9:45 – 10:25am

Depression: Pearls for Management in Primary Care

SPEAKER
Gerald W. Smetana, MD

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► Gerald W. Smetana, MD: No financial relationships to disclose.

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Depression: Pearls for Management in Primary Care

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Learning Objectives
• Discuss the importance of screening for depression in primary care
• Evaluate the efficacy of various antidepressants
• Apply combination antidepressant therapy strategies and distinguish between switching and augmentation of therapy for treatment failures
• Apply the advantages of side effect profiles when selecting antidepressant medications

Key Questions
• Does screening for depression work?
• How long to treat?
• Are newer antidepressants more effective than SSRIs?
• How do side effect profiles differ between drugs?
• Which is better: switching or augmenting?

Question #1
• Does screening for depression work?
• How do I follow up on a positive screening survey?
Does Screening for Depression Work?

- US Preventive Health Services Task Force
- December 2009 Update
- Recommends screening for depression (Grade B recommendation - fair evidence) when resources for Rx and follow up are available
- Good evidence that screening improves the accurate identification of depression in primary care settings and
- Treatment in the primary care setting decreases clinical morbidity

Ann Intern Med 2009;151:784

Accuracy of Non-Psychiatric Physicians Recognition of Depression

- 2007, Walter Reed Army Medical Center
  - 500 pts surveyed, results not disclosed to providers
  - 29% of pts had a mental disorder
  - After 5 years, 66% with identified mental disorder were undiagnosed.

- 2007, St. Mary’s Hospital, Montreal
  - Meta-analysis
  - How well do non-psychiatrists identify depression?
  - Less than half of depressed patients were identified by non-psychiatrists.

Which Screening Tools to Use?

- Multiple available questionnaires
- Administration times range from 1-5 minutes
- In a systematic review of screening tools:
  - Positive likelihood ratio (LR+)
    - 3.3 (range 2.3-12.2)
  - Negative likelihood ratio (LR-)
    - 0.19 (range 0.14-0.35)
  - High sensitivity (80-90%) but only fair specificity (57-85%)

The Rational Clinical Examination. Is this patient clinically depressed? JAMA 2002;287:1160

PHQ-9: Over the Past 2 Weeks, Have You Been Bothered by:

<table>
<thead>
<tr>
<th>Depression Severity</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimal</td>
<td>4</td>
</tr>
<tr>
<td>Mild</td>
<td>5-9</td>
</tr>
<tr>
<td>Moderate</td>
<td>10-14</td>
</tr>
<tr>
<td>Moderately severe</td>
<td>15-19</td>
</tr>
<tr>
<td>Severe</td>
<td>20-27</td>
</tr>
</tbody>
</table>

Simple Screening Tool: Ask Two Questions

1. ‘During the past month, have you often been bothered by feeling down, depressed or hopeless?’
2. ‘During the past month, have you often been bothered by having little interest or pleasure in doing things?’

- 96% sensitive but only 57% specific for at least one positive response
- Recommended by USPSTF

J Gen Intern Med 1997;12:439
Follow up of Screening Tool

- Screening tools
  - High sensitivity
  - Lower specificity
- Some false positives will occur
- Follow up with additional questions to probe for diagnosis of depression
- Consulting family members may add information

At least 4 of the following neurovegetative symptoms (SIG-ECAPS)

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep</td>
<td>Insomnia or sleeping too much</td>
</tr>
<tr>
<td>Interest</td>
<td>Diminished interest or pleasure in most activities</td>
</tr>
<tr>
<td>Guilt</td>
<td>Feelings of guilt or worthlessness</td>
</tr>
<tr>
<td>Energy</td>
<td>Loss of energy or fatigue</td>
</tr>
<tr>
<td>Concentration</td>
<td>Diminished ability to think or concentrate, indecisiveness</td>
</tr>
<tr>
<td>Appetite</td>
<td>Increase or decrease in appetite</td>
</tr>
<tr>
<td>Psychomotor</td>
<td>Psychomotor agitation or retardation</td>
</tr>
<tr>
<td>Suicide</td>
<td>Thoughts of death or suicidal ideation</td>
</tr>
</tbody>
</table>

Suicide Screening Questions

- Three simple questions
  - Do you ever think of hurting yourself or taking your own life?
  - Do you currently have a plan?
  - What is your plan?
- Do not fear that asking questions will suggest the idea of suicide to a patient
- Emergency mental health evaluation if patient can’t contract for safety

Question #2

- What are response rates to initial Rx?
- How long should one continue antidepressant medication?

