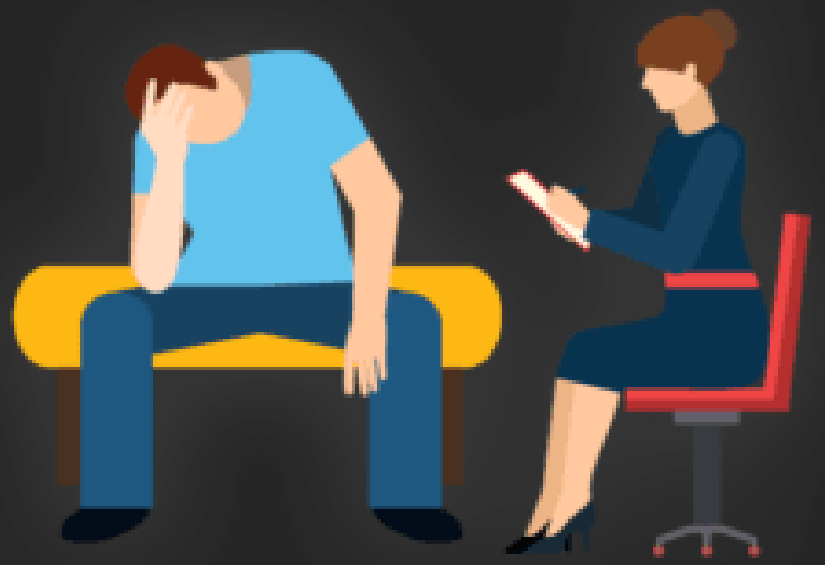
Dr Karamallah S. Mahmood

Antidepressants



NERVOUS SYSTEM DRUGS

TRICYCLIC ANTIDEPRESSANTS, MAO-INHIBITORS, SSRI

TRICYCLIC ANTIDEPRESSANTS

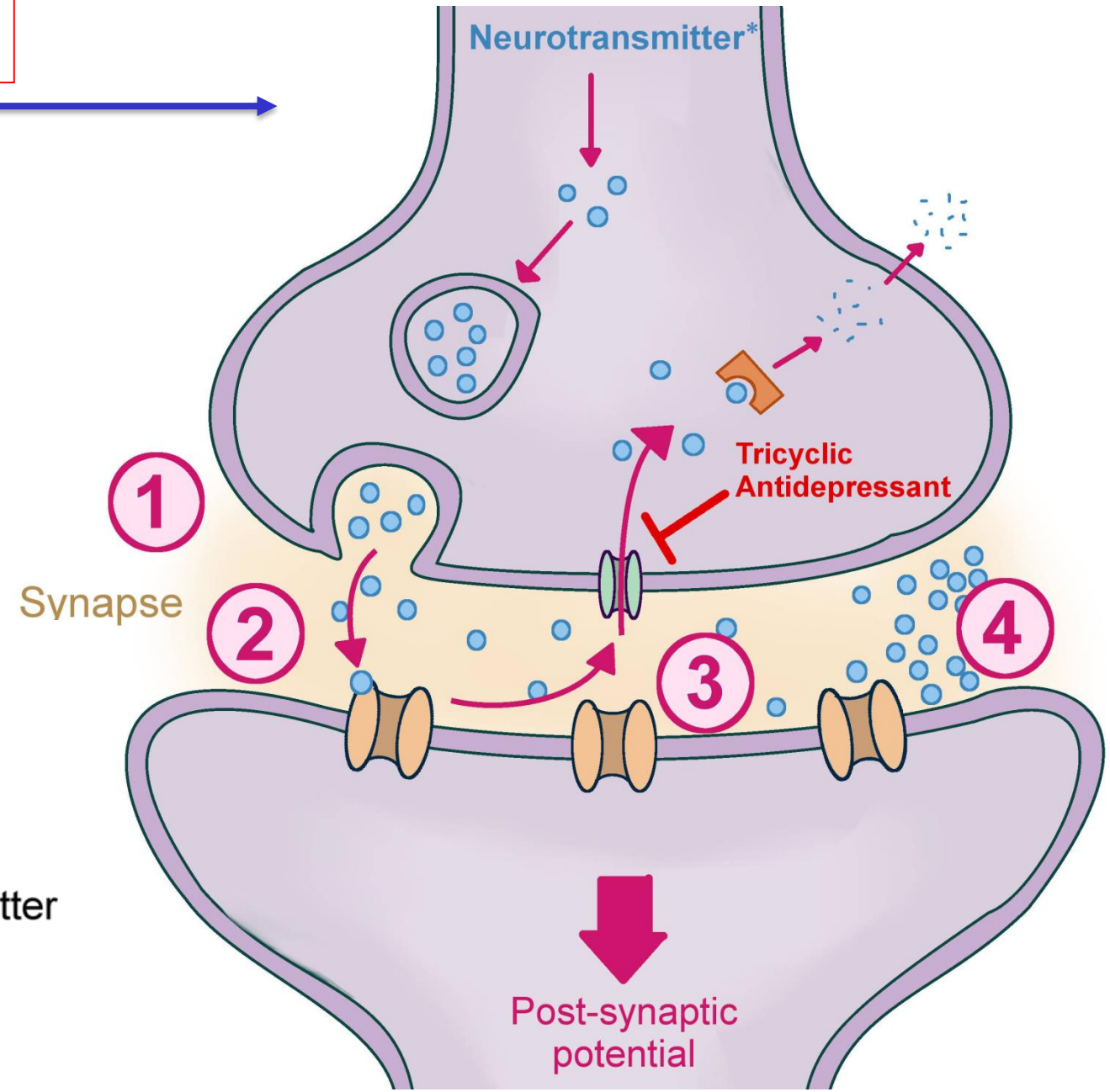
The TCAs block **norepinephrine and serotonin reuptake** into the presynaptic neuron and, thus, if discovered today, might have been referred to as SNRIs, except for their **differences in adverse effects** relative to this newer class of antidepressants.

