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Recognizing & Responding To Inadequately Treated Major Depressive Disorder

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Otsuka Pharmaceutical Development &
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Objectives

- Discuss the burden of MDD on the individual and society
- Explore the negative impact of residual symptoms
- Identify patient and treatment characteristics associated with a poor treatment response
- Discuss strategies to optimize pharmacotherapy

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1. Burden of MDD
2. Residual symptoms in MDD
3. Response to Antidepressant Treatment in MDD
4. Evidence for the Treatment of Patients With MDD and Practical Guidelines
5. Summary

Introduction

- Depression is the most common diagnosis among patients seen by psychiatrists in the US[1]
- MDD is a serious, chronic, disabling illness affecting more than 350 million people worldwide[2]
- MDD results in a substantial burden of disease to both the individual and society[3]
- Residual symptoms are common and cause significant psychosocial and occupational functional impairment[4,5]

1. Duffy FF et al. *Psychiatr Serv*. 2008;59(10):1148-1154;
2. World Health Organization. *Fact Sheet on Depression.* (2012) http://www.who.int/mediacentre/factsheets/fs369/en/index.html;
3. Kessler RC. *Psychiatr Clin North Am.* 2012;35(1):1-14;
4. Romera I et al. *Eur Psychiatry*. 2010;25(1):58-65;
5. Zimmerman M et al. *Compr Psychiatry*. 2007;48(2):113-117.

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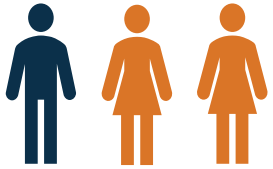
Prevalence Of Depression

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.

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Burden Of MDD

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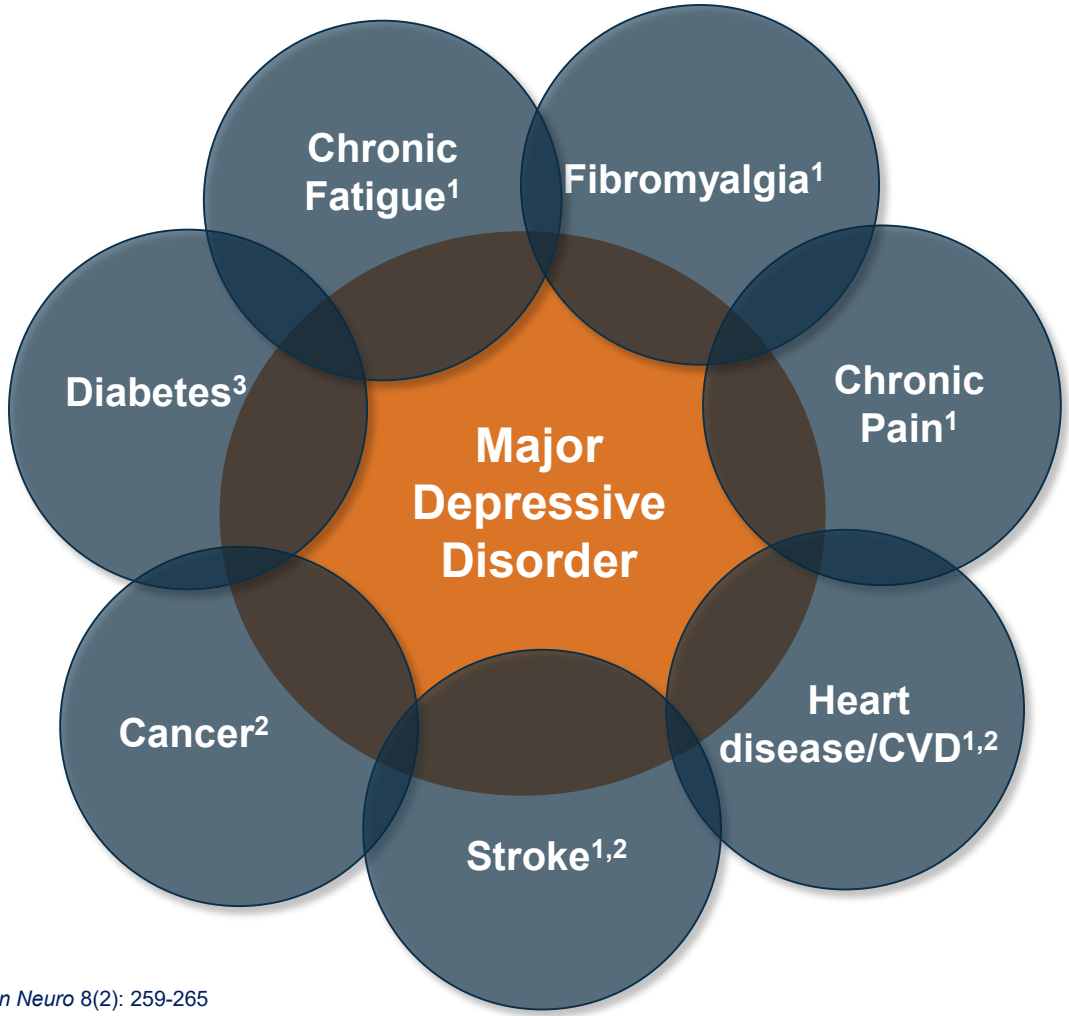
Association Between Depression And Other Medical Illnesses



1. Goodwin G et al. 2006. *Dial Clin Neuro* 8(2): 259-265
2. Kang HJ et al 2015. *Chonnam Med J* 51: 8-18
3. Mezuk B et al 2008. *Diabetes Care* 31: 2383-2390

Depression As A Risk Factor For Heart Disease:
A Scientific Statement From The American Heart Association

- Based on a systematic literature review on depression and adverse medical outcomes after acute coronary syndrome (ACS)
  - 53 studies and 4 meta-analyses met inclusion criteria
- The majority of relevant studies (21/32) suggest that depression is a risk factor for all-cause mortality after ACS.
- The majority of relevant studies (8/12) suggest that depression is a risk factor for cardiac mortality after ACS.
- The American Heart Association panel of authors suggests that depression should be elevated to the status of a risk factor for adverse medical outcomes in patients with ACS.

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Lichtman JH et al. *Circulation*. 2014;129. Epub ahead of print.

Burden Of Disease To The Individual

- 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

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

Total Societal Costs[1] (2010)

Type of cost	Dollars (in billions)	Percentage of Total	% cost increase from 2005
Total costs*	210.5	100.0	21.5
Direct cost	98.8	47	39.2
Inpatient	20.6	10	39.3
Outpatient	38.2	18	42.5
Pharmaceutical	28.1	13	5.4
Suicide-related costs	9.7	5	2.7
Workplace costs	102.0	48	18.2
Absenteeism	23.3	11	8.3
Presenteeism	78.7	37	21.5

*Total costs = direct, suicide-related, and workplace costs.
Note: Cost/case may not equal total cost divided by population estimates due to rounding.

1. Greenberg et al 2015 *J Clin Psych* 76 (2): 155-162

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Lost Productive Time (Hours Per Week)

Type of LPT	MDD*	Expected mean LPT in absence of depression
Absenteeism	1.2 (0.4)	0.4
Presenteeism	7.2 (1.3)	1.1
Total LPT	8.4 (1.3)	1.5
Pain/weakness/fatigue	10.0 (1.2)	5.1
GI complaints	10.7 (1.5)	2.0
Panic/anxiety	9.3 (1.7)	4.1
Faintness/dizziness	8.9 (2.4)	4.5
Autonomic instability	9.5 (1.9)	6.5
Ears ringing/head or nose fullness	8.1 (1.2)	2.8
Sensory or nerve impairment	10.0 (1.4)	3.2
None	5.8 (3.7)	0.8

GI, gastrointestinal; LPT, lost productive time.
*Data reported as mean (standard error) hours per worker per week.
Stewart WF et al. *JAMA*. 2003;289:3135-3144.

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Suicide Risk

- Patients with MDD are roughly 20 times more likely to commit suicide than the general population
- Attempts at suicide among patients with MDD are highly associated with the occurrence and overall severity of MDD symptoms
- Increased time spent depressed is predictive of suicide attempts in this population

Sokero TP et al. *Br J Psychiatry*. 2005;186:314-318.

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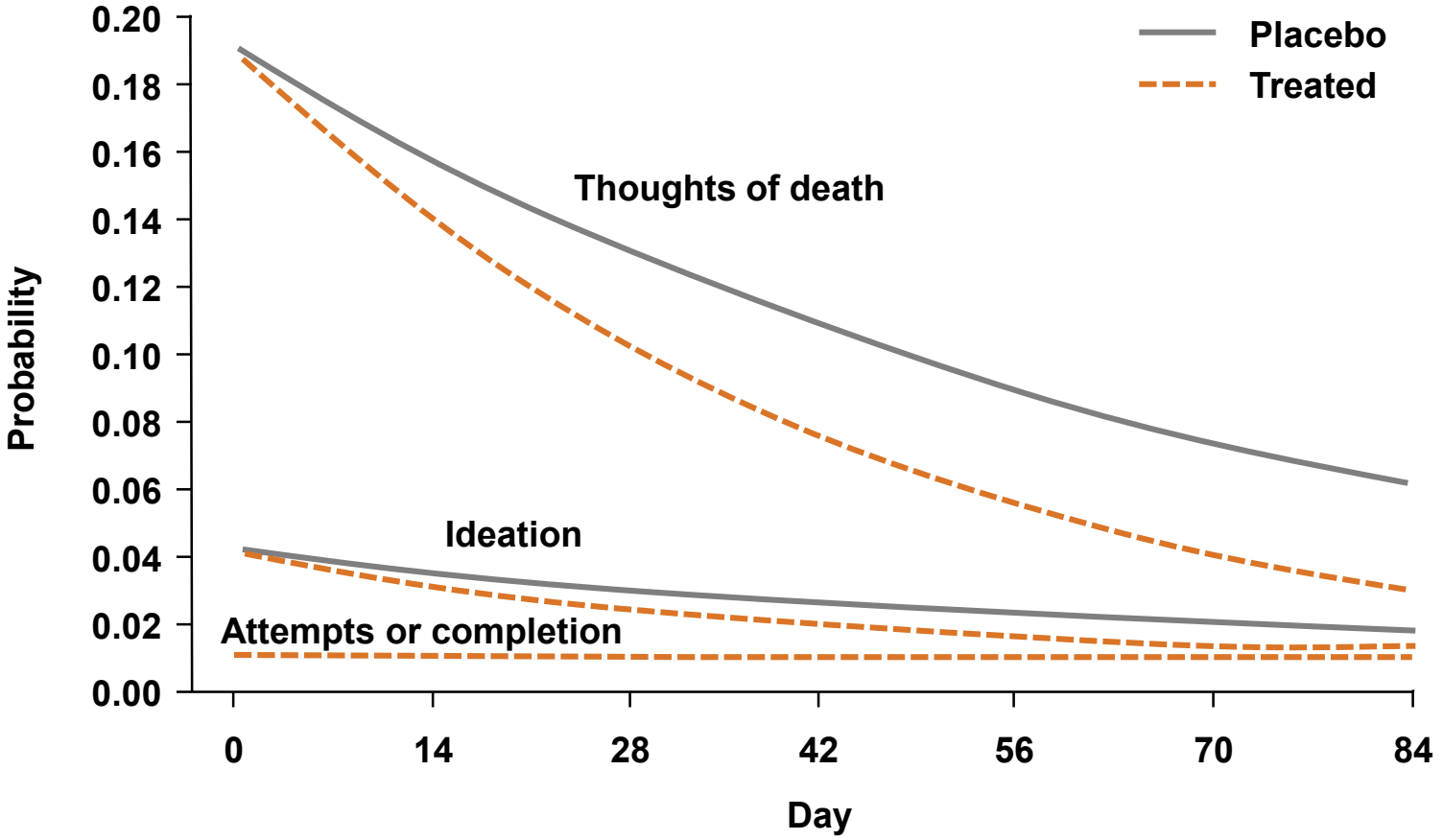
Suicidal Thoughts, Ideations, And Attempts



Note: Data based on 31 randomized controlled trials of antidepressants in patients with MDD.
Gibbons RD et al. *Arch Gen Psychiatry*. 2012;69(6):580-587.

