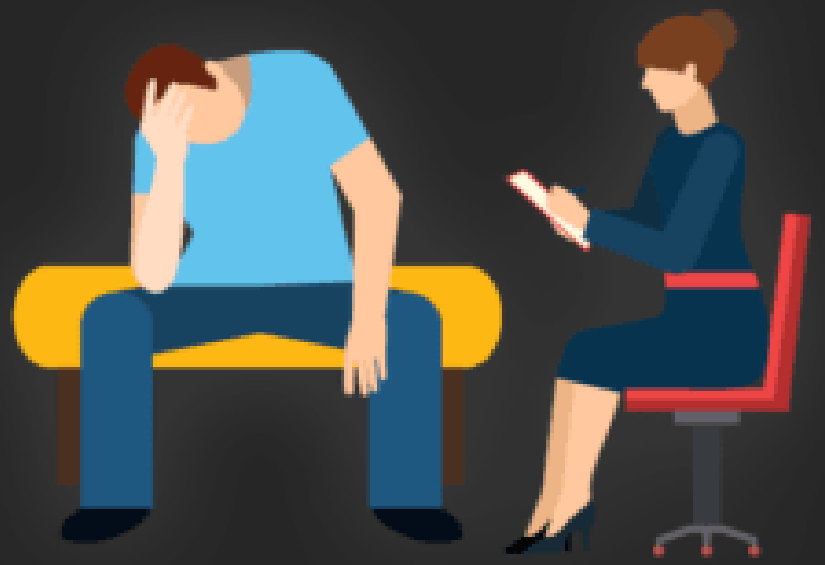
Dr Karamallah S. Mahmood/ PhD Clinical Pharmacology

Antidepressants



NERVOUS SYSTEM DRUGS

TRICYCLIC ANTIDEPRESSANTS, MAO-INHIBITORS, SSRI

OVERVIEW

The symptoms of depression are:

- ✓ feelings of sadness and hopelessness,
- ✓ inability to experience pleasure in usual activities,
- ✓ changes in sleep patterns and appetite,
- ✓ loss of energy,
- ✓ suicidal thoughts.

OVERVIEW

Mania is characterized by the opposite behavior:

- ✓ enthusiasm,
- ✓ anger,
- ✓ rapid thought and speech patterns,
- ✓ extreme self-confidence,
- ✓ impaired judgment.

