

Antidepressants and Drugs for Bipolar Disorder

Pharmacology 210, 2009

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Important note: The corresponding material presented in lecture will cover just the “highlights” of what is in this file. Be sure to study this file in its entirety, and be sure to read the corresponding text chapter(s).

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The Biochemical Basis of Depression

- Signs, symptoms appear to be due to inadequate levels/activity of one or more **biogenic monoamine neurotransmitters** in certain brain regions:
 - **Serotonin** (5-hydroxytryptamine; 5-HT)
 - **Norepinephrine (NE)**
 - **Dopamine (DA)**

“Evidence” for the Biochemical Theory

- **Drugs that deplete brain monoamines, or block their receptors, cause or worsen depression S/Sx.**
- **Drugs that ↑ brain monoamine levels/activities, or mimic their effects, reduce depression S/Sx. *This is how the various antidepressants work.***

The Main Classes of Antidepressants

- **SSRIs**
 - New and now most widely used antidepressant class
 - Certain advantages over older agents
- **Tricyclics** (and some other “heterocyclics”)
 - Until not too long ago, the main group for depression tx.
 - Still used because of cost compared with SSRIs
- **Atypical agents** (e.g., bupropion)
- **MAO inhibitors**
 - Both very old and very new agents
 - Concerns over drug-drug and drug-food interactions (autonomics notes) limit use

Uses of Antidepressants

- **Main**
 - Depression/melancholia
 - Anxiety disorders (some), panic attacks
 - Obsessive/compulsive neuroses
- **Some Others**
 - “Mood stabilizers” in bipolar illness (as alternative to lithium)
 - Adjunct to management of certain types of epilepsy
 - Adjunct to management of chronic pain, neuralgias, migraine

Effects on Mood

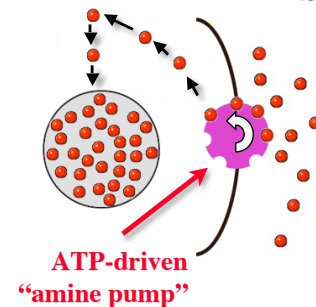
- **Reversal of depression s/sx**
 - slow onset of effect (3-4 weeks, on average, with continued tx.)... these drugs don’t “work overnight.”
- **Increased risk of suicide, other aggressive behaviors (incl. homicide/assault) possible during early tx.**

Selective Serotonin Reuptake Inhibitors (SSRIs)

- **The newest and most-used group of antidepressants**
- **Examples:**
 - Fluoxetine (PROZAC) -- can be considered the prototype
 - Sertraline (ZOLOFT)
 - Citalopram (CELEXA)
 - Escitalopram (LEXAPRO)
 - Paroxetine (PAXIL)
 - Fluvoxamine (LUVOX)

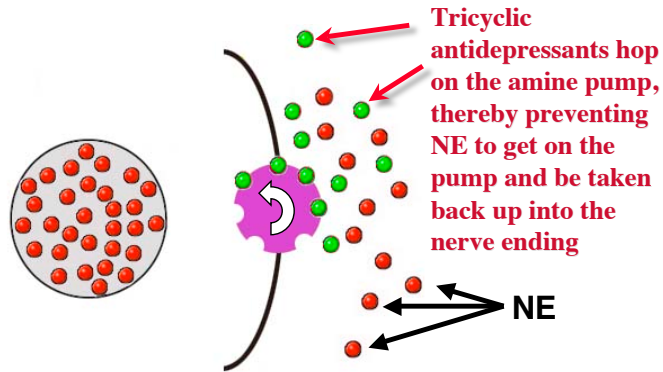
Recall From Your Autonomics Notes...

“Reuptake” is the process by which the actions of NE, released from adrenergic nerves in the SNS, are terminated...



...and a similar reuptake process applies in parts of the CNS, to stopping the actions of NE, serotonin, and dopamine released from their neurons.

