MAJOR DEPRESSIVE DISORDER IN PATIENTS:

Goal Maintenance and Remission: Improving Patient Care and Health Outcomes

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**Consultant:** Forest, Lundbeck, Merck, Neos, Otsuka, Rhodes, Shire, Sunovion, Takeda

**Speakers Bureau:** Forest, Lundbeck, Merck, Otsuka, Shire, Takeda
Learning Objectives

- Connect specific risk factors and symptoms with MDD
- Apply clinical guidelines for the optimal management of MDD with a patient
- Select an appropriate therapeutic intervention by balancing the needs of the patient with an adherence strategy
- Provide MDD patients with educational resources to help them better manage their disease

MDD=major depressive disorder
Outline

קרה של תגובה בלתי מלאה
תמיכה, resta או צמצום? מראיון
שימוש בнструמנט של בדיקת הנחתת הענווה: NNT, NNH
Q & A
Prevalence of Depression

Life Time Prevalence of Depression

Depression in Primary Care

箦 ≈10% of patients are depressed

- Rates vary by:
  - Socioeconomic status
  - Presence of comorbidities
- ≈20% of patients with subthreshold symptoms

PCPs Are the Largest Group of Health Care Providers Prescribing Antidepressants

Percentage of Antidepressants Prescribed by Type of Provider: Aug 2006-July 2007

*Includes general practitioners, obstetrician/gynecologists, and pediatricians.

Data from the National Prescription Audit Plus database of IMS.

PCPs=primary care providers; NPs=nurse practitioners; PAs=physician assistants

Major Depressive Disorder Is as Common as Diabetes and Coronary Heart Disease

*12-month prevalence in patients aged 13 years and older.
†Total serum cholesterol levels ≥240 mg/dL.2

The Health-Related Quality of Life Reported by Patients With Major Depression Is Similar to Congestive Heart Failure, Severe Hepatitis, and Patients on Dialysis

BP=bodily pain; CHF=congestive heart failure; Dialysis=chronic hemodialysis; GH=general health perceptions; MH=mental health; PF=physical functioning; RE=role limitations caused by emotional problems; RP=role limitations due to physical limitations; SF=social functioning; SF-36=36-item Short Form Health Survey; VT=vitality

Medical Differential

Medical conditions with symptoms that overlap with MDD and affect mood, sleep, energy, and cognition:

- Metabolic illness (diabetes mellitus, thyroid dysfunction)
- Chronic medical illness (cancer [pancreatic], chronic pain)
- Sleep apnea, chronic cardiovascular, pulmonary, or immune illness
- Dementia, traumatic brain injury
- Drugs and environmental toxins (e.g., lead poisoning)

MDD=major depressive disorder

MDD and Medical Comorbidities Are Hypothesized to Have Interactive Effects on Patient Prognosis

- MDD is associated with an increased risk of medical comorbidities (eg, CVD, metabolic syndrome, hypertension, sleep disorders)\(^1\)-\(^3\)
- The presence of comorbid medical conditions may impact the MDD patient’s response to treatment
  - Increased morbidity/more severe disease\(^4\),\(^5\)
  - Reduced functional status\(^5\)
  - Increased hospitalization risk\(^5\)
  - Increased mortality\(^5\),\(^6\)
  - Reduced adherence with medication or other forms of treatment (eg, rehabilitation)\(^5\),\(^7\)

- Lower response rates\(^8\)
- Lower rates of recovery/remission\(^5\),\(^8\)
- Increased relapse rates\(^5\)

CVD=cardiovascular disease

Symptoms of Depression

- Depressed mood
- Loss of interest or pleasure
- Diminished ability to think/concentrate or indecisiveness
- Significant change in weight or appetite
- Insomnia or hypersomnia
- Psychomotor agitation or retardation
- Fatigue or loss of energy
- Feelings of worthlessness or excessive guilt
- Suicidal ideation
Suicide

- 10th leading case of death in the US\(^1\)

Suicide risk factors include:

- Depression or other mental illness
- Previous suicide attempts
- Family history of suicide
- Alcohol or drug abuse
- Stressful life event or loss

Primary care providers - unique position

- PCPs interact with suicidal patients more than mental health services
- 2 x more suicide victims had contact with PCPs vs mental health services in the month before their death\(^2\)
- 50% had contact one week prior to death

Various Brain Regions Have Been Theorized to Be Associated With Different MDD Symptoms

Concentration Interest/ Pleasure
Psychomotor Fatigue (mental)
Guilt/Suicidality
Worthlessness
Mood
Guilt/Suicidality
Worthlessness/Mood
Sleep
Appetite
Psychomotor Fatigue (physical)
Psychomotor Fatigue/Energy
Pleasure/Interest
Fatigue/Energy

A=amygdala; BF=basal forebrain; Cb=cerebellum; H=hippocampus; Hy=hypothalamus; NA=nucleus accumbens; PFC=prefrontal cortex; S=striatum; SC=spinal cord; T=thalamus

Changes in Brain Structure and Function Are Observed in Some Patients With MDD

Structural changes (see image): In a voxel-based morphometry and MRI study, patients who met *DSM-IV* criteria for recurrent MDD in full remission (n=27) had gray matter volume similar to healthy controls (n=107)\(^1\)

Compared to currently depressed patients (n=58), remittent MDD patients showed increased gray matter in the superior, middle, and inferior frontal gyri on the left side, the left insula, the precuneus bilaterally, the right inferior and superior parietal lobule, the right superior temporal gyrus, and the pregenual and left subgenual anterior cingulate cortex\(^1\)

Functional changes (no image shown): In a separate meta-analysis of 3 PET studies involving 119 MDD patients and 42 healthy controls, differences in circuit connectivity between antidepressant responders and nonresponders were seen in pathways involving the dorsal lateral prefrontal cortex, orbital frontal cortex, hippocampus, anterior thalamus, and the anterior and subgenual cingulate cortexes\(^2\)

MRI=magnetic resonance imaging; PET=positron emission tomography; DSM= *Diagnostic and Statistical Manual of Mental Disorders*;

Case Study: Ashley

At the urging of her friends, Ashley a single parent comes to see her PCP for a routine visit

“I just don’t feel right. Nothing is enjoyable anymore, even my kids. I’m stressed out having headaches and concentration problems everyday, and I need something to help me sleep.”

“I can’t afford to lose another job!”
Top 3: Sleep, Mood, and Concentration
Prevalence of Symptoms During MDD Episodes

13-year NIMH Study of 1,920 Individuals in the Baltimore Epidemiologic Catchment Area

NIMH=National Institute of Mental Health

Ashley (continued)

- Her PCP orders a CBC, CMP, TSH, and schedules a Comprehensive Physical Exam
- While waiting for her Exam, Ashley fills out a PHQ-9 screener

CBC=complete blood count; CMP=comprehensive metabolic panel; TSH=thyroid stimulating hormone; PHQ=Patient Health Questionnaire
**PHQ-9: Nine-Item Patient Health Questionnaire Designed to Help Primary Care Clinicians Diagnose, Grade, and Follow Depression Symptom Severity**

<table>
<thead>
<tr>
<th>Over the past 2 weeks, how often have you been bothered by any of the following problems?</th>
<th>Not at all</th>
<th>Several Days</th>
<th>More Than Half the Days</th>
<th>Nearly Every Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Little interest or pleasure in doing things</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>2. Feeling down, depressed or hopeless</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>3. Trouble falling asleep, staying asleep, or sleeping too much</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>4. Feeling tired or having little energy</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>5. Poor appetite or overeating</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>6. Feeling bad about yourself - or that you’re a failure or have let yourself or your family down</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>7. Trouble concentrating on things, such as reading the newspaper or watching television</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>8. Moving or speaking so slowly that other people could have noticed, or the opposite - being so fidgety or restless that you have been moving around a lot more than usual</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>9. Thoughts that you would be better off dead or of hurting yourself in some way</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

**Column Totals**

Add Totals Together

9 Items

0 to 3 on each item

Max score of 27

**PHQ-9 score ≥ 10:**

Likely major depression

**Depression score ranges:**

- 0 to 4: minimal
- 5 to 9: mild
- 10 to 14: moderate
- 15 to 19: moderately severe
- ≥ 20: severe

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PHQ-9 is 23, including:

- Insomnia
- Fatigue
- Poor concentration
- Anxiety
- Anhedonia
- Feeling Guilty

No suicidal (or homicidal) thoughts noted

Exam and blood work WNL

What would you do next if you were her provider?