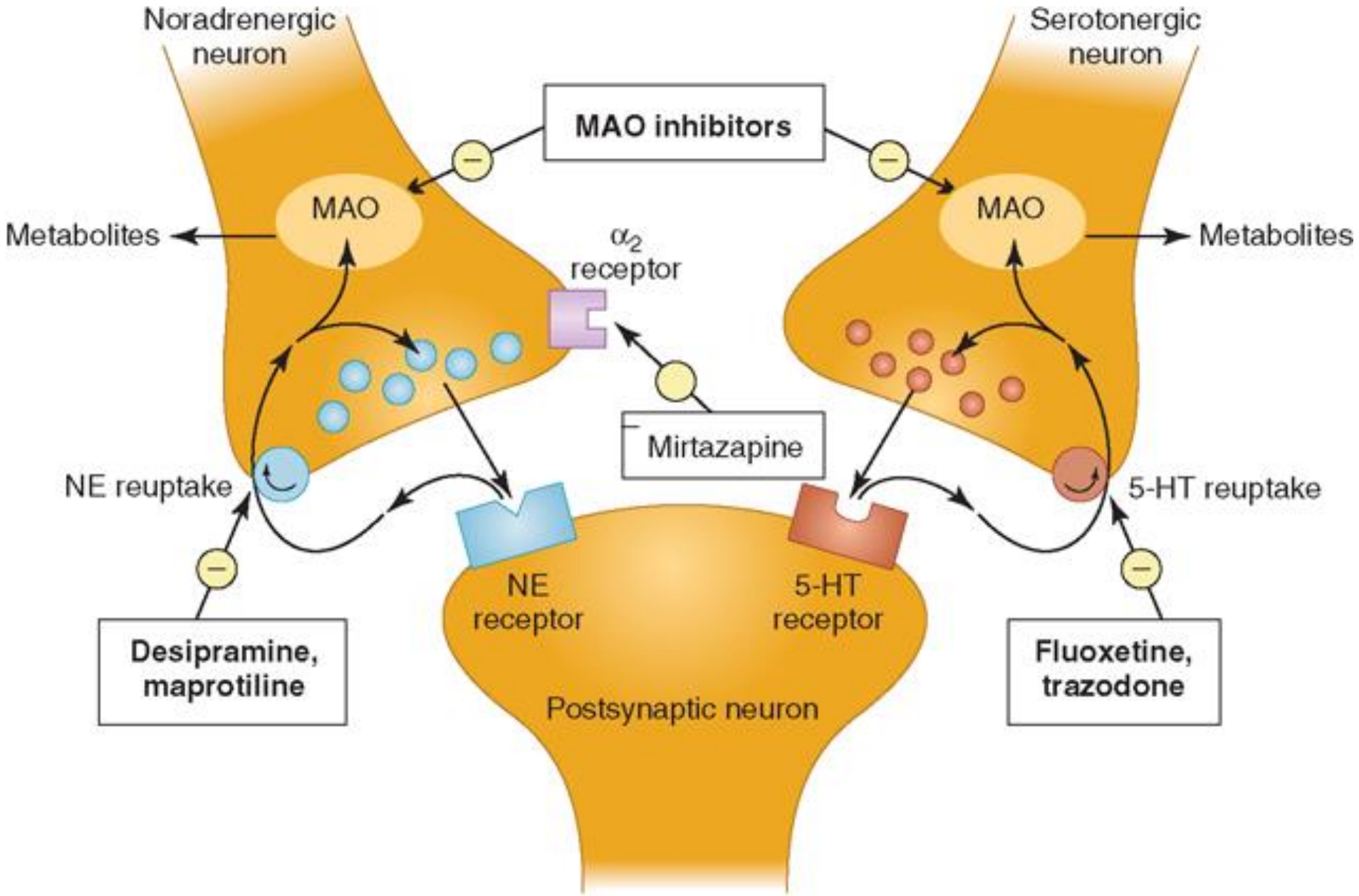
MECHANISM OF ANTIDEPRESSANT DRUGS

Most clinically useful antidepressant drugs potentiate, either directly or indirectly, the actions of **norepinephrine and/or serotonin (5-HT)** in the brain.

This, along with other evidence, led to **the biogenic amine theory**, which proposes that depression is due to a deficiency of monoamines, such as norepinephrine and serotonin, at certain key sites in the brain.

Conversely, the theory proposes that mania is caused by an overproduction of these neurotransmitters.

MECHANISM OF ANTIDEPRESSANT DRUGS



MECHANISM OF ANTIDEPRESSANT DRUGS

However, **the biogenic amine theory** of depression and mania is overly simplistic.

It fails to explain the pharmacological effects of any of the antidepressant and antimania drugs on neurotransmission, which often occur immediately; however, the time course for a therapeutic response occurs over several weeks.

This suggests that decreased reuptake of neurotransmitters is only an initial effect of the drugs, which may not be directly responsible for the antidepressant effects.

SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIs)

- *Citalopram* CELEXA
- *Escitalopram* LEXAPRO
- *Fluoxetine* PROZAC
- *Fluvoxamine* LUVOX CR
- *Paroxetine* PAXIL
- *Sertraline* ZOLOFT

SEROTONIN/NOREPINEPHRINE REUPTAKE INHIBITORS (SNRIs)

- *Desvenlafaxine* PRISTIQ
- *Duloxetine* CYMBALTA
- *Levomilnacipran* FETZIMA
- *Venlafaxine* EFFEXOR

ATYPICAL ANTIDEPRESSANTS

- *Bupropion* WELLBUTRIN, ZYBAN
- *Mirtazapine* REMERON
- *Nefazodone*
- *Trazodone* DESYREL
- *Vilazodone* VIIBRYD
- *Vortioxetine* BRINTELLIX

TRICYCLIC ANTIDEPRESSANTS (TCAs)

- *Amitriptyline*
- *Amoxapine*
- *Clomipramine* ANAFRANIL
- *Desipramine* NORPRAMIN
- *Doxepin* SINEQUAN
- *Imipramine* TOFRANIL
- *Maprotiline* LUDIOMIL
- *Nortriptyline* PAMELOR
- *Protriptyline* VIVACTIL
- *Trimipramine* SURMONTIL

MONOAMINE OXIDASE INHIBITORS (MAOIs)

- *Isocarboxazid* MARPLAN
- *Phenelzine* NARDIL
- *Selegiline* EMSAM
- *Tranylcypromine* PARNATE

SELECTIVE SEROTONIN REUPTAKE INHIBITORS/ SSRI

The SSRIs are a group of antidepressant drugs that specifically inhibit **serotonin reuptake**,

This contrasts with the tricyclic antidepressants (**TCAs**) and serotonin/norepinephrine reuptake inhibitors (**SNRIs**) that nonselectively inhibit the reuptake of norepinephrine and serotonin.

DRUG	UPTAKE INHIBITION	
	Nor-epinephrine	Serotonin
Selective serotonin reuptake inhibitor		
Fluoxetine	0	++++
Selective serotonin/ norepinephrine reuptake inhibitors		
Venlafaxine	++*	++++
Duloxetine	++++	++++
Tricyclic antidepressants		
Imipramine	++++	+++
Nortriptyline	++++	++

SELECTIVE SEROTONIN REUPTAKE INHIBITORS/ **SSRI**

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

The SSRIs include **fluoxetine (the prototypic drug)**, citalopram, escitalopram, fluvoxamine, paroxetine, and sertraline.

