**Antidepressant Pharmacology - An Overview**

**Figure 1.**

![Antidepressant Pharmacology - An Overview](image)

**Figure 1. Targets of Antidepressant Action on Noradrenergic and Serotonergic Neurons.**

In Panel A, targets of action for antidepressants in the noradrenergic system can enhance activity by blockade of the α-adrenergic autoreceptor, blockade of norepinephrine (NE) reuptake at the synaptic cleft, stimulation of α-propionic and β-adrenergic postsynaptic receptors, activation of signal transduction and second messenger pathways, and blockade of monoamine oxidase (MAO), the enzyme involved in NE breakdown. In Panel B, targets of action for antidepressants in the serotonergic system can enhance activity by blockade of 5-HT1A, 5-HT1B, and 5-HT2A autoreceptors, blockade of serotonin receptors at the synaptic cleft, activation of the 5-HT1A postsynaptic receptor, activation of signal transduction and second messenger pathways, and blockade of the 5-HT2A postsynaptic receptor. Monoamine oxidase inhibitors (MAOIs) function by blockade of MAO, the enzyme involved in serotonin breakdown.

Source: NEJM 2005;353:1819-34

**Figure 2.**

![Antidepressant Pharmacology - An Overview](image)
Figure 3: Antidepressant Pharmacology pictures:

Source: Stephen Stahl - Essential Psychopharmacology
Table 1. Antidepressant Mechanism of Action

<table>
<thead>
<tr>
<th>Class</th>
<th>Drugs</th>
<th>Re-uptake Inhibition</th>
<th>Receptor Blockade</th>
<th>Potent CYP enzyme inhibition</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>SRI</td>
<td>NRI</td>
<td>DRI</td>
</tr>
<tr>
<td>SSRI s</td>
<td>Fluoxetine</td>
<td>+++</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fluvoxamine</td>
<td>+++</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Sertraline</td>
<td>+++</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Paroxetine</td>
<td>++++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Citalopram</td>
<td>++</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Escitalopram</td>
<td>++</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>TCAs</td>
<td>Amitriptyline</td>
<td>+++</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Nortriptyline</td>
<td>++</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>NDRI</td>
<td>Bupropion</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>SNRI</td>
<td>Venlafaxine</td>
<td>++</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Duloxetine</td>
<td>++</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>NaSSA</td>
<td>Mirtazapine</td>
<td>++++</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

SRI = serotonin reuptake inhibition; NRI = norepinephrine reuptake inhibition; DRI = dopamine reuptake inhibition

**Drug Class:** SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant; NDRI = norepinephrine dopamine reuptake inhibitor; SNRI = serotonin norepinephrine reuptake inhibitor; NaSSA = noradrenergic and specific serotonergic antidepressant

(+ to (++++) = increasing potency; (-) = weak effect; blank = no effect

Ref: J Clin Psych 2003;64[suppl 13]:5-12
Mayo Clin Proc 2001;76:511-27
Clinical Handbook of Psychotropic Drugs 2004, 14th Ed.

**Figure 4. Action of Mirtazapine:** blocks pre-synaptic alpha-2 receptors on NE and 5-HT neurons which “takes the brakes off” and enhances the release of NE and 5-HT. NE then activates alpha-1 receptors on 5-HT neuron to enhance release of 5-HT.
**Table 2. Clinical Effects of Neurotransmitter Reuptake Blockade**

<table>
<thead>
<tr>
<th>Receptor action</th>
<th>Therapeutic Effects</th>
<th>Possible Side Effects</th>
</tr>
</thead>
</table>
| Norepinephrine Reuptake Inhibition | Antidepressant effects | Tremors  
Tachycardia  
Insomnia, anorexia  
Hypertension  
Augmentation of pressor effects of sympathomimetic amines |
| Serotonin Reuptake Inhibition | Antidepressant effects  
Antianxiety effects  
Anti-OCD effects | GI disturbances (nausea, vomiting, diarrhea, wt loss early on; wt gain later in tx)  
Headache  
Sexual dysfunction  
May see increase in anxiety (early on or with fast dose titration) |
| Dopamine Reuptake Inhibition | Antidepressant effects  
Enhanced motivation  
Enhanced cognition  
Antiparkinsonian  
Mitigation against prolactin elevation  
Psychomotor activation | Aggravation of psychosis |
| Muscarinic (acetylcholine) blockade | (Potentiates drugs with anticholinergic properties eg. Diphenhydramine, TCAs, oxybutynin, H2-blockers) | Dry mouth, Blurred vision, Constipation, Urinary retention  
Sinus tachycardia, QRS changes  
Memory disturbances  
Worsen narrow-angle glaucoma |
| Alpha-1 receptor blockade | (Potentiates antihypertensives with alpha-blocking properties eg. Prazosin, terazosin, labetalol) | Postural hypotension, dizziness, reflex tachycardia  
Sedation |
| H1 (Histamine) blockade | (Potentiates effects of other CNS drugs) | Sedation, drowsiness  
Postural hypotension  
Weight gain |