Is there any new information from DSM-5 to help guide you with her diagnosis or prognosis?
Major Depressive Disorder: Background

▪ How common is “depression” as a symptom in a general family practice?

▪ What are the changes in DSM-5?

▪ Differential diagnosis with other depressive disorders

▪ Other issues in differential diagnosis and comorbidities
Can use this *specifier* for either major depressive disorder or bipolar disorder

Other *specifiers* that can be used in DSM-5 include with anxious distress, with peripartum onset, with seasonal pattern, etc.

Full criteria are met for an MDE and ≥ 3 of the following manic/hypomanic symptoms are present during the majority of days of the current or most recent episode of depression:

↑ Mood; ↑ Self-esteem or grandiosity; ↑ Talkative/pressured speech; Flight of ideas/racing thoughts; ↑ Energy or goal-directed activity; ↑ Activities with high potential for painful consequences; ↓ Need for sleep (not insomnia)

MDE=major depressive episode


Core Symptoms Versus Symptoms That Can Be Observed in Other States

<table>
<thead>
<tr>
<th>Depressive Sx</th>
<th>Non-Specific Sx</th>
<th>Manic/Hypomanic Sx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depressed</td>
<td>Anxiety</td>
<td>Elevated/expansive mood</td>
</tr>
<tr>
<td>Diminished interest or pleasure</td>
<td>Distractibility</td>
<td>Inflated self-esteem</td>
</tr>
<tr>
<td>Slowed physical and emotional reaction</td>
<td>Irritability</td>
<td>Talkativeness</td>
</tr>
<tr>
<td>Fatigue or loss of energy</td>
<td>Indecision</td>
<td>Flight of ideas</td>
</tr>
<tr>
<td>Recurrent thoughts of death</td>
<td>Insomnia</td>
<td>Increased energy/goal-directed activity</td>
</tr>
<tr>
<td></td>
<td>Agitation</td>
<td>Activities with high potential for painful consequences</td>
</tr>
</tbody>
</table>

Sx=symptoms

Mixed features associated with a major depressive episode have been found to be a significant risk factor for the development of bipolar I or bipolar II disorder. As a result, it is clinically useful to note the presence of this specifier for treatment planning and monitoring of response to treatment.
Major Depressive Disorder: Background

How common is “depression” as a symptom in a general family practice?

What are the changes in DSM-5?

Differential diagnosis with other depressive disorders

Other issues in differential diagnosis and comorbidities
What Is Bipolar Depression?

- Bipolar depression is defined by having MDEs and manic/hypomanic episodes
  - Bipolar type I is when there is a history of manic episodes
  - Bipolar type II is when there is a history of hypomanic episodes but no manic episodes
- On cross-sectional examination, the symptoms of an MDE are the same for both major depressive disorder and bipolar disorder
  - Easy to misdiagnose bipolar depression for major depressive disorder
- Patients with bipolar disorder often don’t have any insight into their symptoms of mania or hypomania and often fail to report them as such
- However, patients with bipolar disorder often have insight into depressive symptoms and come for treatment for that reason

How Common Is Bipolar Depression?

- Bipolar disorder prevalence in the US is ~1% for bipolar I and ~1% for bipolar II
- For bipolar type I, the frequency of MDE to manic/hypomanic episodes is 3:1
- For bipolar type II, the frequency of MDE to hypomanic episodes is 39:1
- In long-term studies, patients with bipolar disorder spend half their life in a symptomatic state, usually depression

Misdiagnosis of Bipolar Disorder and Bipolar Depression Is Common

- Up to 69% of persons with bipolar disorder are misdiagnosed initially
  - Mean 3.5 diagnoses and 4 clinicians before receiving the right diagnosis

- Comorbidity is common and can be confusing
  - 50%-70% have at least one comorbid psychiatric or mental condition
  - Examples include anxiety, substance use, obesity, CVD

- As many as 1 in 5 primary care patients who have clinically significant depressive symptoms and are receiving antidepressant treatment actually have bipolar I or bipolar II disorder
More About Misdiagnosis of Bipolar Disorder

- In a community sample of more than 80,000 patients with positive screens for the Mood Disorder Questionnaire (MDQ)
  - 19.8% indicated that they had previously received a bipolar disorder diagnosis
  - 31.2% reported a previous diagnosis of MDD
  - 49.0% had received neither diagnosis

- Common misdiagnoses received by patients with bipolar disorder:
  - 60% unipolar depression
  - 26% anxiety disorder
  - 18% schizophrenia
  - 17% personality disorder
  - 14% substance use disorder

- 35% of patients with bipolar disorder may wait for 10 years or more for an accurate diagnosis

Consequences of Misdiagnosis

- Incorrect treatment
- Incorrect prognosis
- Poor outcomes

Major concern: antidepressant use

- No antidepressant is approved for the treatment of bipolar depression (except for fluoxetine in combination with olanzapine)
- Antidepressant monotherapy can destabilize a person with bipolar depression
  - Induction of mania or hypomania and/or rapid cycling
- Antidepressants do not confer a treatment advantage for acute or enduring response
- However, never say never

Clues to Avoid Misdiagnosis

*Increase your index of suspicion if…*

- **Family history**
  - Higher rates of psychiatric illness and positive for bipolar disorder
- **Course of illness**
  - Onset before age 25 and high number of recurrent episodes
  - Abrupt onset and end of depressive episode
- **Treatment response**
  - Suboptimal outcome with antidepressants
  - Antidepressant-induced mania or hypomania
- **Mania symptoms**
- **Associated features**
  - Chaotic relationships/job environments
  - Substance use

Mixed Features Specifier

- Can use this *specifier* for either major depressive disorder or bipolar disorder
- Full criteria are met for an MDE *and* ≥ 3 of the following manic/hypomaniac symptoms are present during the majority of days of the current or most recent episode of depression:
  - ↑ Mood; ↑ Self-esteem or grandiosity; ↑ Talkative/pressured speech; Flight of ideas/racing thoughts; ↑ Energy or goal-directed activity; ↑ Activities with high potential for painful consequences; ↓ Need for sleep (not insomnia)

Treatment of major depressive disorder with the mixed features specifier should likely be the same as for treatment of bipolar depression (ie, avoidance of antidepressant monotherapy)

Major Depressive Disorder: Background

- How common is “depression” as a symptom in a general family practice?
- What are the changes in DSM-5?
- Differential diagnosis with other depressive disorders
- Other issues in differential diagnosis and comorbidities
Diagnosis - MDD

- Ashley’s family history, disease course (no prior episodes), negative history for manic symptoms, and lack of associated features is negative for Bipolar disease

- MDQ Bipolar screen is negative

- The PCP tells Ashley that she is depressed and prescribes generic Escitalopram 20 mg. daily
Differential Diagnosis: Unipolar or Bipolar?

1. Family history
   - Higher rates of psychiatric illness
   - Positive for bipolar disorder

2. Course of illness
   - Age of 1st mania/depression
   - Duration of episodes
   - Frequency of episodes
   - Seasonality

3. Treatment response
   - Multiple treatment failures
   - Nonresponse or erratic response to antidepressants

4. Mania symptoms
   - Distractibility
   - Insomnia
   - Grandiosity
   - Flight of ideas
   - Activities
   - Pressured speech
   - Thoughtlessness

5. Associated features
   - Unevenness in intimate relationships
   - Frequent career changes
   - Substance use disorders

Key Elements
Longitudinal Assessment of Bipolar Disorder Is Critical

### Screening Tool: Mood Disorder Questionnaire

**1.** Has there ever been a period of time when you were not your usual self and...

- ...you felt so good or so hyper that other people thought you were not your normal self or you were so hyper that you got into trouble?
- ...you were so irritable that you shouted at people or started fights or arguments?
- ...you felt much more self-confident than usual?
- ...you got much less sleep than usual and found you didn’t really miss it?
- ...you were much more talkative or spoke faster than usual?
- ...thoughts raced through your head or you couldn’t slow your mind down?
- ...you were so easily distracted by things around you that you had trouble concentrating or staying on track?
- ...you had much more energy than usual?
- ...you were much more active or did many more things than usual?
- ...you were much more social or outgoing than usual, for example, you telephoned friends in the middle of the night?
- ...you were much more interested in sex than usual?
- ...you did things that were unusual for you or that other people might have thought were excessive, foolish, or risky?
- ...spending money got you or your family into trouble?

