**PHARMACOLOGY & THERAPEUTICS of Antidepressants**

### Monoamines
- **NE**: attention & energy (life of the party)
- **5-HT**: oil in the motor of life (mood, emotion, sleep, appetite, anxiety, obsession)
- **DA**: joy of life

### Receptors: consequences of their antagonism
- **5-HT₂**: improves insomnia, anxiety, akathesia (inner restlessness), sexual dysfunction
- **5-HT₃**: anti-emetic (anti-N/V/D)
- **H₁**: weight gain, sedation
- **M**: constipation, dry mouth, drowsiness, confusion
- **α₁**: orthostatic hypotension

**Tricyclic Antidepressants (TCA’s)**

**2° amines**: desipramine, nortriptyline, protriptyline, amoxapine
- blocks NE > 5-HT reuptake

**3° amines**: imipramine, amitriptyline, doxepin, trimipramine, clomipramine
- blocks 5-HT > NE reuptake

**MOA**: inhibits both NE and 5-HT reuptake carriers

**Immediate action**: ↑NE & ↑5-HT in synapse

**Chronic treatment**: downregulated β-NE & 5-HT receptors, ↑ sensitization of 5-HT receptors → accounts for why onset of action is delayed 4-6 weeks after initiating therapy

**Therapeutic activity**: anti-depressant, anti-panic, anti-obessional

**Receptors affected**: α₁, H₁, M → and their resulting SE (see above “receptors”)

**Other side effects**:
- β-NE stimulation → tremor
- Na⁺ channel blockade → lowers seizure threshold → precipitate or worsen seizures
- Na⁺ channel blockade → cardiac arrhythmia
- May worsen cardiac problems → QTc prolongation, cardiac toxicity, lethal arrhythmias in CAD patients
- Avoid in patients with high suicide risk
- Sexual dysfunction → ↓libido, impaired erection & ejaculation, anorgasmia

**P’kinetics**: good po absorption, highly protein bound, long t½, hepatic metabolism

**Place in therapy**:
- Effective, bad SE profile limits use, used as alternative (moderate to severe pts)
- Avoid in patients with: CHD, seizure risk, elderly, susceptible to anticholinergic effects
- Consider in patients: with neuropathic pain, migraine, fibromyalgia
- Consider 2° amine TCA’s if SE is an issue: less sedation, orthostasis, and anticholinergic effects

### MAOIs

**Monoamine Oxidase Inhibitors (MAOI’s)**

- **Irreversible, nonselective drugs**: phenelzine (hydrzine), isocarboxazid (hydrzide), tranylcypromine
- **Selective MAO-B**: selegiline, moclobemide
- **MOA**: inhibits oxidative deamination (breakdown) of NE, DA, & 5-HT to ↑ their concentration in synapse
- **Pharmacologic effects**: anti-depressive, anti-panic, anti-narcoleptic
- **Two MAO enzyme types**
  - MAO-A → NE, 5-HT, tyramine
  - MAO-B → DA (useful in Parkinson’s)

**Side effects**
- Tyramine effect: potentially fatal hypertensive crisis results if eating tyramine-rich foods (inhibit MAO-A → ↑tyramine → ↑NE → ↑bp)
Common side effects: sleep disturbance, orthostatic hypotension, sexual dysfunction, weight gain

- **Drug interactions:** can cause serotonin syndrome or excessive sympathomimetic activity
  - Avoid: antidepressants, meperidine, dextromethorphan, sympathomimetics, pseudoephedrine
  - Switching to MAOIs: wait two weeks after discontinuing (fluoxetine: wait 5-6 weeks)
- **Place in therapy:** rarely used today, maybe for atypical depression

