PBM-Federal Partners
Board Certification BCPP Webinar: Anxiety Disorders

June 14th, 2017
3:10 PM ET
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Announcements: 3:05 PM ET
PBM-Federal Partners
Board Certification Webinar: Anxiety Disorders
June 14, 2017
3:10 PM ET
Monica Cyr, PharmD, BCPP
Conflict of Interest Disclosures

Materials presented have been developed for study purposes only in preparation for the board certification exam. It is not meant to substitute for clinical practice and other examination preparation courses.

Speaker has no conflicts of interest to disclose.
• List the target symptoms for the following anxiety disorders
  – Generalized Anxiety Disorder (GAD)
  – Panic Disorder
  – Obsessive Compulsive Disorder (OCD)
  – Social Anxiety Disorder
  – Posttraumatic Stress Disorder (PTSD)
Learning Objectives

• Develop a treatment plan for each of the anxiety disorders discussed which include drug selection, dosing, monitoring parameters, treatment goals, and duration of treatment
Anxiety Disorders per DSM-V

- Generalized Anxiety Disorder (GAD)
- Panic Disorder (PD)
- Obsessive Compulsive Disorder (OCD)
- Social Anxiety Disorder (SAD)
- Phobias
• Increased norepinephrine (NE) release
  – 80% of NE transmission occurs in locus ceruleus
    • Hypersensitive?
    • Exaggerated response to stimuli?
• Abnormal serotonergic function in raphe nucleus (brain stem)
  – Serotonin has an inhibitory effect
• Abnormal GABA receptors
  – Inhibitory effect on NE, serotonergic, and dopaminergic pathways
Generalized Anxiety Disorder

• Anxiety/worry occurring most days for at least six months **in more than one situation**
• Difficult to control
• At least 3 of the following symptoms
  - Easily fatigued
  - Irritability
  - Muscle tension
  - Poor concentration
  - Restlessness
  - Sleep disturbance
Clinical Course

- Mean age of onset is 21 years
- High comorbidity with depressive disorders
- Waxing and waning course
Treating GAD

• SSRI’s & SNRI’s are drugs of choice
  – Sertraline & citalopram **NOT FDA-approved** for treatment of GAD

• Common side effects
  – **Beware of activation!**
  – GI
  – Headaches
  – Sexual dysfunction

• May need larger doses than used to treat depression
• Time to response may take up to 12 weeks
## SSRI’s: CYP450 Inhibitors

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<thead>
<tr>
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<th>1A2</th>
<th>2D6</th>
<th>3A4</th>
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<tr>
<td>Citalopram</td>
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<td>+</td>
<td>-</td>
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<tr>
<td>Escitalopram</td>
<td>-</td>
<td>+</td>
<td>-</td>
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<tr>
<td>Fluoxetine</td>
<td>++</td>
<td>+++</td>
<td>+/-</td>
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<tr>
<td>Fluvoxamine</td>
<td>+++</td>
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<td>+</td>
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<tr>
<td>Paroxetine</td>
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<tr>
<td>Sertraline</td>
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## CYP450 Interactions

<table>
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<tr>
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<tbody>
<tr>
<td>Substrate</td>
<td>Duloxetine</td>
<td>Citalopram Escitalopram Fluoxetine Imipramine</td>
<td>TCA’s Duloxetine Fluoxetine Nefazodone Venlafaxine Vortioxetine</td>
<td>Citalopram Escitalopram Levomilnacipran Nefazodone Trazodone Venlafaxine Vilazodone Vortioxetine</td>
</tr>
</tbody>
</table>
SSRI Withdrawal

• Begins within 24 hours of discontinuation and can last up to 2 weeks
• Dizziness
• Headache
• Irritability
• Nausea
Serotonin-Norepinephrine Reuptake Inhibitors

• Venlafaxine
  – Resembles SSRI at doses ≤ 150 mg/day
    • High incidence of nausea
  – Mid-range doses include norepinephrine reuptake inhibition
  – Higher doses also inhibit dopamine reuptake
    • Watch for increased blood pressure

