Psych Congress MasterClass

Beyond Partial Response: Functional and Remission-Based Strategies in MDD

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- This activity has been independently reviewed for balance

Learning Objectives

1. Define partial response and its impact on long-term outcomes, including relapse risk, quality of life, and daily functioning
2. Assess when and how to adjust the dose of an existing antidepressant in the context of partial response to optimize therapeutic benefits while minimizing adverse effects
3. Evaluate best practices associated with treatment augmentation vs switching to address partial response, including when to consider precision serotonin receptor modulators
4. Describe patient-centered strategies to clinical decision-making that go beyond symptom reduction to improve outcomes and overall well-being

Understanding Partial Response in MDD: Clinical and Functional Implications

Background

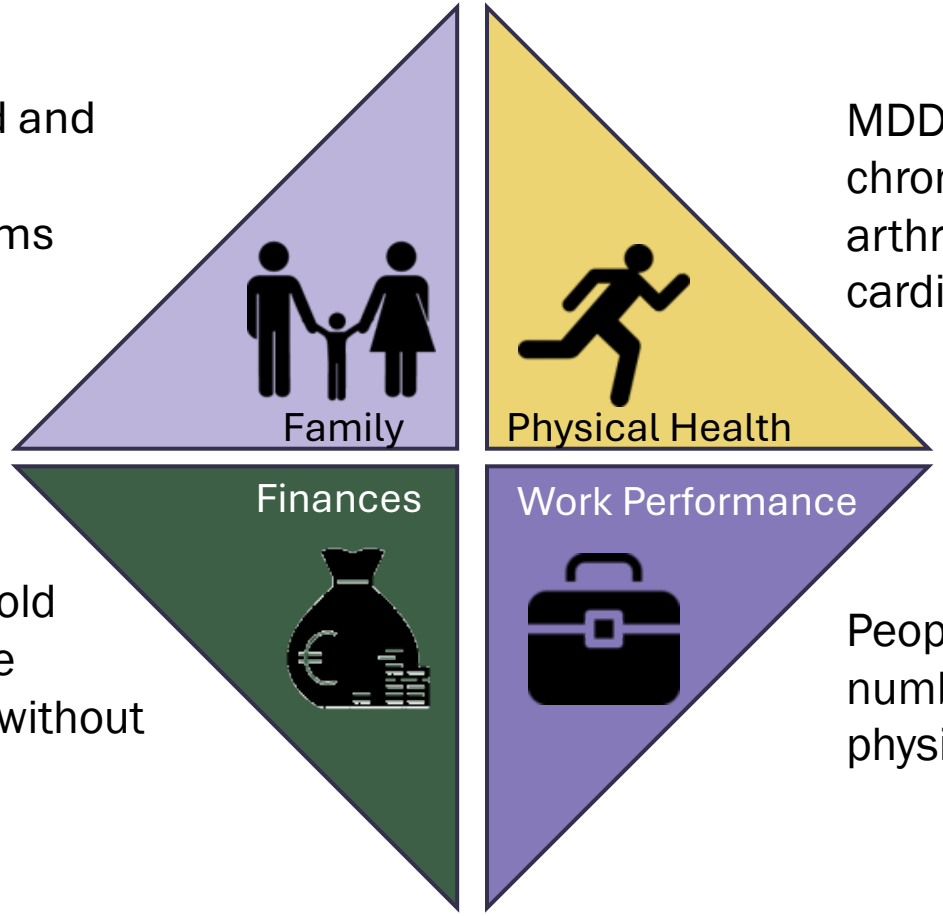
- ~21 million adults in the US had at least 1 major depressive episode, making up 8.3% of U.S Adults in 2021
- 14.5 million adults had at least 1 major depressive episode with severe impairment in the past year as of 2021
- MDD has severe impact on daily functioning and quality of life
- Economic burden of adults with MDD in the US is $326 billion
- Residual symptoms are common and cause significant psychosocial and occupational functional impairment

MDD = major depressive disorder.

National Institute of Mental Health (NIMH). Major Depression. Updated July, 2023. Accessed May 5, 2024. https://www.nimh.nih.gov/health/statistics/major-depression. Greenberg PE, et al. *Pharmacoeconomics*. 2021;39(6):653–665. Romera I, et al. *Eur Psychiatry*. 2010;25(1):58-65. Zimmerman M et al. *Compr Psychiatry*. 2007;48(2):113-117.

The Personal Burden of MDD Can Be Significant and Wide-ranging

Marital dissatisfaction/discord and negative parenting behaviours are strongly related to symptoms of depression



MDD is significantly associated with chronic physical disorders including arthritis, asthma, cancer, diabetes, cardiovascular disease and pain

Personal earnings and household income of people with MDD are substantially lower than those without depression

People with MDD have the highest number of days away from work of any physical or mental disorder

Kessler RC. *Psychiatr Clin North Am*. 2012;35(1):1–14.

Levels of Response to MDD Treatment

Nonresponse: little to no improvement

- < 25% improvement on a depression rating scale

Partial response

- 25% to 49% improvement on a rating scale
- Still have troublesome symptoms affecting functioning

Response

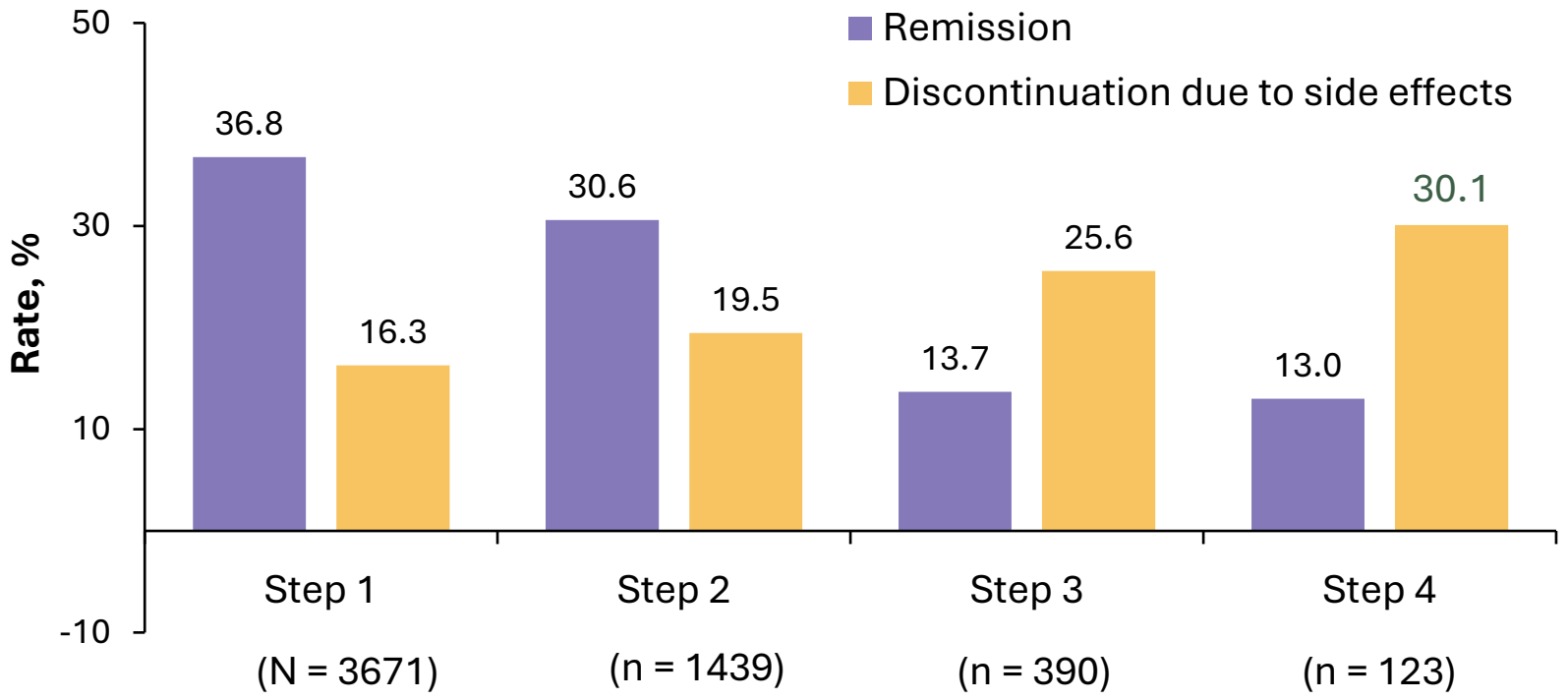
- ≥ 50% improvement on a rating scale, *but not remission*
- Treatment may be needed for residual symptoms

Remission

- Virtually symptom free
- Return to normal functioning

Papakostas GI, et al. *J Clin Psychiatry*. 2020;81:OT19037BR4.

Remission Rates Decreased, While Discontinuation Due to Side Effects Increased in the STAR*D Trial



Each step of therapy included options to switch or augment

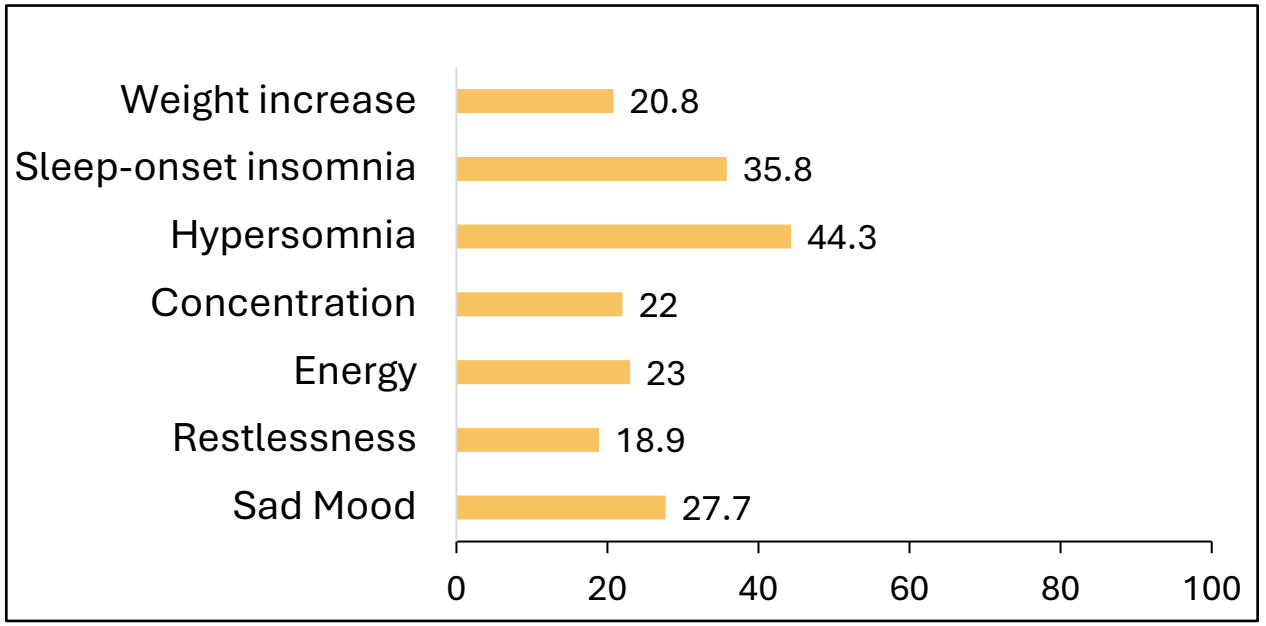
Options included various SSRIs, SNRIs, lithium, T_3, and cognitive therapy

SSRI = selective serotonin reuptake inhibitor; SNRI = serotonin and norepinephrine reuptake inhibitor; T3 = triiodothyronine.

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

Persistent Symptoms* in MDD Remitters are Common and Negatively Affect Outcomes

Proportion of Remitters With Persistent Baseline Symptoms at the End of Step 1 (STAR*D Study)

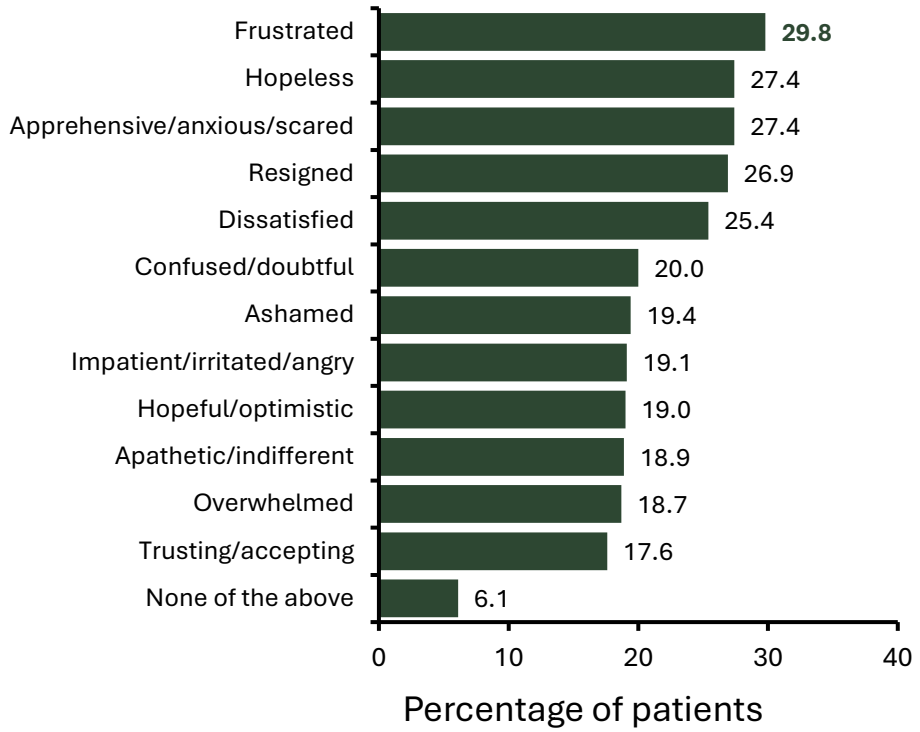


- Residual symptoms increase the risk for suicide and relapse
- Residual symptoms have an adverse impact on psychosocial and occupational functioning

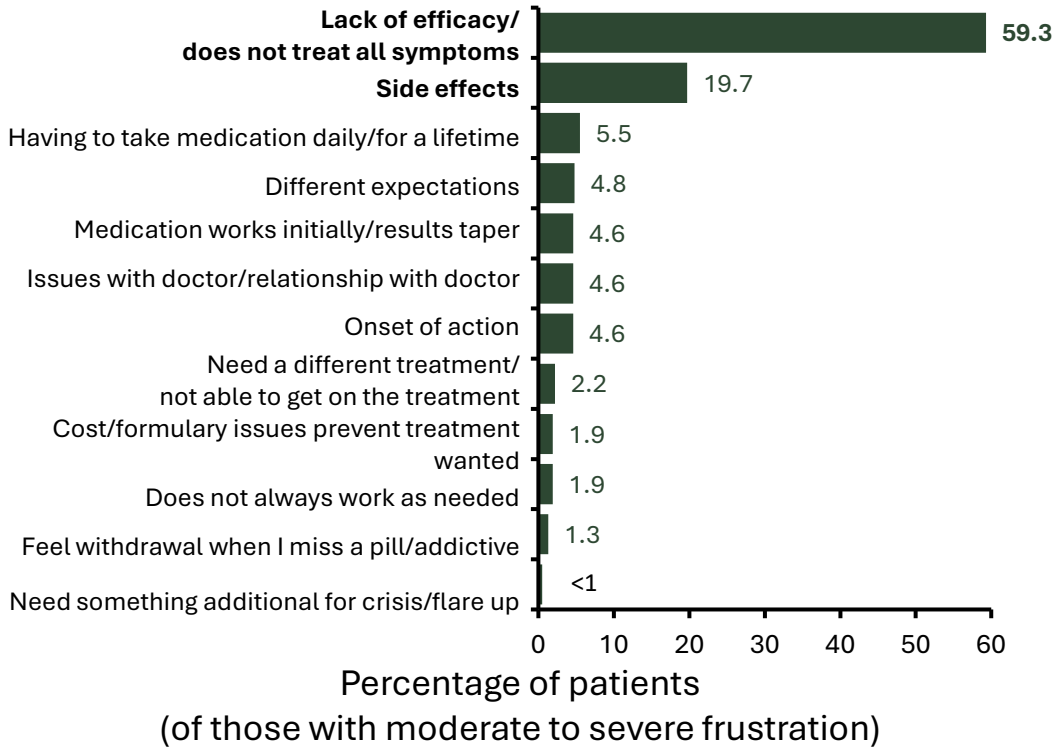
***Persistent symptoms defined as QIDS-SR16 item score ≥1**
QIDS-SR16 = 16-Item Quick Inventory of Depressive Symptomatology-Self Report; STAR*D = Sequenced Treatment Alternatives to Relieve Depression study.
Nierenberg AA, et al. *Psychol Med*. 2010;40(1):41-50. Blier P. *J Clin Psychiatry*. 2013;74(Suppl 2):19-24. Romera I, et al. *BMC Psychiatry*. 2013;13:51.

