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Management of Major Depressive Disorder:

Breaking Through The Barriers

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This program is paid for by Otsuka Pharmaceutical Development & Commercialization, Inc. (OPDC) and Lundbeck, LLC.

Objectives

To understand that Major Depressive Disorder (MDD) is a serious illness leading to decreased overall patient health and quality of life

To investigate the effect of inadequate treatment response in MDD on patients and their families

To recognize predictors of and important considerations for inadequate treatment response in MDD, including the new *DSM-5* specifier for anxious distress

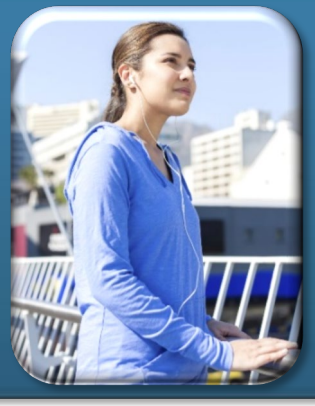
To consider the importance of proactive treatment decisions

MDD is A Serious Illness of The Brain That May Lead to Decreased Patient Health And Quality of Life[1-3]

1.

1. Greer TL, et al. *CNS Drugs*. 2010;24:267-284.
2. Hamilton JP, et al. *Am J Psychiatry*. 2012;169:693-703;
3. Salvadore G, et al. *Neuroimage*. 2011;54(4):2643-2651.

Patients Comment About Their Long Journey With Depression*



"So, I would say, maybe, in 10th grade, in high school, is when I realized I needed to get help for it [depression] because it runs [very] heavily in my mother's side of the family…I didn't want to have this…I got pretty bummed out and it was hard making choices and just going through every day…"

– Anna F, Diagnosed with first MDD episode 10 years ago, but reports longstanding, chronic dysphoria

"…having been a product of depression my whole life and seeing what it did for my mother. She didn't even want a stent put in her arteries. She just said let me die… It's a debilitating disease. And that's why I'm not ashamed of it. If I broke my leg I'd go, get it set."

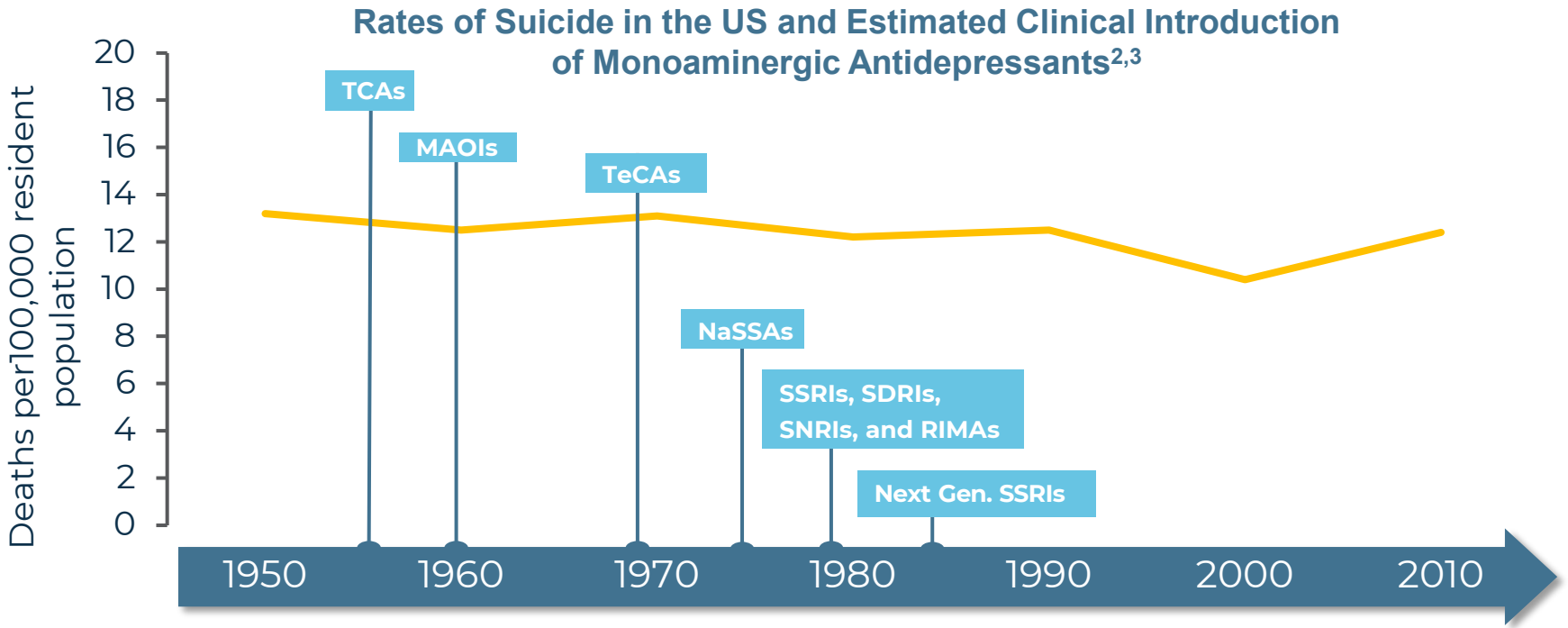
– Sheila M, Multiple documented episodes of MDD

*Pictures and names are fictitious and used for illustrative purposes only.

1. Keeley RD, et al. *BMC Fam Pract*. 2014;15:13.

Increased Availability of Antidepressants Has Had Limited Effects on The Rate of Suicide

- Use of antidepressants among adults 18 to 64 years of age has increased in the US from 2.2% (1988-1994) to 10.6% (2007-2010)[1]
- Depression is present in at least 50% of all suicides; 15% of patients with treated depression eventually die by suicide[2]

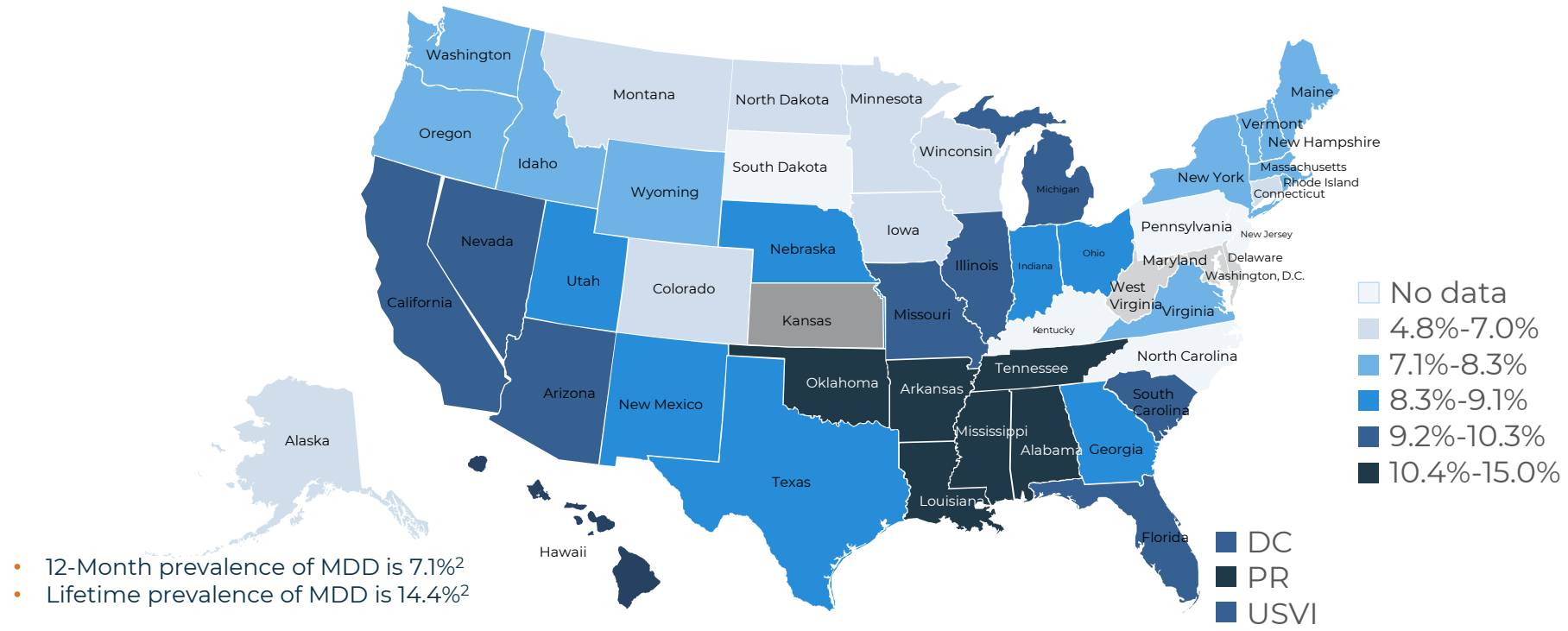


MAOIs=monoamine oxidase inhibitors; NaSSAs=noradrenergic and specific serotonergic antidepressants; RIMAs=reversible and selective inhibitors of MAO; SDRIs=selective dopamine reuptake inhibitors; SNRIs=serotonin and norepinephrine reuptake inhibitors; SSRIs=selective serotonin reuptake inhibitors; TCAs=tricyclic antidepressants; TeCAs=tetracyclic antidepressants.

1. National Center for Health Statistics. Health, United States, 2013: With Special Feature on Prescription Drugs. Hyattsville, MD; 2014.
2. American Association of Suicidology. Depression and Suicide Risk (2014). http://www.suicidology.org/Portals/14/docs/Resources/FactSheets/2011/DepressionSuicide2014.pdf. Accessed December 26, 2014.
3. López-Muñoz F, Alamo C. *Curr Pharm Des*. 2009;15:1563-1586.

Prevalence of Depression Across The United States

Age-standardized* Prevalence Rates of Depression† by State/Territory—
Behavioral Risk Factor Surveillance System, US (2006 and 2008)[1]

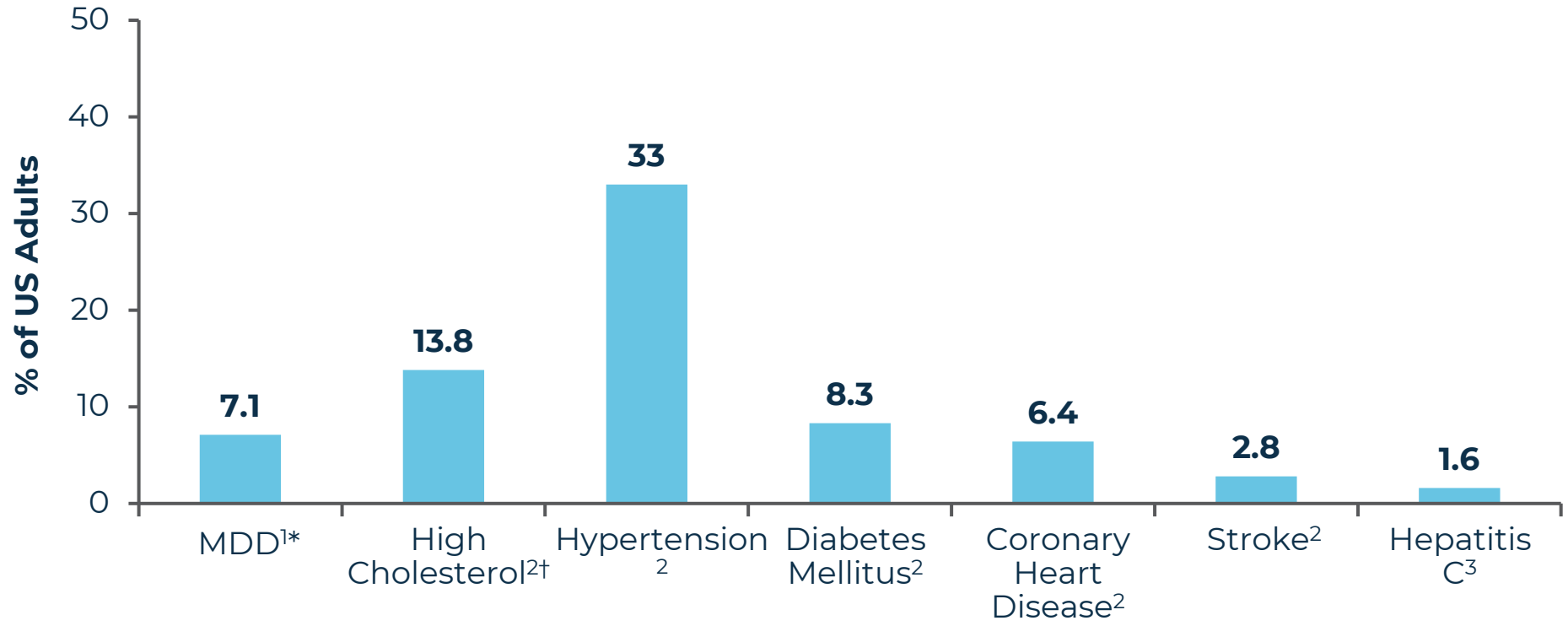


- 12-Month prevalence of MDD is 7.1%[2]
- Lifetime prevalence of MDD is 14.4%[2]

*Age standardized to the 2000 US standard population. †Based on responses to Patient Health Questionnaire 8.

