Depression

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General Internal Medicine
Case

35 F going through a stressful divorce and job transition presents with 1 mo of “depressed mood”, anhedonia, gained 5 lbs, stopped going to the gym. “I come home from work, get in bed, eat potato chips and cry myself to sleep”.

PMH: No prior bouts of depression
<table>
<thead>
<tr>
<th>Over the last 2 weeks</th>
<th>Not at all (0)</th>
<th>Several days (1)</th>
<th>More than ½ days (2)</th>
<th>Nearly every day (3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Little interest or pleasure in doing things</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>2. Feeling down depressed or hopeless</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>3. Trouble stay/falling asleep, sleeping too much</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Feeling tired, or having little energy</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>5. Poor appetite or overeating</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Feeling bad about yourself</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>7. Poor concentration</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. Moving or speaking slowly, OR agitated</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>9. Thoughts of better off dead, or hurting self</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>How difficult?</td>
<td>Not at all</td>
<td>Some</td>
<td>Very</td>
<td>Extremely</td>
</tr>
</tbody>
</table>
# Scoring PHQ-9

## Initial Diagnosis

<table>
<thead>
<tr>
<th>Score</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 to 9</td>
<td>minimal sx</td>
</tr>
<tr>
<td>10 to 14</td>
<td>mild depression</td>
</tr>
<tr>
<td>15 to 19</td>
<td>moderate depression</td>
</tr>
<tr>
<td>&gt; 20</td>
<td>severe depression</td>
</tr>
</tbody>
</table>

## Post 4-6 wks of Rx

<table>
<thead>
<tr>
<th>Score change</th>
<th>Rx response</th>
<th>Rx plan</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓ &gt;5 pts</td>
<td>Adequate</td>
<td>No change</td>
</tr>
<tr>
<td>↓ 2-4 pts</td>
<td>Probably adequate</td>
<td>Consider dose ↑</td>
</tr>
<tr>
<td>↓ 0-1 pts</td>
<td>inadequate</td>
<td>↑ dose, change/ add med</td>
</tr>
</tbody>
</table>

Adapted from [www.depression-primarycare.org](http://www.depression-primarycare.org)
PHQ9: 18 (moderate-severe)

Before you consider treatment what important depression mimic should you screen for prior to making the diagnosis of major depression?

Extra credit if you can give an example of a practical screening question.
Bipolar

- Delayed diagnosis, 7-10 years
- Risk of spurring mania with antidepressants
- Higher morbidity and mortality
- Bipolar I >1 week + social dysfunction
- Bipolar II >4 days +/- dysfunction
- Unipolar depression can look like bipolar depression
### Features of Mania
- Excessive euphoria (especially in hypomania)
- Extreme irritability and distractibility
- Greatly increased energy, restlessness
- Racing, rapidly shifting thoughts
- Rapid, pressured speech
- Decreased need for sleep
- Unrealistic or grandiose beliefs in abilities
- Reckless, impulsive behavior
- Increased sexual drive, risky sexual behavior
- Abuse of drugs or alcohol
- In severe cases, hallucinations, delusions, paranoia

### Features of Bipolar Depression
- Persistent, sad, anxious or empty mood
- Feelings of hopelessness or pessimism
- Feelings of guilt, worthlessness
- Loss of interest in ordinary activities
- Decreased energy, increased fatigue
- Difficulty concentrating or making decisions
- Diminished self-care
- Restlessness or irritability
- Insomnia or oversleeping
- Changes in appetite or weight
- Unexplained aches and pains
- Thoughts of death or suicide

- Any history of mania or hypomania
- Bipolar depression is more anergic, with psychomotor retardation

Jacobs, D.G. et. al. *Screening for Mental Health Inc.*
Bipolar

• Common mania sx
  – Pressured speech, hyperverbosity, physical hyperactivity, decreased sleep, hypersexuality, extravagance

• Less common sx
  – Violence, hyper-religiousity, regression, catatonia

• Screening
  – Ever with 1 wk, ↑mood, ↓sleep, out of control behavior?

**Take Home:** Always screen for Bipolar disorder when you consider treating depression.
Case continued

No evidence of bipolar.

