



# *Advances in Diagnosis, Neurobiology, and Treatment of Mood Disorders*

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# CIAP

CURSO INTERAMERICANO DE ACTUALIZACIÓN EN PSIQUIATRÍA



# The Epidemiology, Differential Diagnosis, and Course of Mood Disorders

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## Disclosures

- **Research/Grants:** National Institutes of Health (NIH)
- **Consultant:** Bracket (Clintara); Fortress Biotech; Gerson Lehrman Group, Inc. (GLG) Healthcare & Biomedical Council; Lundbeck; Mitsubishi Tanabe Pharma Development America; Prismic Pharmaceuticals, Inc.; 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.; Titan Pharmaceuticals, Inc.; Xhale, Inc.
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- **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.

# Audience Response



What percentage of patients with major depression are explicitly recognized as being depressed?

- A. Less than 25%
- B. Between 30% - 40%
- C. Less than 50%
- D. Between 55% - 60%

# Audience Response



Which of the following pairs lists common observer-scored depression rating scales used in mental health?

- A. Hamilton Scale of Depression and Montgomery-Åsberg Depression Rating Scale
- B. Zung Depression Scale and Patient Health Questionnaire-9
- C. Minnesota Multiphasic Personality Inventory and Conners' Rating Scale
- D. Goldberg Depression and Mania Scales and Major Depression Inventory



# Learning Objectives

A decorative graphic in the top right corner of the slide. It features a stylized neuron with a glowing green nucleus and several branching dendrites. The background is a dark teal color with a network of glowing blue lines and dots, suggesting a neural network or data connectivity.

- Define the role of epidemiology and differential diagnosis on the clinical course of mood disorders.
- Translate the latest evidence on the importance of treating patients with mood disorders to remission.
- Implement measurement based care into the clinical management of patients with mood disorders.

*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)*





Canst thou not minister to a mind diseased?  
Pluck from the memory a rooted sorrow,  
Raze out the written troubles of the brain,  
And with some sweet oblivious antidote  
Cleanse the stuffed bosom of that perilous  
Stuff which weighs upon the heart?

**MACBETH**

# 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.

# 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 sadness, 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.

# Major Depressive Disorder: DSM-5 Diagnostic Criteria



Severity/course specifier	Single episode	Recurrent episode*
Mild	296.21 (F32.0)	296.31 (F33.0)
Moderate	296.22 (F32.1)	296.32 (F33.1)
Severe	296.23 (F32.2)	296.33 (F33.2)
With psychotic features	296.24 (F32.3)	296.34 (F33.3)
In partial remission	296.25 (F32.4)	296.35 (F33.4)
In full remission	296.26 (F32.5)	296.36 (F33.5)
Unspecified	296.20 (F32.9)	296.30 (F33.9)

\*For an episode to be considered recurrent there must be an interval of at least 2 consecutive months between separate episodes in which criteria are not met for a major depressive episode.

# 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**

<sup>1</sup>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 the self-critical or pessimistic ruminations seen in MDE. In grief, self-esteem is generally preserved, whereas in MDE 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 the 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

# Major Changes in *DSM-5*

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

Global Burden of Disease and Injury Series

# THE GLOBAL BURDEN OF DISEASE

A comprehensive assessment of mortality and disability from diseases, injuries, and risk factors in 1990 and projected to 2020

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World Health Organization and The World Bank  
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# Depression—A Major Cause of Disability Worldwide

## *DALYs—2000 and 2020*

<u>Rank</u>	<u>2000<sup>1</sup></u>	<u>2020 (Estimated)<sup>2</sup></u>
1	Lower respiratory infections	Ischemic heart disease
2	Perinatal conditions	<b>Unipolar major depression</b>
3	HIV/AIDS	Road traffic accidents
4	<b>Unipolar major depression</b>	Cerebrovascular disease
5	Diarrheal diseases	COPD

DALYs = disability-adjusted life-years.

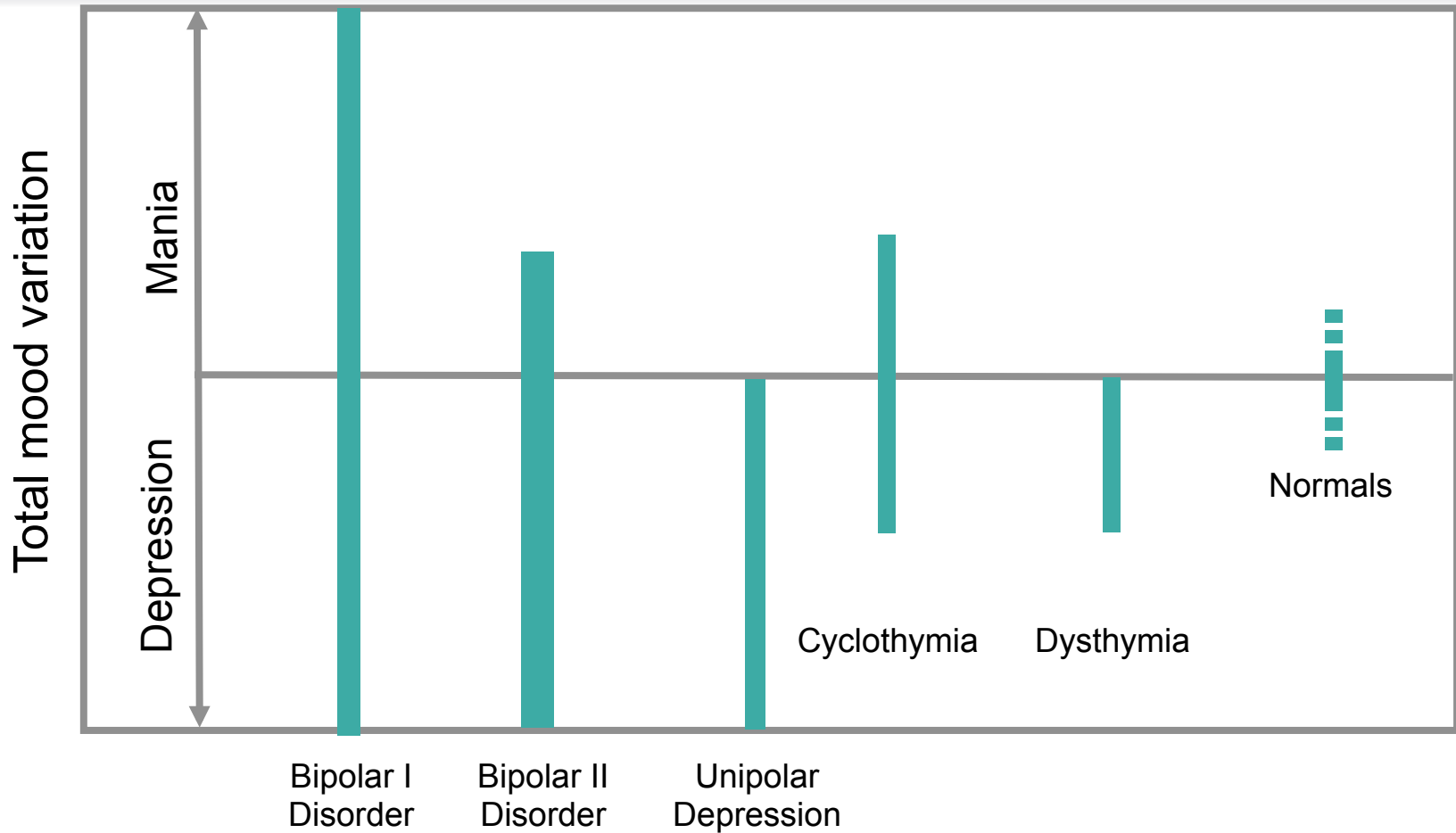
COPD = chronic obstructive pulmonary disease

1. World Health Report 2001. Mental Health: New Understanding, New Hope. Geneva, World Health Organization, 2001.

2. Murray CJL, Lopez AD, eds. The Global Burden of Disease. Boston: Harvard University Press; 1996.



# The Mood-Disorders Spectrum



# Depression is Often Under Diagnosed and Inadequately Treated



- Less than 1/2 of patients with major depression are explicitly recognized as being depressed<sup>1</sup>
- Only about 1/2 of all depressed patients receive some form of therapy for their illness<sup>2</sup>
- Only about 1/4 of depressed patients receive an adequate dose and duration of antidepressant treatment<sup>3</sup>

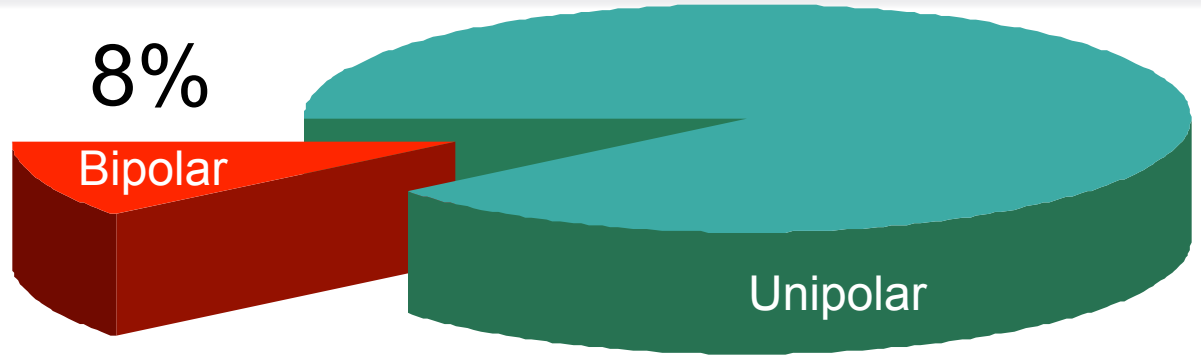
1. AHCPR. Rockville, Md: US Dept of Health and Human Services; 1993. Publication 93-0550.

2. Lepine JP, et al. *Int Clin Psychopharmacol*. 1997;12(1):19-29.

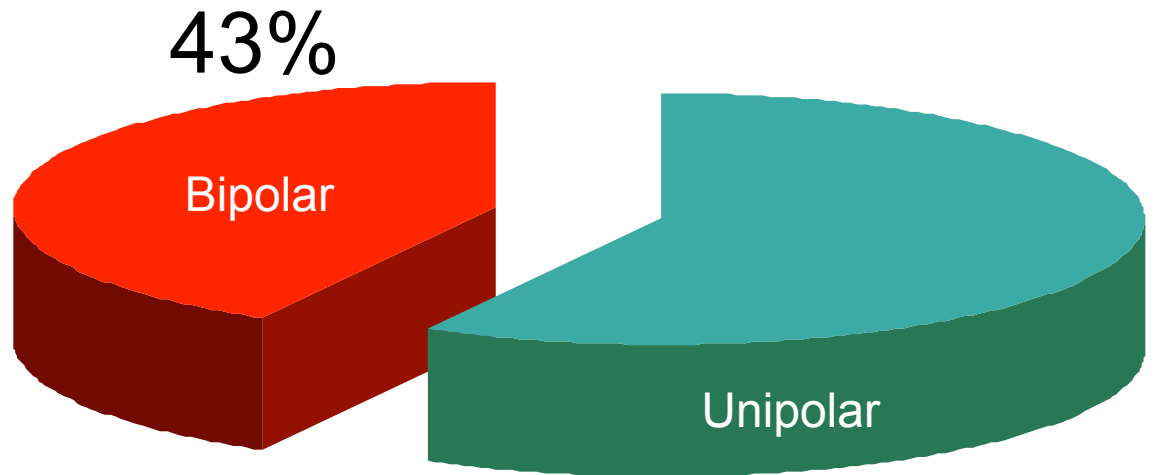
3. Katon W, et al. *Med Care*. 1992;30(1):67-76.