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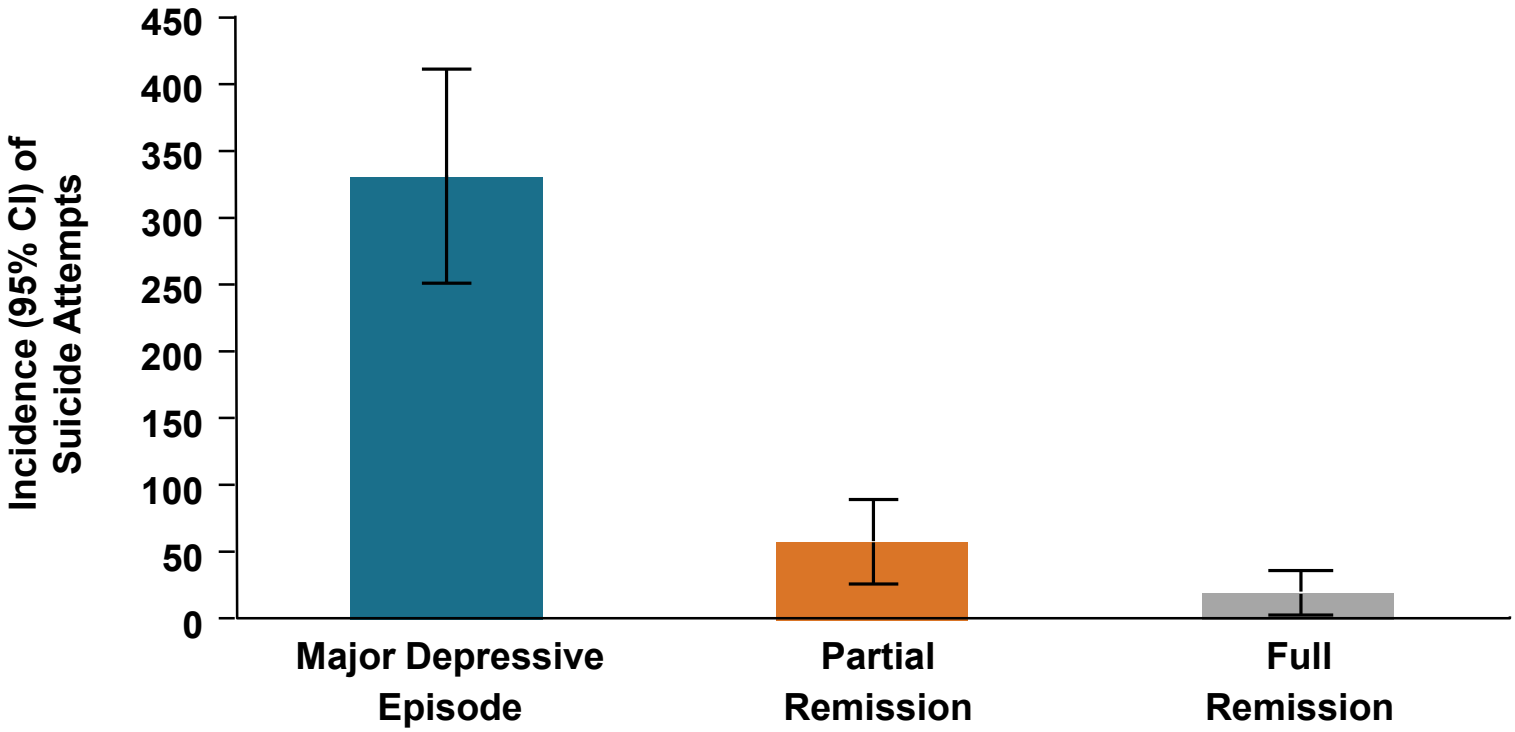
Incidence Of Suicide Attempts



- 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.

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

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Suicide Attempts In MDD: Depression-Related Characteristics

Characteristic	No suicide attempt (n=182)	Suicide attempt (n=16)	P-value
Severity of depression at baseline, n (%)			0.02
Mild	11 (6)	-	
Moderate	99 (54)	4 (25)	
Severe	72 (40)	12 (75)	
Mean (SD) time to full remission, months	4.0 (4.7)	8.1 (7.5)	0.002
Mean (SD) total time in depression, months	4.4 (4.7)	8.6 (7.1)	0.002

- Of the 41 discrete suicide attempts that occurred in the 16 patients over 18 months, 25 occurred during a major depressive episode, 12 during partial remission, and 4 during full remission
- The risk of a suicide attempt was almost 8-fold higher during a major depressive episode compared with a period of full remission (relative risk 7.54)

SD, standard deviation.

Sokero TP et al. *Br J Psychiatry*. 2005;186:314-318.

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Residual Symptoms In MDD

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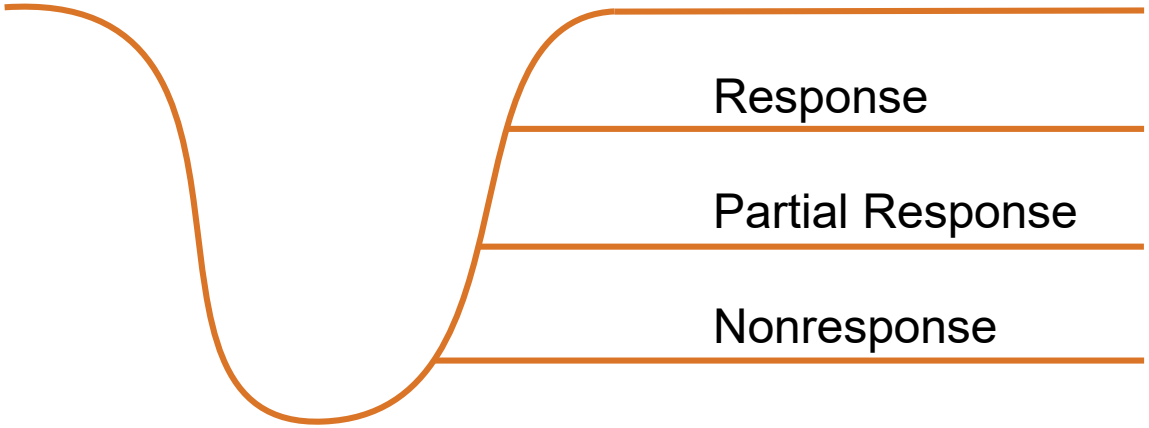
Remission Is The Goal



Remission also defined as attainment of a virtually asymptomatic status (17-item Hamilton Depression Rating Scale [HDRS] score ≤ 7) for at least 2 consecutive weeks.[3]

1. Weisler R et al. *CNS Spectrums*. 2009;14(6):299-313;
2. Nierenberg AA et al. *J Clin Psychiatry*. 2001;62(suppl 16):5-9;
3. Frank E et al. *Arch Gen Psychiatry*. 1991;48:851-855 et al.

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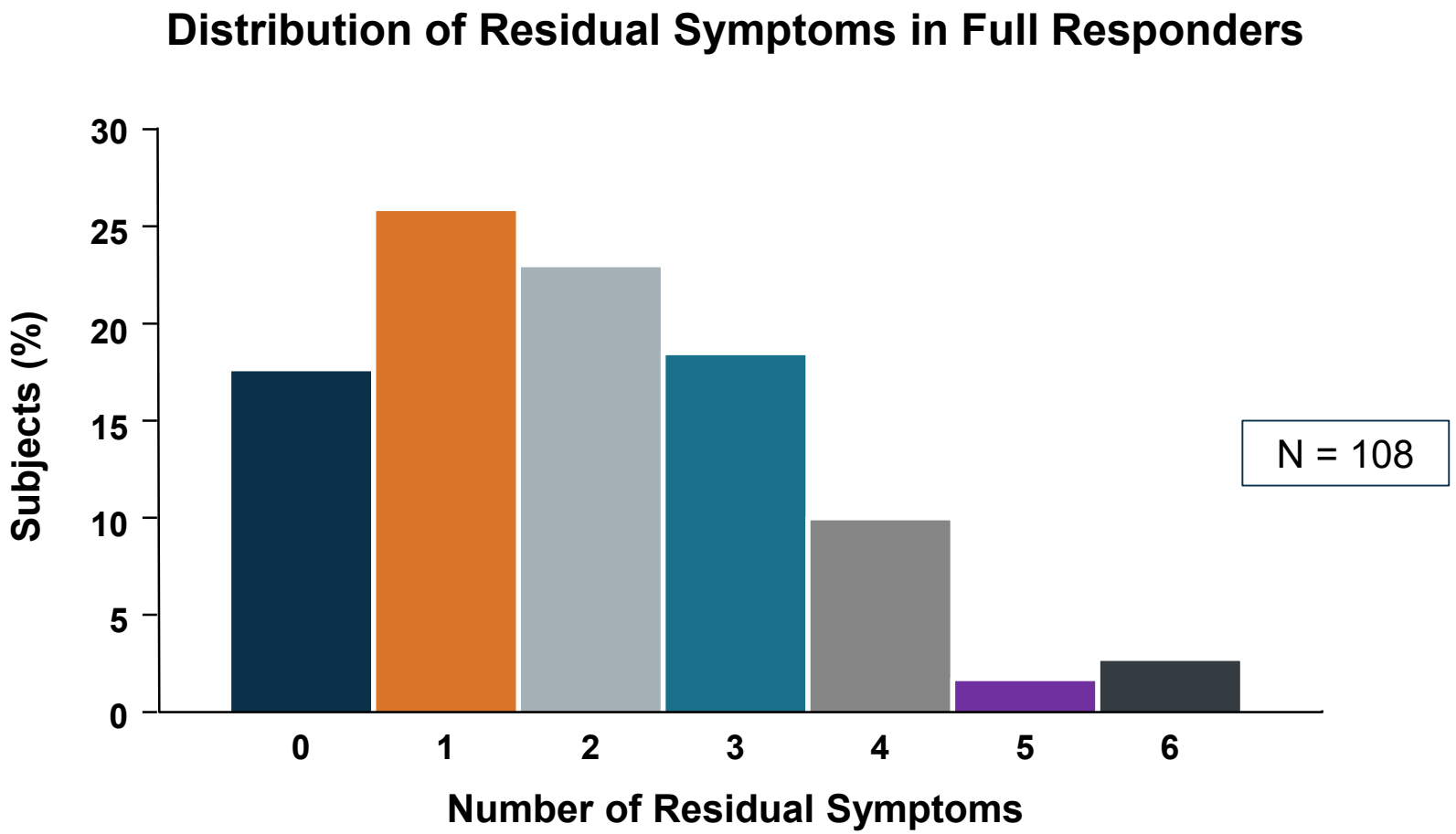
Prevalence Of Residual Symptoms



Nierenberg AA et al. *J Clin Psychiatry*. 1999;60(4):221-225.

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Common Unresolved Or Residual MDD Symptoms

Estimated frequencies[1]:

- Sleep disturbances (44%)
- Fatigue (38%)
- Diminished interest or pleasure (27%)
- Guilt (≈ 25%)
- Concentration difficulties (≈ 25%)
- Disturbances in mood (≈ 15%)
- Weight issues (≈ 15%)
- Disturbances in psychomotor activity (≈ 5%)
- Suicidal ideation (≈ 5%)

Other residual/unresolved MDD symptoms include: core mood symptoms,[2] anxiety,[2,3] irritability and/or inner tension,[3] somatic symptoms (including pain),[2,4] sexual dysfunction,[3] and impairment of work and/or activities[2]

1. Nierenberg AA et al. J Clin Psychiatry. 1999;60(4):221-225.
2. Romera I et al. *BMC Psychiatry*. 2013;13:51;
3. Trivedi MH et al. *J Clin Psychiatry*. 2008;69(2):246-258;
4. Trivedi MH. *J Clin Psychiatry*. 2004:6(Suppl 1)12-16.

