Al-Mustaqbal University College

Pharmacology II 4th stage

Antidepressant Drugs Part 2

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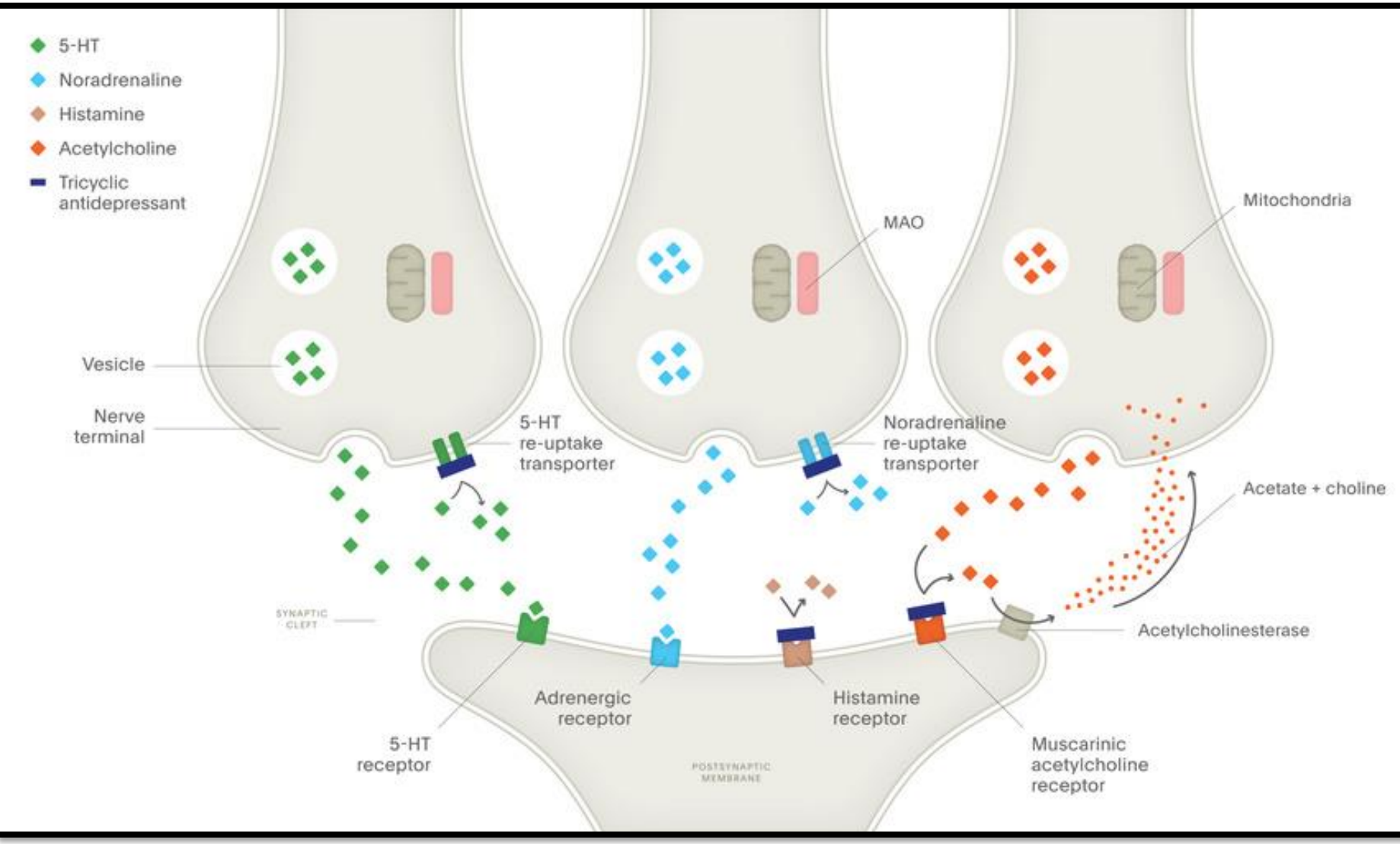
Tricycli antidepressants(TCAs):

Include: imipramine, amitriptyline, clomipramine, doxepin, trimipramine, desipramine, nortriptyline, protriptyline, Maprotiline and amoxapine.