The TCAs include the **tertiary amines** Imipramine (**the prototype drug**), amitriptyline, clomipramine , doxepin, and trimipramine, and the **secondary amines** desipramine and nortriptyline (the N-demethylated metabolites of imipramine and amitriptyline, respectively) and protriptyline.

Maprotiline and amoxapine are related "**tetracyclic**" antidepressant agents and are commonly included in the general class of TCAs.

Patients who do not respond to one TCA may benefit from a different drug in this group.

TCAs/ Mechanism of action



1. Neurotransmitter released in the synapse
2. Neurotransmitter activates post-synaptic receptor
3. Neurotransmitter reuptake is blocked by TA
4. Increased synaptic concentration of Neurotransmitter available to bind to the post-synaptic receptors

==> increased post-synaptic nerve transmission

ırotransmitter = serotonine or norepinephrine

TCAs/ Mechanism of action

1. Inhibition of neurotransmitter reuptake:

TCAs and amoxapine are potent inhibitors of the neuronal reuptake of norepinephrine and serotonin into presynaptic nerve terminals.

Maprotiline and desipramine are relatively selective inhibitors of **norepinephrine** reuptake.

2. Blocking of receptors:

TCAs also block **serotonergic, α-adrenergic, histaminic, and muscarinic** receptors. It is not known if any of these actions produce the therapeutic benefit of the TCAs.

Amoxapine also blocks 5-HT_2 and dopamine D_2 receptors.

TCAs/ Actions

The TCAs elevate mood, improve mental alertness, increase physical activity, and reduce morbid preoccupation in **50% to 70%** of individuals with major depression.

The onset of the mood elevation is slow, **requiring 2 weeks** or longer.

Physical and psychological dependence have been **rarely** reported.

TCAs/ Therapeutic uses

The TCAs are effective in treating **moderate to severe depression**.

Imipramine has been used to control **bed-wetting** in children older than 6 years of age; however, it has largely been replaced by desmopressin and nonpharmacologic treatments.

The TCAs, particularly amitriptyline, have been used to help **prevent migraine** headache and treat **chronic pain** syndromes (for example, neuropathic pain) in a number of conditions for which the cause of pain is unclear.

Low doses of TCAs, especially doxepin, can be used to treat **insomnia**.

