ECHO IDAHO:
Behavioral Health in Primary Care

New Psychiatric Medications

11/20/2024

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College of Pharmacy, Division of Pharmacotherapy & Translational Science

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Declaration of Interests

- "Retired"
  - ✓ Clinical Professor Emeritus
    Division of Pharmacotherapy & Translational Science
    College of Pharmacy
    The University of Texas at Austin
- Appointed
  - ✓ Adjoint Professor
    Pharmacotherapy Educ & Research Center
    Joe R. & Teresa Lozano Long School of Medicine
    UT Health San Antonio
- Psychopharmacology Translational Science Consultant
- Speakers Bureau
  - ✓ BMS
  - ✓ Otsuka PsychU
  - ✓ Neurocrine
  - ✓ Teva
  - ✓ Several professional organizations
- Consultant
  - ✓ Alkermes
  - ✓ BMS
  - ✓ Genomind
  - ✓ Janssen
  - ✓ Lundbeck
  - ✓ Otsuka
- Expert Witness for Both Defendant and Plaintiff

Learning Objectives

Describe the efficacy and safety data of the emerging (Phase 3) and recently approved mental health and neurologic medications

Explain appropriate monitoring requirements, patient education points, and provider education for these agents where known

Discuss the clinical use of these new and emerging medications and where they may fit into current clinical practice

Global Cost Effectiveness of Medications

The Least Expensive Medication is the One that Works

The Most Expensive Medication is the One that Does Not Work

Current Status of New Treatments for Schizophrenia

Ulotaront (TARR1 Agonist)

- ✓ Pivotal Phase 3 Studies DIAMOND 1 & 2 Both Failed
- ✓ Very High Placebo Response
- ✓ Sunovion Withdrew from Co-development Agreement with Otsuka
- ✓ Otsuka Continues Development (Maybe)

Pimavanserin (5-HT_{2A} Receptor Inverse Agonist)

- ✓ Pivotal Phase 3 Studies for Negative Symptoms of Schizophrenia were Negative
- ✓ ADVANCE 2: NSA-16; p=0.4825; Effect Size=0.07)
- ✓ Development Discontinued

Iclepertin (Glycine Transporter 1 Inhibitor)

- ✓ Phase 3 Trial (COGNNEX-3; NCT04860830) Remains Active, Not Recruiting
- ✓ Testing Learning & Memory

Meta-analysis of Schizophrenia Augmentation Studies

- ✓ Na Benzoate & Memantine for Persistent Positive Symptoms: ES small to moderate
- ✓ Risperidone, Tropisetron, Pioglitazone, Minocycline & Memantine for Reducing Negative Symptoms: ES Moderate to Large
- ✓ Clozapine + Antipsychotics for Reducing Negative Symptoms: ES Small to Moderate
- ✓ Clozapine with Added Duloxetine for Reducing Negative Symptoms: ES Large

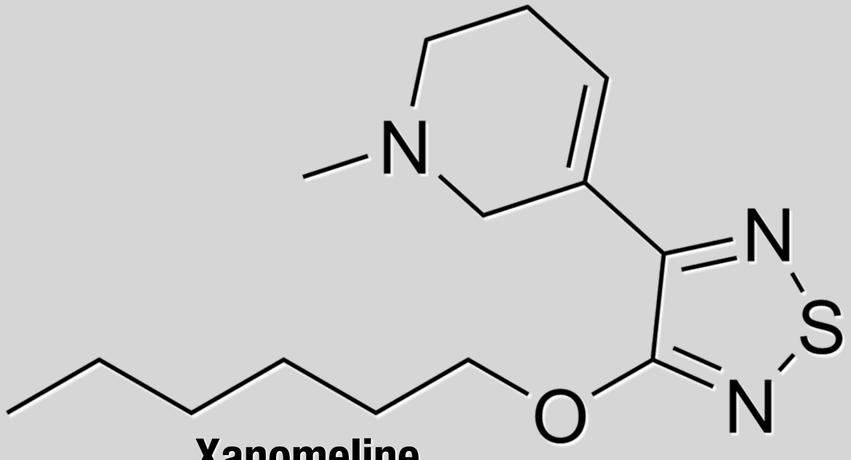
Key: NSA-16 = Negative Symptom Assessment-16. ES = Effect Size. Etchecopar-Etchart D, et al. Comprehensive evaluation of 45 augmentation drugs for schizophrenia: a network meta-analysis. Lancet 2024;69:1–13. https://doi.org/10.1016/j.eclinm.2024.102473

All Muscarinic CNS Agents in Development

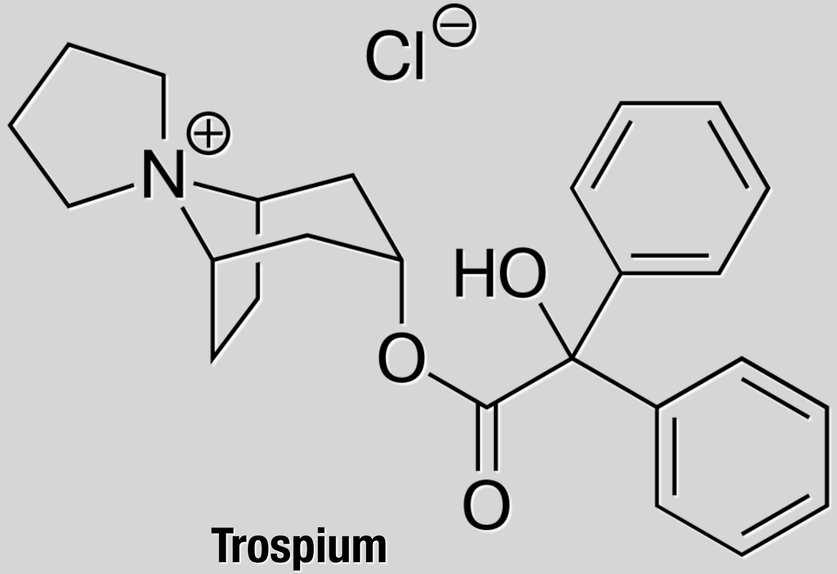
Drug	Company	Target / Properties	Status
KarXT	Karuna/BMS	M1/M4 Agonist (Xanomeline) + Peripheral pan-mAChR Antagonist	Approved
Emraclidine	Cerevel/Abbvie	M4 PAM	Phase 2 (11/11/2024: EMPOWER 1 & 2 Both Placebo Failed)
NBI-1117568	Neurocrine/Nxera	M4 Agonist	Phase 2 (08/24/2024: EC=0.61, p=0.011)
ANAVEX3-71	Anavex	Sigma 1/M1 Agonist	Phase 2 (Part A Completed 10/17/2024)
NBI-1117570	Neurocrine/Nxera	M1/M4 Agonist	Phase 1
NBI-1117567	Neurocrine/Nxera	M1-preferring Agonist	Phase 1
NBI-1117569	Neurocrine/Nxera	M4-preferring Agonist	Phase 1
ML-007C-MA	Maplight	M1/M4 Agonist + Peripheral pan-mAChR Antagonist	Phase 1
NMRA-266	Neumora	M4 PAM	Phase 1 (FDA Hold on 04/15/2024)
Undisclosed	Neurosterix	M4 PAM	Preclinical

Key: Agonist Binds to Receptor Site and Activates Receptor; PAM = Positive Allosteric Modulator, Binds to Non-Receptor Site and Alters Conformation; ES = Effect Size. Kingwell K. Nature Reviews: Drug Discovery 2024;23:647–649. https://doi.org/10.1038/d41573-024-00129-w. Krystal JH, et al. Lancet 2022;400: 2210–20. https://doi.org/10.1016/S0140-6736(22)01990-0; Individual Company Investor Pipeline Sites (Accessed 10/18/2024)

Xanomeline + Trospium (Cobenfy, KarXT, BMS, Karuna)

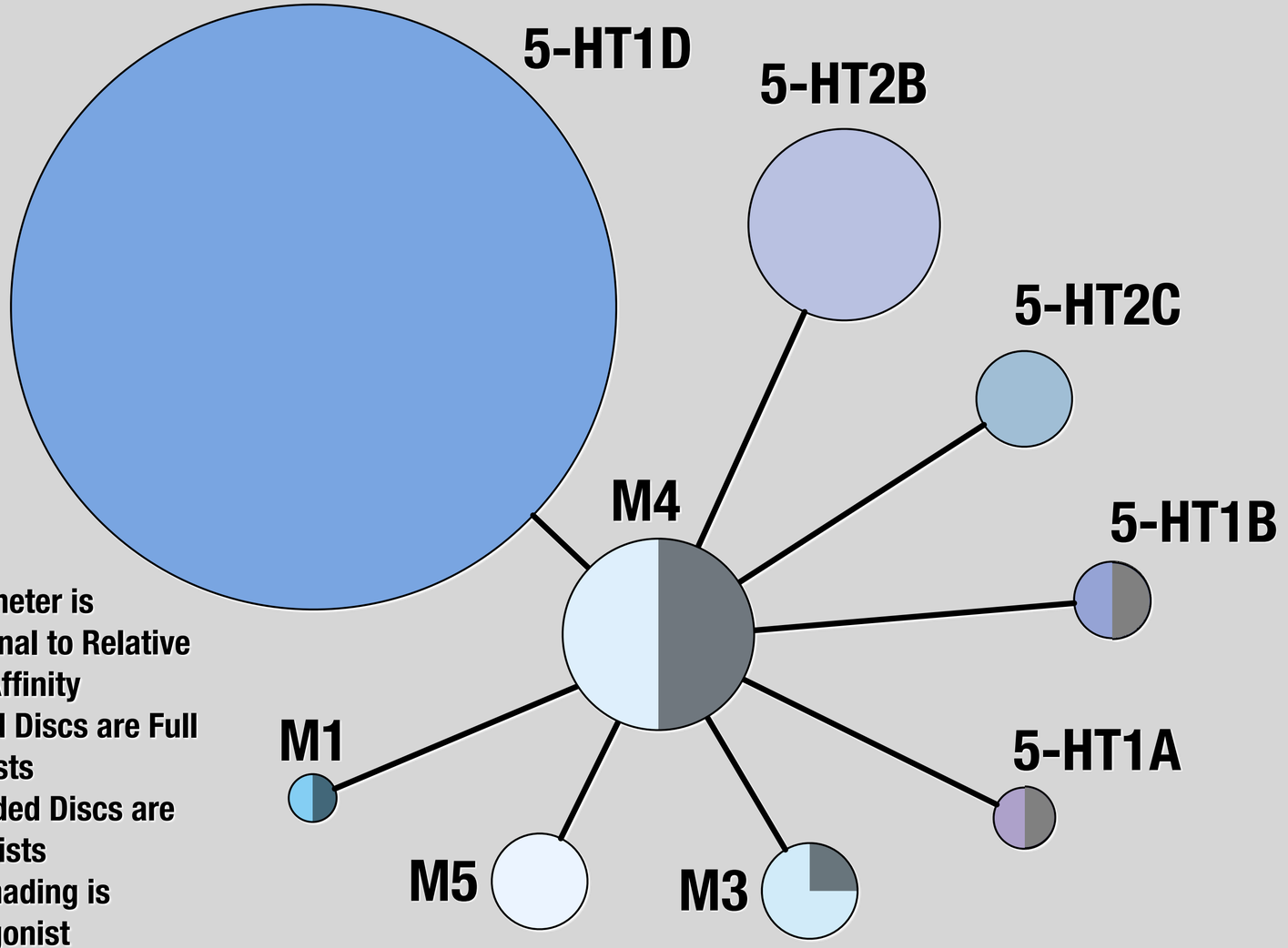


Xanomeline



Trospium

- ✓ Disc Diameter is Proportional to Relative Binding Affinity
- ✓ Unshaded Discs are Full Antagonists
- ✓ 50% Shaded Discs are Full Agonists
- ✓ Partial Shading is Partial Agonist



Receptor Binding Data from Roth BL, et al. The Neuroscientist, 6:252-262, 2000. Science Netwatch 2000;287:5453. https://pdsp.unc.edu/databases/kidb.php
Xanomeline Structures by Chemgirl131, Public domain, via Wikimedia Commons https://commons.wikimedia.org/wiki/File:Xanomeline.png. Trospium Structure is Public Domain https://commons.wikimedia.org/wiki/File:Trospium_chloride.svg

