From Resistance to Response: Evolving Strategies in MDD Management

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Disclosures

Cristina Cusin, MD, has reported the following relevant financial relationships or relationships with ineligible companies of any amount during the past 24 months:

- *Consulting Fees*: Boehringer Ingelheim, Compass Pathways, Janssen
  Research: Abbott, AFSP, Atai, LivaNova, NIMH

Learning Objectives

- Apply measurement-based care tools to identify patients with treatment-resistant depression or patients with major depressive disorder (MDD) who are suboptimally managed
- Differentiate between depression symptoms caused by MDD and those stemming from bipolar disorder, using evidence-based diagnostic criteria and patient history
- Evaluate the risks and benefits of augmentation versus switching strategies for antidepressant treatments to minimize adverse events, focusing on evidence-based treatment strategies
- Develop treatment plans that specifically target the residual symptoms of depression
- Critically evaluate the impact of targeting multiple pathways when treating MDD

Audience Participation

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Definitions

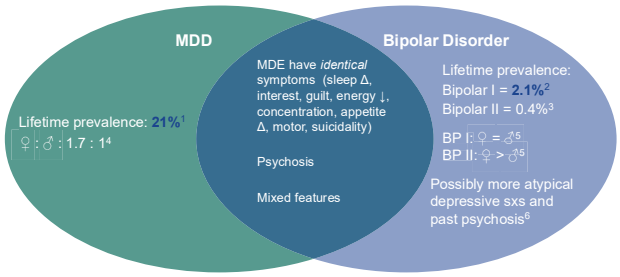
Terminology	Operational Definition
Response	>50% improvement from baseline symptom severity[1]
Partial response	25%-49% improvement from baseline[1]
Remission	Symptoms fall below a minimum threshold to be deemed of little or no clinical significance[1]
Recovery	Remission lasting ≥6 months[1]
Nonresponse	<25% improvement from baseline[1]

Examples of remission:
- 17-item Hamilton Rating Scale for Depression (HAM-D) < 7[1]
- Montgomery-Åsberg Depression Rating Scale (MADRS) score < 10[2]
- Quick Inventory of Depressive Symptoms (QIDS-SR$_{16}$) ≤ 5[3]

Assumptions:
- Correct diagnosis of MDD (R/O bipolar depression; psychosis; negative sxs)
- Appropriate pharmacotherapies – adequate dosing, duration, and adherence
- Absence of confounders – psychoactive substance use, comorbid psychiatric or unstable medical conditions

1. Hawley CJ, et al. *J Affect Disord*. 2002;72(2):177-184. 2. Frank E, et al. *Arch Gen Psychiatry*. 1991;48(9):851-855. 3. Nierenberg AA, et al. *Psychol Med*. 2010;40(1):41-50.

Depression in MDD vs Bipolar Disorder



1. Hasin DS, et al. *JAMA Psychiatry*. 2018;75(4):336-346. 2. Blanco C, et al. *J Psychiatr Res*. 2017;84:310-317. 3. Merikangas KR, Lamers F. *Curr Opin Psychiatry*. 2021;25(1):19-23. 4. Li S, et al. *Ann Gen Psychiatry*. 2023;22(1):53. 5. Altshuler LL, et al. *Am J Psychiatry*. 2010;167(6):708-715. 6. Mitchell PB, et al. *J Clin Psychiatry*. 2001;62(3):212-216.

Measurement-Based Tools to Quantify Depression Symptom Severity, Response, and Remission

PATIENT HEALTH QUESTIONNAIRE-9 (PHQ-9)

Over the last 2 weeks, how often have you been bothered by any of the following problems? (*Use ✔ to indicate your answer*)	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, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself — or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed? Or the opposite — being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3

Scoring:
0-4: None
5-9: Mild
10-14: Moderate
15-19: Moderately Severe
≥20: Severe

Other Depression Rating Scales

Scale	Description
MADRS	10-item scale, each rated 0-6; scores of 7-19 are considered "mild," 20-34 "moderate," and >34 "severe." Developed as a scale that is sensitive to change in symptoms over time.
HAM-D	16-item self- or clinician-rated measure. Scores of 0-5 are "not depressed," 6-10 reflect "mild depression," 11-15 is "moderate," 16-20 is "severe," and scores ≥20 are "very severe."
QIDS	16-item **self- or clinician-rated** measure. Scores of 0-5 are "not depressed," 6-10 reflect "mild depression," 11-15 is "moderate," 16-20 is "severe," and scores ≥20 are "very severe."
BDI	21 **self-report** questions each scored from 0-3 (maximum score of 63); scores of 0-13 = "minimal symptoms," 14-19 = "mild," 20-28 = "moderate," and >29 = "major." The scale captures attitudes and distortions related to the cognitive theory of depression.

