Depression Screening & Treatment in Primary Care: Part One

Physician Overview of Treatment Guidelines

Wednesday, September 14, 2016
We Want To Hear From You!

Type questions into the Questions Pane at any time during this presentation
Patient-Centered Primary Care Institute

Transforming Primary Care: Promote Knowledge Sharing, Facilitate Collaborative Learning, Build Capacity, Create Alignment

Online Modules, Webinars, Website, Learning Collaboratives, Trainings, TA Network
PCPCH Model of Care

Oregon’s PCPCH Model is defined by six core attributes, each with specific standards and measures

- **Access to Care** “Health care team, be there when we need you”
- **Accountability** “Take responsibility for making sure we receive the best possible health care”
- **Comprehensive Whole Person Care** “Provide or help us get the health care, information and services we need”
- **Continuity** “Be our partner over time in caring for us”
- **Coordination and Integration** “Help us navigate the health care system to get the care we need in a safe and timely way”
- **Person and Family Centered Care** “Recognize that we are the most important part of the care team - and that we are ultimately responsible for our overall health and wellness”

Learn more: [http://primarycarehome.oregon.gov](http://primarycarehome.oregon.gov)
Learning Objectives

• Review existing clinical practice guidelines for medication and non-medication treatment of depression, including the research supporting non-medication management

• Provide information on addressing depression for specific populations, including adolescents and older adults
Presenter Introductions

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Chief Medical Officer for Cascadia Behavioral Healthcare
& Medical Director for OHSU's Project ECHO

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Clinical Pharmacy Manager at UnitedHealth Group
& Psychiatric Pharmacy Consultant for OHSU’s Project ECHO
Treatment of Depression in Primary Care
Why Bother?

- The CDC estimates that as many as 5% of those over age 11 have depression

- Roughly 1 in 6 Americans will have meet criteria for Major Depressive Disorder at some point in their lives
  - https://www.icsi.org/guidelines_more/catalog_guidelines_and_more/catalog_guidelines/catalog_behavioral_health_guidelines/depression/

- Depression is Treatable!
Why bother in the Primary Care Setting?

• More than 70% of Americans who seek treatment for depression do so from PCP's

• More than 70% of antidepressants are prescribed in primary care
  • https://www.icsi.org/guidelines_more/catalog_guidelines_and_more/catalog_guidelines/catalog_behavioral_health_guidelines/depression/

• Depressive Symptoms and Severity vary little between Primary Care and specialty care settings
  • http://www.annfammed.org/content/5/2/126.full.pdf
Depression co-occurs

- Risk of depression is much higher in certain medical illnesses
  - 1 out of 20 American adults
  - 3 out of 20 with diabetes
  - 8 out of 20 stroke survivors
  - 4-12 out of 20 people with cancer
  - 13 out of 20 heart attack survivors

What is Depression?

- An abnormally low mood that interferes
- There are several types of depression
  - Major Depressive Disorder
  - Persistent Depressive Disorder
  - Bipolar Depression
  - Substance-induced Mood Disorder
  - Depression due to Medical Illness
  - Depressive Disorder NOS
Major Depressive Disorder

- At least five of the following symptoms have been present during the same 2-week period and represent a change from previous functioning: at least one of the symptoms is either 1) or 2)
- Depressed mood
- Markedly diminished interest
- Significant weight or appetite changes
- Insomnia or hypersomnia
- Psychomotor agitation or retardation
- Fatigue or loss of energy
- Feelings of worthlessness or guilt
- Diminished ability to think or concentrate, or indecisiveness
- Recurrent thoughts of death or suicidal thoughts
SIG E CAPS for Depression

S  sleep decreased (or increased)
I  interest decreased
G  guilt or worthlessness
E  energy decreased
C  concentration difficulties
A  appetite disturbance or weight loss
P  psychomotor agitation or retardation
S  suicidal thoughts

and depressed mood!
When to Screen for Depression

• Family predisposition to depression
• Previous history of any psychiatric disorder
• Two or more chronic diseases
• Stressful home or work environment
• Recent history of major loss (health, relationship, job)
• Multiple vague symptoms, aches, and pains
• Loss of interest in sexual activity
• Older adults
• Everyone?

PHQ-9 helps clarify severity of depression

- PHQ-9 screens for the 9 MDD criteria
  - Score 0-4: No depression symptoms
  - Score 5-9: Minor depression symptoms
  - Score 10-14: Moderate depression symptoms
  - Score 15-19: Moderate to severe depression symptoms
  - Score 20 or more: Severe depression symptoms

- Score of 10 or greater indicates MDD
- Sensitivity – 88%    Specificity – 88%

PHQ-9 for Adolescents

- PHQ-9 works well in adolescents when a cut-off score of 11 is used
  - [http://pediatrics.aappublications.org/content/126/6/1117.full.pdf+html](http://pediatrics.aappublications.org/content/126/6/1117.full.pdf+html)
- Some experts have modified the PHQ-9 for teens, known as the PHQ-A
- Still others recommend an extended depression screening
  - [https://provider.ghc.org/open/caringForOurMembers/patientHealthEducation/screeningSchedules/depressionPHQ9Teen.pdf](https://provider.ghc.org/open/caringForOurMembers/patientHealthEducation/screeningSchedules/depressionPHQ9Teen.pdf)
GDS and CSDD

