Antidepressant Pharmacology – An Overview

Figure 1.

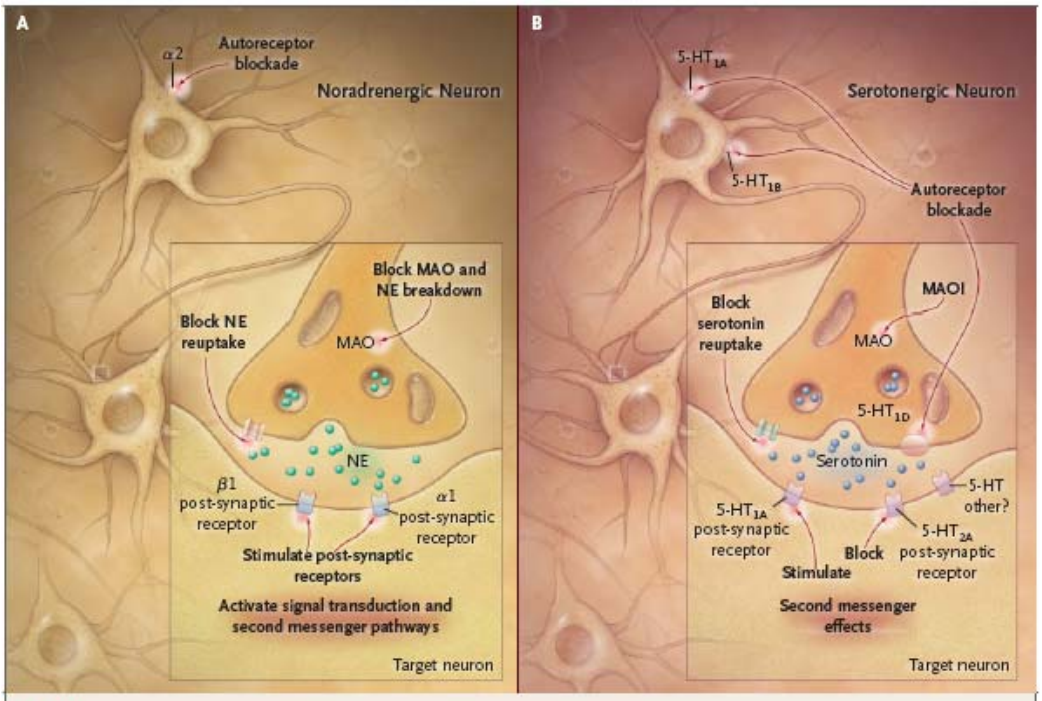


Figure 1. Targets of Antidepressant Action on Noradrenergic and Serotonergic Neurons.

In Panel A, targets of action for antidepressants in the noradrenergic system can enhance activity by blockade of the α_2-adrenergic autoreceptor, blockade of norepinephrine (NE) reuptake at the synaptic cleft, stimulation of α_1-adrenergic and β_1-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-HT_{1A}, 5-HT_{1B}, and 5-HT_{1D} autoreceptors; blockade of serotonin reuptake at the synaptic cleft; activation of the 5-HT_{1A} postsynaptic receptor; activation of signal transduction and second-messenger pathways; and blockade of the 5-HT_{2A} 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.