Pros	Cons
Validated	Often used in clinical trials research; requires training to administer and score
Standardized	Time-intensive
Captures varied symptom domains	May over-weight some symptoms (eg, somatization, sleep in HAM-D) and under-weight others (eg, atypical depressive symptoms in MADRS)

BDI, Beck Depression Inventory; HAM-D, Hamilton Rating Scale for Depression; MADRS, Montgomery-Åsberg Depression Rating Scale; QIDS, Quick Inventory of Depressive Symptomatology.

Another Conceptualization: Staging of Depression

Takes into account # of failed adequate trials and also episode duration, intensity of trials, symptom severity, augmentation trials, modalities (eg, ECT)

Maudsley Staging Parameters and Suggested Scoring Conventions		
Parameter/Dimension	**Parameter Specification**	**Score**
Duration	Acute (≤12 mo) Sub-acute (13-24 mo) Chronic (>24 mo)	1 2 3
Symptom severity at baseline	Subsyndromal Syndromal ▪ Mid ▪ Moderate ▪ Severe without psychosis ▪ Severe with psychosis	1 2 3 4 5
Treatment failures Antidepressants	 Level 1: 1-2 medications Level 2: 3-4 medications Level 3: 5-6 medications Level 4: 7-10 medications Level 5: >10 medications	 1 2 3 4 5
Augmentation	Not used Used	0 1
Electroconvulsive therapy	Not used Used	0 1
Total		15

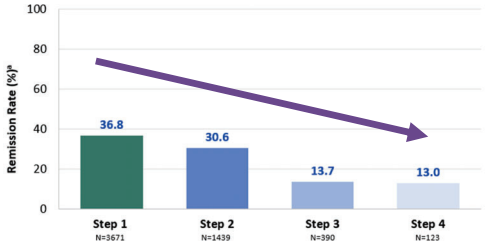
Scoring Treatment Resistance:

3-6: mild
7-10: moderate
11-15: severe

Fekadu A, et al. *J Clin Psychiatry.* 2009;70(2):177-184.

Successive Antidepressant Trials Yield Decreasing Remission Rates: STAR*D…

1-citalopram
2a- switch sertraline vs bupropion vs venlafaxine vs CBT
2b- add bupropion vs buspirone vs CBT
3- switch mirtazapine v nortriptyline
Add lithium, T3
4-venlafaxine/mirtazapine vs tranylcypromine



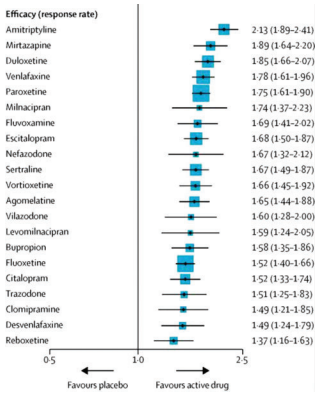
Rush AJ, et al. *Am J Psychiatry.* 2006;163(11):1905-1917.

…And No Particular "Next" Treatment Intervention May Be Better Than Another

Treatment Step	Response, %
Step 2 (n = 1439)	28.5
Switch strategy (n = 789)	27.3
• Bupropion SR (n = 239)	26.1
• Cognitive therapy (n = 62)	30.6
• Sertraline (n = 238)	26.7
• Venlafaxine XR (n = 250)	28.2
Augmentation strategy (n = 650)	29.9
• Bupropion (n = 279)	31.8
• Buspirone (n = 286)	26.9
• Cognitive therapy (n = 85)	34.1

Rush AJ, et al. *Am J Psychiatry.* 2006;163(11):1905-1917.

…As Most Monoaminergic Antidepressants Have Roughly Comparable Likelihoods for MDD Response



Cipriani A, et al. *Lancet*. 2018;391(10128):1357-1366.

