Primary Care Psychopharmacology for Anxiety and Depression

SARAH A. JOHNSON, MD
Outline

Epidemiology
Screening
Basic principles of treatment
Drug-drug interactions
Assessment of treatment response
Other drug classes
Epidemiology
Prevalence of Anxiety and Depressive Disorders Among U.S. Adults

- Annually, 19.1% of US adults meet criteria for an anxiety disorder
- 6.7% meet criteria for Major Depressive Disorder
- Prevalence for both anxiety disorders and depressives disorders among women nearly 2x that among male counterparts
Comorbidity

- ~60% of adults meeting criteria for MDD will have at least one co-occurring anxiety disorder

- Co-occurrence of substance use disorders and both anxiety and depression common
  - alcohol (57% to 80%)
  - substance use (67.6% to 100%)
Widespread, But Undertreated

Anxiety

• 60-65% do not receive treatment

MDD

• 30 to 70% receive no treatment
Insufficient treatment

• Despite the fact that over 30 million Americans receive antidepressant prescriptions every year

  o ~20-30% of patients drop out of treatment prematurely
  o ~25-50% stay on ineffective treatments for too long
Screening
Screening for Depression

• US Preventative Services Task Force (USPSTF) recommends screening for major depressive disorder (MDD) in all adults, including pregnant and postpartum women
Patient Health Questionnaire (PHQ-9)

- 9-item, self-administered validated diagnostic assessment
  - Also used to track outcomes

- Available in Spanish, as well as in a modified version for adolescents

- Score indicates diagnosis and severity
  - 0-4: Not clinically depressed
  - 5-9: Mild depressive symptoms (persistent depressive disorder)
  - 10-14: Mild/moderate symptoms (major depression; 88% sensitivity and specificity)
  - >14: Moderate/severe depression (major depression; 95% specificity)

PHQ-9 is adapted from PRIME MD TODAY, developed by Drs. Robert L. Spitzer, Janet B.W. Williams, Kurt Kroenke, and colleagues, with an educational grant from Pfizer Inc. For research information, contact Dr. Spitzer at rls@cumc.columbia.edu. Use of the PHQ-9 may only be made in accordance with the terms of use available at http://www.pfizer.com. Copyright ©1999 Pfizer Inc. All rights reserved. PRIME MD TODAY is a trademark of Pfizer Inc.
Screening for Anxiety

Used in Collaborative Care Medicaid Program

- GAD – 7 - GAD but also moderately sensitive for Panic DO, SAD, PTSD. 7 Measure self report over previous 2 weeks

Other evidence-based tools

- HARS (HAM-A) – Hamilton Anxiety Rating Scale – clinician administered, more time consuming, more specific regarding physical symptoms

- OASIS – Overall Anxiety Severity and Impairment Scale – 5 measure self report over previous 7 days
## GAD-7

### GAD-7 Anxiety

<table>
<thead>
<tr>
<th>Over the last two 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>0. 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 sleep 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>

Column totals: ____ + ____ + ____ + ____ = Total score

0–4: minimal anxiety
5–9: mild anxiety
10–14: moderate anxiety
15–21: severe anxiety

*seven-item scale (GAD-7) has shown reliability, validity, and adequate sensitivity (89%) and specificity (82%)*
Treatment
Principles of treatment

• Use antidepressants, not minor tranquilizers / benzodiazepines for depression and most anxiety disorders

• Use adequate doses for an adequate amount of time

• Start slow and work with side effects but titrate to an effective dose as needed

• *Change medication* if not effective • Usually after 8 – 10 weeks
Principles of treatment (cont)

• For mild symptoms and impairment, or more severe symptoms in pts declining meds - also refer for talk treatment.

• Robust evidence base for Cognitive Behavioral Therapy (CBT) for anxiety disorders and MDD
CBT

- Identify negative thoughts and thinking errors/cognitive distortions
- Skills based, goal oriented
- Positive results even with short term interventions
- Any patient with symptoms significant enough to warrant medication should be strongly encouraged to engage in therapy.
  - Combined treatment generally superior to medication alone
Keep in mind. . .

