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Inadequately Treated Major Depressive Disorder (MDD)

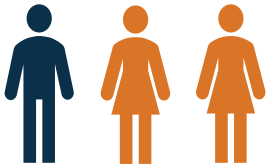
Objectives

- Describe the prevalence of depression in the US
- Highlight the burden of MDD
- Identify inadequately treated MDD and understand how it impacts patients
- Understand which patients are at risk for inadequately treated MDD
- Explain MDD treatment strategies

Prevalence Of Depression

US depression rate by adult age group[2]

	18-25	26-49	50+
Depression Rate	13.1	7.7	4.7



Nearly twice as common in women than in men[1,3]

- Of the adults reporting MDD, 63.8% reported severe impairment, representing 4.5% of adults in the US[2]

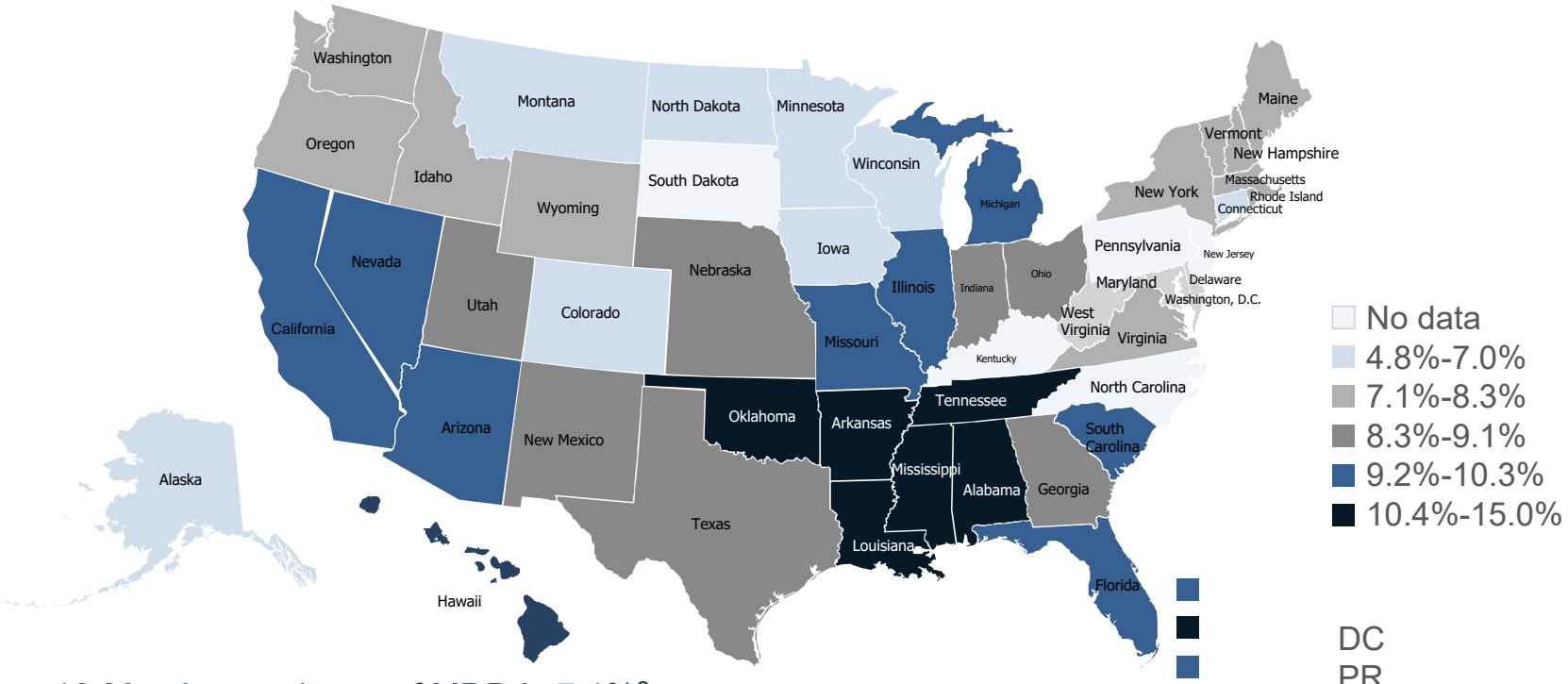
8 years

The projected median time between MDD onset and first contact with a care provider[4]

1. Brody et al 2018 *NCHS Data Brief* No 303
2. https://www.nimh.nih.gov/health/statistics/major-depression.shtml
3. Bogren et al 2018 *Eur Arch Psychiatry Clin Neurosci* 268: 179-189.
4. Wang et al 2005 *Arch Gen Psychiatry* 62: 603-613.

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

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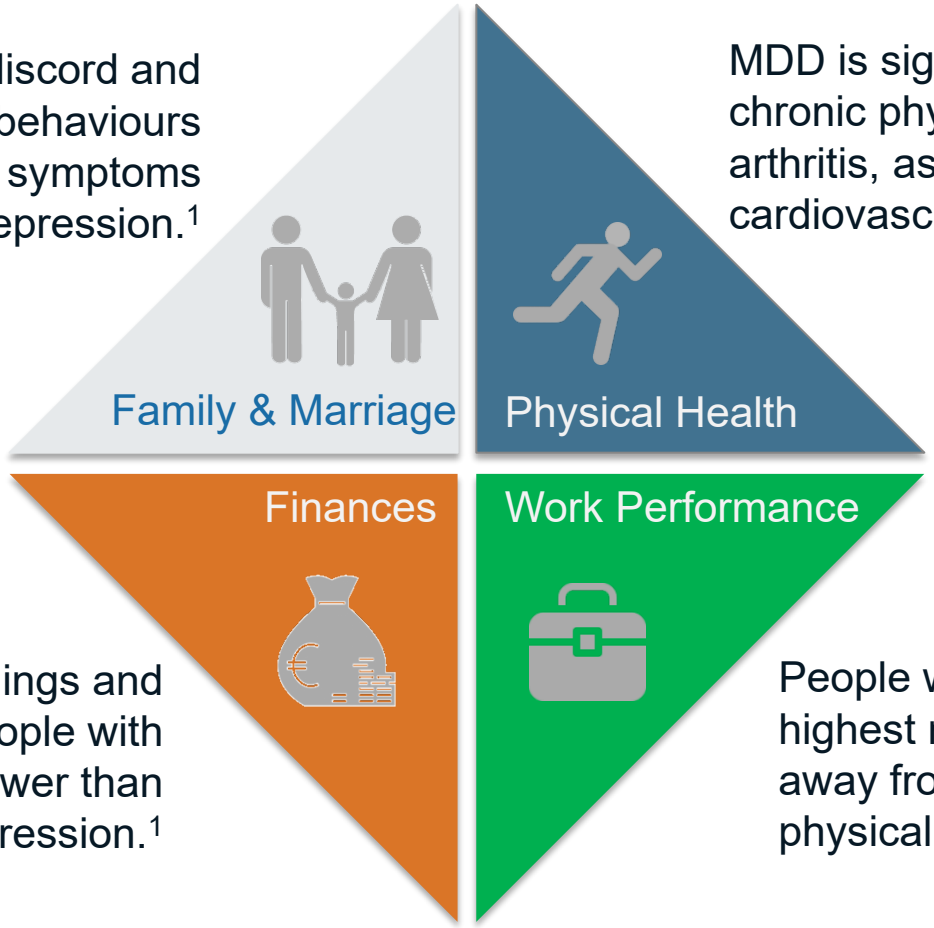
Burden of MDD

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.[1]



MDD is significantly associated with chronic physical disorders including arthritis, asthma, cancer, diabetes, cardiovascular disease and pain.[1]

Personal earnings and household income of people with MDD are substantially lower than those without depression.[1]

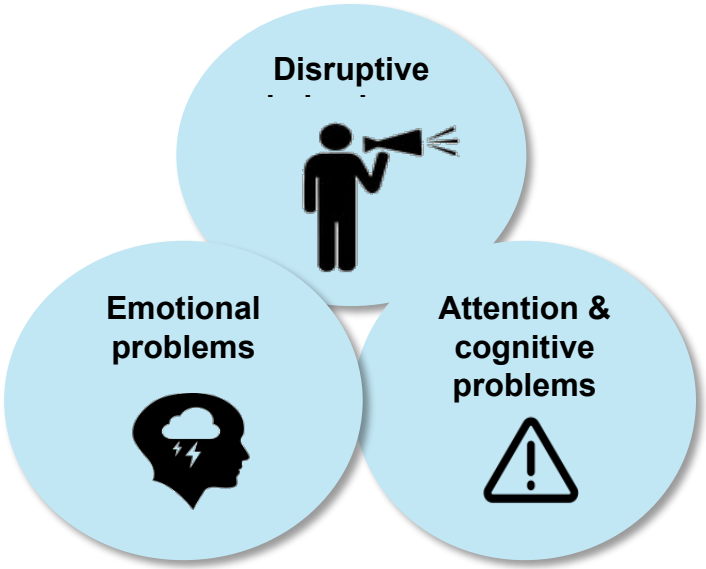
People with MDD have the highest number of days away from work of any physical or mental disorder.[1]

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

Maternal Depression Can Have A Significant Effect On Family

Children of mothers with MDD have increased rates of depression,[1,2] with normal child development disrupted by a lack of warm, consistent and sensitive parenting.[2]

Young children of mothers with depression are at increased risk of:[2]



Improvement in the mothers' depressive symptoms can:[1]

