Primary Care Psychopharmacology for Anxiety Disorders

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Prevalence of Any Anxiety Disorder Among U.S. Adults

- 18% of U.S. adults had any anxiety disorder in the past year – most prevalent class of mental health disorders. Next most prevalent were mood disorders at 9.5%
- Past year prevalence of any anxiety disorder was higher for females (23.4%) than for males (14.3%)
- 31.1% of U.S. adults experience any anxiety disorder at some time in their lives.

Anxiety Disorders

- Generalized Anxiety Disorder (GAD)
- Panic Disorder (PD)
- Social Anxiety Disorder (prev. Social Phobia)
- Agoraphobia
- Specific Phobia

(OCD, PTSD, and Acute Stress Disorder removed from Anxiety Disorders in DM-V)
Widespread But Undertreated

Anxiety disorders are highly treatable, yet only 36.9% of those suffering receive treatment.

(Anxiety and Depression Association of America)
Co-Morbidities

Very high percentage of those with anxiety disorders have:

- depressive disorders – up to 60% may have MDD (Kaufman et al, 2000)
- substance use disorders - anxiety disorders often precede the development of co-occurring alcohol (57% to 80%) and substance use (67.6% to 100%) disorders. (Merikangas, et al 1998)
Natural History of Anxiety Disorders

- Evidence of premorbid anxiousness and overadaptation already in childhood.

- Distressing conditions in the family are more prevalent among subjects with anxiety disorders than among controls.

- Full blown anxiety disorders frequently have onset in teen years to age 30, and can be triggered by life events. The course is often characterized by periodic exacerbations with a chronicity that manifests itself in residual symptoms and milder impairment in social roles even after many years.

(Angst et al, 1991)
Consequences of Anxiety Disorders

Potential for functional impairment across all spheres:

• Family relationships
• Social relationships
• Academic and occupational performance
• Pursuit of leisure activities and self-care
Risk Factors for Anxiety Disorders

- Genetics
- Inhibited temperament/behaviors as child or toddler
- Environment – anxious parents modeling anxious behaviors and overschilding
- Gender – higher prevalence in girls
- Trauma
Basic Neuroscience of Anxiety

[Image of a brain with a highlighted area labeled AMYGDALA]
Regions of the brain involved in the anxiety response

**Amygdala** - stores memories of frightening events and other emotional experiences. In people with anxiety disorders, the amygdala may be so sensitive that it overreacts in situations that aren't threatening.
Regions of the brain involved in the anxiety response

Amygdala

Hippocampus
Regions of the brain involved in the anxiety response

- **Hippocampus** - central role in processing emotions and long-term memories. Trauma may lead to atrophy. Stress may suppress the production of new neurons in the hippocampus.
Regions of the brain involved in the anxiety response
Regions of the brain involved in the anxiety response

• **Locus coeruleus** - an area of the brainstem that helps determine which brain stimuli are worth paying attention to
Neuron to Neuron

Action potential from the pre-synaptic ("sending") cell to the synapse, which then connects to the post-synaptic ("receiving") cell.
Dysregulated Neurotransmitters in Anxiety Disorders

Low Serotonin – also plays a major role in depressive disorders

Overactive or excess stress hormones – Excessive production of stress hormones such as cortisol lead to the physical effects of anxiety – rapid heart beat, sweating, shallow breathing etc

Low levels of GABA - when this calming neurotransmitter is in low supply, we are on edge
SSRIs at the Synapse

- Neurotransmitter
- Synaptic vesicle
- Voltage-gated Ca\(^{2+}\) channel
- Postsynaptic density
- Neurotransmitter transporter
- Receptor
Generalized Anxiety Disorder

Essential features include excessive anxiety or worry that is difficult to control, and takes place across a number of settings and more days than not for at least six months.

- The individual experiences at least three characteristic symptoms including:
  - restlessness or feeling keyed up or on edge
  - being easily fatigued
  - difficulty concentrating or mind going blank
  - irritability
  - muscle tension
  - sleep disturbance (APA, 2013).
Panic Disorder

The essential features are:

• recurrent and unexpected panic attacks

• including physiological changes such as accelerated heart rate, sweating, dizziness, trembling, and chest pain.

• persistent concern, for one month or longer, about having another attack and/or worries about the implications and consequences of the attacks, often with maladaptive behavior pattern to avoid future attacks.

(Distinguish disorder from panic attack specifier)
Social Anxiety Disorder

- Fear of negative evaluation (e.g., being humiliated, embarrassed, or rejected) by others (either unfamiliar or familiar) in performance, interaction, or observation situations.