STAR*D Trial of Citalopram: Time to Response Among Responders

- Mean dose 40 mg qd
- Results at 14 weeks
- Response
  - 47%
- Remission
  - 28%
- Most responders do so by 8 weeks
- Consistent with previous reports

Systematic Review: SSRIs More Alike than Different

Annals of Internal Medicine 2008;149:734-750
Three Treatment Phases

6-12 Weeks
- Acute Treatment

3-12 Months
- Continuation Treatment
  - Prevents relapse

Long term
- Maintenance Treatment
  - Prevents Recurrence

Approach to Relapse After Initial Rx

- Initial Rx may have been too brief
  - Continuation Rx for at least 6-9 months
- Relapse after adequate duration of Rx
  - Suggests need for maintenance Rx
  - At least 2-3 years
- First strategy is to resume the same med that led to initial remission
- Consider psychotherapy in addition to meds

Factors that Support Maintenance Phase Medication

- Two or more previous episodes of depression
- Major depression lasting more than 2 years
- Failed at least two previous taper attempts
- Age >50 or < 20 years
- Psychotic features
- Family history of recurrent depression
- Severe, sudden, or life threatening episode
- H/o suicide attempt

Important Considerations

- Initial med Rx response rates 50%
- Rx for at least 6-9 months
- Withdrawal symptoms if abrupt d/c of SSRIs
- Risk of serotonin syndrome for SSRIs increases with certain drug interactions
- Increased suicidal behavior for SSRIs for patients aged 18-29 years
- Increased risk of GI bleeding for SSRIs in older patients
- Medication probably not beneficial for minor depression

Question #3

- In patients with major depression, are the newer antidepressants (venlafaxine, nefazodone, mirtazapine, bupropion) more effective than SSRIs?

NO!
Systematic Review: Modest Differences in Response Rates Between New and Old Rx

<table>
<thead>
<tr>
<th>New Drug</th>
<th>Compared to</th>
<th>OR for Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mirtazapine</td>
<td>Fluoxetine</td>
<td>1.39</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>1.35</td>
<td></td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>Fluoxetine</td>
<td>1.30</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>1.27</td>
<td></td>
</tr>
<tr>
<td>Bupropion</td>
<td>Fluoxetine</td>
<td>0.82</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>0.73</td>
<td></td>
</tr>
</tbody>
</table>

Lancet 2009;373:746

Acceptability: Marginally Favors Two Old Agents: Sertraline and Escitalopram

<table>
<thead>
<tr>
<th>Drug</th>
<th>Acceptability compared to fluoxetine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Old</td>
<td></td>
</tr>
<tr>
<td>Sertraline</td>
<td>1.14</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>1.19</td>
</tr>
<tr>
<td>New</td>
<td></td>
</tr>
<tr>
<td>Bupropion</td>
<td>1.12</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>0.94</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>0.97</td>
</tr>
</tbody>
</table>

All comparisons p > 0.05

Question #4

- How do side effect profiles differ between drugs?

SSRI Side Effects

Available SSRIs
- Fluoxetine
- Sertraline
- Paroxetine
- Fluvoxamine
- Citalopram
- Escitalopram

Side effects
- Nausea (10%)
- Headaches (10%)
- Sweating (10%)
- Insomnia (15%)
- Sexual side effects (up to 50%)
  - Can minimize with bupropion augmentation
- Drug interactions

Citalopram: 2011 FDA Advisory on Dose and Risk of Arrhythmia

- Risk of QT prolongation and torsades at higher doses
- Do not exceed 40 mg daily
- No more than 20 mg daily for elderly or if liver disease

- Use with caution if CHF, h/o bradyarrhythmia or potential for hypokalemia
- Expanded list of drug interactions

FDA Advisory August 24, 2011
Tricyclic Antidepressants (TCAs)

- Equally effective as SSRIs
- Risk of death in overdose
- Side effects are anticholinergic, fatigue, orthostasis
- Start low: 25 mg at bedtime
- Nortriptyline twice as potent as others
- Consider use if insomnia or chronic pain are major features of depression

