Breaking the Mold: Novel Mechanisms in Psychiatry's New Kids on the Block

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Disclosures

Dr. Kristin Waters, faculty for this CE activity, has no relevant financial relationship(s) with ineligible companies to disclose.

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Learning Objectives

- Describe the unique mechanisms of action of xanomeline-trospium in the management of schizophrenia and dextromethorphan-containing medications in the management of major depressive disorder
- Distinguish between adverse effect profiles of new psychiatric medications compared to traditional antipsychotics and antidepressants
- Identify appropriate candidates for new psychiatric medications based on knowledge of efficacy, safety, and patient-specific factors

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Schizophrenia & Xanomeline/Trospium

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Schizophrenia: Background

- Serious mental illness with prevalence of ~1%
- Associated with a high degree of **morbidity:**
  - Common co-occurring conditions: Cardiovascular disease, dyslipidemia, obesity, hypertension, diabetes, substance use disorders
  - Reduced quality of life
  - Treatment-related adverse effects
  - Homelessness
  - Stigma, social isolation
  - Family/caregiver burden
  - Financial burden
- Among the top 15 leading causes of disability worldwide
- Increased **mortality:** Lifespan may be decreased by an average of 28.5 years

Finnerty MT, et al. *Schizophrenia (Heidelb).* 2024; Olfson M, et al. *JAMA Psychiatry.* 2015; GBD 2016 Disease and Injury Incidence and Prevalence Collaborators. *Lancet.* 2017; Schizophrenia. National Institute of Mental Health. Available from: nimh.nih.gov/health/statistics/schizophrenia

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Schizophrenia: Symptoms

Positive symptoms:	• Hallucinations • Delusions • Disorganized speech • Grossly disorganized or catatonic behavior
Negative symptoms:	• Blunted affect • Alogia • Avolition • Anhedonia • Amotivation
Cognitive symptoms:	• Difficulty maintaining attention • Deficits in working memory and long-term memory • Deficits in executive function

American Psychiatric Association, *DSM-5-TR*, 2013

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Schizophrenia: Pathophysiology

- Heterogenous and not fully understood
- Anatomical changes
- **Neurotransmitter changes:**
  - Dopamine (DA):
    - DA **hyperactivity** in mesolimbic pathway→ positive symptoms
    - DA **hypofunction** in mesocortical pathway (frontal cortex) → negative and cognitive symptoms
  - Dysfunction of serotonin, glutamate, GABA
  - Cholinergic system dysfunction

Robison AJ, et al. *Biol Psychiatry.* 2020
Jimenez-Trejo F, et al. *Front Psychiatry.* 2024

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Schizophrenia Treatment Guidelines

	APA 2020	BAP 2020
First-line	Second-generation antipsychotic (SGA) First-generation antipsychotic (FGA) *Oral or long-acting injectable (LAI)*	SGA FGA (lower dose preferred)
Second-line	SGA FGA *Oral or LAI*	SGA FGA *LAI if pt nonadherent*
Third-line	Clozapine	Clozapine

The American Psychiatric Association Practice Guideline for the Treatment of Patients with Schizophrenia 2020
British Association for Psychopharmacology Evidence-based Guideline for the Treatment of Schizophrenia 2020

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Audience Question 1

What is the mechanism of action of traditional antipsychotic medications in the treatment of schizophrenia?

A. Serotonin receptor antagonism
B. Dopamine receptor antagonism
C. Glutamate receptor antagonism
D. GABA receptor antagonism

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Audience Question 1

What is the mechanism of action of traditional antipsychotic medications in the treatment of schizophrenia?

A. Serotonin receptor antagonism
B. Dopamine receptor antagonism
C. Glutamate receptor antagonism
D. GABA receptor antagonism

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Audience Question 2

What year was the first antipsychotic approved by the FDA?

A. 1944
B. 1954
C. 1964
D. 1974

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Audience Question 2

What year was the first antipsychotic approved by the FDA?

