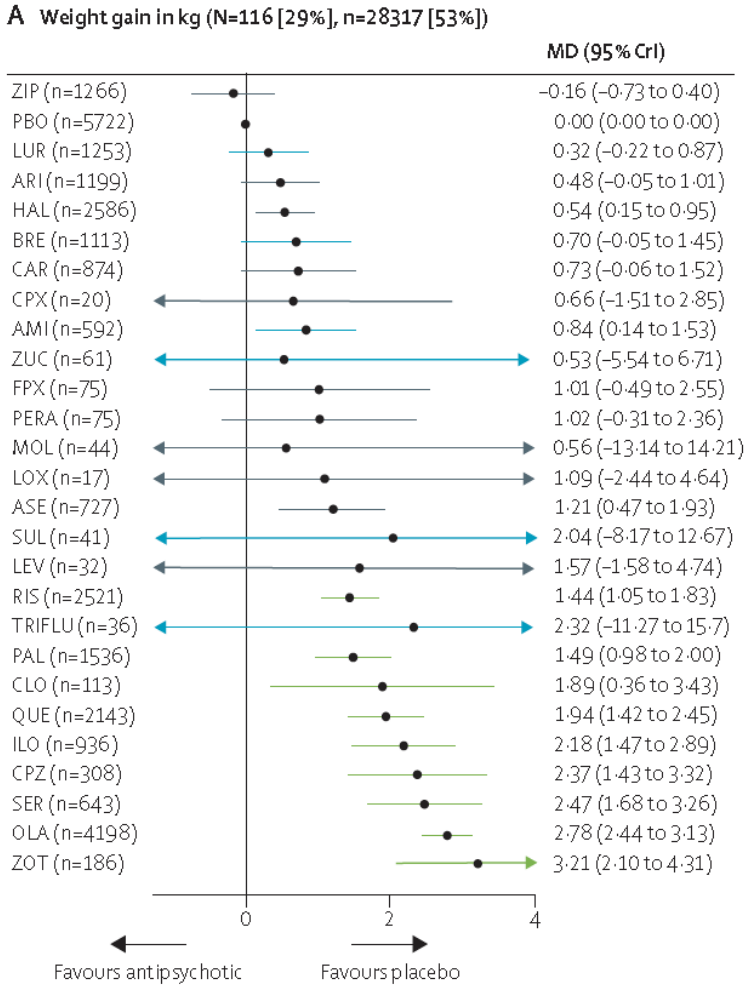
Network of comparisons

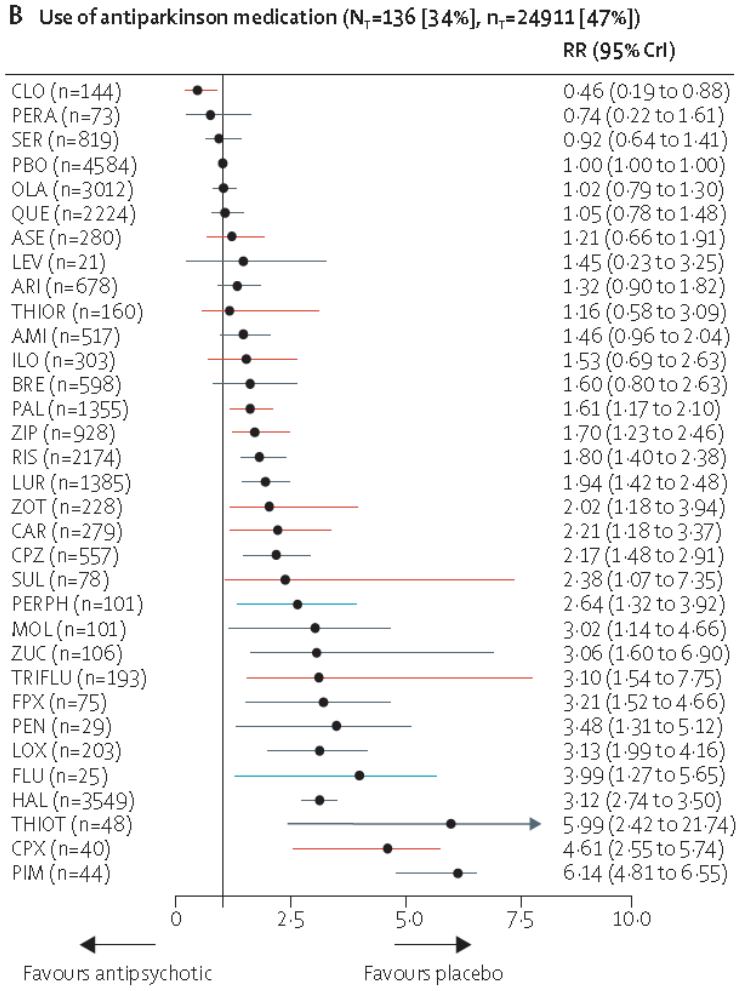
RCT=Randomized Controlled Study.

Huhn M, et al. *Lancet.* 2019;394:939–51.

Antipsychotic Meta-Analysis: Positive Symptom Efficacy, Weight Gain, and Parkinsonism Liability

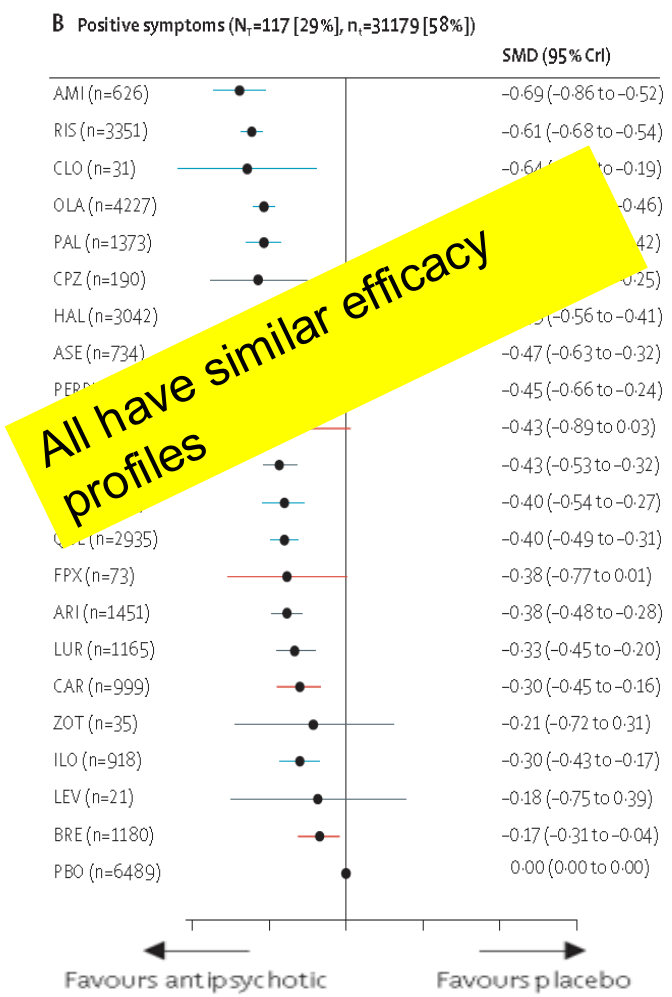


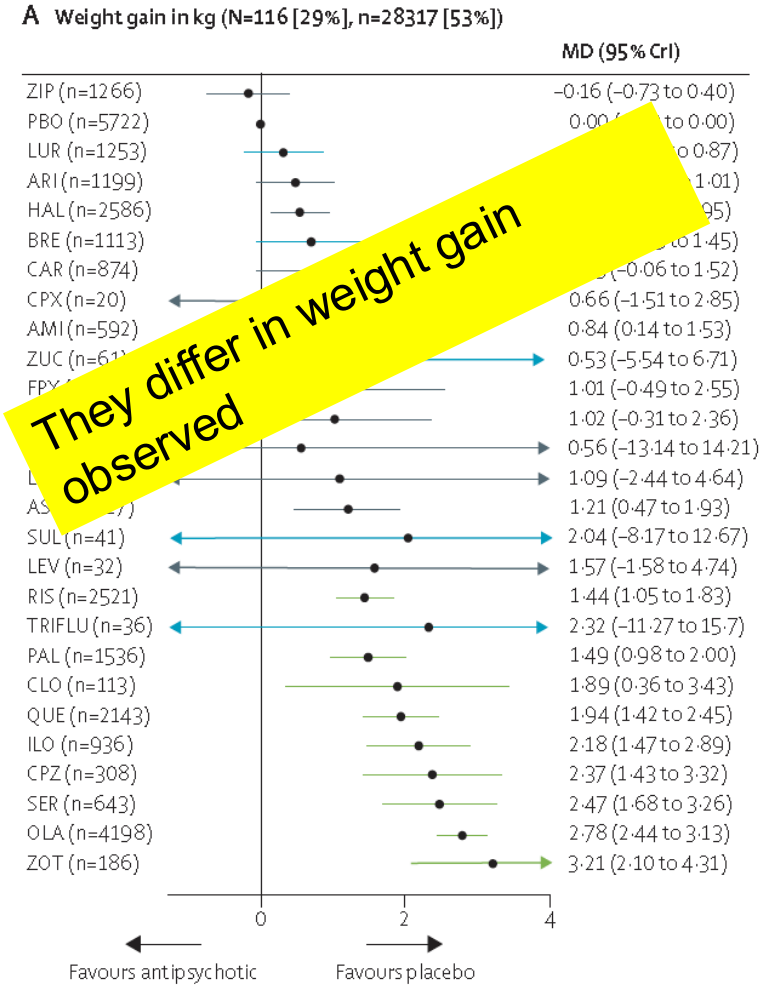


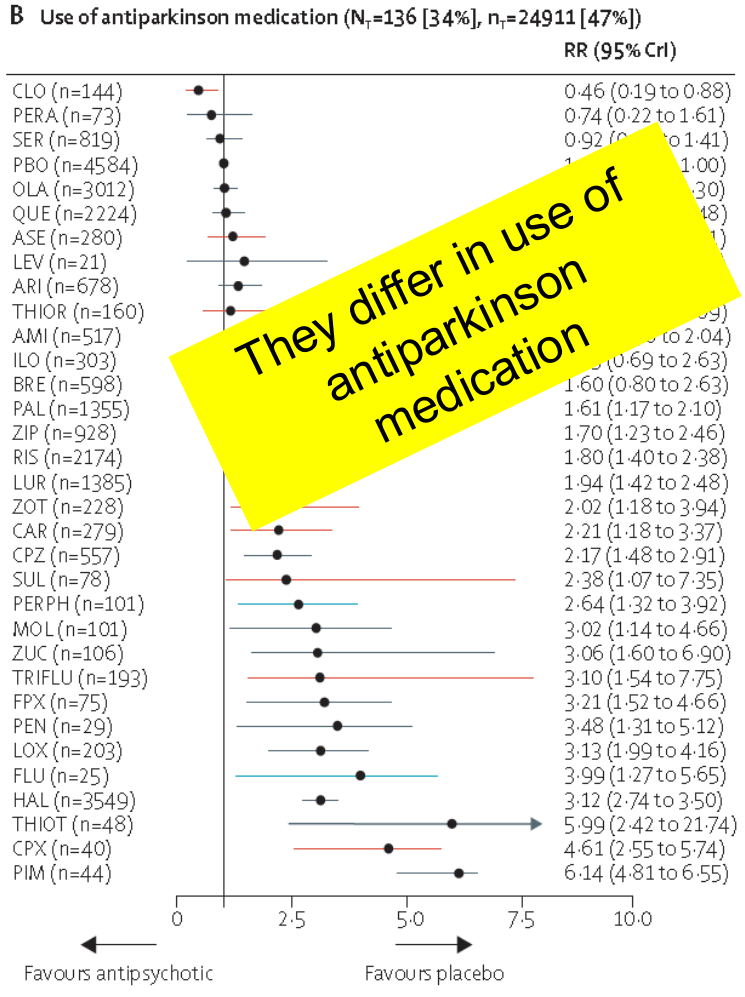


Huhn M, et al. *Lancet*. 2019;394(10202):939–51. doi: 10.1016/S0140-6736(19)31135-3. Epub 2019 Jul 11. Erratum in: *Lancet*. 2019 Sep 14;394(10202):918. PMID: 31303314; PMCID: PMC6891890.