<table>
<thead>
<tr>
<th></th>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**2.** If you checked YES to more than one of the above, have several of these ever happened during the same period of time? Please circle one response only.

<table>
<thead>
<tr>
<th></th>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**3.** How much of a problem did any of these cause you — like being unable to work, having family, money, or legal troubles; getting into arguments or fights? Please circle one response only.

<table>
<thead>
<tr>
<th></th>
<th>No problem</th>
<th>Minor problem</th>
<th>Moderate problem</th>
<th>Serious problem</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Patient screens positive for bipolar disorder if they answer:**

- “YES” to 7 or more of 13 items in section 1
- “YES” for concurrence of symptoms in section 2
- “MODERATE / SERIOUS” life impact in section 3

Diagnosing Unipolar vs Bipolar Disorder: The Critical Role of Outside Observers

Patients Underreport Manic Symptoms

<table>
<thead>
<tr>
<th>Symptom</th>
<th>% Reporting</th>
<th>% Not Reporting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prolonged Sadness</td>
<td>62</td>
<td>21</td>
</tr>
<tr>
<td>Loss of Energy</td>
<td>57</td>
<td>19</td>
</tr>
<tr>
<td>Heightened Mood</td>
<td>37</td>
<td>40</td>
</tr>
<tr>
<td>Increased Activity</td>
<td>35</td>
<td>38</td>
</tr>
</tbody>
</table>

Depression vs Mania

N=600
Ashley Returns 4 Weeks Later

Four weeks later, Ashley returns and states she feels a little better, but is still:

- Anxious, worried and forgetful at work
- Not sleeping well, tired and irritable
- Has a “short fuse” with her kids, friends, co-workers

Repeat PHQ-9 is *still elevated* at 14

*How would you proceed?*
Anxiety in Depressive Patients Results in Worse Outcomes

After 2 years, only 25.1% of patients with comorbid depression/anxiety were disease free, compared with 47.6% and 46%, respectively, of patients with depression only and anxiety only ($P<0.001$).

56.8% of depressed and anxious patients never achieved remission, whereas 24.5% of depressed patients and 41.9% of anxious patients never achieved remission.

-$P$ value based on chi-square statistics for categorical variables and Mann-Whitney nonparametric statistics for continuous variables.

The Generalized Anxiety Disorder-7 Item Scale

GAD-7

<table>
<thead>
<tr>
<th>Over the last 2 weeks, how often have you been bothered by the following problems?</th>
<th>Not at all</th>
<th>Several days</th>
<th>More than half the days</th>
<th>Nearly every day</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Feeling nervous, anxious or on edge</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>2. Not being able to stop or control worrying</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>3. Worrying too much about different things</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>4. Trouble relaxing</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>5. Being so restless that it is hard to sit still</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>6. Becoming easily annoyed or irritable</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>7. Feeling afraid as if something awful might happen</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

(For office coding: Total Score T = 0 + 1 + 2 + 3)

Interpreting the Score:

≥ 10 Possible diagnosis of GAD; confirm by further evaluation
- 5 to 9 = mild anxiety
- 10 to 14 = moderate anxiety
- 15 to 21 = severe anxiety

GAD=generalized anxiety disorder

Developed by Drs. Robert L. Spitzer, Janet B.W. Williams, Kurt Kroenke and colleagues, with an educational grant from Pfizer Inc. No permission required to reproduce, translate, display or distribute.
Irritability Negatively Impacts the Course of MDD in About Half of Patients

Irritable MDD may be associated with:

1. Increased Depressive Severity
2. More Chronic and Severe Course of MDD
3. Poor Impulse Control
4. Higher Rates of Drug Dependence and Anxiety Disorders
5. Greater Psychosocial Impairment
6. Reduced Life Satisfaction

### Screening for Adult ADHD: Self-Report Scale (ASRS-v1.1)

<table>
<thead>
<tr>
<th></th>
<th>Never</th>
<th>Rarely</th>
<th>Sometimes</th>
<th>Often</th>
<th>Very Often</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. How often do you have trouble wrapping up the final details of a project, once the challenging parts have been done?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. How often do you have difficulty getting things in order when you have to do a task that requires organization?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. How often do you have problems remembering appointments or obligations?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. When you have a task that requires a lot of thought, how often do you avoid or delay getting started?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. How often do you fidget or squirm with your hands or feet when you have to sit down for a long time?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. How often do you feel overly active and compelled to do things, like you were driven by a motor?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

If 4 or more marks appear in the darkly shaded boxes, the patient has symptoms highly consistent with Adult ADHD and further investigation is warranted.

US Prevalence of Adult ADHD Compared With Other Psychiatric Disorders

- MDD: 7%
- Adult ADHD: 4.45%
- GAD: 3%
- Bipolar disorder: 2.5%
- Schizophrenia: 1%

ADHD=attention-deficit/hyperactivity disorder; GAD=generalized anxiety disorder; MDD=major depressive disorder

Comorbid Disorders in Adults With and Without ADHD

National Comorbidity Survey Replication (United States)

Prevalence (%)

- Mood Disorder
- Anxiety Disorder
- Substance Abuse Disorder
- Impulse Control Disorder

Patients With Psychiatric Comorbidities: What to Treat First

- Substance use disorder
- Severe mood disorders
- Severe anxiety disorders
- ADHD

Treat other severe psychiatric disorders (eg, Bipolar, MDD, Substance Use, Anxiety Disorder) before treating adult ADHD

If the patient has mild depressive and/or anxiety symptoms, then ADHD can be treated first while monitoring the mood/anxiety symptoms

Question

Spotlight Ashley states she is taking her SSRI daily

Spotlight Her GAD-7 and ADHD screener are both negative, as is her CAGE Questionnaire for substance abuse

Spotlight She is on the maximum dosage of escitalopram (20 mg daily)

If you were her provider, what would you do next?

ADHD=attention-deficient/hyperactivity disorder; GAD=generalized anxiety disorder 7-item scale; SSRI=selective serotonin reuptake inhibitor
Outline

❖ Major Depressive Disorder: Background
❖ A Case of Incomplete Response
❖ **Switch, Stay, or Augment? A Consultation**
❖ Using the Tools of Evidence-Based Medicine: NNT, NNH
❖ Q & A
Switch, Stay, or Augment?  
A Consultation

❖ Was adherence an issue? Identify root causes
❖ If adherent, was efficacy the major problem? Need for remission rather than mere response; need to eliminate residual symptoms
❖ If adherent, was dose appropriate? Was it titrated adequately? Were there drug-drug interactions?
❖ Switch to another antidepressant? Are we throwing the baby out with the bathwater?
❖ Augment with a second-generation antipsychotic? Are we making treatment too complex and perhaps too expensive?
# Root Causes of Partial or Non-Adherence

*Varies From Patient to Patient*

<table>
<thead>
<tr>
<th>Patient-related¹</th>
<th>Environment/ Relationship-related¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Poor insight</td>
<td>• Lack of family/social support</td>
</tr>
<tr>
<td>• Negative attitude toward medication</td>
<td>• Problems with therapeutic alliance</td>
</tr>
<tr>
<td>• Prior non-adherence</td>
<td>• Practical problems</td>
</tr>
<tr>
<td>• Substance abuse</td>
<td>(financial, transportation, etc.)</td>
</tr>
<tr>
<td>• Cognitive impairment</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment-related¹</th>
<th>Societal-related²</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Side effects</td>
<td>• Stigma attached to illness</td>
</tr>
<tr>
<td>• Lack of efficacy/ continued symptoms</td>
<td>• Stigma caused by medication side effects (eg, sexual AEs)</td>
</tr>
</tbody>
</table>

The Case for Remission and for the Elimination of Residual Symptoms
*Mood, Physical, and Cognitive Symptoms*

- Residual symptoms significantly inhibit functionality and increase the risk of relapse and recurrence.
- Most common residual symptoms are fatigue, sleep problems, and cognitive dysfunction.
- Treating these symptoms as target symptoms from baseline increases the patient’s chances of an asymptomatic remission and can improve patients’ functional recovery at work, home, and socially.

Switch, Stay, or Augment?
A Consultation

✶ How to discuss treatment options and adherence

✶ How to inform patient and families about patient education resources
Patient Education Resources

- www.YouAndDepression.net
- National Library of Medicine
- National Institute of Mental Health
  - www.nlm.nih.gov
- American Psychiatric Association
  - www.psych.org
Outline

- Major Depressive Disorder: Background
- A Case of Incomplete Response
- Switch, Stay, or Augment? A Consultation
- Using the Tools of Evidence-Based Medicine: NNT, NNH
- Q & A
The Difference in Remission for a Major Depressive Episode at 6 Weeks for Drug A Versus Drug B Is Highly Statistically Significant.