• Geriatric Depression Scale – Short Form
  – 15 yes or no questions
  – Score greater than 5 suggests depression
  – 92% Sensitivity and 89% Specificity
  
  http://www.healthcare.uiowa.edu/igec/tools/depression/GDS.pdf

• Cornell Scale for Depression in Dementia
  – 19 scaled questions
  – Score of 12 or more indicates probable depression
  – 93% sensitivity, 97% specificity

http://www.primaris.org/sites/default/files/resources/Depression/depression_cornell%20scale%20for%20depression%20final.pdf
Nonpharmacologic Interventions

- Antidepressants are no better than placebo for mild to moderate depression

- Antidepressants may worsen bipolar disorder

- Antidepressants tend to have drug-drug interactions

- Antidepressants can be pretty aversive
Differential Diagnosis

- Other things masquerade as depression
  - Hypothyroidism
  - Sleep deprivation or sleep apnea
  - Medication side effects
  - Vitamin B12, D, or iron deficiencies
  - Anemia
  - Viruses
- So start all treatment with a good work up
Exercise

- Just as effective as sertraline

- High energy expenditure is best, but any exercise is better than no exercise

- Often benefits other comorbid conditions

- At the least, add it to other treatments

- Exercise protects against depression
Sleep Hygiene

- Loss of sleep leads to depression
  - https://www.elsevier.com/books/sleep-and-affect/babson/978-0-12-417188-6

- Treating insomnia with CBT can double chances of recovery from depression

- Start with Sleep Hygiene
  - Regular bed and awake times
  - No naps
  - Keep your room dark and quiet as possible
  - Your bed is only for two things!
Light Therapy

- Appears effective for both SAD and MDD
- The more intense the light, the better
- Ideally, use first thing in the morning
- Follow the package instructions
- May need to monitor for hypomania
- Low-risk, low-cost option
  - [link](http://pro.psychcentral.com/light-therapy-for-depression-does-itwork/002903/html)
  - [link](http://www.psycheducation.org/depression/LightTherapy.htm)
  - [link](http://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/mdd.pdf)
Psychotherapy

- Types effective in acute depression
  - Cognitive Behavioral Therapy
  - Interpersonal Therapy
  - Behavioral Therapies
- As effective as medications in mild to moderate depression
- Beneficial effect more prolonged than medications
- May be preferable for women who want to get pregnant

http://behavioralassociatesla.com/research-on-the-efficacy-of-cbt-treatment/
Behavioral Activation

• Schedule fun!

• Schedule responsibilities
  – http://www.therapistaid.com/content/0022.pdf

• Volunteer

• Engage in your spiritual/religious tradition

• Break things into manageable chunks
Non-Pharmacologic Options for Treatment-Resistant Depression

Four main therapies for Severe MDD
• ECT – Electroconvulsive Therapy
• rTMS – repetitive Transcranial Magnetic Stimulation
• VNS – Vagal Nerve Stimulation
• CBT – Cognitive Behavioral Therapy

Electroconvulsive Therapy

- ECT may be first-line therapy
  - Severe depression with
    - Psychotic Features
    - Catatonia
    - Suicide Risk
    - Food refusal leading to nutritional compromise
    - Severe Medical Illness
  - Those who have previously responded
  - Those who prefer it*
Transcranial Magnetic Stimulation

- Uses MRI-strength magnetic pulses to stimulate superficial cortical neurons
- Requires daily treatments
- Approved by the FDA in 2008
- Not considered a first-line treatment

Vagal Nerve Stimulation

- Only approved for treatment resistant depression
- May work better when used together with medications
- Requires surgical implantation
- Not indicated for first-line treatment

Depression in Primary Care

• Depression is common
• Depression is treatable
• PHQ-9 simplifies detecting and quantifying depression
• The first steps in the treatment of recovery are usually nonpharmacological
Pharmacologic Interventions
# Antidepressant Treatment Selection

<table>
<thead>
<tr>
<th>Severity</th>
<th>PHQ-9 or PHQ-9A score</th>
<th>Psychotherapy</th>
<th>Antidepressant</th>
<th>Combination psychotherapy and antidepressant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe major depression</td>
<td>20–27</td>
<td>Shared decision making</td>
<td>Recommended</td>
<td>Recommended <em>(preferred)</em></td>
</tr>
<tr>
<td>Moderately severe major depression</td>
<td>15–19</td>
<td>Shared decision making</td>
<td>Shared decision making</td>
<td>Shared decision making</td>
</tr>
<tr>
<td>Moderate major depression</td>
<td>10–14</td>
<td>Shared decision making</td>
<td>Shared decision making</td>
<td>Shared decision making</td>
</tr>
<tr>
<td>Indeterminate or mild depression</td>
<td>5–9</td>
<td>Usually not indicated</td>
<td>Usually not indicated</td>
<td>Usually not indicated</td>
</tr>
</tbody>
</table>
# Antidepressant Treatment Selection

