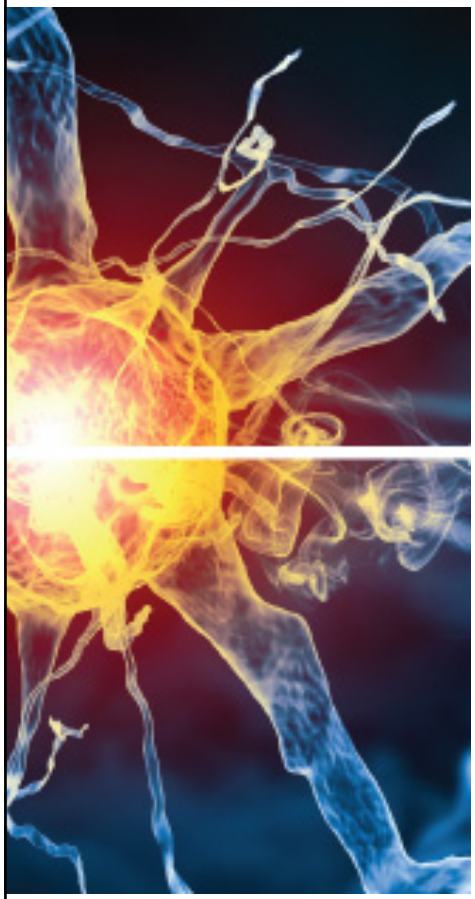
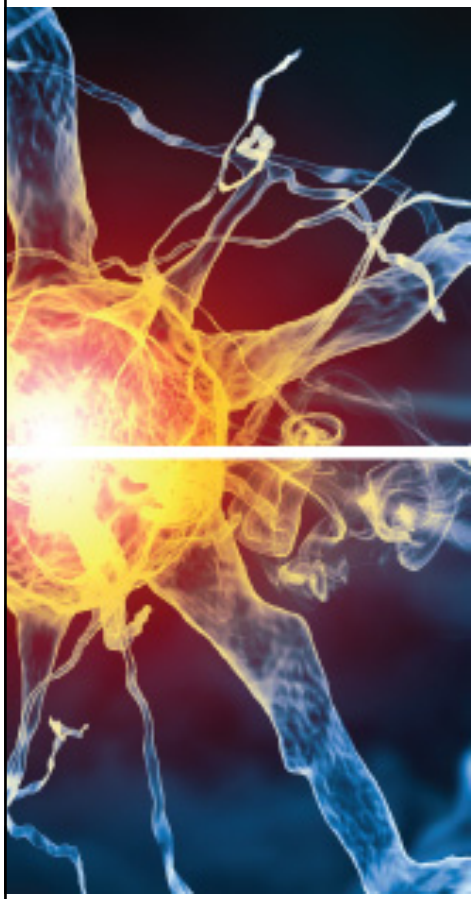


Management of Treatment Resistant Depression:

The Art and the Science



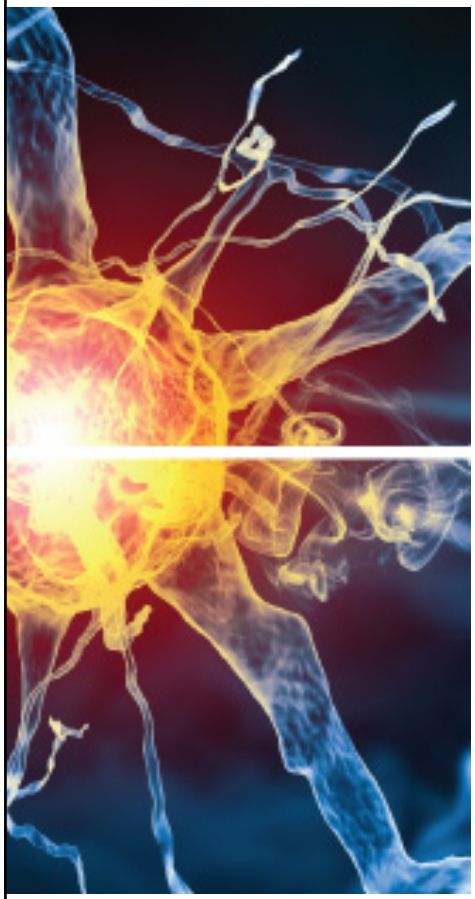
Charles B. Nemeroff, MD, PhD

Leonard M. Miller Professor and Chairman
Department of Psychiatry and Behavioral Sciences
Director, Center on Aging
University of Miami, Miller School of Medicine
Miami, FL

Charles B. Nemeroff, MD, PhD

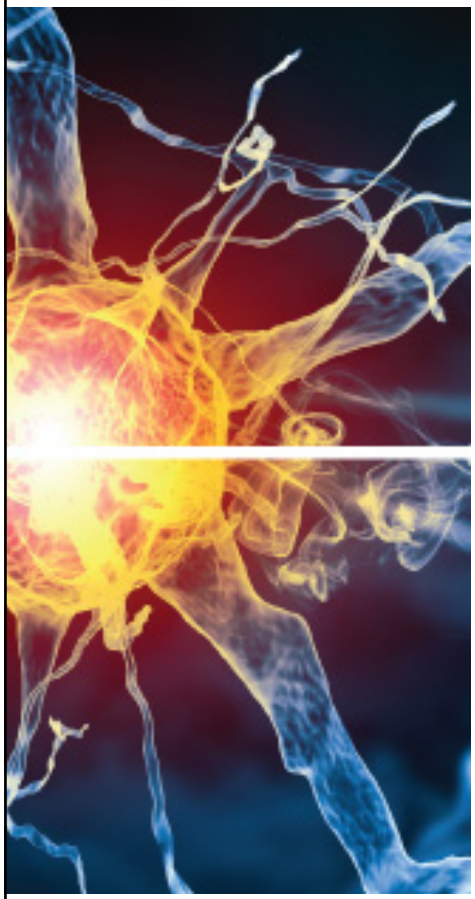
Disclosures

- ***Research/Grants***: National Institutes of Health (NIH), Stanley Medical Research Institute
- ***Consultant***: Bracket (Clintara); Fortress Biotech; Gerson Lehrman Group, Inc. (GLG) Healthcare & Biomedical Council, America; Janssen Research & Development, LLC; MagStim, Inc.; Prismic Pharmaceuticals, Inc.; Sumitomo Dainippon Pharma; Sunovion Pharmaceuticals Inc.; Taisho Pharmaceutical Inc.; Takeda Pharmaceuticals North America, Inc.; Total Pain Solutions (TPS); Xhale, Inc.
- ***Stockholder:*** AbbVie Inc.; Bracket; Celgene Corporation; Intermediate Holding Corp.; Network Life Sciences Inc.; OPKO Health, Inc.; Seattle Genetics, Inc.; Xhale, Inc.
- ***Income Sources or Equity of $10,000 or More***: American Psychiatric Publishing; Bracket (Clintara); CME Outfitters, LLC; Takeda Pharmaceuticals North America, Inc.; Xhale, Inc.
- ***Patents***: Method and devices for transdermal delivery of lithium (US 6,375,990B1) Method of assessing antidepressant drug therapy via transport inhibition of monoamine neurotransmitters by ex vivo assay (US 7,148,027B2)
- ***Scientific Advisory Board***: American Foundation for Suicide Prevention (AFSP); Anxiety Disorders Association of America (ADAA); Bracket (Clintara); Brain & Behavior Research Foundation (BBRF) (formerly National Alliance for Research on Schizophrenia and Depression [NARSAD]); Laureate Institute for Brain Research, Inc. RiverMend Health, LLC; Skyland Trail; Xhale, Inc.
- Board of Directors: American Foundation for Suicide Prevention (AFSP); Anxiety Disorders Association of America (ADAA); GratitudeAmerica, Inc.



1 Learning Objective

Recognize the factors that impact the severity of depression and contribute to treatment resistance.



2 Learning Objective

Develop a strategy for treatment resistant depression utilizing pharmacologic and nonpharmacologic approaches.

All his life he suffered spells of depression, sinking into the brooding depths of melancholia, an emotional state which, though little understood, resembles the passing sadness of the normal man as a malignancy resembles a canker sore.

William Manchester,
The Last Lion, Winston Spencer Churchill, Vol. I: Visions of Glory
(New York: Little, Brown & Company, 1989, p. 23)

Major Depressive Disorder: *DSM-5* Diagnostic Criteria

A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure:

Note: Do not include symptoms that are clearly attributable to another medical condition.

1. Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad, empty, hopeless) or observation made by others (e.g., appears tearful). (Note: In children and adolescents, can be irritable mood.)
2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation).
3. Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day. (Note: In children, consider failure to make expected weight gain.)
4. Insomnia or hypersomnia nearly every day.
5. Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).
6. Fatigue or loss of energy nearly every day.
7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).
8. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).
9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders: DSM-5*. 5th ed. 2013.

Major Depressive Disorder: *DSM-5* Diagnostic Criteria

B. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

C. The episode is not attributable to the physiological effects of a substance or to another medical condition.

Note: Criteria A-C represent a major depressive episode.

Note: Responses to a significant loss (e.g., bereavement, financial ruin, losses from a natural disaster, a serious medical illness or disability) may include feelings of intense sad ness, rumination about the loss, insomnia, poor appetite, and weight loss noted in Criterion A, which may resemble a depressive episode. Although such symptoms may be understandable or considered appropriate to the loss, the presence of a major depressive episode in addition to the normal response to a significant loss should also be carefully considered. This decision inevitably requires the exercise of clinical judgment based on the person's past history of major depressive episodes, whether the symptoms are disproportionately severe given the nature of the loss, and the individual's cultural norms for the expression of distress in the context of loss.

D. The occurrence of the major depressive episode is not better explained by schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional disorder, or other specified and unspecified schizophrenia spectrum and other psychotic disorders.

E. There has never been a manic episode or a hypomanic episode.

Note: This exclusion does not apply if all of the manic-like or hypomanic-like episodes are substance-induced or are attributable to the physiological effects of another medical condition.

American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders: DSM-5*. 5th ed. 2013.

Major Depressive Disorder: *DSM-5* Diagnostic Criteria

Specify:

If the full criteria are currently met for a major depressive episode, specify its current clinical status and/or features:

With anxious distress

With mixed features

With melancholic features

With atypical features

[1]In distinguishing grief from a major depressive episode (MDE), it is useful to consider that in grief the predominant affect is feelings of emptiness and loss, while in MDE it is persistent depressed mood and the inability to anticipate happiness or pleasure. The dysphoria in grief is likely to decrease in intensity over days to weeks and occurs in waves, the so-called pangs of grief. These waves tend to be associated with thoughts or reminders of the deceased. The depressed mood of MDE is more persistent and not tied to specific thoughts or preoccupations. The pain of grief may be accompanied by positive emotions and humor that are uncharacteristic of the pervasive unhappiness and misery characteristic of MDE. The thought content associated with grief generally features a preoccupation with thoughts and memories of the deceased, rather than tl1e self-critical or pessimistic ruminations seen in MOE. In grief, self-esteem is generally preserved, whereas in MOE feelings of worthlessness and self-loathing are common. If self-derogatory ideation is present in grief, it typically involves perceived failings vis à vis the deceased (e.g., not visiting frequently enough, not telling the deceased how much he or she was loved). If a bereaved individual thinks about death and dying, such thoughts are generally focused on the deceased and possibly about "joining" the deceased, whereas in MDE such thoughts are focused on ending one's own life because of feeling worthless, undeserving of life, or unable to cope with tl1e pain of depression.

With mood-congruent psychotic features

With mood-incongruent psychotic features

With catatonic features **Coding note:** Use additional code 781.99 (R29.818).

With peripartum onset

With seasonal pattern (recurrent episode only)

Specify current or most recent episode:

Single episode.

Recurrent episode: Defined as the presence of two or more lifetime major depressive episodes. To be considered separate episodes, there must be an interval of at least 2 consecutive months in which criteria are not met for a major depressive episode.

Specify current severity:

Mild

Moderate

Severe

Specify:

Level of concern for suicide in the current assessment period regardless of current episode or remission status

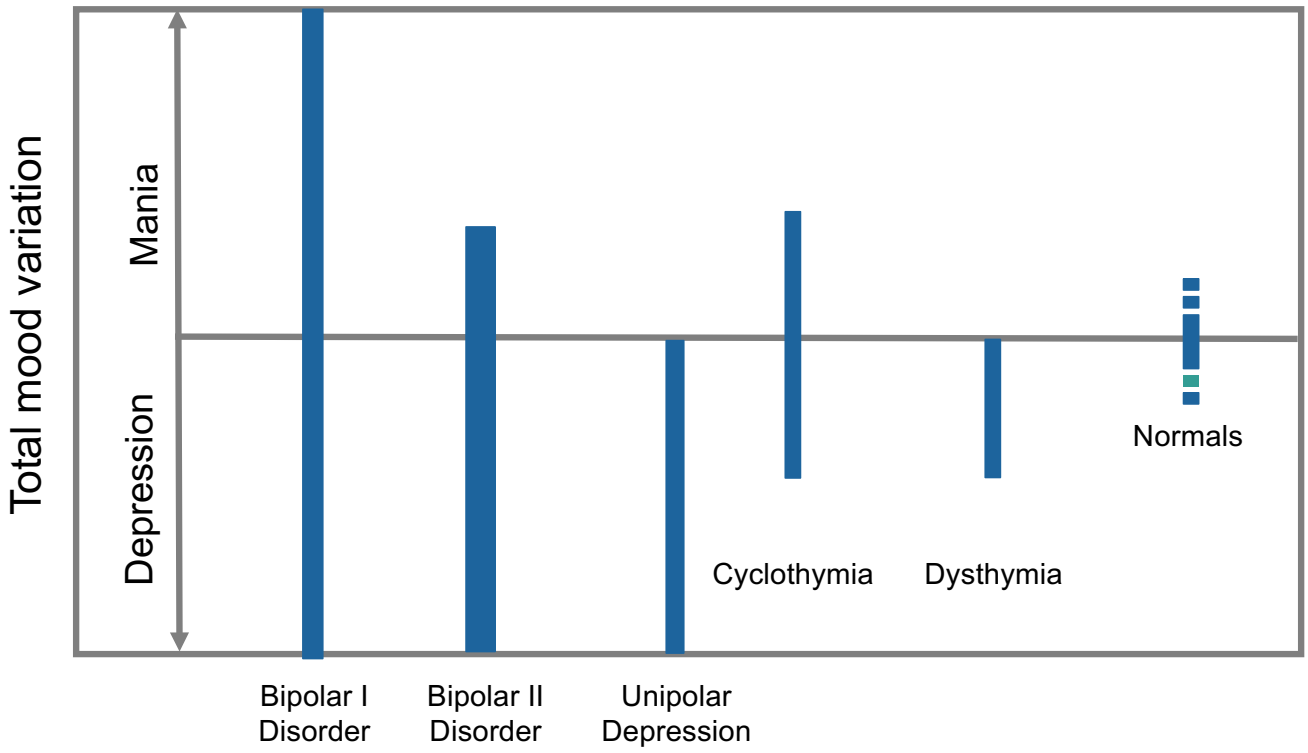
American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders: DSM-5*. 5th ed. 2013.

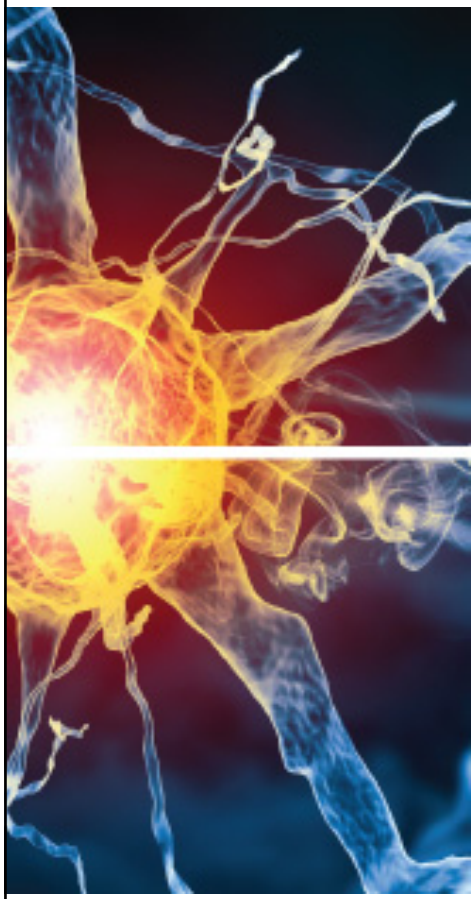
Major Changes in *DSM-5*

- Bereavement
- Elimination of chronic depression
- Severity/course specifier

American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders: DSM-5*. 5th ed. 2013.

The Mood-Disorders Spectrum

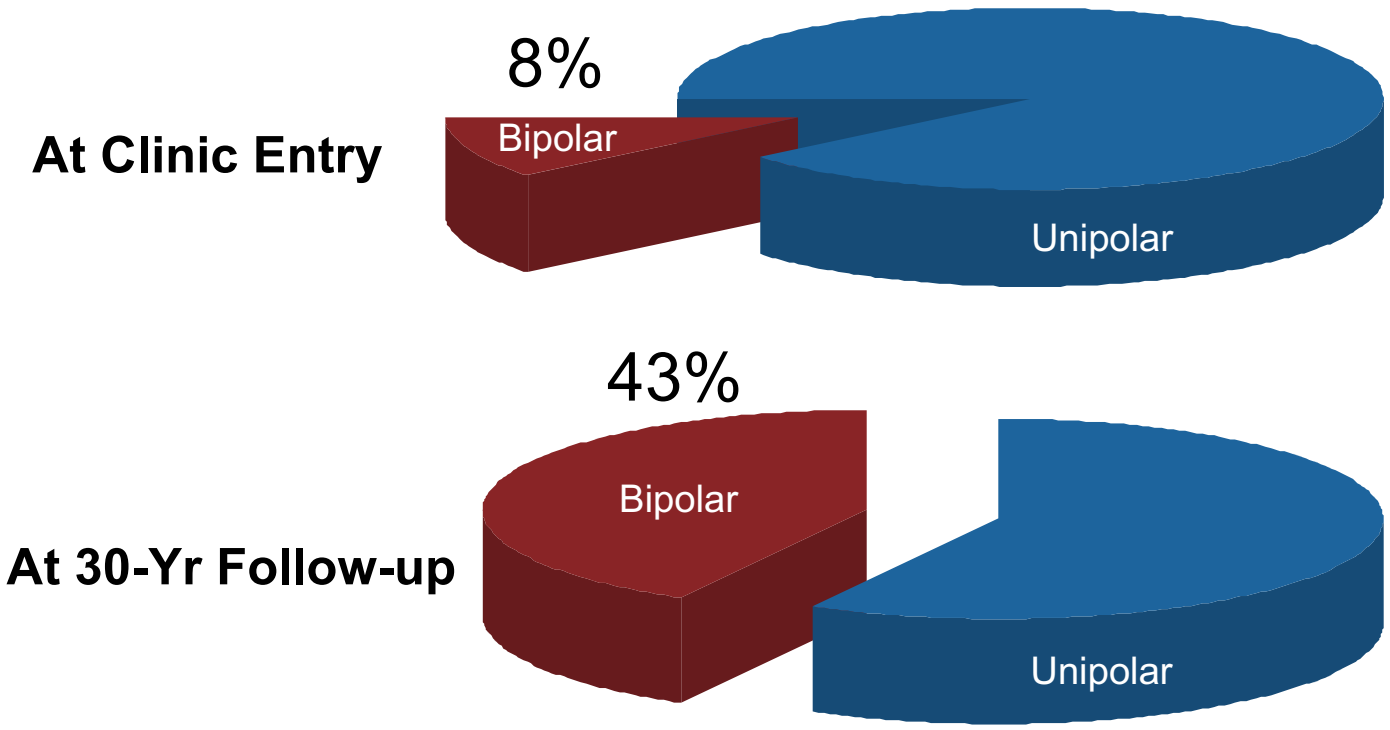




Unipolar vs. Bipolar Depression: Initial Diagnosis

How Often do Unipolar Patients Become Bipolar?

UP:BP



UP = Unipolar; BP = Bipolar

Angst J, Sellaro R. *Biol Psychiatry*. 2000;48:445-457.

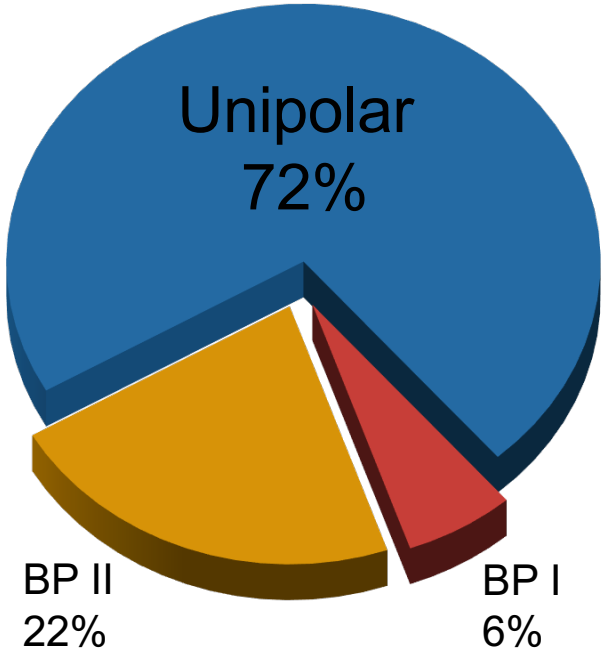
Risk of Bipolar Disorder in Patients Initially Hospitalized for Unipolar Depression

- 15 year follow-up of 74 patients initially hospitalized for unipolar depression
  - 27% had > 1 episode of hypomania (BPII)
  - 19% had > 1 episode of mania (BPI)
  - 80% with psychotic depression became bipolar compared with 34% with nonpsychotic depression

Goldberg JF, et al. *Am J Psychiatry*. 2001;158(8):1265-1270.

Underrecognition of Bipolar Disorder in Psychiatric Clinics

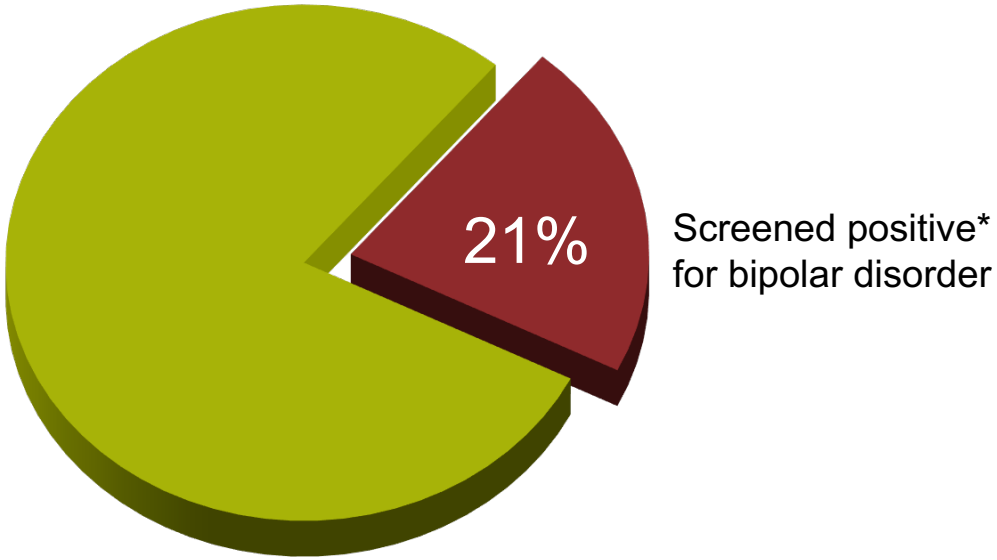
Patients with major depressive episodes in France (n = 250)



Hantouche EG, et al. *J Affect Disord*. 1998;50:163-173.

Underrecognition of Bipolar Disorder in Patients Treated for Depression in a Primary Care Clinic

649 outpatients receiving treatment for depression



*Using the Mood Disorder Questionnaire (MDQ).

Hirschfeld RMA, et al. *J Am Board Fam Pract*. 2005;18:233-239.

Improving Recognition of Bipolar Disorder in Patients Presenting with Depression

- Ask about history of mania and hypomania
- Ask about family history of bipolar disorder
- Involve family members or significant others in the evaluation process
- Administer a screening instrument for bipolar disorder, the Mood Disorder Questionnaire (MDQ)

Hirschfeld RM, Vornik LA. *J Clin Psychiatry*. 2004;65(suppl 15):5-9.

Clinical Clues to Bipolarity in "Unipolar" Depressed Patients

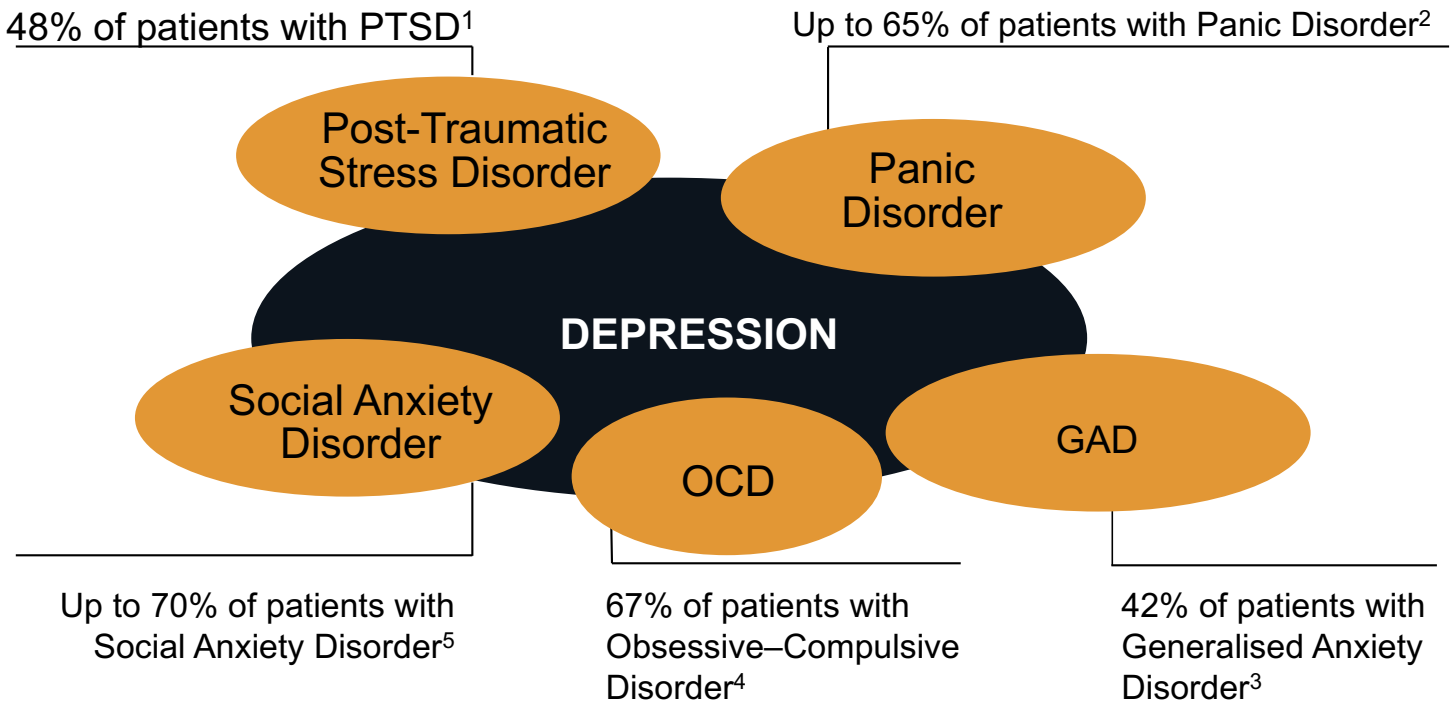
- "Loaded" family history
- Early age of onset (< 25 year-old) with high episode rates
- Psychotic features
- Seasonal pattern
- Antidepressant "misadventures"
  - Treatment-emergent hypomania or agitation
  - Erratic or uneven antidepressant responses
  - Multiple antidepressant failures —"treatment-resistant depression"

Ghaemi SN, et al. *J Psychiatr Pract*. 2001;7:287-297.

Goodwin FK, Jamison KR. *Manic-Depressive Illness*. New York, NY: Oxford University Press, Inc; 1990:56-73.

Comorbidity

Lifetime comorbidity of mood and anxiety disorders



Kessler RC, et al. *Arch Gen Psychiatry* 1995;52(12);1048-1060; DSM-IV-TR™ 2000; Brawman-Mintzer O, et al. *Am J Psychiatry* 1993;150(8):1216-1218.; Rasmussen SA, et al. *J Clin Psychiatry* 1992;53 Suppl:4-10.; Dunner D. *Depress Anxiety* 2001;13(2):57-71.

