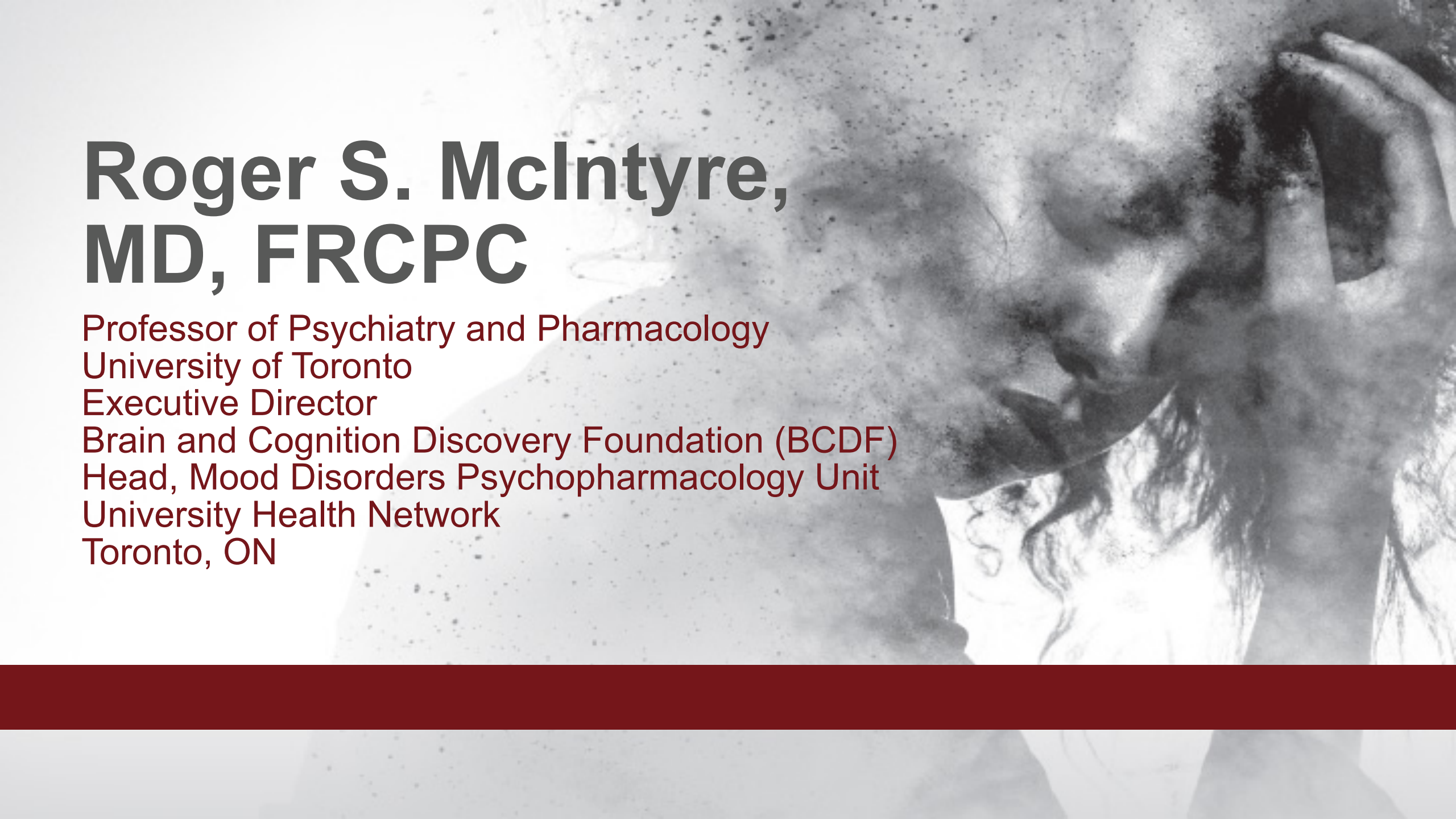
May 16, 2017

INTEGRATED CARE STRATEGIES TO ADDRESS THE IMPACT OF RESIDUAL SYMPTOMS ON FUNCTIONAL OUTCOMES IN MDD

#MDD2017

6:30pm - 8:30pm | Mandalay Bay South Convention Center, Las Vegas | Oceanside D

Provided by CME Outfitters



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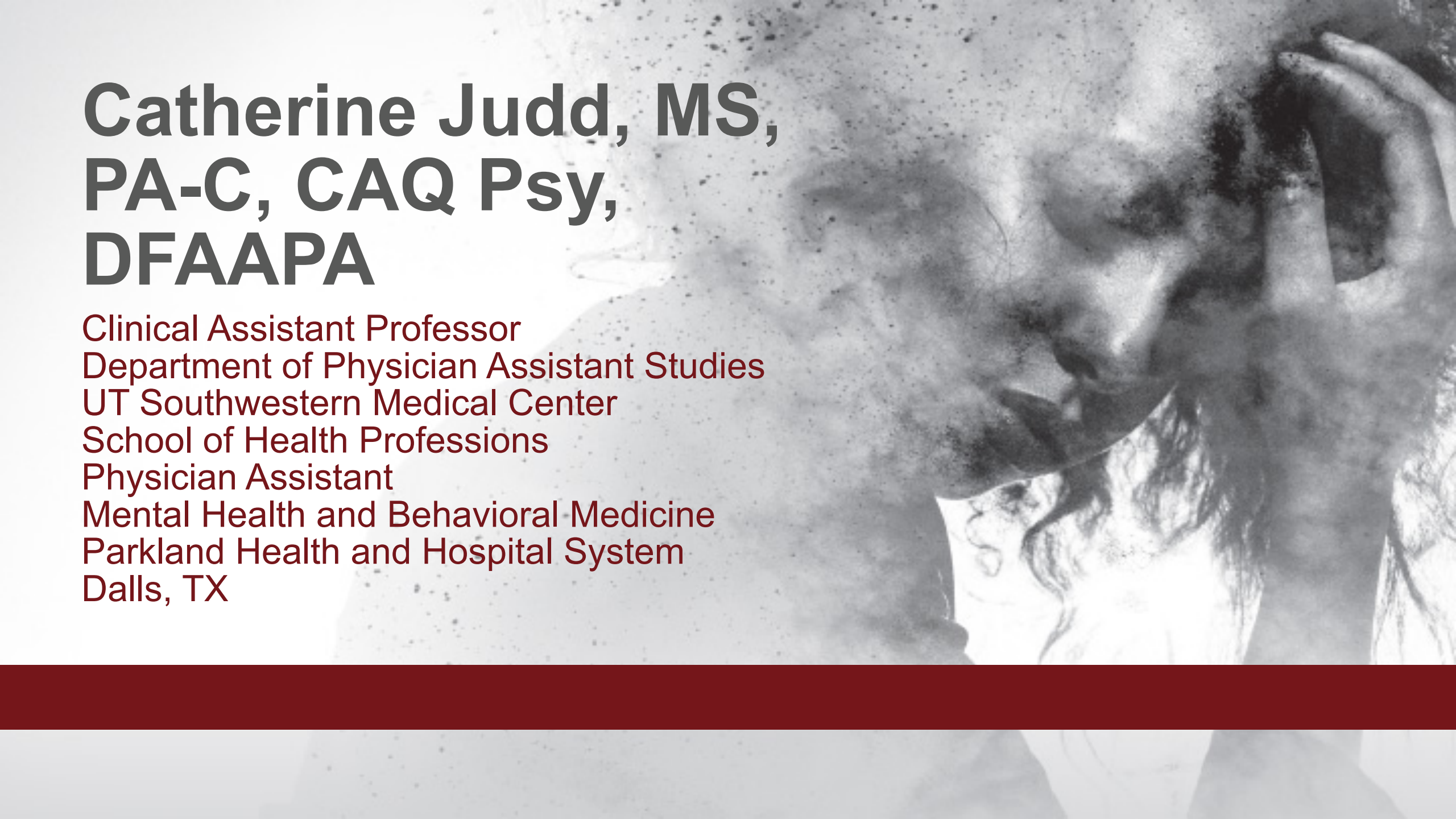

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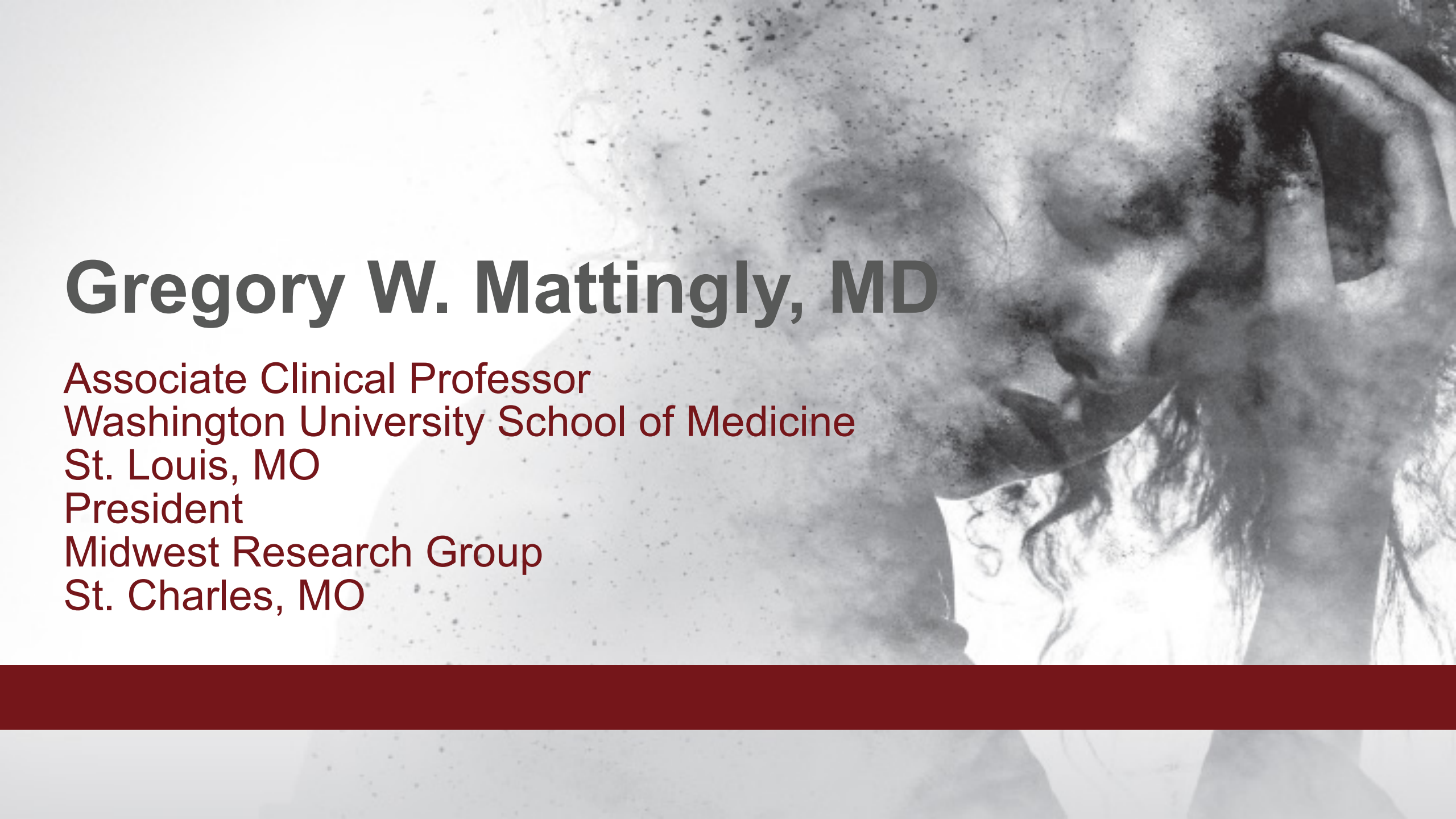

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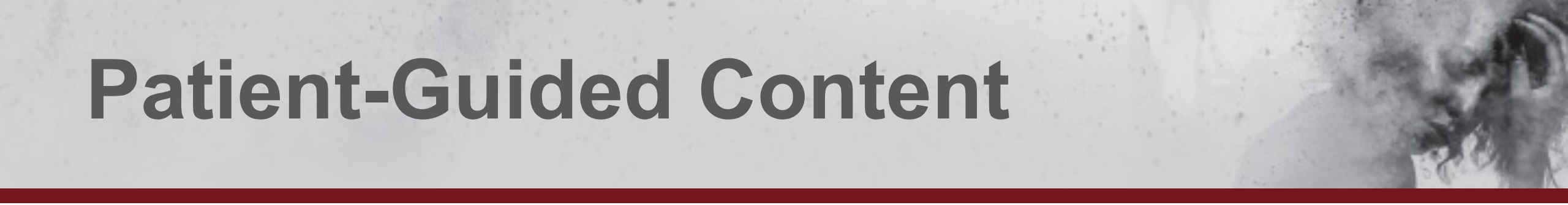
We will be live tweeting from today's symposium – tweet us your questions using #MDD2017

Patient-Guided Content



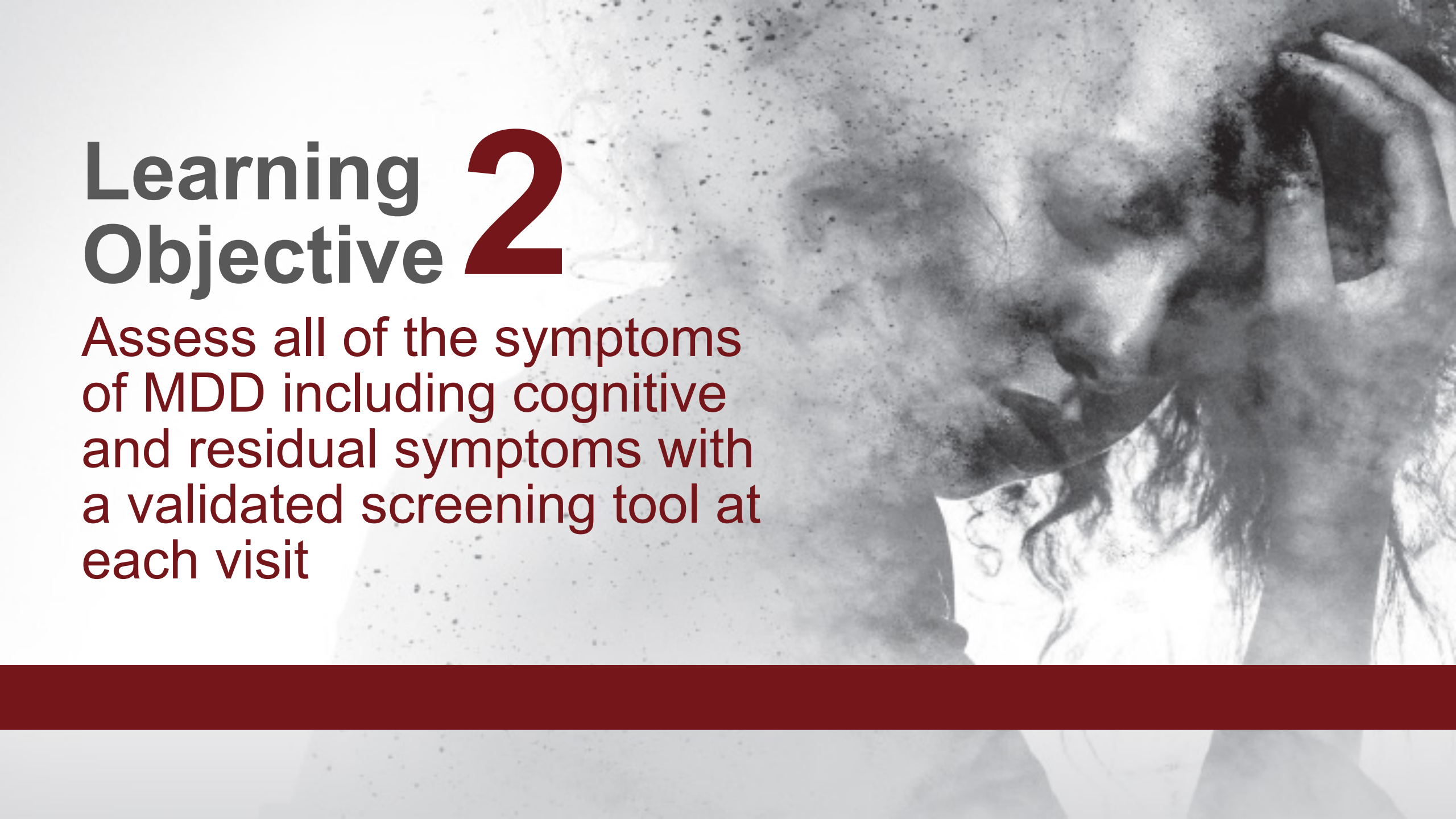
- Developed following a telephone survey of patient leaders who have been diagnosed with major depression
- The survey highlights patients' needs, concerns, and experiences related to MDD

Learning Objective 1

Recognize the relationship between residual cognitive symptoms and functional impairment in patients with MDD

Learning Objective 2

Assess all of the symptoms of MDD including cognitive and residual symptoms with a validated screening tool at each visit



Learning Objective 3

Engage patients in shared decision-making to optimize their treatment options to manage all symptoms of MDD

Major Depressive Disorder (MDD)

- Affects 18 million US residents and 340 million worldwide[1] (16.2% lifetime risk)[2]; 2/3 are female
- Depression is chronic or recurrent
  - 25% to 40% experience a recurrence within 2 years of the index episode[3]
  - 60% experience recurrence after 5 years[3]
  - 20% to 35% of patients who experience one episode of depression have chronic depression[4-6]

1. Greden JF. *J Clin Psychiatry*. 2001;62(suppl 22):5-9.; 2.Kessler RC, et al. *JAMA*. 2003;289:3095-3105.; 3.Keller MB, et al. *Biol Psychiatry*. 1998;44:348-360.; 4. Keller MB, et al. *Am J Psychiatry*. 1982;139:438-442.; 5. Mueller TI, et al. *Psychiatr Clin North Am*. 1996;19:85-102.; 6. Fava M, et al, for the STAR*D Investigators Group. *Psychiatr Clin North Am*. 2003;26:457-494.

Current Treatment in MDD

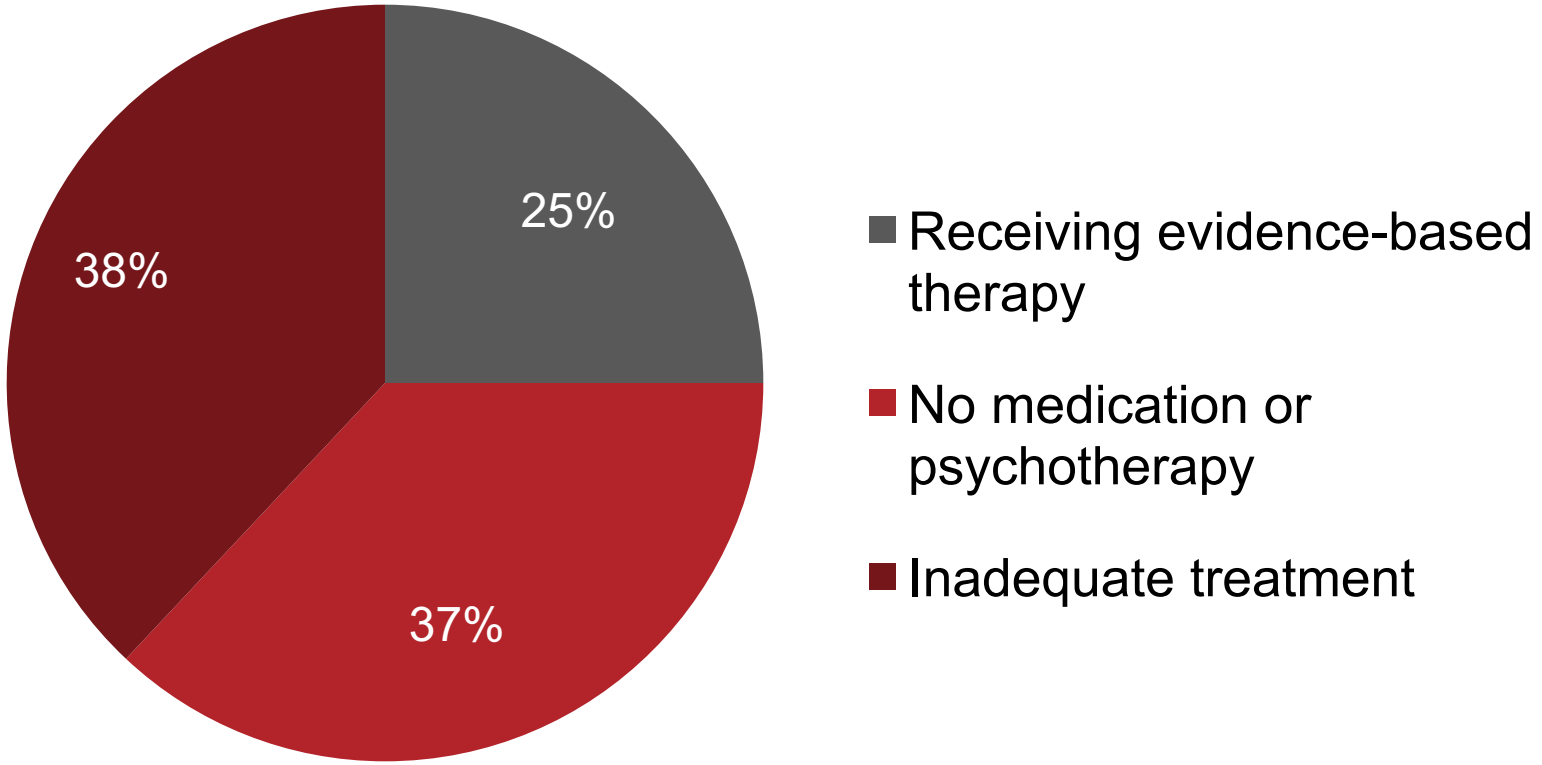
- Data show that only 28% - 33% of patients treated with antidepressant monotherapy reach remission[1]
- The gold standard of remission[2]
  - Hamilton Depression Scale (HAM-D) score of seven or less
  - Nearly asymptomatic