Remember this too? Tricyclic antidepressants (and cocaine), block NE reuptake. NE accumulates in the synapse and so its postsynaptic effects are intensified, prolonged



A similar thing happens in the CNS with SSRIs (selectively ↓ serotonin reuptake) and the tricyclics (↓ reuptake of serotonin, DA, and even NE)

SSRIs

PROTOTYPE: Fluoxetine (PROZAC)

- Main antidepressant effect due to selective ↓ of serotonin reuptake by certain brain neurons, which → ↑ postsynaptic neurotransmitter levels and effects, which → ↓ symptoms
- Uses similar to tricyclics (see later)
 - For most pts, probably no more effective than a tricyclic
 - Probably more effective for some pts with refractory depression

SSRI Side Effects, Toxicity

- Sexual dysfunction is most common SE of SSRIs overall (particularly fluoxetine)
- Others include
 - S/sx. of CNS stimulation (nervousness, irritability, insomnia)
 - Weight gain (after a few week or more of tx.)
 - NO autonomic SEs similar to those described for tricyclics (see later)
- Overdoses rarely fatal, s/sx completely different from what occurs with tricyclics

The “Serotonin Syndrome” An Important DDI Between SSRIs and MAOIs

- Serotonin is metabolically inactivated by MAO
- MAOIs inhibit the inactivation of serotonin, but unlike the situation with NE in the ANS, MAOIs do NOT ↓ serotonin release in the CNS
- SSRIs → ↓ serotonin reuptake from synapses, and in the presence of MAOI this → ↑↑ serotonin levels in synapses and ↑↑ effects on postsynaptic neurons
- S/Sx
 - Altered mental status (confusion, hallucinations)
 - Seizures
 - Overreactive reflexes (hyperreflexia)
 - Fever, profound sweating
- Can occur within hours of combined therapy
- May be fatal, so avoid the interaction

Tricyclic Antidepressants

Prototype: Imipramine (TOFRANIL)

- A large group of older antidepressants that are being used less since introduction of SSRIs, but still are used
- Seem to ↓ depression signs/symptoms by ↓ neuronal reuptake of all the main biogenic amines: DA, NE, 5-HT

Side Effects of Tricyclics

- Variable incidence, severity, depending on drug, dose, and patient
- CNS
 - Sedation - tolerance may develop
 - Manic/hypomanic states
 - ↑ Seizure risk (mainly in patients with epilepsy)
- Peripheral **atropine-like**
 - SEs, CIs = those for atropine
- CV: Orthostatic hypotension + tachycardia
- Variable (usually high) incidence of sexual dysfunction

Tricyclic Toxicity

- Like atropine poisoning (“hot as a furnace, red as a beet, dry as a bone, etc.”): ...delirium, seizures ... plus arrhythmias (consult your autonomics notes!)
- Slow recovery, hard to treat, but many of the “symptomatic and supportive” interventions are same as used for atropine poisoning
- **Arrhythmias associated w/ tricyclic OD** — use physostigmine for antimuscarinic signs/symptoms, *but use extra caution* and anticipate having to control worsening arrhythmias with suitable drugs

Atypical Antidepressants

Example: Bupropion (WELLBUTRIN)

- Claimed to have lowest risk of sexual dysfunction of all other antidepressants (actually seems to ↑ sexual desire)
- **Main risk: seizures/convulsions**, mainly from excessive doses and/or stopping the drug too quickly
- Bupropion marketed under other brand names, used for other purposes (e.g., ZYBAN to help quit smoking), and so it’s relatively easy to get overdoses/toxicity if patient is prescribed (and takes) both.... which must be avoided

MAO Inhibitors for Severe, Refractory Depression

Isocarboxazid (MARPLAN)
Phenelzine (NARDIL)
Tranylcypromine (PARNATE)

MAO Inhibitors

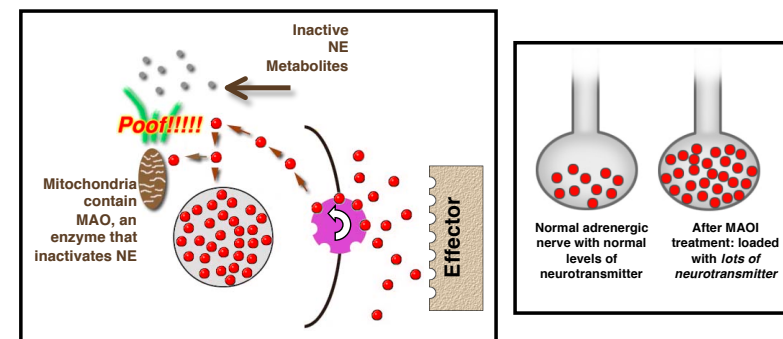
- **Mechanisms of action**
 - Inhibit metabolic inactivation of monoamines (NE, dopamine, serotonin) by MAO in the brain → ↑ neurotransmitter levels in the nerves
 - Unlike the situation in peripheral adrenergic nerves, do NOT ↓ release of neurotransmitters in the CNS, so we get greater neurotransmitter effects because much more neurotransmitter is released into the synapses in the CNS
- **Use: for *severe, refractory depression***
- **Limitations associated with MAOIs**
 - Hypotension (incl. orthostatic) common and usually severe
 - Hypertensive crisis from interaction with common foods, medications that contain mixed- or indirect-acting sympathomimetic
 - Interactions with any drug with atropine-like actions → antimuscarinic poisoning (this includes tricyclic antidepressants!!!)
 - Never use with SSRI (see serotonin syndrome, earlier)

Recall From (and Review) Your Autonomics Notes...

