Al-Mustaqbal University College

Pharmacology II 4th stage

Antidepressant Drugs Part 1

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Depression is characterized by intense feeling of sadness, hopelessness, inability to experience pleasure, changes in sleep patterns and appetite, loss of energy, and suicidal thoughts.

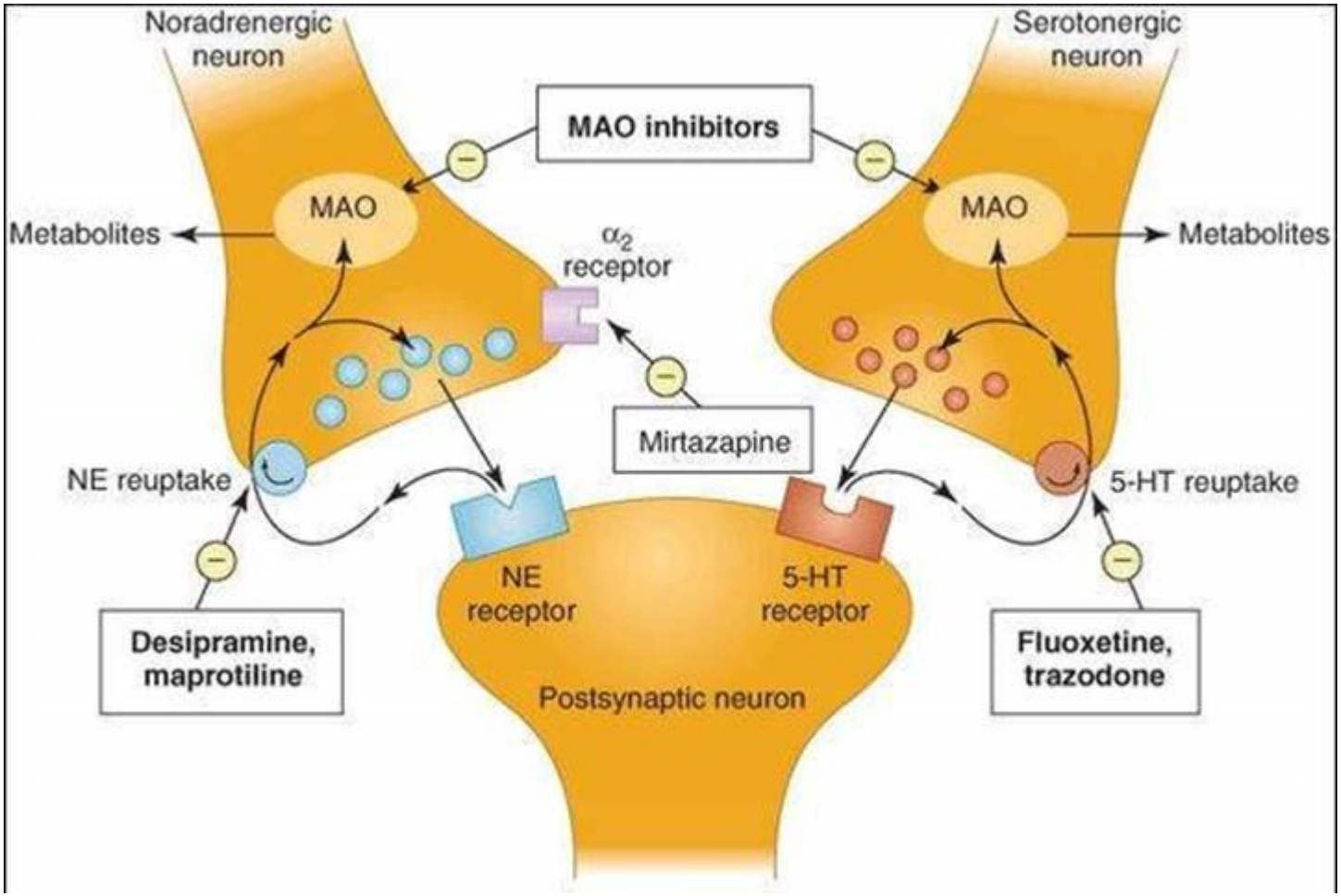
Mania is characterized by the opposite behavior that includes rapid thought and speech patterns, extreme self-confidence, and impaired judgment.