1. Trivedi MH, et al. *Am J Psychiatry*. 2006;163:28-40. PMID: 16390886.

2. Möller HJ. *World J Biol Psychiatry*. 2008;9(2):102-114. PMID: 18428079.

Undertreatment of Patients With MDD

Patients with severe symptoms of MDD



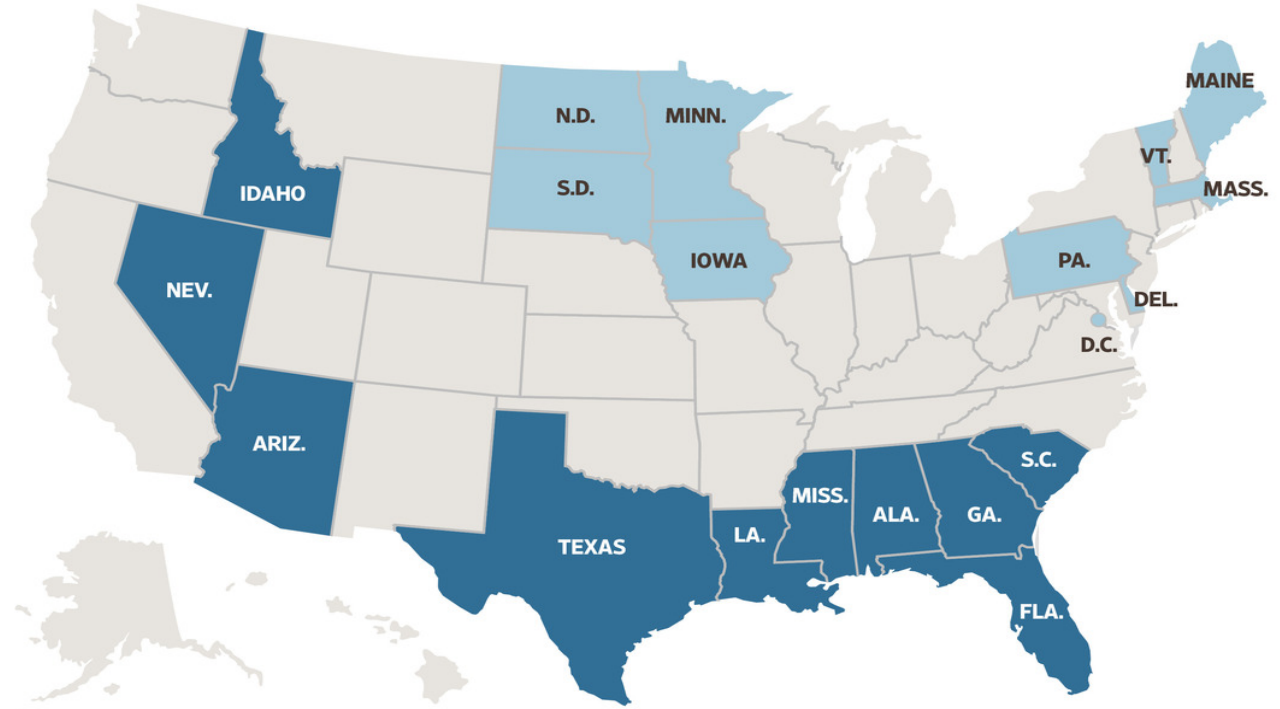
Study based on data from NHANES 2005-2008.

Shim RS, et al. *J Am Board Fam Med*. 2011;24:33-38.

Access to Mental Health Care in the US

Taking Care

How Mental Health America, a patient advocacy group, ranks the states on access to care, from best to worst. The ranking reflects measures including access to insurance, access to treatment, quality and cost of insurance and access to special education.



Best 10

1. Vermont
2. Massachusetts
3. Maine
4. Delaware
5. Iowa
6. North Dakota
7. Pennsylvania
8. Minnesota
9. South Dakota
10. District of Columbia

Worst 10

42. Idaho
43. South Carolina
44. Florida
45. Georgia
46. Arizona
47. Texas
48. Louisiana
49. Alabama
50. Mississippi
51. Nevada

42.5 million
Number of adults in the U.S. who have mental illness (18% of adult population)

1:790
Ratio of mental-health providers to people in the U.S.

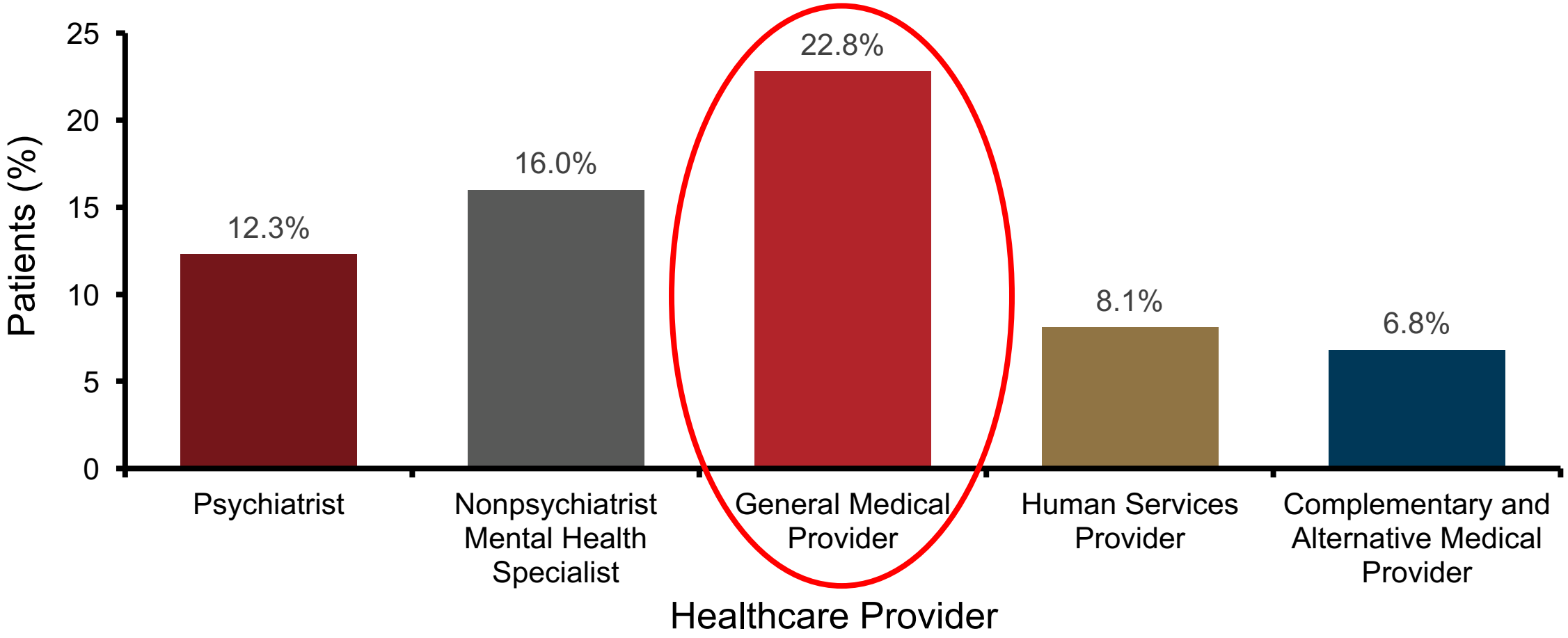
41%
Share of people with mental illness who report receiving treatment

Source: Mental Health America

THE WALL STREET JOURNAL

Available at http://www.wsj.com/articles/where-are-the-mental-health-providers-1424145646

Whom Do Patients See for Mental Health Care?



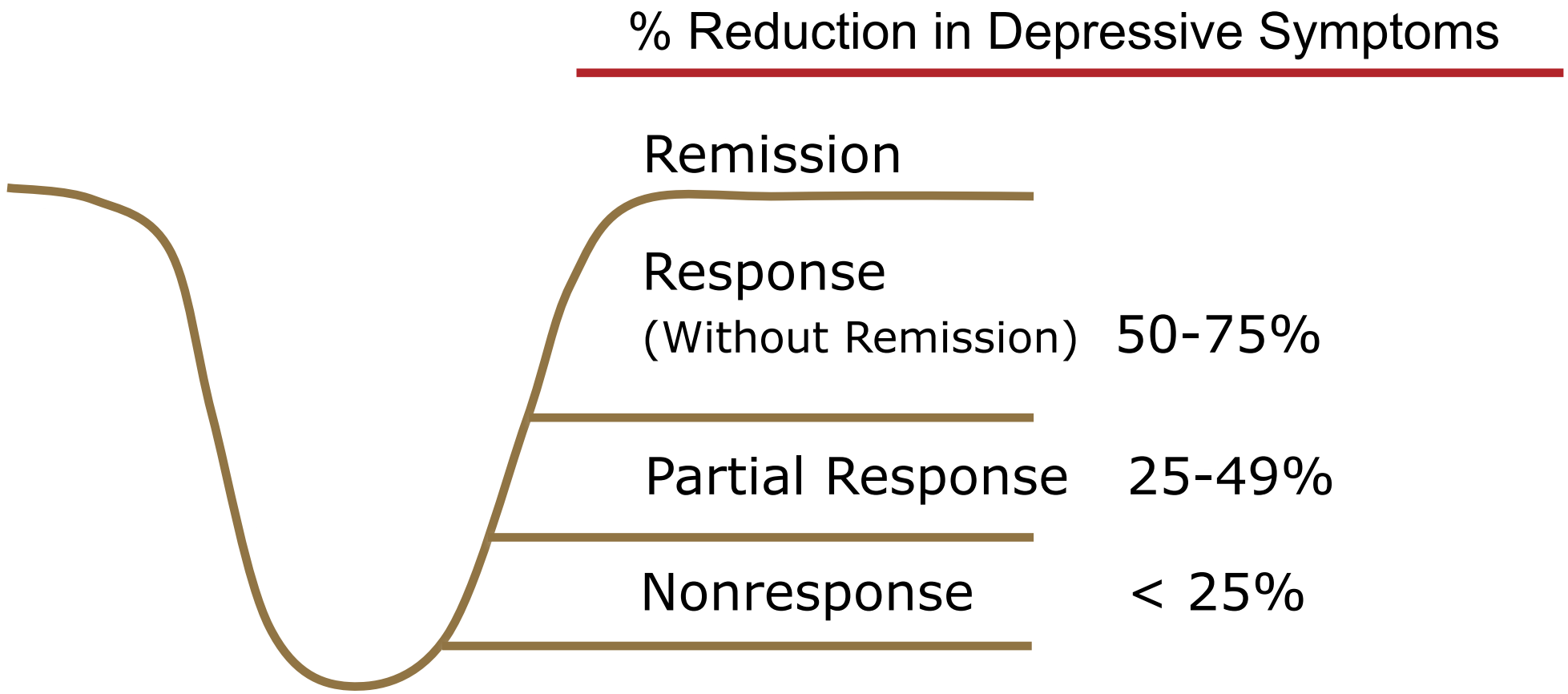
Treatment could be received by > 1 source.

Wang PS, et al. *Arch Gen Psychiatry.* 2005;62(6):629-640.

Patient Survey Question and Responses

- Please share with us how focused they would say their primary care clinician is in ensuring that they experience a complete recovery from depression symptoms, as well as a return to a normal level of functioning. Please be as detailed as possible, and then elaborate on your answer.
  - Honestly I'm not sure that complete remission has ever been part of the conversation. It's typically alleviation of some symptoms, improvement, up to maybe significant improvement, but that complete remission is never really posed as the goal.

Definitions of Remission and Response to Treatment



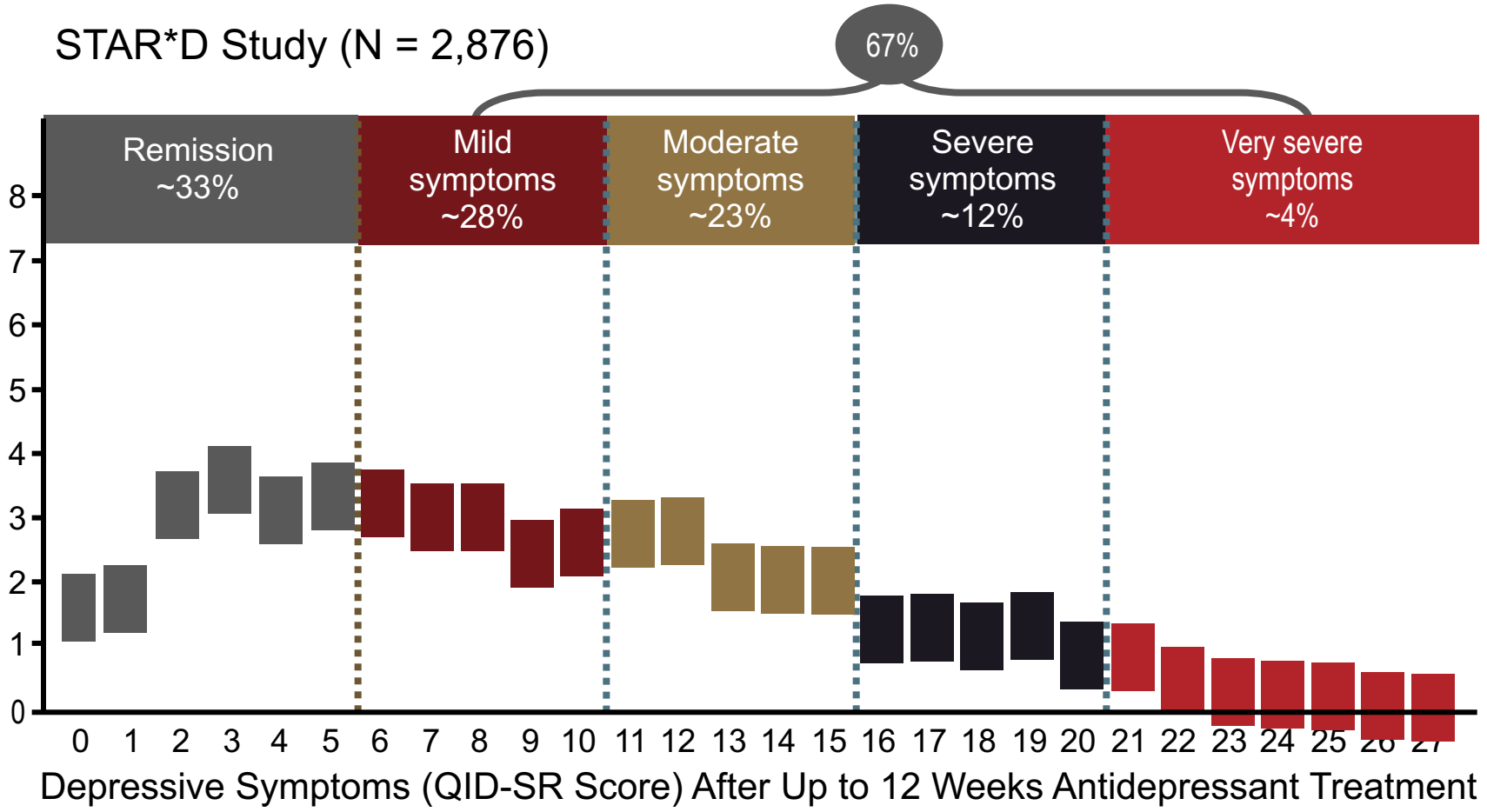
Fava M, et al. *Psychiatr Clin North Am.* 1996;19:179-200.

Factors Affecting the Probability of Achieving Remission

- Pretreatment symptom severity
- Treatment resistance
- Treatment type
- Length of current episode
- Degree of interepisode recovery
- Presence of Axis I, II, or III disorders
- Length of illness
- Treatment nonadherence

Fava M, Davidson KG. *Psychiatr Clin North Am*. 1996;19:179-200.

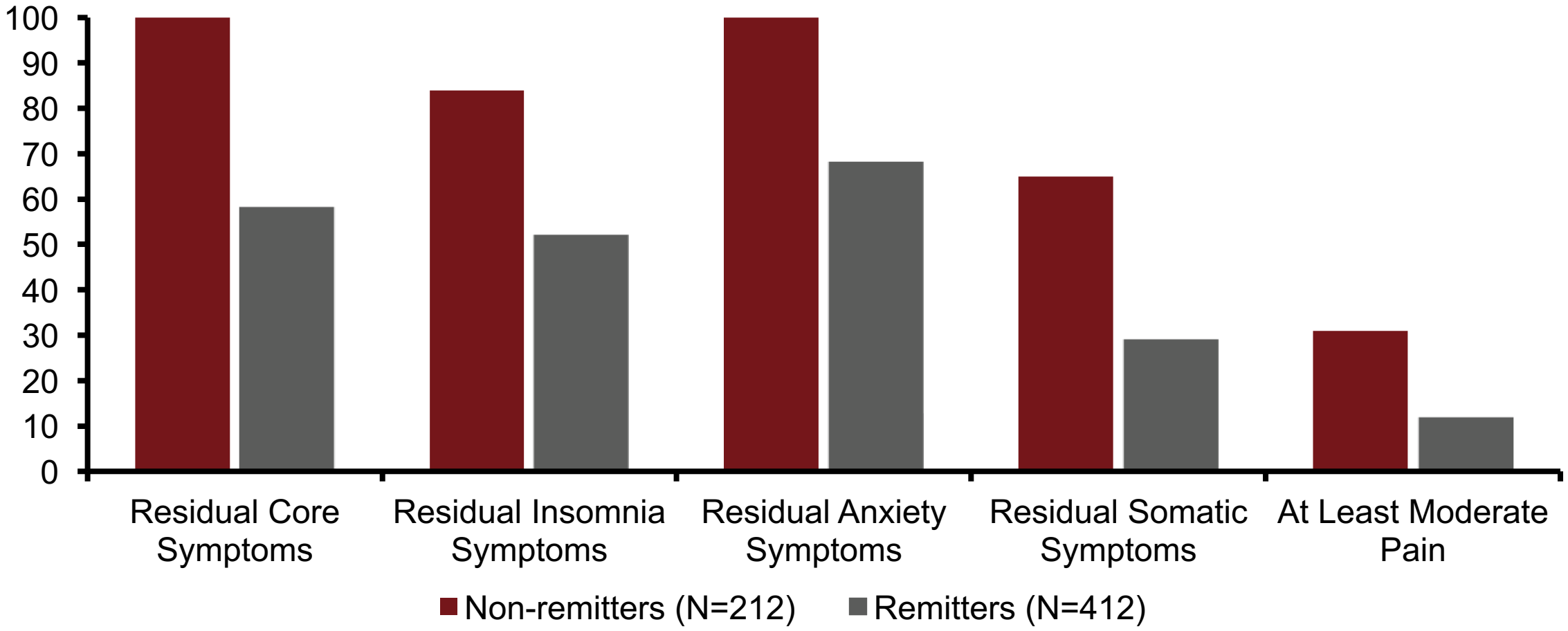
STAR*D: Unresolved Symptoms Following Antidepressant Treatment



STAR*D = Sequenced Treatment Alternatives to Relieve Depression

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

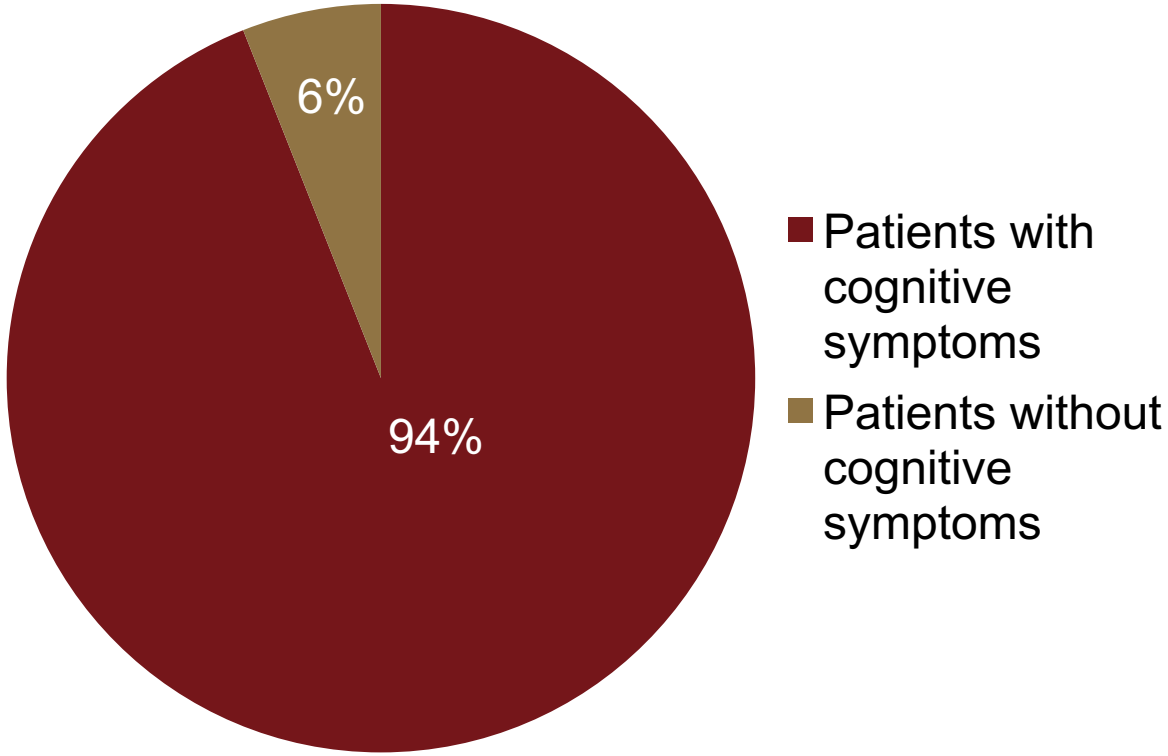
Prevalence of Residual Symptoms by Type in MDD



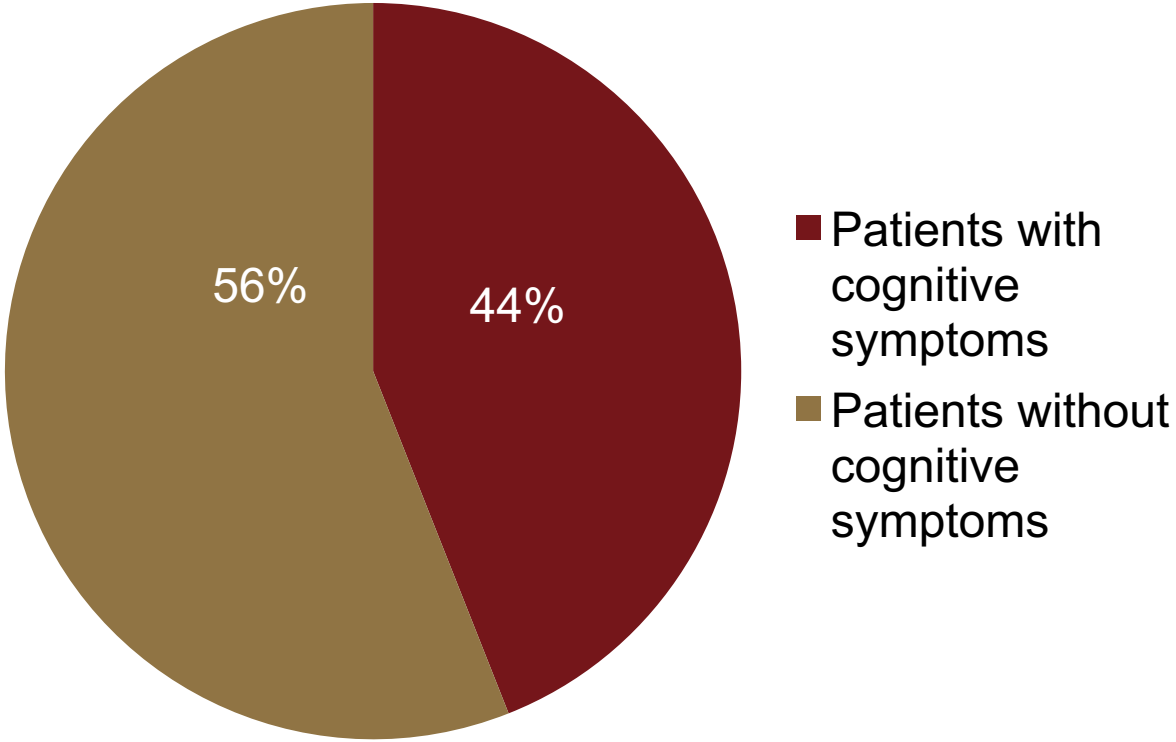
Adapted from Romera I, et al. *BMC Psychiatry*. 2013;13:51.

