Primary Care Psychopharmacology for Anxiety and Depression

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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

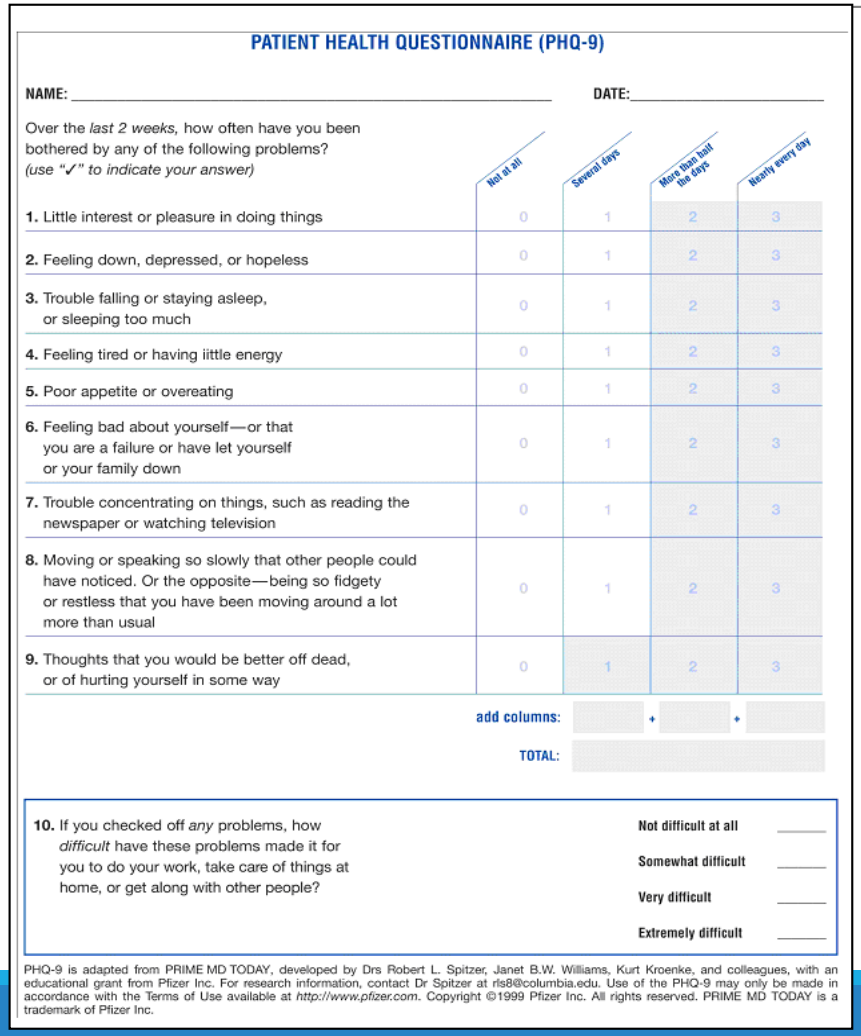
- Despite the fact that over 30 million Americans receive antidepressant prescriptions every year
  - ~20-30% of patients drop out of treatment prematurely
  - ~25-50% stay on ineffective treatments for too long

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)



PATIENT HEALTH QUESTIONNAIRE (PHQ-9)

NAME: _____ DATE: _____

Over the *last 2 weeks*, how often have you been bothered by any of the following problems? *(use "✓" to indicate your answer)*	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself—or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed. Or the opposite—being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead, or of hurting yourself in some way	0	1	2	3
add columns:		+	+	
TOTAL:				

10. If you checked off *any* problems, how *difficult* have these problems made it for you to do your work, take care of things at home, or get along with other people?

- Not difficult at all _____
- Somewhat difficult _____
- Very difficult _____
- Extremely difficult _____

- 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)

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

Over the last two weeks, how often have you been bothered by the following problems?	Not at all	Several days	More than half the days	Nearly every day
1. Feeling nervous, anxious, or on edge	0	1	2	3
2. Not being able to sleep or control worrying	0	1	2	3
3. Worrying too much about different things	0	1	2	3
4. Trouble relaxing	0	1	2	3
5. Being so restless that it is hard to sit still	0	1	2	3
6. Becoming easily annoyed or irritable	0	1	2	3
7. Feeling afraid, as if something awful might happen	0	1	2	3

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. . .