Patients with Inadequate Response to Antidepressant Treatment Often Feel Frustrated by Their Medication

Patients' emotions regarding their medication (n=2,096)*



Patients' reasons for frustration with their medication (n=536)



*Patients could select all emotions that applied.

Mago et al. *BMC Psychiatry*. 2018;18(1):33

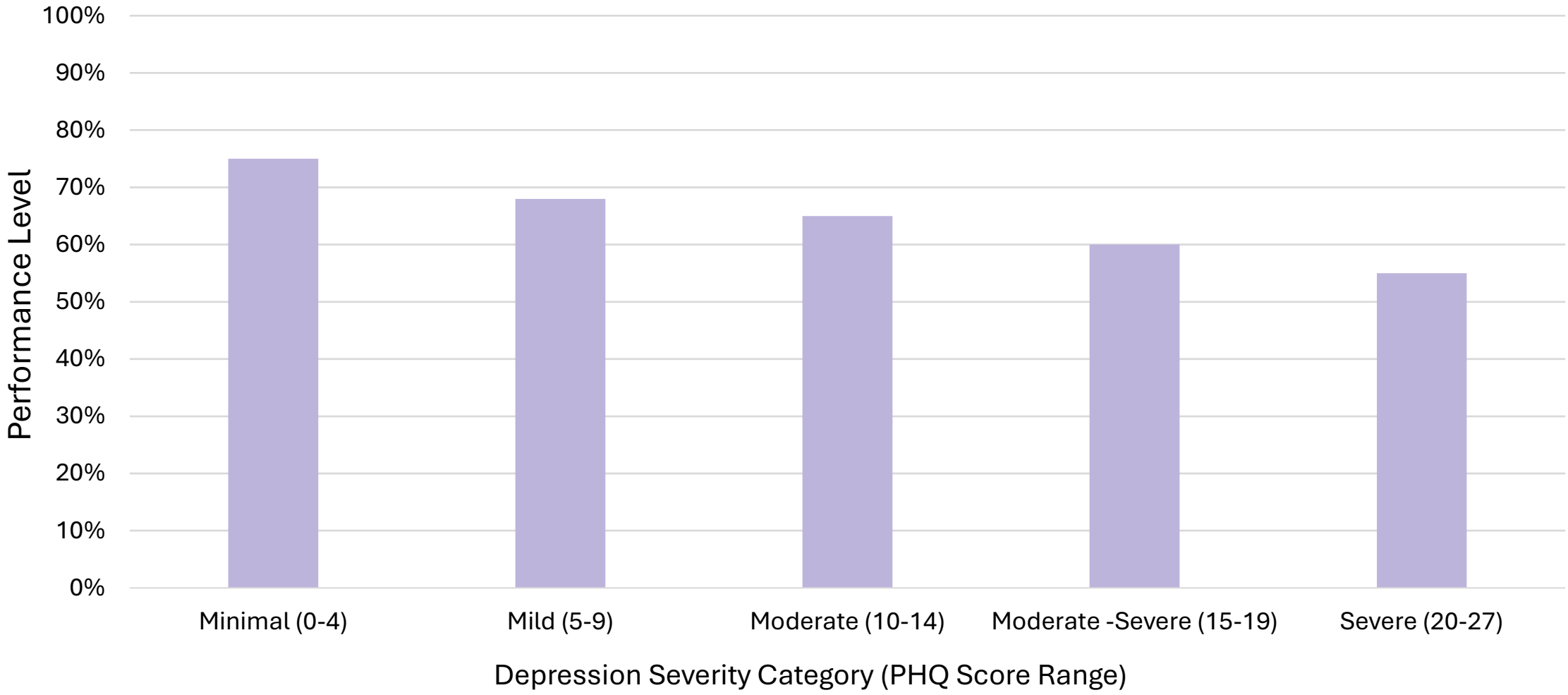
More About Functional Impairment

Absenteeism: workdays missed

Presenteeism: at work but not functioning as needed
("working while ill")

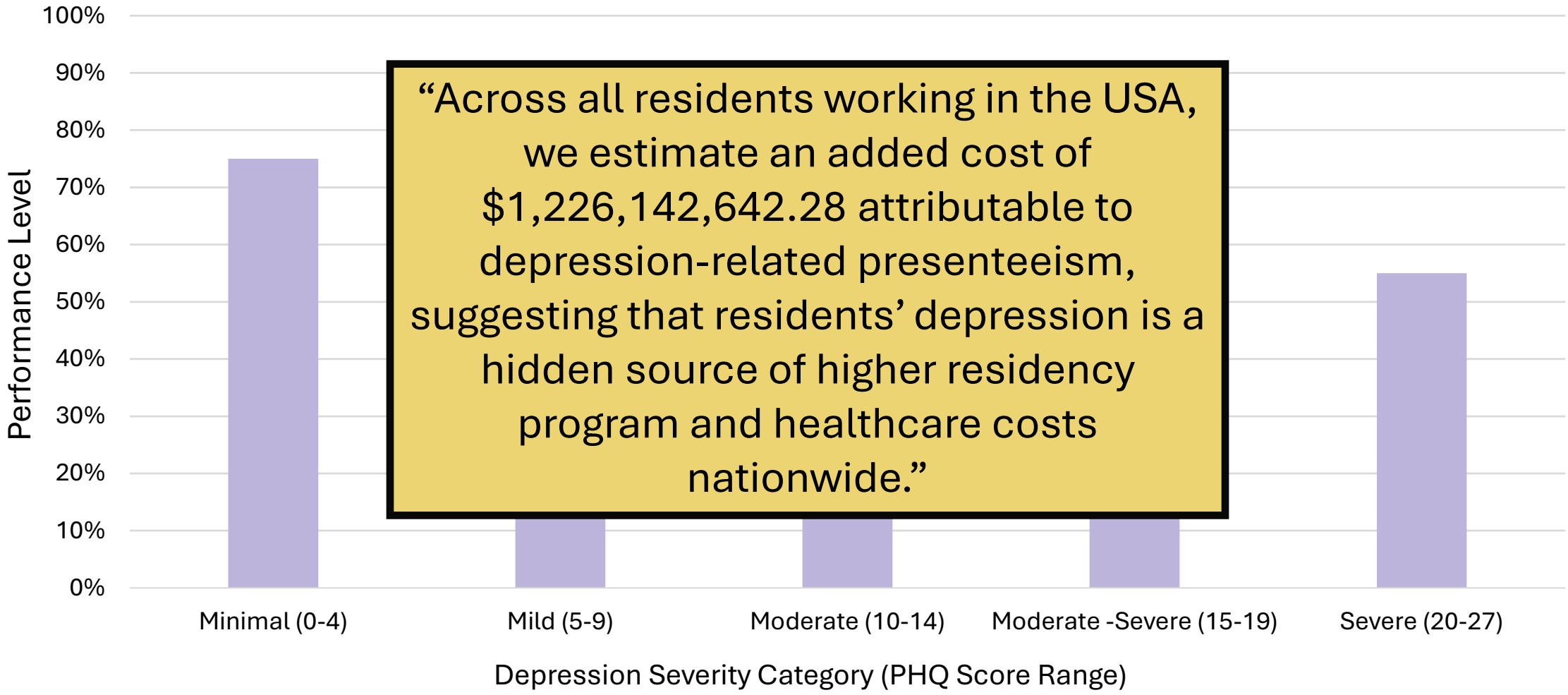
Rosen T, et al. *Acad Psychiatry.* 2018;42(1):84-87.

Depression-Related Presenteeism in Resident Physicians



Rosen T, et al. *Acad Psychiatry.* 2018;42(1):84-87.

Depression-Related Presenteeism in Resident Physicians



"Across all residents working in the USA, we estimate an added cost of $1,226,142,642.28 attributable to depression-related presenteeism, suggesting that residents' depression is a hidden source of higher residency program and healthcare costs nationwide."

Rosen T, et al. *Acad Psychiatry.* 2018;42(1):84-87.

Which Depressive Symptoms Interfere with Occupational Functioning? Defined as a response of "Very much" or "So much that I had to stop working" to the following question: "In the past week, how have the following symptoms interfered with your ability to work?"

Symptom	% of sample experiencing symptom	Mean score	SD	Clinically important interference[1] (%)
Lack of motivation	93	1.78	0.91	59
Low energy	96	1.72	0.87	58
Low mood	98	1.68	0.88	55
Feeling physically slowed down	94	1.50	0.92	52
Anxious/tense/nervous	96	1.55	0.90	50
Trouble concentrating	96	1.48	0.80	45
Sleepy during the day	88	1.31	0.85	40
Trouble with memory	93	1.31	0.77	39
Trouble sleeping at night	84	1.30	0.93	39
Feeling guilty/ashamed	88	1.24	0.97	38
Irritability/anger	91	1.26	0.91	36
Physical pain	76	1.18	1.10	35
Sleeping too much	80	1.26	1.00	31
Poor appetite	69	0.95	0.97	28
Suicidal thoughts	66	0.79	0.92	19

Lam RW, et al. *Depress Res Treat*. 2012;2012:630206.

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Lam RW, et al. *Depress Res Treat*. 2012;2012:630206.

Summary of Individual Disease Burden

Physical

- MDD is a consistent predictor of the subsequent first onset of a variety of chronic physical disorders, including arthritis, asthma, cardiovascular disease, diabetes, chronic pain, and certain types of cancer

Financial

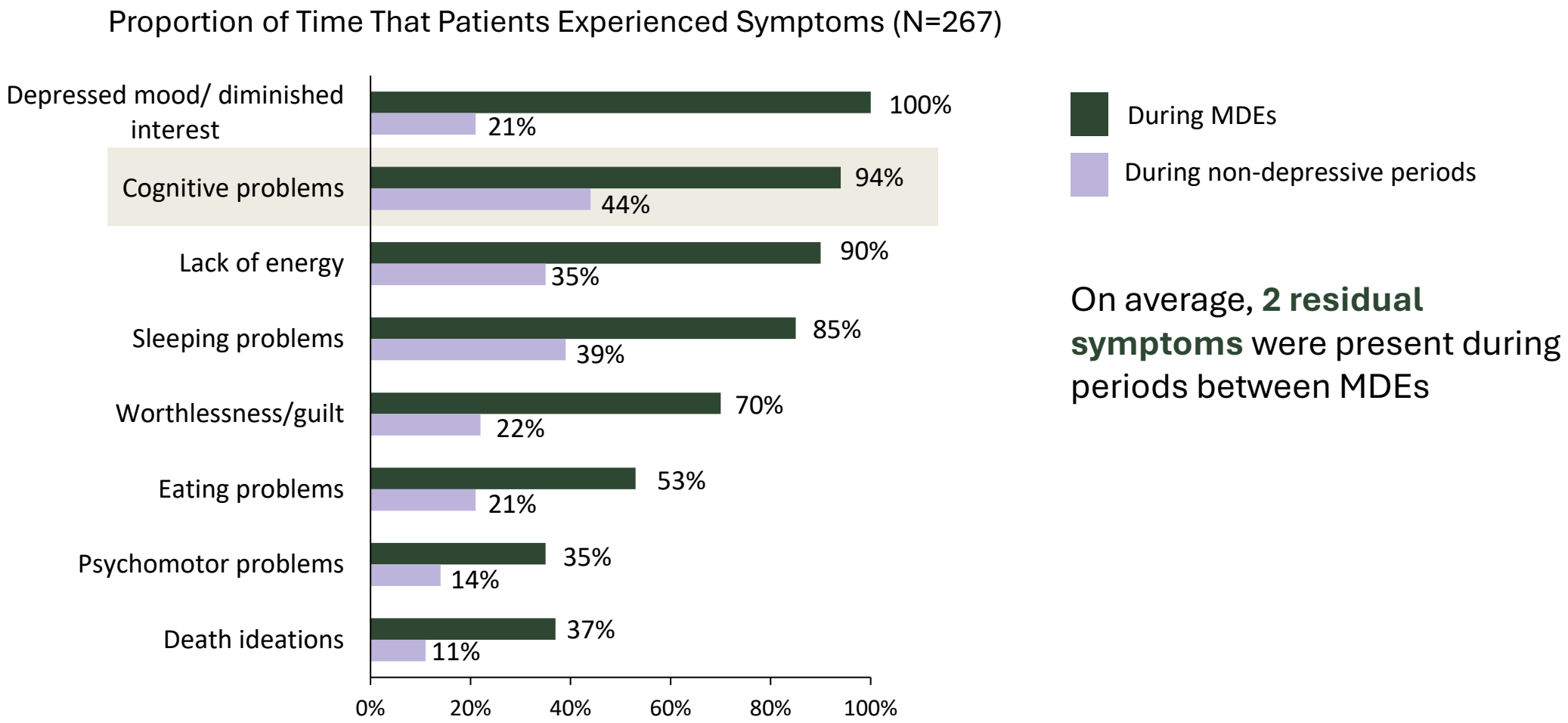
- Incomes of people with MDD are substantially lower than those without depression

Education

- MDD is associated with a 60% elevated risk of failure to complete secondary school than otherwise comparable youth

Kessler RC. *Psychiatr Clin North Am*. 2012;35(1):1-14.

Between Episodes, Cognitive Problems are Experienced More of the Time than Other Symptoms

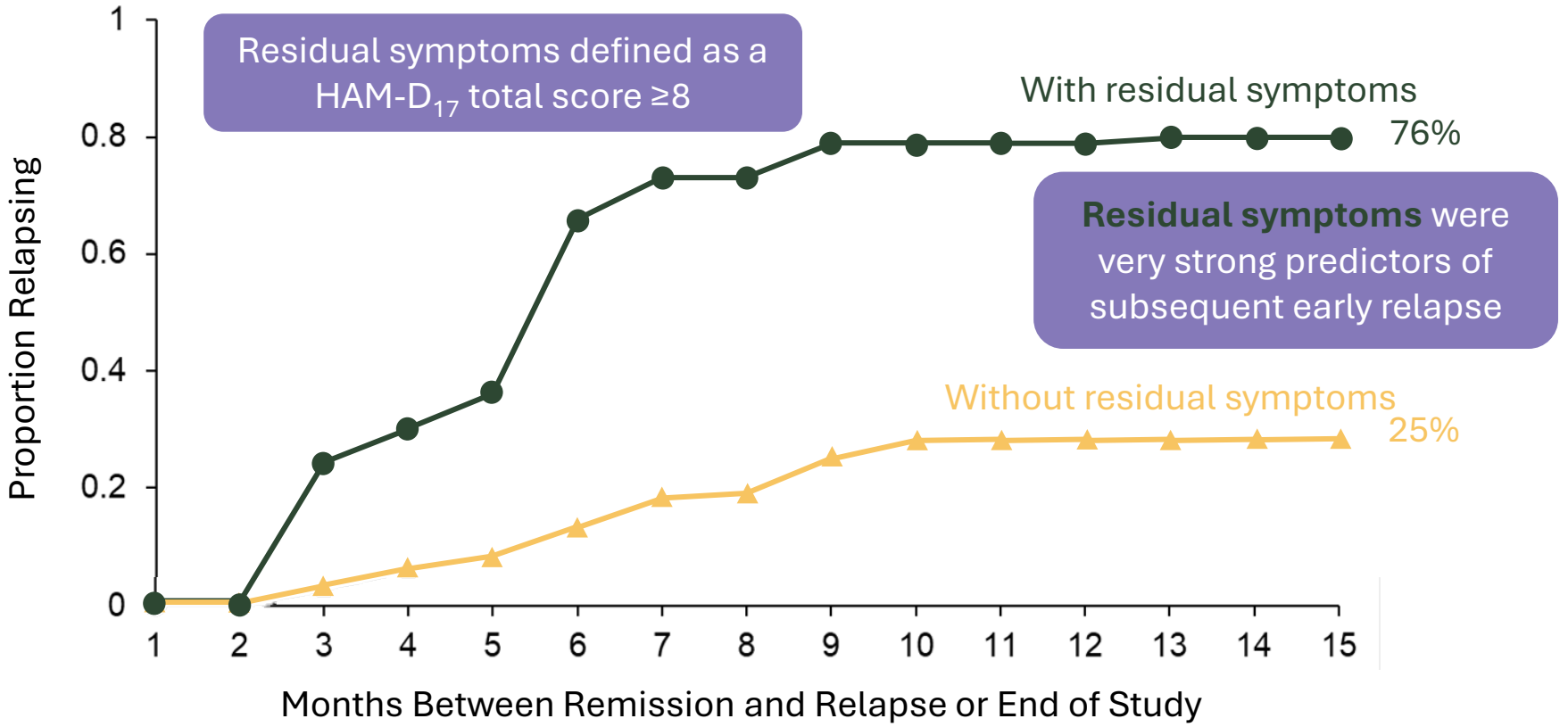


On average, **2 residual symptoms** were present during periods between MDEs

Conradi HJ, et al. *Psychological Medicine*. 2011;41(06):1165-1174. Gualtieri CT, Morgan DW. *J Clin Psychiatry*. 2008;69(7):1122-1130.