Prevalence of Cognitive Symptoms in Depressive Episodes and Periods of Remission

Presenting Symptoms During Depressive Episodes

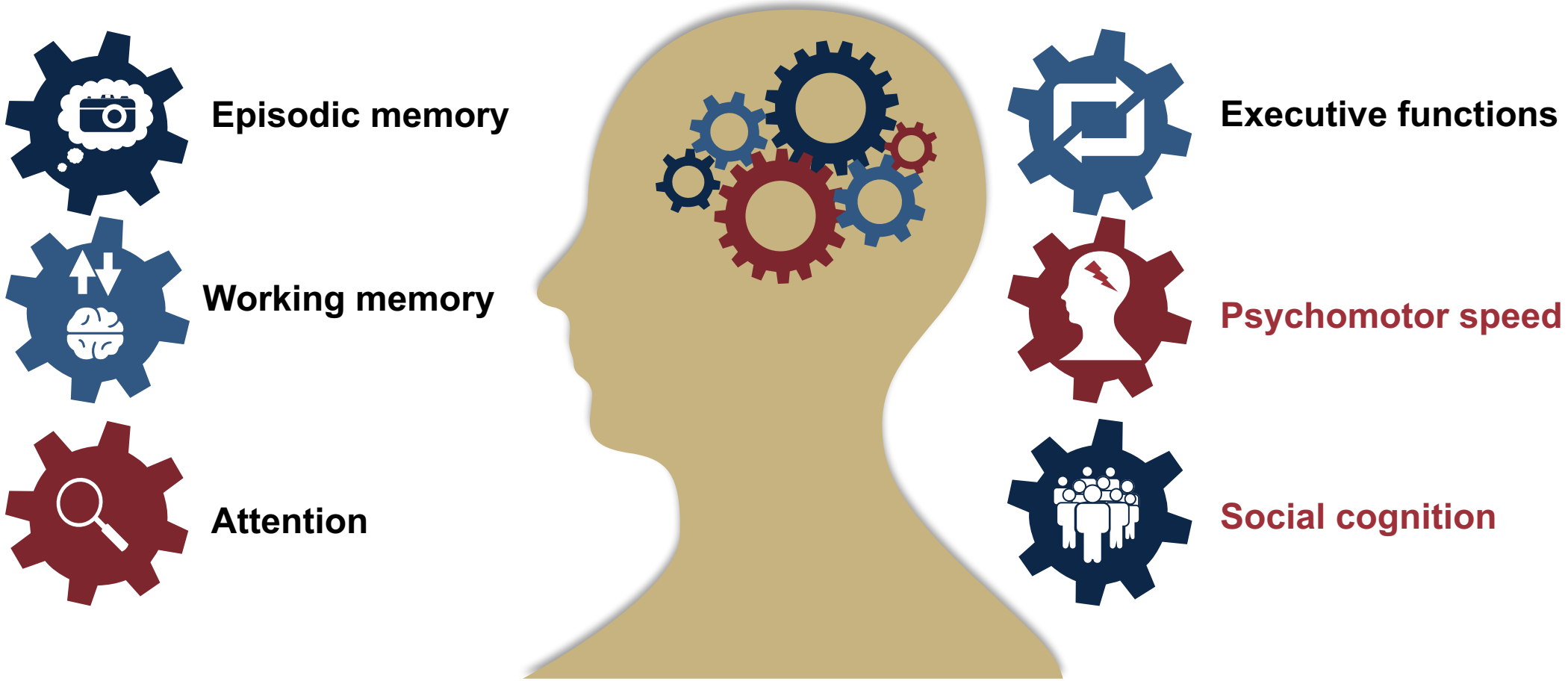


Residual Cognitive Symptoms In Between Depressive Episodes



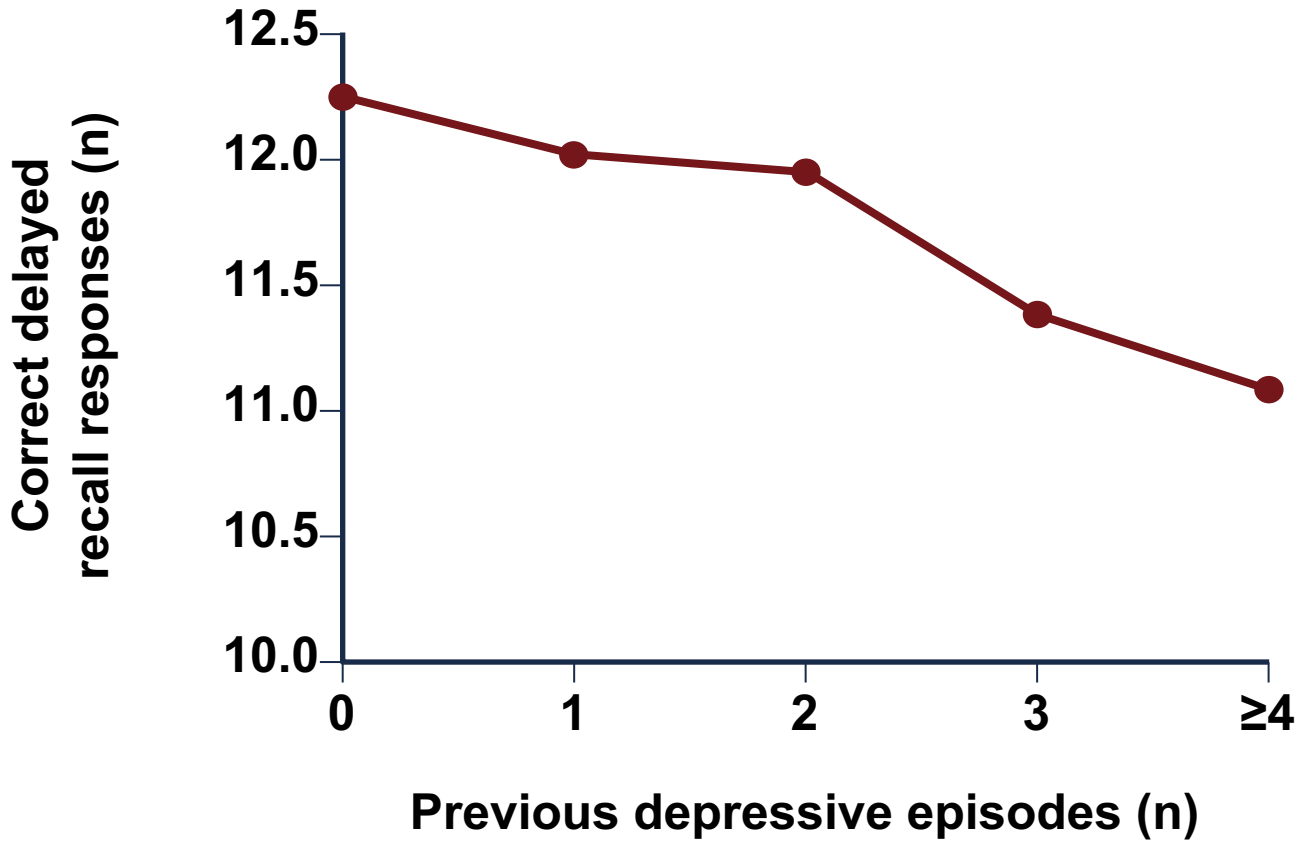
Conradi HJ, et al. *Psychol med*. 2011;41(6):1165-1174.

Key Domains: The Atoms of Cognition



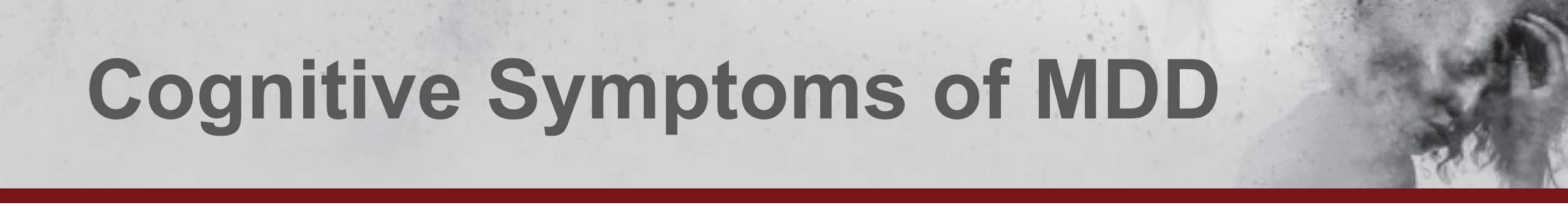
Episode Frequency Increases Cognitive Dysfunction in MDD

- Cognitive dysfunction can persist outside of acute episodes and appears to progress as a function of number of episodes



Gorwood P, et al. *Am J Psychiatry*. 2008;165:731-739.

Cognitive Symptoms of MDD



- May predate onset of MDD episode
- Distinct neurobiology
- Heritable
- Some deficits may improve with antidepressant therapy
- Differences in antidepressant effects on cognition
- Often persist after treatment
- Impact quality of life and functional outcomes

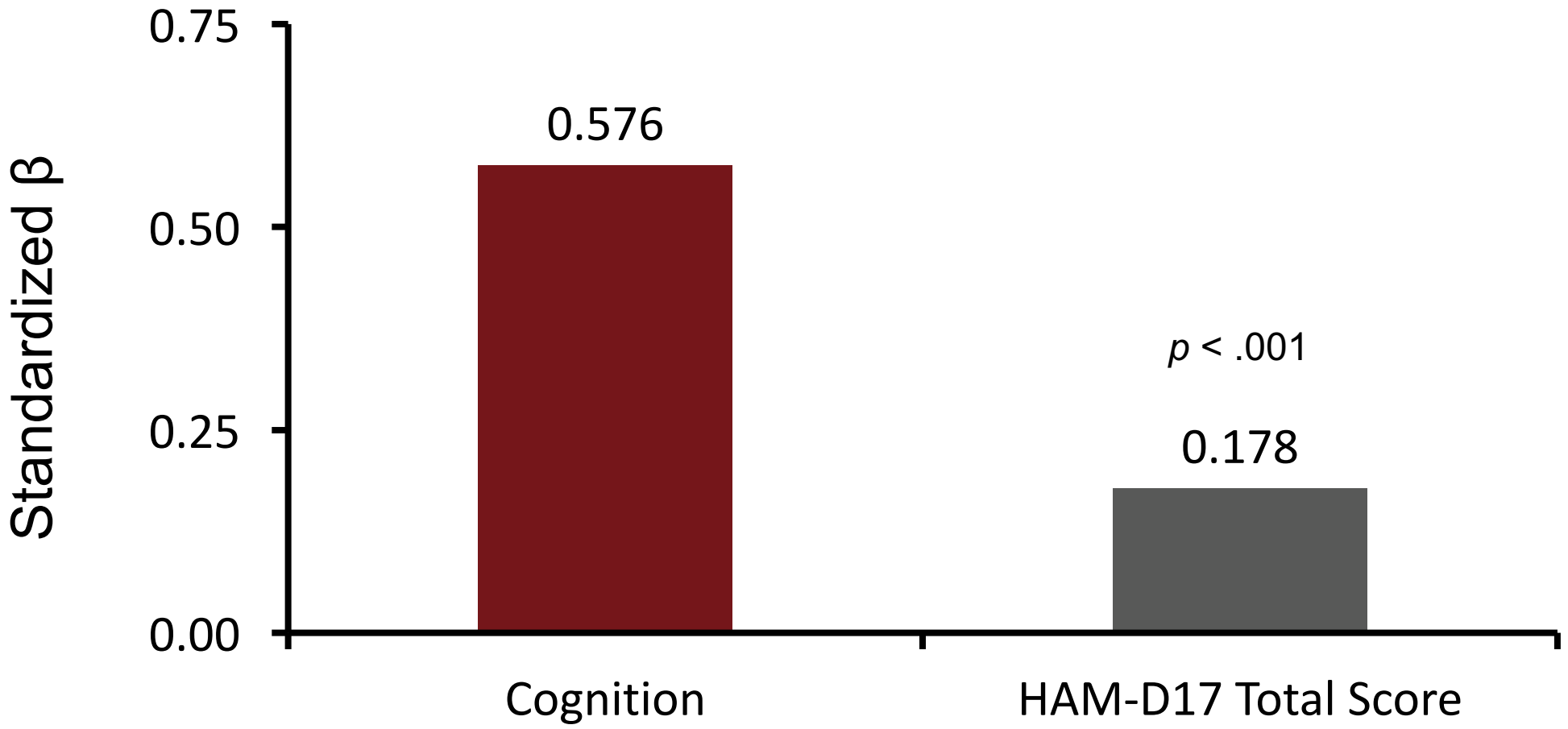
Trivedi M, et al. *J Affect Disord*. 2014;152:19-27.

Determinants of Cognitive Deficit in MDD

- Age
- Age at onset
- Baseline depression severity
- Childhood adversity
- Educational attainment
- Episode frequency
- Illness duration
- MDD subtype
- Medical comorbidity
- Psychiatric comorbidity
- Symptomatic status
- Treatment

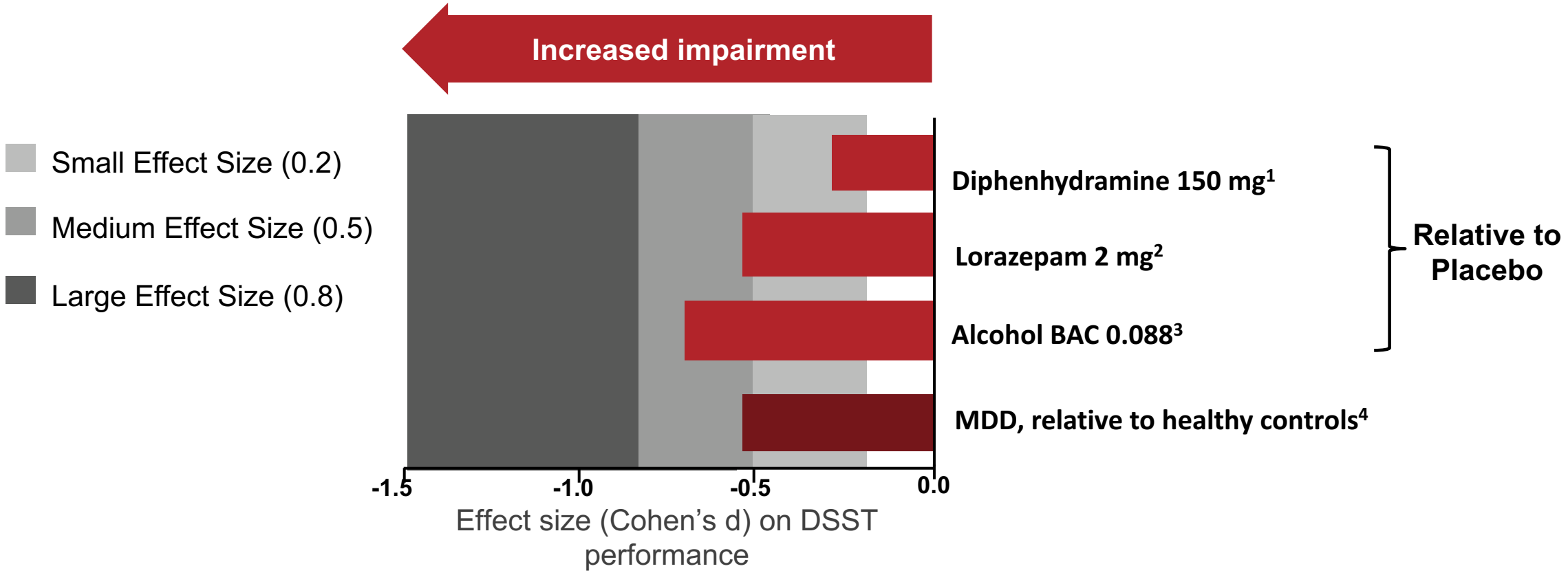
McIntyre RS, et al. *Depress Anxiety*. 2013;30(6):515-527.

Cognitive Measures Account for More Variability in Workplace Functioning than Total Depression Severity



McIntyre RS, et al. *Compr Psychiatry*. 2015;56:279-282.

The Cognitive Symptoms of MDD are Clinically Meaningful



- In a meta-analysis of overall cognitive symptoms in patients with MDD versus healthy controls (22 studies, 1904 subjects on DSST), the effect size decrement on DSST was 0.55 (p <.001)[4]

BAC = Blood Alcohol Concentration; DSST = Digit Symbol Substitution Test; MDD = Major Depressive Disorder.

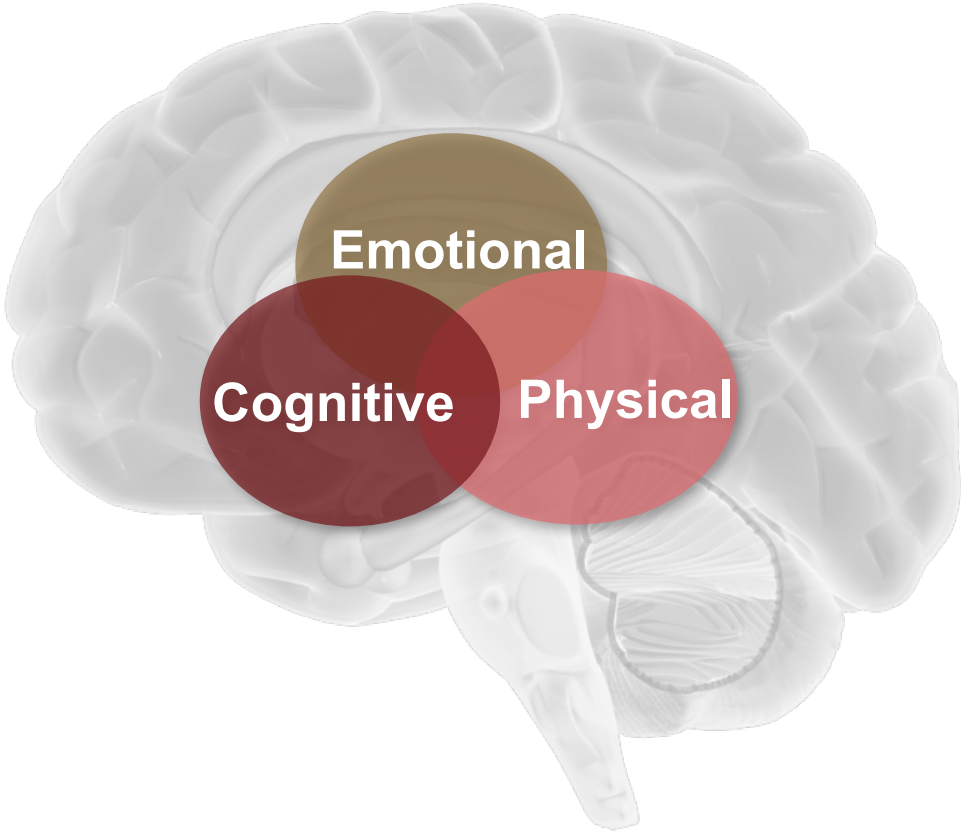
[1]Roth T et al. *J Allergy Clin Immunol*. 1987;80(1):94-98; [2]Pompeia S et al. *Hum Psychopharmacol*. 2008;23(3):183-192; [3]Mattila MJ et al. *J Psychopharmacol*. 1997;11(4):313-317; [4]Snyder HR. *Psychol Bull*. 2013;139(1):81-132.