• Desvenlafaxine
  – Metabolite of venlafaxine
  – Less nausea than venlafaxine
  – Not FDA-approved for treatment of GAD
• Duloxetine
  – Do not use if hepatic failure
• Levomilnacipran (Fetzima)
  – Not FDA-approved for treatment of GAD
  – Most norepinephrine activity of the class
  – Isomer of milnacipran (Sevella)
Tricyclic Antidepressants

• Anticholinergic side effects most significant in elderly especially impact on cognition

• Fatal in overdose (>2gm) due to arrhythmias
  – Be aware of dispense quantities
  – Not good choice post-MI

• Substrates for CYP 2D6
  – Inhibitors can triple plasma concentrations
Mixed Serotonergic Agents

• Trazodone
  – Mostly used for sleep/anxiety
    • Orthostasis
    • Sedation
  – 1 in 5000 risk of priapism

• Nefazodone
  – Risk of hepatic failure
  – Less orthostasis & sedation than trazodone
Bupropion

- Increases dopaminergic transmission
- **No sexual dysfunction**
- May decrease appetite/weight neutral
- Increased risk of anxiety
Clinical Scenario

- VB a 28-year old veteran has been experiencing jitteriness, worry, and insomnia for the past year. He reports being worried about his future, his health, and the economy. He has a good job and stable finances and has no significant health issues. After discussing this with his primary care provider, he is started on citalopram 10mg daily. He has been compliant for the past 8 weeks, but continues to experience these symptoms. What should be done?
  - Change to paroxetine
  - Change to venlafaxine
  - Continue treatment for 4 more weeks
  - Increase dose of citalopram
Benzodiazepines

- Most common modality used to treat anxiety disorders
  - Effective
  - Rapid response
    - “Buzz” often mistaken for therapeutic effect
    - Onset of effect/”buzz” based on lipophilicity
- Increase GABA_A receptor activity
- **Not the drug of choice for ANY psychiatric disorder other than alcohol withdrawal**
  - Potential for dependence/abuse
  - Long-term use may lead to/exacerbate depression
Benzodiazepines

• Considered second-line if failure to tolerate/respond to antidepressants
• Used short-term (2-4 weeks) until response to antidepressant occurs
**Benzodiazepines: Pertinent Properties**

<table>
<thead>
<tr>
<th></th>
<th>Onset of Effect</th>
<th>Half-life</th>
<th>Active Metabolite?</th>
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<tbody>
<tr>
<td>Alprazolam</td>
<td>fast</td>
<td>short</td>
<td>no</td>
</tr>
<tr>
<td>Chlordiazepoxide</td>
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<td>long</td>
<td>yes</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>slow</td>
<td>long</td>
<td>no</td>
</tr>
<tr>
<td>Clorazepate</td>
<td>fast</td>
<td>long</td>
<td>yes</td>
</tr>
<tr>
<td>Diazepam</td>
<td>fastest</td>
<td>long</td>
<td>yes</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>intermediate</td>
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</tr>
<tr>
<td>Oxazepam</td>
<td>intermediate</td>
<td>intermediate</td>
<td>no</td>
</tr>
</tbody>
</table>
Benzodiazepines

• Additive effects with other CNS depressants
  – Can contribute to depression
  – Can cause confusion/memory impairment
• Contraindicated if h/o substance abuse
• Potential for drug interactions
Benzodiazepine Withdrawal

• Withdrawal symptoms (indicate physical dependence)
  – Anxiety
  – Diaphoresis
  – Insomnia
  – Irritability
  – Seizures (within 3-7 days)

• Withdrawal symptoms occur in 40% after 4 weeks of use
  – Increased risk with short half-life/no active metabolite agents which are best for the elderly & those with hepatic impairment
Tapering off benzodiazepines