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Residual Symptoms After Remission: STAR*D

Symptom	At least mild symptoms* (% of patients)	At least moderate symptoms† (% of patients)
Weight increase	71.3	21.7
Mid-nocturnal insomnia	54.9	40.5
Increased appetite	50.6	9.5
Sleep-onset insomnia	29.5	9.7
Sad mood	27.1	0.4
Hypersomnia	24.0	2.4
Energy	22.5	1.7
Concentration/decision making	20.9	0.9
Weight decrease	16.7	4.5
Early morning insomnia	16.6	6.8
Restless	15.2	0.9
Decreased appetite	12.2	0.6
Involvement	9.4	1.8
Outlook self	6.8	0.4
Slowed down	5.8	0.3
Suicidal ideation	1.3	0.3

*Defined as any 16-item Quick Inventory of Depressive Symptomatology, Self-Report (QIDS-SR16) item ≥ 1; †Defined as any QIDS-SR16 item ≥ 2.

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

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Impact Of Residual Symptoms On Patient Functioning And Outcomes

- Residual symptoms cause significant and often persistent psychosocial and occupational functional impairment[1,2,3]
- Patients being treated for MDD who have residual symptoms have an increased risk of depressive relapse[4,5]

Author	N	Time Followed	Relapsed
Paykel[4]	70	15 months	▪ 76% of patients with residual symptoms ▪ 25% of patients with no residual symptoms
Pintor[5]	139	4 years	▪ 91% of patients with partial remission ▪ 51% of patients with complete remission

- Patients with residual symptoms tend to have poor psychosocial functioning[6]

1. Romera I et al. *Eur Psychiatry*. 2010;25(1):58-65;
2. Zimmerman M et al. *Compr Psychiatry*. 2007;48(2):113-117;
3. Fava M. *J Psychopharm.* 2006;20(3):29-34;
4. Paykel ES et al. *Psychol Med*. 1995;25(6):1171-1180;
5. Pintor L et al. *J Affect Disord*. 2004;82(2):291-296;
6. Romera I et al. *BMC Psychiatry*. 2013;13:51.

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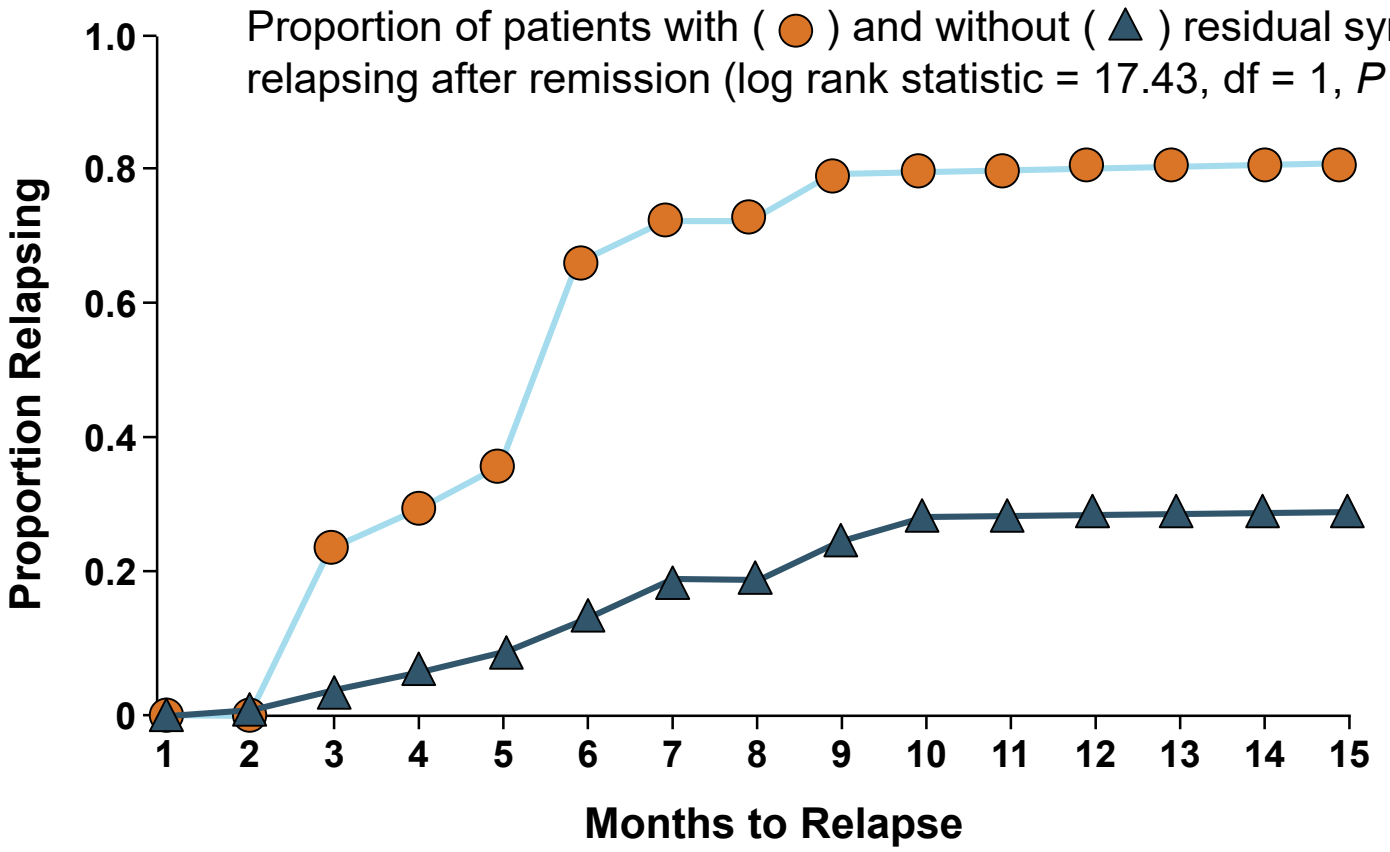
Predictors Of Relapse And Recurrence In MDD



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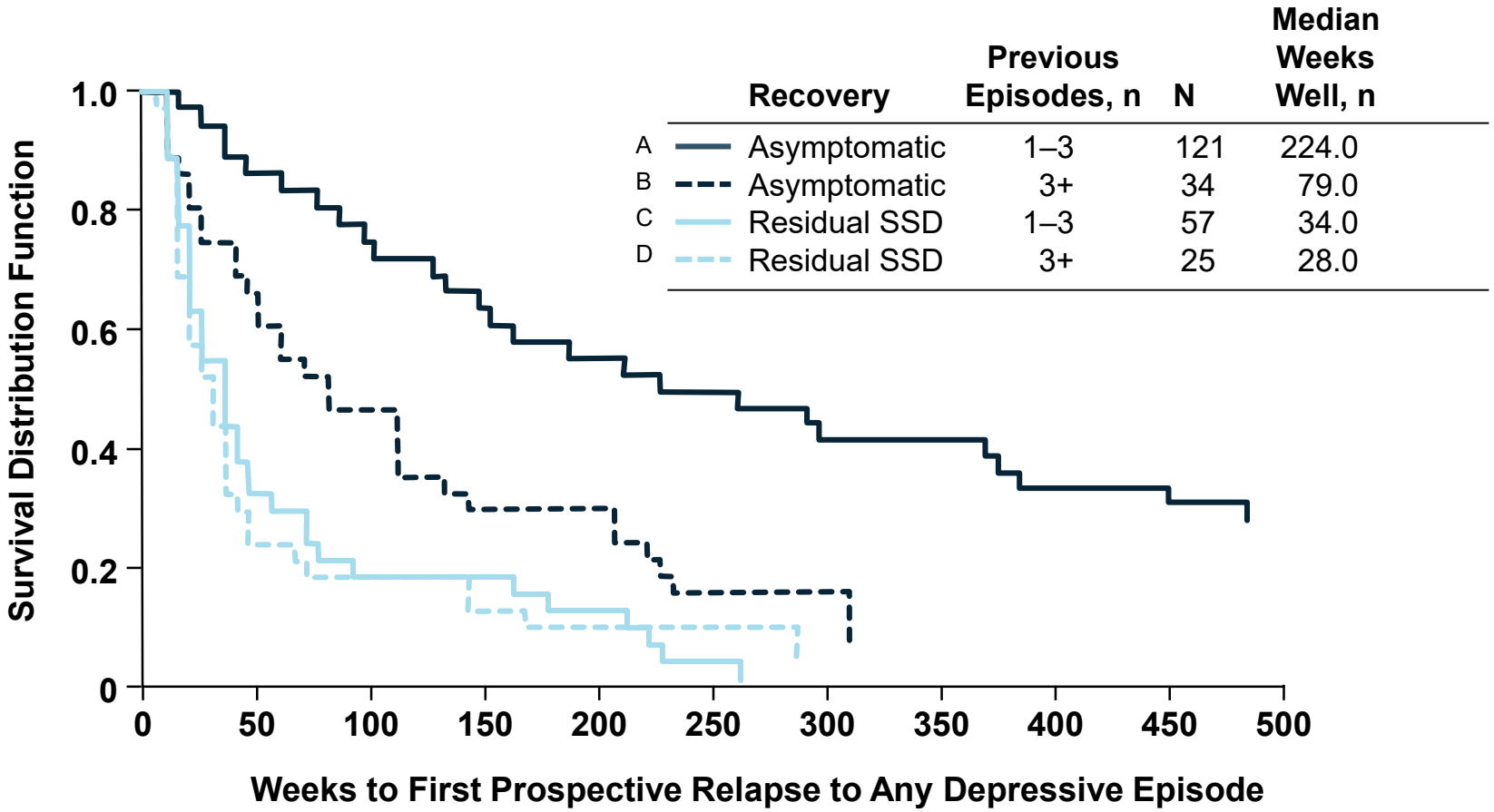
Paykel ES et al. *Psychol Med.* 1995;25:1171-1180.

Predictors Of Relapse And Recurrence In MDD



	Recovery	Previous Episodes, n	N	Median Weeks Well, n
A	Asymptomatic	1–3	121	224.0
B	Asymptomatic	3+	34	79.0
C	Residual SSD	1–3	57	34.0
D	Residual SSD	3+	25	28.0

SSD, Subsyndromal Symptoms of Depression; Survival Distribution Function = Cumulative Proportion of Cases Surviving to Given Time Interval.

Judd LL et al. *J Affect Discord*. 1998;50:97-108.

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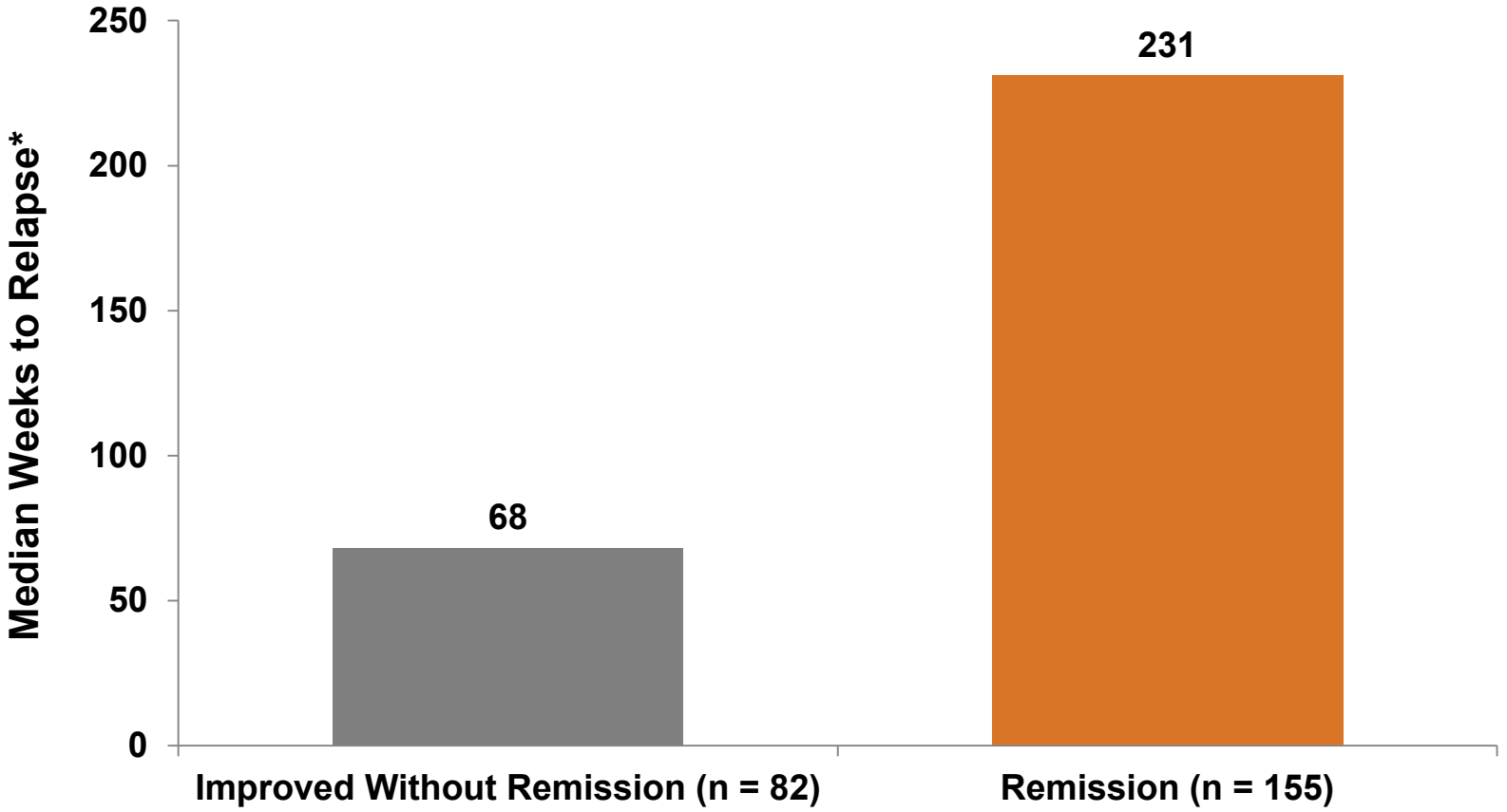
Predictors Of Relapse And Recurrence In MDD



*Relapse defined as onset of new major depressive episode.