- Persists for a minimum duration of at least 6 months.

- The median age of onset of social anxiety disorder in the US is age 13, with 75% of those with social anxiety disorder experiencing the onset at a range of ages 8-15. The onset can either be insidious, or sudden onset triggered by a specific event. (American Psychiatric Association, 2013).
Anxiety as a Physical Phenomenon

- GI symptoms – stomach upset, diarrhea, constipation, nausea, vomiting
- Headaches
- Muscle tension and pain
- Cardiovascular symptoms inc SOB, rapid heartbeat, sweating
- Sleep problems
Differential Diagnosis

Medical Mimics of anxiety disorders:

- Hyperthyroidism
- GI disease
- Heavy metal toxicity
- Asthma
- Headache and CNS syndromes
- Cardiac arrhythmia, MI
- Substance use – especially stimulant and cocaine use
- Lyme disease
Screening/Assessment Tools

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

- **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 Anxiety

Over the last two weeks, how often have you been bothered by the following problems?

<table>
<thead>
<tr>
<th></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>1</td>
<td>Feeling nervous, anxious, or on edge</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>Not being able to sleep or control worrying</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>Worrying too much about different things</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>Trouble relaxing</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>5</td>
<td>Being so restless that it is hard to sit still</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>6</td>
<td>Becoming easily annoyed or irritable</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>7</td>
<td>Feeling afraid, as if something awful might happen</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

**Column totals**  

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 of Anxiety Disorders

- For mild symptoms and impairment, refer for therapy
- Robust evidence base for Cognitive Behavioral Therapy (CBT) for anxiety disorders
CBT

- Identify negative thoughts and thinking errors/cognitive distortions
- Skills based, goal oriented
- Here and now focused
- Positive results even with short term interventions – most trials look at a 12 week intervention
- Any patient with symptoms significant enough to warrant medication should be strongly encouraged to engage in therapy. Combined treatment is often superior to medication alone
Medication Options for Moderate to Severe Anxiety

- Medication decisions informed by:
  - FDA indications
  - Evidence base
  - Family hx
  - Personal hx of prior med trials
  - Side effect profiles
  - Interactions with pt’s current meds
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 – no FDA indicated for anxiety; milnacipran - fibromyalgia)
The Newer Antidepressants

- Vilazodone (Viibryd) – 2011 MDD – SSRI + partial agonist of 5HT1A – akin to ssri + buspirone. May be helpful for co-morbid anxiety but no FDA approvals. Reasonable 3rd line choice.

- Levomilnacipran (Fetzima) -2013 – “NSRI” - ? More benefit for cognitive functions such as concentration, motivation. No FDA approval 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 – this med is an NDRI
- Not FDA approved for use to treat any anxiety disorder
- Anxiety is a common side effect for some
- Use cautiously in patients with depression and comorbid anxiety
Evidence base for SSRI/SNRI meds for anxiety

- SSRI/SNRI medications have best evidence base for medication therapies.

- However, no one agent consistently outperforms the others as a whole in the population. Individuals may respond better to particular agents however.

- SNRIs tend to be used after failure of SSRIs as some pts will have increased anxiety r/t norepinephrine stimulation
Role of Family Hx in selection of SSRI/SSRI in anxiety

- There is no ‘crystal ball’ that tells us what med will work best for a particular patient. Utility of pharmacogenetic testing remains in question.

- Meds 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 differences (polymorphisms)
Prior med response in SSRI/SNRI selection

- Best predictor of future response is past response
- Revisit previously effective drugs at previously effective doses. 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
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 wt gain vs wt loss
  - Elimination half life
Common SSRI Side Effects

• Short term:
  • GI upset / nausea
  • Jitteriness / restlessness / insomnia
  • Sedation / fatigue – switch to night time dosing if persistent
  • Headache / dizziness
  • Wt loss / Wt gain

• Long term:
  • Sexual dysfunction (up to 33%)
  • Weight gain (5 to 10%) vs SNRI
## SSRI/SNRI Side Effects

### A COMPARISON OF DEPRESSION MEDICATIONS

<table>
<thead>
<tr>
<th>Medication</th>
<th>Anticolinergic</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>
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<td>Citalopram/Escitalopram</td>
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<td>1+</td>
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<td>(Celexa/Lexapro)</td>
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<td>1+</td>
<td>1+</td>
<td>1+</td>
<td>3+</td>
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<td>(Prozac)</td>
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<td>Paroxetine</td>
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<td>(Paxil)</td>
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<td>Sertraline</td>
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<td>(Zoloft)</td>
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<tr>
<td>Bupropion</td>
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<td>(Wellbutrin)</td>
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<td>Venlafaxine ER</td>
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<td>1+</td>
<td>2+</td>
<td>0</td>
<td>0</td>
<td>3+</td>
<td>$19</td>
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<td>(Effexor XR)</td>
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</table>