Patients With Residual Symptoms Relapse Faster Than Do Patients Without Residual Symptoms

Proportion of Patients with and Without Residual Symptoms Relapsing After Remission



HAM-D17 = Hamilton Depression Scale 17-item.

Paykel ES, et al. *Psychol Med*. 1995;25:1171-1180.

Patient Health Questionnaire-9

Used to identify treatment response and residual symptoms

Points per item: 0 to 3 (total points, 0-27)

Severity of depression:

- 0 to 4 points: minimal depression
- 5 to 9 points: mild depression
- 10 to 14 points: moderate depression
- 15 to 19 points: moderately severe depression
- 20 to 27 points: severe depression

Over the *last 2 weeks*, how often have you been bothered by any of the following problems?	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
Total score: 0 + __ + __ + __				

Kroenke K, et al. *J Gen Intern Med*. 2001;16:606-613. APA. Accessed March 13, 2023. https://www.apa.org/depression-guideline/patient-health-questionnaire.pdf

But Wait, There's More! Assessing Function is Question "10"

There is an additional item: "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?"

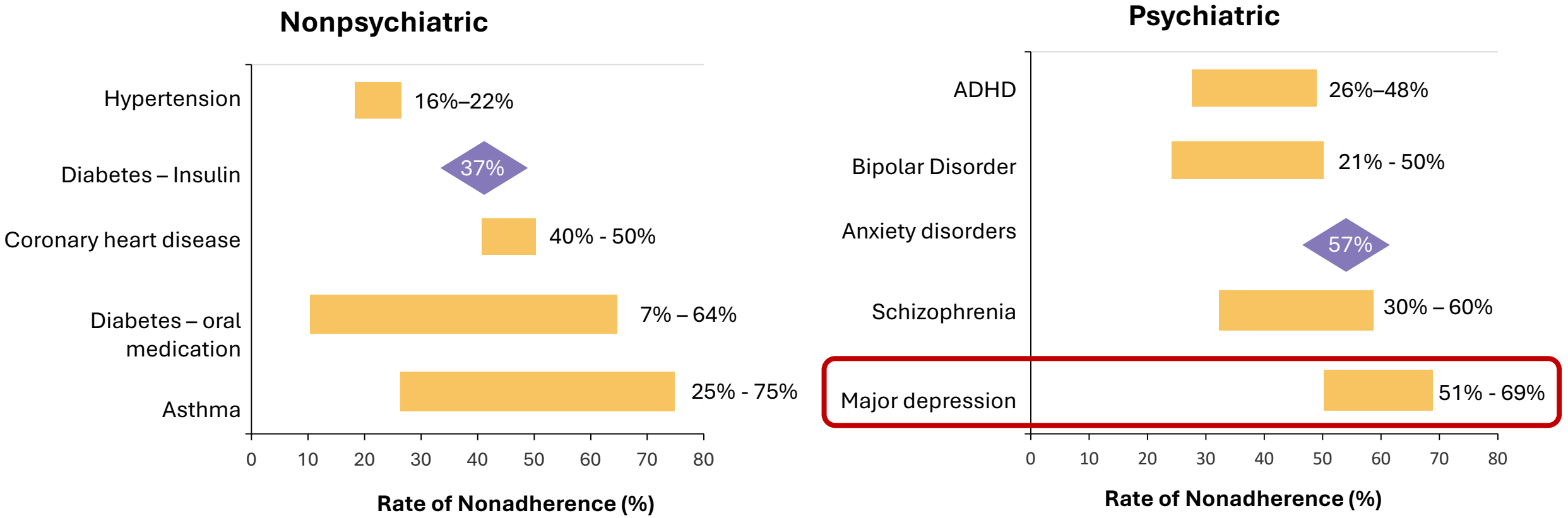
DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. PHQ-9 = Patient Health Questionnaire-9.
Baas KD, et al. *J Affect Disord*. 2011;129:229-235.

Key Learning Points

- MDD is highly prevalent in the United States, upwards of 21 million US Adults experienced at least 1 MDD episode in 2021
- In the real-world STAR*D study, approximately 50% of patients did not achieve response with a first-line antidepressant
- While response is measured as ≥50% improvement, partial response can range from 25%-50% improvement
- Studies have shown that residual symptoms, even when in remission can cause significant impact in psychosocial functioning

Addressing Partial Response in MDD: Optimizing Dose and Augmenting Treatment

First, Assess Adherence Because Many Chronic Conditions Have High Rates of Medication Nonadherence



ADHD = attention-deficit/hyperactivity disorder.

Buckley PF, Foster AE, Patel NC, Wermert A. Adherence to Mental Health Treatment. Oxford American Psychiatry Library. Oxford University Press, New York, 2009, pp 13-15.

My Personal Anecdote – Always Ask About Adherence

- A patient in my practice was being treated with citalopram 80 mg/day from March 2007 for her MDD
- On 8/24/11, the FDA recommended not prescribing doses greater than 40 mg/day due to the risk of dose-dependent QT interval prolongation
- I advised the patient that her dose would need to be reduced to 40 mg/day and that she will need a baseline ECG
- She then told me “Don’t worry Doc, I’ve been taking only 40 mg/day for months now!”
- She revealed to me that this started in April 2011 (well before the FDA advisory), and was primarily motivated by saving money as she purchased her medication out-of-pocket

US Food and Drug Administration. https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-revised-recommendations-celexa-citalopram-hydrobromide-related. Accessed September 15, 2025.
US Food and Drug Administration. https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-abnormal-heart-rhythms-associated-high-doses-celexa-citalopram. Accessed September 15, 2025.

Medication Strategies to Address Non-Response or Inadequate Response to Treatment

- Optimize dose
- Change to another non-MAOI antidepressant
- Augment by adding depression-focused psychotherapy
- Augment by adding a non-MAOI antidepressant or a non-antidepressant medication such as lithium, thyroid hormone, or a **second-generation antipsychotic**

American Psychiatric Association. Practice Guideline for the Treatment of Patients With Major Depressive Disorder. 3rd ed. Arlington, VA: American Psychiatric Association; 2010.

What is the Appropriate Next Step for Partial Responders?

Consider switch if

- Intolerable
- No response
- Patient preference

Consider adding if

- Tolerable
- Partial response
- Patient preference

American Psychiatric Association. Practice Guideline for the Treatment of Patients With Major Depressive Disorder. 3rd ed. Arlington, VA: American Psychiatric Association; 2010. Kennedy SH, et al. *Can J Psychiatry.* 2016;61(9):540-60.

Why Add? Why Not?

When a patient has responded to and has tolerated an antidepressant but has residual symptoms, adjunctive treatment

- Builds upon progress already gained
- Avoids delays inherent in starting over
- Combines different mechanisms of action

But, there are potential risks

- Drug-drug interactions
- Additive side effects
- For adjunctive SGAs, tardive dyskinesia

SGA = second generation antipsychotic.

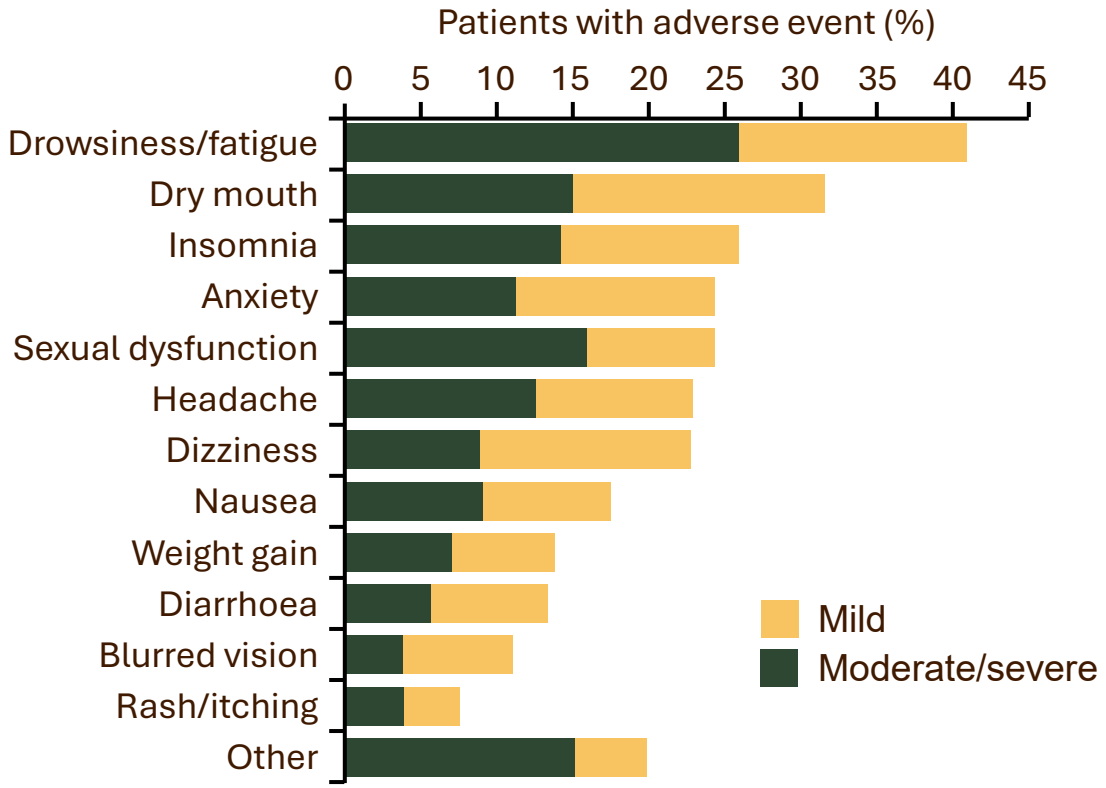
American Psychiatric Association. Practice Guideline for the Treatment of Patients With Major Depressive Disorder. 3rd ed. Arlington, VA: American Psychiatric Association; 2010. Kennedy SH, et al. *Can J Psychiatry*. 2016;61(9):540-60.

Safety and Tolerability of SSRIs

- In a survey of patients with MDD who initiated therapy on an SSRI, adverse events, particularly drowsiness/fatigue, were the most common reasons for discontinuing SSRI treatment within the first 3 months
- All antidepressants are associated with a characteristic collection of adverse events
- Adjunct therapies are also associated with specific adverse events
- In order to promote continuity of drug treatment, and improve patient adherence with antidepressants, novel agents with better tolerability need to be vigorously pursued

There is an unmet need in the treatment of MDD for therapies with improved safety and tolerability

Incidence and severity of SSRI-associated adverse effects during the first 3 months of treatment

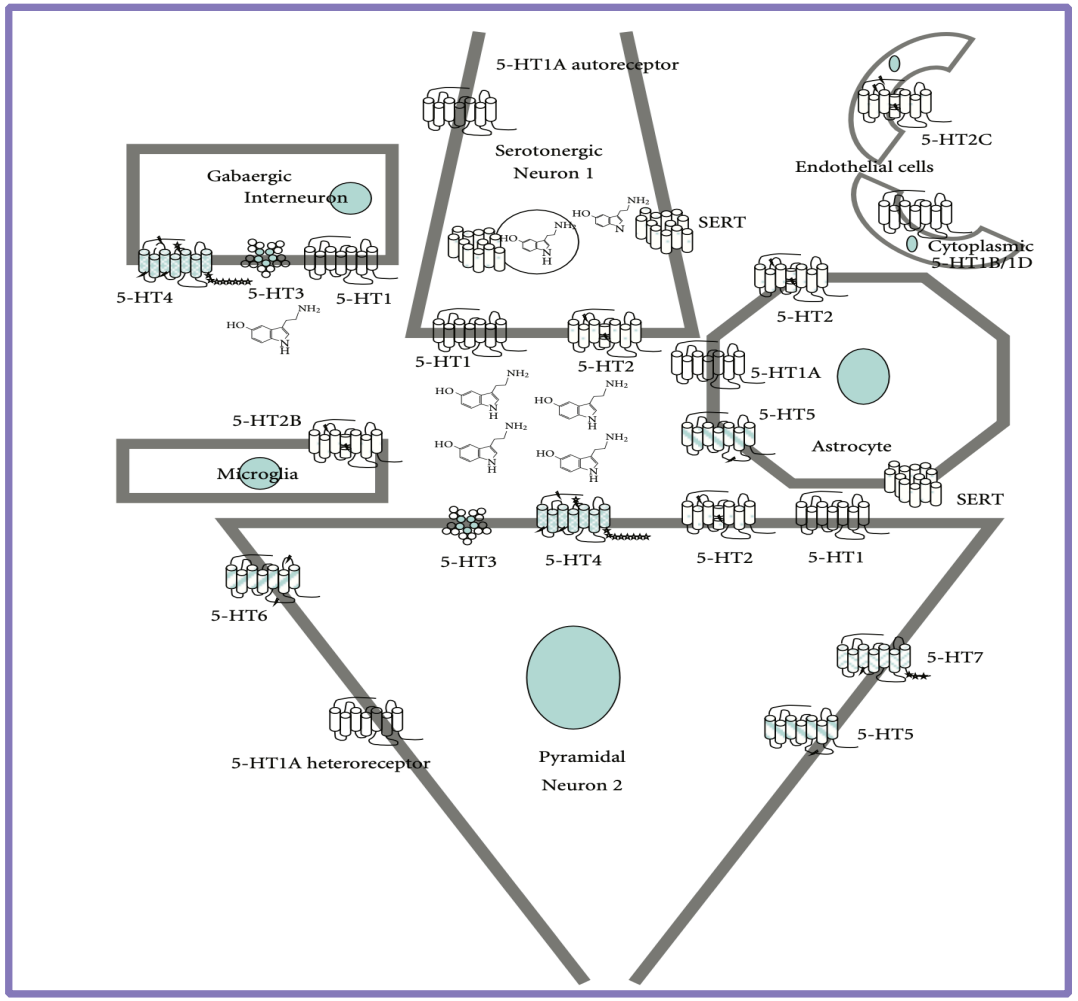


Bull S, et al. *Ann Pharmacother*. 2002;36(4):578–584. Stahl S. Stahl's Essential Psychopharmacology. Neuroscientific Basis and Practical Applications. 4th ed. Cambridge University Press; 2013. Möller H-J. *World J Biol Psychiatry*. 2008;9(2):102–114. Neurotorium. *Major Depressive Disorder-Treatment Principles*. Accessed May 24, 2023. https://neurotorium.org/slidedeck/major-depressive-disorder-treatment-principles/?slide=15483.

Imprecise MOAs of Conventional Serotonergic Antidepressants

- ‘Single action’ Serotonin Reuptake Inhibitors are imprecise, and exert their effects on all receptors in the serotonin system. This creates the challenge of ‘off-target’ activity, thereby creating ‘nuisance’ side-effects.

- As a result, more precise targeting is an urgent clinical goal for both clinicians and patients



MOA = mechanism of action.

Berumen LC, et al. *Scientific World Journal.* 2012;2012:823493.