Commonly Used Depression Symptom Severity Scales in Treatment Research

- Beck Depression Inventory (self-report)
- Hamilton Rating Scale for Depression (clinician-rated)
- Montgomery Asberg Depression Rating Scale (clinician-rated)
- Inventory of Depressive Symptoms (full and quick versions self-report and clinician-rated versions)

Bradley RG, et al. *Arch Gen Psychiatry.* 2008;65(2):190-200.

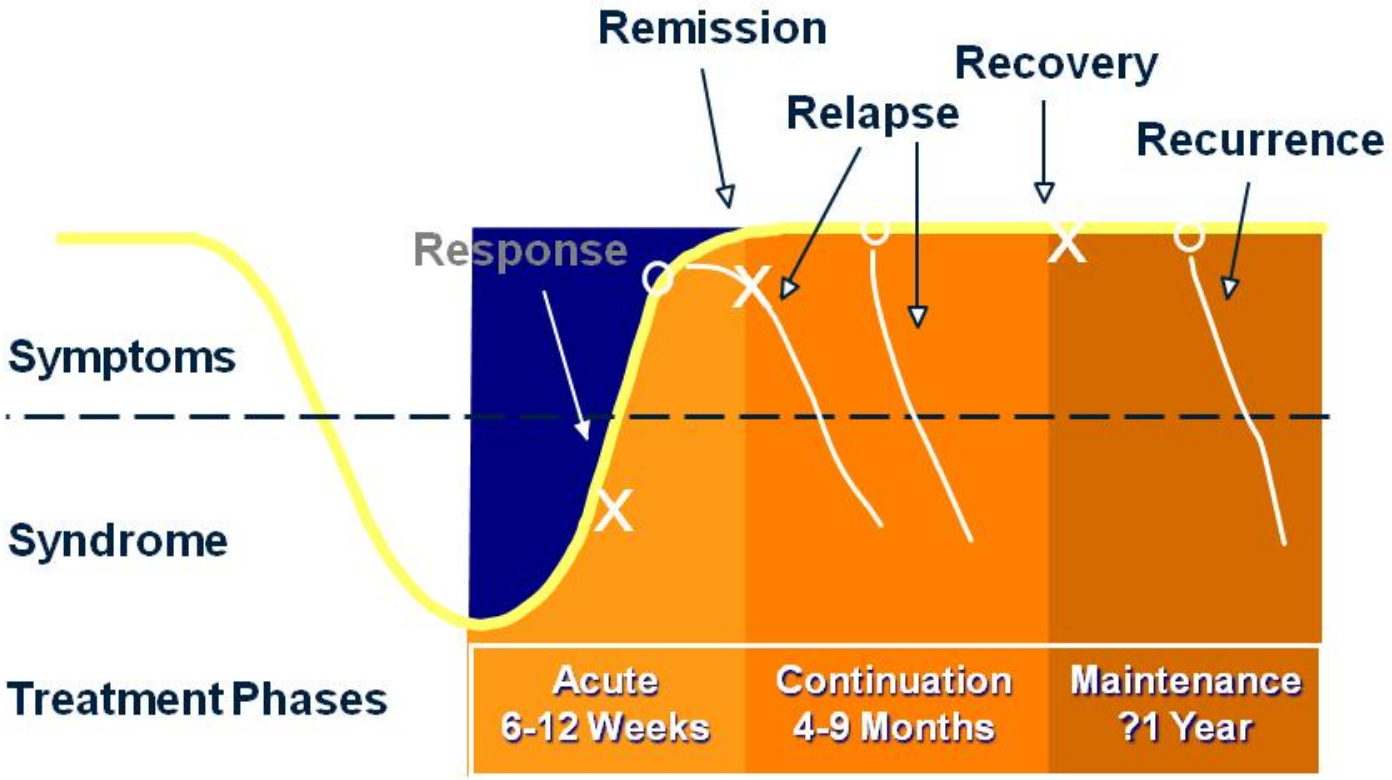
Montgomery-Asberg Depression Rating Scale (MADRS)

Measures 10 symptoms

1. Apparent sadness
2. Reported sadness
3. Inner tension
4. Reduced sleep
5. Reduced appetite
6. Concentration difficulties
7. Lassitude
8. Inability to feel
9. Pessimistic thoughts
10. Suicidal thoughts

Montgomery S, Asberg M. *Br J Psychiatry*. 1979;134:382–389.

Outcome of Depression Treatment: The Five Rs



Outcomes of Treatment

Outcome	Commonly Accepted Definition
Response	Clinical significant reduction in baseline symptom severity
Remission	Absence of symptoms
Recovery	Sustained period of remission following an episode of major depression
Relapse	Return of a major depressive episode during continuation treatment (ie, before recovery)
Recurrence	New episode of depressive following recovery of previous episode

Depression Guideline Panel; 1993. AHCPR publication 93-0550.

Frank E, et al. *Arch Gen Psychiatry*. 1991;48:851-855.

Remission

- Minimal or no symptoms
  - No longer meets diagnostic criteria
- Sustained remission: return to “functional normality”
  - Remission for ≥8 wk usually associated with restoration of daily functioning
  - Typically, cannot be distinguished from those without depression

DSM-IV-TR. Washington, DC: American Psychiatric Association; 2000.

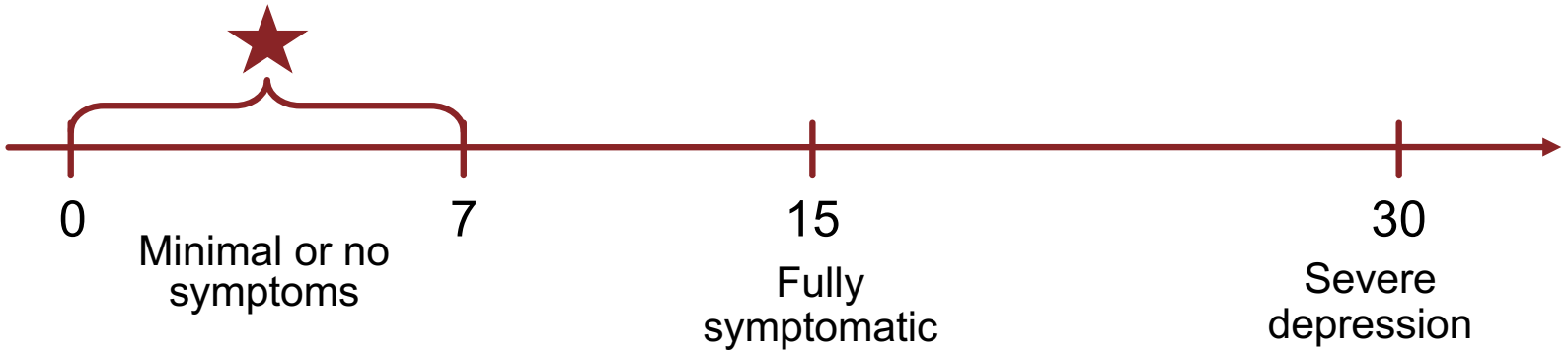
Thase ME, et al. *Br J Psychiatry*. 2001;178:234-241.

Frank E, et al. *Arch Gen Psychiatry*. 1991;48(9):851-855.

Rush AJ, et al. *Psychiatr Ann*. 1995;25:704.

Operational Definition of Remission

Remission = HAM-$D_{17} \leq 7$



Hamilton Depression Rating Scale (HAM-D_{17})

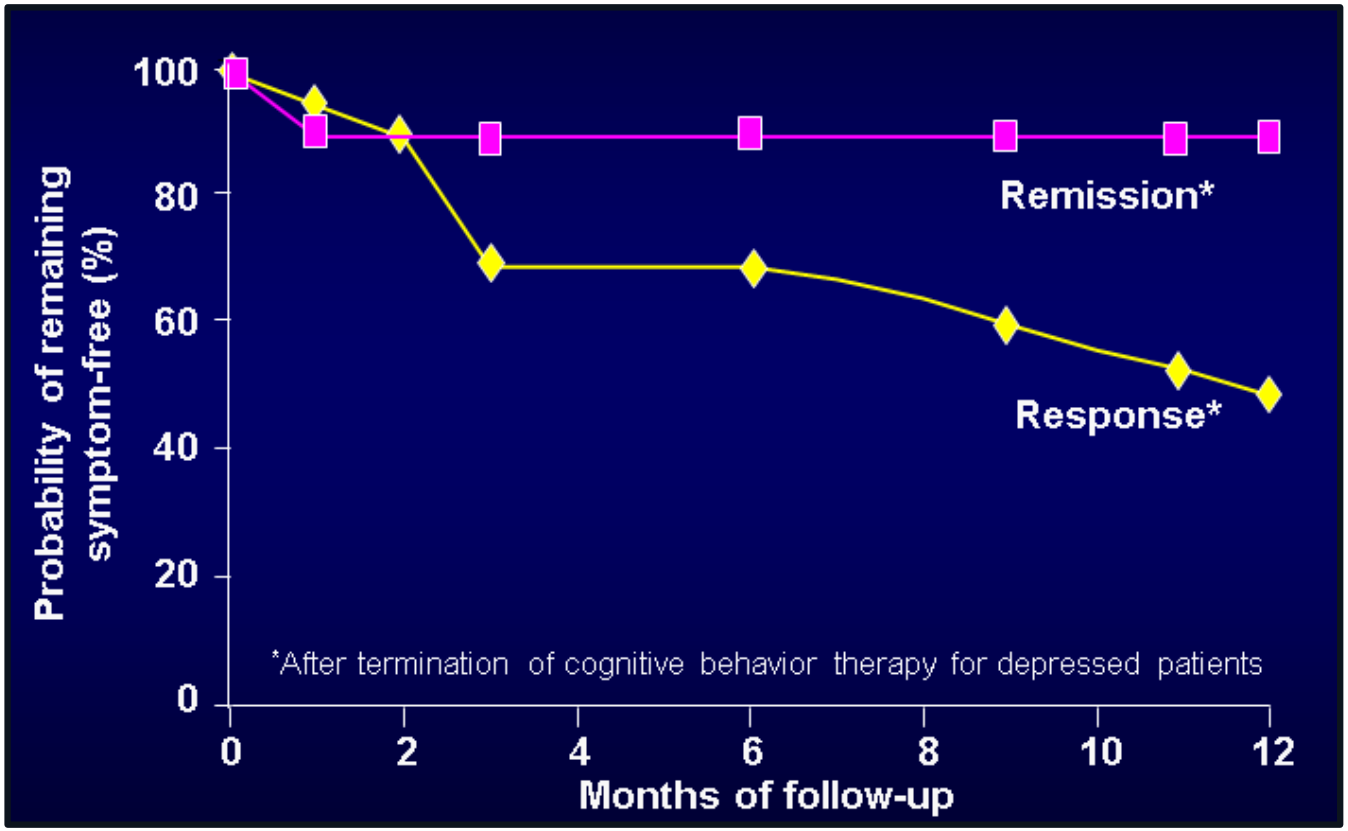
Frank E, et al. *Arch Gen Psychiatry*. 1991;48:851-855.; Rush AJ, et al. *Psychiatr Ann*. 1995;25:704.; American Psychiatric Association. *Practice Guidelines for the Treatment of Patients With Major Depression*. 2nd ed. 2000; Anderson IM, et al. *J Psychopharmacol*. 2000;14:3-20.

Potential Consequences of Failing to Achieve Remission

- Increased risk of relapse and treatment resistance
- Continued psychosocial limitations
- Decreased ability to work and decreased workplace productivity
- Increased cost for medical treatment
- Sustained risk of suicide, substance abuse
- Sustained depression can worsen morbidity/mortality of other conditions

Paykel ES, et al. *Psychol Med.* 1995;25:1171-1180.; Thase ME, et al. *Am J Psychiatry*. 1992;149:1046-1052.; Judd LL, et al. *J Affect Disord*. 1998;59:97-108; Miller IW, et al. *J Clin Psychiatry*. 1998;59:608-619.; Simon GE, et al. *Gen Hosp Psychiatry*. 2000;22:153-162; Druss BG, et al. *Am J Psychiatry*. 2001;158:731-734; Frasure-Smith N, et al. *JAMA*. 1993;270:1819-1825; Penninx BW, et al. *Arch Gen Psychiatry.* 2001;58:221-227; Rovner BW, et al. *JAMA*. 1991;265:993-996.

Achieving Remission Decreases Risk of Relapse



Thase ME, et al. *Am J Psychiatry*. 1992;149:1046-1052.

Depression Worsens Outcomes of Many General Medical Conditions

- Depression worsens morbidity and mortality after myocardial infarction[1,2]
- Depression increases risk for mortality in patients in nursing homes[3]
- Depression worsens morbidity post-stroke[4]
- Depression can worsen outcomes of cancer, diabetes, AIDS, and other disorders[5]

[1]Frasure-Smith N, et al. *JAMA*. 1993;270:1819-1825.; [2]Penninx BW, et al. *Arch Gen Psychiatry*. 2001;58:221-227.; [3]Rovner BW, et al. *JAMA*. 1991;265:993-996.; [4]Pohjasvaara T, et al. *Eur J Neurol*. 2001;8:315-319. [5]Petitto JM, Evans DL. *Depress Anxiety*. 1998;8(suppl 1):80-84.

Risk Factors for Delayed Remission

- Chronicity
  - Longer length of episode
  - Number of previous episodes
- Medical comorbidity
- Older age
- Axis I or II comorbidity
- Severity

Thase ME, et al. *Am J Psychiatry*. 1997;58(suppl 13):23-29.
Nierenberg AA, et al. *J Clin Psychiatry*. 1999;60(suppl 22):7-11.
Thase ME. *J Clin Psychiatry*. 1999;60(suppl 22):3-6.

Potential Obstacles to Attaining Remission in Clinical Practice

- Patients and clinicians are satisfied with partial improvement in symptoms (ie, response but not remission)
- Treatments may not be well tolerated
- Underdosing
- Failure to recognize residual symptoms

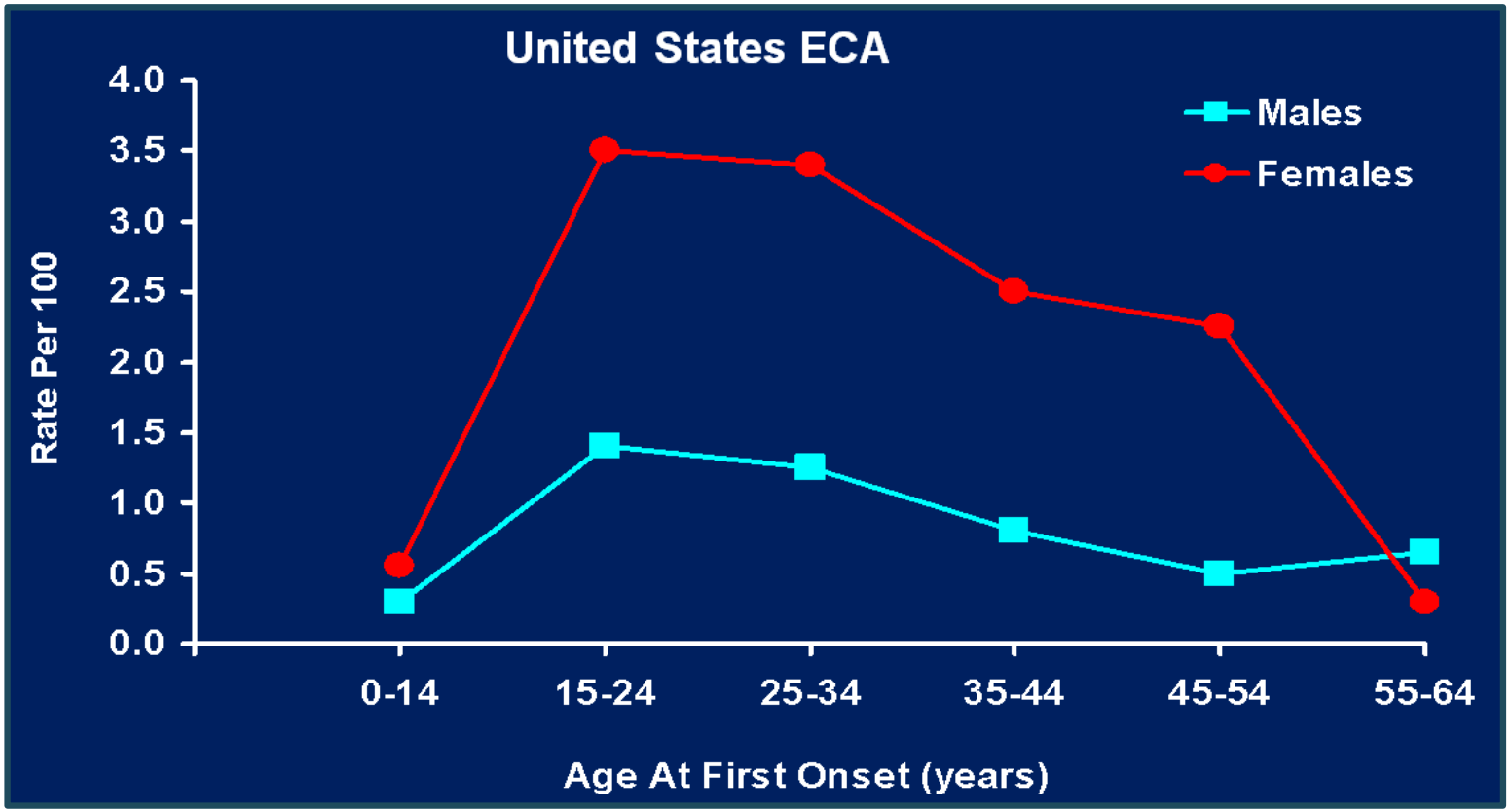
Keller MB, et al. *Arch Gen Psychiatry*. 1992;49(10):809-816.

Increasing the Likelihood of Remission

- Measure outcomes!
- Optimize dose/extend trial
- Selection of antidepressant
- Role of adherence
- Pharmacologic adjuncts
- Role of psychotherapy

Rush AJ, et al. *J Clin Psychiatry*. 1997;58(suppl 13):14-22.
Thase ME, et al. *Am J Psychiatry*. 1999;60(suppl 22):3-6.

Age at First Onset of Major Depression



Weissman MM, et al. *JAMA*. 1996;276(4):293.

Gender Differences in Comorbidities with Depression

More Common in *Men*

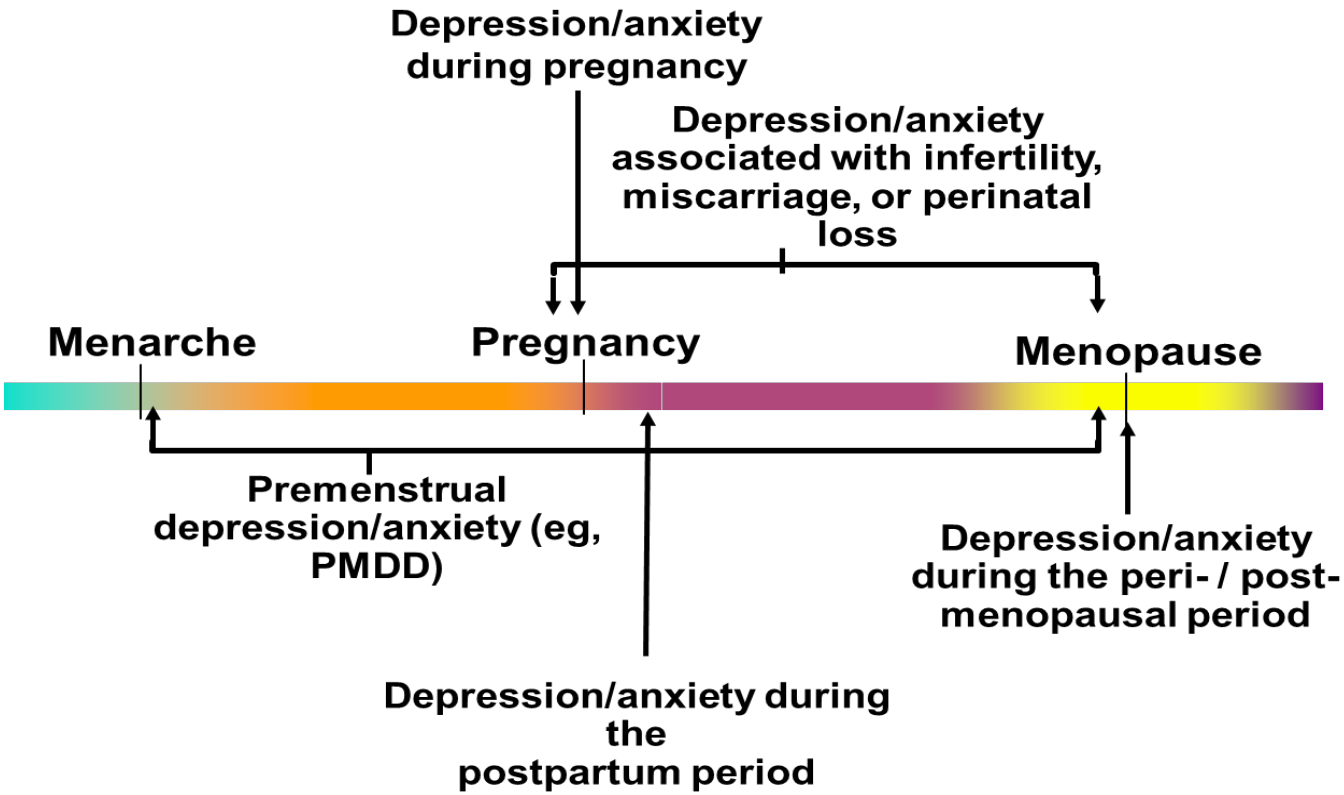
- Alcohol abuse/dependence[1]
- Substance abuse/dependence[1]
  - Stimulant
  - Cannabis
  - Cocaine
  - Hallucinogen

More Common in *Women*

- Panic disorder[1]
- GAD[1]
- Social phobia[2]
- Bulimia[1,2]
- Thyroid disease[3]
- Migraine headaches[3,4]
- Fibromyalgia[3]
- Chronic fatigue syndrome[3]

[1]Kornstein S et al. *Presented at American Psychiatric Association; May 4-9, 1996; New York, NY.*
[2]Fava M, et al. *J Affect Disord.* 1996;38(2-3):129-133.
[3]Kornstein SG. *J Clin Psychiatry.* 2002;63:602-609.
[4]Moldin SO, et al. *Psychol Med.* 1993;23(3):755-761.

Mood and Anxiety Disorders Across the Female Reproductive Cycle



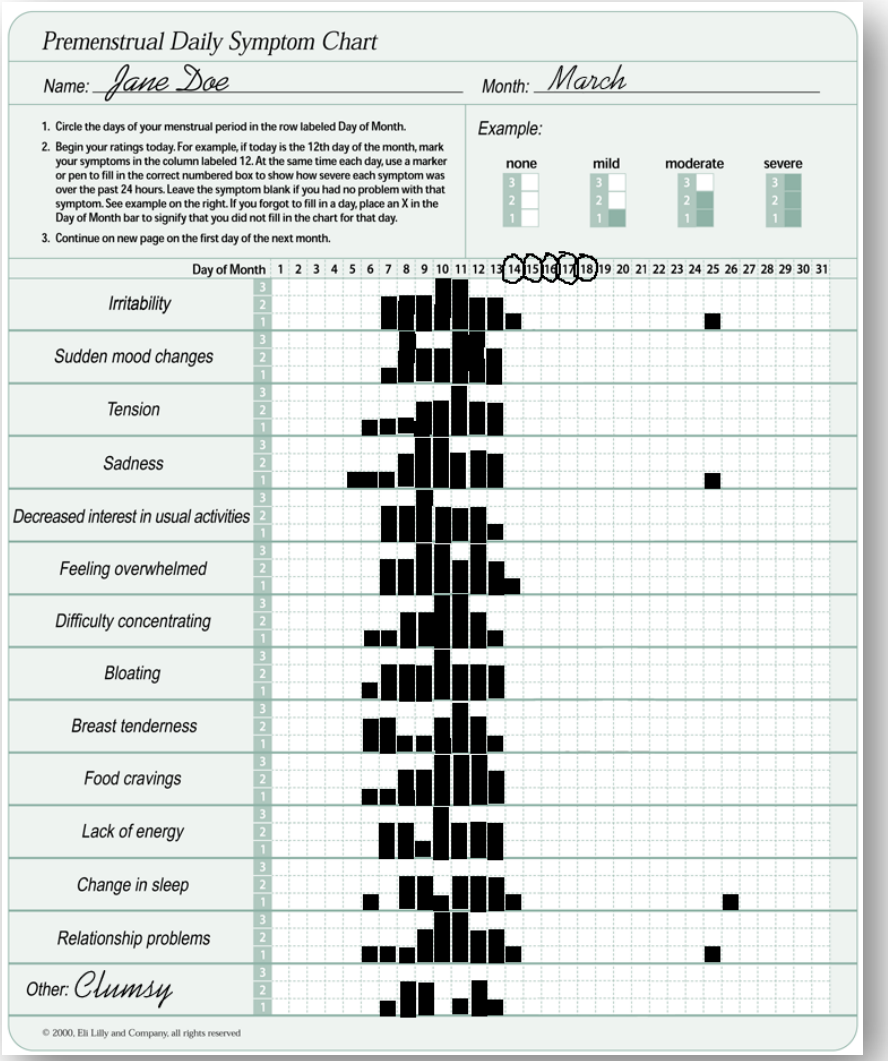
PMDD: Background

- 75% of women report minor, isolated, or occasional premenstrual changes
- 20% – 50% report “premenstrual syndrome”
- 3% – 8% of reproductive-age women have PMDD

PMDD = premenstrual dysphoric disorder

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, fourth edition. 1994. Angst J. *Eur Neuropsychopharmacol*. 1999;9:S144.; Haskett RF. *Prog Neuropsychopharmacol Biol Psychiatry*. 1987;11:129; Johnson SR, et al. *J Reprod Med*. 1988;33:340; Ramcharan S, et al. *J Clin Epidemiol*. 1992;45:377; Rivera-Tovar AD, Frank E. *Am J Psychiatry*. 1990;147:1634.

PMDD



Premenstrual Daily Symptom Chart

Name: Jane Doe Month: March

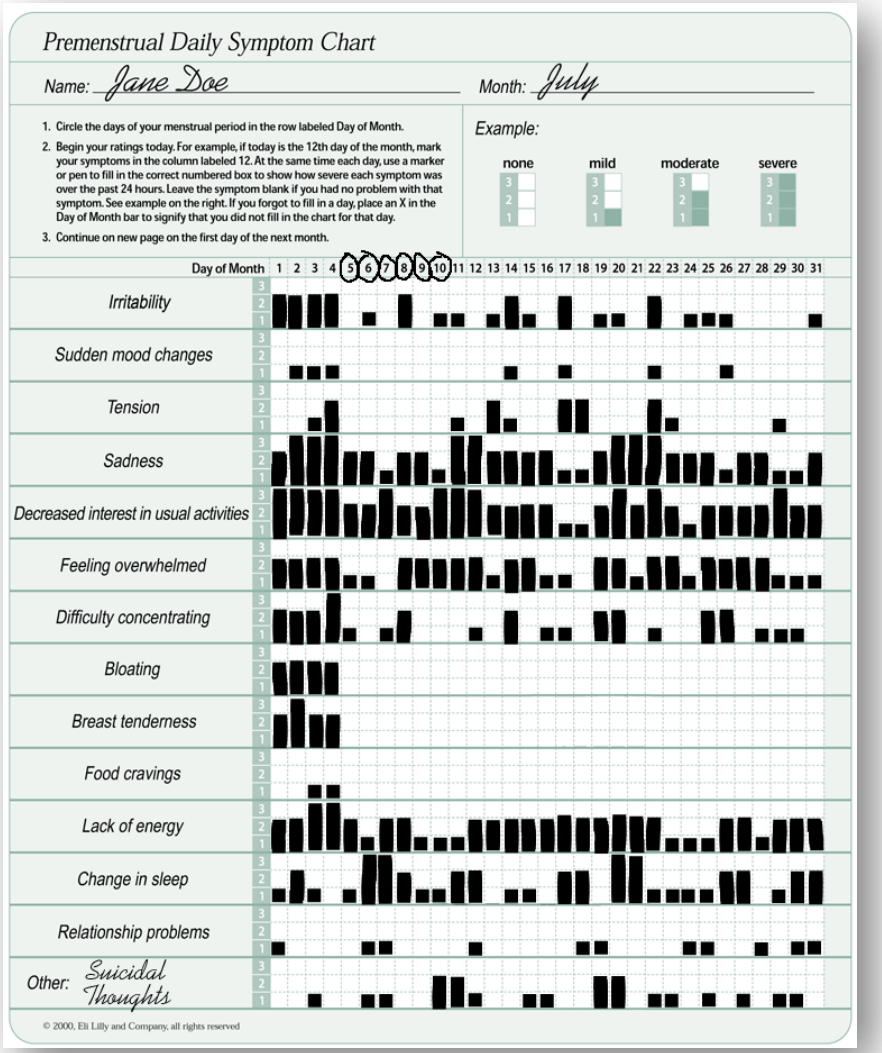
1. Circle the days of your menstrual period in the row labeled Day of Month.
2. Begin your ratings today. For example, if today is the 12th day of the month, mark your symptoms in the column labeled 12. At the same time each day, use a marker or pen to fill in the correct numbered box to show how severe each symptom was over the past 24 hours. Leave the symptom blank if you had no problem with that symptom. See example on the right. If you forgot to fill in a day, place an X in the Day of Month bar to signify that you did not fill in the chart for that day.
3. Continue on new page on the first day of the next month.