Percent of Patients in Remission at 6 Weeks

Drug A: 31%

Drug B: 35%

P<0.0001

The Difference in Remission for a Major Depressive Episode at 6 Weeks for Drug A Versus Drug B Is Highly Statistically Significant, but Clinically Irrelevant.
The Difference in Remission for a Major Depressive Episode at 6 Weeks for Drug A Versus Drug B Is Highly Statistically Significant, but Clinically Irrelevant

How irrelevant is this? Can we quantify this?

Percent of Patients in Remission at 6 Weeks

Drug A

Drug B

P<0.0001

What Is Evidence-Based Medicine?

Clinical Judgment

Relevant Scientific Evidence

Patients’ Values and Preferences

EBM

Evidence-Based Medicine Is About Benefit and Risk: Key Concepts

- $P$ value and statistical significance
- Effect size and clinical significance
Concepts Related to Benefit/Risk: 

\( P \) Value

- This gives an indication of how strong the likelihood is that any difference is NOT due to chance.

- The smaller the \( P \) value, the more convinced you are that something is going on that is not just random.

- This does not state anything about the size or the importance of the nonrandom effect.

- \( P \) value is not the same as effect size.

Concepts Related to Benefit/Risk: Effect Size

- This gives an indication of how big the treatment effect is in terms of reduction in symptoms, or other outcome of interest.

- The greater the effect size, the more convinced you are that the intervention will have a clinically important impact.

- This does not state anything about statistical significance of the observed outcome in a clinical trial.

- Effect size is not the same as $P$ value.

Concepts Related to Benefit/Risk: Effect Size—Number Needed to Treat

- NNT is one measure of effect size
- It is independent of $P$ value and does not say anything about the likelihood of the difference between treatments being due to chance alone
- Helps you judge the clinical significance of a statistically significant result

NNT=number needed to treat

Number Needed to Treat

How many patients would you need to treat with drug A instead of drug B before you would encounter one additional responder, or one additional adverse outcome?

The smaller the NNT, the larger the differences between the 2 drugs, ie, larger numbers mean more patients needed to treat to see the difference in effect.

NNT=number needed to treat

Calculating NNT Is Easy

What is the NNT for an outcome for Drug A vs Drug B?

\[ f_A = \text{frequency of outcome for Drug A} \]
\[ f_B = \text{frequency of outcome for Drug B} \]

Attributable Risk (AR) = \( f_A - f_B \)

NNT = \( \frac{1}{AR} \)

By convention, when not presenting fractions, we round up
the NNT to the next *higher* whole number

For example, Drug A results in remission 50% of the time,
but Drug B results in remission 20% of the time.

\[ \text{NNT} = \frac{1}{[0.50-0.20]} = \frac{1}{0.30} = 3.33 \rightarrow \text{Round up to 4} \]
The Difference in Remission for a Major Depressive Episode at 6 Weeks for Drug A Versus Drug B Is Highly Statistically Significant, but Clinically Irrelevant

How irrelevant is this? Can we quantify this?

Percent of Patients in Remission at 6 Weeks

<table>
<thead>
<tr>
<th>Drug</th>
<th>Percent of Patients in Remission at 6 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug A</td>
<td>P&lt;0.0001</td>
</tr>
<tr>
<td>Drug B</td>
<td></td>
</tr>
</tbody>
</table>

The Difference in Remission for a Major Depressive Episode at 6 Weeks for Drug A Versus Drug B Is Highly Statistically Significant, but Clinically Irrelevant

\[ NNT = \frac{1}{0.315 - 0.305} = \frac{1}{0.01} = 100 \]

NNT = number needed to treat

What Is Number Needed to Harm?

- We would use NNH when referring to an outcome we are trying to avoid.
- It is calculated the same way as NNT.

NNH = number needed to harm; NNT = number needed to treat

NNT and NNH

An intervention should have a small NNT to show the benefit is large and a large NNH to show the risk of harm is small.
What Is a Clinically Important Number Needed to Treat?

- A small NNT of 2 would be a hugely important difference
- Single-digit NNTs are important enough to notice in day-to-day clinical practice
- A large NNT of 100 or more means that there is little difference between choosing drug A or drug B for the outcome measured
- Some NNTs may be clinically important, even if they are relatively large, for example, when the outcome is death
- Some NNTs may be clinically irrelevant, even if they are relatively small, for example, when the outcome is a mild dry mouth

NNT=number needed to treat

## NNT: Examples in Medicine

<table>
<thead>
<tr>
<th>Condition</th>
<th>Treatment</th>
<th>Comparator</th>
<th>Duration of Intervention</th>
<th>Outcome</th>
<th>NNT (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peptic ulcer</td>
<td>Triple therapy</td>
<td>Histamine antagonist</td>
<td>6–10 weeks</td>
<td>Ulcers healed at 6–10 weeks</td>
<td>5</td>
</tr>
<tr>
<td>Venous thromboembolism</td>
<td>Graduated compression stockings</td>
<td>No stockings</td>
<td>Not stated</td>
<td>Episodes of venous thromboembolism</td>
<td>9</td>
</tr>
<tr>
<td>Anticipated preterm delivery</td>
<td>Corticosteroids</td>
<td>No treatment</td>
<td>Before delivery</td>
<td>Risk of fetal RDS</td>
<td>11</td>
</tr>
<tr>
<td>Hypertension in the elderly</td>
<td>Drug treatments</td>
<td>No treatment</td>
<td>&gt; 1 year</td>
<td>Overall prevention of CV event &gt; 5 years</td>
<td>18</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>Aspirin alone</td>
<td>No treatment</td>
<td>1 month</td>
<td>Prevention of one 5-week vascular death</td>
<td>40</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>Thrombolytic therapy 5 hours earlier</td>
<td>Later treatment</td>
<td>Appropriate period</td>
<td>Prevention of one 5-week vascular death</td>
<td>100</td>
</tr>
</tbody>
</table>

CI=confidence interval; CV=cardiovascular; NNT=number needed to treat

http://www.medicine.ox.ac.uk/bandolier/band50/b50-8.html
## NNT: Examples in Psychiatry

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Treatment Comparison</th>
<th>Outcome Measure</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agitation</td>
<td>IM antipsychotics or IM lorazepam vs placebo</td>
<td>40% Reduction in PANSS-EC at 2 hours</td>
<td>2-5</td>
</tr>
<tr>
<td>Acute mania</td>
<td>Valproate or lithium vs placebo</td>
<td>50% Reduction in SADS-M</td>
<td>5</td>
</tr>
<tr>
<td>Bipolar disorder</td>
<td>Lithium vs placebo</td>
<td>Relapse</td>
<td>3</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>Antipsychotic vs placebo</td>
<td>40% Reduction in BPRS or “much improved” CGI scale</td>
<td>2-5</td>
</tr>
<tr>
<td>Panic disorder</td>
<td>SSRI vs placebo</td>
<td>Panic free</td>
<td>3-6</td>
</tr>
<tr>
<td>Obsessive-compulsive disorder</td>
<td>SSRI vs placebo</td>
<td>35% Reduction in Y-BOCS</td>
<td>4-5</td>
</tr>
<tr>
<td>Bulimia nervosa</td>
<td>Antidepressants vs placebo</td>
<td>Remission</td>
<td>9</td>
</tr>
</tbody>
</table>

BPRS=Brief Psychiatric Rating Scale; CGI= Clinical Global Impression Scale; IM=intramuscular; NNT=number needed to treat; PANSS-EC=Positive And Negative Syndrome Scale Excited Component; SADS-M=Schizophrenia and Affective Disorders Scale, Manic Component; SSRI=selective serotonin reuptake inhibitor; Y-BOCS, Yale-Brown Obsessive-Compulsive Scale

Adapted from Pinson L et al. Psychiatr Serv. 2003;54(2):145-146
Let’s Apply This to Three New FDA-Approved Antidepressant Monotherapies for MDD

Vilazodone, levomilnacipran and vortioxetine for major depressive disorder: the 15-min challenge to sort these agents out

In a prior 15-min challenge, we tackled the three new oral anorectic agents (1). This time, we will sort out three new agents that have been approved for the treatment of major depressive disorder. Major depressive disorder is common. Estimated lifetime prevalence rates for major depressive disorder in epidemiological studies have ranged from approximately 13–16% of the USA population, with 12-month prevalence rates of 5.3–6.6%, and with rates that are higher in women than in men (2). Major depressive disorder is associated with significant functional dis-levomilnacipran and vortioxetine can be taken without regard to meals. Nausea is the most frequently encountered adverse event for levomilnacipran and vortioxetine. Diarrhoea is the most commonly encountered adverse event for vilazodone, followed by nausea.

