# 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:

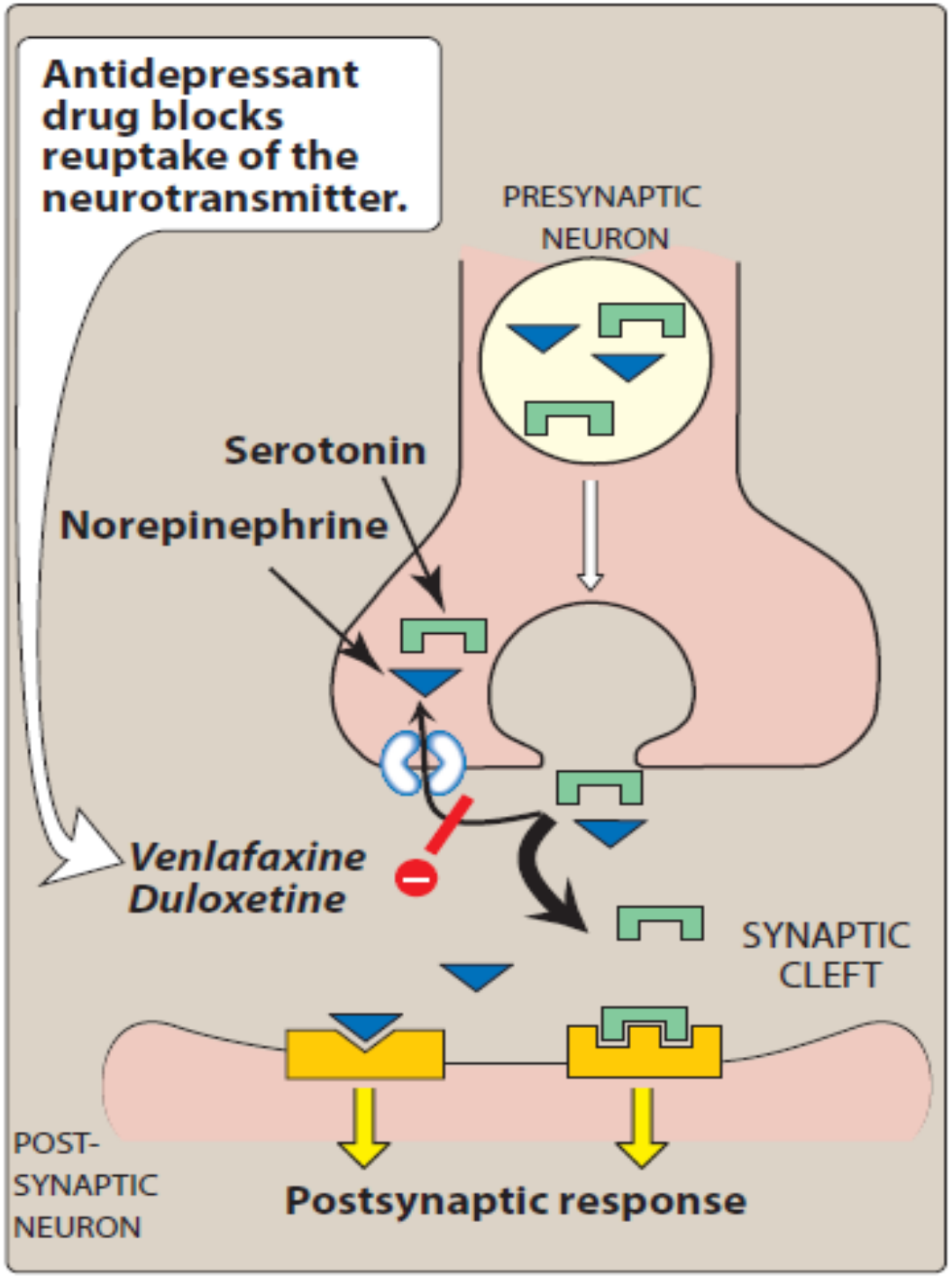
All of the SSRIs have the potential to cause a **discontinuation syndrome** after their abrupt withdrawal, particularly the agents with shorter half-lives and inactive metabolites.