**Other Side Effects:**

**SSRIs in general:** nausea, anxiety, tremor, insomnia, sweating, dry mouth, headache, dizziness, diarrhea, constipation, sexual dysfunction (> 30%), SIADH (hyponatremia)

**Fluoxetine:** most anorexic and stimulating of SSRIs, weight loss; very long half-life (1 week!)

**Fluvoxamine:** most nauseating, constipating and sedating SSRI, many drug interactions

**Paroxetine:** most anticholinergic of SSRIs, increased sexual dysfunction; higher incidence of discontinuation reactions, increased weight gain

**Sertraline:** most diarrhea and male sexual dysfunction

**Citalopram:** fewest drug interactions

**Escitalopram:** less sedation, sweating and sexual dysfunction than citalopram (is the active portion of the citalopram molecule)

**TCAs in general:** tachycardia, hypotension, dizziness, sedation, weight gain, sexual dysfunction, sweating, tremor, ECG abnormalities, seizures, fatal in overdose, dry mouth, constipation

**Venlafaxine:** higher incidence of nausea/vomiting than with SSRIs; agitation, tremor, sweating, headache, as dose increases can cause hypertension; higher incidence of discontinuation reactions; less weight gain than with SSRIs; few drug interactions; sweating, headache, moderate incidence of sexual dysfunction (10-30%)  
**Note:** at doses of less than 150 mg/day behaves mainly like an SSRI; beyond 150-225 mg/day you get increased NE effects
**Duloxetine:** less effect on BP compared to Venlafaxine; otherwise ~similar to Venlafaxine

**Mirtazapine:** dry mouth, sedation, edema, arthralgias, increased appetite, high incidence of weight gain, less sexual dysfunction than SSRIs/SNRIs

**Bupropion:** risk of seizures (0.4%/400 mg/d) – caution in those with seizure history; agitation, insomnia, tremor, sweating, decreased appetite, GI upset, little-no weight gain, less sexual dysfunction than SSRIs/SNRIs, vivid dreams (esp people using for smoking cessation), psychosis

**Antidepressants and Suicidality**
- Suicide is the 9th leading cause of death in Canada
  - 2nd leading cause in people aged 15-34 yrs
  - 3rd leading cause in people aged 35-44 yrs

- Risk factors include depression and other mental illnesses; alcohol and substance abuse
- In the US – the ratio of suicide attempts to completed suicides:
  - General population: 25 attempts : 1 suicide
  - Ages 15-24 yrs: 100-200 attempts : 1 suicide
  - Ages 65 and older: 4 attempts : 1 suicide

Ref: www.statcan.gc.ca and [www.cdc.gov/violenceprevention](http://www.cdc.gov/violenceprevention) summer 2009 newsletter

**Figure 5:**

[Graph showing the relationship between weeks and suicide risk with labels for energy increase, mood improvement, and agitation increase and decrease.

*Figure 1* Temporal course of antidepressant actions

Ref: Nutt DJ. J of Psychopharmacology 2003;17: 355-64
Consider risk of untreated depression:

- Cohort study in Washington and Idaho state looking at claim records from an HMO of over 100,000 pts over 10 yrs showed an increased risk of suicide attempts in the 1 month PRIOR to starting a prescription for antidepressants compared to the few months post.

**Figure 6:**

**Figure 1. Risk of Suicide Attempt or Possible Suicide Attempt Before and After Starting Treatment Among Adolescents and Adults Receiving New Antidepressant Prescriptions From Primary Care Physicians, Receiving New Antidepressant Prescriptions From Psychiatrists, or Starting Individual Psychotherapy for Depression**


FDA 2006 meta-analysis of trials for increased risk of suicide –

**Fluoxetine and Sertraline** had a DECREASED risk of “suicidal ideation or worse” as an outcome

**all other SSRIs, Venlafaxine, Bupropion, Mirtazapine, Duloxetine had NS results**

**Sertraline had a DECREASED risk of “suicide preparation or worse” as an outcome**

**Paroxetine had an INCREASED risk of “suicide preparation or worse”**


**Antidepressants and Cardiac disease:**

Sertraline has been found to be safe for use in depression post MI. Citalopram has been found to be safe for use in depression with CAD.
**Serotonin Syndrome:**
Mild cases may present with tremor, sweating and diarrhea. Severe life-threatening cases may have delirium/agitation, neuromuscular rigidity and hyperthermia.