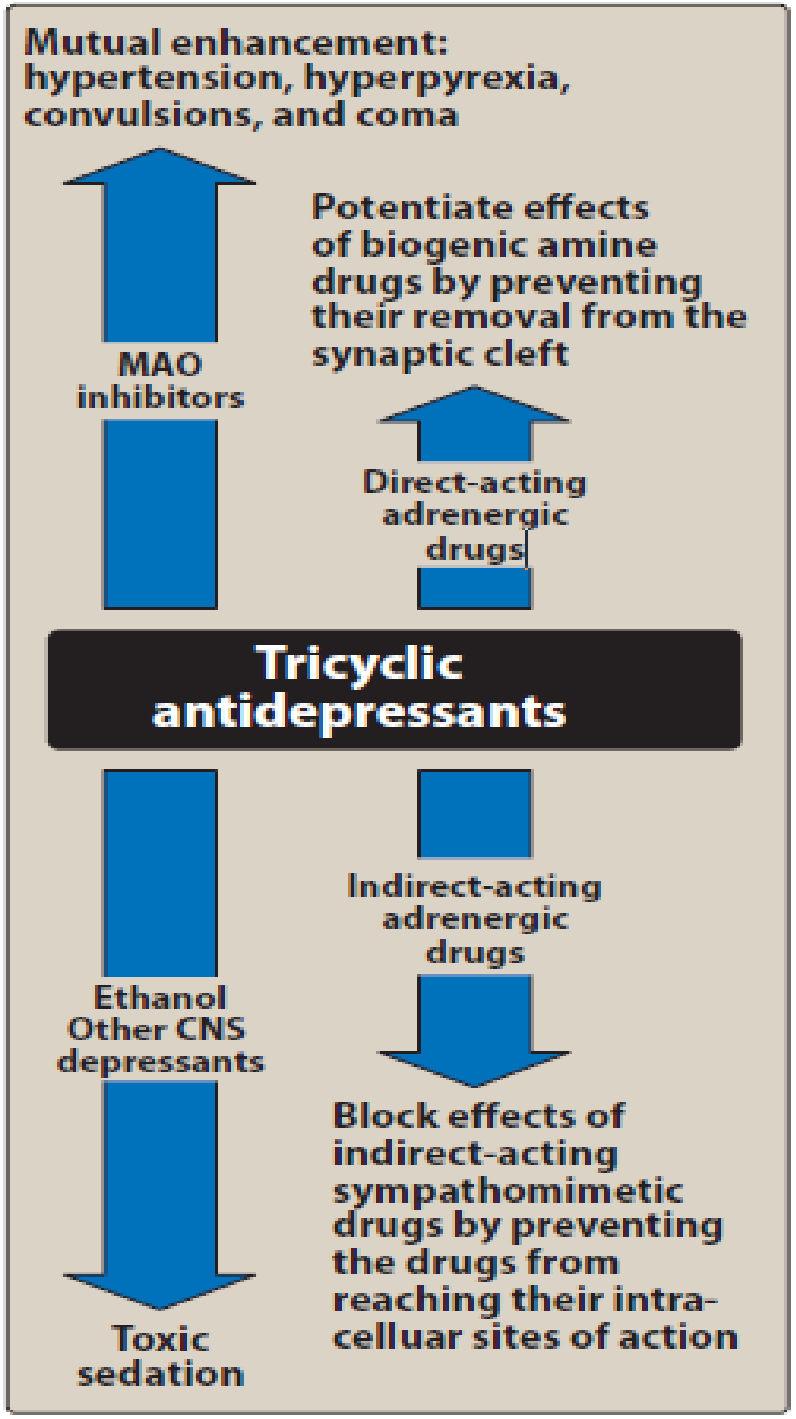
TCAs/ Pharmacokinetics

TCAs are well **absorbed** upon oral administration.

They are widely distributed and readily penetrate into the **CNS**.

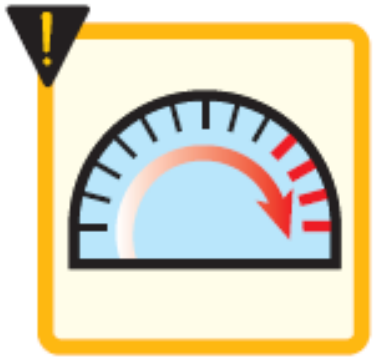
These drugs are metabolized by the **hepatic** microsomal system and conjugated with glucuronic acid.

Ultimately, the TCAs are excreted as inactive metabolites via the **kidney**.