# UP:BP

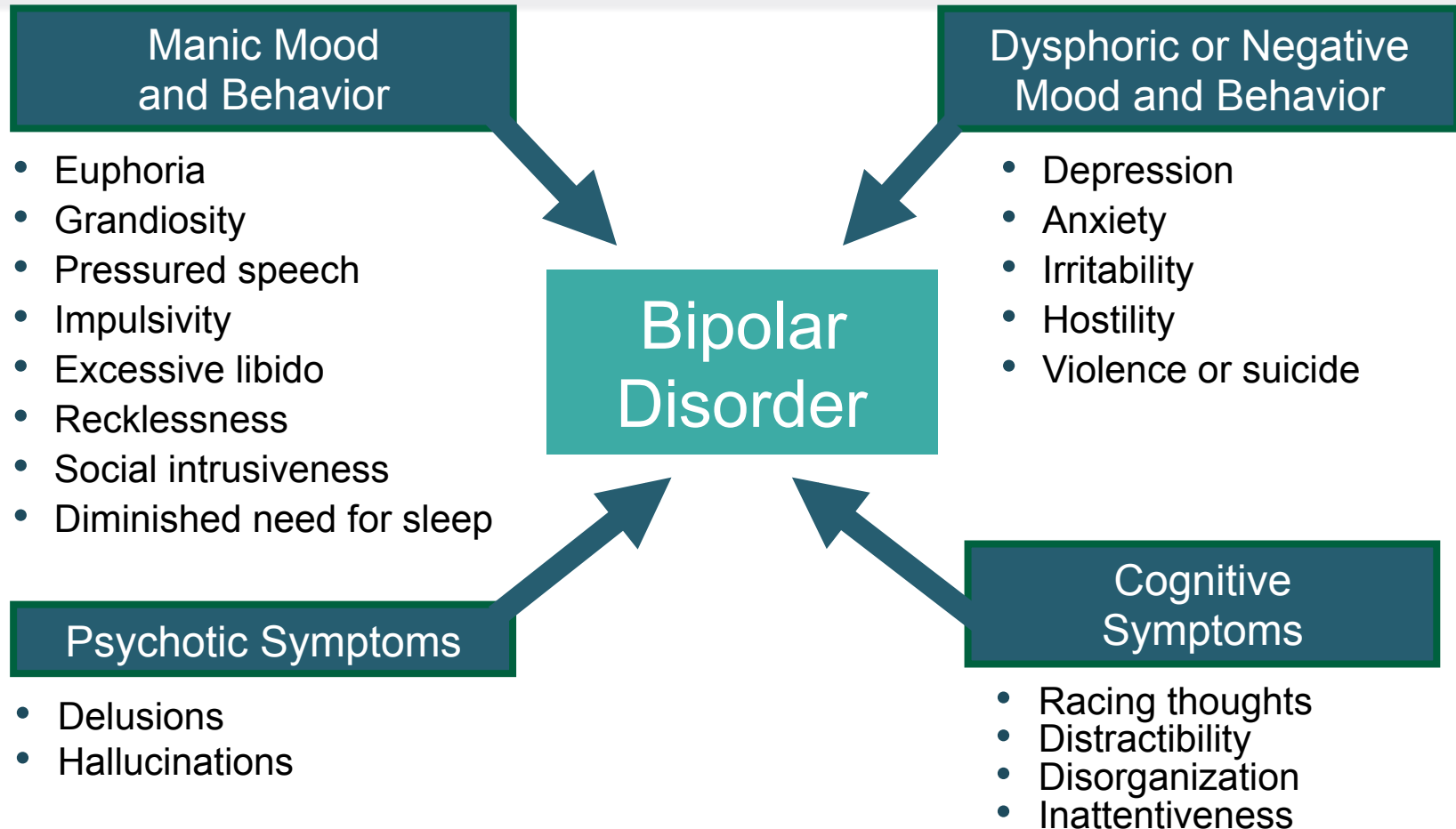
**At Clinic Entry**



**At 30-Yr Follow-up**



# Symptom Domains of Bipolar Disorder



# History of Bipolar Disorder

- **1904:** Kraepelin described symptoms recognized today as bipolar I disorder
- **1949:** Discovery by Cade of lithium's antimanic effects
- **1950s:** Mogens Schou demonstrated short-term and prophylactic efficacy in bipolar I disorder
- **1962:** Bipolar terminology introduced
- **1970s:** Lithium given FDA approval for acute mania and maintenance therapy
- **1980:** Bipolar disorder added to DSM
- **1980s:** The anticonvulsants valproic acid and carbamazepine studied in bipolar disorder
- **1995:** Divalproex given FDA approval for acute mania
- **2000:** Olanzapine given FDA approval for acute mania
- **Present:** Use of a variety of anticonvulsants and atypical antipsychotics in the treatment of bipolar disorder

# Epidemiology of Bipolar Disorder



- Epidemiological Catchment Study<sup>1</sup>  
lifetime prevalence: 1.2%  
(3.3 million people in US)
- National Comorbidity Study<sup>2</sup>  
lifetime prevalence: 1.6%  
(4 million people in US)
- Surgeon General's Report<sup>3</sup>  
lifetime prevalence: 1.7%
- Equal gender distribution<sup>1</sup>

1. Goodwin FK, Jamison KR, 1990.

2. Kessler RC, et al. *Arch Gen Psychiatry*. 1994;51:8-19. PMID: 8279933

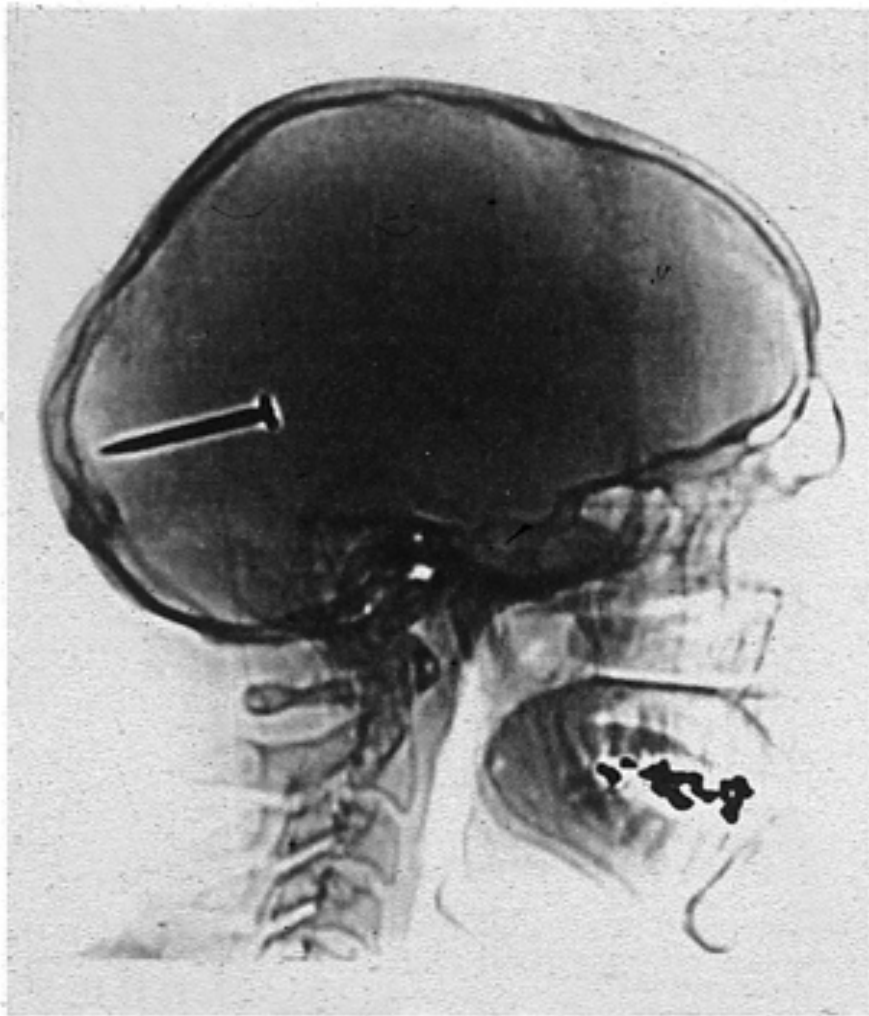
3. Office of the Surgeon General. *Mental Health: A Report of the Surgeon General*. 1999:228.

# Course of Bipolar Illness

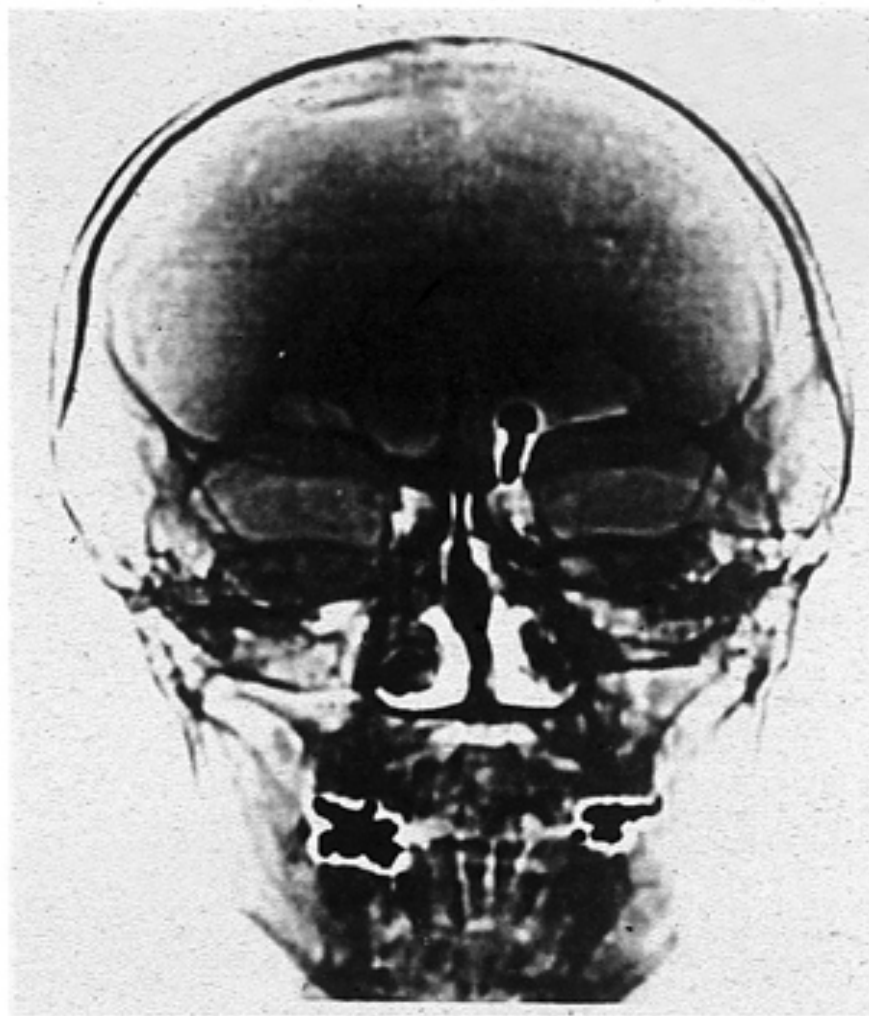


- Peak age of onset: 15 to 24 years<sup>1</sup>
- High recurrence rate: >90% of patients who have a single manic episode will have future episodes<sup>1</sup>
- 10% to 15% of patients will have >10 episodes during their lifetime<sup>1,2</sup>
- Course may vary with clinical subtype of bipolar disorder<sup>3</sup>

1. American Psychiatric Association. *Am J Psychiatry*. 1994;151(suppl 12):1-136.  
2. Goodwin FK, Jamison KR. *Manic-Depressive Illness*. New York, NY: Oxford University Press; 1990.  
3. Müller-Oerlinghausen B, et al. *Lancet*. 2002;359:251-247.