Case-Based Discussion: Case 1

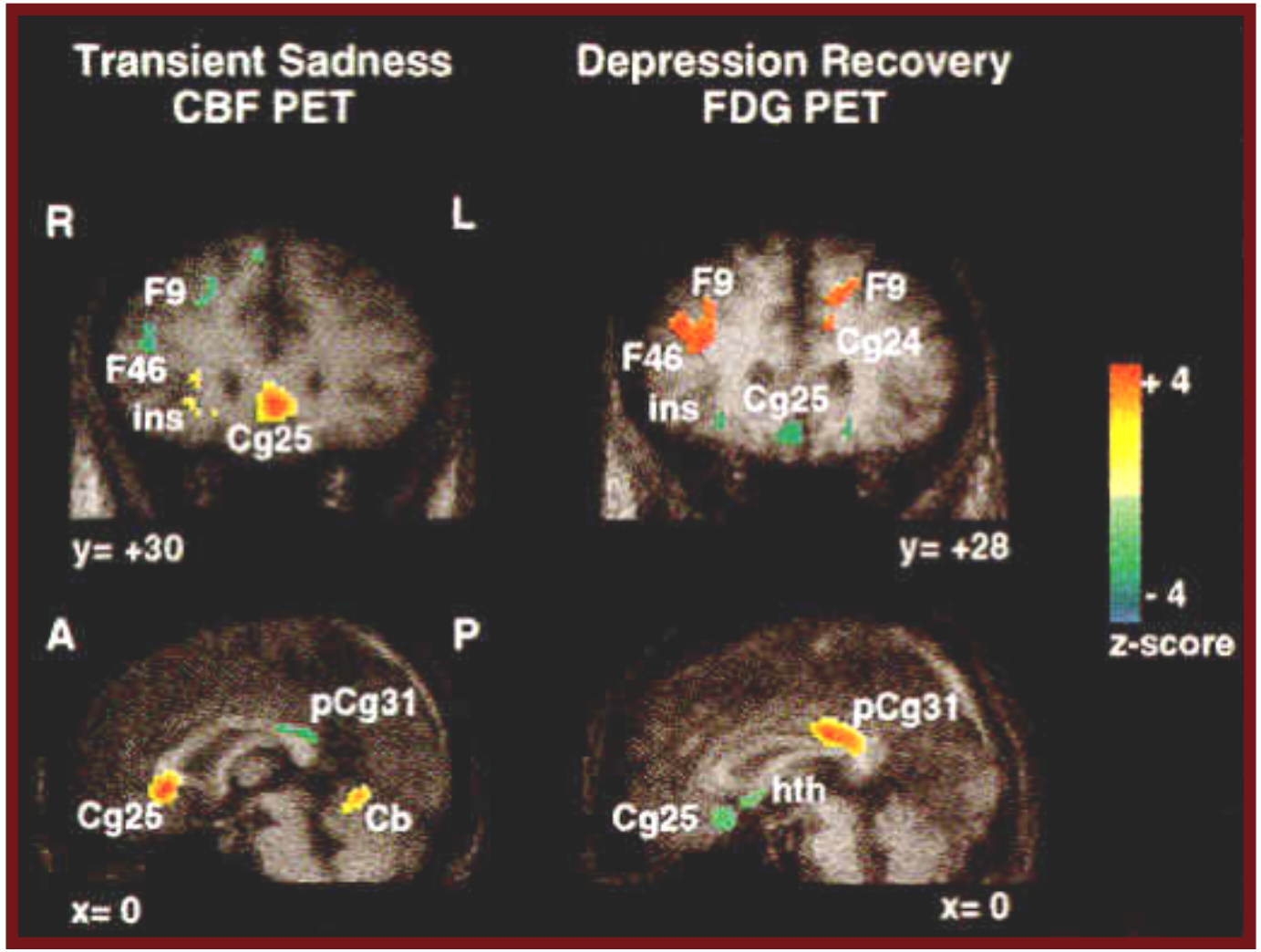
- 36 y/o female; BMI of 27; smoking; uses THC intermittently; single; childless
- Comes to your office in a panic, just written up at her job as a legal assistant
- Diagnosis of MDD recurrent with mixed features specifier
- Partial response to 2 antidepressants
- Labs normal

Changes in the Brain Associated with Depression

- Depression is a neurologic condition which involves emotional, physical and cognitive centers in the brain



Sadness, Depression and Recovery: Reciprocal Limbic-Cortical Function and Mood

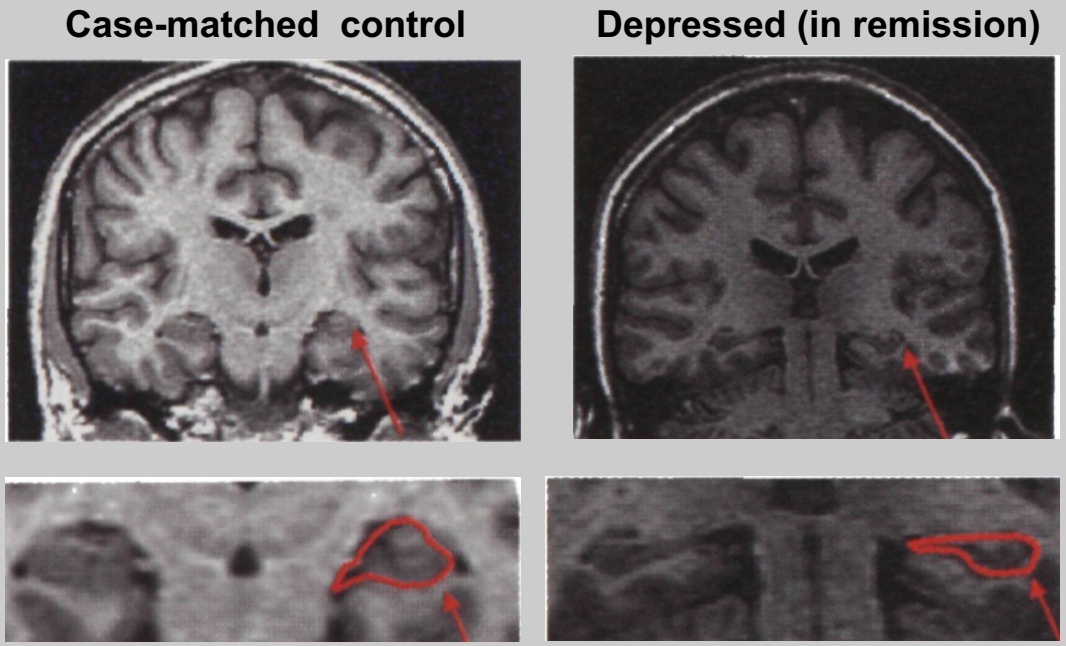


Mayberg HS, et. al. *Am J Psychiatry.* 1999:156:675-682.

MDD is Associated with Reductions in Hippocampal Volume Across All Age Groups

Age Group	Observations
Adolescence[1]	Evidence of abnormalities in the hippocampus in early onset depression
Adulthood[2,3]	Findings are consistent with smaller left hippocampal volume in depression
Old age[4]	Further evidence of structural brain abnormalities in geriatric depression

Atrophy of the hippocampus in patients with depression[3]

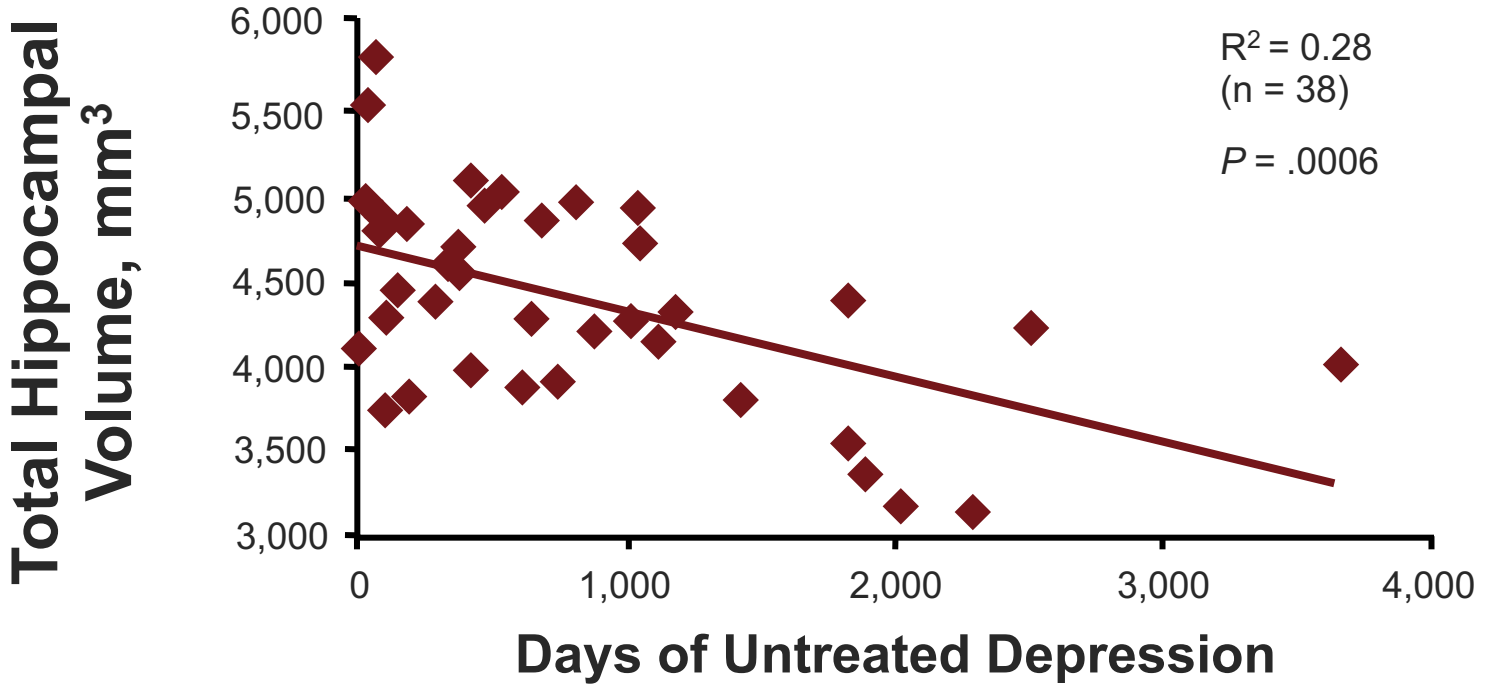


- 19% smaller volume of left hippocampus in patients with treated depression versus non-depressed control subjects
- This represents a statistically significant decrease

1. MacMaster FP, et al. BMC Med. 2004;2:2;
2. Bremner JD, et al. *Am J Psychiatry*. 2000;157(1):115-118;
3. Bremner JD, et al. *CNS Spectr*. 2002;7(2):129-130,135-139;
4. Bell-McGinty S, et al. *Am J Psychiatry*. 2002;159(8):1424-1427.

Hippocampal Volume Correlates With the Duration of Untreated Depression

Imaging studies in depressed patients show that hippocampal volume is inversely related to the length of time the disease went untreated



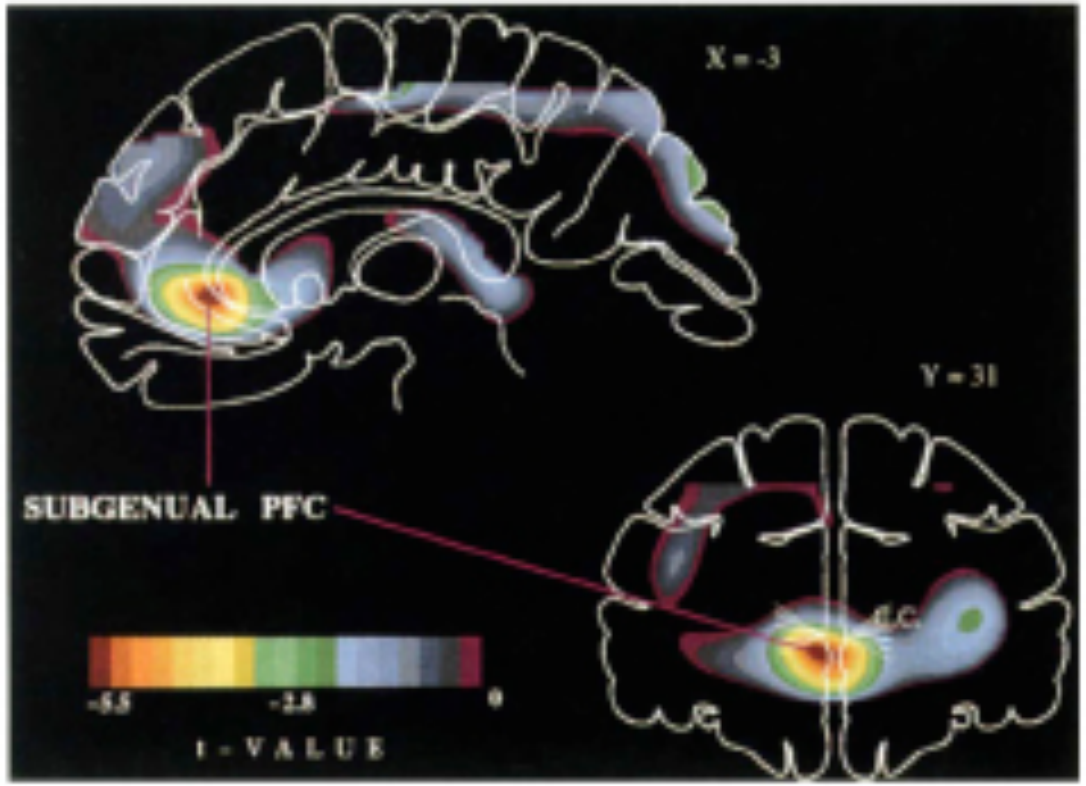
Longer durations of untreated depressive episodes were associated with **reductions in hippocampal volume**

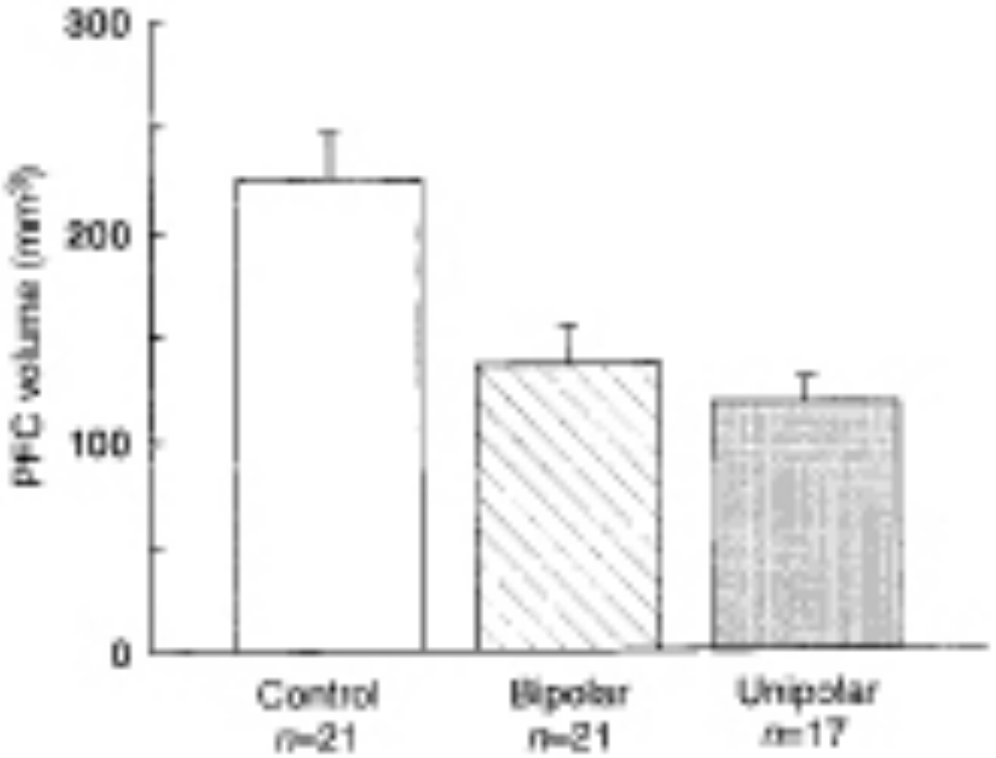
Antidepressants may have a neuroprotective effect during depression

Sheline YI, et al. *Am J Psychiatry*. 2003;160(8):1516-1518.

Recurrent Depression Causes Cell Death

Letters to Nature



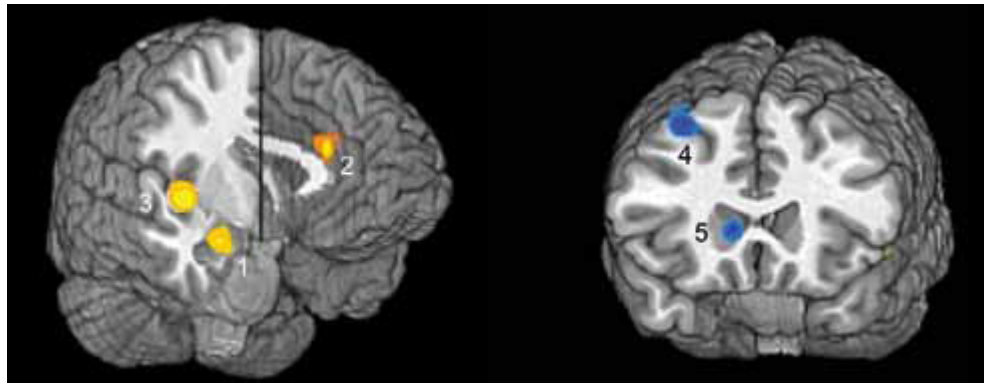


Recurrent depression had a 48% decrease in cell volume

Drevets WC, et al. *Nature*. 1997;386:824-827.

MDD Significantly Changes the Brain's Responses to Negative Stimuli

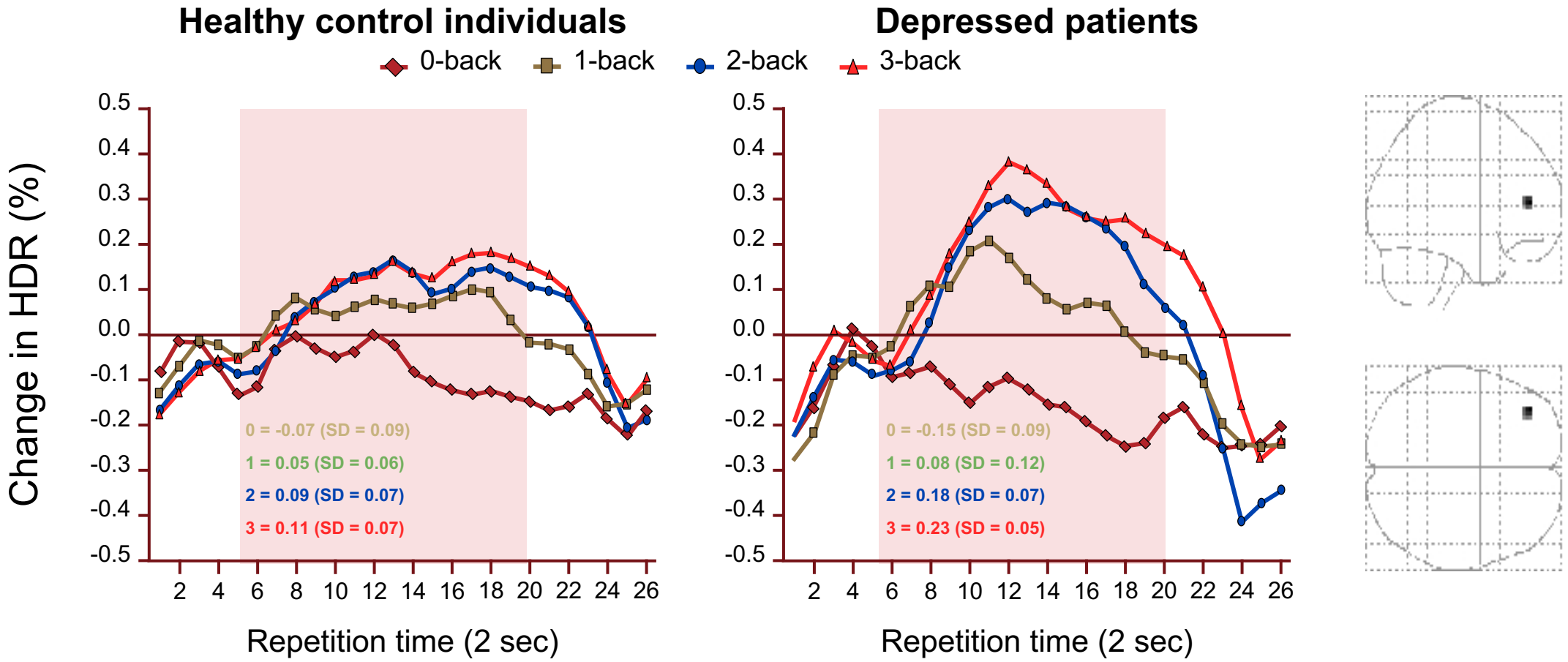
- Compared with healthy subjects, patients with MDD showed higher baseline activity in the pulvinar nucleaus compared with healthy subjects
- In response to negative stimuli:
  - MDD patients showed greater response in the amygdala, insula, and dorsal anterior cingulate cortex, compared with control
  - MDD patients showed lower response in the dorsal stratum and dorsolateral prefrontal cortex, compared with control