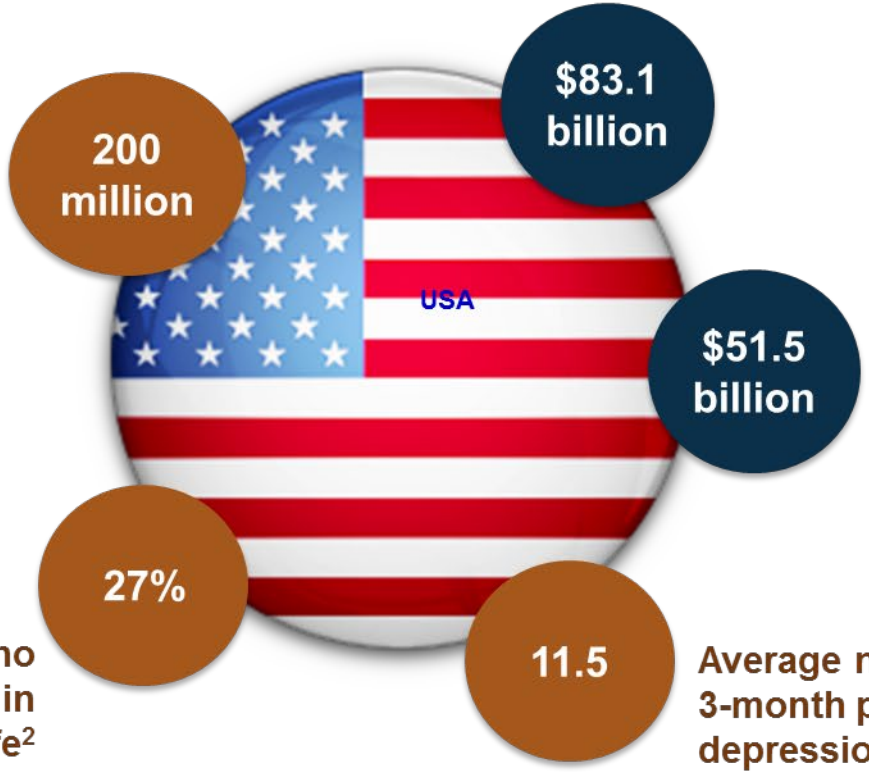
- Improve depressive symptoms and functioning in their children over 12 weeks of treatment
- Improve self-reported parental functioning, including the mothers' ability to talk and listen to their children

The benefits of effectively treating maternal depression could therefore be extended to offspring.[3]

1. Weissman MM et al. *Am J Psychiatry* 2015;1;172(5):450–459;
2. Barker E et al. *BJP* 2012;200:124–129
3. Coiro MJ et al. *Psych Serv* 2012;63:357–363

MDD Has Significant Costs To Society: USA

Estimated number of working days lost each year[2]

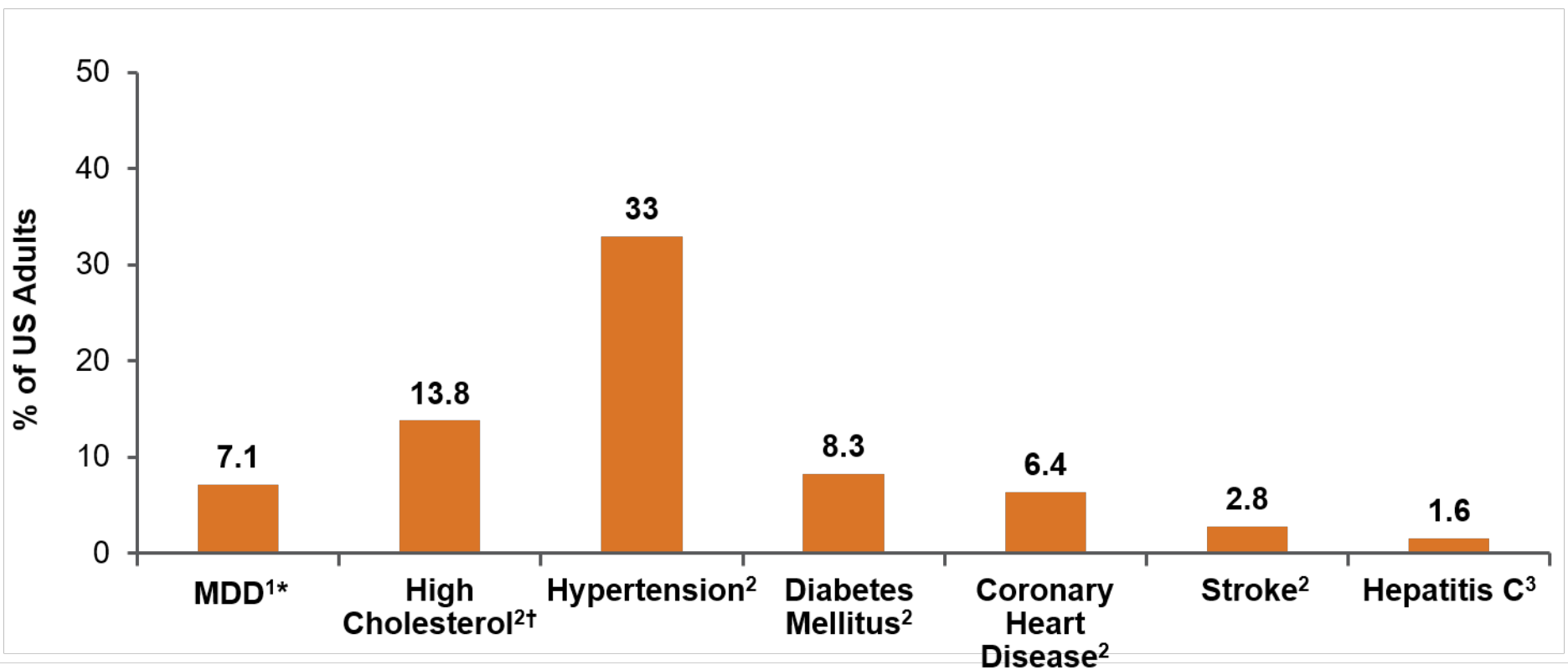


Percentage of patients who reported serious difficulties in work life[2]

Average number of days in a 3-month period that a patient with depression reports reduced productivity at work[2]

1. Greenberg PE et al. *J Clin Psychiatry* 2003;64:1465–1475
2. Centers for Disease Control and Prevention
3. https://www.cdc.gov/workplacehealthpromotion/health-strategies/depression/index.html. Accessed Sep 11 2017

MDD 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

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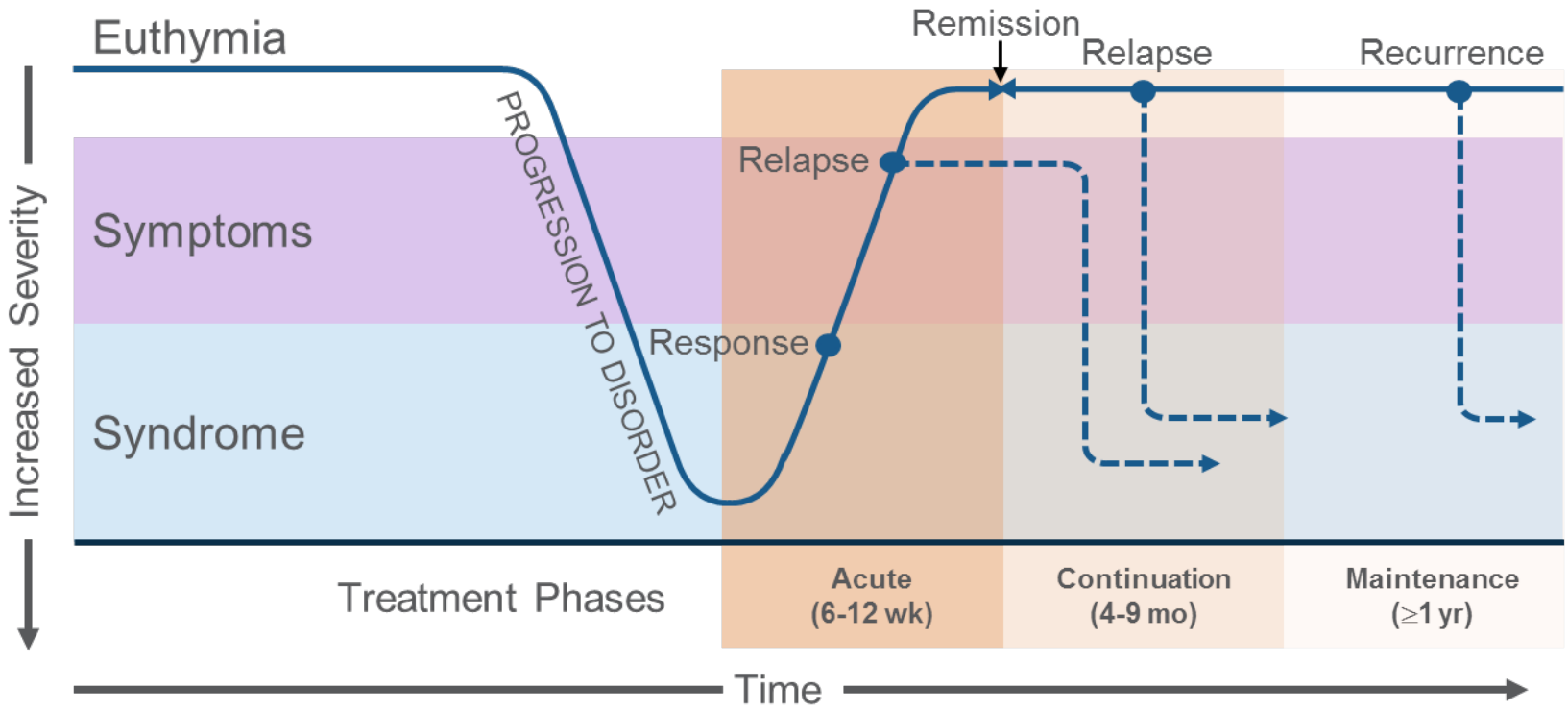
What Is Inadequate Response And How Does It Impact Patients?