Mechanism of Antidepressant Drugs

Most antidepressant drugs potentiate, either directly or indirectly, the actions of in the brain.

This led to the **amine theory**, which states that depression is due to a deficiency of monoamines, such as norepinephrine and serotonin, at certain sites in the brain.

Conversely, the theory states that mania is caused by an overproduction of these neurotransmitters. The pharmacologic effects of any of the antidepressant and antimania drugs on neurotransmission occur immediately, whereas the therapeutic response occurs over several weeks.


Noradrenergic neuron
Serotonergic neuron
MAO inhibitors
MAO
MAO
Metabolites
Metabolites
α_2 receptor
Mirtazapine
NE reuptake
5-HT reuptake
NE receptor
5-HT receptor
Desipramine, maprotiline
Fluoxetine, trazodone
Postsynaptic neuron

Decreased the uptake of neurotransmitter is only an initial effect of the drugs, which may not be directly responsible for the antidepressant effects. It has been proposed that presynaptic inhibitory receptor densities in the brain decrease over a 2- to 4-week period with antidepressant drug use.

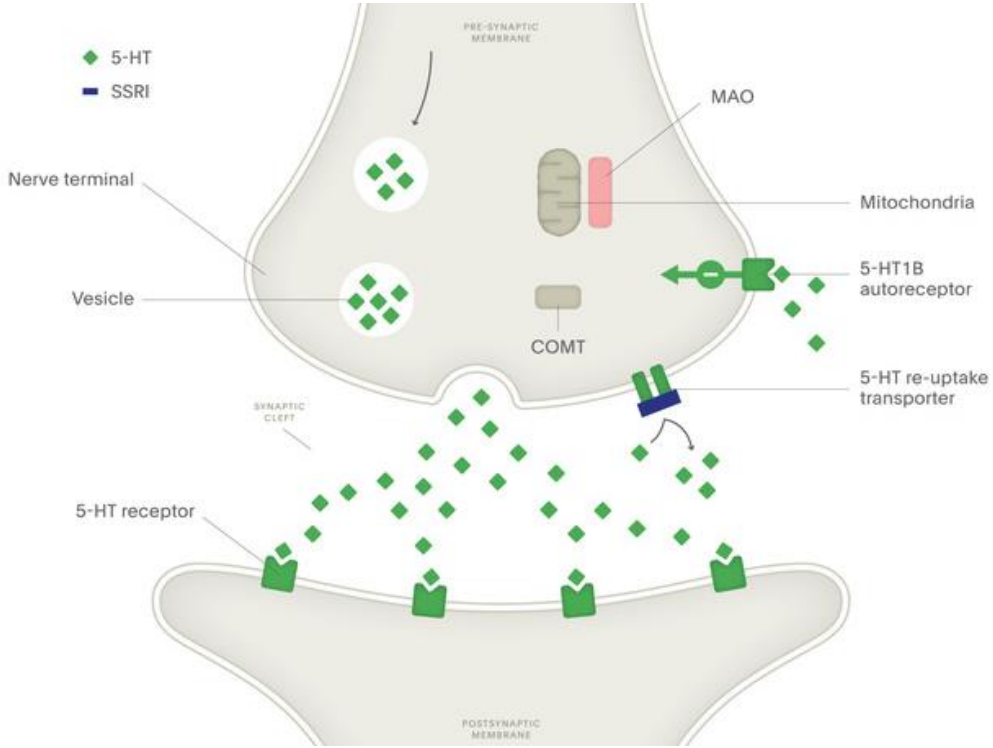
This down-regulation of inhibitory receptors permits greater synthesis and release of neurotransmitters into the synaptic cleft leading to a therapeutic response.

1- selective serotonin reuptake inhibitors (SSRI):

Include:

Fluoxetine [floo-OX-e-teen] (the prototypic drug),
citalopram [sye-TAL-oh-pram],
escitalopram [essye-TAL-oh-pram],
fluvoxamine [floo-VOX-e-meen],
paroxetine [paROX-e-teen],
and sertraline [SER-tra-leen].