Judd LL et al. *J Affect Disord*. 1998.

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Predictors Of Relapse And Recurrence In MDD

Relapse in Patients With Partial and Complete Remission After 24 Months of Follow-up

Type of Remission	Relapse	
	Yes	No
Partial Remission	48 (67.6%)	23 (32.4%)
Complete Remission	17 (15.2%)	95 (84.8%)

All proportions reflect percentage of relapse according to type of remission.

Pintor L et al. *J Affect Disord*. 2003;73:237-244.

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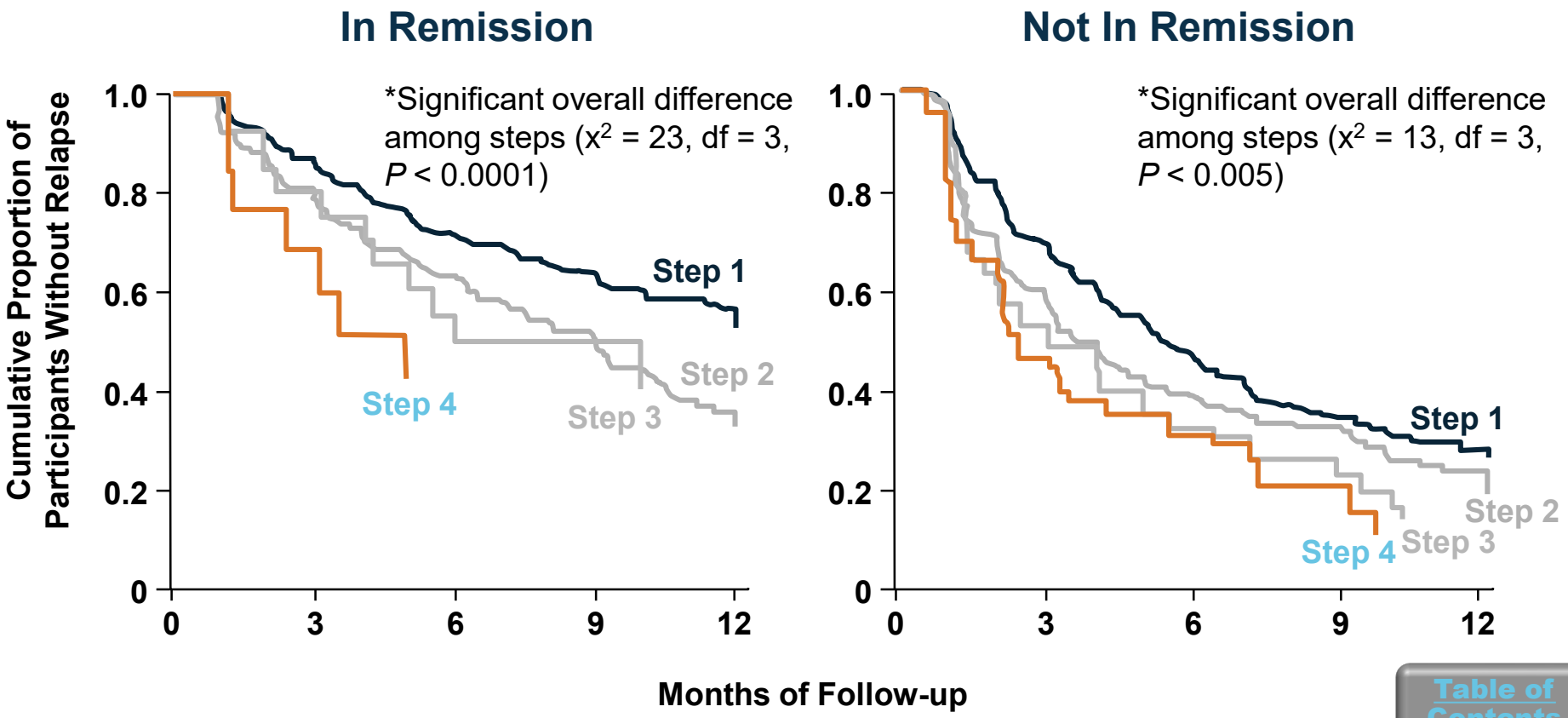
Comparison Of STAR*D Participants

Relapse During Follow-up Phase by Number of Acute Treatment Steps for STAR*D Participants Who Entered Follow-up Phase:



Rush AJ et al. *Am J Psychiatry*. 2006;163:905-1917.

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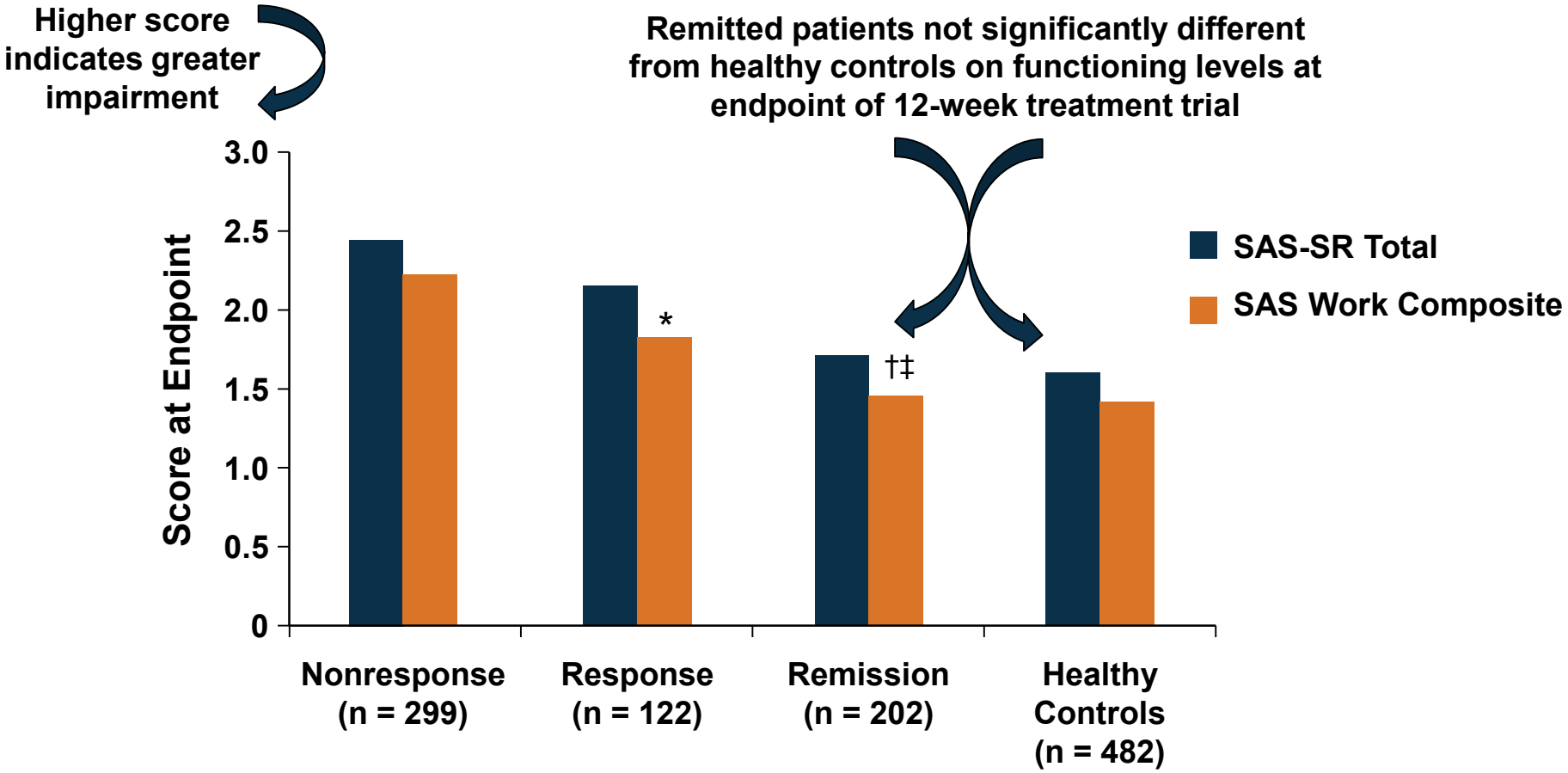
Impact Of Residual Symptoms On Functioning



Significant differences (P ≤ 0.05) for SAS work composite scores between response versus nonresponse (*), remission versus nonresponse (†), remission versus response (‡).
SAS-SR, Social Adjustment Scale-Self Report.
Miller IW et al. *J Clin Psychiatry*. 1998;59:608-619.

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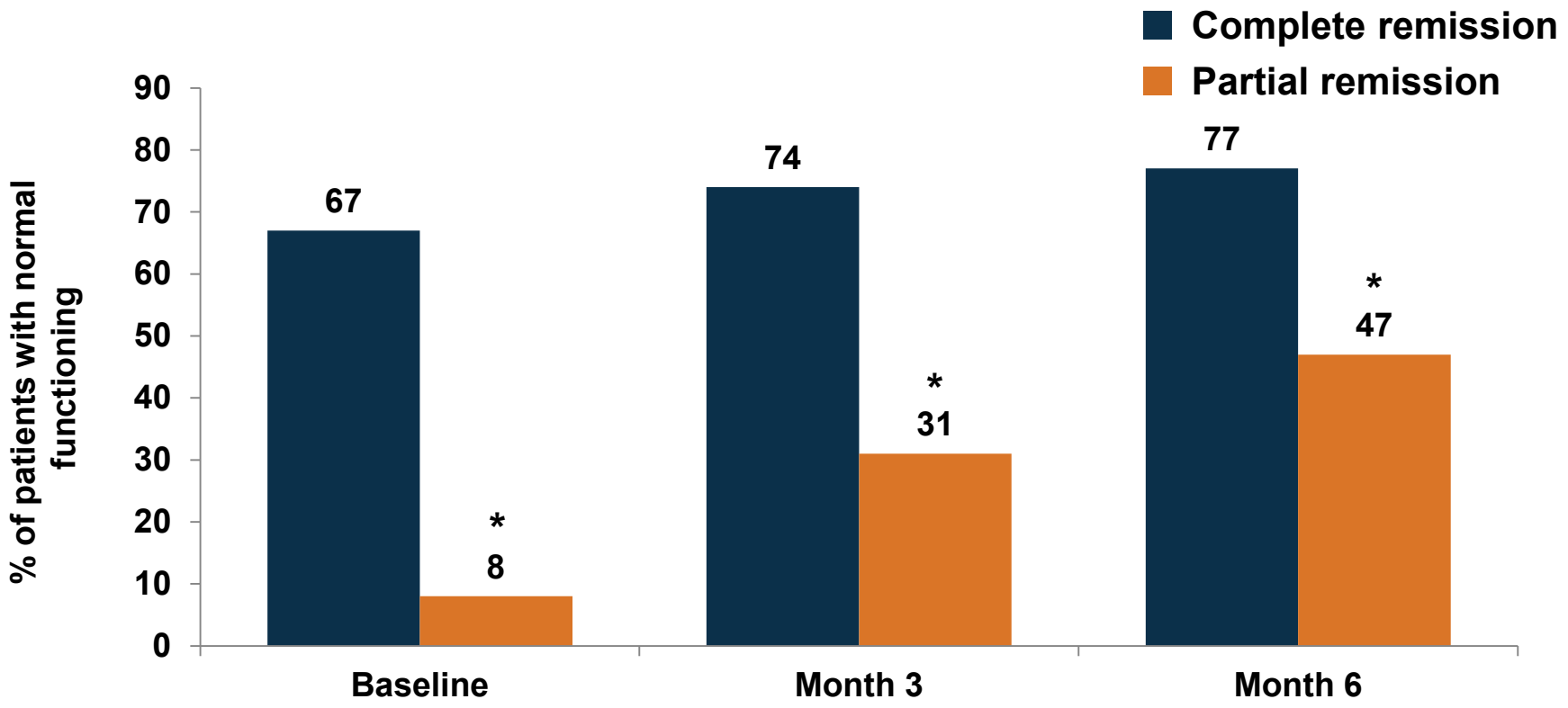
Remission And Functioning



- Normal functioning at endpoint (Month 6) was associated with a complete response at baseline (ie, after 3 months of acute antidepressant treatment).