MDD Is A Complex, Often Recurrent And Remitting Disorder[1]



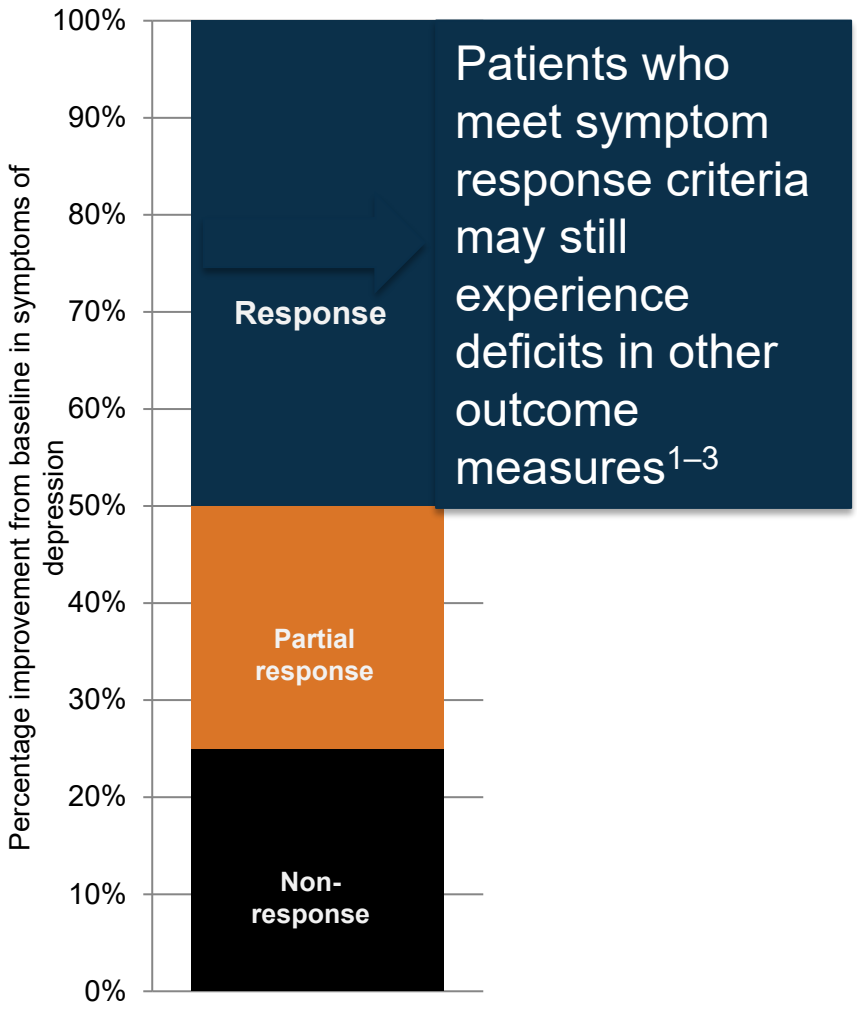
- Following an initial depressive episode, ~50% of patients recover with no further episodes, ~35% of patients suffer from recurrent MDD, and ~15% of patients experience unremitting MDD[3]

1. Nierenberg AA. Am J Manag Care. 2001;7(11 suppl):S353-S366
2. Kupfer DJ. J Clin Psychiatry. 1991;52 (suppl): 28-34
3. Eaton WW, et al. Arch Gen Psychiatry. 2008;65:513-520

Symptomatic Improvement Is Not Always Adequate[1–3]

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

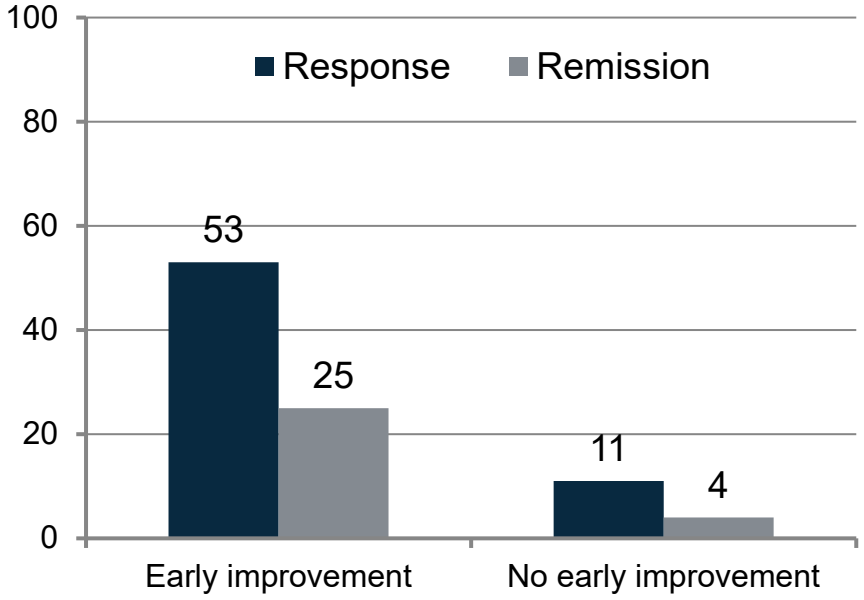
The optimal outcome for a patient with MDD is full symptom recovery with associated improvements in functioning and quality of life.[3]



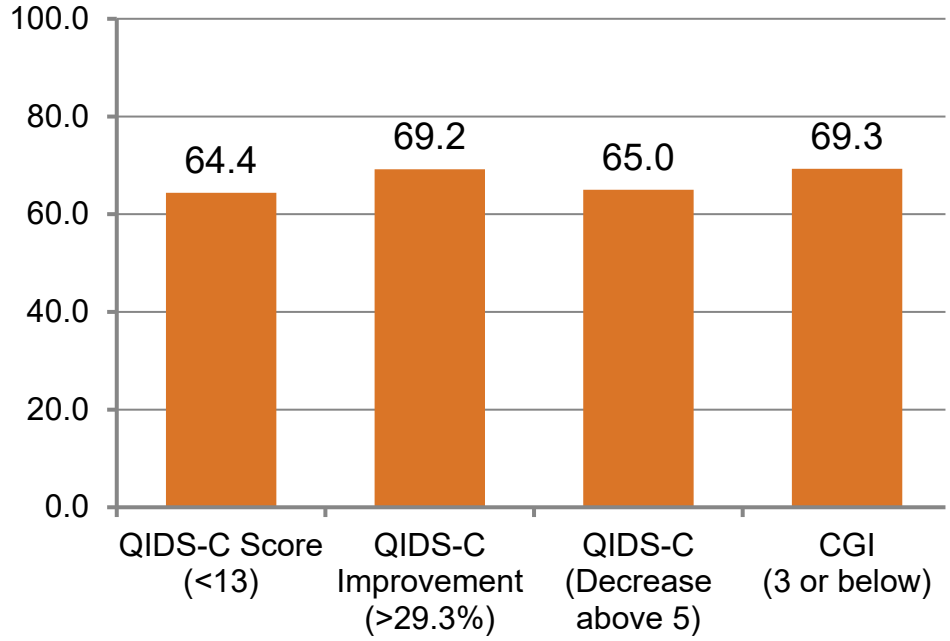
1. Nierenberg AA, DeCecco LM. *J Clin Psychiatry* 2001;62(suppl 16):5–9
2. Angst J et al. *Acta Psychiatr Scand* 1996;93(6):413–419
3. Saltiel PF & Silvershein DI. *Depress Anxiety* 2012;29(7):638–645

Absence Of Early Improvement Is Predictive Of A Failure To Achieve Response Or Remission

Patients who did not achieve a 20% improvement from baseline in HAM-D score within the first 2 weeks of treatment were unlikely to respond or remit at Week 4*[1]



A lack of improvement at 2 weeks consistently predicted a failure to achieve response at 6 weeks, with a negative predictive value of 64–70%†[2]



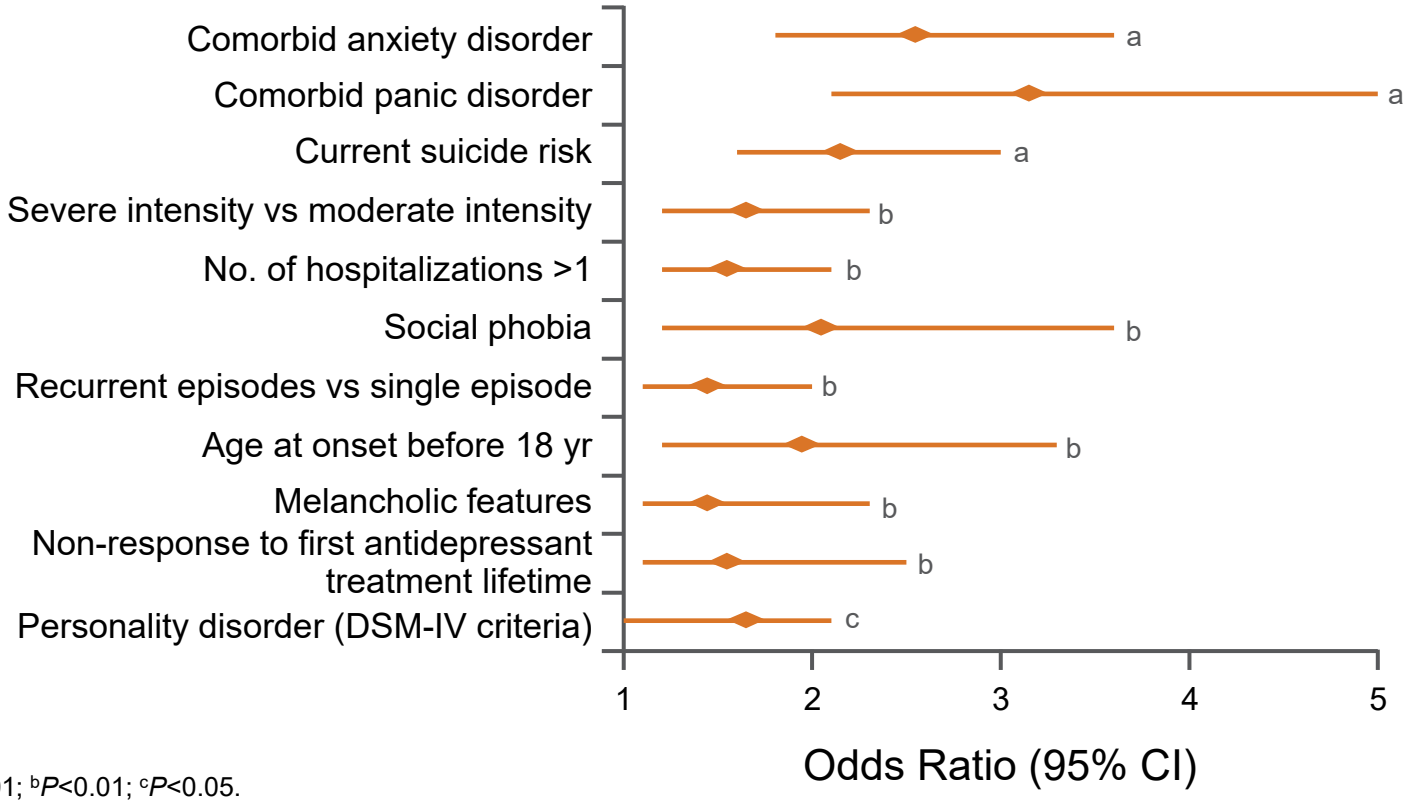
*Early improvers: patients having a reduction in HAM-D score of ≥20% compared with baseline within the first 2 weeks of treatment. Stable responders: patients having a reduction in HAM-D17 score of ≥50% from baseline at 4 weeks of treatment and at all subsequent assessments. Stable remitters: patients having a reduction in HAM-D17 score to ≤7 points at week 4 of treatment and at all subsequent assessments[1]