1. CDC. An estimated 1 in 10 US adults report depression. CDC website. http://www.cdc.gov/features/dsdepression/. Updated March 31, 2011. Accessed December 24, 2014.
2. Kessler RC, et al. *Int J Methods Psychiatr Res*. 2012;21:169-184.

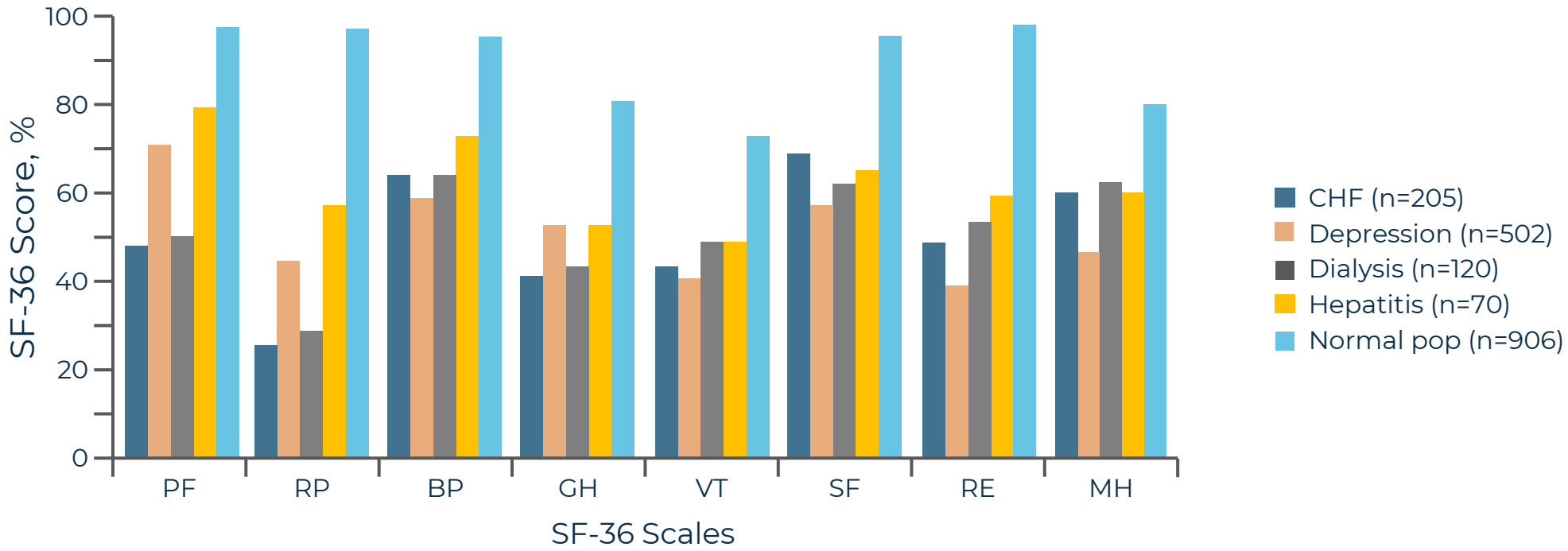
Major Depressive Disorder is as Common as Diabetes And Coronary Heart Disease



*12-month prevalence in patients aged 13 years and older.
†Total serum cholesterol levels ≥240 mg/dL.[2]

1. Kessler RC, et al. *Int J Methods Psychiatr Res*. 2012;21:169-184.
2. Go AS, et al. *Circulation*. 2013;127:e6-e245.
3. Armstrong GL, et al. *Ann Intern Med*. 2006;144:705-714.

The Health-related Quality of Life (QoL) Reported by Patients With Major Depression is Similar to Congestive Heart Failure, Severe Hepatitis, and Dialysis



The SF-36® is a multipurpose, short-form health survey (36 questions). It yields an 8-scale profile of functional health and well-being scores, as well as psychometrically-based physical- and mental-health-summary measures and a preference-based health-utility index. It is a generic measure, as opposed to one that targets a specific age, disease, or treatment group.[2]

BP=bodily pain; CHF=congestive heart failure; Dialysis=chronic hemodialysis; GH=general health perceptions; MH=mental health; PF=physical functioning; RE=role limitations caused by emotional problems; RP=role limitations due to physical limitations; SF=social functioning; SF-36=36-item Short-form Health Survey; VT=vitality

1. Juenger J, et al. *Heart*. 2002;87:235-241; 2. Ware JE Jr. http://www.sf-36.org/tools/sf36.shtml. Accessed Jun 9, 2015.
2. SF-36® is a registered trademark of the Medical Outcomes Trust.

MDD Significantly Changes The Brain's Responses to Negative Stimuli (Measured By fMRI)

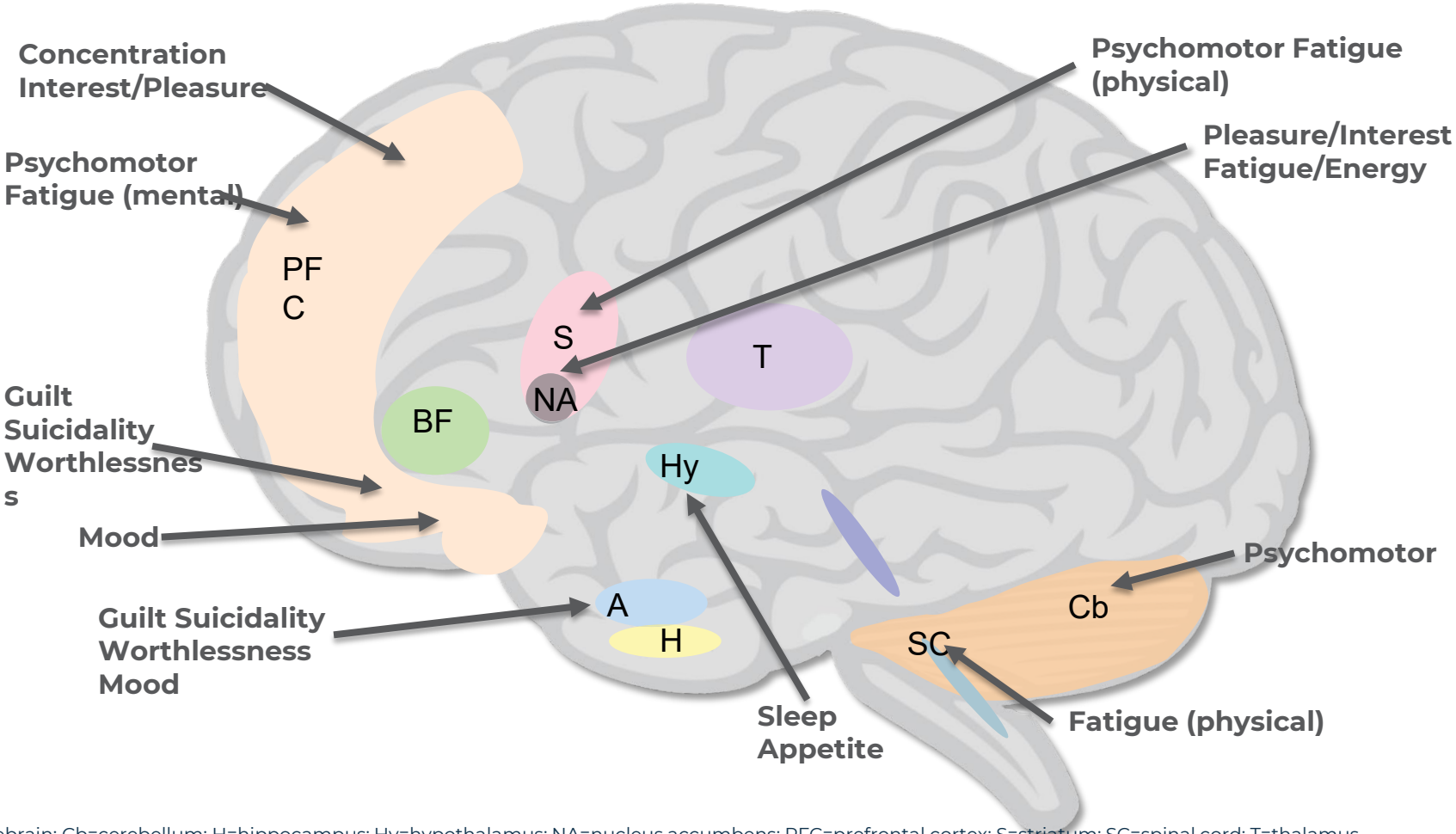
- Compared with healthy subjects, patients with MDD showed higher baseline activity in the pulvinar nucleus

- In response to negative stimuli:
  - MDD patients showed greater response in the amygdala, insula, and dorsal anterior cingulate cortex, compared with control
  - MDD patients showed lower response in the dorsal stratum and dorsolateral prefrontal cortex, compared with control

MDD=major depressive disorder; fMRI=functional magnetic resonance imaging

1. Hamilton JP, et al. *Am J Psychiatry*. 2012;169:693-703.

Various Brain Regions Have Been Theorized to be Associated With Different MDD Symptoms

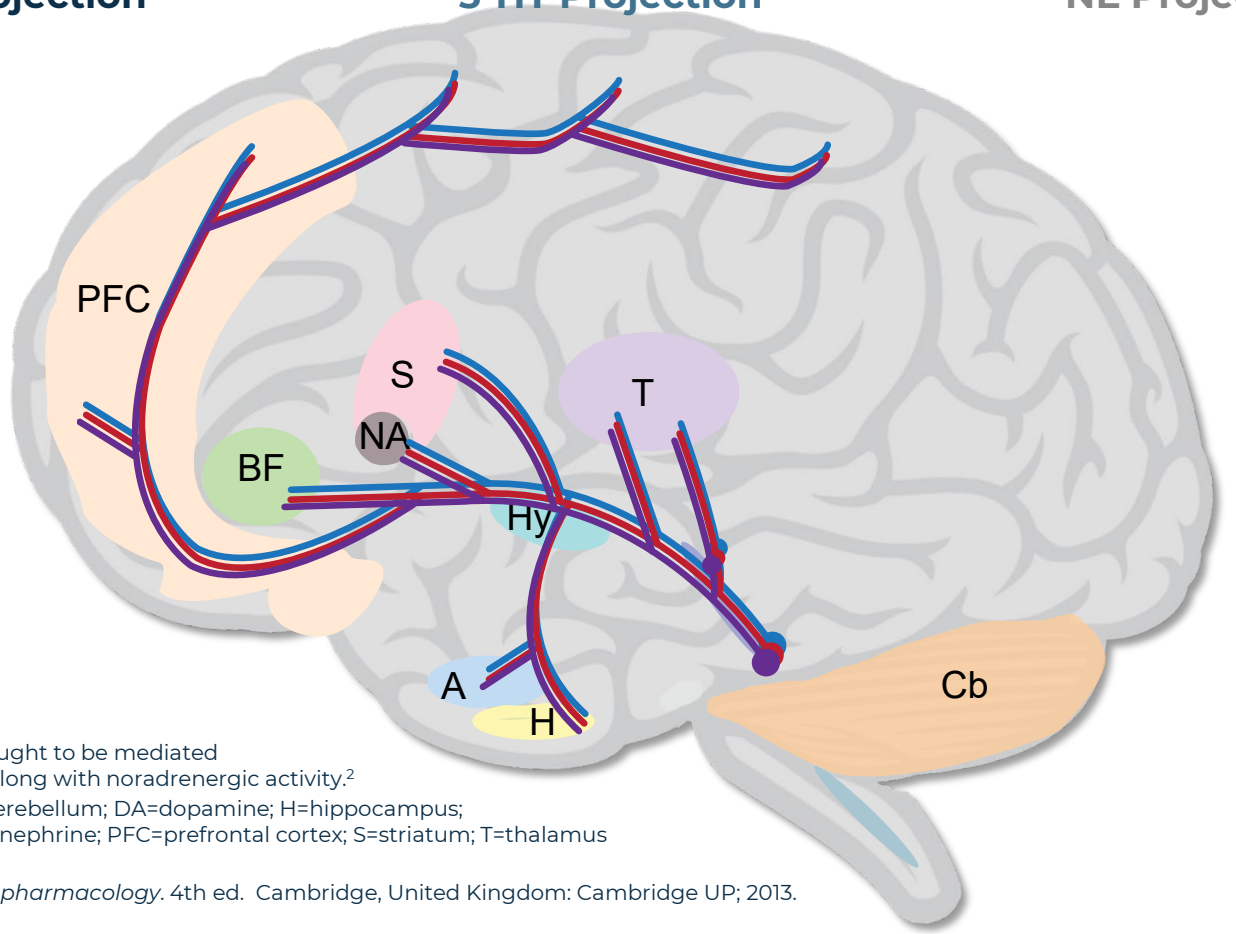


A=amygdala; BF=basal forebrain; Cb=cerebellum; H=hippocampus; Hy=hypothalamus; NA=nucleus accumbens; PFC=prefrontal cortex; S=striatum; SC=spinal cord; T=thalamus

1. Stahl SM. *Stahl's Essential Psychopharmacology*. 4th ed. Cambridge, United Kingdom: Cambridge University Press; 2013.