*Nail in the Brain*



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"Scout" films for a computed tomographic scan of the head show a nail in the brain of a stuporous, inebriated man seen in the emergency department. Examination revealed a mild right hemiparesis, which persisted after he became sober and fully articulate. Nine hours after admission, the patient disclosed that during a depressive episode 12 years earlier, he had attempted suicide with a nail gun directed between his eyes. Aside from right-sided facial droop and a slight limp, the patient had been symptom-free since the suicide attempt; he had had neither seizures nor episodes of loss of consciousness.

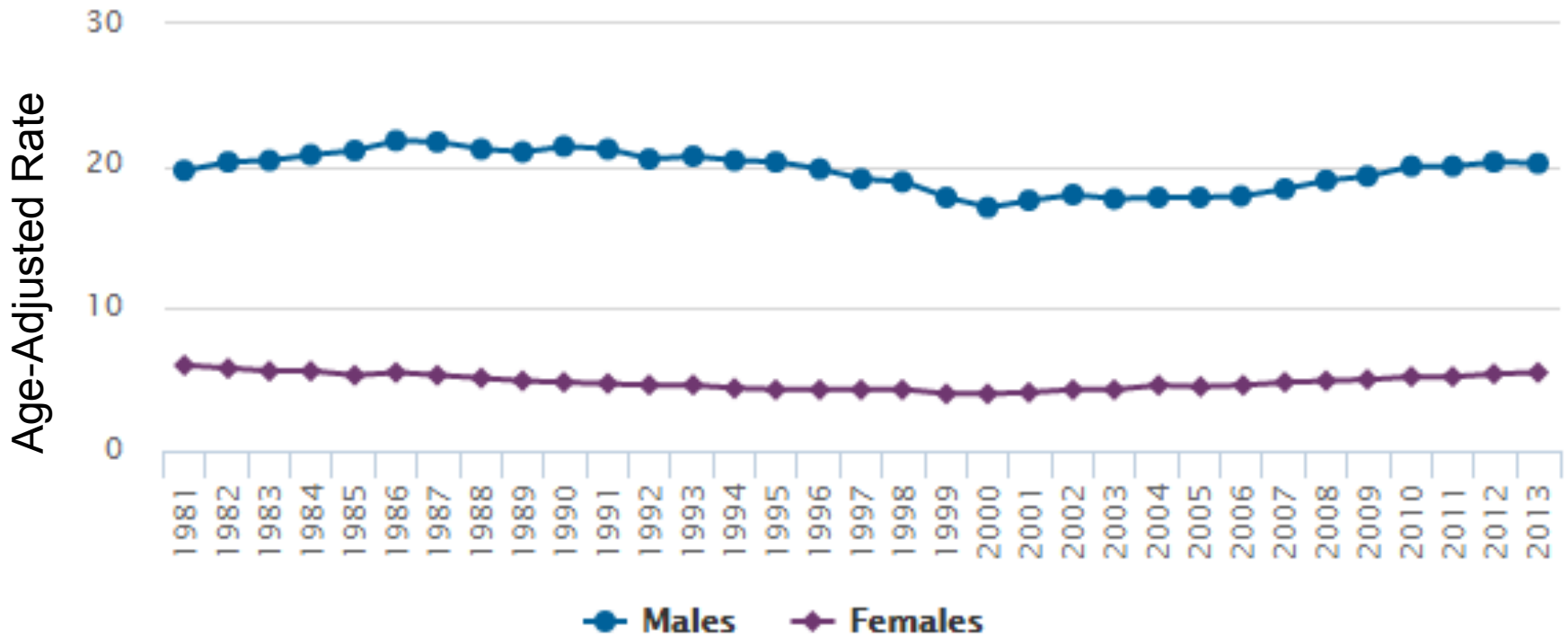


# Facts and Figures...

- The number of suicides in the United States in 2013 was 41,149.
- It exceeds the rate of homicide greatly.
- Suicide is the 10th leading cause of death in the United States.
- Of the 50 states, Florida is # 17 in suicide rate

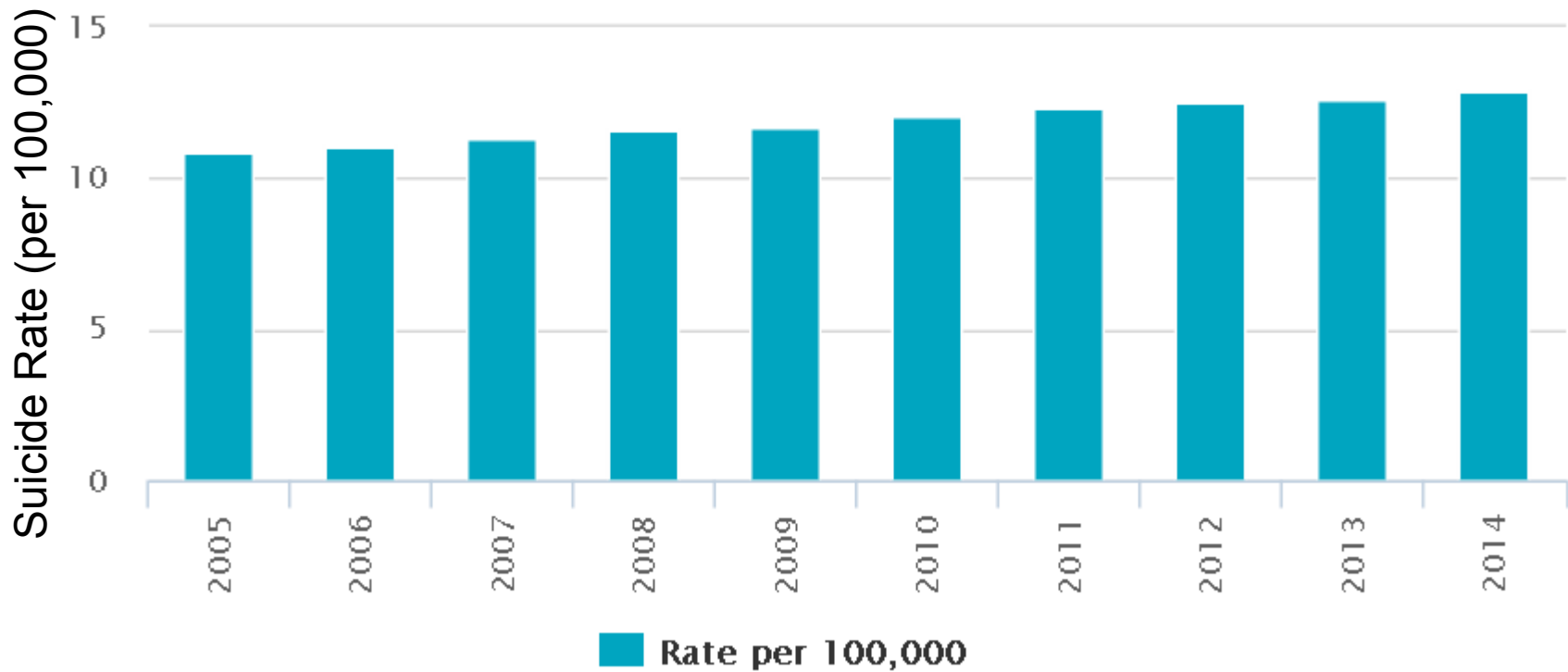
# Facts and Figures...

## Suicide Rates by Sex from 1981 to 2013



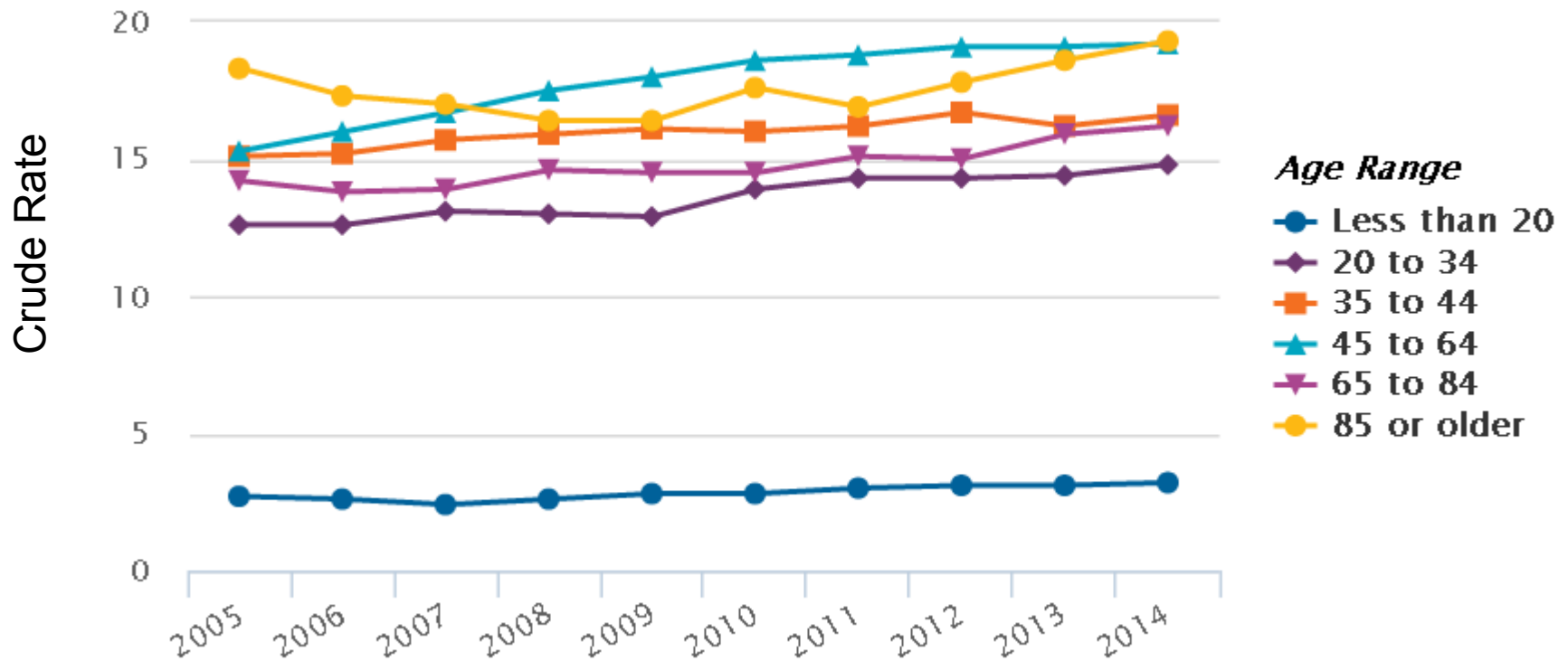
# Facts and Figures...