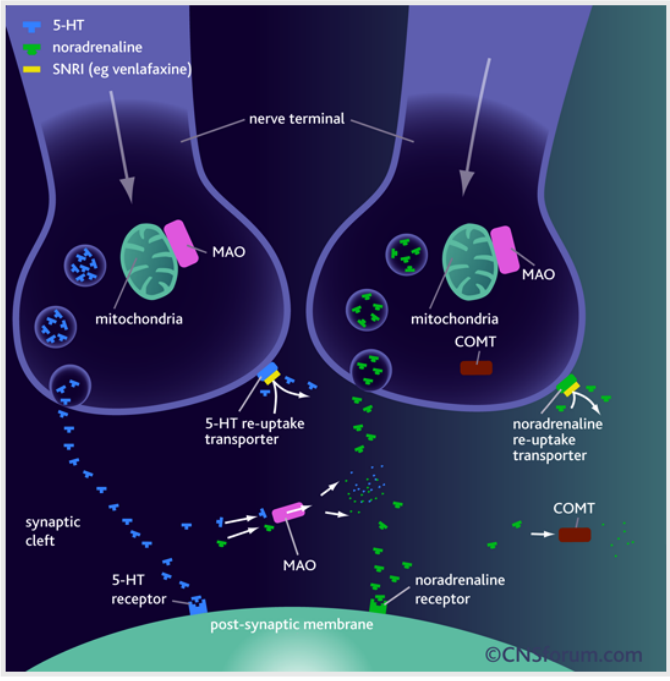
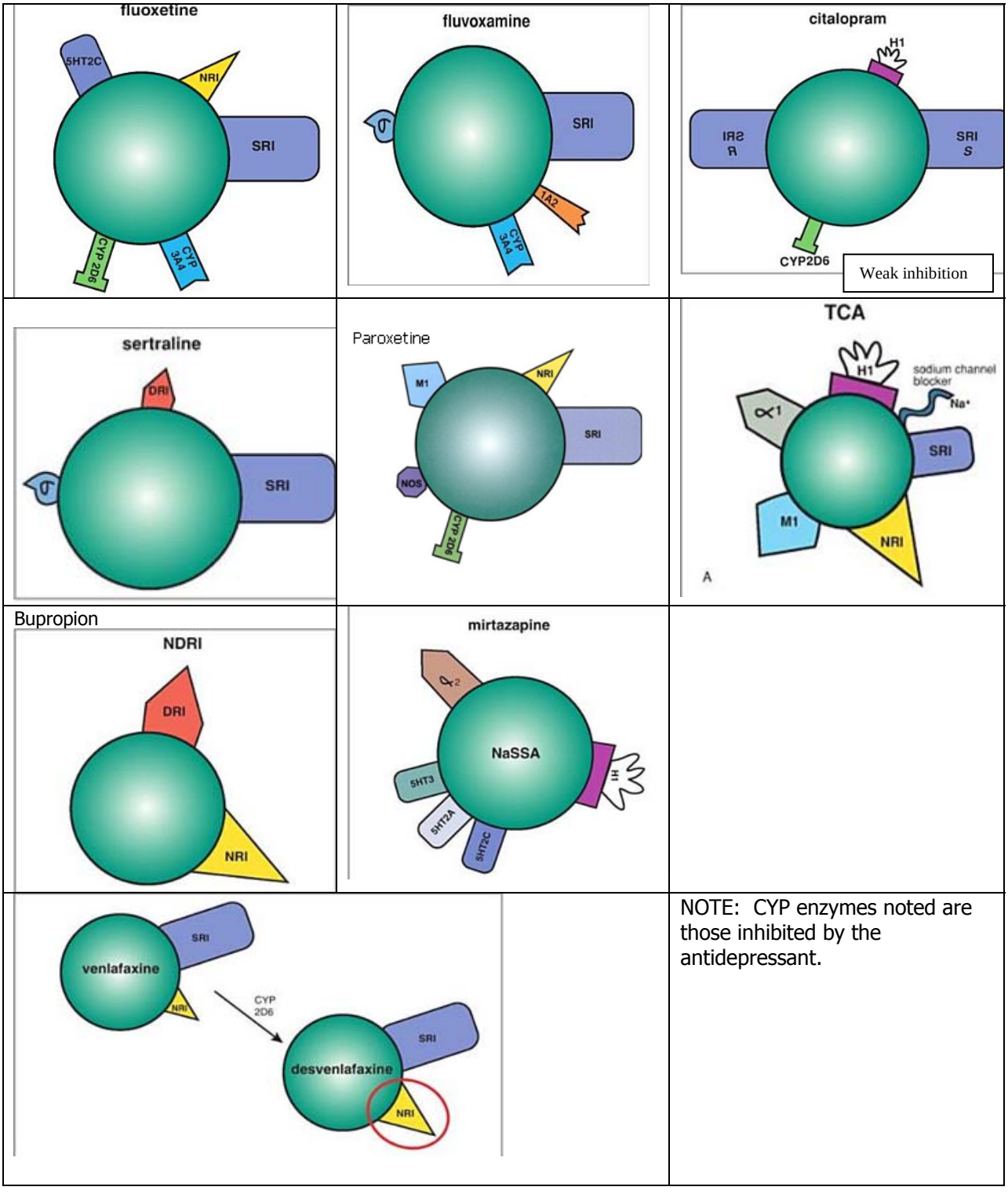