Table 2 outlines the efficacy information from the pivotal acute short-term trials as extracted from prior reviews (3–5). Response is defined as a ≥50% reduction from baseline on the Montgomery-Asberg Depression Rating Scale (MADRS). Remission is
## Vilazodone, Levomilnacipran, Vortioxetine

Table 1 Overview and indications, contraindications, bolded boxed warnings, dosage recommendations, drug interactions and most commonly encountered adverse effects (incidence ≥ 5% and at least twice the rate of placebo), taken from the highlights of prescribing information and section 12.1 (Mechanism of Action) from the product label (6–8)

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Vilazodone</th>
<th>Levomilnacipran</th>
<th>Vortioxetine</th>
</tr>
</thead>
<tbody>
<tr>
<td>US brand name</td>
<td>Vilbyrd</td>
<td>Fetzima</td>
<td>Brintellix</td>
</tr>
<tr>
<td>Initial US approval</td>
<td>2011</td>
<td>2012 (milnacipran, 2009)</td>
<td>2013</td>
</tr>
<tr>
<td>Mechanism of action</td>
<td>The mechanism of the antidepressant effect of vilazodone is not fully understood but is thought to be related to its enhancement of serotonergic activity in the CNS through selective inhibition of serotonin reuptake. Vilazodone is also a partial agonist at serotonergic 5-HT1A receptors; however, the net result of this action on serotonergic transmission and its role in vilazodone’s antidepressant effect are unknown.</td>
<td>The exact mechanism of the antidepressant action of levomilnacipran is unknown, but is thought to be related to the potentiation of serotonin and norepinephrine in the central nervous system, through inhibition of reuptake at serotonin and norepinephrine transporters. Non-clinical studies have shown that levomilnacipran is a potent and selective serotonin and norepinephrine reuptake inhibitor.</td>
<td>The mechanism of the antidepressant effect of vortioxetine is not fully understood, but is thought to be related to its enhancement of serotonergic activity in the CNS through inhibition of the reuptake of serotonin (5-HT). It also has several other activities including 5-HT3 receptor antagonism and 5-HT1A receptor agonism. The contribution of these activities to vortioxetine’s antidepressant effect has not been established.</td>
</tr>
<tr>
<td>Contraindications</td>
<td>Serotonin syndrome and MAOIs: Do not use MAOIs intended to treat psychiatric disorders with vilazodone or within 14 days of stopping treatment with vilazodone. Do not use vilazodone within 14 days of stopping an MAOI intended to treat psychiatric disorders. In addition, do not start vilazodone in a patient who is being treated with linezolid or intravenous methylene blue.</td>
<td>Hypersensitivity to levomilnacipran, milnacipran HCl or any excipient in the levomilnacipran formulation. Serotonin syndrome and MAOIs: Do not use MAOIs intended to treat psychiatric disorders with levomilnacipran or within 7 days of stopping treatment with levomilnacipran. Do not use levomilnacipran within 14 days of stopping an MAOI intended to treat psychiatric disorders. In addition, do not start levomilnacipran in a patient who is being treated with linezolid or intravenous methylene blue.</td>
<td>Hypersensitivity to vortioxetine or any components of the vortioxetine formulation. Do not use MAOIs intended to treat psychiatric disorders with vortioxetine or within 21 days of stopping treatment with vortioxetine. Do not use vortioxetine within 14 days of stopping an MAOI intended to treat psychiatric disorders. In addition, do not start vortioxetine in a patient who is being treated with linezolid or intravenous methylene blue.</td>
</tr>
<tr>
<td>Bolded boxed warnings</td>
<td>Increased risk of suicidal thinking and behaviour in children, adolescents and young adults taking antidepressants. Monitor for worsening and emergence of suicidal thoughts and behaviours. Vilazodone is not approved for use in paediatric patients.</td>
<td>Increased risk of suicidal thinking and behaviour in children, adolescents and young adults taking antidepressants. Monitor for worsening and emergence of suicidal thoughts and behaviours. Levomilnacipran is not approved for use in paediatric patients.</td>
<td>Increased risk of suicidal thinking and behaviour in children, adolescents, and young adults taking antidepressants. Monitor for worsening and emergence of suicidal thoughts and behaviours. Vortioxetine has not been evaluated for use in paediatric patients.</td>
</tr>
</tbody>
</table>

## Vilazodone, Levomilnacipran, Vortioxetine

<table>
<thead>
<tr>
<th>Table 1 Continued</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Generic name</strong></td>
</tr>
<tr>
<td><strong>Dosage</strong></td>
</tr>
<tr>
<td><strong>Drug interactions</strong></td>
</tr>
<tr>
<td><strong>Most commonly encountered adverse effects (incidence ≥ 5% and at least twice the rate of placebo)</strong></td>
</tr>
</tbody>
</table>

MAOI, monoamine oxidase inhibitor.
### Table 2: Efficacy: Response [≥ 50% reduction from baseline on the Montgomery-Asberg Depression Rating Scale (MADRS)] and remission (endpoint MADRS ≤ 10), and number needed to treat (NNT) vs. placebo in acute short-term (6–8 week) studies, as extracted from prior reviews (3–5)

<table>
<thead>
<tr>
<th>Number of informative clinical trials</th>
<th>Response</th>
<th>Remission</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Active Medication</td>
<td>Placebo</td>
</tr>
<tr>
<td>Vilazodone 40 mg/day</td>
<td>2</td>
<td>42.2</td>
</tr>
<tr>
<td>Levomilnacipran 40–120 mg/day</td>
<td>4</td>
<td>45.6</td>
</tr>
<tr>
<td>Vortioxetine 5–20 mg/day</td>
<td>6</td>
<td>48.6</td>
</tr>
</tbody>
</table>

CI, confidence interval; NNT, number needed to treat.

### Table 3: Safety and tolerability: proportion of patients who discontinued the clinical trial(s) because of an adverse event and number needed to harm (NNH) vs. placebo; and incidence of the most commonly encountered adverse events and NNH vs. placebo in acute short-term (6–8 week) studies, as extracted from prior reviews (3–5)

<table>
<thead>
<tr>
<th>% of patients discontinuing because of an adverse event</th>
<th>% of patients with the most commonly encountered adverse event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active Medication</td>
<td>Placebo</td>
</tr>
<tr>
<td>Vilazodone 40 mg/day</td>
<td>7.0</td>
</tr>
<tr>
<td>Levomilnacipran 40–120 mg/day</td>
<td>8.8</td>
</tr>
<tr>
<td>Vortioxetine 5–20 mg/day</td>
<td>6.5</td>
</tr>
</tbody>
</table>

*Although diarrhoea was the most commonly encountered spontaneously reported adverse event, nausea was also common at a rate of 23.4% for vilazodone vs. 5.1% for placebo, producing a NNH of 6 (95% CI 5–8). CI, confidence interval; NNH, number needed to harm.
Let’s Apply NNT and NNH to FDA-Approved Adjunctive Options for MDD

Adjunctive Aripiprazole, Olanzapine, or Quetiapine for Major Depressive Disorder: An Analysis of Number Needed to Treat, Number Needed to Harm, and Likelihood to be Helped or Harmed

Abstract

Objective: To describe the efficacy and safety of adjunctive aripiprazole, olanzapine, and quetiapine for major depressive disorder. Data sources: Published registration study reports, supplemented by clinical trial synopses as disclosed by manufacturers and product labeling. Study selection: All available reports of studies were identified. Data extraction: Descriptions of the principal results and calculation of number needed to treat (NNT) for response and remission and number needed to harm (NNH) for relevant dichotomous adverse outcomes were extracted. Likelihood to be helped or harmed (LHH) was subsequently calculated. Data synthesis: Three registration studies of adjunctive aripiprazole, 5 for olanzapine-fluoxetine combination, and 2 for quetiapine extended-release reveal NNT for response and remission to range from 7 to 14 and 7 to 13, respectively, for adjunctive antipsychotic versus antidepressant monotherapy, depending on the antipsychotic and/or dose. Adverse event profiles for the 3 different adjunctive antipsychotics are more diverse, with adjunctive aripiprazole more strongly associated with akathisia (NNH, 6), adjunctive olanzapine with weight gain (NNH, 3), and adjunctive quetiapine with somnolence (NNH, 5 for 300 mg/d and NNH, 6 for 150 mg/d). Conclusions: Number needed to treat and NNH can be used to quantify efficacy and tolerability outcomes and help place various therapeutic options into clinical perspective. Likelihood to be helped or harmed can illustrate to the clinician and the patient the trade-offs between obtaining potential benefits versus harms. In the case of the adjunctive second-generation antipsychotics approved for treating major depressive disorder, these trade-offs vary greatly among the choices available and require careful, individualized, patient-centered clinical decision making.