Antipsychotic Meta-Analysis: Positive Symptom Efficacy, Weight Gain, and Parkinsonism Liability







Huhn M, et al. *Lancet*. 2019;394(10202):939–51. doi: 10.1016/S0140-6736(19)31135-3. Epub 2019 Jul 11. Erratum in: *Lancet*. 2019 Sep 14;394(10202):918. PMID: 31303314; PMCID: PMC6891890.

Another Way of Measuring Effect Size

Number Needed to Treat (NNT)

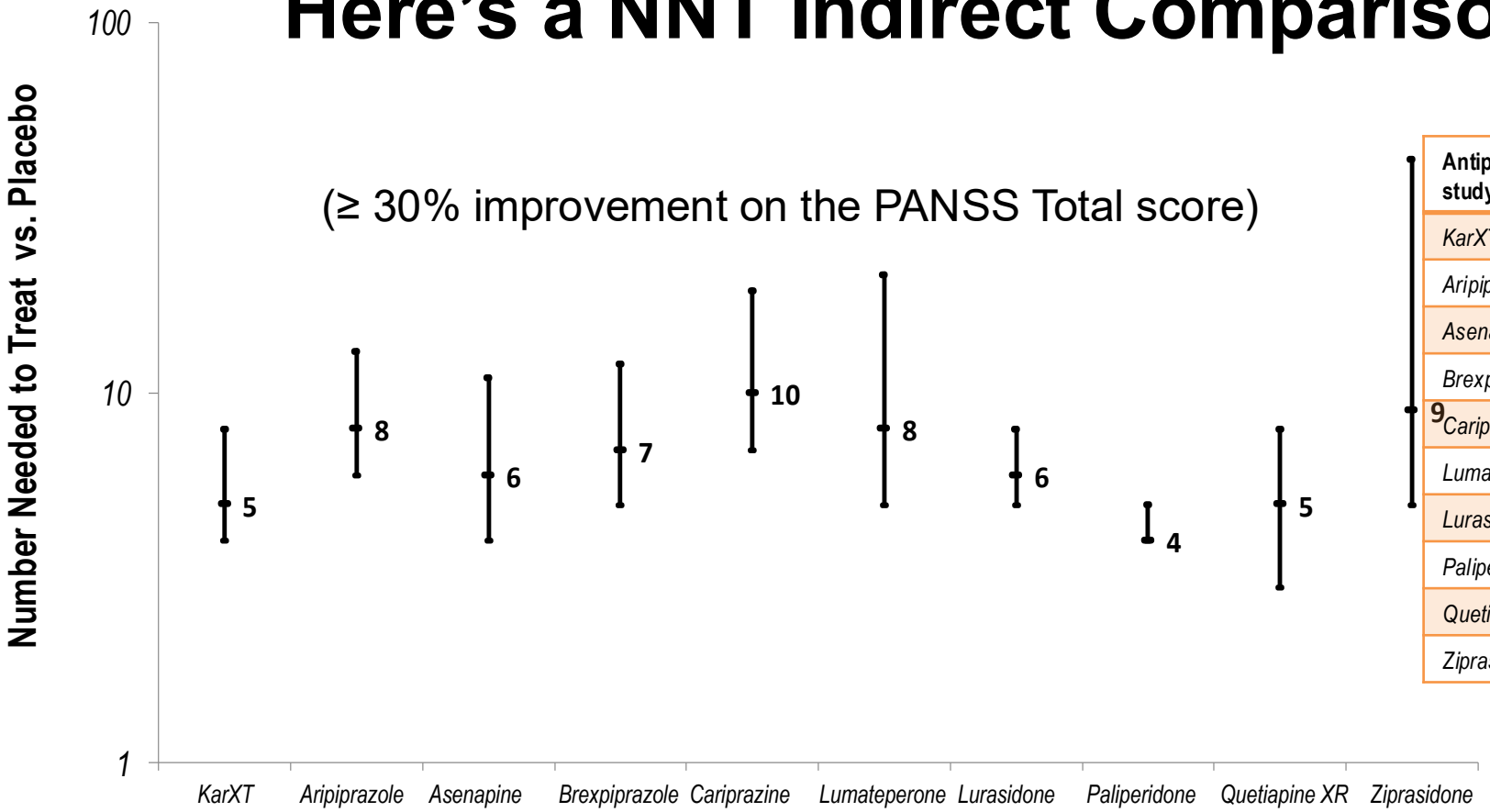
How many patients would you need to treat with Intervention A instead of Intervention B before you would expect to encounter one additional positive outcome of interest?

Number Needed to Harm (NNH)

How many patients would you need to treat with Intervention A instead of Intervention B before you would expect to encounter one additional outcome of interest that you would like to AVOID?

Citrome L. *Acta Psychiatr Scand.* 2010;121(2):94-102.

How Acutely Efficacious Are the SGAs in Schizophrenia? Here's a NNT Indirect Comparison of Response



Antipsychotic, dose, length of study(ies)	Drug n/N (%)	Placebo n/N (%)	NNT (95% CI)
KarXT 125/30 mg/d, 5 weeks	*130/314 (41.4)*	*68/326 (20.9)*	*5 (4-8)*
Aripiprazole 10-30 mg/d, 4-6 weeks	*~301/795 (37.8)*	*~99/404 (24.5)*	*8 (6-13)*
Asenapine 10-20 mg/d, 6 weeks	*~133/272 (49.1)*	*~55/182 (30.4)*	*6 (4-11)*
Brexpiprazole 2-4 mg/d, 6 weeks	*327/718 (45.5)*	*111/358 (31.0)*	*7 (5-12)*
Cariprazine 1.5-6 mg/d, 6 weeks	*274/877 (31.2)*	*93/442 (21.0)*	*10 (7-19)*
Lumateperone 42 mg/d, 4 weeks	*88/224 (39.3)*	*57/221 (25.8)*	*8 (5-21)*
Lurasidone 40-160 mg/d, 6 weeks	*517/1030 (50.2)*	*158/496 (31.9)*	*6 (5-8)*
Paliperidone 6-15 mg/d, 6 weeks	*~441/835 (52.8)*	*~95/356 (26.6)*	*4 (4-5)*
Quetiapine XR 400-800 mg/d, 6 weeks	*182/339 (53.7)*	*35/115 (30.4)*	*5 (3-8)*
Ziprasidone 80-160 mg/d, 6 weeks	*62/207 (30.0)*	*16/91 (17.6)*	*9 (5-43)*

*Response defined as ≥ 30% improvement on the PANSS Total score (KarXT, cariprazine, lumateperone, lurasidone, asenapine, paliperidone, quetiapine XR, one of the three pivotal trials for ziprasidone); ≥ 30% improvement on the PANSS Total score or CGI-I score of 1 (very much improved) or 2 (much improved) (aripiprazole, brexpiprazole). Analogous data for ≥ 30% improvement on PANSS Total score is unavailable for the pivotal trials of risperidone, olanzapine, quetiapine IR, or iloperidone. Abbreviations: CI: confidence interval; CGI-I: Clinical Global Impressions-Improvement; IR: immediate release; NNT: number needed to treat; PANSS: Positive and Negative Syndrome Scale; XR, extended release.

Citrome L, et al. *Neuropsychiatr Dis Treat*. 2025;21:761–773.

How Acutely Tolerable Are the SGAs in Schizophrenia? Here's a NNH "Heat Map"

RED: NNH < 10 higher risk ORANGE: NNH 10-19 intermediate risk GREEN: NNH ≥ 20 lower risk	NNH for weight gain ≥ 7%	NNH for AEs of somnolence and/or sedation	NNH for AEs of akathisia
Lumateperone	122	8	No Difference
Aripiprazole	21	34	31
Asenapine sublingual	35	17	26
Brexpiprazole	17	50	112
Cariprazine (to 6 mg/d)	34	65	15
Iloperidone	10	16	No Difference
Lurasidone	67	11	11
Olanzapine	6	10	25
Paliperidone	35	42	40
Quetiapine Immediate Release	6	15	No Difference
Quetiapine Extended Release	22	7	188
Risperidone (to 8 mg/d)	18	13	15
Ziprasidone	16	13	72

Similar values are expected for acute mania as similar or higher doses are used

Adapted from: Citrome L, et al. *J Clin Psychiatry*. 2023;84:22r14631.

More About Weight Gain

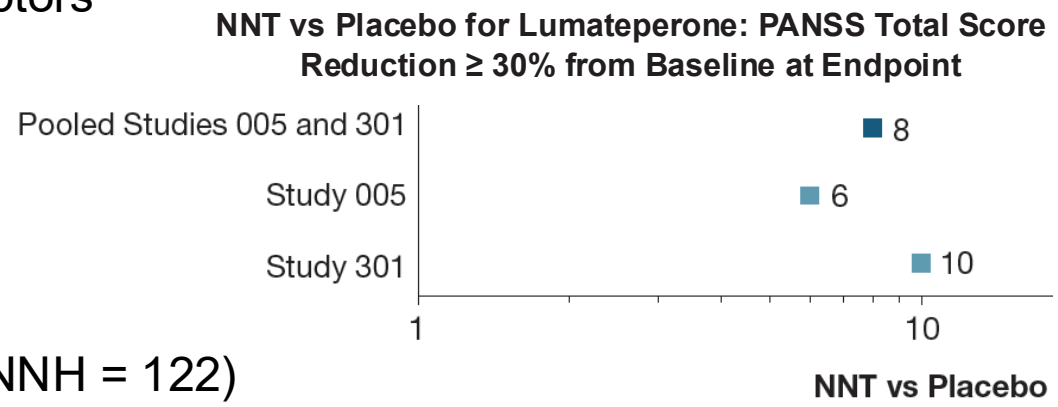
- Almost **all** antipsychotics are associated with weight gain
  - More pronounced in antipsychotic-naïve patients
  - **Can occur over time**
  - Not clearly dose-dependent
- Antipsychotic-related weight gain is **polygenic** and associated with specific genetic variants, especially in genes coding for antipsychotic pharmacodynamic targets
- Nonetheless, there are differences that can be quantified when comparing groups of patients in clinical trials
- “Your individual mileage may vary”

Bak M, et al. *PLoS One.* 2014;9(4):e94112. Zhang JP, et al. *Schizophr Bull.* 2016;42(6):1418-37.

