3. Atypical antidepressants

Bupropion, **mirtazapine**, **nefazodone** & **trazodone**.

- Mixed group that act at several different sites.

Bupropion

- Acts as a weak dopamine & NE reuptake inhibitor.
- Has short half-life.
- Decrease craving & attenuate the withdrawal symptoms for nicotine smoker trying to quit smoking.
- Side effects may include dry mouth, sweating, nervousness, tremor, a very low incidence of sexual dysfunction.
- Has low risk for drug-drug interactions.
- Risk of seizures may occur in higher doses.
- Should be avoided in patients at risk for seizures or who have eating disorders (such as bulimia).

Mirtazapine

- Block presynaptic α_2 receptors enhancing 5-HT & NE neurotransmission.
- Some of its antidepressant activity may due to its ability to block 5-HT2 receptors.
- Neither it cause antimuscarinic (unlike TCAs), nor sexual dysfunction (unlike SSRIs) side effects.
- Increase appetite & weight gain.
- Cause marked sedation (potent antihistaminic activity), an advantage in depressed patients having difficulty sleeping.

Nefazodone and trazodone

- Weak 5-HT reuptake inhibitors.
- Their therapeutic benefit is related to the block of the postsynaptic 5-HT2A receptors.
- Their chronic use may desensitize 5-HT1A presynaptic autoreceptors & thereby, increase 5-HT release.
- Both are sedating (potent H1-blockers).
- **Trazodone** has been associated with priapism.
- **Nefazodone** has been associated with the risk for hepatotoxicity.
- They have mild - moderate α_1-receptor antagonism contributing to orthostasis & dizziness.

4. Tricyclic antidepressants (TCAs)

- Block NE & 5-HT reuptake into the neuron, they differ form SNRIs antidepressants in their adverse effects.
- They include:
  1. The tertiary amines **imipramine** (prototype), **amitriptyline**, **clomipramine**, **doxepin** & **trimipramine**.
  2. The secondary amines **desipramine** & **nortriptyline** (metabolites of **imipramine** & **amitriptyline**) & **protriptyline**.

3. The tetracyclic antidepressant **Maprotiline** & **amoxapine**.

- All have similar therapeutic efficacy.
- Patients who do not respond to one TCA may benefit from another TCA.
- Alternative for patients who do not respond to SSRIs.

Mechanism of action

1. Inhibition of neurotransmitter reuptake:

- TCAs & **amoxapine** are potent reuptake inhibitors of NE & 5-HT into presynaptic nerve terminals.
- At therapeutic doses, they do not block dopamine transporters.

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Therapeutic uses

- Moderate to severe depression.
- Panic disorder.
- **Imipramine** has been used to control bed-wetting in children (older than age 6 years).
- Used cautiously because of the inducement of cardiac arrhythmias & other serious CV problems.
- TCAs, particularly **amitriptyline**, have been used to treat migraine, headache & chronic pain syndromes (eg. neuropathic pain) in which the cause of the pain is unclear.
- Low doses of TCAs, especially **doxepin**, can be used to treat insomnia.

Pharmacokinetics

- Readily penetrate into the CNS. Their lipid solubility also causes these drugs to have variable half lives (eg. 4 - 17 hours for **imipramine**).
- As a result of their variable first-pass metabolism in the liver, TCAs have low & inconsistent bioavailability.
- TCAs may be sensitive to agents that induce or inhibit the CYP450 isoenzymes .

Adverse effects

- Adverse effects due to muscarinic receptors blockage.
- Affect cardiac conduction similarly to **quinidine**, which may precipitate life-threatening arrhythmias.
- Block α -adrenergic receptors, causing orthostatic hypotension, dizziness & reflex tachycardia (most serious problem in elderly adults).
- **Imipramine** is the most likely, and **nortriptyline** the least likely, to cause orthostatic hypotension.
- Sedation (H1 receptors block).
- Weight gain.
- Sexual dysfunction (erectile dysfunction in men & anorgasmia in women), but the incidence is lower than that associated with SSRIs.

Drug interactions:

1. Concomitant use of TCAs & MAOIs cause mutual enhancement that result in HT, hyperpyrexia, convulsion & coma.
2. TCAs potentiate effects of direct-acting adrenergic drugs by preventing their removal from the synaptic cleft.

3. TCAs block the effects of indirect-acting sympathomimetic drugs by preventing the drugs from reaching their intracellular sites of action.
4. TCAs used with ethanol & other CNS depressants may result in toxic sedation.

Precautions :

- TCAs (like all antidepressants) should be used with caution in patients with bipolar disorder, even during their depressed state, because switch to manic behavior may occur .
- TCAs have a narrow therapeutic index (eg. five- six fold the maximal daily dose of **imipramine** can be lethal).
- Depressed patients who are suicidal should be given only limited quantities of these drugs & be monitored closely.
- TCAs may exacerbate unstable angina, BPH, epilepsy and preexisting arrhythmias.
- Used cautiously in very young or very old patients.