†Improvement: patients with a reduction of 20% in the severity of symptoms by week 2. Response: patients witha reduction of at least 50% of the initial QIDS-C score at 6 weeks. QIDS: Quick Inventory of Depressive Symptomatology. QIDS-C score: crude results.. QIDS-C Improvement: percentage of improvement. QIDS-C: points decrease. CGI: Clinical Global Impression scale2

1. Szegedi A et al. *J Clin Psychiatry* 2009;70:344–353. 2. Gorwood P et al. Eur Psychiatry 2013 Aug;28:362-71

Variables Associated With Inadequate Treatment Response In MDD

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



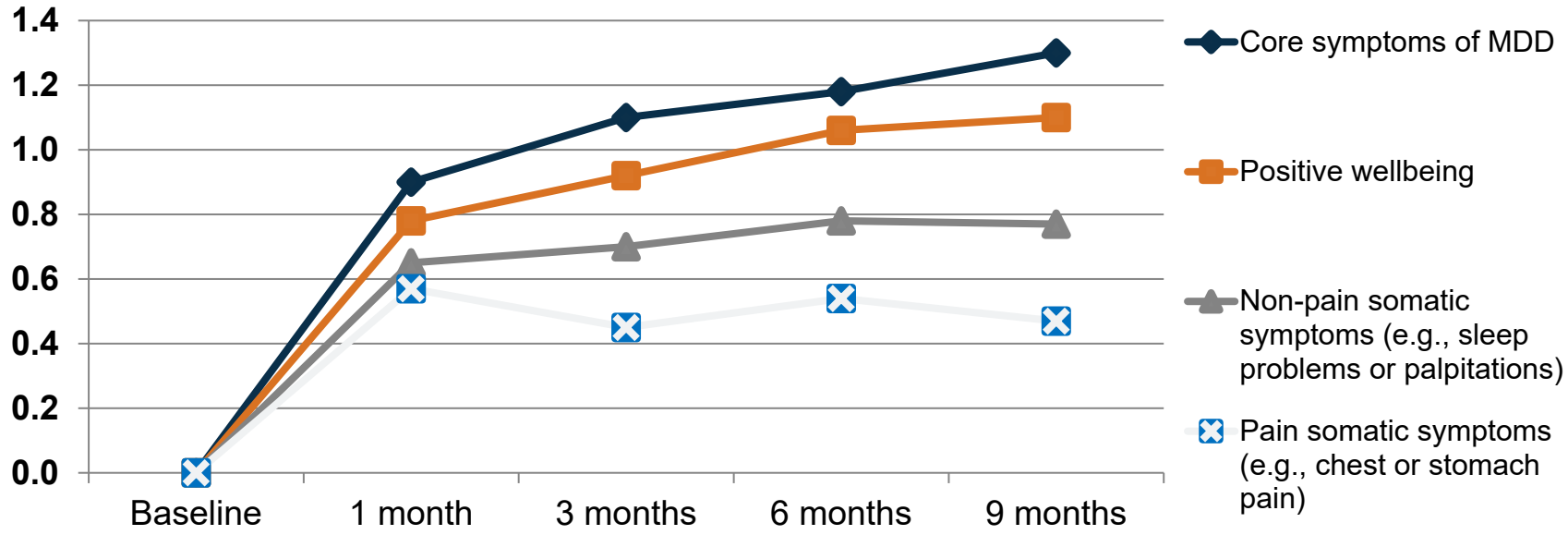
[a]*P*<0.001; [b]*P*<0.01; [c]*P*<0.05.

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

General Well-Being And Somatic Symptoms May Not Improve As Quickly As Core Depressive Symptoms

Time course for improvement of positive wellbeing and the non-pain and pain somatic subscales of the PHQ, compared with the core symptoms of MDD[1]

Open-label, randomised, intention-to-treat trial comparing three SSRIs in primary care patients with MDD (N = 573)



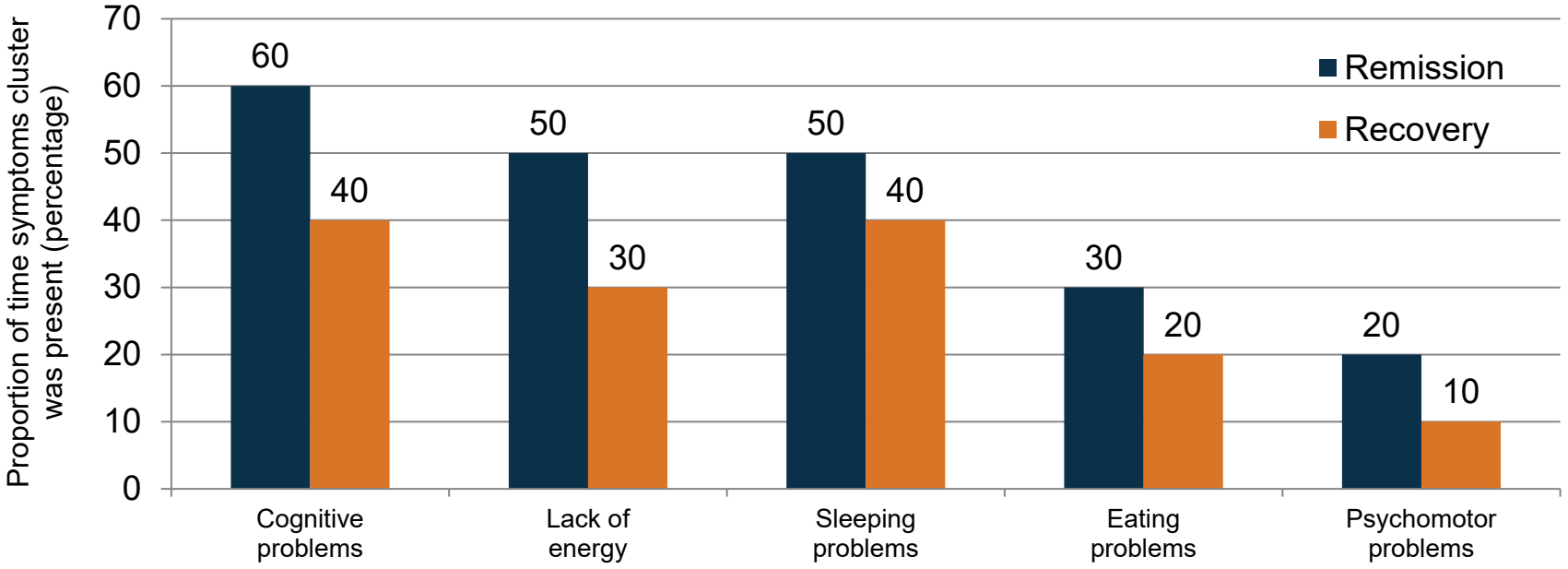
To standardise comparisons among these four domains, change was measured in effect size, which is the mean change divided by the pooled standard deviation for a measure.

PHQ, Patient Health Questionnaire; SSRI, selective serotonin reuptake inhibitor

1. Greco T et al. *J Gen Intern Med* 2004;19:813–818

Functional Impairments May Persist Despite Symptomatic Remission Or Recovery

In a 3-year prospective study of 267 patients with MDD patients still experienced functional symptoms such as cognitive, psychomotor and sleep problems during remission and recovery[1]



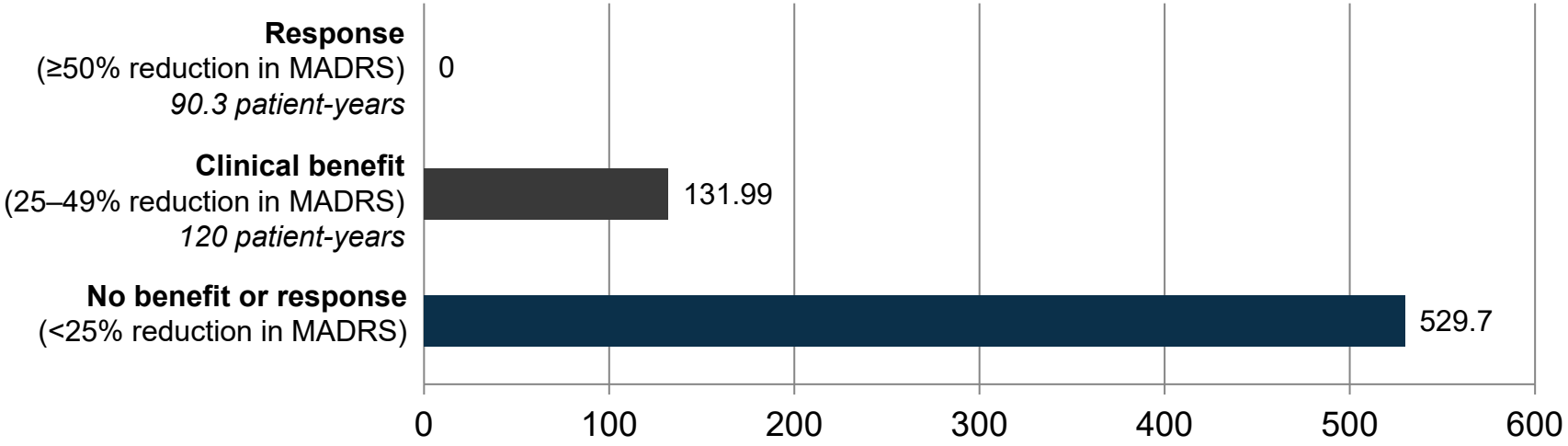
DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition.
Depressed primary care patients (N=267) **(74.2% of whom were receiving antidepressants at baseline)** were monitored over 3 years for the presence or absence of depressive symptom clusters week by week during DSM-IV–defined remissions, recoveries, relapses, and recurrences. The mean proportion of time each symptom cluster was present during 'n' number of phases is shown.