What do you recommend?

a) Bupropion SR
b) Acupuncture
c) Cognitive behavioral therapy (CBT)
d) Venlafaxine
e) Escitalopram
Antidepressant Efficacy

JAMA Jan 2010 meta-analysis of RCTs
• 718 pt. imipramine /paroxetine vs. placebo
• Results: $d$ difference in effect size.
  • $d > 0.2$ min effect, $d > 0.5$ mod effect

<table>
<thead>
<tr>
<th>Severity</th>
<th>$d$</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild-Mod</td>
<td>0.11</td>
<td>16</td>
</tr>
<tr>
<td>Severe</td>
<td>0.17</td>
<td>11</td>
</tr>
<tr>
<td>Very Severe</td>
<td>0.47</td>
<td>4</td>
</tr>
</tbody>
</table>

Fournier JAMA 2010
Antidepressant Medication (ADM) Efficacy

• Most efficacy studies enroll severely depressed
• Paroxetine and imipramine only
• No placebo-washout studies
• Cannot determine if placebo ↓ or ADM ↑ effective

Take Home: Consider a trial of cognitive behavioral therapy, but don’t avoid antidepressants.
Case 1 continued

Her insurance will not cover cognitive behavioral therapy.

What do you recommend?

a) Bupropion
b) St. John’s Wort
c) Fluoxetine
d) Venlafaxine
e) Escitalopram
Antidepressant Guidelines

- $2^{nd}$ generation ADM are equal efficacy
- $1^{st}$ generation = $2^{nd}$ generation efficacy
  - Higher toxicity with TCAs and MAOIs
- Choose Rx based on
  - Side effects
  - Cost
  - Pt preference

2nd Generation ADM

- Lancet Jan 2009 SR of 117 RCTs, 26K pts
- Best Efficacy
  - Mirtazapine > escitalopram > venlafaxine > sertraline
- Best Tolerability
  - Escitalopram > sertraline > citalopram > bupropion
- Least Efficacy and Tolerability
  - Reboxetine, fluvoxamine, paroxetine, duloxetine
- Cochrane Review April 2009 supports

**Take Home:** Consider sertraline and escitalopram

Clinical vs. Statistical Difference

• 2010 meta-analysis of 8 RCT, 2000 pts
  – Citalopram v. escitalopram in MDD
  – MADRS at 8 weeks, response and remission

• Result: Escitalopram superior
  – Difference in MADRS 1.7 pts
  – Response 8.3%, NNT 11.9
  – Remission 17.6%, NNT 5.7

Montgomery et. al. Int. J of Neuropsychopharm Sept 2010
St. John’s Wort

2008 Cochrane Review of 28 RCTs
• Better than placebo (18 PCTs)
  – Larger trials RR 1.28
  – Smaller trials RR 1.87
• Equal efficacy vs. standard antidepressants (17 RTCs)
  – Vs. TCAs/tetracyclic RR 1.02
  – Vs. SSRIs RR 1.0
• Better tolerated (odds of dropout)
  – Vs. TCAs OR 0.24
  – Vs. SSRI OR 0.53

Linde et. al., Cochrane Data. Sys. Rev. 2008, Iss. 4
St. John’s Wort Practical Advice

• Variable preparation
• **Dose** – 500 mg - 1200 mg
• US study (Fava) Hypericum extract *Litchwer LI 160* 3 tabs qday (900 mg). Brand name *Kira*
• **Side-effects** – insomnia, vivid dreams, dizziness, GI discomfort, diarrhea, confusion, sedation, anxiety, irritability, headache, photosensitivity (at higher doses)
• **Drug interactions** – Induces CYP34A, 2C9, 1A2

_Natural Medicines Comprehensive Database (accessed Feb 8, 2009)_
## Side-effects