Example:

	none	mild	moderate	severe
3				
2				
1				

Day of Month	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31
Irritability	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Sudden mood changes	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Tension	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Sadness	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Decreased interest in usual activities	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Feeling overwhelmed	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Difficulty concentrating	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Bloating	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Breast tenderness	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Food cravings	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Lack of energy	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Change in sleep	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Relationship problems	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Other: Clumsy	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1

Depression



Premenstrual Daily Symptom Chart

Name: Jane Doe Month: July

1. Circle the days of your menstrual period in the row labeled Day of Month.
2. Begin your ratings today. For example, if today is the 12th day of the month, mark your symptoms in the column labeled 12. At the same time each day, use a marker or pen to fill in the correct numbered box to show how severe each symptom was over the past 24 hours. Leave the symptom blank if you had no problem with that symptom. See example on the right. If you forgot to fill in a day, place an X in the Day of Month bar to signify that you did not fill in the chart for that day.
3. Continue on new page on the first day of the next month.

Example:

none | mild | moderate | severe

Day of Month 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31

Irritability

Sudden mood changes

Tension

Sadness

Decreased interest in usual activities

Feeling overwhelmed

Difficulty concentrating

Bloating

Breast tenderness

Food cravings

Lack of energy

Change in sleep

Relationship problems

Other: Suicidal Thoughts

Treatment Resistance and Depressive Sub-Types

- Atypical depression
- “Double” depression
- Psychotic depression
- Severe and melancholic depression
- Co-morbidity — psychiatric or medical
- Psychosocial stressors

Current Treatment Options for Depression

Goal = reduce symptoms of depression and return patient to full, active life

Nonpharmacologic

- Psychotherapy
  - Cognitive behavioral therapy
  - Interpersonal therapy
  - Psychodynamic therapy
- Electroconvulsive therapy
- Phototherapy
- Repetitive Transcranial Magnetic Stimulation (rTMS)
- Vagal Nerve Stimulation (VNS)
- Deep Brain Stimulation (DBS)

Pharmacologic

- Antidepressant medications

Depression Guideline Panel. Depression in Primary Care: Vol 1. Detection and Diagnosis. Clinical Practice Guideline No. 5. 1993.

STEPS: Factors to Consider in Antidepressant Selection

- **S**afety
  - Drug-drug interaction potential
- **T**olerability
  - Acute and long term
- **E**fficacy
  - Onset of action
  - Treatment and prophylaxis
- **P**ayment (cost-effectiveness)
- **S**implicity
  - Dosing
  - Need for monitoring

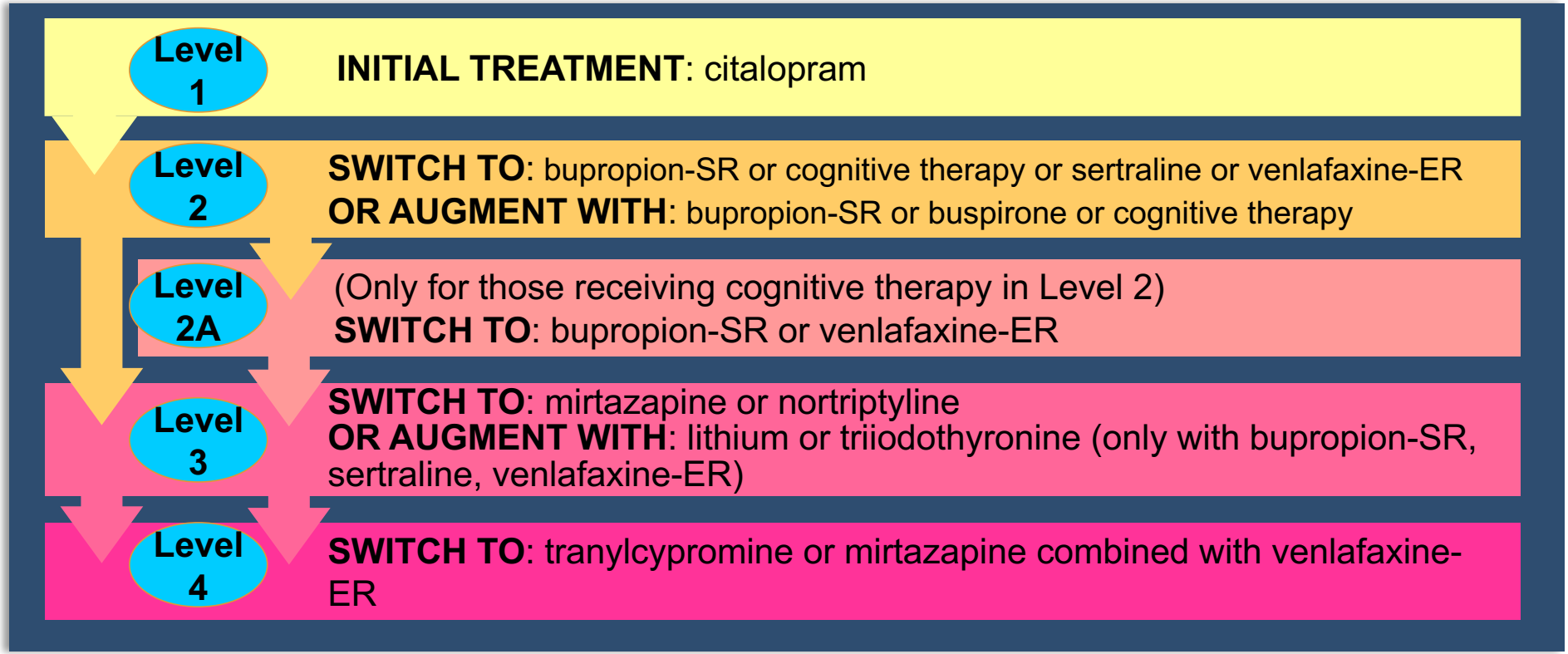
Preskorn SM. *J Clin Psychiatry.* 1997; 58(suppl 6): 3-8.

Evaluation of Outcomes with Citalopram for Depression Using Measurement-Based Care in STAR*D: Implications for Clinical Practice

Madhukar H. Trivedi, M.D., A. John Rush, M.D., Stephen R. Wisniewski, Ph.D., Andrew A. Nierenberg, M.D., Diane Warden, Ph.D., M.B.A., Louise Ritz, M.B.A., Grayson Norquist, M.D., Robert H. Howland, M.D., Barry Lebowitz, Ph.D., Patrick J. McGrath, M.D., Kathy Shores-Wilson, Ph.D., Melanie M. Biggs, Ph.D., G. K. Balasubramani, Ph.D., Maurizio Fava, M.D. and STAR*D Study Team

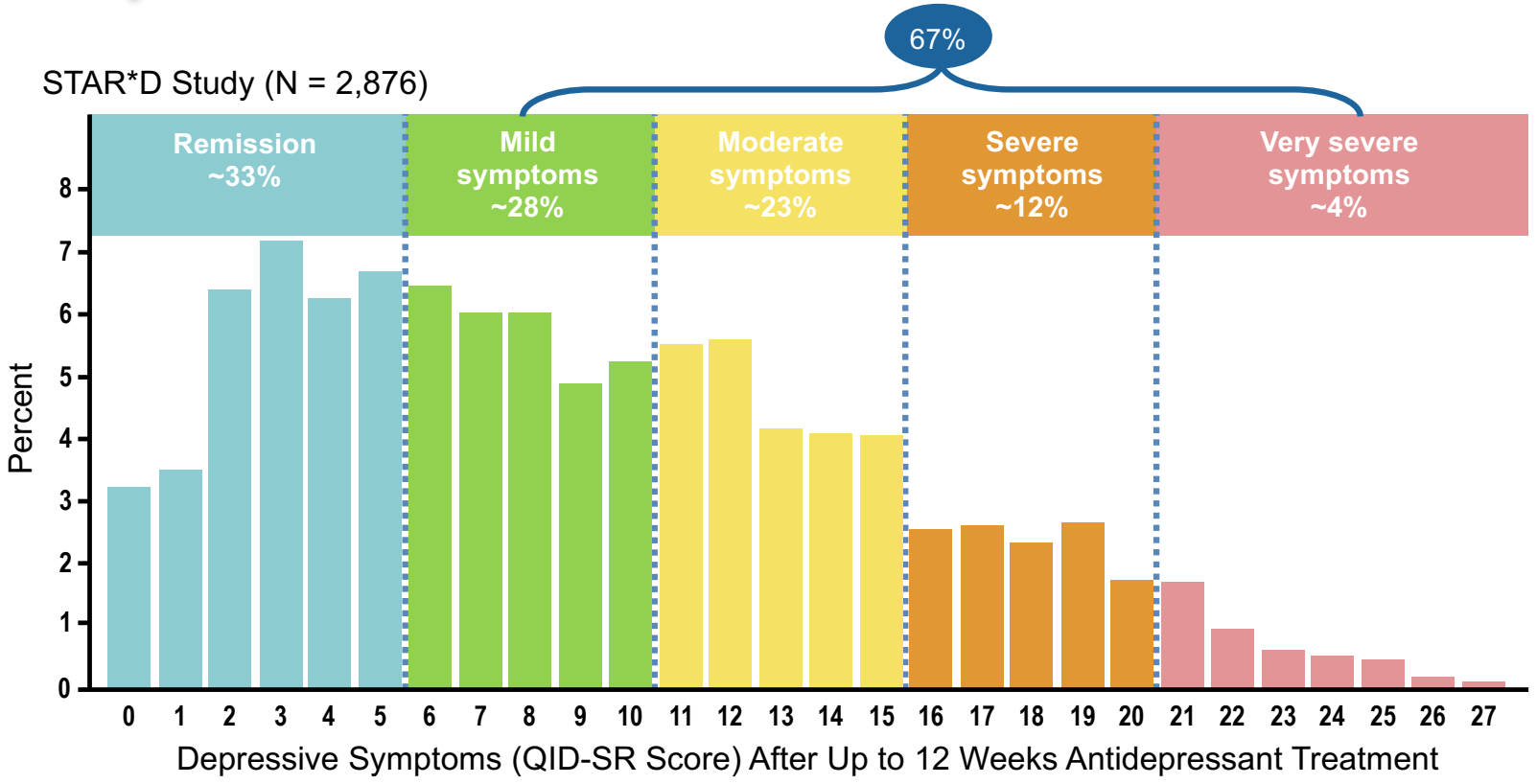
Trivedi M, et al. *Am J Psychiatry* 2006;163:28-40.

STAR*D: Treatment Algorithm Snapshot



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

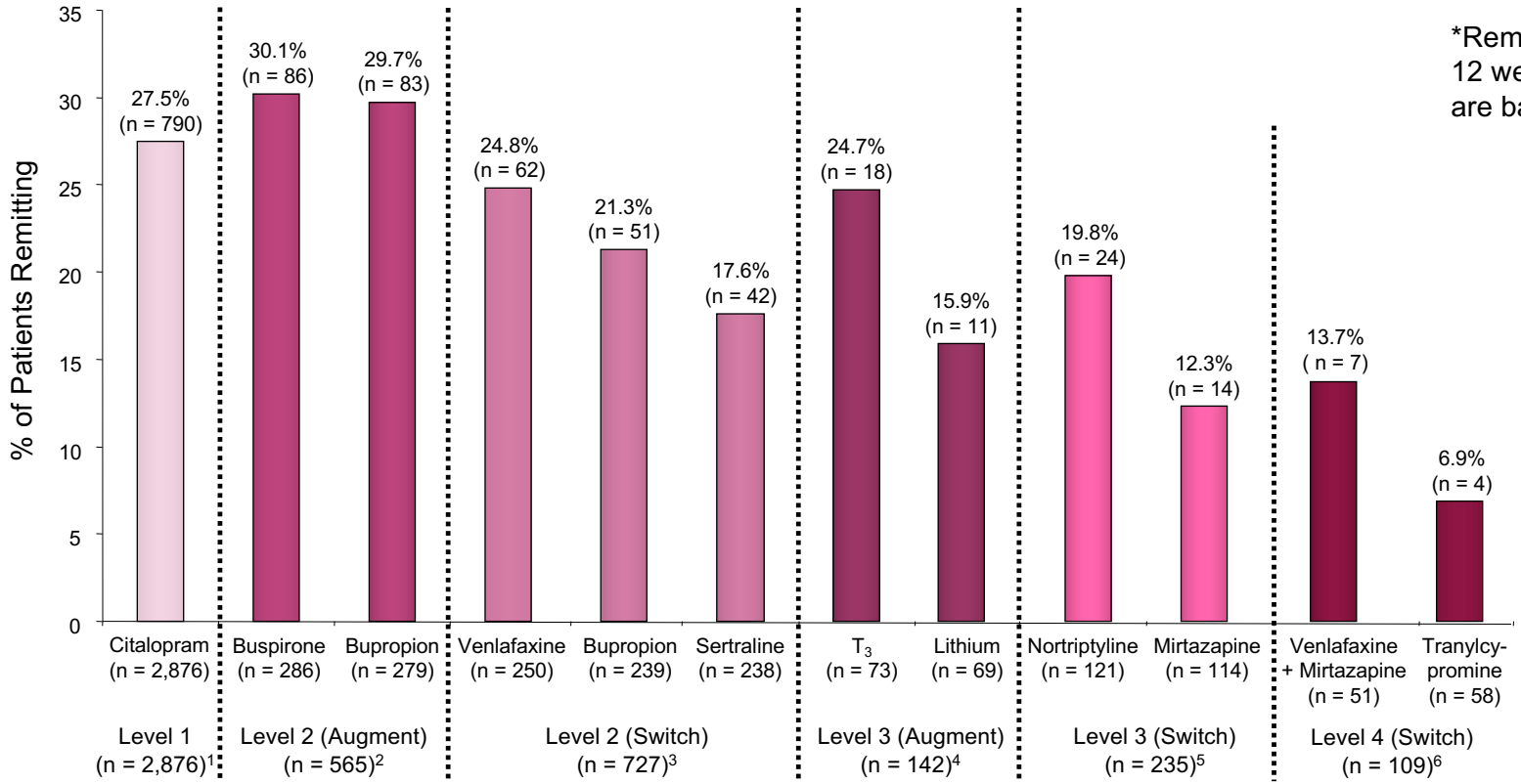
STAR*D: Unresolved Symptoms Following Antidepressant Treatment



STAR*D = Sequenced Treatment Alternatives to Relieve Depression

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

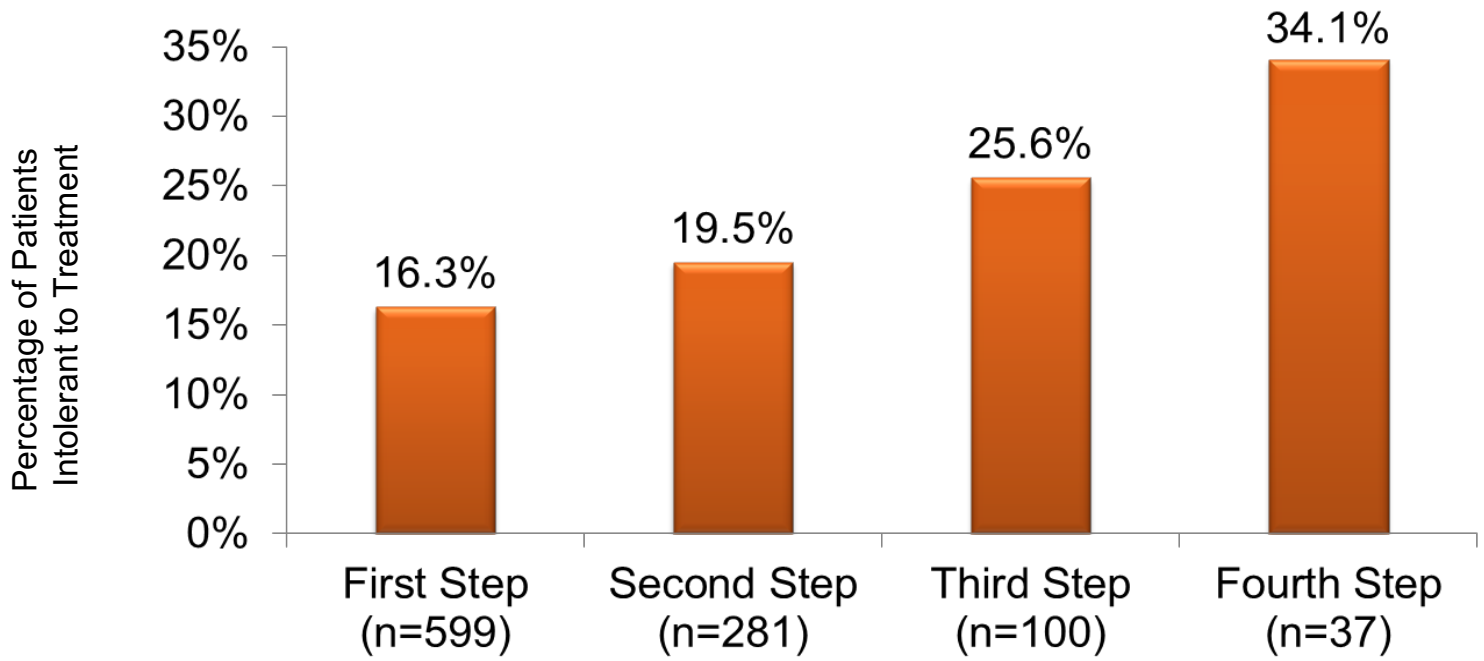
STAR*D Results Demonstrate Diminishing Effectiveness of TRD Treatments



*Remission rates are after 12 weeks of treatment and are based on the $HRSD_{17}$

[1]Trivedi MH, et al. *Am J Psychiatry* 2006;163:28. [2]Trivedi MH, et al. *N Engl J Med* 2006;354:1243. [3]Rush AJ, et al *N Engl J Med* 2006;354:1231.[4]Nierenberg AA, et al. *Am J Psychiatry* 2006;163:1519. [5]Fava M, et al. *Am J Psychiatry* 2006;163:1161. [6]McGrath PJ, et al. *Am J Psychiatry* 2006;163:1531.

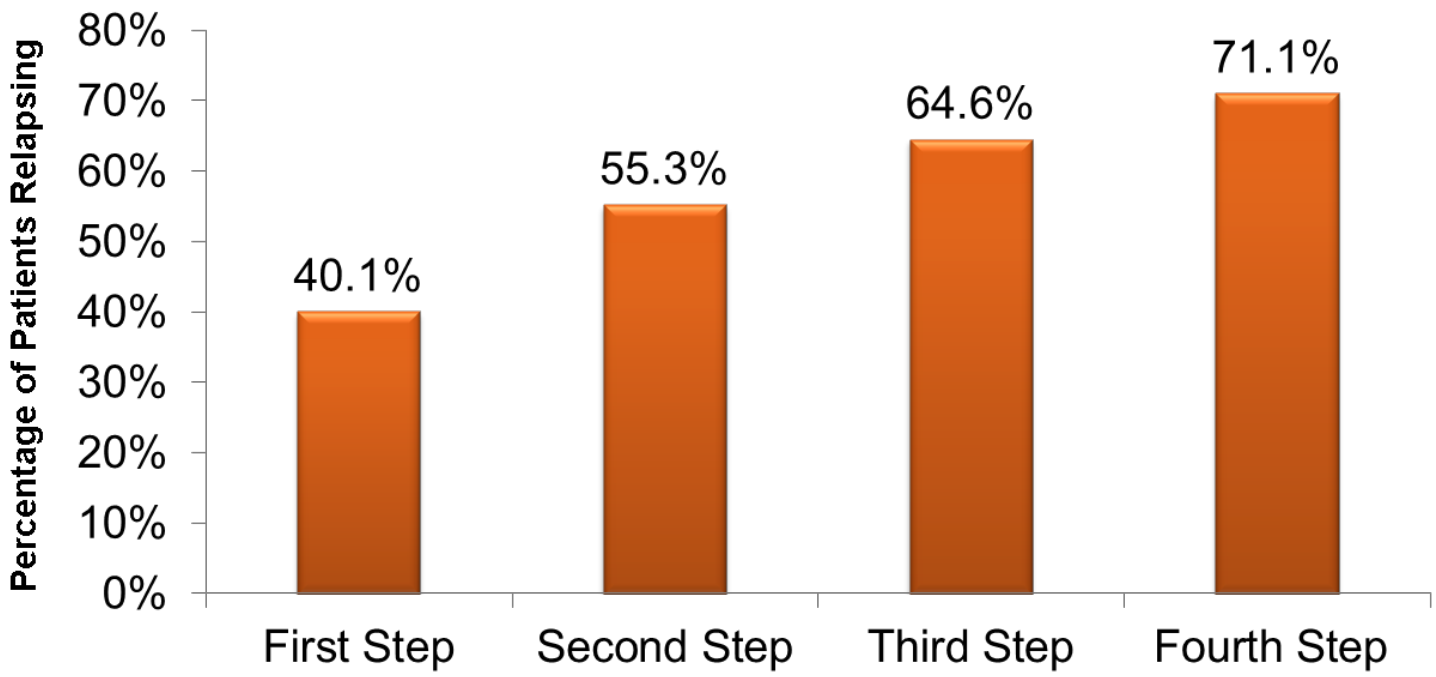
Treatment Intolerance Increases with Each Treatment Level



*Participants were considered to have intolerable side effects if they left the treatment level prior to 4 weeks for any reason or left thereafter citing treatment intolerance as the reason.

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

Relapse Rate Increases with each Treatment Level



*Relapse rate calculated from those who made at least 1 post-baseline call to the interactive voice response system. Treatment step pairwise comparisons showed only Step 1 to be significantly different from the rest ($p < .0001$).

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

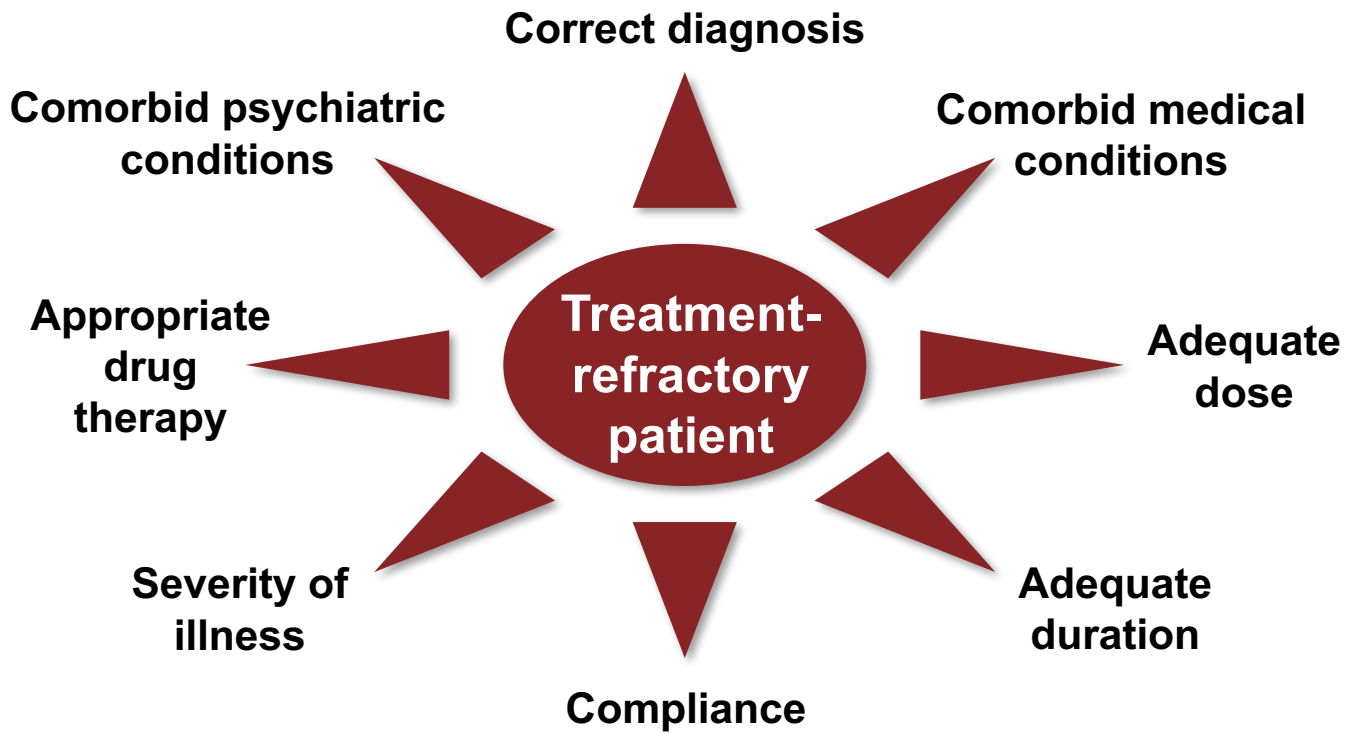
Summary of Challenges in TRD

- High suicide risk[1]
- Significant relapse/recurrence rates with all currently available antidepressant treatments
- High healthcare utilization[2-4]
- Chronic depression is a common manifestation of TRD

1. American Pharmaceutical Association Web site. Accessed June 1, 2017. 2. Russell JM, et al. *J Clin Psychiatry*. 2004;65:341-347. 3. Crown WH, et al. *J Clin Psychiatry*. 2002;63:963-971. 4. Lépine J-P, et al, on behalf of the DEPRES Steering Committee. *Int Clin Psychopharmacol*. 1997;12:19-29.


CURRENTLY ON
EXIT 58A-B
95
1
Zoloft
9
Prozac
Paxil
LAST EXIT
BEFORE TOLL
Buspar
Wellbutrin
Celexa
Xanax

Factors to Consider in Patients Failing First Trial of Antidepressant Monotherapy



Kornstein SG, Schneider RK. *J Clin Psychiatry*. 2001;62 Suppl 16:18-25.

System for Staging Antidepressant Resistance

STAGE 1	Failure of an adequate trial of one class of major antidepressant
STAGE 2	Failure of adequate trials of two distinctly different classes of antidepressants
STAGE 3	Stage II plus failure of a third class of antidepressant, including a TCA
STAGE 4	Stage III plus failure of an adequate trial of MAOI
STAGE 5	Stage IV plus failure of an adequate course of ECT

Adapted from Thase M, Rush J. *J Clin Psychiatry* 2997;58(Suppl 13):23-29.

Childhood Maltreatment Predicts Unfavorable Course of Illness and Treatment Outcome in Depression: A Meta-Analysis

Valentina Nanni, M.D.

Rudolf Uher, M.U.Dr., Ph.D.

Andrea Danese, M.D., Ph.D.

