Antidepressant Agents

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Depression is one of the common psychiatric disorders. It has been found that at every time 5–6% of population is depressed.
Types of depression

1. Reactive depression. (Exogenous).
2. Major depression. (Endogenous).
Antidepressants

1. **Tricyclic anti-depressants (TCAs).**
   - Imipramine, desipramine, nortriptyline, protryptyline, amytriptiline, doxepin.

2. **Atypical anti-depressants.**
   - New TCAs, amoxapine, bupropion, maprotiline, nomifensine, mianserin.

3. **Selective serotonin reuptake inhibitors (SSRIs).**
   - Fluoxetine, sertraline, paroxetine, trazodone.

4. **Monoamine oxidase inhibitors (MAOIs).**
   - Isocarboxacid, phenelzine, tranylcypromine.
I. Tricyclic antidepressants (TCA)

- TCA are structurally similar to the phenothiazine antipsychotics and share many of their pharmacological actions.
- Include imipramine, amitriptyline, desimipramine, nortriptyline, and protriptyline.
1. Mechanism of Action of TCA

• TCA potentiate the actions of biogenic amines, presumably by inhibiting reuptake of the amines in the presynaptic neurons.
• TCA have both antihistamine $H_1$ and alpha-adrenergic blocking actions.
• TCA possess antimuscarinic action and block the reuptake of serotonin.
Pharmacokinetics of TCA

• TCA are well absorbed orally. They are lipid soluble and penetrate all tissues and have long half-lives. They are metabolized by liver enzymes and many of the metabolites are pharmacologically active. Excretion is via the kidney.
Pharmacologic Effects of TCA

• **1- Amine uptake blockade:** TCA block NE uptake transporters in the CNS and peripherally in the A.N.S. This increases sympathetic activity.

• **2- Sedation:** is a common effect with TCA. Some may have CNS stimulant effects.

• **3- Antimuscarinic effects:** Atropine-like actions.

• **4- C.V. effects:** postural hypotension due to alpha-blockade, arrhythmia due to depression of cardiac conduction.

• **5- Seizures:** TCA lowers the convulsive threshold with overdoses
Figure 12.4
Onset of therapeutic effects of the major antidepressant drugs (tricyclic antidepressants, selective serotonin re-uptake inhibitors, and monoamine oxidase inhibitors) requires several weeks.
Clinical Uses of TCA

- **Major depressive disorders**: TCA are considered the treatment of choice for major depression. The various TCA are equivalent at appropriate doses with regards to their overall efficacy.

- **Nocturnal enuresis**: Bed wetting in children with imipramine.

- **Obsessive-compulsive neurosis**: accompanied by depression, and phobic-anxiety syndromes, chronic pain, and neuralgia may respond to TCA.
Adverse Effects of TCA

- Resemble those of the phenothiazines.
- 1- **Antimuscarinic effects.** Occur both centrally and peripherally. Patients with prostatic hypertrophy and glaucoma are cautioned. Tolerance develop to this effect.
- 2- **Postural hypotension** and cardiac arrhythmias
- 3- **Manic excitement and delirium** occur in patients with bipolar depression.
- 4- **The elderly** may suffer from dizziness and muscle tremor.
- 5- **Seizures, ventricular arrhythmias** and death can result from overdoses.
- 6- **combination of MAO-inhibitors** and TCA should be avoided.
Precautions with TCA use

• TCA should be used with caution in manic-depressive patients, since they may unmask manic behavior.

• TCA have narrow therapeutic index. Depressed patients with suicidal intents should be given limited quantities of these drugs.
Heterocyclics

- Venlafaxine:
  - Inhibits serotonin and at higher doses inhibits NE and dopamine reuptake. Has fewer adverse effects than TCA.

- Duloxetine:
  - Not indicated in patients with end stage renal diseases. Can cause nausea, vomiting, diarrhea, dizziness and somnolence, sweating and sexual dysfunctions. It can be used for depression accompanied by neuropathic pain.
Atypical Antidepressants

• Have actions at several sites. Include Bupropion, Mirtazapine nafazodone and Trazodone. They are not better than TCA or SSRIs but their adverse effects are different.

1. Bupropion

• mechanism of action unknown. It decreases the craving for nicotine in tobacco abusers. May produce dry mouth, sweating, tremor, and seizures
2. Mirtazapine

- It can block 5-HT$_2$ and $\alpha_2$ receptors. It is sedative due to its antihistaminic activity, but has no atropine-like actions. It does not interfere with sexual activity. Increased appetite and weight gain can occur.

3. Nefazodone and 4. Trazodone

- Weak inhibitors of 5-HT reuptake. They block 5-HT$_1$ presynaptic autoreceptors, and so increase 5-HT release. They are sedating due to antihistamine effect. Trazodone causes priapism.
Selective Serotonin Re-uptake Inhibitors (SSRIs)

- specifically inhibit serotonin re-uptake having 300- to 3000-fold greater selectivity for 5-HT transporter as compared to NE transporter. SSRIs have little ability to block DA transporter. In addition they have little blocking activity at muscarinic, α-adrenergic, and histamine H₁ receptors. Therefore common adverse effects associated with TCA such as orthostatic hypotension, sedation, dry mouth and blurred vision, are not seen with SSRIs
SSRIs

• SSRIs because of their relative safety and fewer AR have largely replaced TCA and MAOI as the drug of choice in treating depression.