1) Amygdala; **2)** Dorsal anterior cingulate cortex; **3)** Insula and superior temporal gyrus; **4)** Dorsolateral prefrontal cortex; **5)** Caudate body

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

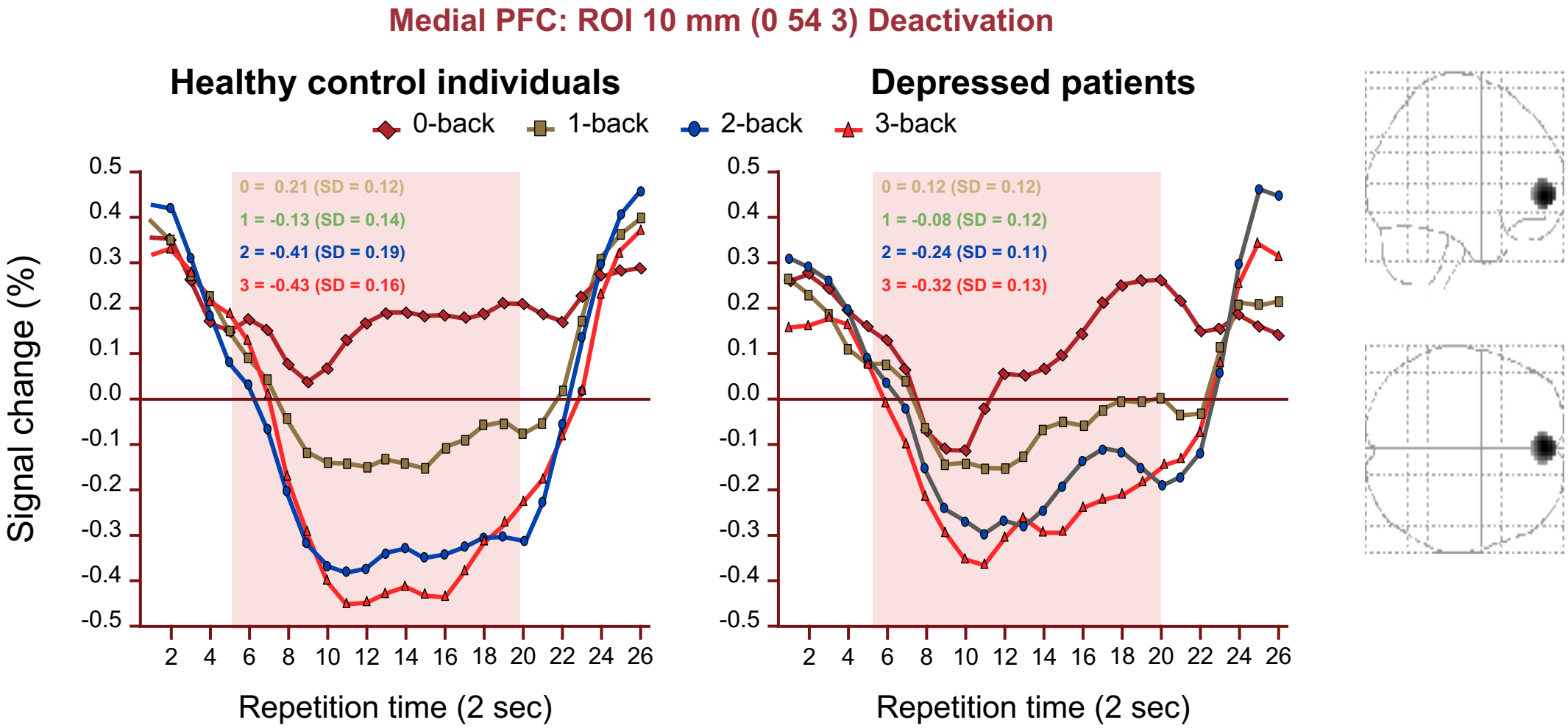
DLPFC Activation, Depression and the N-back Task



DLPFC = dorsolateral prefrontal cortex; BA = Brodmann area; ROI = region of interest; HDR = haemodynamic response; SD = standard deviation

Harvey PO, et al. *Neuroimage.* 2005;26(3):860-869.

Medial PFC and Cognitive Effort



PFC = prefrontal cortex; ROI = region of interest; SD = standard deviation

Harvey PO, et al. *Neuroimage*. 2005;26(3):860-869.

Evidence of Pharmacotherapies Improving Cognition in MDD

	Learning and Memory	Attention/ Concentration	Executive Function	Processing Speed
Duloxetine	1			
Erthyropoietin*	2	2	2	2
Lisdexamfetamine*			2	
Modafinil*	3	3	3	3
Others (eg, SSRIs, SNRIs, and bupropion)	3	3	3	3
Vortioxetine	1	1	1	1

1 = replicated placebo-controlled trial evidence with demonstration of independent effect; **2** = single placebo-controlled trial evidence with demonstration of independent effect; **3** = uncontrolled evidence (e.g., lacking placebo, case-series) with lack of demonstration of independent effect

* erthyropoietin, lisdexamfetamine, and modafinil are not FDA-approved for MDD

McIntyre RS et al. CNS Drugs. 2015;29:577-589.

Cognitive Dysfunction Seems to Normalize Following CBT

Sad facial expression processing[1]

Patients > controls in amygdala, hippocampus and a lower activity in the anterior and posterior cingulate gyri
Normalization of activity following CBT

Self-referential processing of words[2]

Patients > controls in medial prefrontal cortex during processing of negative words
Normalized following 12 weeks of group CBT

Depression associated with altered prefrontal response during a cognitive control task[3]

Normalized following behavioural activation

But involves repeat testing without control group and, therefore, difficult to isolate cause and effect relative to symptom change

CBT = cognitive behavioural therapy.

[1]Fu CH, et al. *Biol Psychiatry.* 2008;64:505-512; [2]Yoshimura S, et al. *Soc Cogn Affect Neurosci*. 2014;9(4):487-493; [3]Dichter GS, et al. *J Affect Disord*. 2010;126(1-2):236-244.

Patient Survey Question and Responses

- In what way does the primary care clinician monitor the effectiveness of their drug therapy treatment for depression? How often does this monitoring occur (e.g., every visit, some visits, etc.) and would they say that this frequency of monitoring is appropriate or not? Please be as detailed as possible, and then elaborate on your answer.
  - Typically the medication is prescribed and they say wait four to six to eight weeks to see if it's helping. If you have any adverse reactions obviously call your doctor immediately, but the follow up, the burden for that falls on the patient to schedule that to initiate the questions, to raise questions about concerns, about side-effects or whether the medication's ineffective. There really isn't proactive follow-up on behalf of the provider to address questions or concerns.
  - I would say that one of the biggest concerns or complaints for people in my community regarding the effectiveness of a particular drug therapy treatment would be the lack of follow up in general. You're making an appointment, and it might be three months or six months before you see a primary care physician again. So, there's not a lot of monitoring that occurs.

Assessing Clinical Outcomes in MDD Care

- Monitoring symptom resolution requires rapport with your patient
- Open conversations asking about continuing symptoms without making patient feel like a failure (problem of wanting to please the provider)
- State that “it is very common for patients to still have some lingering symptoms after the medication has been in place for awhile. Let’s talk about what you still struggle with…”

Why Is Measurement-Based Care Important?

- Depression treatment in real-world practice often does not follow evidence-based guidelines
- Improving the care delivery system improves outcomes for depressed patients in both primary care and specialty care (provides a “common language”)
- MBC is a feasible strategy to improve delivery of antidepressant care
- It works—in STAR*D, guideline recommendations to improve care delivery were followed in over 85% of visits

Williams JW, et al. *Gen Hosp Psychiatry*. 2007;29: 91-116.
Trivedi MH, et al. *Arch Gen Psychiatry*. 2004;61:669-680.
Trivedi MD, et al. *Drug Alcohol Depend*. 2007;88(suppl 2):S61-S71.

Facilitating Adherence

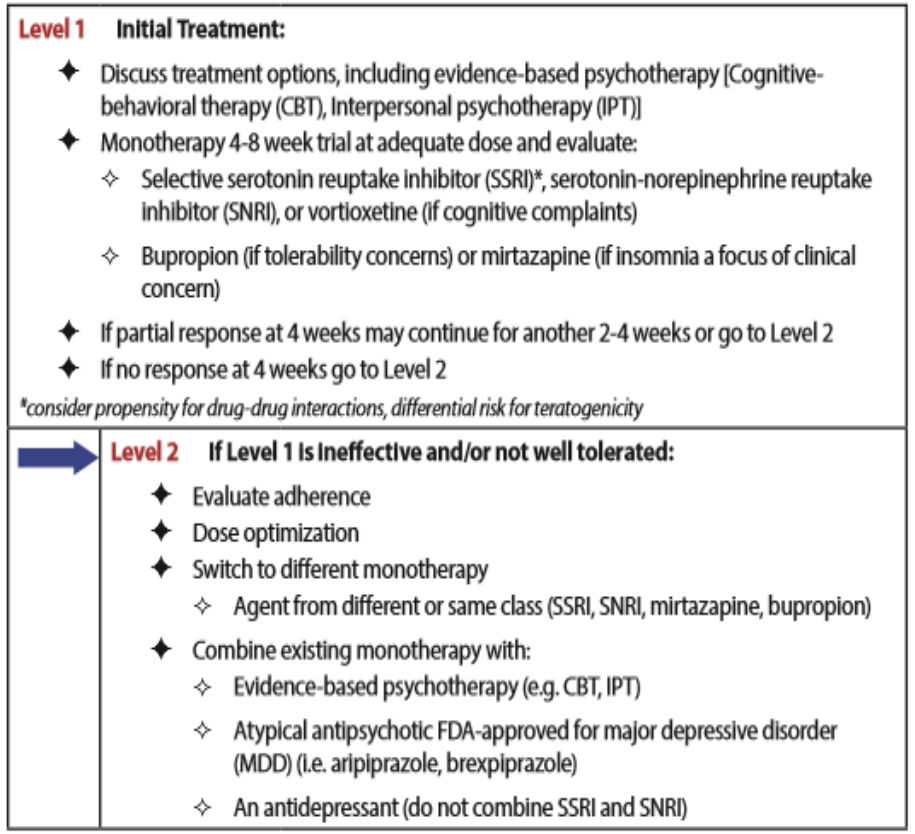
- Maintain open communication with patient
- Strengthen therapeutic alliance
- Use part of the treatment visit to address medication/treatment adherence
- Determine patient's motivation to take prescribed medications
- Identify barriers and address them (eg, side effects, cost, embarrassment, lack of family support)

USA Medicaid Guideline Recommends Screening and Evaluation of Multidimensions of MDD 2016

The goals of acute treatment are safety, response to therapy, patient psychoeducation, and to begin the process of symptomatic, syndromal, and functional recovery

Assess for:

- Prior history of hypomania/mania
- Psychiatric and medical comorbidities (e.g. substance use disorders, anxiety disorders, obesity, diabetes)
- Presence of specifiers; notably psychosis, mixed features, suicidality
- Presence of cognitive dysfunction (e.g., memory complaints; difficulty with concentration, making decisions, and thinking clearly)



Level 1 **Initial Treatment:**

- Discuss treatment options, including evidence-based psychotherapy [Cognitive-behavioral therapy (CBT), Interpersonal psychotherapy (IPT)]
- Monotherapy 4-8 week trial at adequate dose and evaluate:
  - Selective serotonin reuptake inhibitor (SSRI)*, serotonin-norepinephrine reuptake inhibitor (SNRI), or vortioxetine (if cognitive complaints)
  - Bupropion (if tolerability concerns) or mirtazapine (if insomnia a focus of clinical concern)
- If partial response at 4 weeks may continue for another 2-4 weeks or go to Level 2
- If no response at 4 weeks go to Level 2

*consider propensity for drug-drug interactions, differential risk for teratogenicity

Level 2 **If Level 1 is ineffective and/or not well tolerated:**

- Evaluate adherence
- Dose optimization
- Switch to different monotherapy
  - Agent from different or same class (SSRI, SNRI, mirtazapine, bupropion)
- Combine existing monotherapy with:
  - Evidence-based psychotherapy (e.g. CBT, IPT)
  - Atypical antipsychotic FDA-approved for major depressive disorder (MDD) (i.e. aripiprazole, brexpiprazole)
  - An antidepressant (do not combine SSRI and SNRI)

McIntyre RS, et al. Florida Best Practice Psychotherapeutic Medication Guidelines for Adults. 2015; Available at www.medicaidmentalhealth.org.

Treatment of Major Depressive Disorder With Mixed Features (cont.)

Level 2 **If Level 1 is ineffective and/or not well tolerated:**

- Reassess for hypomania/mania
- Dose optimization of medication used in Level 1
- Switch to different monotherapy SGA or mood stabilizer
- Antidepressant monotherapy from different or same class
- Combine existing antidepressant with different SGA
- Combine SGA or mood stabilizer with antidepressant

Level 3 **If Levels 1 and 2 are ineffective and/or not well tolerated:**

- Consider electroconvulsive therapy (ECT) or transcranial magnetic stimulation (TMS)
- Alternative antidepressants, including tricyclic antidepressant (TCA), monoamine oxidase inhibitor (MAOI), or first generation antipsychotic (FGA)

McIntyre RS, et al. Florida Best Practice Psychotherapeutic Medication Guidelines for Adults. 2015; Available at www.medicaidmentalhealth.org.

Assessment Tools for Depression

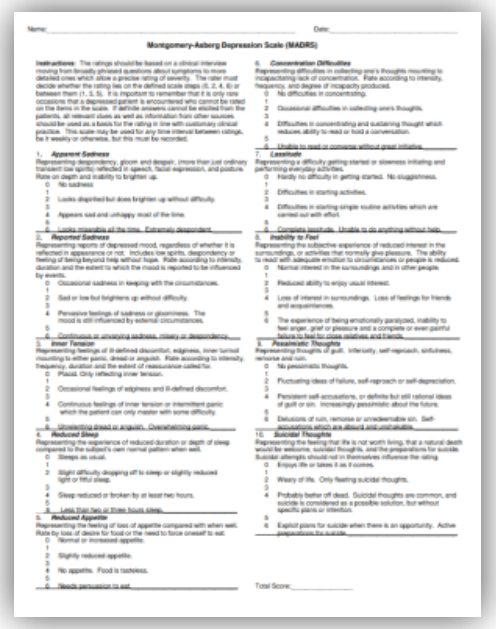
- Beck Depression Inventory (BDI)[1]
  - 21-question self-report inventory
  - Remission: < 9
- Hamilton Rating Scale for Depression (HAMD)[2]
  - 17 or 21-item scale given by health care professionals
  - Remission: HAMD17 < 7
- Patient Health Questionnaire (PHQ-9)[3]
  - 9-item scale based; patient administered
  - Remission: < 4
- Quick Inventory of Depressive Symptoms-Self Report (QIDS-SR) or Clinician Administered (QIDS-C)[2]
  - 16-item scale
  - Remission: < 5
- Montgomery-Asberg Depression Rating Scale (MADRS)[2]
  - 10-item scale
  - Remission: < 10

1. Beck AT, et al. *Arch Gen Psychiatry*. 1961;4:561-571; 2. Trivedi MH. *Prim Care Companion J Clin Psychiatry*. 2004;6(Suppl 1):12-16;
3. Kroenke K, et al. *J Gen Intern Med*. 2001;16:606-613.

Depression Rating Scales Measure Symptom Reduction in Clinical Trials, But are Rarely Used in Clinical Practice[1]

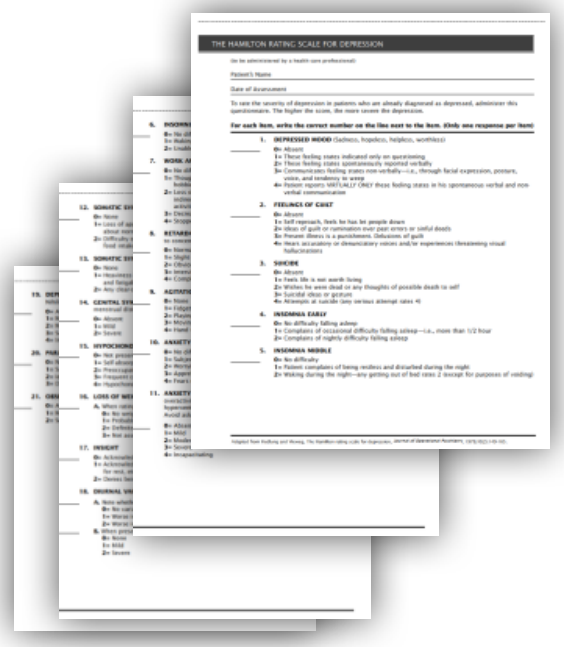
MADRS[2]

Depressive symptoms


Montgomery-Asberg Depression Scale (MADRS)

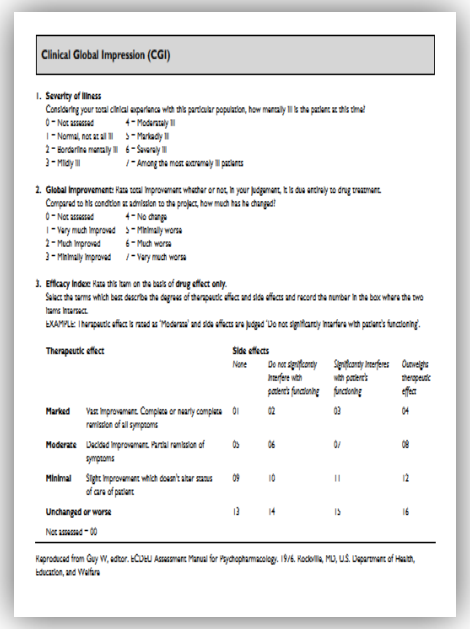
HAM-D[3]

Depressive, anxious, and somatic symptoms


THE HAMILTON RATING SCALE FOR DEPRESSION

CGI-S[1]

Global illness


Clinical Global Impression (CGI)

CGI-S = Clinical Global Impression-Severity scale; HAM-D = Hamilton Depression Rating Scale; MADRS = Montgomery–Åsberg Depression Rating Scale.

1. Busner J, et al. *Psychiatry.* 2007;4(7)28-37;
2. Montgomery SA, et al. *Br J Psychiatry*. 1979;134:382-389;
3. Hamilton M. *J Neurol Neurosurg Psychiatry*. 1960;23:56-62.

PHQ-9 Designed to Help Primary Care Clinicians Diagnose Depression and Grade Symptom Severity

- 9 Items
- 0 to 3 on each item
- Max score of 27

The Patient Health Questionnaire (PHQ-9)

Over the last 2 weeks, how often have you been bothered by any of the following problems?	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself—or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed. Or the opposite—being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3

If you circled **any** problems on this questionnaire so far, mark how **difficult** these problems have made it for you to do your work, take care of things at home, or get along with other people.

- ☐ Not difficult at all
- ☐ Somewhat difficult
- ☐ Very difficult
- ☐ Extremely difficult

ADD COLUMNS _____ + _____ + _____

TOTAL _____

For healthcare professionals: Because this questionnaire relies on patient self-report, all responses should be verified by the clinician. A definitive diagnosis should be made on clinical grounds, taking into account how well the patient understood the questionnaire, as well as other relevant information from the patient. Be sure to exclude response to a significant loss, substance abuse, or other medical condition.

Kroenke K, et al. *J Gen Intern Med*. 2001; 16(9):606-613; Kroenke K, et al. *Psychiatr Ann*. 2002; 32(9):509-515.

The THINC-It Cognition Tool Incorporates Several Tests in 1 Simple Program

Tests

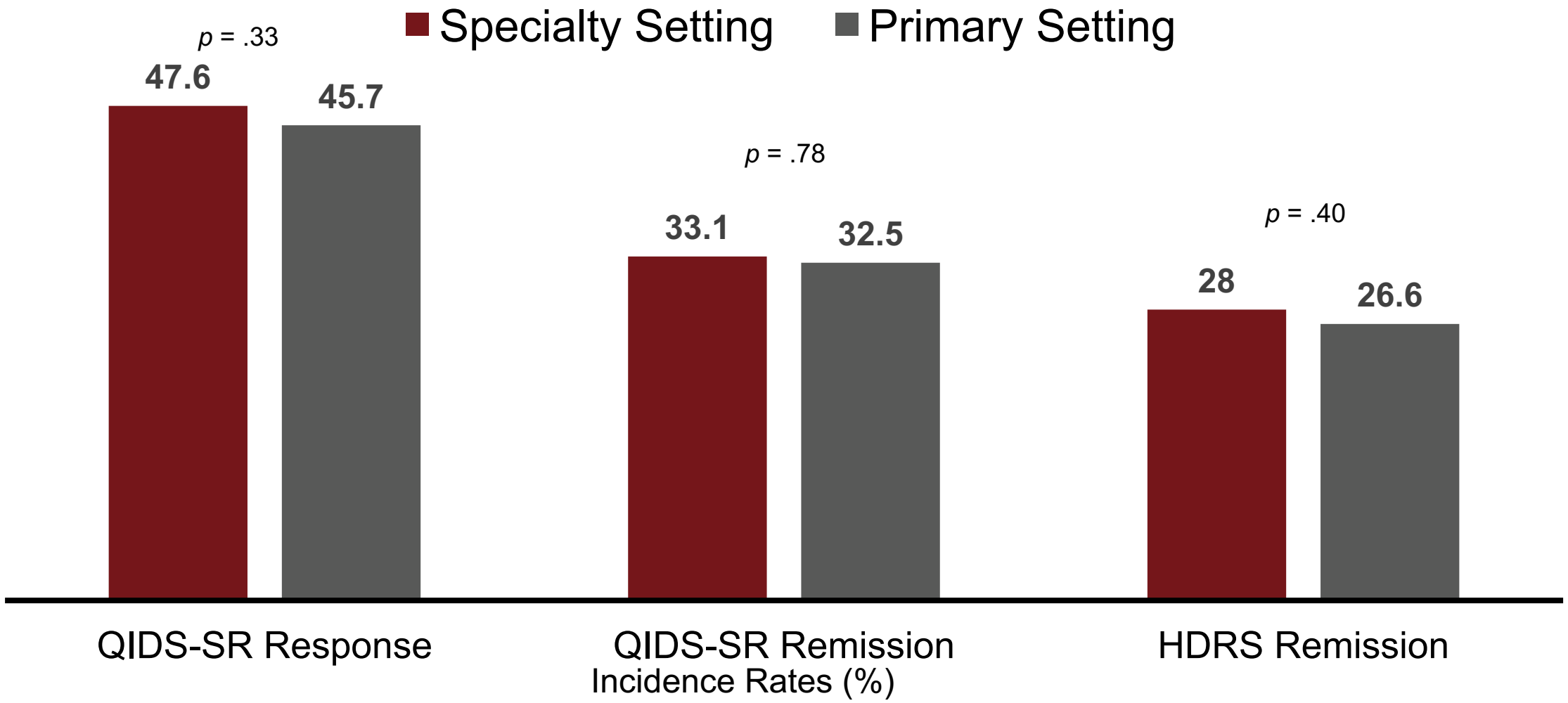
- DSST
- Choice Reaction Time task
- Trail Making Test – B
- 2-back memory task
- Perceived Deficits Questionnaire 5 item version

Tests are included in animated format in 1 program for use on desktop / tablet computers

- Patient completes themselves
- ~15 minutes
- Immediate clinical report

McIntyre RS, et al. *Curr Opin Psychiatry*. 29(1):48-55; Harrison JE. Measuring the mind: detecting cognitive deficits and measuring cognitive change in patients with depression. In *Cognitive Impairment in Major Depressive Disorder. Clinical Relevance, Biological Substrates, and Treatment Opportunities*. 2016.