A. 1944
B. 1954
C. 1964
D. 1974

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Audience Question 3

Which of the following symptoms of schizophrenia is more likely to respond to treatment with an antipsychotic?

A. Anhedonia
B. Concentration difficulties
C. Auditory hallucinations
D. Blunted affect

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Robison AJ, et al. *Biol Psychiatry.* 2020
Jimenez-Trejo F, et al. *Front Psychiatry.* 2024

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First-Generation Antipsychotics

- "Typical" antipsychotics
- Block post-synaptic D_2 receptors
- Longer receptor occupancy compared to SGAs
  - Other receptors may be affected → differences in **adverse effect profiles**

Generic Name	Brand Name	Potency
Chlorpromazine	Thorazine	Low
Thioridazine	Mellaril	Low
Loxapine	Loxitane	Mid
Perphenazine	Trilafon	Mid
Fluphenazine	Prolixin	High
Trifluoperazine	Stelazine	High
Thiothixene	Navane	High
Haloperidol	Haldol	High

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Generic Name	Brand Name
Aripiprazole	Abilify
Asenapine	Saphris
Brexpiprazole	Rexulti
Cariprazine	Vraylar
Clozapine	Clozaril
Iloperidone	Fanapt
Lumateperone	Caplyta
Lurasidone	Latuda
Paliperidone	Invega
Olanzapine	Zyprexa
Olanzapine/Samidorphan	Lybalvi
Quetiapine	Seroquel
Risperidone	Risperdal
Ziprasidone	Geodon

Second-Generation Antipsychotics

- "Atypical" antipsychotics
- Block D_2 and 5-HT_2 receptors
  - Some have partial D_2 and/or partial 5-HT_{1A} agonism

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Antipsychotic Adverse Effects

Extrapyramidal symptoms	Metabolic symptoms • Weight gain • Glucose intolerance • Lipid abnormalities	QTc prolongation	Hyperprolactinemia
Sedation	Orthostatic hypotension	Anticholinergic effects	Sexual dysfunction

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Robison AJ, et al. *Biol Psychiatry.* 2020; Jimenez-Trejo F, et al. *Front Psychiatry.* 2024

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Schizophrenia and the Cholinergic System

- Cholinergic system plays role in multiple processes including sensory processing and perception, cognition, memory, emotional regulation, and motivation
  - Modulates dopamine release in striatum
  - Acetylcholine acts on nicotinic channels and muscarinic receptors
- Evidence growing that schizophrenia is associated with changes in cholinergic neurotransmission
  - Lower cholinergic receptor levels = more severe clinical or cognitive symptoms
  - Significant decrease in muscarinic M1 and M4 receptor densities in striatum, hippocampus, and frontal and cingulate cortices

Saint-Georges Z, et al. *Mol Psychiatry.* 2025

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Xanomeline/ Trospium (Cobenfy™)

- FDA-approved for schizophrenia in September 2024
- **Xanomeline: M1/M4 dual muscarinic receptor agonist**
  - Technically not considered an antipsychotic
  - Indirect effects on dopamine activity:
    - **M1 agonism:**
      - Improves dopamine signaling in cortex and striatum → reduces positive, negative, and cognitive symptoms
    - **M4 agonism:**
      - Helps control excessive dopamine in mesolimbic pathway → reduce positive symptoms and minimize motor adverse effects
      - Also stabilizes cognition via reduction in glutamate transmission

Nair S, et al. *Acta Neuropsychiatr.* 2025

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Why Trospium?