Dose-Response Relationships for SSRI Efficacy in MDD

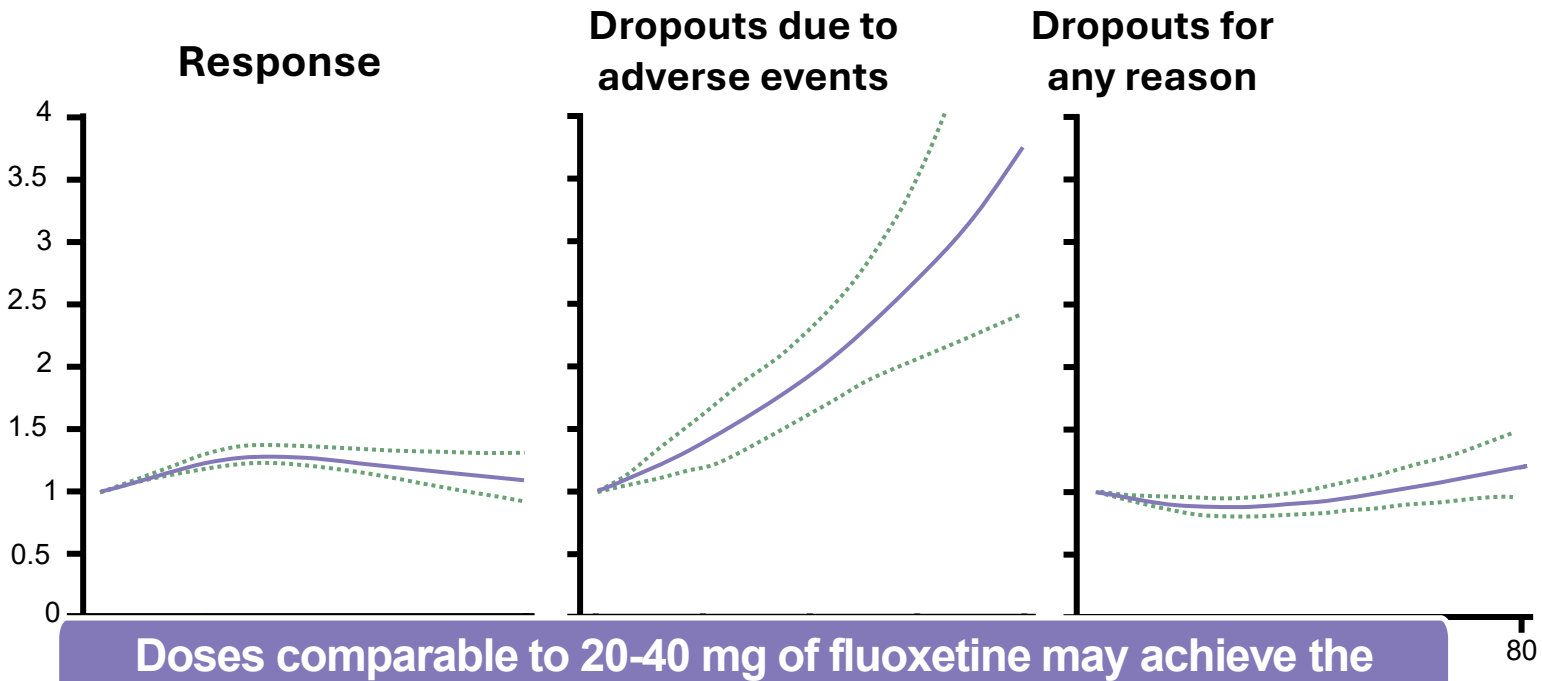
More is Not Always Better...

KEY FINDINGS:

Gradual improvement up to **20–40 mg with a plateau/decline at higher doses**

More dropouts due to adverse events with higher doses

Approximate optimal doses	
Citalopram	20-40 mg
Escitalopram	10-20 mg
Fluoxetine	20-40 mg
Paroxetine	17-34 mg
Sertraline	50-100 mg

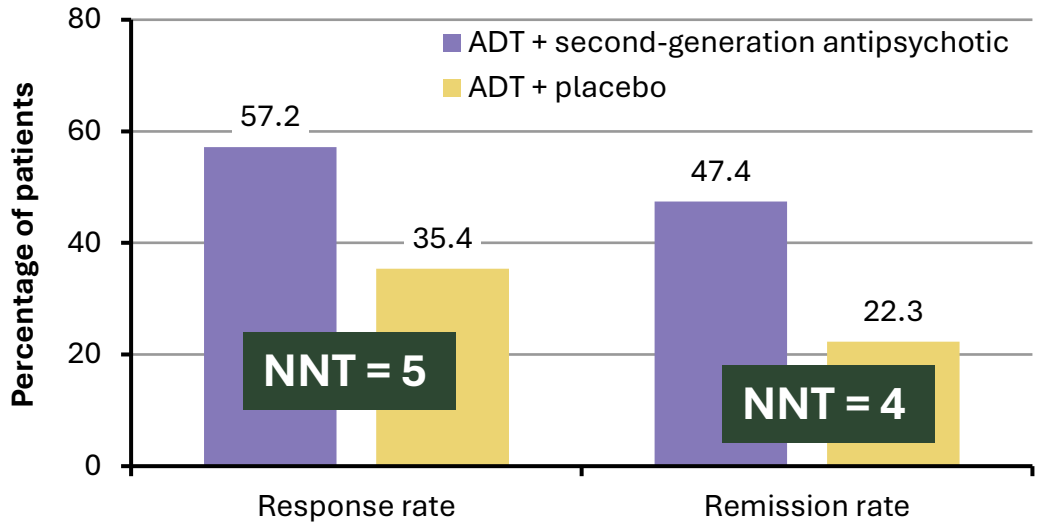


Doses comparable to 20-40 mg of fluoxetine may achieve the optimal balance between efficacy, tolerability, and acceptability.

Furukawa TA, et al. *Lancet Psychiatry*. 2019;6(7):601-609. Hayasaka Y, et al. *J Affect Dis*. 2015;180:179-184.

Adjunctive Treatment with Antipsychotics Can Increase the Likelihood of Response and Remission

Among patients with inadequate response (n=1,500), response and remission rates were higher for patients who received adjunctive treatment with a second-generation antipsychotic agent than for those who received adjunctive placebo



Even in patients showing minimal response to 8 weeks of ADT, 6 weeks of adjunctive antipsychotic treatment significantly reduced time to response and remission compared with patients who received adjunctive placebo[2,b]

Meta-analysis of 10 RCTs assessing adjunctive treatment with an atypical antipsychotic together with standard antidepressants for MDD, where response is defined as ≥50% improvement from baseline in the primary outcome measure (remission definitions varied); bpooled analysis of three RCTs assessing adjunctive treatment with aripiprazole together with antidepressants for MDD, where minimal response is defined as <25% improvement from baseline in MADRS Total score; ADT=antidepressant treatment

Papakostas et al. *J Clin Psychiatry.* 2007;68:826–831. Nelson et al. *Int Clin Psychopharmacol.* 2012;27(3):125–133.

But, how acutely tolerable are the SGAs in MDD? Here's a NNH "Heat Map"

RED: NNH < 10 higher risk ORANGE: NNH 10-19 intermediate risk GREEN: NNH ≥ 20 lower risk	NNH for weight gain ≥ 7%	NNH for AEs of somnolence and/or sedation	NNH for AEs of akathisia
Aripiprazole	24	43	5
Brexpiprazole	52	24	15
Cariprazine (all doses ≥ 1 mg/d)	131	32	12
Olanzapine-Fluoxetine	3	10	167
Quetiapine Extended Release	38	5	91

Citrome L, et al. *J Affect Disord*. 2025;369:1238-1247.

Key Learning Points

- Addressing inadequate response can be accomplished by assessing adherence, optimizing dose, adding depression-focused psychotherapy, and considering switch/augmentation medication strategies
- Tolerability considerations are important when personalizing care

Addressing Partial Response in MDD: The Lost Art of Switching?

Evaluating When Switching is Preferable

Is there an ineffective response?

- Complete lack of response? Lack of response in certain domains (ie, anhedonia, cognition)?

Are there intolerable/dangerous AEs?

- Emotional numbing/blunting, weight gain, sexual dysfunction, GI issues, QTc prolongation, etc.

Are there new safety concerns?

- New concomitant medication? New medical issue?

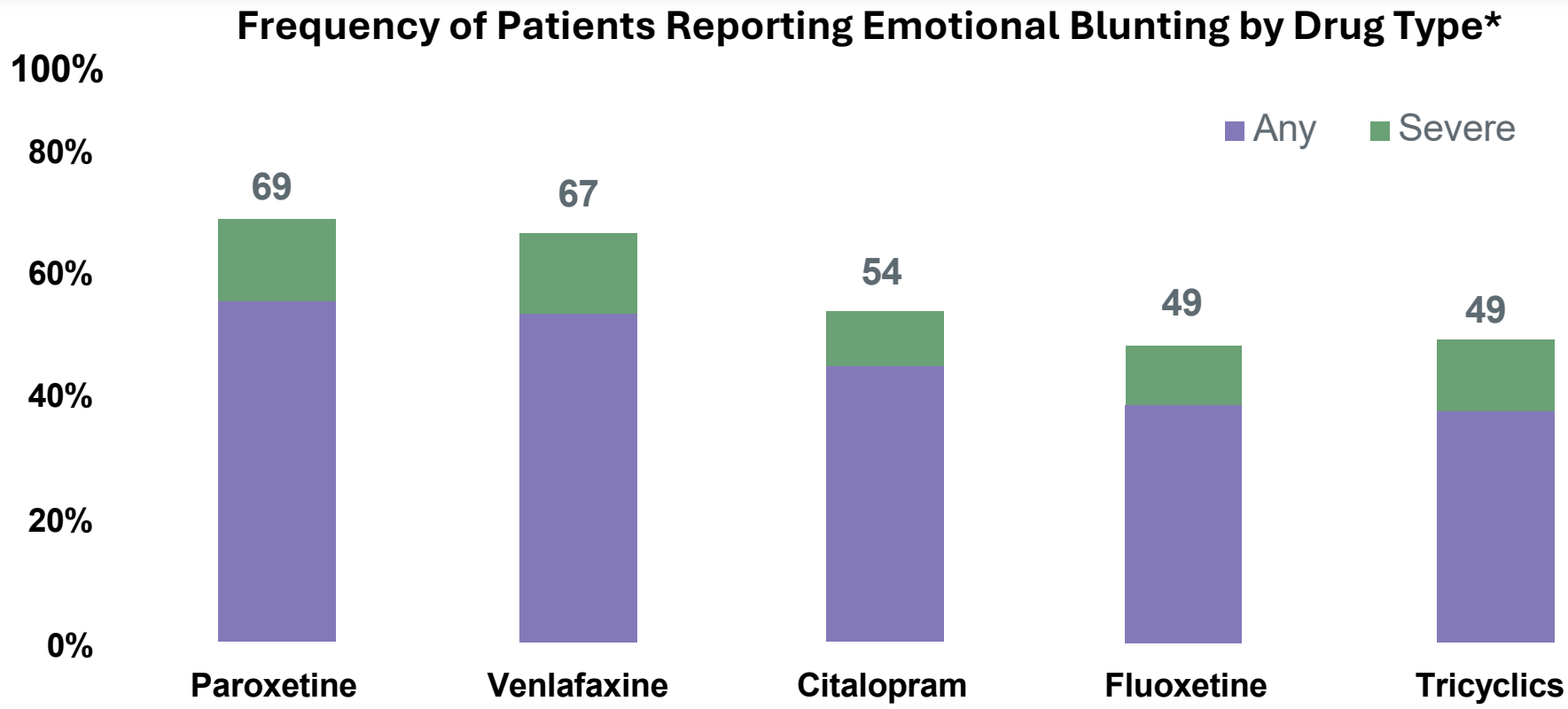
What does the patient prefer?

- Time of dosing? Desire for pregnancy?

AE = adverse event.

Why Switch? The Majority of Patients Experienced Emotional Blunting while Taking Commonly Used Antidepressants

An online questionnaire about experiences with, and beliefs about, antidepressants was completed by 1829 adults who had been prescribed antidepressants in the last five years



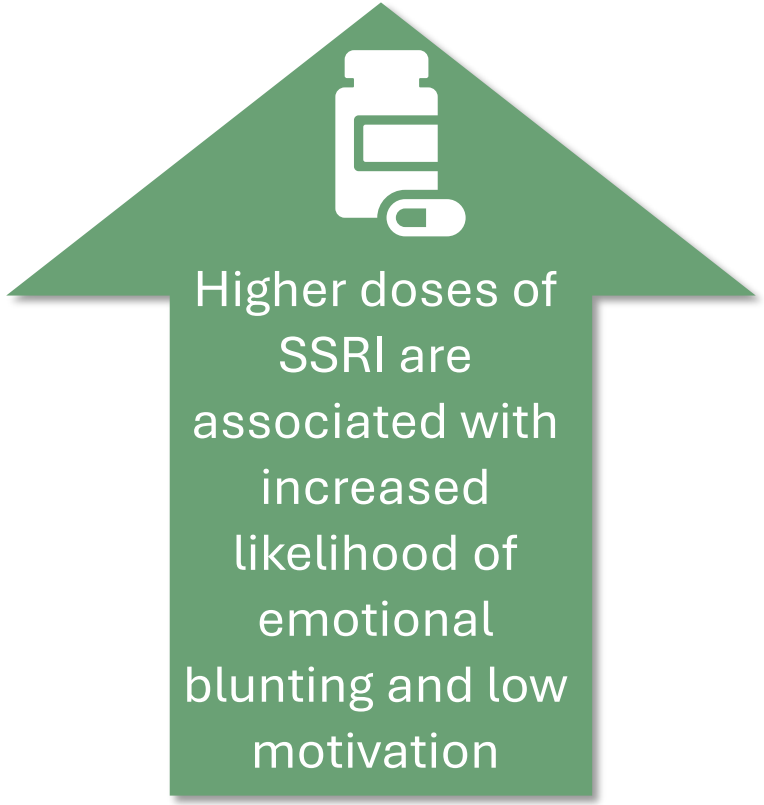
*Eight side-effects were analyzed by drug type, including: feeling emotionally numb, feeling not like myself, reduction in positive feelings, caring less about others, sexual difficulties, failure to reach orgasm, suicidality, withdrawal effects.

Read J, et al. *Psychiatry Res*. 2014;216:67–73.

Why Switch? The Likelihood of Emotional Blunting And Low Motivation with SSRIs / SNRIs

Clinical characteristics of SSRI-induced indifference:*

- **Low insight in the afflicted** with regards to low motivation
- **Delayed or insidious onset**
- Related to SSRI dosing, with **higher doses** being more likely to **precipitate the symptoms**
- Completely resolvable with a **lowering and/or discontinuation of the SSRI**



***SSRI-induced indifference refers to indifference both on a behavioural level (ie, decreased motivation) as well as on an emotional level (ie, emotional blunting).**

Sansone RA, et al. *Psychiatry*. 2010;7:14–18.

Clinical Factors to Consider when Switching

Factors to consider in selecting an antidepressant

Patient Factors

- **Clinical features and dimensions**
- **Comorbid conditions**
- **Response and side effects during previous use of antidepressants**
- Patient preference

Medication Factors

- Comparative efficacy
- **Comparative tolerability (potential side effects)**
- Potential interactions with other medications
- Simplicity of use
- Cost and availability

Most common factors influencing antidepressant selection in patients with depression who received a new antidepressant (n=1137)

1st — Presence of a **specific symptom** or **symptom profile**

2nd — Avoidance of specific **side effects**

3rd — Presence of a **comorbid condition**

4th — Prior **treatment history**, including previous positive/negative response

Kennedy SH, et al. *Can J Psychiatry*. 2016;61:540–60; Zimmerman M, et al. *Am J Psychiatry*. 2004;161(7):1285-128

Rationale for Choice of Antidepressant Switches

References

Strategies for Switching

Direct switch

- Stop the current antidepressant and start the new one the following day
- Pay attention to interaction risks, half-life and MOA

Taper and switch immediately

- Gradually reduce current antidepressant and start the new one immediately after discontinuation

Taper and switch following washout

- Gradually reduce current antidepressant, wait for washout period (5 half-lives of medication), start new medication immediately following washout period (think MAOI)

Cross-taper

- Gradually decrease current antidepressant while slowly starting and increasing new antidepressant over 1-4 weeks
- Pay attention to interaction risks

However, there are other factors to consider...

MECHANISM OF ACTION

TCAs

Primary MOA: inhibit the reuptake of serotonin and norepinephrine

- Competitive antagonists at muscarinic, histamine (H1), and cholinergic (alpha-1, alpha-2) receptors

common side effects

Drowsiness, blurred vision, constipation, dry mouth

SSRIs

Primary MOA: inhibit the reuptake of serotonin via SERT (serotonin transporter)

common side effects

GI upset, sexual AE, sleep changes, emotional numbing/blunting, weight gain

SNRIs

Primary MOA: inhibit the reuptake of both norepinephrine via NET and serotonin via SERT

common side effects

Nausea, dry mouth, sweating, constipation

Serotonin Modulators

Primary MOA: inhibit the reuptake of serotonin and a partial agonist of specific serotonin receptor subtypes

common side effects

GI upset, trouble sleeping

MOA=Mechanism of Action; TCA=Tricyclic Antidepressants; SSRI=Selective Serotonin Reuptake Inhibitor; SERT=Serotonin Transporter; GI=Gastrointestinal, SNRI=Selective Norepinephrine Reuptake Inhibitor; NET=Norepinephrine Transporter

Moraczewski J, et al., Tricyclic Antidepressants. In: *StatPearls*. Treasure Island (FL): StatPearls Publishing; August 17, 2023; Stahl SM. *J Affect Disord*. 1998;51(3):215-235. Fanelli D, et al. *Neurol Int*. 2021;13(4):497-509.

Within-Class vs. Between-Class Switches

Within-Class Switches

Changing from one antidepressant to another within the same class

i.e., SSRI → SSRI, SNRI → SNRI

Pros:

Familiar mechanism

Potentially less ***NEW*** AEs

Predictability

Response and AEs may be similar therefore more predictable

Cons:

Limited efficacy change

Between-Class Switches

Changing from one antidepressant of a particular class to a different class

i.e., SSRI ↔ SNRI, SSRI to Other, SNRI to Other

- Pros:
  - New Mechanism
  - Targets different neurotransmitter systems
    - May be more effective or more tolerable if the first medication was ineffective or intolerable
  - Offers wider range of medications to choose from
- Cons:
  - Uncertain efficacy and tolerability
    - May not respond
    - May introduce new AEs
    - Body may require more time to adjust

Ruhe HG, et al. *J Clin Psychiatry*. 2006;67(12):1836-55.