- Escitalopram (Lexapro) is the S isomer of citalopram. Citalopram is cheaper.
- Has the longest half-life. Therefore, caution with using in elderly.
- Shortest half-life. **Pregnancy class D**
- Has many other indications besides depression such as panic disorder.
- Frequently used as adjunct to SSRIs for depression. Also used for tobacco cessation. Can decrease seizure threshold.
- May increase blood pressure.
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 for suicide-related events

- Approximately two people out of every 100 treated with an SSRI will have a “suicide-related” event compared to one person out of every 100 treated with placebo (Hammad, 2004).

- The definition of “Suicide-related” events is variable depending on the study and have included: short term suicidal ideation; persistent suicidal ideation; self-harm without suicide intent; self-harm with suicide intent. This variability of definitions makes it difficult to evaluate the incidence of actual suicide directed behaviors. Best available data from controlled trials and health record databases alike show that SSRI treatment significantly decreases suicidal ideation and suicide attempts in young people (Cheung et al., 2006).
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 – mirtazapine, trazodone
Progression of Serotonin Syndrome

Symptoms

- Diarrhoea
- Sweating
- Akathisia
- Ataxia

Mild symptoms:
- Tremor
- Myoclonus
- Confusion
- Convulsions

Life threatening
SSRIs/SNRIs and interactions with other meds

- Impact on hepatic enzymes: Cytochrome P450 – esp CYP2D6 inhibition can cause higher plasma levels of other drugs
  - Elderly
  - Pts on antiretrovirals
  - Biggest offenders are fluoxetine and fluvoxamine
  - Escitalopram, citalopram, venlafaxine have no CYP450 effects
- Impact on QT interval, seizure threshold – citalopram, bupropion
<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><strong>Serotonin reuptake inhibitors</strong></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><strong>Serotonin and norepinephrine reuptake inhibitors</strong></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>
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. More rapid titration risks 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. Not all pts will respond at lower end of dose range
### SSRI/SNRI Dosing in Anxiety Disorders

<table>
<thead>
<tr>
<th>Medication</th>
<th>Initial Dose Range</th>
<th>Increment Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoxetine</td>
<td>20 – 80mg</td>
<td>10 – 20mg</td>
</tr>
<tr>
<td>Sertraline</td>
<td>50 – 200mg</td>
<td>25 to 50mg</td>
</tr>
<tr>
<td>Citalopram</td>
<td>10 – 40mg</td>
<td>10 mg</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>10 – 20 mg</td>
<td>5 to 10 mg</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>10 – 60mg</td>
<td>10 mg</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>75 – 225mg</td>
<td>37.5 – 75mg</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>60 – 120mg</td>
<td>30mg</td>
</tr>
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</table>
Approach to Discontinuing an SSRI/SNRI

- 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, more likely with
SSRI/SNRI Alternatives or Augmenting Agents

- For patients who fail or don’t tolerate SSRI/SNRIs
- For Bipolar patients with anxiety
- For patients in whom SSRI/SNRI deliver partial but not sufficient relief from anxiety symptoms
TCAs for Anxiety

- amitriptyline, desipramine, clomipramine, doxepin, etc.

- Lethality in overdose
- High side effect burden
- Need for blood monitoring
- Specialty use in OCD, as well as sleep and chronic pain
Benzodiazepines

• Modulate GABA-ergic pathways

• While effective in the short-term treatment of severe anxiety and panic disorders, evidence shows that continuing them beyond four to six weeks often results in loss of efficacy and development of tolerance and dependence, therefore whenever possible, avoid use.