- Xanomeline studied in 1990s for Alzheimer's disease
  - Significant improvement in cognition but high dropout rate related to ADEs
  - Most common ADEs:
    - Nausea
    - Vomiting
    - Dyspepsia
    - Increased salivation
    - Diaphoresis
    - Chills
    - Elevated liver enzymes, biliary transaminase
- Trospium = muscarinic receptor antagonist in peripheral tissues
  - Goal is to mitigate cholinergic ADEs of xanomeline
  - Does not cross blood-brain barrier

Bodick NC, et al. *Arch Neurol.* 1997;54:465-73
Breier A, et al. *Psychopharmacology (Berl).* 2023;240(5):1191-8

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Xanomeline/Trospium (X/T): Efficacy

	EMERGENT-1	EMERGENT-2	EMERGENT-3
Trial phase	2	3	3
Study duration	5 weeks		
Patient population	Adults 18-65 years* with **schizophrenia** with an acute exacerbation of psychotic symptoms **requiring hospitalization within 2 months** of screening • Baseline PANSS total score ≥ 80 and ≤ 120 (moderately to severely ill)[‡] **Pertinent exclusion criteria:** First-episode psychosis, history of resistance to antipsychotic treatment		
Study design	Randomized, double-blind, multi-site, inpatient, placebo-controlled		
Treatment	X/T vs. placebo twice daily (flexible dosing) • Continued use of as-needed anxiolytics permitted		
Primary outcome	Change from baseline to week 5 in PANSS total score		
PANSS: Positive and Negative Syndrome Scale			

*EMERGENT-1 included adults 18-60 years
[‡] Other criteria included score of ≥ 4 on at least 2 out of 4 PANSS positive scale items, Clinical Global Impression-Severity score of ≥ 4

Kaul I, et al. *J Clin Psychiatry.* 2025
Kaul I, et al. *Schizophrenia (Heidelb).* 2024

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X/T: Efficacy (EMERGENT-1, -2, -3)

Pertinent baseline characteristics			
		X/T (n=314)	**Placebo (n=326)**
Age (years), mean ± SD		44.6 ± 10.7	43.7 ± 11.3
Male, n (%)		233 (74.2)	250 (76.7)
Race, n (%)	**Asian**	4 (1.3)	2 (0.6)
	Black	225 (71.7)	221 (67.8)
	Native Hawaiian or Other Pacific Islanders	1 (0.3)	1 (0.3)
	White	83 (26.4)	98 (30.1)
	Other	1 (0.3)	4 (1.2)
United States, n (%)[a]		295 (93.9)	300 (92.0)
PANSS total score, mean ± SD		97.5 ± 9.0	97.0 ± 8.9
[a]Other study site locations = Ukraine			

Kaul I, et al. *J Clin Psychiatry.* 2025
Kaul I, et al. *Schizophrenia (Heidelb).* 2024

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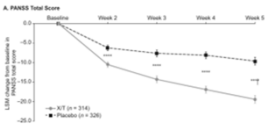
X/T: Efficacy (EMERGENT-1, -2, -3)

- X/T resulted in a 9.9-point greater reduction in total PANSS score at week 5 compared to placebo
  - Improvement observed at week 2 (earliest timepoint measured)
  - Greater reduction in positive symptoms than negative symptoms



	X/T (n=314)	Placebo (n=326)	Difference (95% CI)	Cohens d	p value
PANSS total score, LSM (SE)	-19.4 (1.0)	-9.6 (1.0)	-9.9 (-12.4, -7.3)	0.65	<0.0001

LSM: least squares mean
SE: standard error

Kaul I, et al. *Schizophrenia (Heidelb).* 2024

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X/T: Efficacy in Open Label Studies

- 2 open-label extension studies:
  - EMERGENT-4 (53 weeks)
  - EMERGENT-5 (56 weeks)
- Non peer-reviewed results of EMERGENT-4 include:
  - Much lower completion rate (~23%) than EMERGENT-1, -2, and -3
    - ~11% did not complete due to a treatment-emergent adverse effect (TEAE)
  - >50% experienced a TEAE
  - Continued improvements in PANSS scores
    - LSM improvement in PANSS score of 9.0 points for patients who had received X/T in the acute studies (n=19)