5. Monoamine oxidase inhibitors (MAOIs)

- MAO is a mitochondrial enzyme found in nerve, gut & liver.
- Neuronal MAO act as a "safety valve" to oxidatively deaminate & inactivate any excess neurotransmitter (NE, dopamine & serotonin).
- MAOIs may irreversibly or reversibly inactivate the enzyme, permitting neurotransmitter accumulation within the presynaptic neuron & its leak into the synaptic space.
- This is believed to cause activation of NE & 5-HT receptors, and it may be responsible for the indirect antidepressant action of these drugs.
- Four MAOIs are currently available for treatment of depression:

Phenelzine ; **Tranylcypromine**; **Isocarboxazid** & **Selegiline** (it was prior approved for Parkinson disease, but is now also approved for depression)

- Use of MAOIs is limited due to the complicated dietary restrictions.

Mechanism of action

- Most MAOIs, such as **phenelzine**, cause irreversible inactivation of MAO, increasing stores of NE, 5-HT & dopamine within the neuron.
- They inhibit not only MAO in the brain, but also MAO in the liver & gut that catalyze oxidative deamination of drugs & potentially toxic substances, such as tyramine, which is found in certain foods, therefore MAOIs show a high incidence of drug-drug & drug-food interactions.
- **Selegiline** is the first antidepressant available as a transdermal patch that may produce less inhibition of gut & hepatic MAO at low doses because it avoids first-pass metabolism.

Actions

- MAO is fully inhibited after several days of treatment, but antidepressant action of the MAOIs, like that of the SSRIs & TCAs, is delayed several weeks.
- **Selegiline** & **tranylcypromine** have an amphetamine- like stimulant effect that may produce agitation or insomnia.

Therapeutic uses

- Depression in patients who are unresponsive or allergic to TCAs or who experience strong anxiety.
- Patients with low psychomotor activity may benefit from the stimulant properties of the MAOIs.
- Phobic states.
- A special subcategory of depression, called atypical depression (characterized by labile mood, rejection sensitivity & appetite disorders), may respond preferentially to MAOIs.

Pharmacokinetics

- The antidepressant effects require at least 2 to 4 weeks of treatment).
- Enzyme regeneration, when irreversibly inactivated, varies, but it usually occurs several weeks after termination of the drug. Thus, when switching antidepressant agents, a minimum of 2 weeks of delay must be allowed after termination of MAOI therapy & the initiation of another antidepressant from any other class.

Adverse effects

Severe & often unpredictable side effects, due to drug-food & drug-drug interactions, limit the widespread use of MAOIs (last-line agents).

- MAOIs interfere with degradation of tyramine obtained from the diet such as, aged cheeses & meats, chicken liver, pickled or smoked fish (such as anchovies or herring) & red wines.
- Tyramine causes the release of large amounts of stored catecholamines from nerve terminals, resulting in what is termed a "hypertensive crisis," with signs & symptoms such as occipital headache, stiff neck, tachycardia, nausea, HT, cardiac arrhythmias, seizures &, possibly, stroke.
- Thus, tyramine-containing foods should be avoided.
- **Phentolamine** & **prazosin** are helpful in the management of tyramine-induced HT.

Note: Treatment with MAOIs may be dangerous in severely depressed patients with suicidal tendencies.

- Other possible side effects include drowsiness, orthostatic hypotension, blurred vision, dry mouth, dysuria & constipation.
- MAOIs & SSRIs should not be coadministered due to the risk of the life-threatening "serotonin syndrome."
- Both types of drugs require washout periods of at least 2 weeks before the other type is administered, with the exception of **fluoxetine**, which should be discontinued at least 6 weeks before a MAOI is initiated.
- Combination of MAOIs and **bupropion** can produce seizures.

Treatment of mania and bipolar disorder

A. Lithium

- **Lithium salts** are used prophylactically for treating manic-depressive patients & in the treatment of manic episodes &thus, are considered "mood stabilizers."
- Effective in treating 60 - 80 % of patients exhibiting mania & hypomania.

Note: **Lithium** is believed to interferes with the resynthesis (recycling) of phosphatidylinositol bisphosphate (PIP2), leading to relative depletion of PIP2 in neuronal membranes of the CNS (PIP2 levels in peripheral membranes are unaffected).

- **Lithium** is given orally & the ion is excreted by the kidney.
- Lithium salts can be toxic.
- Their safety factor & therapeutic index are extremely low & comparable to those of **digoxin**.
- Common adverse effects may include headache, dry mouth, polydipsia, polyuria, polyphagia, GI distress (give **lithium** with food), fine hand tremor, dizziness, fatigue, dermatologic reactions & sedation.

Note: The diabetes insipidus that results from taking **lithium** can be treated with **amiloride**.

- Higher plasma levels **of lithium** may cause ataxia, slurred speech, coarse tremors, confusion & convulsions.
- Thyroid function may be decreased (should be monitored).
- **Lithium** causes no noticeable effect on normal individuals.
- It is not a sedative, euphoriant, or depressant.

B. Other drugs

- Several antiepileptic drugs, including, most notably, **carbamazepine**, **valproic acid** & **lamotrigine**, have been identified & FDA approved as mood stabilizers, & have been successfully used in the treatment of bipolar disorder.
- Other agents that may improve manic symptoms include the older (eg. **chlorpromazine** & **haloperidol**) & newer antipsychotics.
- Atypical antipsychotics (**risperidone**, **olanzapine**, **ziprasidone**, **aripiprazole**, **asenapine** & **quetiapine**) have also received FDA approval for the management of mania.
- Benzodiazepines are also frequently used as adjunctive treatments for the acute stabilization of patients with mania.