Actions of MAO Inhibitors

- **In peripheral sympathetic nervous system**
 - **NE builds up** because its metabolic breakdown by MAO is ↓ ...but
 - **NE release in response to normal neural stimulation also ↓ ↓**, leading to ↓ BP (antihypertensive effect) and other s/sx
- **In CNS**
 - NE, dopamine, serotonin build up **but neurotransmitter release is not ↓** (accounts for antidepressant action)

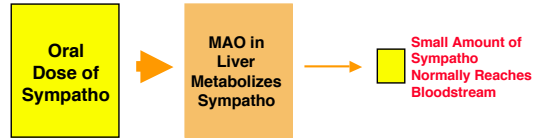
Recall From (and Review) Your Autonomics Notes...



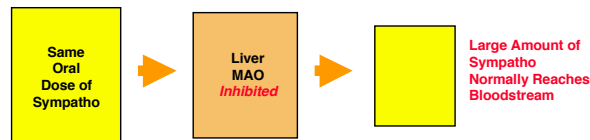
- **In the peripheral sympathetic nervous system**
 - **NE builds up** because its metabolic breakdown by MAO is ↓ ...but
 - **NE release in response to normal neural stimulation also ↓ ↓**, leading to ↓ BP (antihypertensive effect) and other s/sx

Recall From Your Autonomics Notes...

MAO Is Also Found in The Liver, Metabolizes Mixed- and Indirect-Acting Sympathos



Inhibit hepatic MAO, mixed- and indirect-acting sympathos cause a much bigger systemic effect



Bipolar Illness (Manic-Depressive Illness)

- Mood swings ... schizophrenic episodes cycling with episodes of depression
- Swings generally not related to identifiable triggering events in the patient's life
- Tx. often involves antipsychotics, antidepressants, and lithium (or another “mood-stabilizing” drug)

Bipolar Illness: Lithium (Li⁺)

- Main use as mood stabilizing drug in bipolar illness, to prevent manic phase
 - Antipsychotic drugs, not lithium or other mood-stabilizing drugs, are indicated for treating acute manic (psychotic) phase of bipolar illness
 - Effective 60-70% of time
- Use of Li as mood-stabilizing drug declining as use of other agents (e.g., certain drugs mainly used as anticonvulsants) with fewer common SEs is increasing

Common Side Effects That Can Occur When Serum Lithium Levels are “Therapeutic”

- **GI:** nausea, vomiting, diarrhea, appetite loss are common but usually disappear
- **Neurologic:** fatigue, muscle weakness, headache
- **Polyuria** sufficient to cause dehydration unless other measures are taken to prevent it (hydration, certain diuretics; see text); potential nephrotoxicity
- **Hypothyroidism** (possibly with benign goiter, occurs because lithium can ↓ iodine uptake by thyroid gland)

Lithium Toxicity

- Fairly common, as are side effects:
- Very low margin of safety
- Typical progression of toxicity....
 - Initially nausea, vomiting, diarrhea weakness, fine tremor
 - Then confusion, coarse muscle tremor, hyperreflexia
 - Then profound ↓ BP, seizures, coma, death

Lithium and Sodium

- Renal Na depletion → lithium retention, ↑ **risk of lithium SE or toxicity**
- Renal Na retention (or excess Na intake) → ↑ lithium excretion, ↓ lithium levels and ↓ effects
- Consistency of daily Na intake (and loss) important for consistent effects

Mood-Stabilizing Anticonvulsants As Lithium Alternatives for Bipolar Illness (Prophylaxis)

- Valproic acid (DEPAKENE), carbamazepine (TEGRETOL) and some of the newer anticonvulsants are being used increasingly as lithium alternatives
- Generally are effective, associated with fewer *milder*/common side effects than lithium, but some toxicities can be serious
- See notes, text, on “Anticonvulsant Drugs”