Depression Outcomes Using Measurement-Based Care in Primary Care and Specialty Settings



QIDS-SR = Quick Inventory of Depressive-Self-Report; HDRS = Hamilton Depression Rating Scale

Gaynes BN, et al. *J Gen Intern Med*. 2008;23:551-560.

Effective Management of MDD

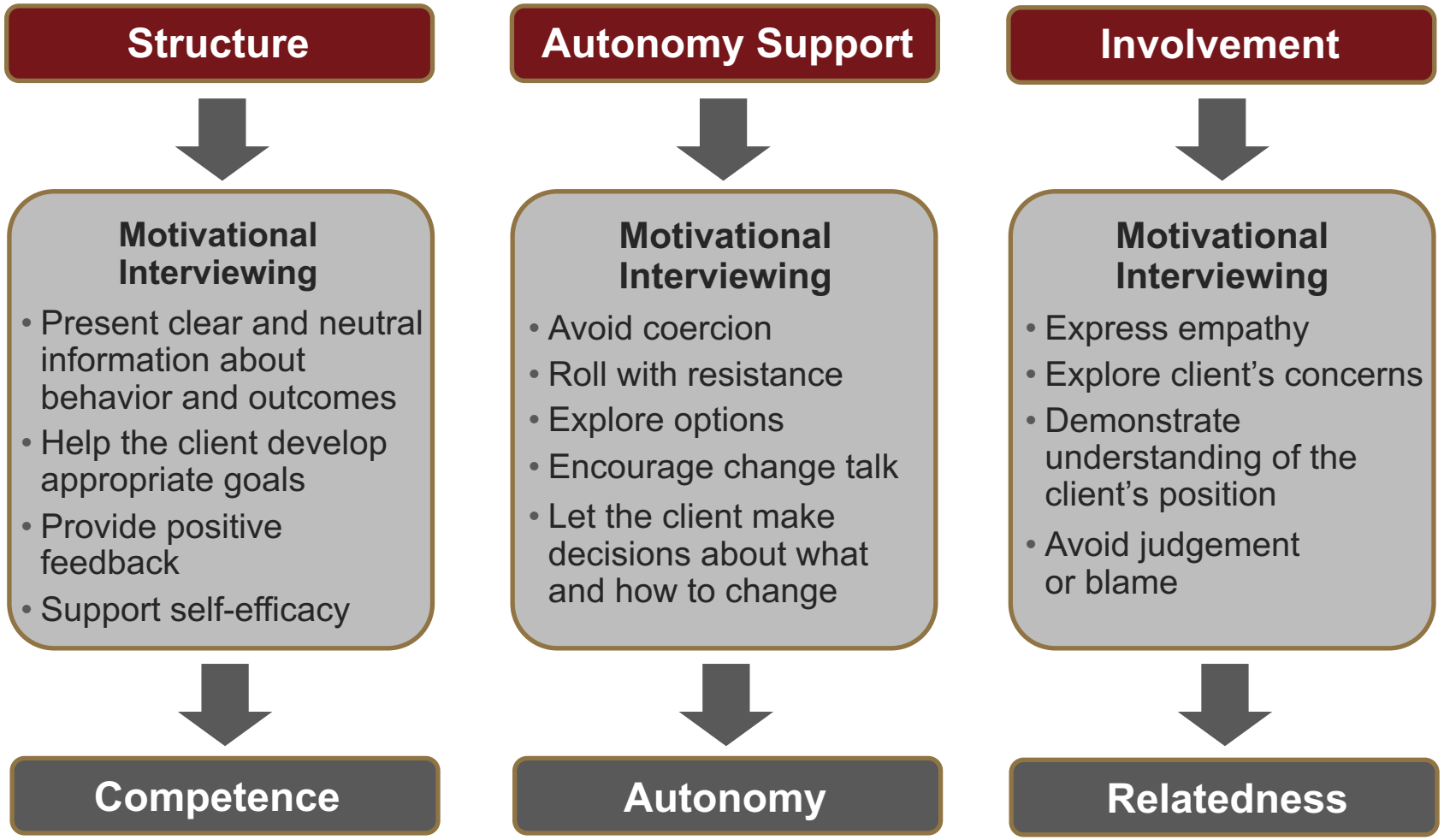
- Early identification
- Pharmacotherapy
- Treatment broker
  - Psychotherapy
  - Group therapy
  - Case management
  - Clinic team coordination
- Matching symptoms with neural circuits
- Comorbid depression (asthma, cardiac, diabetes)

Moller MD. *Curr Psychiatr*. 2017;16(4):15-16, 18-20; Ritsema TS, et al. *Prev Chronic Dis.* 2014;11:130175; Saur CD, et al. *J Am Psychiatr Nurses Assoc*. 2002;8:159-167

Patient Survey Question and Responses

- Speaking on behalf of patients within your online community who have been diagnosed with major depression and are receiving drug therapy treatment for their depression in the primary care setting, would they say that their primary care clinician (e.g., PCP, PA or NP) did or did not involve them in deciding on a treatment strategy for their depression? And, if so, how involved do they feel their primary care clinician enabled them to be during the decision-making process?
  - It's kind of typical to just decide for the patient. Here's your prescription, there you go. There's very little involving patients in the conversation of treatment. I've heard from a number of patients if they go in armed with questions or suggestions, it's usually not received well by the doctors.
  - As far as I see with some of the patients in my community, I would say that their PCPs generally struggle as far as whether or not to choose to be the physician that handles that part of their care. The ones that I think do choose to, often don't give them as much information as they could.

A Pathway to Shared Decision Making



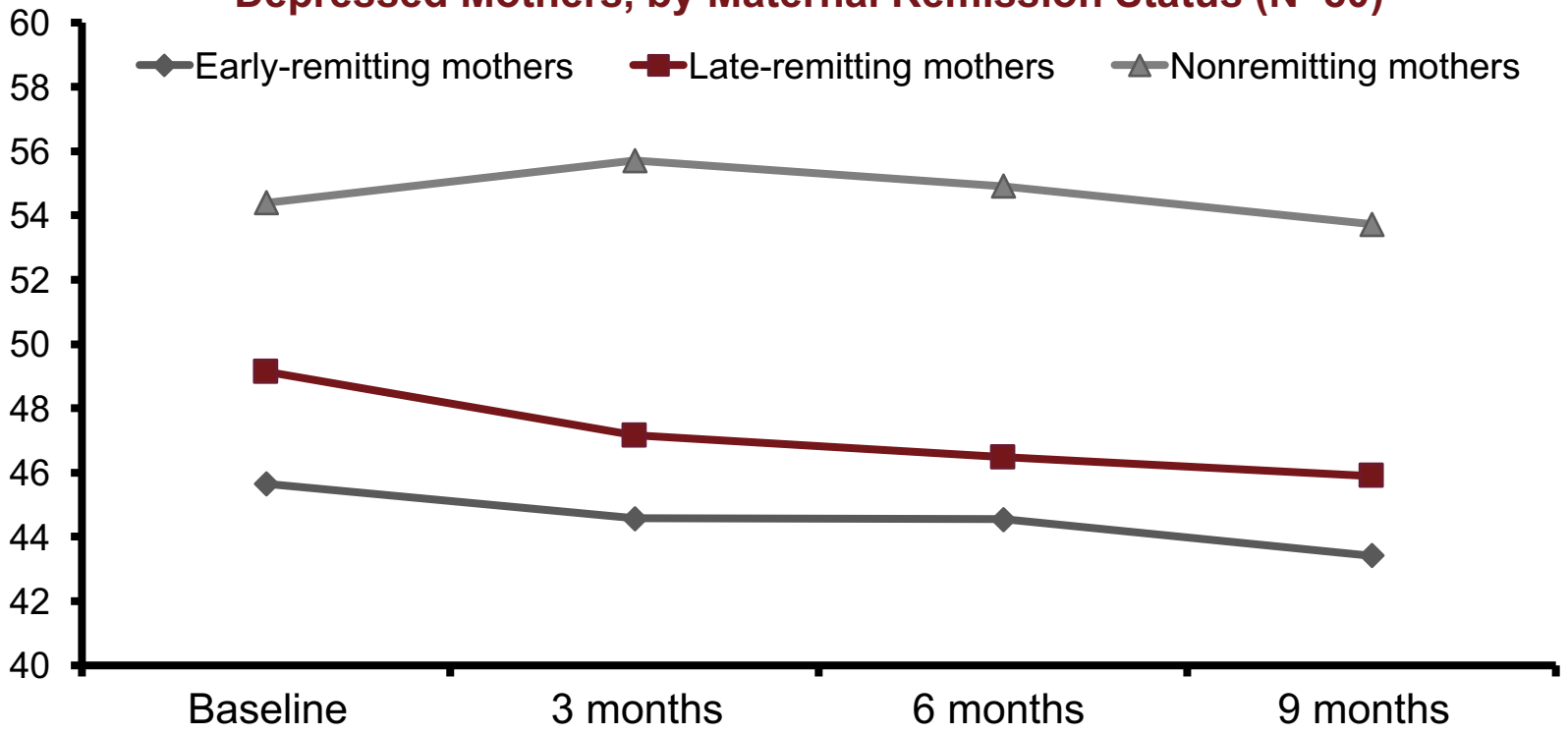
Markland D, et al. *J Soc Clin Psychol* . 2005;24:811-831.

SMART Goals

- Measurement-based care
- Return the brain to normal function
- Recognize cognitive deficits
- Shared decision-making

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: $p = .005$; late vs nonremitting: $p = .002$)[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.

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

Questions & Answers

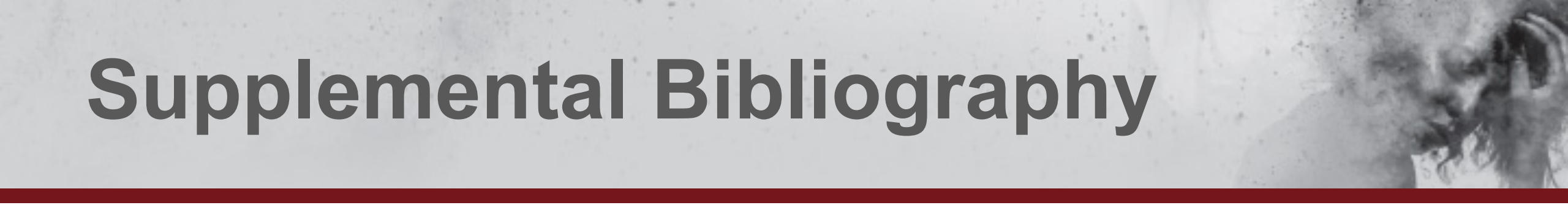
Thank You!

Don’t forget to fill out the forms and collect your credit.

Downloadable Resources

Downloadable resources will be available at **www.cmeoutfitters.com/MDD2017resources**

Supplemental Bibliography



[1]Raskin J, et al. *J Clin Psychopharmacol*. 2008;28(1):32-38.

[2]Herrera-Guzmán I, et al. *Psychiatry Res*. 2010;177(3):323-329.

[3]Herrera-Guzmán I, et al. *J Affect Disord*. 2010.;123(1-3):341-350.

[4]Cassano GB, et al. *J Clin Psychiatry*. 2002;63(5):396-402.

[5]Ferguson JM, et al. *Int Clin Psychopharmacol*. 2003;18(1):9-14.

[6]Constant EL, et al. *Depress Anxiety*. 2005;21(2):78-89.

[7]Jeon HJ, et al. *J Clin Psychopharmacol*. 2014;34(2):218-225.

Reference Slides

Risks of Pharmacotherapies Associated with Improving Cognition in MDD

	Warnings/Precautions
Duloxetine	Suicidal thoughts, hepatotoxicity, serotonin syndrome, orthostatic hypotension; contraindicated in with monoamine oxidase inhibitors (MAOs) *(See prescribing information for full listing)*[1]
Erthyropoietin*	Hypertension, seizures, increased mortality, myocardial infarction, stroke and thromboembolism *(See prescribing information for full listing)*[2]
Lisdexamfetamine*	Serious cardiovascular reactions, blood pressure and heart rate increases, psychiatric adverse reactions, suppression of growth, anorexia, diarrhea, nausea, insomnia *(See prescribing information for full listing)*[3]
Modafinil*	Headache, nausea, anxiety, back pain, dyspepsia, use caution in patients with history of depression, psychosis, or mania *(See prescribing information for full listing)*[4]
Vortioxetine	Nausea, constipation, vomiting; serotonin syndrome, increased risk of bleeding when used with NSAIDs, aspirins or other agents affecting coagulation *(See prescribing information for full listing)*[5]

*erthyropoietin, lisdexamfetamine, and modafinil are not FDA-approved for MDD

[1]Duloxetine [package insert]. Drugs@FDA Website. 2004; [2]Erthyropoietin [package insert]. Drugs@FDA Website. 1989; [3]Lisdexamfetamine [package insert]. Drugs@FDA Website. 2007; [4]Modafinil [package insert]. Drugs@FDA Website. 1998; [5]Vortioxetine [package insert]. Drugs@FDA Website. 2013.

Risks of Pharmacotherapies Associated with Improving Cognition in MDD (cont.)

	Warnings/Precautions
Escitalopram	Insomnia, ejaculation disorder, nausea, fatigue, somnolence, decreased libido; serotonin syndrome, risk of suicide *(See prescribing information for full listing)*[1]
Fluoxetine	Anorexia, anxiety, decreased libido, nausea; suicidality, serotonin syndrome, seizures, hypnonatremia *(See prescribing information for full listing)*[2]
Paroxetine	Asthenia, nausea, decreased appetite, somnolence, ejaculatory disturbance, tremor; contraindicated in MOAIs; seizures, suicide, activation of mania/hypomania *(See prescribing information for full listing)*[3]
Reboxetine*	Seizures, contraindicated in MOAIs, orthostatic hypotension, serotonin syndrome *(See prescribing information for full listing)*[4]
Sertraline	Nausea, diarrhea, ejaculation failure, tremor, dyspepsia, decreased appetite; serotonin syndrome, increased risk of bleeding *(See prescribing information for full listing)*[5]
Tianeptine*	Gastralgia, abdominal pain, anorexia, nausea, asthenia, tachycardia, myalgia; contraindicated in MOAIs. (*See prescribing information for full listing)*[6]

***reboxetine and tianeptine are not FDA-approved for MDD**

[1]Escitalopram [package insert]. Drugs@FDA Website. 2002; [2]Fluoxetine [package insert]. Drugs@FDA Website. 1987; [3]Paroxetine [package insert]. Drugs@FDA Website. 1992; [4]Reboxetine [package insert]. Drugs@FDA Website. 2011; [5]Sertraline [package insert]. Drugs@FDA Website. 1991; [6]Tianeptine [package insert]. Drugs@FDA Website. 2008.

Risks Associated with Off-Label Use of Agents to Treat MDD

	Warnings/Precautions
Lithium*	Tremor, polyuria, nausea, diarrhea, vomiting, muscular weakness, ataxia, blurred vision, cardiac arrhythmia, hypotension, impotence/sexual dysfunction *(See prescribing information for full listing)*[1]
Liothyronine (T3)*	Headache, irritability, nervousness, cardiac arrthymia, increased bowel motility, skin reactions; drug interactions with oral anticoagulants, insulin or oral hypoglycemics, tricyclic antidepressants, vasopressors, ketamine, estrogen, oral contraceptives *(See prescribing information for full listing)*[2]
Quetiapine*	Somnolence, dry mouth, constipation, dizziness, increased appetite, dyspepsia, weight gain, fatigue, dysarthria, nasal congestion, tachycardia *(See prescribing information for full listing)*[3]

***lithium, liothyronine (T3), and quetiapine are not FDA-approved for MDD**

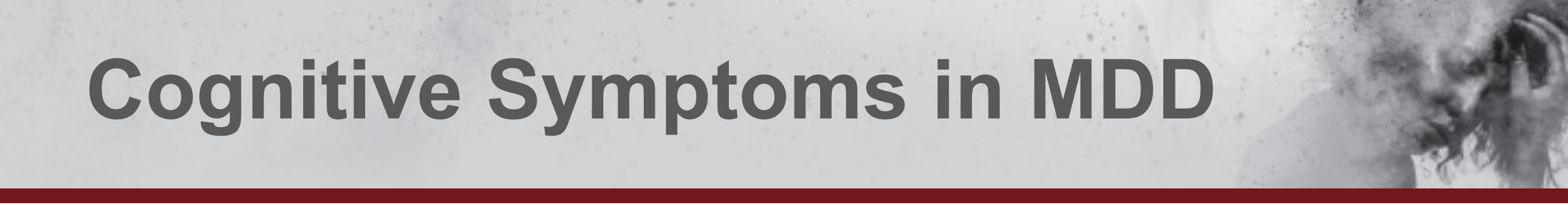
[1]Lithium [package insert]. Drugs@FDA Website. 1970; [2]Liothyronine (T3) [package insert]. Drugs@FDA Website. 2002; [3]Quetiapine [package insert]. Drugs@FDA Website. 1997.

4 Key Domains of Cognitive Function in MDD

ATTENTION DOMAIN	**The ability to focus on several possible objects or trains of thought**
Real-life manifestations:	Difficulty with concentration, focus, attention
MEMORY DOMAIN	**Includes visual and verbal memory, episodic memory (time and places), semantic memory (meaning of things)**
Real-life manifestations:	Forgetfulness, word-finding difficulties
EXECUTIVE FUNCTION DOMAIN	**Includes inhibition, working memory, mental flexibility, verbal fluency, planning, and problem-solving**
Real-world manifestations:	Indecisiveness: inability to prioritize, multi-task, make decisions, or plan
PSYCHOMOTOR SPEED DOMAIN	**The time to perform motor actions that arise from mental activity (e.g., reaction time, information-processing speed, and slowed speech)**
Real-world manifestations:	Slow processing, slow speech, slow response

American Psychiatric Association. Diagnostic and Statistical Manual (5th ed.). 2013

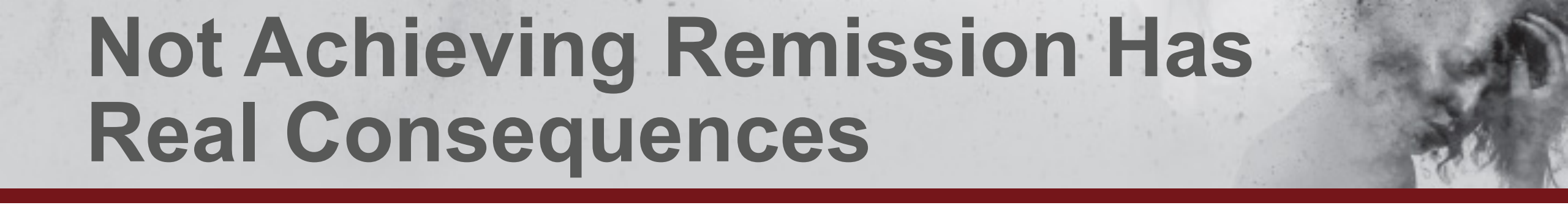
Cognitive Symptoms in MDD



- Among the core symptom domains included in the diagnostic criteria for a major depressive episode[1]
- > 30% of patients who otherwise responded to antidepressant therapy report residual cognitive symptoms (forgetfulness, inattentiveness, mental slowing, apathy, and word-finding difficulty)[2]
- Prevalence:
  - Among all adults with MDD: 30% - 40%[1]
  - Among MDD patients > 65 years old: 50% - 60%[2]

[1]Poletti S, et al. *J Affect Disord*. 2014;156:144:149; [2]Fava M, et al. *J Clin Psychiatry*. 2006;67:1754-1759.