Ramey O, et al. *Ann Pharmacother.* 2025
Nair S, et al. *Acta Neuropsychiatr.* 2025
Bristol-Myers Squibb. An extension study to assess long-term safety, tolerability, and efficacy of KarXT in adult patients with Schizophrenia (EMERGENT-4). Clinicaltrials.gov identifier: NCT04659174. Updated October 28, 2024. Accessed November 13, 2025. https://clinicaltrials.gov/study/NCT04659174?intr=Xanomeline%20and%20Trospium%20Chloride%20Capsules&rank=1

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ARISE Trial

- Not published in full
- 6-week, randomized, double-blind, placebo-controlled, multicenter, **outpatient** study
- X/T as **adjunctive treatment** in adults with schizophrenia with inadequate response to current antipsychotic
  - No statistically significant improvement in PANSS score compared to placebo in primary analysis
  - Post-hoc analysis showed that patients receiving antipsychotics other than risperidone did have a statistically significant reduction in PANSS score when X/T was added

Nair S, et al. *Acta Neuropsychiatr.* 2025
Bristol-Myers Squibb. A Study to Assess Efficacy and Safety of Adjunctive KarXT in Subjects With Inadequately Controlled Symptoms of Schizophrenia (ARISE) Clinicaltrials.gov identifier: NCT05145413. Updated March 28, 2025. Accessed November 13, 2025. https://www.clinicaltrials.gov/study/NCT05145413

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X/T: Safety (EMERGENT-1, -2, -3)

- Early trial discontinuation: 27.6% in X/T group and 22.7% in placebo group:
  - Most common reason = withdrawal of consent
- Most commonly reported treatment-emergent adverse effects (TEAEs) occurred within the first 7 days of X/T treatment and resolved by end of treatment

%	X/T (n=340)	Placebo (n=343)
Early trial discontinuation due to TEAE	5.9	4.4
≥ 1 TEAE	67.9	51.3
Nausea	18.5	3.8
Constipation	17.1	6.1
Dyspepsia	15.9	4.7
Vomiting	13.5	1.7
Hypertension	8.5	1.7

Kaul I, et al. *J Clin Psychiatry.* 2025

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X/T: Safety (EMERGENT -1, -2, -3)

Body weight changes:

- Minimal, less than in placebo group

Movement disorders:

- Very rare
- 1.5% in X/T group

Kaul I, et al. *J Clin Psychiatry.* 2025

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X/T Dosing & PK

- **Initial dosing:**
  - Xanomeline 50 mg/trospium chloride 20 mg by mouth BID for ≥ 2 days
  - May then increase to xanomeline 100 mg/trospium chloride 20 mg by mouth BID for ≥5 days
- **Max dose:**
  - Xanomeline 125 mg/ trospium chloride 30 mg by mouth BID
- **Dose adjustments:**
  - Not recommended in moderate or severe renal impairment, mild hepatic impairment
  - Contraindicated in moderate to severe hepatic impairment
- **PK parameters (xanomeline):**
  - **Absorption:** 2 hours
    - AUC increased ~30% by high-fat meal
  - Hepatically metabolized via CYP450
    - Substrate of CYP2D6, CYP2B6, CYP1A2, CYP2C9, CYP2C19
    - Inhibitor of CYP3A4
  - Excretion: 78% renal, 12% fecal
  - Elimination half-life: 5 hours

Cobenfy (xanomeline and trospium chloride) [package insert]. Bristol Myers Squibb, 2014. Accessed November 13, 2025. https://packageinserts.bms.com/pi/pi_cobenfy.pdf

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X/T: Key Takeaways

- Statistically and clinically reduced PANSS total scores in three 5-week RCTs
  - Improvements in positive and negative symptoms
  - Results from open-label extension trials not fully available → long-term safety and efficacy not established
- Study assessing role as adjunctive treatment did not demonstrate statistically significant benefit (results not fully available)
- Most common TEAEs are gastrointestinal
  - Nausea, constipation, dyspepsia, vomiting
- Not associated with some TEAEs related to traditional antipsychotics
  - Movement disorders, weight gain

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X/T: Current Place in Therapy