1. Conradi HJ et al. Depress Anxiety. 2012;29:638–645

Patients With Inadequate Response Are At Increased Rate Of Suicide

In an observational, open-label study of 300 patients with treatment-resistant depression* receiving treatment of any kind (pharmacological or non-pharmacological), patients who did not achieve response had high rates of suicidal ideation. [1]

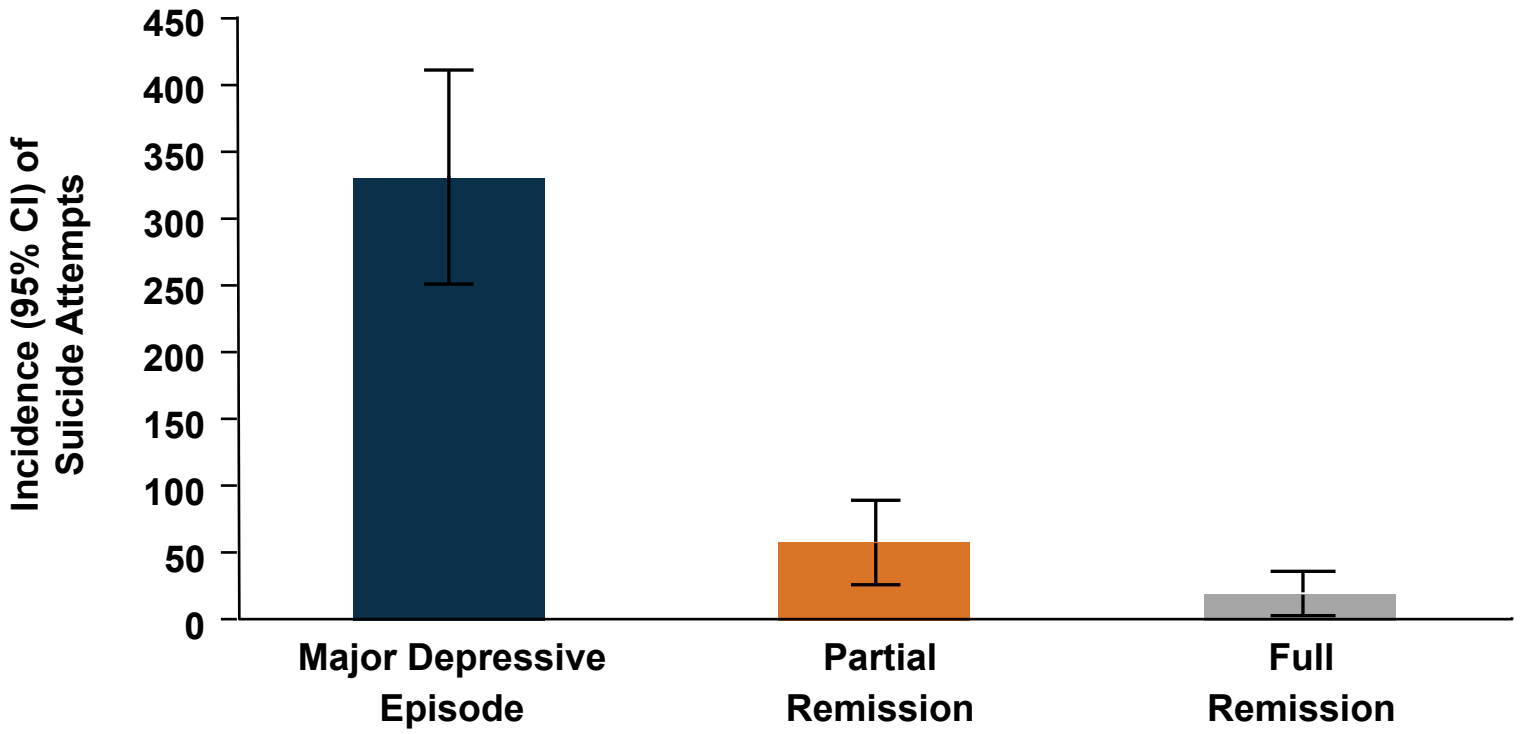
Suicidal ideation rate (MADRS item 10 score ≥4) per 1000 person-years[1]



*Patients had an inadequate response to four or more adequate antidepressant treatments prior to enrolment in the study.

1. Olin B et al. *PLoS One* 2012;7(10):e48002

Incidence Of Suicide Attempts



- Over 5 years follow-up, risk of suicide attempts was 21-fold during a major depressive episode compared with full remission (N=332 vs 16 per 1,000 patient-years)

Note: Data indicate the incidence rate per 1000 patient-years based on Poisson distribution.

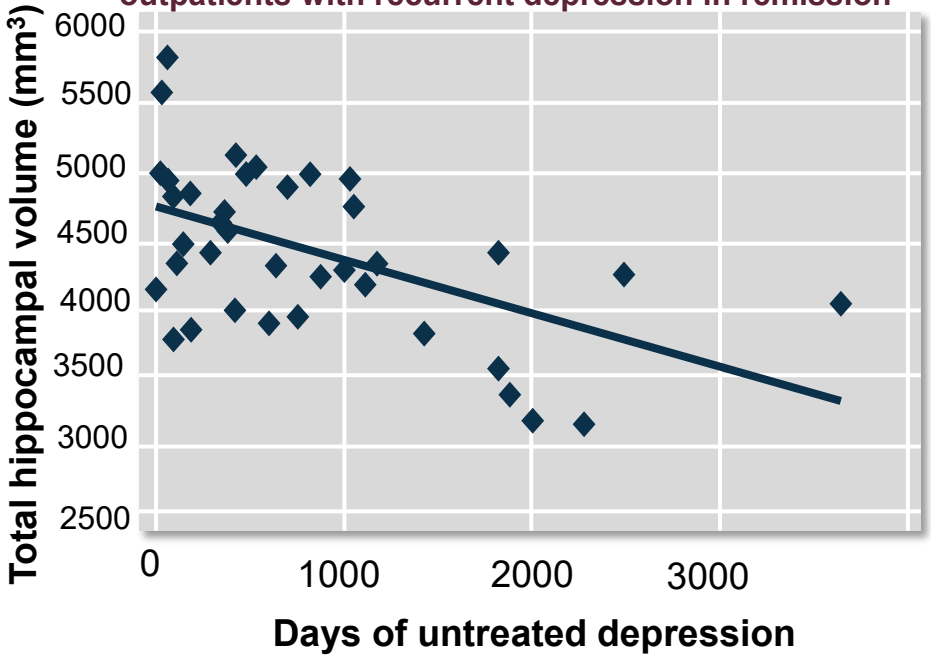
1. Holma KM et al. *Am J Psychiatry*. 2010;167:801-808.

There Is An Established Association Between Long-Term Untreated Depression And Structural Changes In The Brain

An MRI study of changes in hippocampal volume over time demonstrated:

- Longer durations of untreated depression were associated with greater reductions in hippocampal volume[1]
- Over a three-year period, patients in remission had less volume decline in the left hippocampus, anterior cingulum and dorsomedial prefrontal cortex compared with patients not in remission[2]

Relationship between hippocampal volume and days of untreated depression in 38 female outpatients with recurrent depression in remission[3]



Early intervention may help to prevent the **cumulative damage and neuroplastic changes** that occur with repeated episodes of depression and worsen the clinical course[1–3]

Remission determined according to DSM-IV criteria

1. Sheline et al. *J Neurosci* 1999;19(12):5034–5043; 2. Frodl et al. *Arch Gen Psychiatry* 2008;65(10):1156–1165;
3. Sheline et al *Am J Psychiatry* 2003;160:1516–1518

