



Addressing Unresolved Symptoms of Major Depressive Disorder (MDD)

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Objectives



Understand why many patients with MDD continue to experience unresolved symptoms following first-line treatment

1



Understand why the optimal outcome for a patient with MDD involves full symptom recovery

2



Discuss different strategies commonly used to address inadequate response to treatment

3

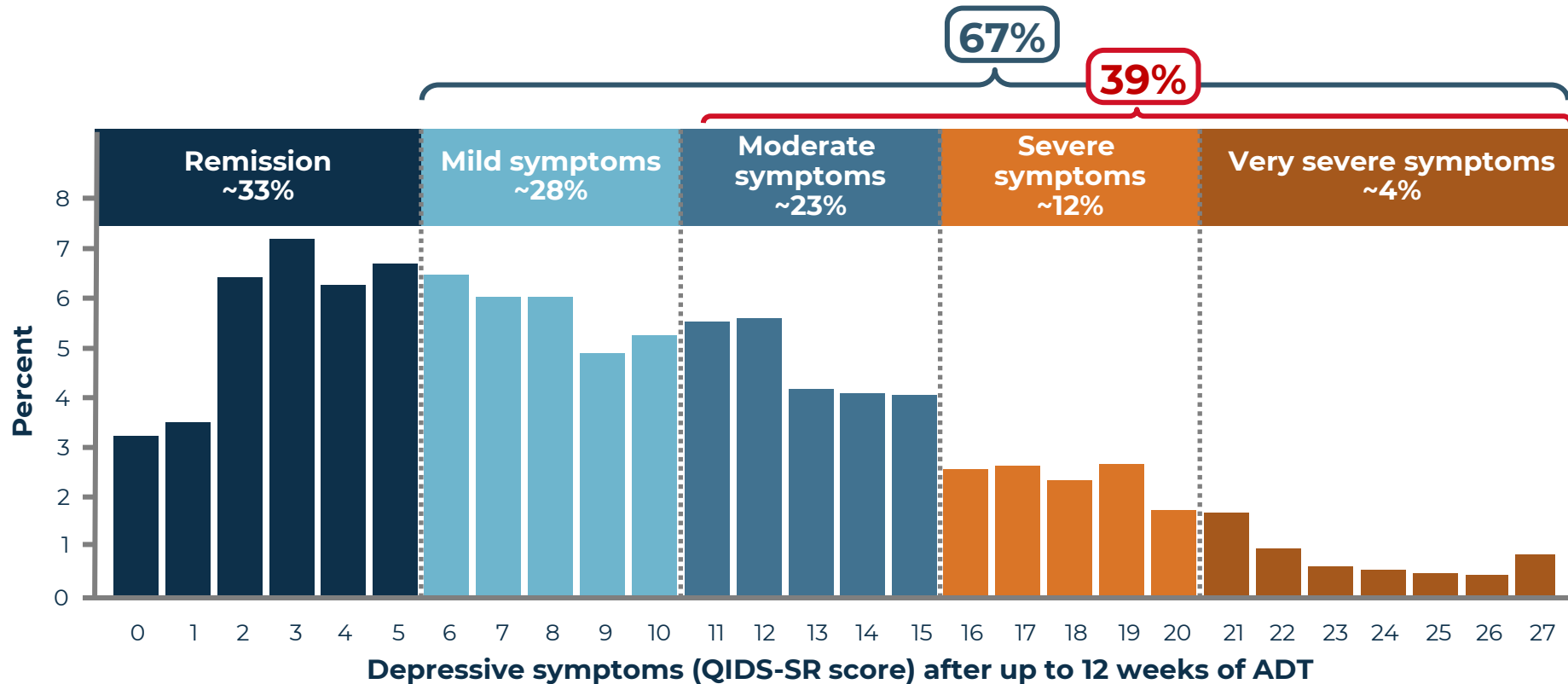


Learn how adjunctive atypical antipsychotics (AAPs) fit into the treatment paradigm for patients with MDD

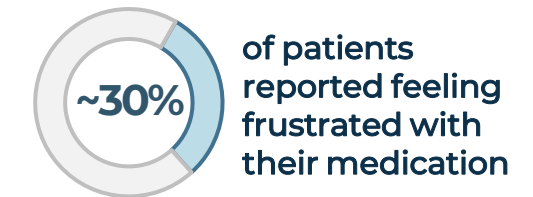
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Unresolved Symptoms of MDD Following Monotherapy Antidepressant Treatment (ADT) Are Common^{1,2}

Approximately **two out of three** patients with MDD had unresolved symptoms following treatment with first-line antidepressants (N=2876)



In a separate study,^{2,a}



Frustration led patients to:

- ~36% Ask about alternative medication options
- ~34% Consider alternative therapeutic approaches
- ~33% Want to quit taking medication altogether

^aIn an online international survey conducted in 2016 of patients (n=2096) with MDD with inadequate response to antidepressant treatment.

QIDS-SR=Quick Inventory of Depressive Symptomatology–Self-Report.

1. Trivedi MH, et al. *Am J Psychiatry*. 2006;163(1):28-40.
2. Mago R, et al. *BMC Psychiatry*. 2018;18(1):33.

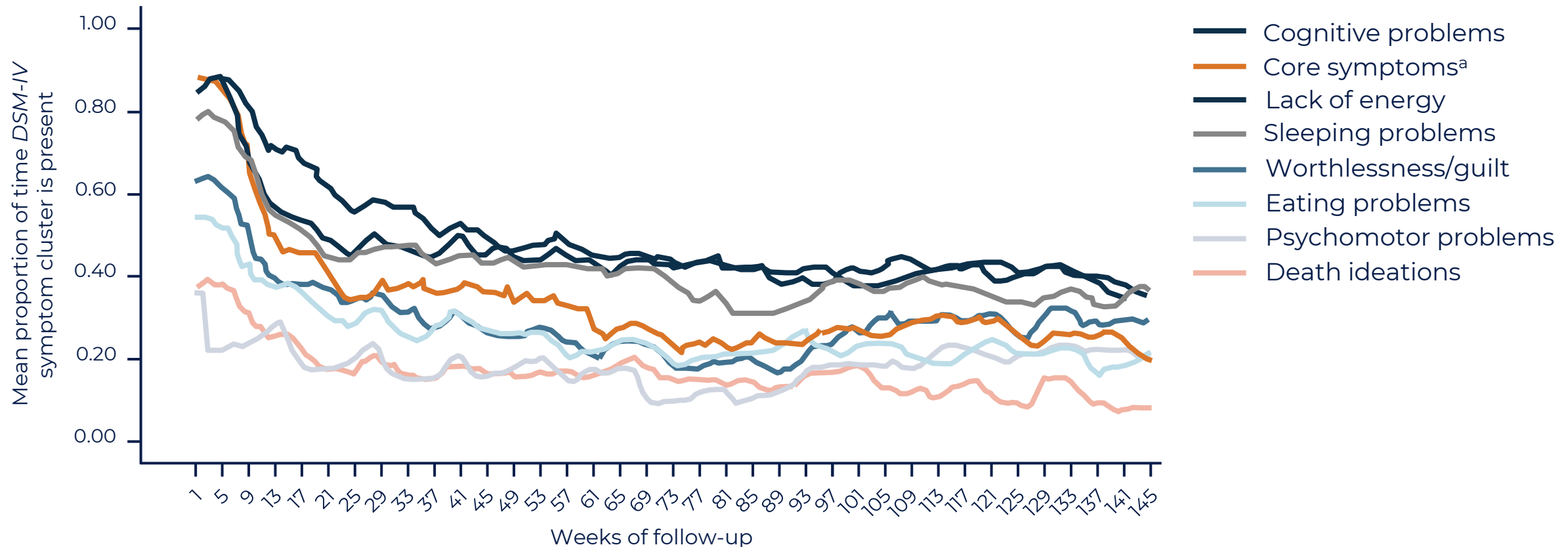
Polling Question

In your clinical experience, which of the following unmet needs have you recognized as the main concern with antidepressant treatment (ADT)?