- Unclear
- Possible candidates for X/T may include adults with schizophrenia with:
  - Intolerable adverse effects from antipsychotics
    - Especially metabolic or movement-related
  - Cognitive impairment, negative symptoms → although more improvement in positive symptoms in trials
  - Treatment-resistant? (adjunct)
- Cost concerns
  - List price: $1850 for 30-day supply

Nair S, et al. *Acta Neuropsychiatr.* 2025

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Audience Question 4

Which of the following patients with schizophrenia would be the best candidate for treatment with xanomeline/trospium? (assume no other PMH)

A. A 28 y/o patient who has been treated with 5 antipsychotics over the past 3 years and was recently started on clozapine
B. A 21 y/o patient who was just diagnosed with schizophrenia and has never received treatment with an antipsychotic previously
C. A 34 y/o patient who responded well to olanzapine but discontinued due to weight gain

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Audience Question 4

Which of the following patients with schizophrenia would be the best candidate for treatment with xanomeline/trospium? (assume no other PMH)

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Audience Question 5

Which adverse effect is more likely to occur during treatment with xanomeline/trospium compared to standard antipsychotics?

A. Dystonic reactions
B. Nausea
C. Dyslipidemia
D. Hyperprolactinemia

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Audience Question 5

Which adverse effect is more likely to occur during treatment with xanomeline/trospium compared to standard antipsychotics?

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B. Nausea
C. Dyslipidemia
D. Hyperprolactinemia

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Depression & Dextromethorphan

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Major Depressive Disorder (MDD): Background

- One of the most common psychiatric disorders in the United States
  - Affects more than 1 out of 5 people (20.6% lifetime prevalence)
  - ~60% receive treatment
- Most pts have ≥ 1 co-occurring condition
  - Medical, psychiatric, substance use disorders
- High degree of morbidity
  - Loss of productivity, disability
  - Decreased quality of life
  - High economic burden
- Significant increase in mortality

Hasin DS, et al. *JAMA Psychiatry.* 2018
Zhang Z, et al. *JAMA Network Open.* 2023

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MDD: Symptoms

Sleep changes	Loss of interest	Guilt	Energy changes
Concentration impairment	Appetite changes	Psychomotor agitation/slowing	Suicidal ideation or actions

American Psychiatric Association, *DSM-5-TR*, 2013

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MDD: Pathophysiology

- Complex and heterogeneous
- Several hypotheses:
  - Monoamine hypothesis
    - Deficiencies in serotonin, norepinephrine, dopamine
  - Dysregulation hypothesis
    - Dysregulation of neurotransmitters: Serotonin, norepinephrine, dopamine, glutamate, adenosine
  - Hypothalamic-pituitary-adrenal (HPA) axis dysfunction
  - Inflammatory hypothesis
  - Genetic/epigenetic anomaly hypothesis
  - Structural and functional brain remodeling

Cui L, et al. *Signal Transduct Target Ther.* 2024

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Audience Question 6

Which of the following are considered first-line treatments for MDD? Select all that apply.

A. Vortioxetine (Trintellix)
B. Fluoxetine (Prozac)
C. Bupropion (Wellbutrin)
D. Amitriptyline (Elavil)
E. Dextromethorphan/bupropion (Auvelity)
F. Esketamine (Spravato)
G. Mirtazapine (Remeron)

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MDD Treatment Guidelines

- Psychotherapy can be first-line for mild to moderate MDD

Place in Therapy	Antidepressant or Antidepressant Class
First-line	• Selective serotonin reuptake inhibitors (SSRIs) • Serotonin norepinephrine reuptake inhibitors (SNRIs) • Bupropion • Mirtazapine • Vortioxetine • Vilazodone • Trazodone[#]
Second-line	• Switch to alternate first-line therapy • Add a second antidepressant or augmentation (next slide) • Tricyclic antidepressants (TCAs) • **Dextromethorphan-bupropion**[¶]
Electroconvulsive therapy may be appropriate at any stage	