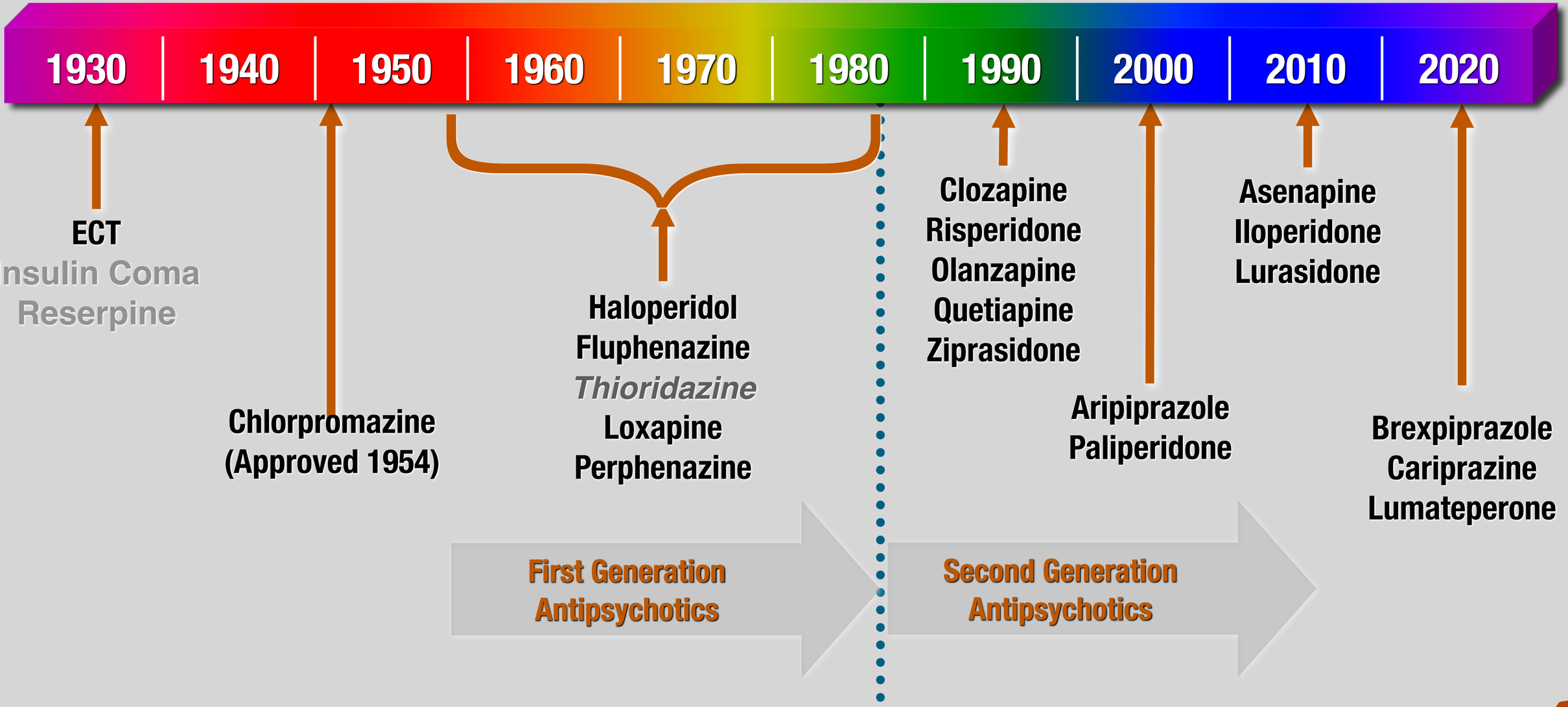
Xanomeline + Trospium (X+T) is the First in a New FDA Category of Medications

"Antipsychotic" Does Not Appear in the Product Label Even Once

The FDA Approved Product Label Describes X+T as: "…a Combination of Xanomeline, a Muscarinic Agonist, and Trospium Chloride, a Muscarinic Antagonist, Indicated for the Treatment of Schizophrenia in Adults"

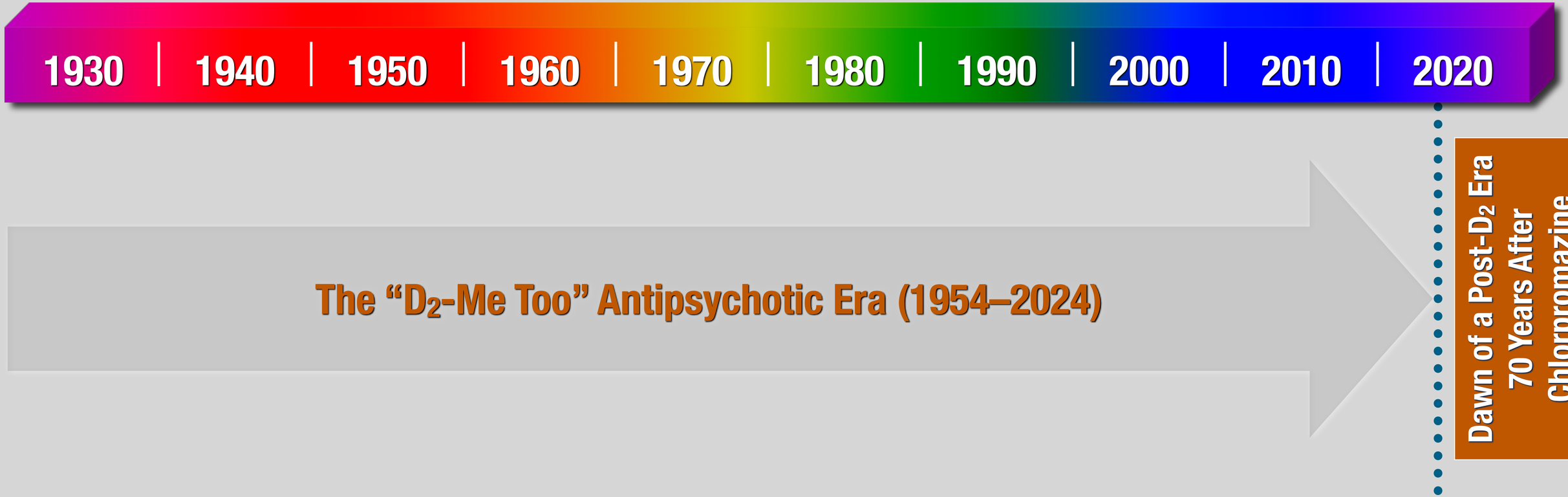
Cobenfy Product Label 1629-US-2400371, Karuna, BMS, Princeton, NJ 08543 09/2024

Timeline of FDA Approved Medications for Schizophrenia

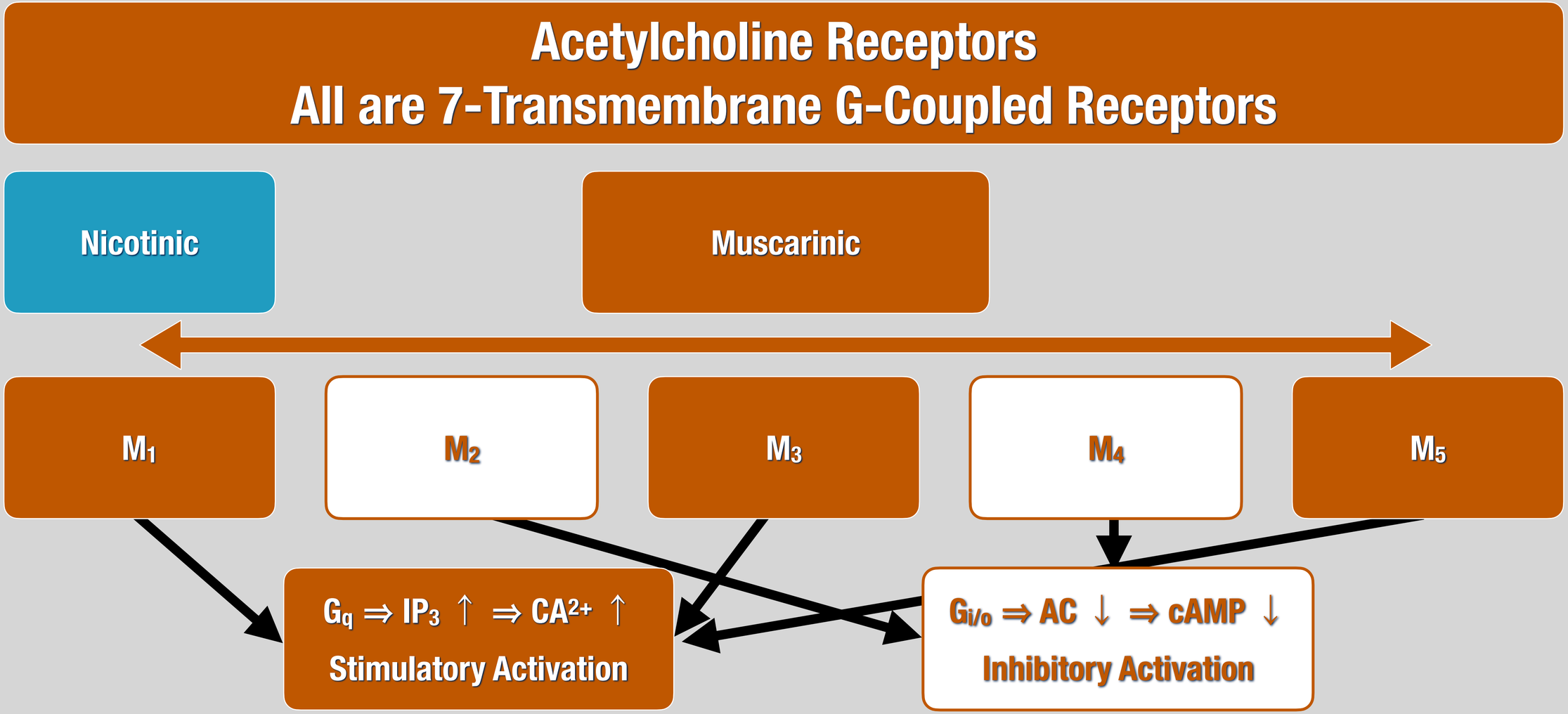


Key: Light Shading = No Longer Used; Italic = Brand Withdrawn, Generic Avaliable.
For FDA Approved Agents see Drug@FDA https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm
Also see List of Antipsychotics https://en.wikipedia.org/wiki/List_of_antipsychotics

The Muscarinic Agonists Are Indicated for the "Treatment of Schizophrenia"