Mechanism of action

1. Inhibition of the neuronal reuptake of norepinephrine and serotonin into presynaptic nerve terminals causing increased concentrations of monoamines in the synaptic cleft, and resulting in antidepressant effects.

2- Blocking of receptors: TCAs also block serotonergic, α-adrenergic, histaminic, and muscarinic receptors. However, actions at these receptors are probably responsible for many of the untoward effects of the TCAs. Amoxapine also blocks the D_2 receptor.


5-HT
Noradrenaline
Histamine
Acetylcholine
Tricyclic antidepressant
MAO
Mitochondria
Vesicle
Nerve terminal
5-HT re-uptake transporter
Noradrenaline re-uptake transporter
Acetate + choline
SYNAPTIC CLEFT
Acetylcholinesterase
Adrenergic receptor
Histamine receptor
5-HT receptor
Muscarinic acetylcholine receptor
POSTSYNAPTIC MEMBRANE

Actions:

1. mood elevation.
2. Improvement of mental alertness.
3. Increase physical activity.
4. The onset of mood elevation is slow requiring 2 weeks or longer.

6. Do not produce CNS stimulation or mood elevation in normal individuals.
7. Physical and psychological dependence has been rarely reported.
8. These drugs can be used for prolong treatment of depression.

Therapeutic uses

- treatment of moderate to sever major depression.
- Panic disorder.
- Imipramine has been used to control bed-wetting in children (older than 6 years) but with caution because of the inducement of cardiac arrhythmias.
- Treatment of migraine headache and chronic pain.

Pharmacokinetics:

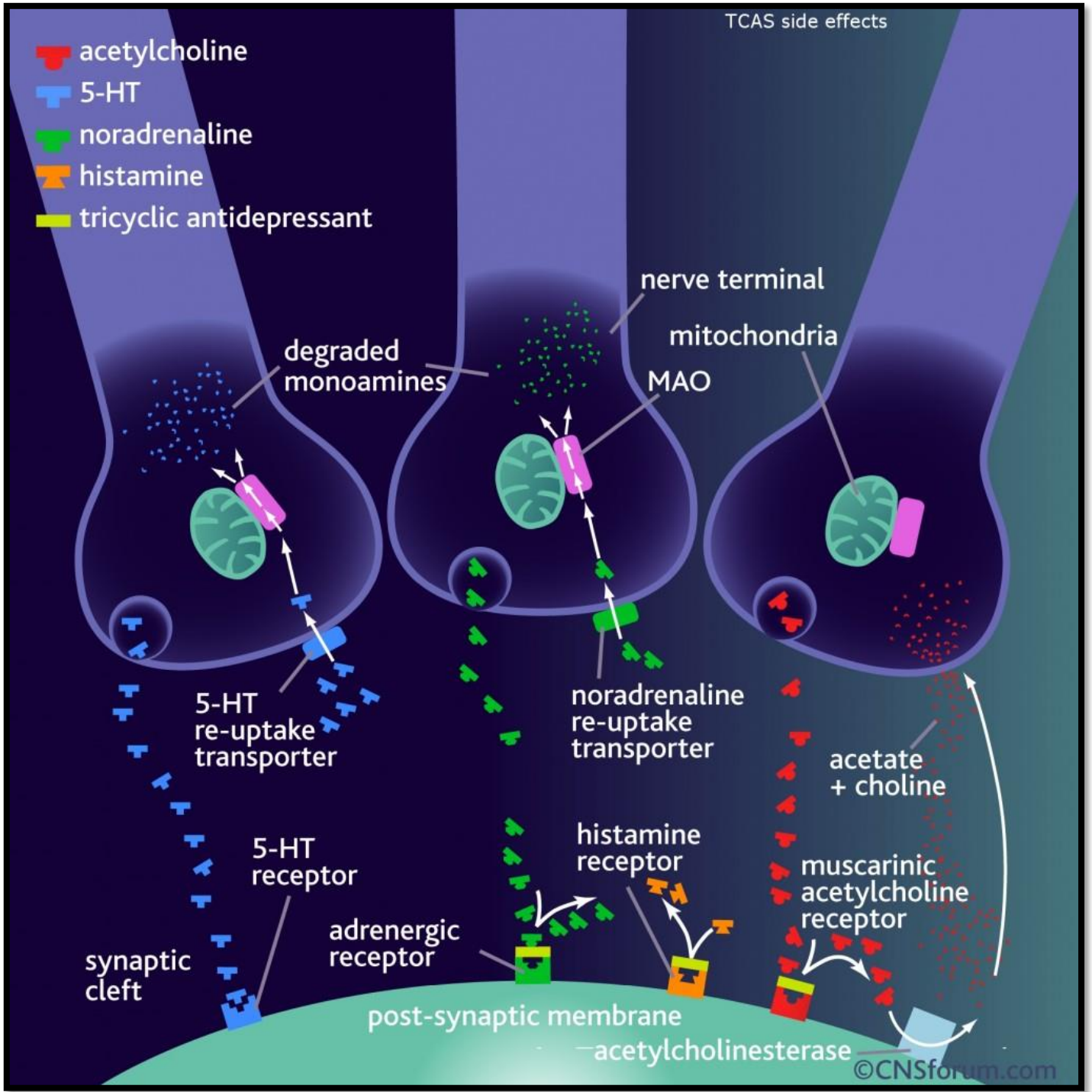
TCAs are well absorbed upon oral administration; and because of their lipophilic nature, are widely distributed and readily penetrate into CNS.