• More than 30-50% of patients will experience complete treatment response

• 50-70% of patients will require at least one adjustment to treatment in order to experience an improvement in their symptoms
Treatment of Moderate to Severe Anxiety/Depression

• SSRIs/SNRIs have the best evidence base for medication therapies.

• No agent consistently outperforms the others.

• Individuals may respond better to particular agents.

• SNRIs tend to be used after failure of SSRIs due to potential for more side effects.
SSRI/SNRI at the Synapse

- Neurotransmitter
- Synaptic vesicle
- Voltage-gated $\text{Ca}^{2+}$ channel
- Postsynaptic density
- Neurotransmitter transporter
- Receptor
SSRI/SNRI Drugs Approved For Anxiety Disorders in Adults

• **GAD**: paroxetine, escitalopram, duloxetine, venlafaxine

• **Panic Disorder**: fluoxetine, paroxetine, sertraline, venlafaxine

• **SAD**: sertraline, paroxetine, fluvoxamine CR, venlafaxine

(Citalopram, desvenlafaxine, levomilnacipran – not FDA indicated for anxiety; milnacipran - fibromyalgia)
<table>
<thead>
<tr>
<th>Medication</th>
<th>Brand Names</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citalopram</td>
<td>Celexa</td>
<td>Depression</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>Lexapro</td>
<td>Depression, GAD</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>Prozac, Sarafem,</td>
<td>Bulimia nervosa, depression, OCD, panic disorder, PMDD</td>
</tr>
<tr>
<td></td>
<td>Selfemra</td>
<td></td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>Luvox</td>
<td>OCD, social phobia</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>Paxil, Pexeva</td>
<td>Depression, GAD, OCD, panic disorder, PTSD, PMDD, social phobia</td>
</tr>
<tr>
<td>Sertraline</td>
<td>Zoloft</td>
<td>Depression, OCD, panic disorder, PTSD, PMDD, social phobia</td>
</tr>
<tr>
<td>Vilazodone</td>
<td>Viibryd</td>
<td>MDD</td>
</tr>
<tr>
<td>Drug 1</td>
<td>Drug 2</td>
<td>Indications</td>
</tr>
<tr>
<td>-------------</td>
<td>-----------</td>
<td>--------------------------------------------------</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>Cymbalta</td>
<td>Depression, diabetic neuropathy, fibromyalgia, GAD, musculoskeletal pain, osteoarthritis</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>Effexor</td>
<td>Depression, GAD, panic disorder, social phobia</td>
</tr>
<tr>
<td>Desvenlafaxine</td>
<td>Pristiq</td>
<td>Depression</td>
</tr>
<tr>
<td>Levomilnacipran</td>
<td>Fetzima</td>
<td>Depression</td>
</tr>
</tbody>
</table>
New antidepressants

• Vilazodone (Viibryd): 2011 MDD – SSRI + partial agonist of 5HT1A (ssri + buspirone) May be helpful for comorbid anxiety but no FDA approvals. Reasonable 3rd line choice

• Levomilnacipran (Fetzima): 2013 – “NSRI” - More benefit for cognitive functions such as concentration, motivation. (Not FDA approved for anxiety disorders)

• Vortioxetine (Brintellix – now Trintellix): 2013 – multimodal mechanism. Increases Serotonin, dopamine, norepinephrine

• All may be helpful, but not first line due to lack of FDA approvals and cost
What about bupropion?

• No serotonergic effects (NDRI)

• Not FDA approved for use to treat any anxiety disorder

• Anxiety is a common side effect

• Use cautiously in patients with depression and comorbid anxiety
Medication Choice for Moderate to Severe Anxiety and/or Depression

Medication decisions informed by:

• FDA indications

• Evidence base

• Personal hx of prior med trials

• Family hx

• Side effect profiles

• Safety in the event of overdose

• Interactions with pt’s current meds
SSRI/SNRI selection

• Prior response is best predictor of future response

• Revisit previously effective drugs at previously effective doses.
  o Titration still required

• SSRI/SNRI tachyphylaxis (‘poop out’) may occur, but loss of response may also be related to other factors such as poor adherence
Role of Family History

- There is no ‘crystal ball’ that tells us what medication will work best.