• Take into account duration of therapy and psychological dependence
• Usually can decrease dose by 25% without withdrawal
  – Decrease remaining dose by 25% per week until at 50% of initial dose then slowly taper by about 10% per week
  – Switch to longer acting benzodiazepine?
Discontinuing Therapy

• Withdrawal?
• Recurrence?
• Rebound?
BZD: Pregnancy/Lactation

• No proven teratogenic effect in humans
  – Animal studies show otherwise
• Use later in pregnancy can lead to withdrawal symptoms in the infant
• Rapidly absorbed into breast milk
• Half-life increased in infants
Buspirone

• 5-HT\textsubscript{1A} partial agonist
  – Increases serotonergic transmission
• As effective as benzodiazepines
  – Not perceived as effective in patients previously treated with benzodiazepines due to *slow onset of action/no “buzz” effect*
• Requires BID to TID dosing due to short half-life
  – Start with 7.5mg BID and increase to max dose up to 60 mg/day
• Not effective PRN!
Buspirone

- Considered second-line therapy
- No cognitive side effects
- No risk of dependence
- No antidepressant effect
- Avoid in lactation
Antihistamines

- Beware anticholinergic side effects in the elderly!
- Do not use during first trimester
- Do not use during lactation
Pregabalin

• Schedule V
• Some risk of abuse/dependence
• Some evidence supporting in GAD
• Not FDA-approved
Antipsychotics

• Second-generation antipsychotics more commonly used
  – Not FDA-approved for anxiety
  – Quetiapine often used in low doses
    • Antihistamine effects
    • Assess risk/benefits
# GAD Treatment Hierarchy

<table>
<thead>
<tr>
<th>Line</th>
<th>Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First-Line</strong></td>
<td>SSRI’s, SNRI’s</td>
</tr>
<tr>
<td><strong>Second-Line</strong></td>
<td>Benzodiazepines, Buspirone, TCA’s</td>
</tr>
<tr>
<td><strong>Alternatives</strong></td>
<td>Hydroxyzine, Quetiapine, Pregabalin</td>
</tr>
</tbody>
</table>
Duration of Treatment

• Tends to be recurrent
• Treat for one year beyond response
  – Taper off gradually
• Consider cognitive behavioral therapy
• Clinician-rated
• 14 items scored from 0 to 4
• Assesses severity of anxiety symptoms
  – Mild: 0-17
  – Moderate: 18-24
  – Severe: 25-30
• Response
  – At least 25% decrease in score
• Remission
  – At least 70% decrease in score OR
  – Total score <7
Self-rated Measures

• Used for screening
• Beck Anxiety Inventory (BAI)
  – More specific for panic symptoms
• Penn State Worry Questionnaire (PSWQ)
  – More focused toward worry
• Zung Self-rated Anxiety Scale
Panic Disorder

• Panic attack followed by at least one month of at least one of the following
  – Worry about having another attack
  – Worry about consequences of attack
  – Change in behavior for fear of having another attack

• Agoraphobia
  – Anxiety about being in places/situations from which it may be difficult to escape or obtain help if a panic attack occurs
Panic Attack

- Chest pain
- Increased heart rate
- Tremor
- Sweating
- Nausea
- Fear of dying
- Shortness of breath
- Dizziness/feeling faint
- Parasthesias
- Derealization
- Fear of going crazy
## PD Treatment Hierarchy

<table>
<thead>
<tr>
<th>First-Line</th>
<th>FDA-Approved</th>
<th>Not FDA-Approved</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Fluoxetine</td>
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<tr>
<td></td>
<td>Sertraline</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Paroxetine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Venlafaxine XR</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Second-Line</th>
<th>Alprazolam</th>
<th>TCA’s</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Clonazepam</td>
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</table>

<table>
<thead>
<tr>
<th>Alternatives</th>
<th>MAOI’s</th>
</tr>
</thead>
</table>
Monitoring Parameters

• Number and severity of panic attacks
• Anticipatory anxiety
• Avoidance
  – May respond more slowly than above symptoms
• Expect some response within 4 weeks
  – Maximum response may take 12 weeks
Course of Treatment