<table>
<thead>
<tr>
<th>Drug</th>
<th>Diarrhea</th>
<th>Dizziness</th>
<th>Headache</th>
<th>Insomnia</th>
<th>Nausea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bupropion</td>
<td>8.7</td>
<td>12.5</td>
<td>27.2</td>
<td>11-40</td>
<td>9-24</td>
</tr>
<tr>
<td>Citalopram</td>
<td>8</td>
<td>up to 14</td>
<td>up to 18</td>
<td>up to 15</td>
<td>21</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>7-13</td>
<td>6-17</td>
<td>NR</td>
<td>8-16</td>
<td>11</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>6-14</td>
<td>4-7</td>
<td>24</td>
<td>7-14</td>
<td>15-18</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>12</td>
<td>2-11</td>
<td>16.6</td>
<td>9-26</td>
<td>20-30</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>NR</td>
<td>NR</td>
<td>14.5</td>
<td>NR</td>
<td>22.2</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>8.8</td>
<td>12</td>
<td>12</td>
<td>8</td>
<td>↑appetite 17</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>18</td>
<td>4-6</td>
<td>17-27</td>
<td>up to 24</td>
<td>26</td>
</tr>
<tr>
<td>Sertraline</td>
<td>13-24</td>
<td>6-17</td>
<td>25</td>
<td>12-28</td>
<td>13-30</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>5.5</td>
<td>11-24</td>
<td>25-38</td>
<td>14-24</td>
<td>22-58</td>
</tr>
</tbody>
</table>

*Adapted from Hansen, Annals Int Med 2005 and Micromedex 2010*
Side-effects with Clear Associations

• Sexual dysfunction
  – Sertraline > venlafaxine > citalopram > paroxetine
  – No effect with bupropion, mirtazapine

• Nausea and vomiting
  – Venlafaxine highest

• Weight gain
  – Highest with mirtazapine and paroxetine

• Diarrhea
  – Highest with sertraline

Serretti et al, J Clin Psychopharmacol 2009
Which Side-Effects Are Associated with SSRIs?

a) GI bleeding
   - SSRI OR 1.4-2, SSRI + NSAID OR 1.2-6.3 (RR 3.3-15), SSRI + NSAID + PPI OR 0.39-1.3

b) Fracture
   - OR 1.95 osteoporeetic fx for SSRI

c) Arrhythmia
   - QTc prolongation, ↑ risk Torsades

d) Falls
   - OR 1.7 SSRI and antipsychotics, OR 0.9 narcotics

e) Hemorrhagic stroke
   - 45%↑RR CVA, absolute ↑1%/y (3->4%), WHI

FDA recommends lowering Celexa's maximum daily dose

The Food and Drug Administration is recommending that patients taking the antidepressant Celexa (citalopram hydrobromide) take no more than 40mg a day. The FDA says anything more can cause abnormal heart rhythms, and studies show there is no therapeutic benefit with doses higher than 40mg. The recommendation includes generic versions of the drug.

**TAKE HOME:**
- ↓ Citalopram to 40 mg or less
- ↓ to 20 mg or < if hepatic failure, > 60, CYP 2C19 low metabolizers, on cimetidine
- Do not use in prolonged QT.
- Caution in CHF, bradycardia, low K, low Mg, or concurrent meds
Case 2

45 F presents with anhedonia, depressed mood, sleep disturbance, irritability, and decreased concentration. She was tried on fluoxetine but had worsening sleep. She was switched to citalopram for 2 months and doesn’t feel better.
Does She Have Treatment Resistant Depression (TRD)?

A. Yes, she’s failed two anti-depressants
B. No, she’s only tried one class of meds
C. Maybe, it depends on the doses and duration of her treatment, as well as prior treatment
D. It doesn’t matter what you call it, you plan to switch her meds
Is This TRD?

• Confirm the diagnosis of major depression
• Grade severity and duration of symptoms
• Grade level of response to medication, or therapy
• Check for adequacy of dose, and duration of medication, medication adherence
Grading Response To Rx

TRD - Non-response despite 2 meds from different classes at adequate dose and duration

- Non-response <25%
- Partial response 25-50%
- Response >50%
- Remission Asx x 2 weeks
- Recovery Sx free x 6 months
Predictors of TRD

• Co-morbid axis I and axis II disorders
• Subtypes of depression
  – Psychotic: hallucinations and delusions
  – Atypical: weight gain, hypersomnia
  – *Melancholic: predominant anhedonia
• Medical co-morbidity
  – Somatic symptoms vs. confirmed diagnosis
• Prolonged prior bouts of MDE

* Not a predictor of TRD
Predictors of TRD

- Psychiatric admissions
- Severity of symptoms
- Number of prior therapies tried
- Duration between onset of symptoms and treatment
- Ongoing substance abuse
- Mild to moderate alcohol consumption
- Poor social support
Co-morbid Psychiatric Conditions

• Generalized anxiety disorder (SSRI)
  – Last 6 mo, anxious/worried most of the time?