These drugs specifically inhibit serotonin reuptake. This contrasts with the tricyclic antidepressants that nonselectively inhibit the uptake of norepinephrine and serotonin. Both of these antidepressant drug classes exhibit little ability to block the dopamine transporter.



Moreover, the SSRIs have little blocking activity at muscarinic, α--adrenergic, and histaminic H1 receptors.

Therefore, common side effects that associated with tricyclic antidepressants, such as orthostatic hypotension, sedation, dry mouth, and blurred vision, are not commonly seen with the SSRIs.

Q- SSRIs are considered as the drugs of choice in treating depression. **Why?**

Actions

The SSRIs block the reuptake of serotonin, leading to increased concentrations of the neurotransmitter in the synaptic cleft and, increased **postsynaptic neuronal activity**.

Antidepressants, including SSRIs, typically take at least 2 weeks to produce significant improvement in mood, and maximum benefit may require up to 12 weeks or more.

Note: These drugs do not usually produce central nervous system (CNS) stimulation or mood elevation in normal individuals.

Therapeutic uses

- depression.
- Obsessive- compulsive disorder (fluvoxamine is effective).
- Panic disorder.
- Generalized anxiety disorder; social anxiety disorder.
- Premenstrual syndrome.
- Bulimia nervosa (fluoxetine is effective).

Pharmacokinetics

All of SSRIs are well absorbed after oral administration.

Food increases absorption of sertraline only. Metabolism by P_{450}-dependent enzymes and glucuronide or sulfate conjugation occur extensively.

Fluoxetine has longer half life (50 hrs) and available as a sustained release preparation allowing once weekly dosing.

Fluoxetine and paroxetine are potent inhibitors of a hepatic cytochrome p_{450} responsible for the elimination of TCA drugs, neuroleptic, some antiarrhythmic, β-adrenergic antagonist drugs.

Adverse effects

1. nausea, vomiting, diarrhea.
2. Headache, anxiety.
3. Sweating.
4. Weakness and fatigue.
5. Sexual dysfunction.
6. Changes in weight.
7. Sleep disturbances.

Choose the one best answer.