Deficits In Monoamine Neurotransmitter Systems Are Hypothesized to Mediate Behavioral Effects of MDD[1,2]

DA Projection **5-HT Projection** **NE Projection**

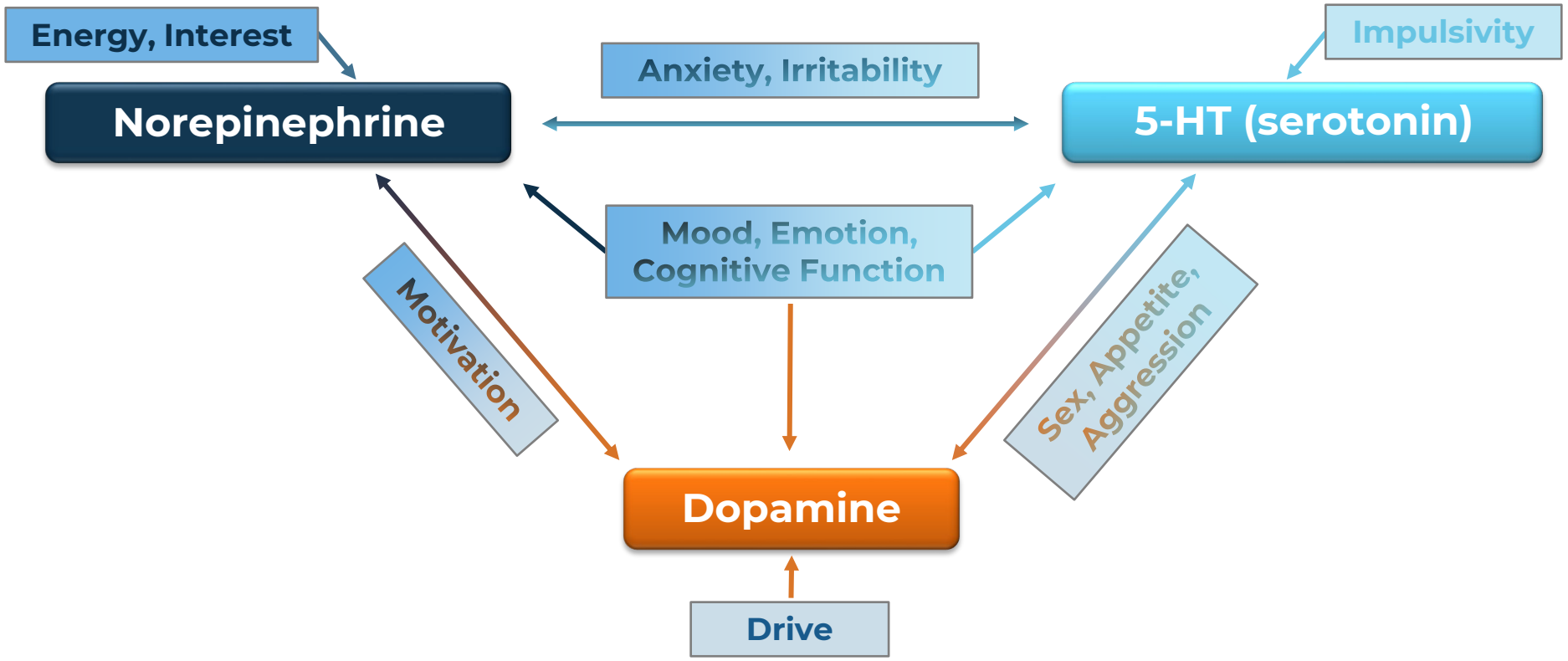


Antidepressant effects of available medications are thought to be mediated through modulating serotonin and dopamine activity along with noradrenergic activity.[2]

5-HT=serotonin; A=amygdala; BF=basal forebrain; Cb=cerebellum; DA=dopamine; H=hippocampus; Hy=hypothalamus; NA=nucleus accumbens; NE=norepinephrine; PFC=prefrontal cortex; S=striatum; T=thalamus

1. Adapted from: Stahl SM. *Stahl's Essential Psychopharmacology*. 4th ed. Cambridge, United Kingdom: Cambridge UP; 2013.
2. Roiser JP, et al. CNS Spectr. 2013;18:139-49.
3. Stahl SM. *Stahl's Essential Psychopharmacology*. 4th ed. Cambridge, United Kingdom: Cambridge University Press; 2013.

Overlap Between Monoamine Neurotransmitter Systems Plays A Role in Emotional Behavior



1. Zajecka J, et al. *J Clin Psychiatry*. 2013;74:407-414.

Changes in Brain Structure And Function Are Observed in Some Patients With MDD

- A recent meta-analysis of fMRI studies suggests that changes in the way negative and positive emotions are processed in MDD are associated with functional changes in the dorsal lateral prefrontal cortex, anterior and dorsal cingulate cortex, amygdala, striatum and cerebellum[1]
  - It is unclear whether changes in brain volume are the result of the disease or treatments
- In a study comparing healthy controls (n=107) to patients with current depression (n=58) using voxel-based morphometry and high-resolution MRI, depressed patients showed reduced gray matter volume in the left inferior (VLPFC) frontal gyrus and the right middle (DALPFC) and superior (DMPFC) frontal gyri [2]

DALPFC=dorsal anterolateral prefrontal cortex; DMPFC=dorsomedial prefrontal cortex; fMRI=functional magnetic resonance imaging; HC=healthy control; VLPFC=ventrolateral prefrontal cortex

1. Groenewold NA et al. *Neurosci Biobehav Rev*. 2013;37:152-163.
2. Salvadore G, et al. *Neuroimage*. 2011;54:2643-2651

Inadequate Treatment Response in MDD

Patients With MDD May Face A Long Journey

- The phases of treatment for depression are typically defined as acute (~6-12 weeks), continuation (~4-9 months), and maintenance (≥ 1 year)[1]
- Even patients who respond to treatment and who are diagnosed as being in remission may still relapse periodically, and recurrences of depressive symptoms may still occur during long-term maintenance therapy[1]
- These relapses may vary markedly in severity and may occur during any phase of treatment[1]
- Following an initial depressive episode, ~50% of patients recover with no further episodes, ~35% of patients suffer from recurrent MDD, and ~15% of patients experience unremitting MDD[2]

1. Kupfer DJ. *J Clin Psychiatry*. 1991;52 (suppl): 28-34.
2. Eaton WW, et al. *Arch Gen Psychiatry*. 2008;65:513-520.

Patients Comment About Their Long Journeys With Depression*

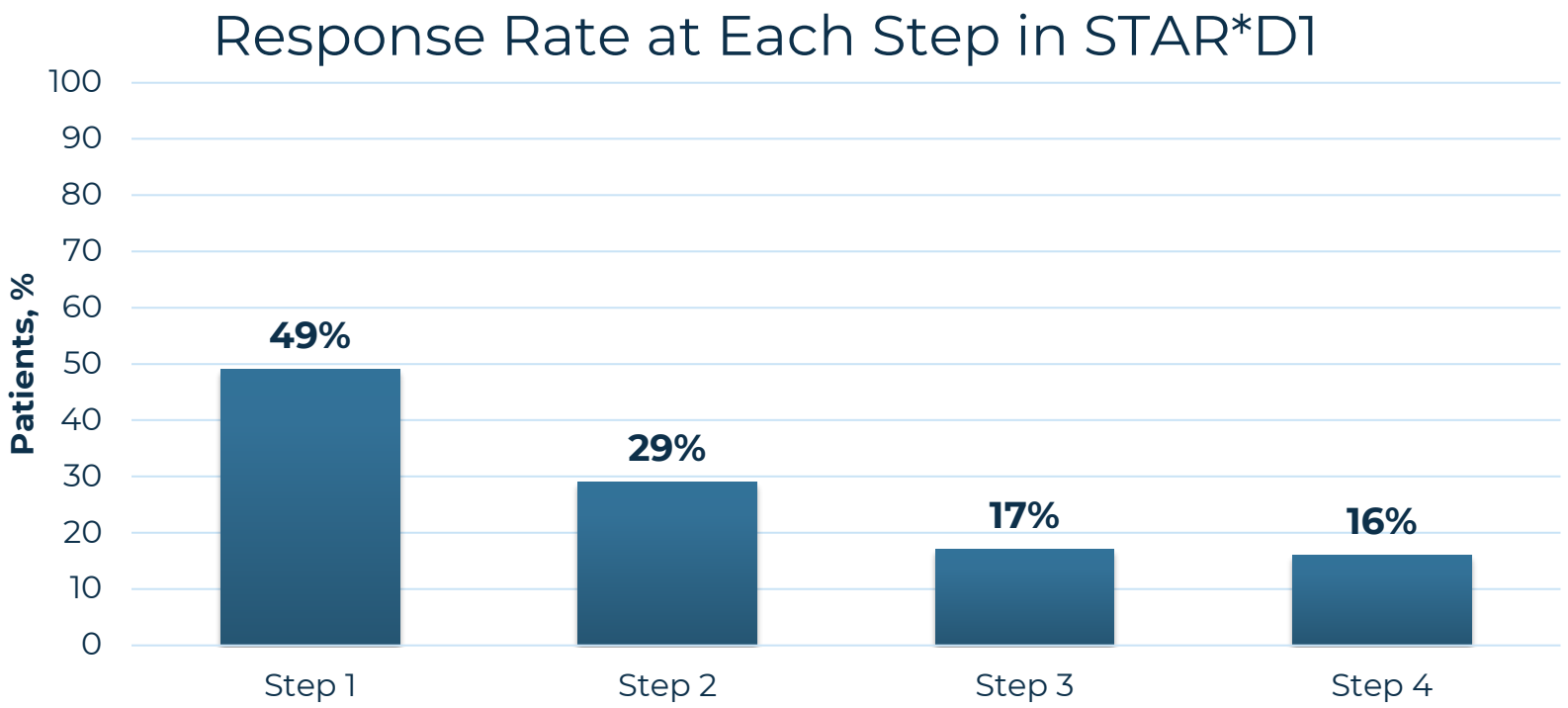
"I did go on medication then and was on it for about 6 months and then went off it…I think that was why I stopped because it wasn't helping…But I was going to a different doctor then—one of those who rush you in and rush you out and this pill is going to cure everything. And it didn't."

– Anna F, a depressed patient with inadequate treatment response

*Pictures and names are fictitious and used for illustrative purposes only.

1. Keeley RD, et al. *BMC Fam Pract.* 2014;15:13.

Less Than Half of Patients With MDD May Respond to Initial Therapy



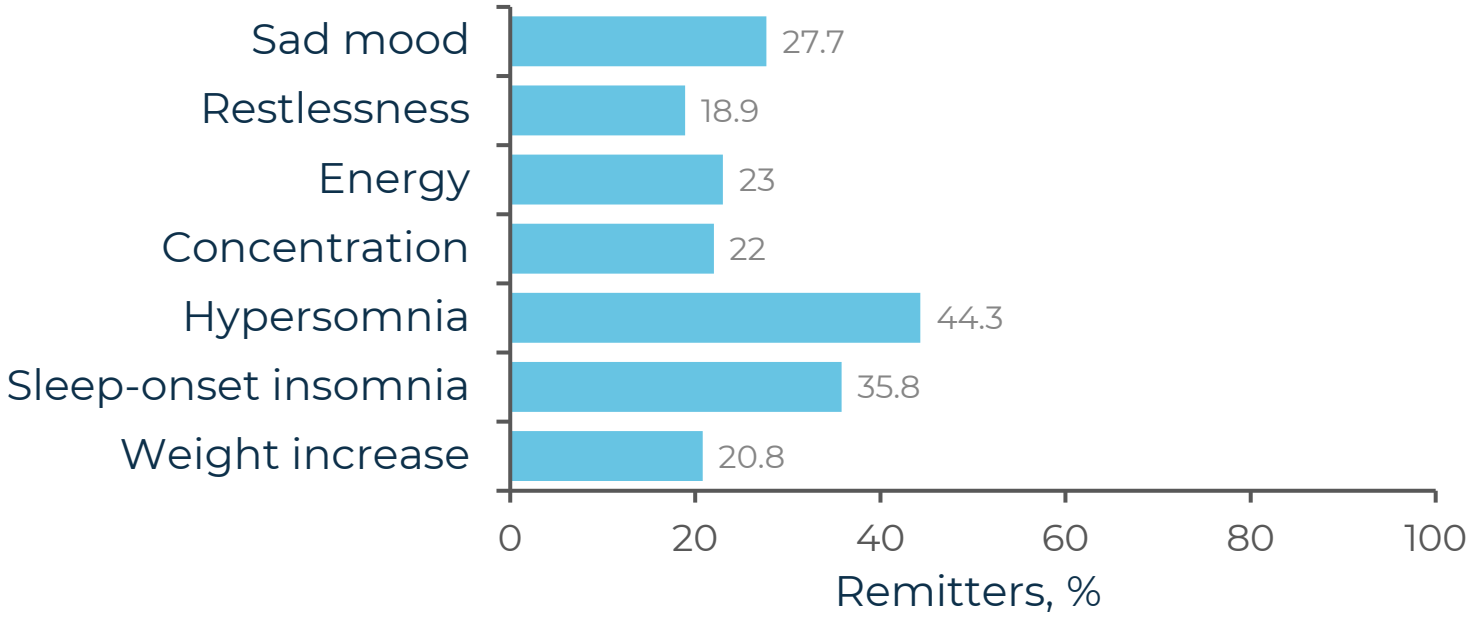
Coping skills may need to be assessed in patients who fail to respond to adequate doses of multiple classes of antidepressant therapy[2]

STAR*D=Sequenced Treatment Alternatives to Relieve Depression

1. Rush AJ, et al. *Am J Psychiatry*. 2006;163:1905-1917.
2. Keitner GI, et al. *Psychiatr Clin North Am*. 2012;35:249-265.

