REAL PSYCHIATRY

An Educational Experience Designed for and by
APPs on the Frontline of Modern Practice

THE CHANGING FACE OF MAJOR DEPRESSIVE DISORDER TREATMENT

NEW PARADIGMS AND EMERGING STRATEGIES

— JANUARY 13, 2024 —

Project Overview

- In the past several years, multiple novel treatments for major depressive disorder (MDD) have emerged that represent a shift from traditional monoaminergic-based approaches to new, **multitargeted mechanisms**.
- These unique strategies allow for an expanded therapeutic arsenal including agents that can be more **rapid-acting and impactful for difficult-to-treat depression phenotypes**.
- Such developments, however, have outpaced treatment guidelines, leaving an **unmet need** for education on the optimal use of these newly approved therapies.

- **OBJECTIVE:** To help clinicians navigate novel agents and strategies to optimize the modern therapeutic management of MDD and its many phenotypes.
  - This activity will utilize expert-led case-based discussion to provide guidance on clinical decision making where there is a scarcity of formal recommendations or guidelines.

FACULTY

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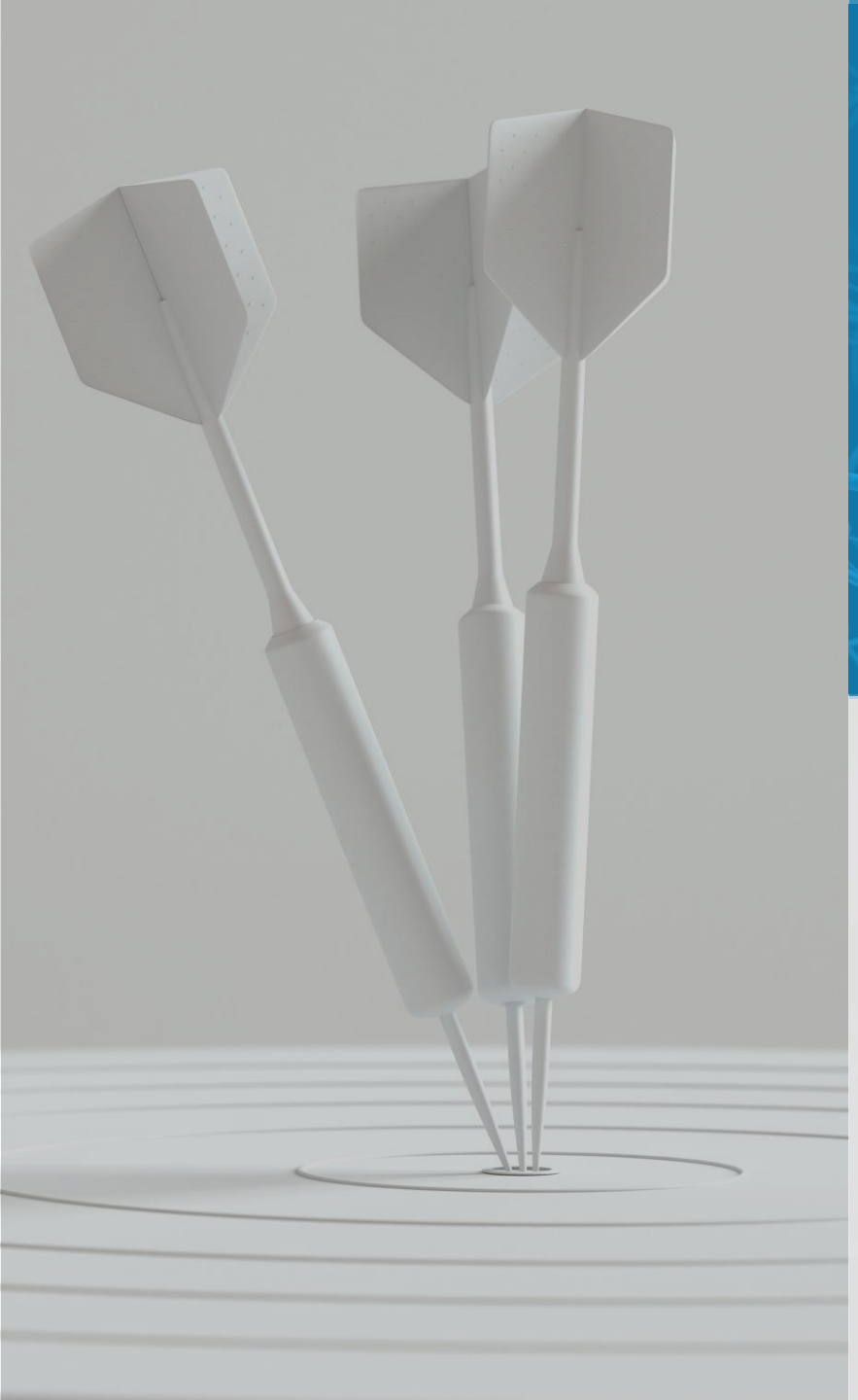


MODULE -1-

SHIFTING CONVENTION:

NEW AND MULTITARGETED MECHANISMS

CASE 1*

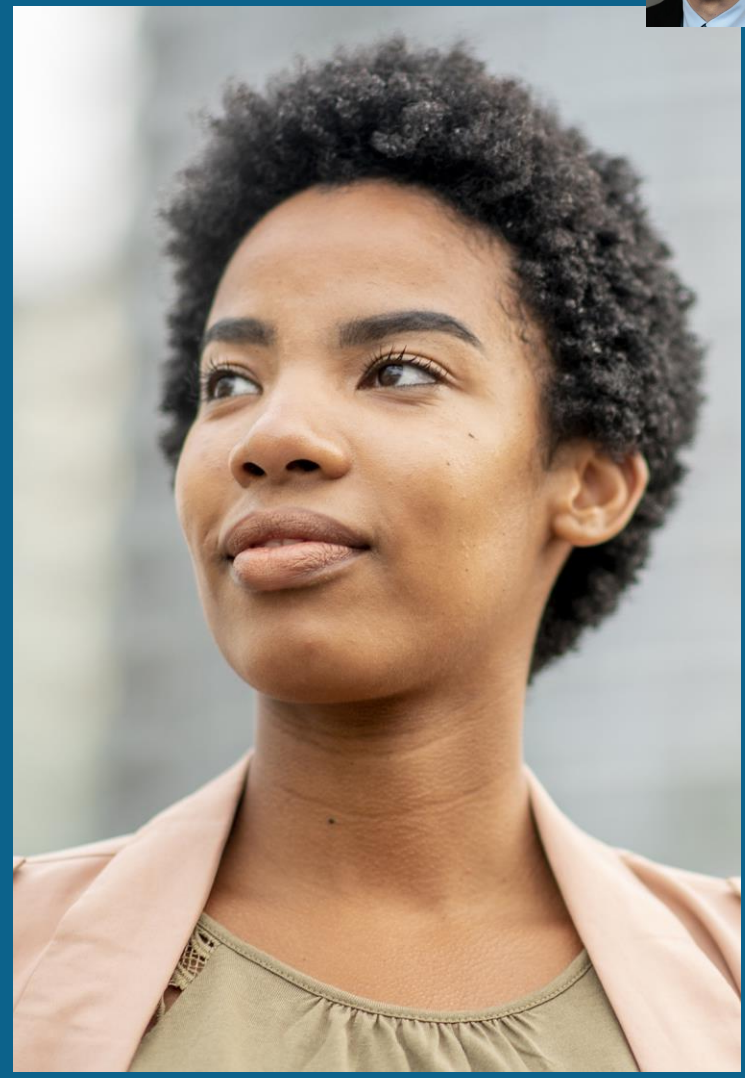
PRESENTATION

Sandra, a 26-year-old female with a history of MDD, presents for routine follow-up. She reports continued depressed mood and being unengaged with life.

ASSESSMENTS:

GAD-7	PHQ-9	MDQ
19/21	18/27	1/13

NEXT STEP: MEDICATION REVIEW



*Fictionalized representation based on a real medical case.

GAD-7: General Anxiety Disorder Screener 7; **MDQ:** Mood Disorder Questionnaire; **PHQ-9:** Patient Health Questionnaire-9

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CASE 1*
MEDICATIONS

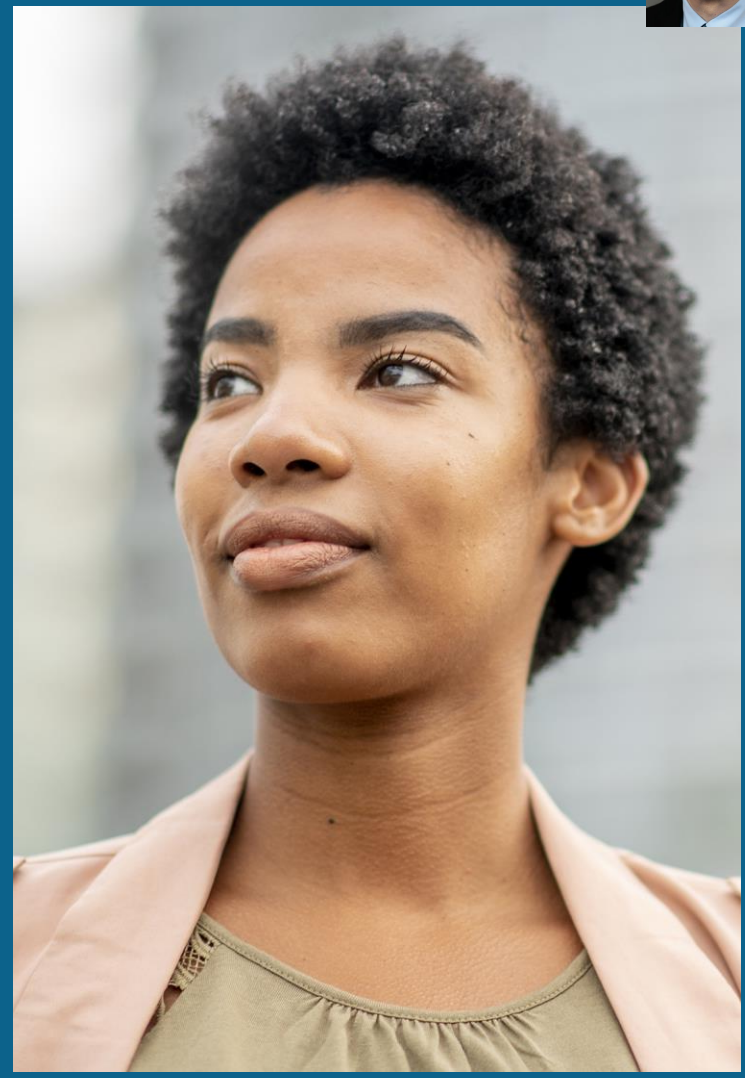
What should we be thinking about when considering her next steps?