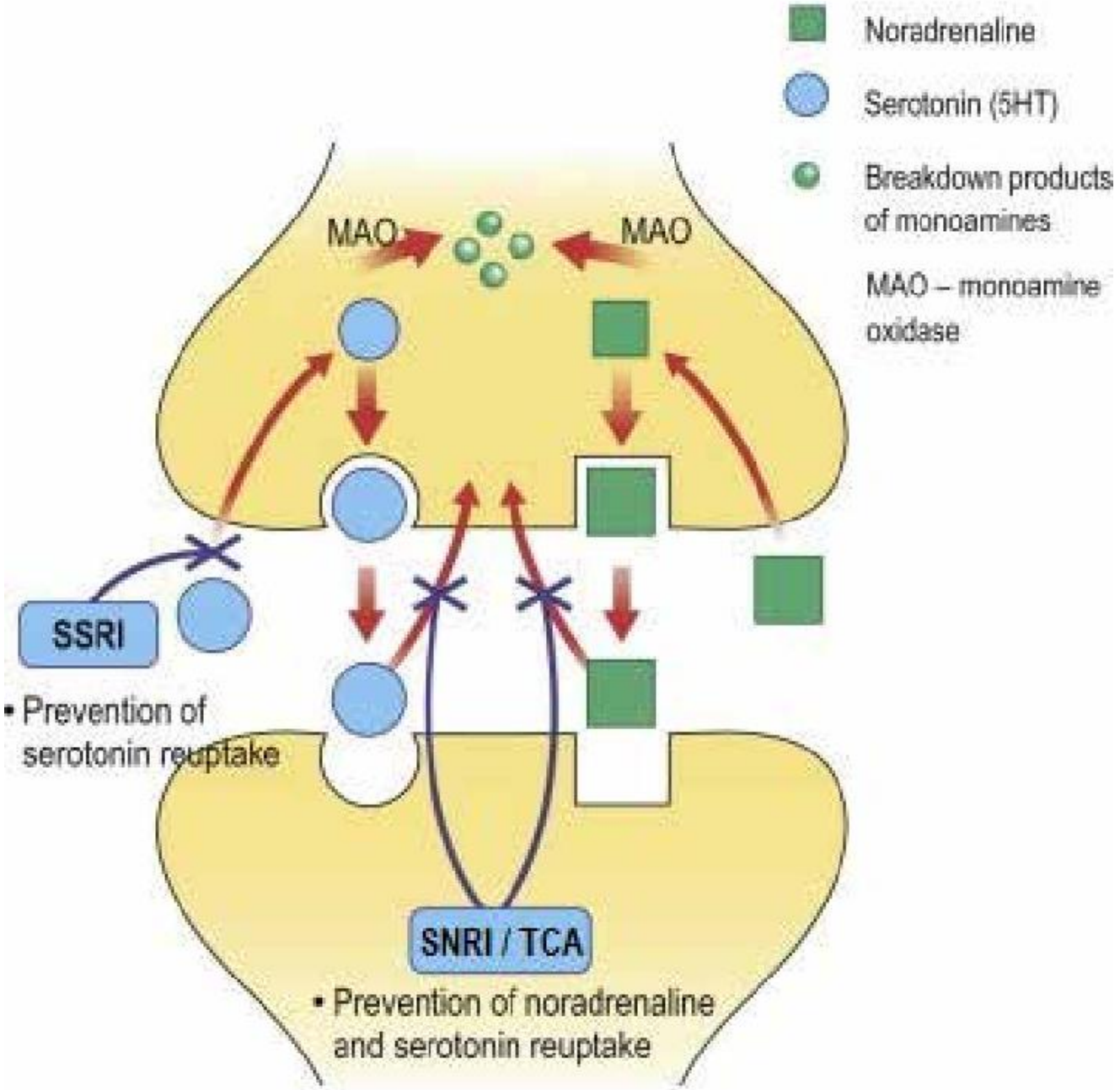
A 36-year-old man presents with symptoms of compulsive behavior. He realizes that his behavior is interfering with his ability to accomplish his daily tasks but cannot seem to stop himself. Which drug would be most helpful to this patient?

A. Desipramine
B. Paroxetine
C. Amitriptyline
D. Selegiline

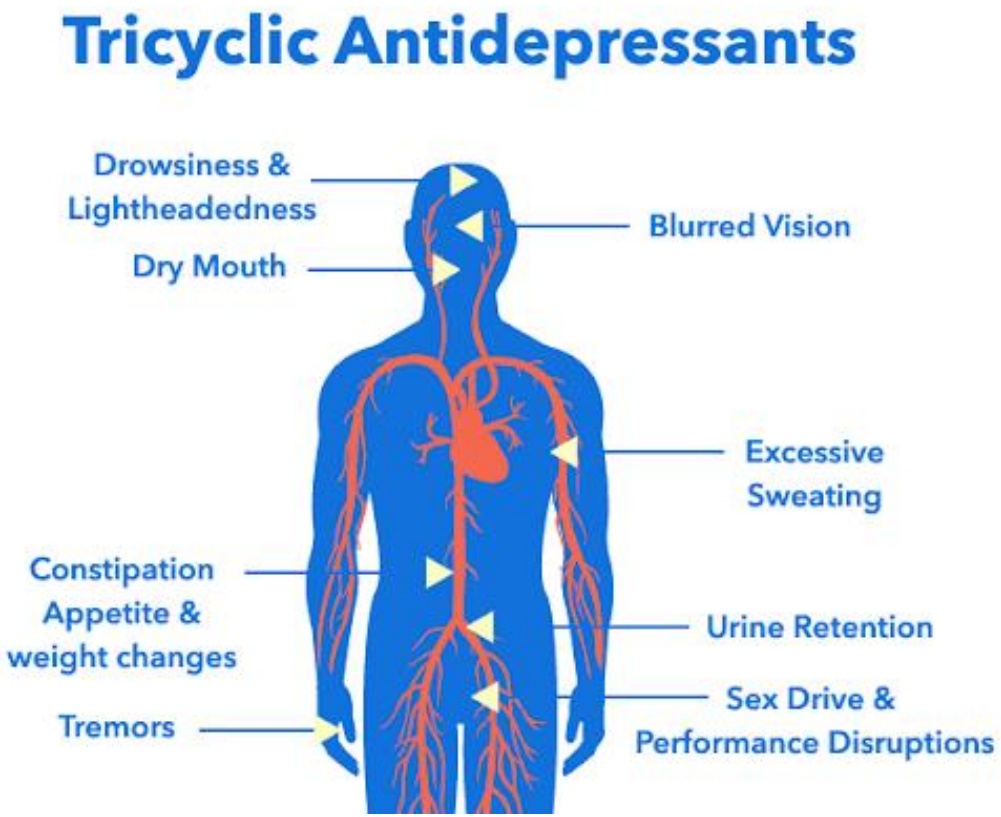
Correct answer = B. SSRis are particularly effective In treating obsessive-compulsive disorder, and paroxetlne Is approved for this concition.