Persistent Symptoms[a] in MDD Remitters are Common and Negatively Affect Outcomes

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



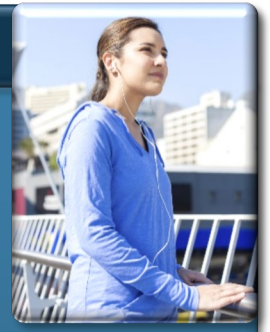
- Residual symptoms increase the risk for suicide and relapse[1]
- Residual symptoms have an adverse impact on psychosocial and occupational functioning[2, 3]

[a]Persistent symptoms defined as QIDS-SR_{16} item score ≥1.

1. Nierenberg AA, et al. *Psychol Med*. 2010;40:41-50.
2. Blier P. *J Clin Psychiatry*. 2013;74(Suppl 2):19-24.
3. Romera I, et al. *BMC Psychiatry*. 2013;13:51.

Potentially Significant Unresolved Symptoms May Persist in Patients Who Meet Treatment Response Criteria*

Case 1: Anna F



- Feelings of guilt over past errors (2 points)
- Moderate somatic anxiety (2 points)
- Hypochondriasis: self-absorbed with body (1 point)
- Slight psychomotor retardation (1 point)

Case 2: Sheila M

- Psychological anxiety: apprehensive attitude apparent in face or speech (3 points)
- Agitation: hand wringing, nail biting, biting of lips (2 points)
- Nightly difficulty falling asleep (2 points)

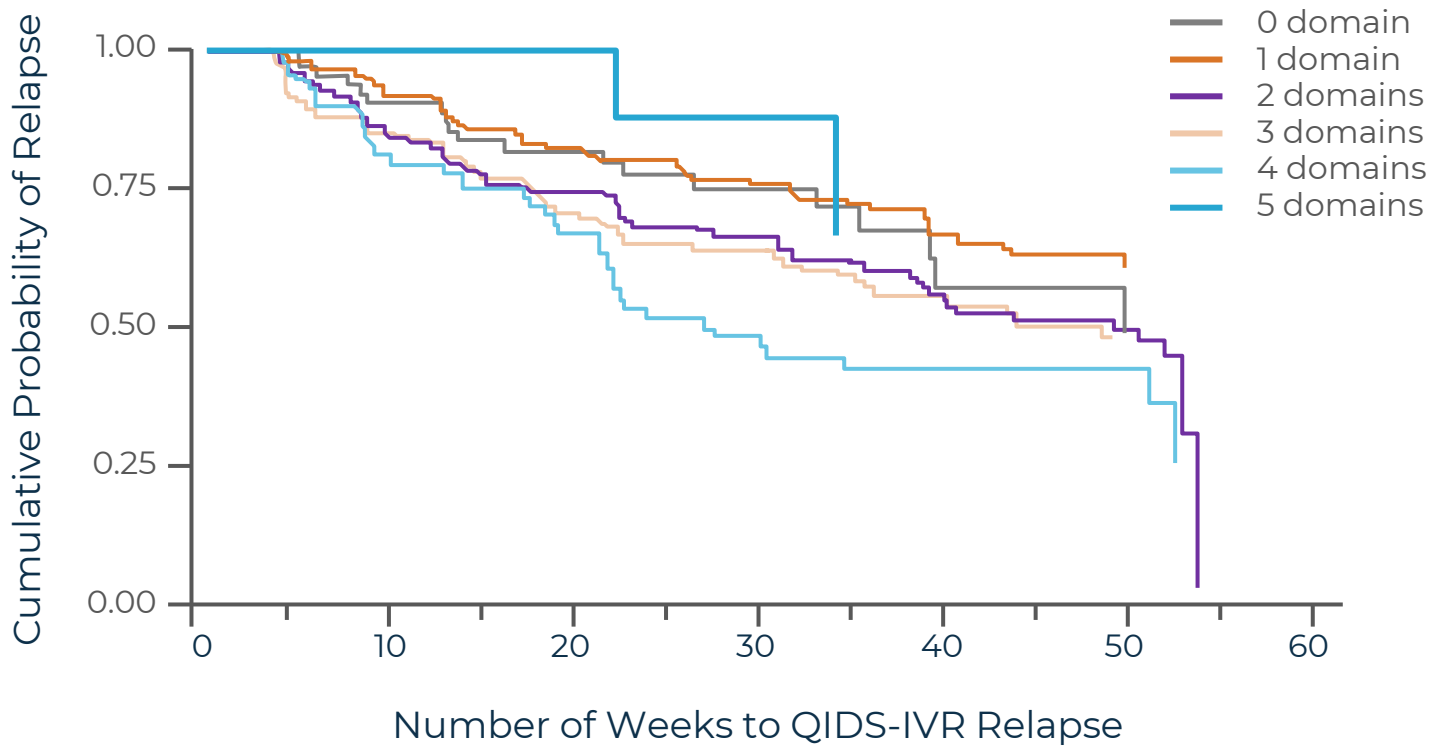
- Based on results of a large, naturalistic study, a reduction of approximately 50% on HAM-D, MADRS, or BDI is considered the gold standard for defining treatment response criteria[a]

*Pictures and names are fictitious and used for illustrative purposes only.
[a]Corresponding to a Clinical Global Impression Severity rating of 1 (normal).
BDI=Beck Depression Inventory; HAM-D=Hamilton Depression Rating Scale; MADRS=Montgomery-Åsberg Depression Rating Scale

1. Riedel M, et al. *J Psychiatr Res*. 2010;44:1063-1068.

Persistent Symptoms Increase The Risk of Relapse in MDD Remitters

An increasing number of residual symptom domains leads to an increased risk of relapse (x2 [5]=17.7155, *P*=0.0033)



Symptom domains:

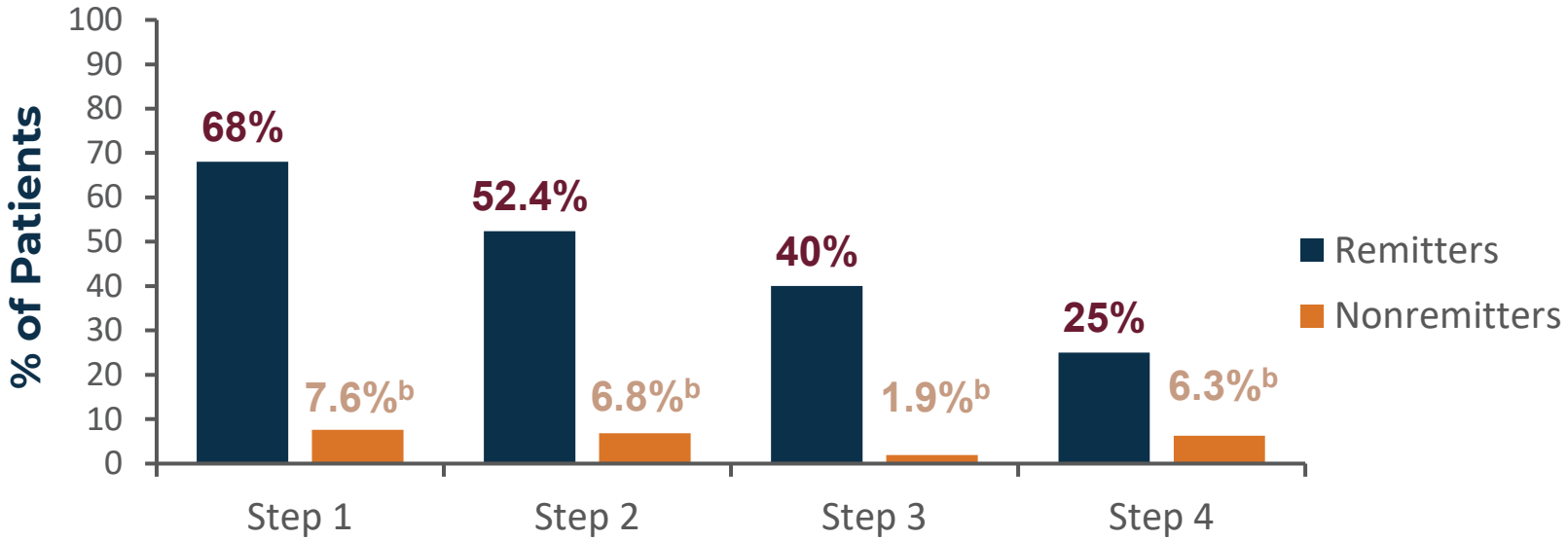
- Sleep disturbance
- Sad mood
- Appetite/weight
- Concentration
- Outlook
- Suicidal ideation
- Involvement
- Energy/fatigue
- Psychomotor

QIDS-IVR=Quick Inventory of Depressive Symptomatology, Self Report—Interactive Voice Response

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

QoL And Functioning Are Reduced For MDD Patients Even With Multiple Steps of MDD Therapy

Remitters and Nonremitters Within Normal QoL During Step Therapy for Depression (Q-LES-Q[a])[1]



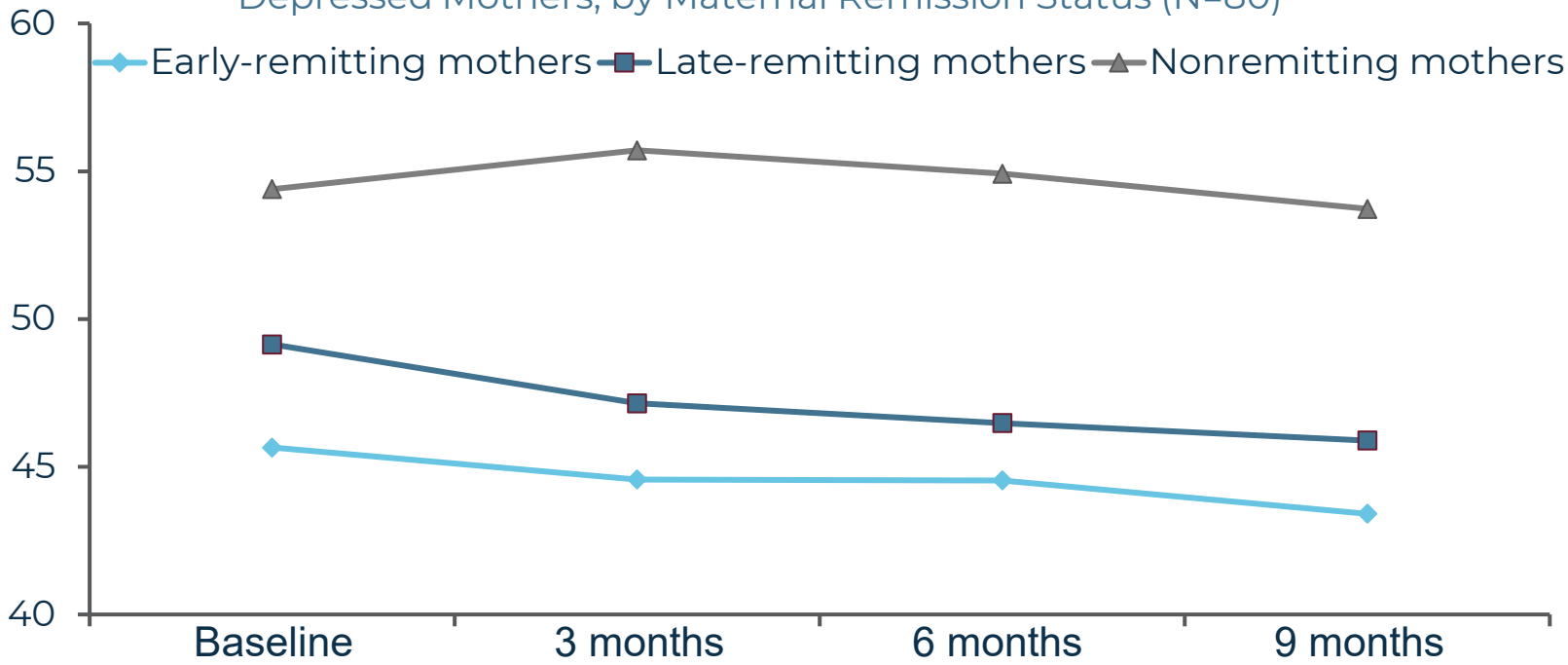
- Nonremitters show more pronounced impairment in functioning than do remitters following treatment[2]

[a]As measured by Q-LES-Q short version; "normal" defined as Q-LES-Q within 10% of community norms (≥70.47).
[b]*P*<0.001 vs remitters.
Q-LES-Q=Quality of Life, Enjoyment, and Satisfaction Questionnaire

1. IsHak WW, et al. *Acta Psychiatr Scand*. 2015;131:51-60.
2. IsHak WW, et al. *Dialogues Clin Neurosci*. 2014;16:171-183.

Remission Status Of MDD Patients Has Significant Effects on Family Members

Decrease in Problem Behaviors and Symptoms for Children of Depressed Mothers, by Maternal Remission Status (N=80)[a]



Children of early- and late-remitting mothers significantly improved compared with those of nonremitting mothers (early vs nonremitting: *P*=0.005; late vs nonremitting: *P*=0.002)[b]

[a]Only data for the 9 months following remission is shown, due to high dropout rate among non-remitters prior to month 12.
[b]Child Behavior Checklist was used; higher scores = greater number or severity of symptoms.