TCAs/ Adverse effects

Weight gain



Urinary retention

Arrhythmias

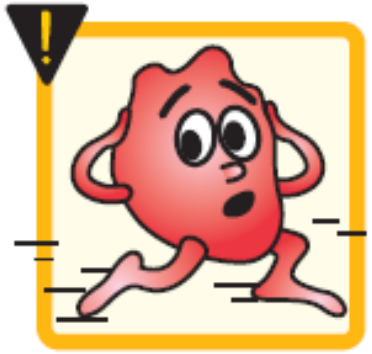
Dry mouth

Blurred vision

Nausea

Constipation

Tachycardia



Drowsiness

TCAs/ Adverse effects

Blockade of **muscarinic receptors** leads to blurred vision, xerostomia (dry mouth), urinary retention, sinus tachycardia, constipation, and aggravation of glaucoma.

These agents affect cardiac conduction similarly to quinidine and may precipitate life-threatening arrhythmias in an overdose situation.

The TCAs also block **α-adrenergic receptors**, causing orthostatic hypotension, dizziness, and reflex tachycardia. Imipramine is the most likely, and nortriptyline the least likely, to cause orthostatic hypotension.

Sedation may be prominent, especially during the first several weeks of treatment, and is related to the ability of these drugs to block histamine H1 receptors.

Weight gain is a common adverse effect of the TCAs. **Sexual dysfunction** occurs in a minority of patients, and the incidence is lower than that associated with the SSRIs.

TCAs/ Adverse effects …. Cont.

TCAs (like all antidepressants) should be used with caution in patients with bipolar disorder, even during their depressed state, because antidepressants may cause a switch to manic behavior.

The TCAs have **a narrow therapeutic index** (for example, five- to sixfold the maximal daily dose of imipramine can be lethal).

MONOAMINE OXIDASE INHIBITORS/ MAOI

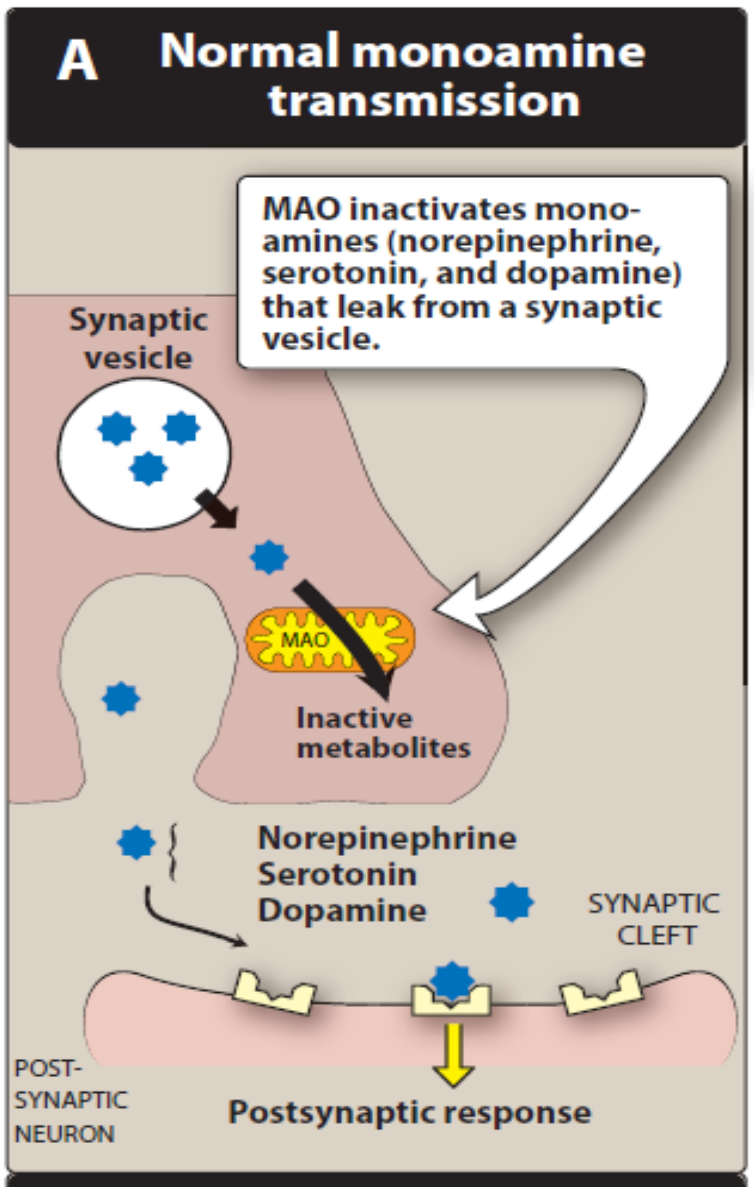
MAO is a mitochondrial enzyme found in nerve and other tissues, such as the gut and liver.