Two Newer Options and Information About Weight Gain

Lumateperone

- **Lumateperone** (initially approved December 2019) is a D2/5HT2A antagonist with 60× higher affinity to 5-HT2A than D2 receptors
  - Dopaminergic + Serotonergic + Glutamatergic Actions
    - D2 Autoreceptor (Presynaptic) Partial Agonism + Low-Occupancy Postsynaptic D2 Antagonism
    - 5HT2A Antagonism + SERT Inhibition
    - D1-Dependent (Indirect) NMDA/AMPA Modulation
- Placebo-level effect on weight gain ≥7% in acute studies (NNH = 122)
  - In a 1-year open-label safety study 24% of patients showed a ≥7% decrease in body weight and 8% showed a ≥7% increase in body weight



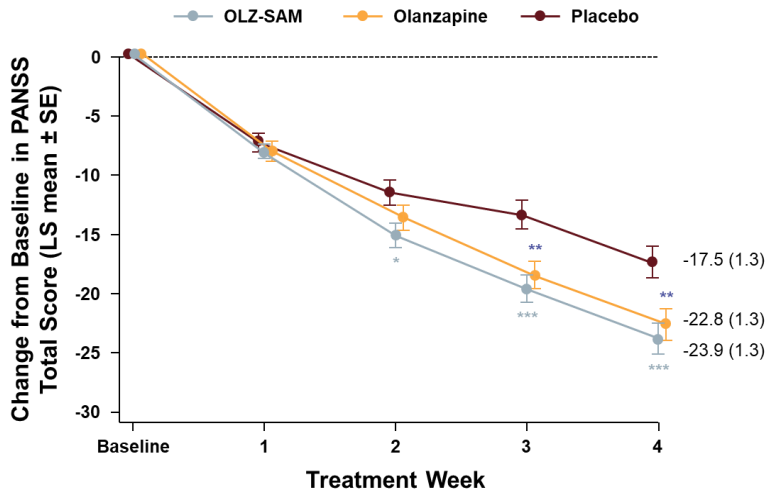
Lumateperone prescribing information. Drugs@FDA: FDA Approved Drugs. Accessed March 6, 2024. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/209500Orig1s000TOC.cfm.
Citrome L. *J Clin Psychiatry*. 2023;84(2):22r14631; Correll CU, et al. *JAMA Psychiatry*. 2020;77(4):349-358; Satlin A, et al. *Schizophr Bull.* 2020;46(Suppl 1):S214.

Two Newer Options and Information About Weight Gain

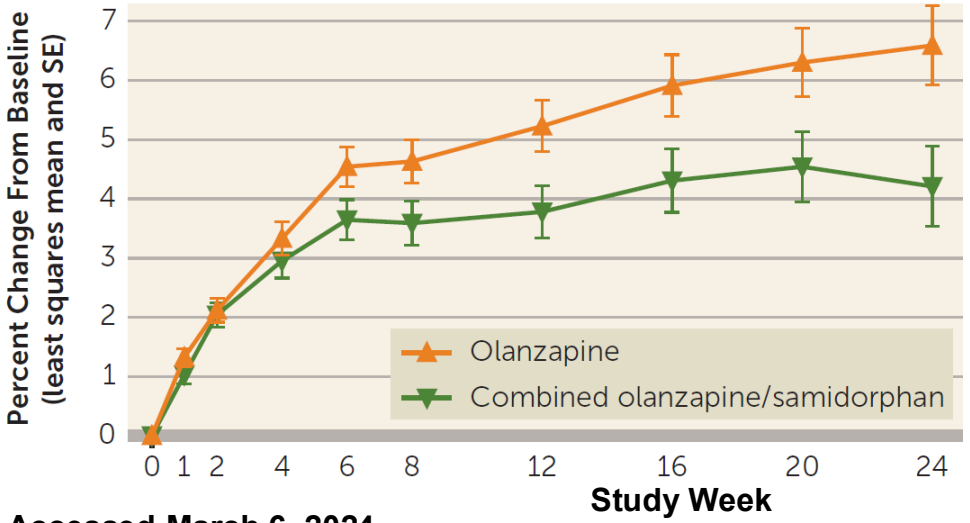
Olanzapine-Samidorphan

- **Olanzapine-samidorphan** (initially approved in May 2021) is a combination of olanzapine (available for 25+ years) and samidorphan, an opioid receptor antagonist
  - Mitigates **at least some** of the weight gain expected with the use of olanzapine alone
  - Patients taking olanzapine-samidorphan combination experienced a 50% lower risk of gaining ≥7% or ≥10% of body weight relative to olanzapine at week 24

Change in PANSS Total Score in Acute Study



Change in Body Weight in 24-Week Study



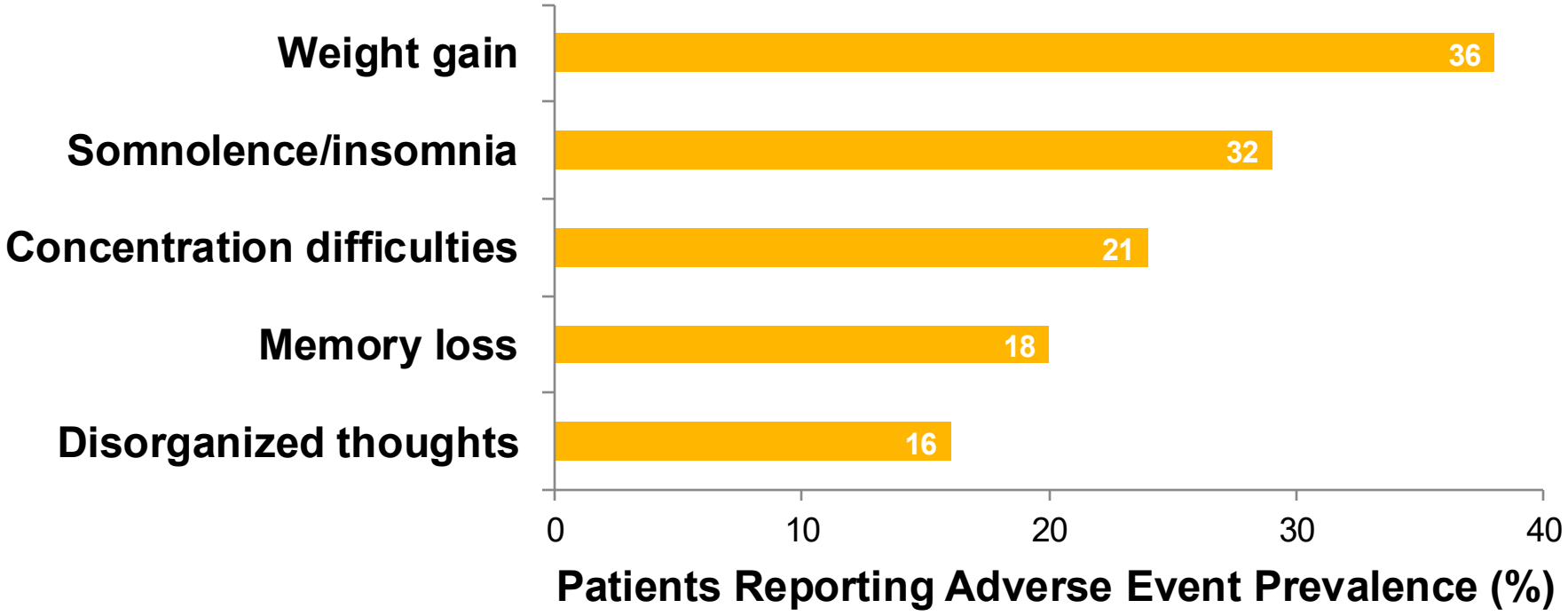
Olanzapine-samidorphan prescribing information. Drugs@FDA: FDA Approved Drugs. Accessed March 6, 2024. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/213378Orig1Orig2s000TOC.cfm;
Citrome L. *Current Psychiatry*. 2022;21(1):35-40; Potkin SG, et al. *J Clin Psychiatry*. 2020;81(2):19m12769; Correll CU, et al. *Am J Psychiatry*. 2020;177(12):1168-1178.

Clinical Implications of Adverse Effects

- Impact on quality of life
- Patient perspective
- Provider perspective

Adverse Events Considered by Patients to Have Most Negative Effect on Quality of Life

Patients rated metabolic consequences of medication to contribute to morbidity, low quality of life, and low satisfaction with care



The UNITE survey was an internet-based multinational survey with 1155 respondents with schizophrenia from 11 countries

McIntyre RS. *J Clin Psychiatry*. 2009;70(Suppl 3):5-11.

Eye of the Beholder: Reverberations from Side Effects

Influencing patient response →

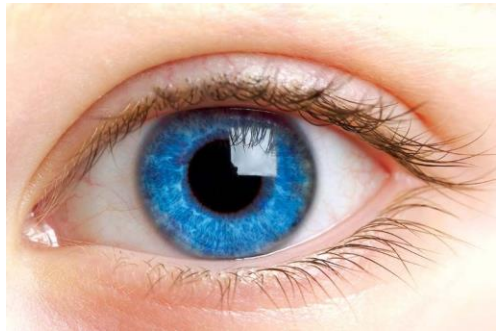
Side Effect Appears

Subjective Distress

Adherence Impact

Objective Severity

Safety and Risk



Influencing clinician response →

Weiden PJ, et al. *J Clin Psychiatry*. 2007;68(Suppl 6):14-23.