### SSRI's

<table>
<thead>
<tr>
<th>Selective Serotonin Reuptake Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drugs:</strong> fluoroxetine, paroxetine, fluvoxamine, sertraline, citalopram, escitalopram</td>
</tr>
<tr>
<td><strong>MOA:</strong> inhibition of 5-HT reuptake carrier</td>
</tr>
<tr>
<td><strong>Immediate action:</strong> ↑5-HT accumulation in synapse</td>
</tr>
<tr>
<td><strong>Chronic treatment:</strong> downregulation of 5-HT2 and β-receptors</td>
</tr>
<tr>
<td><strong>Therapeutic effects:</strong> antidepressant, anti-obessional, social anxiety, PMS symptoms, appetite suppression</td>
</tr>
</tbody>
</table>
| **Side effects:**
  - Often due to subtypes of 5-HT receptors (agonistic activity)
    - 5-HT2: insomnia, agitation, anxiety, panic, sexual dysfunction, akathisia
    - 5-HT3: GI issues (N/D), headache
    - Common but transient: jitteriness, insomnia, restlessness, GI issues
  - **Serotonin syndrome:** combining SSRI + SNRI + other drugs*
    - *Other drugs: MAOIs, dextromethorphan, meperidine, tramadol, sympathomimetics
    - Clinical manifestations
      - Cognitive/behavioral: confusion, disorientation, irritability, headaches
      - ANS: hyperthermia, diaphoresis, hypertension, diarrhea, tachycardia
      - Neuromuscular: hyperflexia, myoclonus, rigidity, tremor, ataxia
      - Sexual: ↓libido, impaired arousal, anorgasmia, delayed ejaculation
  - **Discontinuation syndrome:** abrupt d/c leads to bad things
    - Shows up particularly in drugs with short t½
    - Clinical manifestations: electric-shock sensations, jitteriness, anxiety, nausea, headache, dizziness, impaired concentration, flu-like, insomnia
| **Drug profiles:**
  - Activating properties: fluoxetine > sertraline > citalopram > paroxetine
  - Fluoxetine: preferred in patients with psychomotor retardation, AM dosed to ↓insomnia
  - Paroxetine: preferred in patients with psychomotor activation, HS dosed to ↓sedation (anti-ACh)
  - Sertraline, citalopram: preferred in patients with multiple meds, less drug interactions
  - Hepatic enzyme inhibition (drug-drug interactions): paroxetine > norfluoxetine > fluoxetine > sertraline > citalopram
| **Place in therapy:** drug of choice, tolerable, safe (no significant anti-ACh or anti-α effects), not lethal in overdose, generics, drug of choice in patients with comorbid anxiety disorder

### SNRI’s

<table>
<thead>
<tr>
<th>Serotonin Norepinephrine Reuptake Inhibitors</th>
</tr>
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<tbody>
<tr>
<td><strong>Venlafaxine (Effexor):</strong> blocks reuptake of both 5-HT and NE (and DA at high doses) by inhibiting reuptake carrier</td>
</tr>
<tr>
<td><strong>MOA:</strong> blocks reuptake of both 5-HT and NE by inhibiting reuptake carrier</td>
</tr>
<tr>
<td><strong>Low doses:</strong> blocks 5-HT &gt; NE (at low doses acts like SSRI’s)</td>
</tr>
<tr>
<td><strong>Higher doses:</strong> blocks NE &gt; 5-HT, and DA</td>
</tr>
<tr>
<td><strong>Side effects:</strong> no effect on M, α1, or H1 receptors</td>
</tr>
<tr>
<td><strong>Dose related</strong></td>
</tr>
<tr>
<td>- Low doses (&lt;150mg/day): Similar SE profile to SSRI’s</td>
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<tr>
<td>- High doses: NE related effects (↑bp, sweating, ↑HR, tremor, urinary retention)</td>
</tr>
<tr>
<td>- Avoid in patients with uncontrolled hypertension</td>
</tr>
<tr>
<td><strong>Discontinuation syndrome</strong></td>
</tr>
<tr>
<td><strong>Compared to SSRI’s</strong></td>
</tr>
<tr>
<td>- Benefit: dual action</td>
</tr>
<tr>
<td>- Results unclear: maybe faster response, higher remission rates</td>
</tr>
</tbody>
</table>
**Desvenlafaxine (Pristiq)**
- Active metabolite of venlafaxine
- MOA and SE similar to venlafaxine
- Difference from venlafaxine: not a substrate for CYP2D6, so no significant drug interactions

**Duloxetine (Cymbalta)**
- MOA: inhibition of both NE and 5-HT reuptake carriers
- Co-indication: diabetic neuropathy
- Drug interactions: due to CYP2D6
- SE: monitor BP, liver toxicity

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**Atypical Antidepressants**

### Heterocyclics
- **2nd generation**: trazodone, bupropion
- **3rd generation**: mirtazapine, nefazodone

### Trazodone
- MOA: inhibits 5-HT reuptake carrier, antagonizes 5-HT₂ & α₁-NE receptors
- SE: sedation, dry mouth, hypotension, priapism
  - Often used for sedating effect in patients with insomnia as adjunct to SSRI