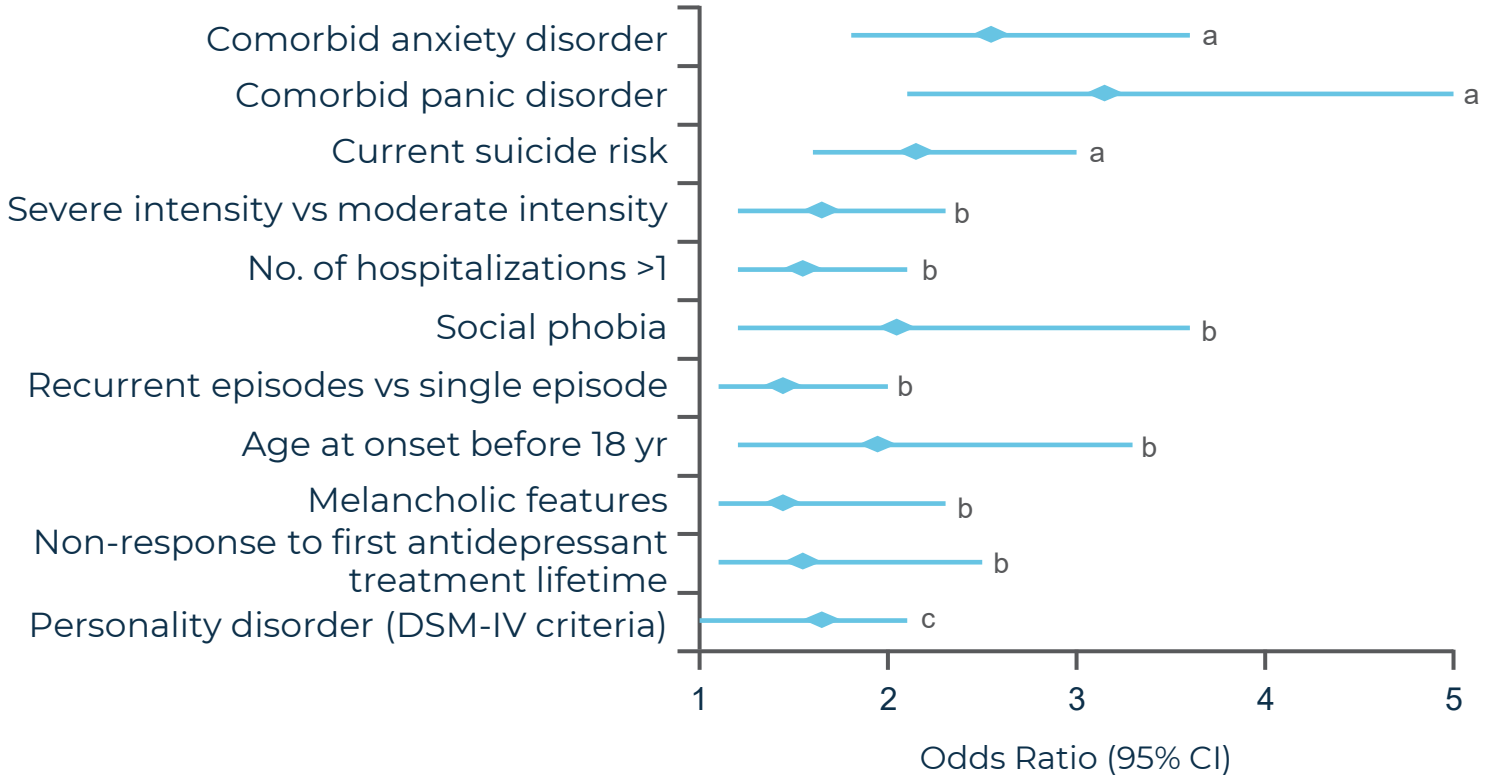
1. Wickramaratne P, et al. *Am J Psychiatry*. 2011;168:593-602.

Predictors of Inadequate Response in MDD, Including The DSM-5 Specifier For Anxious Distress[1-2]

1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Arlington, VA: American Psychiatric Publishing; 2013.
2. Souery E, et al. *J Clin Psychiatry*. 2007;68:1062-1070.

Variables Associated With Inadequate Treatment Response In MDD

Factors Associated With Treatment Resistance (Initial Univariable Logistic Regression Using Nonresistance/Resistance as the Dependent Variable) N=702

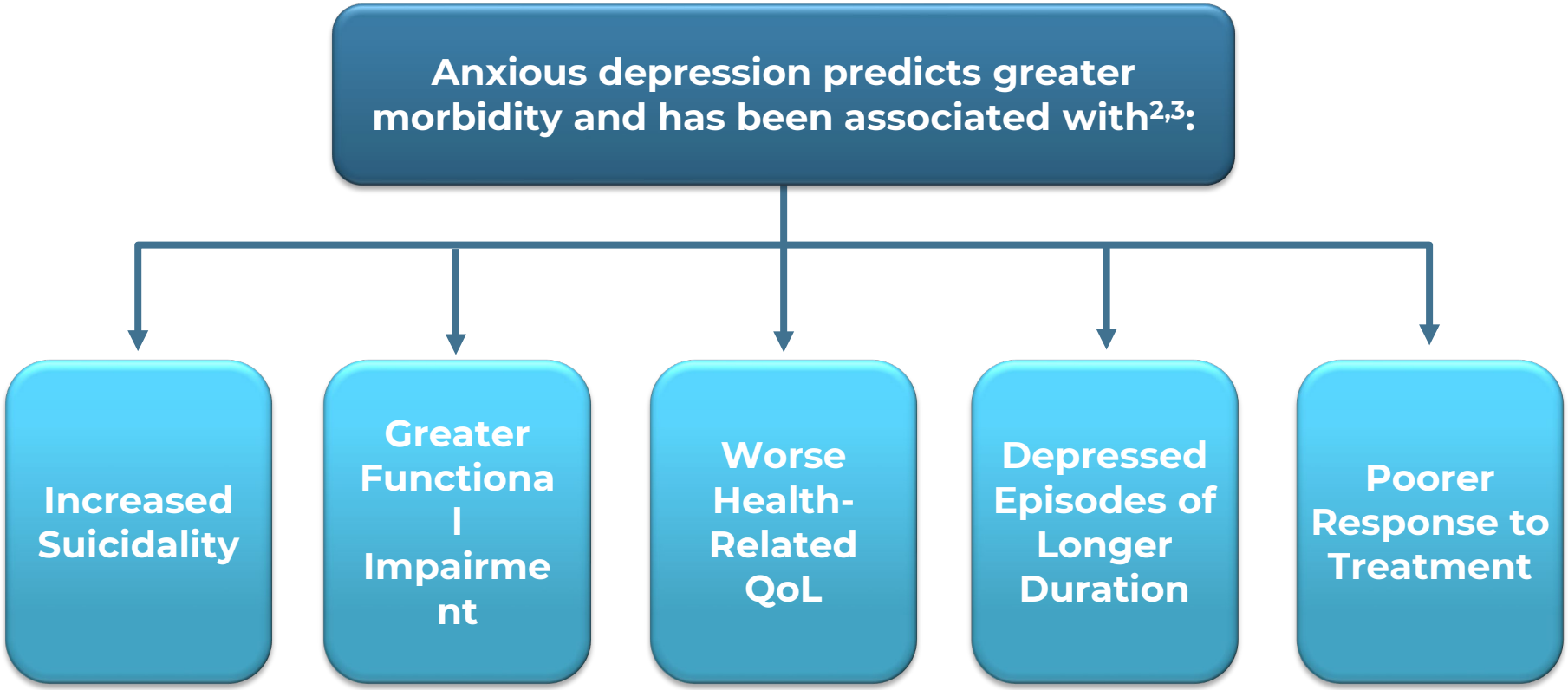


[a]*P*<0.001; [b]*P*<0.01; [c]*P*<0.05.

CI=confidence interval; DSM-IV=

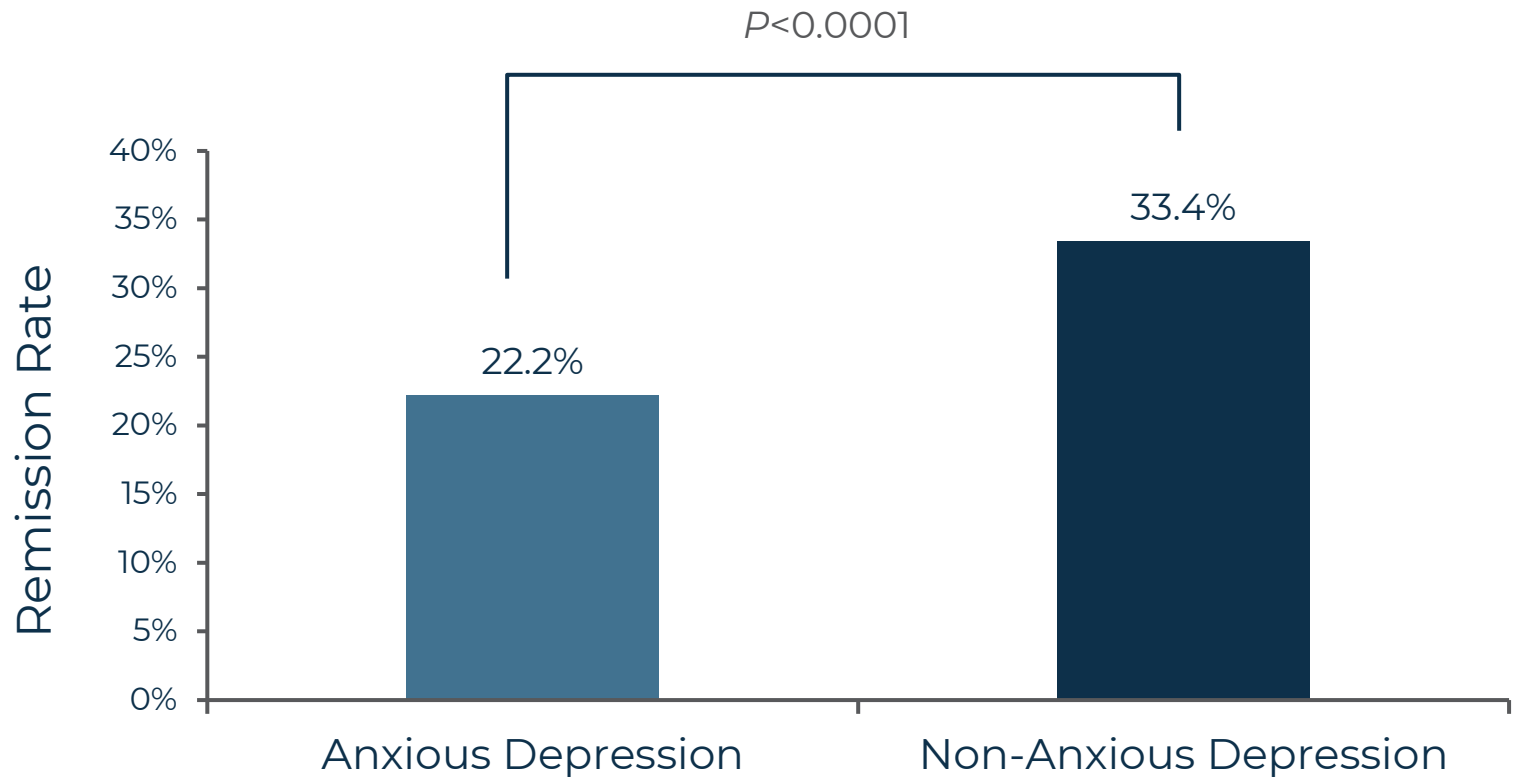
1. Souery E, et al. *J Clin Psychiatry*. 2007;68:1062-1070.

At Least Half Of Patients With Depression Can Have Symptoms of Anxious Depression, Which May Worsen Their Prognosis[1,2]



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.