- A** Limited specific efficacy with first-line therapies
- B** Intolerable side effects
- C** Inconsistent treatment response
- D** Relatively slow onset of action
- E** Need for second-line treatment modalities

Persistence of Unresolved Symptoms Following ADT

Presence of Unresolved Symptoms During 3-Year Follow-up Period (N=267)



^aCore symptoms are depressed mood/diminished interest.

1. Conradi HJ, et al. *Psychol Med*. 2011;41(6):1165-1174.

ADT=antidepressant treatment. DSM-IV=Diagnostic and Statistical Manual of Mental Disorders, 4th Ed.

A Greater Number of Residual Symptom Domains Corresponds to a Greater Probability of Relapse in MDD Remitters

Probability of Relapse in the Year Following Acute Remission

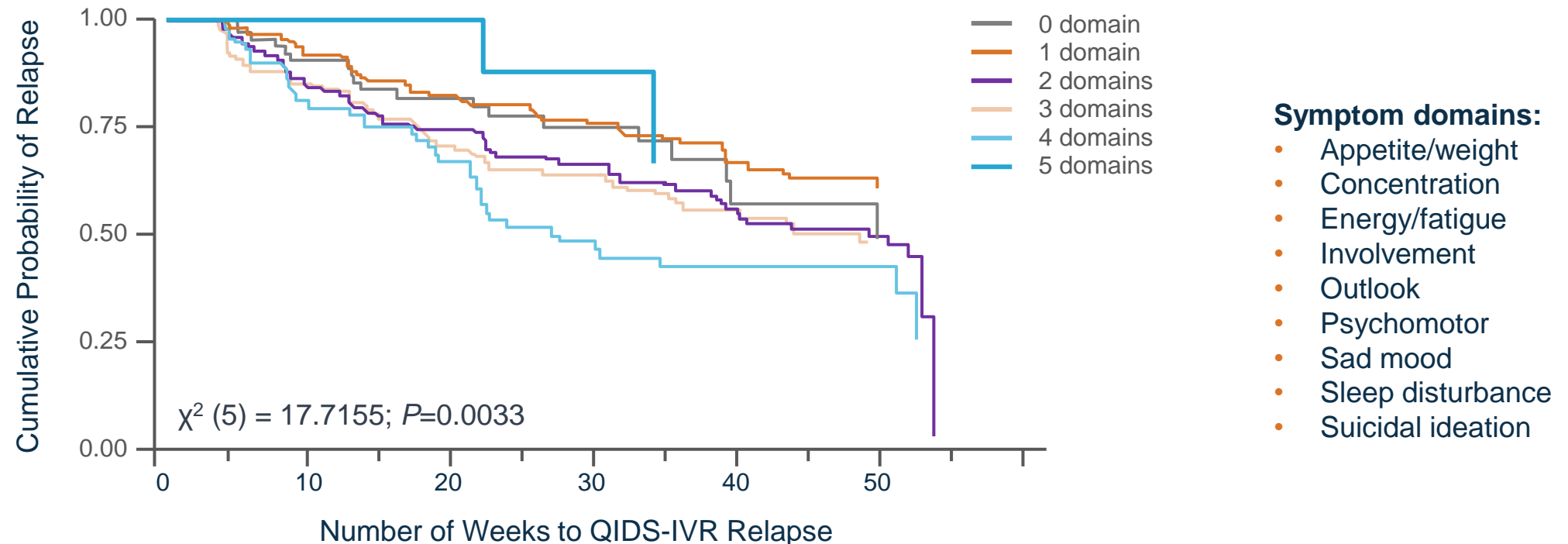


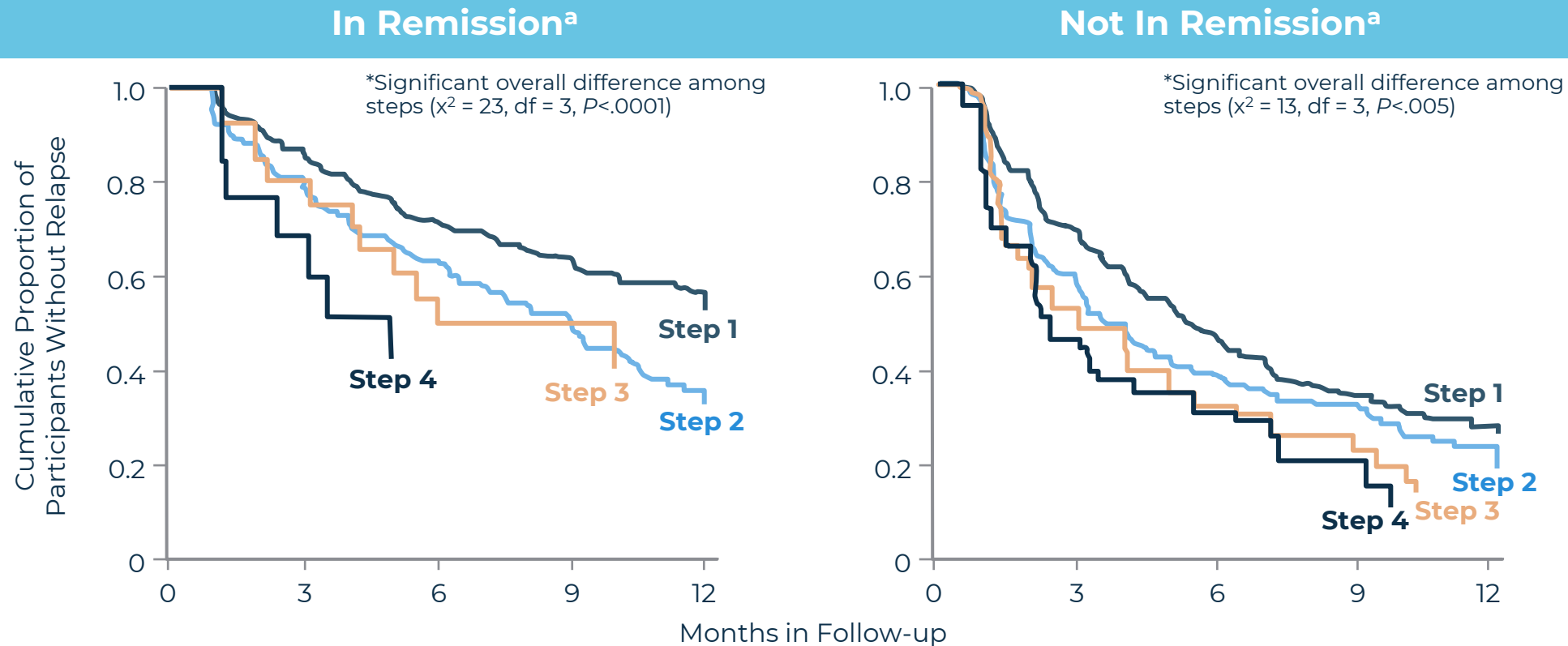
Image: Copyright © 2009 Cambridge University Press. Reprinted with the permission of Cambridge University Press.

MDD=major depressive disorder. QIDS-IVR=Quick Inventory of Depressive Symptomatology, Self Report—Interactive Voice Response.