Note: Normal functioning defined as a Social and Occupational Functioning Assessment Scale score ≥ 80.
*$P < 0.001$.

Romera I et al. *Eur Psychiatry*. 2010;25:58-65.

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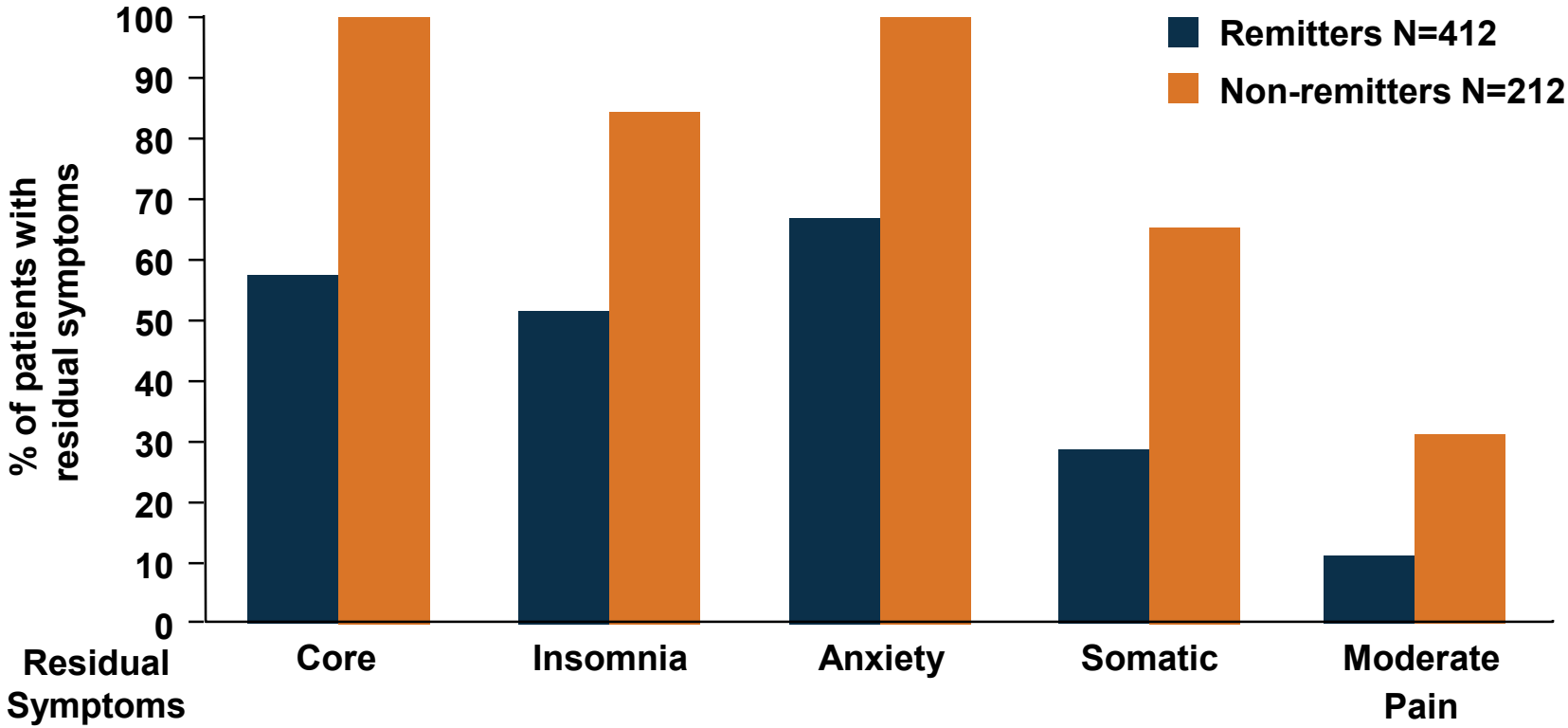
Residual Symptoms And Functioning



- Normal functioning at endpoint (Month 3) was associated with the absence of core mood symptoms (OR 8.7; 95% CI, 4.6–16.7) and insomnia symptoms (OR 1.8; 95% CI, 1.2–2.7)

CI, confidence interval; OR, odds ratio.

Romera I et al. *BMC Psychiatry*. 2013;13; 51.

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Remission As Goal Of Treatment

- Only approximately 28% of patients treated for MDD achieve remission* following treatment with a single antidepressant[1]
- Partial response (indicated by a 25% to 49% reduction in depressive symptoms) is common[2]
- Patients not achieving a full remission typically suffer from troubling residual symptoms[2]
- Even patients considered to be fully remitted report experiencing at least one residual symptom[3,4]
- Ideally, the goal of treatment for MDD is for patients to achieve full remission[5]

*Remission defined as a score of ≤5 on the Hamilton Depression Rating Scale.

1. Trivedi MH et al. *Am J Psychiatry*. 2006;163:28-40;
2. Fava M. *J Psychopharm*. 2006;20(3):29-34;
3. Paykel ES et al. *Psychol Med*. 1995;25(6):1171-1180;
4. Nierenberg AA et al. *Psychol Med*. 2010;40(1):41-50;
5. Trivedi M. *Psychiatry Weekly*. May 21, 2007.

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Significant Challenges Exist Surrounding The Treatment Of MDD

- **There is significant unmet need in the treatment of MDD:**
  - under-treatment due to misdiagnosis or underdiagnosis[1]
  - low rates of adherence and persistence to therapy,[2] potentially influenced by:
    - slow onset of action: antidepressants require 4–6 weeks to achieve full therapeutic effect[3]
    - lack of efficacy: a significant proportion of patients fail to remit or only partially remit despite adequate therapy[4,5]
    - poor tolerability: adverse events associated with pharmacologic agents may reduce adherence and persistence[3]
  - low rates of guideline-concordant follow up[6]

1. Nierenberg. *Am J Manag Care*. 2001(suppl 11):353-66;
2. Cantrell, et al. *Med Care*. 2006;44(4):300-303;
3. Gelenberg, et al. American Psychiatric Association. Practice guideline for the treatment of patients with major depressive disorder. 2010;
4. Olchanski, et al. *Clin Ther*. 2013;35(4):512-22;
5. Nierenberg, et al. *Psychol Med*. 2010;40(1):41-50;
6. Chen, et al. *Gen Hosp Psych*. 2010;32:360-367.

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Real-World Studies Show That <1/2 Of Patients With MDD Receive An Adequate Course Of Therapy

- **A study of commercially insured people found that only 21.7% of those diagnosed with MDD received an adequate course of therapy[1] [a]:**
  - greater depressive symptom severity, functional impairment, duration of depression, and comorbidities were associated with higher probability of adequate treatment
- **A national telephone survey found that only 25.3% of patients with a depressive disorder received an adequate course of therapy[2] [b, c]:**
  - patients with comorbid anxiety disorder were more likely to receive appropriate treatment

a. Defined as: (1) ≥ 4 outpatient visits with a physician for pharmacotherapy, including either an antidepressant or mood stabilizer for ≥ 30 days; or (2) ≥ 8 outpatient visits for psychotherapy lasting ≥30 minutes each.
b. Defined as receiving at least the minimum therapeutic dose of an antidepressant medication for ≥ 2 months.
c. Defined as ≥ 4 visits with a mental health specialist or PCP that included counseling for mental health problems.

1. Kessler, et al. *JAMA*. 2003;289(23):3095-3105;
2. Young, et al. *Arch Gen Psychiatry*. 2001;58(1):55-61.

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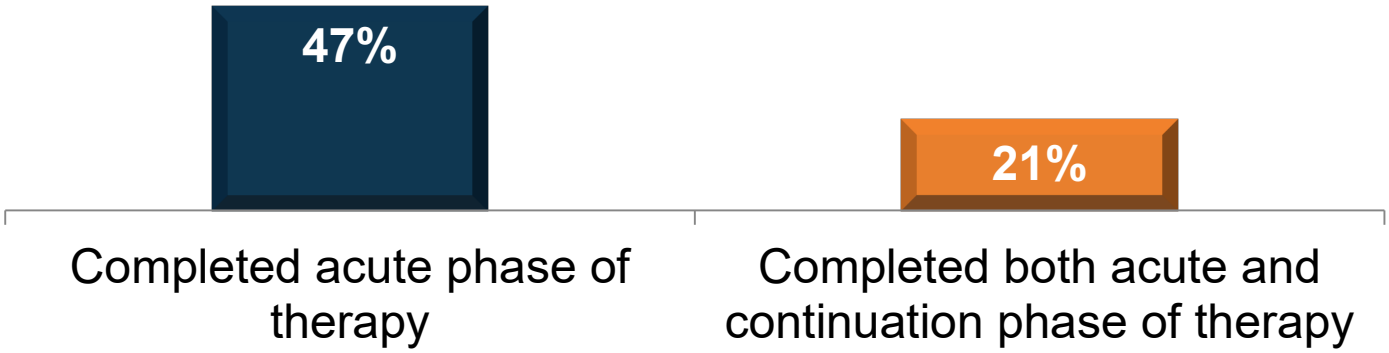
Adherence To Therapy Is A Key Issue In Treating Patients With MDD

- **The association between prescriber specialty, follow-up visits, and proportion of patients to complete antidepressant regimen was estimated retrospectively using data from a large national health plan (N = 4102)[1]:**
  - overall, less than half of patients completed the acute phase of therapy and approximately only 1/5 completed both the acute and continuation phase[1]
- **These results suggest improved adherence to antidepressants is seen when proper provider support is in place and patients participate in frequent follow-up**



Chen, et al. *Gen Hosp Psych.* 2010;32:360-367.

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The Majority Of Patients Are Nonadherent

- **APA Guidelines recommend that newly diagnosed patients remain on therapy for 6–9 months, yet over 40% of patients discontinue within 3 months[1]:**
  - studies show that ≤ 50% of MDD patients are adherent over the first 6 months of therapy, and 30% discontinue within the first month[2]
  - premature discontinuation is associated with a 77% increase in the risk of a relapse[3]

Physicians should check for nonadherence before assuming the drug is not effective

1. Cantrell, et al. *Med Care*. 2006;44(4):300-303;
2. Liu, et al. *Clinicoecon Outcomes Res*. 2011;3:63-72;
3. Melfi, et al. *Arch Gen Psychiatry*. 1998;55(12):1128-32.