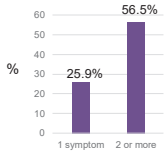
Prevalence of Residual Symptoms After Treatment for Major Depression

After **partial response**:

- 15-month follow-up of 54 patients from 1990s:
- **>75% had residual somatic symptoms**, fatigue, psychic anxiety, depressed mood, sexual dysfunction; over half had guilt or insomnia[1]

After **remission** (HAM-D < 7):

- 8-week open trial of fluoxetine (N = 215) for MDD
- <20% were symptom-free[2]
- Most common residual symptoms:
  - Sleep disturbance (44%)
  - Fatigue (38%)
  - Lack of interest (27%)



1. Paykel ES. *Psychopathology*. 1998;31(1):5-14. 2. Nierenberg AA, et al. *J Clin Psychiatry*. 1999;60(4):221-225.

Residual Depressive Symptoms After Acute Response in STAR*D

- Citalopram responders who did not remit had, on average, 5 residual symptom domains[1]

Residual Symptom Domain	Prevalence
Insomnia	94.6%
Sad mood	70.8%
Poor concentration	69.6%

- >90% of citalopram *remitters* had at least 1 residual symptom (median = 3)[2]

Residual Symptom Domain	Prevalence
Weight increase	71.3%
Middle insomnia	54.9%
Poor concentration	69.6%

- Remitters before week 6 had fewer residual symptoms[2]
- # of residual symptoms was associated with higher probability of relapse[2]

1. McClintock SM, et al. *J Clin Psychopharmacol*. 2011;31(2):180-186. 2. Nierenberg AA, et al. *Psychol Med*. 2010;40(1):41-50.

Residual/Subsyndromal Symptoms Hasten Syndromal Relapse in MDD

NIMH Collaborative Depression Study

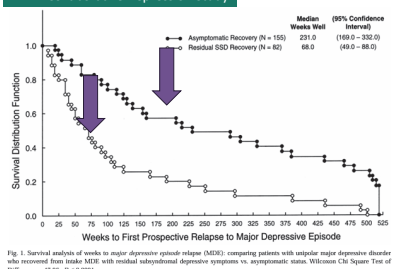
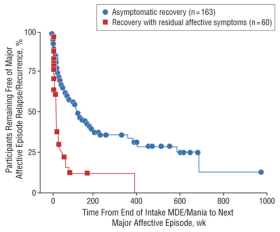


Fig. 1. Survival analysis of weeks to *major depressive episode* relapse (MDE): comparing patients with unipolar major depressive disorder who recovered from intake MDE with residual subsyndromal depressive symptoms vs. asymptomatic status. Wilcoxon Chi Square Test of Difference = 47.96; $P < 0.0001$.

Residual subsyndromal depression:
- 3x faster time until MDE relapse as compared to full remitters

Judd LL, et al. *J Affect Disord*. 1998;50(2-3):97-108.

Residual Symptoms and Episode Relapse in Bipolar Disorder



Survival analysis of weeks to first major affective episode relapse or recurrence in individuals with bipolar I or bipolar II disorder, comparing participants with asymptomatic recovery vs participants with recovery with residual affective symptoms from their intake major depressive episode (MDE) or mania. Significance of difference in overall survival distribution: Wilcoxon $\chi^2 = 35.81$; $P < 0.001$; hazard ratio, 3.36; 95% confidence interval, 2.25-4.98. Median weeks well: asymptomatic recovery, 123 (95% confidence interval, 89-179); recovery with residual affective symptoms, 24 (95% confidence interval, 19-31).

Judd LL, et al. *Arch Gen Psychiatry*. 2008;65(4):386-394.

Which STAR*D Residual Depressive Symptoms Best Predicted Relapse?

	Crude hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)[a]
Sleep onset insomnia	1.280 (1.167–1.403)[b]	1.001 (0.889–1.128)
Mid-nocturnal insomnia	1.225 (1.115–1.346)[b]	1.049 (0.941–1.169)
Early morning insomnia	1.292 (1.168–1.429)[b]	1.050 (0.933–1.203)
Hypersomnia	1.253 (1.106–1.420)[b]	**1.190 (1.044–1.356)[c]**
Sad mood	1.581 (1.409–1.774)[b]	1.125 (0.943–1.342)
Appetite change	1.350 (1.240–1.471)[b]	1.084 (0.960–1.224)
Weight change	1.286 (1.180–1.400)[b]	**1.127 (1.005–1.264)[c]**
Impaired concentration/decision-making	1.492 (1.317–1.624)[b]	1.066 (0.901–1.258)
Negative self-view	1.282 (1.132–1.452)[b]	1.010 (0.868–1.174)
Suicidal ideation	1.650 (1.354–2.011)[b]	1.172 (0.923–1.490)
Lack of involvement	1.462 (1.315–1.625)[b]	1.118 (0.969–1.289)
Loss of energy	1.445 (1.315–1.587)[b]	1.112 (0.975–1.269)
Slowed down	1.650 (1.414–1.924)[b]	1.045 (0.839–1.302)
Restlessness	1.501 (1.337–1.686)[b]	**1.197 (1.031–1.390)[c]**

[a] Adjusted for age, gender, length of the current episode, and number of the past episodes
[b] $p < 0.001$
[c] $p < 0.05$ shown in bold
CI confidence interval, *QIDS-SR*$_{16}$ 16-item Quick Inventory of Depressive Symptomatology, self-report

Sakurai H, et al. *Psychopharmacology (Berl)*. 2017;234(16):2453-2461.