1. Nierenberg AA, et al. *Psychol Med*. 2010;40:41-50.

In the STAR*D Study, Patients With Unresolved Symptoms of MDD Had Higher Relapse Rates Than Patients in Remission

RELAPSE DURING FOLLOW-UP PHASE BY NUMBER OF ACUTE TREATMENT STEPS FOR STAR*D PARTICIPANTS WHO ENTERED THE FOLLOW-UP PHASE:

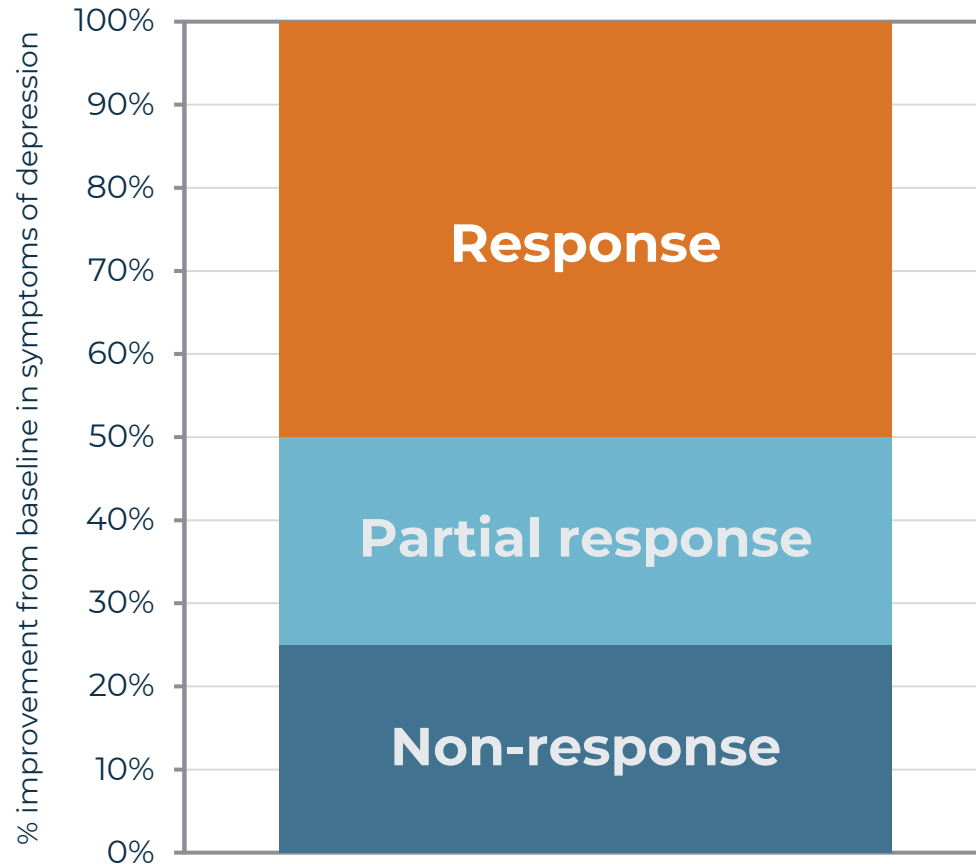


^aRemission defined as QIDS-SR score ≤ 5 .

MDD=major depressive disorder. QIDS-SR=Quick Inventory of Depressive Symptomatology-Self-Report. STAR*D=Sequenced Treatment Alternatives to Relieve Depression.

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

Symptomatic Improvement Is Not Always Adequate¹⁻³



Patients who meet response criteria may experience deficits in other outcomes¹⁻³:

- Unresolved symptoms
- Functional impairments
- Quality of life impairments
- Failure to achieve goals



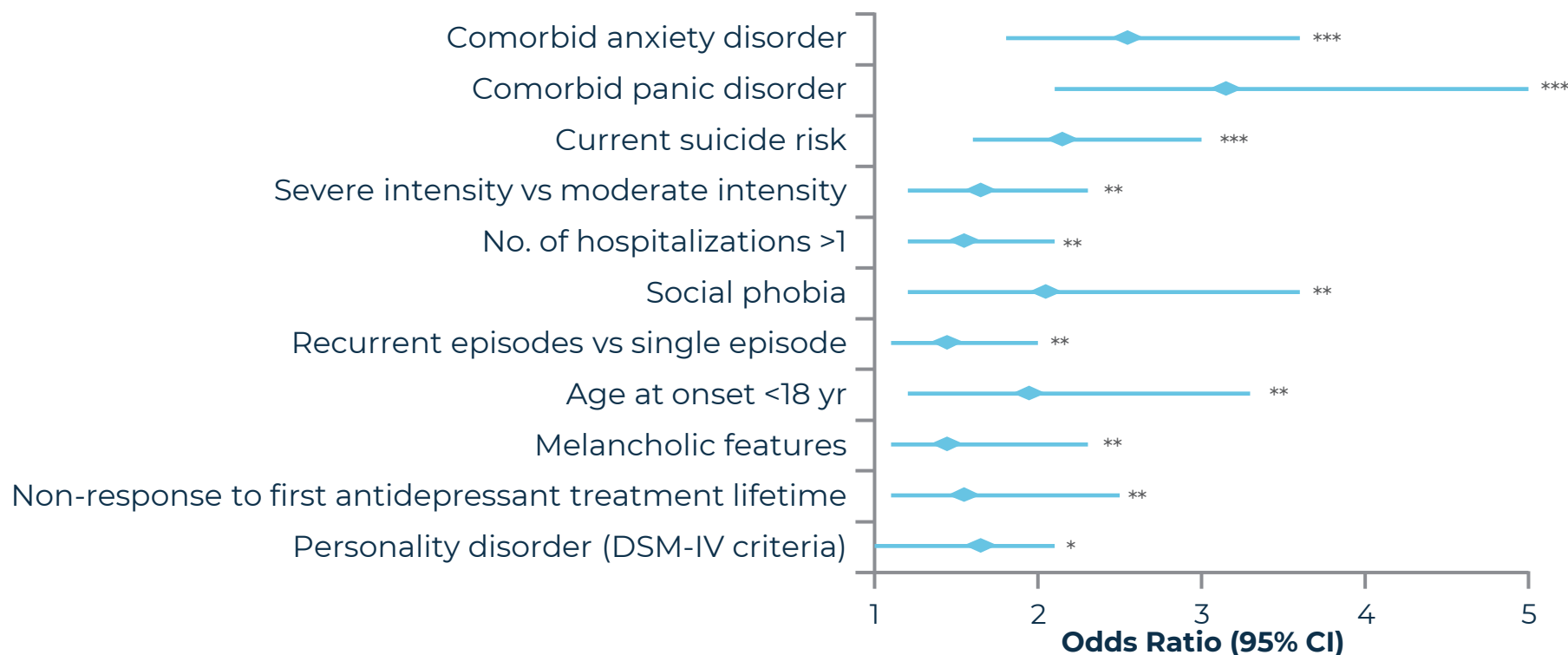
The **optimal outcome** for a patient with MDD is **full symptom recovery** with associated **improvements in functioning and quality of life**³

MDD=major depressive disorder.

1. Nierenberg AA, DeCecco LM. *J Clin Psychiatry*. 2001;62(suppl 16):5-9.
2. Angst J, et al. *Acta Psychiatr Scand*. 1996;93(6):413-419.
3. Saltiel PF, Silvershein DI. *Depress Anxiety*. 2012;29(7):638-645.

Eleven Different Clinical Factors Have Been Associated With Inadequate Response in MDD¹

Comorbid anxiety disorder was the most power clinical factor associated with treatment resistance^a in MDD (N=702)