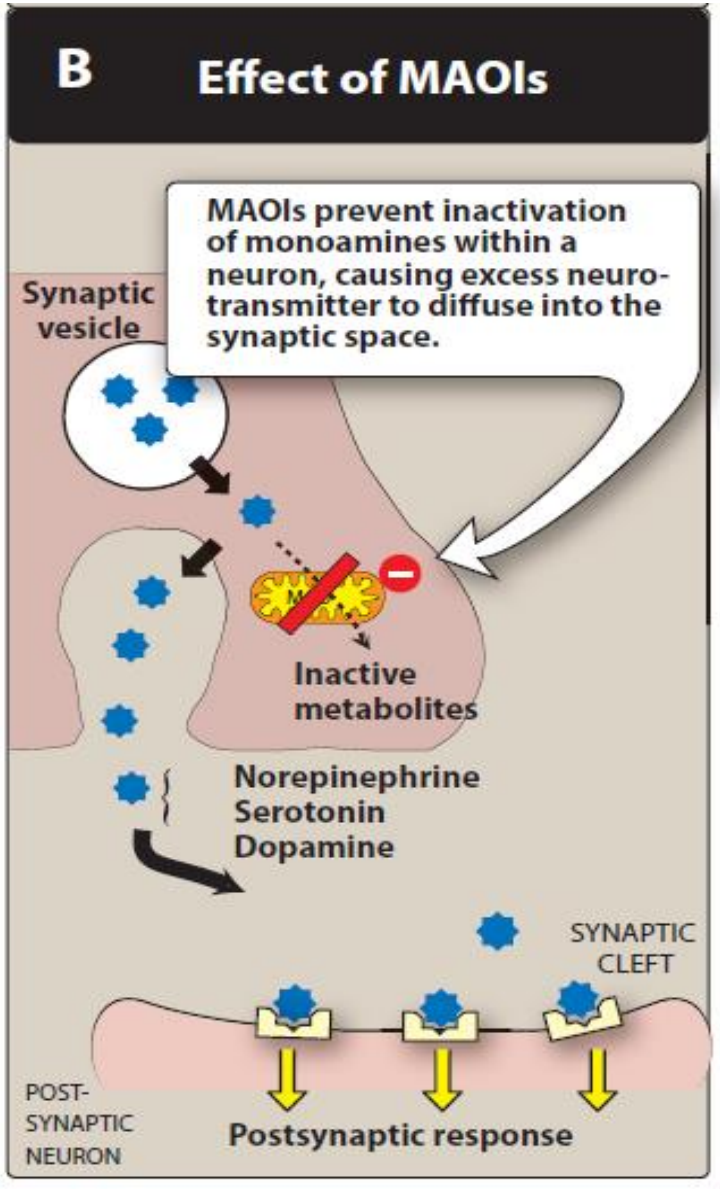
In the neuron, MAO functions as a "**safety valve**" to oxidatively deaminate and inactivate any excess neurotransmitters (for example, norepinephrine, dopamine, and serotonin) that may leak out of synaptic vesicles when the neuron is at rest.

The MAOIs may **irreversibly or reversibly** inactivate the enzyme, permitting neurotransmitters to escape degradation and, therefore, to accumulate within the presynaptic neuron and leak into the synaptic space.

The four MAOIs currently available for treatment of depression include **phenelzine, tranylcypromine, isocarboxazid, and selegiline.**

MAOI/ Mechanism of action





MAOI/ Mechanism of action

Although MAO is fully inhibited after several days of treatment, the antidepressant action of the MAOIs, like that of the SSRIs, SNRIs, and TCAs, is delayed **several weeks**.

Selegiline and tranylcypromine have an amphetamine-like stimulant effect that may produce agitation or insomnia.