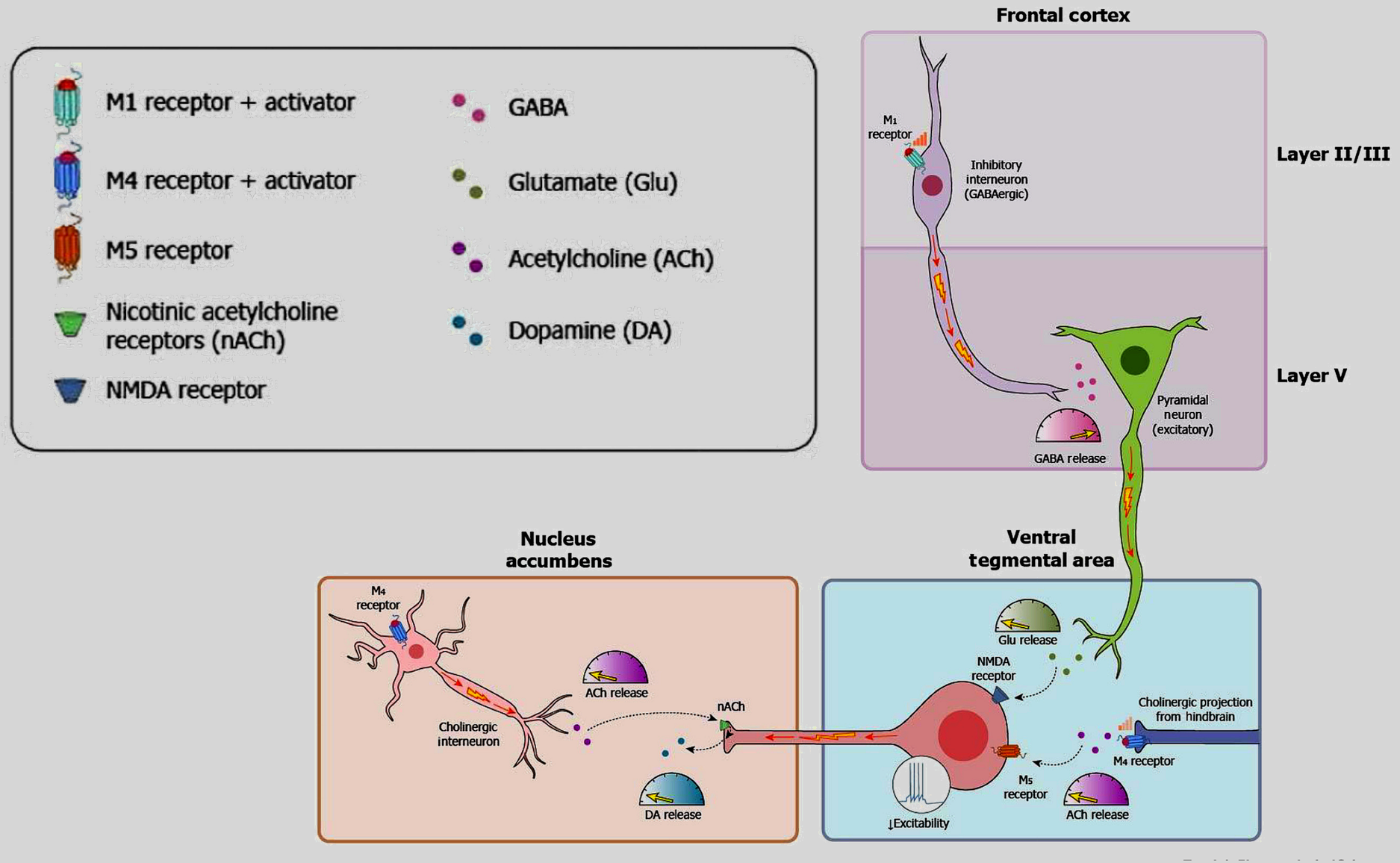


Simplified Acetylcholine Receptor Pharmacology



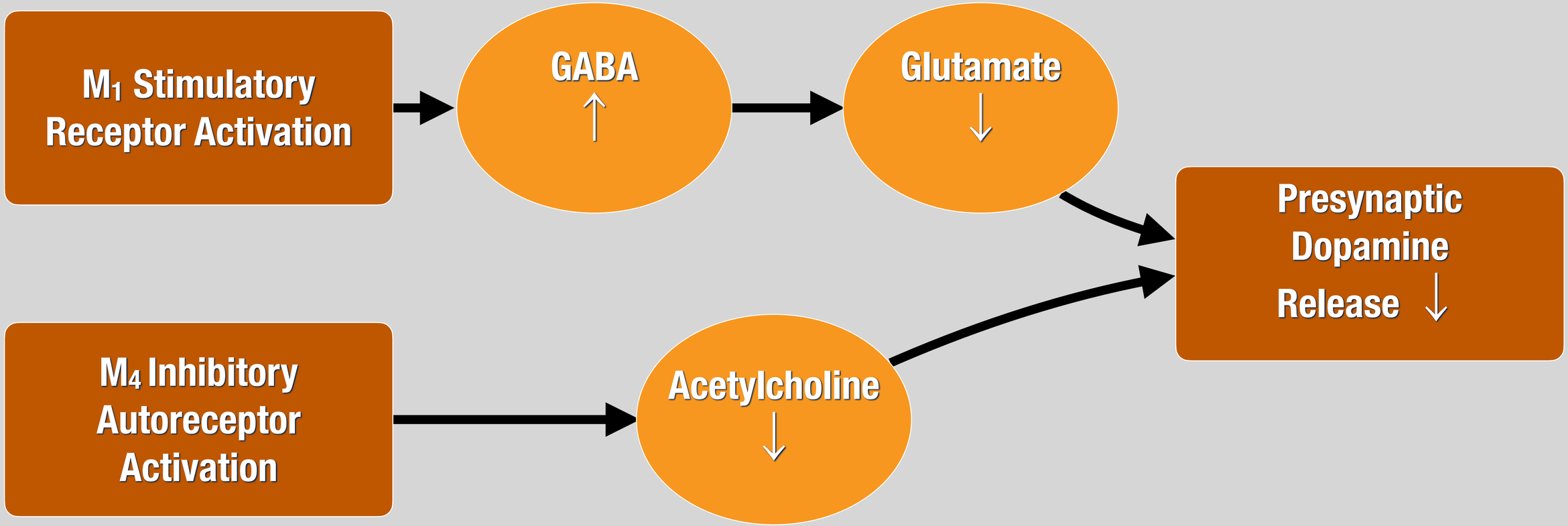
Yohn SE, et al. Trends in Pharmaceutical Sciences. 2022;43(12):1098–1112. https://doi.org/10.1016/j.tips.2022.09.006. Paul SM, et al. Am J Psychiatry 2022;179(9):611–627. https://doi.org/10.1176/appi.ajp.21101083. Picciotto MR, et al. Neuron. 2012;76(1):116-129. http://dx.doi.org/10.1016/j.neuron.2012.08.036. StatPearls. Updated 04/10/2023. Accessed 10/13/2024. https://www.ncbi.nlm.nih.gov/books/NBK557825/

Acetylcholine Wiring Diagram in Brain



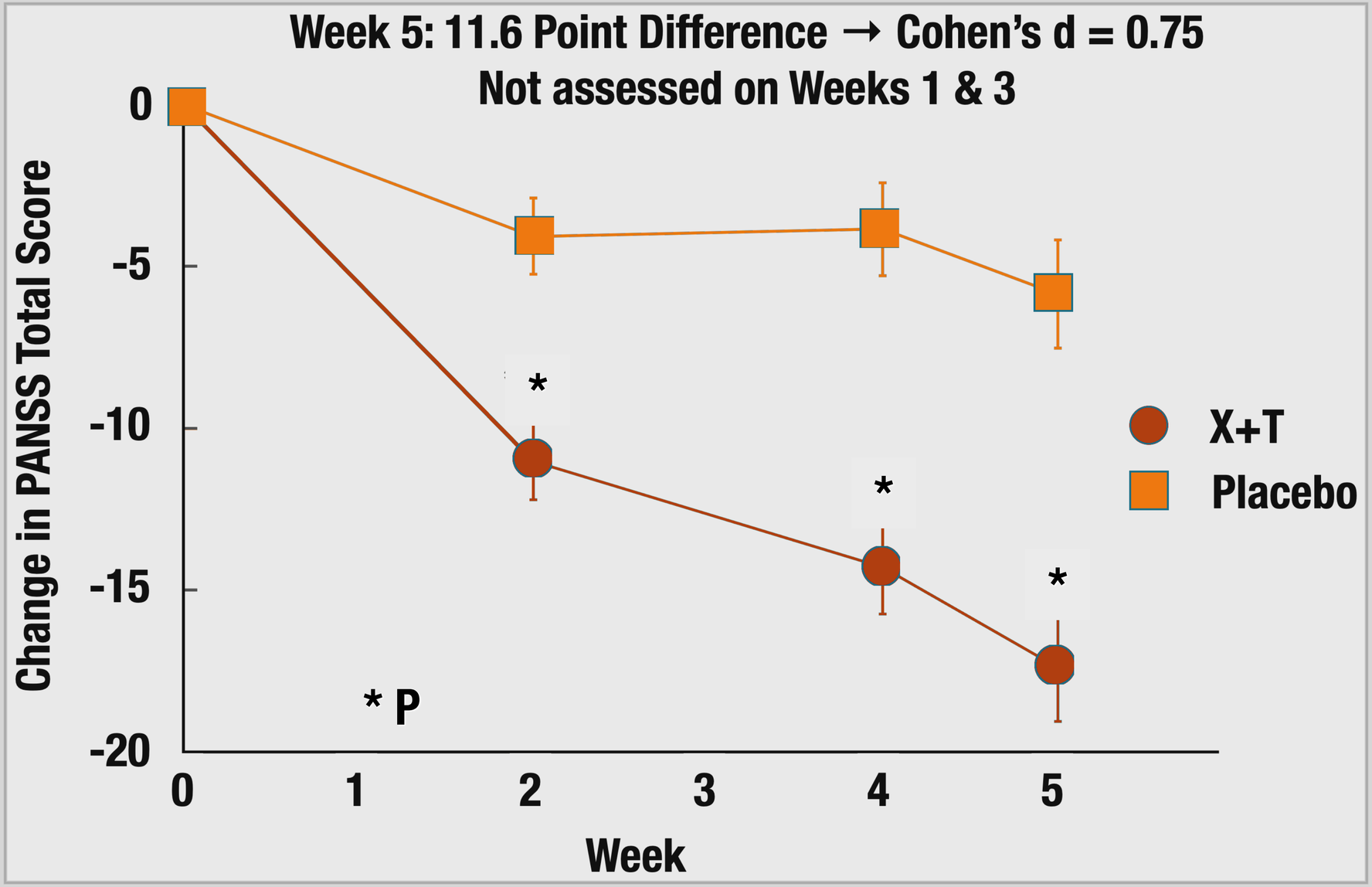
Adapted from Yohn SE, Weiden PW, Felder CC, Stahl SM. Muscarinic acetylcholine receptors for psychotic disorders: bench-side to clinic. Trends in Pharmaceutical Sciences. 2022;43(12):1098–1112. https://doi.org/10.1016/j.tips.2022.09.006

Using a Presynaptic Mechanism for a Predominately Presynaptic Disorder



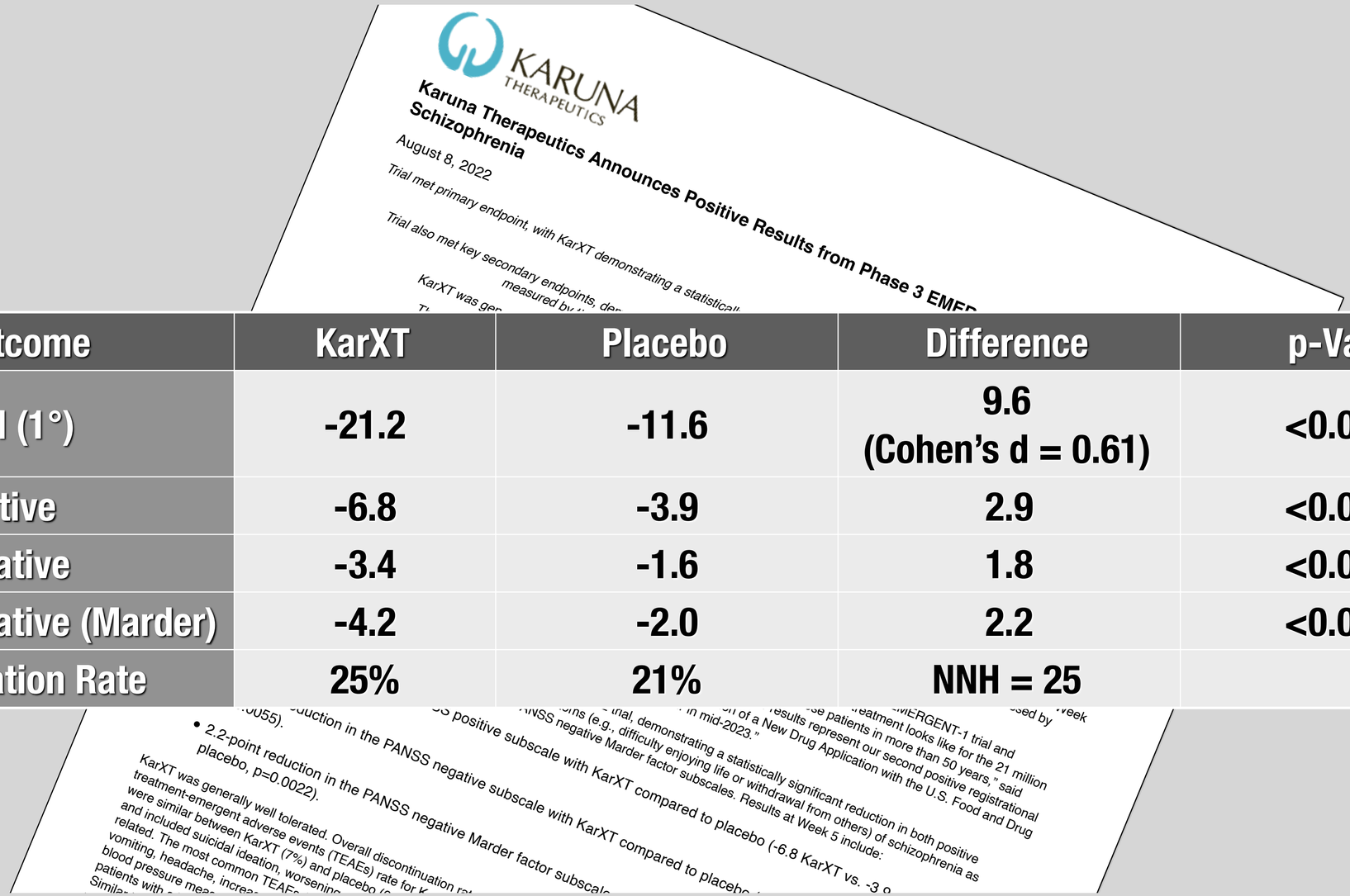
Paul SM, et al. Am J Psychiatry 2022;179(9):611–627. https://doi.org/10.1176/appi.ajp.21101083. Picciotto MR, et al. Neuron. 2012;76(1):116-129. http://dx.doi.org/10.1016/j.neuron.2012.08.036.