[#]VA guidelines only
[¶]CANMAT guidelines only

Canadian Network for Mood and Anxiety Treatments (CANMAT) 2023 Update on Clinical Guidelines for Management of Major Depressive Disorder in Adults, 2024
VA/DoD Clinical Practice Guideline. The Management of Major Depressive Disorder. 2022

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Augmentation Strategies

- Recommended adjunctive treatments differ across guidelines
- Common augmentation strategies:
  - Non-pharmacologic therapies
  - Second-generation antipsychotics
  - IV ketamine
  - Intranasal esketamine
  - Lithium
  - Triiodothyronine

Canadian Network for Mood and Anxiety Treatments (CANMAT) 2023 Update on Clinical Guidelines for Management of Major Depressive Disorder in Adults, 2024
VA/DoD Clinical Practice Guideline. The Management of Major Depressive Disorder. 2022

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First-Line Antidepressant Adverse Effects

Anxiety	Insomnia, sedation	Headache	Nausea
Diarrhea	Anorexia	Sexual dysfunction	Diaphoresis

Boxed warning: Suicidal thoughts/behaviors in pts <25 years of age

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Unique Bupropion Adverse Effects

- Rare risk of seizures (0.1-0.4%)
- Insomnia, activation, anxiety
- Hypertension
- Tachycardia
- Constipation
- Tremor
- Dizziness
- Xerostomia

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Antidepressant Response

- First-line antidepressants take from 4 to 6 weeks to achieve an effect
- Many patients with MDD do not respond adequately to initial pharmacologic treatment
  - **Approximately 1 in 3 patients will not achieve remission**
- Treatment-resistant depression generally defined as $\geq$ 2 unsuccessful antidepressant trials

Voineskos D, et al. *Neuropsychiatr Dis Treat.* 2020

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Audience Question 7

Current first-line pharmacologic treatment options for MDD act on which of the following neurotransmitters? Select all that apply.

A. Serotonin
B. Norepinephrine
C. Dopamine
D. Glutamate
E. GABA

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  - Genetic/epigenetic anomaly hypothesis
  - Structural and functional brain remodeling

Cui L, et al. *Signal Transduct Target Ther.* 2024

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Glutamate and MDD

- Glutamate: Main excitatory neurotransmitter in CNS
- Activates N-methyl-D-aspartate (NMDA) receptors in neurons → contributes to synaptic loss
  - Plays role in mediating interaction between CNS and astrocytes
- Pathogenesis of MDD linked to:
  - Abnormal glutamate levels in cortex
  - Abnormal NMDA receptor expression and signaling

Morguchi S, et al. *Mol Psychiatry.* 2019
Feyissa AM, et al. *Neuropsychopharmacol Biol Psychiatry.* 2009
Cui L, et al. *Signal Transduct Target Ther.* 2024

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NMDA Receptor Antagonists in MDD

IV ketamine

Intranasal esketamine

Dextromethorphan

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DTX HBr/ Bupropion HCl (Auvelity®)

- FDA-approved for MDD in 2022
- Dextromethorphan (DTX) mechanism of action in MDD:
  - Non-competitive NMDA receptor antagonist
  - Sigma-1 receptor agonist
    - Neuroprotective effects

Eskandari K, et al. *Pharmaceuticals (Basel).* 2025
Auvelity (dextromethorphan HBr and bupropion HCl) [package insert]. Axsome, 2022. Accessed November 14, 2025. www.axsome.com/wp-content/uploads/2024/11/auvelity-prescribing-information.pdf

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Why Bupropion?