• They include fluoxetine, citalopram, escitalopram, fluvoxamine, paroxetine and sertraline
<table>
<thead>
<tr>
<th>DRUG</th>
<th>UPTAKE INHIBITION</th>
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<tr>
<td></td>
<td>Nor-</td>
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<td>epinephrine</td>
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<td>Selective serotonin re-uptake inhibitor</td>
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<td><em>Fluoxetine</em></td>
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<td>Selective serotonin/norepinephrine re-uptake inhibitors</td>
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<td><em>Venlafaxine</em></td>
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<td><em>Duloxetine</em></td>
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<td>Tricyclic antidepressant</td>
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<td><em>Imipramine</em></td>
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**Figure 12.3**
Relative receptor specificity of some antidepressant drugs. *Venlafaxine* inhibits norepinephrine re-uptake only at high doses. ++++ = very strong affinity; +++ = strong affinity; ++ = moderate affinity; + = weak affinity; 0 = little or no affinity.
Actions of SSRIs

• Inhibit reuptake of 5-HT leading to increased concentration of serotonin in the synaptic cleft and increased postsynaptic neuronal activity.

• Antidepressants, including SSRIs typically take 2 weeks to produce improvement in mood and may require 12 weeks or more. However none of the antidepressants is uniformly beneficial. About 40% of patients respond well to treatment. Patients who do not respond to one drug may respond to another drug, and approximately 80% or more will respond to at least one antidepressant drug. Antidepressants do not elevate mood in normal subjects.
Therapeutic Uses of SSRIs

- Used in depression,
- Obsessive compulsive disorders (fluvoxamine)
- Panic disorders
- Generalized anxiety
- Premenstrual dysphoric disorders
- Bulimia nervosa
Pharmacokinetics

• All SSRIs are well absorbed from GIT. Food has little effect on absorption. All are well distributed with large $V_d$. Most have long plasma half-life. Metabolized by liver and excreted in urine.

• **Fluoxetine:** Has longer half-life about 50 hours and available as sustained release preparations allowing once-weekly dosing. Also it is metabolized to norfluoxetine which is active having a half-life of 10 days.

• **Fluoxetine and paroxetine:** are potent enzyme inhibitors

• Paroxetine and sertraline are partly excreted in bile
Adverse effects of SSRIs

- **Sleep disturbance**: Paroxetine and fluvoxamine are sedating, while fluoxetine is activating causing insomnia.
- **Sexual dysfunction**: Loss of libido, delayed ejaculation, anorgasmia.
- **Uses in children and teenagers**: One out of 50 children becomes suicidal as a result of use of SSRIs.
- **Overdose**: Fluoxetine may cause seizures. They cause “serotonin syndrome” characterized by hyperthemia, muscle rigidity, clonic muscle twitching and changes in mental status in the presence of MAOIs.
Figure 12.5
Some commonly observed adverse effects of selective serotonin re-uptake inhibitors.
Monoamine oxidase inhibitors (MAOIs)

- phenelzine (Nardil)
- isocarboxazid (Marplan)
- tranylcypromine (Parnate)
- selegiline (Deprenyl)
MAO INHIBITORS

Mechanism of action:
Inhibit MAO enzymes (non-selective):
1) Irreversible MAO inhibitors
   Phenelzine and isocarboxazid => hydrazides.
2) Reversible MAO Inhibitors. **RIMA** (reversible inhibitor of monoamine oxidase A)
   Tranylcypromine => non-hydrazide,
   prolonged blockade, but reversible within 4hr.

Decrease metabolism of most biogenic amines (**NE**, **5HT**, **DA**, tyramine, octopamine).
MAO INHIBITORS

Mechanism of action (con’t):

Acute administration causes:

- ↑ NE and 5-HT in synaptic terminals in brain but ↓ NE in PNS. ↓ NE synthesis.
- Acute euphoria
- Suppressed REM sleep.

Chronic administration causes:

- ↓ NE-stimulated cAMP in brain.
- Down regulation of β receptors.
- Down regulation of 5-HT\textsubscript{2} receptors.
MAO INHIBITORS

MAO-A → NE, 5-HT, Tyramine
MAO-B → DA

Selective MAOIs:

Inhibitors MAO-A

- Moclobemide, Clorgyline

Inhibitors of MAO-B.

- Deprenyl, Selegiline
Wine-and-Cheese Reaction

- Fatal interaction with tyramine-containing foods (fermented foods in particular, such as wine and cheese).

- ↓ MAO-A => ↑ Tyramine in the body => ↑ NE in circulation => induces hypertensive crisis => can lead to intracranial bleeding and other organ damage.
MAO INHIBITORS

Negative drug interactions with:

Any drug metabolized by MAOs* including SSRIs, TCAs and meperidine, alcohol, CNS depressants, sympathomimetics, phenylephrine (O/C nasal decongestants), amphetamines, and other indirect-acting adrenergic drugs.

* Interaction with drugs metabolized by MAOs (e.g. Meperidine (opioid analgesics) => hyperpyrexia or “hyperexcitation syndrome” involving high fever, delirium and hypertension).
MAO INHIBITORS

Other side effects:

- Hypotension
- Hepatotoxicity.
- Sedation.
THANK YOU