KAR-XT Change in PANSS Total Score from Baseline (Phase 2)



Data from Brannan SK, et al. N Engl J Med 2021;384:717–26. https://doi.org/10.1056/NEJMoa2017015

X+T Phase 3 Trial in Schizophrenia (EMERGENT-2) Top Line Results


KARUNA THERAPEUTICS

Karuna Therapeutics Announces Positive Results from Phase 3 EMER
Schizophrenia

August 8, 2022

Trial met primary endpoint, with KarXT demonstrating a statistical

Trial also met key secondary endpoints, de
measured by

KarXT was ge

ERGENT-1 trial and
treatment looks like for the 21 million
results represent our second positive registrational
of a New Drug Application with the U.S. Food and Drug
in mid-2023."

trial, demonstrating a statistically significant reduction in both positive
NSS negative Marder factor subscales. Results at Week 5 include:

0055).

- 2.2-point reduction in the PANSS negative Marder factor subscale with KarXT compared to placebo, p=0.0022).

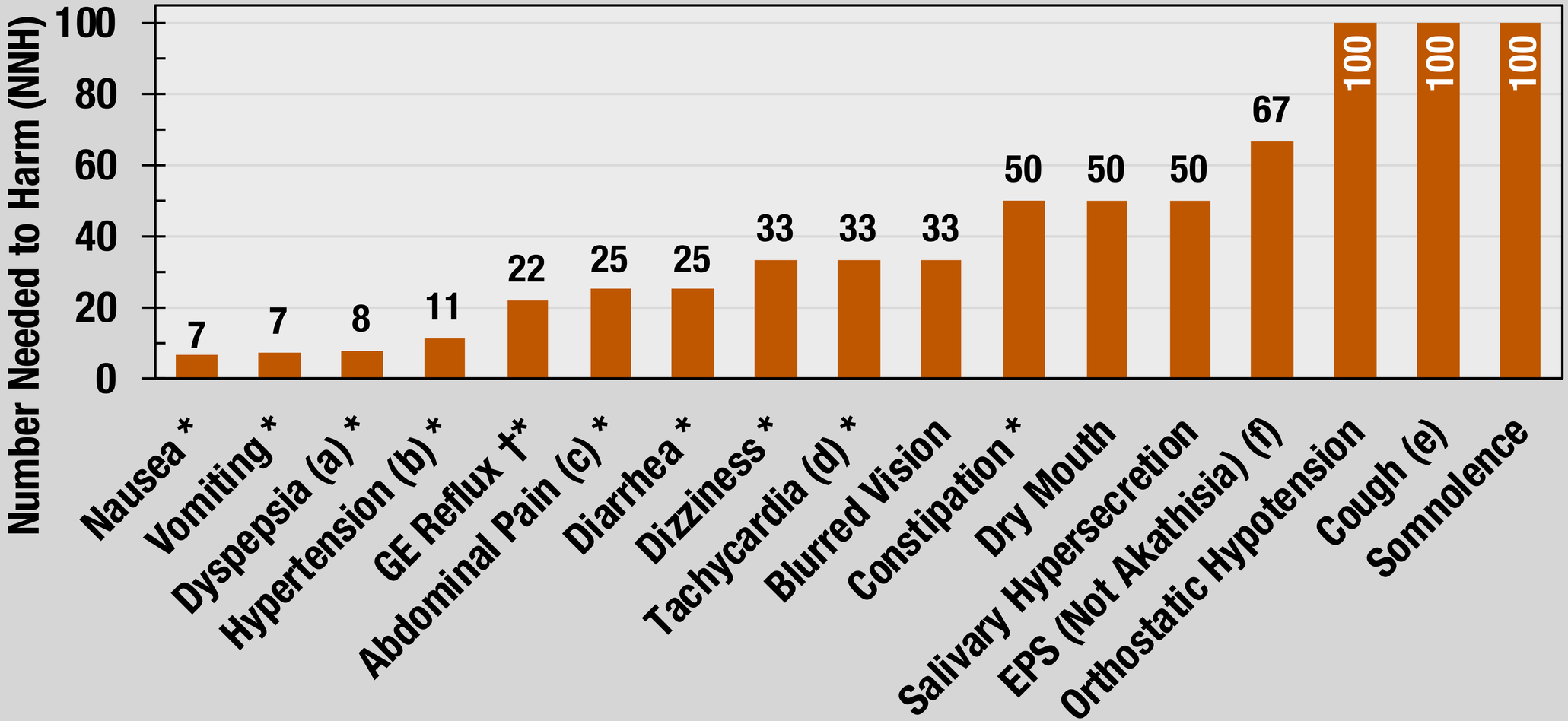
S positive subscale with KarXT compared to placebo

KarXT was generally well tolerated. Overall discontinuation ra
treatment-emergent adverse events (TEAEs) rate for K
were similar between KarXT (7%) and placebo (
and included suicidal ideation, worsening
related. The most common TEAE
vomiting, headache, increa
blood pressure mea
patients with
Simila

Outcome	KarXT	Placebo	Difference	p-Value
PANSS Total (1°)	-21.2	-11.6	9.6 (Cohen's d = 0.61)	<0.0001
PANSS Positive	-6.8	-3.9	2.9	<0.0001
PANSS Negative	-3.4	-1.6	1.8	<0.0055
PANSS Negative (Marder)	-4.2	-2.0	2.2	<0.0022
Discontinuation Rate	25%	21%	NNH = 25	

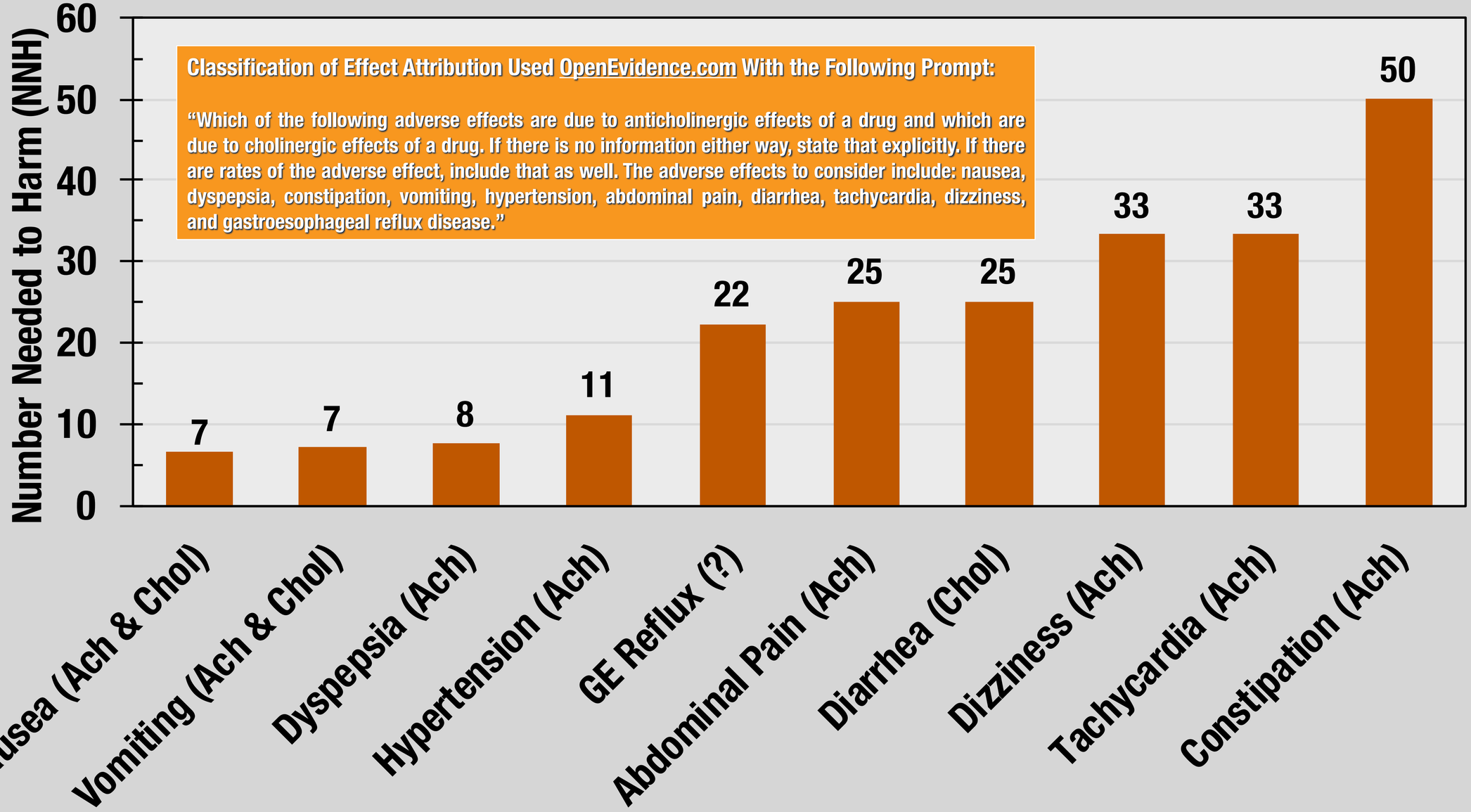
Karuna Press Release "Karuna Therapeutics Announces Positive Results from Phase 3 EMERGENT-2 Trial of KarXT in Schizophrenia" https://investors.karunatx.com/news-releases/news-release-details/karuna-therapeutics-announces-positive-results-phase-3-emergent (Accessed 08/08/2022)

X+T Adverse Effects ≥2%



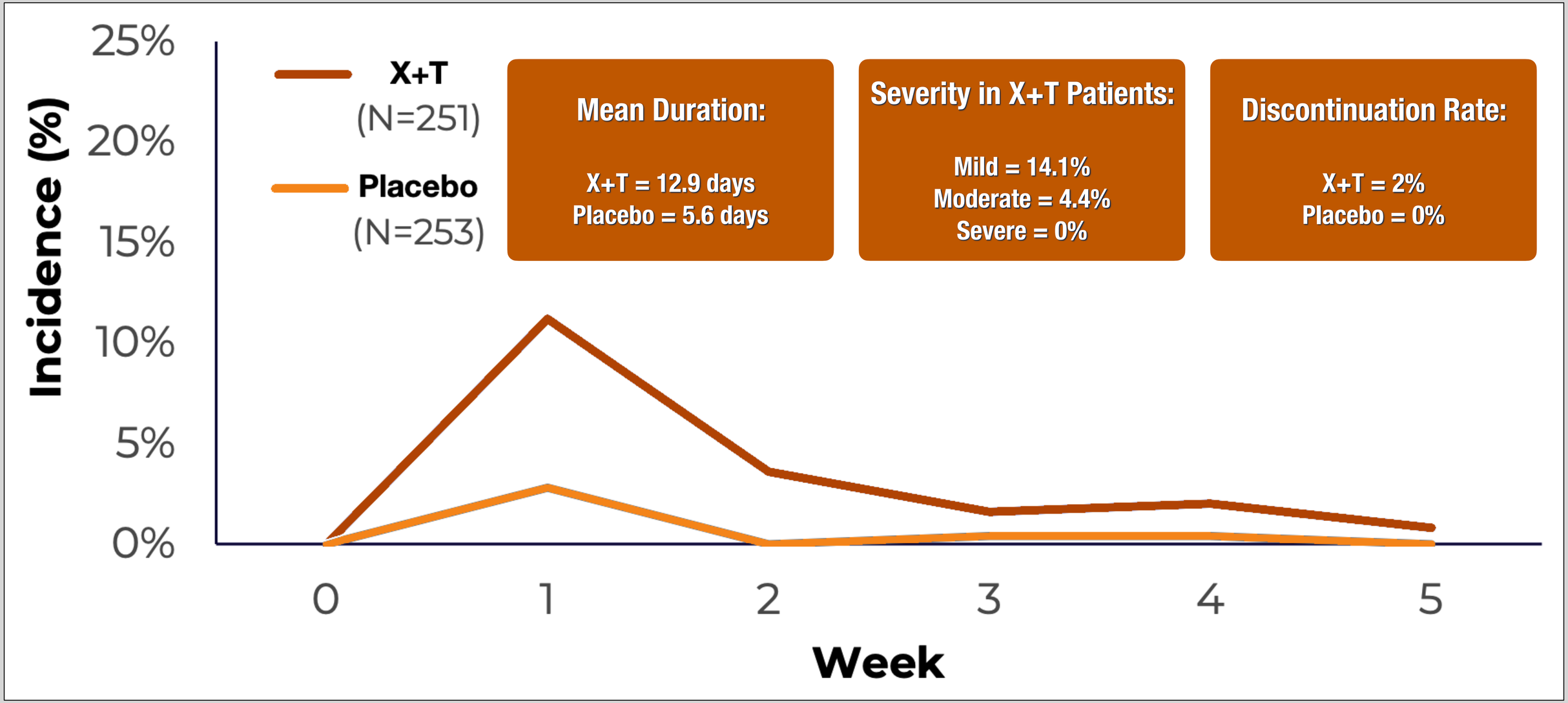
Key: * = Common Drug Related Adverse Effect (>5% in Any Group & Twice Placebo); † = Gastroesophageal Reflux Disease; a = Dyspepsia includes dyspepsia, esophageal discomfort; b = Hypertension includes hypertension, blood pressure increased, labile hypertension, orthostatic hypertension; c = Abdominal Pain includes abdominal discomfort, abdominal pain upper, abdominal pain, abdominal pain lower, abdominal tenderness; d = Tachycardia includes tachycardia, heart rate increased, sinus tachycardia; e = Cough: includes cough, productive cough; f = EPS (non-akathisia) includes dyskinesia, drooling, dystonia, extrapyramidal disorder, muscle contraction involuntary, muscle spasms; NNH = 1 / (Experimental Rate - Control Rate); Data from Cobenfy Product Label 1629-US-2400371, 09/2024, Bristol Myers Squibb, Princeton, NJ 08543