Not Achieving Remission Has Real Consequences



Effect on Disease Course

- Higher risk of relapse
- Increased rate of recurrence
- Shorter course of well intervals
- Fewer symptom-free weeks
- Increased risk of suicide

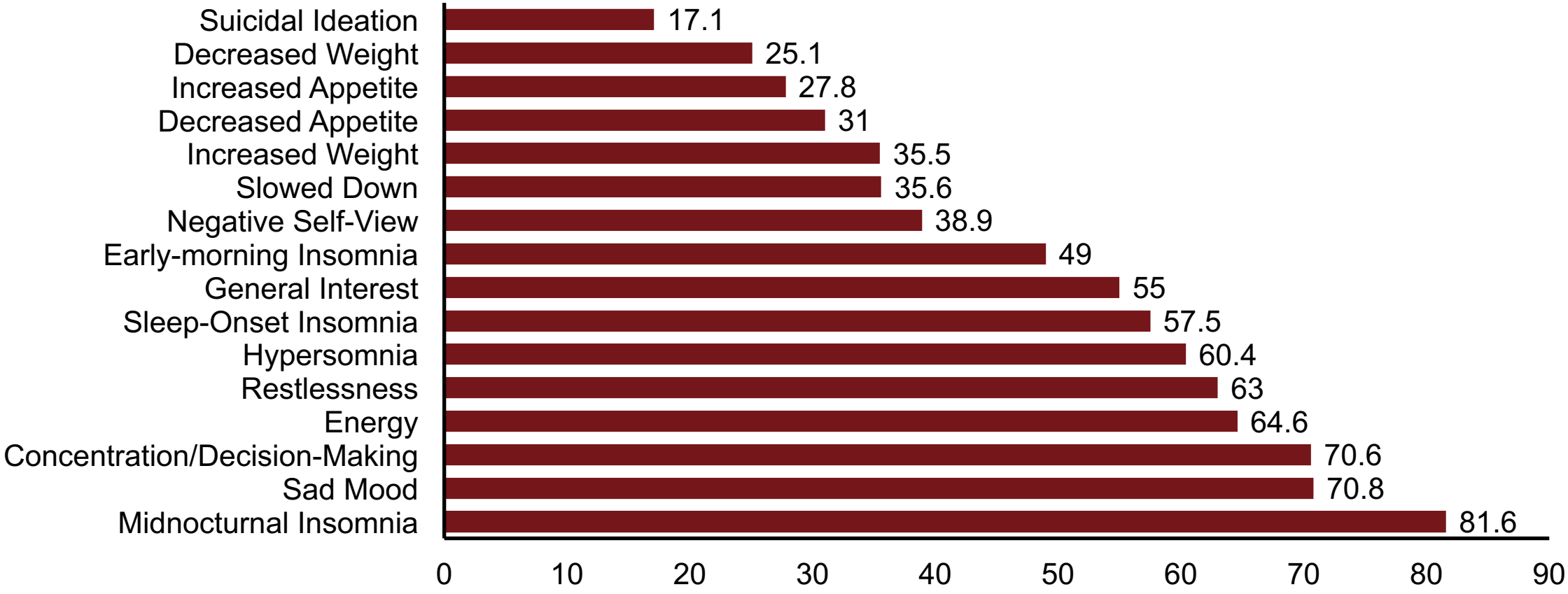
Effect on Direct and Indirect Costs

- Medical, psychiatric, emergency care
- More psychiatric hospitalizations
- More benefits received through welfare or disability insurance
- Increased work impairment

Judd LL, et al. *Am J Psychiatry.* 2000;157:1501-1504; Paykel ES, et al. *Psychol Med*. 1995;25:1171-1180.

What Does Failure to Remit Look Like in Those Who Respond to an Antidepressant?

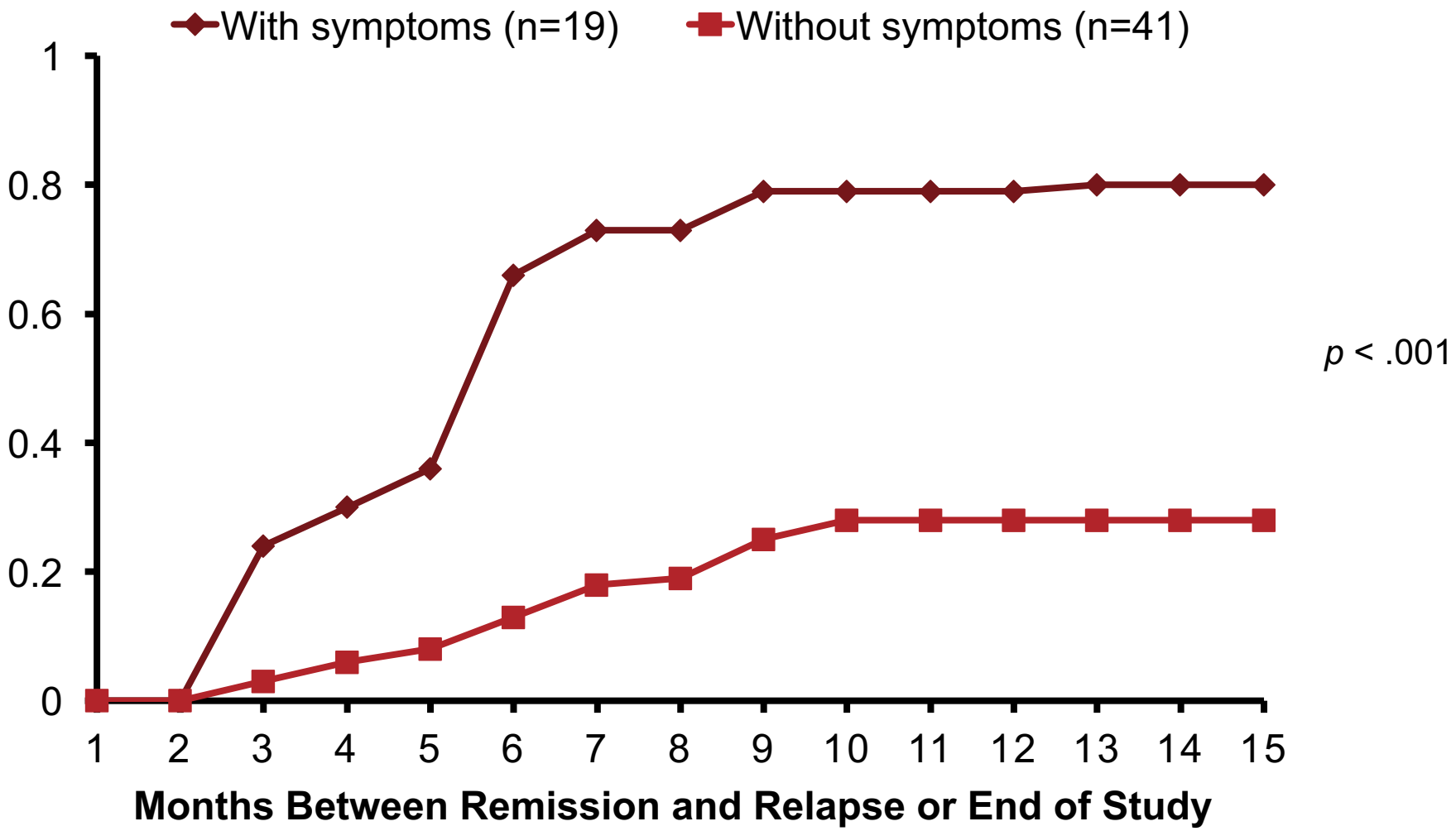
Proportion of responders who had symptoms at baseline that persisted at exit*



*Percentages are reported as the remaining percent of those with each symptom at baseline that continued to have the symptoms at exit. Response was defined as $\geq$ 50% reduction in QIDS-SR_{16}. Presence of symptoms was indicated by a QIDS-SR_{16} domain score $\geq$ 1.

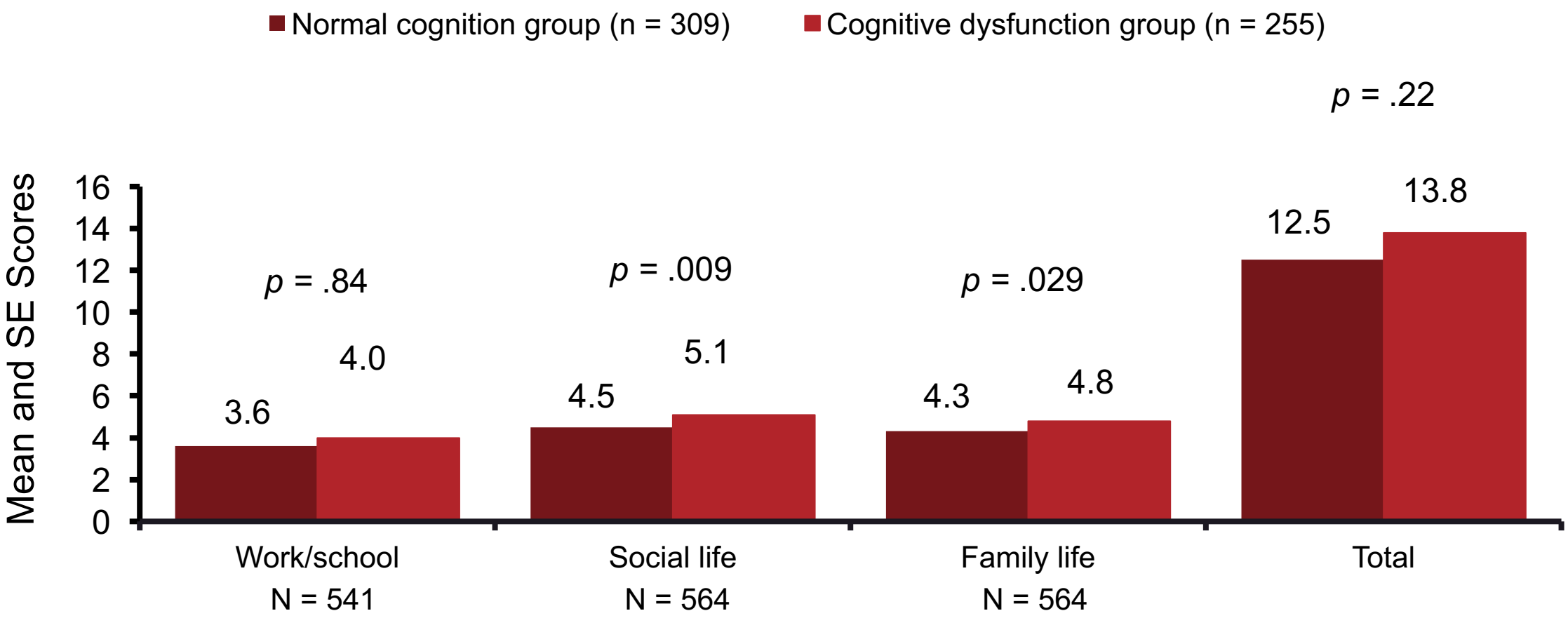
McClintock SM, et al. *J Clin Psychopharmacol*. 2011;31:180-186.

Residual Symptoms Increase Risk of Relapse After Remission



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

Association Between Cognitive Function, Disability, and Quality of Life in Patients Treated for Depression



In relation to the normal cognition group, the cognitive dysfunction group showed: worse mean SF-12 scores of utility, mental component, and physical component significantly greater mean days lost in week (0.84 vs. 0.55 days); worse WPAI scores (not statistically significant)

Kurlander JL, et al. Eur Neuropsychopharmacol. 2013;23(suppl 2):S284-S285.

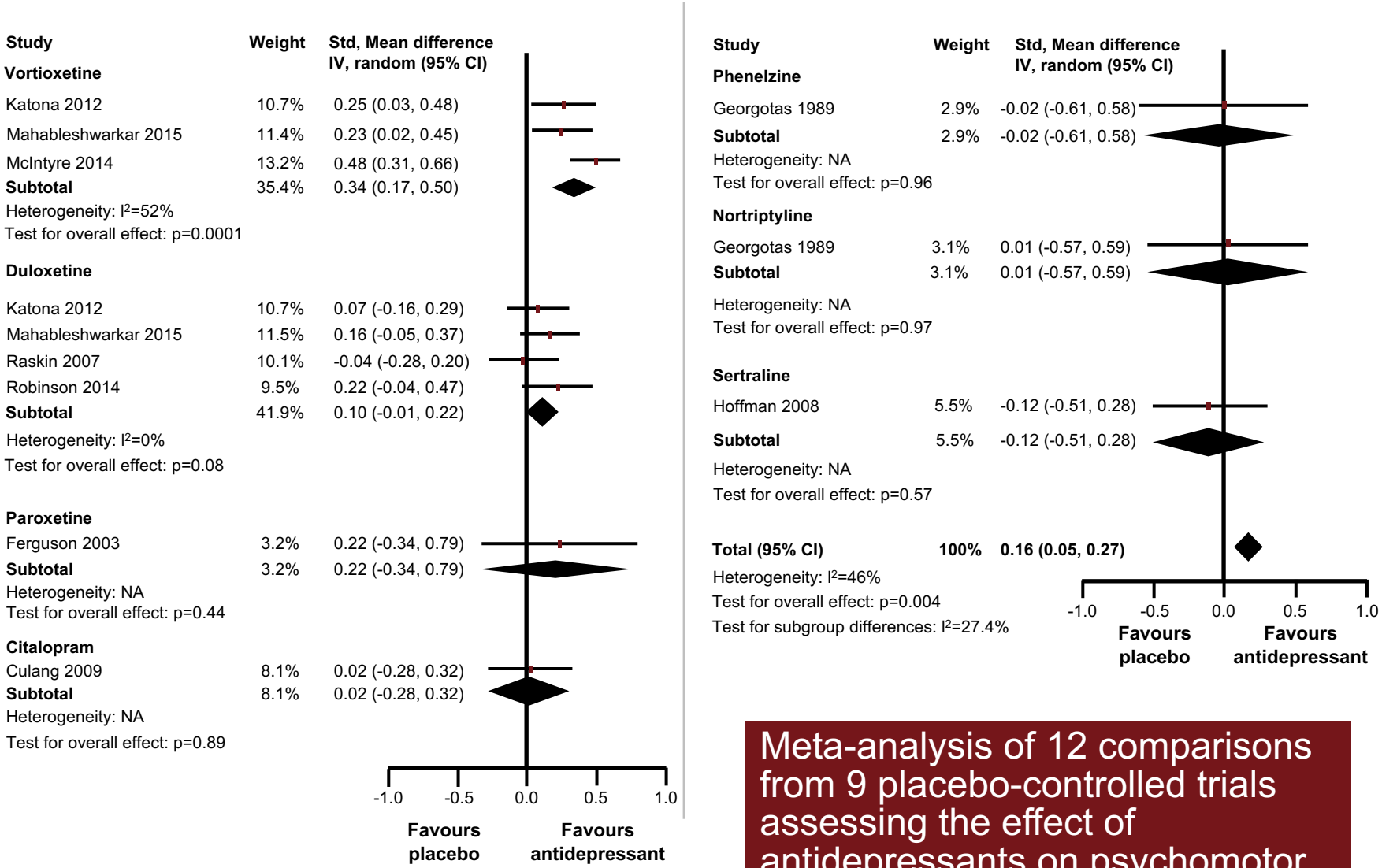
Effect of Antidepressants on Cognitive Improvement

Treatment (reference)	Patient Population	Cognitive Improvements
Duloxetine (Raskin, 2008[1]; Herrera-Guzmán, 2010[2])	207 elderly MDD patients	Verbal learning and memory improved
Escitalopram (Herrera-Guzmán, 2010[3])	37 adults with MDD	Improved episodic memory, working memory, mental processing speed, and motor performance
Fluoxetine (Cassano, 2002[4])	119 elderly MDD patients	Attention, verbal learning, and memory improved
Paroxetine (Cassano, 2002[4])	123 elderly MDD patients	Attention, verbal learning, and memory improved
Reboxetine* (Ferguson, 2003[5])	25 adults with MDD	Improved sustained attention and speed of cognitive functioning
Sertraline (Constant, 2005[6])	20 adults with MDD	Improved psychomotor slowing associated with inttentional and executive functions
Tianeptine* (Jeon, 2014[7])	82 adults with MDD	Improved neurocognitive functions, especially in commission errors and working memory

*Reboxetine and tianeptine are not FDA-approved for MDD

See supplemental bibliography.

Differences Exist Between Antidepressants' Effects on the Cognitive Domain

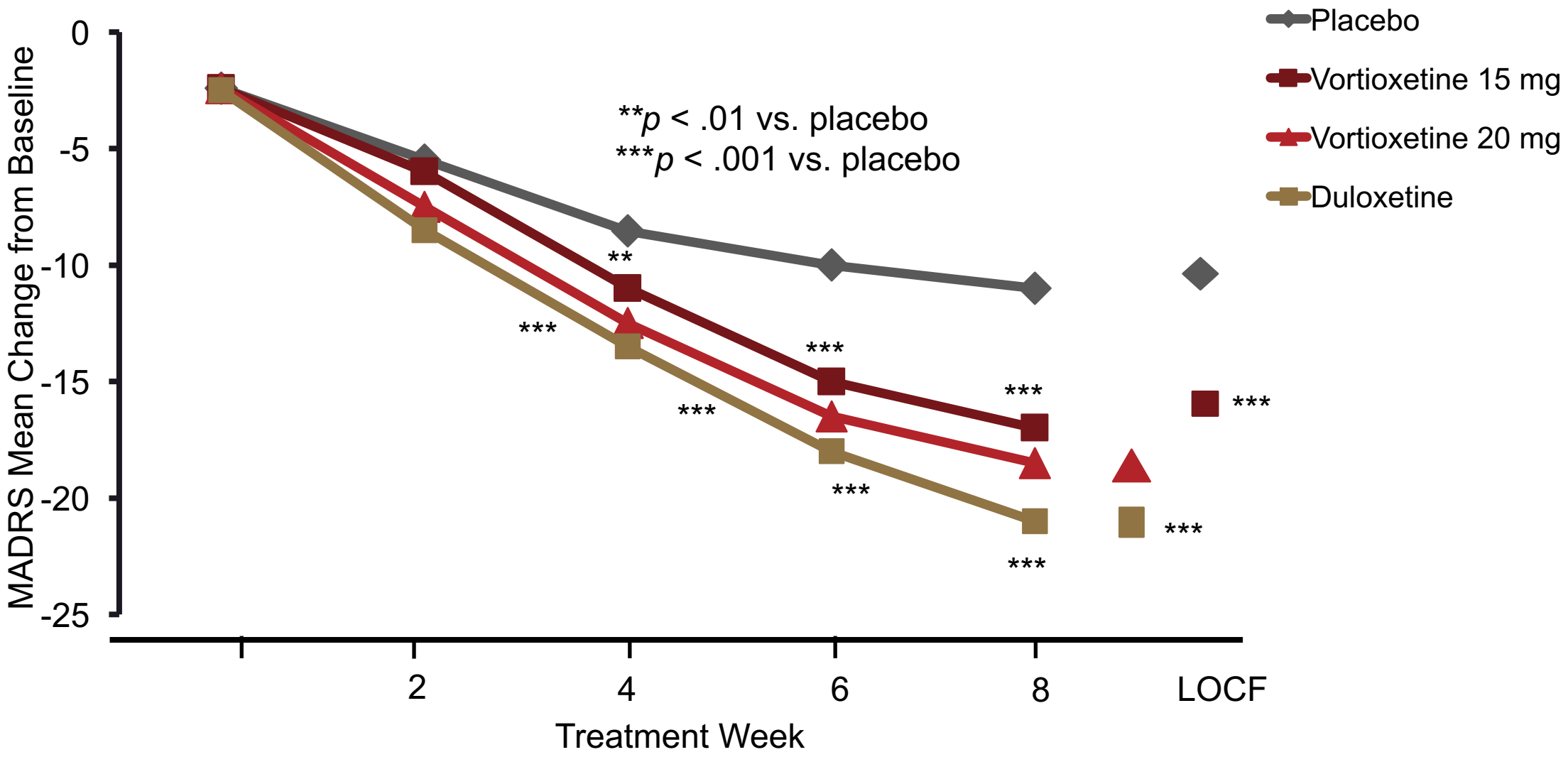


Meta-analysis of 12 comparisons from 9 placebo-controlled trials assessing the effect of antidepressants on psychomotor speed: pooled effects

Antidepressants n = 1660; placebo n = 875; CI = confidence interval; NA = not applicable

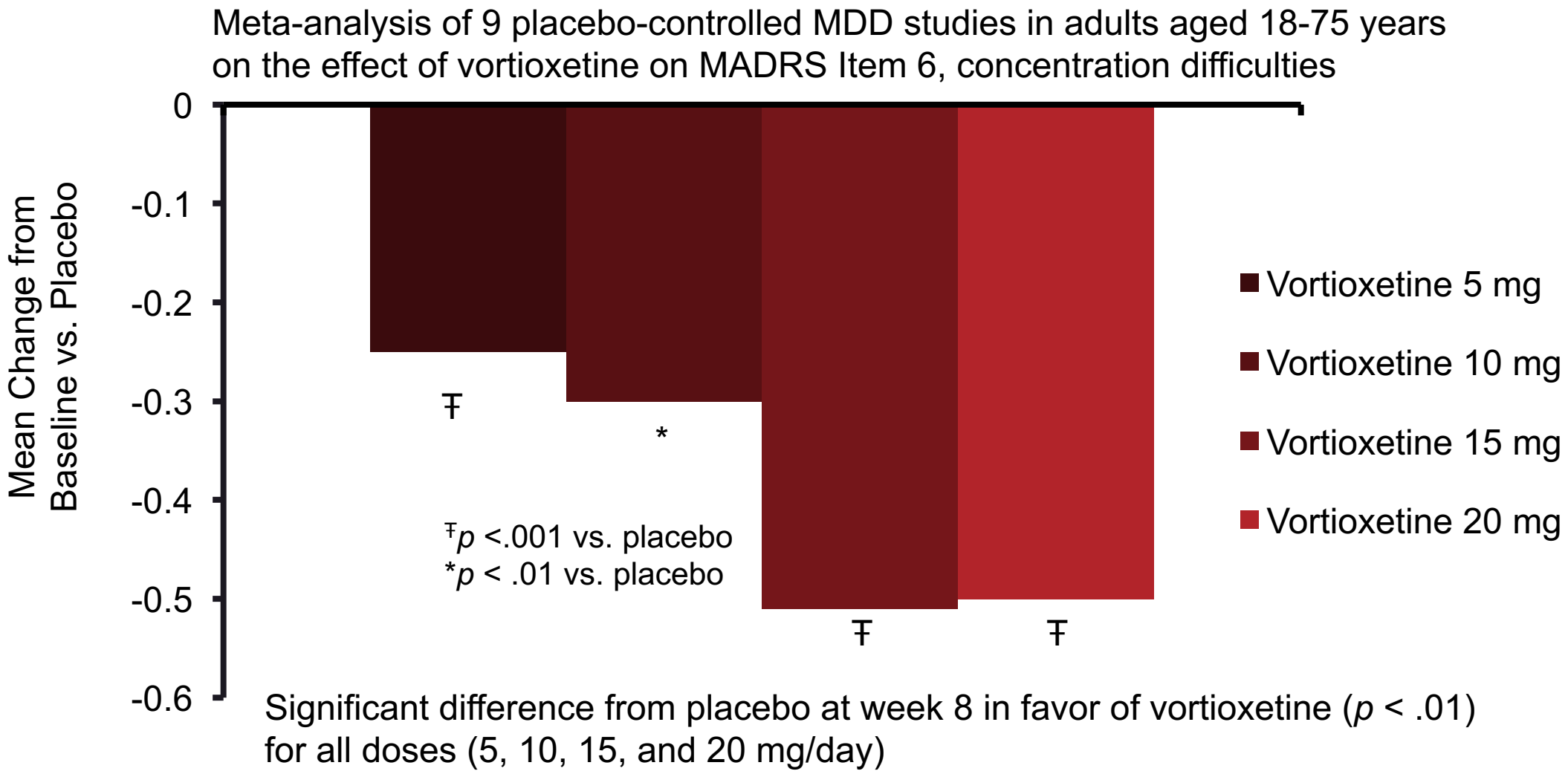
Rosenblat J, et al. *Int J Neuropsychopharmacol.* 2015;19(2):1-13.