- Utility of pharmacogenetic testing remains questionable.

- Medications that have been effective and well tolerated in a first degree relative should be prioritized.

- Evidence from family studies indicates that response to specific antidepressants can be affected by genetic polymorphisms.
SSRI/SNRI selection based on attribute and side effect profiles

Tailor drug choice to fit the needs of your patient based on attributes and most common side effects of the various agents.

- Sedating vs energizing
- Likelihood of weight gain vs weight loss
- Elimination half life
# A Comparison of Depression Medications

<table>
<thead>
<tr>
<th></th>
<th>Anti-colinergic</th>
<th>Sleepy</th>
<th>Insomnia/Agitation</th>
<th>Orthostatic Hypotension</th>
<th>QT</th>
<th>GI</th>
<th>Weight Gain</th>
<th>Sexual</th>
<th>Approx. cost per month</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SSRI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Citalopram/ Escitalopram</td>
<td>0</td>
<td>0</td>
<td>1+</td>
<td>1+</td>
<td>1+</td>
<td>1+</td>
<td>1+</td>
<td>3+</td>
<td>$4</td>
<td>$20 Escitalopram (Lexapro) is the S isomer of citalopram. Citalopram is cheaper.</td>
</tr>
<tr>
<td>Fluoxetine (Prozac)</td>
<td>0</td>
<td>0</td>
<td>2+</td>
<td>1+</td>
<td>1+</td>
<td>1+</td>
<td>1+</td>
<td>3+</td>
<td>$4</td>
<td>Has the longest half life. Therefore, caution with using in elderly.</td>
</tr>
<tr>
<td>Paroxetine (Paxil)</td>
<td>1+</td>
<td>1+</td>
<td>1+</td>
<td>2+</td>
<td>1+</td>
<td>1+</td>
<td>2+</td>
<td>4+</td>
<td>$4</td>
<td>Shortest half life. Pregnancy class D</td>
</tr>
<tr>
<td>Sertraline (Zoloft)</td>
<td>0</td>
<td>0</td>
<td>2+</td>
<td>1+</td>
<td>1+</td>
<td>1+</td>
<td>1+</td>
<td>3+</td>
<td>$10</td>
<td>Has many other indications besides depression such as panic disorder</td>
</tr>
<tr>
<td>Bupropion (Wellbutrin)</td>
<td>0</td>
<td>0</td>
<td>2+</td>
<td>0</td>
<td>1+</td>
<td>1+</td>
<td>0</td>
<td>0</td>
<td>$30</td>
<td>Frequently used as adjunct to SSRIs for depression. Also used for tobacco cessation. Can decrease seizure threshold</td>
</tr>
<tr>
<td><strong>SNRI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Venlafaxine ER (Effexor XR)</td>
<td>0</td>
<td>0</td>
<td>2+</td>
<td>0</td>
<td>1+</td>
<td>2+</td>
<td>0</td>
<td>3+</td>
<td>$19</td>
<td>May increase blood pressure</td>
</tr>
</tbody>
</table>
SSRI Side Effects

Short term:
- GI upset / nausea
- Jitteriness / restlessness / insomnia
- Sedation / fatigue – switch to night time dosing if persistent
- Headache

Long term:
- Sexual dysfunction (up to 33%)
- Weight gain (5 to 10%)
Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of an antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber.
SSRIs and the risk of suicide

• Increase the risk of ‘suicide related events’ (SI/SA) from 1 in 100 to 2 in 100 for children, adolescents and young adults.