Eye of the Beholder: Reverberations from Side Effects

Influencing patient response →

Low energy/sedation is subjective and influences patient

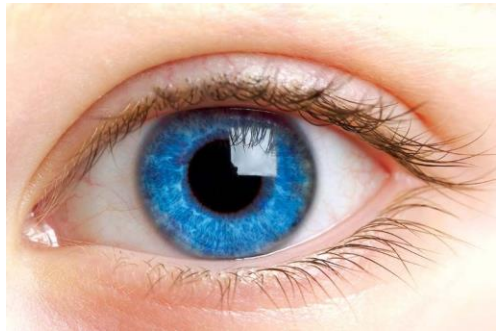
Side Effect Appears

Subjective Distress

Adherence Impact

Objective Severity

Safety and Risk

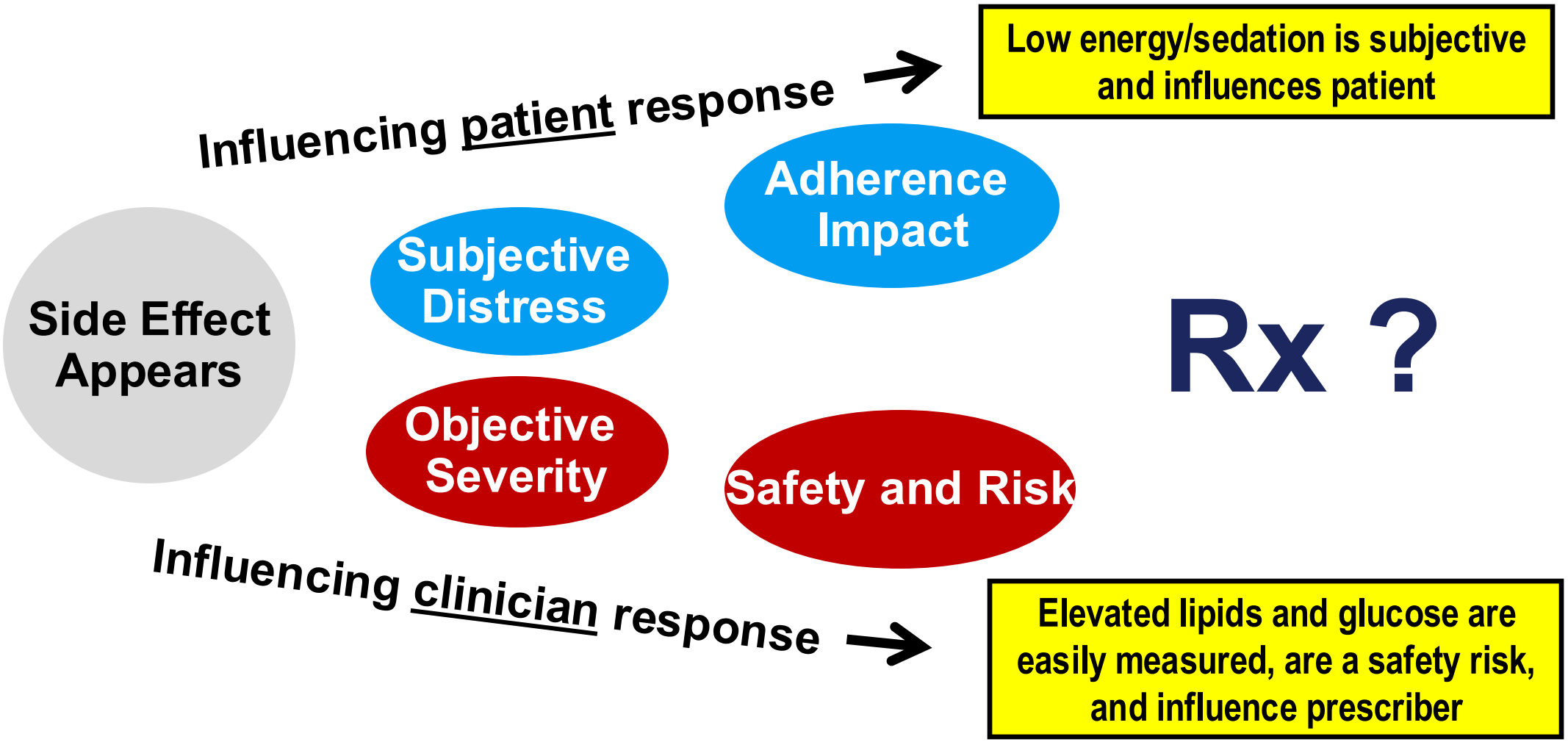


Influencing clinician response →

Elevated lipids and glucose are easily measured, are a safety risk, and influence prescriber

Weiden PJ, et al. *J Clin Psychiatry*. 2007;68(Suppl 6):14-23.

Eye of the Beholder: Reverberations from Side Effects



Weiden PJ, et al. *J Clin Psychiatry*. 2007;68(Suppl 6):14-23.

Key Learning Points

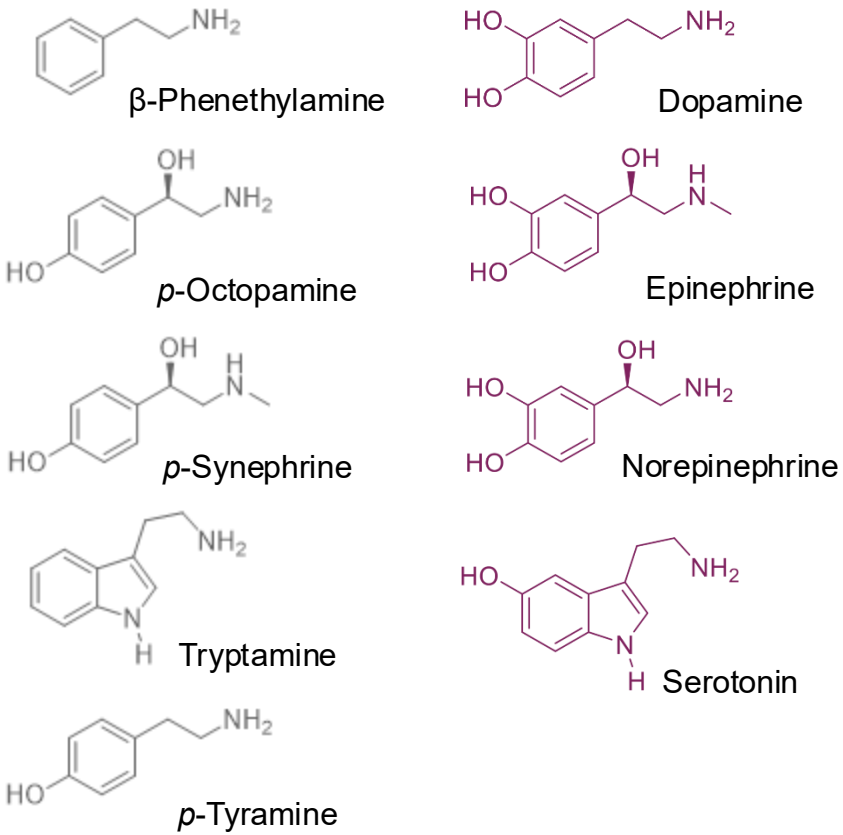
- First generation antipsychotics are limited by drug-induced movement disorders in general
- Second generation antipsychotics are limited by weight gain, sedation, and akathisia
- However, there is much heterogeneity in tolerability profiles
- New options offer differing tolerability profiles

Indirect Modulation of Dopamine Activity via Non-D2 Receptors

What Are Trace Amines and TAARs?

- **Trace amines** (TAs):
  - Endogenous chemical messengers, referred to as ”false neurotransmitters” because they are not released from synaptic vesicles when the neuron fires
    - Serve as true neurotransmitters in invertebrates
  - Structurally similar to monoamine neurotransmitters, eg, dopamine, norepinephrine, serotonin
    - Expressed at levels at least 100-fold lower than corresponding neurotransmitters
    - Present in food (significant amounts in seafood, cured meats, wine, cheese, and chocolate)
    - Produced by human microbiota
- **Trace amine-associated receptors** (TAARs):
  - In 2001, TAs were found to selectively activate a family of receptors called TAARs that are located in the CNS and periphery.
    - TAARs are predominantly intracellular receptors that modulate neurotransmission of dopamine, serotonin and glutamate.
    - Most studied is TAAR1

Traditional TAs **Monoamine Neurotransmitters**

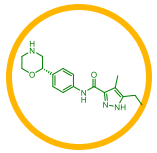


Adapted from Dedic N, et al. Int J Mol Sci. 2021;22(24):13185

Nair PC, et al. Mol Psychiatry. 2022;27(1):88-94; Gainetdinov RR, et al. Pharmacol Rev. 2018;70(3):549-620; Dedic N, et al. Int J Mol Sci. 2021;22(24):13185; Dodd S, et al. Neurosci Biobehav Rev. 2021;120:537-541.

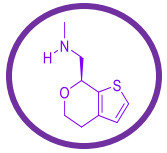
Investigational TAAR1 Compounds in Clinical Trials

- Two investigational TAAR1 compounds reached Phase 2/3 clinical trials for the treatment of schizophrenia and other psychiatric conditions
- Each have different receptor pharmacology:



Ralmitaront*: TAAR1 partial agonist

  - 2 recently-terminated Phase 2 trials in schizophrenia and schizoaffective disorder (acute exacerbation, and augmentation for negative symptoms)



Ulotaront: TAAR1 agonist with 5-HT_{1A} agonist activity

  - Phase 2 complete in schizophrenia; Phase 3 program: 2 negative trials
  - adjunctive MDD and GAD clinical trials ongoing

*NOTE: Limited information about ralmitaront available publicly.

5-HT_{1A}=serotonin receptor type 1A; GAD=generalized anxiety disorder; MDD=major depressive disorder; TAAR1=trace amine associated receptor 1.

Dedic N, et al. *J Pharmacol Exp Ther*. 2019;371(1):1-14; Dedic N, et al. *Int J Mol Sci*. 2021;22(24):13185; https://clinicaltrials.gov/search?term=ralmitaront; Koblan KS, et al. *N Engl J Med.* 2020;382:1497-1506; Correll CU, et al. *NPJ Schizophr.* 2021;7(1):63.

Emraclidine Phase 2B EMPOWER Studies vs Phase 1B Study

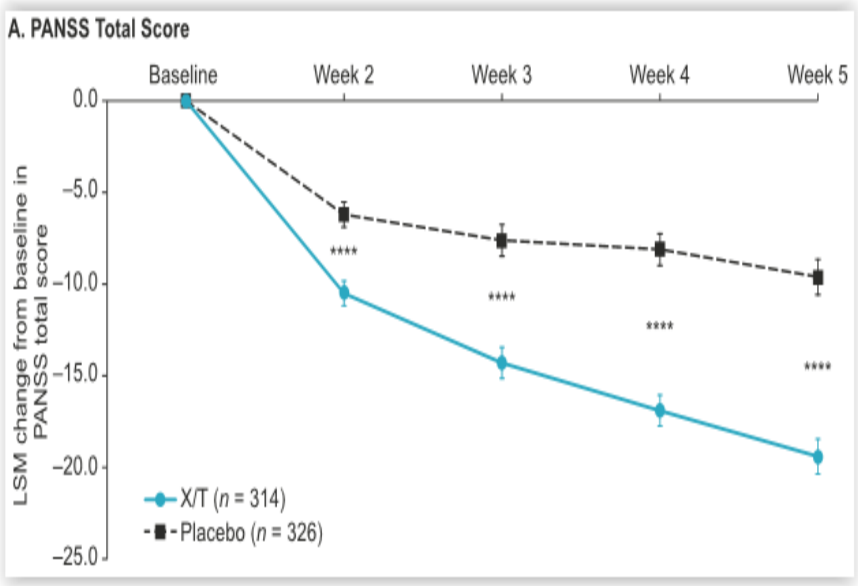
	EMPOWER-1			EMPOWER-2		
	Placebo (N= 127)	**Emraclidine 10mg QD (N = 125)**	**Emraclidine 30mg QD (N = 127)**	**Placebo (N = 128)**	**Emraclidine 15mg QD (N = 122)**	**Emraclidine 30mg QD (N = 123)**
Baseline (SD)	98.3 (8.2)	97.6 (7.6)	97.9 (7.9)	97.4 (8.2)	98.0 (8.5)	97.2 (7.8)
LS Mean (95% CI)	**-13.5** (-17.0, -10.0)	**-14.7** (-18.1, -11.2)	**-16.5** (-20.0, -13.1)	**-16.1** (-19.4, -12.8)	**-18.5** (-22.0, -15.0)	**-14.2** (-17.6, -10.8)
Phase 1B Study	**Placebo (N= 27)**	**Emraclidine 30mg QD (N = 27)**	**Emraclidine 20mg BID (N = 27)**			
Baseline (SD)	93 (8.8)	93 (7.3)	97 (7.9)			
LS Mean (SE)	**-6.8 (3.8)**	**-19.5 (3.9)**	**-17.9 (3.9)**			