Figure 3: Antidepressant Pharmacology pictures:



NOTE: CYP enzymes noted are those inhibited by the antidepressant.

Source: Stephen Stahl - Essential Psychopharmacology

Table 1. Antidepressant Mechanism of Action

Class	Drugs	Re-uptake Inhibition			Receptor Blockade			Potent CYP enzyme *inhibition*		
		SRI	NRI	DRI	Hist	Musc	Alpha1	2D6	2C19	1A2
SSRIs	Fluoxetine	+++	-					√		
	Fluvoxamine	+++	-					√	√	√
	Sertraline	+++	-	+		-	-		√	
	Paroxetine	++++	+	+		++		√		
	Citalopram	++	-					(√) weak		
	Escitalopram	++	-							
TCAs	Amitriptyline	+++	++	-	++	++++	++	√	√	
	Nortriptyline	++	++++	-	+	+	+			
NDRI	Bupropion	-	-	+						
SNRI	Venlafaxine	++	-							
	Duloxetine	++	-							
NaSSA	Mirtazapine				++++	-	-			

SRI = serotonin reuptake inhibition; **NRI =** norepinephrine reuptake inhibition; **DRI =** dopamine reuptake inhibition
Drug Class: SSRI= selective serotonin reuptake inhibitor; TCA= tricyclic antidepressant; NDRI= norepinephine 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.