• Mechanism is unclear:
  ◦ Activation of underlying Bipolar Disorder?
  ◦ Increase in Agitation and impulsivity?
  ◦ Enough improvement to act on suicidal thoughts?
Drug-drug interactions
SSRIs/SNRIs and interactions with other meds

Concomitant administration with other serotonergic drugs and risk for serotonin syndrome

- Triptans
- Tramadol
- Other antidepressants (SSRI/SNRI, TCA, MAOI)
- Commonly used off label sleep meds – mirtazepine, trazodone
Serotonin syndrome

- Diarrhoea
- Sweating
- Akathisia
- Ataxia

Mild symptoms: Tremor, Myoclonus, Confusion, Convulsions

Life threatening:
Drug-drug interactions

- Impact on cytochrome P450 – esp CYP2D6 inhibition can cause higher plasma levels of other medications
  - Biggest offenders are fluoxetine and fluvoxamine
  - Escitalopram, citalopram, venlafaxine have no CYP450 effects

- Patients most frequently impacted:
  - Elderly
  - Patients on antiretroviral medications

- Impact on QT interval, seizure threshold – citalopram, bupropion
Drug-drug interactions: best practices

• If patient is on a drug with a narrow therapeutic window (e.g., digoxin, warfarin, theophylline, antiarrhythmics, lithium, TCAs, anticonvulsants)

  ➔ check a serum level of that drug when a steady state of the antidepressant is reached or if there are side effects

• When in doubt, consult a pharmacist.
Characteristics of an adequate structured SSRI/SNRI trial

- Start at beginning of adult dose range, though some patients will require slower titration.

- Due to delayed onset of effect (2 - 6 weeks), limit dose increases to monthly.
  - Rapid titration may lead to agitation and other intolerable side effects, but may be undertaken by specialists or in the inpatient setting.

- Persist with one agent prior to switching until adequate symptom control, dose range is exhausted or intolerable side effect develops.
SSRI/SNRI Dosing

- Fluoxetine 20 – 60mg, 10 – 20mg increments
- Sertraline 50 – 200mg, 25 to 50mg increments
- Citalopram 10 – 40mg, 10 mg increments
- Escitalopram 10 – 20 mg, 5 to 10 mg increments
- Paroxetine 10 – 60mg, 10 mg increments
- Venlafaxine 75 – 300mg, 37.5 – 75mg increments
- Duloxetine 60 – 120mg, 30mg increments
Assessing treatment response
Response Rates

• ~30% placebo rate in both adolescents and adults

• Overall response rates to antidepressants are about 65% for MDD at the highest

• True antidepressant response rate in MDD is about 35%, but may be somewhat higher for some anxiety disorders
Defining Clinical Improvement

**PHQ-9** score < 10 (i.e., no or mild depression) or a current PHQ-9 score that is <50% of the patient’s baseline score, ideally over an 8–12 week period

**GAD-7** score < 10 (no or mild anxiety) or a current GAD-7 score that is < 50% of baseline score over 8–12 weeks
When and how to stop antidepressants

- All adults should be treated for 6-9 months following treatment response.
- Those at high risk for relapse should be treated for at least 24 months.
- Maintenance treatment should be at full dose.
- Make relapse prevention plan.
- Taper antidepressants slowly to avoid discontinuation syndrome.
### What to do with a non-responder/partial responder

<table>
<thead>
<tr>
<th>Adjust</th>
<th>Adjust dosage until response/side effects/MDD reached</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consider</td>
<td>Consider switch to another agent – lack of response to one does not predict lack of response to another</td>
</tr>
<tr>
<td>Assess</td>
<td>Assess adherence</td>
</tr>
<tr>
<td>Reevaluate</td>
<td>Reevaluate diagnosis</td>
</tr>
</tbody>
</table>
General Office Strategies for Optimizing Adherence

- Provide rationale for use
- Careful attention to side-effects
- Address fear of dependence and loss of control
- Enlist family support
- Address concerns in relation to patient’s prior experience with medication
- Increase contact with brief phone check-ins
- Specific instructions (take regardless of symptom change, don’t stop on own)
When to Stop or Switch Medications

- Intolerable side effects
- Dangerous interactions with necessary medications
- The medication was not indicated to start with (i.e. wrong diagnosis)
- Medication has been at maximum therapeutic dose without improvement for 4-6 weeks
Approach to Discontinuing SSRI/SNRI’s

For brief trials without benefit or discontinuation due to side effects, quick taper is appropriate, or immediate cessation for serious side effect.

When discontinuing therapy after benefit (at least 6 to 12 months), gradual taper is highly recommended to prevent abrupt and severe relapse of symptoms.

- Slow taper over several months gives best chance of maintaining remission.