Specific Drug Side Effects Vary Between Old and New Drugs

<table>
<thead>
<tr>
<th></th>
<th>Anti-cholinergic</th>
<th>Fatigue</th>
<th>Insomnia</th>
<th>GI</th>
<th>Wt Gain</th>
</tr>
</thead>
<tbody>
<tr>
<td>TCA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td></td>
</tr>
<tr>
<td>Nortriptyline</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>SSRIs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Citalopram</td>
<td>++</td>
<td>+</td>
<td>+++</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sertraline</td>
<td>++</td>
<td>+++</td>
<td>++</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bupropion</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>++</td>
<td>+++</td>
<td>++</td>
<td></td>
<td>++</td>
</tr>
</tbody>
</table>

Effect on Body Weight is An Important Consideration

<table>
<thead>
<tr>
<th>Weight Gain</th>
<th>Neutral</th>
<th>Weight Loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mirtazapine</td>
<td>Citalopram</td>
<td>Fluoxetine</td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>Duloxetine</td>
<td>Bupropion</td>
</tr>
<tr>
<td>Doxepin</td>
<td>Escitalopram</td>
<td></td>
</tr>
<tr>
<td>Trazodone</td>
<td>Sertraline</td>
<td>Venlafaxine</td>
</tr>
</tbody>
</table>

Sexual Side Effects Vary

<table>
<thead>
<tr>
<th>Incidence Sexual Dysfunction</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 10%</td>
<td>Bupropion</td>
</tr>
<tr>
<td>10-30%</td>
<td>Mirtazapine</td>
</tr>
<tr>
<td>&gt; 30%</td>
<td>Citalopram</td>
</tr>
<tr>
<td></td>
<td>Duloxetine</td>
</tr>
<tr>
<td></td>
<td>Venlafaxine</td>
</tr>
</tbody>
</table>

Prescribing Tips

- Mirtazapine
  - Very sedating
  - Useful if insomnia
  - Constipation
  - Weight gain
- Bupropion
  - Activating
  - Can cause insomnia
  - Least sexual effects
  - May promote weight loss
- Venlafaxine
  - Side effect profile similar to SSRIs
  - More fatigue
  - Higher morbidity in OD than SSRIs
- Nefazodone
  - Case reports of liver failure
  - Do not recommend for use in primary care

Question #5

- What is the approach to SSRI non-responders?
- Switch to another medication in the same class?
- Switch classes?
- Augment with another agent?
Before Modifying Drug Regimen:

- Inquire about side effects (particularly sexual) that prevent adherence
- Consider adding psychotherapy to medication
- Consider alcohol or drug abuse (dual diagnosis)
- Reconsider correct diagnosis of depression, exclude bipolar or PTSD

Treatment Failures: Switch or Augment?

If no response to first SSRI, choices include:

- Change to another SSRI
- Switch to new class
- Augment by adding second drug

Selection of second SSRI is empiric. My recommendation due to prescriber comfort and cost

STAR*D: Citalopram Treatment Failures: No Difference Between Switch to Bupropion, Sertraline, or Venlafaxine

Switch: Therapy and Meds Comparable
Augment: Medication More Effective and Faster

Reasons to Seek Psychiatric Consultation

- Failure to respond to trial of two different medications
- Patient actively suicidal
- Suggestion of bipolar disorder
- Presence of psychotic features
- Patient preference
- Co-morbid medical, psychiatric, or substance use disorder
- Treatment resistant depression with psychomotor retardation that may warrant ECT

Summary

- Screen with simple two question tool
- Exclude suicidality
- Acute, continuation, and maintenance medication
- SSRIs: 50% response, 30% remission
- Response rates similar for all SSRIs
- Risk of relapse if Rx < 6-9 months
- No difference in remission rates for newer agents when compared to SSRIs
Summary

• Use SSRIs as first choice for most patients
• Side effect profiles important in drug choice
  - Weight loss or gain
  - Sedation
  - Sexual side effects
• Switch or augment probably comparable
• Meds work more quickly than cognitive Rx

“In sooth, I know not why I am so sad: It wearies me; you say it wearies you; But how I caught it, found it, or came by it, What stuff ’tis made of, whereof it is born, I am to learn; And such a want-wit sadness makes of me, That I have much ado to know myself.”

Antonio, in
William Shakespeare
The Merchant of Venice
Act 1, Scene 1