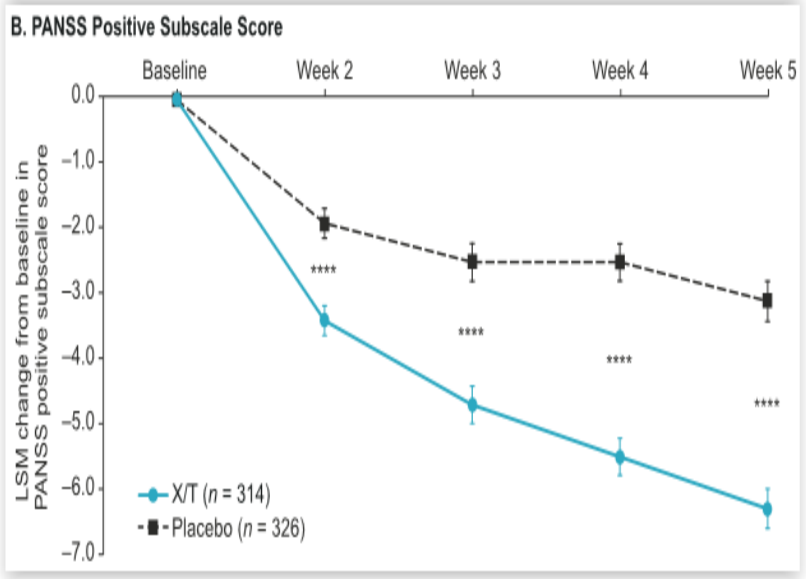
In the EMPOWER phase 2B trials, emraclidine was well-tolerated with a safety profile comparable to that observed in the Phase 1b trial.
The most commonly reported adverse events in EMPOWER-1 and EMPOWER-2, respectively, were:

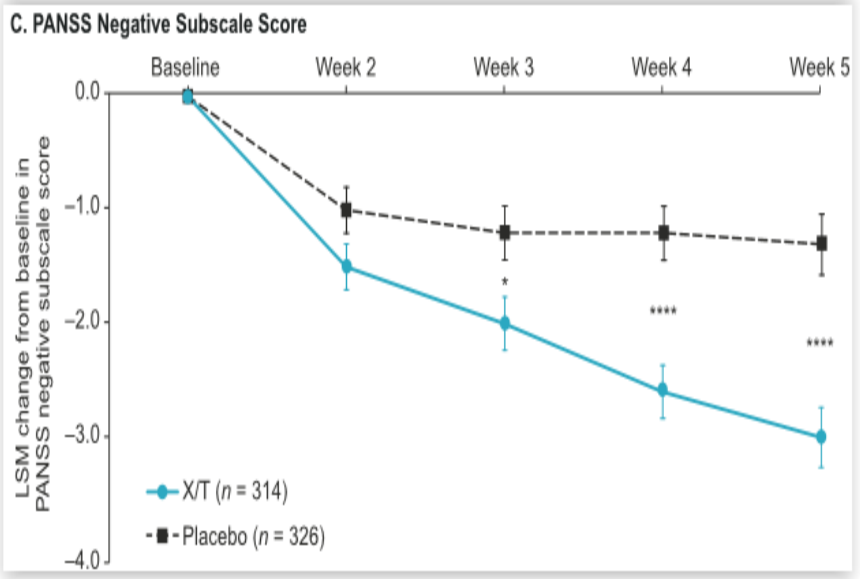
- Headache (9.4% and 10.8% in placebo, 14.1% in EMPOWER-1 10mg and 14.6% in EMPOWER-2 15mg, and 13.2% and 13.0% in 30mg),
- Dry mouth (2.3% and 0.8% in placebo, 3.9% in EMPOWER-1 10mg and 0.8% in EMPOWER-2 15mg, and 9.3% and 5.3% in 30mg), and
- Dyspepsia (3.1% and 1.5% in placebo, 3.9% in EMPOWER-1 10mg, and 3.1% in EMPOWER-2 15mg, and 7.8% and 2.3% in 30mg).

https://news.abbvie.com/2024-11-11-AbbVie-Provides-Update-on-Phase-2-Results-for-Emraclidine-in-Schizophrenia, accessed 11.11.2024; Krystal JH, et al. Lancet. 2022 Dec 17;400(10369):2210-2220.

EMERGENT 1-3 Trials: Pooled Results Across PANSS Total, Positive, and Negative Scores







XT: xanomeline-trospium chloride

Kaul I et al. Schizophrenia (Heidelb). 2024 Nov 2;10(1):102.
Pooled data from:
Brannan SK, et al. *N Engl J Med.* 2021;384(8):717-726; Karuna Therapeutics. Data on file; Kaul I, et al. *Lancet.* 2024;403(10422):160-170; Kaul I, et al. *JAMA Psychiatry.* 2024; 81(8):749-756.

EMERGENT 1-3 Trials: Treatment Emergent Adverse Events From Baseline to Week 5

Variable	X/T (n = 340)	Placebo (n = 343)
Any treatment-related AE, n (%)	176 (51.8)	101 (29.4)
Serious treatment-related AE, n (%)	1 (0.3)[a]	0
Treatment-related AEs reported in ≥2% of people in the xanomeline/trospium group and at least twice the placebo rate, n (%)		
Nausea	58 (17.1)	11 (3.2)
Constipation	51 (15.0)	18 (5.2)
Dyspepsia	41 (12.1)	8 (2.3)
Vomiting	37 (10.9)	3 (0.9)
Hypertension[b]	20 (5.9)	4 (1.2)
Dry mouth	17 (5.0)	5 (1.5)
Tachycardia	16 (4.7)	7 (2.0)
Abdominal pain	16 (4.7)	5 (1.5)
Dizziness	15 (4.4)	6 (1.7)
Gastroesophageal reflux disease	9 (2.6)	1 (0.3)
Vision blurred	8 (2.4)	1 (0.3)

[a]Psychotic disorder (n = 1).
[b]Hypertension is the MedDRA preferred term, defined as a resting mean pulmonary artery pressure ≥25 mm Hg, and is not necessarily reflective of clinical hypertension.
Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities, X/T = xanomeline/trospium.

Kaul I et al. J Clin Psychiatry. 2025 Feb 26;86(1):24m15497.

EMERGENT 1-3 Trials: Movement Disorder Adverse Events From Baseline to Week 5

	X/T (n = 340)	Placebo (n = 343)
EPS TEAEs related to trial medication		
Any related EPS TEAE,[a] n (%)	5 (1.5)	1 (0.3)
Akathisia	2 (0.6)	1 (0.3)
Dyskinesia	1 (0.3)	0
Dystonia	1 (0.3)	0
Extrapyramidal disorder	1 (0.3)	0
Movement scales scores change from baseline		
SAS total score mean change from baseline to week 5 ±SD	−0.1 ± 0.62	−0.1 ± 0.63
BARS total score mean change from baseline to week 5 ±SD	−0.1 ± 0.90	−0.1 ± 0.84
AIMS total score of items 1–7 mean change from baseline to week 5 ±SD	0.0 ± 0.66	0.0 ± 0.15

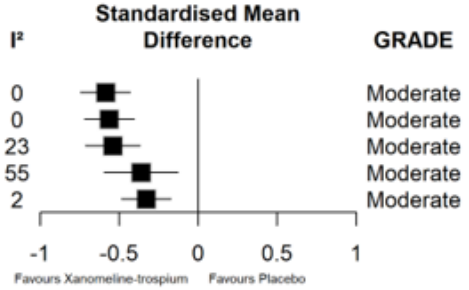
[a]Related EPS TEAEs included any new onset of dystonia, dyskinesia, akathisia, or extrapyramidal disorder reported at any time after the first dose of trial medication and that was deemed related to trial medication by the investigator.

Abbreviations: AIMS = Abnormal Involuntary Movement Scale, BARS = Barnes Akathisia Rating Scale, EPS = extrapyramidal symptom, SAS = Simpson-Angus Scale, TEAE = treatment-emergent adverse event, X/T = xanomeline/trospium.

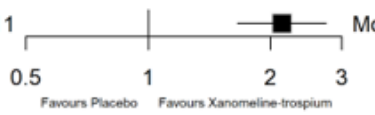
Kaul I et al. J Clin Psychiatry. 2025 Feb 26;86(1):24m15497.

EMERGENT 1-3 Trials: Meta-Analyzed Efficacy and Tolerability Outcomes

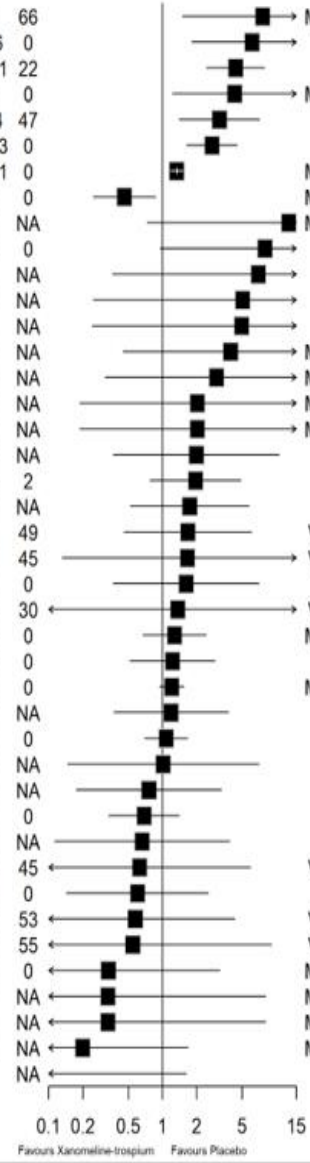
Outcome	N Studies	SMD (95% CI)	P-value	I²	GRADE
PANSS positive symptom subscore	3	-0.59 (-0.75;-0.43)	<0.0001	0	Moderate
PANSS total score	3	-0.56 (-0.72;-0.40)	<0.0001	0	Moderate
CGI-S	3	-0.54 (-0.71;-0.37)	<0.0001	23	Moderate
PANSS Marder negative symptom subscore	3	-0.36 (-0.60;-0.13)	0.0025	55	Moderate
PANSS negative symptom subscore	3	-0.33 (-0.49;-0.17)	<0.0001	2	Moderate



Outcome	N Studies	RR (95% CI)	P-value	I²	GRADE
Response	3	2.13 (1.66;2.75)	<0.0001	11	Moderate