Abrupt cessation can cause discontinuation syndrome, though less likely with fluoxetine due to long elimination half life.
SSRI/SNRI Switching Strategies

• Direct switch: stop the 1st antidepressant abruptly and start new antidepressant the next day.

• Taper & switch immediately: gradually taper the 1st antidepressant, then start the new antidepressant immediately after discontinuation.

• Taper & switch after a washout: gradually withdraw the 1st antidepressant, then start the new antidepressant after a washout period.

• Cross-tapering: taper the 1st antidepressant (usually over 1-2 weeks or longer), and build up the dose of the new antidepressant simultaneously.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Half out of body in</th>
<th>99% out of body in</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serotonin reuptake inhibitors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>paroxetine (Paxil)</td>
<td>24 hours</td>
<td>4.4 days</td>
</tr>
<tr>
<td>sertraline (Zoloft)</td>
<td>26 hours</td>
<td>5.4 days</td>
</tr>
<tr>
<td>escitalopram (Lexapro)</td>
<td>27 to 32 hours</td>
<td>6.1 days</td>
</tr>
<tr>
<td>citalopram (Celexa)</td>
<td>36 hours</td>
<td>7.3 days</td>
</tr>
<tr>
<td>fluoxetine (Prozac)</td>
<td>Four to six days</td>
<td>25 days</td>
</tr>
<tr>
<td>Serotonin and norepinephrine reuptake inhibitors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>venlafaxine (Effexor)</td>
<td>5 hours</td>
<td>1 day</td>
</tr>
<tr>
<td>duloxetine (Cymbalta)</td>
<td>12 hours</td>
<td>2.5 days</td>
</tr>
</tbody>
</table>
Key Educational Messages for Patients and Families

- SSRI/SNRIs only work if taken every day.
- SSRI/SNRIs are not addictive.
- Benefits from medication occur slowly.
- Continue medication even after you feel better.
- Mild side effects are common and usually improve over time.
- If you’re thinking about stopping the medication, call prescriber first.
- Sometimes it takes a few tries to find the right medication.
Other drug classes
Benzodiazepines

• Modulate GABA-ergic pathways

• Continuing them beyond four to six weeks often results in loss of efficacy and development of tolerance and/or dependence.

• The risk of dependence increases with dose and duration of therapy.

NOT FIRST LINE AND NOT FOR LONG-TERM USE
Benzodiazepines

Risks

• Misuse/abuse/dependence

• Depression and worsening impulse control

• Overdoses, especially when used with EtoH, opiates, opiate agonists, other sedating meds

• Risks of abrupt withdrawal – seizure, death

• Short and long term effects on cognition

• Increased risks for falls, especially in the elderly
Possible Reasonable Short Term Uses of Benzodiazepines

• Severe Panic Disorder where time limited prn use may be beneficial while waiting for SSRI to take effect

• Brief use when starting and SSRI/SNRI to counteract transient medication induced anxiety/jitteriness.

• Isolated use for Specific Phobia exposure – like fear of flying or dental procedures

• Use should always be PRN and not scheduled
Beta Blockers

• Consider for panic disorder, performance anxiety as an alternative to benzodiazepines to calm the autonomic nervous system

• Beta blockers do not have the cognitive side effects, sedation or fatigue of benzos, and avoid potential for abuse and overdose

• Can cause/exacerbate depression

• Propanolol 10mg prn and titrate as needed, tolerated
Lifestyle/Self-Care Interventions for Anxiety and Depressive Disorders

- Sleep hygiene
- Exercise – prescribe it!
- Limit/eliminate caffeine
- Meditation, yoga
- Reduce/eliminate use of alcohol and drugs
- Diet: reduce sugar, refined carbs
- Address medical needs: DM, Chronic pain etc
Consider Psychiatry Referral

- Cases that are difficult diagnostically
- Failure to respond to 2-3 adequate trials of SSRI/SNRIs combined with CBT as evidenced by persistent significant functional impairment
- Multiple complicating comorbidities (substance use or dependence, eating disorders)
- Suicidality
- Any question of psychosis or bipolarity
Questions?