X+T CDRAE Only



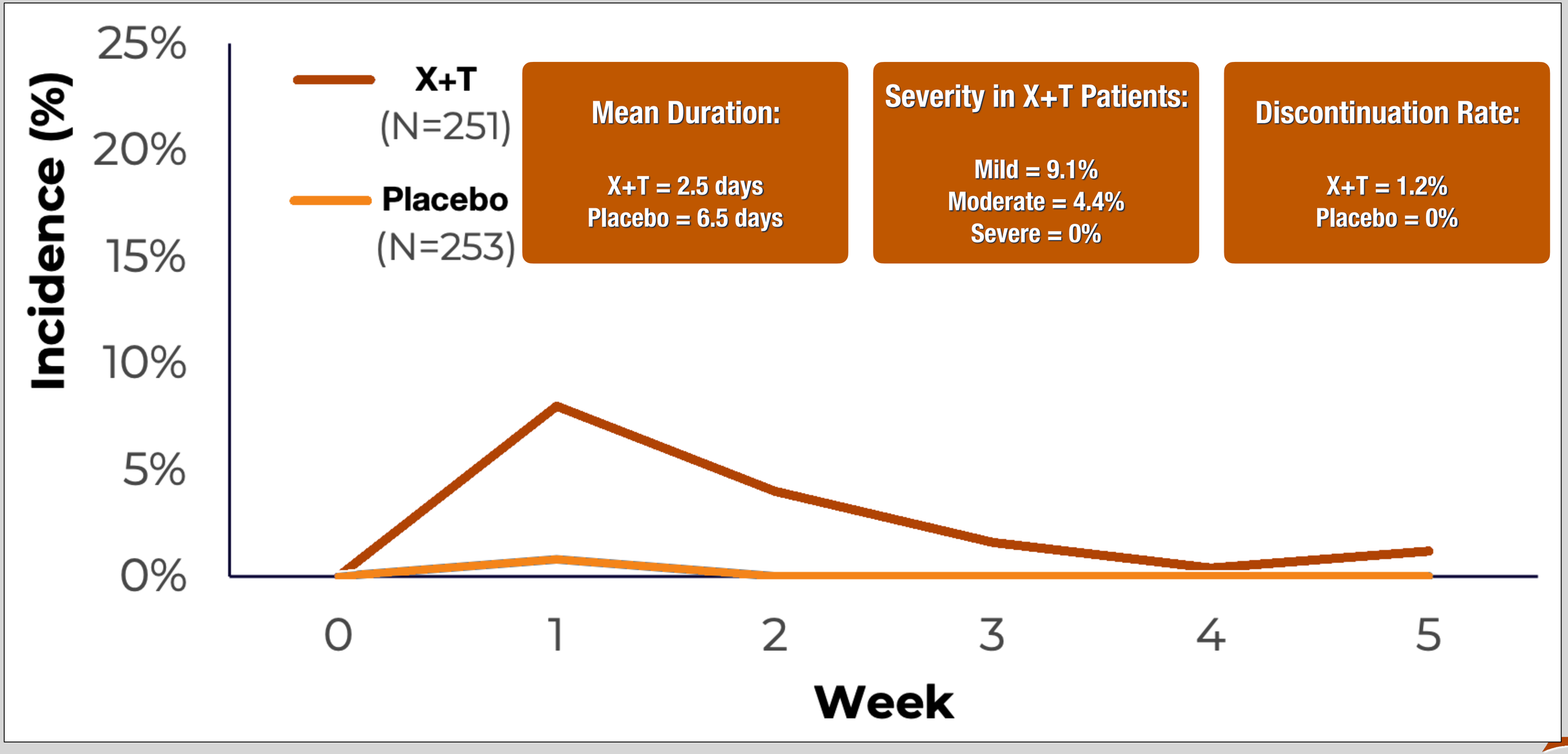
Key: CDRAE = Common Drug Related Adverse Effect (>5% in Any Group & Twice Placebo); Ach = Likely Anticholinergic Effect; Chol = Likely Cholinergic Effect; NNH = 1 / (Experimental Rate - Control Rate); Data from Cobenfy Product Label 1629-US-2400371, 09/2024, Bristol Myers Squibb, Princeton, NJ 08543

X+T Nausea Incidence by Week



Data from Brannan S, et al. Poster Presentation at NEI; 11/9–12/2023, Colorado Springs, CO. Antiemetics (Most Often, Ondansetron was Used) by 4% of All Patients.

X+T Vomiting Incidence by Week



Mean Duration:

X+T = 2.5 days
Placebo = 6.5 days

Severity in X+T Patients:

Mild = 9.1%
Moderate = 4.4%
Severe = 0%

Discontinuation Rate:

X+T = 1.2%
Placebo = 0%

Data from Brannan S, et al. Poster Presentation at NEI; 11/9–12/2023, Colorado Springs, CO. Antiemetics (Most Often, Ondansetron was Used) by 4% of All Patients.

Warnings & Precautions

- Urinary Retention
- Decreased Gastrointestinal Motility
- Increases Heart Rate
- Hepatic Impairment
- Angioedema
- Anticholinergic Adverse Reactions with Renal Impairment
- Biliary Disease
- Narrow Angle Glaucoma
- Central Nervous System

Data from Cobenfy Product Label 1629-US-2400371, 09/2024, Bristol Myers Squibb, Princeton, NJ 08543

Antipsychotic Warnings & Precautions that are Absent

No Boxed Warnings

Tardive Dyskinesia or Other Movement Disorders

No

Metabolic Disorders or Weight Gain

QT Prolongation

Data from Cobenfy Product Label 1629-US-2400371, 09/2024, Bristol Myers Squibb, Princeton, NJ 08543

Pharmacokinetics Summary

Parameter	Xanomeline	Trospium
Time to Peak Concentration	2 hours	1 hour
Maximum Concentration (Low or High Fat)	Unchanged	↓ 70–75%
AUC	Low Fat Unchanged; High Fat ↑ 30%	Low or High Fat ↓ 85–90%
Oral Volume of Distribution	10,800 L	531 L
Plasma Protein Binding	~95%	~80%
Elimination Half-life	5 hours	6 hours
Apparent Clearance	1950 L/hr	796 L/hr
Renal Clearance	0.085 L/hr	21 L/hr
Metabolic Pathways		
CYP 450	1A2, 2B6, 2C9, 2C19, 2D6	Unlikely
Other	FM01, FM03	Esther Hydrolysis, Glucuronic Acid Conjugation (not fully characterized)
Urine Excretion		
Total	78%	Unknown
Unchanged	<0.01%	85–90%
Tubular Secretion	Unknown	Yes
Fecal Excretion		
Total	12%	Unknown
Unchanged	Unknown	Unknown

Key: High-fat high-calorie meal is 800-1000 calories, 50% from fat; a low-fat meal is 400-500 calories, 25% from fat. Data from Cobenfy Product Label 1629-US-2400371, 09/2024, Bristol Myers Squibb, Princeton, NJ 08543

Dosing Recommendations

Time Frame	Dosing	Comments
Before Starting & as Clinically Indicated		✓ Liver Enzymes ✓ Bilirubin
Starting Dose 0 → ≥2 Days	✓ X+T 50 mg/20 mg BID	✓ Empty Stomach (1 hr AC or 2 hr PC)
Interim Dose in Adults >2 Days for ≥5 Days (Maximum in Geriatric)	✓ X+T 100 mg/20 mg BID	✓ Empty Stomach (1 hr AC or 2 hr PC)
Maximum Dose ≥7 Days	✓ X+T 125 mg/30 mg BID	✓ Empty Stomach (1 hr AC or 2 hr PC) ✓ ↑ Dose if Needed & Well-tolerated

Check for Contraindications Before Considering X+T

- ✓ Urinary Retention
- ✓ Moderate (Child-Pugh B) or Severe (Child-Pugh C) Hepatic Impairment
- ✓ Gastric Retention
- ✓ History of Hypersensitivity to Components (Xanomeline or Trospium)
- ✓ Untreated Narrow-angle Glaucoma

🤔

Slower Titration May ↓ Incidence of Some Adverse Effects

Based on Cobenfy Product Label 1629-US-2400371, 09/2024, Bristol Myers Squibb, Princeton, NJ 08543

Clinically Significant Drug Interactions

Type of Interaction	Effect	Management
Strong Inhibitors of CYP2D6	✓ Xanomeline is Metabolized by CYP2D6 ✓ Inhibitors will Increase Plasma Concentrations	✓ Monitor for Increased Frequency or Severity of Adverse Reactions (Cholinergic)
Sensitive Substrates of CYP3A4	✓ Xanomeline Transiently Inhibits CYP3A4 Locally in the Gut, but not Systemically ✓ Sensitive Substrates of CYP3A4 may have Increased Plasma Concentrations when Administered Orally	✓ Monitor for Increased Frequency or Severity of Adverse Reactions from Orally Administered Sensitive Substrates
Drugs Eliminated by Active Tubular Secretion (ATS)	✓ Trospium is Eliminated by ATS ✓ Drugs which Compete for ATS may Increase Plasma Concentrations	✓ Monitor for Increased Frequency or Severity of Adverse Reactions to Trospium (Anticholinergic) ✓ Monitor for Increased Frequency or Severity of Adverse Reactions to Other ATS Eliminated Drugs
Substrates of P-glycoprotein (PGP)	✓ Xanomeline Transiently Inhibits PGP Locally in the Gut, but not Systemically ✓ Substrates of PGP may have Increased Plasma Concentrations when Administered Orally	✓ Monitor for Increased Frequency or Severity of Adverse Reactions to Oral Narrow Therapeutic Index Substrates of PGP
Antimuscarinic Drugs	✓ Additive Antimuscarinic Activity	✓ Monitor for Increased Frequency or Severity of Anticholinergic Adverse Reactions when used with Concomitantly Administered Antimuscarinic Drugs
Effect on Absorption of Orally Administered Drugs	✓ Altered Gastrointestinal Motility may Alter Absorption of Some Orally Administered Concomitant Medications	✓ Monitor and Adjust the Dose of Concomitant Orally Administered Drugs Based on Clinical Response and Tolerability

Metformin Study: Trospium ↓; Metformin Unchanged. Based on Cobenfy Product Label 1629-US-2400371, 09/2024, Bristol Myers Squibb, Princeton, NJ 08543