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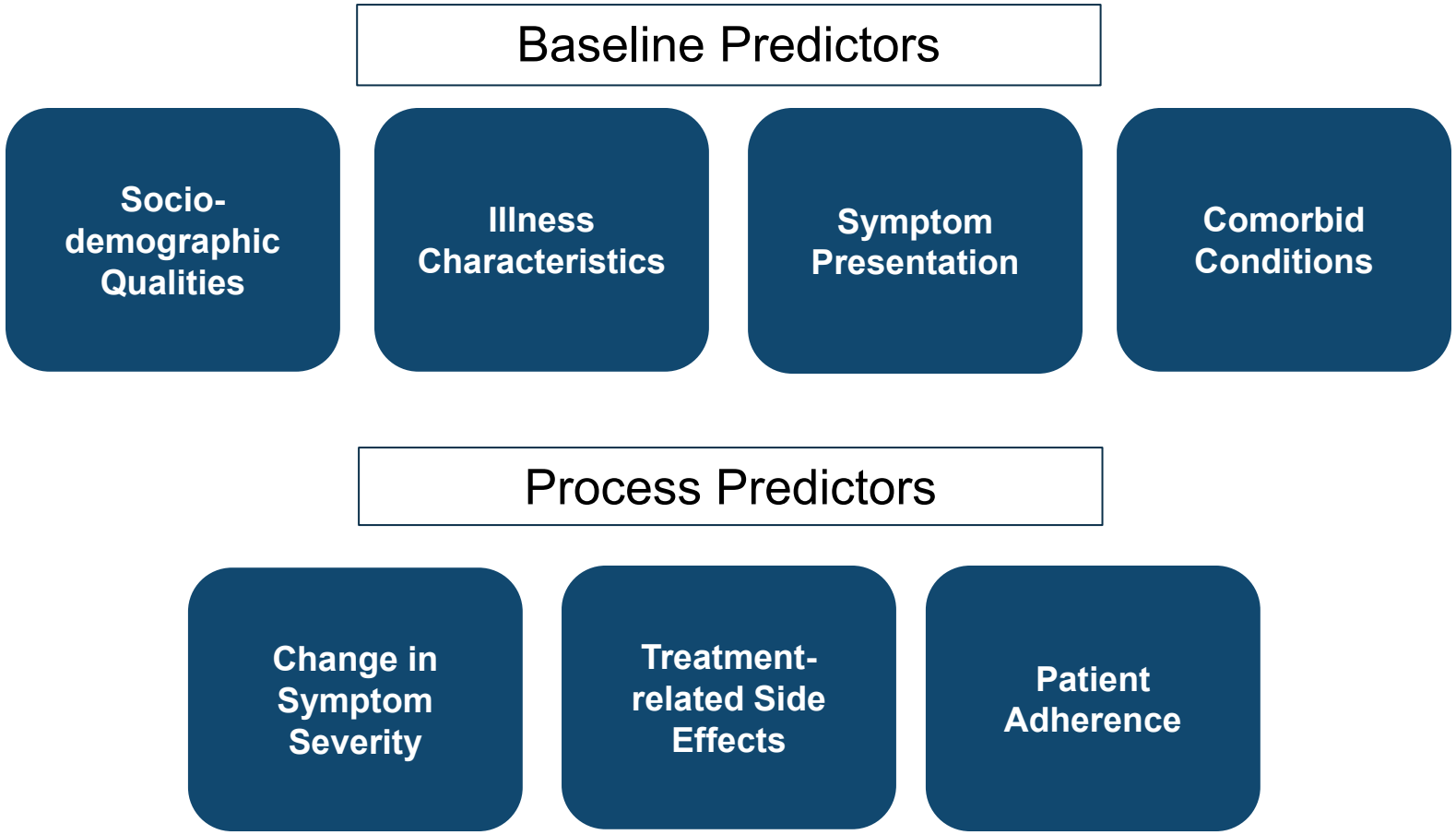
Which Patients Are Most Likely To Experience Inadequate Response?

Predicting Patient Response To Antidepressant Treatment



1. Trivedi M. *Psychiatry Weekly*. May 21, 2007

Baseline Characteristics Associated With A Poor Response To Antidepressant Treatment

- Living alone
- Greater severity of depression
- Unemployed
- Lower income
- Higher neuroticism
- Anxious features
- Comorbid medical condition and/or personality disorder
- Longer duration of illness

1. Trivedi M. *Psychiatry Weekly*. May 21, 2007

Baseline Characteristics Associated With A Better Response To Antidepressant Treatment

- Married or cohabitating[1]
- Employment[2]
- Higher level of education[1]
- Negative family history of depression[1]
- Higher quality of life[1]
- Lower number of depressive episodes[1]
- Shorter illness histories[1]

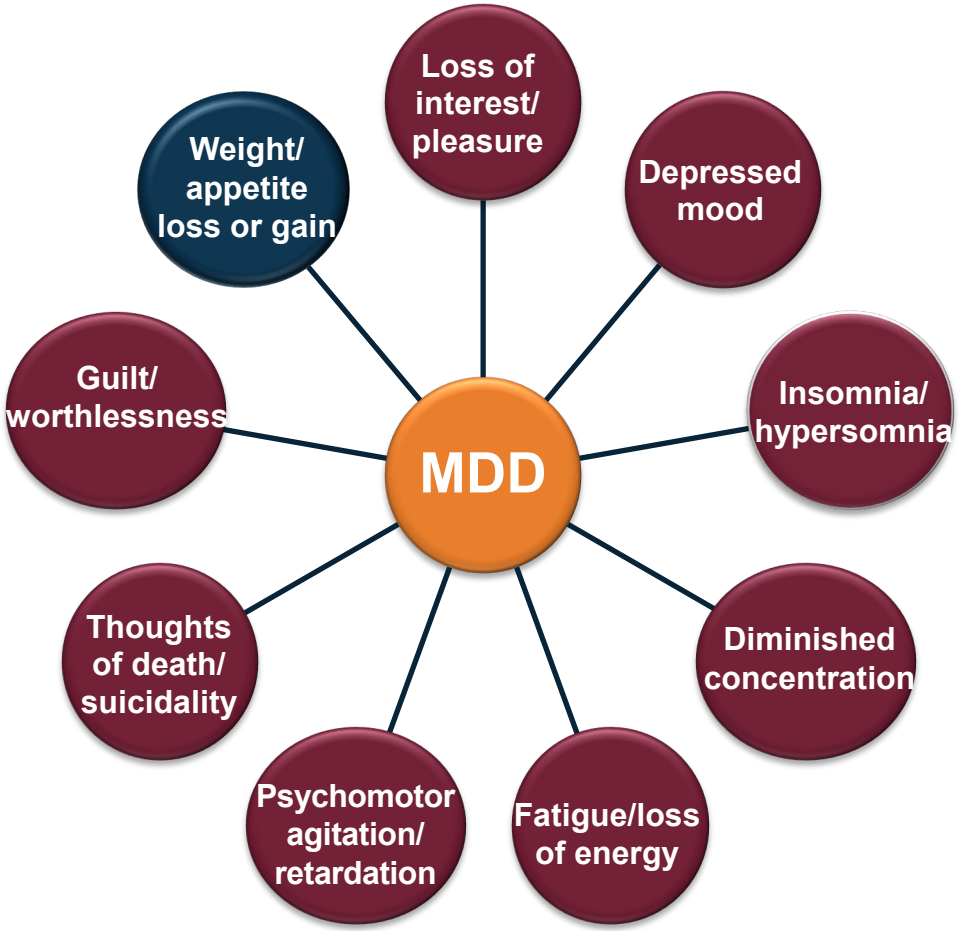
1. Trivedi M. *Psychiatry Weekly*. May 21, 2007
2. van der Lem R, et al. *Soc Psychiatry Psychiatr Epidemiol*. 2013;48(6):975-984

At Least Half Of Patients With MDD Experience Symptoms Of Anxiety, Which May Worsen Prognosis

Anxious depression predicts greater morbidity and has been associated with:

1. Fava M et al. Am J Psychiatry 2008;165:342–351
2. Zimmerman M et al. J Clin Psychiatry 2014;75:601–607
3. Trivedi MH et al. Am J Psychiatry 2006;163:28–40

The Clinical Importance Of Anxiety Symptoms Is Now Recognized In Diagnostic Criteria For MDD



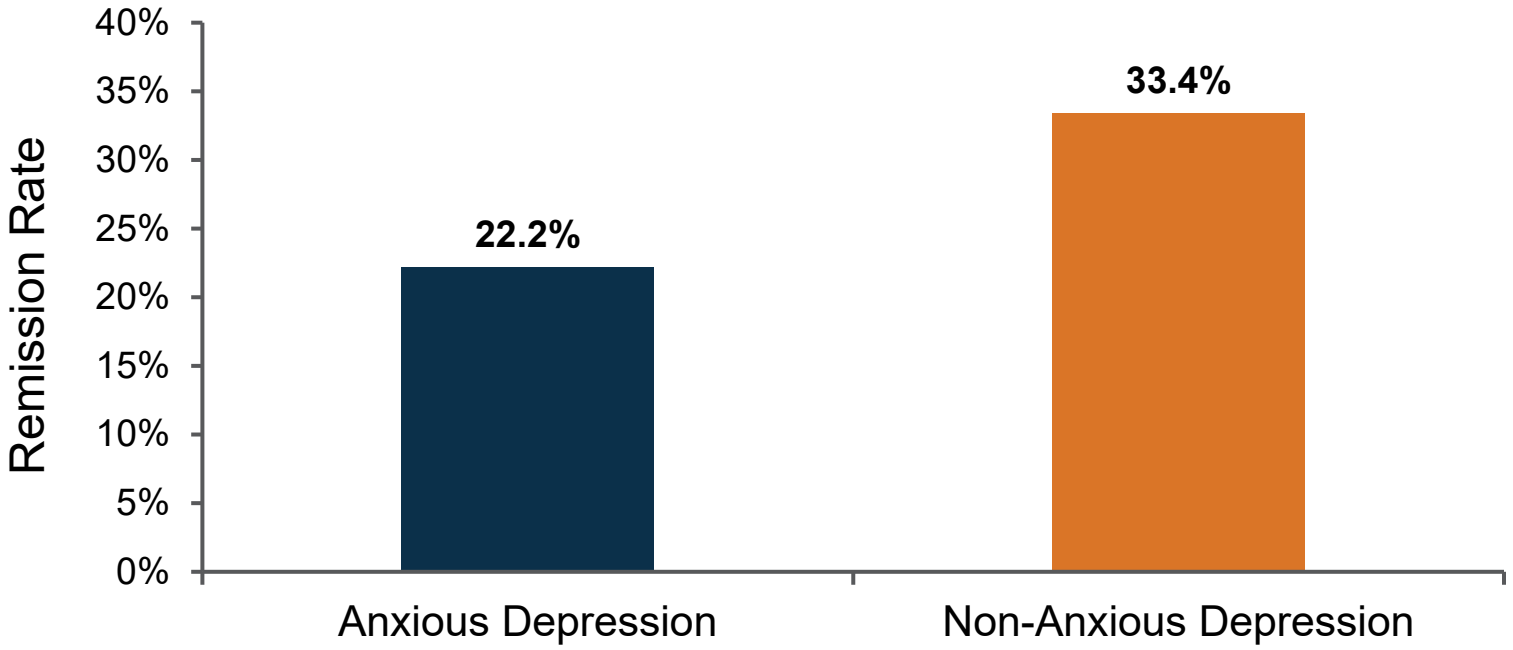
Anxious distress:[1]