Have long half life for e.g. 4-17 hrs for imipramine. The initial period of treatment is typically 4-8 weeks. The dose can be gradually reduced unless relapse occurs. TCAs are metabolized in the liver and excreted in urine.

Adverse effects

Antimuscarinic effects: blockade of Ach receptors leads to blurred vision, xerostomia (dry mouth), urinary retention, constipation, aggravation of glaucoma and epilepsy.

Cardiovascular: increased catecholamine activity results in cardiac overstimulation, slowing of atrioventricular conduction.


TCAS side effects
acetylcholine
5-HT
noradrenaline
histamine
tricyclic antidepressant
nerve terminal
mitochondria
degraded monoamines
MAO
5-HT re-uptake transporter
noradrenaline re-uptake transporter
acetate + choline
histamine receptor
5-HT receptor
muscarinic acetylcholine receptor
adrenergic receptor
synaptic cleft
post-synaptic membrane
acetylcholinesterase
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Orthostatic hypotension and reflex tachycardia: due to α-adrenergic receptors blocking.

Sedation: during the first several weeks.

Weight gain and sexual dysfunction.

Narrow therapeutic index; 5-6 fold the maximal daily dose may be lethal.

Choose the one best answer.

A 51-year-old woman with symptoms of major depression also has angle-closure glaucoma. Which antidepressant should be avoided in this patient?

A. Amitriptyline
B. Bupropion
C. Mirtazapine
D. Fluvoxamine

Correct answer = A. Because of its potent antimuscarinic activity.

Choose the one best answer.

Which antidepressant is the most sedating?

A. Bupropion
B. Duloxetine
C. Doxepin
D. Venlafaxine

Correct answer = c. Doxepin is the most sedating of the list due to its histamine-blocking activity.

Monoamine oxidase inhibitors(MAOIs)

Monoamine oxidase (MAO) is a mitochondrial enzyme found in nerve and other tissues such as gut and liver.

In the neuron MAO functions as a safety valve that deaminate and inactivate any excess neurotransmitter molecules
(norepinephrine, dopamine and serotonin).