2- *Serotonin-Norepinephrine Reuptake Inhibitors*

Venlafaxine and duloxetine selectively inhibit the re-uptake of both serotonin and norepinephrine. These agents may be effective in treating depression in patients in whom SSRIs are ineffective, in addition to treat the painful symptoms that associate depression such as backache and muscle aches.


Noradrenaline
Serotonin (5HT)
Breakdown products of monoamines
MAO – monoamine oxidase
MAO
MAO
SSRI
• Prevention of serotonin reuptake
SNRI / TCA
• Prevention of noradrenaline and serotonin reuptake

SNRIs associated with less side effects than TCA, Why?



The SNRIs, unlike the tricyclic antidepressants, have little activity at adrenergic, muscarinic, or histamine receptors.

A. Venlafaxine

Venlafaxine is a potent inhibitor of serotonin reuptake and, at **medium to higher doses**, is an inhibitor of norepinephrine re-uptake. It is also a mild inhibitor of dopamine reuptake at high doses. Venlafaxine has minimal inhibition of the cytochrome P_{450}.

The most common side effects of venlafaxine are: nausea, headache, sexual dysfunction, dizziness, insomnia, sedation, and constipation. At high doses, there may be an increase in blood pressure and heart rate.

B. Duloxetine

Duloxetine inhibits serotonin and norepinephrine reuptake at all doses.

Q- Duloxetine should not be administered to patients with hepatic insufficiency, Why?

A- Because it is extensively metabolized in the liver to numerous metabolites.

Metabolites are excreted in the urine. Food delays the absorption of the drug.

Gastrointestinal side effects are common including: nausea, dry mouth, and constipation. Insomnia, dizziness, somnolence, and sweating are also seen.