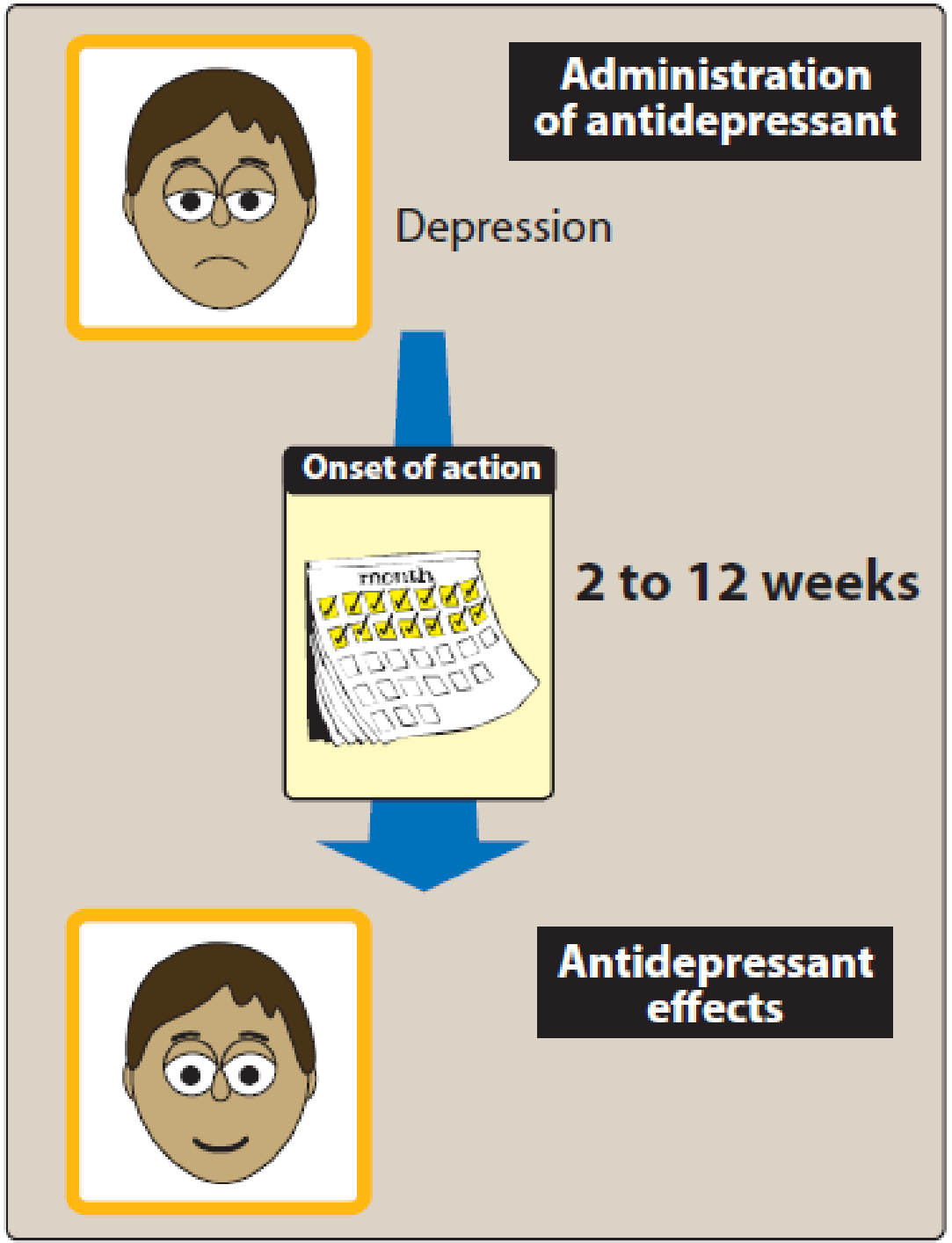
Escitalopram is the pure S-enantiomer of citalopram.

SSRI/ Actions

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

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**.

Patients who do not respond to one antidepressant may respond to another, and approximately 80% or more will respond to at least one antidepressant drug.



SSRI/ Therapeutic uses

The primary indication for SSRIs is depression, for which they are as effective as the TCAs.

A number of other psychiatric disorders also respond favorably to SSRIs, including:

- Obsessive–compulsive disorder,
- Panic disorder,
- Generalized anxiety disorder,
- Posttraumatic stress disorder,
- Social anxiety disorder,
- Premenstrual dysphoric disorder,
- Bulimia nervosa (**only fluoxetine is approved for bulimia**).

SSRI/ Pharmacokinetics

All of the SSRIs are well absorbed after oral administration.

The majority of SSRIs have plasma half-lives that range between 16 and 36 hours.

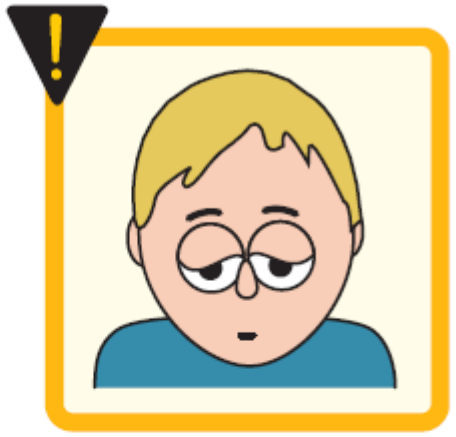
Fluoxetine differs from the other members of the class by having a much **longer half-life** (50 hours), and the half life of its active metabolite S-norfluoxetine is quite long, averaging 10 days.

Fluoxetine and paroxetine are potent **inhibitors of a CYP450** isoenzyme (CYP2D6) responsible for the elimination **of TCAs, antipsychotic drugs, and some antiarrhythmic and β-adrenergic antagonist drugs**.