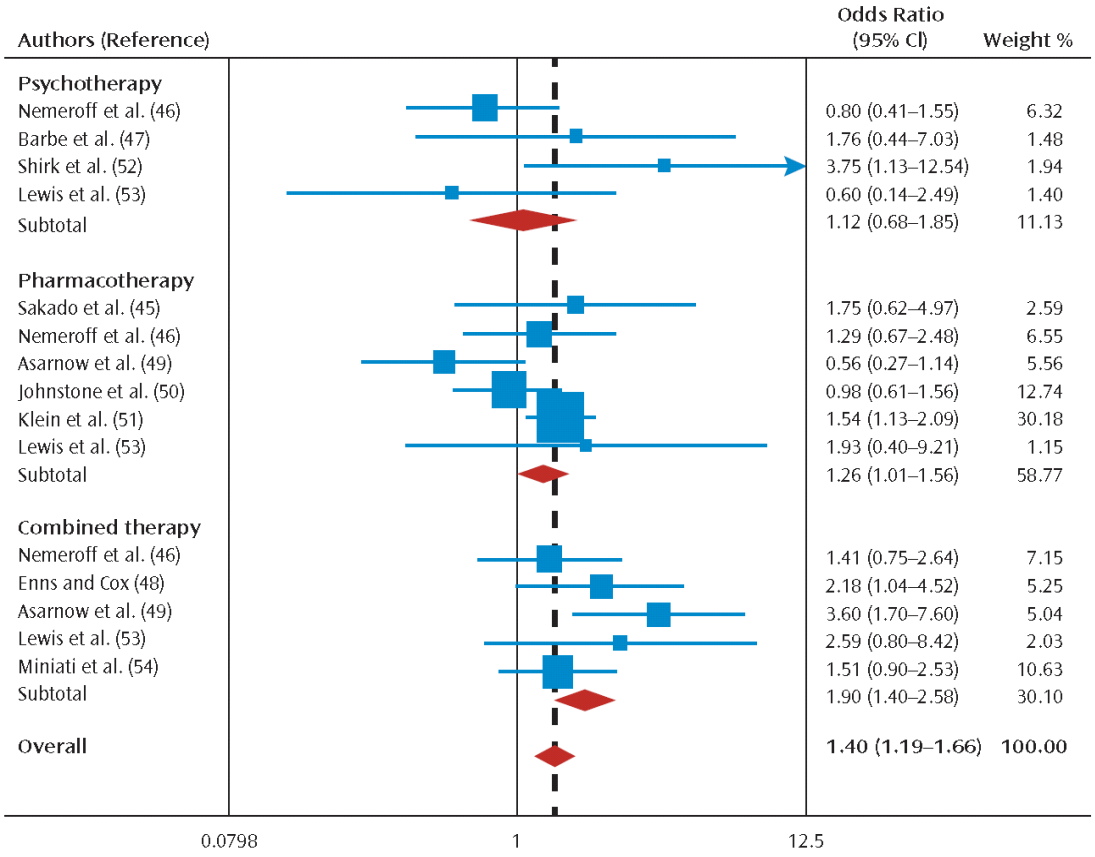
Objectives: Evidence suggests that childhood maltreatment may negatively affect not only the lifetime risk of depression but also clinically relevant measures of depression, such as course of illness and treatment outcome. The authors conducted the first meta-analysis to examine the relationship between childhood maltreatment and these clinically relevant measures of depression.

Results: A meta-analysis of 16 epidemiological studies (23,544 participants) suggested that childhood maltreatment was associated with an elevated risk of developing recurrent and persistent depressive episodes (odds ratio=2.27, 95% confidence interval [CI]=1.80–2.87). A meta-analysis of 10 clinical trials (3,098 participants) revealed that childhood maltreatment was associated with lack of response or remission during treatment for depression (odds ratio=1.43, 95% CI=1.11–1.83). Meta-regression analyses suggested that the results were not significantly affected by publication bias, choice of outcome measure, inclusion of prevalence or incidence samples, study quality, age of the sample, or lifetime prevalence of depression.

Conclusions: Childhood maltreatment predicts unfavorable course of illness and treatment outcome in depression.

Nanni V, et al. *Am J Psychiatry* 2012;169:141–151.

Meta-Analysis of Clinical Trials Investigating the Association Between Childhood Maltreatment & Treatment Outcomes of Depression (Fixed Effects)



Nanni V, et al. *Am J Psychiatry* 2012;169:141–151.

Reasonable Strategies for Stage I Resistant Depression (Non-Remission to One Treatment)

- Switch within same class
- Switch across classes
- Augmentation strategies
- Focused Management of Residual Symptoms

Switching vs. Augmentation

Switching (typically used in nonresponders)

- **Advantages**
  - A simpler strategy than augmentation, conducive to compliance
  - Lower risk of drug interactions
  - Fewer side effects
- **Disadvantages**
  - Delays onset of action of second agent

Augmentation (typically used among partial responders at maximal doses)

- **Advantages**
  - Avoids loss of benefit already achieved
  - More rapid response
  - Allows the maximization of each drug trial before considering other options
- **Disadvantages**
  - Not conducive to compliance
  - Higher risk of drug interactions

Nelson JC. *J Clin Psychiatry* 1998;59(suppl 16):13-19; Thase ME, et al. *J Clin Psychiatry* 1998;59(suppl 5):5-12.

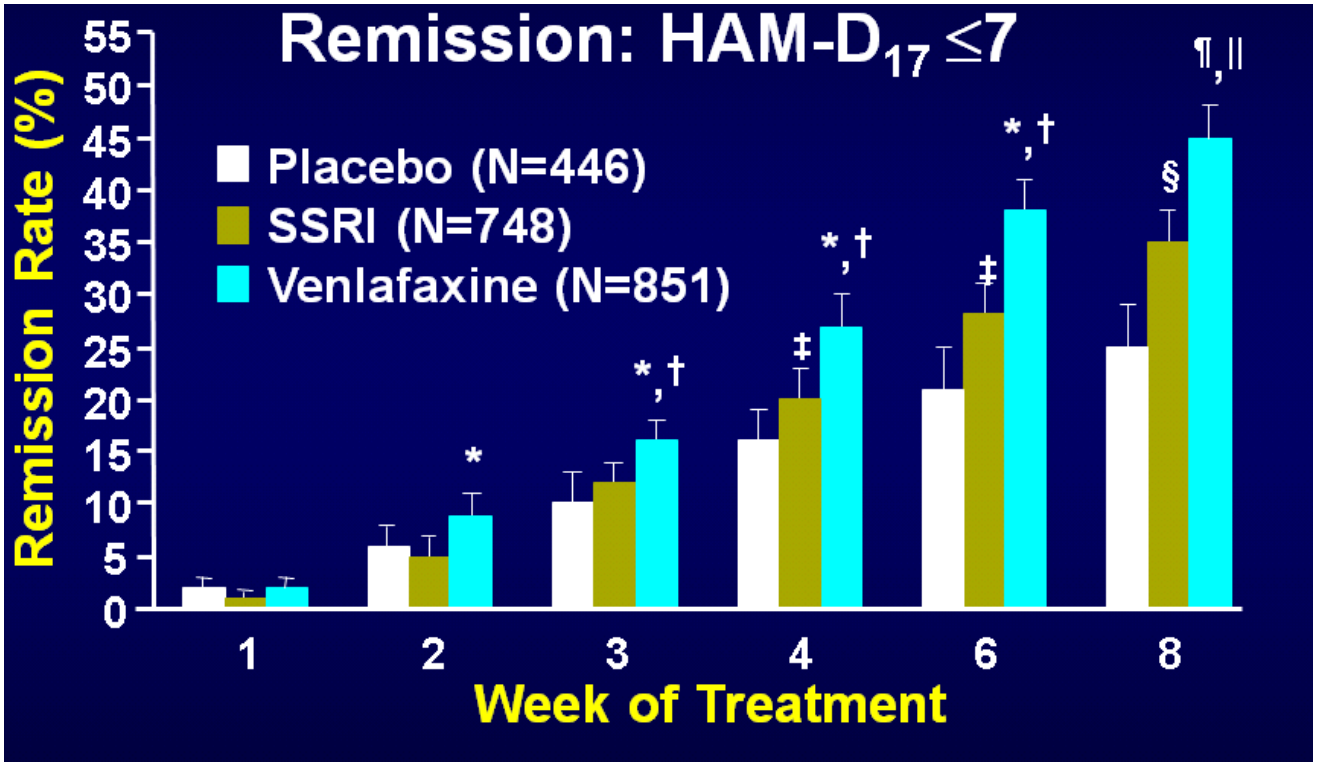
Raising Antidepressant Dose

- Popular choice when presented with
  - Antidepressant partial responder
  - Antidepressant nonresponder
- Studies show mixed results from increasing SSRI dose
- Some SSRIs show flat dose-response curves

Switching Agents

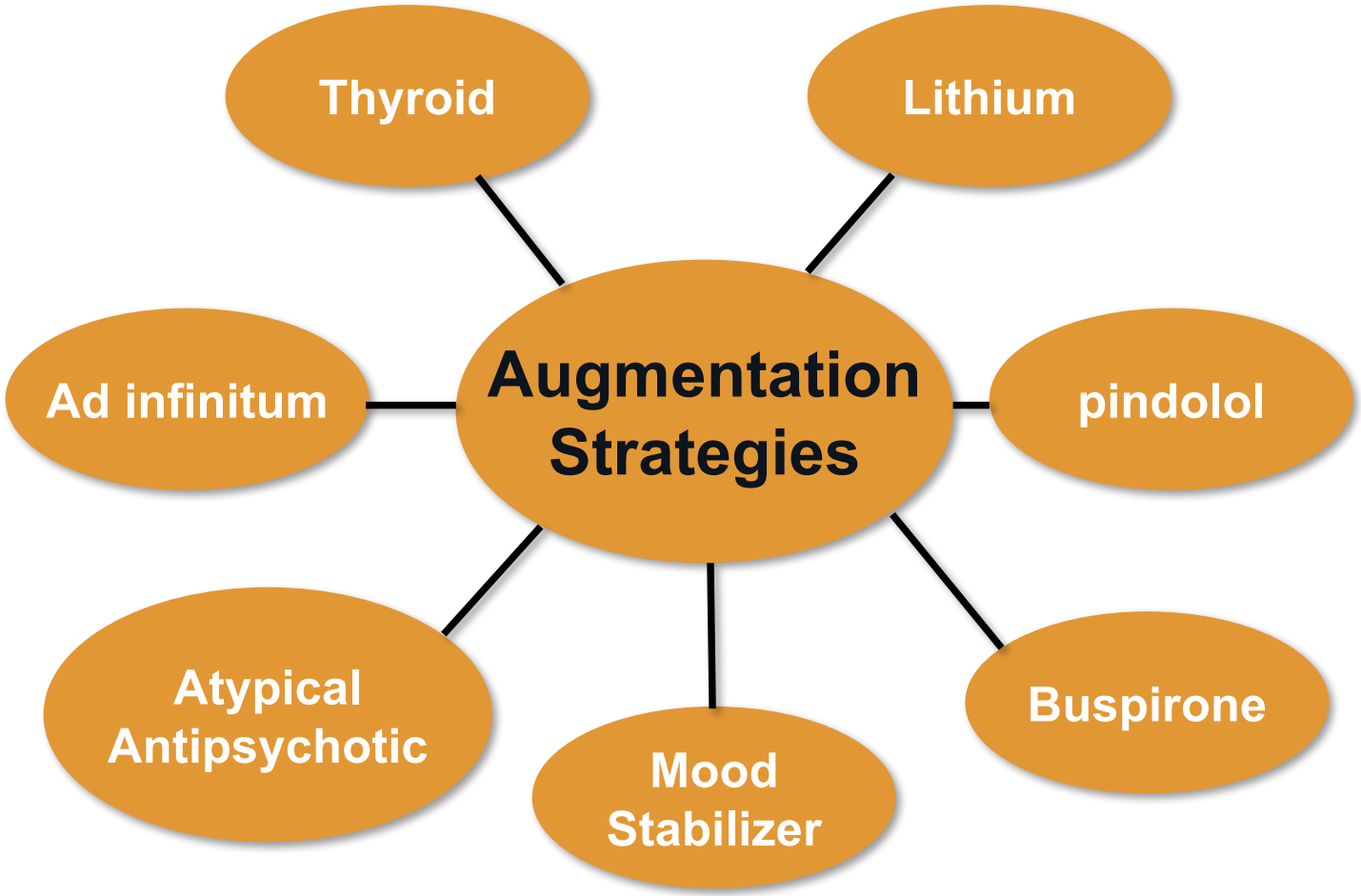
- Switching to different antidepressant with distinct pharmacologic profile
  - TCAs to SSRIs
  - SSRIs to SNRIs
- Switching to antidepressant within the same class
  - SSRIs to SSRIs

Pooled Analysis of Venlafaxine vs. SSRIs in Depressed Patients

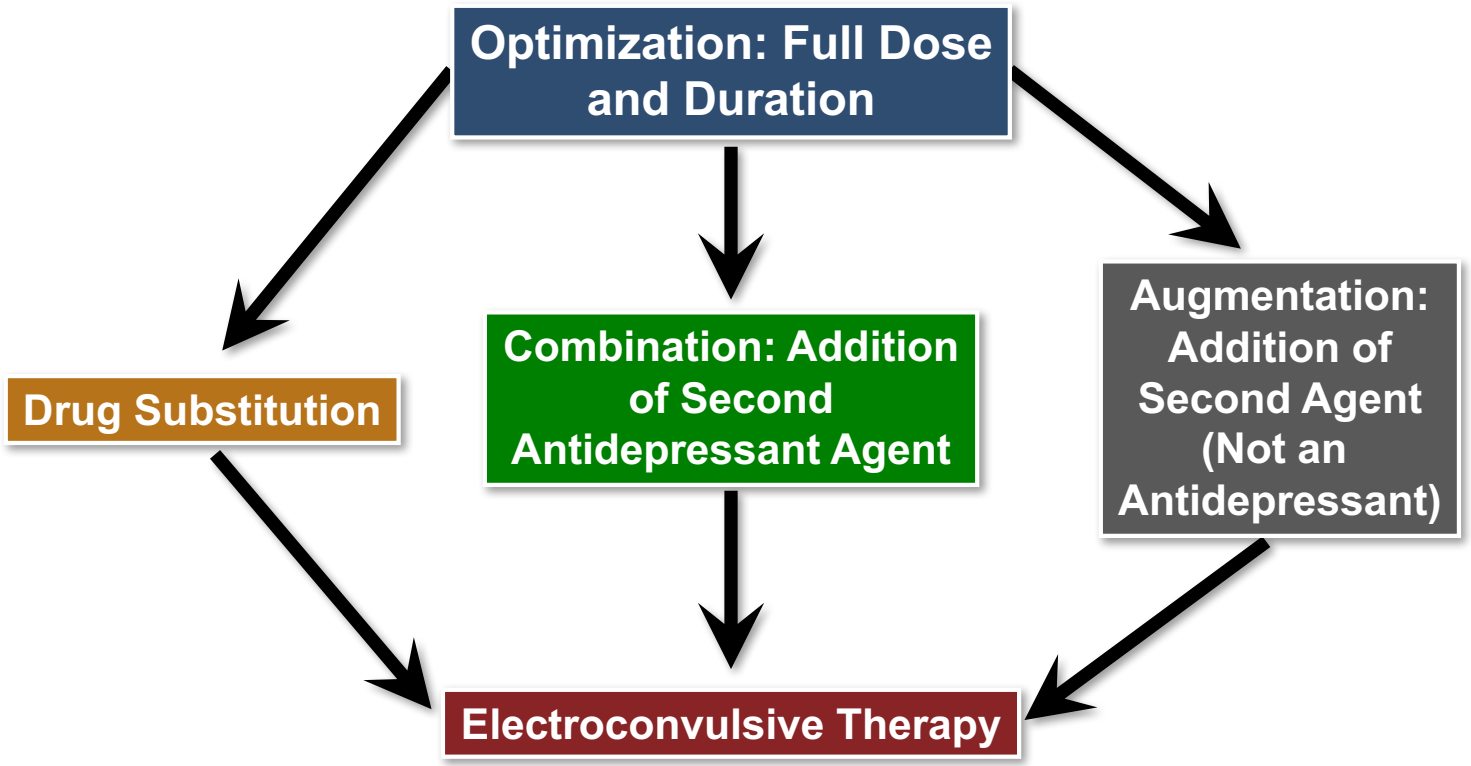


*p⊠0.05 venlafaxine vs. SSRI; †p⊠0.05 venlafaxine vs. placebo; ‡*p* ⊠ 0.05 SSRI vs. placebo; §*p* < 0.001 SSRI vs. placebo; §*p* < 0.001 venlafaxine vs. SSRI; ||*p* < .001 venlafaxine vs. placebo;

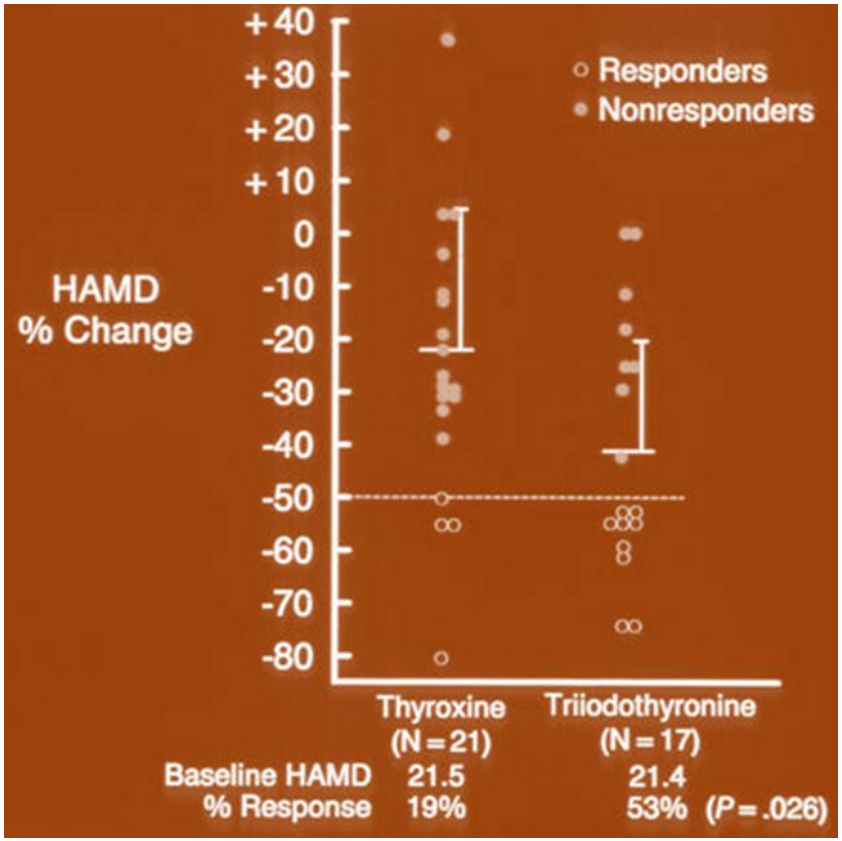
Thase ME, Entsuah R, Rudolph RL. Br J Psychiatry. 2001;178:134-141.


Thyroid
Lithium
Ad infinitum
Augmentation Strategies
pindolol
Atypical Antipsychotic
Mood Stabilizer
Buspirone

Strategies for Antidepressant Nonresponse



T3 vs T4 Augmentation Therapy



Joffe RT, et al. *Arch Gen Psychiatry.* 1993;50(5):387-393.

Triiodothyronine Augmentation in the Treatment of Refractory Depression: A Meta-Analysis

Ronnie Aronson, MD; Hilary J. Offman, MD; Russell T. Joffe, MD; C. David Naylor, MD, PhD

Aronson R, et al. Arch Gen Psychiatry. 1996;53:842-848.

Lithium Carbonate Addition in Tricyclic Antidepressant-Resistant Unipolar Depression

Correlations with the neurobiologic actions of tricyclic antidepressant drugs and lithium ion on the serotonin system

Claude de Montigny, MD, PhD, FRCP(C);
Gerard Cournoyer, MD;
Raymond Morissette, MD, FRCP (C);
Robert Langlois, MD, CSPQ;
Gilles Caille, PhD

de Montigny C, et al. *Arch Gen Psychiatry*. 1983;40:1327-1334.

Effect of Adding Lithium to TCA Therapy

Pretreatment (No. of Observations)	Mean HAMD Score (% improvement)		
	Pre-TCA Baseline	Before Li Addition	48 Hours after Li Addition
Amitriptyline (16)	24.8	20.7 (16)	8.6* (58)
Imipramine (12)	24.8	24.2 (2)	7.7* (68)
Trimipramine (6)	23.7	20.2 (19)	9.8** (51)
Desipramine (4)	19.0	15.7 (17)	4.0*** (74)
Doxepin (4)	25.7**	16.7 (37)	6.0** (64)
TOTAL (42)	**24.2*** **	**20.8 (15)**	**7.8* (62)**

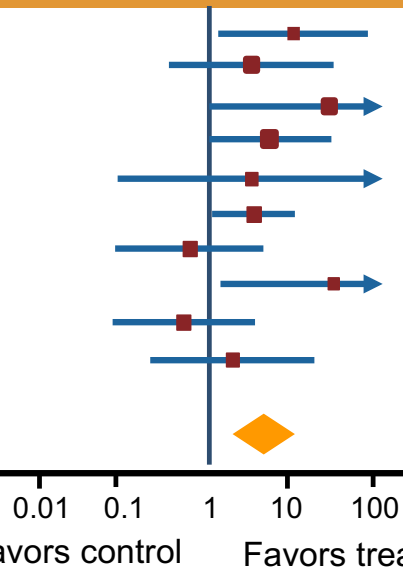
*$p < .001$ vs scores before Li addition
**$p < .05$ vs scores before Li addition
***$p < .001$ vs scores before Li addition

de Montigny C, et al. *Arch Gen Psychiatry*. 1983;40:1327-1334.

Placebo Controlled Lithium Augmentation Studies – Meta-Analysis

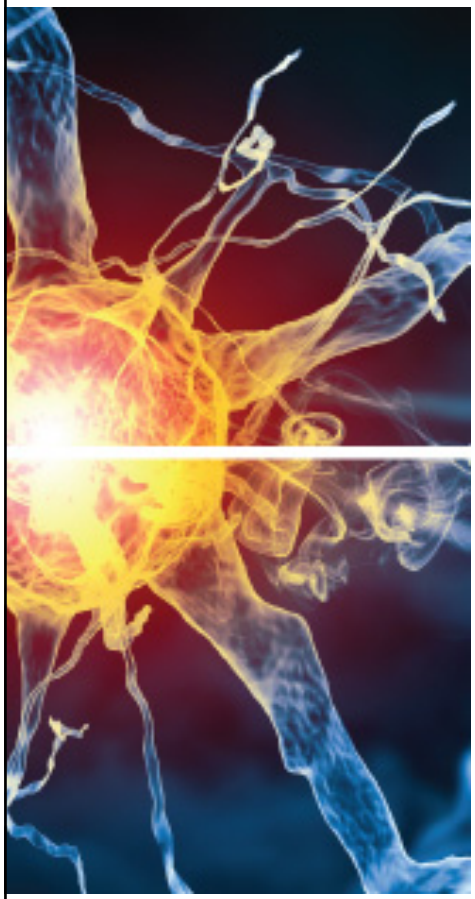
Meta-analysis of 10 augmentation studies
Overall pooled rates of response: lithium 53/131 or 40.5% vs 24/138 or 17.4%

Study or sub-category	Treatment n/N	Control n/N	OR (fixed) 95% CI	Weight %	OR (fixed) 95%CI
Bauman 1996	6/10	2/14		4.48	9.00 [1.27, 63.89]
Browne 1990	3/7	2/10		6.33	3.00 [0.35, 25.87]
Heninger 1983	5/8	0/7		1.38	23.57 [1.00, 556.08]
Joffe 1993	9/17	3/16		9.78	4.88 [1.01, 23.57]
Kantor 1986	1/4	0/3		2.61	3.00 [1.09, 9.48]
Katona 1995	15/29	8/32		24.69	3.21 [1.09, 9.48]
Nierenberg 2003	2/18	3/17		18.44	0.58 [0.08, 4.01]
Schoepf 1989	7/14	0/13		1.74	27.00 [1.35, 541.57]
Stein 1993	2/16	4/18		22.15	0.50 [0.08, 3.19]
Zusky 1988	3/8	2/8		8.40	1.80 [0.21, 15.41]
Total (95% CI)	131	138		100.00	3.11 [1.80, 5.37]



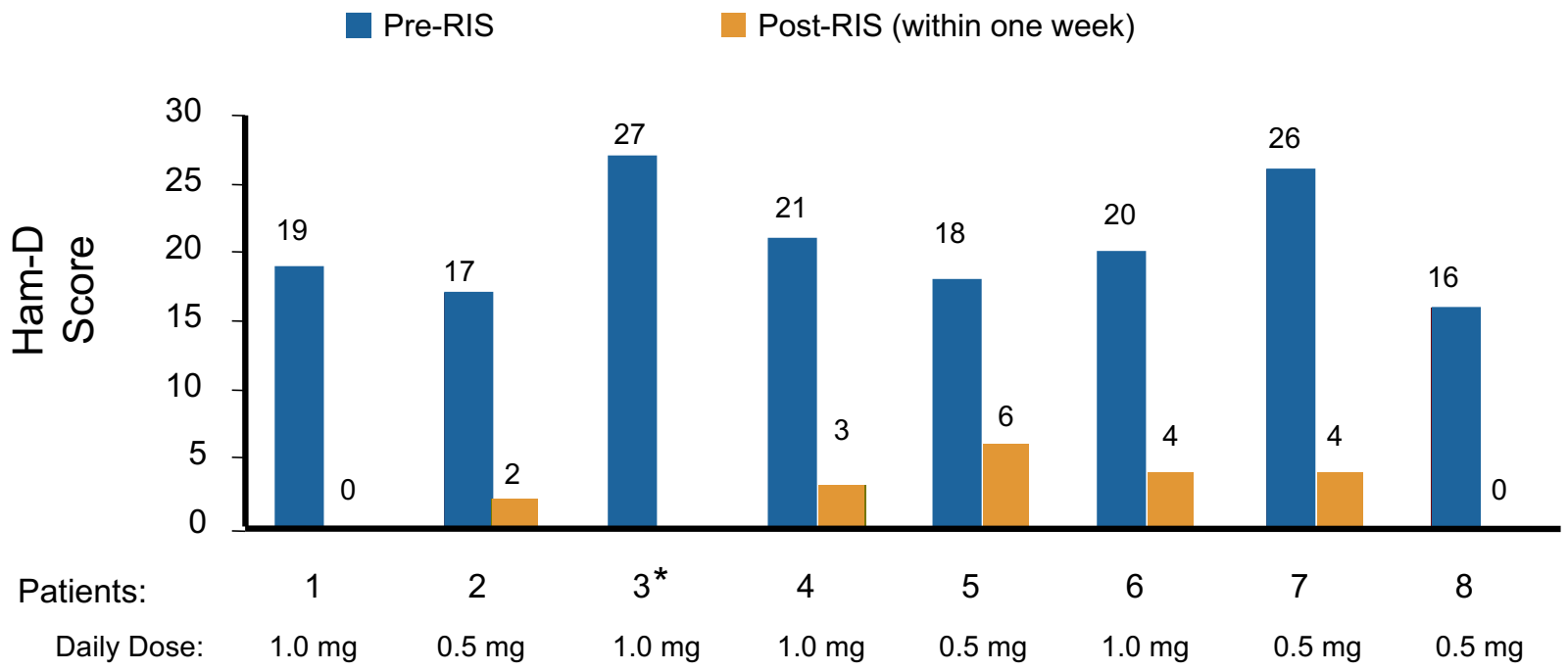
Total events: 53 (Treatment), 24 (Control)
Test for heterogeneity: $Chi^2 = 11.90$, df = 9 ($p = 22$), $I^2 = 24.4\%$
Test for overall effect: $Z = 4.06$ ($p < .0001$)

Crossley NA, Bauer M. *J Clin Psychiatry.* 2007;68:935-940.