What Does the Evidence Say?

- Brain imaging shows that serotonin receptors are saturated quickly and even at low doses
- Suggests potential benefit in use of ADTs with varying activity
- Favors augmentation or use of Precision Serotonin Receptor Modulators
- There is no strong clinical evidence showing that switching ***between-class*** is better or worse than switching ***within-class*** when it comes to SSRI/SNRI/TCA
- Response and Remission Rates vary widely
  - Response Rate – 12%-86%
  - Remission Rate – 7%-82%
- Number of ADT prior is associated with lower chances of success regardless of switching method

Ruhe HG, et al. *J Clin Psychiatry*. 2006;67(12):1836-55.

Switching Pharmacotherapies

Advantages

- Adherence
- Cost
- Lower risk of drug-drug interactions
- Loss of adverse effects from ineffective treatment

Disadvantages

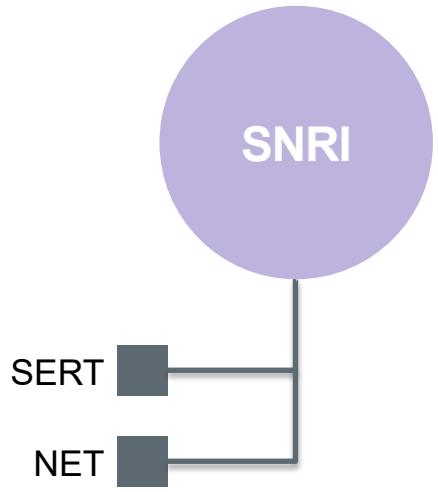
- Withdrawal (if switching from serotonergic to non-serotonergic agent)
- Potential loss of therapeutic benefit of first-line agent

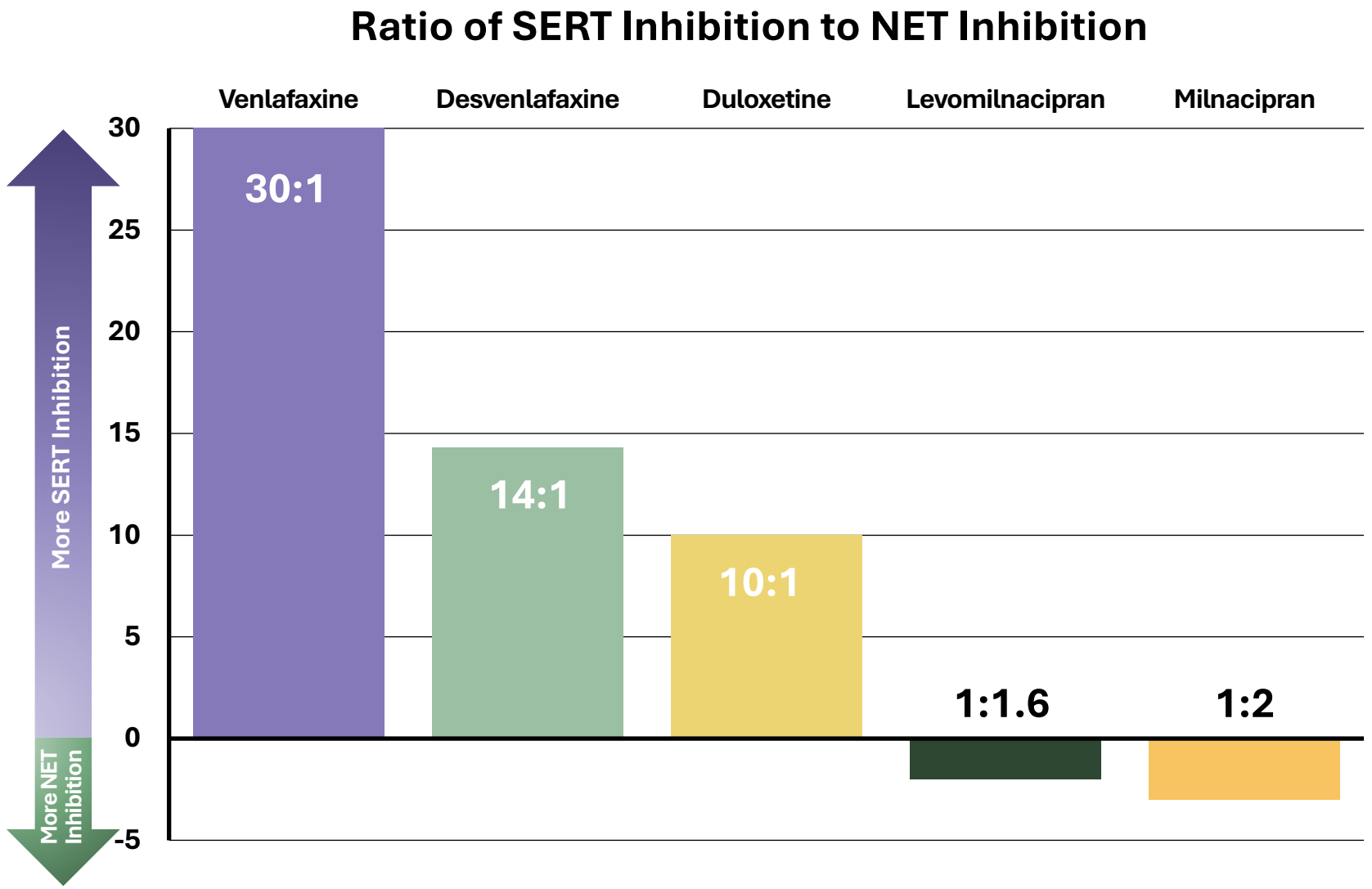
Papakostas GI. *J Clin Psychiatry*. 2009;70 Suppl 6:16-25.

Summary of Evidence for SNRIs

References

MOA of SNRIs



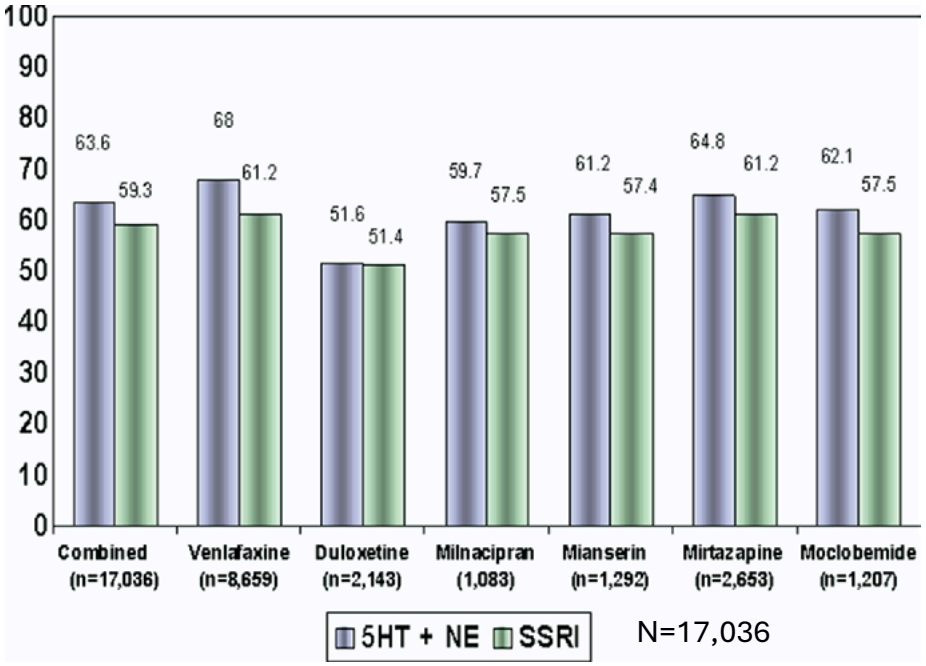


SERT = Serotonin Reuptake Transporter; NET = Norepinephrine Reuptake Transporter

Macaluso M, et al (eds.) *Antidepressants: From Biogenic Amines to New Mechanisms of Action. Vol. 250.* Springer;2019.

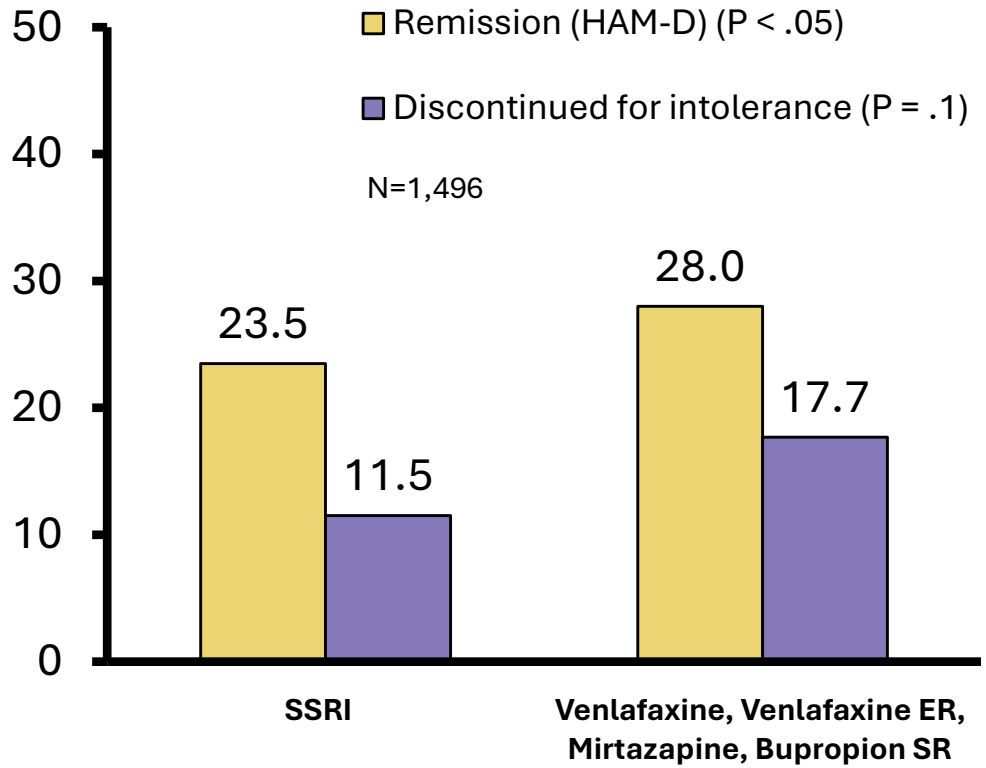
Switching from SSRI → SSRI vs. SSRI → Non-SSRI

Pooled 2007 Meta-Analysis: SSRI vs SNRI



Difference in efficacy between the two treatment groups was small and its clinical relevance (if any)could not be determined.

Pooled 2008 Meta-Analysis: SSRI→SSRI vs. SSRI→SNRI

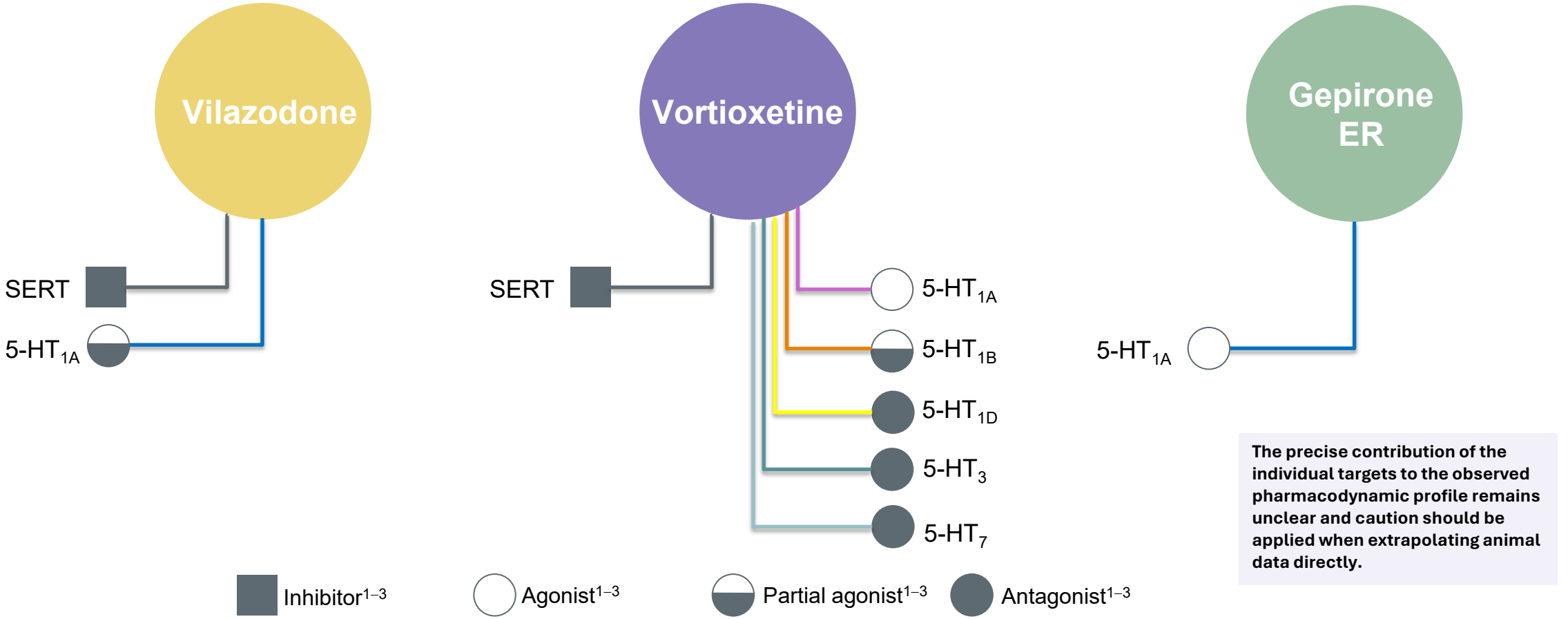


HAM-D = Hamilton Rating Scale for Depression.

Papakostas GI, et al. *Biol Psychiatry.* 2007;62:1217–1227. Papakostas GI, et al. *Biol Psychiatry*. 2008;63(7):699-704.

Summary of Evidence for Precision Serotonin Receptor Modulators

Three ‘Precision’ Based Serotonergic Antidepressants

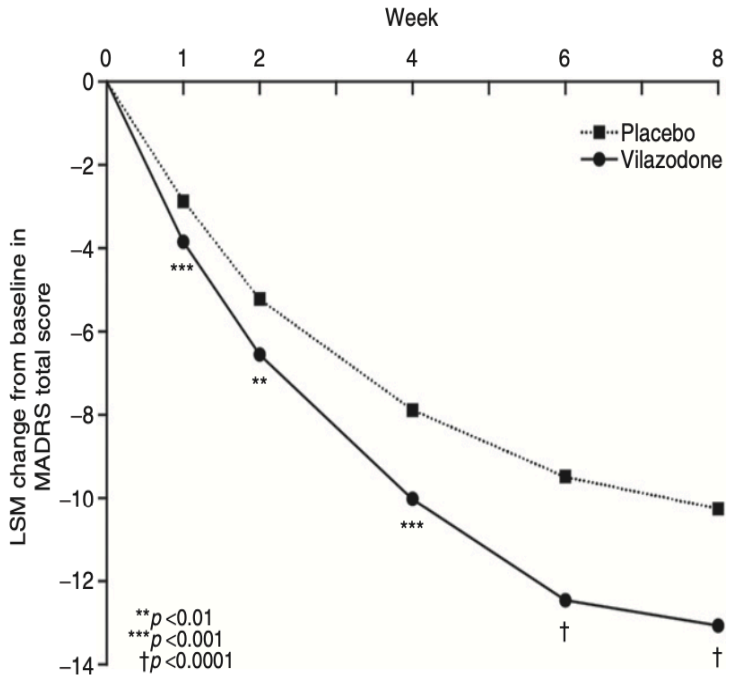


The precise contribution of the individual targets to the observed pharmacodynamic profile remains unclear and caution should be applied when extrapolating animal data directly.

HT = hydroxytryptamine.