<table>
<thead>
<tr>
<th>Modality</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>NNT for 1 Positive Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychotherapy</td>
<td>Effective and safe—no physical side effects</td>
<td>Possible increased number of visits/copays</td>
<td>Vs. placebo = 7</td>
</tr>
<tr>
<td></td>
<td>Benefit continues after active therapy is completed</td>
<td></td>
<td>Sustained effect (2 yrs post-therapy) = 5-6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CBT vs. other psychotherapies = NS</td>
</tr>
<tr>
<td>Antidepressant</td>
<td>Achieves greater improvement than psychotherapy in the first 2 months, after which results are equivalent</td>
<td>Medication side effects</td>
<td>Vs. placebo = 5-7</td>
</tr>
<tr>
<td></td>
<td>More effective than psychotherapy in severe depression</td>
<td>Possible increased suicidal ideation</td>
<td>Vs. psychotherapy = NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No long-term effect after medication is discontinued</td>
<td>One 2nd-Gen antidepressant vs. another = NS</td>
</tr>
<tr>
<td>Combination Therapy</td>
<td>Same as above</td>
<td>Same as above</td>
<td>Vs ATDs alone = 4-10</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Vs. ATDs alone—high severity = 5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Vs. ATDs alone—low severity = NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Vs. psychotherapy alone = 4</td>
</tr>
</tbody>
</table>
### Available Antidepressants

<table>
<thead>
<tr>
<th><strong>SSRIs</strong></th>
<th><strong>SNRIs</strong></th>
<th><strong>Others</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Brintellix</strong> (vortioxetine) B</td>
<td><strong>Cymbalta</strong> (duloxetine) G</td>
<td><strong>Wellbutrin</strong> (bupropion) G</td>
</tr>
<tr>
<td><strong>Celexa</strong> (citalopram) G</td>
<td><strong>Effexor</strong> (venlafaxine) G</td>
<td>Bupropion is a weak inhibitor of DA, NE and 5HT reuptake</td>
</tr>
<tr>
<td><strong>Lexapro</strong> (escitalopram) G</td>
<td><strong>Fetzima</strong> (levomilnacipran) B</td>
<td><strong>Remeron</strong> (mirtazapine) G</td>
</tr>
<tr>
<td><strong>Luvox</strong> (fluvoxamine) G</td>
<td><strong>Pristiq</strong> (desvenlafaxine) B,G</td>
<td>Mirtazapine ↑central noradrenaline and 5HT activity by antagonizing central presynaptic α2 adrenergic autoreceptors and heteroreceptors</td>
</tr>
<tr>
<td><strong>Paxil</strong> (paroxetine) G</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Prozac</strong> (fluoxetine) G</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Viibryd</strong> (vilazodone) B</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Zoloft</strong> (sertraline) G</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Selectively inhibit the reuptake of serotonin (5HT) at the presynaptic neuronal membrane

Inhibit serotonin and norepinephrine reuptake

G=Generic; B=Brand
Role of Neurotransmitters

NOREPINEPHRINE
- Attention
- Motivation
- Pleasure
- Reward

DOPAMINE
- Alertness
- Energy

SEROTONIN
- Mood
- Anxiety
- Obsessions and Compulsions
Choosing an Initial Antidepressant

Because there is comparable efficacy between and within classes of medications, the initial selection of antidepressants is based largely on the following considerations:

• Anticipated side effects
• Safety and tolerability of side effects for individual patients
• Patient preference
• Quantity and quality of clinical trial data
• Cost
Initial Treatment Selection

- Comparative effectiveness
- Side effects
- Drug interactions
- Patient preference
- Cost
Summary of the Evidence

- Effectiveness and efficacy were similar between all second generation antidepressants.
  - Roughly a 60% overall response rate
    - Overall mean weighted effect size = 0.37 (95% CI, 0.33-0.41) from published PCB controlled studies. For unpublished studies, the effect size is 0.15 (95% CI, 0.08-0.22).
    - (0.2 indicates small, 0.50 moderate, and 0.80 large differences between interventions)
  - Discontinuation rates and response and remission rates did not differ substantially.
  - Minor differences in onset of action, tolerability, side effects and significant differences in cost may affect treatment choices.

www.ohsu.edu/drugeffectiveness/reports/final.cfm
FDA black box warning for all patients aged 24 years or younger

- Warning that antidepressant medications may sometimes increase suicidal ideation in children, adolescents, and young adults (aged 18 – 24 years) during initial treatment (generally first 1-2 months) and at times of dose changes.

- A pooled analysis of placebo controlled trials suggests:
  - For patients <18 years of age: 14 additional cases of suicidal ideation per 1,000 patients (NNH=71)
  - For patients 18-24 years of age: 5 additional cases of suicidal ideation per 1,000 patients (NNH = 200)

- Families/caregivers should be alerted about the need to monitor patients daily for the emergence of agitation, irritability and unusual changes in behavior.

- Providers should follow-up with patients a minimum of 3x during the first 2 months. More frequent contact may be needed with high-risk patients.