MAOI/ Therapeutic uses

The MAOIs are indicated for depressed patients who are unresponsive or allergic to TCAs and SSRIs or who experience strong anxiety.

Because of their risk for drug–drug and drug–food interactions, the MAOIs are considered **last-line agents** in many treatment settings.

MAOI/ Pharmacokinetics

These drugs are well absorbed after oral administration.

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 and the initiation of another antidepressant from any other class.

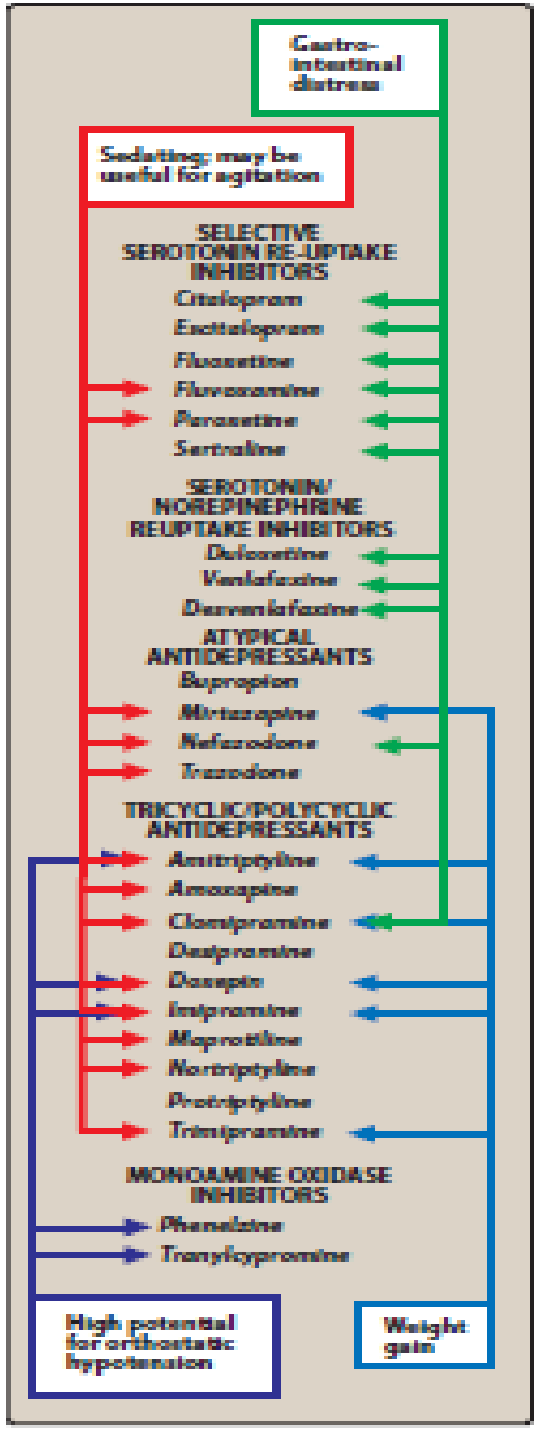
MAOIs are hepatically metabolized and excreted rapidly in urine.

MAOI/ Adverse effects

Tyramine, which is contained in foods, such as **aged** cheeses and meats, chicken liver, pickled or smoked fish, and red wines, is normally **inactivated by MAO in the gut**.

Individuals receiving a MAOI are unable to **degrade tyramine** obtained from the diet.

Tyramine causes the release of large amounts of stored **catecholamines** from nerve terminals, resulting in a hypertensive crisis, with signs and symptoms such as occipital headache, stiff neck, tachycardia, nausea, hypertension, cardiac arrhythmias, seizures, and, possibly, stroke.



MAOI/ Adverse effects

Patients must, therefore, be educated to avoid tyramine-containing foods.

Phentolamine and prazosin are helpful in the management of tyramine-induced hypertension.