- DTX rapidly and extensively metabolized via CYP2D6
  - Limits bioavailability and clinical utility
- **Combination with bupropion (CYP2D6 inhibitor) increases plasma concentrations and prolongs half-life of DTX**

Majeed A, et al. *Expert Opin Emerg Drugs.* 2021
Eskandari K, et al. *Pharmaceuticals (Basel).* 2025
Auvelity (dextromethorphan HBr and bupropion HCl) [package insert]. Axsome, 2022. Accessed November 14, 2025. www.axsome.com/wp-content/uploads/2024/11/auvelity-prescribing-information.pdf

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DTX/Bupropion: Efficacy

	GEMINI study
Trial phase	3
Study duration	6 weeks
Patient population	Adults 18-65 years of age with MDD experiencing a depressive episode of ≥ 4 weeks and a MADRS score of ≥ 25 and CGI-S score ≥ 4 **Pertinent exclusion criteria:** Bipolar disorder, treatment-resistant depression, substance use disorder within past year, clinically significant risk of suicide
Study design	Randomized, double-blind, placebo-controlled, multi-center
Treatment	DTX-bupropion vs. placebo orally (once daily x 3 days then BID)
Primary outcome	Change from baseline to week 6 in MADRS total score
MADRS: Montgomery-Asberg Depression Rating Scale CGI-S: Clinician Global Impression-Severity	

Iosifescu DV, et al. *J Clin Psychiatry.* 2022.

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DTX/Bupropion: Efficacy

Pertinent baseline characteristics			
		DTX/Bupropion (n=156)	**Placebo (n=162)**
Age, mean y (SD)		42.1 (12.80)	41.2 (13.77)
Male, n (%)		61 (39.1)*	45 (27.8)
Race, n (%)	**White**	84 (53.8)	92 (56.8)
	Black or African-American	58 (37.2)	54 (33.3)
	Asian	9 (5.8)	8 (4.9)
	Multiple	3 (1.9)	2 (1.2)
	Other	2 (1.3)	6 (3.7)
MADRS total score, mean (SD)		33.6 (4.43)	33.2 (4.36)
*Significantly more males enrolled in treatment group vs. placebo			

Iosifescu DV, et al. *J Clin Psychiatry.* 2022.

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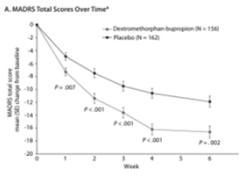
DTX/Bupropion: Efficacy

- **Primary endpoint:** DTX/bupropion resulted in a 3.87 point greater reduction in MADRS score at 6 weeks compared to placebo
  - Difference started at week 1
- Dropout rate 24.1% in treatment group vs. 10.4% in placebo group



	DTX/Bupropion (N=156)	Placebo (N=162)	LSM difference (95% CI)	p-value
MADRS total score change, LSM (SE)	-15.9 (0.9)	-12.0 (0.9)	-3.87 (-1.39 to -6.36)	0.002
LSM: least squares mean SE: Standard error				

Iosifescu DV, et al. *J Clin Psychiatry.* 2022.

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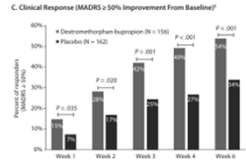
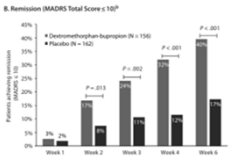
DTX/Bupropion: Efficacy

- Significantly higher rates of response (≥ 50% reduction in MADRS) and remission (MADRS score ≤ 10) in DTX/bupropion group vs. placebo at week 6
  - **Response:** 54.0% vs. 34.0%
  - **Remission:** 39.5% vs. 17.3%





Iosifescu DV, et al. *J Clin Psychiatry.* 2022.

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DTX/Bupropion: Safety

n (%)	DTX/bupropion (N=162)	Placebo (N=164)
Any adverse event	100 (61.7)	74 (45.1)
Adverse event leading to discontinuation	10 (6.2)	1 (0.6)
Dizziness	26 (16.0)	10 (6.1)
Nausea	21 (13.0)	14 (8.5)
Headache	13 (8.0)	6 (3.7)
Diarrhea	11 (6.8)	5 (3.0)
Somnolence	11 (6.8)	5 (3.0)
Dry mouth	9 (5.6)	4 (2.4)
Hyperhidrosis	8 (4.9)	0

Iosifescu DV, et al. *J Clin Psychiatry.* 2022.