- Untreated depression may also lead to suicidal behavior/ideation
Common Adverse Effects

SSRIs
- Nausea
- Vomiting
- Dizziness
- Insomnia
- Agitation
- Headache
- Sexual dysfunction

SNRIs
- Nausea
- Vomiting
- Dizziness
- Insomnia
- Anxiety
- Headache
- Somnolence
- Decreased appetite
- Sexual dysfunction

Others
- Bupropion:
  - Headache
  - Agitation
  - Weight loss
  - Insomnia
  - Nausea
- Mirtazapine:
  - Dizziness
  - Diarrhea
  - Increased appetite (weight gain)
  - +/- Drowsiness
  - Dry mouth
## Common Adverse Effects

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>Coping Strategies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>Take with food or divide the dose (half with breakfast, half with lunch) Suck on sugarless hard candy Drink plenty of fluids Try antacids</td>
</tr>
<tr>
<td>Fatigue, drowsiness</td>
<td>Brief nap during the day Regular physical activity Avoid driving or operating dangerous machinery until the fatigue passes Take ATD 1 to 2 two hours before bedtime</td>
</tr>
<tr>
<td>Insomnia</td>
<td>Take ATD in the morning Avoid caffeinated food and drinks Regular physical activity</td>
</tr>
<tr>
<td>Dizziness</td>
<td>Rise slowly from sitting or standing positions Use handrails, canes or other sturdy items for support Avoid driving or operating machinery Avoid caffeine, tobacco and alcohol Drink plenty of fluids Take your antidepressant at bedtime</td>
</tr>
</tbody>
</table>
## Common Adverse Effects

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>Coping Strategies</th>
</tr>
</thead>
</table>
| Dry mouth                     | Sip water regularly or suck on ice chips  
                                   Chew sugarless gum or suck on sugarless hard candy  
                                   Avoid caffeine  
                                   Breathe through your nose, not your mouth  
                                   Brush your teeth twice a day, floss daily and see your dentist regularly.  
                                   Consider a moisturizing mouth spray or another product that might stimulate saliva production |
| Blurry vision                 | Consider use of eyedrops to relieve dryness  
                                   Get an eye exam to see whether blurred vision caused by an antidepressant may be worsened by an underlying eye problem  
                                   Consider alternative antidepressant |
| Constipation                  | Drink plenty of water  
                                   Eat high-fiber foods or a fiber supplement  
                                   Get regular exercise  
                                   Consider stool softeners |
| Agitation, restlessness, anxiety | Get regular exercise  
                                   Practice deep-breathing exercises, muscle relaxation or yoga  
                                   Consult your doctor about temporarily taking a relaxing or sedating medication or switching to an antidepressant that isn't as stimulating |
ATDs and Sexual Dysfunction

- Serotonin-enhancing antidepressants have been associated with diminished sexual desire, delayed sexual arousal, and muted or absent orgasm.
- Interesting article on the ability of ATDs to jeopardize romantic love and marriage:
  www.medscape.org/viewarticle/482059
### ATD Induced Sexual Dysfunction

<table>
<thead>
<tr>
<th>Antidepressant</th>
<th>Type of Sexual Dysfunction</th>
<th>Incidence*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venlafaxine</td>
<td>Impaired ejaculation, delayed/absent orgasm</td>
<td>12%</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>Impaired ejaculation, delayed/absent orgasm</td>
<td>13-28%</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>Impaired ejaculation, delayed/absent orgasm</td>
<td>2-8%</td>
</tr>
<tr>
<td>Sertraline</td>
<td>Impaired ejaculation, delayed/absent orgasm</td>
<td>14%</td>
</tr>
<tr>
<td>Citalopram</td>
<td>Impaired ejaculation, delayed/absent orgasm, decreased libido</td>
<td>1-6%</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>Impaired ejaculation, delayed/absent orgasm, decreased libido, and erectile impairment</td>
<td>2-11%</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>Decreased libido</td>
<td>2-6%</td>
</tr>
<tr>
<td>Bupropion</td>
<td>Decreased libido</td>
<td>1-3%</td>
</tr>
</tbody>
</table>

*Based on spontaneous report in clinical trials*
ATD Induced Sexual Dysfunction

• STAR*D findings (14-week study)
  • Decreased libido => 54%
  • Difficulty achieving orgasm => 36%
  • Erectile dysfunctions => 37% (males)

• Cross sectional survey of new SSRI or SNRI starts found treatment-emergent sexual dysfunction in approximately 50% of patients
ATD Induced Sexual Dysfunction

- General Approach:
  - Unresponsive to SSRI or troubled by SSRI-induced sexual dysfunction => bupropion
  - SSRI responders who suffer from sexual dysfunction:
    - Decrease the dose (those w/ high dose or in remission)
    - Wait for spontaneous remission (wait 2 to 8 weeks)
    - Switch to a non-SSRI
    - Switch to a different SSRI
    - Use a second drug to offset the adverse effect (e.g. bupropion, phosphodiesterase inhibitors)
    - Drug holiday (short half lives)
ATD Induced Sexual Dysfunction

Key Points

- Serotonergic antidepressant incidence may be as high as 50-80%.
- Lowest level of sexual dysfunction with non-serotonergic antidepressants.
- Patients should be routinely asked about sexual adverse effects. May affect ATD adherence.
- Best way to avoid is the use of non-serotonergic antidepressants = bupropion
• Healthcare system study
  • Amitriptyline, bupropion, citalopram, duloxetine, escitalopram, fluoxetine, mirtazapine, nortriptyline, paroxetine, sertraline, or venlafaxine use between 2/1/1990 and 12/1/2011
  • Citalopram used as reference antidepressant
  • Only statistically significant difference:
    • Nortriptyline, amitriptyline, bupropion < citalopram
FDA issued a warning in 2011 about the risk of QT prolongation with citalopram at doses higher than 40mg/day. The following year, a maximum dose of 20mg/day for specific patient groups was advised.