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Urgency To Treat Residual Symptoms

- Residual depressive symptoms are associated with an increased risk of relapse and poor psychosocial functioning[1,2]
- Adequate pharmacological intervention early in the disease is important to reduce the amount of the time in a depressed state, thereby decreasing the risk of suicide[1,2]

1. Fava M. *J Psychopharmacology*. 2006;20(3):29-34.
2. Sokero TP et al. *Br J Psychiatry*. 2005;186:314-318.

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Response To Antidepressant Treatment In MDD

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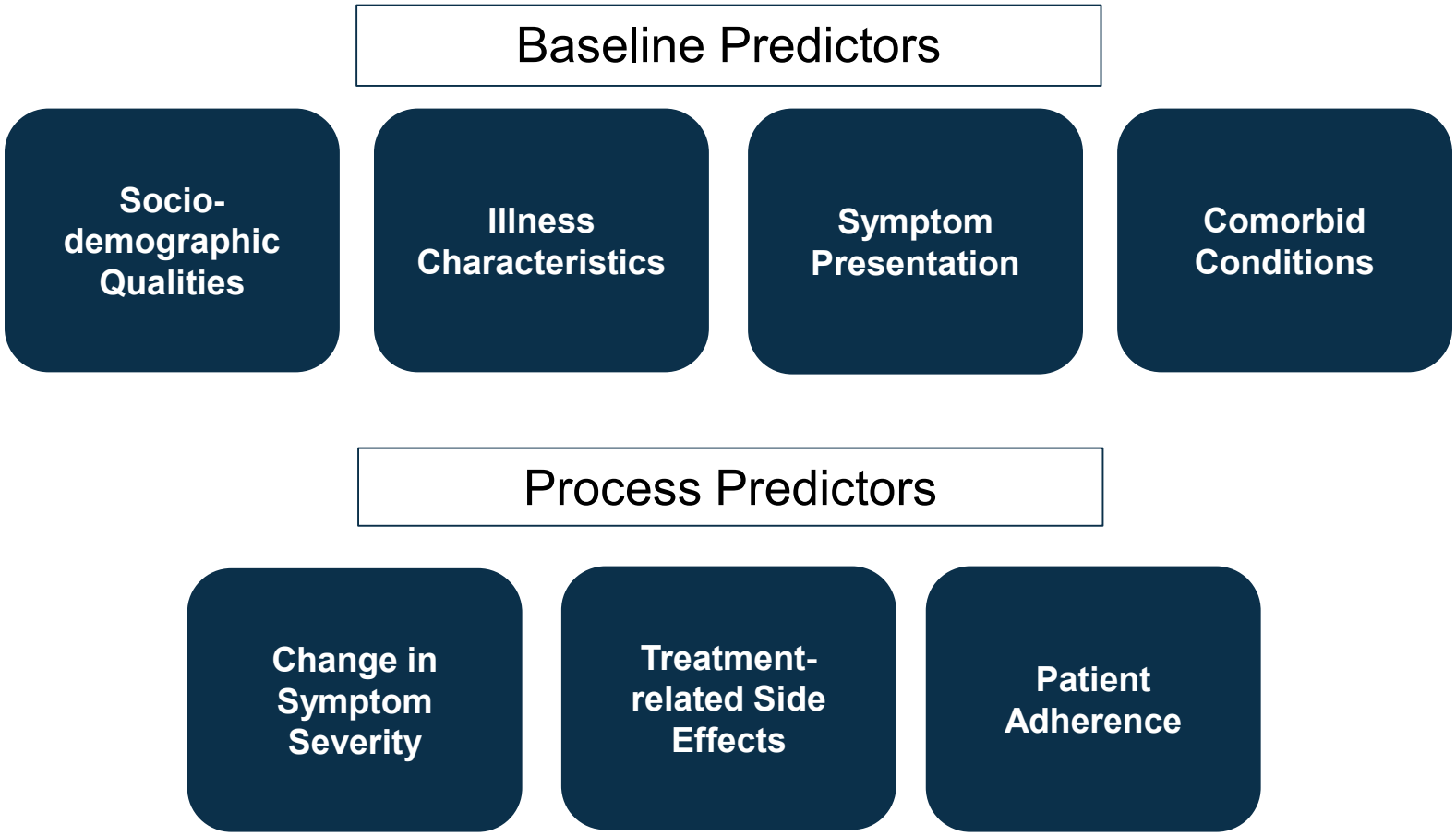
Predicting Patient Response To Antidepressant Treatment



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

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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

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

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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.

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The Delayed-Onset Hypothesis Of Antidepressant Treatment

- Initially believed that antidepressants take approximately 1 month for full antidepressant activity, with a delayed onset of action of at least 2 weeks[1]
- Methodological issues:
  - Few prospective trials; majority of data based on post-hoc analyses, meta-analyses, and naturalistic studies[1]
  - Randomized trials rely on significant drug/placebo differences in mean rating scale scores, which do not detect early significant symptom changes in individuals[1]
  - Frequently used instruments such as the HAM-D are not very sensitive to treatment change[1]
  - The weekly/bi-weekly measurements are too infrequent to detect early changes[1]
  - The current cut-off point for a response of 50% improvement from baseline may be too strict to detect slight, but significant, early changes[1]
    - A 20% cut-off may be more accurate, although somewhat arbitrarily determined[2]

1. Möller HJ et al. *Medicographia*. 32;2010:139-145.
2. Ahn YM. *Medicographia*. 32;2010:161.

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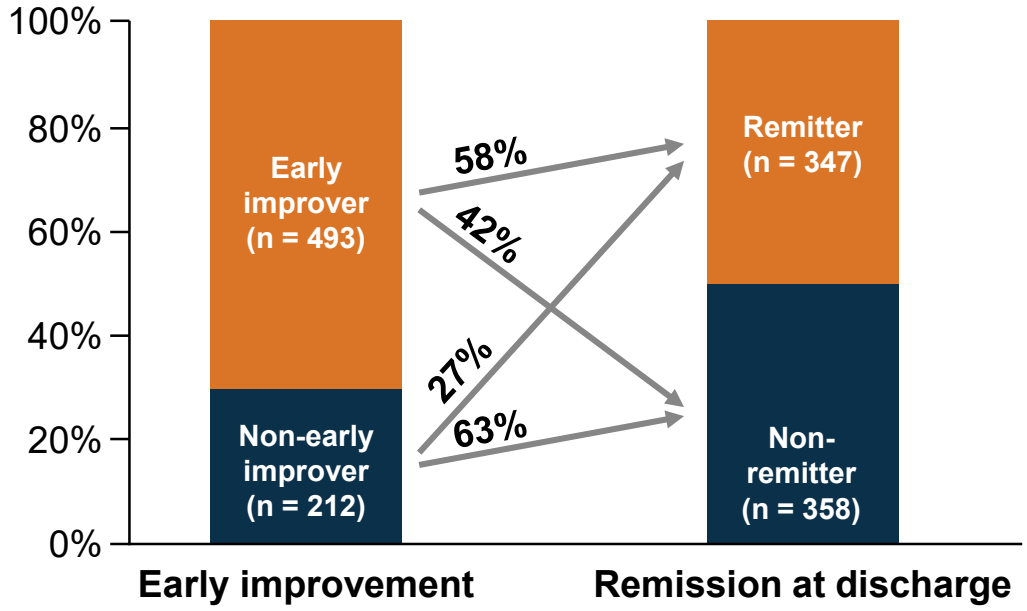
Early Improvement Is Common And Predicts Remission



- Earlier onset of response before 2 weeks is common and highly predictive of later outcome[1-3]
- If no improvement is observed after 2 weeks, treatment should be adjusted or changed immediately[4]

1. Henkel V et al. *J Affect Disord*. 2008;115:439-449;
2. Nierenberg AA et al. *Am J Psychiatry*. 1995; 152:1500-1503;
3. Szegedi A et al. *J Clin Psychiatry*. 2009;70:344-353;
4. Möller HJ et al. *Medicographia*. 32;2010:139-144.

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Identifying The Inadequately Treated Patient

- Measurement tools for assessing severity of depression used during the first 2–4 weeks of antidepressant treatment can accurately predict the likelihood of a response or lack of response to treatment after a longer term (8 weeks)[1]
- Assessment tools to evaluate changes in symptom states during the first 4 weeks of treatment can also predict treatment response at 12 weeks[2]
  - Dividing the HAM-D-17 into symptom clusters (mood, sleep/psychic anxiety, appetite, and somatic anxiety/weight) and evaluating change scores at 4 weeks correctly assigned up to 70% of patients as late responders or nonresponders at 12 weeks

1. Nirenberg AA et al. *Am J Psychiatry*. 2000;157:1423-1428;
2. Trivedi MH et al. *J Clin Psychiatry*. 2005;66(8):1064-1070.

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Evidence For The Treatment Of Patients With MDD And Practical Guidelines

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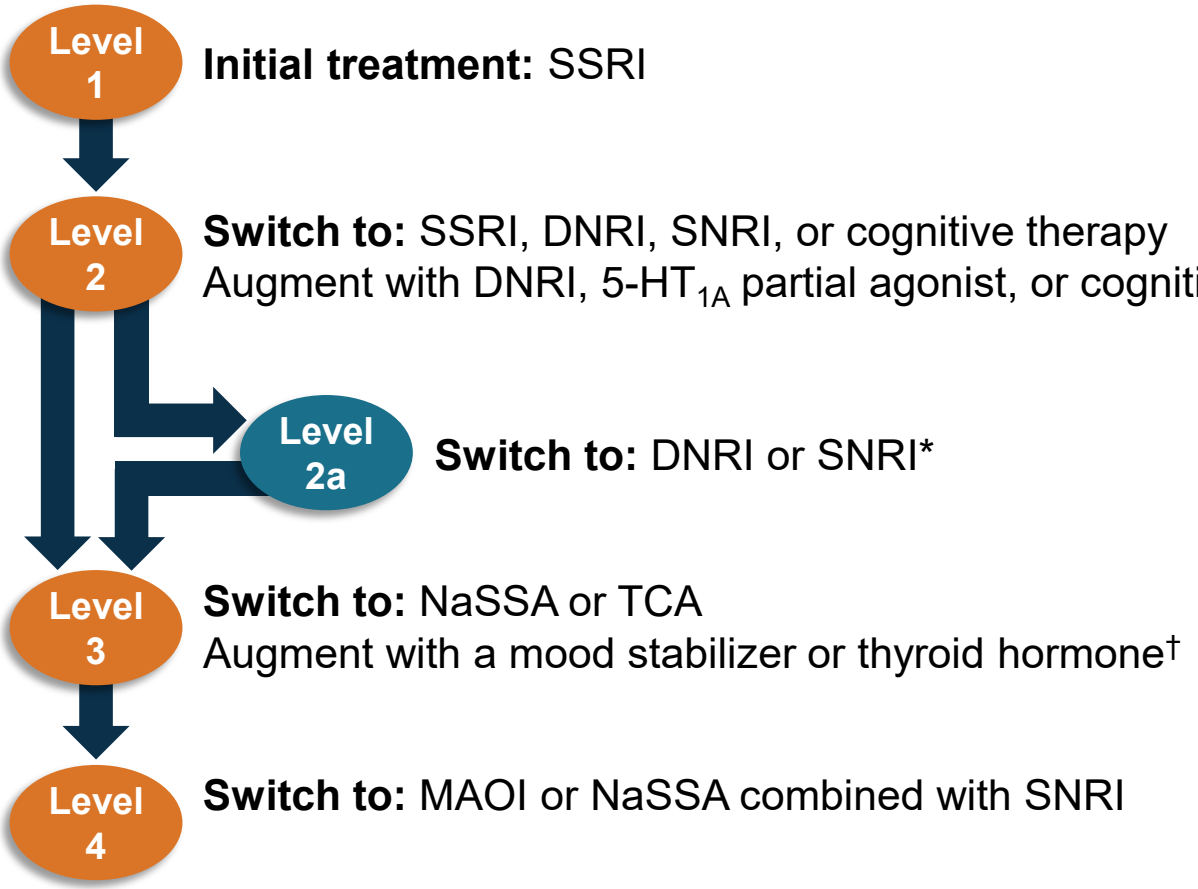
STAR*D Treatment Algorithm: Examining Different Treatment Strategies In A "Real-World" Setting



*Only for those who failed cognitive therapy; †Only with DNRI, SSRI, or SNRI.