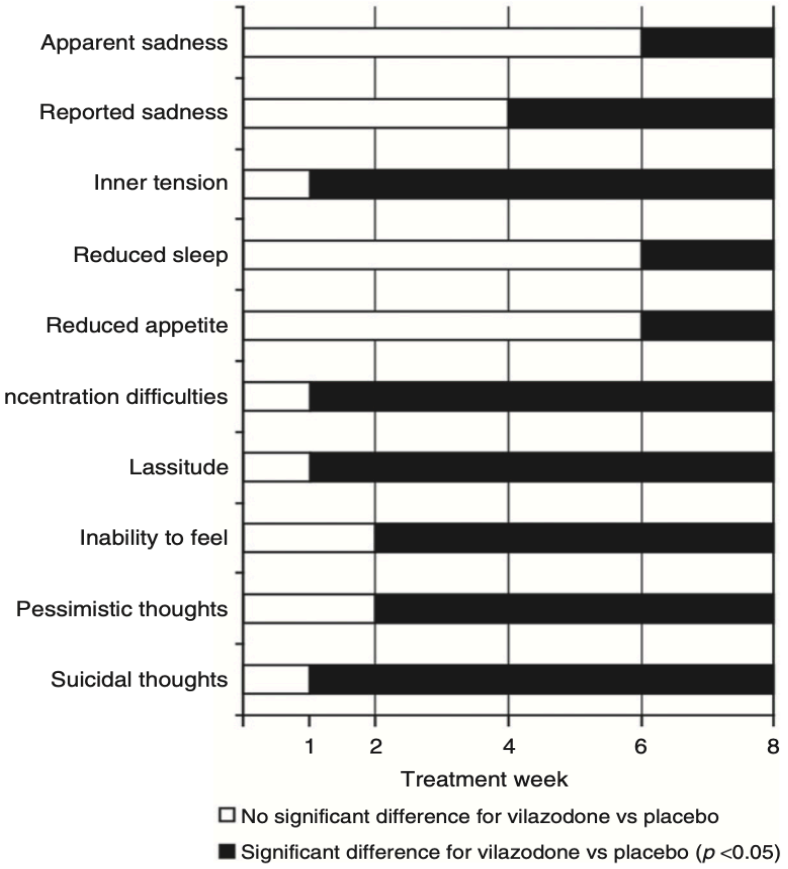
Bang-Andersen B, et al. *J Med Chem*. 2011;54:3206-3221. Sanchez C, et al. *Pharmacol Ther*. 2015;145:43-57. Vortioxetine Prescribing Information. Drugs@FDA: FDA-Approved Drugs. Accessed January 10, 2024. www.accessdata.fda.gov/scripts/cder/daf/.

Vilazodone: Rapidly and Broadly Efficacious Precision Antidepressant



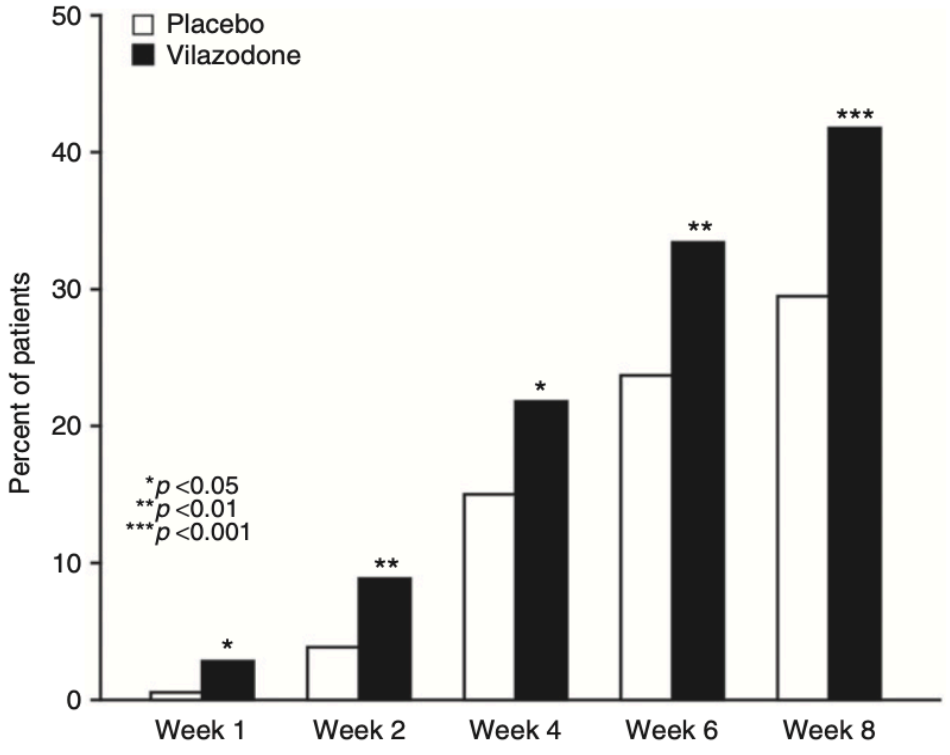
Least squares mean change from baseline in MADRS total score (pooled ITT population; LOCF). ITT, intent-to-treat; LOCF, last observation carried forward; LSM, least squares mean, MADRS, Montgomery–Asberg Depression Rating Scale.

Statistical separation of vilazodone from placebo on the MADRS single items (pooled ITT population; LOCF). When the difference in LSM change became statistically significant in favor of vilazodone versus placebo is denoted by the color change from white to black on each bar; the difference remained significantly until the end of the study. ITT, intent-to- treat; LOCF, last observation carried forward; LSM, least squares mean, MADRS, Montgomery–Asberg Depression Rating Scale.



Jain R, et al. *Current Medical Research and Opinion.* 2014;30:2, 263-270.

Vilazodone: Rapidly and Broadly Efficacious Precision Antidepressant (cont'd)



Cumulative Response Rate (by week)

Conclusion:

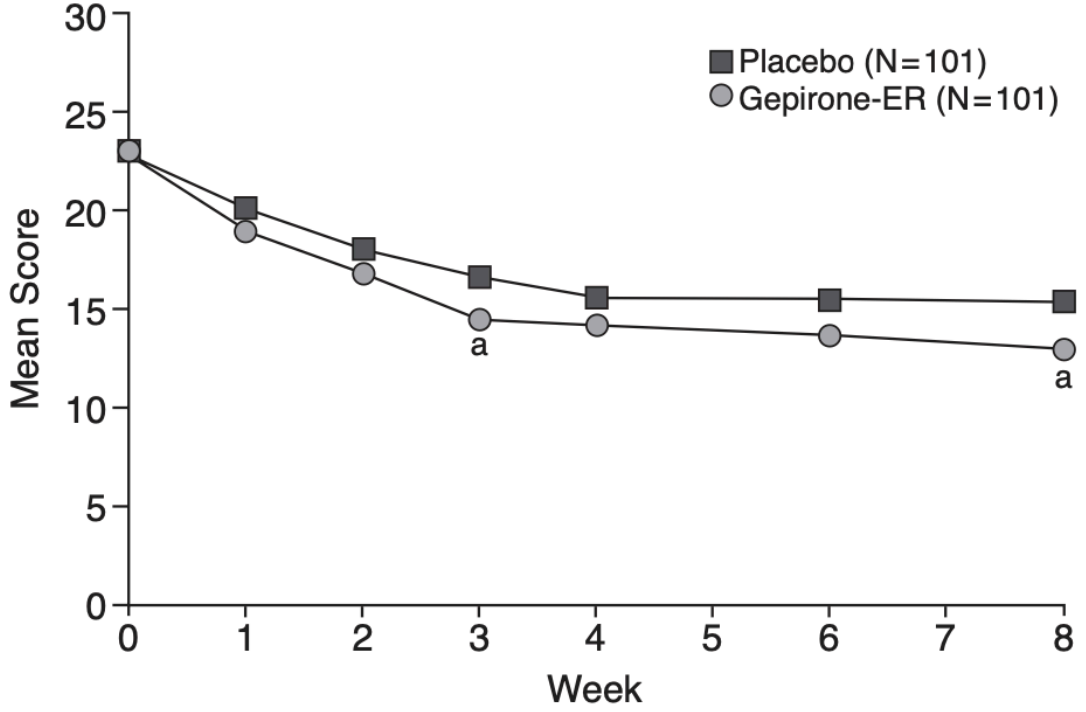
"Retrospective analyses of pooled data from two randomized, controlled trials suggest that vilazodone is an effective antidepressant treatment that was associated with early and persistent symptomatic improvement and rates of response. Early and sustained improvement and response are important clinical outcomes that may be associated with positive long-term treatment implications." – Jain R. et al.

Jain R, et al. *Current Medical Research and Opinion.* 2014;30:2, 263-270.

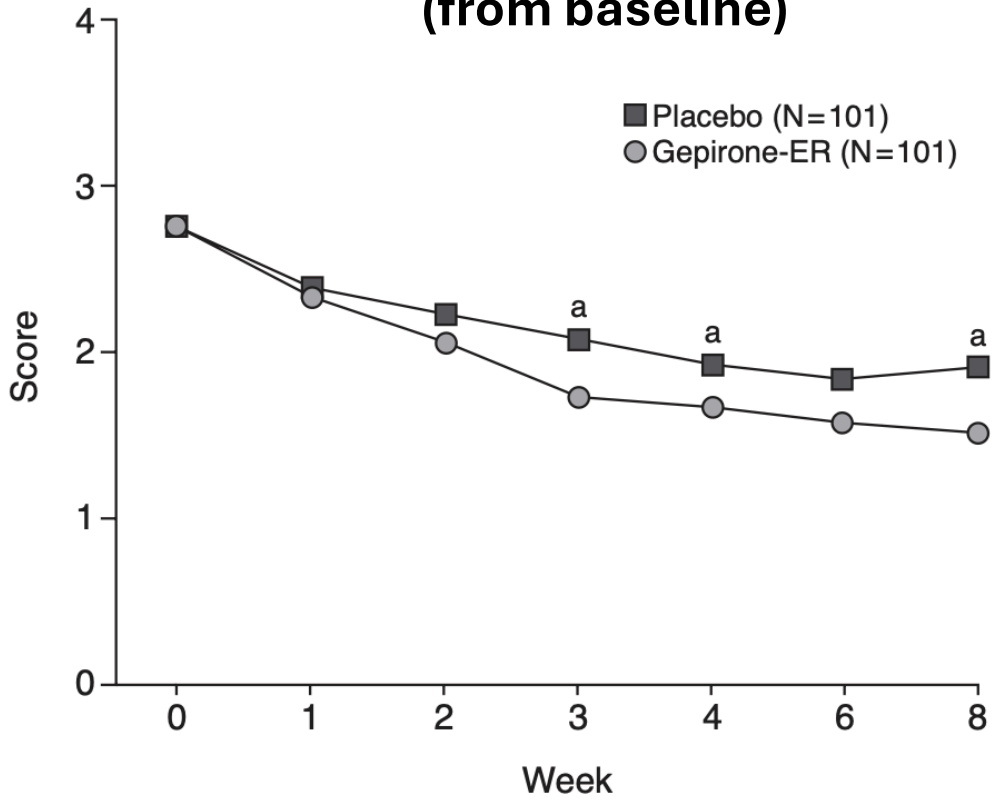
Gepirone ER

FDA Approved – Not Yet Commercialized

MDD trial: 18-70 age range
Entry criteria = HAM-D 17, 20 or greater



HAM-D Item 1 Scores
(from baseline)



Feiger AD, et al. *J Clin Psychiatry.* 2003;64:243-249. FDA. Drugs@FDA: FDA Approved Drugs. Accessed January 10, 2023. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/021164s000lbl.pdf

Gepirone ER (cont'd)

FDA Approved – Not Yet Commercialized

Figure 5. Percentage of Patients Achieving a Remission (HAM-D-17 total score ≤ 7) (LOCF)

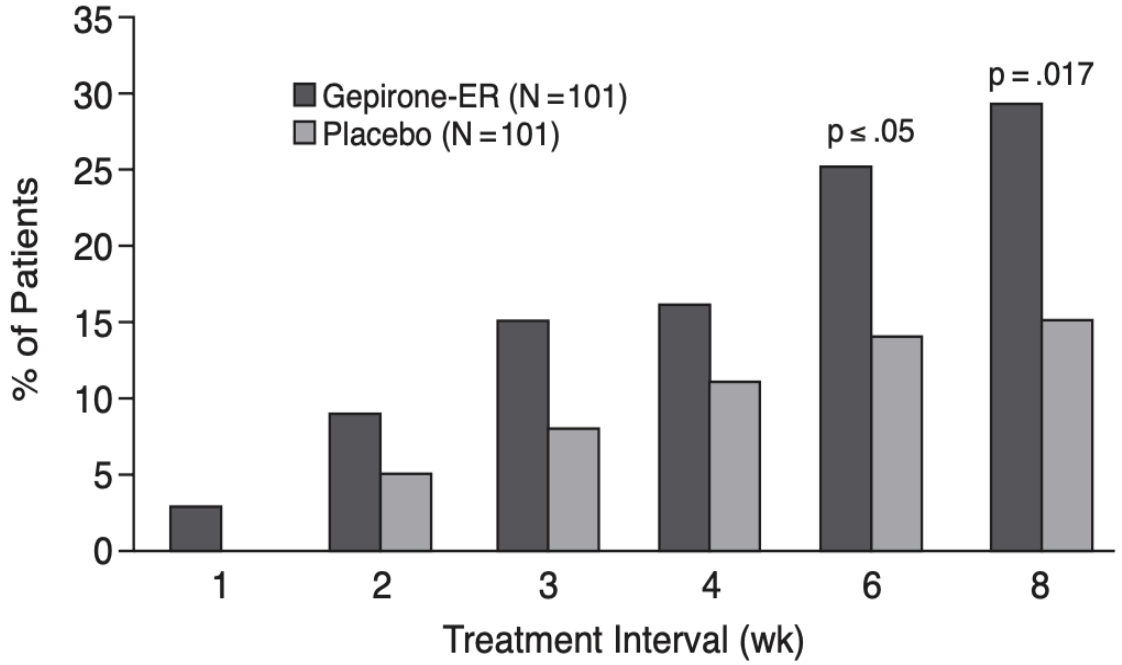


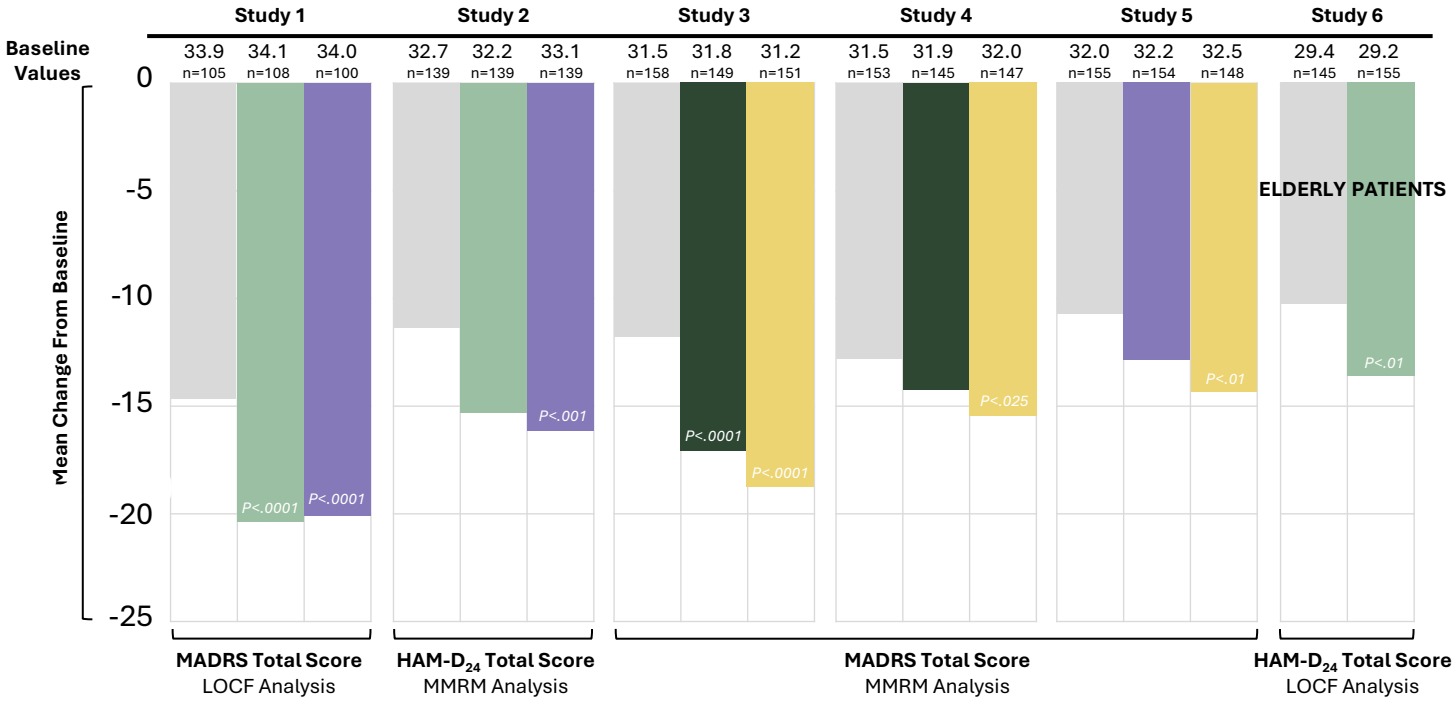
Table 5. Incidence of Adverse Events Occurring in at Least 5% of Patients in the Gepirone-ER Group and at Least Twice the Frequency of the Placebo Group (%)

Adverse Event	Gepirone-ER (N = 102)	Placebo (N = 106)	p Value[a]
Dizziness	52.0	11.3	< .001
Nausea	35.3	14.2	< .001
Insomnia	19.6	6.6	.007
Nervousness	10.8	5.7	.211
Vomiting	9.8	4.7	.186
Dry mouth	9.8	3.8	.101
Abdominal pain	9.8	1.9	.017
Dyspepsia	7.8	3.8	.245
Paresthesia	5.9	1.9	.164

[a]p Value from Fisher exact test.
Abbreviation: ER = extended release.