Citalopram blood levels are influenced by variants in CYP2C19

Retrospective cohort study used data from 748 adults (318 with exposure to citalopram or escitalopram) evaluated with CYP P450 genotyping

- Extensive metabolizers had a significantly shorter QTc
- Serum concentration of citalopram was not found to be associated with QTc prolongation

**Bottom line:** Use caution in prescribing citalopram at doses higher than 20 mg in patients who may have increased levels of citalopram in the blood (>60 yrs, hepatic impairment, poor 2C19 metabolizers, concomitant 2C19 inhibitors. Use caution in patients with congenital long QT syndrome, bradycardia, hypokalemia or hypomagnesemia, recent acute MI, or uncompensated heart failure. Additional clinical monitoring (EKG) is recommended for patients taking >40 mg citalopram.
### SSRI Enzyme Inhibition

<table>
<thead>
<tr>
<th>DRUG</th>
<th>CYP450 ISOENZYME</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1A2</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td></td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>****</td>
</tr>
<tr>
<td>Sertraline</td>
<td></td>
</tr>
<tr>
<td>Paroxetine</td>
<td></td>
</tr>
<tr>
<td>Citalopram</td>
<td></td>
</tr>
<tr>
<td>Escitalopram</td>
<td></td>
</tr>
</tbody>
</table>

Other notable enzyme modification: duloxetine is a moderate inhibitor of 2D6, bupropion is a strong inhibitor of 2D6, St. John’s Wort is a 2C9, 2C19, and 3A4,5,7 inducer. Brintellix, Fetzima and Viibryd do not appear to inhibit or induce isoenzymes.
# Clinically Relevant Drug Interactions

<table>
<thead>
<tr>
<th>SSRI</th>
<th>Interacting Drug</th>
<th>Possible Effect(s)</th>
<th>Importance and Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>Alcohol</td>
<td>Increased CNS depression</td>
<td>Advise caution in early stage of treatment</td>
</tr>
<tr>
<td>All</td>
<td>Benzodiazepines</td>
<td>Increased sedation. Fluoxetine and paroxetine may reduce metabolism</td>
<td>Advise caution</td>
</tr>
<tr>
<td>All</td>
<td>Warfarin</td>
<td>Increased INR and increased bleeding risk due to antiplatelet effect</td>
<td>Monitor INR</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>Metoprolol and propranolol</td>
<td>Increased beta-blocking effects, bradycardia</td>
<td>Monitor HR</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>Buspirone</td>
<td>Serotonin syndrome and theoretical lowering of seizure threshold</td>
<td>Monitor concurrent use</td>
</tr>
<tr>
<td>All</td>
<td>Antiepileptics, CBZ, phenytoin</td>
<td>Increased plasma concentrations of carbamazepine and phenytoin</td>
<td>Monitor plasma levels. Adjust dose if necessary.</td>
</tr>
<tr>
<td>All</td>
<td>NSAIDs</td>
<td>Increased risk of GI bleeding</td>
<td>Assess risk in those with additional RFs</td>
</tr>
</tbody>
</table>
## Clinically Relevant Drug Interactions

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<th>Importance and Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>MAOIs</td>
<td>Hypertensive crisis</td>
<td>Avoid concurrent use. Washout is essential.</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>Clozapine, haloperidol, risperidone</td>
<td>Increase AP plasma concentrations</td>
<td>Monitor for dose related adverse effects and reduce AP if needed</td>
</tr>
<tr>
<td>Paroxetine</td>
<td></td>
<td>Serotonin syndrome, lowering of seizure threshold</td>
<td>Use combination very cautiously, especially at high dose. Alternative analgesics are preferable</td>
</tr>
<tr>
<td>All</td>
<td>Tramadol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>TCAs</td>
<td>Increased TCA plasma concentrations, increase risk of adverse effects. Risk of serotonin syndrome with clomipramine</td>
<td>Increases can be around 3-4x or more. Start w/ lowest TCA dose and monitor.</td>
</tr>
<tr>
<td>All</td>
<td>Sibutramine</td>
<td>Increase risk of CNS toxicity</td>
<td>Avoid</td>
</tr>
</tbody>
</table>
## Clinically Relevant Drug Interactions

<table>
<thead>
<tr>
<th>SSRI</th>
<th>Interacting Drug</th>
<th>Possible Effect(s)</th>
<th>Importance and Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>Antiarrhythmic drugs</td>
<td>Increased plasma concentrations leading to toxicity</td>
<td>Greatest with fluoxetine and paroxetine. Refer to individual prescribing information</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>Protease inhibitors (ritonavir)</td>
<td>Increase in both drug concentrations. Cases of serotonin syndrome with fluoxetine have been reported.</td>
<td>Monitor for serotonin syndrome</td>
</tr>
<tr>
<td>Paroxetine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>Lithium</td>
<td>Neurotoxic symptoms and serotonin like syndrome occasionally reported</td>
<td>Addition of Li to SSRI can be beneficial and is usually uneventful.</td>
</tr>
<tr>
<td>All</td>
<td>Selegilene</td>
<td>HTN, CNS excitation, serotonin syndrome</td>
<td>Avoid</td>
</tr>
<tr>
<td>All</td>
<td>St. John’s Wort</td>
<td>Serotonin syndrome</td>
<td>Avoid</td>
</tr>
<tr>
<td>All</td>
<td>Sumatriptan</td>
<td>Cases of dyskinesias with fluoxetine. Occasional reports of serotonin syndrome</td>
<td>Typically not a problem, but monitoring is recommended at start</td>
</tr>
</tbody>
</table>
Citalopram and escitalopram—least likely SSRIs to cause CYP450 drug interactions