Outcome	N Studies	RR (95% CI)	P-value	I²	GRADE
Vomiting	3	7.60 (1.50; 38.57)	0.014	66	Moderate
Hypertension	2	6.13 (1.81; 20.76)	0.0036	0	High
Nausea	3	4.39 (2.44; 7.87)	<0.0001	22	High
Dry mouth	2	4.31 (1.23; 15.11)	0.022	0	Moderate
Dyspepsia	3	3.16 (1.41; 7.12)	0.0054	47	High
Constipation	3	2.72 (1.63; 4.55)	0.00013	0	High
Any TEAE	3	1.33 (1.18; 1.51)	<0.0001	0	Moderate
Weight gain (≥7%)	3	0.46 (0.25; 0.87)	0.016	0	Moderate
Vision blurred	1	12.90 (0.73;226.54)	0.08	NA	Moderate
GERD	2	7.94 (0.95; 66.30)	0.056	0	Low
Salivary hypersecretion	1	6.94 (0.36;133.08)	0.2	NA	Low
Decreased appetite	1	5.06 (0.25;103.84)	0.29	NA	Low
Suicidal ideation	1	4.96 (0.24;102.30)	0.3	NA	Low
Heart rate increased	1	3.97 (0.45; 35.01)	0.21	NA	Moderate
Orthostatic hypotension	1	2.98 (0.31; 28.23)	0.34	NA	Moderate
Hyperhidrosis	1	2.02 (0.19; 21.91)	0.56	NA	Moderate
Increased GGT (>2x ULN)	1	2.02 (0.19; 21.91)	0.56	NA	Moderate
Abdominal pain	1	1.98 (0.37; 10.64)	0.42	NA	Low
Dizziness	2	1.95 (0.78; 4.90)	0.15	2	Low
Abdominal discomfort	1	1.74 (0.52; 5.78)	0.37	NA	Low
Diarrhea	3	1.67 (0.46; 6.05)	0.44	49	Very low
Akathisia	2	1.66 (0.13; 20.90)	0.7	45	Very low
Serious AE	3	1.61 (0.37; 7.02)	0.53	0	Low
Increased ALT (>3x ULN)	2	1.36 (0.10; 18.90)	0.82	30	Very low
Intolerability-related discontinuation	3	1.27 (0.67; 2.41)	0.46	0	Moderate
Somnolence	2	1.22 (0.52; 2.89)	0.65	0	Low
All-cause discontinuation	3	1.20 (0.94; 1.55)	0.15	0	Moderate
Anxiety	1	1.19 (0.37; 3.80)	0.77	NA	Low
Headache	3	1.07 (0.69; 1.66)	0.75	0	Low
Sedation	1	1.01 (0.15; 7.02)	0.99	NA	Low
Increased weight	1	0.76 (0.17; 3.29)	0.71	NA	Low
Insomnia	3	0.69 (0.34; 1.41)	0.31	0	Low
Back pain	1	0.66 (0.11; 3.89)	0.65	NA	Low
Tachycardia	2	0.63 (0.07; 5.94)	0.69	45	Very low
Severe AE	2	0.60 (0.14; 2.52)	0.49	0	Low
Agitation	2	0.58 (0.08; 4.32)	0.59	53	Very low
Psychotic disorder	2	0.55 (0.03; 9.07)	0.67	55	Very low
Increased AST (>3x ULN)	2	0.33 (0.04; 3.18)	0.34	0	Moderate
Appendicitis	1	0.33 (0.01; 8.04)	0.5	NA	Moderate
Schizophrenia	1	0.33 (0.01; 8.04)	0.5	NA	Moderate
Toothache	1	0.20 (0.02; 1.67)	0.14	NA	Moderate
Arthralgia	1	0.09 (0.01; 1.61)	0.1	NA	High



Fabiano N et al. Eur Neuropsychopharmacol. 2024 Dec 25;92:62-73.

ARISE Trial: Xanomeline-Trospium (XT) vs Placebo: LS Mean Change (LE) From Baseline to Week 6

	Outcome	*XT* + APD	Placebo + APD	LSMD (95% CI)	p-value
mITT Population, N		190	196		
Primary Endpoint	Change in PANSS Total Score	-14.3 (1.01)	-12.2 (0.98)	-2.0 (-4.5, 0.5)	0.11
Key Secondary Endpoint	Change in PSP Score	5.3 (0.75)	5.9 (0.73)	-0.6 (-2.4, 1.2)	0.52*
Secondary Endpoint	Change in CGI-S	-0.6 (0.06)	-0.5 (0.06)	-0.1 (-0.3, 0.04)	0.14*
Post-Hoc Subgroup Analysis					
Risperidone	Change in PANSS Total Score	(N=60) -11.3 (2.13)	(N=69) -12.3 (2.10)	1.1 (-3.7, 5.9)	0.66*
Non-Risperidone	Change in PANSS Total Score	(N=130) -15.1 (1.18)	(N=127) -11.7 (1.17)	-3.4 (-6.3, -0.5)	0.03*

APD = Antipsychotic background drug; PANSS = Positive and Negative Syndrome Scale; PSP = Personal and Social Performance Scale; CGI-S = Clinical Global Impressions Severity Scale; mITT = modified intent-to-treat; SE = Standard Error; LSMD = Least Squares Mean Difference; Non-Risperidone group includes paliperidone, aripiprazole, ziprasidone, lurasidone and cariprazine.
*p-value is nominal, not adjusted for multiplicity.

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, accessed 04.22.2025

M4 Positive Allosteric Modulator Emraclidine Phase 1B Study: Efficacy Results in Change from Baseline to Week 6

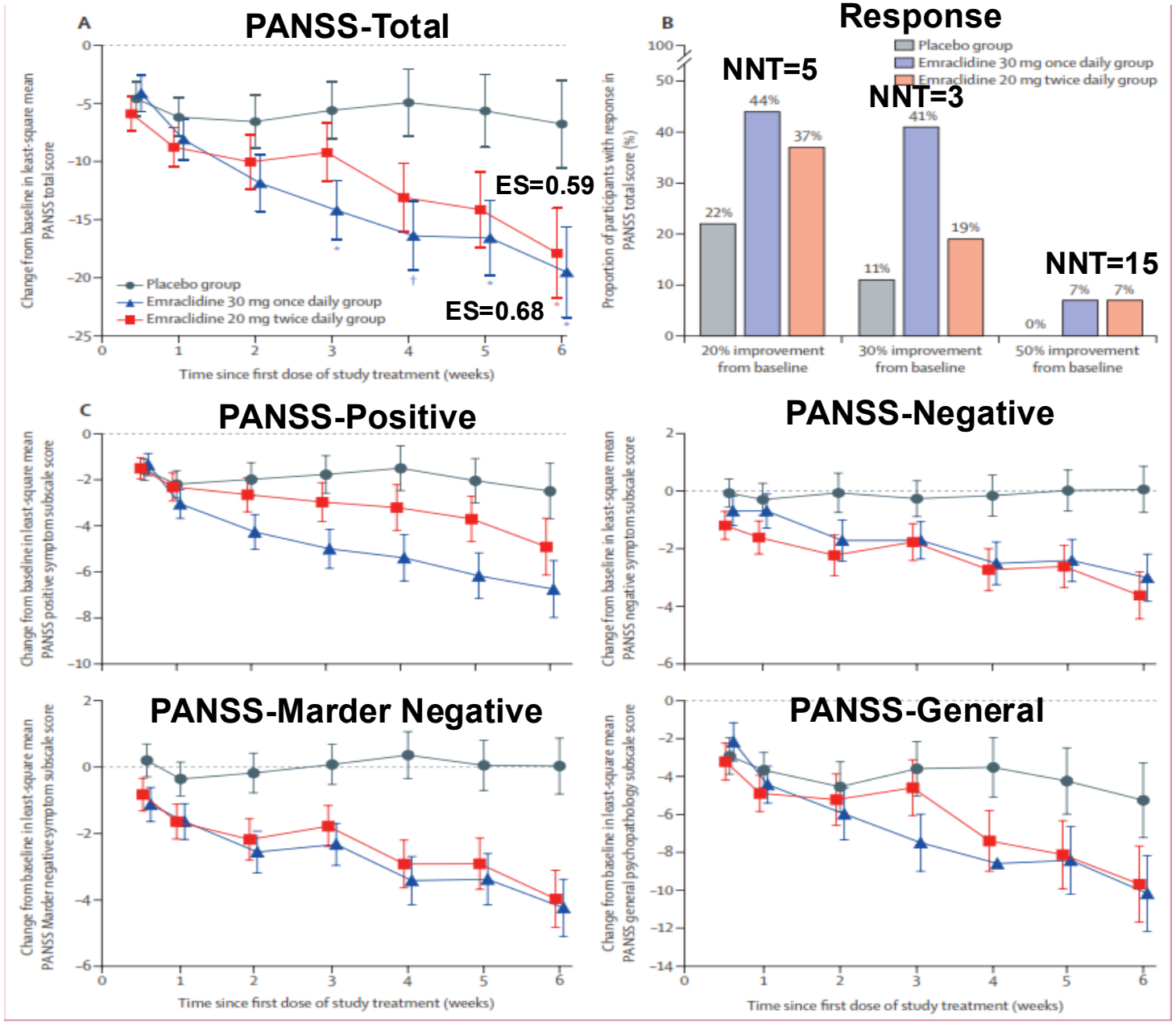


Figure 3: **PANSS scores in participants in part B**
(A) Change in mean PANSS total over time. (B) Proportion of participants with a response in PANSS score. (C) Change in PANSS subscale scores over time. Error bars show SE. PANSS=Positive and Negative Syndrome Scale. *Nominal p<0·05. †Nominal p<0·01.