## Suicide Rates by Year

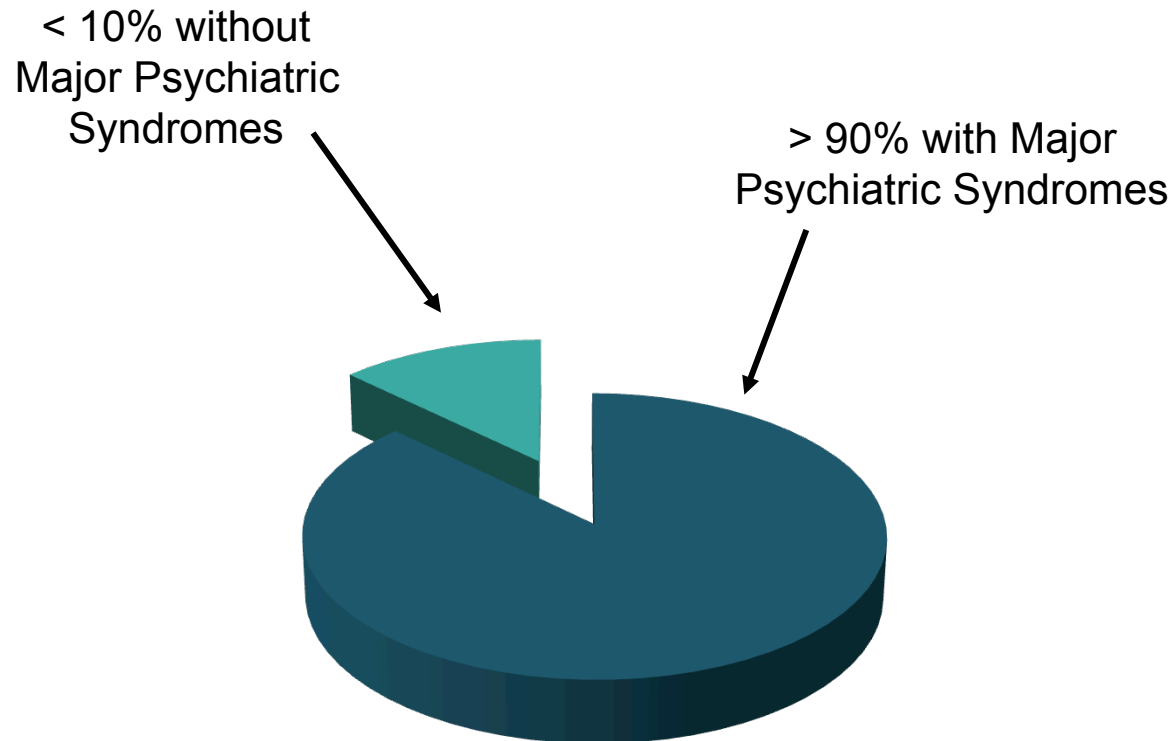


# Facts and Figures...

## Suicide Rates by Age from 2005 to 2014



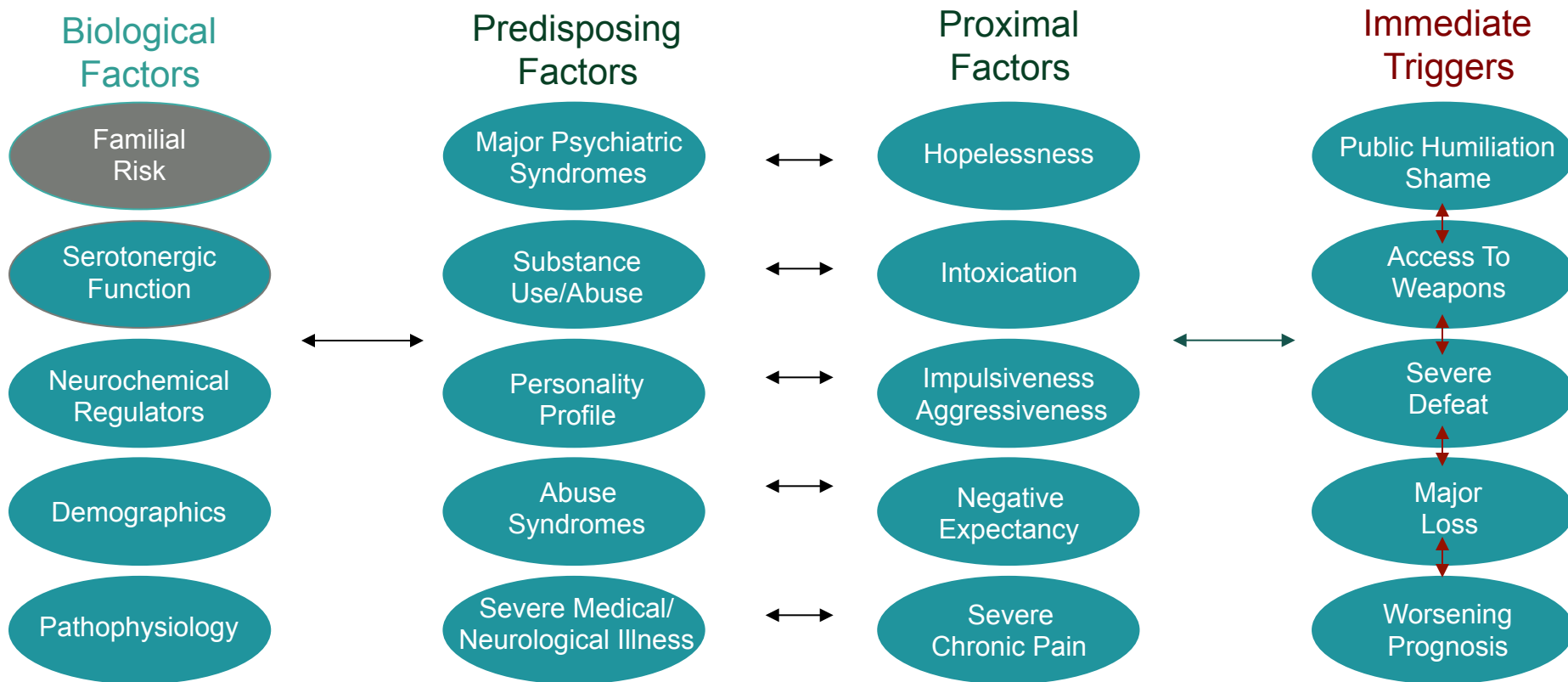
# Suicide Deaths and Major Psychiatric Syndromes



A number of psychological autopsy studies have found that approximately 90% of all completed suicides could be retrospectively diagnosed with a major mental disorder.

# Suicide is an Outcomes that Requires Several Things to go Wrong All at Once

There is No One Cause of Suicide and No Single Type of Suicidal Person

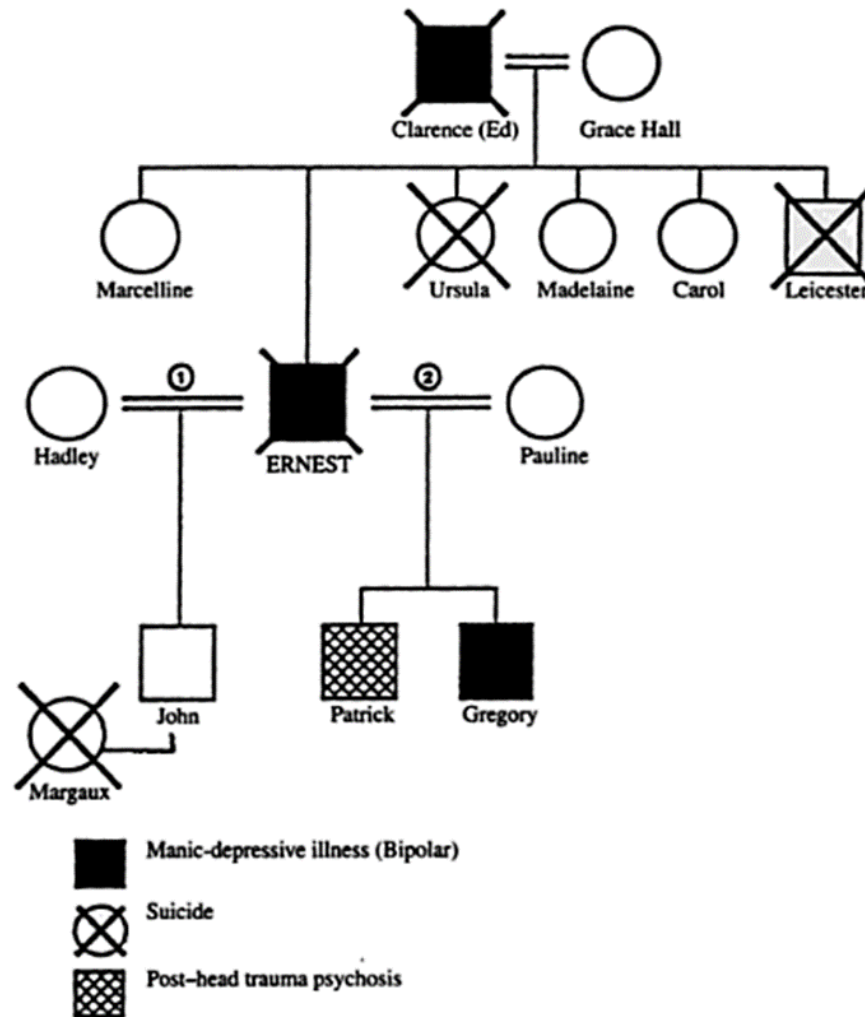


# Triggering Events



- Loss of social support (friends, family)
- Loss of identity/meaning (job, career, financial, legal problems)
- Loss of independence/autonomy, or function (major health problem)
- Acute psychiatric symptoms (psychosis, depression, panic...)
- Loss of hope/Sense of failure
- Date of a significant past interpersonal loss:  
Anniversary reaction

# Ernest Hemingway



Adapted from Jamison (1993:229) Copyright 1993 by Kay Redfield Jamison. Adapted by permission.