• Acute Phase
  – 1 to 3 months
  – Consider change in therapy if no response at 6 to 8 weeks

• Maintenance Phase
  – 12 months beyond remission of symptoms
  – Continue beyond 12 months if residual symptoms

• Discontinuation Phase
  – Decision based on various factors
  – Taper over 4 to 6 month period
Clinical Scenario

• OP is a 21 yo who has been on lorazepam 1mg TID for the past 14 months to treat panic attacks. Over this time, the number of panic attacks has greatly decreased, but he continues to experience anxiety prior to exams. He has decided he no longer needs therapy and has decreased to PRN use for the past 3 weeks. He currently reports feeling nervous, tremors, poor sleep, and dizziness. How should OP be treated now?
Clinical Scenario

- OP has GAD, start paroxetine.
- OP is having withdrawal symptoms. Change to diazepam and taper gradually.
- OP is having withdrawal symptoms, resume a lower dose of lorazepam and taper over the next several months.
- OP is relapsing. Have him resume PRN use of lorazepam.
Obsessive Compulsive Disorder

• Persistent obsessions with attempts to ignore, suppress, or neutralize them
  – Intrusive
  – Cause distress

• Repetitive behaviors performed in response to obsessive thoughts in order to decrease anxiety or distress

• Obsessions and/or compulsions occur for at least one hour daily
Clinical Course

- Often present to non-psychiatric providers to treat associated symptoms (i.e., chapped hands) due to shame
- Often precipitated by stressful event
  - Sudden onset in 50%
- High incidence of depressive comorbidity
Clomipramine

• Considered gold-standard
• Start with 25 mg daily
• Increase weekly by 25 md/day
• Target dose at least 100 mg/day
• Maximum dose 250 mg/day
• Side effects may limit use
• Does not appear to be teratogenic
  – Withdrawal may manifest in newborn
• Excreted in breast milk
  – Use with caution
• Fluvoxamine SSRI of choice
  – Strong CYP 1A2 inhibitor
• Also FDA-approved for OCD
  – Fluoxetine
  – Paroxetine
  – Sertraline
<table>
<thead>
<tr>
<th><strong>Medication</strong></th>
<th><strong>mg/day</strong></th>
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<tbody>
<tr>
<td>Fluoxetine</td>
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<tr>
<td>Fluvoxamine</td>
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<tr>
<td>Paroxetine</td>
<td>60</td>
</tr>
<tr>
<td>Sertraline</td>
<td>200</td>
</tr>
</tbody>
</table>
Common OCD Rating Scale

- Yale-Brown OCB Scale (Y-BOCS)
- 10-items scored from 0 to 4
- Assesses severity of symptoms
  - Mild: 8-15
  - Moderate: 16-23
  - Severe: 24-31
  - Extremely severe: 32-40
Assessing Response

• Response
  – At least 25% reduction in Y-BOCS score

• Remission
  – Y-BOCS score of less than 9
Antipsychotics

• May be used to augment antidepressant treatment
  – Haloperidol
  – Risperidone
  – Aripiprazole
Course of Treatment

• Onset of effect takes 6 to 8 weeks
• Maximum response may take 12 weeks
• Have patient keep symptom diary
• Consider augmentation if only partial response is achieved
• Treat for at least 1 year before considering taper
• High relapse rates
  – Consider life-long treatment
## OCD Treatment Hierarchy

<table>
<thead>
<tr>
<th>First-line</th>
<th>SSRI</th>
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</table>

<table>
<thead>
<tr>
<th>Second-line</th>
<th>SSRI</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Alternate SSRI Clomipramine</td>
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</table>

<table>
<thead>
<tr>
<th>Alternative</th>
<th>SSRI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Augment with antipsychotic</td>
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</table>
• A persistent fear of acting in an anxious or embarrassing manner when in social situations involving unfamiliar people or possible scrutiny by others.
• Individual realizes anxiety is excessive or not reasonable.
• Situations are endured with much distress or avoided.
Rating Scales