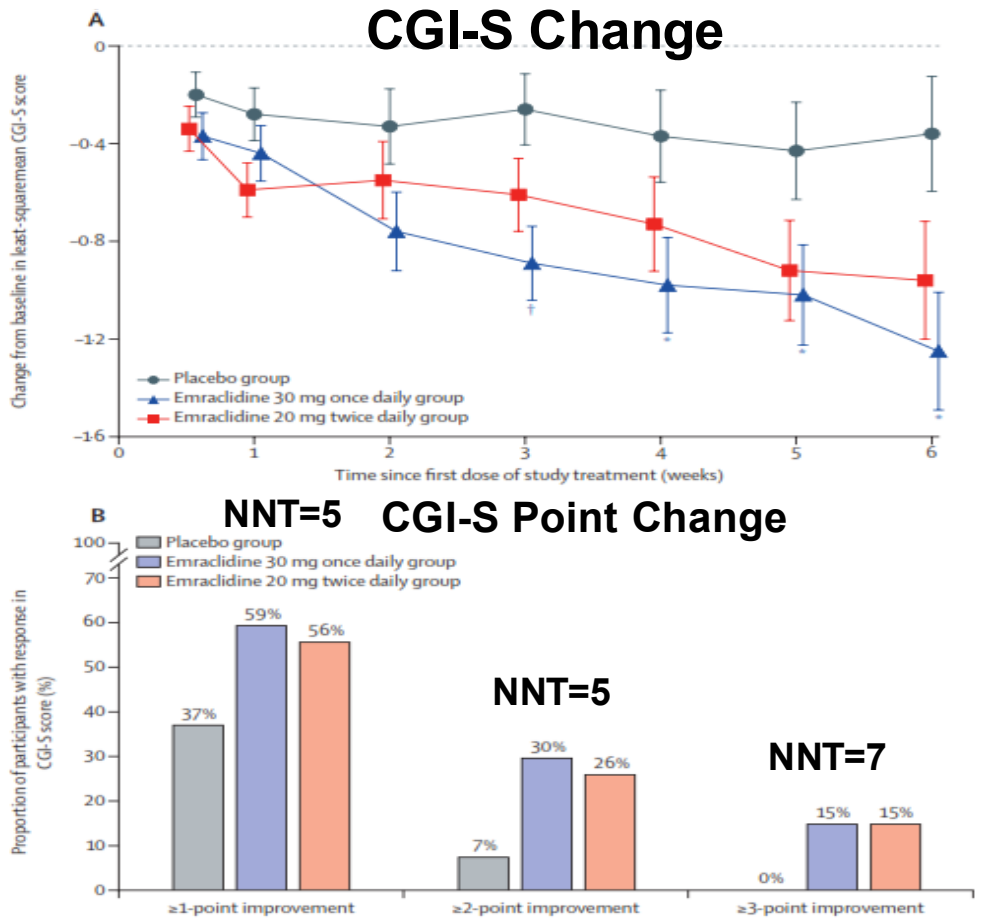


Figure 4: **CGI-S scores in participants in part B**
(A) Change in mean CGI-S score over time. (B) Proportion of participants with a response in CGI-S score. Error bars show SE. CGI-S=Clinical Global Impression of Severity. *Nominal p<0·05. †Nominal p<0·01.

Krystal JH, et al. Lancet. 2022 Dec 17;400(10369):2210-2220.

M4 Positive Allosteric Modulator Emraclidine: Adverse Event Results in Part B of a Phase 1B Study

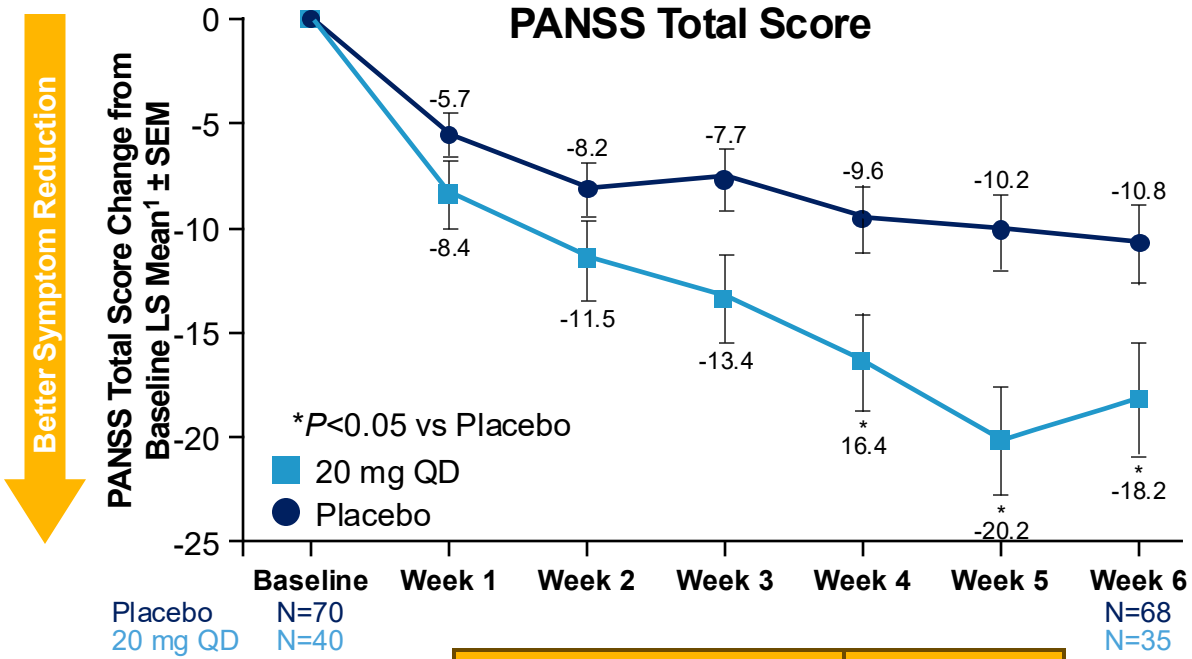
	Placebo group (n=27)	Emraclidine 30 mg once daily group (n=27)	Emraclidine 20 mg twice daily group (n=27)
Any adverse event	14 (52%)	14 (52%)	15 (56%)
Adverse events related to study drug	10 (37%)	7 (26%)	12 (44%)
Adverse events of special interest	3 (11%)	2 (7%)	4 (15%)
Serious adverse events	0	2 (7%)	1 (4%)
Adverse events leading to study discontinuation	0	2 (7%)	1 (4%)
Adverse events that occurred in at least 5% of participants receiving emraclidine where percent incidence was greater with emraclidine than with placebo			
Headache	7 (26%)	8 (30%)	7 (26%)
Nausea	1 (4%)	2 (7%)	2 (7%)
Back pain	1 (4%)	2 (7%)	1 (4%)
Blood creatinine phosphokinase increased	0	1 (4%)	2 (7%)
Dizziness	0	1 (4%)	2 (7%)
Dry mouth	0	3 (11%)	0
Somnolence	0	1 (4%)	2 (7%)

Data are n (%).

Krystal JH, et al. Lancet. 2022 Dec 17;400(10369):2210-2220.

Once-Daily M4 Receptor Agonist (NBI-111568) Significantly Reduced PANSS Total Score at Week 6

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



Placebo: -10.8 pts NBI-'568 20 mg: -18.2 pts*	Effect Size d=0.61

AEs Occurring in ≥ 5% of NBI111758620 Group		
	Placebo N=70	NBI-'568 20 mg N=40
Somnolence	3%	13%
Dizziness	1%	13%
Headache	20%	3%
Nausea	3%	5%
Constipation	3%	5%
Discontinuation due to AEs	5% across all dose arms vs. 4.3% for placebo	

Few drug-induced movement disorders reported
Weight change was similar to placebo

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

Two Phase 3 studies in schizophrenia are in progress and expected to complete Q4 2027

QD = once daily; BID = twice daily; LS = Least Squares; SEM = Standard Error of the Mean; TE = treatment-emergent; AE =adverse event; D/C = discontinuations.

Nash A, et al. Once-Daily NBI-1117568, a Highly Selective Orthosteric M 4 Muscarinic Receptor Agonist, Demonstrates Meaningful Improvements in PANSS Total Score and Is Well Tolerated in Adults With Schizophrenia: Phase 2 Study Results. Presented at the ASCP Annual Meeting May 27-30, 2025; Scottsdale, AZ.https://clinicaltrials.gov/study/NCT06963034. Accessed 8-20–25.
https://clinicaltrials.gov/study/NCT07105098. Accessed 8-20-25.

Other Muscarinic Receptor Modulators in Development

Clinical					
Company	**Compound name**	**Target**	**Mode of action**	**Indication**	**Stage of development**
Karuna Therapeutics (recently acquired by BMS)	KarXT	M_1/M_4	Muscarinic Agonists + peripherally restricted mAChR antagonist	SCZ and AD psychosis	Phase 3
AbbVie (previously Cerevel Therapeutics)	Emraclidine	M_4	PAM	SCZ	Phase 2
Neurocrine Biosciences	NBI-1117568	M_4	Agonist	SCZ	Phase 2
Anavex Life Sciences	ANAVEX3-71	Sigma $1/M_1$	Agonist/PAM	SCZ and AD cognition	Phase 2
Neurocrine Biosciences	NBI-1117570	M_1/M_4	Agonist	SCZ	Phase 1
MapLight Therapeutics	ML-007	M_1/M_4	Muscarinic Agonists + peripherally restricted mAChR antagonist	SCZ and AD	Phase 1
Neumora Therapeutics	NMRA-266	M_4	PAM	SCZ	Phase 1
Pre-clinical					
Company	**Compound Name**	**Target**	**Mode of Action**	**Indication**	
Addex Therapeutics	–	M_4	PAM	SCZ	
NeuroSolis	NSX-0527	M_1/M_4	Agonist	SCZ and AD	
	NSX-0559				
NeuShen Therapeutics	NS-136	M_4	PAM	SCZ	
Cerevel Therapeutics	–	M_4	Agonist	SCZ and AD	
Neurocrine Biosciences	NBI-1117569	M_4	Agonist	SCZ	
Suven Life Sciences	SUVN-17016031	M_1	PAM	PD dementia	
	SUVN-L8203032	M_4	PAM	SCZ	
	SUVN-16107	M_1	PAM	Cognition	
	SUVNI-1307014	M_1	PAM	AD	
Asceneuron	–	M_1	Agonist	Frontotemporal dementia	

AD, Alzheimer's disease; mAChR, muscarinic acetylcholine receptor; PAM, positive allosteric modulator; PD, Parkinson's disease; SCZ, schizophrenia.

Yohn SE, et al.. Front Psychiatry. 2024 Oct4;15:1421554.