CURRENT MEDICATIONS

- ❑ Escitalopram 20mg
- ❑ Bupropion XL 150 mg

PAST MEDICATIONS

- ❑ Sertraline 150 mg **(no therapeutic effect)**
- ❑ Fluoxetine 80 mg **(increased anxiety)**
- ❑ Aripiprazole 5 mg **(akathisia)**



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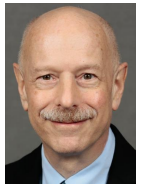


REIMAGINING TREATMENT OF DEPRESSION

SSRIs and SNRIs are the most common first-line medications for depression

LIMITATIONS OF OLDER THERAPIES[1,2]

Focus on ***monoamine modulation***

Slower onset of action

Broad indication for MDD

Limited impact for severe depression or TRD

BENEFITS OF NEWER THERAPIES[1,2]

Broader spectrum of activity

New mechanisms of action

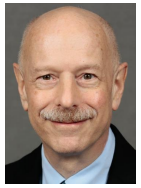
Faster onset of action

Indications for *specific MDD phenotypes*

Options for severe depression and *TRD*

1. Marwaha S et al. Novel and emerging treatments for major depression. *Lancet.* 2023;401(10371):141-153. **2.** Borbély É et al. Novel drug developmental strategies for treatment-resistant depression. *Br J Pharmacol.* 2022;179(6):1146-1186.

SNRI serotonin-norepinephrine reuptake inhibitor; **SSRI:** selective serotonin reuptake inhibitor; **TRD:** treatment-resistant depression



SSRIs AND SNRIs
PROS AND CONS

PROS

- **Older generics** are **inexpensive**
- Clinicians are **comfortable/ experienced with using them** due to their long history of clinical use

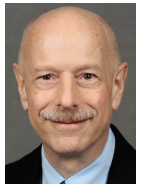
CONS[1,2]

- Significant side effects can interfere with daily life
- Can take weeks to work
- Many patients do not respond

SSRI	SPECTRUM OF SIDE EFFECTS*	SNRI
	OVERLAP	
Restlessness[1] (*not seen in all SSRIs*)	Serotonin syndrome[3]	Blood pressure elevation[2]
QT_c prolongation (*citalopram*)[1]	Suicidal ideation / suicidality[4]	Hepatic injury (*duloxetine*)[2]
	Emotional blunting[5]	
	Weight gain[2]	
	Sexual dysfunction[2]	
	GI distress[2]	
	Bleeding risk[2]	

**Note:* *Side effects vary between agents and must be evaluated individually*

1. Edinoff AN et al. Selective serotonin reuptake inhibitors and adverse effects: a narrative review. *Neurol Int.* 2021;13(3):387-401. **2.** Wang SM et al. Addressing the side effects of contemporary antidepressant drugs: a comprehensive review. *Chonnam Med J.* 2018;54(2):101-112. **3.** Cooper J et al. Predicting serotonin toxicity in serotonin reuptake inhibitor overdose. *Clin Toxicol (Phila).* 2023;61(1):22-28. **4.** Coupland C et al. Antidepressant use and risk of suicide and attempted suicide or self harm in people aged 20 to 64: cohort study using a primary care database. *BMJ*. 2015;350:h517. **5.** Ma H et al. Emotional blunting in patients with major depressive disorder: a brief non-systematic review of current research. *Front Psychiatry*. 2021;12:792960.



REIMAGINING TREATMENT OF DEPRESSION

New treatment strategies are emerging to help improve and expand clinical efficacy to a **wider range of depression phenotypes**[1,2]

LIMITATIONS OF OLDER THERAPIES[1,2]

Focus on ***monoamine modulation***

Slower onset of action

Broad indication for MDD

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Indications for ***specific MDD phenotypes***

Options for severe depression and ***TRD***

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SNRI serotonin-norepinephrine reuptake inhibitor; **SSRI:** selective serotonin reuptake inhibitor; **TRD:** treatment-resistant depression

TREATMENT CONSIDERATION

DEPRESSION PHENOTYPES

STEP 1: BE CERTAIN ABOUT THE SOURCE OF DEPRESSION TO DETERMINE OPTIMAL THERAPY!

TYPES OF DEPRESSION*

- **MDD**
  - EVALUATE FOR PSYCHOTIC SYMPTOMS
- **BIPOLAR DEPRESSION**
  - RULE OUT BIPOLAR DISORDER
    - Remember what you learned in our module on ***Bipolar Depression!***
- **POSTPARTUM DEPRESSION**
  - CLINICAL HISTORY
- **TREATMENT-RESISTANT DEPRESSION**
  - CLINICAL HISTORY
  - MEDICATION HISTORY
- **CAUSED BY ANOTHER MEDICAL CONDITION OR THERAPY**
  - CLINICAL HISTORY AND PHYSICAL EXAM

*This is not an exhaustive list of depression subtypes but is meant to illustrate variable clinical scenarios that will be discussed in this presentation.

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CASE 1*

DIAGNOSIS

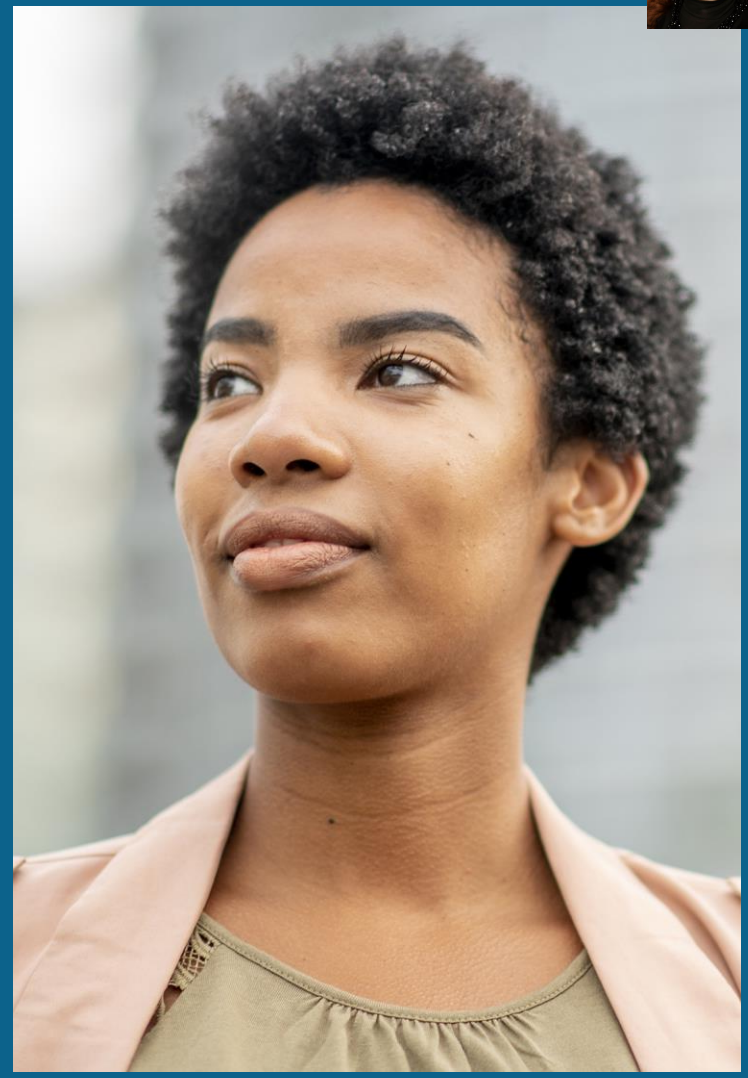
CASE CONTINUED:

- Sandra, 26-year-old female with a history of MDD despite trials with multiple antidepressants
- BD ruled out through the MDQ and clinical history *(remember our bipolar depression module!)*

TRUE MDD

	Medication	Efficacy / side effects	Neurotransmitter targeted
Current	Escitalopram	No benefit	Serotonin
	Bupropion	No benefit	Norepinephrine | dopamine
Past	Sertraline	No benefit	Serotonin
	Fluoxetine	Increased anxiety	Serotonin
	Aripiprazole	Akathisia	Dopamine

How could we approach treatment of this patient?