Venlafaxine—less likely than duloxetine to cause drug interactions

Bupropion—can lower the seizure threshold, potent 2D6 enzyme inhibitor
### Comparative Benefits
- Similar efficacy, effectiveness, and QOL
- Onset of action
  - Mirtazapine > citalopram, fluoxetine, paroxetine, & sertraline
- Response rates similar after 4 weeks of tx
- Remission rates similar
- Efficacy does not differ in older adults
- Fluoxetine daily = fluoxetine weekly (response and remission rates)
- Paroxetine IR = paroxetine CR (response and adherence rates)
- Similar efficacy for treating anxiety and depression in MDD with anxiety sx
- Paroxetine=duloxetine (pain scores for patients with depression)

### Comparative Adverse Effects
- Nausea and vomiting: Venlafaxine has a 52% higher incidence than SSRIs as a class
- Weight gain: Mirtazapine > citalopram, fluoxetine, paroxetine, sertraline (1.8 – 6.6 lbs after 6-8 wks)
- Diarrhea: Sertraline > bupropion, citalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine & venlafaxine
- Discontinuation Rates: Duloxetine & venlafaxine > SSRIs
- Withdrawal Symptoms: Paroxetine & venlafaxine > other SSRIs; Lowest with fluoxetine
- Sexual Dysfunction: Bupropion < escitalopram, fluoxetine, paroxetine, and sertraline; Paroxetine > other SSRIs
First-Line Treatment Selection

<table>
<thead>
<tr>
<th>Adult*</th>
<th>Pregnant or Breastfeeding</th>
<th>Adolescent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Escitalopram</td>
<td>Fluoxetine Sertraline</td>
<td>Escitalopram Fluoxetine Sertraline</td>
</tr>
<tr>
<td>Fluoxetine Sertraline</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Elderly—use lower initial doses and slower titration.
Be aware of potential drug-drug interactions.
# First-Line Treatment Selection

<table>
<thead>
<tr>
<th>Drug</th>
<th><strong>Initial dose</strong></th>
<th><strong>Titration schedule (after adequate trial)</strong></th>
<th><strong>Usual therapeutic dose range</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Bupropion XL</td>
<td>150 mg daily in the morning</td>
<td>Increase to 300 mg qd</td>
<td>300 – 450 mg</td>
</tr>
<tr>
<td>Citalopram</td>
<td>10 mg qd X 7 days, then increase to 20 mg qd</td>
<td>Increase to 40 mg, if clinically appropriate</td>
<td>20 – 40 mg</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>5 mg qd X 7 days, then increase to 10 mg qd</td>
<td>Increase to 20 mg daily</td>
<td>10 – 20 mg</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>10 mg qd before noon X 7 days, then increase to 20 mg qd before noon</td>
<td>Increase by 20 mg increments at 4-week intervals</td>
<td>20 – 60 mg</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>15 mg qhs X 7 days, then increase to 30 mg daily</td>
<td>Increase to 45 mg daily if needed (may need to give in the morning)</td>
<td>15 – 45 mg</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>10 mg qd X 7 days, then increase to 20 mg qd</td>
<td>Increase by 10 mg increments at 4-week intervals</td>
<td>10 – 50 mg</td>
</tr>
<tr>
<td>Sertraline</td>
<td>50 mg qd X 7 days, then increase to 100 mg qd</td>
<td>Increase in 50 mg increments at 4-week intervals</td>
<td>50 – 150 mg</td>
</tr>
<tr>
<td>Venlafaxine XR</td>
<td>75 mg qd with food X 7 days, then increase to 150 mg qd</td>
<td>Increase to 225 mg daily</td>
<td>75 – 225 mg</td>
</tr>
</tbody>
</table>
Defining the Goals of Treatment

• **Response** = a clinically significant degree of depressive symptom reduction following treatment initiation.
  – When used clinically, response implies that the treatment has caused the response.
  – Response criteria must be met for 3 consecutive weeks.

• **Remission** = the virtual absence of depressive symptoms.
  – 3 consecutive weeks must pass, during which each week is characterized by the virtual absence of depressive symptoms, before remission can be ascribed.
  – Remission may end with either relapse or recovery.
# Progressive ATD Treatment

<table>
<thead>
<tr>
<th>Level</th>
<th>Treatment</th>
<th>Choices</th>
<th>Remission Rate</th>
<th>Relapse Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Monotherapy</td>
<td>SSRI</td>
<td>30%</td>
<td>33.5%</td>
</tr>
<tr>
<td>2</td>
<td>Switch</td>
<td>Different SSRI, bupropion SR or venlafaxine XR</td>
<td>25%</td>
<td>47.4%</td>
</tr>
<tr>
<td></td>
<td>Augment</td>
<td>Bupropion SR</td>
<td>30%</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Switch</td>
<td>Mirtazapine or nortriptyline</td>
<td>12-20%</td>
<td>42.9%</td>
</tr>
<tr>
<td></td>
<td>Augment</td>
<td>Lithium or thyroid (T3)</td>
<td>16%</td>
<td>25%</td>
</tr>
<tr>
<td>4</td>
<td>Switch</td>
<td>MAOI or venlafaxine + mirtazapine</td>
<td>6.9%</td>
<td>&gt;50%</td>
</tr>
</tbody>
</table>

Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study
Adequate Antidepressant Trials

The first selection may have the most impact.