• Obsessive compulsive (SSRI)
  – Intrusive/recurrent thoughts
  – Ritualistic behavior to relieve anxiety

• Eating disorders (SSRI)
  – Are you satisfied with your eating habits?

• Dementia (non-TCA)
  – MMSE, Mini-Cog
Case 2 continued

45 F presents with anhedonia, depressed mood, sleep disturbance, irritability, and decreased concentration, PHQ9 20. She was titrated to fluoxetine 60 mg for 4 weeks but had worsening sleep, then switched to citalopram 40 mg for 2 months. She had < 25% improvement of her symptoms on both meds. A previous bout of depression in college was treated with notripylline 150 mg for 8 weeks without improvement.
What Would You Do?

A. D/C citalopram and start escitalopram (lexapro)
B. ↑ citalopram dose to 60 mg qd
C. D/C citalopram and start venlafaxine (effexor)
D. Continue citalopram and add aripiprazole (abilify)
E. Continue citalopram and add bupropion (wellbutrin)
STAR-D Overview

- 2870 patients non-psychotic depression
  - 75% hx of recurrent depression
- Mimicked “real-life” practice
- Focused on remission (HDRS <7)
- Level 1: citalopram up to 60 mg
  - 27.5% remission, 47% response
- Level 2: augmentation vs. switch meds
- Level 3: augmentation vs. switch meds
- Level 4: MAOI vs. combo antidepressants

*Nierenberg et al. 163 (9): 1519. (2006)*
STAR-D Level 2

Augmentation
- 565 adults resistant to 12 wks citalopram (55 mg)
- Bupropion SR (400 mg) OR Buspirone* (60 mg)
- HDRS remission 30%
- Drop out - 12.5% bupropion and 20.6% buspirone

Switch Meds
- 727 adults resistant to 14 wks citalopram, switched
- Bupropion SR (400 mg) 21-25%
- Venlafaxine ER (375 mg) 25%
- Sertraline (200 mg) 17-26%

Take Home: Bupropion + citalopram improved remission

Take Home: 2nd SSRI vs. change in class = efficacy

1) Trivedi M et al, NJEM 354 (12) 3/06.
2) Rush J et al, NJEM 354 (12) 3/06.
STAR-D Level 3

Augmentation

- 142 pt, mean 9.6 wks
- On bupropion SR, sertraline, venlafaxine XR, citalopram + buspirone, citalopram + bupropion SR.
- Augmenting agent remission
  - T3* (45 mcg) 24.7%
  - Lithium* (860 mg) 15.9%
- Side effects Li > T3, OR 2.0 p=0.04

Switch Medication

- 114 pt randomly assigned for 14 wks
  - Mirtazapine (60 mg) 12.3%
  - Nortriptyline (200 mg) 19.8%
- Not statistically significant for remission
- No difference in tolerability

Take Home: T3 is efficacious and tolerated

Take Home: Lower yield with 3rd antidepressant

STAR-D Level 4

- Failed 3 antidepressant medications
- 109 pts random assignment, open-label
- Remission rates
  - Tranylcypromine (37 mg) 6.9%
  - Venlafaxine XR (210 mg) + mirtazapine (36 mg) 13.7%

Take Home: Poorer response after failing 3 meds

McGrath et al. 163 (9): 1531. (2006)
TRD - Anxious Depression

• **Level 1** (53% w/ anxiety)
  – ↓ remission 22% vs. 33%
  – Similar dose but ↑ SE frequency (26% vs. 21%), severity (19% vs. 12%)
  – ↑ time to remission/response

• **Level 2**
  – Switch remission rates worse
    • Bupropion 10% vs. 34%
    • Sertraline 8% vs. 28%
    • Venlafaxine 12% vs. 36%
  – Augmentation remission rates worse
    • + Bupropion 18% vs. 37%
    • + Buspirone 9% vs. 39%