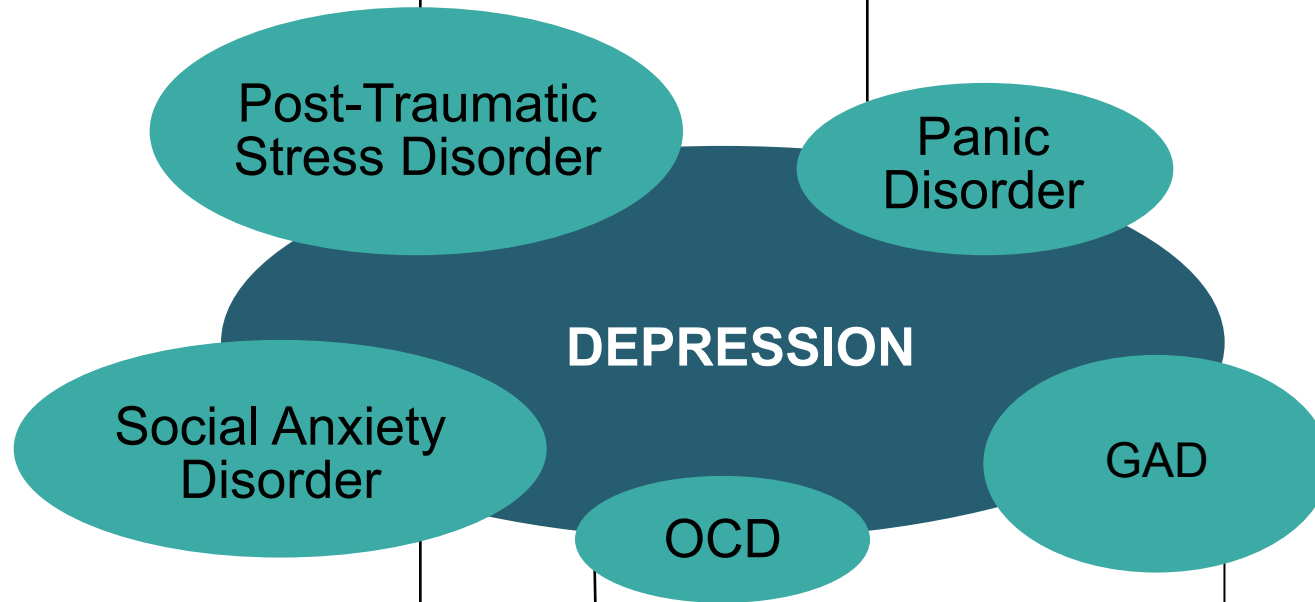


# Comorbidity

## Lifetime comorbidity of mood and anxiety disorders

48% of patients with PTSD<sup>1</sup>

Up to 65% of patients with Panic Disorder<sup>2</sup>



Post-Traumatic  
Stress Disorder

Panic  
Disorder

**DEPRESSION**

Social Anxiety  
Disorder

GAD

OCD

Up to 70% of patients with  
Social Anxiety Disorder<sup>5</sup>

67% of patients with  
Obsessive–Compulsive  
Disorder<sup>4</sup>

42% of patients with  
Generalised Anxiety  
Disorder<sup>3</sup>

# 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)

# 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

# Measuring the Severity of Depression and Remission in Primary Care: Validation of the HAM-D-7 Scale



Roger S. McIntyre, Jakub Z. Konarski,  
Deborah A. Mancini, Kari A. Fulton,  
Sagar V. Parikh, Sophie Grigoriadis,  
Larry A. Grupp, David Bakish, Marie-  
Josee Filteau, Chris Gorman, Charles B.  
Nemeroff, Sidney H. Kennedy

# The 7-item Hamilton Depression Rating Scale

<p><b>1. Depressed mood (sadness, the blues, weepiness)</b></p> <ul style="list-style-type: none"><li>• Have you been feeling down or depressed this past week?</li><li>• How often have you felt this way, and for how long?</li></ul>	<ul style="list-style-type: none"><li><input type="checkbox"/> Absent</li><li><input type="checkbox"/> Indicated only on questioning</li><li><input type="checkbox"/> Spontaneously reported verbally</li><li><input type="checkbox"/> Communicates nonverbally (facial expression, posture, voice, tendency to weep)</li><li><input type="checkbox"/> Patient reports <i>virtually only</i> these feeling states in spontaneous verbal and nonverbal communication</li></ul>
<p><b>2. Feelings of guilt (self-criticism, self-reproach)</b></p> <ul style="list-style-type: none"><li>• In the past week, have you felt guilty about something you've done, or that you've let others down?</li><li>• Do you feel you're being punished by being sick?</li></ul>	<ul style="list-style-type: none"><li><input type="checkbox"/> Absent</li><li><input type="checkbox"/> Self-reproach (letting people down)</li><li><input type="checkbox"/> Ideas of guilt or rumination over past errors or sinful deeds</li><li><input type="checkbox"/> Present illness seen as punishment; delusions of guilt</li><li><input type="checkbox"/> Hears accusatory or denunciatory voices or experiences threatening visual hallucinations</li></ul>
<p><b>3. Interest, pleasure, level of activities (work and activities of daily living)</b></p> <ul style="list-style-type: none"><li>• Are you as productive at work and at home as usual?</li><li>• Have you felt interested in doing things that usually interest you?</li></ul>	<ul style="list-style-type: none"><li><input type="checkbox"/> No difficulty</li><li><input type="checkbox"/> Fatigue, weakness or thoughts of incapacity (related to activities, work or hobbies)</li><li><input type="checkbox"/> Loss of interest in activities (directly reported or indirectly through listlessness, indecision and vacillation)</li><li><input type="checkbox"/> Decrease in actual time spent in activities or in productivity</li><li><input type="checkbox"/> Stopped working because of current illness</li></ul>
<p><b>4. Tension, nervousness (psychological anxiety)</b></p> <ul style="list-style-type: none"><li>• Have you been feeling more tense or nervous than usual this week?</li><li>• Have you been worrying a lot?</li></ul>	<ul style="list-style-type: none"><li><input type="checkbox"/> No difficulty</li><li><input type="checkbox"/> Subjective tension and irritability</li><li><input type="checkbox"/> Worrying about minor matters</li><li><input type="checkbox"/> Apprehensive attitude apparent in face or speech</li><li><input type="checkbox"/> Fears expressed without questioning</li></ul>

# The 7-item Hamilton Depression Rating Scale

<p><b>5. Physical symptoms of anxiety (somatic anxiety)</b></p> <ul style="list-style-type: none"><li>• How much have these things been bothering you in this past week?</li></ul> <p>DON'T RATE IF SYMPTOMS ARE CLEARLY DUE TO MEDICATION:</p> <ul style="list-style-type: none"><li>• In the past week, have you had any of these symptoms?</li></ul> <ul style="list-style-type: none"><li>— Gastrointestinal: dry mouth, gas, indigestion, diarrhea, cramps, belching</li><li>— Cardiovascular: heart palpitations, headaches</li><li>— Respiratory: hyperventilation, sighing</li><li>— Having to urinate frequently</li><li>— Sweating</li></ul>	<ul style="list-style-type: none"><li><input type="checkbox"/> Absent</li><li><input type="checkbox"/> Mild</li><li><input type="checkbox"/> Moderate</li><li><input type="checkbox"/> Severe</li><li><input type="checkbox"/> Incapacitating</li></ul>
<p><b>6. Energy level (somatic symptoms)</b></p> <ul style="list-style-type: none"><li>• How has your energy been this past week?</li><li>• Have you felt tired?</li><li>• Have you had any aches or pains or felt any heaviness in your limbs, back or head?</li></ul>	<ul style="list-style-type: none"><li><input type="checkbox"/> None</li><li><input type="checkbox"/> Heaviness in limbs, back or head (backache, headache, muscle aches; loss of energy and fatigability)</li><li><input type="checkbox"/> Any clear-cut symptom rates 2 points</li></ul>
<p><b>7. Suicide (ideation, thoughts, plans, attempts)</b></p> <ul style="list-style-type: none"><li>• Have you any thoughts life is not worth living or you'd be better off dead?</li><li>• Have you thoughts of hurting or killing yourself?</li><li>• Have you done anything to hurt yourself?</li></ul>	<ul style="list-style-type: none"><li><input type="checkbox"/> Absent</li><li><input type="checkbox"/> Feels life is not worth living</li><li><input type="checkbox"/> Wishes to be dead (or any thoughts of possible death to self)</li><li><input type="checkbox"/> Suicidal ideas or gestures</li><li><input type="checkbox"/> Attempts at suicide (any serious attempt rates 4)</li></ul>
	<p style="text-align: right;"><b>Total score:</b></p>

**Background:** Symptomatic remission is the optimal outcome in depression. **A brief, validated tool for symptom measurement that can indicate when remission has occurred in mental health and primary care settings is unavailable. We evaluated a 7-item abbreviated version (HAMD-7) of the 17-item Hamilton Depression Rating Scale (HAMD-17)** in a randomized controlled clinical trial of patients with major depressive disorder being cared for in primary care settings.

**Methods:** We enrolled **454 patients across 47 primary care settings who met DSM-IV-TR criteria for a major depressive disorder. Of these, 410 patients requiring antidepressant medication were randomized to have their symptoms rated with either HAMD-7 ( n= 205) or HAMD-17 ( n= 205) as the primary measurement tool.** The primary outcome was the proportion of patients who achieved a-priori defined responses to 8 weeks of therapy using each instrument.

**Results:** Of the 205 participants per group, 67% of those evaluated with HAMD-7 were classified as having responded to therapy (defined as a 50% reduction from the pretreatment score), compared with 74% of those evaluated with HAMD-17 (  $p= 0.43$ ). The difference between the groups' changes in scores from baseline (pretreatment) to endpoint was significant (  $p < 0.001$ ), without a main effect of group (  $p= 0.84$ ) or group-by-time (  $p= 0.83$ ) interaction. The HAMD-7 test was brief to administer (e.g., 3–4 min for 85% of the primary care physicians evaluated), which facilitated the efficient and structured evaluation of salient depressive symptoms.

**Interpretation:** **The abbreviated HAMD-7 depression scale is equivalent to the HAMD-17 in assessing remission in patients with a major depressive disorder undergoing drug therapy.**

# Outcomes of Treatment

<b>Outcome</b>	<b>Commonly Accepted Definition</b>
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



# Remission



- Minimal or no symptoms
  - No longer meets diagnostic criteria
- Sustained remission: return to “functional normality”
  - Remission for  $\geq 8$  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.

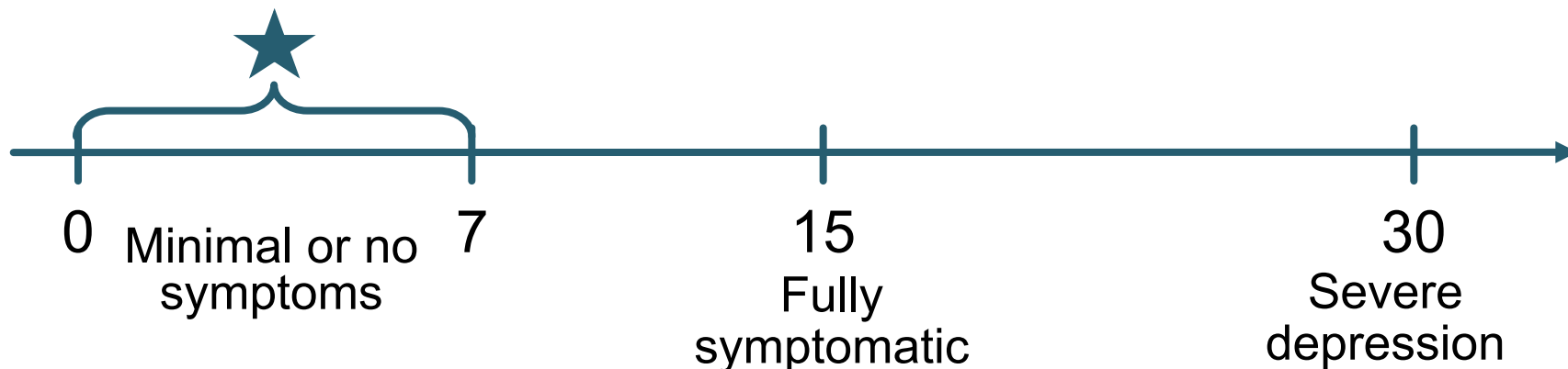
Thase ME, et al. *Br J Psychiatry*. 2001;178:234-241.