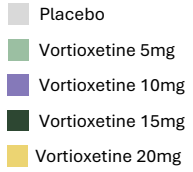
Feiger AD, et al. *J Clin Psychiatry.* 2003;64:243-249. FDA. Drugs@FDA: FDA Approved Drugs. Accessed January 10, 2023. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/021164s000lbl.pdf

Vortioxetine: Significantly Improves Depressive Symptoms Compared to Placebo



Primary endpoints in 6 randomized, placebo-controlled, double-blind, 6- to 8-week studies (5 mg to 20 mg once daily) in adult MDD patients

- 5 studies in adult patients (aged 18-75)
- 1 study focused on elderly patients (aged 64-88)

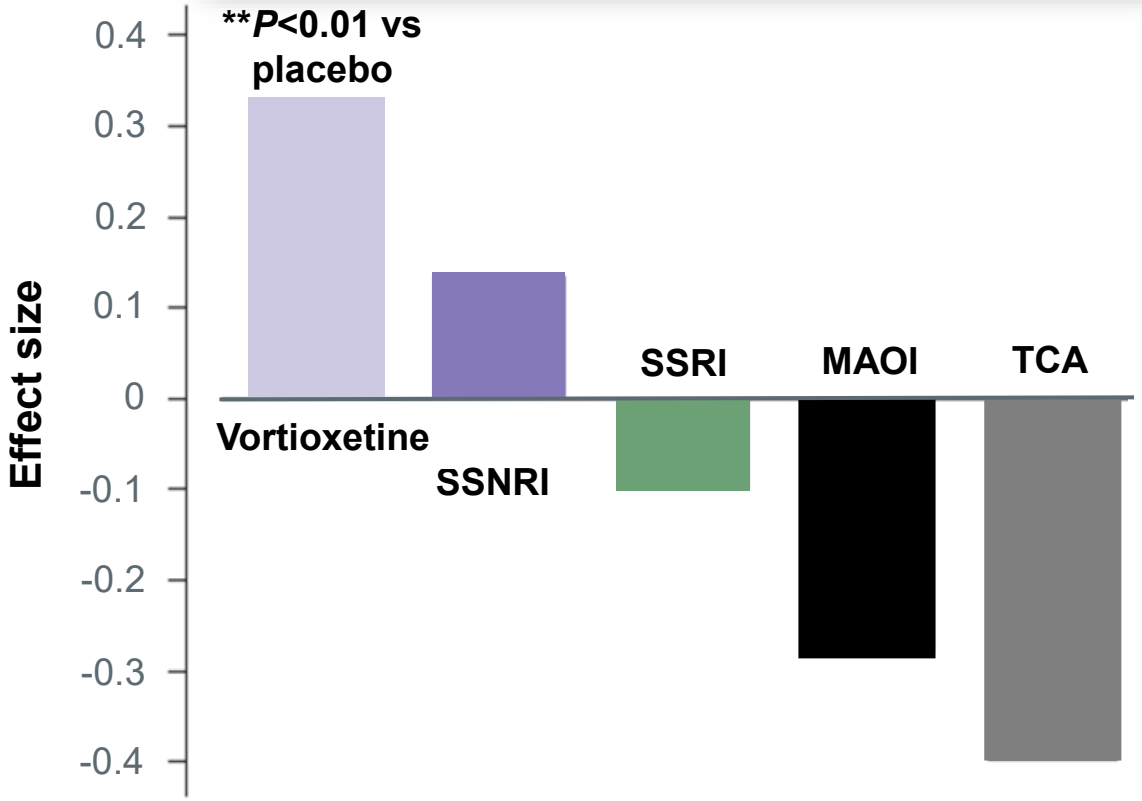


LOCF, last observation carried forward; MADRS, Montgomery-Åsberg Depression Rating Scale; MMRM, mixed model for repeated measures.

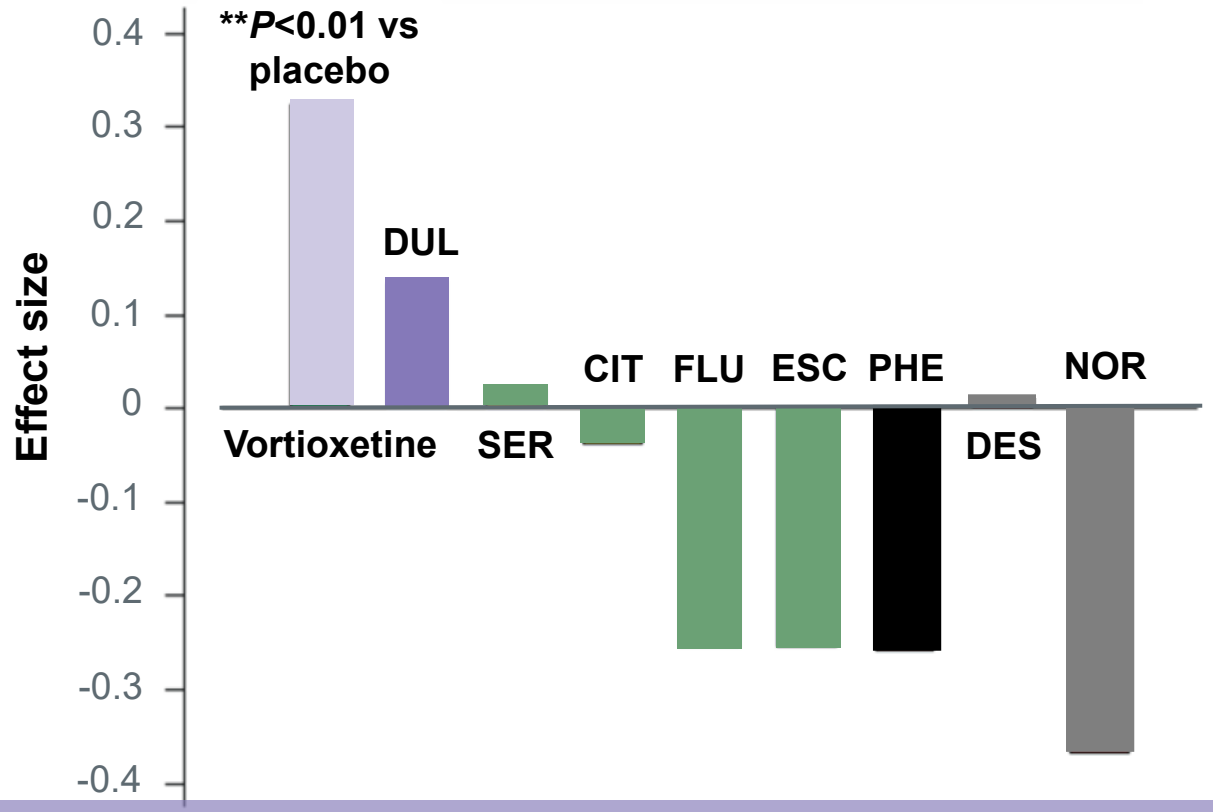
Alvarez E, et al. *Int J Neuropsychopharmacol*. 2012;15(5):589-600. Henigsberg N, et al. *J Clin Psychiatry*. 2012;73(7):953-959. Boulenger JP, et al. *Int Clin Psychopharmacol*. 2014;29(3):138-149. Mahableshwarkar AR, et al. *Psychopharmacology (Berl)*. 2015;232(12):2061-2070. Jacobsen PL, et al. *J Clin Psychiatry*. 2015;76(5):575-582. Katona C, et al. *Int Clin Psychopharmacol*. 2012;27(4):215-223.

Vortioxetine Significantly Improved Cognitive Function in MDD

Standardized Effect Size Relative to Placebo by Antidepressant Therapeutic Classes



Standardized Effect Size Relative to Placebo by Individual Antidepressants



Vortioxetine was the only antidepressant with a statistically significant positive effect on cognitive performance

CIT = citalopram; DES = desipramine; DSST = Digit Symbol Substitution Test; DUL = duloxetine; ESC = escitalopram; FLU = fluoxetine; MAOI = monoamine oxidase inhibitor; MDD = major depressive disorder; NOR =nortriptyline; PHE =phenelzine; RCT = Randomized controlled trial; SER = sertraline; SNRI = serotonin-noradrenaline reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant.

Baune BT, et al. *Int J Neuropsychopharmacol.* 2018;21(2):97-107.

Vortioxetine: Safety and Tolerability

Adverse Reactions Occurring in >2% of Patients Treated with Any Vortioxetine Dose AND at least 2% Greater Than Incidence in Placebo-Treated Patients

Adverse Effect	VOR 5mg/d %	VOR 10mg/d %	VOR 15mg/d %	VOR 20mg/d %	Placebo %
Nausea	21	26	32	32	9
Diarrhea	7	7	10	7	6
Dry Mouth	7	7	6	8	6
Constipation	3	5	6	6	3
Vomiting	3	5	6	6	1
Flatulence	1	3	2	1	1
Dizziness	6	6	8	9	6
Abnormal dreams	<1	<1	2	3	1
Pruritus	1	2	3	3	1

Dose	Discontinuation Incidence
5mg/d	5%
10mg/d	6%
15mg/d	8%
20mg/d	8%
Placebo	4%

Nausea was the most common AE reported as a reason for discontinuation

≥95% reported mild to moderate nausea

Discontinuation due to nausea **2.2%** across all doses vs. **0.3%** in placebo group

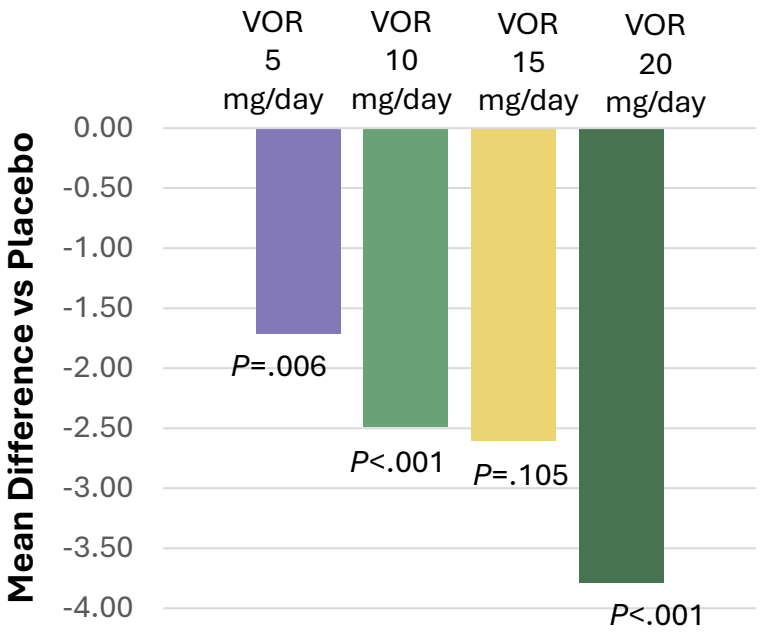
NNH 52

Vortioxetine PI. Drugs@FDA: FDA-Approved Drugs. Accessed August 2025. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/204447s021s022lbl.pdf.

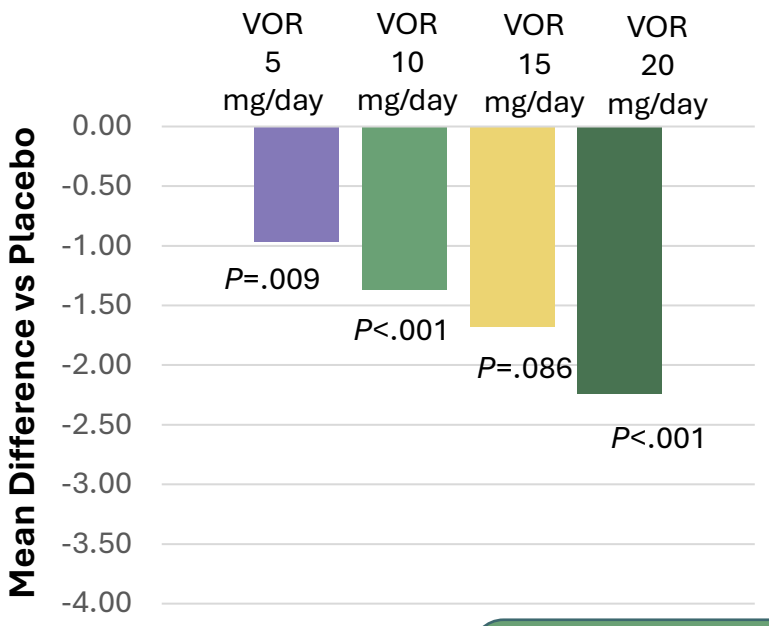
Vortioxetine Significantly Improved Depressive Symptoms, Anhedonia, and Functioning

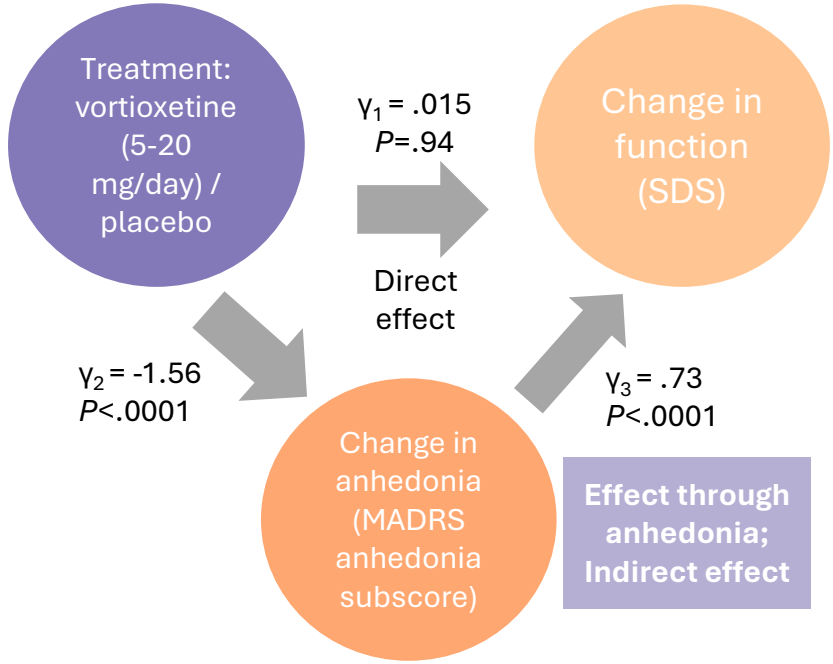
Pooled analysis of all 11 short-term, placebo-controlled studies

MADRS total score



MADRS anhedonia subscale score





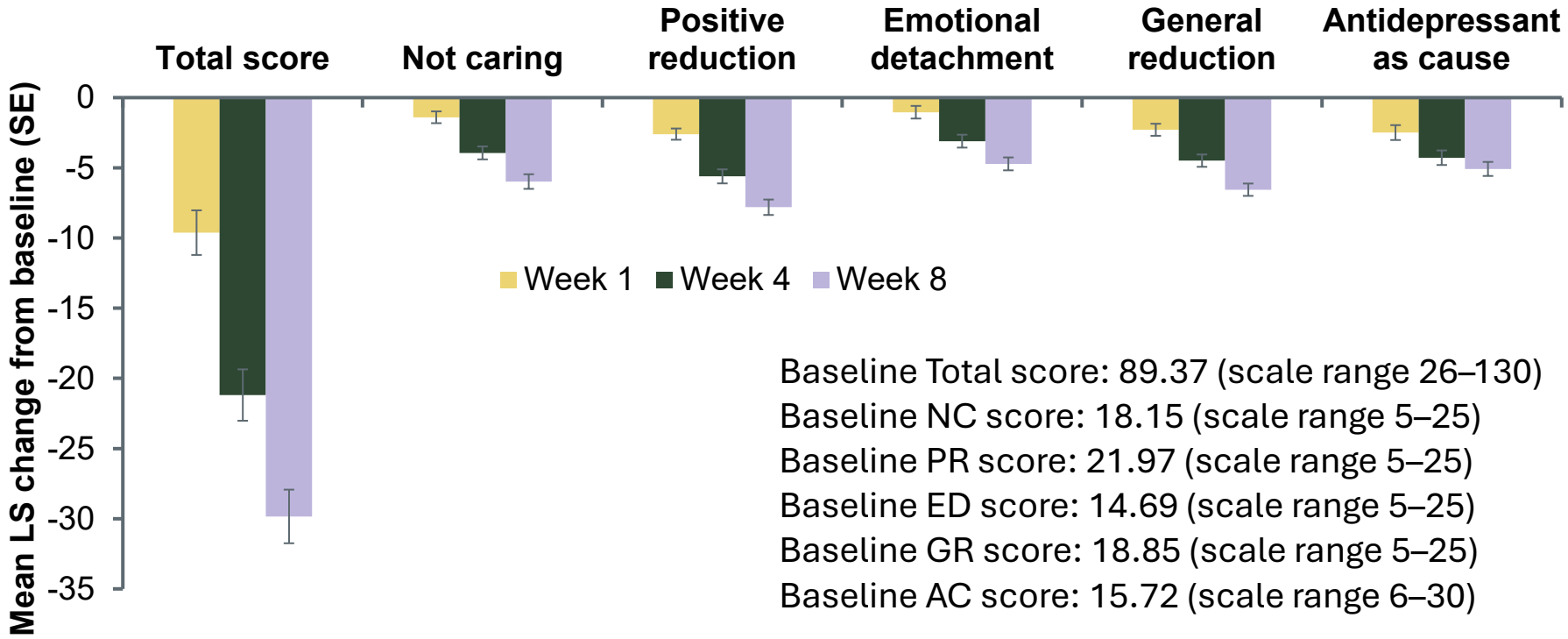
Vortioxetine-associated **improvements in functioning** appear to be **driven mostly by the effect** of vortioxetine **on anhedonia.**

- n=4988 patients with MDD and n=495 in the active-comparator study
- Improvements in functioning associated with vortioxetine were driven by the effect of treatment on MADRS anhedonia factors

McIntyre RS, et al. *Neuropsychiatr Dis Treat*. 2021;17:575-585.