Remission Rates are Significantly Lower in Patients With Anxious Depression Following The First Antidepressant Treatment[a]

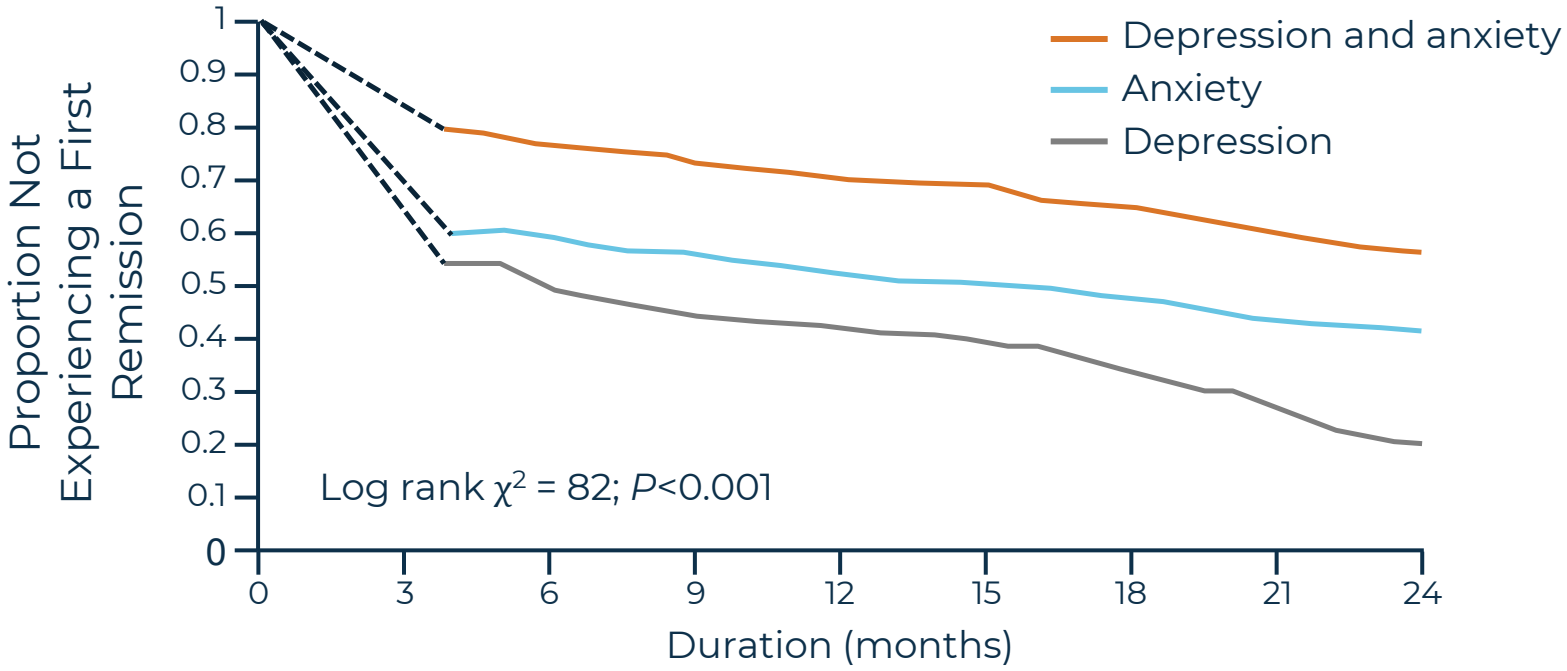


N=2876

[a]Remission was defined as a score ≤7 on the HAM-D17.

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

Time to First Remission Found to Be Longer in Patients With Co-occurring Depression And Anxiety[a]

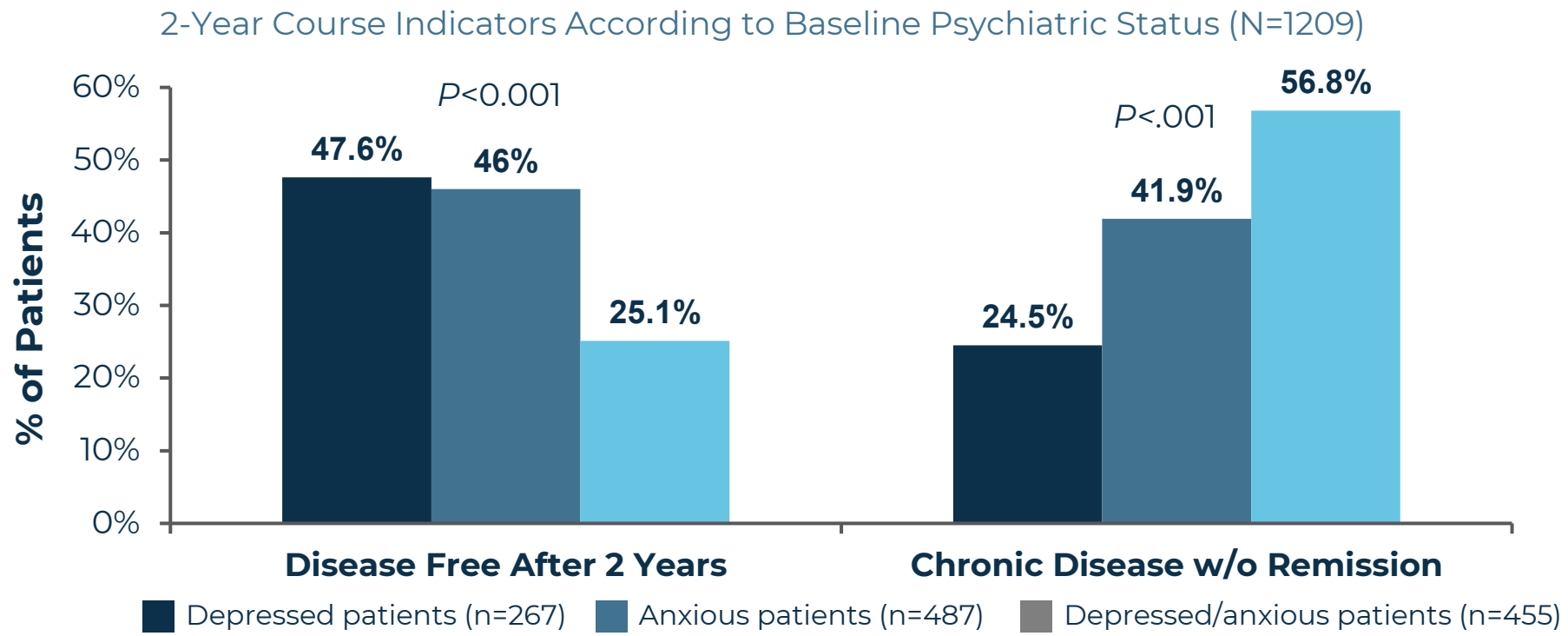


- Median time to remission in the depression group was 6 months for depression versus 12 months for comorbid depression and anxiety
- Median time to remission in the anxiety group was 16 months for anxiety and 24 months for comorbid depression and anxiety

[a]Survival 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.

Anxiety in Depressive Patients Results in Worse Outcomes

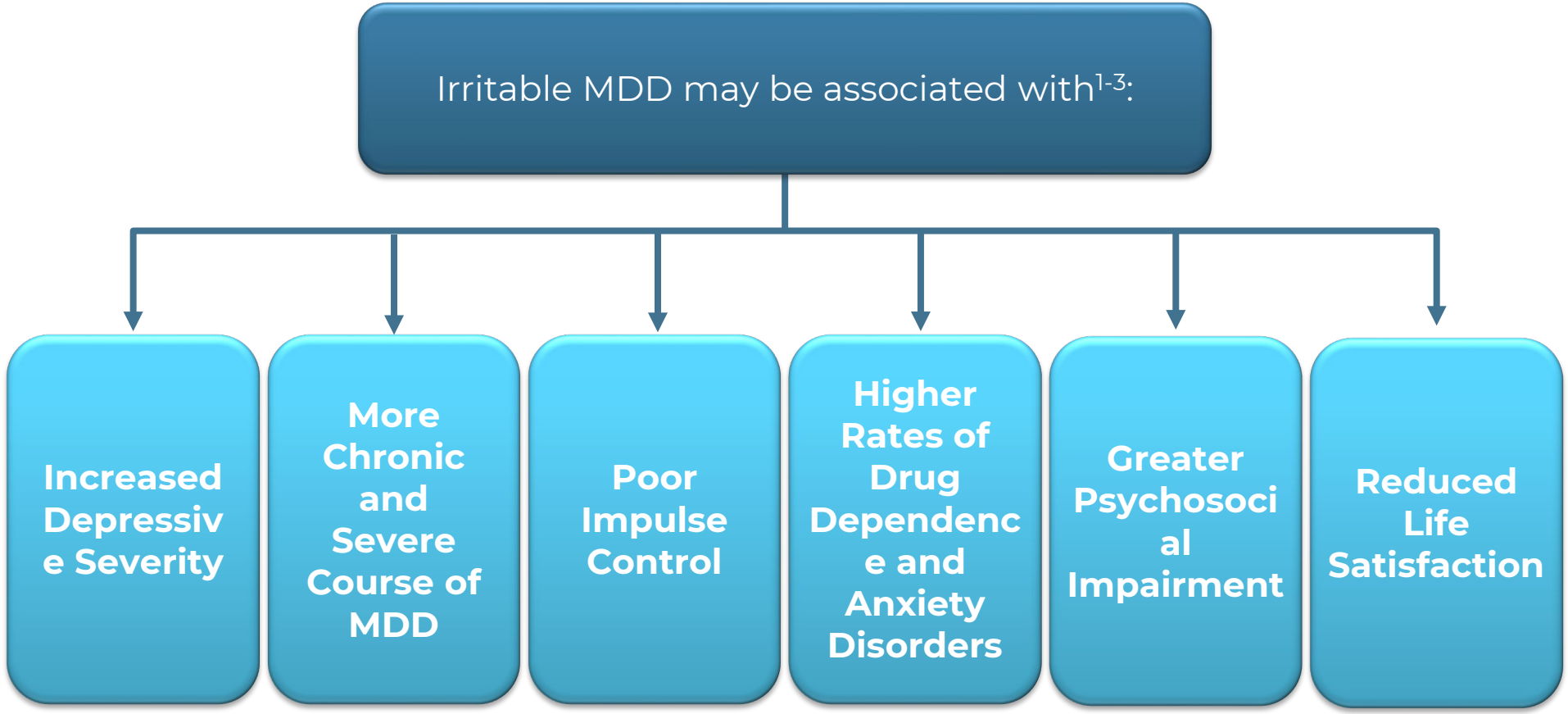


- After 2 years, only 25.1% of patients with comorbid depression/anxiety were disease free, compared with 47.6% and 46%, respectively, of patients with depression only and anxiety only (*P*<0.001)
- 56.8% of depressed and anxious patients never achieved remission, whereas 24.5% of depressed patients and 41.9% of anxious patients never achieved remission

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.

Irritability Negatively Impacts the Course Of MDD in About Half of Patients[1-3]



MDD=major depressive disorder

1. Fava M, et al. *Mol Psychiatry*. 2010;15:856-867.
2. Judd LL, et al. *JAMA Psychiatry*. 2013;70:1171-1180.
3. Perlis RH, et al. *Acta Psychiatr Scand*. 2009;119(4):282-289.

MDD Patients With Irritability Are at Increased Risk For Earlier And Longer Disease Course

Onset and Course of Irritable and Non-Irritable DSM-IV/CIDI MDD

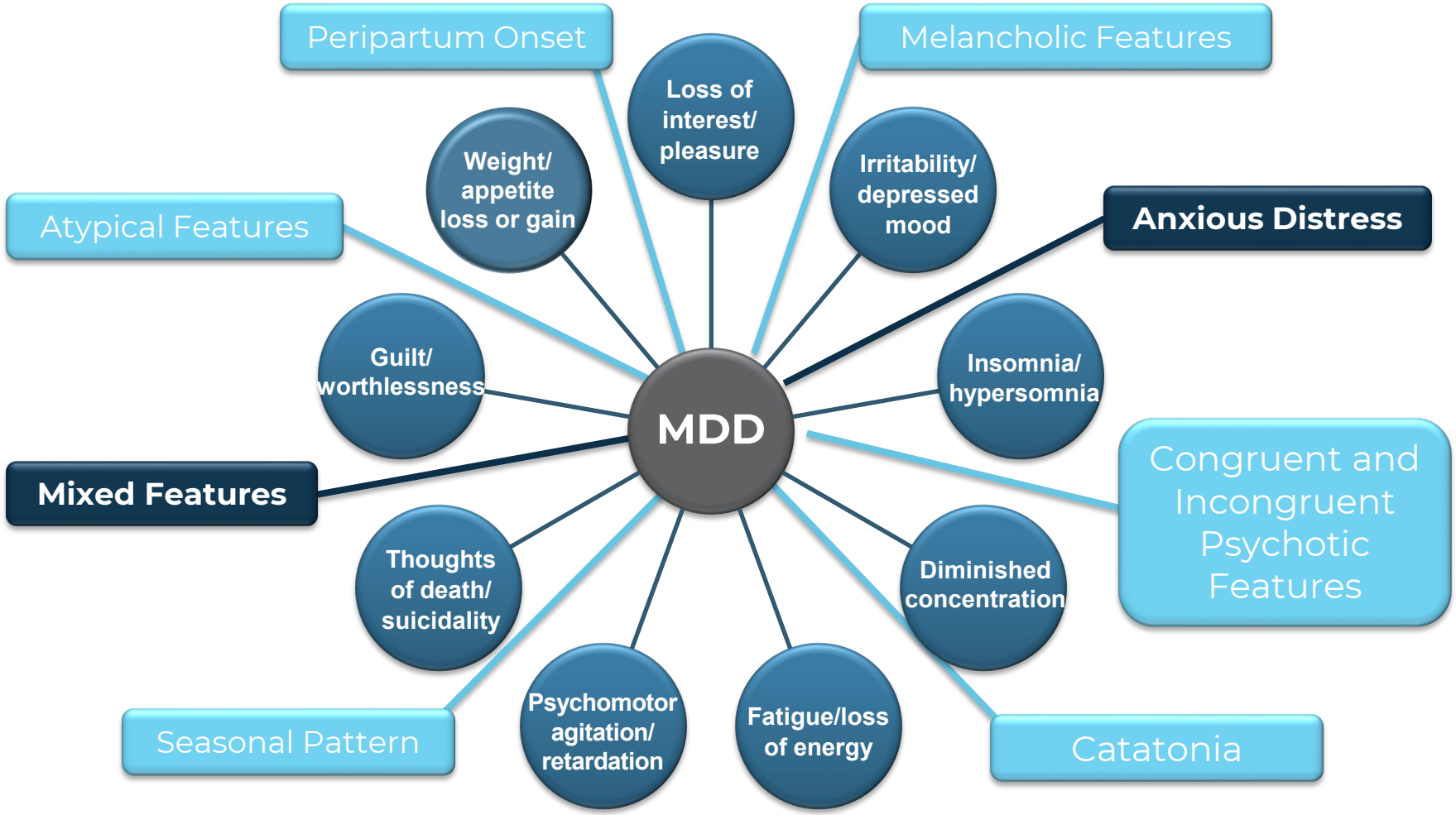
	Irritable		Non-irritable MDE		
	Est	(SE)	Est	(SE)	F/χ^2
Mean age of onset	26.7[a]	(0.7)	31.3	(0.9)	13.7[a,b]
Mean years in episode	5.7	(0.5)	5.1	(0.9)	0.1[b]
12-month: lifetime	40.3[a]	(2.7)	28.8	(1.6)	9.0[a,c]
Prevalence (n)[d]	(497)		(480)		