Commonly Prescribed Drugs in the USA that have Active Tubular Secretion

Captopril
- ✓ ACE inhibitor
- ✓ OAT1

Enalaprilate
- ✓ ACE Inhibitor
- ✓ Active Metabolite of Enalapril
- ✓ OAT1

Lisinopril
- ✓ ACE Inhibitor
- ✓ OAT1

Losartan
- ✓ ARB
- ✓ OAT1

Valsartan
- ✓ ARB
- ✓ OAT1

Hydrochlorothiazide
- ✓ Thiazide Diuretic
- ✓ OAT1, OAT3, OCT2, & MATE2-K

Eliminated by Active Tubular Secretion

Pravastatin
- ✓ Low Potency Statin
- ✓ OAT1

Furosemide
- ✓ Loop Diuretic
- ✓ OAT1

Simvastatin
- ✓ Statin
- ✓ OAT1

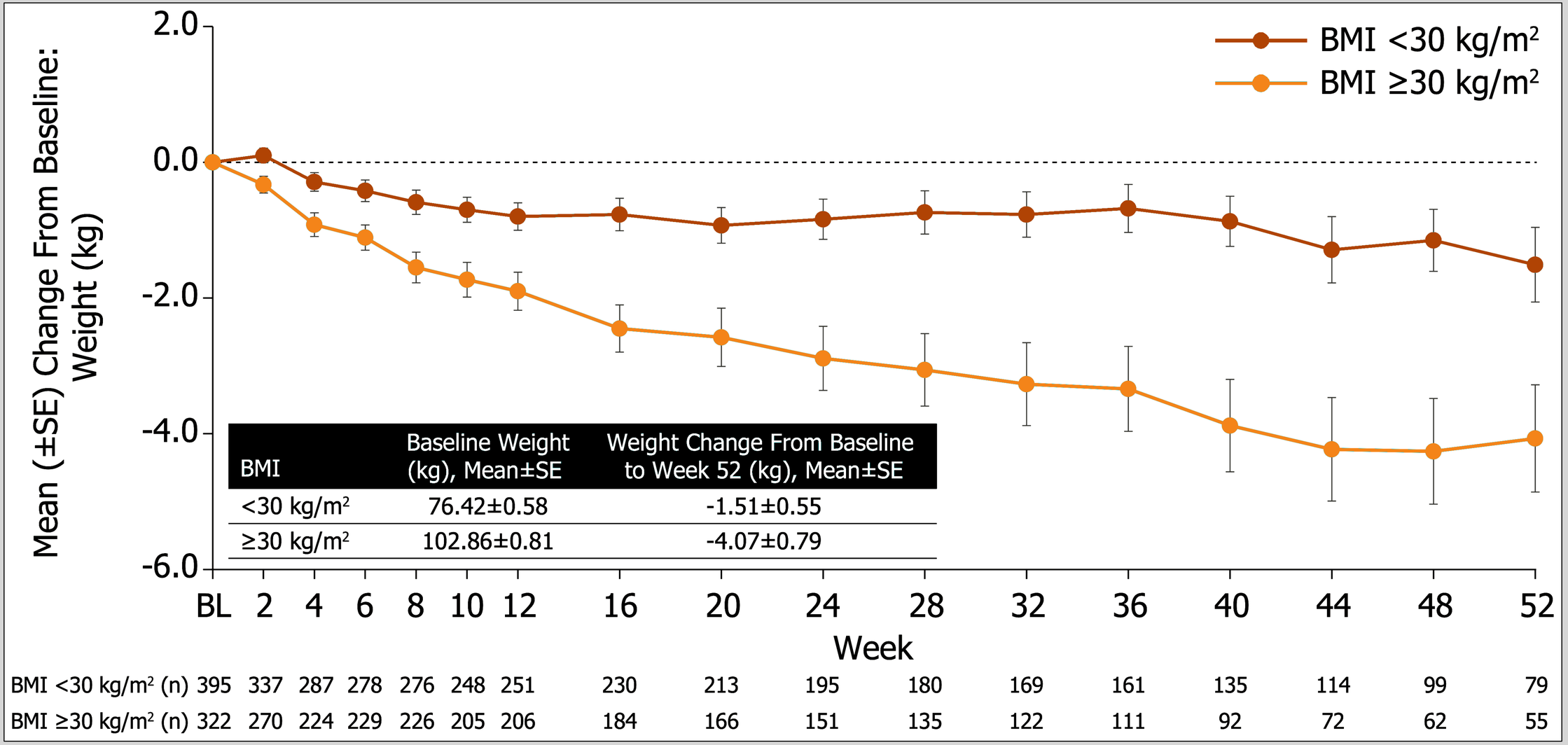
Key: OAT1 = Organic Anion Transporter-1; OAT3 = Organic Anion Transporter-3; OCT2 = Organic Cation Transporter-2; ARB =Angiotensin Receptor Blocker; ACE = Angiotensin-converting Enzyme; MATE2K = Multidrug and Toxin Extrusion 2KAli SS, et al. Fundamental & Clinical Pharmacology. 2012;26(2):175-9. https://doi.org/10.1111/j.1472-8206.2011.01012.x. Yin J, et al. Am J Physiology Renal Physiology. 2019;317(4):F805-F814. https://doi.org/10.1152/ajprenal.00141.2019. Mihaila SM, et al. Toxins. 2020;12(6):E391. https://doi.org/10.3390/toxins12060391. Ivanyuk A, et al. Clin Pharmacokinet 2017;56:825–892. https://doi.org/10.1007/s40262-017-0506-8.

P-glycoprotein (PGP) Interactions

Inhibitors	Inducers	Substrates	Decreased Expression
Amiodaron	Carbamazepine	Colchicine	Alzheimer's Disease
Clarithromycin	Dexamethasone	Ciclosporin	Inflammatory Bowel Diseases
Ciclosporin	Doxorubicin	Dibigatran	
Colchicine	Nefazodone	Digoxin	
Diltiazem	Phenobarbital	Diltiazem	
Erythromycin	Phenytoin	Fexofenadine	
Felodipine	Prazosin	Indinavir	
Ketoconazole	Rifampin	Morphine	
Lansoprazole	St. John's wort	Sirolimus	
Omeprazole (Other Proton-Pump Inhibitors)	Tenofovir		
Nifedipine	Tipranavir		
Paroxetine	Trazodone		
Reserpine	Vinbalstine		
Saquinavir			
Sertraline			
Quinidine			
Tamoxifen			
Verapamil			
Duloxetine			

Wikipedia p-Glycoprotein https://en.wikipedia.org/wiki/P-glycoprotein (Accessed 10/17/2024)

X+T Weight Changes Over One Year



BMI	Baseline Weight (kg), Mean±SE	Weight Change From Baseline to Week 52 (kg), Mean±SE
<30 kg/m²	76.42±0.58	-1.51±0.55
≥30 kg/m²	102.86±0.81	-4.07±0.79

BMI <30 kg/m² (n)	395	337	287	278	276	248	251	230	213	195	180	169	161	135	114	99	79
BMI ≥30 kg/m² (n)	322	270	224	229	226	205	206	184	166	151	135	122	111	92	72	62	55

Claxton A, et al. Long-Term Metabolic Outcomes Associated With KarXT (Xanomeline and Trospium) - Interim Results From Pooled, Long-Term Safety Studies EMERGENT-4 and EMERGENT-5 (Poster AAPP 2024)

Currently Studied Population Demographics: Basically, the Same as all New Agents

Median age = 46 years (19 to 65)

Female = 25%, Male = 75%

White = 31%
Black or African American = 68%
Other (or not reported) = 1%

Moderately to Markedly Ill
(PANSS Baselines = 97–98)

What Questions Remain to be Answered about X+T

- Long-term Efficacy
- Long-term Adverse Effects
- Pregnancy (Exposure Registry)
- Lactation (No Data)
- Pediatric Use (All Patients ≥19 y/o)
- Geriatric Use (All Patients ≤65 y/o)
- Moderate to Severe Renal Impairment (eGFR <60 mL/min)
- Hepatic Impairment (Mild → Not Recommended; Contraindicated → Moderate &
- Refractory Patients
- New Patients
- Other Indications Beyond Schizophrenia

Olanzapine LAI (TV-44749) Results from Phase 3 Study in Schizophrenia

Uses Same MedinCell Subcutaneous LAI Technology as TEVA's Risperidone LAI

- ✓ Study Start Date 01/24/2023
- ✓ Study Completion Date is 10/16/2025 (Estimated)

Study Design

- ✓ Period 1: 8 Week R-DB-PC
- ✓ Period 2: OL Olanzapine ≤48 Week (Ongoing)
- ✓ 1 Month Injection Interval

Positive DB Outcomes at Week 8

- ✓ Primary: PANSS Total Score
- ✓ Key Secondaries: CGI-S, PSP
- ✓ No Evience of PDSS

Olanzapine LAI Dose Group	Δ PANSS (p<0.0001)	Δ CGI-S (p<0.0001)	Δ PSP (p<0.02)
318 mg (~10 mgday PO)	-9.69	-0.53	4.63
425 mg (~15 mg/day PO)	-11.25	-0.61	3.15
531 mg (~20 mg/day PO)	-9.71	-0.47	4.93

Key: Δ = Change from Baseline; PSP = Personal and Social Performance Scale; PDSS = Postinjection Delirium / Sedation Syndrome; Kuntz L. <https://www.psychiatrictimes.com/view/tev-749-demonstrates-no-incidence-of-postinjection-delirium-sedation-syndrome-in-new-data> <https://clinicaltrials.gov/study/NCT05693935> Accessed 10/19/2024

Olanzapine LAI (TV-44749)
Phase 3 Study Shows Positive DB Results

Olanzapine LAI Dose Group	PANSS Δ (p<0.0001)	CGI-S (p<0.0001)	PSP (p<0.02)
318 mg (~10 mgday PO)	-9.69	-0.53	4.63
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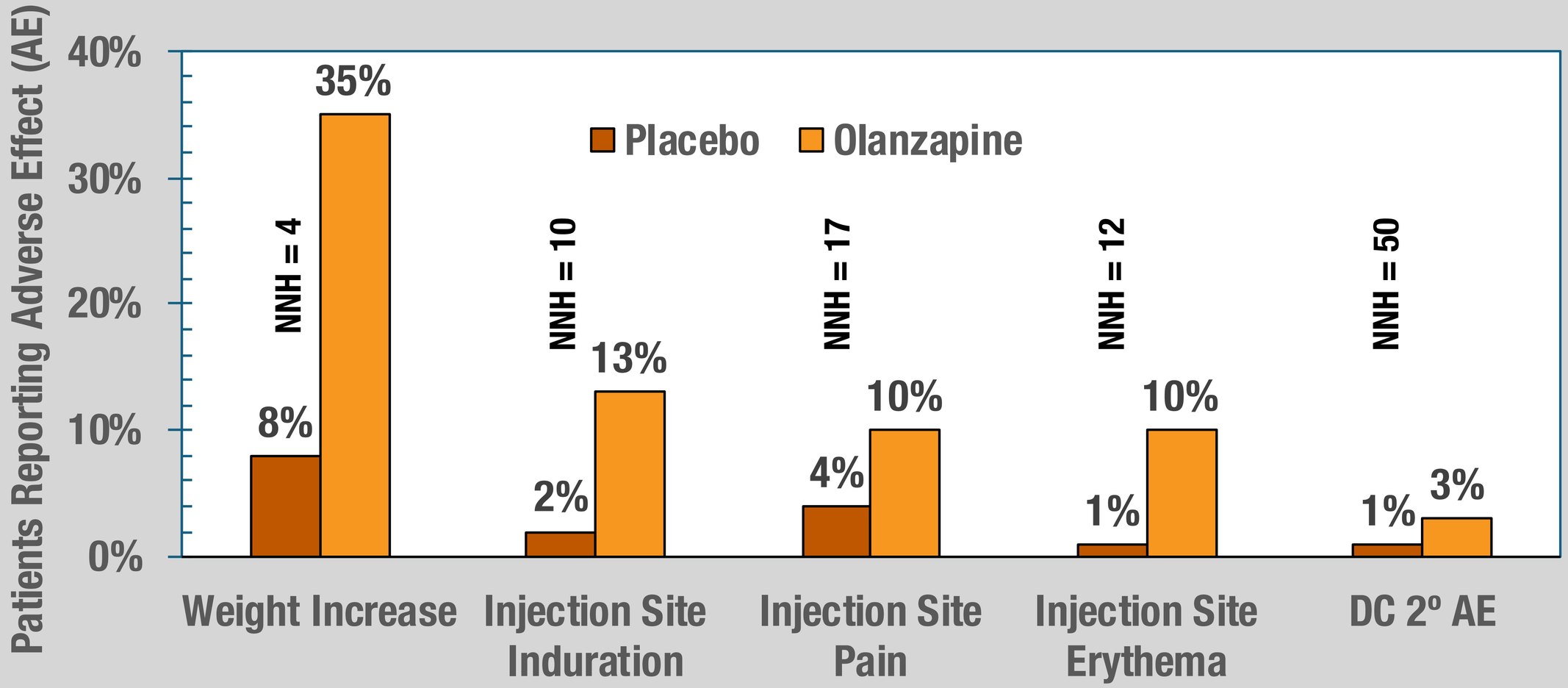
Olanzapine LAI (TV-44749) Adverse Effects During 8-Week Double-Blind Period (> Placebo)



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FDA Approves Foscarbidopa + Foslevodopa 10/17/2024 for Adults Living with Advanced Parkinson's Disease

Foscarbidopa + Foslevodopa are Injectable Prodrugs of Carbidopa and Levodopa for Subcutaneous Administration via Infusion Pump (Preferably in the Abdomen)

Maximum Recommended Daily Dosage is 3,525 mg of Foslevodopa (Equivalent to ~2,500 mg Levodopa