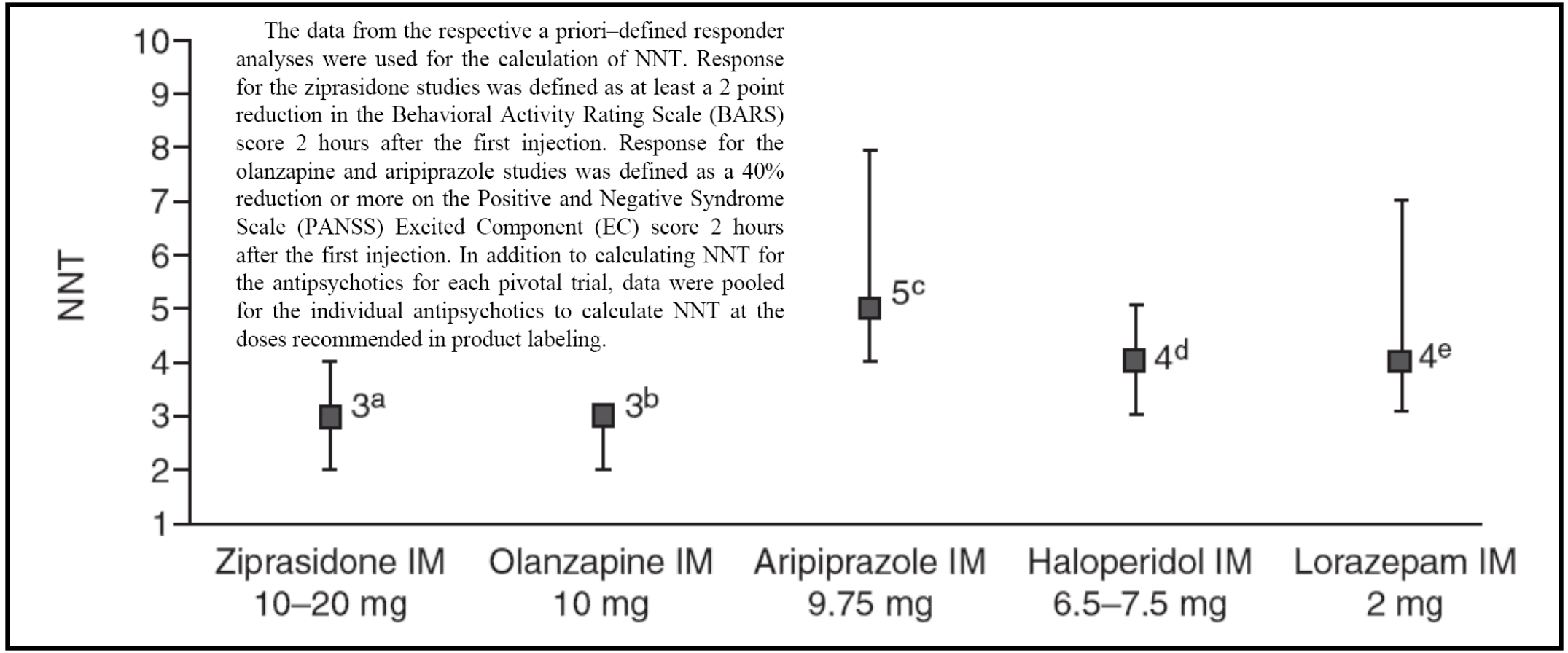
Formulations Other Than Oral Pills

Diverse Formulations Other Than Pills

- Fast-acting IM olanzapine and ziprasidone for agitation
- Inhaled loxapine powder for agitation
- Long-Acting Injectable (LAIs)
- Sublingually absorbed asenapine
- Transdermal asenapine

How Do IM Treatments for Acute Agitation Compare Against Placebo?

Responders at 2 hours as defined a priori by each manufacturer



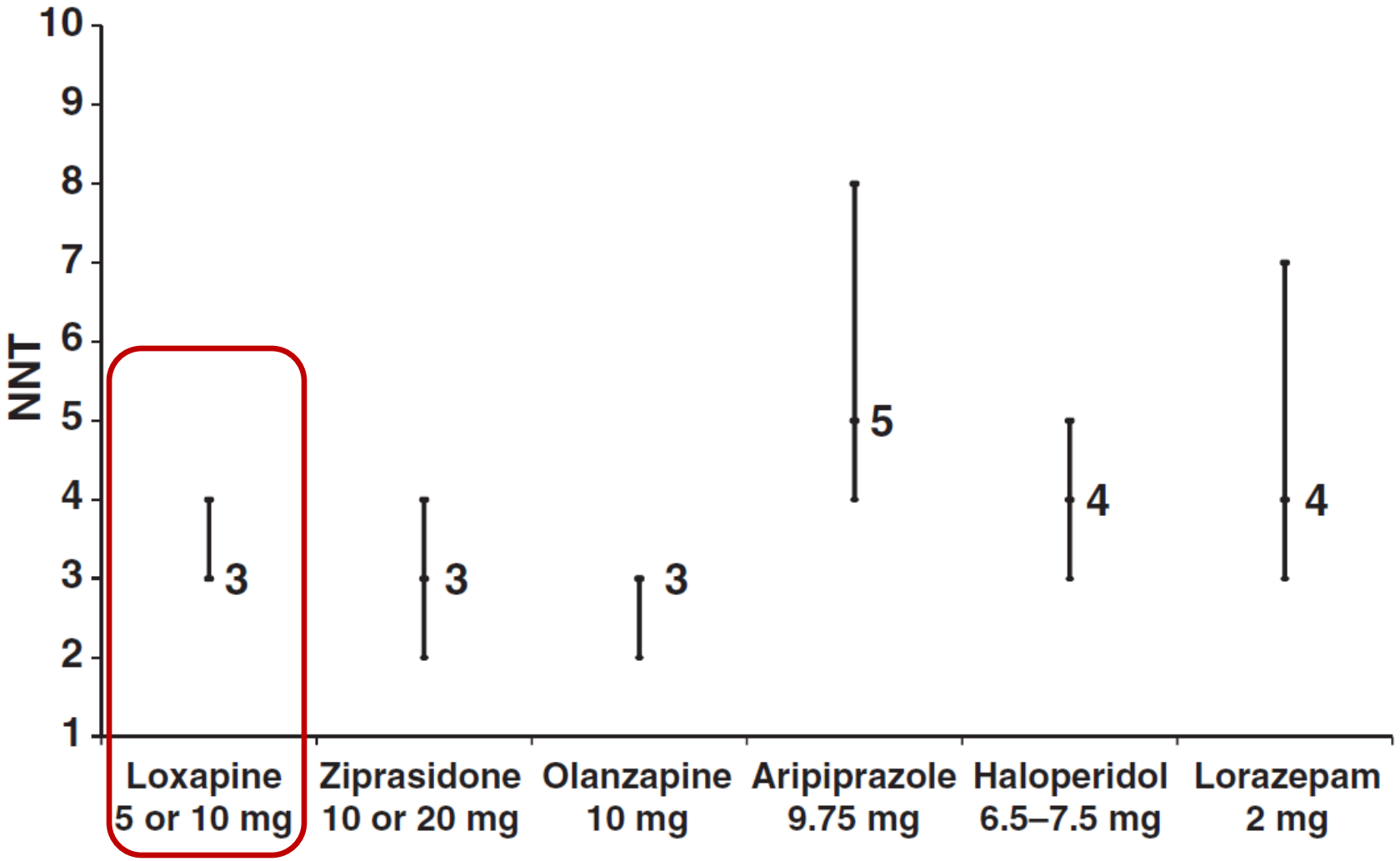
Citrome L. *J Clin Psychiatry*. 2007;68(12):1876-1885.

Inhaled Loxapine Powder

- Indicated for the acute treatment of agitation associated with schizophrenia or bipolar I disorder in adults, as established in RCTs
  - Schizophrenia (2; one was a Phase 3 pivotal study)
  - Bipolar mania (1)
- Rapid onset of efficacy
- Dosage 10 mg; only a single dose within a 24-hour period administered only by a health care professional in an enrolled health care facility
- Favorable EPS profile
- **Cautions**: Bronchospasm – REMS (Risk Evaluation and Mitigation Strategy) requirement!

Citrome L. *Current Psychiatry*. 2013;12(2):31-36. Lesem MD, et al. *Br J Psychiatry*. 2011;198(1):51-58.

NNT vs Placebo for Response at 2 Hours?



Citrome L. *Int J Clin Pract*. 2011;65(3):330-340.

Formulations of Long-Acting Injectable Antipsychotics Approved in the United States

- **First-generation antipsychotics**
  - Haloperidol decanoate
  - Fluphenazine decanoate
- **Second-generation antipsychotics**
  - Risperidone- or paliperidone-containing formulations
    - Risperidone microspheres (2 products, each administered every 2 weeks)
    - Risperidone subcutaneous (2 products, one administered every month*, the other every month or every 2 months)
    - Risperidone ISM*
    - Paliperidone palmitate (2 products, one administered every month, the other administered every month, every 3 months, or every 6 months)
  - Aripiprazole-containing formulations
    - Aripiprazole monohydrate (administered every month or every 2 months)
    - Aripiprazole lauroxil (administered every month, every 6 weeks, or every 2 months)
  - Olanzapine pamoate (administered every 2 weeks or every month)

*Discontinued or never commercialized in the US

Citrome L. CNS Spectr. 2025;30(1):e73.

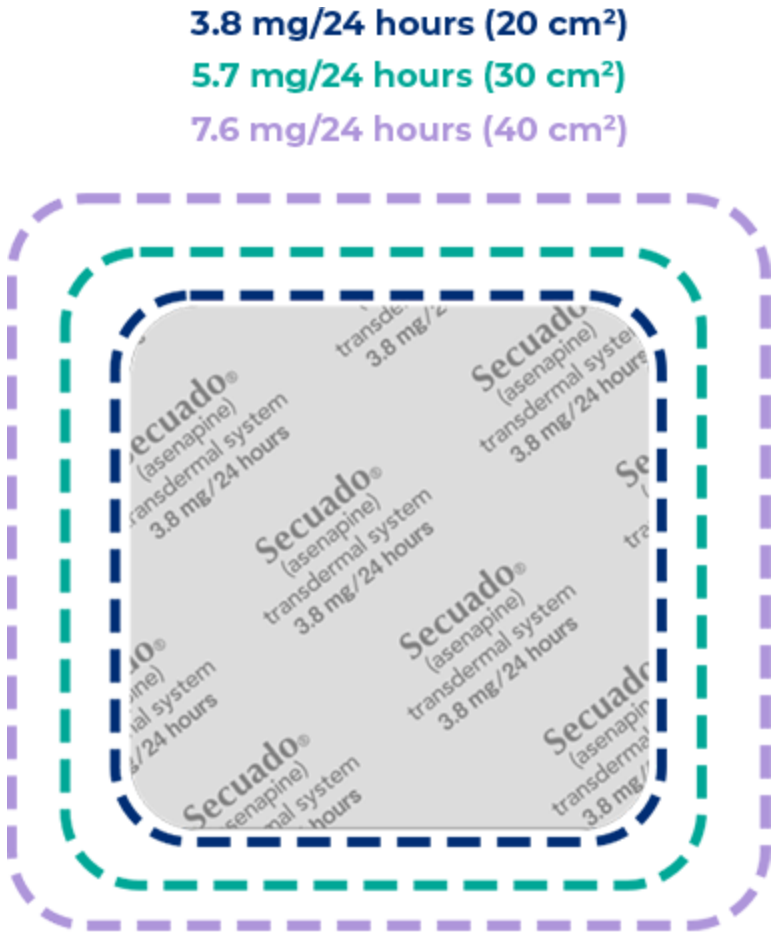
Sublingual Asenapine

- Approved by the FDA in 2009 for treatment of
  - Acute schizophrenia
  - Acute mania or mixed episodes associated with bipolar I disorder
- Administered sublingual BID, with no food or liquid for 10 minutes after administration in order to maximize bioavailability – not absorbed when swallowed
- "The only way to cheek it is to swallow it"
  - Drinking water sooner than 10 minutes after administration of sublingual asenapine can reduce its bioavailability
  - A 19% reduction in plasma exposure was observed following water administration at two minutes
- Time to peak concentration: 0.5-1.5 hours

Musselman M, et al. Ther Adv Psychopharmacol. 2021;11:20451253211035269.

Transdermal Asenapine

- Approved by the FDA in 2019 for the treatment of schizophrenia in adults
- Efficacy was established in a registrational study examining acutely ill inpatients with schizophrenia
- The patch needs to changed once daily



PATCH NOT ACTUAL SIZE.

Musselman M, et al. Ther Adv Psychopharmacol. 2021;11:20451253211035269.