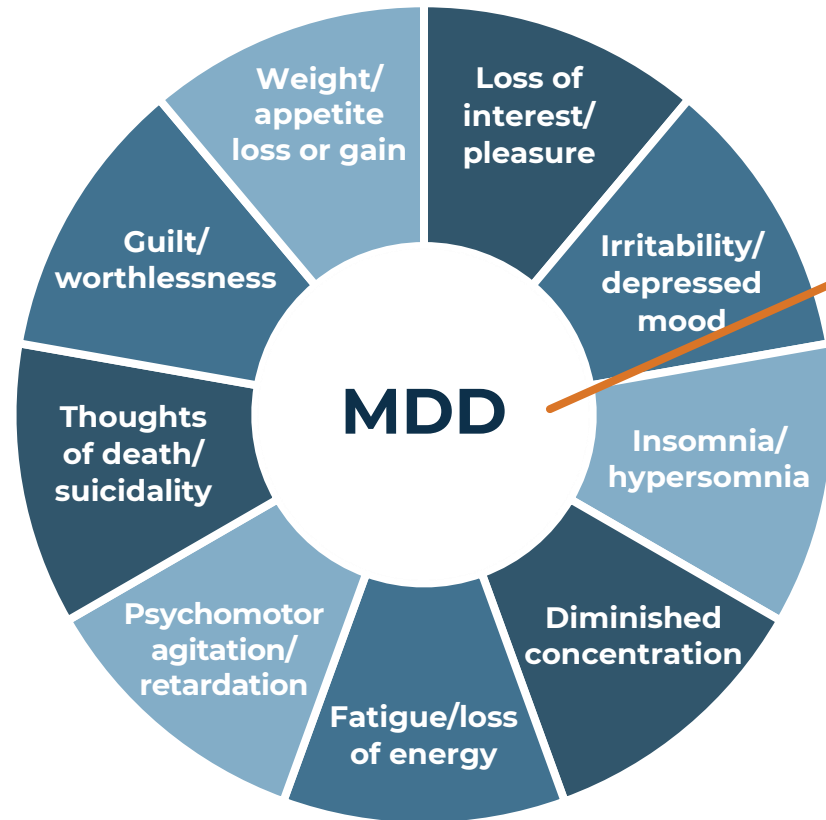
* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

^aInitial uni-variable logistic regression using nonresistance/resistance as the dependent variable.

CI=confidence interval. DSM-IV=Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. MDD=major depressive disorder.

1. Souery E, et al. *J Clin Psychiatry*. 2007;68:1062-1070.

Inclusion Of The Anxious Distress Specifier in the DSM-5-TR Highlights Its Clinical Implications










Anxious distress specifier

- Feeling keyed up or tense
- Feeling unusually restless
- Difficulty concentrating because of worry
- Fear that something awful may happen
- Feeling that the individual might lose control of himself or herself

DSM-5-TR=Diagnostic and Statistical Manual of Mental Disorders, 5th Edition, Text Revision. MDD=major depressive disorder.

1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Arlington, VA: American Psychiatric Publishing; 2013.

Clinical Tools Can Help in Assessment of Anxious Distress in MDD

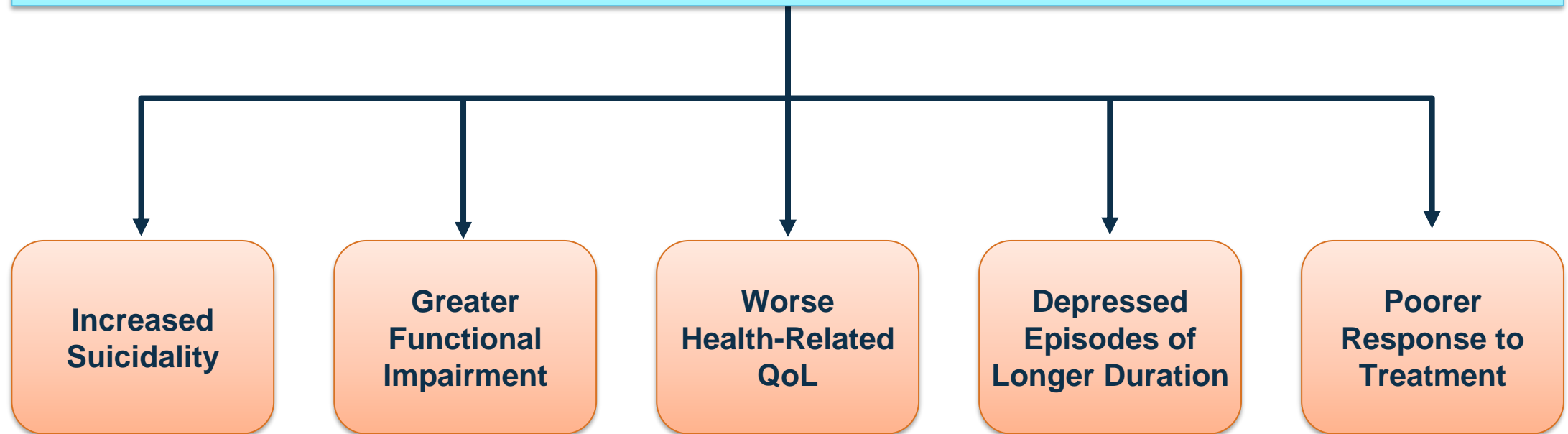
Clinical Assessments	Self Assessments	
MADRS, IDS-SR, HAM-D	GAD-7, HAM-A	
Tension – MADRS item 3 (inner tension) ≥ 3	GAD-7¹ A 7-item tool that rates the severity of anxiety Each item is given a score of 0 to 3 based on frequency of symptoms The total score is rated as:  Minimal: 1 to 4  Mild: 5 to 9  Moderate: 10 to 14  Severe: 15 to 21	HAM-A² A 14-item tool that rates the severity of anxiety Each item is given a score of 0 to 4 based on level of severity The total score is rated as:  Mild: <17  Moderate: 18 to 24  Moderate to severe: 25 to 30
Restlessness – IDS-SR item 24 (feeling restless) ≥ 2		
Concentration – MADRS item 6 (concentration difficulties) ≥ 3		
Apprehension – HAM-D item 10 (anxiety – psychic) ≥ 3		

DSM-5-TR=Diagnostic and Statistical Manual of Mental Disorders, 5th Edition, Text Revision. GAD-7=Generalized Anxiety Disorder-7. HAM-A=Hamilton Rating Scale for Anxiety. HAM-D=Hamilton Depression Rating Scale. IDS-SR=Inventory of Depressive Symptomatology-Self Report. MADRS=Montgomery-Åsberg Depression Rating Scale. MDD=major depressive disorder.

1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Arlington, VA: American Psychiatric Publishing; 2013.
2. Thase M, et al. *Neuropsych Dis Tx*. 2019;15:37-45.
3. MIRECC. Accessed November 11, 2022. https://www.mirecc.va.gov/cih-visn2/Documents/Clinical/GAD_with_Info_Sheet.pdf
4. Thompson E. *Occup Med (Lond)*. 2015;65(7):601.

At Least Half of Patients With Depression Can Have Symptoms of Anxious Depression, Which May Worsen Their Prognosis^{1,2}

Anxious depression predicts greater morbidity and has been associated with^{2,3}:



QoL=quality of life.

1. Trivedi MH, et al. *Am J Psychiatry*. 2006;163:28-40.

2. Fava M, et al. *Can J Psychiatry*. 2006;51:823-835.

3. Zimmerman M, et al. *J Clin Psychiatry*. 2014;75:601-607

Time to First Remission Found to Be Longer in Patients With Co-occurring Depression and Anxiety^a

Median time to remission

- Depression group:
 - 6 months for depression
 - 12 months for comorbid depression and anxiety
- Anxiety group:
 - 16 months for anxiety
 - 24 months for comorbid depression and anxiety