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TREATMENT GUIDELINES

MDD

- Guidelines ***do not usually include newly approved agents***[1,2]
- When to initiate combination and escalation of therapy depends on ***clinical severity***[1]

FIRST-LINE THERAPY[1,2]

- SSRI
- SNRI
- NDRI
- "Atypical" antidepressants

Inadequate response

SECOND-LINE THERAPY[1,2]

- ***Combination therapy***
- Switch to ***another class of antidepressants***
- Switch to / augment with ***psychotherapy***
- Augment with a ***second-generation antipsychotic***

1. Qaseem A et al. Nonpharmacologic and pharmacologic treatments of adults in the acute phase of major depressive disorder: a living clinical guideline from the American College of Physicians. *Ann Intern Med.* 2023;176(2):239-252. **2.** American Psychological Association PsycExtra® Database. APA clinical practice guideline for the treatment of depression across three age cohorts. 2019. Accessed January 4, 2024. https://www.apa.org/depression-guideline

SNRI: serotonin-norepinephrine reuptake inhibitor
SSRI: selective serotonin reuptake inhibitor
NDRI: norepinephrine-dopamine reuptake inhibitor

CASE 1
TREATMENT OPTIONS

THINK ABOUT DIFFERENT TREATMENT APPROACHES

Consider targeting different neurotransmitters!

SECOND-LINE THERAPY[1,2]

- ***Combination therapy***
- Switch to ***another class of antidepressants***
- Switch to / augment with ***psychotherapy***
- Augment with a ***second-generation antipsychotic***

1. Qaseem A et al. Nonpharmacologic and pharmacologic treatments of adults in the acute phase of major depressive disorder: a living clinical guideline from the American College of Physicians. *Ann Intern Med.* 2023;176(2):239-252. **2.** American Psychological Association PsycExtra® Database. APA clinical practice guideline for the treatment of depression across three age cohorts. 2019. Accessed January 4, 2024. https://www.apa.org/depression-guideline

SNRI: serotonin-norepinephrine reuptake inhibitor
SSRI: selective serotonin reuptake inhibitor
NDRI: norepinephrine-dopamine reuptake inhibitor

NEW MECHANISMS FOR DEPRESSION

BEYOND GENERICS: BRANDED FDA-APPROVED AGENTS

MDD

- Combination of dextromethorphan + bupropion
- Vortioxetine
- Adjunctive cariprazine
- Adjunctive brexpiprazole

TRD

- Esketamine nasal spray

POSTPARTUM DEPRESSION

- Zuranolone*
- Brexanolone

BIPOLAR DEPRESSION

- Cariprazine
- Lumateperone

TRD: treatment-resistant depression

**Commercially available as of 12/14/23*

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NEW MECHANISMS FOR DEPRESSION

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BIPOLAR DEPRESSION

- Cariprazine
- Lumateperone

May be utilized as ***first-line therapy***

TRD: treatment-resistant depression

AUDIENCE POLL

How does the combination of **dextromethorphan and bupropion** work **synergistically**?

a) Both act on NMDA receptor antagonism

b) Dextromethorphan extends the half-life of bupropion

c) Bupropion inhibits the metabolism of dextromethorphan

d) Bupropion increases norepinephrine and dopamine levels while dextromethorphan impacts serotonin levels

e) I do not know / I am unsure.

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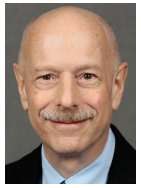


DEXTROMETHORPHAN–BUPROPION

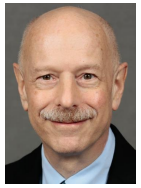
MECHANISM[1,2]

SYNERGISTIC PHARMACOLOGY:

- *Bupropion **inhibits the metabolism of dextromethorphan** to achieve therapeutic levels*

	SYNAPTIC PLASTICITY	SEROTONIN MODULATION	NE MODULATION
NMDA antagonism / glutaminergic pathways	✓	✗	✗
Sigma-1 agonism	✓	✓	✗
Serotonin reuptake inhibitor	✗	✓	✗
Norepinephrine (NE) reuptake inhibitor	✗	✗	✓

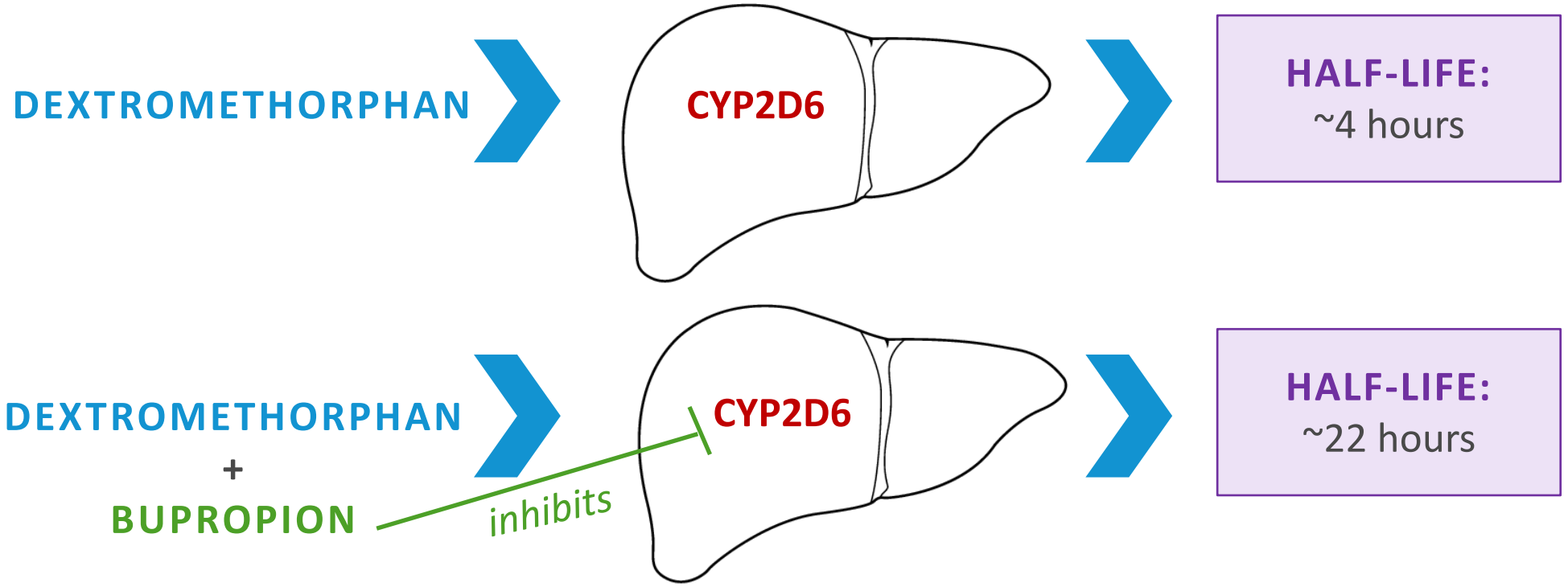
1. Shad MU. Recent Developments in pharmacotherapy of depression: bench to bedside. *J Pers Med.* 2023;13(5):773.
2. Stahl SM. Dextromethorphan/bupropion: a novel oral NMDA (N-methyl-d-aspartate) receptor antagonist with multimodal activity-addendum. *CNS Spectr*. 2020;25(6):803.



DEXTROMETHORPHAN – BUPROPION

PHARMACOKINETICS

Synergistic pharmacokinetics to extend half-life



IS A SINGLE COMBINATION PILL BETTER THAN BEING PRESCRIBED BOTH MEDS INDIVIDUALLY?

1. McCarthy B et al. Dextromethorphan-bupropion (Auvelity) for the treatment of major depressive disorder. *Clin Psychopharmacol Neurosci.* 2023;21(4):609-616.

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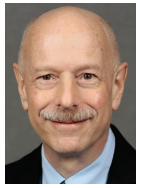


SYNERGISTIC AGENT VS POLYPHARMACY?

1 + 1 = 1? ❯ **Useless polypharmacy**

1 + 1 = 2? ❯ **Additive effects**

1 + 1 = 3? ❯ **Synergy!**

DEXTROMETHORPHAN–BUPROPION

EFFICACY

STUDY DESIGN

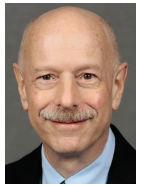
- 80 patients with moderate/severe MDD treated with dextromethorphan-bupropion 45mg/105mg (n=43) or bupropion 105mg (n=37) BID for 6 weeks