At least two symptoms among:

- 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 him/herself

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

Remission Rates Are Significantly Lower In Patients With Anxious Depression Following The First Antidepressant Treatment[1]



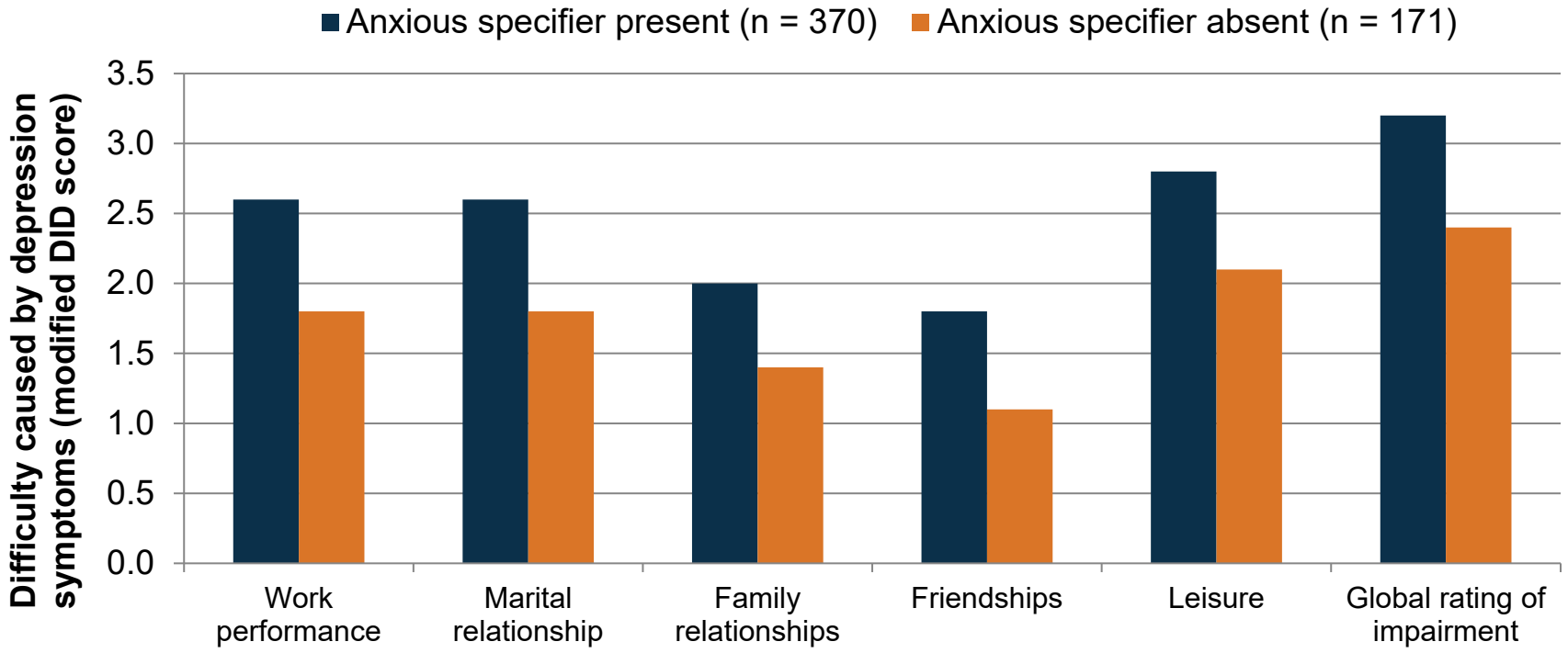
N=2876

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

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

Anxiety Symptoms Decrease Functioning For Patients With MDD

Patients with the DSM-5 anxious distress specifier had greater impairment of quality of life and greater functional impairment compared with those who did not[1]



*p < 0.001

DID, Diagnostic Inventory for Depression

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

Patients With MDD And Symptoms Of Irritability May Have An Earlier And More Persistent Disease Course

Patients with MDD and irritability symptoms have a significantly earlier onset of disease and a higher 12-month lifetime prevalence of MDD than those who are not irritable

	MDD with irritability symptoms (n = 497)	MDD without irritability symptoms (n = 480)	
	Estimated (SE)		p
Mean age of onset, years	26.7 (0.7)*	31.3 (0.9)	<0.001
Mean years in episode	5.7 (0.5)	5.1 (0.9)	0.75
Ratio 12-month:lifetime prevalence, %	40.3 (2.7)*	28.8 (1.6)	0.004

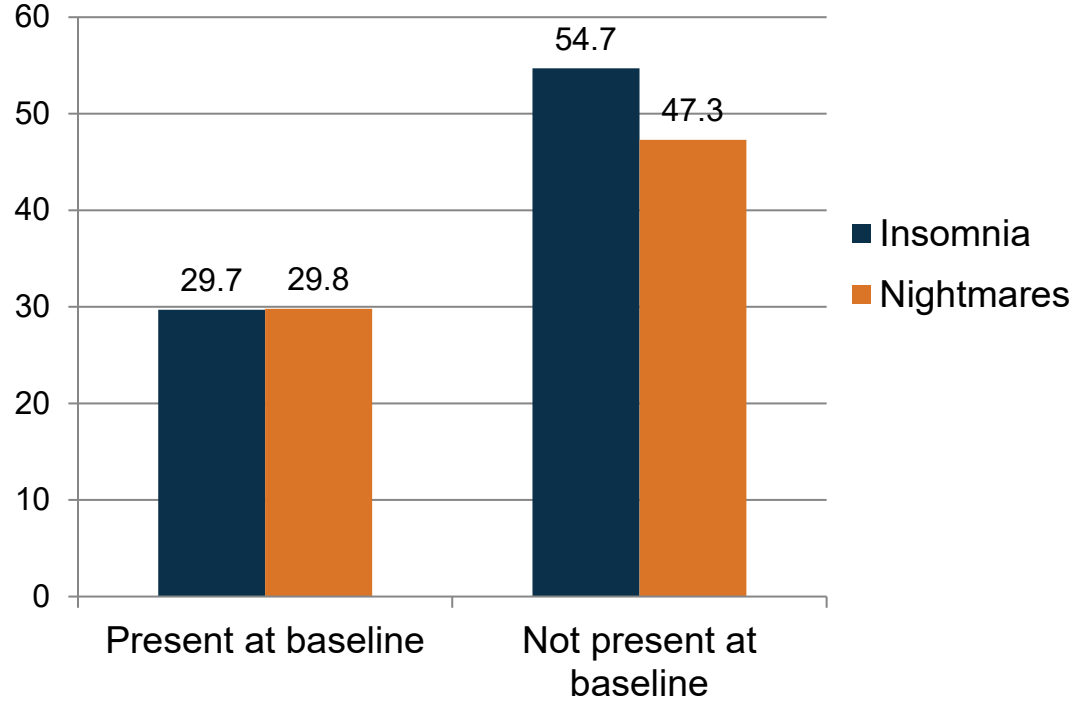
*The reported sample sizes are unweighted and assessed in the part 1 sample

SE, standard error

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

Sleep Disturbances Are A Significant Problem For Patients With MDD And Negatively Impact Outcomes

Patients with insomnia or nightmares at baseline were significantly less likely to achieve remission at 12 months compared with those without these sleep disturbances.[1]



*p < 0.001 vs no insomnia at baseline

Insomnia is believed to occur in 60–80% of patients with depression[2]

Residual symptoms of sleep disturbance may predict relapse[3,4]

1. Li SX et al. *Sleep* 2012;35:1153–1161
2. Luca A et al. *Clin Interv Aging* 2013;8:1033–1039
3. Mendlewicz J. *World J Biol Psychiatry* 2009;10:269–275. 4. Dombrovski A. *J Affect Disord* 2007;103:77–82

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MDD Management Strategies

Management Of Inadequate Response: Practice Guidelines

Substantial clinical confidence | Moderate clinical confidence | Low clinical confidence | No clinical confidence