**Take Home:** Screen for anxiety, treat longer, get help
Practical Advice

**Liothyronine* (T3)**
- Start T3 (liothyronine) 12.5-50 mcg qday
- 35% response, 30% remission
- Better in atypical depression, worse for melancholic depression
- Monitoring
  - No recommendation per psych
  - Consider checking TSH in 6 wks

**Lithium**
- Start at 150 mg PO BID
- Average dose 600 mg to 800 mg
- Check a trough level in one week
- Aim for 0.4-0.8 mmol/L
- Watch for common side-effects
  - Tremor, mild cognitive impairment
  - Diarrhea, nausea, anorexia
  - Thirst/urinary frequency
  - Weight gain, fatigue
Adjunctive Antipsychotics

- **FDA approved**
  - Aripiprazole (Abilify) $530/mo
    - Start 2-5 mg, ave. 10mg, max 15-20mg
  - Quetiapine XR (Seroquel XR) $500/mo
    - 300mg qday
  - Olanzepine (Zyprexa) $275-700/mo, Olanzepine/fluoxetine (Symbyax) $300-575/mo
    - Low dose = high dose efficacy. Start 1-5 mg, ave. 5-12mg, max 20 mg

- **Non FDA approved**
  - Risperdone (Risperdol)
  - Ziprasidone (Geodon)

Connolly et al, Drugs 2011:71 (1) 43-64
### Adjunctive Antipsychotics

<table>
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<tr>
<th>Med</th>
<th>Response</th>
<th>Remission</th>
<th>NNT</th>
</tr>
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<tbody>
<tr>
<td>aripiprazole</td>
<td>32-46%</td>
<td>17-26%</td>
<td>5-10</td>
</tr>
<tr>
<td>olanzapine</td>
<td>27-60%</td>
<td>NR</td>
<td>2-9</td>
</tr>
<tr>
<td>quetiapine</td>
<td>56-59%</td>
<td>46%</td>
<td>7-8</td>
</tr>
</tbody>
</table>

- **Risks** – **Black box warning!** discontinuation 6%
  - Tardive dyskinesia, NMS, hyperglycemia/DM, orthostasis, body temperature, dysphagia
  - Akathisia (25%), restlessness, insomnia, constipation, fatigue. Pregnancy class C, lactation unknown- possibly unsafe

- **Duration** – no evidence for maintenance
- **Monitor** – FBG, lipids, +/- CBC

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Anything Else?

Winners
• Moderate exercise + meds
  RCT n=33, resp 21%, rem 26%
• Bright light therapy
• Psychotherapy
• Possibly dual therapy + mirtazapine at initiation
  – Remission 45-50% vs. 25%
  – Fluoxetine, venlafaxine, bupropion

Losers
• Lamotrigine solo or aug.
• Buspirone
• Stimulants
  – Insufficient evidence
  – Methylphenidate, amphetamines, modafinil
Practical Advice

• Duration of treatment
  – >6 weeks needed at dose for 1/3 to respond

• Changing meds
  – Cross taper between classes
  – SSRI to SSRI, OK to use equivalent dose in new med, and d/c old
  – Full washout after SSRI if starting MAOI

• Augmentation
  – TCAs use low dose 15-30 mg, check level
Serotonin Syndrome

• Symptoms and signs
  - **Neuro:** confusion, hyperreflexia, ataxia, rigidity, ocular clonus, Babinski, dilated pupils
  - **CV:** tachycardia, HTN
  - **GI:** vomiting, diarrhea
  - **Autonomic:** fever, diaphoresis

• Meds
  - SSRI, TCA, MAOI, Li, buspirone, triptans, L-dopa, odansetron, dextromethorphan, meperidine, linezolid
Take Home Points

• Consider psychotherapy first for mod. depression
• Consider sertraline and escitalopram for initial choice (discuss side-effects)
• Consider St. John’s wort
• Beware of serotonin syndrome
• Consider augmenting with bupropion or T3 for TRD. Any class is okay for switching meds
• Remember drug interactions and metabolism