SSRI/ Adverse effects

Nausea

Drowsiness

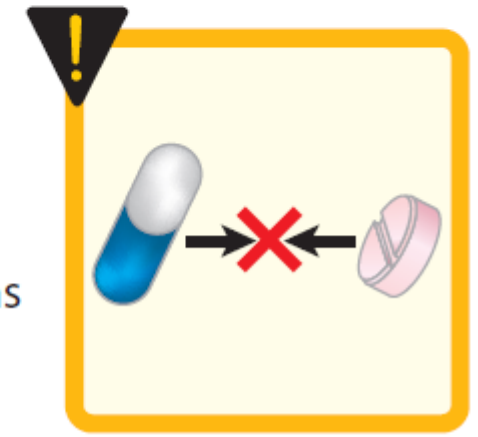


Sexual dysfunction

Anxiety

Insomnia

Drug interactions



SSRI/ Adverse effects

1. Sleep disturbances:

Paroxetine and fluvoxamine are generally more sedating than activating, and they may be useful in patients who have difficulty sleeping.

Conversely, patients who are fatigued or complaining of excessive somnolence may benefit from one of the more activating SSRIs, such as **fluoxetine or sertraline**.

2. Sexual dysfunction:

Sexual dysfunction, which may include loss of libido, delayed ejaculation, and anorgasmia, is common with the SSRIs.

SSRI/ Use in children and teenagers

Antidepressants should be used cautiously in children and teenagers, because of **suicidal ideation** as a result of SSRI treatment.

Fluoxetine, sertraline, and fluvoxamine are approved for use in children to treat obsessive–compulsive disorder, and **fluoxetine and escitalopram** are approved to treat childhood depression.

SSRI/ Overdose:

Overdose with SSRIs **does not** usually cause cardiac **arrhythmias**, with the exception of citalopram, which may cause QT prolongation.

Serotonin syndrome may include the symptoms of hyperthermia, muscle rigidity, sweating, myoclonus (clonic muscle twitching), and changes in mental status and vital signs.

SSRI/ Discontinuation syndrome:

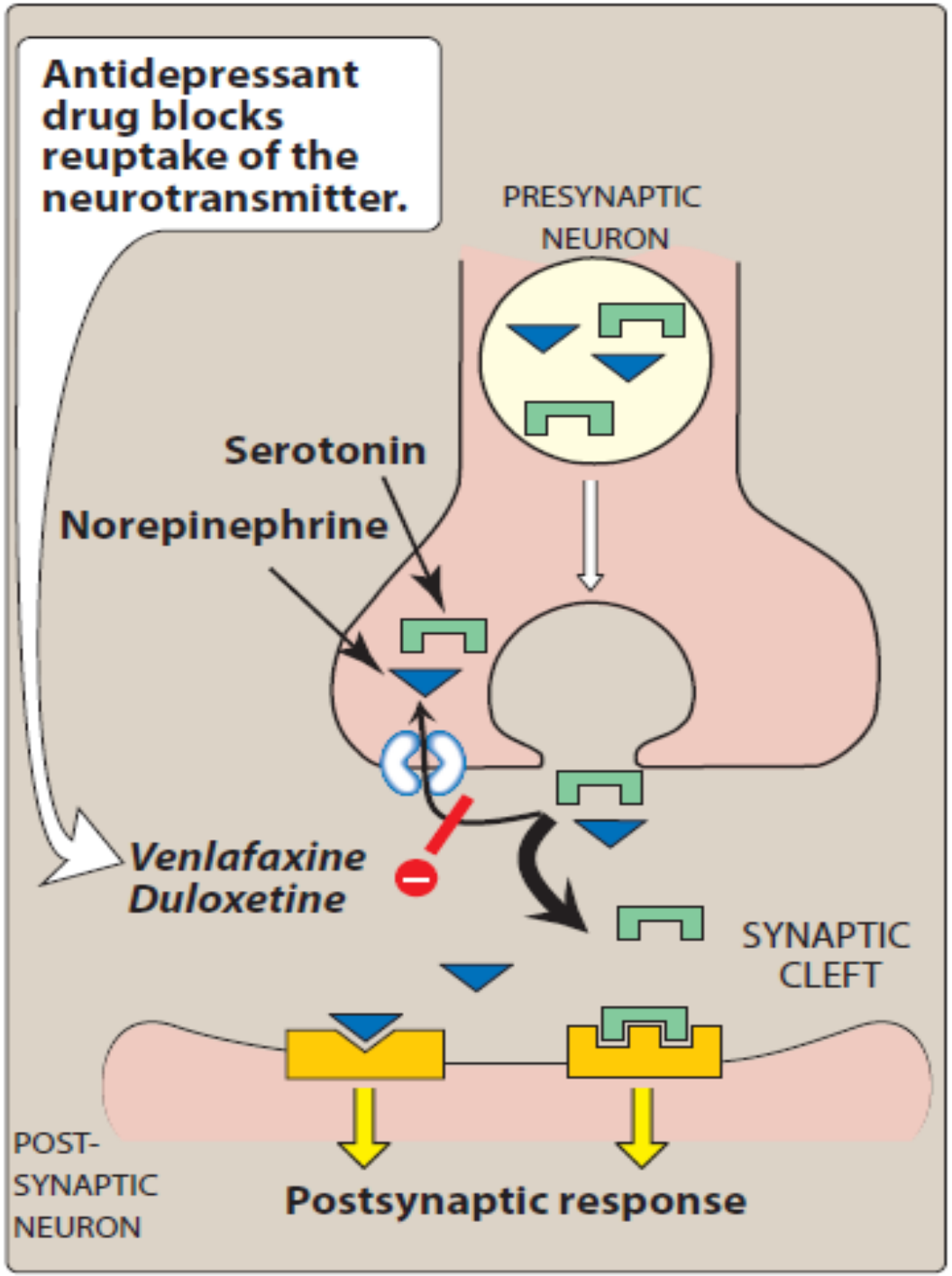
All of the SSRIs have the potential to cause a **discontinuation syndrome** after their abrupt withdrawal, particularly the agents with shorter half-lives and inactive metabolites.

Possible signs and symptoms of SSRI discontinuation syndrome include headache, malaise, and flu-like symptoms, agitation and irritability, nervousness, and changes in sleep pattern.

SEROTONIN/NOREPINEPHRINE REUPTAKE INHIBITORS/ SNRIs

Venlafaxine, desvenlafaxine , levomilnacipran, and duloxetine inhibit the reuptake of both **serotonin and norepinephrine**.

SNRIs may be effective in treating depression in patients in whom SSRIs are ineffective.



SNRIs

Furthermore, depression is often accompanied by **chronic painful symptoms**, such as backache and muscle aches, **against which SSRIs are also relatively ineffective !!!!!!**.

This pain is, in part, modulated by serotonin and norepinephrine pathways in the central nervous system (CNS).

The SNRIs, unlike the TCAs, have little activity at α-adrenergic, muscarinic, or histamine receptors and, thus, have fewer of these receptor-mediated adverse effects than the TCAs.

SNRIs

Venlafaxine and desvenlafaxine

Venlafaxine and desvenlafaxine (demethylated metabolite of venlafaxine) are a potent inhibitor of serotonin reuptake and, at **medium to higher doses, is an inhibitor of norepinephrine reuptake**.

Venlafaxine has minimal inhibition of the CYP450 isoenzymes and is a substrate of the CYP2D6 isoenzyme.

The most common side effects of venlafaxine are nausea, headache, sexual dysfunction, dizziness, insomnia, sedation, and constipation.