**Figure 7:**

![Figure 7](image1)

**Figure 8:**

**Table 1. Drugs and Drug Interactions Associated with the Serotonin Syndrome.**

<table>
<thead>
<tr>
<th>Drugs associated with the serotonin syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selective serotonin-reuptake inhibitors: sertraline, fluoxetine, fluvoxamine, paroxetine, and citalopram</td>
</tr>
<tr>
<td>Antidepressant drugs: trazodone, nefazodone, buspirone, clomipramine, and venlafaxine</td>
</tr>
<tr>
<td>Monoamine oxidase inhibitors: pheelazine, moclobemide, clorgiline, and selegiline</td>
</tr>
<tr>
<td>Antihypertensives: valproate</td>
</tr>
<tr>
<td>Analgesics: meperidine, fentanyl, tramadol, and pethidine</td>
</tr>
<tr>
<td>Antihistamines: sedatives, granisetron, and metoclopramide</td>
</tr>
<tr>
<td>Anticholinergic drugs: sumatriptan</td>
</tr>
<tr>
<td>Bariatric medications: sibutramine</td>
</tr>
<tr>
<td>Antibiotics: linezolid (a monoamine oxidase inhibitor) and ritonavir (through inhibition of cytochrome P-450 enzyme methyl isomerase 3A4)</td>
</tr>
<tr>
<td>Over-the-counter cough and cold remedies: decongestants</td>
</tr>
<tr>
<td>Drugs of abuse: methylenedioxymethylamphetamine (MDMA, or “ecstasy”), beta-acid diethylamide (LESD), 5-methoxyisopropyltryptamine (“fox methoxy”), Syrian rue, both monoamine oxidase inhibitors</td>
</tr>
<tr>
<td>Dietary supplements and herbal products: tryptophan, Hypericum perforatum (St. John’s wort), Panax ginseng (ginseng)</td>
</tr>
<tr>
<td>Other: lithium</td>
</tr>
</tbody>
</table>

**Drug interactions associated with severe serotonin syndrome**

- Zoloft, Prozac, Sarafem, Luvox, Palox, Cava, Desyrel, Sarzone, Buprop, Anaf. manil, Effekor, Nirdil, Maneix, Marpall, Depakote, Demerol, Duragesic, Sublimaze, Upram, Talwin, Zofran, Exilril, Reglan, Imitrex, Meridia, Redux, Pondmin, Zyvo, Novit, Parnate, Tofedil, Remeron |

| Pheneze X and meperidine |
| Tranylcypromine and imipramine |
| Pheneze X and selective serotonin-reuptake inhibitors |
| Paroxetine and buspirone |
| Linezolide and citalopram |
| Moclobemide and selective serotonin-reuptake inhibitors |
| Tranadil, verapamil, and mitazapine |

**Discontinuation Reactions with Antidepressants:**
Occurs in approximately 20% of pts after abrupt discontinuation of an antidepressant medication that was taken for at least 6 wks.
Symptoms typically appear within 3 days of stopping the agent.

**FINISH** – Mnemonic to recognize Discontinuation Syndrome:
- F lu-like symptoms (fatigue, lethargy, malaise, muscle aches, diarrhea)
- I nsomnia
- N ausea
- I mbalance (gait instability, dizziness, lightheadedness, vertigo)
- S ensory disturbances (paresthesias, “electric shock” sensations, visual disturbances)
- H yperarousal (anxiety, agitation)

Symptoms are usually mild and self-limiting – lasting 1-2 weeks. If intolerable – they will be extinguished with the resumption of the antidepressant agent.
Can occur with SSRIs (except NOT with fluoxetine), TCAs, MAOIs, Venlafaxine, Duloxetine, Mirtazapine and Trazodone.
Higher risk with agents with a shorter half-life: Paroxetine, Venlafaxine, Duloxetine

**Management** – use a slower tapering course, if not possible switch to Fluoxetine


**Common Antidepressant Doses** - See RxFiles table or Clinical Handbook of Psychotropic Drugs

**General Comments regarding Drug Interactions**
- Carbamazapine is a strong inducer of CYP P450 enzymes and it lowers the levels of most SSRI’s, Trazodone, Mirtazapine, and Venlafaxine
- SSRIs affect platelet aggregation and can therefore increase the antiplatelet effects of drugs like aspirin, clopidogrel, prasugrel; because of this action there is an increased risk of GI bleeds. This is very important when given in combination with NSAIDs (risk of GI bleeds higher than with either SSRI or NSAID alone).
- MAOIs will increase the effects of all other antidepressants and combinations are considered contraindicated. Can lead to serotonin syndrome and hypertensive emergencies.
  - Note: Linezolid (antibiotic) has weak MAOI properties and can cause serotonin syndrome; macrolides (clarithromycin) can also increase levels of SSRIs
- Tramadol has weak SSRI properties and there are case reports of serotonin syndrome when given in combination with SSRI’s.
- Cigarette smoking can decrease the levels of Mirtazapine and Duloxetine through induction of CYP 1A2
- Antiretrovirals (ex. Ritonavir) may be potent enzyme inducers and could lower levels of certain antidepressants.
- Triptans (migraine medications, eg. Sumatriptan, Rizatriptan) can lead to serotonin syndrome
- Paroxetine inhibits CYP 2D6 – can lower metabolism of Risperidone; Tramadol to its active components

**Useful Readings:**
Mann JJ. Medical management of depression. NEJM 2005;353:1819-34
Belmaker RH and Agam G. Major depressive disorder. NEJM 2008;358:55-68