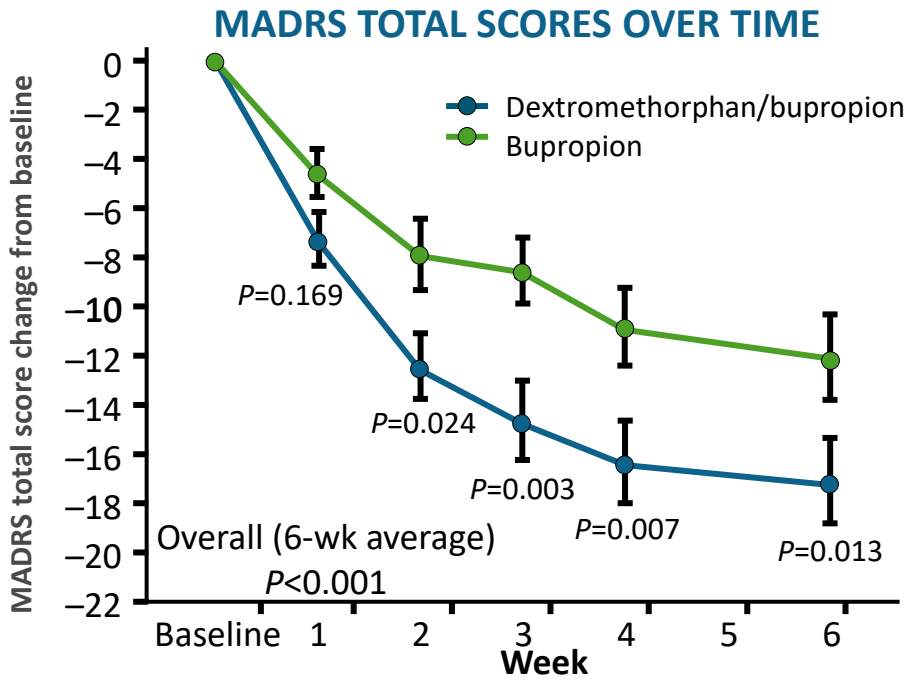
RESULTS

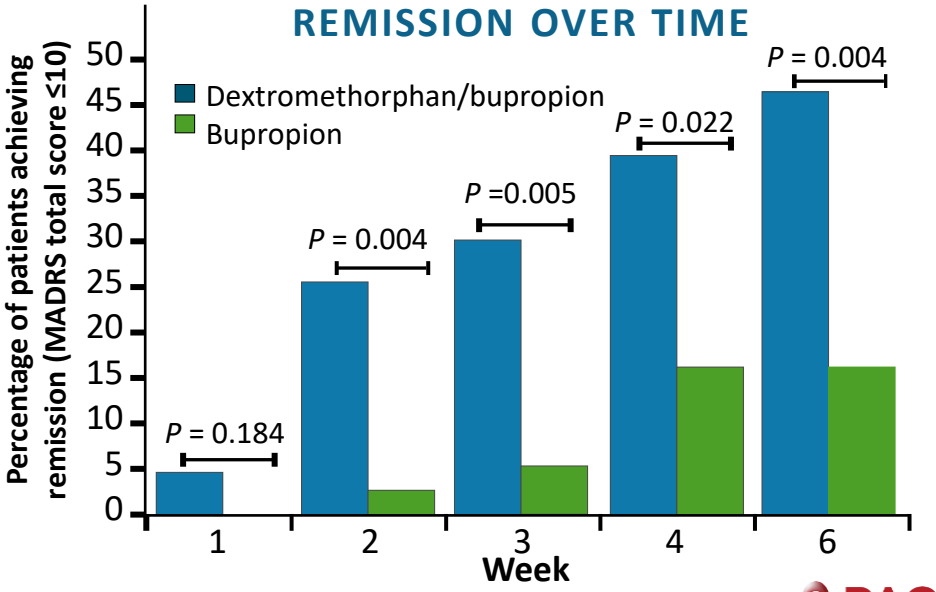
- Dextromethorphan-bupropion associated with significant improvement in:
  - **MADRS**
  - **Remission rates**

SAFETY

- **Common side effects:** dizziness, nausea, anxiety
- **No serious adverse events requiring hospitalization**







1. Tabuteau H et al. Effect of AXS-05 (dextromethorphan-bupropion) in major depressive disorder: a randomized double-blind controlled trial. *Am J Psychiatry*. 2022;179(7):490-499.

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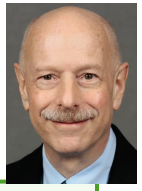
VORTIOXETINE



MECHANISM OF ACTION

- Multimodal mechanism
  - Serotonergic
  - Glutamate
  - GABA
  - Dopamine
  - Acetylcholine
  - Histamine

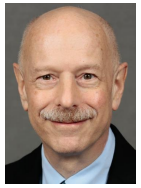
	AGONIST	PARTIAL AGONIST	ANTAGONIST	INHIBITOR
5-HT$_{1A}$	✓			
5-HT$_{3}$			✓	
5-HT$_{7}$			✓	
5-HT$_{1D}$			✓	
5-HT$_{1B}$		✓		
SERT				✓

PHARMACOKINETICS

- **T$_{max}$:** 7 to 11 hours
- **Half-life:** 59 to 69 hours, a *long half-life*
- **Hepatic metabolism** (*know your inducers/inhibitors)*

1. Chen G et al. Vortioxetine: clinical pharmacokinetics and drug interactions. Clin Pharmacokinet. 2018;57(6):673-686.

SERT: serotonin transporter



VORTIOXETINE
CLINICAL EFFICACY

*Vortioxetine not only improves depressive symptoms but also improves **cognitive symptoms**[1]*

STUDY DESIGN

- Meta-analysis (3-randomized controlled trials)
- Findings related to Digit Symbol Substitution Test (DSST)
- DSST scores adjusted for changes in Montgomery-Åsberg Depression Rating Scale (MADRS)

RESULTS

- **Moderate effect size for DSST** relative to placebo: SES=0.24 (95%CI, 0.12-0.35; *P*<0.0001)

*Vortioxetine may have a more **favorable side effect profile** compared with other antidepressants*[2]

- **Less sexual dysfunction**
  - Possibly due to 5-HT_{1A} agonism
- **Low risk of treatment-emergent suicidal ideation**
- **Low risk of discontinuation syndrome**
  - Due to long half-life

WHICH PATIENTS WOULD BENEFIT MOST FROM THE COGNITIVE IMPROVEMENTS SEEN IN VORTIOXETINE?

1. McIntyre RS et al. The effects of vortioxetine on cognitive function in patients with major depressive disorder: a meta-analysis of three randomized controlled trials. *Int J Neuropsychopharmacol.* 2016;19(10):pyw055. **2.** Rao TSS et al. Antidepressants and sexual dysfunction: is vortioxetine among the exceptions? *J Psychosexual Health*. 2022;4(3):155-156.

SES: standardized effect size

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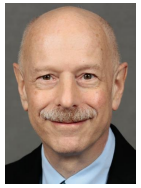
CARIPRAZINE
ADJUNCTIVE THERAPY



MECHANISM OF ACTION[1]

10-fold higher affinity for D_3 vs D_2 receptor

Nigrostriatal D_3 blockade associated with:

- **Improved reward processing**
- **Precognitive/ antidepressant effects**

5-HT_{2B} antagonism /5-HT_{1A} agonism

Antidepressant effects

PHARMACOKINETICS[2]

T_{max} = 3 to 6 hours

Half-life = 1 to 3 weeks
(major metabolite)

SAFETY[3,4]

Treatment-emergent adverse effects

Akathisia
Restlessness
Sedation
Dizziness
Nausea

CLINICAL EFFICACY[4]

- Significant improvements in **depressive symptoms** vs placebo at 6 weeks

(MADRS change: -14.1 vs -11.5; P=0.0050)

- Remission rates not significantly different

CONCLUSION

Cariprazine is an efficacious long-acting adjunctive therapy to antidepressants that is generally well-tolerated

1. Stahl SM et al. Cariprazine as a treatment across the bipolar I spectrum from depression to mania: mechanism of action and review of clinical data. *Ther Adv Psychopharmacol*. 2020;10:1-11. **2.** VRAYLAR (cariprazine). Prescribing information. AbbVie; 2022. Accessed 12.18.23. **3.** Earley W et al. Cariprazine treatment of bipolar depression: a randomized double-blind placebo-controlled phase 3 study. *Am J Psychiatry.* 2019;176(6): 439-448. **4.** Sachs GS et al. Adjunctive Cariprazine for the Treatment of Patients With Major Depressive Disorder: A Randomized, Double-Blind, Placebo-Controlled Phase 3 Study. *Am J Psychiatry*. 2023;180(3):241-251.

MADRS: Montgomery-Asberg Depression Rating Scale

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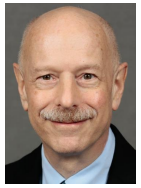


BREXPIPRAZOLE
ADJUNCTIVE THERAPY

MECHANISM OF ACTION[1-3]

- D_2 partial agonist
  - *Reduces motor symptoms vs. D_2 antagonism*
  - **Lower intrinsic activity than aripiprazole**
- 5-HT_{1A} partial agonist
  - *Antidepressant effect*
- 5-HT_{2A} antagonist
  - *Reduces motor symptoms*
  - *Antidepressant effect*
  - **Greater affinity than aripiprazole**
- H_1 receptor
  - *Sedation*
  - **Lower affinity than aripiprazole**

PHARMACOKINETICS[3]

T_{max} = 4 hours
Half-life = 91 hours
Time to steady state = 10 to 12 days

SAFETY[1-3]

Common side effects
Akathisia
Sedation
Weight gain

May improve side effect profile vs aripiprazole

CLINICAL EFFICACY[1]

Significant reductions in depressive symptoms for patients with inadequate response to 1-3 antidepressants vs placebo

(MADRS score: LSMD = -3.21 points; P=0.0002)

CONCLUSION

*Brexiprazole is a **safe and efficacious adjunctive treatment for MDD** that **may have a more favorable side effect profile than aripiprazole** although head-to-head comparisons are lacking*

LSMD: least-square mean difference; **MADRS:** Montgomery-Asberg Depression Rating Scale