SEROTONIN/NOREPINEPHRINE REUPTAKE INHIBITORS/ SNRIs

B. Duloxetine

Duloxetine inhibits serotonin and norepinephrine reuptake at all doses.

GI side effects are common with duloxetine, including nausea, dry mouth, and constipation. Insomnia, dizziness, somnolence, sweating, and sexual dysfunction are also seen.

Duloxetine may increase blood pressure or heart rate.

Duloxetine is a moderate **inhibitor of CYP2D6** isoenzymes and may increase concentrations of drugs metabolized by this pathway, such as antipsychotics.

SEROTONIN/NOREPINEPHRINE REUPTAKE INHIBITORS/ SNRIs

C. Levomilnacipran

Levomilnacipran is an enantiomer of milnacipran (an older SNRI used for the treatment of depression in Europe and fibromyalgia in the United States).

The adverse effect profile of levomilnacipran is similar to other SNRIs.

It is primarily **metabolized by CYP3A4**, and, thus, activity may be altered by inducers or inhibitors of this enzyme system.

ATYPICAL ANTIDEPRESSANTS

A. Bupropion

Bupropion is a weak **dopamine and norepinephrine** reuptake inhibitor that is used to alleviate the symptoms of depression.

Bupropion is also useful for decreasing cravings and attenuating withdrawal symptoms of nicotine in patients trying to **quit smoking**.

Side effects may include dry mouth, sweating, nervousness, tremor, and a dose-dependent increased risk for seizures. **It has a very low incidence of sexual dysfunction, WHY?.**

However, bupropion may inhibit CYP2D6 and, thus, increase exposure to substrates of this isoenzyme.
Use of bupropion should be avoided in patients at risk for seizures or those who have eating disorders such as bulimia.

ATYPICAL ANTIDEPRESSANTS

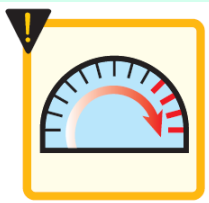
B. Mirtazapine

Mirtazapine enhances **serotonin and norepinephrine** neurotransmission by serving as an **antagonist at presynaptic α2 receptors.**

Additionally, some of the antidepressant activity may be related to antagonism at 5-HT2 receptors.

It is sedating because of its potent **antihistaminic** activity, but it **does not cause the antimuscarinic** side effects of the TCAs, or interfere with sexual function like the SSRIs.