Vortioxetine and Duloxetine vs. Placebo: Change in MADRS From Baseline



Boulenger JP, et al. *Int Clin Psychopharmacol*. 2014;29(3):138-149.

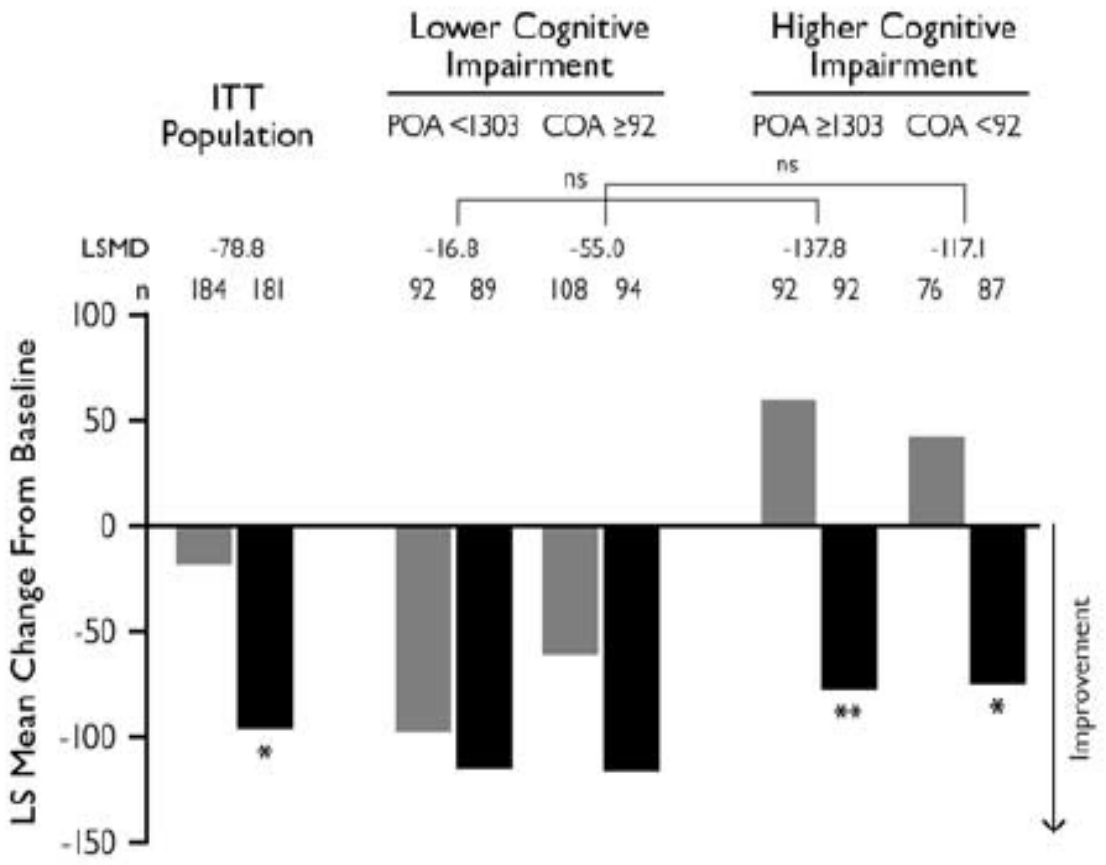
Cognitive Function Assessed by Clinician Ratings



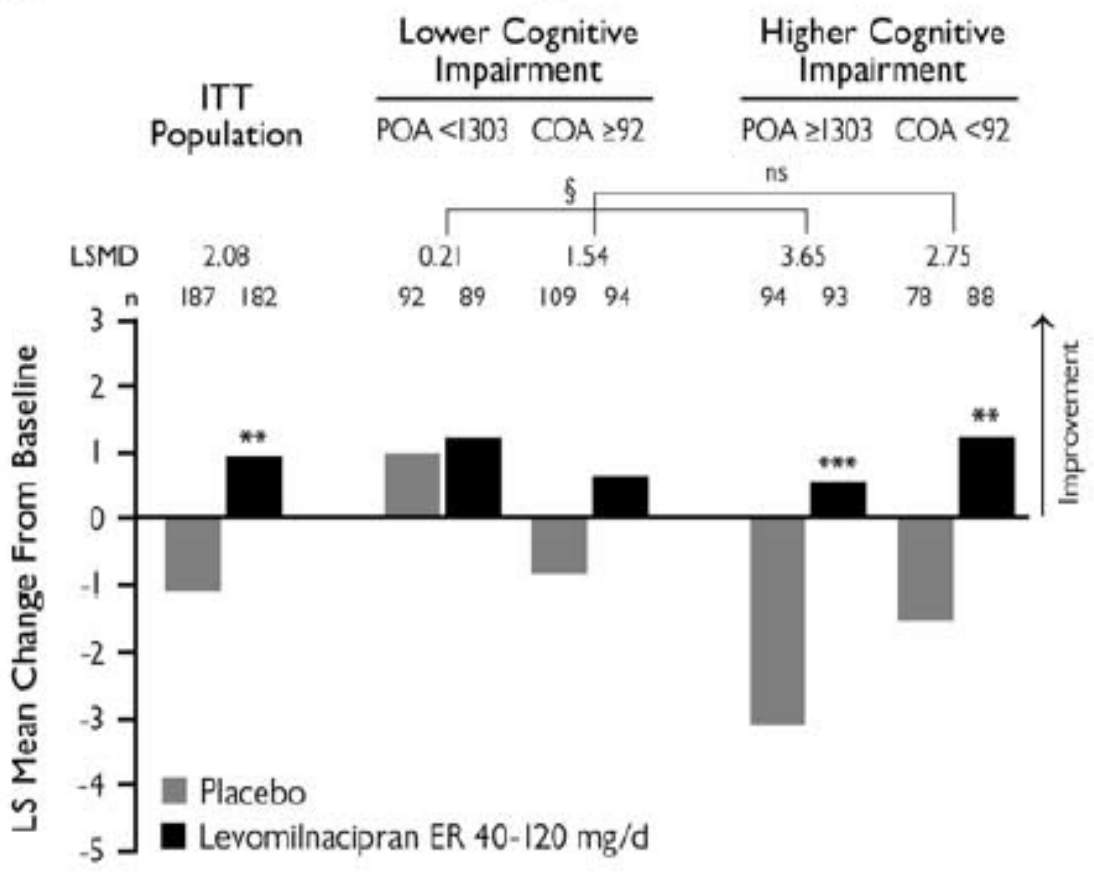
Keefe RS, et al. *Eur Neuropsychopharmacol*. 2013;23(suppl 2):S402-S403; Boulenger JP, et al. *Int Clin Psychopharmacol*. 2014;29(3):138-149.

Levomilnacipran Improves Measures of Attention in MDD

Power of Attention



Continuity of Attention

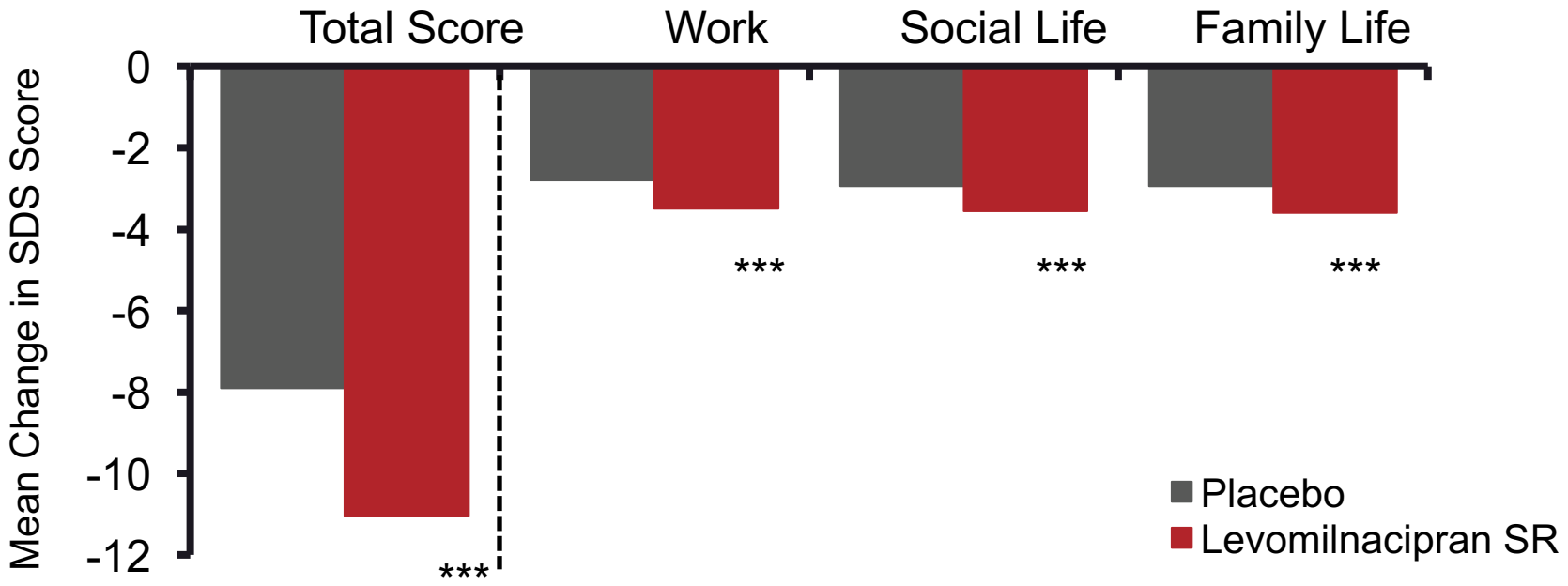


*p < .05; **p < .01; ***p <.001

Wesnes KA, et al. *Int Clin Psychopharmacol*. 2017;32:72-79.

Levomilnacipran SR and Functional Change in MDD

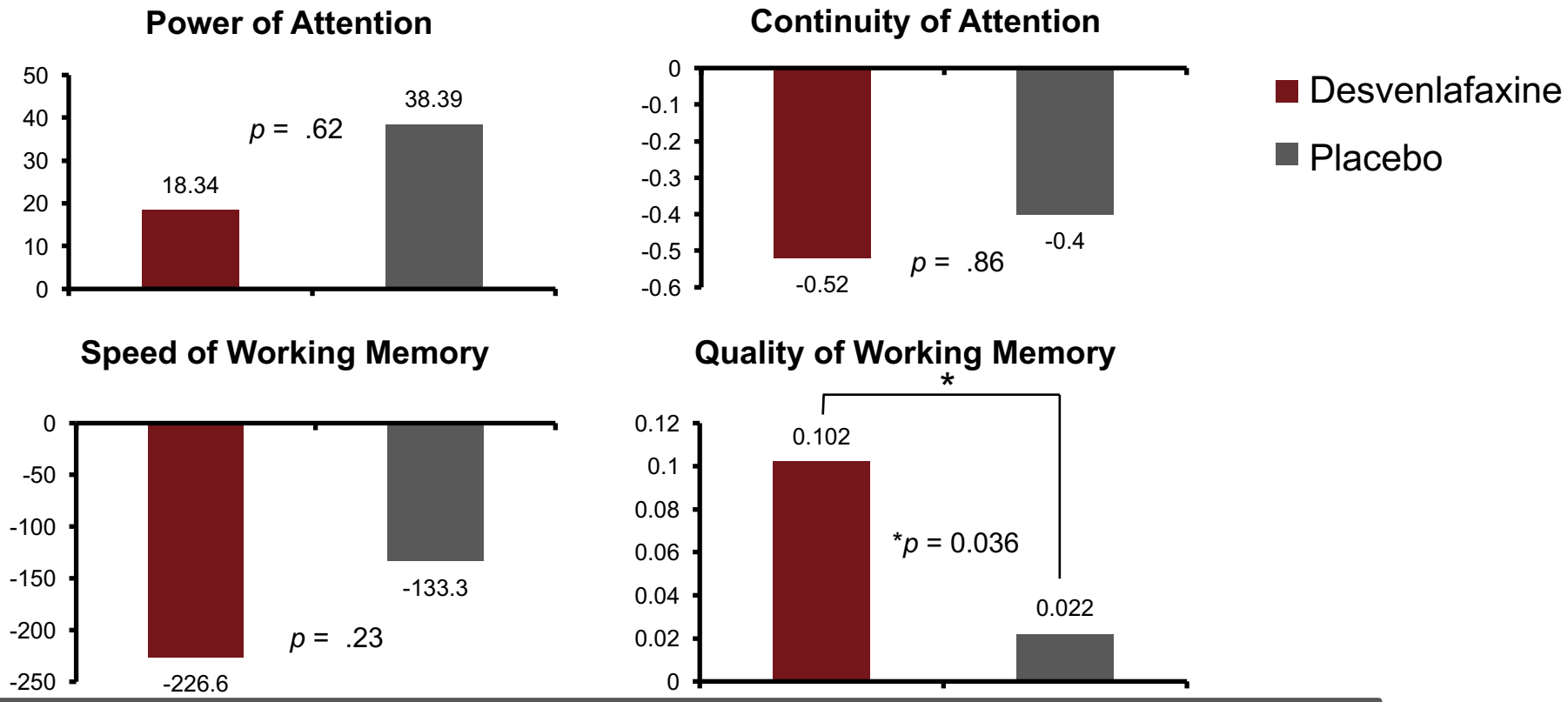
- Sheehan Disability Scale Change from Baseline to Week 10
- (Mixed-effects model for repeated measures)



***p < .0001; N = 553

Montgomery SA, et al. J Clin Psychiatry. 2013;74(4):363-369.

Effect of Desvenlafaxine on Cognitive Symptoms in Employed MDD Patients, Post-hoc Analysis



Only significant difference between desvenlafaxine and placebo is in CDR system composite measure "quality of working memory".

Quality of working memory: The sum of the SIs from numeric and spatial working memory, which reflects the ability to hold information successfully in working memory.

CDR = cognitive drug research; SI = sensitivity index; N = 81

Reddy S, et al. *J Psychopharmacol*. 2016;30(6):559-567.

Alternate Therapeutic Strategies to Address Cognitive Symptoms

Therapeutic Approach	Influence on Emotional Symptoms*	Influence on Cognitive Impairment*	Psychiatric Disorders Targeted
Cognitive behavioral therapy	↑ →	±	Mainly depression (anxiety disorders)
Cognitive remediation therapy	±/↑ ←	↑	Mainly schizophrenia (depression)
Deep-brain stimulation or electroconvulsive therapy	↑ →	±/↓	Major depression
Repetitive transcranial magnetic stimulation	±/↑ →	±/↑	Mainly depression (autism, schizophrenia)
Currently available pharmacotherapy	↑ →	↑/±/↓	Schizophrenia, depression, bipolar disorder, anxiety disorders
Improved drugs (alone and in combination with above strategies)	↑ ↔	↑	Dependent on mechanism of action

* ↑ = improvement; ↓ = worsening; ± = no marked change

Milan ML, et al. *Nat Rev Discov*. 2012;11(2):141-168.

Treatment of Major Depressive Disorder (cont.)

Level 3 **If Levels 1 and 2 are ineffective and/or not well tolerated:**

- Evaluate adherence
- Seek psychiatric consultation
- (SSRI or SNRI) + quetiapine (tolerability concerns)*
- (SSRI or SNRI) + (lithium or T3)*
- (SSRI or SNRI) + (L-methylfolate or S-adenosylmethionine)
- Tricyclic antidepressant (TCA)
- Monoamine oxidase inhibitor (MAOI)
- Electroconvulsive therapy (ECT)
- Transcranial magnetic stimulation (TMS)

Level 4 **If Levels 1 – 3 are ineffective and/or not well tolerated:**

- Re-evaluate diagnosis if patient has failed to respond to two or more treatments
- Monoamine oxidase inhibitor (MAOI) augmentation **(AVOID CONTRAINDICATED COMBINATIONS)**
- L-methlyfolate augmentation
- Triple drug combination (little evidence exists supporting or refuting this strategy)
  - (SSRI or SNRI) + mirtazapine + bupropion
  - (SSRI or SNRI) + mirtazapine + lithium
  - (SSRI or SNRI) + bupropion + second generation antipsychotic (SGA)
- Other neuromodulatory approaches (e.g. vagus nerve stimulation)

* quetiapine, lithium, and T3 (liothyronine) are not FDA-approved for MDD

McIntyre RS, et al. Florida Best Practice Psychotherapeutic Medication Guidelines for Adults. 2015; Available at www.medicaidmentalhealth.org.

Treatment of Major Depressive Disorder With Mixed Features

Mixed features are subsyndromal hypomanic features defined according to the DSM-5.

Assess for:

- Prior history of hypomania/mania
- Psychiatric and medical comorbidities (e.g. substance use disorders, anxiety disorders, obesity, diabetes)

Level 1 **Initial Treatment:**

- Minimal evidence for treating major depressive disorder (MDD) with mixed features specifier
- Discuss treatment options, including evidence-based psychotherapy [Cognitive-behavioral therapy (CBT), Interpersonal psychotherapy (IPT)]
- Consider second generation antipsychotic (SGA) or mood stabilizer (e.g. lithium)
- Antidepressant monotherapy 4-8 week trial at adequate dose and evaluate (antidepressant monotherapy in MDD with subsyndromal hypomania may be associated with a higher rate of suboptimal therapeutic outcomes when compared to MDD without subsyndromal hypomania):
  - Selective serotonin reuptake inhibitor (SSRI) (consider propensity for drug-drug interactions, differential risk for teratogenicity), serotonin-norepinephrine reuptake inhibitor (SNRI), or vortioxetine (if cognitive complaints)
  - Bupropion (if tolerability concerns) or mirtazapine (if insomnia a focus of clinical concern)
- For all Level 1 treatments, if partial response at 4 weeks, may continue for another 4 weeks or go to Level 2
- For all Level 1 treatments, if no response at 4 weeks, go to Level 2

McIntyre RS, et al. Florida Best Practice Psychotherapeutic Medication Guidelines for Adults. 2015; Available at www.medicaidmentalhealth.org.

Impact of Collaborative Care Models on Depression Outcomes

- A plurality of trials have evaluated collaborative care models for depression
- Two 2012 systematic reviews evaluated a total of 69 randomized trials of collaborative care
  - Consistently more effective than traditional model
    - Higher response to treatment
    - Higher remission rates
    - Improved treatment adherence
    - Improved quality of life and functional status

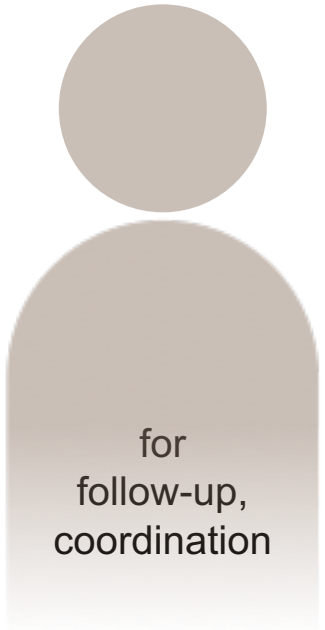
Thota AB, et al. *Am J Prev Med*. 2012;42(5):525-538.
Jacob V, et al. *Am J Prev Med*. 2012;42(5):539-549.

The DIAMOND Model

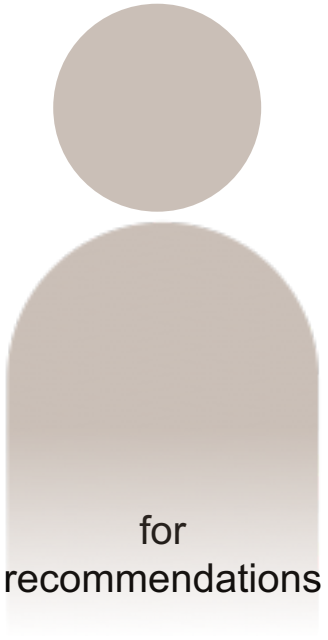
- Consists of 4 processes:
  - Standardized assessment and monitoring (PHQ-9)
  - Registry for tracking patients
  - Stepped care for intensifying and changing treatment
  - Measures to prevent relapse

Introduces 2 new players:

Care Manager



Consulting Psychiatrist



Pietruszewski P. *Psychiatr Serv*. 2010;61(10):1042-1044.