Defining Treatment-Resistant Depression

No universal or consensus definition

Most commonly used definition is **"a minimum of 2 prior treatment failures and confirmation of prior adequate dose and duration"**[1]

FDA-approved interventions:

- Intranasal esketamine: "not responded adequately to at least **2 different antidepressants** of adequate dose and duration"
- Olanzapine-fluoxetine combination: patients who do not respond to **2 separate trials** of different antidepressants of adequate dose and duration in the current episode
- Transcranial magnetic stimulation
- Vagus nerve stimulation: nonresponse to **4 or more medications**, ECT, or both

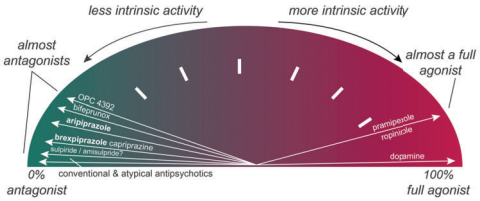
1. Gaynes BN, et al. *Depress Anxiety*. 2020;37(2):134-145.

Atypical Antipsychotics That Are FDA-Approved for Add-On Therapy After Incomplete Response to an Antidepressant in MDD (ie, not necessarily TRD)

Agent	Adjunctive Therapy Dosing in MDD	What About Bipolar Depression?
Aripiprazole	2-5 mg/day initially; target = 5-10 mg/day; max 15 mg/day	2 (-) trials
Brexpiprazole	0.5-1 mg/day; target = 2 mg/day; max 3 mg/day	No data
Cariprazine	Target = 1.5 mg/day; max = 3 mg/day	FDA-approved (same dosing)
Olanzapine (+ Fluoxetine)	6 or 12 mg/day	FDA-approved (same dosing)
Quetiapine XR	Initially 50 mg/day; target = 150-300 mg/day (max = 300 mg/day)	FDA-approved (target = 300 mg/day)

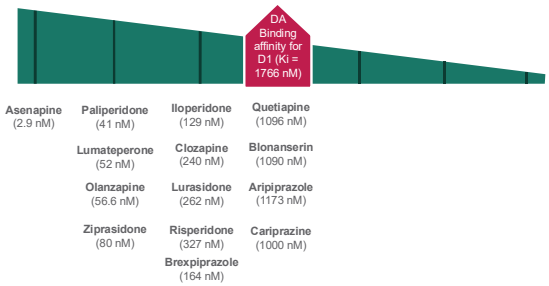
Off-label and/or unstudied as adjunctive therapy in MDD: asenapine, risperidone, iloperidone, lurasidone, ziprasidone
Under review as adjunctive therapy in MDD: lumateperone

Dopamine Partial Agonists



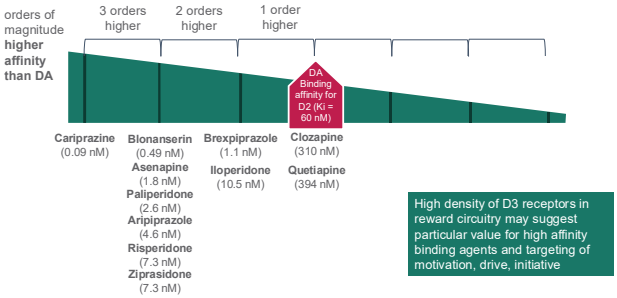
	Aripiprazole	Brexpiprazole	Cariprazine
	Ki (nM)	Ki (nM)	Ki (nM)
D2	3.3	0.30	0.49
D3	0.8 – 9.7	1.1	0.85
5HT2A	3.4 – 35	0.47	18.8
5HT1A	1.7 – 5.6	0.12	2.6

Antipsychotics: D1 Receptor Modulation



1. Stahl SM. *CNS Spectr.* 2017;22(5):375-384. 2. Snyder GL, et al. *Psychopharmacology (Berl).* 2015;232(3):605-621.

Antipsychotics: D3 Receptor Modulation



High density of D3 receptors in reward circuitry may suggest particular value for high affinity binding agents and targeting of motivation, drive, initiative

Stahl SM. *CNS Spectr.* 2017;22(5):375-384.