Vortioxetine Improves Emotional Blunting Following SSRI/SNRI Treatment

Change from baseline in ODQ domain scores (FAS, MMRM)



Baseline Total score: 89.37 (scale range 26–130)
Baseline NC score: 18.15 (scale range 5–25)
Baseline PR score: 21.97 (scale range 5–25)
Baseline ED score: 14.69 (scale range 5–25)
Baseline GR score: 18.85 (scale range 5–25)
Baseline AC score: 15.72 (scale range 6–30)

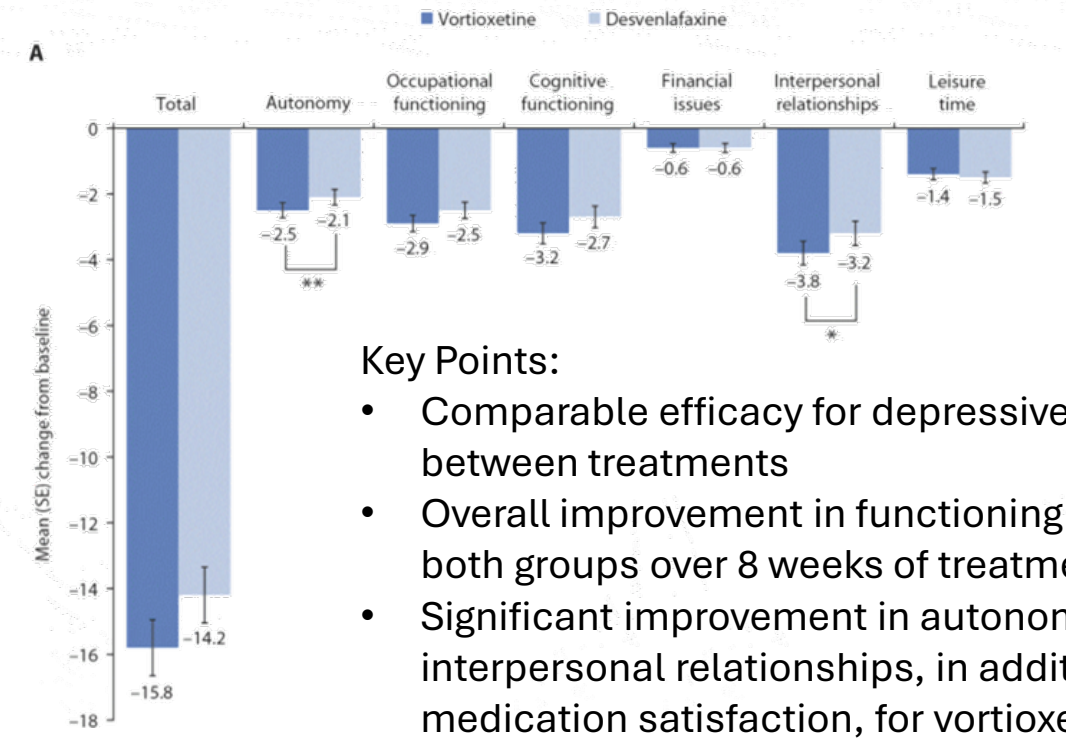
In adults with MDD with partial response to SSRI/SNRI treatment, there was **significant improvement in emotional blunting, overall functioning, motivation and energy, cognitive performance, and depressive symptoms after 8 weeks of treatment with vortioxetine 10-20 mg/day**

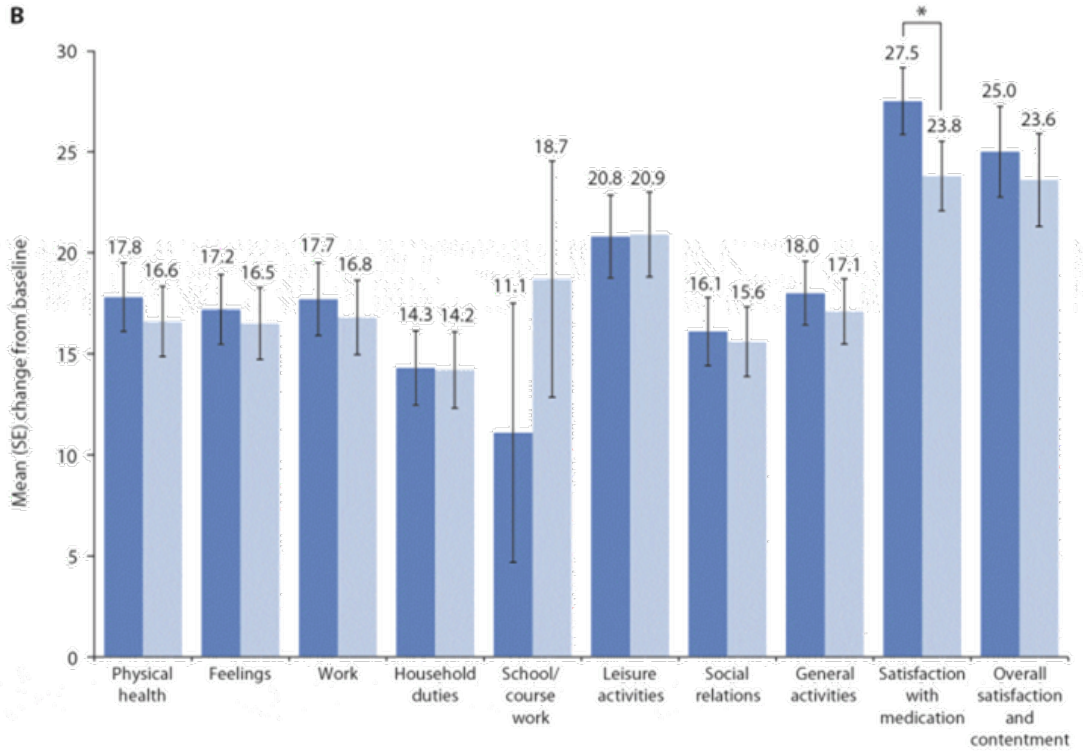
***nominal p<0.05; **nominal p≤0.001; ***nominal p<0.0001.**
AC = antidepressant as cause; ED = emotional detachment; FAS = full analysis set; GR = general reduction; LS = least square; NC = not caring; ODQ =Oxford Depression Questionnaire; PR = positive reduction.
Fagiolini A, et al. *J Affect Disord.* 2021;283:472-479.

Vortioxetine vs Desvenlafaxine in Patients with Partial Response to SSRI Treatment

VIVRE Study: Participants with MDD aged 18-65 who were experiencing a partial response to SSRI monotherapy treated with a SNRI (desvenlafaxine) or a serotonin modulator (vortioxetine) for 8 weeks

Figure 2. Change From Baseline to Week 8 for (A) FAST Total and Domain Scores[a] and (B) Q-LES-Q Percentage Scale Scores[b] (Analysis of Covariance, Observed Cases)





Key Points:

- Comparable efficacy for depressive symptoms between treatments
- Overall improvement in functioning was seen in both groups over 8 weeks of treatment
- Significant improvement in autonomy and interpersonal relationships, in addition to greater medication satisfaction, for vortioxetine-treated patients

McIntyre RS, et al. *J Clin Psychiatry.* 2023;84(4):23m114780.

Summary of Evidence for Other Antidepressants as Monotherapy

Evidence for Bupropion

Bupropion – NDRI

- Used for over 20 years
- Meta-analysis revealed 27 trials evaluating bupropion for MDD ranging from 6-44 weeks
  - 21 double-blinded and RCT
  - Showed efficacy in 24/27 trials comparable to efficacy of SSRI/SNRI/TCA
  - "…as tolerable as other common antidepressants"
- Associated with lower risk of sexual AEs and weight gain compared to traditional ADT
- Reports of insomnia, anxiety, and GI upset
- Contraindicated in seizures and eating disorders
- Caution with concomitant CYP2D6 inhibitors/medications metabolized viaCYP2D6 pathway

Patel K, et al. *Ther Adv Psychopharmacol*. 2016;6(2):99–144.

Evidence for Mirtazapine

Mirtazapine – Atypical tetracyclic antidepressant (TCA)

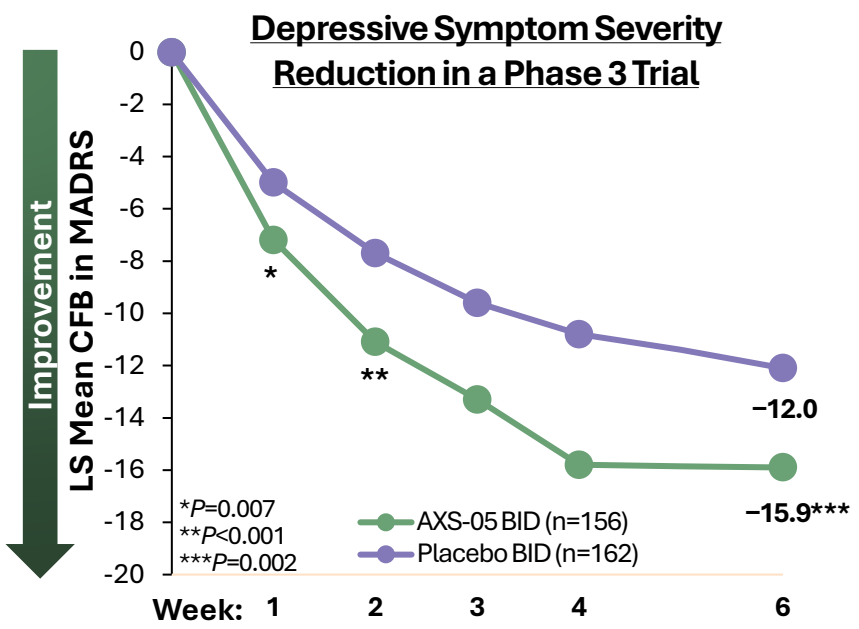
- Meta-analysis of 21 ADTs found response rate at ~50% (similar to other commonly prescribed ADT)
- 2016 retrospective study found remission rate to be 36.8% in real-world clinical use
- No proven efficacy or safety over SSRI/SNRI/TCA
- Strong antihistamine
- AEs include sedation, increased appetite and wt gain
- Does not inhibit Cytochrome P450 (CPY450) enzymes and thus has fewer drug-drug interactions

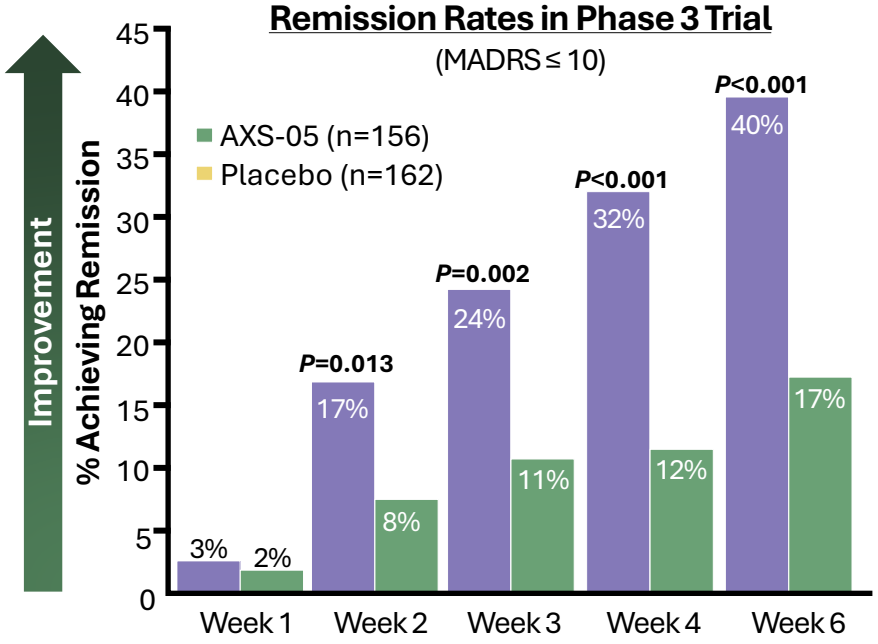
Mirtazapine: Update on efficacy, safety, dose response. Therapeutics Initiative. https://www.ti.ubc.ca/2021/05/06/129-mirtazapine-update-on-efficacy-safety-dose-response/. Accessed September 15, 2025. Tsutsumi T, et al. *Neuropsychiatr Dis Treat*. 2016;12:2533–2538. Jilani TN, et al. *Stat Pearls*. Treasure Island (FL); 2025.

AXS-05 (Dextromethorphan/Bupropion) Clinical Snapshot

Dextromethorphan is an oral NMDA antagonist and sigma-1 agonist; Bupropion acts as an inhibitor of its metabolism by Cytochrome 2D6

Remission rate of AXS-05 was ~3x that of bupropion at week 6 in a phase 2 active controlled trial





Adverse Events ≥ 5%

	AXS-05	Placebo
Dizziness	**16%**	**6%**
Nausea	**13%**	**9%**
Headache	**8%**	**4%**
Diarrhea	**7%**	**3%**
Somnolence	**7%**	**3%**
Dry mouth	**6%**	**2%**
Sexual dysfunction	**6%**	**0%**
Hyperhidrosis	**5%**	**0%**
D/C due to AEs	**4%**	**0%**
Weight change	**-0.4 lb**	**+1.0 lb**

BID = twice daily; D/C = discontinuation; AE = Adverse Event

Iosifescu DV, et al. *J Clin Psychiatry.* 2022;83(4):21m1434. Tabuteau H, et al. *Am J Psychiatry*. 2022;179(7):490-499.

Key Learning Points

- There are many things to consider while making a decision to switch antidepressants when addressing partial response including method, AEs, comorbidities and concomitant medications
- Use of SSRIs and SNRIs may worsen cognitive function, contribute to emotional blunting, sexual dysfunction, and leave anhedonia untreated
- Precision Serotonin Receptor Modulators demonstrate efficacy in areas that SSRIs and SNRIs worsen/don't address, such as functional improvement

Panel Discussion

TOPIC 1:

Early Improvement as a Resilience Signal Predicting Later Remission to Antidepressant Treatment

Panel Discussion

TOPIC 2:

Clinical Decision-Making: Choosing the Best Strategy (Dose Optimization, Augmentation, or Switching)

Panel Discussion

TOPIC 3:

Personalizing Treatment Based on
Patient Characteristics, Preferences, and Comorbidities

Practical Take Aways

- Early improvement may predict likelihood for remission
- When a patient is experiencing partial response, use a shared decision-making approach to decide whether to augment or switch
- Consider using a Precision Serotonin Modulator in patients with partial response, especially when they are experiencing cognitive symptoms, anhedonia, and sexual dysfunction/emotional blunting from previous therapy

Q&A