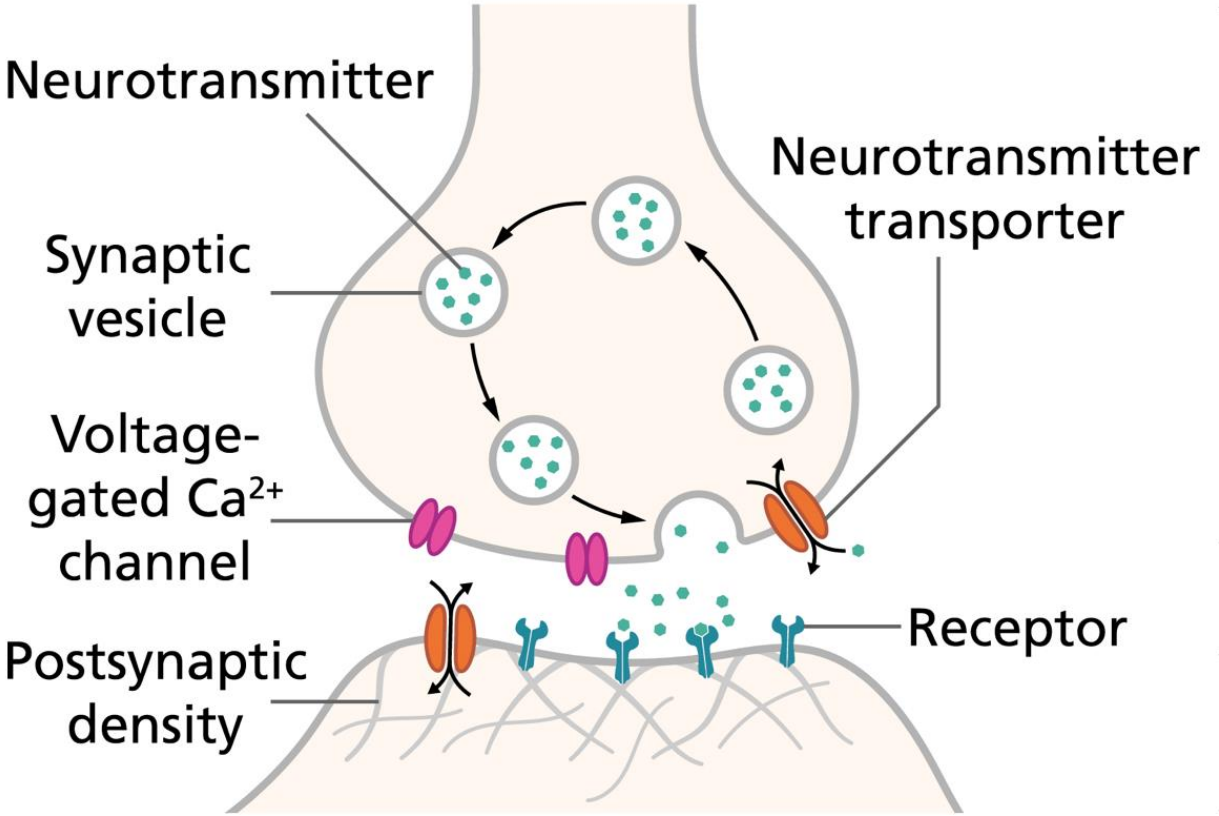
- More than 30-50% of patients will experience complete treatment response

- 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

- SSRI/SNRI medications have 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



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)

Citalopram	Celexa	Depression
Escitalopram	Lexapro	Depression, GAD
Fluoxetine	Prozac, Sarafem, Selfemra	Bulimia nervosa, depression, OCD, panic disorder, PMDD
Fluvoxamine	Luvox	OCD, social phobia
Paroxetine	Paxil, Pexeva	Depression, GAD, OCD, panic disorder, PTSD, PMDD, social phobia
Sertraline	Zoloft	Depression, OCD, panic disorder, PTSD, PMDD, social phobia
Vilazodone	Viibryd	MDD

SSRI FDA Indications

Duloxetine	Cymbalta	Depression, diabetic neuropathy, fibromyalgia, GAD, musculo-skeletal pain, osteoarthritis
Venlafaxine	Effexor	Depression, GAD, panic disorder, social phobia
Desvenlafaxine	Pristiq	Depression
Levomilnacipran	Fetzima	Depression

SNRI FDA Indications

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 seratonergic 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.
  - 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

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

SSRI/SNRI Side Effects

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%)

FDA “Black Box” Warning

WARNING: SUICIDALITY AND ANTIDEPRESSANT DRUGS

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?