DNRI, dopamine and norepinephrine reuptake inhibitor; MAOI, monoamine oxidase inhibitor; NaSSA, noradrenergic and specific serotonergic antidepressant; SNRI, serotonin norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; STAR*D, Sequenced Treatment Alternatives to Relieve Depression;
TCA, tricyclic antidepressant.

Rush AJ et al. *Am J Psychiatry*. 2003;160(2):237.

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STAR*D Results

Symptom Remission[a] (% Patients)

Level 1[1,2]	SSRI (n = 3671)				28%		
Level 2[3-5]	SSRI (n = 238)	DNRI (n = 239)	SNRI (n = 250)	Cognitive Therapy (n = 36)	DNRI + SSRI (n = 279)	5HT-1A Partial Agonist + SSRI (n = 286)	Cognitive Therapy + SSRI (n = 65)
	18%	21%	25%	25%	30%	30%	23%
Level 3[6,7]	NaSSA (n = 114)		TCA (n = 121)		Mood Stabilizer +ADT (n = 69)	Thyroid Hormone +ADT (n = 73)	
	12%		20%		16%	25%	
Level 4[8]	MAOI (n = 58)		NaSSA + SNRI (n = 51)				
	7%		14%				

Note: Trial was not designed to directly compare switch or augmentation medication treatments.
[a]Defined by exit score ≤ 7 on the HAM-D17.

ADT, antidepressant therapy; HAM-D17, 17-item Hamilton Depression Rating Scale.

1. Rush AJ et al. Am J Psychiatry. 2006;163:1905-1917;
2. Trivedi MH et al. *Am J Psychiatry*. 2006;163(1):28-40;
3. Rush AJ et al. *N Engl J Med*. 2006;354(12):1231-1242;
4. Thase ME et al. *Am J Psychiatry*. 2007;164(5):739-752;
5. Trivedi MH et al. *N Engl J Med*. 2006;354(12):1243-1252;
6. Fava M et al. *Am J Psychiatry*. 2006;163 (7):1161-1172;
7. Nierenberg AA et al. *Am J Psychiatry*. 2006;163(9):1519-1530;
8. McGrath PT et al. *Am J Psychiatry*. 2006;163(9):1531-1541.

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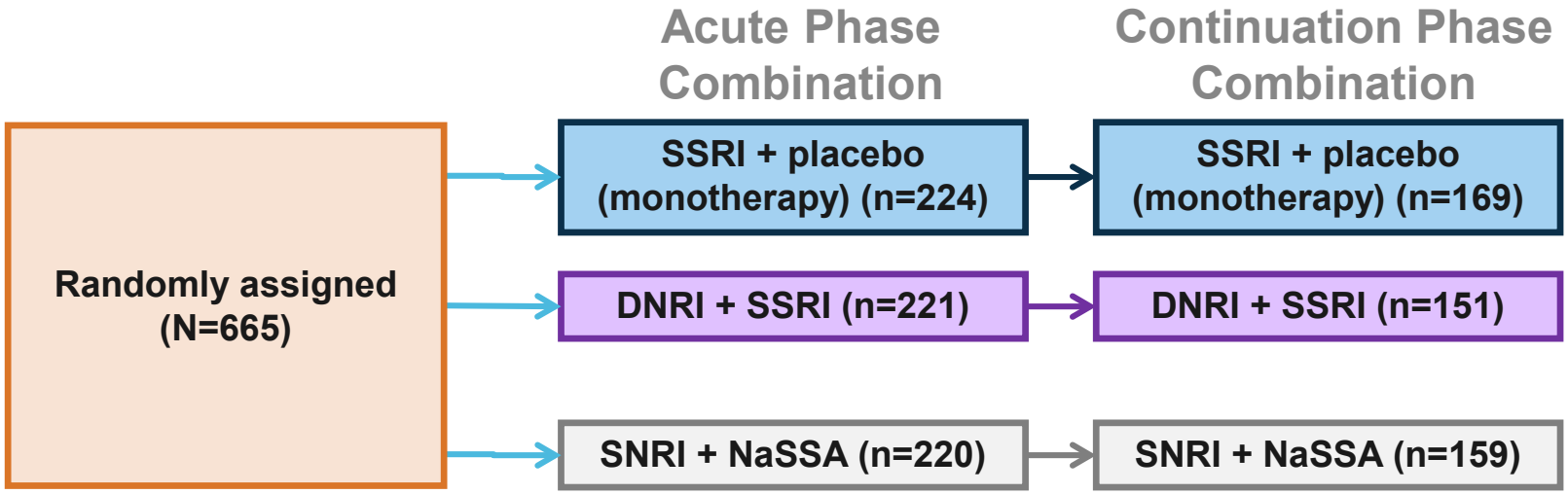
Combining Medications To Enhance Depression Outcomes (CO-MED) Study Design



DNRI, dopamine and norepinephrine reuptake inhibitor; NaSSA, noradrenergic and specific serotonergic antidepressant; SNRI, serotonin norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

Rush AJ et al. *Am J Psychiatry*. 2011;168(7):689-701.

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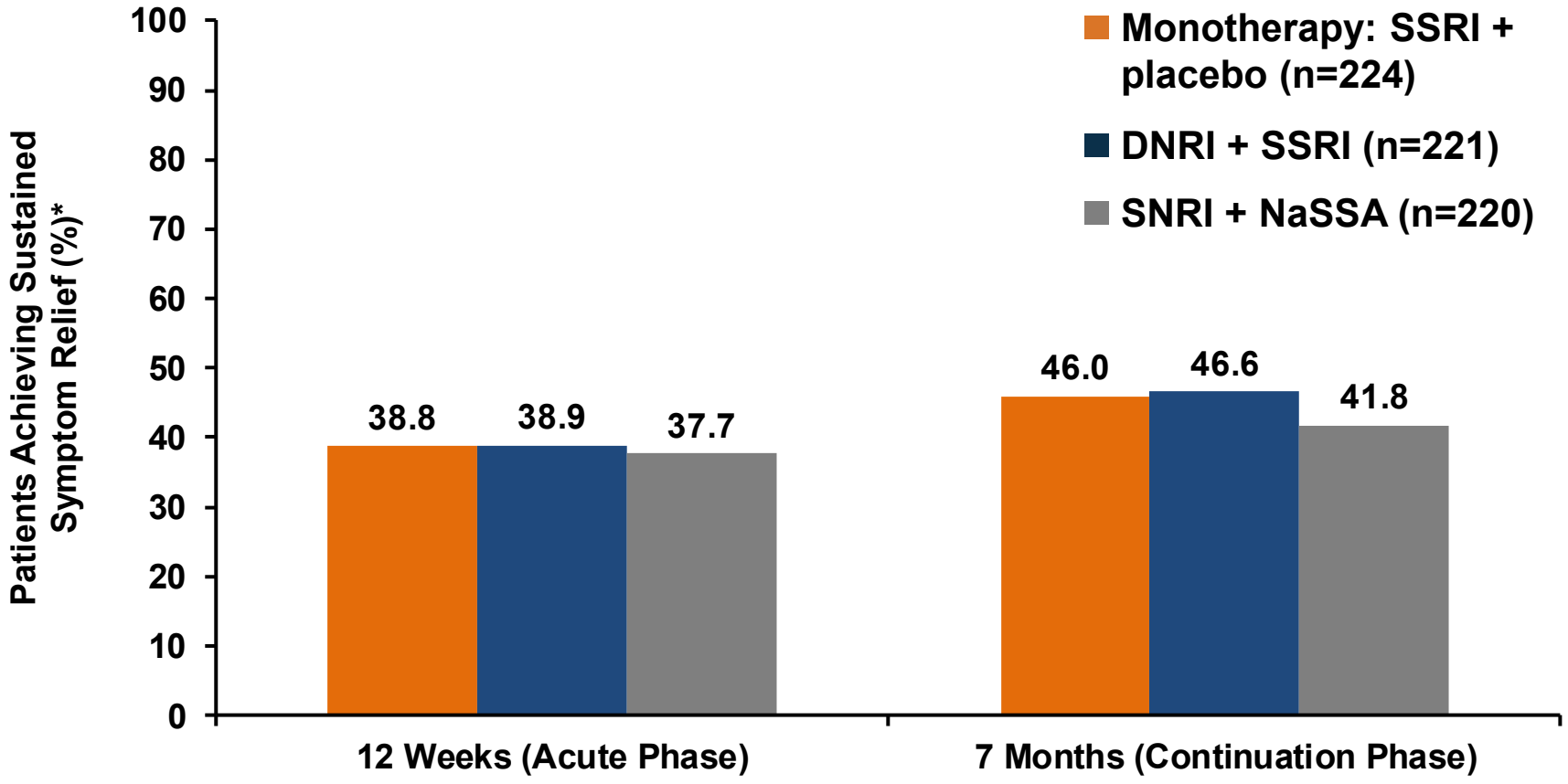
CO-MED Results: Percentage Of Patients Achieving Sustained Symptom Relief



*Defined as scores of <8 and <6 on the 16-item Quick Inventory of Depressive Symptomatology—Self-Report (QIDS-SR16) at the last two consecutive assessments.

Rush AJ et al. Am J Psychiatry. 2011;168(7):689-701.

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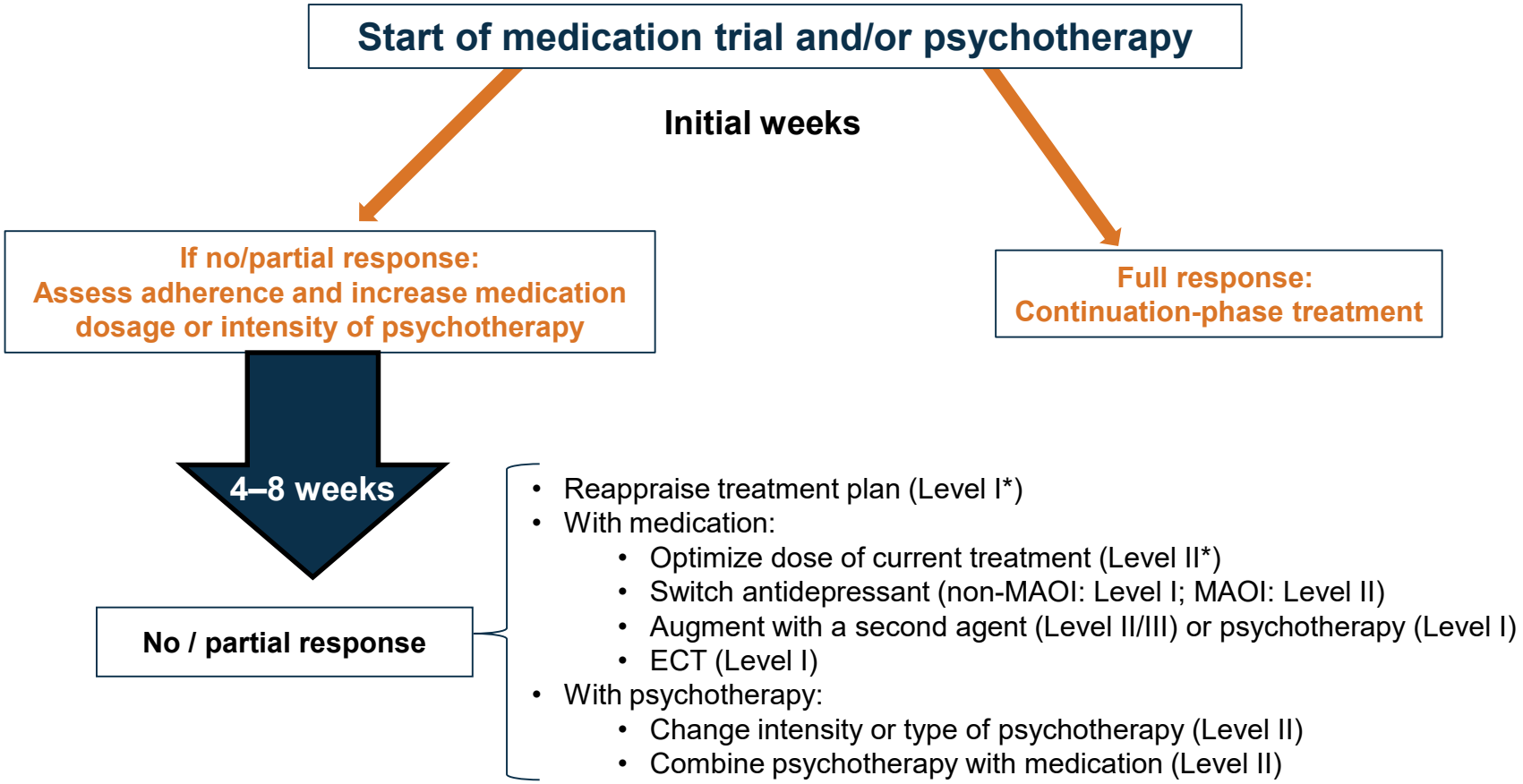
Revised APA Guidelines For The Acute-Phase Treatment Of MDD



*Level I = recommended with substantial clinical confidence; Level II = recommended with moderate clinical confidence; (Level III = may be recommended on the basis of individual circumstances).