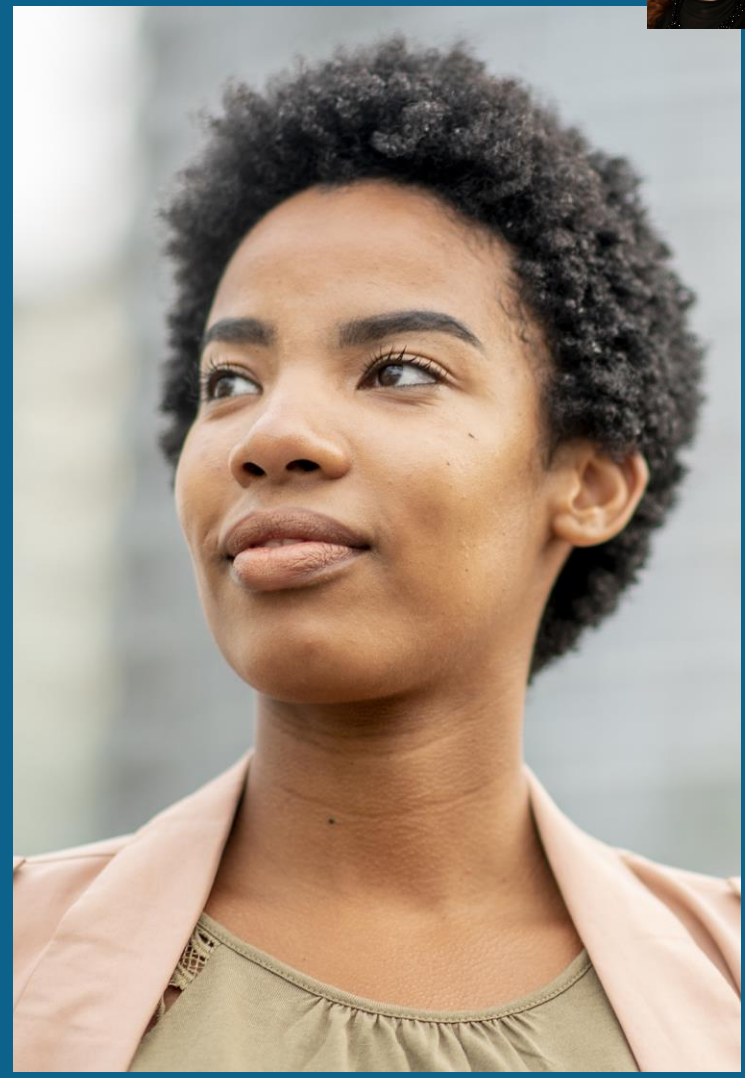
1. Diefenderfer LA, Iuppa C. Brexpiprazole: A review of a new treatment option for schizophrenia and major depressive disorder. *Ment Health Clin*. 2018;7(5):207-212. 2. Fornaro M et al. Brexpiprazole for treatment-resistant major depressive disorder. *Expert Opin Pharmacother*. 2019;20(16):1925-1933. 3. Edinoff AN et al. Brexpiprazole for the Treatment of Schizophrenia and Major Depressive Disorder: A Comprehensive Review of Pharmacological Considerations in Clinical Practice. *Psychopharmacol Bull*. 2021;51(2):69-95.

CASE 1*

RESOLUTION

- **DISCONTINUED** bupropion
- **LOWERED** escitalopram to 10 mg x2 weeks
  - Then **DISCONTINUED**
- **STARTED** dextromethorphan-bupropion

WHAT IF YOU DETERMINE THIS PATIENT HAS TRD?



*Fictionalized representation based on a real medical case.

TRD: treatment-resistant depression

PACE Partners for Advancing Clinical Education EFFICIENT

AUDIENCE POLL

Which class of medications are you most likely to prioritize for **treatment-resistant depression**?

a) NMDA receptor antagonists (e.g., esketamine)
b) Neuroactive steroids (e.g., zuranolone, brexanolone)
c) Synergistic pharmacotherapy (e.g., dextromethorphan-bupropion)
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NEW MECHANISMS FOR DEPRESSION

BEYOND GENERICS: BRANDED FDA-APPROVED AGENTS

MDD	TRD	POSTPARTUM DEPRESSION	BIPOLAR DEPRESSION
• Combination of dextromethorphan + bupropion • Vortioxetine • Adjunctive cariprazine • Adjunctive brexpiprazole	• Esketamine nasal spray	• Zuranolone *Commercially available as of 12/14/23* • Brexanolone	• Cariprazine • Lumateperone

TRD: treatment-resistant depression

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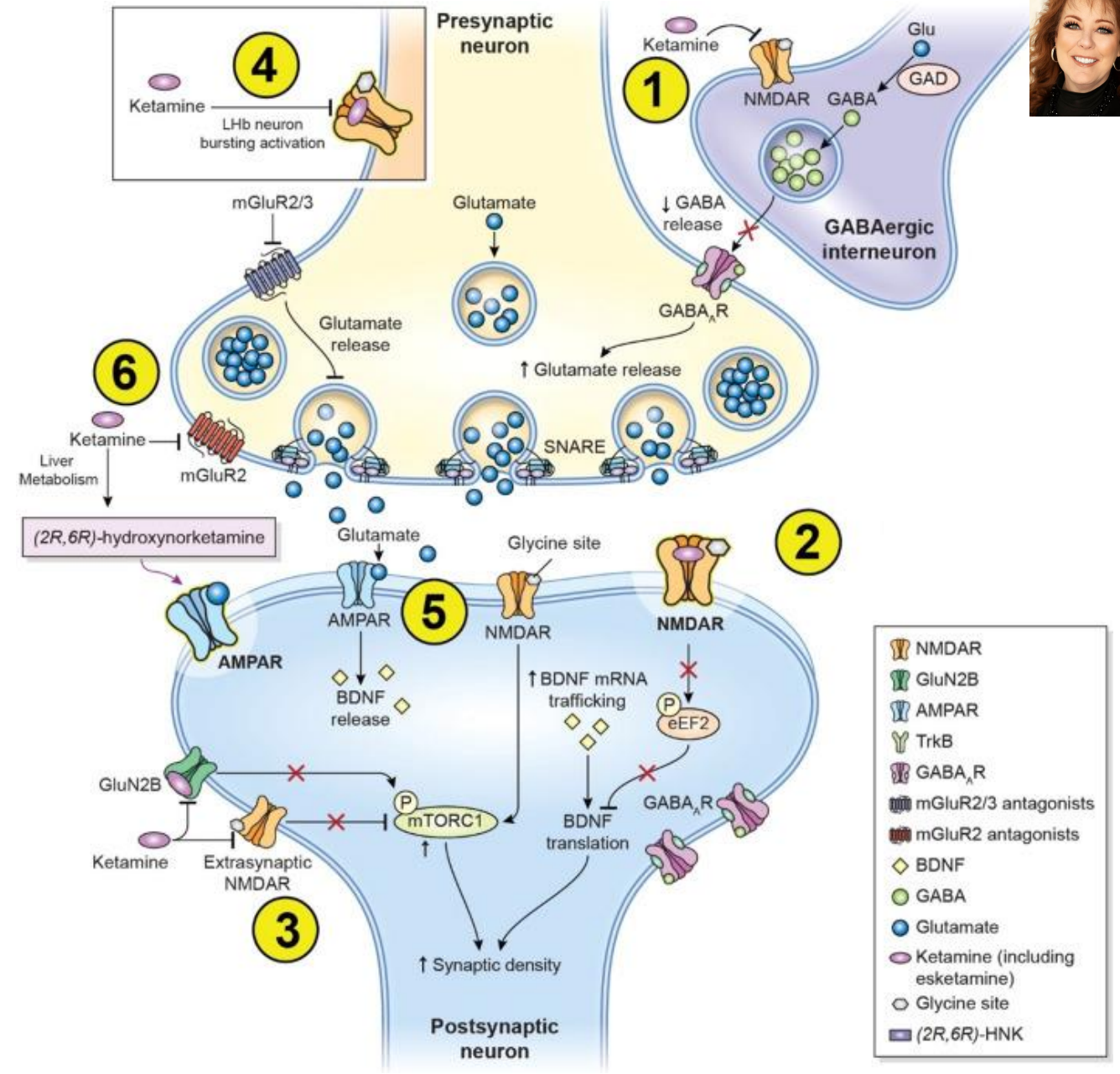
NMDA RECEPTOR ANTAGONISM

MECHANISM OF ACTION

- **NMDA receptor antagonist**
  - Promotes ***synaptogenesis and neuroplasticity*** believed to contribute to antidepressant effects

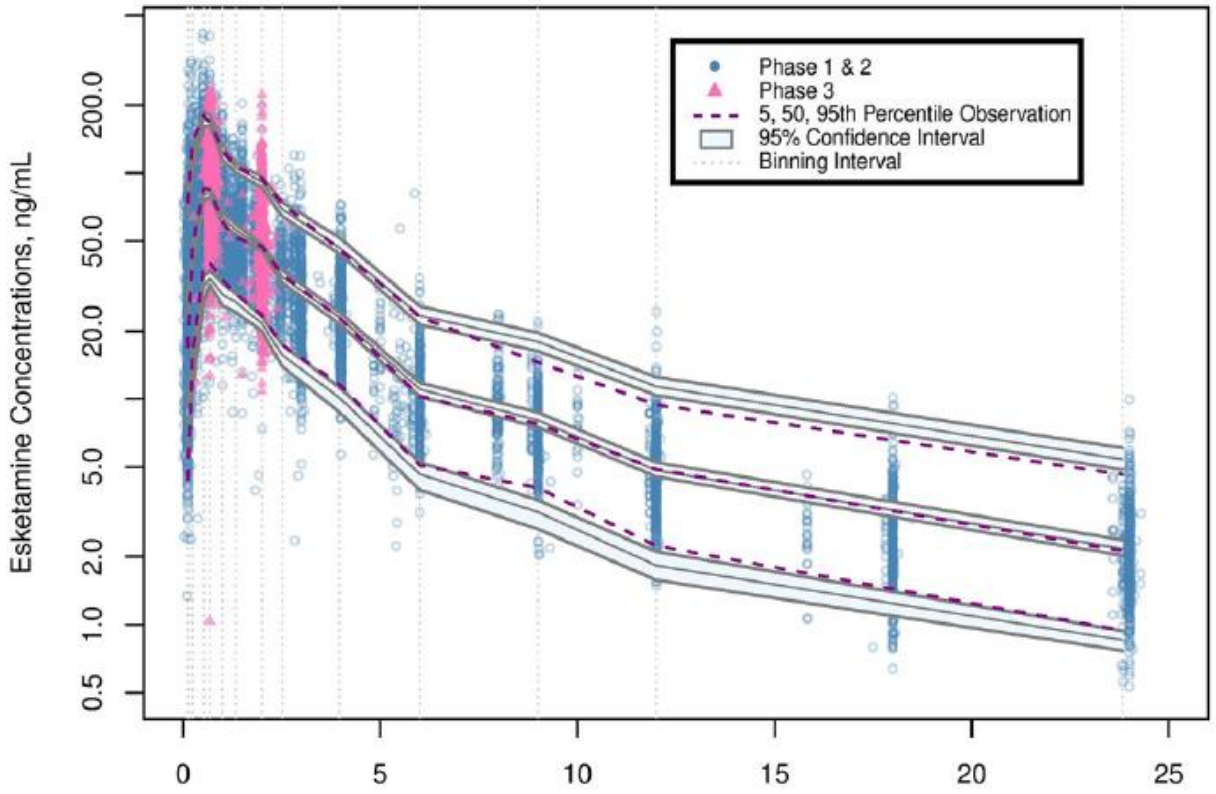


1. Yavi M et al. Ketamine treatment for depression: a review. *Discov Ment Health.* 2022;2(1):9..

ESKETAMINE INTRANASAL SPRAY

PHARMACOKINETICS

- **Limited oral bioavailability: ~18.6%[1]**
  - Undergoes extensive first-pass metabolism
- **Greater intranasal bioavailability: 45% to 50%[1]**
  - Bypasses first-pass metabolism
- **T_{max}** (time to maximum plasma concentration): ~20 to 40 minutes[2]
- **Half-life:** ~7 to 12 hours[1,2]



Perez-Ruixo C et al. *Clin Pharmacokinet*. 2021;60(4):501-516.