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DTX/Bupropion: Safety

- No identified risk of:
  - Psychotomimetic effects
  - Weight gain
  - Sexual dysfunction
  - Suicidal behaviors
  - Withdrawal
- Carries the boxed warning regarding increased risk of suicidal thoughts and behaviors for patients <25 years of age

Iosifescu DV, et al. *J Clin Psychiatry.* 2022.

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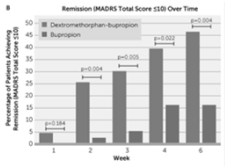
Is Bupropion Doing All the Work?

- Comparison of DTX/bupropion vs. bupropion alone showed significant improvements over 6 weeks with DTX/bupropion in:
  - Change in MADRS
    - -13.7 points vs. -8.8 points
  - Remission rates



Tabuteau H, et al. *Am J Psychiatry.* 2022

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However…..

- In an unpublished study comparing DTX/bupropion to bupropion in **treatment-resistant MDD**:
  - Statistically significant improvement in MADRS score in DTX/bupropion group at weeks 1 and 2 but results were not statistically significant at week 6

Biospace. Axsome Therapeutics [Internet]. Biospace; 2020 [cited November 15, 2025]. Available from: https://www.biospace. com/article/releases/axsome-therapeutics-announces-topline-results-of-the-stride-1-phase-3-trial-in-treatment-resistant- depression-and-expert-call-to-discuss-clinical-implications

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DTX/Bupropion Dosing & PK

- **Dosing:**
  - Dextromethorphan HBr 45 mg/bupropion HCl 105 mg (1 tablet) by mouth once daily in morning x 3 days followed by:
  - 1 tablet by mouth BID given at least 8 hours apart
- **Dose adjustments:**
  - Renal impairment (GFR 30 to 59 mL/minute/1.73m^2): 1 tablet daily
    - GFR <30: Use not recommended
  - Severe hepatic impairment: Use not recommended
  - Concomitant strong CYP2D6 inhibitors: 1 tablet daily
- **Metabolism:**
  - DTX: CYP2D6
    - Substrate of CYP2D6
  - Bupropion: CYP2B6
    - Inhibitor of CYP2D6
- **Renal excretion**
  - DTX: 45-83%
  - Bupropion: 87%
- **Elimination half-life:**
  - DTX: 22 hours
  - Bupropion: 15 hours

Auvelity (dextromethorphan HBr and bupropion HCl) [package insert]. Axsome, 2022. Accessed November 14, 2025. www.axsome.com/wp-content/uploads/2024/11/auvelity-prescribing-information.pdf

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DTX/Bupropion: Key Takeaways

- DTX/bupropion demonstrated statistically and clinically meaningful reductions in MADRS total score in phase 3 trial compared to placebo
  - Higher rates of response and remission
  - Improvements were observed **earlie**r than what is typically expected from traditional oral antidepressants
  - Patient population somewhat limited
- Most common adverse effects include dizziness, diarrhea, nausea, and headache
  - Concerns about abuse → not observed in trial but excluded patients with substance use disorders

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DTX/Bupropion: Current Place in Therapy

- Second-line in CANMAT treatment guidelines
- May be appropriate for patients requiring more rapid symptom control or those with intolerable adverse effects from other antidepressants
- No published clinical trials have demonstrated role as an **adjunctive** medication or in:
  - Treatment-resistant depression
  - Bipolar depression
- Cost concerns:
  - ~$1400 for 30-day supply

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Audience Question 8

Which of the following patients with MDD would be the best candidate for treatment with dextromethorphan/bupropion?

A. A pt who has been previously treated with escitalopram but discontinued due to sexual dysfunction
B. A pt who has been previously treated with escitalopram, venlafaxine XR, and mirtazapine with inadequate response
C. A pt with cocaine use disorder who has never received pharmacologic treatment for depression

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Breaking the Mold: Novel Mechanisms in Psychiatry's New Kids on the Block

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Session Code

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