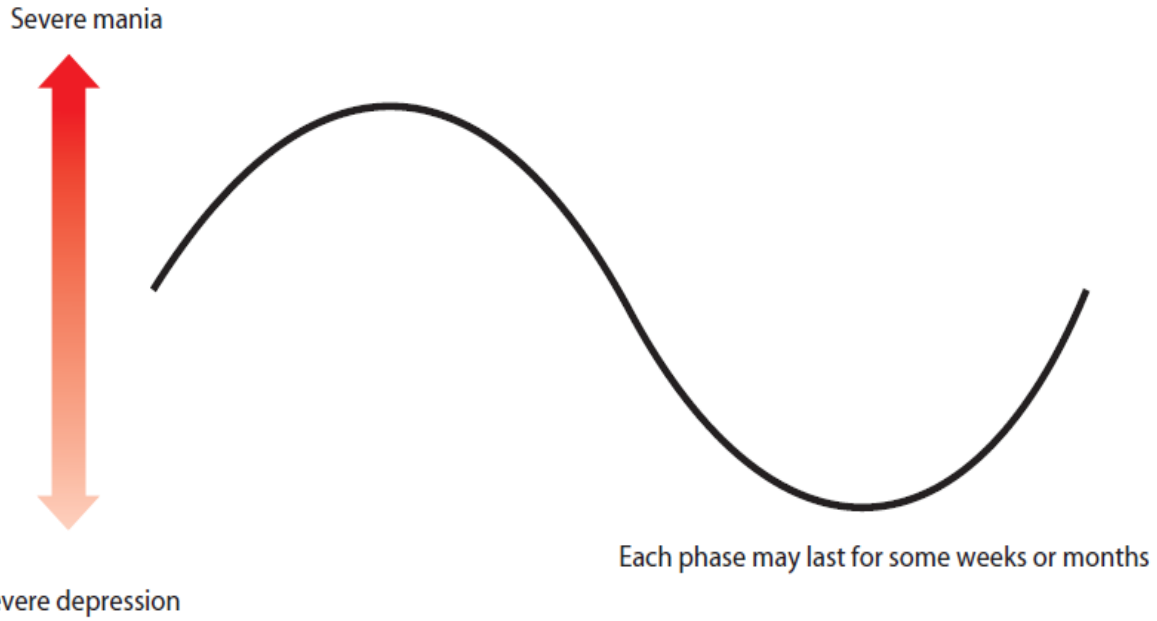
Other possible side effects of treatment with MAOIs include drowsiness, orthostatic hypotension, blurred vision, dry mouth, and constipation.

In addition, the MAOIs have many other critical drug interactions, and caution is required when administering these agents concurrently with other drugs.

TREATMENT OF MANIA AND BIPOLAR DISORDER

The treatment of bipolar disorder has increased in recent years, due to increased recognition of the disorder and also an increase in the number of available medications for the treatment of mania.

Bipolar disorder (manic-depressive illness) is characterised by mood changes which swing between mania and depression.



TREATMENT OF MANIA AND BIPOLAR DISORDER

A. Lithium

Lithium salts are used **acutely and prophylactically** for managing bipolar patients.

Lithium is effective in treating 60% to 80% of patients exhibiting **mania and hypomania**.

Although many cellular processes are altered by treatment with lithium salts, the mode of action is **unknown**.

The therapeutic index of lithium is extremely low, and lithium salts can be toxic.

Common adverse effects may include headache, dry mouth, polydipsia, polyuria, polyphagia, GI distress (give lithium with food), fine hand tremor, dizziness, fatigue, dermatologic reactions, and sedation.

TREATMENT OF MANIA AND BIPOLAR DISORDER

A. Lithium

Adverse effects due to higher plasma levels may indicate toxicity and include ataxia, slurred speech, coarse tremors, confusion, and convulsions.

Thyroid function may be decreased and should be monitored.

Unlike other mood stabilizers, lithium is **renally eliminated**, and though caution should be used when dosing this drug in renally impaired patients, it may be the best choice in patients with hepatic impairment.

TREATMENT OF MANIA AND BIPOLAR DISORDER

B. Other drugs

Several **antiepileptic** drugs, including carbamazepine, valproic acid, and lamotrigine, have been approved as mood stabilizers for bipolar disorder.

Other agents that may improve manic symptoms include the older (chlorpromazine and haloperidol) and newer **antipsychotics**.

The **atypical antipsychotics** risperidone, olanzapine, ziprasidone, aripiprazole, asenapine, and quetiapine are also used for the management of mania.

Quetiapine, lurasidone, and the combination of olanzapine and fluoxetine have been approved for bipolar depression.