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

• NOT FIRST LINE AND NOT FOR LONGTERM USE
Benzodiazepines Risks

- Misuse/abuse/dependence
- Depression and worsening impulse control
- Risk for overdose, especially when combined with alcohol, opiates, opiate agonists or other sedating meds. Use of a benzo with an opiate at least doubles the risk of death from respiratory depression.
- Risks of abrupt withdrawal – seizure, death
- Short and long term effects on cognition – inhibits memory encoding, interferes with exposure response
- 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
Buspirone

- Novel anxiolytic agent with very complex mechanism of action, but likely main neuropharmacologic effects are mediated by the 5-HT1A receptors.
- FDA approved for adults for GAD
- BID to TID dosing (range 10mg – 60mg TDD)
- May be helpful in treating SSRI/SNRI induced sexual side effects
- Associated with less drowsiness, fatigue, nervousness, depression and sleep disturbance than BZD.
Buspirone Side Effects

Usually mild and infrequent but may include:

- dizziness, headache, blurred vision
- feeling restless or nervous
- nausea, dry mouth, upset stomach
- insomnia, strange dreams
- stuffy nose, sore throat
- Tinnitus
- Sedation, fatigue
Gabapentin

Acts on GABA system of inhibitory neurotransmission (GABA agonist)

• off label for use in anxiety disorders

• not hepatically metabolized so minimal drug-drug interactions

• may assist with alcohol craving

• not a potent mood stabilizer

• While not a controlled substance – has potential for abuse, though preferred in clinical practice to use of pregabalin, due to it being controlled substance

• useful in taper of benzodiazepines

• BID – TID dosing (Target is 900mg in divided doses, some pts need higher doses)
Potential side effects of gabapentin

- Class warning for all AEDs for suicidal thinking
- Dizziness, drowsiness, weakness, tired feeling
- Nausea, diarrhea, constipation
- Blurred vision
- Headache
- Breast swelling
- Dry mouth
- Loss of balance or coordination
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.

- Propanolol 10mg prn and titrate as needed, tolerated.
Atypical Antipsychotic Agents

- Sedating agents such as quetiapine, olanzapine, and risperidone are sometimes used off label for anxiety.

- Use with caution due to class risks including Neuroleptic Malignant Syndrome, Tardive Dyskinesia, metabolic effects such as weight gain and adverse effects on glucose metabolism and lipids.

- If utilized, keep doses low to minimize risk of side effects.
Hydroxyzine

• Antihistamine – histamine H1 receptor agonist
  • an approved anxiety treatment in adults
  • use for generalized tension, anticipatory anxiety, possibly panic – benefit over placebo for GAD
  • 50-100mg up to QID, per labeling but mostly used PRN

• Side effects – sedation, wt gain, dizziness, drowsiness, blurred vision, dry mouth, stomach upset, headache. Rarely, anticholinergic toxicity
Mirtazepine

tetracyclic antidepressant

open label study support in adults with GAD, panic disorder

consider if need sedation and appetite stimulation
• Dosing – start at 7.5mg at hs, may increase to BID dosing.
• MDD = 45mg

• Side effects: drowsiness, dizziness; strange dreams; vision changes; dry mouth; constipation; increased appetite; weight gain
Reasons to Stop or Switch Medications

• Intolerable side effects
• Dangerous interactions with necessary medications
• The medication was not indicated to start with (ie wrong diagnosis)
• Medication has been at maximum therapeutic dose without improvement for 4-6 weeks
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 week or longer), and build up the dose of the new antidepressant simultaneously.
Key Educational Messages for Patients and Families

- SSRI/SNRIs only work if taken every day
- SSRI/SNRIs are not addictive
- Benefits from medication appear slowly
- Continue medication even after you feel better
- Mild SE 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
<table>
<thead>
<tr>
<th>Lifestyle/Self-Care Interventions for Anxiety Disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Sleep hygiene</td>
</tr>
<tr>
<td>• Exercise – prescribe it!</td>
</tr>
<tr>
<td>• Limit/eliminate caffeine</td>
</tr>
<tr>
<td>• Meditation, yoga</td>
</tr>
<tr>
<td>• Reduce/eliminate use of alcohol and drugs</td>
</tr>
</tbody>
</table>
Summary of Recommendations

• Screen for anxiety disorders in primary care settings (GAD-7) – they are the most common mental health disorder but under-detected and undertreated.

• Refer mild cases for CBT alone

• Trial SSRIs as first line agents (combined with CBT) for moderate to severe cases. Absent intolerable side effects, explore the entire dose range before abandoning an agent as ineffective. Adherence is crucial.

• SNRIs are 2nd line agents after failing 2 SSRIs, because of side effect profiles and risk for discontinuations syndrome

• Other meds (buspar, mirtazepine, antihistamines, beta blockers, atypical antipsychotics, rare cautious benzos) but may be useful as adjunct treatment, or in some cases primary treatment for those who have inadequate or intolerant responses to SSRI/SNRIs.
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, depressive disorders with suicidality, eating disorders)
- Any question of psychosis or bipolarity