Augmentation with Atypical Antipsychotics

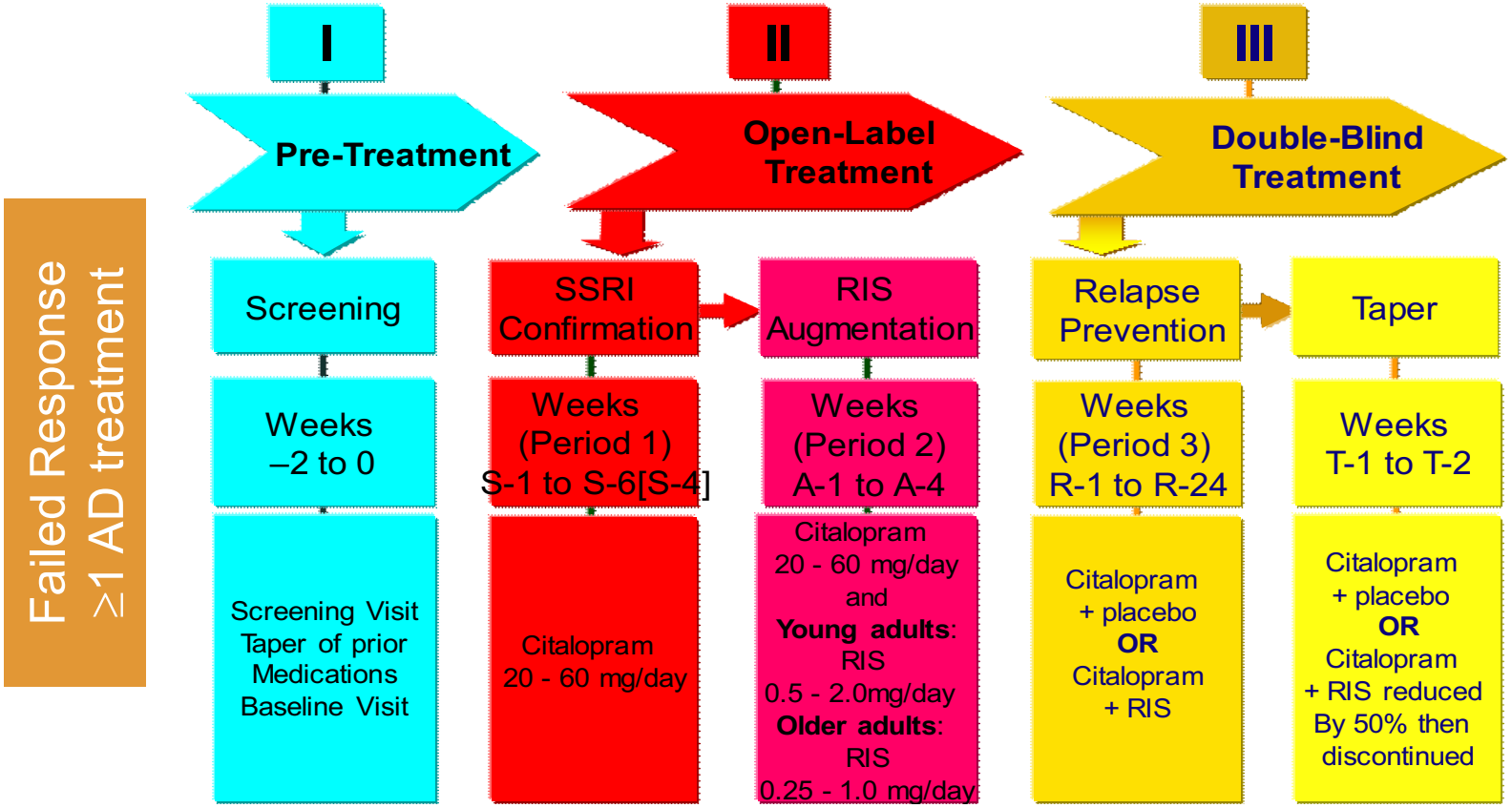
Risperidone Augmentation in Patients Non-Responsive to an SSRI



*No return visit or Ham-D score; patient and referring psychiatrist noted complete remission

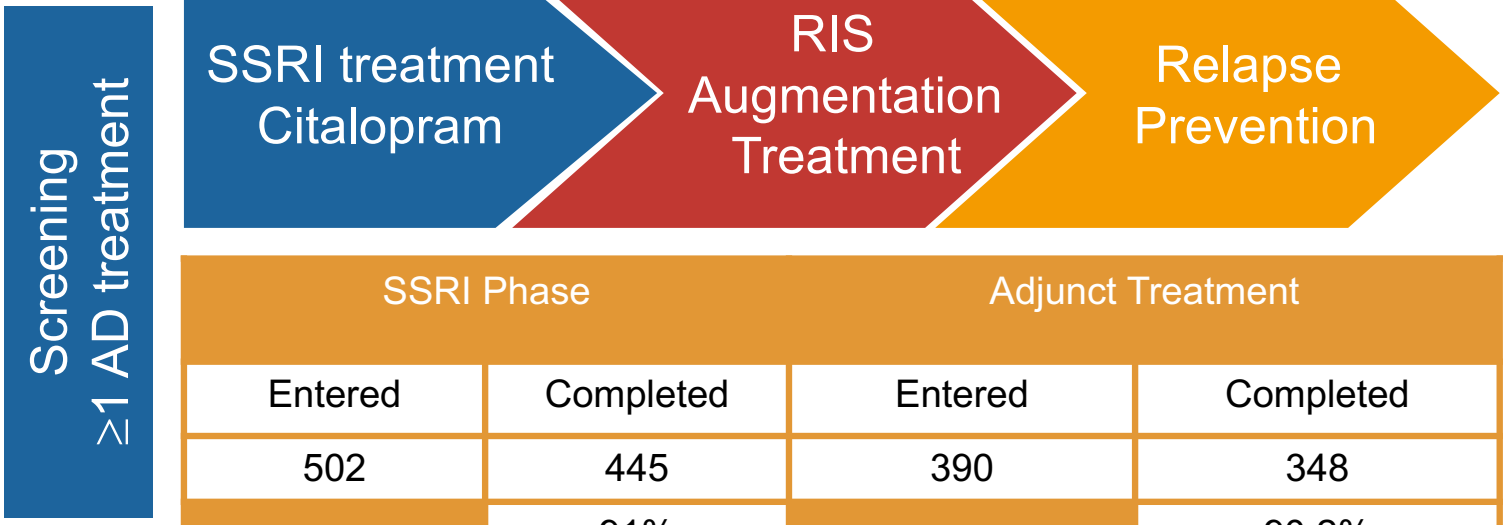
Ostroff RB, Nelson JC. *J Clin Psychiatry*. 1999;60(4):256-259,

Risperidone Treatment of Citalopram Nonresponders: Trial Design



Rapaport MH, et al. *Neuropsychopharmacology*. 2006;31(11):2505-2513.

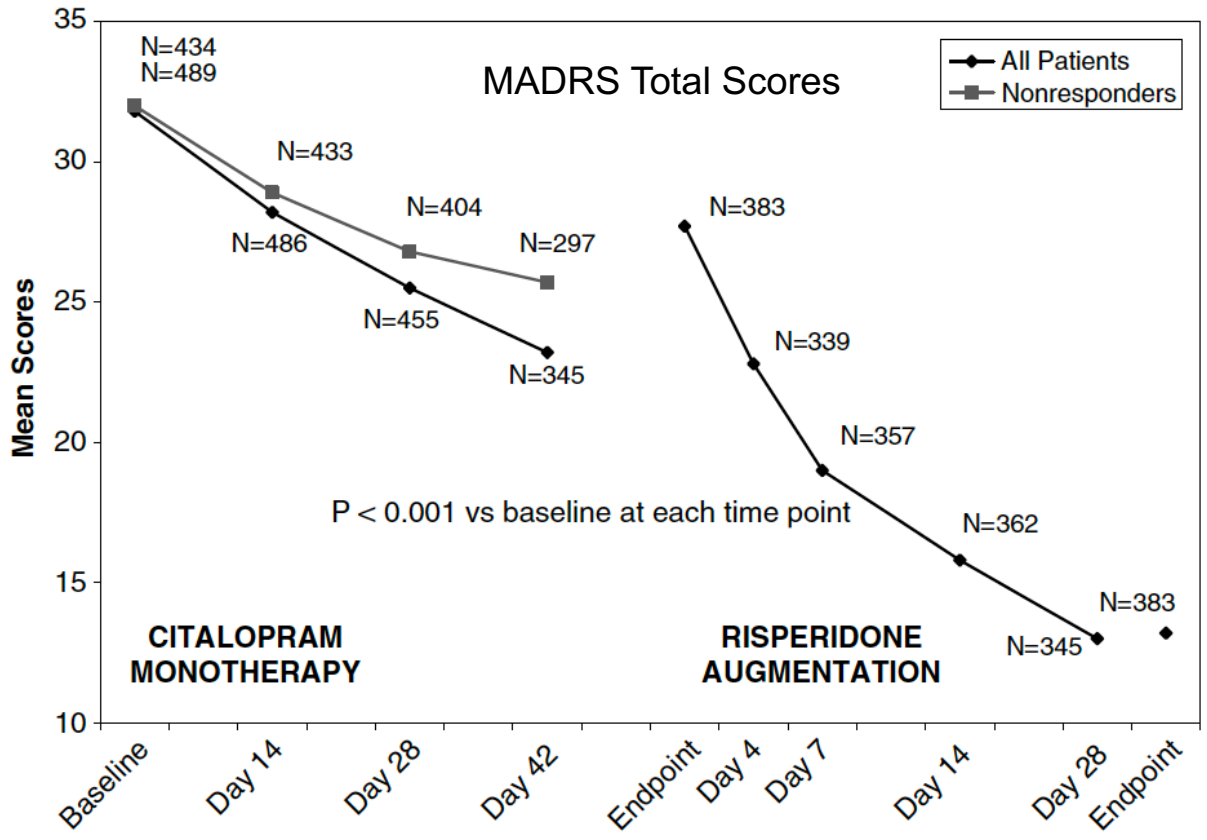
Study Conduct



SSRI Phase		Adjunct Treatment	
Entered	Completed	Entered	Completed
502	445	390	348
	91%		90.2%

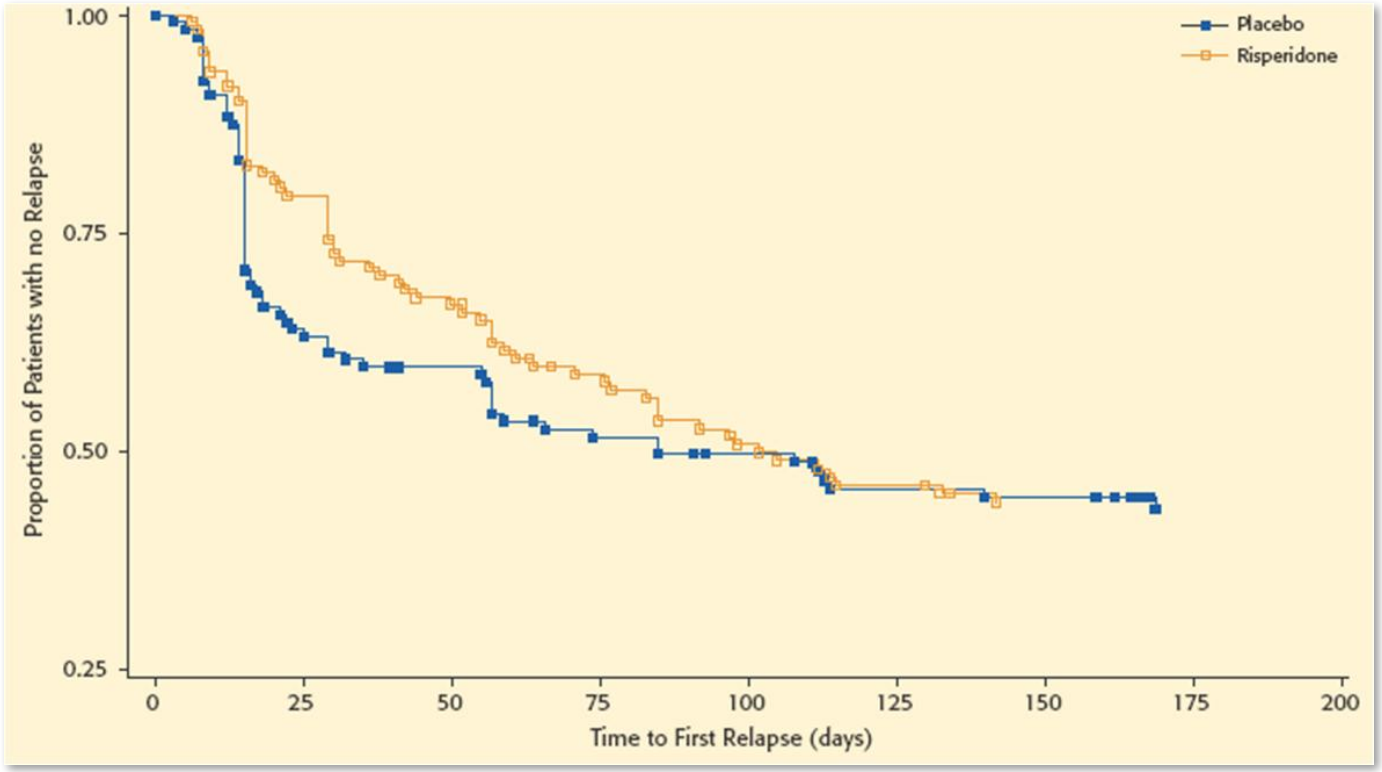
Rapaport MH, et al. *Neuropsychopharmacology*. 2006;31(11):2505-2513.

Remission at Period Endpoints



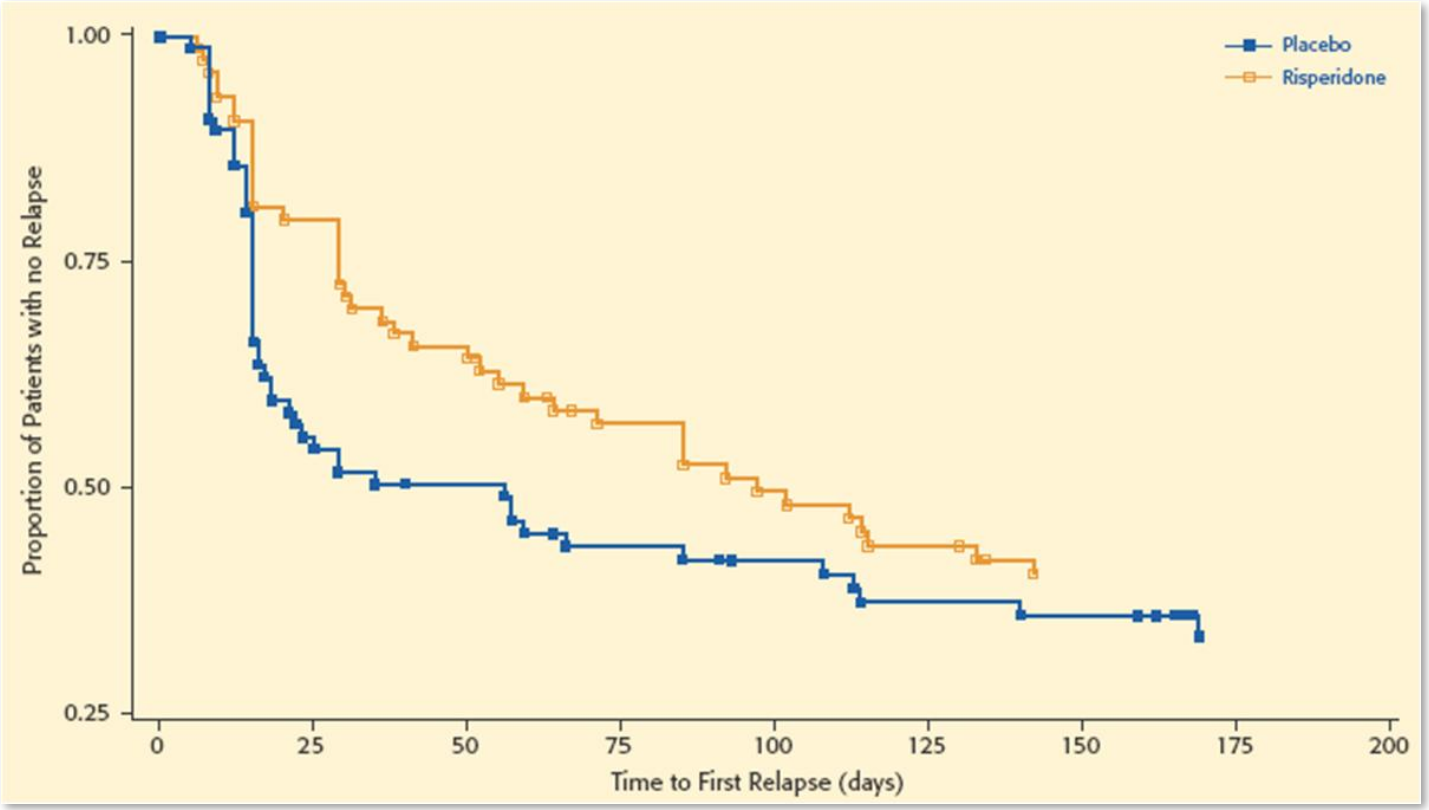
Rapaport MH, et al. *Neuropsychopharmacology*. 2006;31(11):2505-2513.

Kaplan-Meier Estimates of the Time to Relapse in Nonresponders (<50% Reduction in HAM-D Scores)



Nemeroff CB, et al. Presented at the 43rd Annual Meeting of the American College of Neuropsychopharmacology (ACNP). December 12-15, 2004, San Juan, Puerto Rico.

Kaplan-Meier Estimates of the Time to Relapse in Patients Who were Fully Nonresponsive (<25% Reduction in HAM-D Scores)



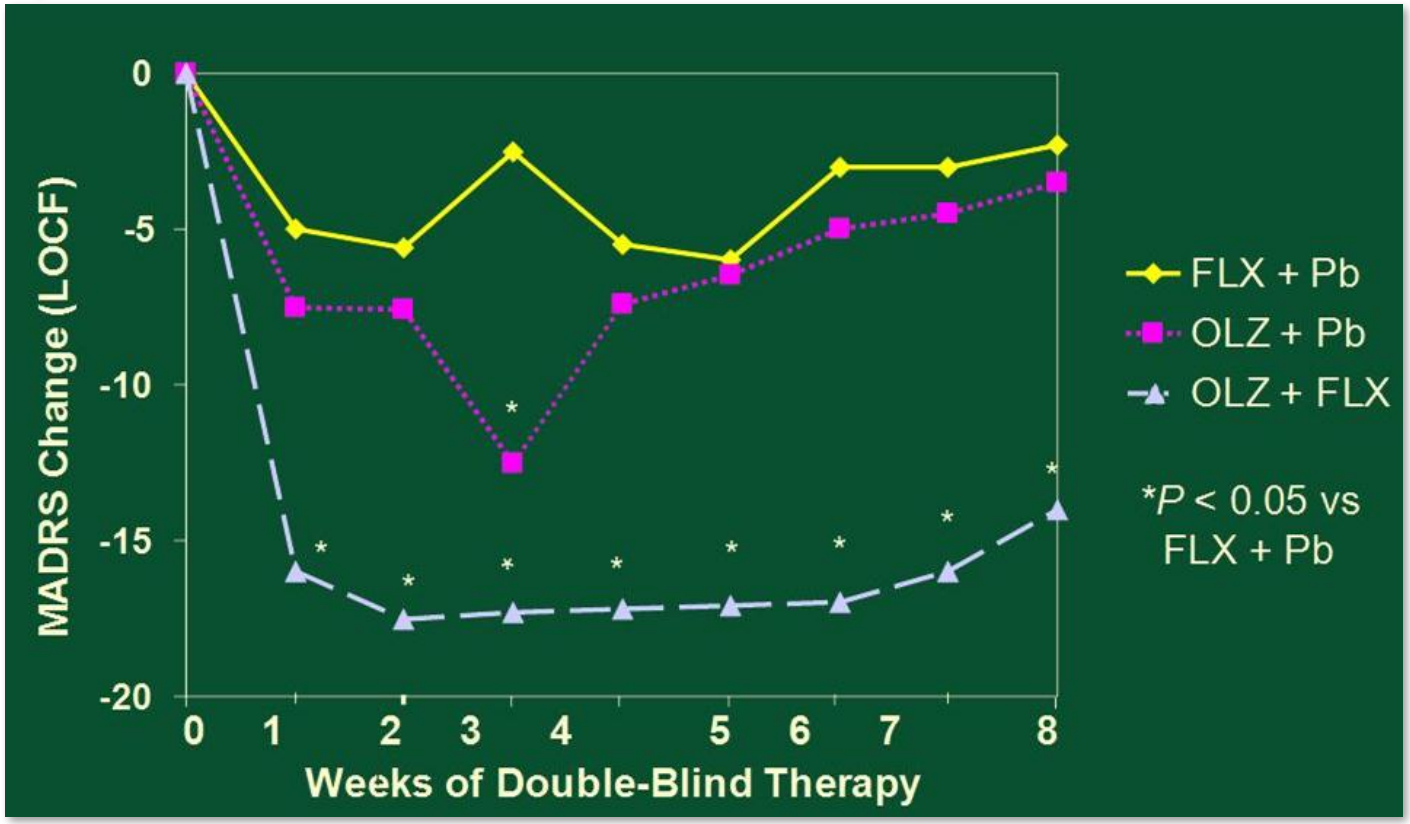
Nemeroff CB, et al. Presented at the 43rd Annual Meeting of the American College of Neuropsychopharmacology (ACNP). December 12-15, 2004, San Juan, Puerto Rico.

Olanzapine and Fluoxetine in Treatment-Resistant Major Depression

- Patients: MDD without psychotic features (n = 28)
- Treatment resistance
  - One SNRI and one SSRI for four weeks at adequate dose
  - Fluoxetine run-in (six weeks) at 40 – 60 mg/d (< 30% improvement on the HAM-D-21)
- Eight-week, double-blind treatment
  - Fluoxetine (20 – 60 mg/d) + placebo (n = 10)
  - Olanzapine (5 – 20 mg/d) + placebo (n = 8)
  - Olanzapine + fluoxetine (n = 10)
  - Eight-week olanzapine + fluoxetine open-label

Shelton RC, et al. *Am J Psychiatry*. 2001;158(1):131-134.

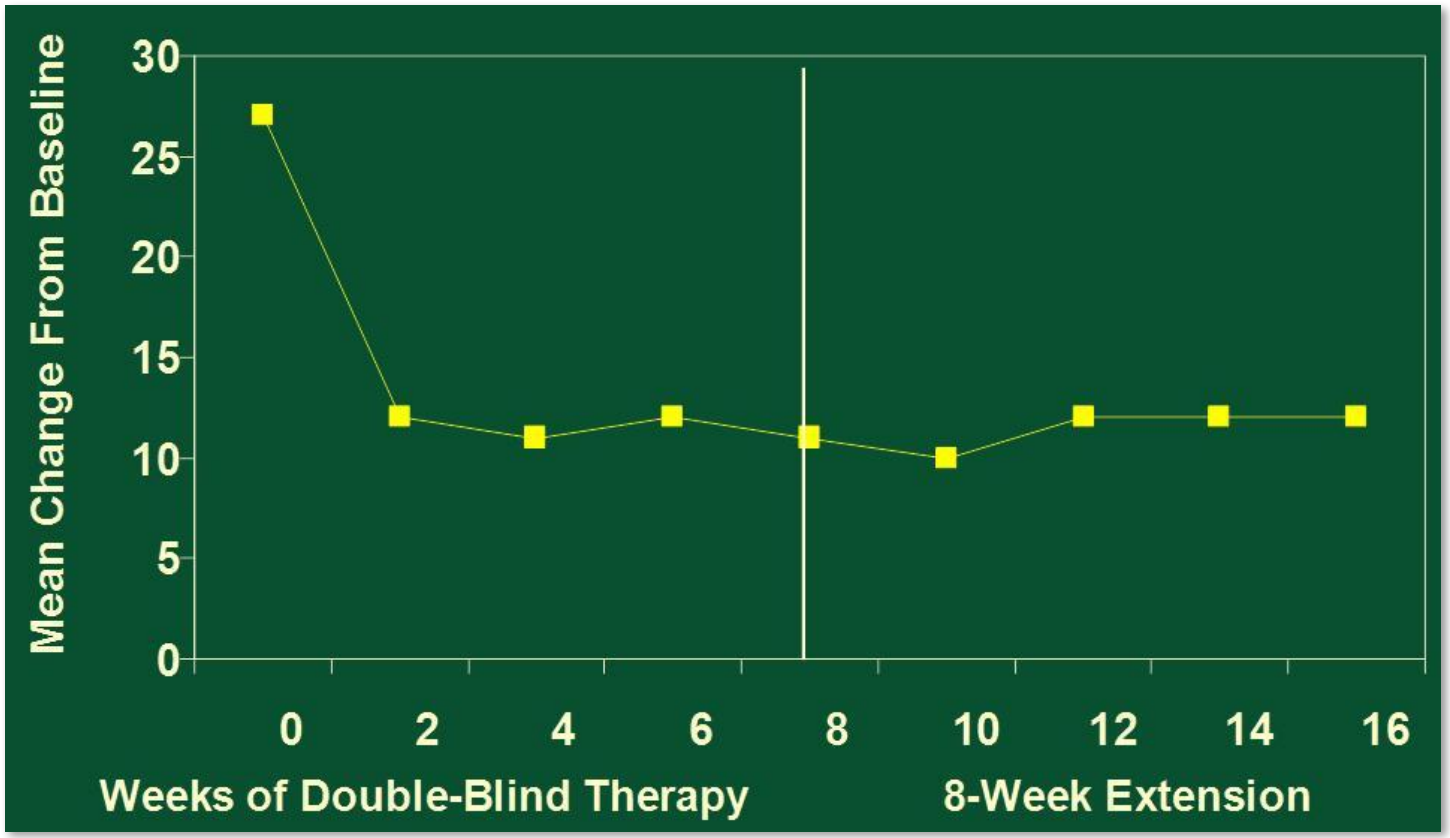
MADRS Score: Mean Change From Baseline (LOCF)



N = 28

Shelton RC, et al. *Am J Psychiatry*. 2001;158(1):131-134.

HAM-D-21 Total: Continuation Data

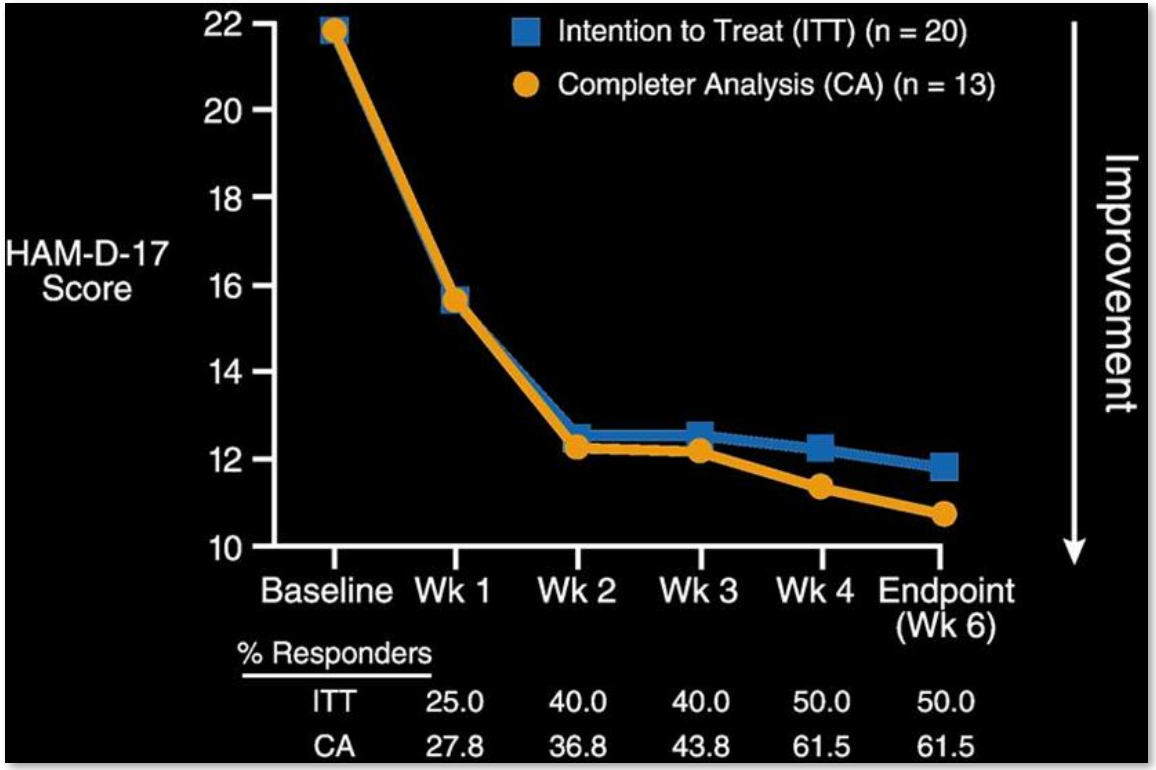


N = 28

Shelton RC, et al. *Am J Psychiatry*. 2001;158(1):131-134.