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

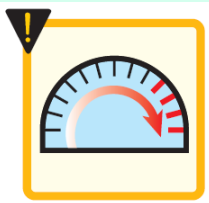
## B. Mirtazapine

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.

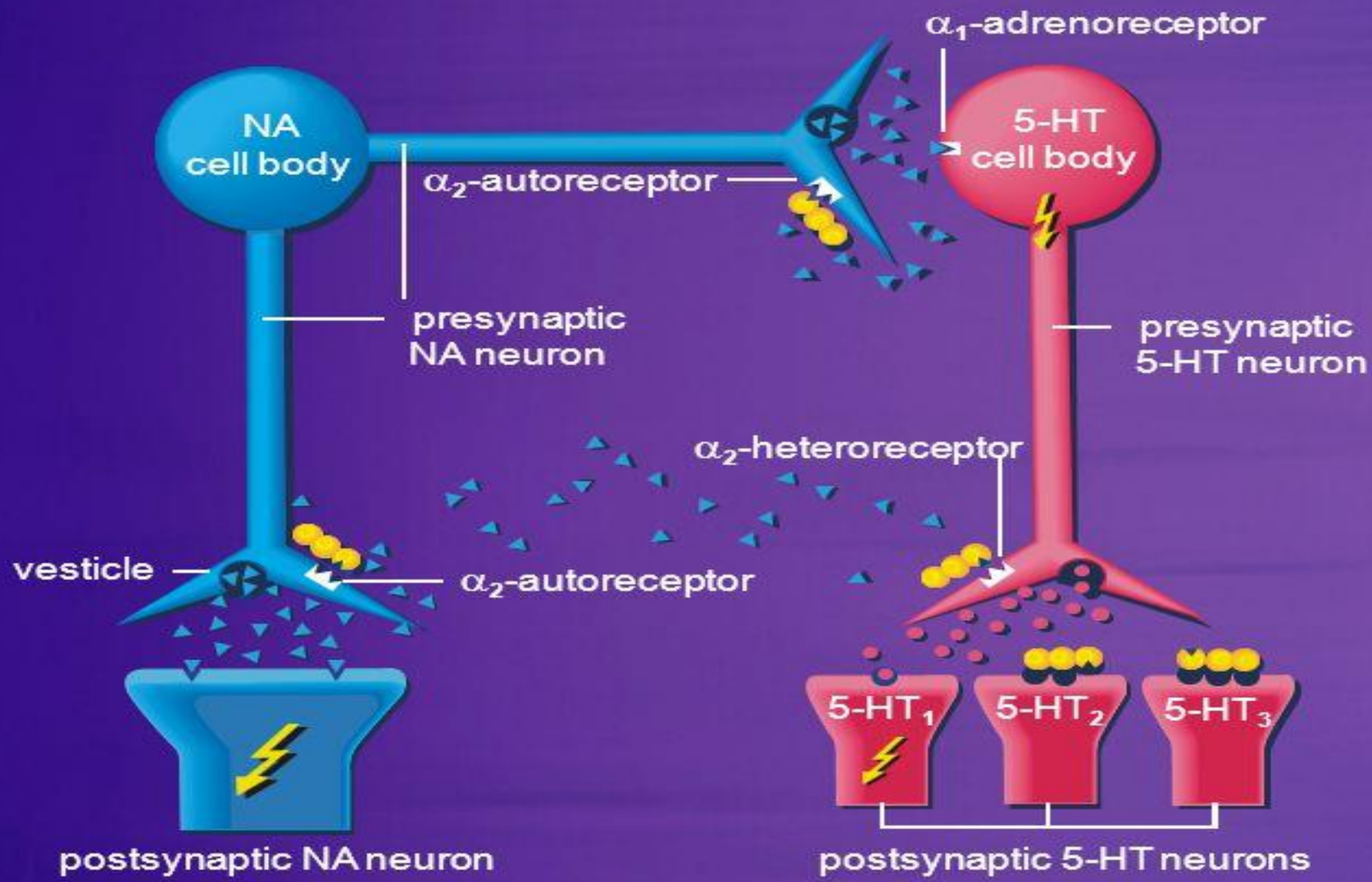
Increased appetite and weight gain frequently occur.



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.