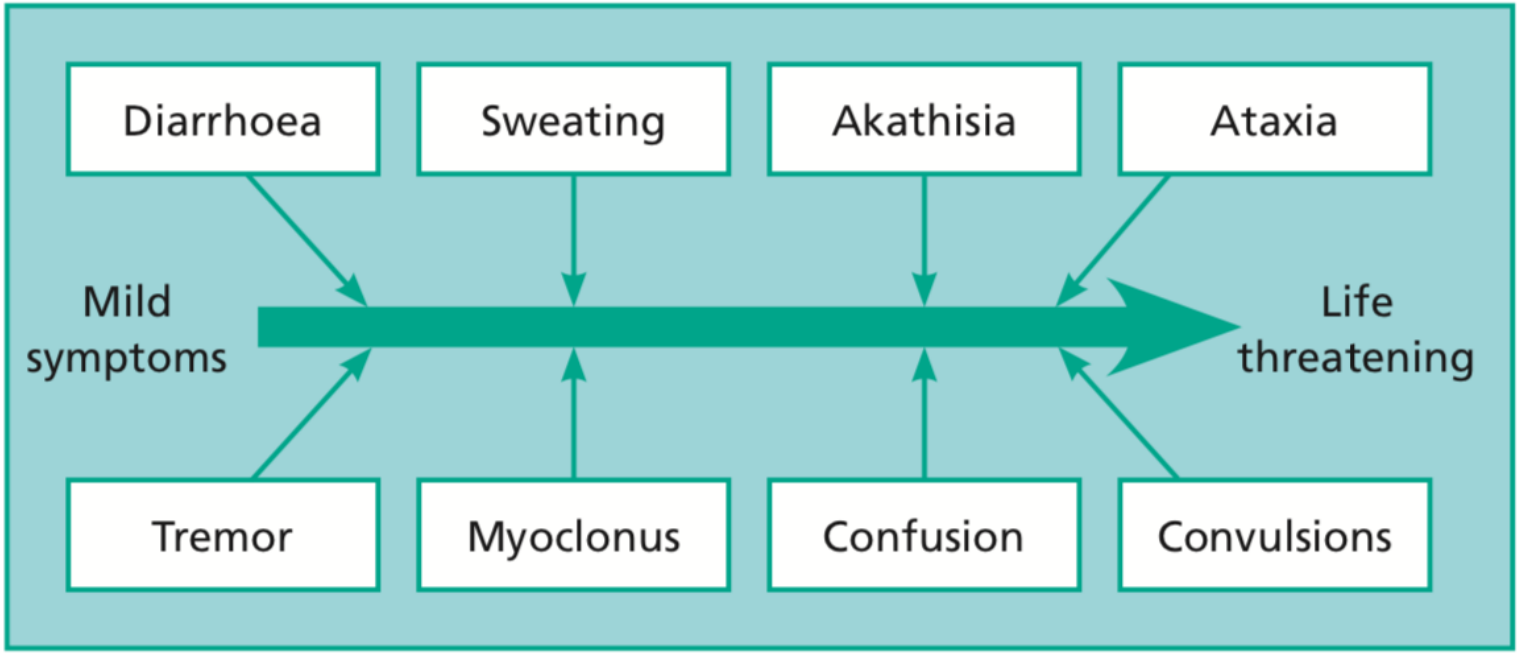
Drug-drug interactions

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



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

Adjust	Adjust dosage until response/side effects/MDD reached
Consider	Consider switch to another agent – lack of response to one does not predict lack of response to another
Assess	Assess adherence
Reevaluate	Reevaluate diagnosis

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.

Antidepressant drugs and their half-lives*		
Drug	**Half out of body in**	**99% out of body in**
Serotonin reuptake inhibitors		
paroxetine (Paxil)	24 hours	4.4 days
sertraline (Zoloft)	26 hours	5.4 days
escitalopram (Lexapro)	27 to 32 hours	6.1 days
citalopram (Celexa)	36 hours	7.3 days
fluoxetine (Prozac)	Four to six days	25 days
Serotonin and norepinephrine reuptake inhibitors		
venlafaxine (Effexor)	5 hours	1 day
duloxetine (Cymbalta)	12 hours	2.5 days

Half lives of commonly prescribed drugs

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?