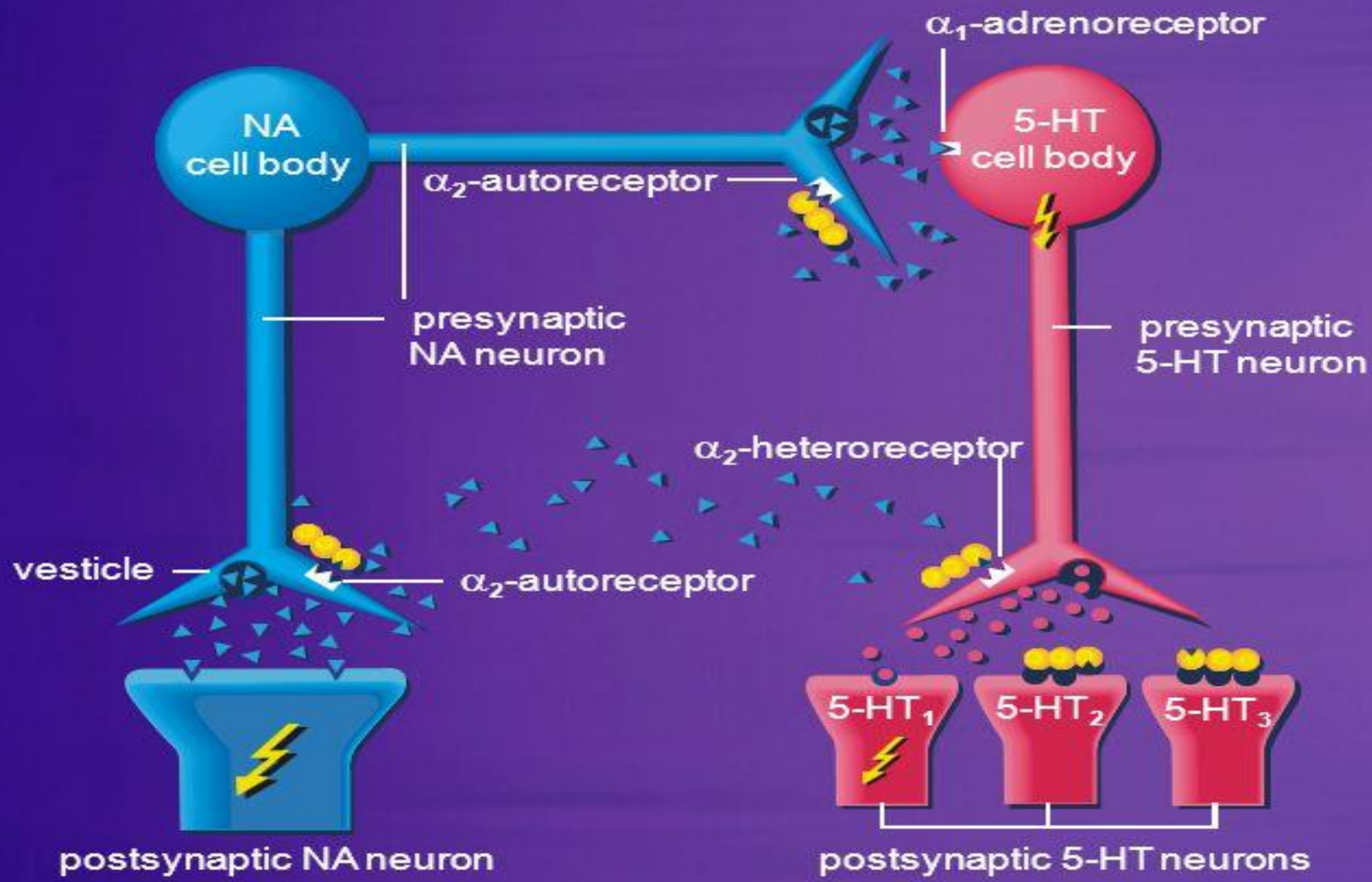
Increased appetite and weight gain frequently occur.



Weight gain

Sedation

Mirtazapine – Mechanism of action



ATYPICAL ANTIDEPRESSANTS

C. Nefazodone and trazodone

These drugs are weak inhibitors of **serotonin reuptake**.

Their therapeutic benefit appears to be related to their ability to **block postsynaptic 5-HT2a receptors**.

Both agents are sedating, probably because of their potent **histamine H1-blocking** activity.

Trazodone is commonly used off-label for the management of **insomnia**.

Trazodone has been associated with **priapism**, and nefazodone has been associated with a risk for **hepatotoxicity**.

Both agents also have mild to moderate **α1 receptor antagonism**, contributing to orthostasis and dizziness.

ATYPICAL ANTIDEPRESSANTS

D. Vilazodone

- ✓ Vilazodone is a **serotonin** reuptake inhibitor and a **5-HT1a partial agonist**.
- ✓ Although the extent to which the 5-HT1a receptor activity contributes to its therapeutic effects is unknown, this possible mechanism of action renders it unique from that of the SSRIs.
- ✓ The adverse effect profile of vilazodone is similar to the SSRIs, including a risk for discontinuation syndrome if abruptly stopped.

E. Vortioxetine

- ❑ Vortioxetine utilizes a combination of **serotonin** reuptake inhibition, **5-HT$_{1\alpha}$ agonism**, and **5-HT$_3$ and 5-HT$_7$ antagonism**.
- ❑ The common adverse effects include nausea, vomiting, and constipation, which may be expected due to its serotonergic mechanisms.