Switching vs Augmentation in MDD

SWITCH	AUGMENT
1 failed trial	2 or more failed antidepressant trials
Poorly tolerated side effects to initial antidepressant	Initial antidepressant well tolerated
<25% improvement in symptoms on initial antidepressant (nonresponse)	≥25% improvement in symptoms on initial antidepressant (partial response)
Less severe symptoms, functional impairment	More severe symptoms, functional impairment
Patient preference to switch	**Patient preference** for adding medication

Kennedy SH, et al. *Can J Psychiatry.* 2016;61(9):540-560.

ASCP Task Force on the Deprescribing of Psychotropic Medications

Delphi Panel Recommendation	% Agreement (95% CI)
"**Discontinue** a medication if it has **failed** to produce **at least a partial response** (>25% reduction in overall symptomatology), or **clinically meaningful** significant improvement in **at least 1 core target symptom** (eg, suicidal ideation, insomnia, anxiety) after a conventionally defined adequate trial"	87% (0.77-0.97)

Goldberg JF, et al. 2025 ASCP Annual Meeting. Poster W68.

Symptom-Targeted Approach to Managing Residual Depressive Symptoms

Symptom Domain	Viable Targeted Strategies
Anxiety	Adjunctive buspirone, CBT, short-term benzodiazepines
Fatigue	(Ar)modafinil, stimulants, bupropion
Insomnia	Orexin receptor antagonists
Low self-worth/self-esteem	CBT
Suicidal ideation	(Es)ketamine
Suicidal behavior	Lithium
Impulsivity, mood instability	Lithium, lamotrigine, divalproex

Menza M, et al. *J Clin Psychiatry*. 2003;64(5):516-523.

Switch or Augment? Other Factors to Consider

Factor	Comment
# of failed trials in the current episode	Few treatments for depression have been studied in the setting of *multiple* previous nonresponses
Are there viable alternatives?	Some treatments may have unique efficacy (eg, ketamine, ECT, MAOIs, lithium)
Tolerability	Are adverse effects bothersome or medically significant? Manageable/tolerable or do risks outweigh benefits?
Severe or unique symptom targets	eg, suicidal behavior and lithium; pain and noradrenergic agents
Comorbidities	eg, stimulants and ADHD; anxiolytics
Timing of making a change	Sometimes safer to retain an existing partially effective treatment and not discontinue until a new replacement treatment has demonstrated efficacy

Goldberg JF, Stahl SM. *Clinical Reasoning and Decision-Making in Psychiatry*. Cambridge University Press; 2024.

Switch or Augment? Other Factors to Consider

Consideration	Comment
Trial length	Expect an inkling of improvement (20%) by 2 weeks, but adequate trial may be 6-12 weeks in chronic or treatment-resistant patients
Adequate dosing	Subtherapeutic ≠ adequate
Pharmacogenetics	Suspect ultrarapid metabolizers for a given substrate if no response + no adverse effects at optimal doses; response to prior substrates of the same metabolic enzyme?
Adequate adherence	Never assume – NEED TO ASK
Comorbidities	Depression + comorbid anxiety disorders required >6 weeks to determine efficacy in STAR*D; **substance use disorder** comorbidity tends to greatly diminish treatment responsivity

Goldberg JF, Stahl SM. *Clinical Reasoning and Decision-Making in Psychiatry*. Cambridge University Press; 2024.

Treatment of SSRI-Resistant Depression: A Meta-Analysis Comparing Within- Versus Across-Class Switches

George I. Papakostas, Maurizio Fava, and Michael E. Thase

Background: Two broad treatment options exist for switching antidepressants for depressed patients who fail to respond to a selective serotonin reuptake inhibitor (SSRI): either a second course of SSRI therapy or a different class of antidepressants. The goal of the present work was to conduct a meta-analysis of studies comparing these two switch strategies.

Methods: Several sources were searched for randomized clinical trials comparing these two switch strategies.

Results: Data from four clinical trials ($n = 1496$) were combined using a random-effects model. Patients randomized to switch to a non-SSRI antidepressant (bupropion, mirtazapine, venlafaxine) were more likely to experience remission than patients switched to a second SSRI (risk ratio = 1.29, $p = .007$). Pooled remission rates were 28% (for non-SSRIs) and 23.5% (for SSRIs). There was also a nonsignificant trend ($p = .1$) in the rate of discontinuation due to intolerance favoring the within-class switch strategy (risk ratio = 1.23). There was no difference in response rates between the two treatment groups.