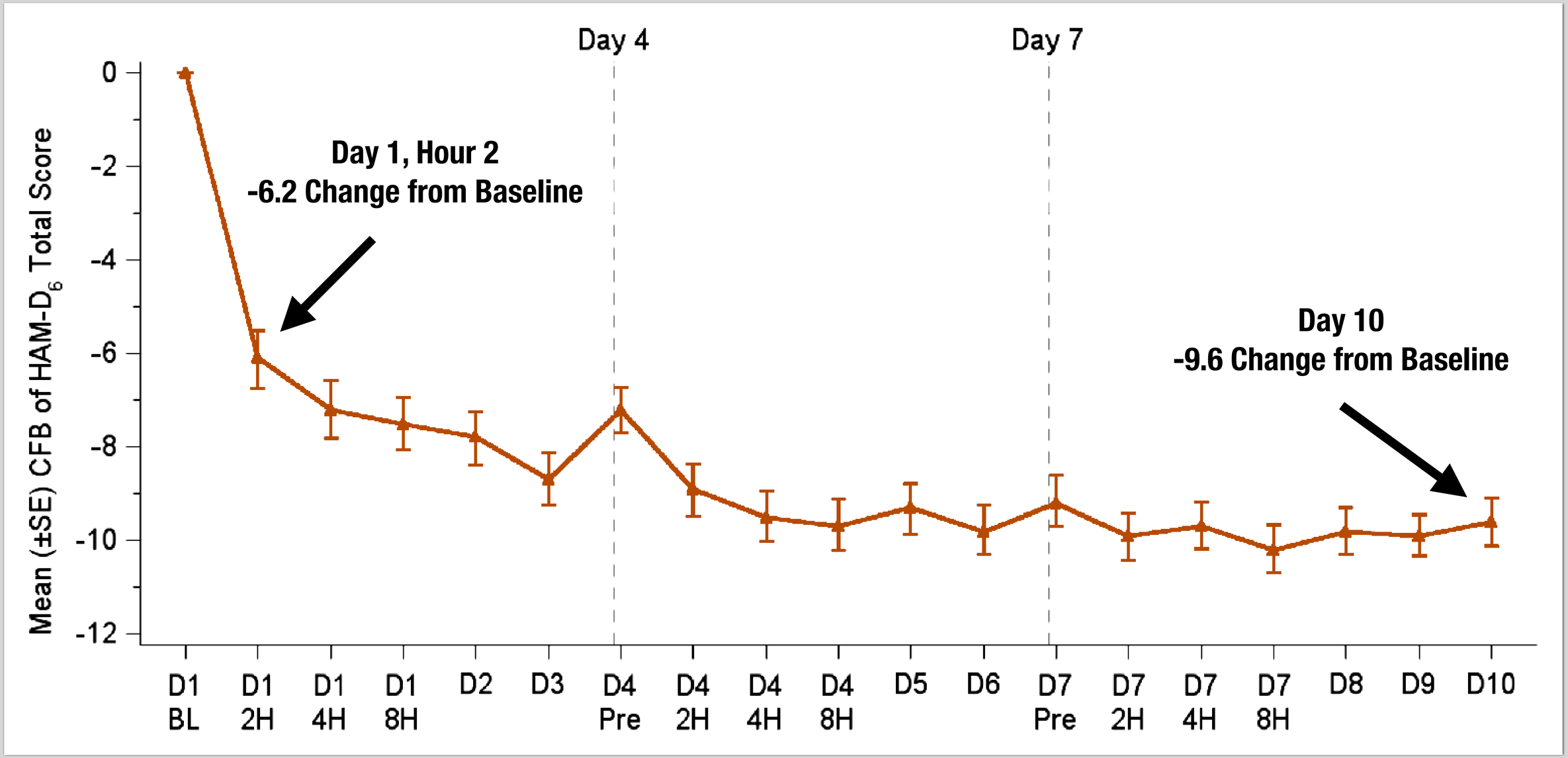
Vyalev Product Label 20065527, Abbvie, North Chicago, IL 60064, 10/2024

SPN-820 for Depression

- Oral, First in Class, Intracellular Modulator of mTORC1
- Increases BDNF & Other Downstream Modulators in Animal Models
- Increases Dendritic Spines in Animal Models (Marker for Neuroplasticity)
- Prior Phase 1b Study Significantly Improved Depressive Symptoms after Single Dose

Key: BDNF = Brain Derived Neurotrophic Factor. Supernus Pipeline Site; Phase 2a Study Report 10/17/2024 <https://ir.supernus.com/static-files/ab65cf23-b874-4b16-819b-13eb197962e7> (Accessed 10/18/2024)

SPN-820 Phase 2a for Depression



Key: SE = Standard Error of the Mean; CBF = Change from Baseline, HAM-D_6 = Hamilton Depression Scale, 6-Item Version; MCT = Meaningful Clinical Threshold is 2–3 points; Doses Administered Day 1, 4, and 7. Phase 2a Study Report 10/17/2024 <https://ir.supernus.com/static-files/ab65cf23-b874-4b16-819b-13eb197962e7> (Accessed 10/18/2024)

Lykos Pulls Off a Phoenix-like Rebirth for PTSD Psychedelic

FDA Rejects NDA for Midomafetamine (MDMA) 08/09/2024

Psychopharmacology Retracts 3 Articles Due to Unethical Conduct 08/10/2024

Lykos Reduces Staff by 75% 08/15/2024

Founder & President of Parent Company Leaving Board 08/15/2024

FDA Initiates Probe of Studies 08/23/2024

New Interim CEO and Chief Medical Officer 09/05/2024

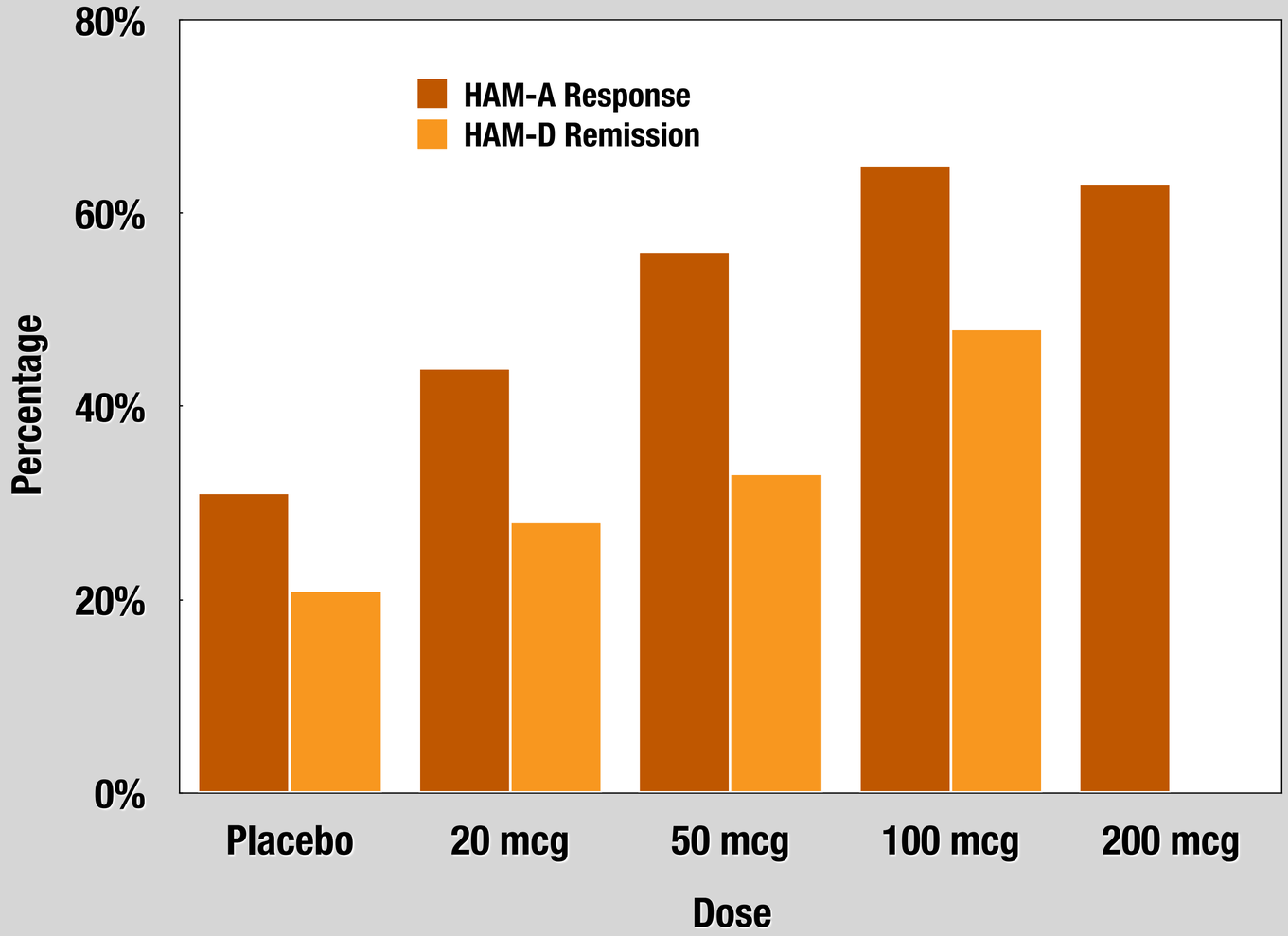
“Productive Meeting” with FDA Outlined Steps Forward 10/18/2024

https://www.fiercebiotech.com/biotech/lykos-accepts-fdas-view-reviving-mdma-treatnents-fortunes-requires-fresh-trial (Accessed 10/21/2024)
Psychopharmacology 2020;237:2485–2497 https://doi.org/10.1007/s00213-020-05548-2. Whyte LE. Wall Street Journal 10/23/23 https://www.wsj.com/health/healthcare/fda-widens-probe-of-ecstasy-based-drug-studies-510307b0?mod=latest_headlines

MM-120 (LSD; MindMed) Top Line Results in Phase 2B for GAD

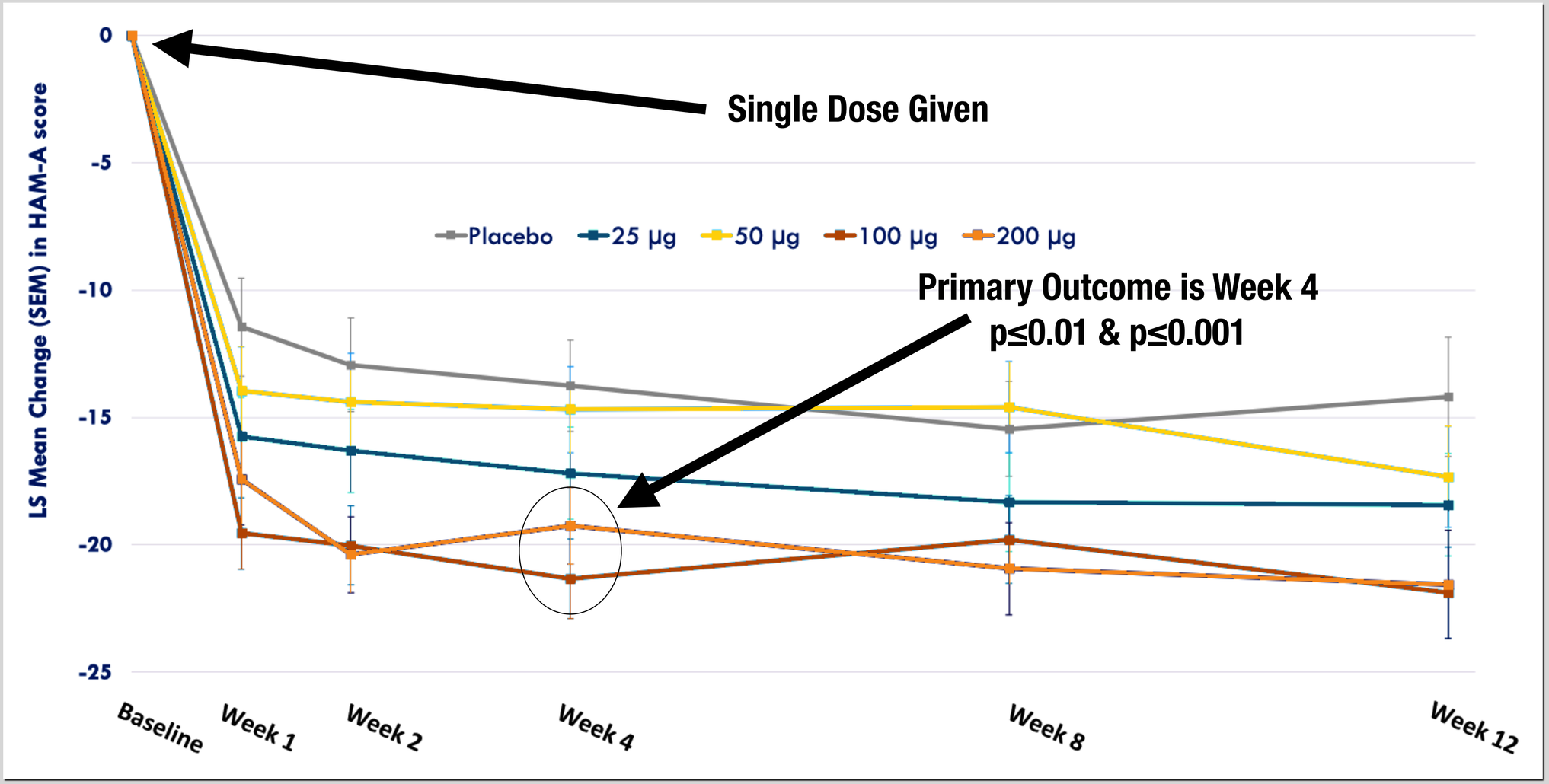
LSD Tartrate

- ✓ Five Groups: Placebo, 25 mcg, 50 mcg, 100 mcg, 200 mcg (Single Dose)
- ✓ 12-Week Study; HAM-A Primary Outcome at Week 4
- ✓ Monotherapy
- ✓ No “Assisted Therapy”
- ✓ Continuous Monitoring While Dosed (No Therapy)
- ✓ Provided Music, Eye Shades, Reading,



https://clinicaltrials.gov/study/NCT05407064 (Accessed 10/21/2024); Investor Presentation MindMed 03/07/2024 <https://d1io3yog0oux5.cloudfront.net/_00d810b1ae2a46c703778efe361a12e8/mindmed/db/2265/21423/pdf/MindMed's+Conference+Call+and+Webcast+on+MM120+for+Generalized+Anxiety+Disorder+(GAD);+March+2024_FINAL.pdf> (Accessed 10/21/2024)

