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Antidepressant Drugs

• Margaret Gnegy
• Professor
• Department Pharmacology
The Bottom Line

- There is a strong interrelationship between serotonergic and noradrenergic neurons and they regulate each others’ activities.

- Most antidepressant drugs enhance serotonergic and noradrenergic activity in the brain but they take weeks to work.

- A common mechanism of antidepressant drug action is to block monoamine reuptake.

- Each type of antidepressant has characteristic side effects which strongly influence which one is prescribed.

- Long term antidepressant treatment may lead to trophic effects on neuron remodeling and production of important growth factors.
Monoamine Theory of Depression

- Deficiency of aminergic transmission in the CNS might be causative of depression
- An excess of aminergic transmission could result in mania
The Norepinephrine Synapse

**Synthesis:**
- Tyrosine hydroxylase
- Aromatic amino acid decarboxylase
- Dopamine beta hydroxylase

**Metabolism:**
- Monoamine oxidase
- Catecholamine-O-methyltransferase

Adapted from Feldman, et al., Principles of Neuropsychopharmacology, Sinauer, 1997, p. 280
The Serotonin Synapse

Synthesis:
- Tryptophan hydroxylase
- Aromatic amino acid decarboxylase

Metabolism:
- Monoamine oxidase
- L-5-Hydroxytryptophan decarboxylase

Innervation of the brain by serotonin and norepinephrine neurons involves similar pathways.
Targets for drugs affecting serotonergic system

Siegel et al. eds. Basic Neurochemistry, 7th Ed. p. 236
Drugs used in the treatment of depression

Selective serotonin reuptake inhibitors: fluoxetine, sertraline

Other heterocyclic drugs: bupropion, trazodone, venlafaxine

MAO inhibitors: phenelzine, moclobemide

Tricyclic antidepressant drugs: amitriptyline, imipramine, desipramine

Electroconvulsive shock
Most, but not all, antidepressants affect monoamine uptake.
Effects of antidepressants on serotonergic cells

There is much the same regulation of noradrenergic cells

Tricyclic antidepressant drugs

PHENOTHIAZINE STRUCTURE

DIBENZOCYCLOHEPTENE DERIVATIVES

IMINODIBENZYL DERIVATIVES

R' = (CH₂)₃ - N - CH₃  
R'' = (CH₂)₃ - NH - CH₃  

Imipramine (Tofranil®)  
Desipramine (Norpramin®, Pertofrane®)  

R' = CH(CH₂)₂ - N - CH₃  
R' = CH(CH₂)₂ - NH - CH₃  

Amitriptyline (Elavil®)  
Nortriptyline (Aventyl®)  
Protriptyline (Vivactil®, Triptil®)  

Source Undetermined
Side effects of TCA’s

- Antimuscarinic: xerostomia, dizziness, mental clouding, constipation, blurred vision
- Cardiovascular: orthostatic hypotension, arrhythmias
- Sedation
- Weight gain
- Extreme CNS depression: suicide
Monoamine Oxidase Inhibitors

Very efficacious in depression

2-3 times a day dosing

Must have tyramine free diet

Interactions with other agents that affect monoaminergic systems
Side effects and drug interactions of MAOIs

- CNS effects: hallucinations, agitation, convulsions
- Cardiovascular: orthostatic hypotension
- Sedation
- Prolongs CV effects of indirectly-acting sympathomimetic amines, food with tyramine
- Should not be given with TCAs or SSRIs
- Potentiate effect of other CNS depressants
The mechanism of potentiation of cardiovascular effects of tyramine: the cheese effect
Selective serotonin reuptake inhibitors (SSRI)
Adverse effects of SSRIs

• Those due to activation of serotonin receptors
  – Nausea
  – Sexual effects
  – Agitation or restlessness
Atypical Antidepressants

- Desyrel
- Trazodone
- Bupropion
- Wellbutrin
- Xyban
- Remeron
- Mirtazapine
Selective serotonin and norepinephrine uptake inhibitors

- Venlafaxine (Effexor)
- Duloxetine (Cymbalta)
Selective Norepinephrine Uptake Inhibitors (SNRI)

Atomoxetine
Strattera

Reboxetine
Edronax
## Potencies of antidepressants at Human Monoamine transporters

<table>
<thead>
<tr>
<th>Drug</th>
<th>NET</th>
<th>SERT</th>
<th>DAT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ki (nM)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>34.5</td>
<td>4.3</td>
<td>3200</td>
</tr>
<tr>
<td>Desipramine</td>
<td>0.83</td>
<td>17.5</td>
<td>3200</td>
</tr>
<tr>
<td>Sertraline</td>
<td>417</td>
<td>0.293</td>
<td>25</td>
</tr>
<tr>
<td>Bupropion</td>
<td>52,600</td>
<td>9100</td>
<td>526</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>11.2</td>
<td>1.55</td>
<td>-</td>
</tr>
</tbody>
</table>
**In vitro** acute receptor affinity of selected antidepressant drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>mAChR</th>
<th>H1 R</th>
<th>α₁ R</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline</td>
<td>17.9</td>
<td>1.1</td>
<td>27</td>
</tr>
<tr>
<td>Desipramine</td>
<td>106</td>
<td>110</td>
<td>130</td>
</tr>
<tr>
<td>Sertraline</td>
<td>625</td>
<td>24,000</td>
<td>370</td>
</tr>
<tr>
<td>Bupropion</td>
<td>40,000</td>
<td>6700</td>
<td>4550</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>3000</td>
<td>2300</td>
<td>8300</td>
</tr>
</tbody>
</table>