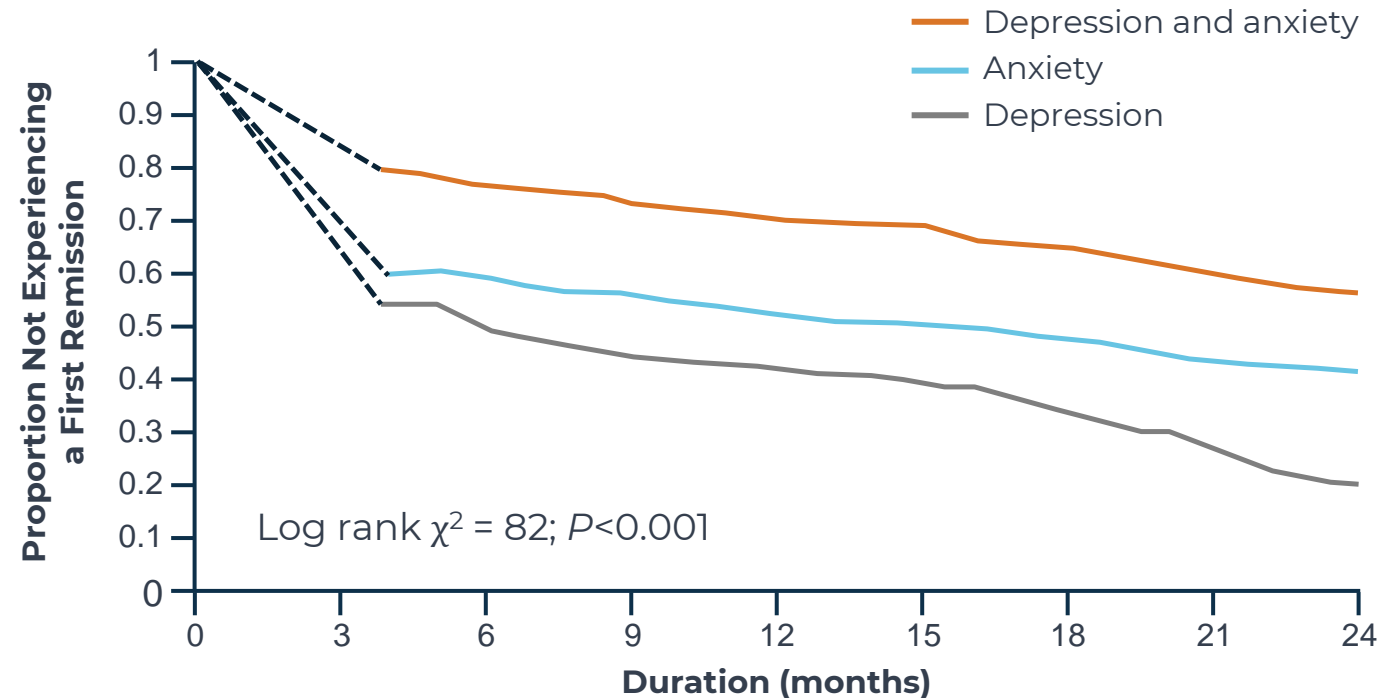


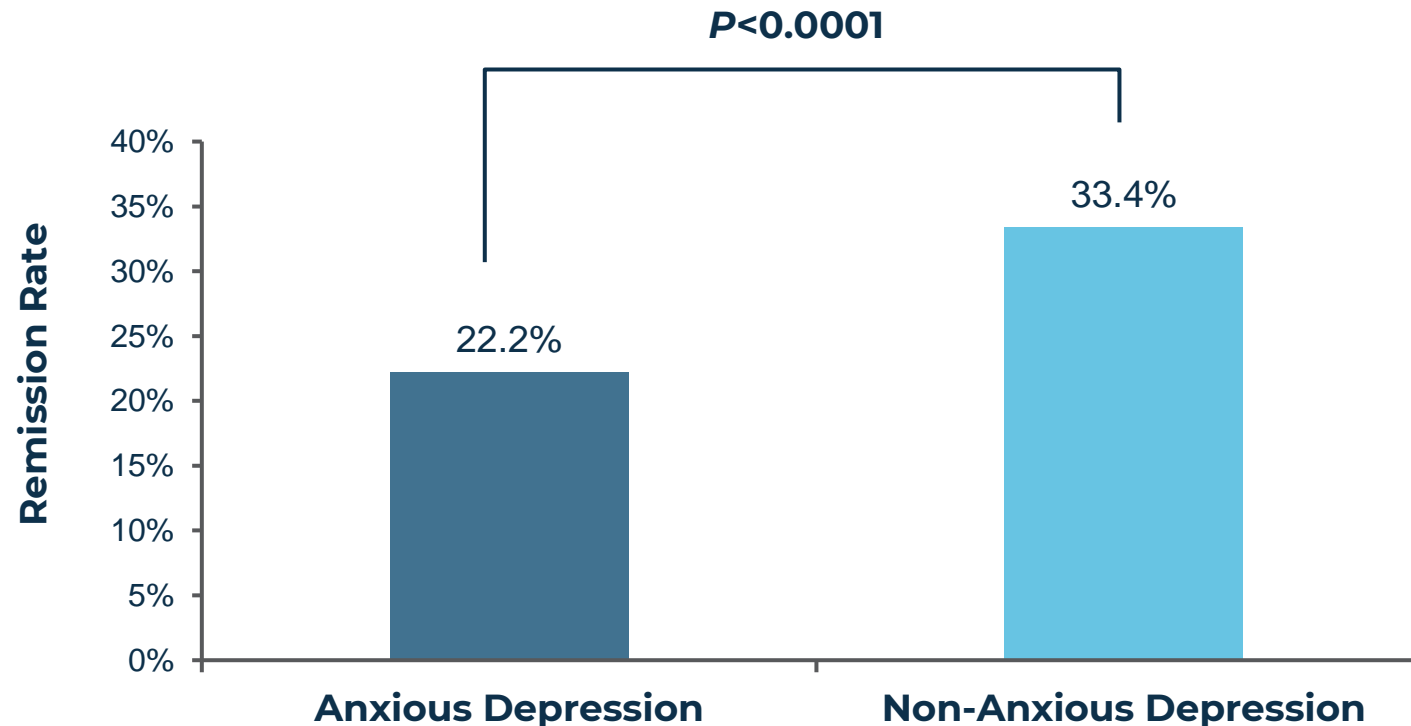
Image reprinted from *J Affect Disord* Vol 133 Penninx B et al. © 2011 with permission from Elsevier.

^aSurvival curve illustrating time until first remission across baseline psychiatric status (n=1209). The dotted lines (-----) are projected lines since, by definition, no remission could have occurred within the first 3-month period.

1. Penninx B, et al. *J Affect Disord*. 2011;133:76-85.

Remission Rates Are Significantly Lower in Patients With Anxious Depression Following The First Antidepressant Treatment^a

Patients with anxious depression were **~50% less likely to achieve remission** than those with non-anxious depression (N=2876)



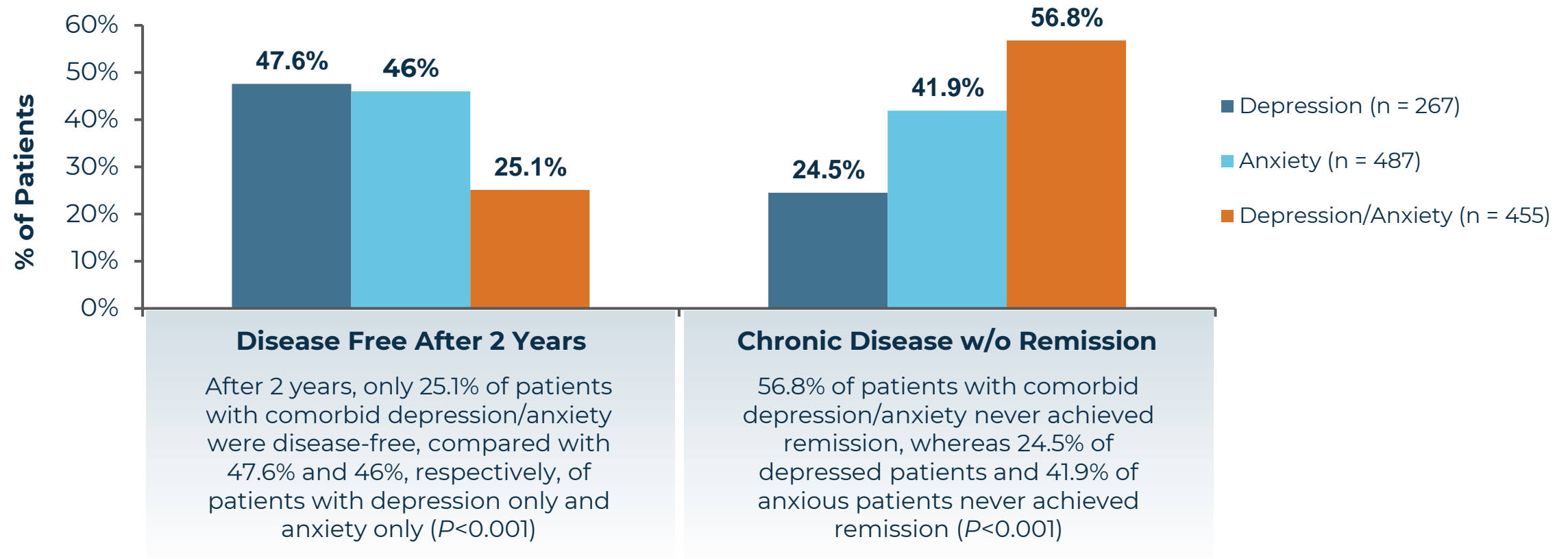
^aRemission was defined as a score ≤ 7 on the HAM-D17.