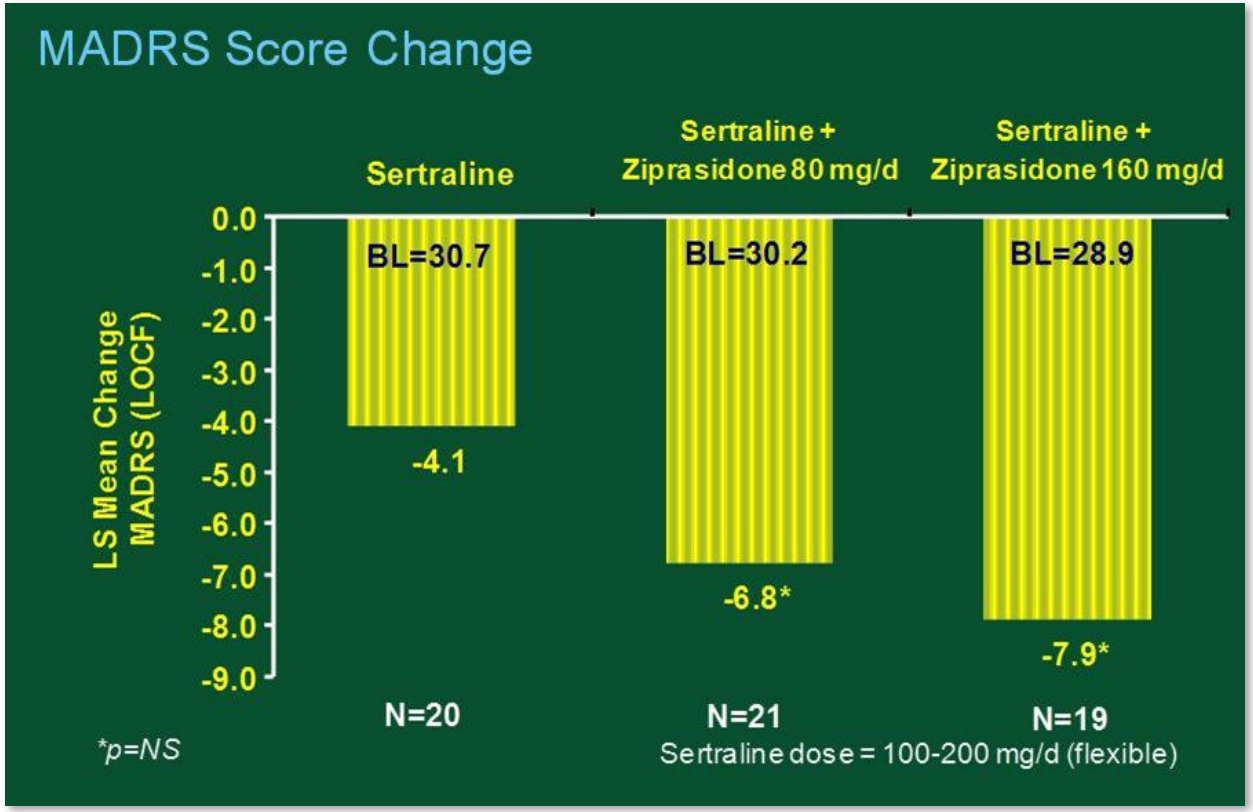
Ziprasidone Augmentation in Treatment-Resistant Depression: Improvement in HAM-D-17 Scores

Ziprasidone titrated up to 160 mg/day



Papakostas GI, et al. *J Clin Psychiatry* 2004;65(2):217-221.

Adjunctive Ziprasidone in TRD: A Randomized, Double-Blind, 8-Week, Pilot Study



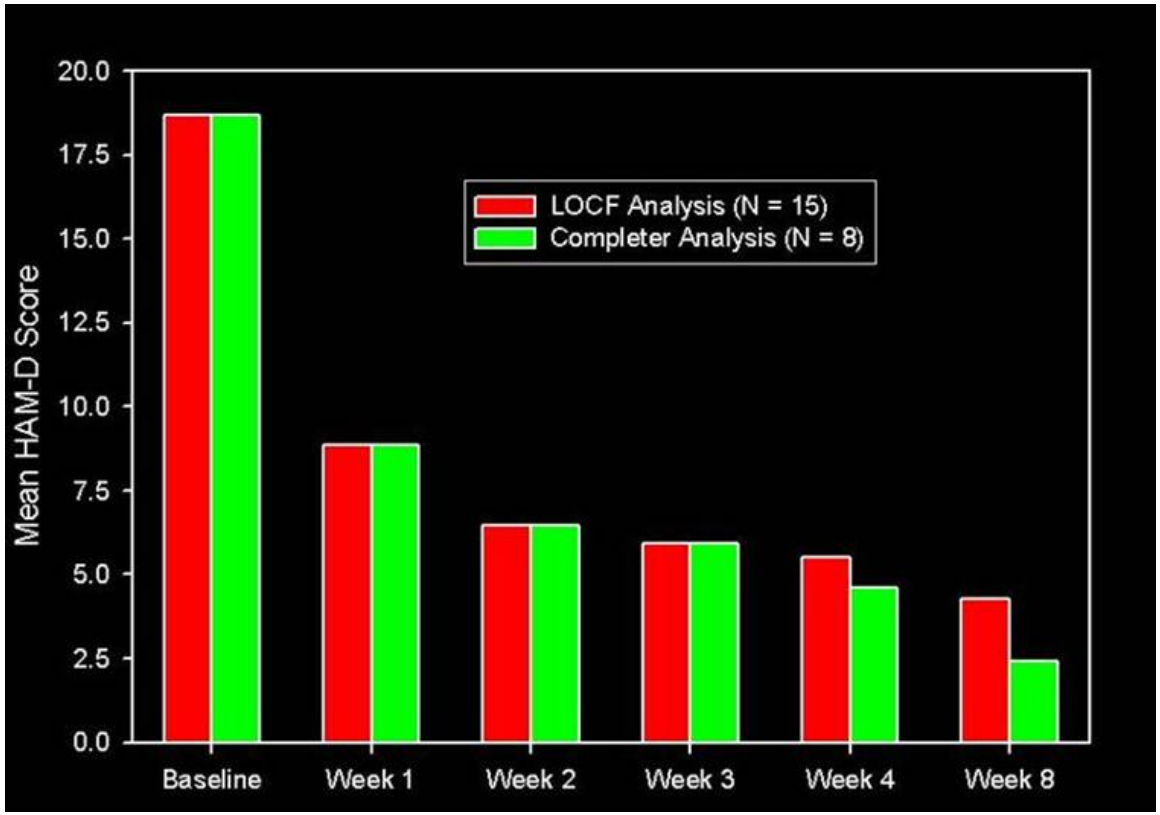
Dunner D, et al. Presented at the 55th Institute of Psychiatric Services. October 29-November 2, 2003, Boston, MA.

Aripiprazole Augmentation of Antidepressants for the Treatment of Partially Responding and Non-Responding Patients with Major Depressive Disorder

Jeffrey S. Simon, MD
Charles B. Nemeroff, MD, PhD

Simon JS, Nemeroff CB. *J Clin Psychiatry*. 2005;66:1216-1220.

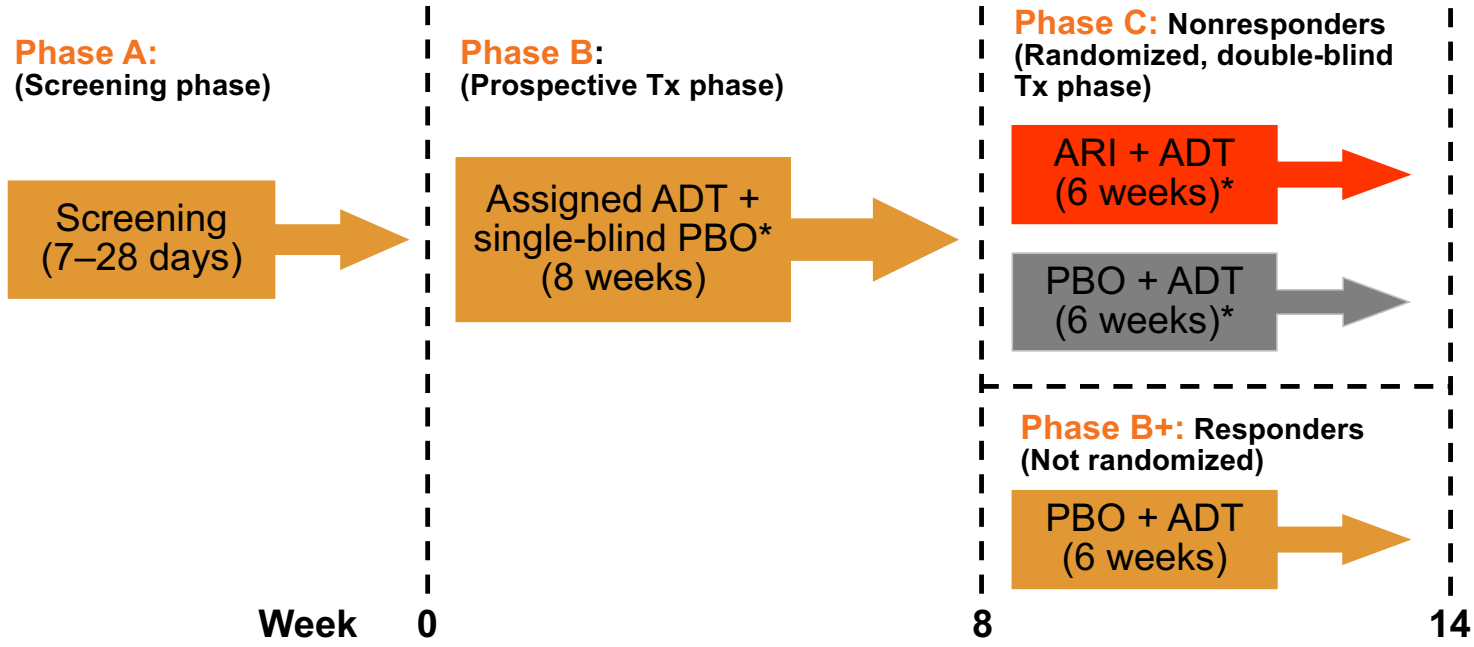
Total Scores on the 17-item HAM-D for Major Depressive Disorder Patients Receiving Augmentation Therapy with Aripiprazole



Simon JS, Nemeroff CB. *J Clin Psychiatry*. 2005;66:1216-1220.

Adjunctive Aripiprazole in Treatment-Resistant Depression

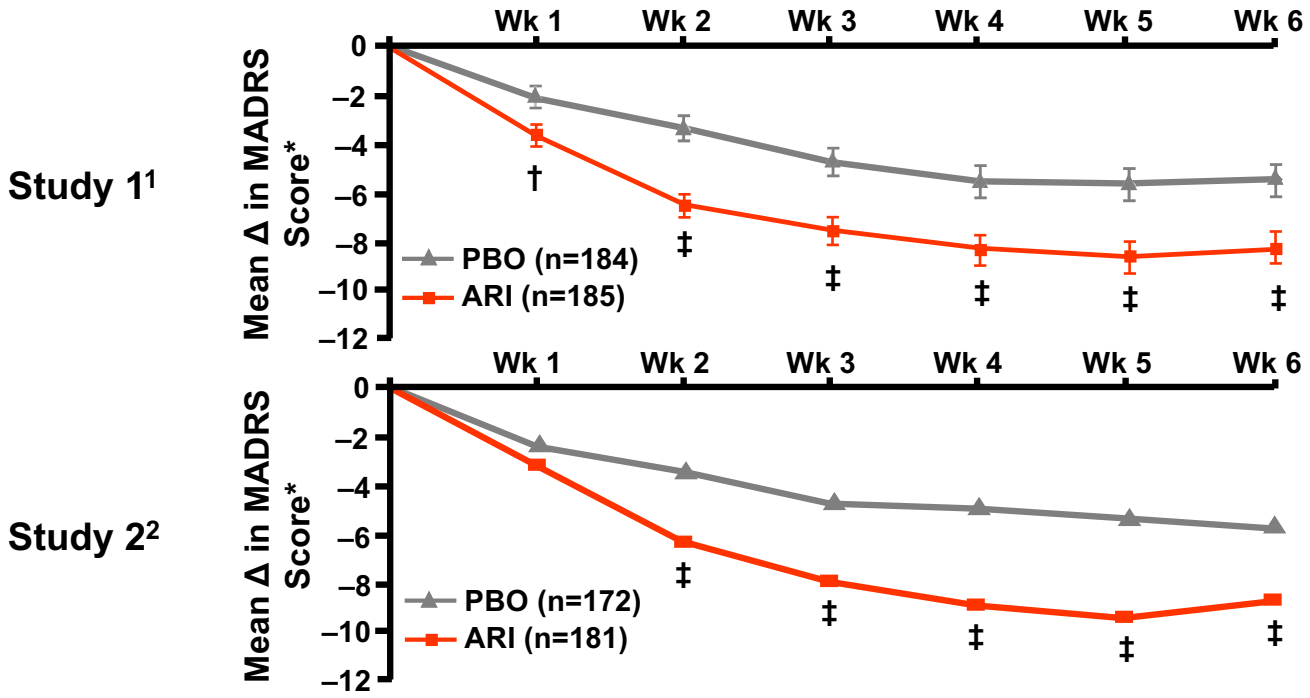
Study Design[1,2]



*There was no significant treatment-by-ADT interaction observed in either study (*P*=.472).
ADT = antidepressant therapy.

1. Thase ME et al. Presented at: Society of Biological Psychiatry 61st Annual Convention & Scientific Program. Toronto, Canada: May 18-20, 2006.
2. Berman RM, et al. Presented at: 2007 Annual Meeting of the American Psychiatric Association. San Diego, Calif: May 19-24, 2007.

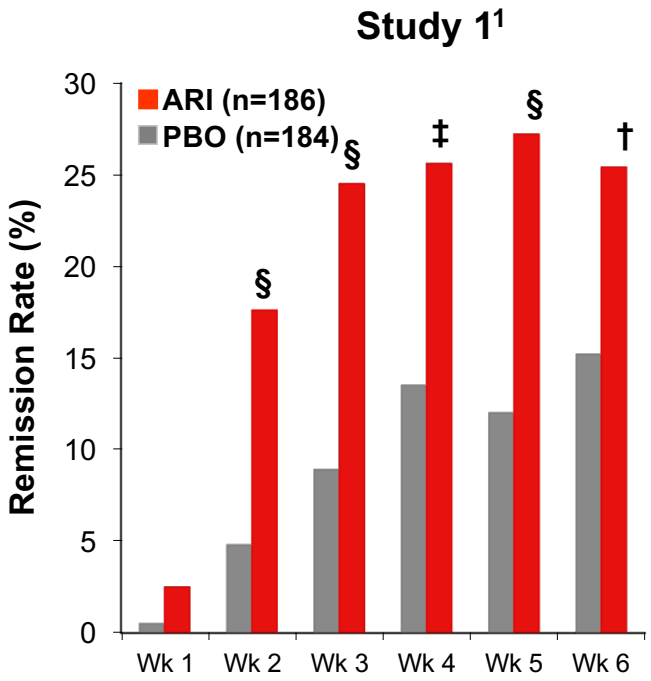
Mean Change in MADRS Total Score (LOCF)

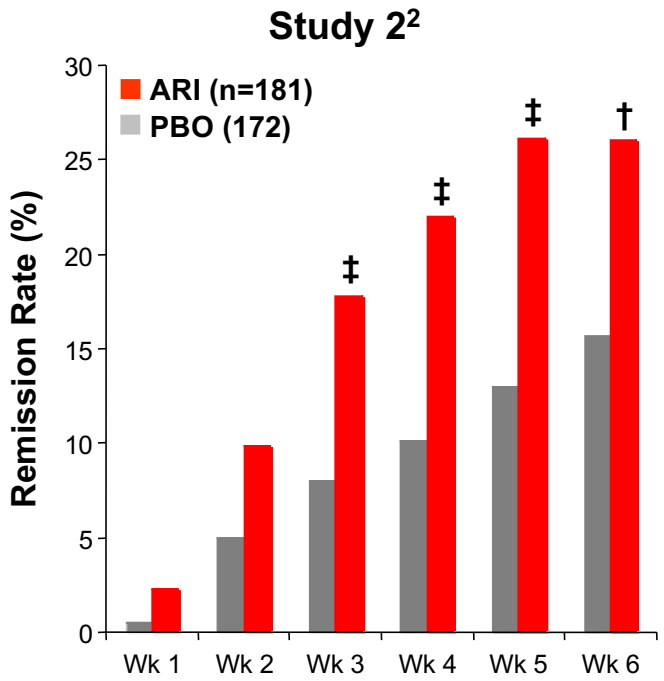


*From end of prospective treatment phase; †*P*<.01; ‡*P*<.001.
MADRS total score reduction in ARI vs PBO groups at study end for study 1 and study 2 was –8.5, –8.8 vs –5.7, –5.8, respectively.

1. Thase ME et al. Presented at: Society of Biological Psychiatry 61st Annual Convention & Scientific Program. Toronto, Canada: May 18-20, 2006.
2. Berman RM, et al. Presented at: 2007 Annual Meeting of the American Psychiatric Association. San Diego, Calif: May 19-24, 2007.

MADRS Remission Rates*





*Remission = MADRS total score ≤10 and 50% reduction in MADRS total score from end of prospective phase to study end; †$P < .05$; ‡$P < .01$; §$P < .001$.

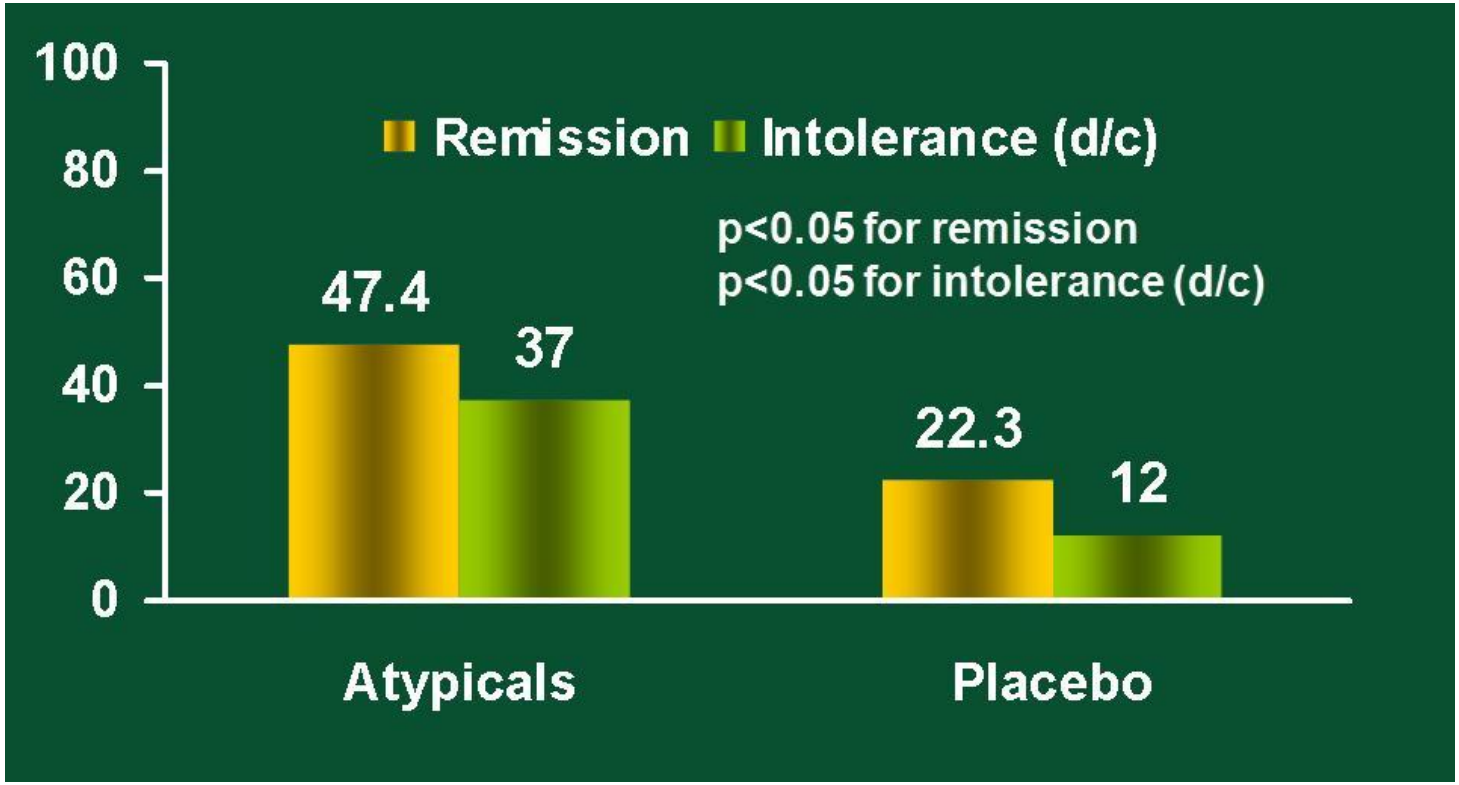
1. Thase ME et al. Presented at: Society of Biological Psychiatry 61st Annual Convention & Scientific Program. Toronto, Canada: May 18-20, 2006.
2. Berman RM, et al. Presented at: 2007 Annual Meeting of the American Psychiatric Association. San Diego, Calif: May 19-24, 2007.

Atypical Antipsychotic Augmentation Randomized Clinical Trials (RCTs)

Shelton et al 2001	Olanzapine	Fluoxetine	8
Shelton et al 2005	Olanzapine	Fluoxetine	12
Corya et al 2006	Olanzapine	Fluoxetine	12
Keitner et al 2006	Risperidone	Various	4
Khullar et al 2006	Quetiapine	SSRI or SNRI	8
Mattingly et al 2006	Quetiapine	SSRI or SNRI	8
McIntyre et al 2006	Quetiapine	SSRI or SNRI	8
Thase et al 2006	Olanzapine	Fluoxetine	8
Thase et al 2006	Olanzapine	Fluoxetine	8
Gharabawi et al 2006	Risperidone	Various	6

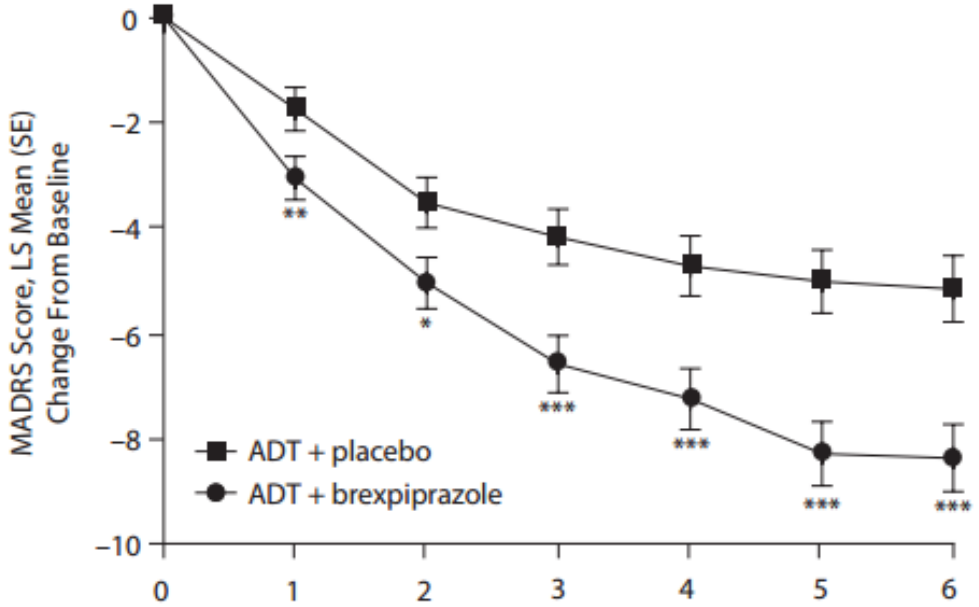
Papakostas GI, et al. *J Clin Psychiatry*. 68(6):826-831.

Atypical Antipsychotic Augmentation in TRD: Meta-analysis of 10 RCTs* (n = 1,500)



Papakostas GI, et al. *J Clin Psychiatry*. 68(6):826-831.

Adjunctive Brexpiprazole: LS Mean (SE) Change from Baseline in MADRS Score for Efficacy Population per Final Protocol

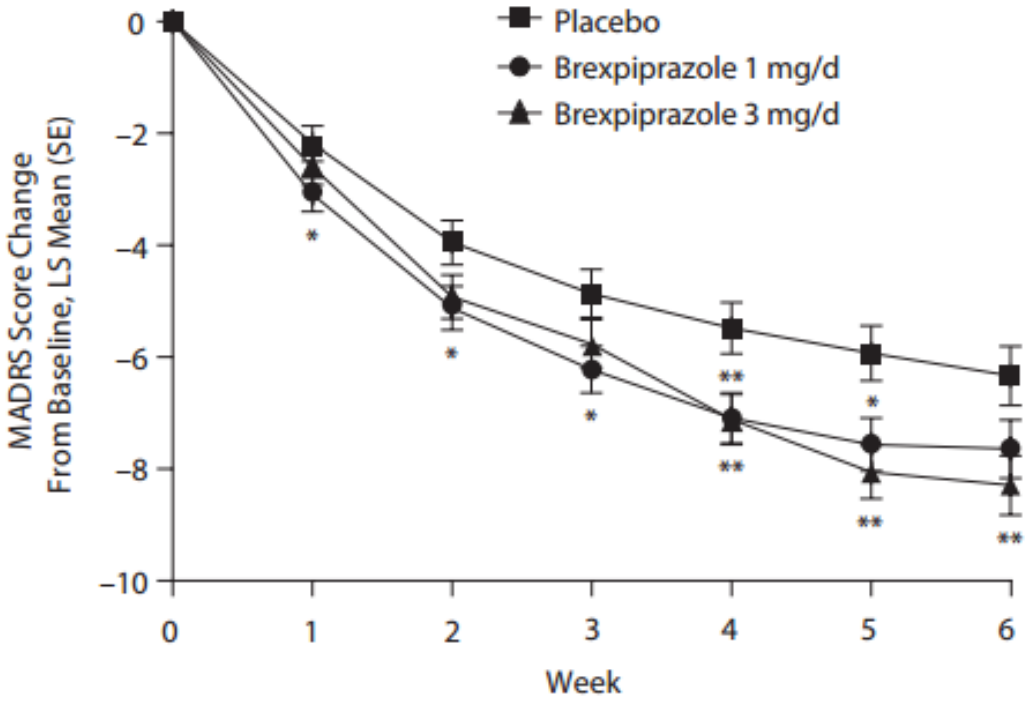


- Baseline mean MADRS scores were 27.3 for ADT + placebo (n = 178) and 26.9 for ADT + brexpipraole (n = 175)
- *P* values based on mixed model repeated-measures analysis
- $*p < .05$
- $**p < .01$
- $***p < .001$

ADT = antidepressant treatment; LS = least squares; MADRS = Montgomery-Asberg Depression Rating Scale; SE = standard error

Thase ME, et al. *J Clin Psychiatry* 2015;76(9):1224-1231.

Adjunctive Brexpiprazole (1mg and 3 mg): LS Mean (SE) Change from Baseline in MADRS Score



- Baseline mean MADRS scores were 26.5 for ADT + placebo (n = 203) and 26.9 for ADT + brexpiprazole 1 mg (n = 211), and 26.5 for ADT + brexpiprazole 3 mg (n = 213)
- *P* values based on mixed model repeated-measures analysis
- $*p < .05$
- $**p < .01$

ADT = antidepressant treatment; LS = least squares; MADRS = Montgomery-Asberg Depression Rating Scale; SE = standard error

Thase ME, et al. *J Clin Psychiatry* 2015;76(9):1232-1240.

Lurasidone Monotherapy in the Treatment of Bipolar I Depression: A Randomized, Double-Blind, Placebo-Controlled Study

Antony Loebel, M.D.

Josephine Cucchiaro, Ph.D.

Robert Silva, Ph.D.

Hans Kroger, M.P.H., M.S.

Jay Hsu, Ph.D.

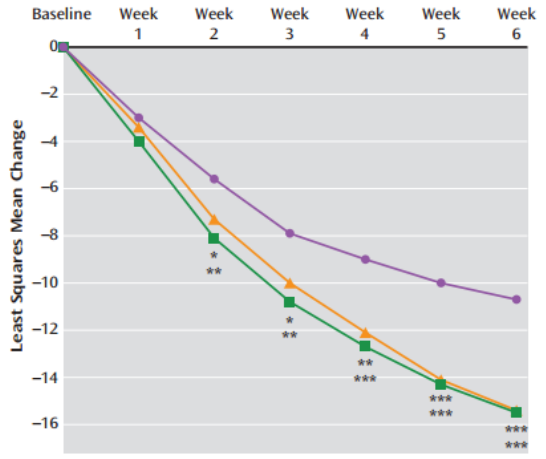
Kaushik Sarma, M.D.

Gary Sachs, M.D.

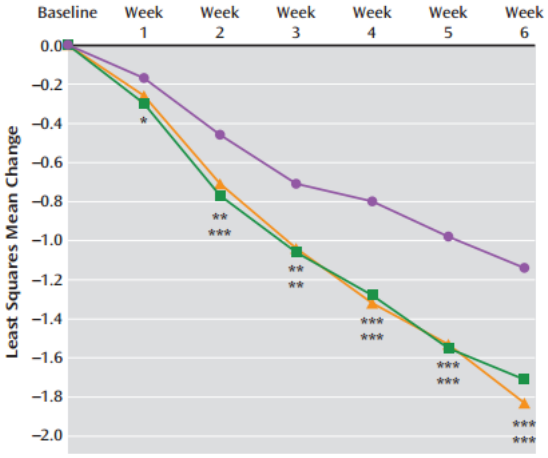
Loebel A, et al. *Am J Psychiatry* 2014;171:160-168.