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

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Revised APA Guidelines: Augmentation Recommendations For No/Partial Response To Antidepressant Therapy

Augmentation Options*	Level of Clinical Confidence (I-III)‡
Psychotherapy	I
Second Antidepressant Therapy†	II
Atypical Antipsychotic	
Thyroid Hormone	
Mood Stabilizer	
Anticonvulsant	III
Psychostimulant	
Omega-3 Fatty Acid	
Folic Acid	
Anxiolytic or Sedative/Hypnotic	

*Classes of medication have been used in this table to replace some of the specific drug names.
†Includes non-MAOI and MAOI antidepressants.
‡Level I = recommended with substantial clinical confidence; Level II = recommended with moderate clinical confidence; (Level III = may be recommended on the basis of individual circumstances).
Adapted from American Psychiatric Association. Practice Guideline for the Treatment of Patients With Major Depressive Disorder. 3rd ed. Arlington, VA: American Psychiatric Association; 2010.

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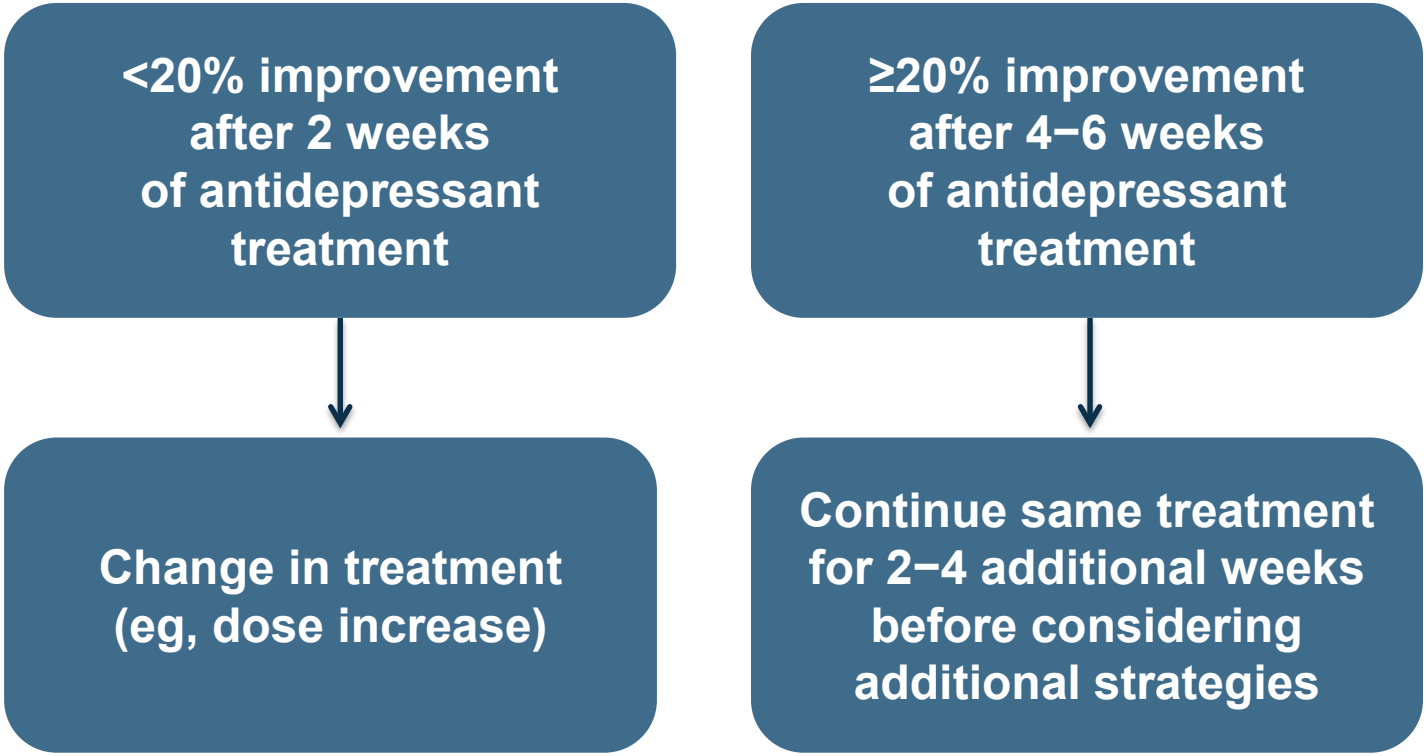
Treatment Guidelines: CANMAT



Lam RW et al. *J Affect Disord*. 2009;117 (Suppl 1):S26-43.

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CANMAT: Recommendations For Nonresponse Or Incomplete Response To Initial ADT

First-line (Level 1 or Level 2 evidence, plus clinical support*)

- Switch to an agent with evidence for superiority
  - SSRIs [Level 1]
  - SNRIs [Level 1-2]
  - Noradrenergic-serotonin modulator [Level 2]
- Add on another agent
  - Mood stabilizer [Level 1]
  - Atypical antipsychotics [Level 1-2]

Second-line (Level 3 evidence or higher, plus clinical support*)

- Add on another agent
  - DNRI [Level 2]
  - Noradrenergic-serotonin modulator [Level 2]
  - Atypical antipsychotic [Level 2]
  - Thyroid hormone [Level 2]
- Switch to an agent with evidence for superiority, but with side effect limitations
  - TCAs [Level 2]
  - MAO inhibitors [Level 2]

Third-line (Level 4 evidence or higher, plus clinical support*)

- Add on another agent
  - Serotonin 5-HT_{1A} receptor partial agonist [Level 2]
  - Psychostimulant [Level 2]
  - Stimulants [Level 3]
  - Atypical antipsychotic [Level 3]

Level of Evidence Criteria

1=At least 2 RCTs with adequate sample sizes, preferably placebo controlled, and/or meta-analysis with narrow confidence intervals.

2=At least 1 RCT with adequate sample size and/or meta-analysis with wide confidence intervals.

3=Nonrandomized, controlled prospective studies or case series or high quality retrospective studies.

4=Expert opinion/consensus.

*Treatments with higher Levels of Evidence may be downgraded to lower Lines of Treatment due to clinical issues such as side effect or safety profile.

Not all products in the therapeutic categories listed are indicated for adjunctive treatment in adult patients with MDD with an inadequate response to antidepressant therapy.

Classes of medication have been used to replace some of the specific drug names. Levels of evidence and recommendations are represented for individual agents and should not be extrapolated to other agents in the same class. Please see the CANMAT Guidelines for further information on the specific drug recommendation options.

Lam RW et al. *J Affective Disord*. 2009;117(suppl 1):S26-S43.

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International Consensus Statement On Optimizing Antidepressant Therapy

- Begin pharmacotherapy with an SSRI, SNRI, or DNRI
- After reaching a minimally effective dose, wait roughly 2–4 weeks to assess symptomatic improvement and tolerability before deciding how to optimize therapy:

Increase the Dose (for inadequate improvement but acceptable tolerability)

Maintain the Current Dose (for adequate improvement and acceptable tolerability)

Decrease the Dose (for adequate improvement but poor tolerability)

Switch to a Different Agent (for inadequate improvement and poor tolerability)

DNRI, dopamine and norepinephrine reuptake inhibitor; NaSSA, noradrenergic and specific serotonergic antidepressant; SNRI, serotonin norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

Nutt DJ et al. *J Clin Psychiatry*. 2010;71(suppl E1):e08.

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International Consensus Statement On Optimizing Antidepressant Therapy (cont)

- Assessment of symptomatic improvement and tolerability should occur every 2 weeks and at each assessment. Reasonable treatment options for partial or lack of efficacy include:

Modifying the antidepressant dose

Switching to a different antidepressant

Switching to augmentation/ combination strategies

- Augmentation/combination strategies include mood stabilizers, atypical antipsychotics, thyroid hormone, NaSSA, or DNRI

DNRI, dopamine and norepinephrine reuptake inhibitor; NaSSA, noradrenergic and specific serotonergic antidepressant.
Nutt DJ et al. *J Clin Psychiatry*. 2010;71(suppl E1):e08.

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Non-Pharmacologic Therapies For MDD

Categories of Care	Care Strategies
Psychotherapy	Cognitive Behavioral Therapy (CBT)[1]
	Interpersonal Therapy[1]
	Group Therapy[1]
	Problem Solving Therapy[1]
	Future Directed Therapy (FDT)[2]
Alternative Mind-Body Therapy	Relaxation techniques (breathing exercises, meditation, etc.)[3]
	Yoga, tai chi, qigong[3]
Family/Caregiver Involvement	Family/caregiver involvement in the patient treatment plan facilitates day to day management of chronic difficulties of depression[4]
Web-Based Intervention	Deprexis (an interactive program that integrates multiple therapeutic approaches to depression)[5]

1. American Psychiatric Association. Practice Guideline for the Treatment of Patients With Major Depressive Disorder. 3rd ed. Arlington, VA: American Psychiatric Association; 2010;
2. Vilhauer JS et al. *Innov Clin Neurosci.* 2013;10(3):12-2;
3. Bertisch SM et al. *J Psychosom Res.* 2009;66(6):511-519;
4. Justin RG. *Prim Care Companion. J Clin Psychiatry.* 2001;3(6):267;
5. Meyer B et al. *J Med Internet Res.* 2009;11(2):e15.

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Challenges And Integrated Care Strategies For MDD

- Patient is feeling somewhat better following antidepressant treatment initiation but complains of lingering feelings of depressed mood
- Patient is feeling better with antidepressant therapy but complains of insomnia or aches and pains
- Patient is in obvious need of social support but is not interested in, or does not have access to, help (such as a support group)
- Patient complains that family members do not understand what they are going through and think family members are just angry and frustrated with them
- Patient is partially responding to antidepressant but expresses feelings of hopelessness and a general low satisfaction with life

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Measurement-Based Care

- Among practitioners, clinical treatment of depression is often associated with wide variations in dosage and duration of treatment[1]
- Measurement-based care was developed as a systematic approach to evaluate patient progress and eliminate variability in patient treatment among physicians
  - In STAR*D, measurement-based care included the routine measurement of symptoms and side effects at each treatment visit; a treatment manual was used by treating physicians that detailed precisely when and how to modify medication regimens or doses based on results of assessments[2]
- A wide variety of physician-rated and patient-rated scales are currently available to evaluate patient symptoms, functioning ability, treatment progress, and side effects[3]
  - For more information, please see: http://www.outcometracker.org/scales_library.php

1. Trivedi MH et al. *Neuropsychopharmacology*. 2007;32(12):2479-2489.;
2. Trivedi MH et al. *Am J Psychiatry*. 2006;163(1):28-40;
3. Zimmerman M. http://www.outcometracker.org/scales_library.php. Accessed October 1, 2013.

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Summary

- MDD is a serious, chronic, disabling illness affecting hundreds of millions of individuals worldwide
- Use of assessment tools and measurement-based care may facilitate patient-physician dialogue
- Residual symptoms are common and cause significant psychosocial and occupational functional impairment
- Over 90% of MDD patients experience residual symptoms during the course of treatment
  - These patients are at increased risk for depressive relapse
- Patients with residual symptoms, relapse, and/or suicidality should receive increased vigilance and a more aggressive treatment approach (including combination therapy, psychotherapy, cognitive behavioral therapy, etc)

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