Conclusions: These results suggest a modest yet statistically significant advantage in remission rates when switching patients with SSRI-resistant depression to a non-SSRI rather than an SSRI antidepressant. With the number needed to treat (NNT) statistic as one indicator of clinical significance, nearly 22 SSRI nonresponders would need to be switched to a non-SSRI rather than a second SSRI antidepressant to obtain one additional remitter. This difference falls well below the mark of NNT = 10 suggested by the United Kingdom's National Institute of Clinical Excellence but nonetheless might be of public health relevance given the large number of SSRI-resistant patients switched to an SSRI versus a non-SSRI antidepressant.

Biol Psychiatry. 2008;63(7):699-704.

Intervention Strategies for Residual MDD Symptoms

Longer time on drug:

- In STAR*D, patients with MDD who had high baseline anxiety usually responded after
- 6 weeks of treatment[1]
- In chronic major depression, 40% of sertraline or imipramine partial remitters
- after 12 weeks of acute treatment converted to full remission after an additional 16 weeks[2]

	Response at weeks 5-8	Response at weeks 9-12
Active drug	21.6%	9.9%
Placebo	13.0%	2.4%
NNT	11	17

1. Fava M, et al. *Am J Psychiatry*. 2008;165(3):342-351. 2. Koran LM, et al. *J Affect Disord*. 2001;65(1):27-36.

Intervention Strategies for Residual MDD Symptoms

Supratherapeutic dosing:

- Unlikely to convert a nonresponse to a full response…but might fine-tune a partial response without necessarily jeopardizing tolerability

Meta-analysis of 9 MDD studies with supratherapeutic dosing (n = 1273) [1]

	SMD	Response	All-cause Dropout
All studies	0.053 *P* = 0.598	OR = 1.124 *P* = 0.532	OR = 0.964 *P* = 0.885
Adult MDD, SSRIs	0.079 *P* = 0.432	OR = 0.110 *P* = 0.559	OR = 0.909 *P* = 0.598
All MDD	0.098 *P* = 0.305	OR = 1.167 *P* = 0.426	OR = 0.964 *P* = 0.885

1. Rink L, et al. *J Clin Psychiatry*. 2018;79(3):17r11693.

What About Just Adding Bupropion?

- Meta-analysis of 7 trials: no better outcome with adjunctive bupropion than SSRI or SNRI alone (SMD = 0.10)[1]
- STAR*D:
  - Citalopram nonresponders randomized to adjunctive bupropion or buspirone had similar response rates
  - Bupropion had greater reduction and overall scores in QIDS-SR depression ratings and lower dropout by Week 12[2]

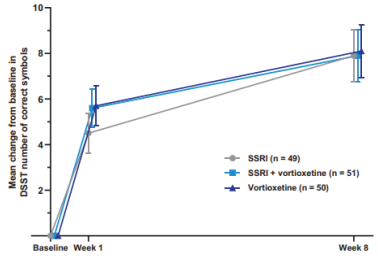
1. Henssler J, et al. *JAMA Psychiatry*. 2022;79(4):300-312. 2. Trivedi MH, et al. *N Engl J Med*. 2006;354(12):1243-1252.

Examples of Neurotransmitter Systems Believed to Be Involved in Major Depression

System	Location	Receptors	Function
Serotonin	Raphe nucleus	SERT, 5HT1A, 5HT2A, 5HT2C, 5HT3, 5HT7	Mood, anxiety, feeding
Norepinephrine	Locus coeruleus	NET, alpha-2	Attention
Dopamine	Prefrontal cortex	DAT, D1, D2, D3, D4, D5	Attention, reward
Glutamate	Cortex, thalamus	Glu	Arousal, mood
Gamma aminobutyric acid (GABA)	Hippocampus, thalamus, basal ganglia, hypothalamus, brainstem	GABA-A	Anxiety, sedation, mood
Acetylcholine	Cortex/anterior cingulate	M2	Mood
Opiate	Cortex, limbic system, brainstem	MOR, KOR	Mood, reward
Melatonin	Hypothalamus, raphe nucleus, locus coeruleus	M1, M2	Mood, sleep/circadian rhythms
Orexin	Hypothalamus	OX1R, OX2R	Mood, sleep

Goldberg JF, Stahl SM. *Practical Psychopharmacology*. Cambridge University Press; 2021. Jeon WJ, et al. *Curr Neuropharmacol*. 2015;13(6):739-749.