MM-120 Appears to Have Sustained Benefit from Single Dose Monotherapy



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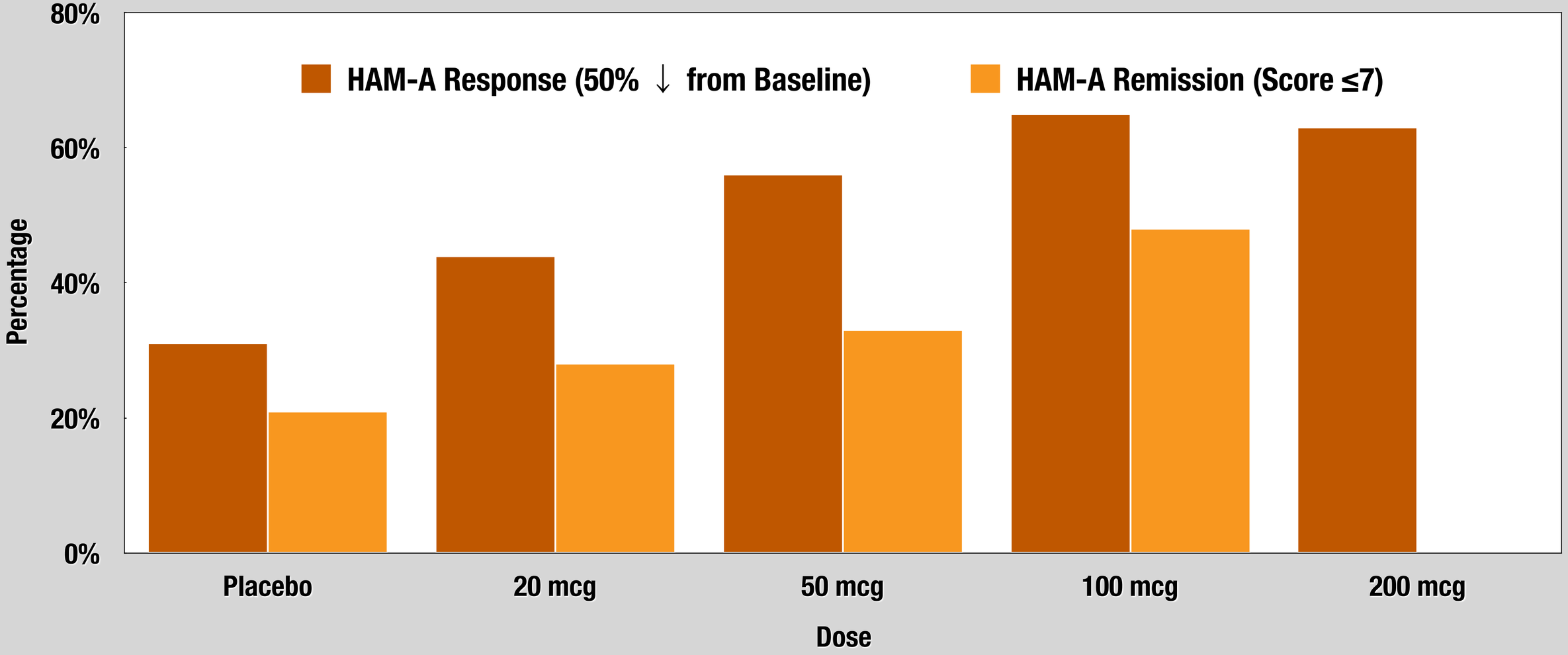
MM-120 Categorical Outcomes at Week 12



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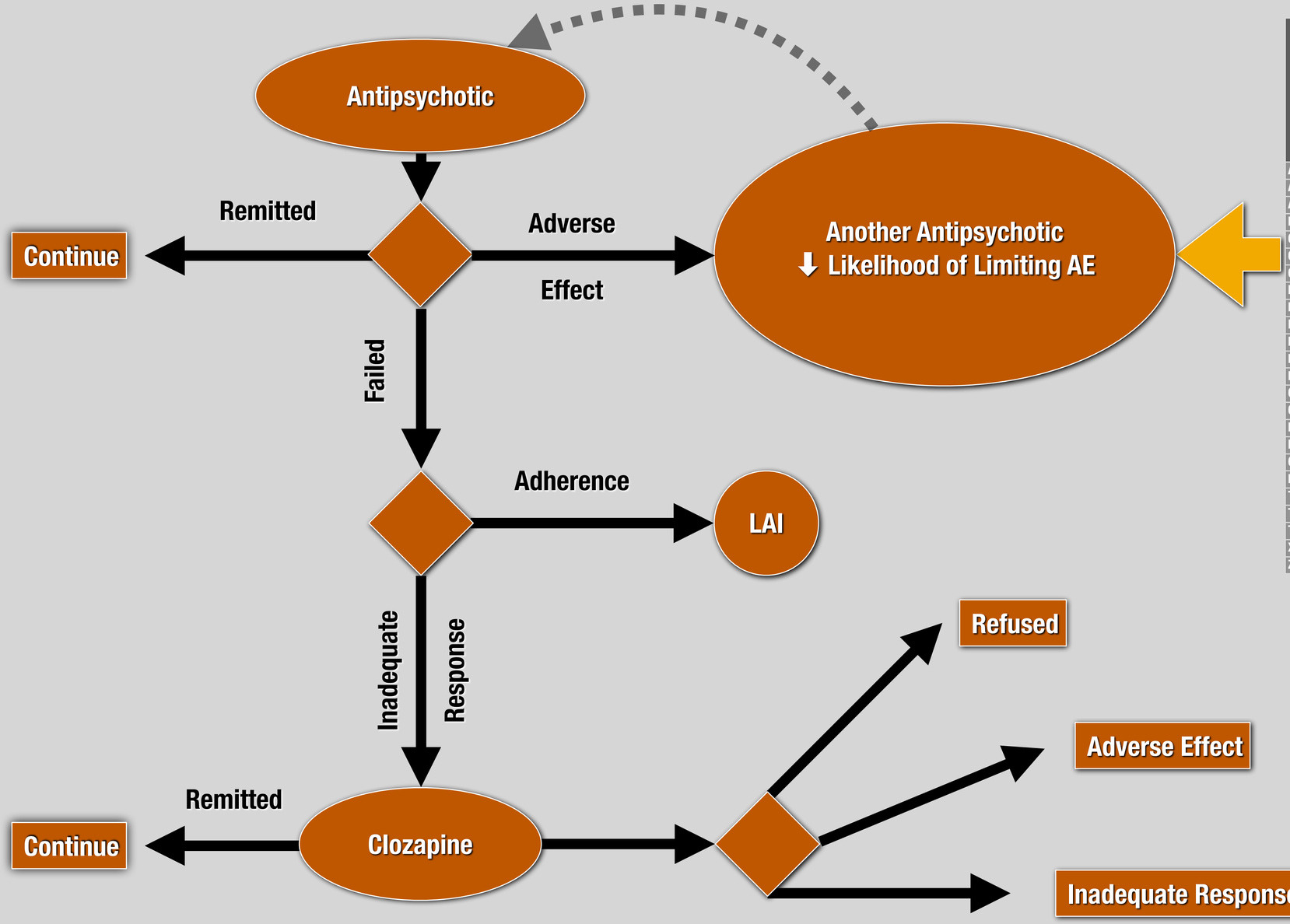
Adverse Effect Comparison of Medications for Schizophrenia

Drug	Sedation	Anticholinergic	Akathisia	Drug Induced Parkinsonism	Orthostasis	Weight Gain	Cholinergic	Agranulocytosis	Seizures	Diabetes	Dyslipidemia	Prolactin	QT Prolongation
Aripiprazole	1	1	2	0	2	1	0	0	0	0	0	0	0
Amisulpride	1	0	3	1	1	1	0	0	0	1	1	3	3
Asenapine	3	0	2	1	1	1	0	0	0	1	0	1	2
Brexpiprazole	1	0	1	0	2	1	0	0	0	0	0	0	0
Cariprazine	2	0	3	2	1	1	0	0	0	0	0	0	0
Chlorpromazine	3	3	3	3	4	3	0	1	3	1	1	2	2
Clozapine	4	3	0	0	3	4	0	3	4	3	2	0	2
Fluphenazine	1	1	6	4	1	1	0	1	1	1	1	3	2
Haloperidol	1	0	4	4	0	1	0	1	1	1	1	3	2
Iloperidone	3	0	1	1	4	3	1	0	0	1	1	1	3
Loxapine	3	2	4	2	3	1	0	1	2	1	1	2	1
Lumateperone	3	0	0	0	1	0	0	0	0	0	0	1	2
Lurasidone	2	0	4	2	1	0	0	0	0	1	0	2	0
Olanzapine	3	2	1	0	1	4	0	0	2	3	3	1	2
Olanzapine + Samidorphan	3	2	1	0	1	2	0	0	2	3	3	1	2
Paliperidone	1	1	1	0	2	2	0	0	0	1	1	4	1
Perphenazine	2	2	4	1	2	1	0	1	1	1	1	2	2
Quetiapine	3	2	1	0	2	2	0	0	1	1	1	0	2
Risperidone	2	1	3	2	2	2	0	0	1	1	2	4	2
Thioridazine	3	4	2	1	3	1	0	1	0	1	1	2	4
Thiothixene	1	1	3	3	1	1	0	1	1	1	1	3	1
Trifluoperazine	1	1	5	3	2	1	0	1	1	1	1	3	1
Xanomeline + Trospium	1	3	0	0	0	0	2	0	0	0	0	0	0
Ziprasidone	3	2	2	1	1	0	0	0	0	1	1	2	3

Key: Color Code: Green (lower number) is Less Risk, Graded through Yellow (median) to Red (highest number) with Highest Risk. Differences of 1 Rank are Equivocal, Differences of 2 are Likely Clinically Signifiant. Columns are in Order of Common Patient Complaints (Left to Right). Updated from Saklad SR, "Antipsychotic Adverse Effects Comparison" Platform Presentation at CPNP (now AAPP) 2021. <https://aapp.org/ed/course/antipsychotic-adverse-effects-comparison>

Treatment of Psychotic Symptoms



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Amisulpride	1	0	3	1	1	1	0	0	0	1	1	3	3
Asenapine	3	0	2	1	1	1	0	0	0	1	0	1	2
Brexpiprazole	1	0	1	0	2	1	0	0	0	0	0	0	0
Cariprazine	2	0	3	2	1	1	0	0	0	0	0	0	0
Chlorpromazine	3	3	3	3	4	3	0	1	3	1	1	2	2
Clozapine	4	3	0	0	3	4	0	3	4	3	2	0	2
Fluphenazine	1	1	6	4	1	1	0	1	1	1	1	3	2
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Lurasidone	2	0	4	2	1	0	0	0	0	1	0	2	0
Olanzapine	3	2	1	0	1	4	0	0	2	3	3	1	2
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Quetiapine	3	2	1	0	2	2	0	0	1	1	1	0	2
Risperidone	2	1	3	2	2	2	0	0	1	1	2	4	2
Thioridazine	3	4	2	1	3	1	0	1	0	1	1	2	4
Thiothixene	1	1	3	3	1	1	0	1	1	1	1	3	1
Trifluoperazine	1	1	5	3	2	1	0	1	1	1	1	3	1
Xanomeline + Trospium	1	3	0	0	0	0	2	0	0	0	0	0	0
Ziprasidone	3	2	2	1	1	0	0	0	0	1	1	2	3

Learning Objectives

Describe the efficacy and safety data of the emerging (Phase 3) and recently approved mental health and neurologic medications

Explain appropriate monitoring requirements, patient education points, and provider education for these agents where known

Discuss the clinical use of these new and emerging medications and where they may fit into current clinical practice