HAM-D17, =7-item Hamilton Depression Rating Scale.

1. Fava M, et al. *Am J Psychiatry*. 2008;165:342-351.

Anxiety in Depressive Patients Has Been Associated With Worse Outcomes

2-YEAR COURSE INDICATORS ACCORDING TO BASELINE PSYCHIATRIC STATUS (N=1209)



P value based on chi-square statistics for categorical variables and Mann Whitney nonparametric statistics for continuous variables.

1. Penninx B, et al. *J Affect Disord.* 2011;133:76-85.

Polling Question

In your clinical practice, what is your preferred second-line treatment strategy when your first-choice antidepressant treatment (ADT) is ineffective?

- A Increase dose and optimize current ADT
- B Switch to a different ADT (SSRI or SNRI)
- C Switch to a DNRI
- D Stay on same ADT and combine with another ADT (SSRI or SNRI)
- E Stay on same ADT and augment with a DNRI
- F Stay on same ADT and augment with a non-ADT (AAP)

AAP=atypical antipsychotic. DNRI=dopamine/norepinephrine reuptake inhibitor. SNRI=serotonin/norepinephrine reuptake inhibitor. SSRI=selective serotonin reuptake inhibitor.



American Psychiatric Association Practice Guideline for the Treatment of Patients With MDD (2010)¹

INITIAL TREATMENT

Mild to moderate MDD



PT

OR



ADT

(SSRI, SNRI, or atypical ADT)

Moderate to severe MDD



PT

&



ADT

(SSRI, SNRI, or atypical ADT)

INADEQUATE RESPONSE...

...TO PT

- Consider changing intensity or type of PT
- Consider adding ADT

...TO ADT

- Increase dose, switch ADT, or augment with PT or another pharmacologic agent
- For patients whose symptoms do not adequately respond to pharmacotherapy, consider ECT

ADT=antidepressant therapy. ECT=electroconvulsive therapy. MDD=major depressive disorder. PT=psychotherapy. SNRI=serotonin-norepinephrine reuptake inhibitor. SSRI=selective serotonin reuptake inhibitor.

1. American Psychiatric Association. *Practice Guideline for the Treatment of Patients With Major Depressive Disorder*. 3rd ed. 2010.

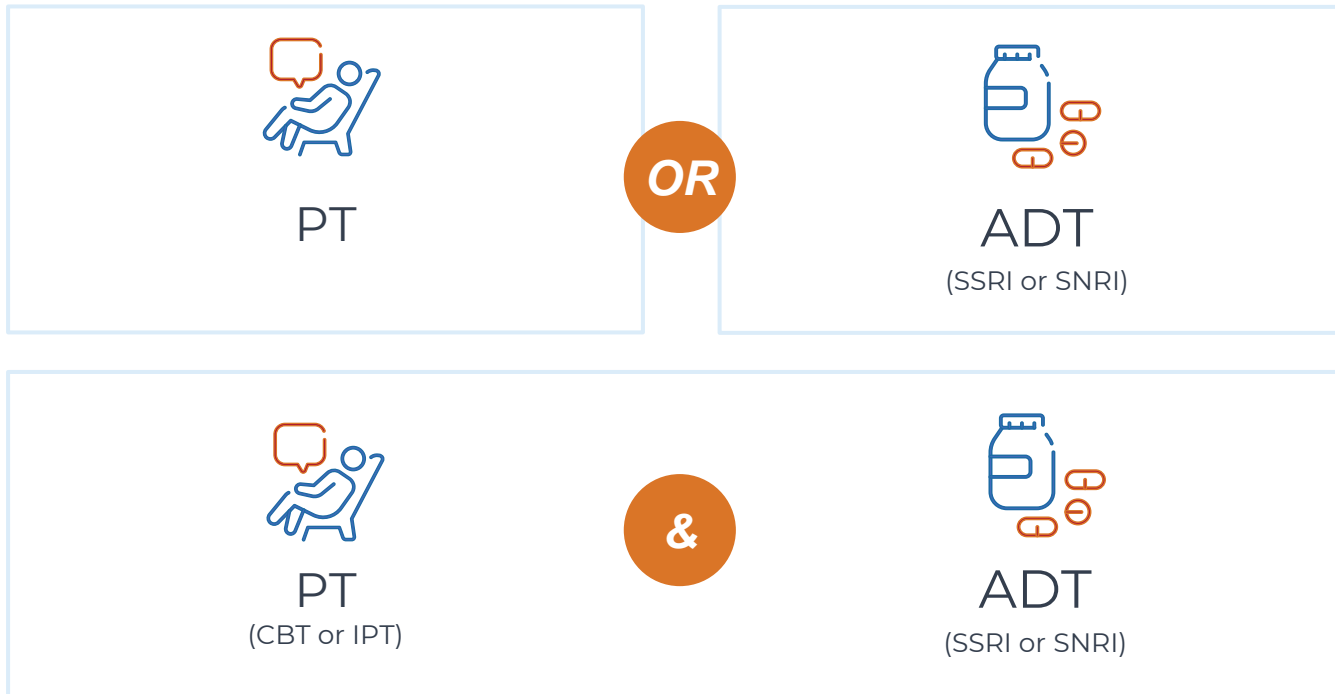


American Psychological Association Clinical Practice Guideline for the Treatment of Patients With MDD (2019)¹

INITIAL TREATMENT



INADEQUATE RESPONSE...



- Switch from ADT alone to cognitive therapy alone
- Switch to another ADT

ADT=antidepressant therapy. CBT=cognitive behavioral therapy. IPT=interpersonal psychotherapy. MDD=major depressive disorder. PT=psychotherapy. SNRI=serotonin-norepinephrine reuptake inhibitor. SSRI=selective serotonin reuptake inhibitor.

1. American Psychological Association. *APA Clinical Practice Guideline for the Treatment of Depression Across Three Age Cohorts*. 2019. Accessed October 29, 2022. <https://www.apa.org/depression-guideline>.

Combining/Augmenting ADTs That Target Different Monoamines May Be More Effective Than Switching¹

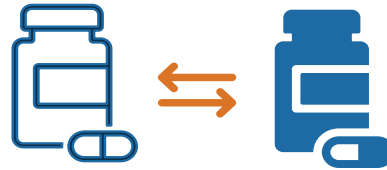
Data suggest that switching antidepressant therapies is frequently ineffective, whereas combining antidepressant therapies with different monoamine profiles may be more effective¹⁻⁴:

DOSE ESCALATION



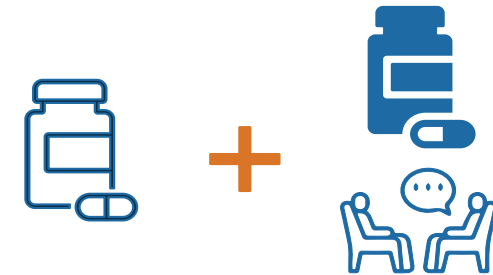
Studies suggest that dose escalation after initial nonresponse may not be particularly effective^{5,6}

SWITCHING ADT



Studies have shown similar efficacy between switching ADTs and continuing with the current ADT^{1,a}

COMBINING/AUGMENTING WITH ADT



Evidence supports improvement over monotherapy^{2,3,b,c}

^aIn the STAR*D trial, nearly 75% of patients with MDD who were switched to a second ADT failed to achieve remission.³

^bCombining a reuptake inhibitor with an α_2 antagonist was more effective than other combinations.⁴

^cGuidelines also suggest that psychotherapy should be added or increased when appropriate and that the diagnosis should be re-evaluated if clinically warranted.⁷






ADT=antidepressant therapy. MDD=major depressive disorder. STAR*D=Sequenced Treatment Alternatives to Relieve Depression.