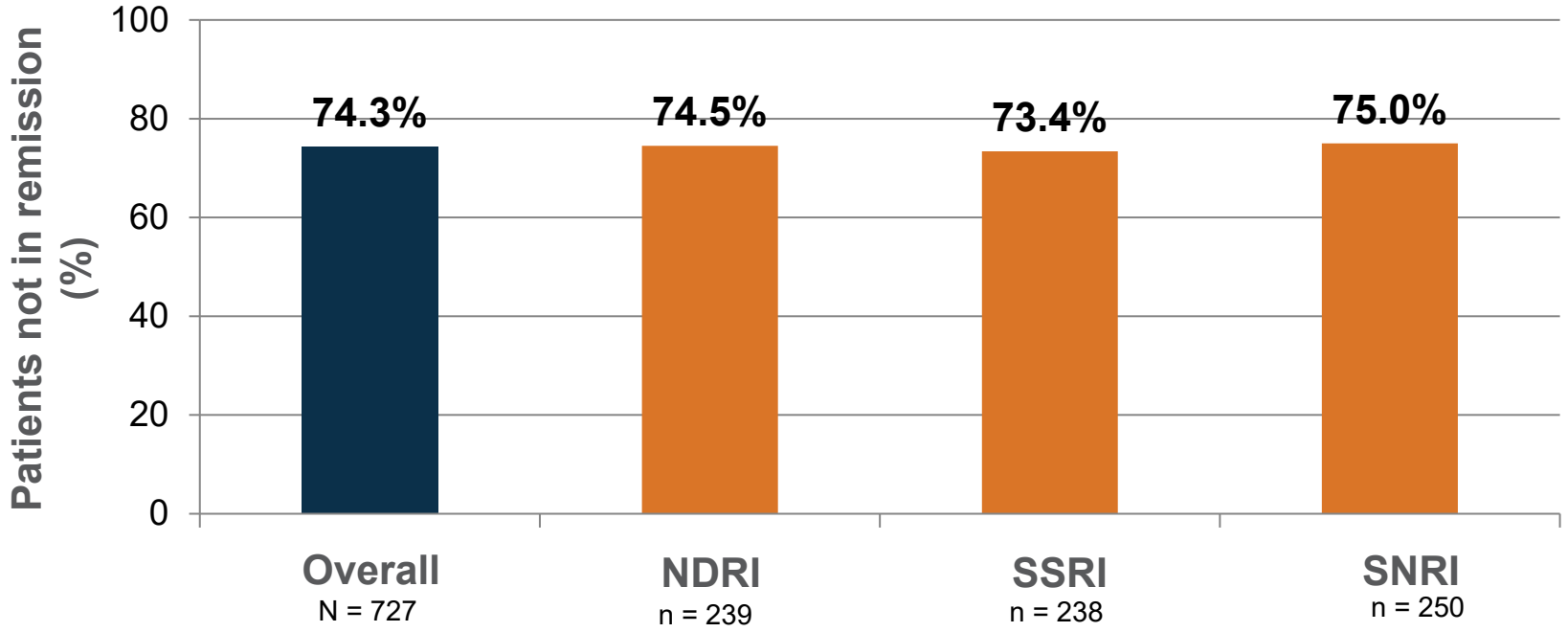
Strategy	APA[1]	NICE[2]	BAP[3]	WFSBP[4]	CANMAT[5]
Optimise current therapy					
Switch to another antidepressant		Depending on agent			Depending on agent
Combination antidepressant pharmacotherapy					
Adjunct treatment with a second agent or psychotherapy	Antipsychotic Mood stabilizer Psychotherapy Benzodiazepines	Antipsychotics Mood stabilizer Benzodiazepines	Antipsychotics Mood stabilizer Psychotherapy	Antipsychotics Mood stabilizer Psychotherapy Benzodiazepines	Antipsychotics Mood stabilizer Psychotherapy

APA, American Psychiatric Association; BAP, British Association for Psychopharmacology; CANMAT, Canadian Network for Mood and Anxiety Treatments; NICE, National Institute for Health and Clinical Excellence; SPC, summary of product characteristics; WFSBP, World Federation of Societies of Biological Psychiatry

1. American Psychiatric Association. Practice Guideline for the Treatment of Patients With Major Depressive Disorder. 3rd ed. Arlington, VA: American Psychiatric Association. 2010; 2. National Collaborating Centre for Mental Health. Depression the Treatment and Management of Depression in Adults. Updated ed. London, UK: The British Psychological Society and The Royal College of Psychiatrists. 2010; 3. Cleare A et al. *J Psychopharmacol* 2015;29(5):459–525: 4. Bauer M et al. *World J Biol Psychiatry* 2013;14:334–385. 5. Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 Clinical Guidelines for the Management of Adults with Major Depressive Disorder. *Can J Psychiatry* 2016;61(9): 510–87.

Switching Antidepressant May Not Improve Outcomes For Patients With Inadequate Response

In the STAR-D trial, nearly 75% of patients with MDD who were switched to second line anti-depressant still failed to achieve remission.



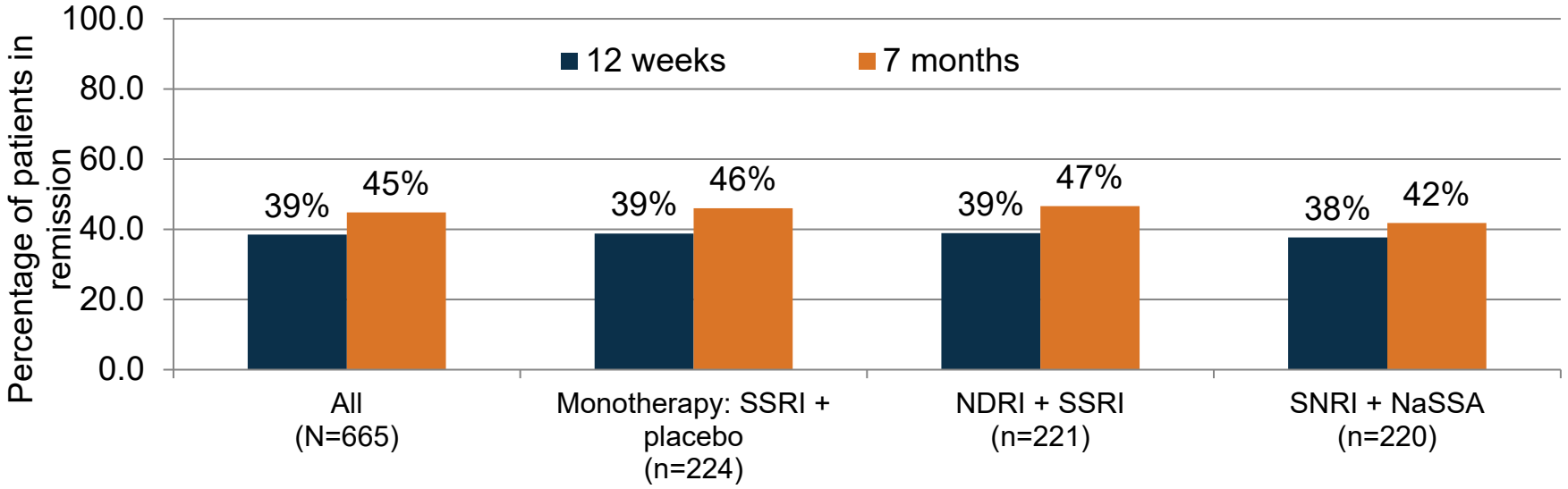
Remission defined as QIDS-SR_{16} score ≤5 at exit from the indicated treatment step.

NDRI, Norepinephrine–dopamine reuptake inhibitor; SNRI, serotonin–norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; STAR*D, Sequenced Treatment Alternatives to Relieve Depression

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

Combination Antidepressant Therapy Compared To Antidepressant Monotherapy: A Prospective Trial

In a prospective trial of 655 patients with MDD, combination therapy with two antidepressants did not improve outcomes when compared with antidepressant mono-therapy, and in some cases increased the risk of adverse events[1]



QIDS-SR = Quick Inventory of Depressive Symptomatology–Clinician-Rated. SSRI, selective serotonin reuptake inhibitor; NDRI, norepinephrine–dopamine reuptake inhibitor; SNRI, serotonin–norepinephrine reuptake inhibitor; NaSSA, noradrenergic and specific serotonergic antidepressant. Remission defined as at least one of the last two consecutive QIDS-SR scores ≤5 and the other ≤7.

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

Practice Guidelines: Adjunctive Treatment Strategies To Address Inadequate Response

Substantial clinical confidence | Moderate clinical confidence | Low clinical confidence | No clinical confidence

Strategy	APA[1]	NICE[2]	BAP[3]	WFSBP[4]	CANMAT[5]
Adjunct treatment with a second agent or psychotherapy	**Antipsychotics** *Individual RCTs: 10* ***Total N<3000***	**Antipsychotics** *Individual RCTs: 10* ***Total N: <2600***	**Antipsychotics** *Individual RCTs: 6* ***Total N: <3400***	**Antipsychotics** *Individual RCTs: 14* ***Total N<5300***	**Antipsychotics** *Individual trials not cited*
	*(M) Nelson, 2009; **N<3500***	*No meta-analyses cited*	*(M) Nelson, 2009; **N<3500*** *(M) Spielmans, 2013; **N<3600***	*(M) Nelson, 2009; **N<3500*** *(P) Bauer, 2010; **N<1000*** *(C) Komossa, 2010; **N<6900***	*(M) Komossa, 2010; **N<3300*** *(M) Nelson, 2009; **N<3500*** *(M) Spielmans, 2013; **N<3600*** *(M) Wen, 2014; **N<3900*** *(NM) Zhou, 2015; **N<4500***
	Mood Stabilizer *Individual RCTs: 1* ***Total N<150***	**Mood Stabilizer** *Individual RCTs: 10* ***Total N<450***	**Mood Stabilizer** *Individual RCTs: 2* ***Total N<850***	**Mood Stabilizer** *Individual RCTs: 4* ***Total N<300***	**Mood Stabilizer** *Individual RCTs: 3* ***Total N<100***
	*(M) Bauer, 1999; **N<350*** *(M) Crossley, 2007; **N<300*** *(P) Austin, 1991; **N<100***	*No meta-analyses cited*	*(M) Crossley, 2007; **N<300***	*(M) Crossley, 2007; **N<300***	*(M) Nelson, 2014; **N<300***

Estimates based on available data on adjunctive treatment with a non-antidepressant drug; studies included are listed in the slide notes; Meta-analyses (M), Network meta-analysis (NM), pooled analyses (P) and Cochrane Reviews (C) comprise some of the listed RCTs and there is overlap in the studies included in each M, P and C analysis. APA, American Psychiatric Association; BAP, British Association for Psychopharmacology; NICE, National Institute for Health and Clinical Excellence; RCT, randomized, controlled trial; SPC, summary of product characteristics; WFSBP, World Federation of Societies of Biological Psychiatry

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Conclusions

- MDD is a serious disease that has wide ranging impact on person, family and society.[1–7]
- More than half of patients do not achieve MDD symptom remission following the first round of treatment. [3]
- Inadequate treatment response may lead to substantial negative patient outcomes.[11]
- Individuals with MDD and comorbid irritability or anxiety may have a worse prognosis, which led to the creation of an "anxious distress" specifier in the DSM-5. [6-8]
- Proactive, targeted treatment decisions may be important. [9-10]

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