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

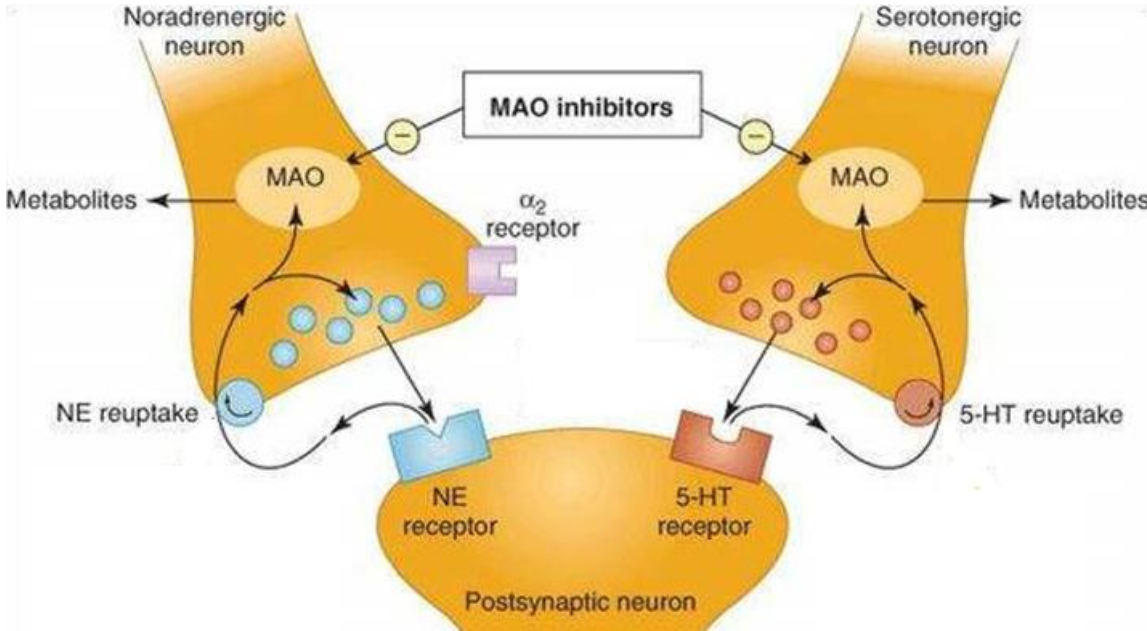
MAOIs include: phenelzine, isocarboxazide and tranylcypromine.

Q- Why Uses of MAOIs now is limited?
A- because of dietary restriction required in patients taking MAOIs.

Mechanism of action

Most MAOIs such as isocarboxazide and phenelzine form stable complexes with MAO enzyme causing irreversible inactivation.

This results in increased stores of norepinephrine, serotonin and dopamine within the neuron and subsequent diffusion of excess neurotransmitter into synaptic cleft.



Actions

Although MAO is fully inhibited after several days of treatment, the antidepressant action of MAOI like that of TCA and SSRIs is delayed several weeks.

Phenelzine and tranycypromine have mild amphetamine like stimulant effect.

Therapeutic use

- used in depressed patients who are unresponsive or allergic to TCA or who are experience strong anxiety.
- Patients with low psychomotor activity may benefit from the stimulant properties of MAOIs.
- Treatment of phobic states.
- Atypical depression.

Pharmacokinetics

These drugs are well absorbed orally, but antidepressant effects requires at least 2-4 weeks of treatment.

When switching antidepressant agent a minimum of 2 weeks of delay must be allowed after termination of MAOI therapy and initiation another antidepressant.

MAOIs are metabolized and excreted rapidly in urine.