1. Bschor T, et al. *J Clin Psychiatry*. 2018;79(1):16r10749.
2. Rush AJ, et al. *Am J Psychiatry*. 2006;163(11):1905-1917.
3. Henssler J, et al. *Can J Psychiatry*. 2016;61(1):29-43.
4. Henssler J, et al. *JAMA Psychiatry*. 2022;79(4):300-312.

5. Dold M, et al. *Psychother Psychosom*. 2017;86(5):283-291.
6. Ruhé HG, et al. *Br J Psychiatry*. 2006;189:309-316.
7. American Psychiatric Association. 3rd ed. 2010

Polling Question

In your clinical practice, what is your preferred adjunctive strategy for patients with MDD who have a partial response to monotherapy with ADT?

-  A Atypical antipsychotics
-  B Mood stabilizers
-  C Benzodiazepines
-  D Psychotherapy
-  E Augment by adding an antidepressant

ADT=antidepressant treatment. MDD=major depressive disorder.

Some Clinical Evidence Supports Augmenting Reuptake Inhibitors With Different Drug Classes and Psychotherapy¹⁻⁵

Adjunctive Treatment	APA ¹	NICE ²	BAP ³	WFSBP ⁴	CANMAT ⁵
Antipsychotics*	●	●	●	●	●
Mood stabilizers	●	●	●	●	●
Benzodiazepines	●	●		●	
Psychotherapy	●		●	●	●

*Augmentation with antipsychotics is the most studied adjunct therapy in patients with MDD⁶

Clinical confidence

● Substantial ● Moderate ● Low ● None

APA=American Psychiatric Association. BAP=British Association for Psychopharmacology. CANMAT=Canadian Network for Mood and Anxiety Treatments. NICE=National Institute for Health and Care Excellence. WFSBP=World Federation of Societies of Biological Psychiatry.

1. American Psychiatric Association. 3rd ed. 2010.

2. National Collaborating Centre for Mental Health (UK). British Psychological Society; 2010.

3. Cleare A, et al. *J Psychopharmacol*. 2015;29(5):459-525.

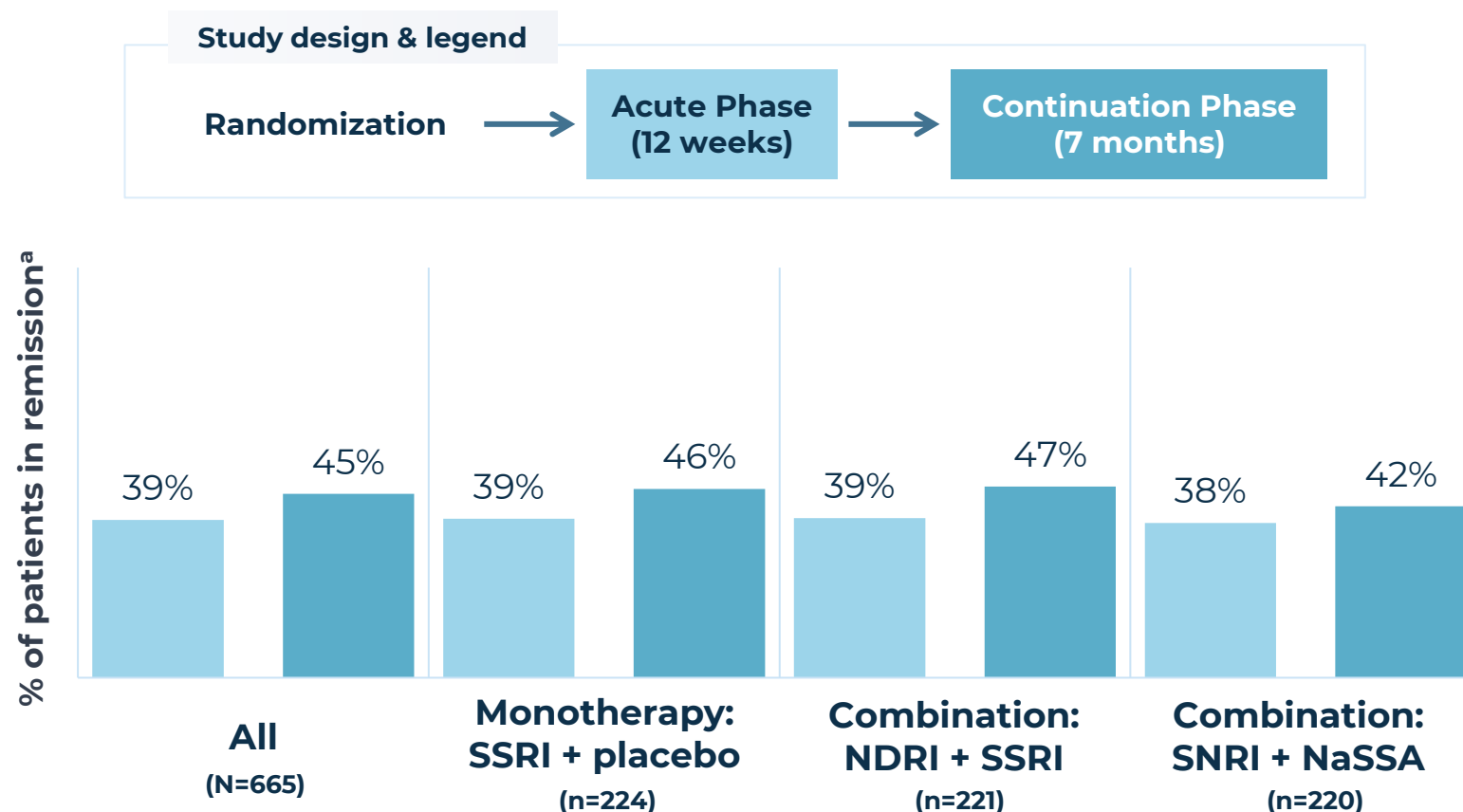
4. Bauer M, et al. *World J Biol Psychiatry*. 2013;14(5):334-385.

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

6. Nuñez NA, et al. *J Affect Disord*. 2022;302:385-400.

Combining ADTs With Similar Monoamine Profiles May Not Improve Outcomes¹

In a prospective trial of **665 patients** with MDD, **combination therapy with two antidepressants did not improve outcomes** when compared with antidepressant monotherapy, and in some cases increased the risk of adverse events¹



^aRemission defined as at least one of the last two consecutive QIDS-SR scores ≤ 5 and the other ≤ 7 .

ADT=antidepressant therapy. NaSSA=noradrenergic and specific serotonergic antidepressant. NDRI=norepinephrine–dopamine reuptake inhibitor. QIDS-SR=Quick Inventory of Depressive Symptomatology–Clinician-Rated. SNRI=serotonin–norepinephrine reuptake inhibitor. SSRI=selective serotonin reuptake inhibitor.

1. Rush AJ et al. *Am J Psychiatry* 2011;168:689–701.

Higher Response and Remission Rates Seen With AAP Augmentation Versus DNRI Augmentation or ADT Monotherapy¹

IN A 12-WEEK FOLLOW-UP OF AN RCT PATIENTS WITH MDD (N=1522):

Patients with unresolved symptoms were separated into three treatment groups:

- Switch to a DNRI
- Augment ADT with a DNRI
- Augment ADT with an AAP

Augmentation with an AAP was superior in response and remission rates compared to:

- Switching ADTs to a DNRI
- Augmenting current ADT with a DNRI

	Response %	Remission %
Switch to a DNRI	62.4%	22.3%
Augment current ADT with a DNRI	65.6%	26.9%
Augment current ADT with an AAP	74.3%	28.9%

AAP=atypical antipsychotic. ADT=antidepressant therapy. DNRI=dopamine and norepinephrine reuptake inhibitor. MDD=major depressive disorder. RCT=randomized controlled trial.