Keywords: antipsychotic; aripiprazole; clinical trials; major depressive disorder; likelihood to be helped or harmed; number needed to harm; number needed to treat; olanzapine; quetiapine

NNT=number needed to treat; NNH=number needed to harm; FDA=U.S. Food and Drug Administration; MDD=major depressive disorder

Adjunctive Aripiprazole: NNT

Table 1. Aripiprazole Registration Trials for Adjunctive Use in the Acute Treatment of Major Depressive Disorder: NNT

<table>
<thead>
<tr>
<th>Study</th>
<th>Response</th>
<th></th>
<th>NNT (95% CI)</th>
<th>Remission</th>
<th></th>
<th>NNT (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adjunctive Aripiprazole n/N (%)</td>
<td>Placebo n/N (%)</td>
<td></td>
<td>Adjunctive Aripiprazole n/N (%)</td>
<td>Placebo n/N (%)</td>
<td></td>
</tr>
<tr>
<td>Berman et al(^a) (2009)</td>
<td>81/174 (46.6%)</td>
<td>45/169 (26.6%)</td>
<td>5 (4–10)</td>
<td>64/174 (36.8%)</td>
<td>32/169 (18.9%)</td>
<td>6 (4–12)</td>
</tr>
<tr>
<td>Marcus et al(^b) (2008)</td>
<td>60/185 (32.4%)</td>
<td>32/184 (17.4%)</td>
<td>7 (5–16)</td>
<td>47/185 (25.4%)</td>
<td>28/184 (15.2%)</td>
<td>10 (6–49)</td>
</tr>
<tr>
<td>Berman et al(^c) (2007)</td>
<td>61/181 (33.7%)</td>
<td>41/172 (23.8%)</td>
<td>11 (6–207)</td>
<td>47/181 (26.0%)</td>
<td>27/172 (15.7%)</td>
<td>10 (6–54)</td>
</tr>
<tr>
<td>Pooled</td>
<td>202/540 (37.4%)</td>
<td>118/525 (22.5%)</td>
<td>7 (5–11)</td>
<td>158/540 (29.3%)</td>
<td>87/525 (16.6%)</td>
<td>8 (6–13)</td>
</tr>
</tbody>
</table>

Response defined as a ≥ 50% decrease from end of prospective treatment phase in MADRS total score. Remission defined as MADRS Total score of ≤ 10 and a ≥ 50% reduction in MADRS total score from end of prospective treatment.

NNT=number needed to treat

## Table 2. Aripiprazole Registration Trials for Adjunctive Use in the Acute Treatment of Major Depressive Disorder: NNH

<table>
<thead>
<tr>
<th>Event</th>
<th>Adjunctive Aripiprazole n/N (%)</th>
<th>Placebo n/N (%)</th>
<th>NNH (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discontinuation because of an adverse event</td>
<td>21/547 (3.8%)</td>
<td>8/538 (1.5%)</td>
<td>43 (24–225)</td>
</tr>
<tr>
<td>Weight gain of ≥ 7% from baseline (randomization)</td>
<td>27/547 (5.0%)</td>
<td>4/538 (0.8%)</td>
<td>24 (17–45)</td>
</tr>
<tr>
<td>Akathisia</td>
<td>123/547 (22.5%)</td>
<td>22/538 (4.1%)</td>
<td>6 (5–7)</td>
</tr>
<tr>
<td>Blurred vision</td>
<td>25/358 (7.0%)</td>
<td>6/348 (1.7%)</td>
<td>19 (13–44)</td>
</tr>
<tr>
<td>Constipation</td>
<td>20/365 (5.5%)</td>
<td>11/362 (3.0%)</td>
<td>41 (NS)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>46/547 (8.4%)</td>
<td>21/538 (3.9%)</td>
<td>23 (14–61)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>43/547 (7.9%)</td>
<td>16/538 (3.0%)</td>
<td>21 (14–46)</td>
</tr>
<tr>
<td>Restlessness</td>
<td>66/547 (12.1%)</td>
<td>13/538 (2.4%)</td>
<td>11 (8–16)</td>
</tr>
</tbody>
</table>

NNH = number needed to harm

### Table 3. OFC Registration Trials for the Acute Treatment of Major Depressive Disorder: NNT

<table>
<thead>
<tr>
<th>Study</th>
<th>Response</th>
<th></th>
<th></th>
<th>Remission</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OFC n/N (%)</td>
<td>Fluoxetine n/N (%)</td>
<td>NNT (95% CI)</td>
<td>OFC n/N (%)</td>
<td>Fluoxetine n/N (%)</td>
<td>NNT (95% CI)</td>
</tr>
<tr>
<td>Shelton et al(^{18}) (2001)(^a)</td>
<td>6/10 (60%)</td>
<td>1/10 (10%)</td>
<td>2 (2–7)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Shelton et al(^{19}) (2005)(^b)</td>
<td>40/146 (27.5%)</td>
<td>41/142 (28.9%)</td>
<td>-72 (NS)</td>
<td>25/146 (16.9%)</td>
<td>19/142 (13.3%)</td>
<td>28 (NS)</td>
</tr>
<tr>
<td>Corya et al(^{20}) (2006)(^c)</td>
<td>100/230 (43.5%)</td>
<td>19/56 (33.9%)</td>
<td>11 (NS)</td>
<td>69/230 (30.0%)</td>
<td>10/56 (17.9%)</td>
<td>9 (5–203)</td>
</tr>
<tr>
<td>Thase et al(^{17}) (2007)—Study 1(^d)</td>
<td>37/101 (36.6%)</td>
<td>30/102 (29.4%)</td>
<td>14 (NS)</td>
<td>24/101 (23.8%)</td>
<td>18/102 (17.6%)</td>
<td>17 (NS)</td>
</tr>
<tr>
<td>Thase et al(^{17}) (2007)—Study 2(^e)</td>
<td>43/97 (44.3%)</td>
<td>30/101 (29.7%)</td>
<td>7 (4–76)</td>
<td>30/97 (30.9%)</td>
<td>16/101 (15.8%)</td>
<td>7 (4–29)</td>
</tr>
<tr>
<td>Pooled from above</td>
<td>226/584 (38.7%)</td>
<td>121/411 (29.4%)</td>
<td>11 (7–30)</td>
<td>148/574 (25.7%)</td>
<td>63/401 (15.7%)</td>
<td>10 (7–20)</td>
</tr>
<tr>
<td>Pooled from Trivedi et al(^{21}) (2009)(^f)</td>
<td>181/450 (40.3%)</td>
<td>94/339 (27.8%)</td>
<td>8 (6–17)</td>
<td>115/450 (25.5%)</td>
<td>59/339 (17.3%)</td>
<td>13 (8–40)</td>
</tr>
</tbody>
</table>

NNT = number needed to treat; OFC = olanzapine/fluoxetine combination
## Table 4. OFC Registration Trials for the Acute Treatment of Major Depressive Disorder: NNH