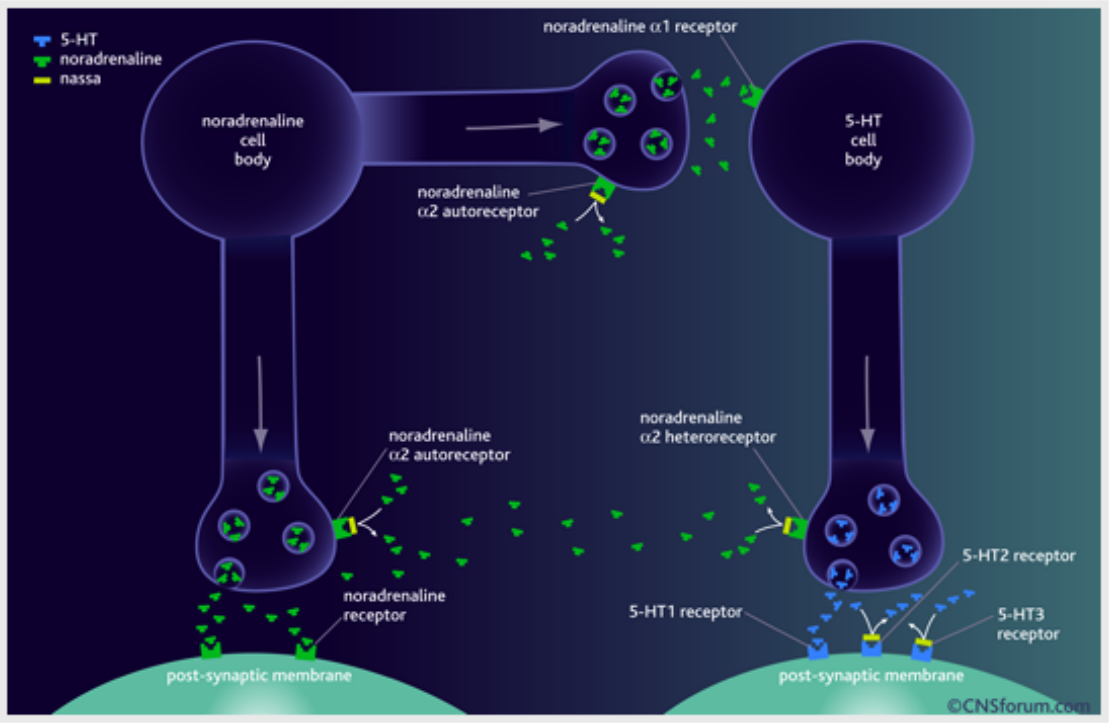


Table 2. Clinical Effects of Neurotransmitter Reuptake Blockade

Receptor action	Therapeutic Effects	Possible Side Effects
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	(Potentiate 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 summer 2009 newsletter

Figure 5:

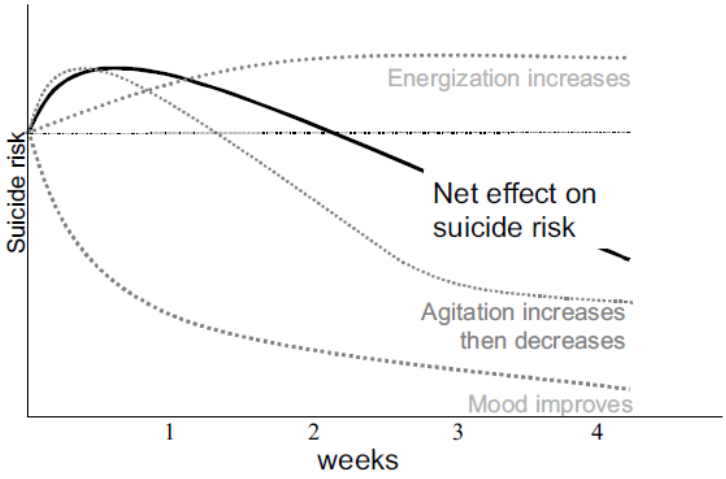


Figure 1 Temporal course of antidepressant actions

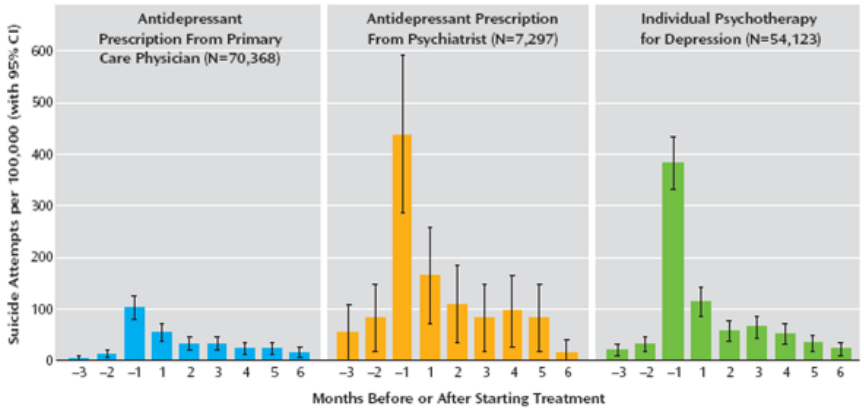
Ref: Nutt DJ. J of Psychopharmacology 2003;17: 355-64

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



Ref: Simon GE, Savarino J. Am J Psych 2007;164:1029-34.

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, Venlafaxafine, 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"

Ref: Stone M et al. BMJ 2009;339:b2880 online (print p.431-4); Barbui C et al. EBMH 2008;11:34-36.