Adverse effects

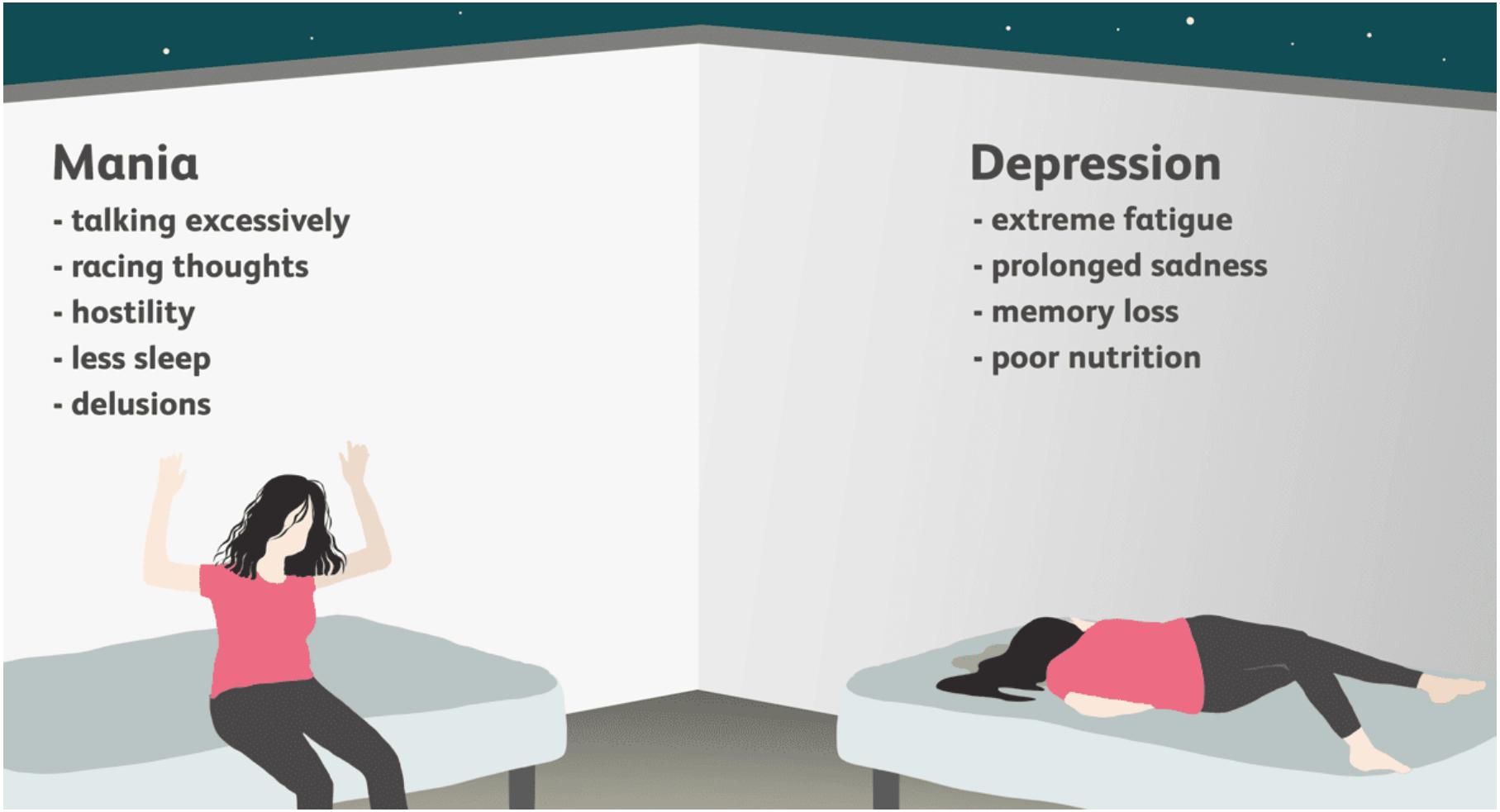
sever and often unpredictable side effects limit the widespread use of MAOIs. For example **tyramine** containing food such as aged cheese, chicken liver, beer and red wines, is nortmally metabolized by MAO in the gut.

Tyramine causes the release of large amounts of stored catecholamines from nerve terminals resulting in headache, tachycardia, nausea, hypertension, cardiac arrhythmia; patients must be educated to avoid tyramine containing food.

Other side effects are drowsiness, orthostatic hypotension, blurred vision, dry mouth, dysurea and constipation.

MAOIs and SSRIs should not be coadministered due to the risk of life threatening "serotonin syndrome ".

Bipolar Disorder



Treatment of Mania and Bipolar Disorder

Lithium salts are used prophylactically for treating manic-depressive patients and in the treatment of manic episodes and, thus, is considered as mood stabilizer.

Lithium is believed to attenuate signaling via receptors coupled to the phosphatidylinositol bisphosphate (PIP2) second-messenger system.

Lithium interferes with the resynthesis (recycling) of PIP2, leading to its relative depletion in neuronal membranes of the CNS.

PIP2 levels in peripheral membranes are unaffected by lithium.

Lithium salts have **therapeutic index are extremely Low** comparable to those of digitalis.

Note:

The **therapeutic index** (**TI**; also referred to as **therapeutic ratio**) is a quantitative measurement of the relative safety of a drug.

It is a comparison of the amount of a therapeutic agent that causes the [therapeutic effect] to the amount that causes toxicity.