- Minimum trial duration = 6 weeks
- Average trial duration = 8 weeks
- Newly recommended trial duration = 12-14 weeks

**Ensure adequate dose, duration and adherence**
Switching Strategies

<table>
<thead>
<tr>
<th>Initial drug</th>
<th>Fluoxetine</th>
<th>Other SSRI</th>
<th>SNRI</th>
<th>Mirtazapine</th>
<th>Nefazodone</th>
<th>Bupropion</th>
<th>MAOI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoxetine</td>
<td></td>
<td></td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Other SSRI</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>SNRI</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Nefazodone</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Bupropion</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>MAOI</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>

Key: (1) direct switch probably safe; (2) cross-taper recommended; (3) washout period advisable
## Augmentation Strategies

<table>
<thead>
<tr>
<th>Augmentation Agent</th>
<th>Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lithium</td>
<td>Studied dose range = 600-1200 mg/d Superior to placebo Majority of studies with TCAs Data weaker with SSRIs Consider adverse effects, potential toxicity, and need for serum monitoring</td>
</tr>
<tr>
<td>Thyroid Hormone (T3)</td>
<td>Hypothesized to work by enhancing noradrenergic neurotransmission or correcting a brain bioenergetic deficiency. Target dose = 50 mcg/d Well tolerated, few adverse effects Much of the data involves TCAs, not SSRIs Baseline and regular monitoring is recommended May work even in euthyroid individuals</td>
</tr>
</tbody>
</table>
Augmentation Strategies

<table>
<thead>
<tr>
<th>Augmentation Agent</th>
<th>Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bupropion</td>
<td>STAR*D found similar results compared with buspirone augmentation, but fewer side effects. Mean dosage was 267 mg/d</td>
</tr>
<tr>
<td>Buspirone</td>
<td>STAR*D found similar results compared with bupropion, but more adverse effects. Mean dosage was 41 mg/d</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>STAR*D studied as an addition to venlafaxine extended-release compared with MAOI tranylcypromine. Low efficacy for both agents, mirtazapine was better tolerated</td>
</tr>
</tbody>
</table>
## Augmentation Strategies

<table>
<thead>
<tr>
<th>Augmentation Agent</th>
<th>Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mood Stabilizers</td>
<td>Topiramate—one small placebo-controlled trial showed significant improvement in depression compared with placebo</td>
</tr>
<tr>
<td></td>
<td>Lamotrigine—Augmentation studies have been negative</td>
</tr>
<tr>
<td></td>
<td>VPA—small favorable study</td>
</tr>
<tr>
<td>Stimulants</td>
<td>Studies of stimulants for ATD augmentation have been negative (including studies of methylphenidate, modafinil, and atomoxetine), despite their initial euphorigenic effect</td>
</tr>
<tr>
<td>Pindolol</td>
<td>Positive open-label trials and a small placebo-controlled trial. Results from larger placebo-controlled trials have been negative</td>
</tr>
<tr>
<td>Sex hormones</td>
<td>Mixed results; concern about long-term adverse effects. Most convincing for testosterone in men with low levels.</td>
</tr>
</tbody>
</table>
# Augmentation Strategies

<table>
<thead>
<tr>
<th>Augmentation Agent</th>
<th>Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atypical Antipsychotics</td>
<td>Effectiveness needs to be balanced with high rate of adverse effects. Few long-term efficacy and safety data; no studies that directly compare them with other augmentation agents</td>
</tr>
<tr>
<td></td>
<td>Overall: Odds ratio (OR) = 1.69 for response with AAP compared to placebo; OR = 2.00 for remission; OR = 3.91 for discontinuation because of adverse effects</td>
</tr>
<tr>
<td></td>
<td>Aripiprazole: Improved response and remission rates compared to placebo, with an average dose of 11 to 12 mg/d. Some trials only showed improvement in clinician-rated scales, not patient-rated scales. High rate of akathisia.</td>
</tr>
</tbody>
</table>
## Augmentation Strategies

<table>
<thead>
<tr>
<th>Augmentation Agent</th>
<th>Data</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Atypical Antipsychotics</strong></td>
<td>Quetiapine XR: Significant response in MADRS compared to placebo. Significant adverse effects include sedation and weight gain.</td>
</tr>
<tr>
<td></td>
<td>Olanzapine: 2 positive and 3 negative trials in placebo-controlled olanzapine-fluoxetine studies. Weight gain is a significant issue.</td>
</tr>
<tr>
<td></td>
<td>Risperidone: 2 placebo-controlled trials with advantage over placebo and 1 with negative results. A long-term augmentation study showed no difference from placebo in time to relapse or relapse rate.</td>
</tr>
<tr>
<td></td>
<td>Brexpiprazole: 2, 6-week trials. Only 2 mg dose superior to placebo on MADRS in one of the studies.</td>
</tr>
</tbody>
</table>
## Augmentation Strategies

<table>
<thead>
<tr>
<th>Augmentation Agent</th>
<th>Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Others</td>
<td>Glutamate neurotransmission via NMDA receptor antagonism. IV ketamine has strong placebo-controlled data in acute antidepressant treatment. Produces a rapid, but transient antidepressant effect. Results of memantine monotherapy were negative. Riluzole (a glutamate release inhibitor that increases glutamate uptake into glial cells) has some evidence of efficacy in small open-label trials</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Antidepressant Withdrawal

Occurs with most antidepressants if the dose is not tapered.