1. Perez-Ruixo C et al. Population pharmacokinetics of esketamine nasal spray and its metabolite noresketamine in healthy subjects and patients with treatment-resistant depression. *Clin Pharmacokinet*. 2021;60(4):501-516.2. Salahudeen MS et al. Esketamine: new hope for the treatment of treatment-resistant depression? A narrative review. *Ther Adv Drug Saf.* 2020;11:2042098620937899.

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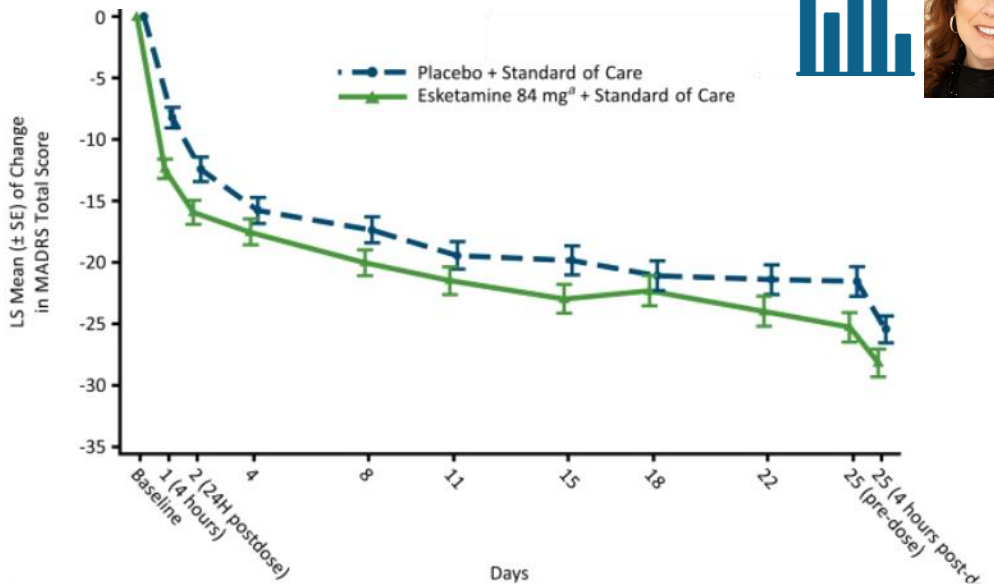
ESKETAMINE NASAL SPRAY
CLINICAL EFFICACY

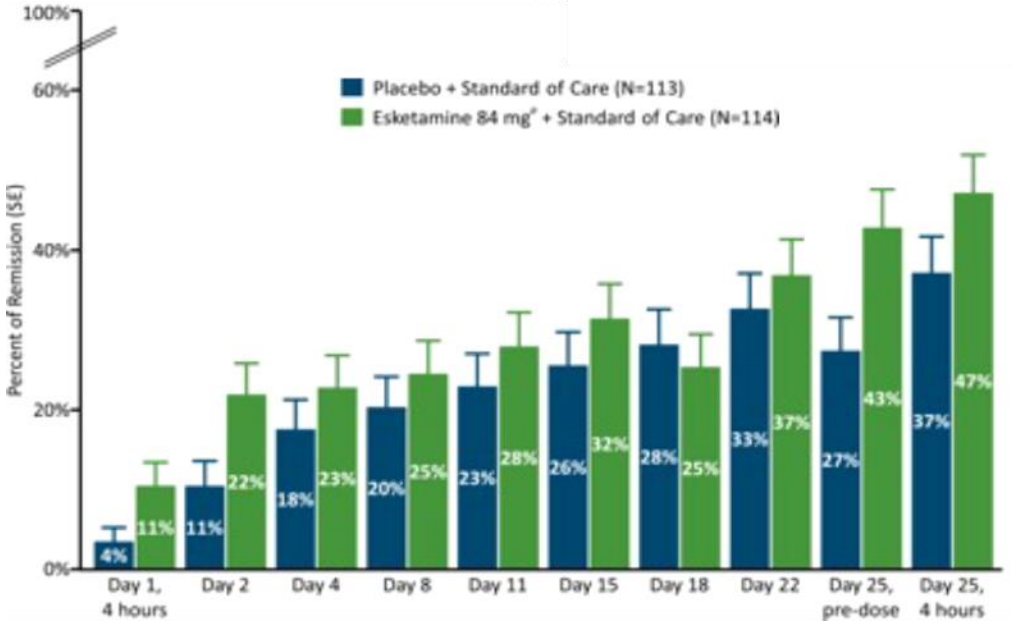
STUDY DESIGN

- 183 patients with MDD and suicidal ideation with intent
- ~1:1 randomization of esketamine 84 mg IN vs placebo + SOC ADT

RESULTS WITH ESKETAMINE

- **Greater improvement in depressive symptoms**
  - First 24 hours: LSMD in MADRS total score: –3.9; *P*=0.006)
  - Difference **evident at 4 hours through 25 days**
- **Greater remission rates** (difference of ~11%)





SAFETY

- ***Reduction in severity of suicidality***
- ***Common side effects:*** dizziness (41.2%), dissociation (38.6%), somnolence (22.8 %), sedation (14.0%)
- ***Emerging side effects:*** depersonalization / derealization (7.9%), increased blood pressure (peaks at 40 minutes)

1. Ionescu DF et al. Esketamine Nasal Spray for Rapid Reduction of Depressive Symptoms in Patients With Major Depressive Disorder Who Have Active Suicide Ideation With Intent: Results of a Phase 3, Double-Blind, Randomized Study (ASPIRE II). *Int J Neuropsychopharmacol*. 2021;24(1):22-31

ADT: antidepressant therapy; **CGI-SS-r**: clinical global impression-severity of suicidality-revised; **IN:** intranasal; **LSMD:** least square mean difference; **MADRS:** Montgomery-Åsberg Depression Rating Scale; **SOC:** standard of care

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AUDIENCE POLL

Which class of medications are you most likely to recommend as first-line therapy for **postpartum depression**?

a) NMDA receptor antagonists (e.g., esketamine)
b) Neuroactive steroids (e.g., zuranolone, brexanolone)
c) Synergistic pharmacotherapy (e.g., dextromethorphan-bupropion)
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AUDIENCE POLL

Which class of medications are you most likely to recommend as first-line therapy for **postpartum depression**?

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*Commercially available as of 12/14/23

TRD: treatment-resistant depression

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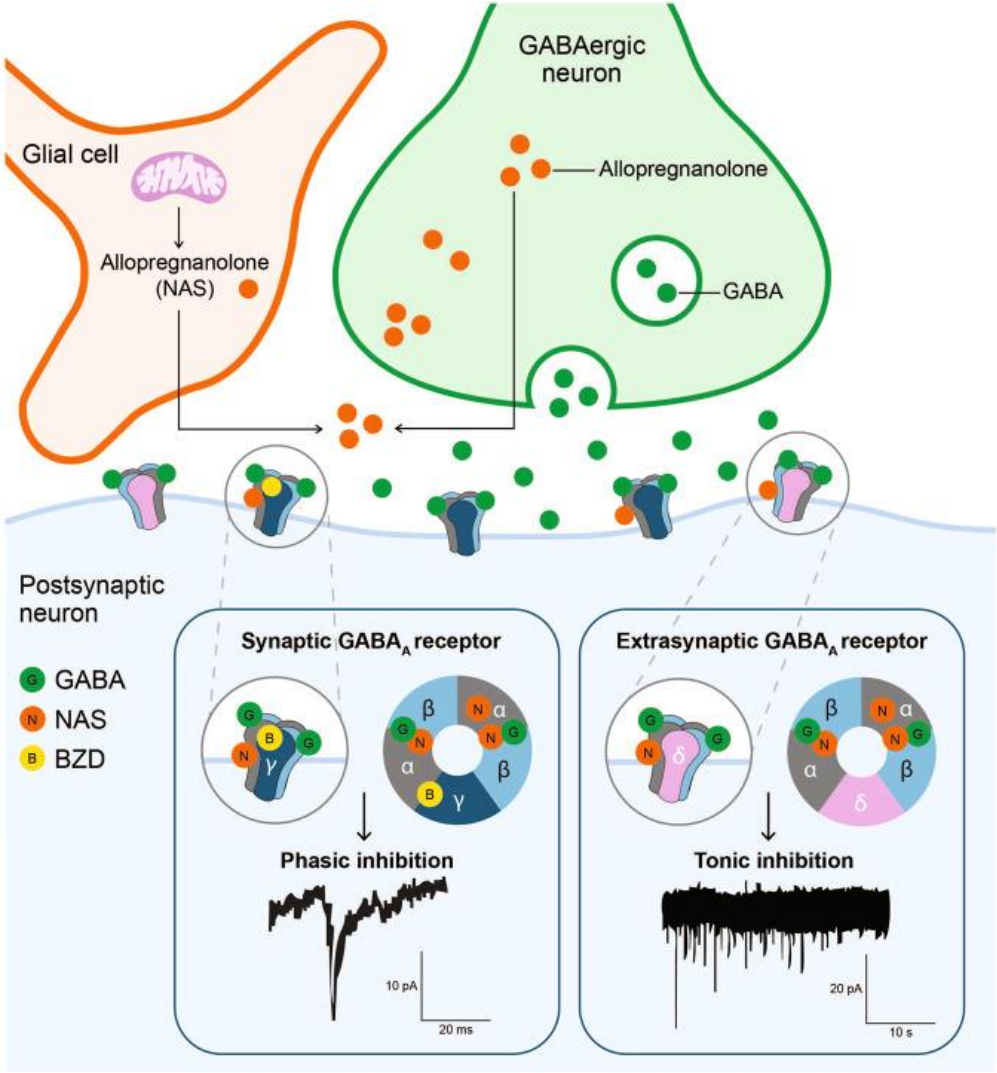
BREXANOLONE/ZURANOLONE
MECHANISM