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:

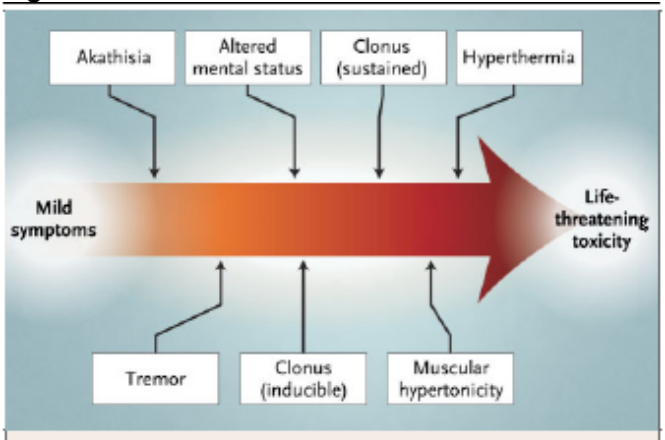


Figure 1. **Spectrum of Clinical Findings.**
Manifestations of the serotonin syndrome range from mild to life-threatening. The vertical arrows suggest the approximate point at which clinical findings initially appear in the spectrum of the disease, but all findings may not be consistently present in a single patient with the serotonin syndrome. Severe signs may mask other clinical findings. For example, muscular hypertonicity can overwhelm tremor and hyperreflexia.

Figure 8:

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

Drugs associated with the serotonin syndrome

Selective serotonin-reuptake inhibitors: sertraline, fluoxetine, fluvoxamine, paroxetine, and citalopram
Antidepressant drugs: trazodone, nefazodone, buspirone, clomipramine, and venlafaxine
Monoamine oxidase inhibitors: phenelzine, moclobemide, clorgiline, and isocarboxazid
Anticonvulsants: valproate
Analgesics: meperidine, fentanyl, tramadol, and pentazocine
Antiemetic agents: ondansetron, granisetron, and metoclopramide
Antimigraine drugs: sumatriptan
Bariatric medications: sibutramine
Antibiotics: linezolide (a monoamine oxidase inhibitor) and ritonavir (through inhibition of cytochrome P-450 enzyme isoform 3A4)
Over-the-counter cough and cold remedies: dextromethorphan
Drugs of abuse: methylenedioxymethamphetamine (MDMA, or "ecstasy"), lysergic acid diethylamide (LSD), 5-methoxydiisopropyltryptamine ("foxy methoxy"), Syrian rue (contains harmine and harmaline, both monoamine oxidase inhibitors)
Dietary supplements and herbal products: tryptophan, *Hypericum perforatum* (St. John's wort), Panax ginseng (ginseng)
Other: lithium

Drug interactions associated with severe serotonin syndrome

Zoloft, Prozac, Sarafem, Luvox, Paxil, Celexa, Desyrel, Serzone, Buspar, Anafranil, Effexor, Nardil, Manerix, Marplan, Depakote, Demerol, Duragesic, Sublimaze, Ultram, Talwin, Zofran, Kytril, Reglan, Imitrex, Meridia, Redux, Pondimin, Zyvox, Norvir, Parnate, Tofranil, Remeron

Phenelzine and meperidine
Tranylcypromine and imipramine
Phenelzine and selective serotonin-reuptake inhibitors
Paroxetine and buspirone
Linezolide and citalopram
Moclobemide and selective serotonin-reuptake inhibitors
Tramadol, venlafaxine, and mirtazapine

Ref: Bower EW and Shannon M. NEJM 2005;352:1112-20.

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

Ref: Warner CH et al. Am Fam Phys 2006;74:449-56.

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
Stahl SS. Selecting an antidepressant by using mechanism of action to enhance efficacy and avoid side effects. J Clin Psych 1998;59(suppl 18):23-29.