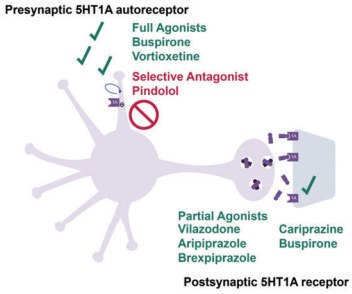
Residual Cognitive Symptoms in Partially Remitted MDD: Role for Vortioxetine (5HT7 Antagonist)?



No added benefit with vortioxetine over SSRI alone

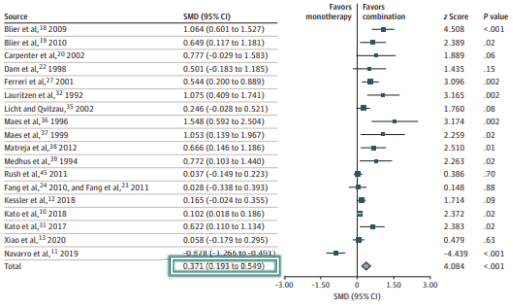
Nierenberg AA, et al. *J Affect Disord*. 2019;250:35-42.

5HT1A Partial Agonism



Goldberg JF, Stahl SM. *Practical Psychopharmacology*. Cambridge University Press; 2021.

Alpha 2A Autoreceptor Antagonists as Antidepressant Adjuncts



Henssler J, et al. *JAMA Psychiatry*. 2022;79(4):300-312.

5HT2A/Alpha 2A Blockade as Antidepressant Adjunct in MDD

Mirtazapine

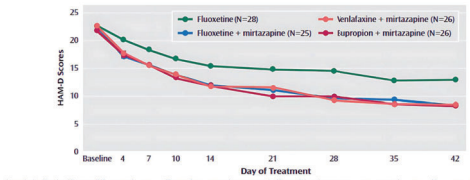
Dosing:

Mirtazapine 30 mg/day

Fluoxetine 20 mg/day

Bupropion 150 mg/day

Venlafaxine 225 mg/day

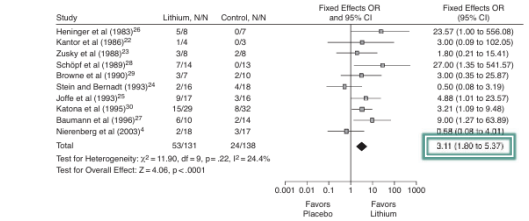


* Statistically significant difference between fluoxetine monotherapy and all combination treatment groups (F=3.87; df=3, 101, p=0.011).

Other 5HT2A antagonists with antidepressant properties: second-generation antipsychotics; nefazodone; trazodone

Blier P, et al. *Am J Psychiatry*. 2010;167(3):281-288.

Don't Forget About Lithium Augmentation



[a]Pooling of patients responding to augmentation therapy. Fixed effects model used.[9]

Crossley NA, Bauer M. *J Clin Psychiatry*. 2007;68(6):935-940.

Looking Beyond Poly-Monoaminergic Mechanisms to Target Residual Symptoms

Anti-glutamatergics:

- Original database with IN esketamine was (by design) augmentation to new antidepressant starts; no existing database specifically examining augmentation after partial response to traditional antidepressant

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Anti-glutamatergics:

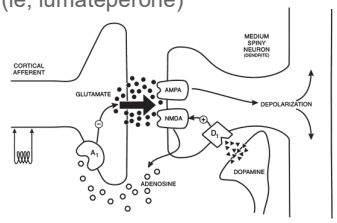
- Original database with IN esketamine was (by design) augmentation to new antidepressant starts; no existing database specifically examining augmentation after partial response to traditional antidepressant
- Bupropion + dextromethorphan as an uncompetitive NMDA receptor antagonist + sigma-1 receptor agonist
- In real-world practice, >70% of treatment initiations occur "off label" as add-on therapy to an SSRI or SNRI (claims database N = 22,288)[1]

1. Muzyk A, et al. *J Med Econ*. 2024;27(1):1003-1010.

Looking Beyond Poly-Monoaminergic Mechanisms to Target Residual Symptoms

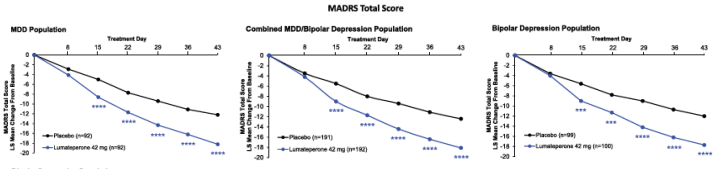
Anti-glutamatergics:

- D1 post-synaptic blockade indirectly modulates glutamatergic transmission[1] (ie, lumateperone)



Harvey J, Lacey MG. *J Neurosci*. 1997;17(14):5271-5280.