KEY FACTORS CONTRIBUTING TO PPD

Decreased levels of allopregnanolone (neuroactive steroid)	GABAergic deficit

NEUROACTIVE STEROIDS[1]

- Positive allosteric modulators (PAMs) of $GABA_A$ receptors
- Potentiate phasic and tonic inhibition of postsynaptic responses
- Aim to replace deficient neuroactive steroids and improve GABAergic neurotransmission
- Rapidly-acting



1. Cutler AJ et al. Understanding the mechanism of action and clinical effects of neuroactive steroids and GABAergic compounds in major depressive disorder. *Transl Psychiatry*. 2023;13(1):228.

PPD: postpartum depression

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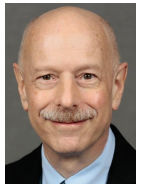

NEW MECHANISMS FOR DEPRESSION

BEYOND GENERICS: BRANDED FDA-APPROVED AGENTS

MDD

- Combination of dextromethorphan + bupropion
- Vortioxetine
- Adjunctive cariprazine
- Adjunctive brexpiprazole

TRD

- Esketamine nasal spray

POSTPARTUM DEPRESSION

- Zuranolone

Commercially available as of 12/14/23

- Brexanolone

BIPOLAR DEPRESSION

- Cariprazine
- Lumateperone

Remember what you learned in "Turning the Tide in Bipolar Depression"

TRD: treatment-resistant depression

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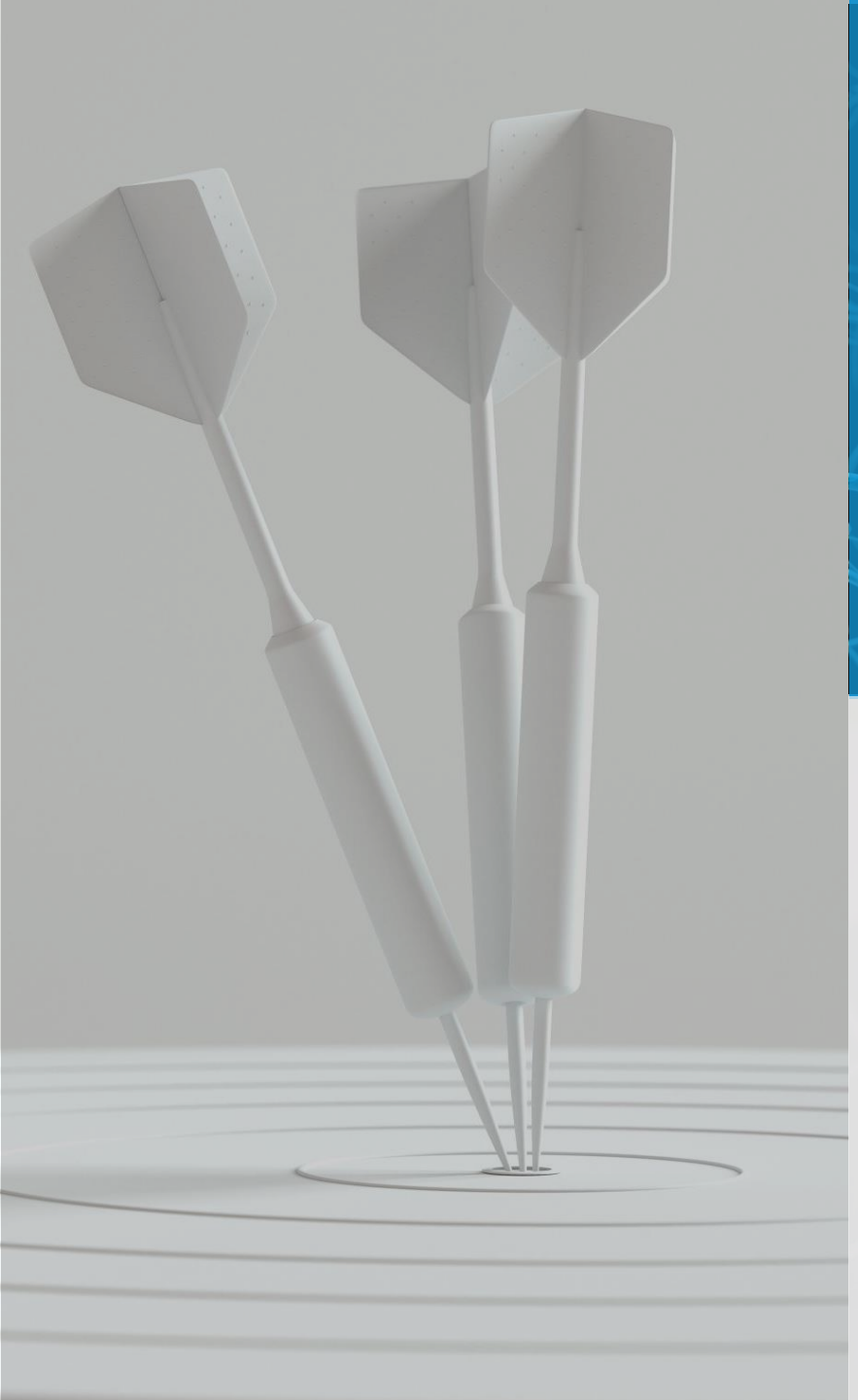
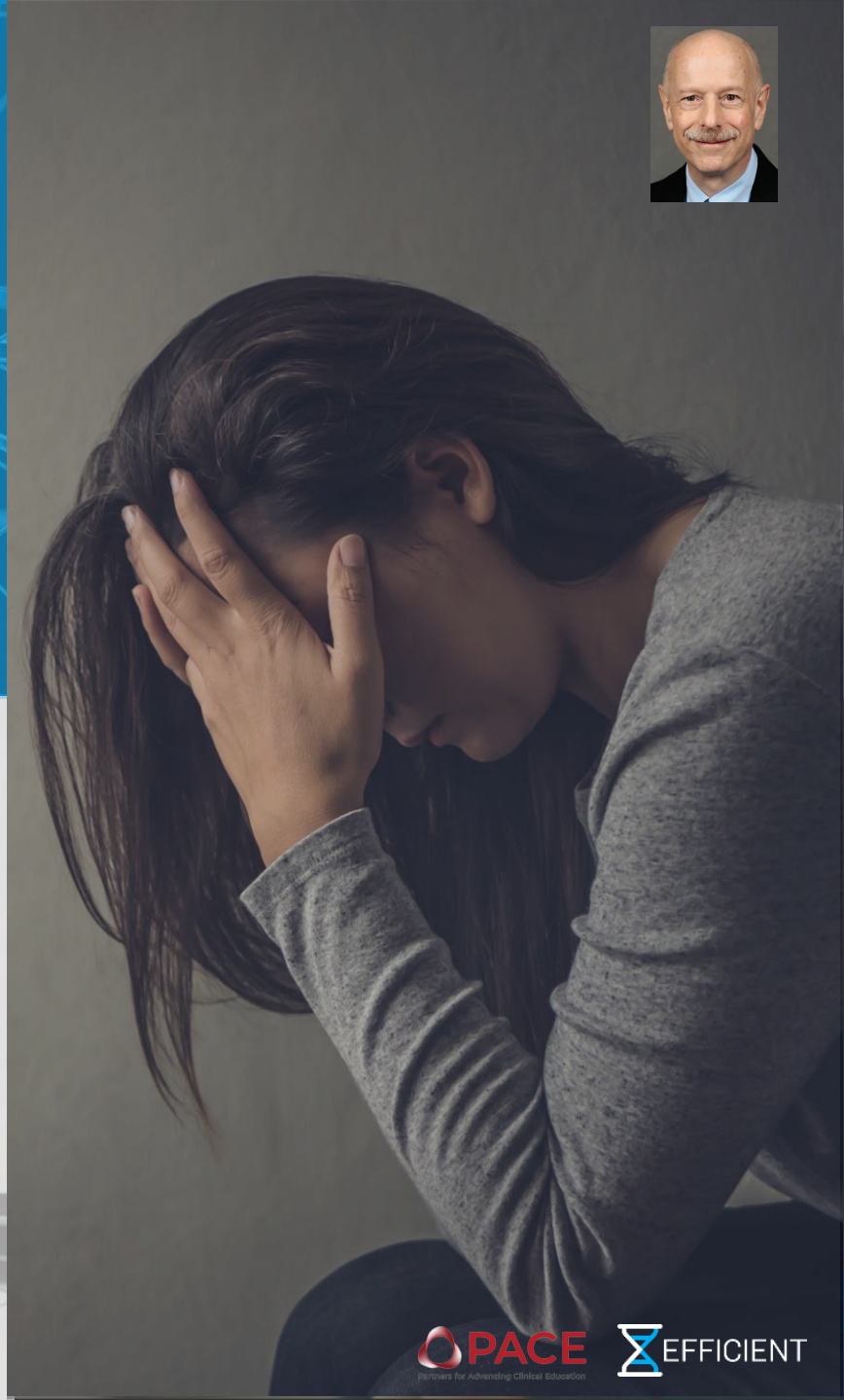
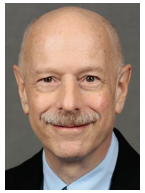