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

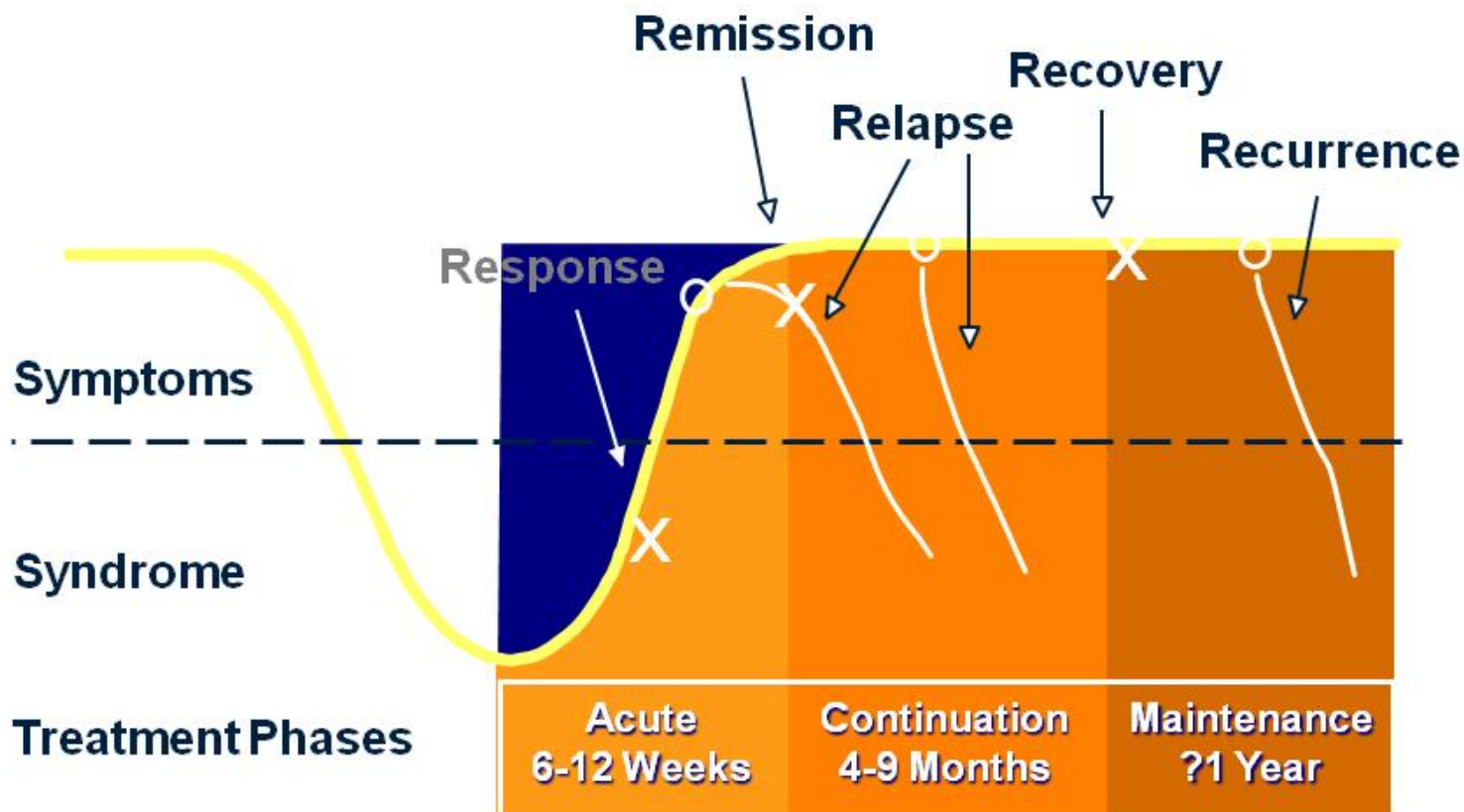
Remission =  $\text{HAM-D}_{17} \leq 7$



Hamilton depression rating scale (HAM-D<sub>17</sub>)

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.

# Outcome of Depression Treatment: The Five Rs



Reproduced with permission from Kupfer DJ. *J Clin Psychiatry*. 1991;52(suppl 5):28-34. Copyright 2002, Physicians Postgraduate Press.

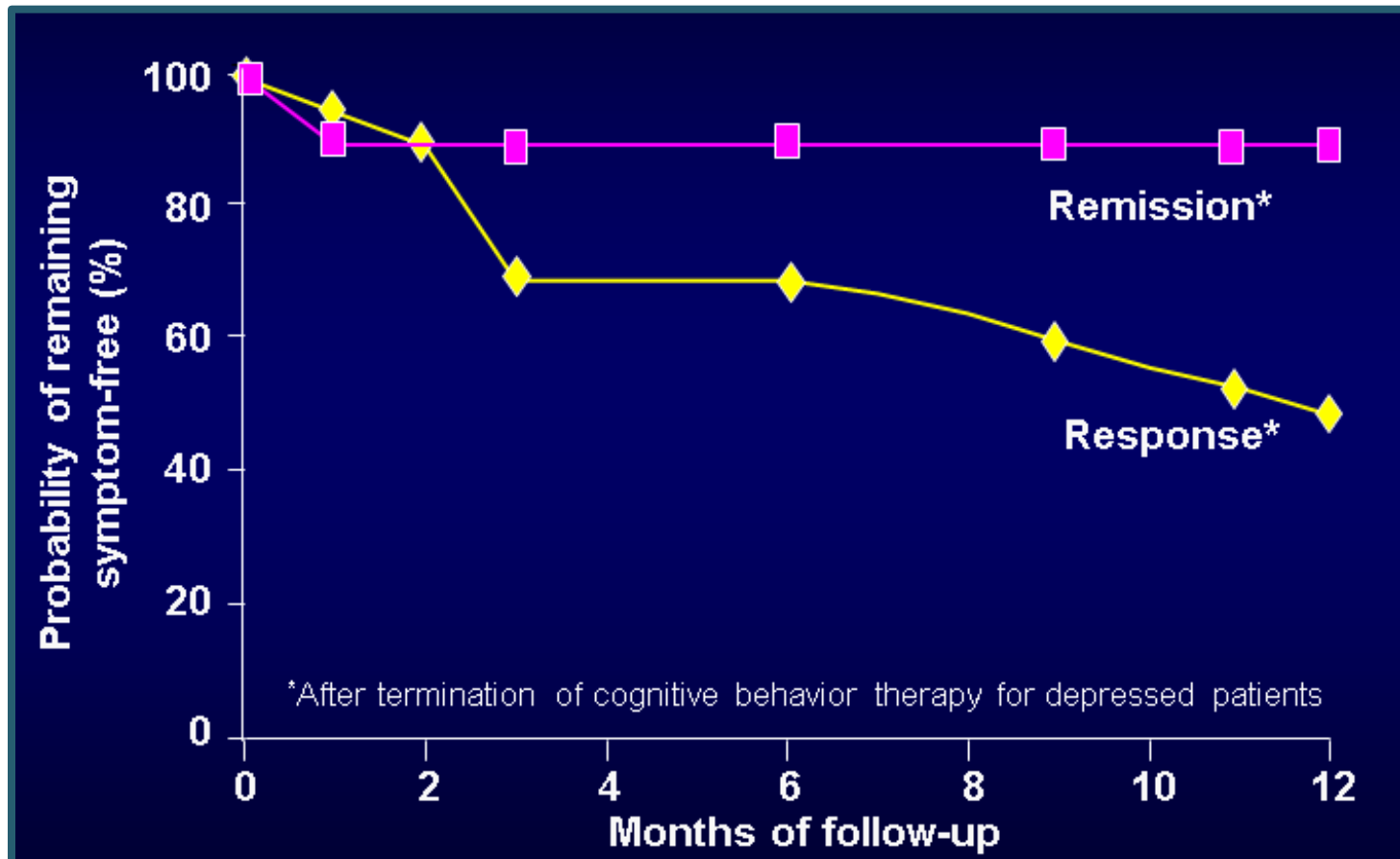
# Potential Consequences of Failing to Achieve Remission



- 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(6):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(3):153-162.; Druss BG, et al. *Am J Psychiatry*. 2001;158(5):731-734.; Frasure-Smith N, et al. *JAMA*. 1993;270(15):1819-1825.; Penninx BW, et al. *Arch Gen Psychiatry*. 2001;58(3):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.

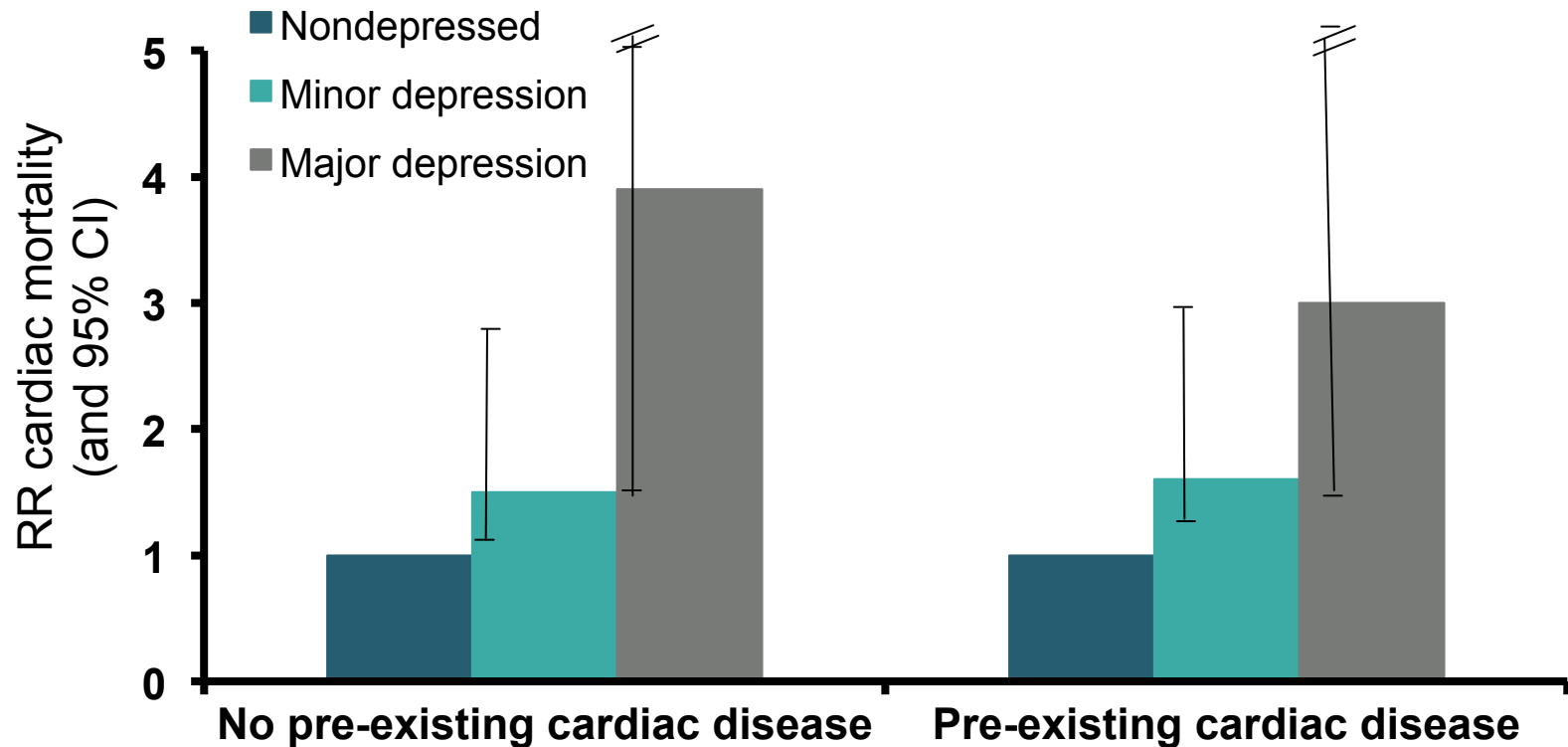
# Depression Worsens Outcomes of Many General Medical Conditions



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

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.