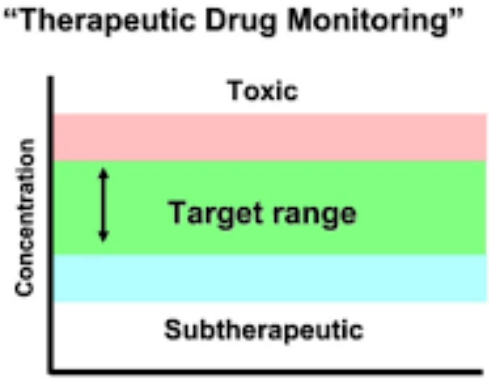


Figure 1A. Dose-Response Curves for Wide Therapeutic Index Medications

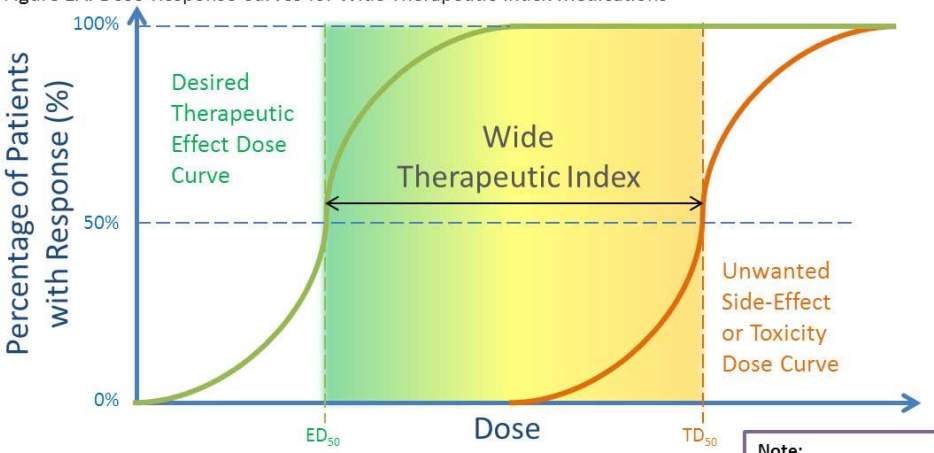
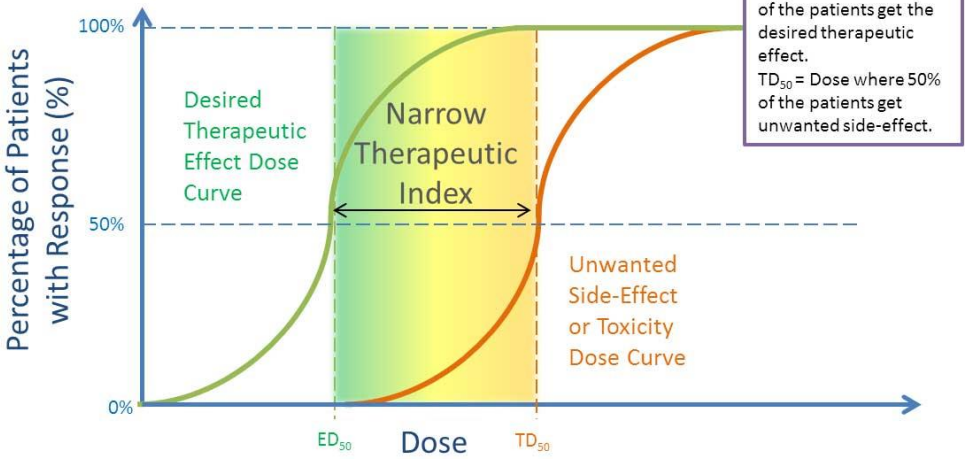


Figure 1B. Dose-Response Curves for Narrow Therapeutic Index Medications



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

Thyroid function may be decreased and should be monitored.

Choose the one best answer.

Which mood-stabilizing agent is most likely to decrease the thyroid function?

A. Carbamazepine
B. Lithium
C. Valproic acid
D. Chlorpromazine

Several antiepileptic drugs, including carbamazepine, valproic acid, and lamotrigine, have been identified as mood stabilizers and have been used in the treatment of bipolar disorder.

The atypical antipsychotics (risperidone, olanzapine, ziprasidone, aripiprazole, and quetiapine) also used in the management of mania.

References

Lippincott Illustrated Reviews: Pharmacology. 7TH ed, Wolters Kluwer.


Thank You