MODULE
— 2 —

MODERN PARADIGMS FOR PHARMACO-THERAPY

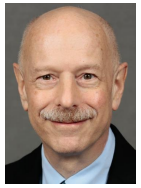




THERAPEUTIC MONITORING

MY PRACTICE

FREQUENCY	• Depends on the medication, but can be done at every visit - Weekly for fast-acting agents (e.g., esketamine [twice weekly doses during induction phase], dextromethorphan-bupropion) to monitor treatment response
ASSESSMENT	• Subjective testing - Patient reports such as PHQ-9
HOW YOU DETERMINE MEDICATION FAILURE	• Lack of symptom improvement • Intolerable side effects • Worsening symptoms • Partial response



PHQ-9

- **Scoring:** 0 to 3 per item (total score range from 0 to 27)
- **Severity of depression** based on scoring:
  - 0 – 4: minimal depression
  - 5 – 9: mild depression
  - 10 – 14: moderate depression
  - 15 – 19: moderately severe depression
  - 20 – 27: severe depression

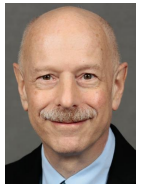
Scale: https://www.apa.org/depression-guideline/patient-health-questionnaire.pdf
Scoring: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1495268/

Over the last 2 weeks, how often have you been bothered by the following?	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, hopeless	0	1	2	3
3. Trouble falling/staying asleep, or sleeping too much	0	1	2	3
4. Poor appetite or overeating	0	1	2	3
5. Feeling bad about yourself (e.g., like a failure, let your family down)	0	1	2	3
6. Trouble concentrating on things (e.g., newspaper, TV)	0	1	2	3
7. Moving/speaking noticeably more slowly? OR more fidgety/restless	0	1	2	3
8. Thoughts that you would be better off dead/hurting yourself	0	1	2	3

If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all	Somewhat difficult	Very difficult	Extremely difficult
☐	☐	☐	☐

Note: Representation. For the full Patient Health Questionaiire-9 (PHQ-9), see https://www.apa.org/depression-guideline/patient-health-questionnaire.pdf



THERAPEUTIC DRUG MONITORING

PLASMA LEVEL MONITORING

- *NOT standard of care!*

How, if at all, should this be used?

MEDICATION	DOSAGE FREQUENCY	REFERENCE RANGE LOWER LIMIT	REFERENCE RANGE UPPER LIMIT	CRITICAL VALUE	DDI*
IN THE MEDICAL RECORD:					
ARIPIPRAZOLE Abilify	5 mg	97 150 ng/mL	500 ng/mL		▲
ATOMOXETINE Strattera	100 mg	173 200 ng/mL	1000 ng/mL		▲
ESCITALOPRAM Lexapro	10 mg	73 50 ng/mL	110 ng/mL		▲
NOT IN THE MEDICAL RECORD:					
OXYCODONE Roxicodone	Not in medical record	25 5 ng/mL	100 ng/mL	200 ng/mL	▲

Reference Range:
Detected concentration inside

10,1 Within Range 999 Out of Range

***Drug-Drug Interaction (DDI):** See details on the following pages.

Major - The use of these medications together is contraindicated. Rare exceptions may exist.

Moderate- The use of these medications together may be contraindicated in a select group of patients. The patient should be monitored for possible manifestations of the interaction.

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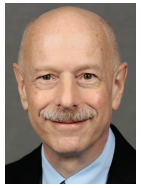

PRIOR AUTHORIZATION TIPS FOR BRANDED RX

1

(dextromethorphan HBr and bupropion HCl) extended-release tablets 45mg/105mg

1. Ensure the patient has the **correct ICD-10 diagnosis** (MDD, single episode or recurrent or in remission)
2. Provide the **appropriate dosing information** (dose, frequency, quantity, supply)
3. Check history of prior therapy
   - Prescribed antidepressants that **satisfy step therapy** include:
     - Sertraline
     - Escitalopram
     - Fluoxetine
     - Buproprion
     - Trazodone
     - Duloxetine
     - Venlafaxine
     - Citalopram
     - Mirtazapine
     - Buspirone
     - Paroxetine

2

(esketamine) CIII
28 mg nasal spray

- Partnered with **CoverMyMeds**
- Offers electronic prior authorization support for pharmacy benefit access

3

(cariprazine) capsules
1.5mg•3mg•4.5mg•6mg

- **Quick to complete** takes 3-5 minutes to submit PA using PARx
- PARx 'PASS' system ensures accurate and complete PA submissions
- Simple to use / easy to understand

4

brexpiprazole 2mg tablets

- Partnered with **CoverMyMeds**
- Majority of decisions are determined within 24 hours

5

vortioxetine
5mg•10mg•20mg tablets

- **Available in ~85% of commercially insured patients** in the United States without prior authorization
- PARx solutions help to assist in the PA submission

1. Axsome Therapeutics. Auvelity-specific considerations for prior authorizations and step edits. 2022. Accessed January 4, 2024. https://www.auvelityhcp.com/prior-authorization-flashcard.pdf
2. Janssen Pharmaceuticals. SPRAVATO® (esketamine). Healthcare professional website. 2023. Accessed January 4, 2024. https://www.spravatohcp.com/patient-support
3. AbbVie Inc. VRAYLAR Support and Resources. Accessed January 4, 2024. https://www.abbvieaccess.com/brand/vraylar
4. Otsuka Pharmaceuticals. REXULTI® (brexpiprazole) | Savings & Cost Information. 2023. Accessed January 4, 2024. https://www.rexulti.com/savings-cost
5. Takeda Pharmaceuticals. Savings Info & Support | TRINTELLIX (vortioxetine). 2023. Accessed January 4, 2024. https://www.trintellixhcp.com/access-savings.

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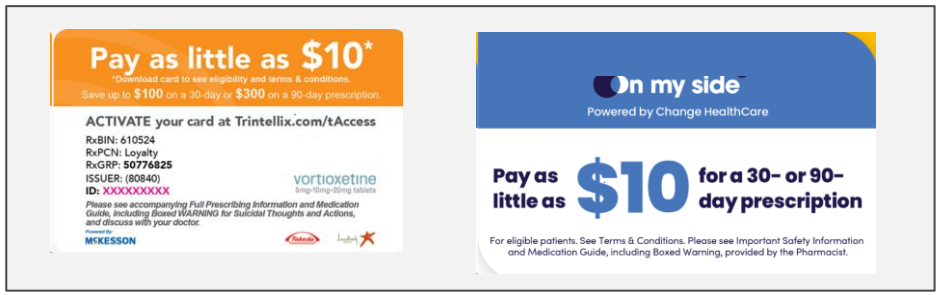
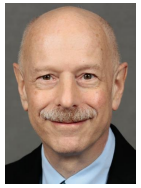
TIPS TO ACCESS
BRANDED RXs

Check your options to reduce medication costs!

Remember, there's almost always a card for new meds!





BRANDED AGENTS	COPAY/SAVINGS CARD?	PATIENT-ASSISTANCE PROGRAMS?	GOVERNMENT INSURANCE COVERAGE?
Dextromethorphan + bupropion[1]	✓	✓	Covered by most Medicare prescription plans (typically tier 4)
Intranasal esketamine[2]	✓	✓	Covered by most Medicare prescription plans
Vortioxetine[3]	✓	✓	Covered by all Medicare prescription plans (typically tier 4)
Brexpiprazole[4]	✓	✓	Covered by most Medicare/ Medicaid prescription plans*
Cariprazine[5]	✓	✓	Covered by most Medicare/ Medicaid prescription plans*

**Medicare low-income subsidy and/or uninsured benefits available as well to select patients*

1. Axsome Therapeutics. Savings Card - Auvelity (dextromethorphan-bupropion). 2022. Accessed January 4, 2024. https://www.auvelity.com/savings-card
2. Janssen Pharmaceuticals. SPRAVATO® (esketamine). Healthcare professional website. 2023. Accessed January 4, 2024. https://www.spravatohcp.com/patient-support
3. Takeda Pharmaceuticals. Savings Info & Support | TRINTELLIX (vortioxetine). 2023. Accessed January 4, 2024. https://www.trintellixhcp.com/access-savings.
4. Otsuka Pharmaceuticals. REXULTI® (brexpiprazole) | Savings & Cost Information. 2023. Accessed January 4, 2024. https://www.rexulti.com/savings-cost
5. AbbVie Inc. Commercial, Medicare, & Medicaid Coverage | VRAYLAR® (cariprazine). Accessed January 4, 2024. https://www.vraylarhcp.com/formulary-coverage

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KEY TAKEAWAYS

- Most therapies for MDD focus on the monoaminergic neurotransmitter modulation of serotonin, norepinephrine, and dopamine using single agents
- Newer agents are now available that impact **glutaminergic, GABAergic, and/or combination** neural pathways to affect neural plasticity
- There are new FDA-approved agents that specifically treat **treatment-resistant, postpartum, and bipolar depression** with favorable side effect profiles


Q&A