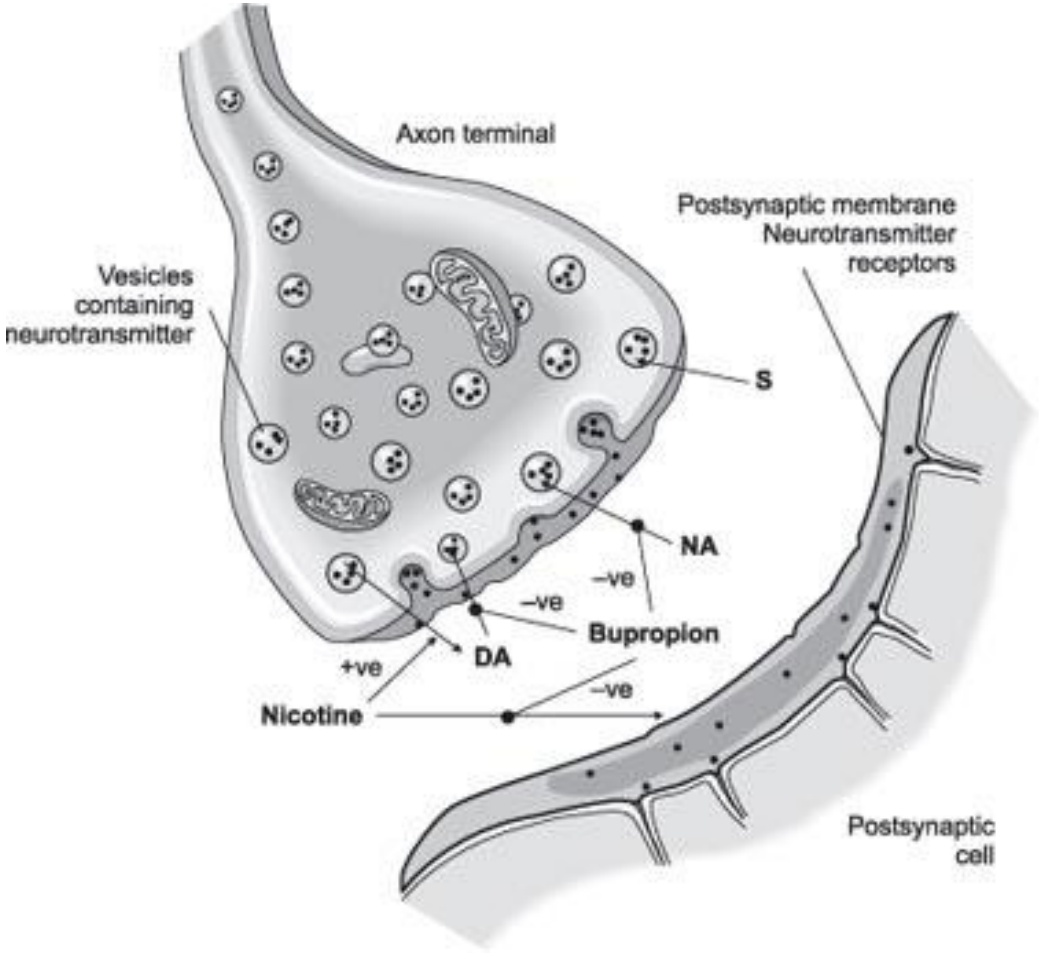
Sexual dysfunction also occurs along with the possible risk for an increase in either blood pressure or heart rate.

Atypical Antidepressants

They are not more efficacious than the tricyclic antidepressants or SSRIs.

A. Bupropion

This drug acts as a weak dopamine and norepinephrine reuptake inhibitor to alleviate the symptoms of depression. Its short half-life may require more than once-a-day dosing or the administration of an extended-release formulation.



