ANTIDEPRESSANTS

	MECHANISM OF ACTION	SIDE EFFECTS	DRUG INTERACTIONS	OTHER POINTS

TRICYCLIC ANTIDEPRESSANTS
Tertiary amines / **Secondary amines**
Imipramine ------> Despiramine
Amitryptyline -------> Nortriptyline
Trimipramine -------> Protrityline
Clomipramine
Doxepine
	• Blocks the neuronal uptake of the biogenic amines 5-HT and/or NA
	  ○ 3° amines preferentially block 5-HT uptake
	  ○ 2° amines preferentially block NE uptake
	  ○ DOUBTS WITH THIS MECHANISM
	• Down-regulation of 5-HT receptors in the brain
		In general, SEs for tertiary > secondary TCAs
		• Anticholinergic, muscarinic blockade: constipation, blurred vision, dry mouth, drowsiness
		• α_1 receptor blockade: dizziness, orthostatic hypotension, reflex tachycardia, drowsiness
		• H_1, ACh & adrenergic antagonism: sedation
		• Overdose: blockade of Na channels = hyperpyrexia, arrhythmias, hypertension, delirium, seizures, and coma
		• Conversion to (hypo)mania
			• MAOI
			• Guathenidine
			• Clonidine
			• Adrenergics
			• CNS depressants
			• Agents that bind plasma protein
				• TCAs do not elevate mood in normal subjects
				• Not reinforcing = not drugs of abuse

SELECTIVE SEROTONIN RECEPTOR INHIBITORS (SSRIS)
• Fluoxetine
• Fluvoxamine
• Paroxetine
• Sertraline
• Citalopram
• Escitalopram
	• Selective in blocking the neuronal uptake of 5-HT preferentially in the somatodendritic area of serotonin neurons
	• Increased 5-HT in the somatodendritic area of the 5-HT neuron → 5-HT_{1A} receptor down-regulation → more 5-HT neuron impulses (spike activity) ➔ more 5-HT release from axon terminals
		• Generally, SSRIs are better tolerated than TCAs
		  ○ << anticholinergics, sedation and dizziness
		  ○ >> insomnia, anxiety, agitation
		• GI distress: constipation, diarrhea
		• Sexual dysfunction
			• MAOI
			• CNS depressants
			• Other antidepressants (serotonin syndrome)
				• 25-30% of depressed patients treated with TCA do not respond
				  ○ Of these, 60-65% respond to SSRI
				  ○ Converse is also true

5-HT, NA (and DA) REUPTAKE BLOCKERS (SNRI)
• Desvenlafaxine
• Venlafaxine
• Duloxetine
• Levomilnacipran*
	• Inhibits reuptake of 5-HT, NA (dose-dependent)
	  ○ Low-doses: SSRI
	  ○ Medium doses: NA uptake blocked
	  ○ Higher doses: similar to bupropion
	• Weak, if any, cholinergic or H_1 receptor blockade
		• Nausea
		• Drowsiness
		• Dizziness
		• HTN (at higher doses)
		• Sexual dysfunction
		• Headache
		• Anxiety
			• Duloxetine should not be co-administered with drugs that potently inhibit CYP1A2 (cimetidine, ticlopidine, ciprofloxacin)	• LEVOMILNACIPRAN: exerts more balanced reuptake inhibitory action of 5-HT & NE
				  ○ SEs: nausea, dry mouth, constipation, hyperhidrosis, headache, dizziness, tachycardia, insomnia, erectile dysfunction

NA and DA REUPTAKE INHIBITORS (NDRIS): • Bupropion	• Blocks NE and DA re-uptake ○ Blockade of DA uptake > NE uptake • Metabolite more potent in blocking NE reuptake than parent compound	• In general, fewer SEs than TCAs or SSRIs • Insomnia, CNS stimulation, headache, nausea, seizures • Less sexual dysfunction compared with SSRIs • Only marginal weight gain, orthostatic hypotension		
5-HT_{2A} ANTAGONIST & 5-HT REUPTAKE INHIBITOR (SARIs) • Trazodone	• Potent blocker of 5-HT_{2A} receptors ○ Reduces anxiety, insomnia and myoclonus • Moderate 5-HT receptor blockade, but less than TCAs or SSRIs • Also blocks α and H_1 receptors • Little or no ability to block NE reuptake	• Orthostatic hypotension • Sedation		
5-HT MODULATOR & STIMULATOR • Vortioxetine	• Inhibits 5-HT reuptake • 5-HT_{1B} partial agonist • 5-HT_3, 5-HT_7 & 5-HT_{1D} antagonist	• Nausea • Headache • Dizziness • Dry mouth • Increased nasopharyngitis	• Use in caution with CYP2D6 inhibitors (bupropion, paroxetine, fluoxetine)	

NA and SPECIFIC 5-HT ANTAGONIST (NaSSas)
• Mirtazapine
	• α_2 antagonism at:
	  ○ Presynaptic α_2 autoreceptors on NE neurons = enhances NE transmission
	  ○ Presynaptic α_2 heteroreceptors on 5-HT neurons = enhances 5-HT transmission
		MOA → RX AND SIDE EFFECTS:
		• 5-HT_{2A} antagonism: anxiolytic action, sedation, ↓ sexual dysfunction
		• 5-HT_{2C} antagonism: anxiolytic action, weight gain
		• 5-HT_3 antagonism: no nausea
		• H_1 antagonism: weight gain, sedation
			•	• May enhance sedative effects of BZDs, alcohol
				• Relatively safe drug, few drug interactions
				• Does not cause serotonin syndrome
				• No significant effects on CV system even at high doses

MONOAMINE OXIDASE INHIBITORS (MAOIs)
• Tranylcypromine
• Isocarboxadize
	• Irreversible, non-selective inhibitors of MAO
	• Two weeks required for enzyme to regenerate
	  ○ Acute: enhancement of biogenic amine transmission
	  ○ Chronically: down-regulate 5-HT, NE and DA receptors
		• Agitation
		• Orthostatic hypotension
		• Sexual dysfunction
		• Weight gain
			• Serotonin syndrome with any agent that blocks 5-HT uptake (= hyperpyrexia, hyperexcitability, motor restlessness, coma, death)
			• Hypertensive crisis with any tyramine-containing foods & beverages (=N, V, HA, palpitations, cerebral hemorrhage, death)
				• **REVERSIBLE MAO_A INHIBITOR (RIMAs):** Meclobemide
				  ○ In presence of RIMA, accumulation of NE caused by tyramine can displace RIMA off MAO = MAO can now catabolize NE & prevent accumulation
				  ○ Less potential for "tyramine" interaction
				  ○ Less potential for serotonin syndrome??