Serotonin discontinuation syndrome

F = flu-like symptoms
I = insomnia
N = nausea
I = imbalance
S = sensory disturbances
H = hyperarousal
Antidepressant Withdrawal

- May be difficult to distinguish from depression relapse.

- Antidepressant withdrawal syndrome is characterized by the time-locked emergence of new, defined and quantifiable signs and symptoms, which develop on cessation or reduction of an antidepressant that has been taken for more than a few weeks.
Antidepressant Withdrawal

Symptoms

• Typically start 24 to 72 hours after the last antidepressant dose (peaking at 1 week).
• Typically resolve within 1 to 3 weeks.
• Severe and disabling withdrawal syndrome seen in 5% of patients.

Treatment

• Tapering the dose can decrease the symptoms.
• Restarting the antidepressant should make the symptoms go away.
• Slower tapers may then be necessary
  • Depends on drug and patient
Antidepressant Withdrawal

- **Less likely**: Fluoxetine
- **Likely**: Sertraline, Citalopram, Escitalopram, Duloxetine, Vilazodone
- **Most likely**: Venlafaxine, Desvenlafaxine, Paroxetine
OTC Alternatives

St. John’s Wort

- Superior to placebo at 300-1800mg/day (maybe)
- More tolerable than low-dose TCA’s
- Formulations are not standardized
- Watch out for drug-drug interactions
  - especially oral contraceptives
- Watch out for sun!
OTC Alternatives

Other alternatives require more research

- **S-Adenosyl Methionine (SAMe)**
  - Some studies show benefit similar to TCA's
  - Formulations are not standardized
- **Omega-3 Fatty Acids**
  - EPA better than DHA
  - Use 3 grams per day
- **Folate and L-methyl-folate**
  - Useful as an adjunct to medications
<table>
<thead>
<tr>
<th>Drug</th>
<th>Average Dose</th>
<th>Average Cost*</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brintellix (vortioxetine)</td>
<td>20mg QD</td>
<td>$270</td>
<td>Brand only</td>
</tr>
<tr>
<td>Bupropion XL</td>
<td>150mg BID</td>
<td>$28</td>
<td></td>
</tr>
<tr>
<td>Citalopram</td>
<td>20mg QD</td>
<td>$5</td>
<td>LCA, $</td>
</tr>
<tr>
<td>duloxetine</td>
<td>30mg QD</td>
<td>$35</td>
<td></td>
</tr>
<tr>
<td>Escitalopram</td>
<td>10mg QD</td>
<td>$12</td>
<td></td>
</tr>
<tr>
<td>Fetzima (levomilnacipran)</td>
<td>40mg QD</td>
<td>$268</td>
<td>Brand only</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>20mg QD</td>
<td>$5</td>
<td>LCA</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>100mg BID</td>
<td>$14</td>
<td></td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>30mg QD</td>
<td>$13</td>
<td></td>
</tr>
<tr>
<td>Paroxetine</td>
<td>20mg QD</td>
<td>$9</td>
<td>LCA, $</td>
</tr>
<tr>
<td>Pristiq, Khedezla, desvenlafaxine</td>
<td>100mg QD</td>
<td>$268, $140</td>
<td>$$ generic</td>
</tr>
<tr>
<td>Sertraline</td>
<td>100mg QD</td>
<td>$9</td>
<td>LCA</td>
</tr>
<tr>
<td>Venlafaxine XR</td>
<td>150mg QD</td>
<td>$17</td>
<td></td>
</tr>
<tr>
<td>Viibryd (vilazodone)</td>
<td>40mg QD</td>
<td>$210</td>
<td>Brand only</td>
</tr>
</tbody>
</table>

*GoodRx.com price comparison; LCA=low cost alternative; $=Walmart $4/$10 generic
Summary

• Best chance for success (remission) with antidepressant tx may be with first trial
  • Use at an adequate dose for an adequate duration
• Goal of treatment is remission
• Sequential approach to pharmacologic treatment is best and favors monotherapy when possible.
• Most antidepressants require tapering in order to avoid withdrawal
Additional Resources

• OHSU ECHO
  – Adult Psychiatric Medication Management
  – Child Psychiatry
  • http://www.ohsu.edu/xd/health/for-healthcare-professionals/telemedicine-network/for-healthcare-providers/ohsu-echo/index.cfm

• OPAL-K

• IMPACT Model
  • http://aims.uw.edu/impact-improving-mood-promoting-access-collaborative-treatment
What Questions Do You Have?

Type questions into the Questions Pane at any time during this presentation.
Thank You!

Please complete the post-webinar survey

**Depression Screening & Treatment in Primary Care: Part Two**
Workflow and Engaging the Clinical Team

Wednesday, October 5, 2016
8:00 to 9:00am

Register at PCPCI.org!