- In this study, irritable patients tended to have an earlier onset of disease, a longer course of disease, and a higher 12-month lifetime prevalence of MDD

[a]Significant difference between irritable and non-irritable cases at the 0.05 level, 2-sided test.
[b]F-test with 1 and 953 degrees of freedom.
[c]χ2-test with 1 degree of freedom.
[d]The reported sample sizes are unweighted and assessed in the part 1 sample.
CIDI=Composite International Diagnostic Interview; Est=estimated; SE=standard error; MDD=major depressive disorder

1. Fava M, et al. *Mol Psychiatry*. 2010;15:856-867.

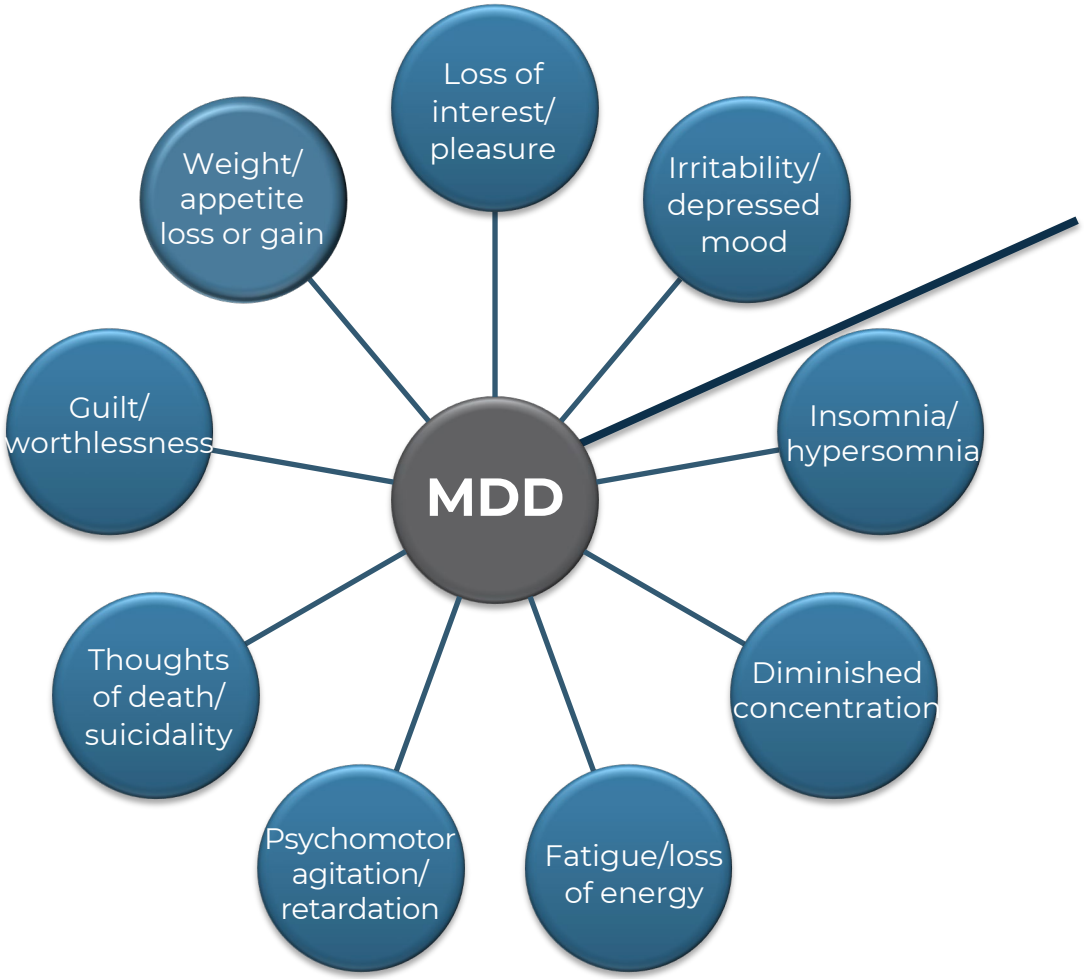
The *DSM-5* Delineated 2 New Specifiers in MDD: Anxious Distress and Mixed Features



MDD=major depressive disorder; DSM-5=diagnostic and statistical manual 5th edition

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

Inclusion Of The Anxious Distress Specifier Highlights Its Clinical Implications



Anxious distress specifier:

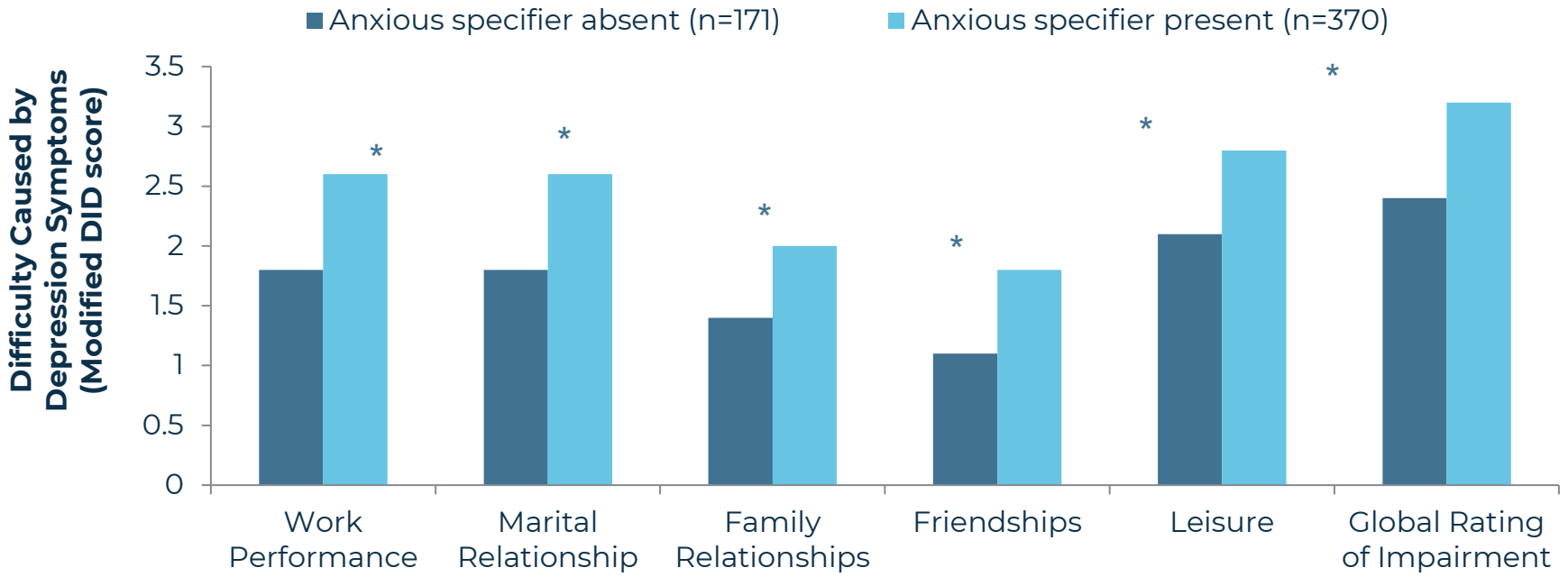
- Feeling keyed up or tense
- Feeling unusually restless
- Difficulty concentrating because of worry
- Fear that something awful may happen
- Feeling that the individual might lose control of himself or herself

MDD=major depressive disorder

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

Anxious Distress Decreases Functioning In Patients With MDD

Patient-reported Psychosocial Function Impairment Based on *DSM-5* Anxious Distress Specifier



- Patients who met the anxious distress specifier had greater impairment of QoL and greater functional impairment compared with those who did not

*P<0.001.

CUDOS-A=Clinically Useful Depression Outcome Scale–Anxious Distress Specifier Subscale; DID=Diagnostic Inventory for Depression; MDD=major depressive disorder; QoL=quality of life

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

Proactive Treatment

Brain Structure And Function of Patients With Full Remission VS Controls

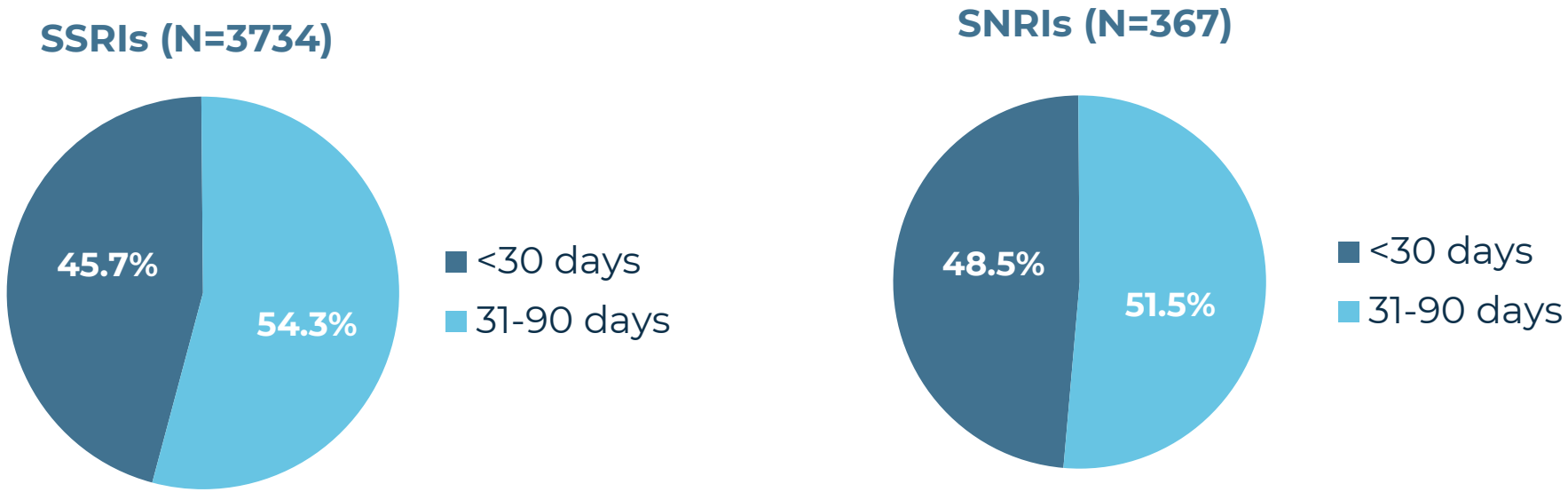
- Structural changes: In a voxel-based morphometry and MRI study, patients who met *DSM-IV* criteria for recurrent MDD in full remission (n=27) had gray matter volume similar to healthy controls (n=107)[1]
- Compared to currently depressed patients (n=58), remittent MDD patients showed increased gray matter in the superior, middle, and inferior frontal gyri on the left side, the left insula, the precuneus bilaterally, the right inferior and superior parietal lobule, the right superior temporal gyrus, and the pregenual and left subgenual anterior cingulate cortex[1]

Functional changes: In a separate meta-analysis of 3 PET studies involving 119 MDD patients and 42 healthy controls, differences in circuit connectivity between antidepressant responders and nonresponders were seen in pathways involving the dorsal lateral prefrontal cortex, orbital frontal cortex, hippocampus, anterior thalamus, and the anterior and subgenual cingulate cortexes[2]