# Depression Increases Risk of Cardiac Mortality



# 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

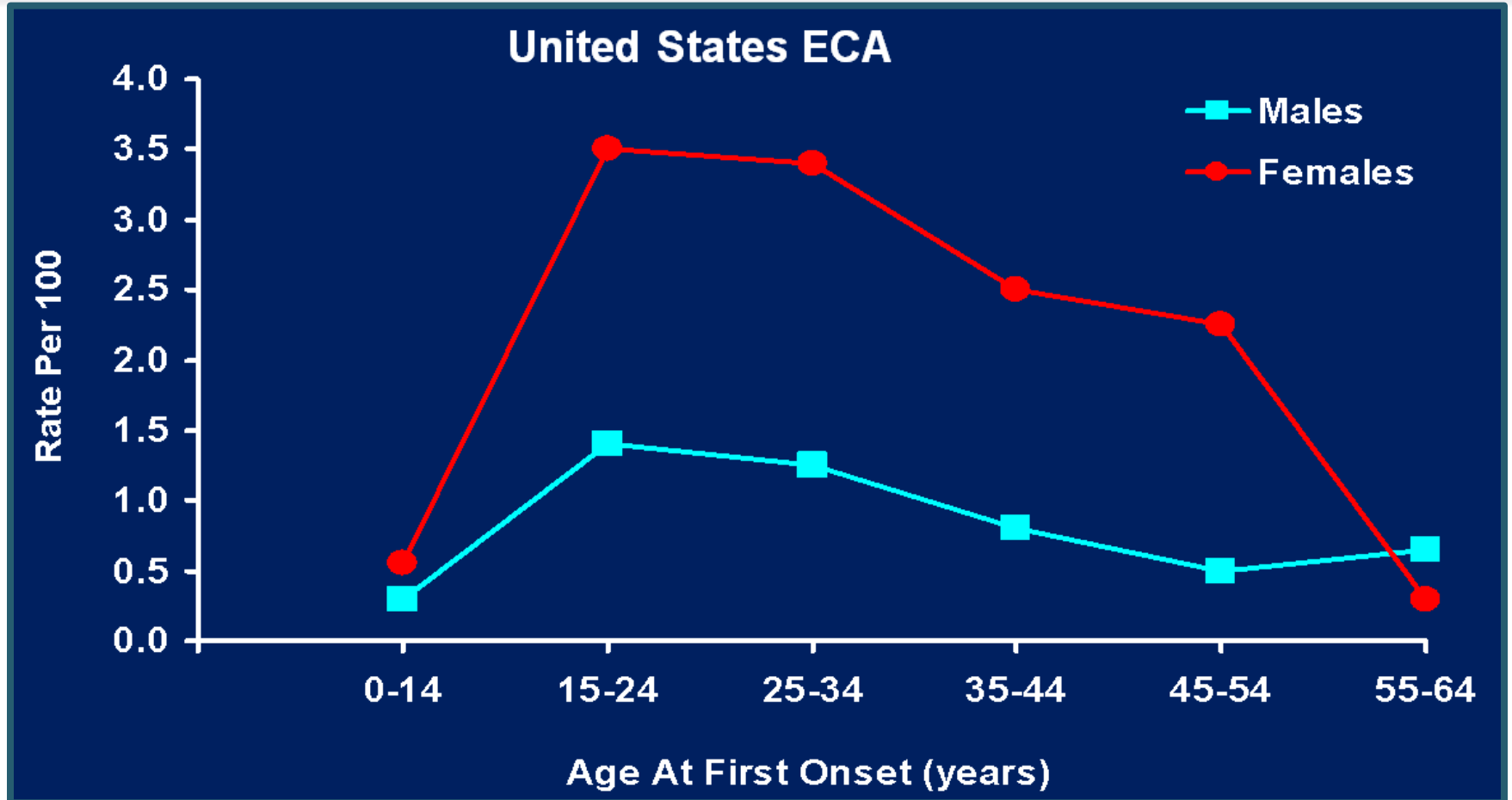
# Increasing the Likelihood of Remission



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

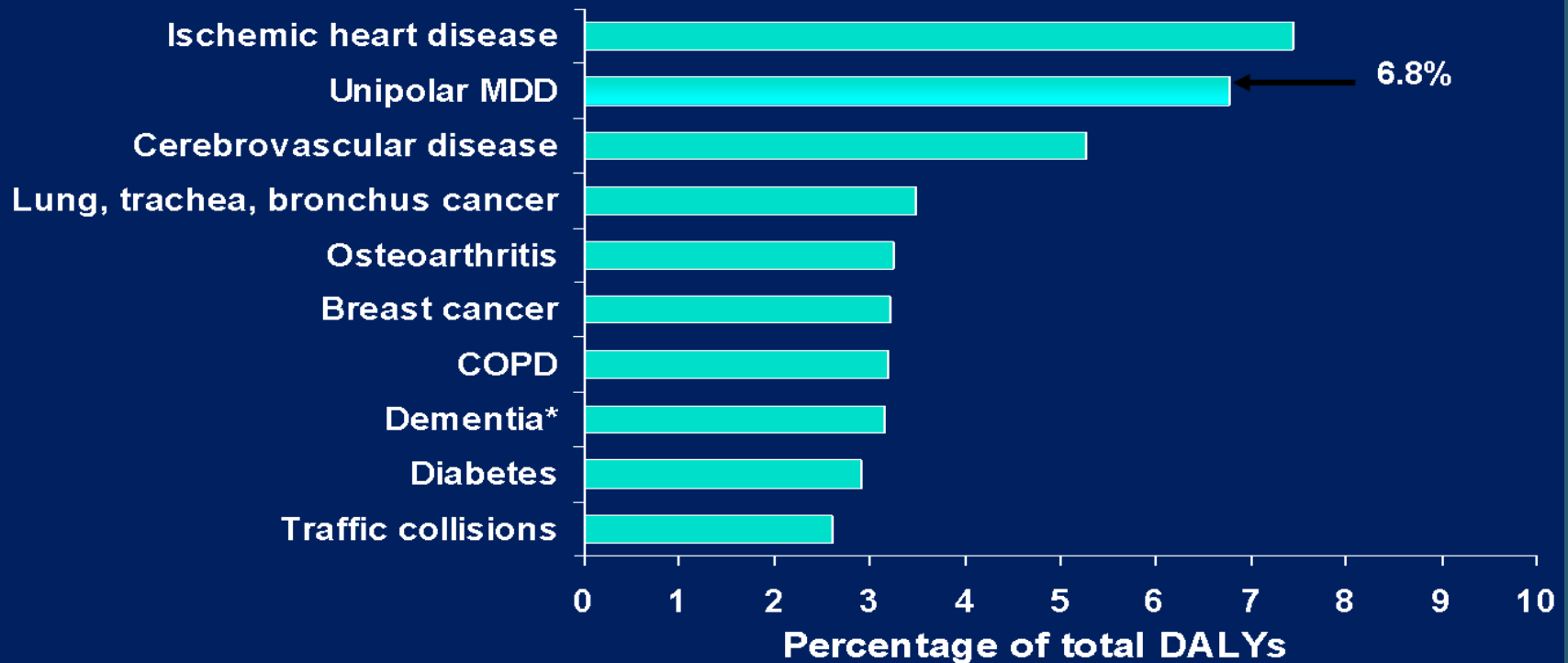
Rush AJ, et al. *J Clin Psychiatry*. 1997;58(suppl 13):14-22.  
Thase ME, et al. *Am J Psychiatry*. 1999;60(suppl 22):3-6.

# Age at First Onset of Major Depression



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

# Leading Causes of Disease Burden for Women in the United States



*MDD = major depressive disorder; COPD = chronic obstructive pulmonary disease; DALY = disability-adjusted life-year.*

*\*Also includes other degenerative and hereditary CNS disorders.*

Michaud CM, et al. *JAMA*. 2001;285(5):535-539. PMID: 11176854.

# Gender Differences in Comorbidities with Depression



## More Common in *Men*

- Alcohol abuse/dependence<sup>1</sup>
- Substance abuse/dependence<sup>1</sup>
  - Stimulant
  - Cannabis
  - Cocaine
  - Hallucinogen

## More Common in *Women*

- Panic disorder<sup>1</sup>
- GAD<sup>1</sup>
- Social phobia<sup>2</sup>
- Bulimia<sup>1,2</sup>
- Thyroid disease<sup>3</sup>
- Migraine headaches<sup>3,4</sup>
- Fibromyalgia<sup>3</sup>
- Chronic fatigue syndrome<sup>3</sup>

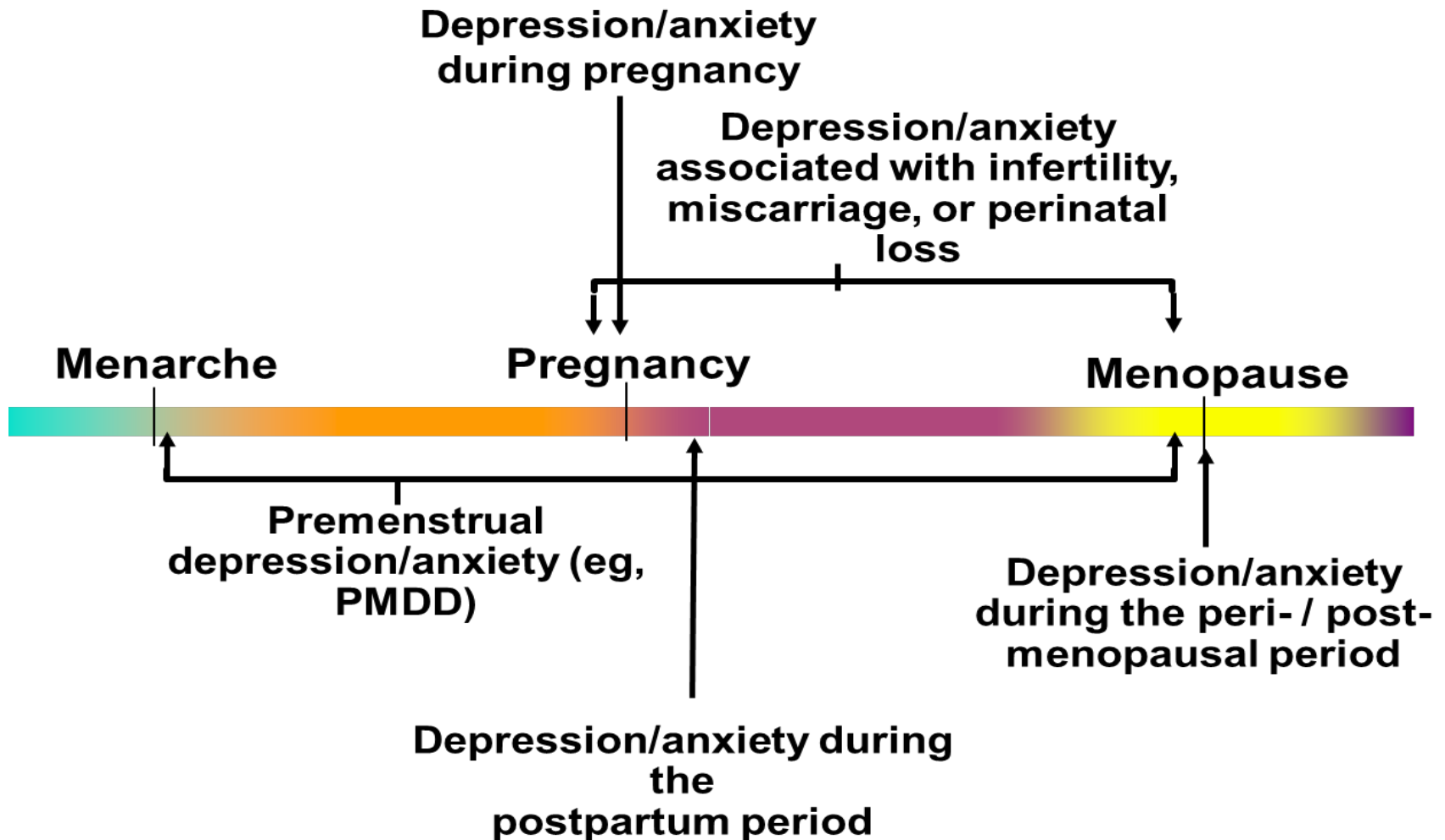
<sup>1</sup>Kornstein S et al. *Presented at American Psychiatric Association; May 4-9, 1996; New York, NY.*

<sup>2</sup>Fava M, et al. *J Affect Disord.* 1996;38(2-3):129-133.