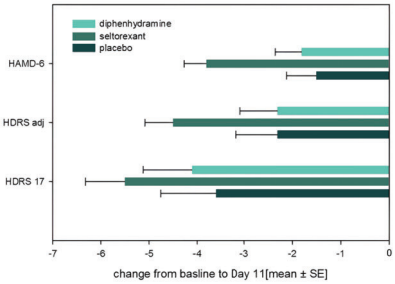
Adjunctive Lumateperone in Major Depressive Disorder With Mixed Features



Durgam S, et al. *J Clin Psychopharmacol*. 2025;45(2):67-75.

Looking Beyond Poly-Monoaminergic Mechanisms to Target Residual Symptoms

Selective Orexin-2 Receptor Antagonist: Seltorexant



HAM-D_{17} LSMD: -22 (95% CI = -4.35 to 0.05), $P < 0.05$

Recourt K, et al. *Transl Psychiatry*. 2019;9(1):216.

Summary

- A majority of patients with MDD experience incomplete remissions with standard antidepressant pharmacotherapies
- Ensure accurate diagnoses, appropriate pharmacotherapies, adequate adherence, adequate trials, and address comorbidities
- Favor the augmentation of partial responses and switch strategies after failure to achieve even partial response (≤25% improvement from baseline)
- Use measurement-based care to quantify outcomes
- Emerging role for multimodal treatment pathways and novel neurotransmitter systems to address incomplete response and residual symptoms of major depression

Audience Participation

Your mobile device can be used to participate in polling and to download today's presentation. Join in by scanning the QR code!

A 35-year-old patient with major depressive disorder (MDD) has been on an SSRI for 8 weeks. The patient reports mild improvement but continues to experience persistent depressive symptoms that impair daily functioning. As their clinician, which measurement-based care tool would be most appropriate to guide the next treatment decision?

A. Patient Health Questionnaire-9 (PHQ-9) to quantify symptom severity and response
B. Mini-Mental State Examination (MMSE) to assess cognitive impairment
C. Glasgow Coma Scale (GCS) to evaluate consciousness levels
D. CAGE questionnaire to assess alcohol use disorder

A 28-year-old patient presents with depressive symptoms, including fatigue, low mood, and difficulty concentrating. Their history reveals episodes of increased energy, decreased need for sleep, and impulsive spending that lasted for several days. Which diagnosis should be considered before initiating antidepressant treatment?

A. Generalized anxiety disorder, due to overlapping symptoms with depression
B. Treatment-resistant MDD, requiring immediate antidepressant augmentation
C. Bipolar disorder if the patient meets DSM-5 syndromal criteria
D. Persistent depressive disorder, given the chronic nature of symptoms

A 47-year-old patient with MDD has been on 10 mg escitalopram (SSRI) for 10 weeks with partial improvement but continues to struggle with anhedonia and fatigue. The patient denies severe side effects and has no history of previous treatment failures. What is the most appropriate next step in managing this patient's depression?

A. Discontinue escitalopram and switch to a TCA
B. Add an atypical antipsychotic with antidepressant properties
C. Increase escitalopram to the maximum dose despite partial response
D. Discontinue antidepressant therapy and reassess in 3 months

A 38-year-old patient with treatment-resistant MDD has failed 2 SSRI trials and continues to experience severe anhedonia. The clinician is considering a medication that targets multiple neurotransmitter pathways to optimize efficacy. Which of the following treatments would be the most appropriate choice?

A. Continue the SSRI and wait for additional response
B. Switch to desvenlafaxine
C. Augment with intranasal esketamine
D. Prescribe a benzodiazepine to help with anhedonia

Lumateperone, which is being studied as an adjunctive treatment for Major Depressive Disorder (MDD), acts on several neurotransmitter systems relevant to mood regulation. Which of the following is not directly modulated by lumateperone?

A. Dopaminergic transmission via D1 receptor phosphorylation pathways
B. Histaminergic modulation through H1 receptor inverse agonism
C. Glutamatergic signaling through indirect NMDA receptor facilitation
D. Serotonergic balance through 5-HT2A antagonism and serotonin reuptake inhibition

Audience Question & Answer

Thank You!

You will receive an email this week with a link to download your certificate.