PET=positron emission tomography

1. Salvadore G, et al. *Neuroimage*. 2011;54:2643-2651.
2. Seminowicz DA, et al. *Neuroimage*. 2004;22:409-418

Many Non-Responders Remain On Ineffective Therapy For Longer Than Recommended

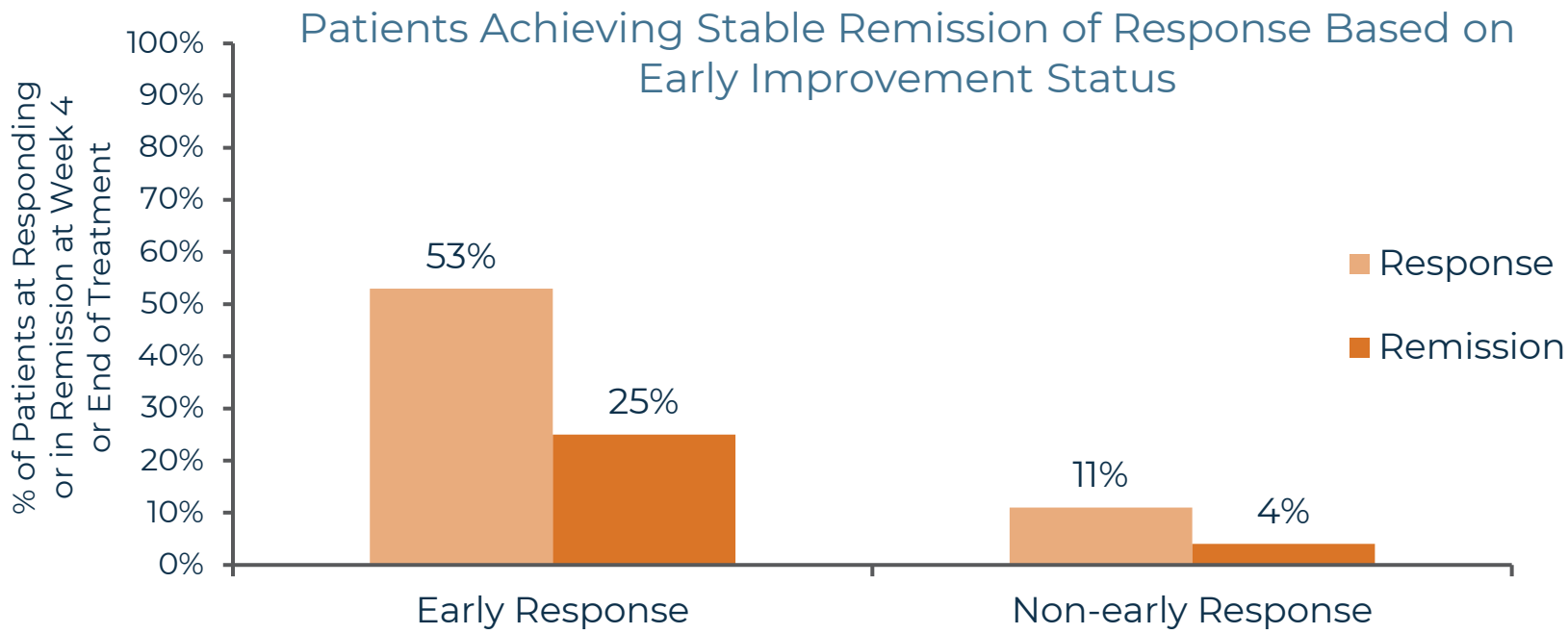


- Study of US patients treated for a depressive disorder (N=56,521), in which 8.6% (n=4844) switched their antidepressant during the first 90 days of therapy[1]
  - 2.4% (n=1333) added an adjunctive antipsychotic
- Prolonging the time to effective antidepressant therapy may have a negative effect on the doctor-patient relationship[2]

SNRIs=Serotonin and Norepinephrine Reuptake Inhibitors; SSRIs=Selective Serotonin Reuptake Inhibitors.

1. Marcus S, et al. *Psychiatric Services*. 2009;60:617-623.
2. Moller HJ, et al. *Medicographia*. 2010;32:139-144.

Early Patient Response in MDD Could be Predictive of Overall Response



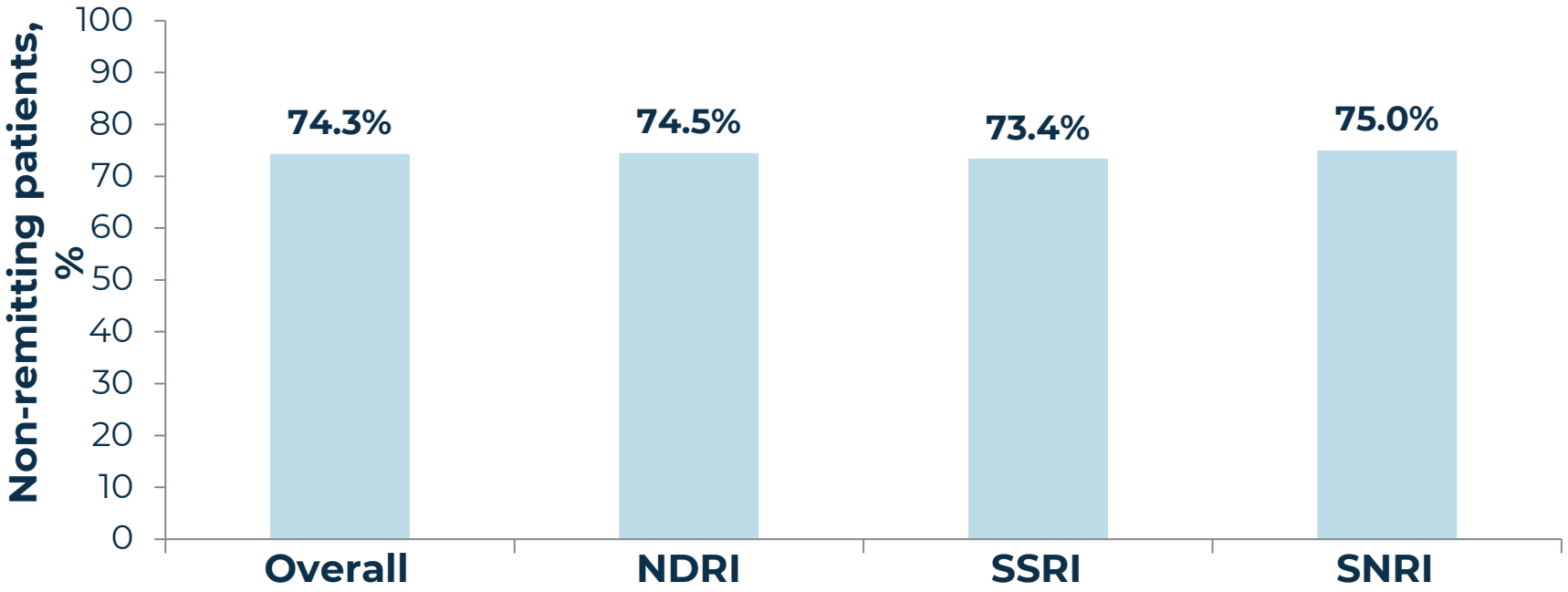
- Early response: patients having a reduction in HAM-D_{17} score of ≥20% compared with baseline within the first 2 weeks of treatment
- Stable responders: patients having a reduction in HAM-D_{17} score of ≥50% from baseline at 4 weeks of treatment and at all subsequent assessments
- Stable remitters: patients having a reduction in HAM-D_{17} score to ≤7 points at week 4 of treatment and at all subsequent assessments

HAM-D=Hamilton Depression Rating Scale

1. Szegedi A, et al. *J Clin Psychiatry*. 2009;70:344-353.

Switching Antidepressant Therapy May Not Lead to Remission For All MDD Patients

Patients Not Achieving Remission Following Switch From a Primary SSRI



- Nearly 75% of patients with MDD who were switched to a 2nd-line antidepressant did not achieve remission in the STAR*D trial

[a]Remission defined as QIDS-SR16 score ≤5 at exit from the indicated treatment step

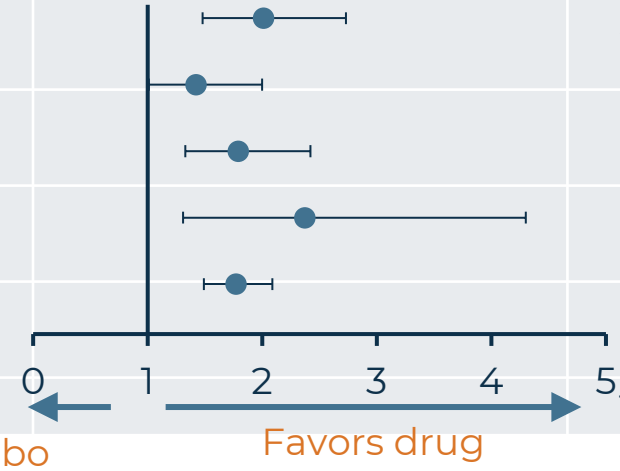
NDRI=Norepinephrine-Dopamine Reuptake Inhibitors; SNRIs=Serotonin and Norepinephrine Reuptake Inhibitors; SSRIs=Selective Serotonin Reuptake Inhibitors.

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

The Use of Adjunctive Atypical Antipsychotics in MDD is Supported By Clinical Evidence[1]

Efficacy of adjunctive treatment with atypical antipsychotics (N=3549)[2,a]

Drug	Treatment n/N	Placebo n/N	Odds Ratio (95% CI)
Atypical Antipsychotic 1	142/540	79/525	2.01 (1.48–2.73)
Atypical Antipsychotic 2/SSRI	135/584	88/537	1.42 (1.01–2.00)
Atypical Antipsychotic 3	231/645	78/332	1.79 (1.33–2.42)
Atypical Antipsychotic 4	48/199	18/164	2.37 (1.31–4.30)
Overall	556/1968	263/1558	1.77 (1.49–2.09)

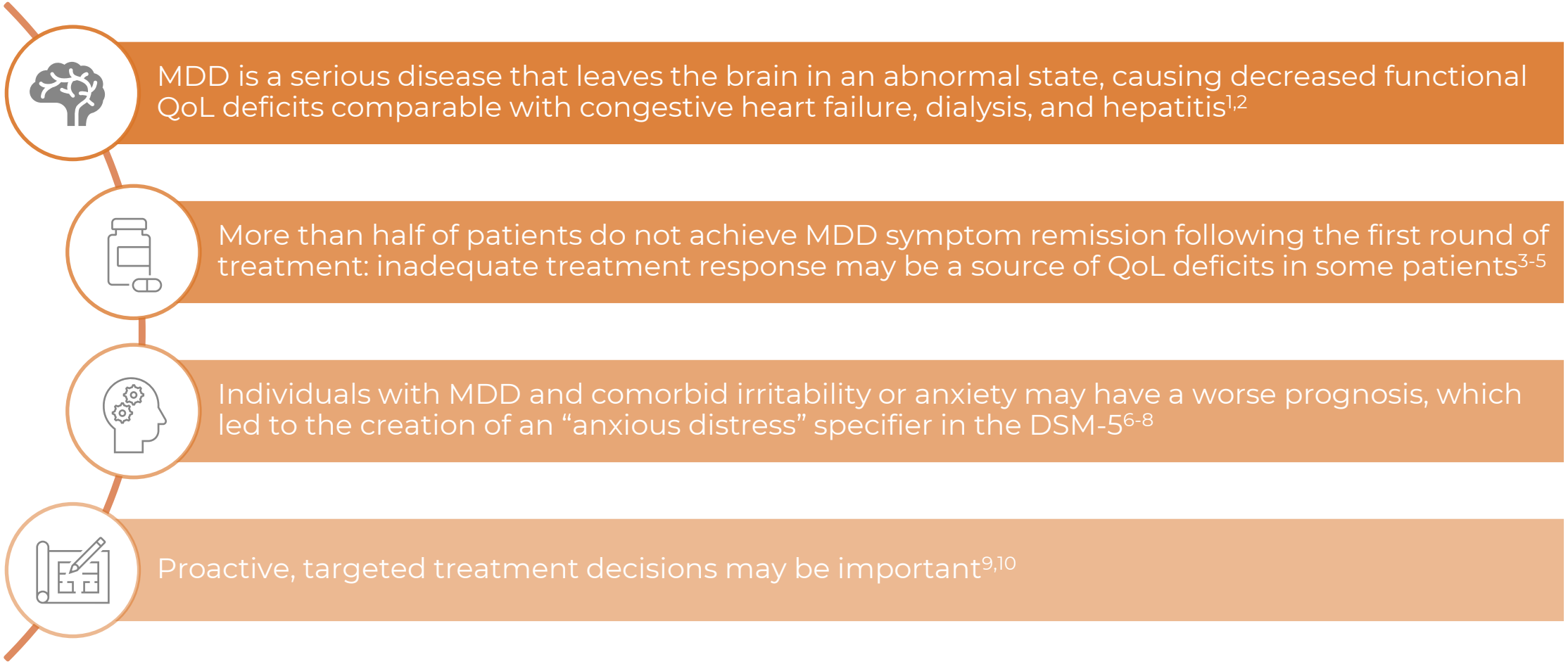


- MDD patients receiving adjunctive antipsychotics were more likely to show efficacy and remission[b] compared to placebo[2]
- However, use of atypical antipsychotics adjunctive therapy in MDD has been associated with akathisia, weight gain, abnormal metabolic lab results, and sedation[2]

[a]Data are from a systematic review of the efficacy and safety profiles of atypical antipsychotic medications used for the adjunctive treatment of depression;
[b]Definition of remission varied across 14 studies.
MDD=major depressive disorder

1. Connolly KR, et al. *Drugs*. 2011;71:43-64.
2. Spielmans GI, et al. *PLoS Med* 2013;10:e1001403.

Conclusions



1. Hamilton JP, et al. *Am J Psychiatry*. 2012;169:693-703.
2. Juenger J, et al. *Heart*. 2002;87:235-241.
3. Rush AJ, et al. *Am J Psychiatry*. 2006;163:1905-1917.
4. IsHak WW, et al. *Acta Psychiatr Scand*. 2015;131:51-60.
5. Keitner GI, et al. *Psychiatr Clin North Am*. 2012;35:249-265.
6. Penninx BW, et al. *J Affect Disord*. 2011;133:76-85.
7. Fava M, et al. *Mol Psychiatry*. 2010;15:856-867.
8. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Arlington, VA: American Psychiatric Publishing; 2013.
9. Szegedi A, et al. *J Clin Psychiatry*. 2009;70:344-353.
10. Phillips JL, et al. *J Clin Psychiatry*. 2012;73:625-631.

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