<sup>3</sup>Kornstein SG. *J Clin Psychiatry.* 2002;63:602-609.

<sup>4</sup>Moldin SO, et al. *Psychol Med.* 1993;23(3):755-761.

# Mood and Anxiety Disorders Across the Female Reproductive Cycle





# Postpartum Depression (PPD)



- 10% to 15% in adults\*
- 26% of adolescents†

\*Stowe Z., Nemeroff C. *Am J Obstet Gynecol.* 1995; 173(2): 639-645.

†Troutman and Cutrona. *J Abnorm Psychol.* 1990; 99(1): 69.



# Depressive Disorders After Miscarriage

- >33% severely depressed\*
- ↑ duration of pregnancy = ↑ risk of depressive disorder\*
- Treat ***depressive disorders*** if reaction beyond expected grief and bereavement

\*From Janssen JH, et al. *Am J Psychiatry*. 1996;153(2): 226-230.

# 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. *Eur Neuropsychopharmacol*. 1999;9:S144; Haskett. *Prog Neuropsychopharmacol Biol Psychiatry*. 1987;11(2-3): 129-135.; Johnson SR, et al. *J Reprod Med*. 1988;33(4):340-346.; Ramcharan S, et al. *J Clin Epidemiol*. 1992;45(4): 377-392.; Rivera-Tovar AD, Frank E. *Am J Psychiatry*. 1990;147(12):1634-1636.

# 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:



	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	
<i>Irritability</i>	3																																
	2																																
	1																																
<i>Sudden mood changes</i>	3																																
	2																																
	1																																
<i>Tension</i>	3																																
	2																																
	1																																
<i>Sadness</i>	3																																
	2																																
	1																																
<i>Decreased interest in usual activities</i>	3																																
	2																																
	1																																
<i>Feeling overwhelmed</i>	3																																
	2																																
	1																																
<i>Difficulty concentrating</i>	3																																
	2																																
	1																																
<i>Bloating</i>	3																																
	2																																
	1																																
<i>Breast tenderness</i>	3																																
	2																																
	1																																
<i>Food cravings</i>	3																																
	2																																
	1																																
<i>Lack of energy</i>	3																																
	2																																
	1																																
<i>Change in sleep</i>	3																																
	2																																
	1																																
<i>Relationship problems</i>	3																																
	2																																
	1																																
<i>Other: Clumsy</i>	3																																
	2																																
	1																																

# Depression

## Premenstrual Daily Symptom Chart

Name: Jane Doe Month: July

- Circle the days of your menstrual period in the row labeled Day of Month.
- 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.
- Continue on new page on the first day of the next month.

**Example:**

3	
2	
1	

**none**

3	
2	
1	

**mild**

3	
2	
1	

**moderate**

3	
2	
1	

**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 2 1																																
Sudden mood changes	3 2 1																																
Tension	3 2 1																																
Sadness	3 2 1																																
Decreased interest in usual activities	3 2 1																																
Feeling overwhelmed	3 2 1																																
Difficulty concentrating	3 2 1																																
Bloating	3 2 1																																
Breast tenderness	3 2 1																																
Food cravings	3 2 1																																
Lack of energy	3 2 1																																
Change in sleep	3 2 1																																
Relationship problems	3 2 1																																
Other: <u>Suicidal Thoughts</u>	3 2 1																																

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# Premenstrual Exacerbation (PME)

- Prospective Monthly Charting for accurate Diagnosis
- Worsening of symptoms during luteal phase of menstrual cycle
- Distinction from PMDD is presence of ongoing symptoms during follicular phase of cycle
- Premenstrual exacerbation of symptoms may be seen with many disorders, including
  - Anxiety disorders
  - Eating disorders
  - Substance abuse
  - Seizures
  - Migraines
  - Asthma

PMDD = premenstrual dysphoric disorder.

Endicott J. *J Affect Disord.* 1993;29(2-3):193-200.

# Depressive Disorders in Children

## Prevalence of Depressive Disorders in Children\*

- Preschool children – 0.8%
- School-aged prepubertal children – 2.0%
- Adolescents – 4.5%

## Key Issues†

- Distinguish between depressive disorders and behavioral disorders
- Depressive disorders before age 20 often associated with recurrent mood disorders in adulthood
- 30% of adolescents hospitalized with severe major depressive disorder develop bipolar disorder

\*Weller EB, Weller RA. In: *Psychiatric Disorders in Children and Adolescents*. 1990: 3-20.

†Depression Guideline Panel. *Depression in Primary Care: Volume 1*. Detection and Diagnosis. 1993: 1-65.

Giles DE, Jarrett RB, Biggs MM, et al. *Am J Psychiatry*. 1989; 146: 765-767.

Strober M, Carlson G. *Arch Gen Psychiatry*. 1982; 39(5): 549-555.

# Depressive Disorders in Older Age



- Occur in approximately 15% of population >65 years old
- May mimic dementia
- Comorbid somatic symptoms
- Not due to “old age”
- Require appropriate treatment

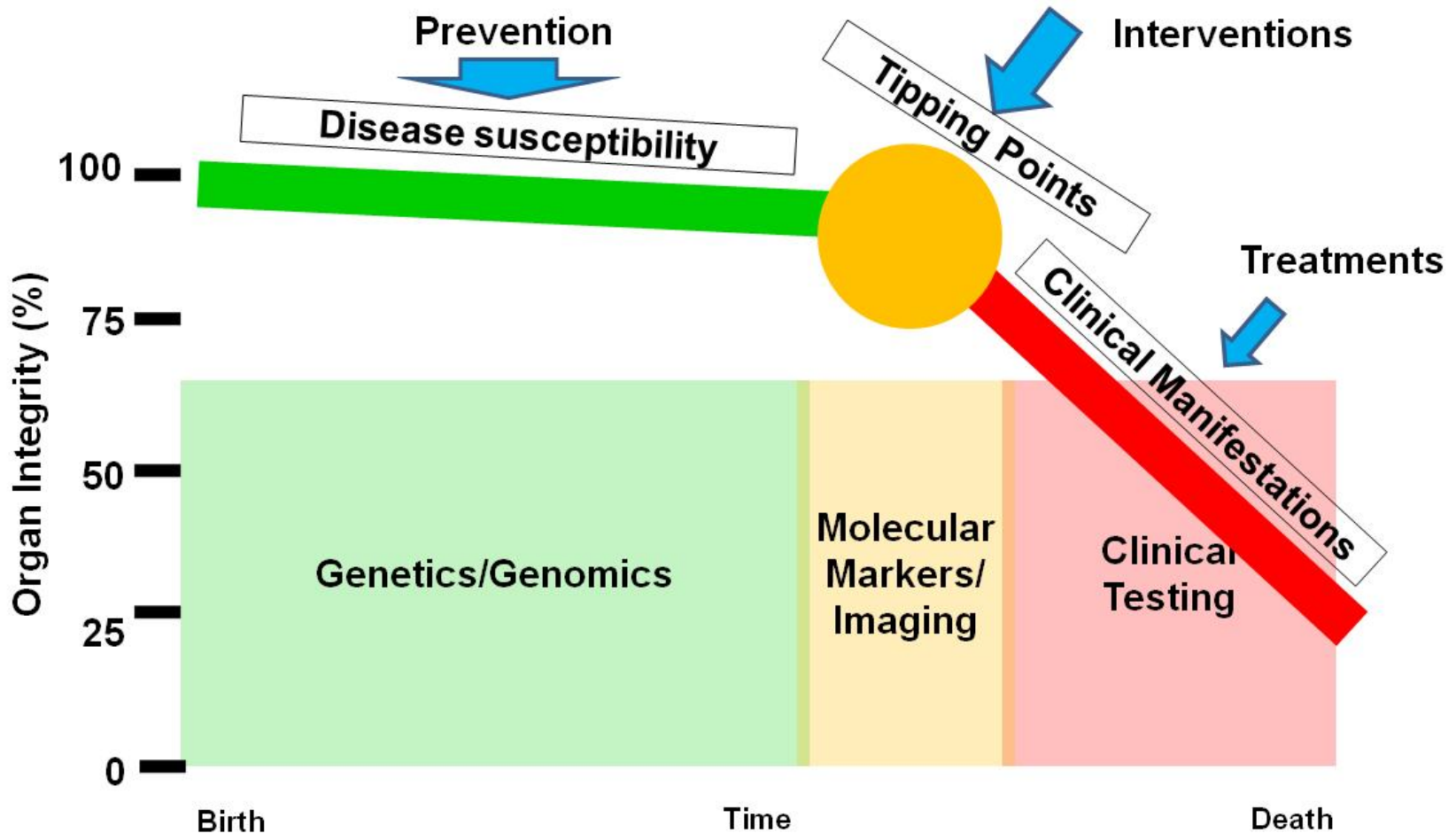
# Treatment Resistance and Depressive Sub-Types



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



# 21st Century Medicine



# Risk Factors for Depressive Disorders

- Family History of depressive disorders
- Prior personal history of a depressive disorder
- Female gender
- Life stressor (eg, bereavement, chronic financial problems)
- Certain personality traits
- Loss of parents at an early age
- Childhood abuse
- Alcohol or drug abuse
- Anxiety disorders
- Neurologic disorders (eg, Parkinson's, Alzheimer's, stroke)
- Primary sleep disorders

# Audience Response



What percentage of patients with major depression are explicitly recognized as being depressed?

- A. Less than 25%
- B. Between 30% - 40%
- C. Less than 50%
- D. Between 55% - 60%

# Audience Response



Which of the following pairs lists common observer-scored depression rating scales used in mental health?

- A. Hamilton Scale of Depression and Montgomery-Åsberg Depression Rating Scale
- B. Zung Depression Scale and Patient Health Questionnaire-9
- C. Minnesota Multiphasic Personality Inventory and Conners' Rating Scale
- D. Goldberg Depression and Mania Scales and Major Depression Inventory



Questions?