1. Mohamed S, et al. JAMA. 2017;318(2):132-145.

Remission Rates Are Higher With AAP Augmentation Versus Monotherapy¹

In a meta-analysis of 11 RCTs consisting of 3341 patients with MDD, AAP augmentation showed superior efficacy compared to monotherapy, and effect size positively correlated with severity of TRD¹

Remission Rates			
	AAP n/N	Monotherapy n/N	Odds Ratio ^a (95% CI)
Non-TRD	32/49	39/53	0.89 (0.69-1.14)
TRD 1	248/753	85/434	1.55 (1.25-1.92)
TRD 2	54/198	34/203	1.63 (1.11-2.38)
TRD 2-4	281/931	127/720	1.68 (1.40-2.03)

With regards to **quality of life and functioning**, certain atypical antipsychotics have been shown to be **significantly more beneficial than placebo²**, with **small-to-moderate effect sizes (g: .22-.49)³**

*Odds ratio >1=superior to placebo.

CI=confidence interval. n/N, number of patients achieving remission/total number of patients. AAP=atypical antipsychotic. TRD=treatment-resistant depression (number after indicates number of antidepressant treatment failures within the current depressive episode). RCT=randomized controlled trial..

1. Wang HR, et al. *Int J Neuropsychopharmacology*. 2015;18(8):pyv023.

2. Zhou X, et al. *Int J Neuropsychopharmacology*. 2015;18(11):pyv060.

3. Spielmans GI, et al. *PLoS Med*. 2013;10(3):e1001403.

Considerations for Augmentation With Atypical Antipsychotics (AAPs)

POTENTIAL ADVANTAGES¹⁻⁶



Maintain any therapeutic benefit of the first-line agent^{1,2}



Enhance antidepressant effect^{1,3}



Increase remission rates^{1,3}



Avoid withdrawal symptoms due to switching²

&

Counteract ADT side effects²



Certain AAPs target three MDD-related monoamines⁴



AAPs can act synergistically with reuptake inhibitors⁶

POTENTIAL DISADVANTAGES^{2,5,7}



Additional daily medications⁵



Additional side effects²



Stigma associated with antipsychotics⁷

AAP=atypical antipsychotic. ADT=antidepressant therapy. MDD=major depressive disorder.

1. American Psychiatric Association. 3rd ed. 2010.

2. Papakostas GI. *J Clin Psychiatry*. 2009;70(suppl 6):16-25.

3. National Collaborating Centre for Mental Health (UK). 2010.

4. Grinchii D, et al. *Int J Mol Sci*. 2020;21(24):9532.

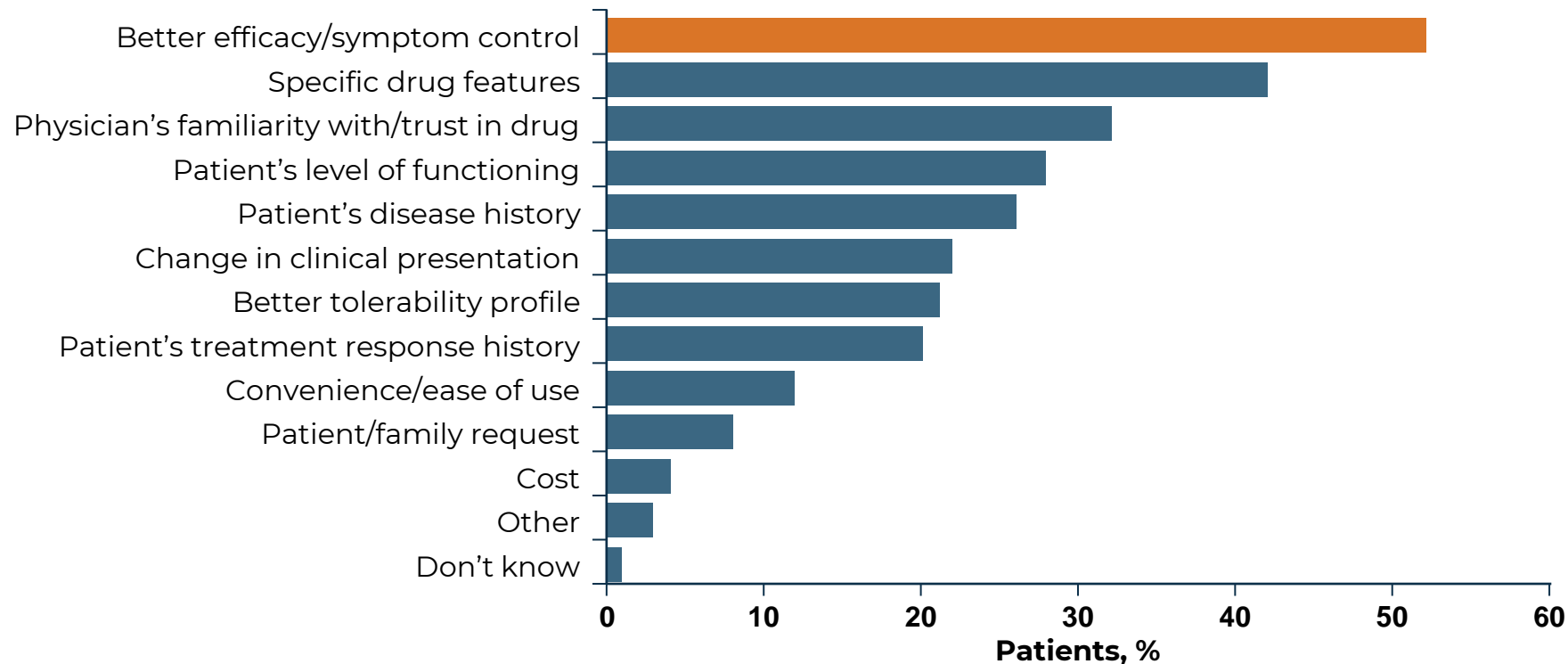
5. Ghaed-Sharaf M, et al. *BMC Psychol*. 2022;10(1):12.

6. Stahl SM. 4th ed. 2013.

7. Townsend M, et al. *Patient Prefer Adherence*. 2022;16:373-401.

Practitioners' Reasons For Deciding To Prescribe An Adjunctive Antipsychotic Medication

Better efficacy/symptom control was the most frequently cited reason for prescribing an adjunctive antipsychotic medication in patients with MDD and an inadequate response to ADT (N=411)^a



^aOtsuka-funded case review study; surveyed psychiatrists and primary care physicians (n=411) based in the United States and Europe.

1. McIntyre RS, et al. *Adv Ther*. 2015;32:429-444.

Summary



Following first-line treatment, many patients with MDD continue to experience unresolved symptoms¹

1



The presence of unresolved symptoms often leads to poor outcomes, even if remission is achieved²

2



Switching ADT monotherapies to address residual symptoms is frequently ineffective³

3



Augmentation with AAPs, the most studied adjunctive therapy in patients with MDD, may provide better symptom control⁴⁻⁶

4

AAP, atypical antipsychotic; ADT, antidepressant therapy; MDD, major depressive disorder.

1. Trivedi MH, et al. *Am J Psychiatry*. 2006;163(1):28-40.
2. Zajecka J, et al. *J Clin Psychiatry*. 2013;74(4):407-414.
3. Bschor T, et al. *J Clin Psychiatry*. 2018;79(1):16r10749.

4. Nuñez NA, et al. *J Affect Disord*. 2022;302:385-400.
5. Rush AJ, et al. *Am J Psychiatry*. 2006;163(11):1905-1917.
6. Henssler J, et al. *Can J Psychiatry*. 2016;61(1):29-43