Ki (nM)

Source Undetermined
Absorption, Distribution and Metabolism

• Most antidepressants are well absorbed
• Once absorbed they are widely distributed
• Most are metabolized by cytochrome P450 system, then glucuronidation
• A number of them have active metabolites:
  – Bupropion (to amphetamine-like compounds)
  – Fluoxetine $\rightarrow$ norfluoxetine ($t_{1/2} = 10$ days)
• Most take several days to be eliminated
• Short half-lives: venlafaxine (3-6 hrs) and bupropion (14 hrs)
Interactions with Cytochrome P$_{450}$ enzymes

- Metabolism of most ADs dependent on hepatic P$_{450}$s
- Some ADs inhibit metabolic clearance of other drugs, may produce clinically significant drug-drug interactions
  - Fluoxetine & fluvoxamine inhibit CYP2C9 (NSAIDS), CYP2D6 (Antidepressants, antipsychotics, β-blockers)
  - Sertraline and fluoxetine increase levels of benzodiazepines, clozapine and warfarin
## Antidepressants: Dose and side effects

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mg/day</td>
<td>Sedation</td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>100-200</td>
<td>+++</td>
</tr>
<tr>
<td>Desipramine</td>
<td>100-200</td>
<td>±</td>
</tr>
<tr>
<td>Sertraline</td>
<td>50-150</td>
<td>±</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>80-100</td>
<td>±</td>
</tr>
<tr>
<td>Bupropion</td>
<td>200-300</td>
<td>0 (agitation)</td>
</tr>
<tr>
<td>Trazodone</td>
<td>150-200</td>
<td>+++</td>
</tr>
</tbody>
</table>

Source Undetermined
Tolerance and Physical Dependence

• Some tolerance develops to sedative and autonomic effects of TCAs
• Some tolerance develops to initial nausea from SSRIs
• Physical dependence following abrupt withdrawal
Drug-drug interactions with antidepressants

- Metabolism of most antidepressants is through hepatic CYPs
- Some antidepressants can inhibit CYPs
- SSRIs especially will compete with metabolism of other drugs
- Antidepressants potentiate the effects of alcohol and probably other sedatives
Withdrawal effects

• Occurs upon abrupt discontinuation of an antidepressant that has been taken for \( \geq 6 \) wks

• Typical symptoms of antidepressant discontinuation syndrome: flu-like symptoms, malaise, insomnia, nausea, imbalance, sensory disturbances, and hyperarousal.
  – Can be serious with MAO inhibitors

• More likely with a longer duration of treatment and a shorter half-life of the treatment drug

• Recurrence of morbidity
Safety throughout life cycle

- Generally safe throughout pregnancy but will get into breast milk
- Risk-benefit ration in children uncertain
- More effective in adolescents
- Risks in geriatric patient higher due to decreased metabolic clearance
Danger of suicide

• Tricyclic antidepressants

• MAO inhibitors

• SSRIs???
# Use of antidepressant drugs in outpatients

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Other indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitryptyline</td>
<td>Chronic pain, delusions, insomnia, migraine, postherpetic neuralgia</td>
</tr>
<tr>
<td>Desipramine</td>
<td>Attention deficit disorder, bulimia, diabetic neuropathy, postherpetic neuralgia</td>
</tr>
<tr>
<td>Sertraline</td>
<td>Obsessive compulsive disorder, panic disorder, post-traumatic stress disorder, anxiety</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>Anxiety, insomnia</td>
</tr>
<tr>
<td>Bupropion</td>
<td>Attention-deficit disorder, smoking cessation, post-traumatic stress disorder</td>
</tr>
<tr>
<td>Trazodone</td>
<td>Insomnia</td>
</tr>
</tbody>
</table>
Melatonin is synthesized and released from the pineal at night in response to stimulus from the suprachiasmatic nucleus (SCN) of the hypothalamus, the major circadian pacemaker in the brain.
Melatonin receptor agonists

Both drugs are agonists at MT1 and MT2 receptors
MT1 Rs are GPCRs that inhibit adenylyl cyclase, predominant receptor in brain
MT2 Rs inhibit soluble guanylate cyclase
3D brain image shows hippocampus (arrows), which is about 10% smaller in people with a history of depression.

Hippocampus of depressed patients has lower levels of brain derived neurotrophin (BDNF) than controls.
normal survival & growth

stress

upward regulation of glucocorticoid

BDNF

downward regulation of BDNF

atrophy & decreased survival

increased vulnerability

Anti-depressant

upward regulation of NE & 5-HT

BDNF

downward regulation of BDNF

increased survival & growth
Antidepressant therapies can lead to production of proteins including BDNF
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Slide 9: Siegel et al. eds. Basic Neurochemistry, 7th Ed. p. 236
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Slide 22: Source Undetermined (Both Images)
Slide 23: Source Undetermined (Both Images)
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