Change from Baseline in Key Measures

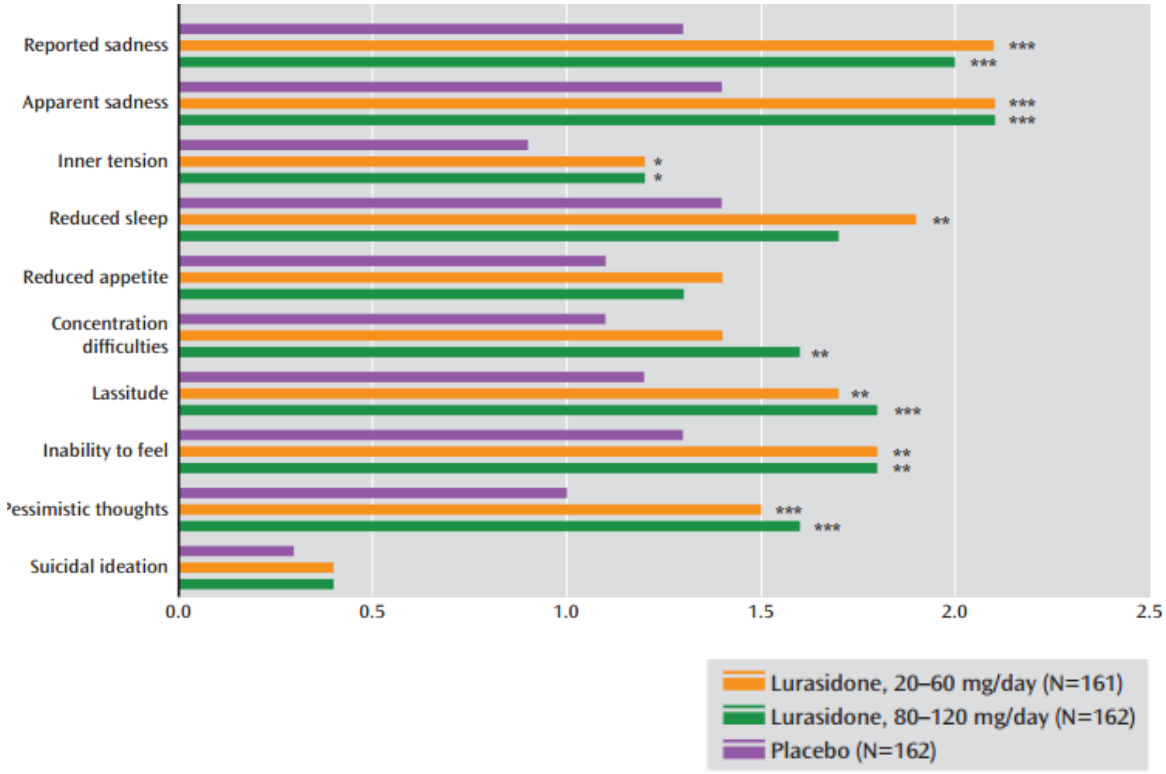
MADRS Total Score



CGI Depression Severity Score



Individual MADRS Item Scores Week 6



Mean MADRS scores at baseline were 30.3 (SD – 4.9), 30.6 (SD = 4.9), 30.5 (SD = 5.0) for lurasidone 20-60 mg, lurasidone 80-120 mg, and placebo, respectively.; Mean CGI scores at baseline were 4.52 (SD = .62), 4.55 (SD = .64), and 4.48 (SD = .61) for lurasidone 20-60 mg, lurasidone 80-120 mg, and placebo, respectively *p < .05, **p < .01, ***p < .001

Loebel A, et al. *Am J Psychiatry* 2014;171:160-168.

An 8-Week Randomized, Double-Blind, Placebo-Controlled Evaluation of the Safety and Efficacy of Cariprazine in Patients With Bipolar I Depression

Suresh Durgam, M.D., Willie Earley, M.D., Alan Lipschitz, M.D., Hua Guo, Ph.D., István Laszlovszky, Pharm.D., György Németh, M.D., Eduard Vieta, M.D., Ph.D., Joseph R. Calabrese, M.D., Lakshmi N. Yatham, M.B.B.S., F.R.C.P.C.

Durgam S, et al. *Am J Psychiatry.* 2016;173(3):271-281.

MAO Inhibitors: Other Association Practice Guidelines

- MAOI treatment recommended for patients with atypical major depression
  - British Association for Psychopharmacology[1]
  - Texas Medication Algorithm Project (TMAP)[2]
  - Agency for Health Care Policy and Research (AHCPR)[3]

1. Anderson IM, et al. *Psychopharmacol* 2000;14:3-20.
2. Trivedi M, et al. *J Clin Psychiatry* 2001;62(suppl 6):22-29.
3. AHCPR Publication No. 99-E014;1999. Available at https://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0010310/. Accessed June 2, 2017.

Optimizing Current Treatments

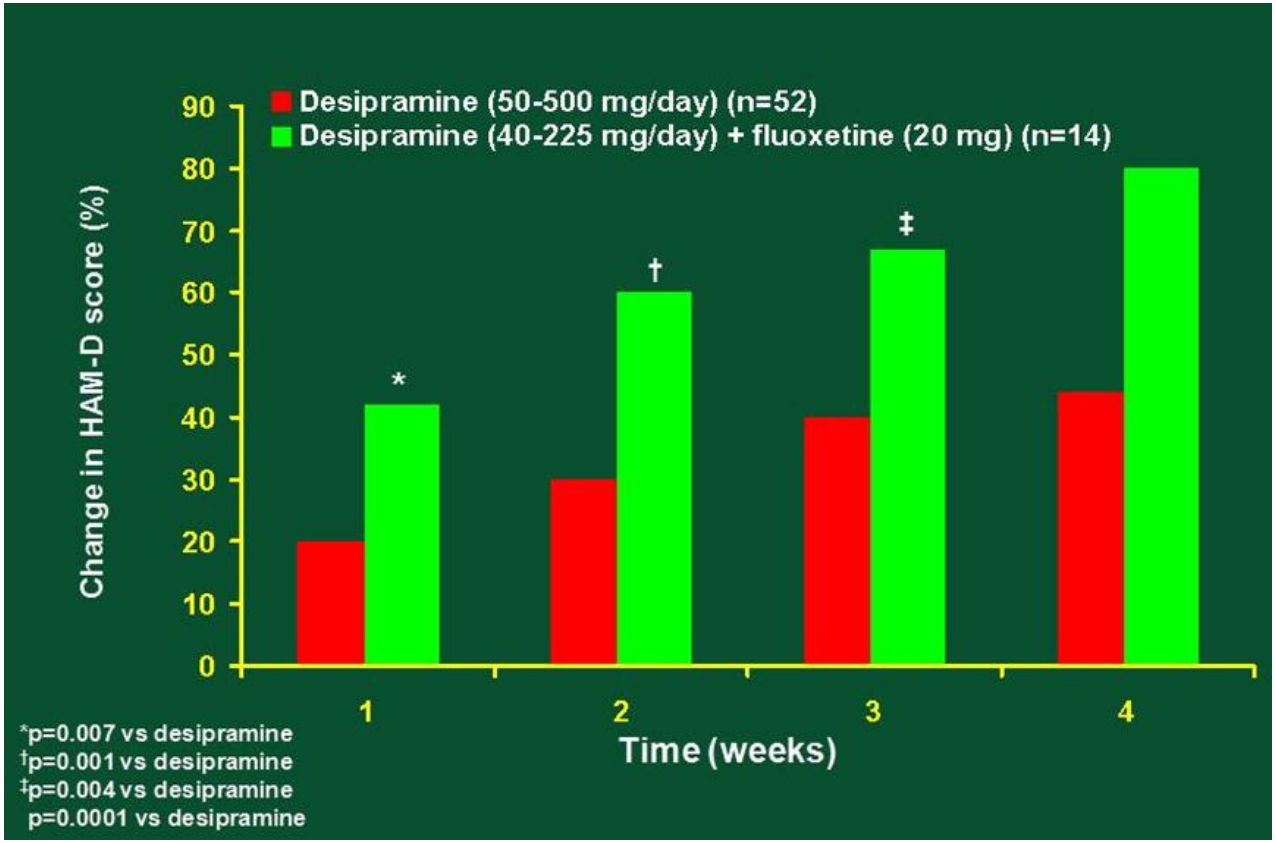
- Monoamine oxidase inhibitors effective for depression[1]
  - Diet restrictions, drug-drug interactions limit utility
- Transdermal selegiline
  - Efficacious for depression[2,3]
  - No diet restrictions at 6mg/day
  - Limitations:
    - Diet restrictions required at higher doses
    - Drug-drug interactions still a concern

1. Krishnan KR, in Textbook of Psychopharmacology, Schatzberg and Nemeroff (eds), 1998
2. Amsterdam JD. *J Clin Psychiatry*, 2003;64(2):208-214.
3. Bodkin JA, Amsterdam JD. *Am J Psychiatry* 2002;159(11):1869-1875.

Combination Therapy

- Combining two antidepressants with well-established efficacy
- Two well-established agents from different classes
- Evoke dual-action approach
- TCAs + SSRIs

Desipramine Alone and an Combination with Fluoxetine



Nelson JC, et al. *Arch Gen Psychiatry.* 191;48(4):303-307.

SSRI + MIRTAZAPINE: A Double-Blind, Placebo-Controlled Study of Antidepressant Augmentation with Mirtazapine

- RCT followed preliminary positive results
- N = 26 outpatients with partial or nonresponse on SSRI (83%), bupropion or venlafaxine at “maximum recommended or tolerated doses”
- Mean pre-combination treatment 19.4 wks
- Mirtazapine 15 mg/d x 1 wk, then 30 mg/d

Carpenter LL, *Biol Psychiatry.* 2002;51(2):183-188.

Carpenter LL, *J Clin Psychiatry*. 1999:60(1):45-49.

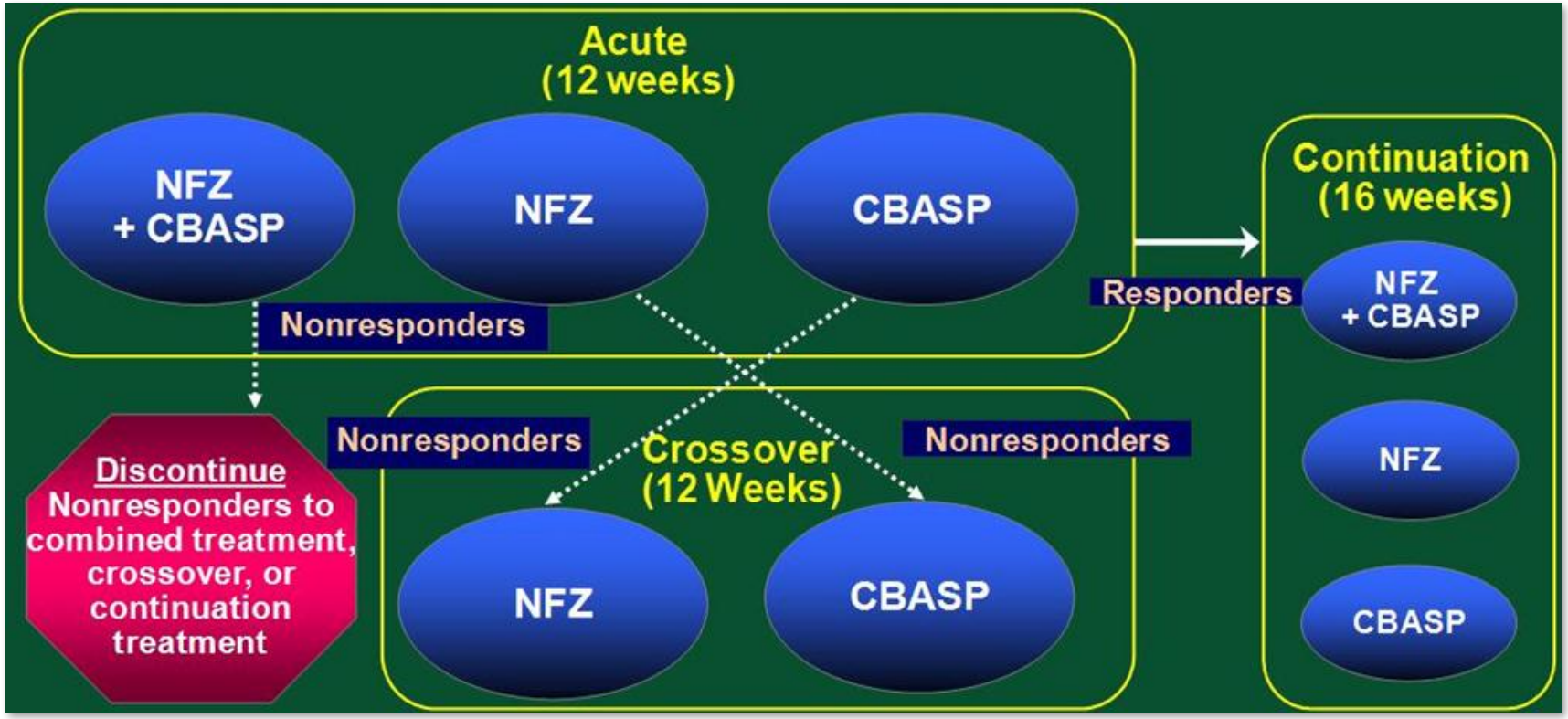
A Double-blind, Placebo-Controlled Study of Antidepressant Augmentation with Mirtazapine

- Response rates: Mirtazapine 63.6% vs Placebo 20%
- Remission rates: Mirtazapine 45.5% vs Placebo 13.3%
- Discontinuation for adverse events similar to placebo
- Most frequent side effect = weight gain
- Concerns:
  - No data on effect of mirtazapine alone
  - Switch from ineffective SSRI in another study showed 37.8% remission with mirtazapine

Carpenter LL, *Biol Psychiatry.* 2002;51(2):183-188.

Thase ME, et al. Poster presented at Institute of Psychiatric Services. October 25-29, 2000. Philadelphia, PA.

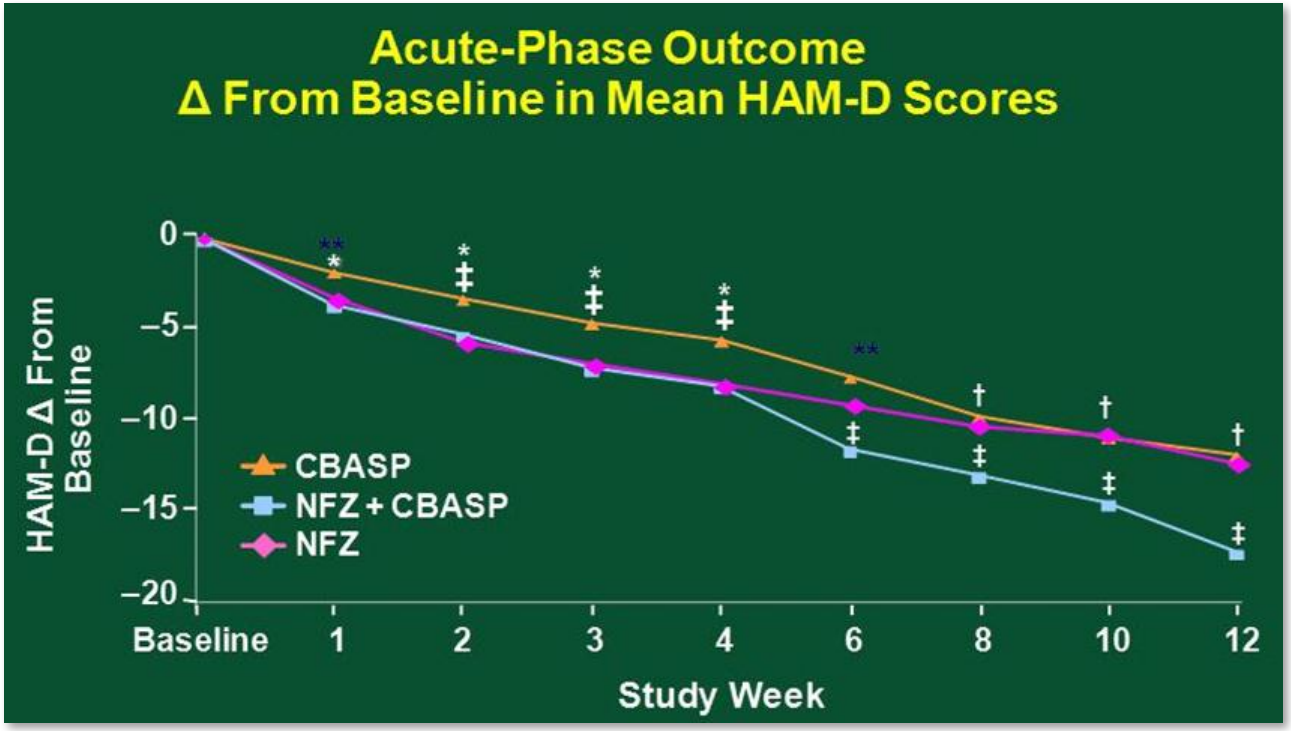
Nefazodone/CBASP Chronic Depression Study



CBASP = Cognitive Behavioral Analysis System of Psychotherapy; NFZ = nefazodone.

Keller MB, et al. *N Engl J Med*. 2000;342(20):1462-1470; Schatzberg AF, et al. *Arch Gen Psychiatry*. 2005;62:513-520.

Nefazodone/CBASP Chronic Depression Study



Observed cases, least-squares (LS) means.; *P < .05, NFZ vs. CBASP; †P < .01, NFZ + CBASP vs. CBASP; ‡P < .01, NFZ + CBASP vs. NFZ. No statistical difference between NFZ vs NFZ + CBASP through Week 4.

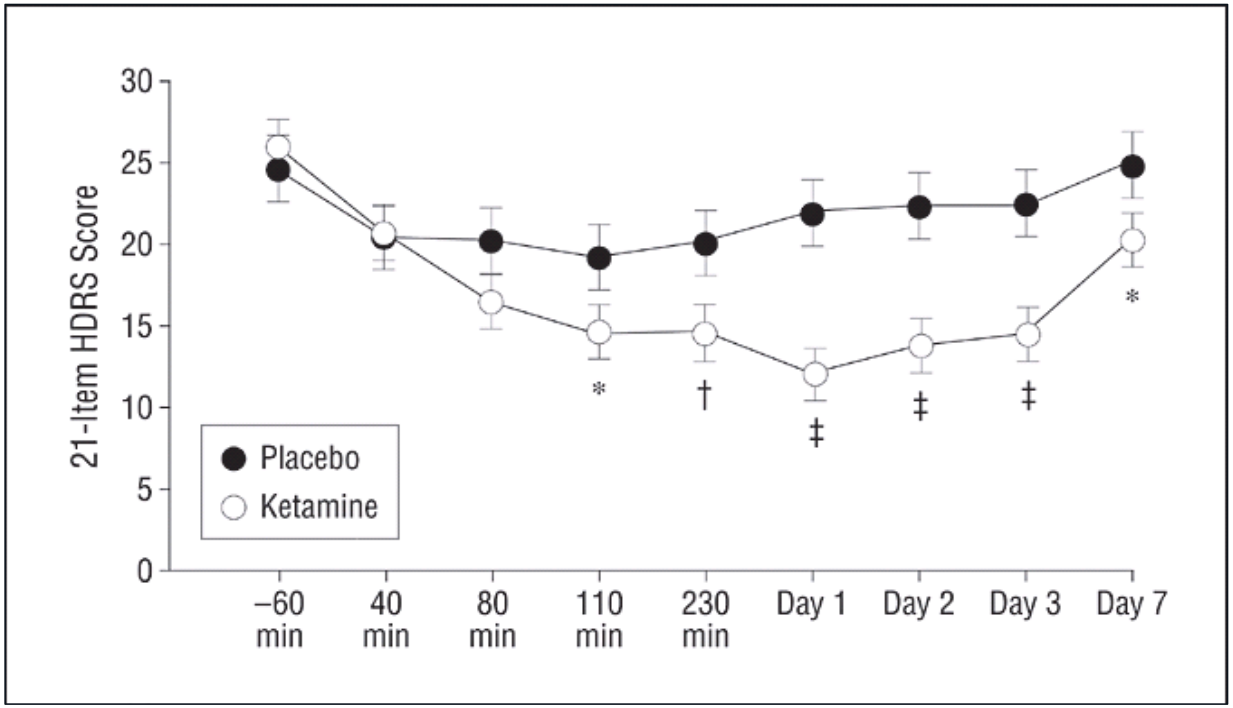
Keller MS, et al. *N Engl J Med* 2000;342(20):1462-1470.

Ketamine*

- Anesthetic agent
- Used intravenously primarily
- Used for chronic pain
- N-methyl-D-aspartate antagonist
- Can cause psychotic-like symptoms
- Acute antidepressant efficacy not sustained

*Not approved by the US FDA for MDD

Ketamine*: Change in the 21-item Hamilton Depression Rating Scale (HDRS)

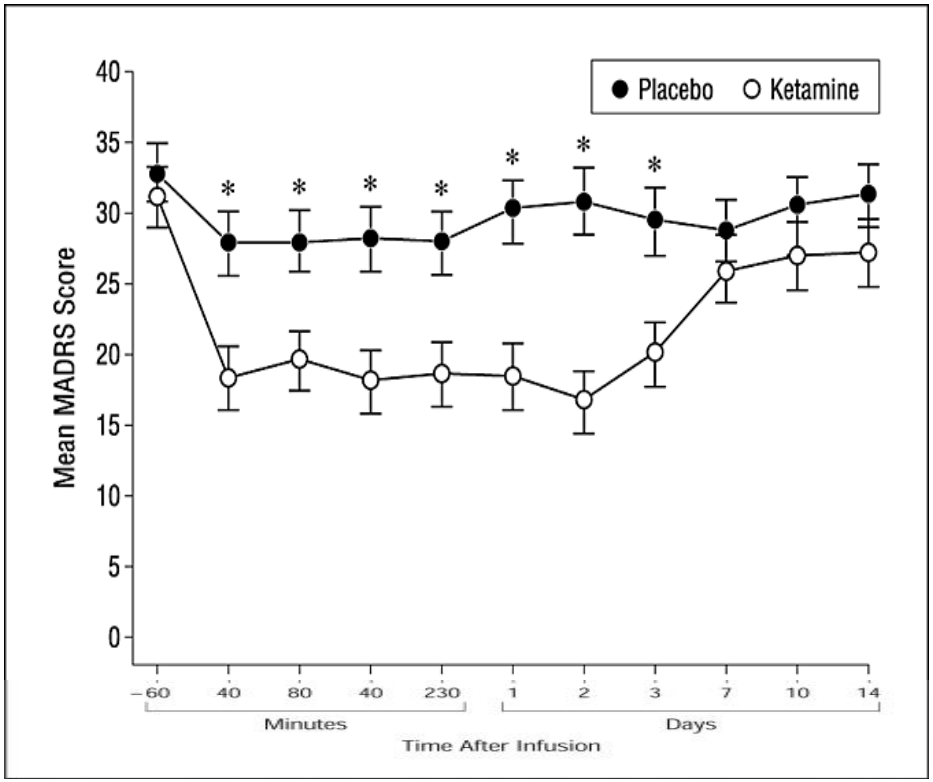


The 21-item Hamilton Depression Rating Scale (HDRS) over 1 week (n = 18)

*Not approved by the US FDA for MDD

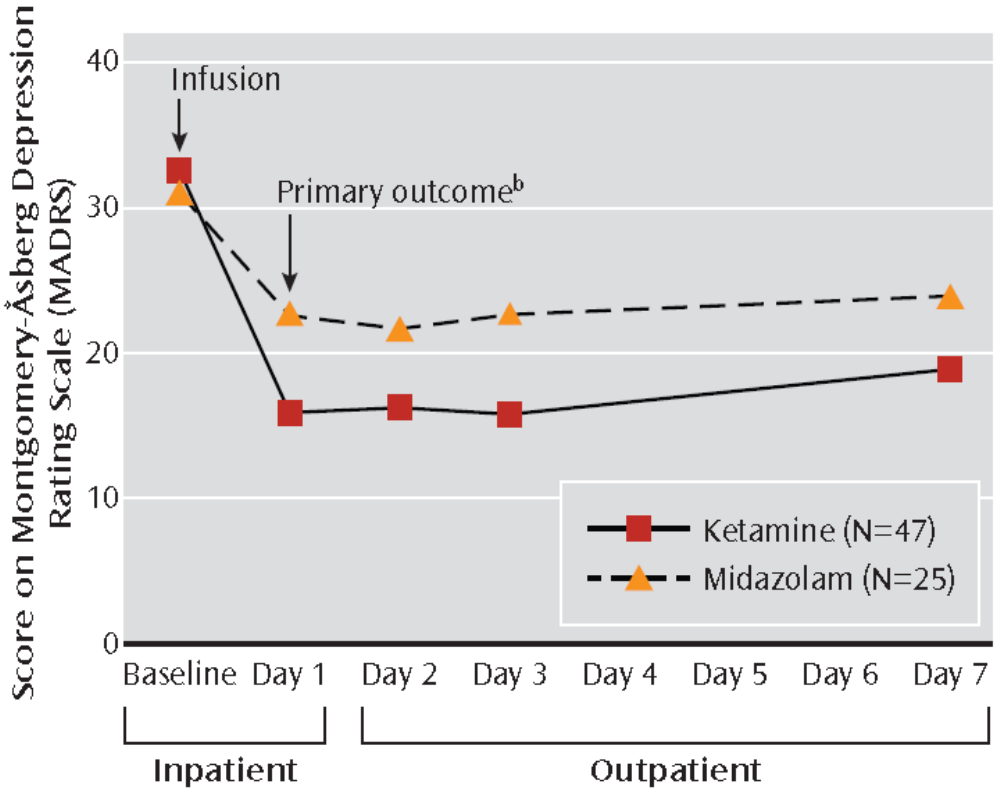
Zarate CA, et al. *Arch Gen Psychiatry* 2006;63:856-864.

Change in Depression Scale Scores During 2 Weeks in Patients with Bipolar Disorder Given Placebo and Ketamine (n = 18)



Diazgranados, N et al. *Arch Gen Psychiatry* 2010; 67:793-802.

Change in Depression Severity Over Time in Patients with TRD Given a Single Infusion of Ketamine* or Midazolam



- Modified intention-to-treat group. MADRS scores range from 0-60 with higher scores indicating greater severity of symptoms.
- Reduction in MADRS score 24 hours after infusion was the primary outcome measure and was significantly greater for the ketamine group than for the midazolam group ($p \leq 0.002$).

*Not approved by the US FDA for MDD

Murrough JW, et al. *Am J Psychiatry*. 2013;170(10):1134-1142.

Ketamine and Other NMDA Antagonists: Early Clinical Trials and Possible Mechanisms in Depression

D. Jeffrey Newport, M.D., M.S., M.Div., Linda L. Carpenter, M.D., William M. McDonald, M.D., James B. Potash, M.D., M.P.H., Mauricio Tohen, M.D., Dr.P.H., M.B.A., Charles B. Nemeroff, M.D., Ph.D., The APA Council of Research Task Force on Novel Biomarkers and Treatments

*Not approved by the US FDA for MDD

Newport, JD, et al. *Am J Psychiatry.* 2015;172(10):950-966.

Conclusions

- The antidepressant efficacy of ketamine, and perhaps E-cycloserine and rapastinel, holds promise for the future glutamate-modulating strategies; however, the in-effectiveness of other NMDA antagonists suggests that any forthcoming advances will depend on improving our understanding of ketamine's therapeutic benefit, couple with its potential for abuse and neurotoxicity, suggest that its use in the clinical setting warrants cautions.

*Not approved by the US FDA for MDD

Newport, JD, et al. *Am J Psychiatry.* 2015;172(10):950-966.

Use of ECT in Patients with MDD

- Patients with MDD most likely to benefit from ECT
  - Patients with delusions[1]
  - Elderly patients[1]
  - Patients presenting with high suicide risk[1]
  - Patients with history of poor response to pharmacotherapy[2]
  - Patients with history of responsiveness to ECT[2]
  - Patients who choose it[2]
  - Patients with bipolar disorder[3]
- ECT is a treatment typically used for MDD after multiple treatments have been poorly tolerated or do not yield a therapeutic response

1. Fink M, Bailine S. *Am J Managed Care*. 1998;4:107-112.; 2. Weiner RD, Krystal AD. In: Gabbard GO, ed. *Treatments of Psychiatric Disorders*. Washington, DC: American Psychiatric Press; 2001:1267-1293.; 3. Kahn DA, et al. *J Psychiatr Pract*. 2000;6:197-211.