• Clinician rated
  – Liebowitz Social Anxiety Scale (LSAS)

• Self-rated
  – Social Phobia and Anxiety Inventory (SPAI)
  – Social Phobia Inventory (SPIN)
Mean age of onset 15 years
  – Treatment often delayed for 10 years
High incidence of concurrent anxiety, depression, or substance abuse
Without treatment, course is often life-long
FDA-Approved Treatments

• Paroxetine
• Sertraline
• Venlafaxine
  – Doses >75 mg/day showed no additional benefit
# SAD Treatment Hierarchy

| First-line | SSRI’s  
Venlafaxine XR |
<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Second-line</td>
<td>Benzodiazepines</td>
</tr>
<tr>
<td>Alternatives</td>
<td>Gabapentin, MAOI’s, Pregabalin</td>
</tr>
</tbody>
</table>
PTSD: DSM-V CRITERIA

• Exposure to traumatic event
• At least one intrusive symptom
  – Nightmares
  – Intrusive thoughts
  – Flashbacks
• Avoidance of reminders of traumatic event
• Negative cognitions/moods associated with traumatic event
• Hyperarousal symptoms
Posttraumatic Stress Disorder

- SSRI’s or venlafaxine are drugs of choice
  - Maximize dose
  - Time course to response 12 weeks
Alternative Therapies for PTSD

- **TCA’s**
  - Minimal supporting data
- **Mirtazapine**
- **Benzodiazepines**
  - **NOT proven helpful**
  - Do not allow for effective psychotherapy
  - Increase risk of depression
- **Prazosin**
  - Targets nightmares
  - Does not cause sedation!
- **Antipsychotics**
  - Not recommended
Therapeutic goals

- Response: 50% decrease in symptoms
- Remission: 70% decrease in symptoms
RP is a 68 year old Vietnam veteran who has recently been diagnosed with PTSD. He is reluctant to start medication, but agrees to a trial of fluoxetine 20mg daily as his wife can no longer tolerate his anger, jitteriness, and isolation. He presents for follow-up 2 weeks later stating that the medication made him feel worse and he feared he would harm somebody if he continued to take it. What should you do?

- Change to sertraline 100mg PO daily
- Add quetiapine 200mg PO at bedtime
- Add lorazepam 1mg PO BID
- Decrease fluoxetine to 10mg PO daily
• Antidepressants are the drugs of choice to treat anxiety disorders
  – Dosing must be adjusted to minimize initial anxiety and maximized to provide adequate response
  – A therapeutic trial tends to be longer than when treating depression (12 weeks vs. 6 weeks)
  – Therapeutic goals vary based on disorder
• Anxiety disorders tend to be recurrent and may require long-term treatment
• Benzodiazepines are NOT the drug of choice for any psychiatric disorders other than alcohol withdrawal
• Benzodiazepine withdrawal may mimic anxiety
QUESTIONS?

Monica Cyr, PharmD, BCPP
Outpatient Pharmacy Manager
VA Maine HCS
Reminders

• All board certification webinars will be held on Wednesday @ 3:10 ET
• Adobe Connect Link: PBM-Federal Partners BCPP Board Certification Prep Webinars
• All webinars are taped & posted to the BCPP Moodle Board Certification Study Group Child Course
• Upcoming June BCPP Board Certification Study Group Webinars
  – 6/21/17-Bipolar Disorder
  – 6/28/17-Neurocognitive Disorders

Don’t Forget the June PBM Monthly Webinar: Update on Hepatitis C
Tues: 6/20/17 @ 3 PM ET
Remember, a different Adobe Connect Link is used for the monthly PBM Webinar Series: See below: http://va-eerc-ees.adobeconnect.com/pbm-monthly-webinars/
• Clinical Practice Review for GAD. https://www.adaa.org/resources-professionals/practice-guidelines-gad

