Antidepressants Classification, and Side effects

Antidepressants do **not cure** depression but are used to **alleviate symptoms** , often over long durations to prevent **relapse or recurrence** . They are primarily used in **major depressive disorder (MDD)** , **dysthymia** , and other psychiatric conditions such as **anxiety disorders** and **bipolar disorder** .

Understanding Depression

Depression is more than just sadness—it involves **persistent low mood, anhedonia, fatigue, sleep disturbances** , and **somatic complaints** . It may be:

- **Reactive (situational)** : Linked to external life events.
- **Endogenous (biological)** : Without identifiable cause, possibly due to neurotransmitter imbalance.
- **Part of bipolar disorder** : Alternates with mania.

Biological Basis: The Monoamine Hypothesis

The prevailing theory suggests that **deficiency of monoamines** (especially **serotonin [5-HT]** , **norepinephrine [NE]** , and **dopamine [DA]**) in synaptic clefts contributes to depression. Antidepressants work by **increasing monoamine availability** in the central nervous system.

Goals of Antidepressant Therapy

- **Acute phase** : Achieve symptom remission.
- **Continuation phase** : Prevent relapse.
- **Maintenance phase** : Prevent recurrence, especially in chronic or recurrent cases.

Classes of Antidepressants

1. Tricyclic Antidepressants (TCAs)

Examples : Imipramine, Amitriptyline, Nortriptyline, Desipramine, Clomipramine, Doxepin, Trimipramine
Mechanism : Inhibit reuptake of **5-HT and NE** , increasing their synaptic levels.

Therapeutic Use :

- Moderate to severe depression
- Neuropathic pain, fibromyalgia
- Nocturnal enuresis (Imipramine)

Adverse Effects :

- **Anticholinergic** : Dry mouth, constipation, urinary retention
- **Cardiotoxicity** : Prolonged QT, arrhythmias (especially in overdose)
- **Sedation** , weight gain
- **Orthostatic hypotension**
- **Lowered seizure threshold**

Clinical Note : Dangerous in **overdose** —monitor ECG and consider use of **activated charcoal or sodium bicarbonate** for TCA toxicity.

2. Monoamine Oxidase Inhibitors (MAOIs)

Examples :

- **Non-selective irreversible** : Phenelzine, Tranylcypromine
- **Reversible MAO-A inhibitor** : Moclobemide

Mechanism : Inhibit **MAO-A and/or MAO-B** , preventing monoamine breakdown.

Indications :

- Atypical depression
- Treatment-resistant depression
- Social phobia

Adverse Effects :

- Hypertensive crisis with **tyramine-rich foods** ("cheese reaction")
- CNS stimulation: Insomnia, agitation
- Orthostatic hypotension
- Dangerous **drug interactions** with SSRIs, TCAs, sympathomimetics ? serotonin syndrome or hypertensive crisis

Clinical Note : **5-week washout** required when switching from fluoxetine to MAOIs due to fluoxetine’s long half-life.

3. Selective Serotonin Reuptake Inhibitors (SSRIs)

Examples : Fluoxetine, Sertraline, Citalopram, Escitalopram, Paroxetine, Fluvoxamine
Mechanism : Selectively inhibit **5-HT reuptake** , increasing its availability.

Indications :

- Major depression
- Generalized anxiety disorder (GAD)
- Panic disorder, OCD, PTSD
- PMDD, bulimia nervosa

Adverse Effects :

- GI upset (nausea, diarrhea)
- Sexual dysfunction (? libido, anorgasmia)
- Insomnia or somnolence
- Serotonin syndrome (especially with polypharmacy)

Clinical Note : **Fluoxetine** has the longest half-life; **paroxetine** is more sedating. SSRIs are **first-line agents** due to better safety and tolerability.

4. Atypical Antidepressants

a. **Bupropion**

- **Mechanism** : Inhibits **NE and DA reuptake**
- **Indications** : Depression, **smoking cessation**
- **Advantage** : No sexual side effects
- **Contraindicated** in **epilepsy** and **eating disorders**

b. **Mirtazapine**

- **Mechanism** : ?2-antagonist ? ? NE and 5-HT; also antagonizes 5-HT2 and 5-HT3 receptors
- **Effects** : Sedation and weight gain (good for anorexia or insomnia)

c. **Trazodone**

- **Mechanism** : 5-HT2 antagonist, weak SSRI
- **Use** : Insomnia (lower doses)
- **Adverse effect** : **Priapism**

d. **Venlafaxine, Duloxetine** (SNRIs)

- **Mechanism** : Inhibit **5-HT and NE** reuptake
- **Use** : Depression, anxiety, **neuropathic pain**

5. Tricyclic Anxiolytics

Examples : Doxepin, Dosulepin

- Similar to TCAs but with **milder antidepressant activity** .
- Useful in **mild depression with anxiety** .
- Faster onset but similar side effects as TCAs.

Key Clinical Considerations

- **Onset of Action** : 2–4 weeks to notice significant effects.
- **Trial Duration** : Minimum of **6 weeks** before considering a switch.
- **Continuation** : 6–12 months post-remission; longer for recurrent depression.
- **Discontinuation** : Taper slowly to avoid withdrawal symptoms.

High-Yield Notes

- SSRIs are **first-line** due to their **favorable side effect profile** .
- **MAOIs** are last-resort due to food and drug interactions.
- **TCAs** are effective but limited by **cardiotoxicity and anticholinergic effects** .
- **Bupropion** is ideal for patients with sexual dysfunction or needing help with smoking cessation.
- Monitor for **serotonin syndrome** when combining serotonergic drugs (triad: **mental status changes, autonomic instability, neuromuscular abnormalities**).
- Always assess for **suicidal ideation** , especially at treatment initiation.