Efficacy of ECT in MDD and TRD

- The acute effect of ECT in MDD is well established
  - Continuation therapy is required to prevent relapses[1]
  - In 1 recent study, within 24 weeks of achieving remission (HAMD reduced by 60% and ≤10), 64% of patients had relapsed[2]
- TRD is predictive of post-ECT relapse
  - Patients with TRD are at high risk for relapse within 1 year following ECT response[3]
    - Only 32% of patients with TRD maintained their response during the year after ECT treatment[4]

[1]Sackeim HA, et al. *JAMA*. 2001;285:1299-1307. [2]Prudic J, et al. *Biol Psychiatry*. 2004;55: 301-312. [3]Sackeim HA, et al. *J Clin Psychopharmacol*. 1990;10:96-104. [4]Sackeim HA, et al. *Arch Gen Psychiatry*. 2000;57:425-434.

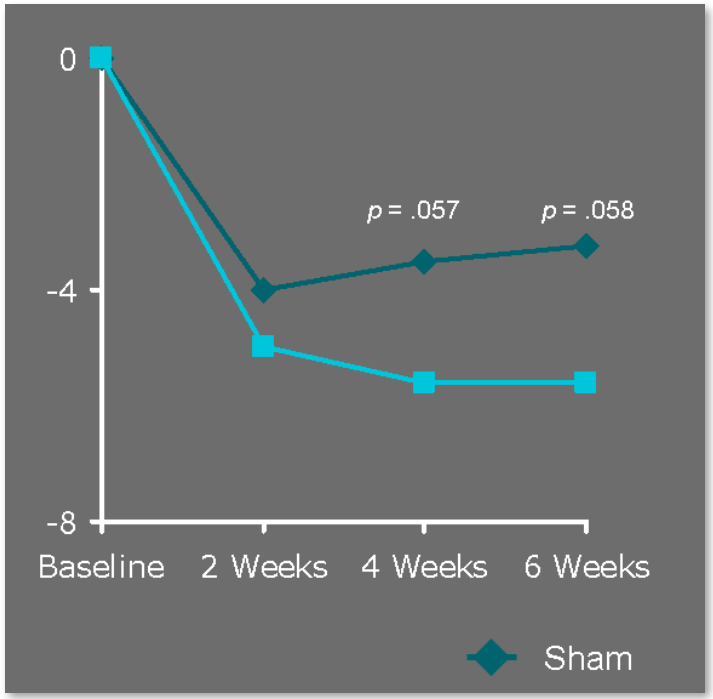
Transcranial Magnetic Stimulation (TMS or rTMS)

- rTMS approved by the FDA for patients who have failed 1 antidepressant trial
- A series of focal electrical pulses are delivered to the cortex via an electro- magnetic coil placed on the scalp
- Non-surgical and potentially amenable to administration in the office setting

rTMS in Major Depression

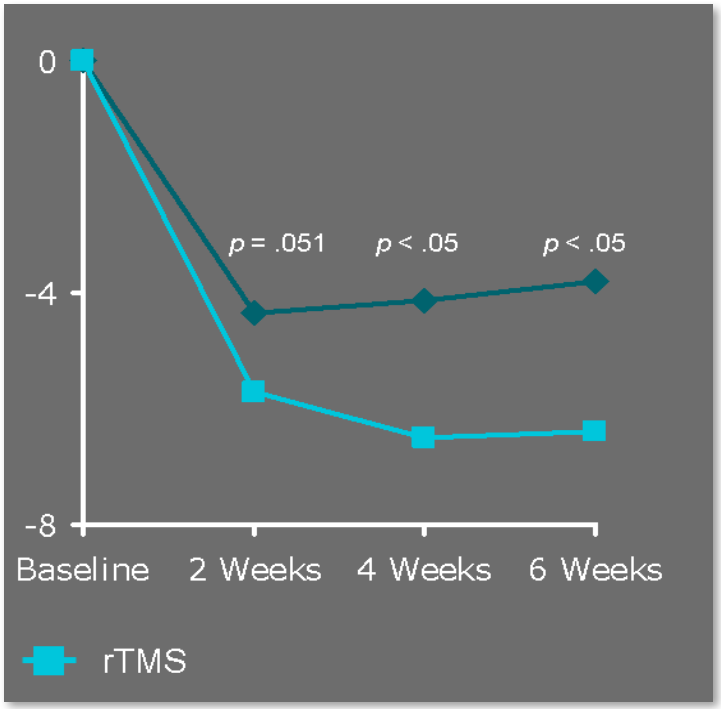
MADRS Total Score

Baseline to Endpoint Change, LOCF Analysis



HAM-D-24 Total Score

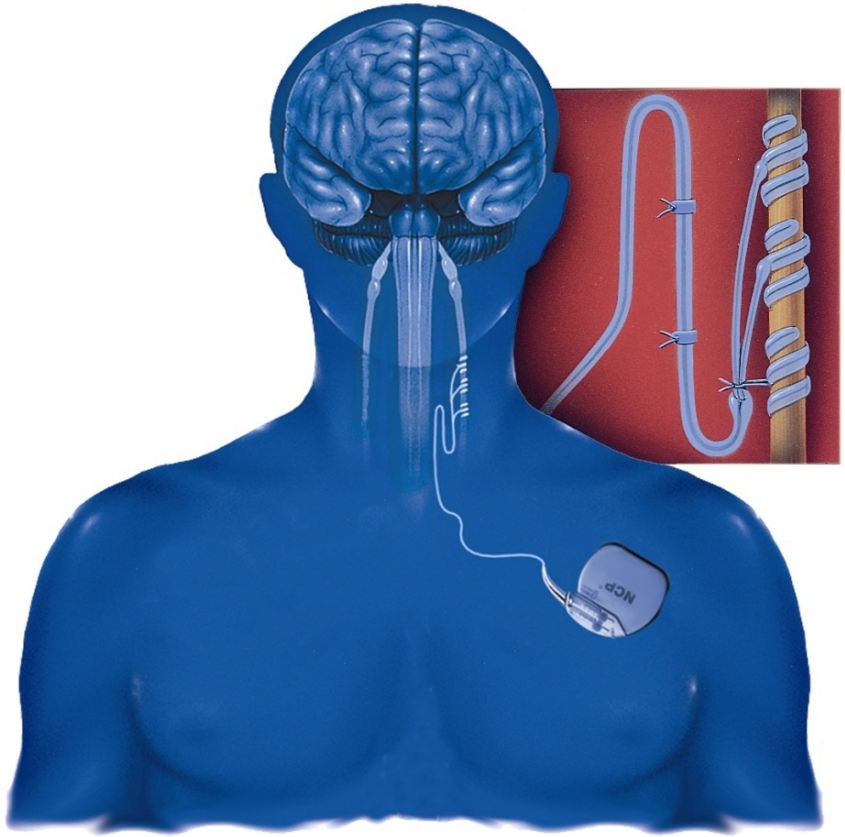
Baseline to Endpoint Change, LOCF Analysis



O'Reardon JP, et al. *Biol Psychiatry.* 2007;11:1208-1216.

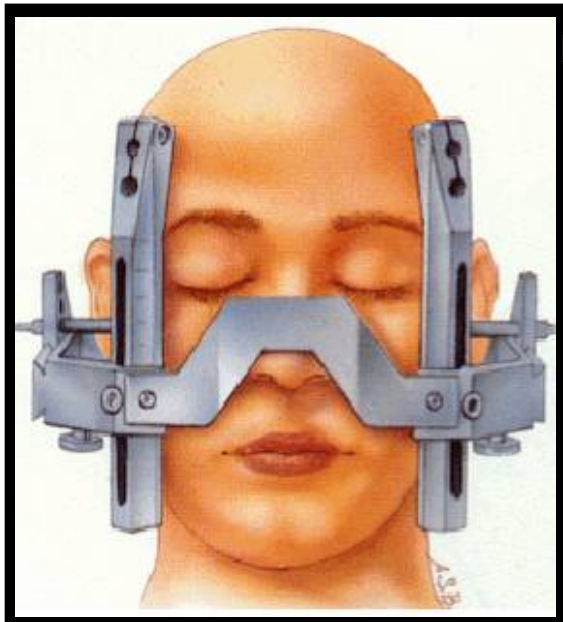
Vagus Nerve Stimulation (VNS)

- FDA-approved (1997) for treatment of medication-refractory epilepsy
- FDA-approved (2005) for treatment of depression that has not responded to four or more medications
- Achieved by implanting a pulse generator attached to (usually) the left vagus nerve

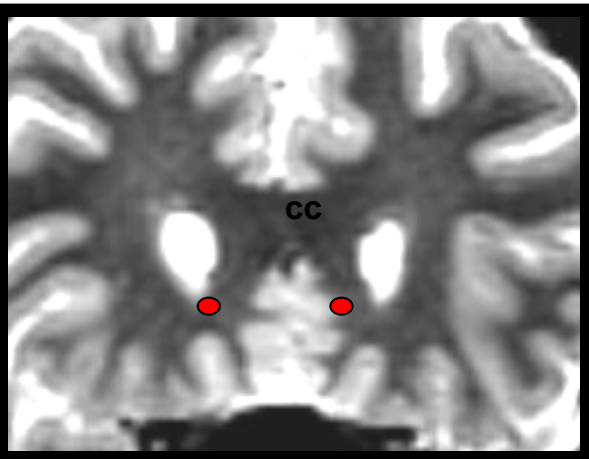


Deep Brain Stimulation (DBS)

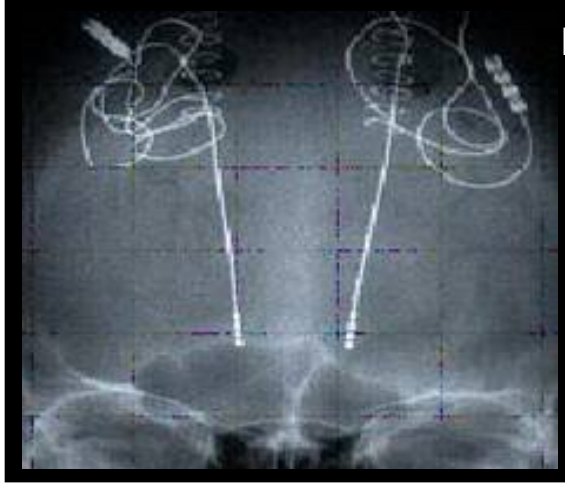
- FDA-approved for the treatment of essential tremor, Parkinson's Disease and dystonia
- Involves (often bilateral) implantation of an electrode into a specific neural structure
  - Different structures chosen for different disorders
  - Side effects often related to site of stimulation
- Stimulation is controlled by a pulse generator implanted in the chest wall



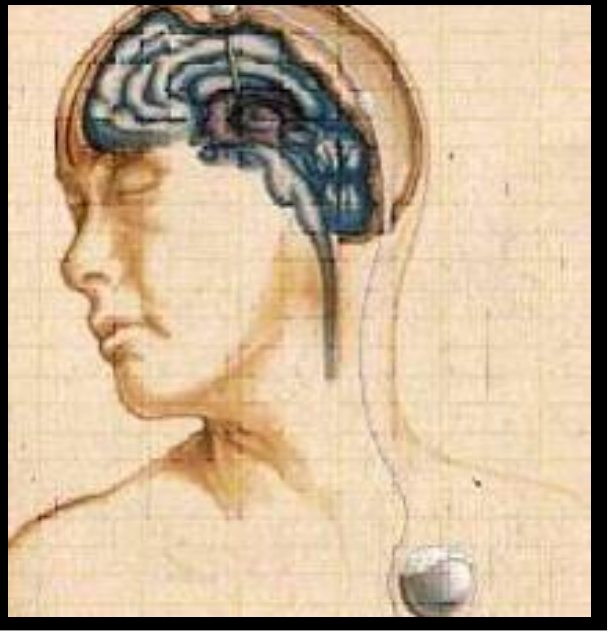
FRAME



TARGET



IMPLANTS



ENTIRE SYSTEM

DBS

- Open study of DBS for depression[1]
  - Target: Brodmann Area 25 white matter (based on imaging and other data)
  - 6 patients with extensively treatment-refractory depression
  - 4 of 6 patients responded by 6 months
    - 2 were remitters
  - All 4 remained responders at 12 months[2]
    - 3 were remitters
  - DBS well tolerated with no stimulation-related adverse events
- Confirmatory trial underway at Emory

1. Mayberg HS, et al. *Neuron*. 2005;45(5)”651-660.
2. Mayberg HS, et al. Presented at 2005 Society for Neuroscience annual meeting, program no. 678.17.

Basis for the Hypothesis that Inflammation and an Activated Innate Immune Response may Play a Role in Depression

- Patients with depression (both medically ill and medically healthy) have been found to exhibit all the cardinal features of inflammation.
  - Increased peripheral blood and csf innate immune cytokines (IL-6 and TNF-alpha most reliable)
  - Increased acute phase reactants (CRP most reliable)
  - Increased chemokines
  - Increased cellular adhesion molecules
- In the majority of studies, inflammatory markers decrease with successful antidepressant therapy (“state marker”).

Basis for the Hypothesis that Inflammation may Play a Role in Depression

- Positive correlation between depressive symptom severity and innate immune cytokines
- Elevated innate immune cytokines predict poor response to antidepressant therapies and are elevated in patients with treatment resistance. Cytokine gene polymorphisms (IL-1, TNF) predict antidepressant treatment response.
- Administration of innate immune cytokines (esp. IL-1, TNF-alpha, and IL-6, as well as IFN-alpha) produce behavioral changes in laboratory animals and humans that resemble major depression.
- Inhibition of cytokine signaling has been found to alleviate depressive and anxiety behaviors in patients with inflammatory disorders and in laboratory animals.

Etanercept and clinical outcomes, fatigue, and depression in psoriasis: double-blind placebo-controlled randomised phase III trial

Stephen Tyring, Alice Gottlieb, Kim Papp, Ken Gordon, Craig Leonardi, Andrea Wang, Deepa Lalla, Michael Woolley, Angelika Jahreis, Ralph Zitnik, David Cella, Ranga Krishnan

Improvement in symptoms of depression were not correlated with objective measures of skin clearance or joint pain

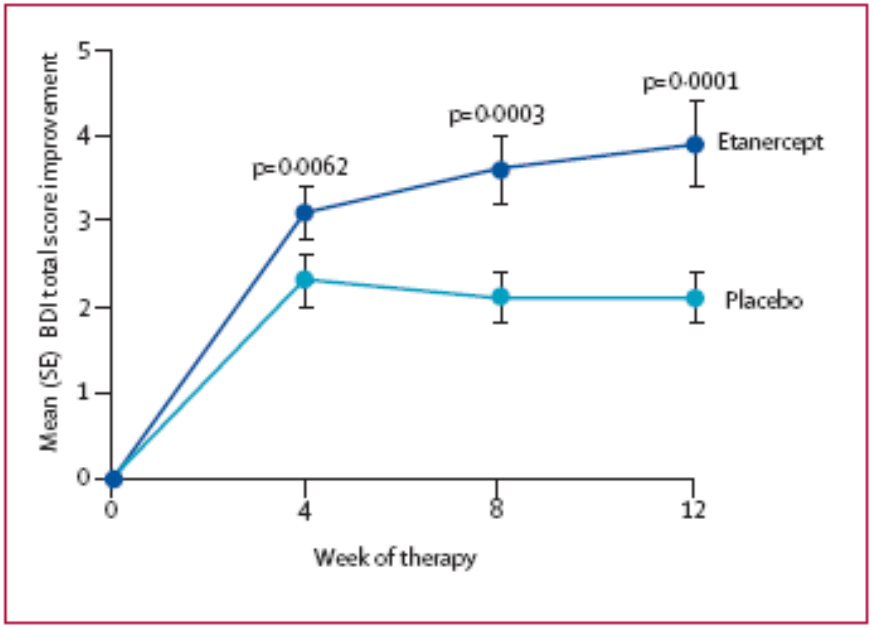
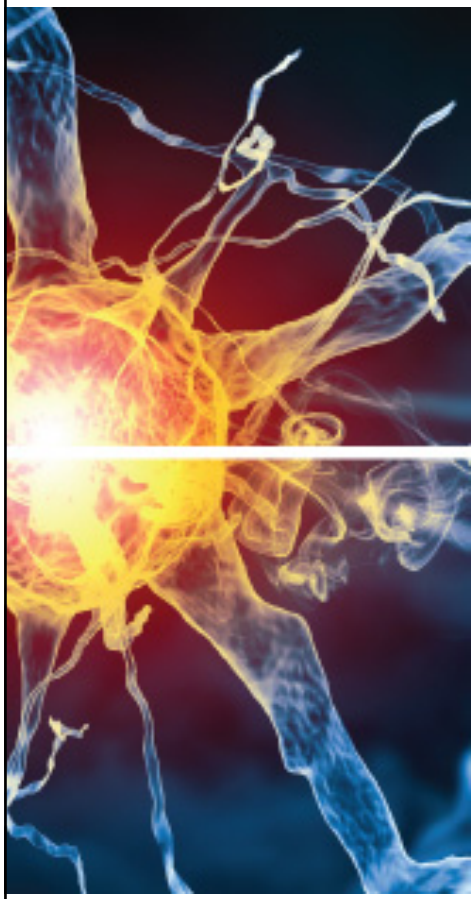


Figure 2: Improvement from baseline in BDI over time
p values for comparison between etanercept and placebo groups.

Tyring S, et al. *Lancet.* 2006;367(9504):29-35.

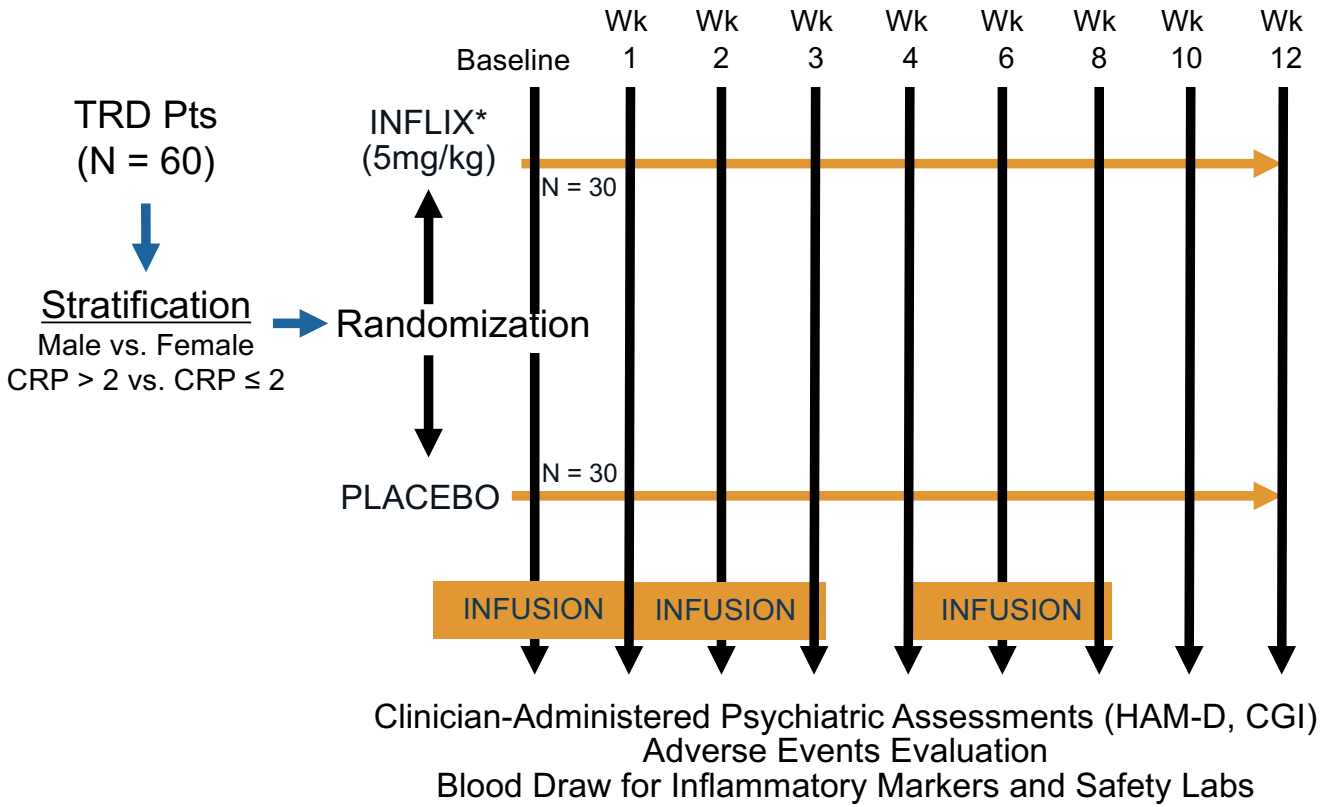


Testing the Cytokine Hypothesis of Depression

Does blockade of inflammatory cytokines reverse depression in patients with treatment-resistant depression (TRD)?

Raison CL, et al. *Arch Gen Psychiatry*. 2012;3:1-11.

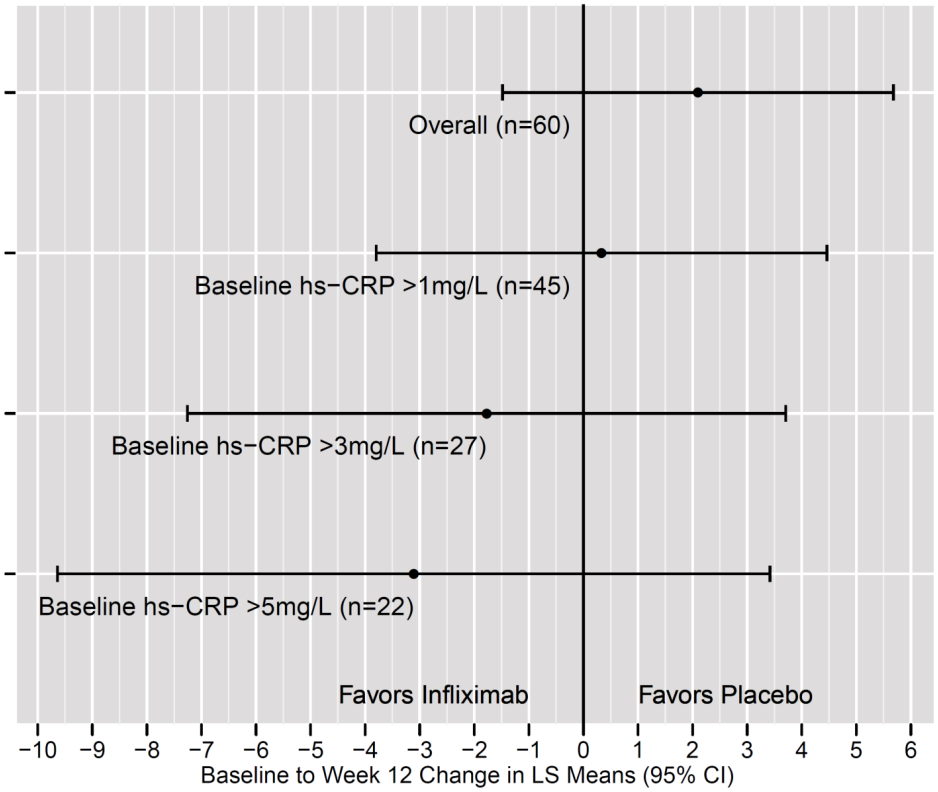
Double-Blind, Parallel-Group, Randomized Design



*Off label use

Raison CL, et al. *Arch Gen Psychiatry*. 2012;3:1-11.

Change in HAM-D-17 Score from Baseline to Week 12 (Infliximab*-Placebo) in TRD Patients Subgrouped By Baseline Plasma hs-CRP



*Off label use

Standardized Effect Size = 0.41 favoring infliximab* at CRP > 5mg/L

Raison CL, et al. *Arch Gen Psychiatry*. 2012;3:1-11. PMID: 22945416.

Review

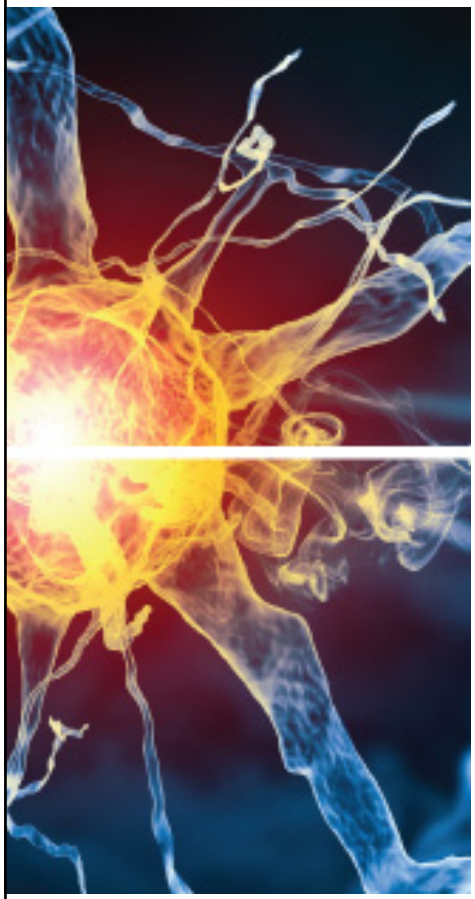
Mesenchymal stem cells: environmentally responsive therapeutics for regenerative medicine

Matthew B Murphy[1], Kathryn Moncivais[1] and Arnold I Caplan[2]

Mesenchymal stem cells (MSCs) are partially defined by their ability to differentiate into tissues including bone, cartilage and adipose *in vitro*, but it is their trophic, paracrine and immunomodulatory functions that may have the greatest therapeutic impact *in vivo*. Unlike pharmaceutical treatments that deliver a single agent at a specific dose, MSCs are site regulated and secrete bioactive factors and signals at variable concentrations in response to local microenvironmental cues. Significant progress has been made in understanding the biochemical and metabolic mechanisms and feedback associated with MSC response. The anti-inflammatory and immunomodulatory capacity of MSC may be paramount in the restoration of localized or systemic conditions for normal healing and tissue regeneration. Allogeneic MSC treatments, categorized as a drug by regulatory agencies, have been widely pursued, but new studies demonstrate the efficacy of autologous MSC therapies, even for individuals affected by a disease state. Safety and regulatory concerns surrounding allogeneic cell preparations make autologous and minimally manipulated cell therapies an attractive option for many regenerative, anti-inflammatory and autoimmune applications.

Experimental & Molecular Medicine (2013) **45,** e54; doi:10.1038/emm.2013.94; published online 15 November 2013

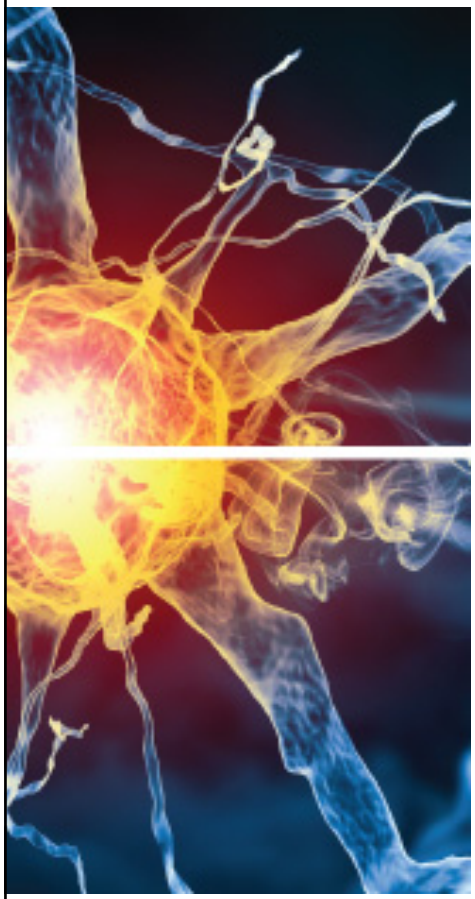
Murphy MB, et al. *Exp Mol Med*. 2013;15;45:e54.



We propose the first study of mesenchymal stem cell therapy for the treatment of refractory depression.

Antidepressant Augmentation Strategies

- Vagus nerve stimulation
- Electroconvulsive therapy
- Lithium
- Thyroid hormone (T3)
- Atypical antipsychotics
- Stimulants
- Buspirone
- Modafinil
- Carbamazepine
- Divalproex sodium
- Lamotrigine
- Dopamine agonists (eg, pramipexole)
- Estrogen replacement
- Buprenorpine
- SAMe
- Inositol
- Phototherapy
- Psychotherapy (time-limited)
- Cognitive-behavioral therapy
- Cognitive-behavioral analysis system
- Interpersonal therapy



Questions & Answers