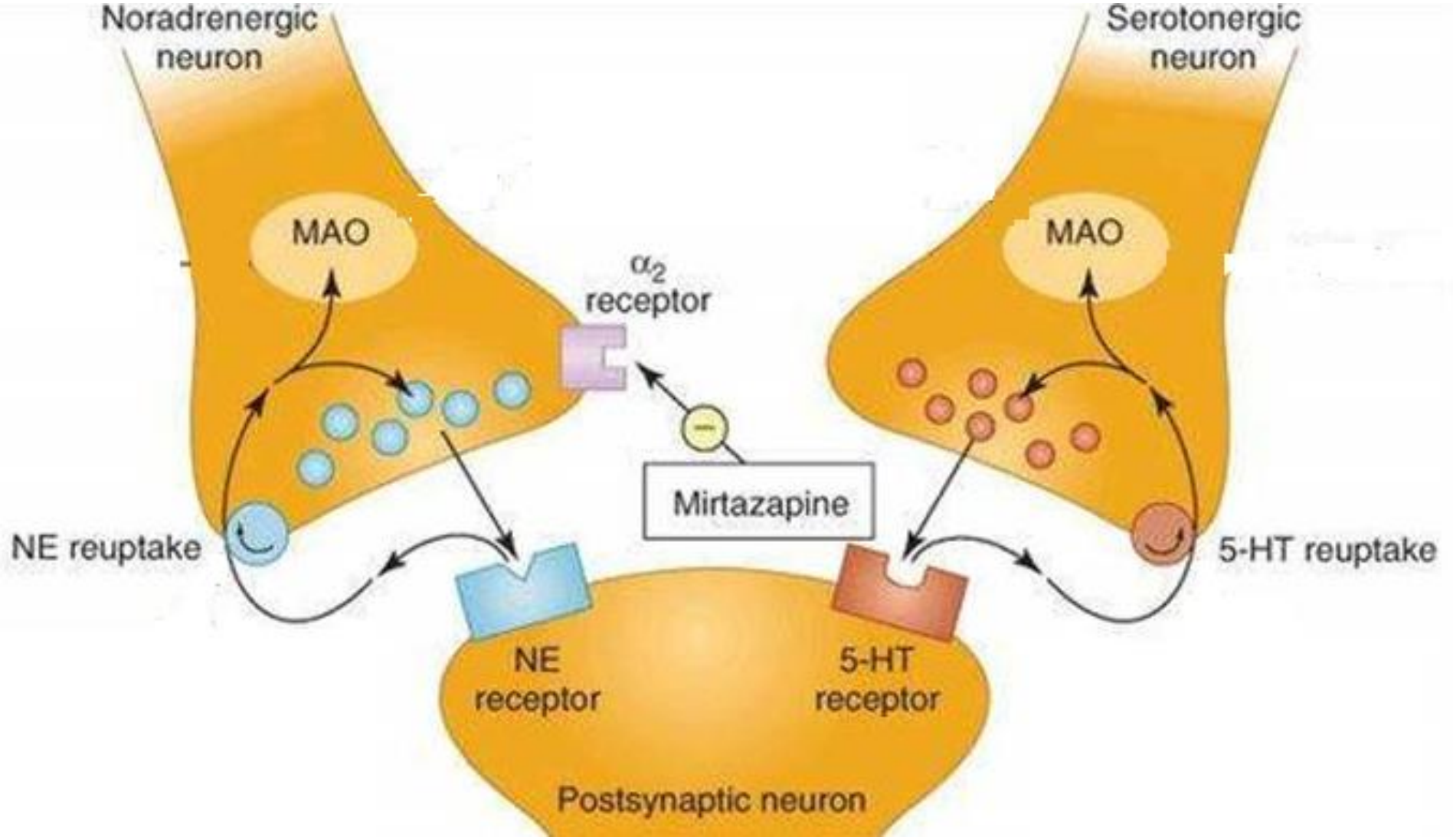
Side effects may include dry mouth, sweating, nervousness, tremor and an increased risk for seizures at high doses.

B. Mirtazapine

- This drug enhances serotonin and norepinephrine neurotransmission by its ability to block presynaptic α_2 receptors.

- It is a sedative because of its potent antihistaminic activity, but

- it does not cause the antimuscarinic side effects of the tricyclic antidepressants,
- or interfere with sexual functioning, as do the SSRIs.
- Increased appetite and weight gain frequently occur.


Noradrenergic neuron
Serotonergic neuron
MAO
MAO
α_2 receptor
Mirtazapine
NE reuptake
5-HT reuptake
NE receptor
5-HT receptor
Postsynaptic neuron

Choose the ONE best answer.

Case: A 55-year-old teacher was diagnosed with depression. After 6 weeks of therapy with fluoxetine, his symptoms improved, but he complains of sexual dysfunction.

Which of the following drugs might be useful for management of depression in this patient?

A. Sertraline
B. Citalopram
C. Mirtazapine
D. Lithium

Correct answer = C. Mirtazaplne Is largely free from sexual side effects. However, sexual dysfunction commonly occurs with SSRis {sertraline and citalopram), as well as with TCAs and SNRis. Lithium is used for the treatment of mania and bipolar disorder.

C. Nefazodone and trazodone

These drugs are weak inhibitors of serotonin reuptake. They block postsynaptic 5-HT_{2A} receptors. With chronic use, these agents may desensitize 5-HT_{1A} presynaptic autoreceptors and, thereby, increase serotonin release.

Both agents are sedating, probably because of their potent H1-blocking activity. Nefazodone has been associated with the risk for hepatotoxicity.

References

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


Thank You