<table>
<thead>
<tr>
<th>Event</th>
<th>OFC n/N (%)</th>
<th>Fluoxetine n/N (%)</th>
<th>NNH (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discontinuation because of an adverse event</td>
<td>55/473 (11.6%)</td>
<td>9/352 (2.6%)</td>
<td>12 (9–18)</td>
</tr>
<tr>
<td>Weight gain of ≥ 7% from baseline (randomization)</td>
<td>191/473 (40.4%)</td>
<td>8/352 (2.3%)</td>
<td>3 (3–3)</td>
</tr>
<tr>
<td>Disturbance in attention</td>
<td>26/473 (5.5%)</td>
<td>12/352 (3.4%)</td>
<td>48 (NS)</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>88/473 (18.6%)</td>
<td>23/352 (6.5%)</td>
<td>9 (7–13)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>66/473 (14.0%)</td>
<td>33/352 (9.4%)</td>
<td>22 (12–430)</td>
</tr>
<tr>
<td>Hypersomnia</td>
<td>29/473 (6.1%)</td>
<td>7/352 (2.0%)</td>
<td>25 (15–67)</td>
</tr>
<tr>
<td>Increased appetite</td>
<td>115/473 (24.3%)</td>
<td>22/352 (6.3%)</td>
<td>6 (5–8)</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>53/473 (11.2%)</td>
<td>4/352 (1.1%)</td>
<td>10 (8–15)</td>
</tr>
<tr>
<td>Sedation</td>
<td>40/473 (8.5%)</td>
<td>10/352 (2.8%)</td>
<td>18 (12–38)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>74/473 (15.6%)</td>
<td>23/352 (6.5%)</td>
<td>11 (8–21)</td>
</tr>
<tr>
<td>Tremor</td>
<td>46/473 (9.7%)</td>
<td>22/352 (6.3%)</td>
<td>30 (ns)</td>
</tr>
<tr>
<td>Weight increased</td>
<td>132/473 (27.9%)</td>
<td>25/352 (7.1%)</td>
<td>5 (4–7)</td>
</tr>
</tbody>
</table>

NNH=number needed to harm; OFC=olanzapine/fluoxetine combination

## Adjunctive Quetiapine: NNT

### Table 5. Quetiapine Registration Trials for Adjunctive Use in the Acute Treatment of Major Depressive Disorder: NNT

<table>
<thead>
<tr>
<th>Study</th>
<th>Response</th>
<th>Adjunctive Quetiapine 150 mg n/N (%)</th>
<th>Adjunctive Quetiapine 300 mg n/N (%)</th>
<th>Placebo n/N (%)</th>
<th>NNT (95% CI) for 150 mg/d</th>
<th>NNT (95% CI) for 300 mg/d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bauer et al²² (2009)</td>
<td></td>
<td>92/166 (55.4%)</td>
<td>93/161 (57.8%)</td>
<td>74/160 (46.3%)</td>
<td>11 (NS)</td>
<td>9 (5–156)</td>
</tr>
<tr>
<td>El-Khalili et al²³ (2010)</td>
<td></td>
<td>74/143 (51.7%)</td>
<td>86/146 (58.9%)</td>
<td>66/143 (46.2%)</td>
<td>19 (NS)</td>
<td>8 (5–79)</td>
</tr>
<tr>
<td><strong>Pooled</strong></td>
<td></td>
<td>166/309 (53.7%)</td>
<td>179/307 (58.3%)</td>
<td>140/303 (46.3%)</td>
<td>14 (NS)</td>
<td>9 (5–24)</td>
</tr>
</tbody>
</table>

### Remission

<table>
<thead>
<tr>
<th>Adjunctive Quetiapine 150 mg n/N</th>
<th>Adjunctive Quetiapine 300 mg n/N</th>
<th>Placebo n/N</th>
<th>NNT (95% CI) for 150 mg/d</th>
<th>NNT (95% CI) for 300 mg/d</th>
</tr>
</thead>
<tbody>
<tr>
<td>69/166 (41.6%)</td>
<td>65/161 (40.4%)</td>
<td>50/160 (31.3%)</td>
<td>10 (NS)</td>
<td>11 (NS)</td>
</tr>
<tr>
<td>60/143 (42.0%)</td>
<td>77/146 (52.7%)</td>
<td>47/143 (32.9%)</td>
<td>11 (NS)</td>
<td>6 (4–12)</td>
</tr>
<tr>
<td><strong>129/309 (41.8%)</strong></td>
<td><strong>142/307 (46.2%)</strong></td>
<td><strong>97/303 (32.1%)</strong></td>
<td><strong>11 (6–48)</strong></td>
<td><strong>7 (5–16)</strong></td>
</tr>
</tbody>
</table>

NNT=number needed to treat

## Adjunctive Quetiapine: NNH

<table>
<thead>
<tr>
<th>Event</th>
<th>Adjunctive Quetiapine 150 mg/d n/N (%)</th>
<th>Adjunctive Quetiapine 300 mg/d n/N (%)</th>
<th>Placebo n/N (%)</th>
<th>NNH (95% CI) for 150 mg/d</th>
<th>NNH (95% CI) for 300 mg/d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discontinuation because of an adverse event</td>
<td>28/315 (8.9%)</td>
<td>48/312 (15.4%)</td>
<td>7/309 (2.3%)</td>
<td>16 (10–33)</td>
<td>8 (6–12)</td>
</tr>
<tr>
<td>Weight gain of ≥ 7% from baseline (randomization)</td>
<td>9/315 (2.9%)</td>
<td>18/312 (5.8%)</td>
<td>5/309 (1.6%)</td>
<td>81 (NS)</td>
<td>25 (15–83)</td>
</tr>
<tr>
<td>Constipation</td>
<td>18/315 (5.7%)</td>
<td>33/312 (10.6%)</td>
<td>11/309 (3.6%)</td>
<td>47 (NS)</td>
<td>15 (10–33)</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>86/315 (27.3%)</td>
<td>124/312 (39.7%)</td>
<td>24/309 (7.8%)</td>
<td>6 (4–8)</td>
<td>4 (3–4)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>45/315 (14.3%)</td>
<td>34/312 (10.9%)</td>
<td>12/309 (3.9%)</td>
<td>10 (7–17)</td>
<td>15 (9–34)</td>
</tr>
<tr>
<td>Sedation</td>
<td>41/315 (13.0%)</td>
<td>54/312 (17.3%)</td>
<td>13/309 (4.2%)</td>
<td>12 (8–23)</td>
<td>8 (6–12)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>71/315 (22.5%)</td>
<td>81/312 (26.0%)</td>
<td>11/309 (3.6%)</td>
<td>6 (5–8)</td>
<td>5 (4–6)</td>
</tr>
</tbody>
</table>

NNH=number needed to harm

Brexpiprazole for MDD – NNT and NNH?

When the results for adjunctive brexpiprazole 1, 2, and 3 mg from the two phase 3 MDD trials are pooled together, 23.2% of the patients receiving brexpiprazole were responders, vs 14.5% for placebo, for a NNT of 12 (95% CI 8–26)

Discontinuation rates because of an AE were 2.6% for brexpiprazole and 0.7% with placebo, for a NNH of 53 (95% CI 30–235)

AE of akathisia was 8.5% for brexpiprazole vs 2.1% for placebo, for a NNH of 16 (95% CI 12–25)

Increase in body weight of ≥ 7% at any time post-baseline was seen in 3.9% for brexpiprazole vs 1.9% with placebo, for a NNH of 52 (ns)

AE=adverse events; CI=confidence interval; MDD=major depressive disorder; NNT=number needed to treat; NNH=number needed to harm; ns=not significant

Circling Back: Monotherapies for MDD

Likelihood to be helped or harmed, response vs discontinuation because of an adverse event, pooled data for each antidepressant

<table>
<thead>
<tr>
<th>Antidepressant</th>
<th>NNT vs. placebo for response (prior to rounding)</th>
<th>NNH vs. placebo for discontinuation because of an adverse event (prior to rounding)</th>
<th>LHH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duloxetine</td>
<td>5.7</td>
<td>24.5</td>
<td>4.3</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>6.7</td>
<td>30.7</td>
<td>4.6</td>
</tr>
<tr>
<td>Levomilnacipran</td>
<td>9.8</td>
<td>18.2</td>
<td>1.8</td>
</tr>
<tr>
<td>Sertraline</td>
<td>5.3</td>
<td>6.5</td>
<td>1.2</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>5.7</td>
<td>7.8</td>
<td>1.4</td>
</tr>
<tr>
<td>Vilazodone</td>
<td>8.0</td>
<td>26.1</td>
<td>3.3</td>
</tr>
<tr>
<td>Vortioxetine</td>
<td>8.4</td>
<td>42.7</td>
<td>5.1</td>
</tr>
</tbody>
</table>

Citrome, L. Vortioxetine for major depressive disorder: an indirect comparison with duloxetine, escitalopram, levomilnacipran, sertraline, venlafaxine, and vilazodone, using number needed to treat, number needed to harm, and likelihood to be helped or harmed. Journal of Affective Disorders (2016), doi:10.1016/j.jad.2016.02.042
NNT for response, NNH for discontinuation because of an adverse event, and 95% confidence intervals, pooled data for each antidepressant.