### Nefazodone
- Mostly similar to trazodone, except for the following points
  - MOA: blocks reuptake of both 5-HT & NE (not just 5-HT as in trazodone) → SARI class
  - More effective for depression-related anxiety & insomnia, less likely to have sexual dysfunction
  - SE: sedation, GI complaints, dry mouth, constipation
  - Black box warning: liver toxicity (potent CYP3A4 inhibitor)

### Vilazodone
- MOA: SSRI + partial 5-HT₁A agonist
- Therapeutic effects: major depressive disorder
- SE: no sexual dysfunction

### Bupropion
- MOA: (unsure), inhibition of NE (metabolite action) and DA (parent drug action) reuptake carriers
- SE: mild psychomotor agitation (very activating), insomnia, seizures (!), psychosis (mesolimbic DA activity), CNS stimulation, appetite inhibition
- Place in therapy: alternative for those who can’t tolerate sexual dysfunction, weight gain, sedation
  - Not effective: anxiety disorder
  - Avoid: patients with anorexia, insomnia, risk of seizures
  - Particularly useful: patients with weight gain, hypersomnia, psychomotor retardation, ADHD, smokers wanting to quit

### Mirtazapine
- MOA: antagonist of α₂ autoreceptors → ↑NE & ↑5-HT
- Therapeutic effects: “The Designer Antidepressant”
  - 5HT₁A: antidepressant, anxiolytic
  - 5HT₂A: anxiolytic, sleep restoring, no sexual dysfunction
  - 5HT₂C: anxiolytic, weight gain
  - 5HT₃: no GI problems, no nausea
  - H₁: anxiolytic, sedation, weight gain, drowsiness
- Place in therapy: useful when insomnia or agitation is prominent, anorexic patients
  - 5-HT₂ blockade: rarely sexual dysfunction, reduces anxiety in depressed patients

### Amoxapine
- MOA: inhibition of both NE & 5-HT reuptake carriers
- SE: sedation (anti-H₁), extrapyramidal side effects (from its metabolite)

### Maprotiline
- MOA: selective NE reuptake inhibitor
- SE: sedation (anti-H₁), orthostatic hypotension (anti-α₁-NE), seizures
<table>
<thead>
<tr>
<th></th>
<th>Monoamines blocked</th>
<th>Psychiatric disorders treated</th>
<th>Adverse effects</th>
<th>Place in therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>TCA’s</td>
<td>NE, 5-HT</td>
<td>Depression, panic, obsession</td>
<td>Weight gain, sedation, anticholinergic, orthostatic hypotension, tremor, seizure, cardiac, suicide, sexual</td>
<td><em>Not used much today</em></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Neuropathic pain, migraine, fibromyalgia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Tyramine effect, sleep disturbance, orthostatic hypotension, sexual, weight gain, drug interactions causing serotonin syndrome</td>
<td><em>Not used much today</em></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Possibly atypical depression</td>
</tr>
<tr>
<td>MAOI’s</td>
<td>NE, 5-HT, DA</td>
<td>Depression, panic, narcolepsy</td>
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</tr>
<tr>
<td>SSRI’s</td>
<td>5-HT</td>
<td>Depression, obsession, social anxiety, PMS sx, appetite</td>
<td>Insomnia, agitation, panic, sexual, akathisia, GI, headache, serotonin syndrome, d/c syndrome</td>
<td>Drug of choice</td>
</tr>
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<td>Especially in patients with comorbid anxiety disorder</td>
</tr>
<tr>
<td>SNRI’s</td>
<td>5-HT, NE, (DA)</td>
<td>Depression</td>
<td>Dose related (5-HT, NE), d/c syndrome</td>
<td>Diabetic neuropathy</td>
</tr>
<tr>
<td>Trazodone</td>
<td>5-HT</td>
<td>Depression</td>
<td>Sedation, dry mouth, hypotension, priapism</td>
<td>Sedating effect in insomniacs</td>
</tr>
<tr>
<td>Bupropion</td>
<td>NE, DA</td>
<td>Depression</td>
<td>Activating, insomnia, seizures, psychosis, ↓appetite</td>
<td>Pts with weight gain, hypersomnia, ADHD, smokers</td>
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<tr>
<td>Mirtazapine</td>
<td>5-HT</td>
<td>Depression, anxiety</td>
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<td>Maprotiline</td>
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