Circling Back: Monotherapies for MDD

NNT for response, NNH for discontinuation because of an adverse event, and 95% confidence intervals, pooled data for each antidepressant.


Citrome, L., Vortioxetine for major depressive disorder: an indirect comparison with duloxetine, escitalopram, levomilnacipran, sertraline, venlafaxine, and vilazodone, using number needed to treat, number needed to harm, and likelihood to be helped or harmed. Journal of Affective Disorders (2016), doi:10.1016/j.jad.2016.02.042
Limitations of Using NNT/NNH

❖ It is most valid to calculate from a randomized controlled trial with identical conditions for all drugs under study

❖ Results are only calculable for binary or dichotomous events that are either present or absent, and do not apply to continuous variables such as the value of a blood test

❖ However, values with clinically significant thresholds, such as weight gain $\geq 7\%$ from baseline can be expressed as a NNT because the data has been dichotomized

NNT=number needed to treat; NNH=number needed to harm
Best Practices When Using NNT/NNH

- Need to calculate from high quality studies (GIGO)
- Outcomes need to be clinically meaningful in order to be clinically interpretable
- Be mindful of the rates that were used to calculate the NNT
  - A NNT of 10 when it is calculated from rates of 20% vs 10% is a very different clinical scenario than when the rates are 80% vs 70%
- Be mindful of the 95% confidence interval
  - The narrower the interval, the more precise the estimate
- Be mindful of study duration—6-week studies can’t easily be compared with 12-week studies

NNT=number needed to treat; NNH=number needed to harm

Back to the Case

- Switch?
  - Different class?
- Stay?
  - Change the dose? Simply wait?
- Augment?
  - Which adjunctive treatment?

Clinical Judgment

Relevant Scientific Evidence

Patients’ Values and Preferences

EBM
Trade-offs vary greatly and treatment selection or medication switching will require careful, individualized, patient-centered decision making.

NNT (and NNH) can help interpret treatment response in terms of both efficacy and tolerability.

What is the final treatment strategy for Ashley? Should she switch, stay, or augment? 

NNT=number needed to treat; NNH=number needed to harm
Key Messages

- MDD is common and should be approached with the same gravity as cardiovascular disease and other chronic illnesses.

- Recognition and diagnosis in primary care are challenging:
  - Overlapping symptoms with other conditions including bipolar disorder.
  - Misdiagnosis of bipolar disorder is common, and distinguishing between conditions is essential.

- Patient education on MDD characteristics and available treatments are necessary components of treatment.

- In cases of incomplete response to treatment, identifying root causes is important for choosing among “switch, stay, or augment.”

- Use the best evidence available when selecting treatment with an understanding that a statistically significant trial result is not always clinically meaningful.
Q & A
# PHQ-9: Nine-Item Patient Health Questionnaire

**Designed to Help Primary Care Clinicians Diagnose, Grade, and Follow Depression Symptom Severity**

<table>
<thead>
<tr>
<th>Over the past 2 weeks, how often have you been bothered by any of the following problems?</th>
<th>Not At all</th>
<th>Several Days</th>
<th>More Than Half the Days</th>
<th>Nearly Every Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Little interest or pleasure in doing things</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>2. Feeling down, depressed or hopeless</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>3. Trouble falling asleep, staying asleep, or sleeping too much</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>4. Feeling tired or having little energy</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>5. Poor appetite or overeating</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>6. Feeling bad about yourself - or that you're a failure or have let yourself or your family down</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>7. Trouble concentrating on things, such as reading the newspaper or watching television</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>8. Moving or speaking so slowly that other people could have noticed. Or, the opposite - being so fidgety or restless that you have been moving around a lot more than usual</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>9. Thoughts that you would be better off dead or of hurting yourself in some way</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

**PHQ-9 score ≥ 10:** Likely major depression

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

**Depression score ranges:**
- 0 to 4: minimal
- 5 to 9: mild
- 10 to 14: moderate
- 15 to 19: moderately severe
- ≥ 20: severe

---

Mood Disorder Questionnaire

<table>
<thead>
<tr>
<th>1. Has there ever been a period of time when you were not your usual self and...</th>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>...you felt so good or so hyper that other people thought you were not your normal self or you were so hyper that you got into trouble?</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>...you were so irritable that you shouted at people or started fights or arguments?</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>...you felt much more self-confident than usual?</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>...you got much less sleep than usual and found you didn't really miss it?</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>...you were much more talkative or spoke faster than usual?</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>...thoughts raced through your head or you couldn't slow your mind down?</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>...you were so easily distracted by things around you that you had trouble concentrating or staying on track?</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>...you had much more energy than usual?</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>...you were much more active or did many more things than usual?</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>...you were much more social or outgoing than usual, for example, you telephoned friends in the middle of the night?</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>...you were much more interested in sex than usual?</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>...you did things that were unusual for you or that other people might have thought were excessive, foolish, or risky?</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>...spending money got you or your family into trouble?</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>

2. If you checked YES to more than one of the above, have several of these ever happened during the same period of time? Please circle one response only.

| YES | NO |

3. How much of a problem did any of these cause you — like being unable to work; having family, money, or legal troubles; getting into arguments or fights? Please circle one response only.

| No problem | Minor problem | Moderate problem | Serious problem |

Patient screens positive for bipolar disorder if they answer:
- “yes” to seven or more items in section 1
- “yes” in section 2
- “moderate or serious problem” in section 3

Screening for Adult ADHD: Self-Report Scale (ASRS-v1.1)

<table>
<thead>
<tr>
<th>Question</th>
<th>Never</th>
<th>Rarely</th>
<th>Sometimes</th>
<th>Often</th>
<th>Very Often</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. How often do you have trouble wrapping up the final details of a project, once the challenging parts have been done?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. How often do you have difficulty getting things in order when you have to do a task that requires organization?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. How often do you have problems remembering appointments or obligations?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. When you have a task that requires a lot of thought, how often do you avoid or delay getting started?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. How often do you fidget or squirm with your hands or feet when you have to sit down for a long time?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. How often do you feel overly active and compelled to do things, like you were driven by a motor?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

If 4 or more marks appear in the darkly shaded boxes, the patient has symptoms highly consistent with Adult ADHD and further investigation is warranted.

# The Generalized Anxiety Disorder-7 Item Scale

## GAD-7

<table>
<thead>
<tr>
<th>Over the last 2 weeks, how often have you been bothered by the following problems?</th>
<th>Not at all</th>
<th>Several days</th>
<th>More than half the days</th>
<th>Nearly every day</th>
</tr>
</thead>
<tbody>
<tr>
<td>01. Feeling nervous, anxious or on edge</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>02. Not being able to stop or control worrying</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>03. Worrying too much about different things</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>04. Trouble relaxing</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>05. Being so restless that it is hard to sit still</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>06. Becoming easily annoyed or irritable</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>07. Feeling afraid as if something awful might happen</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

(Use "✓" to indicate your answer)

## Interpreting the Score:

- \( \geq 10 \) Possible diagnosis of GAD; confirm by further evaluation
- 5 to 9 = mild anxiety
- 10 to 14 = moderate anxiety
- 15 to 21 = severe anxiety

(For office coding: Total Score \( T_{\text{____}} \) = \( ____ + ____ + ____ \))

GAD=generalized anxiety disorder

Developed by Drs. Robert L. Spitzer, Janet B.W. Williams, Kurt Kroenke and colleagues, with an educational grant from Pfizer Inc.
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Extra slides –
do not delete
Differential Diagnosis

1/3 of bipolar disorder in the general population is misdiagnosed as unipolar depression

Use a Bipolar Screen such as the Mood Disorder Questionnaire whenever a patient presents with MDD symptoms

Unipolar depression is a diagnosis of exclusion

Hirschfeld RM et al. (2003), J Clin Psychiatry 64(1):53-59; Das AK et al. (2005), JAMA 293(8):956-963
Why Does It Matter if Bipolar Disorder Is Misdiagnosed?

Correct Diagnosis as a Phase of Bipolar Disorder

Treatment per Guidelines for Bipolar Disorder (Mood Stabilizers, Lithium, Atypical Antipsychotics)

Misdiagnosis as Unipolar Depression

Antidepressant Monotherapy and the Possibility of Emergence of Mania and Rapid Cycling