Lecture 5 + 6

Overview: Alzheimer's Disease

- is a neurodegenerative disorder characterized by
1. impairment of memory and
2. cognitive function together
3. with mood and personality changes.
- is the most common cause of dementia in the elderly.

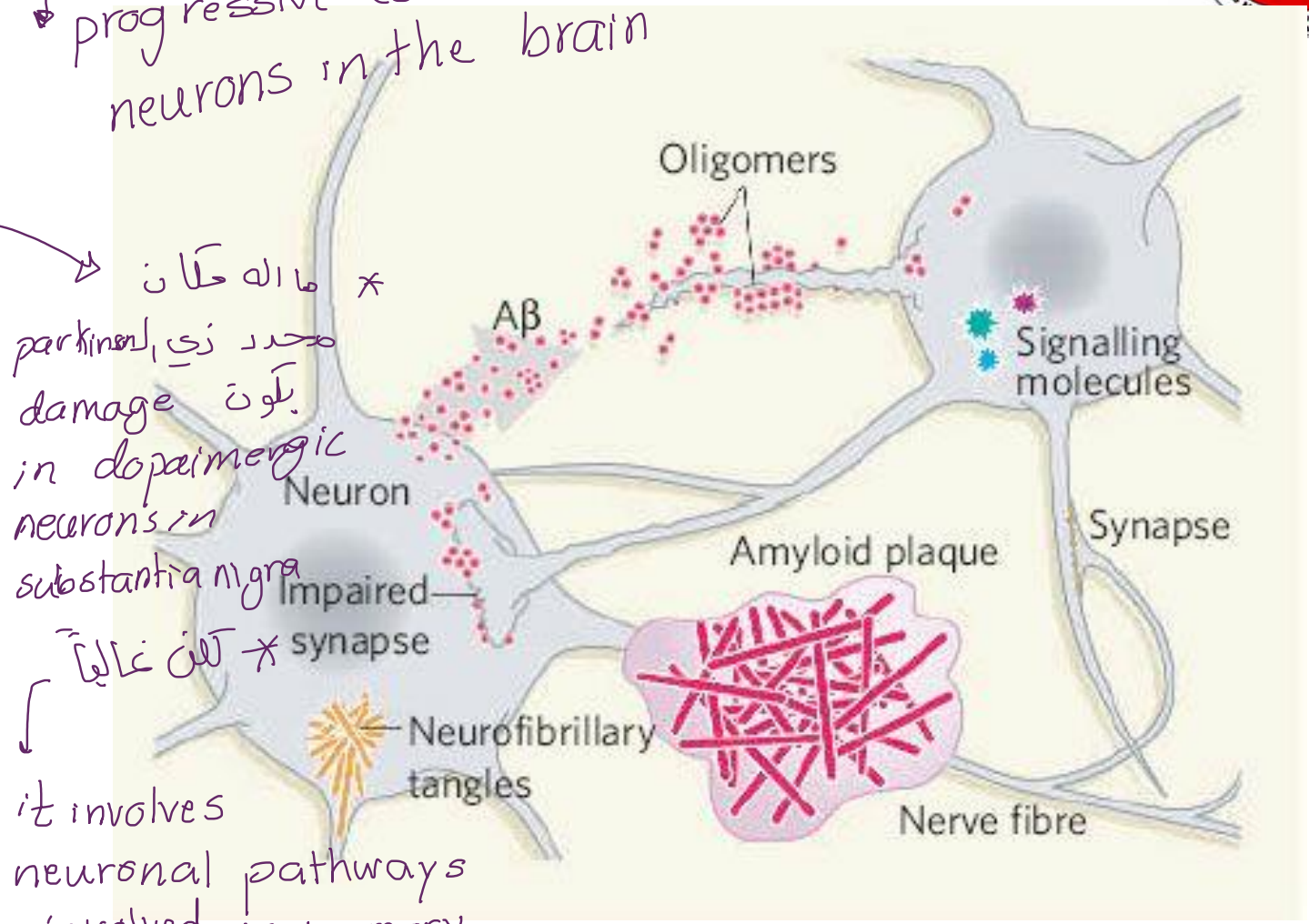
"parkinson's + Alzheimer's"

progressive continuous damage of neurons in the brain

* مالة حكان محدد زي parkinson بكون damage in dopaimergic neurons in substantia nigra

* كتير غالبا

it involves neuronal pathways involved in memory



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Alzheimer's Disease: Pathophysiology

- Dementia of Alzheimer's disease has three distinct features:

1. Accumulation of senile plaques (β-amyloid accumulations)
2. Formation of numerous neurofibrillary tangles
3. Loss of cortical neurons (cholinergic neurons)

↳ is toxic and leads to neuronal damage

Alzheimer's Disease

Strategy of therapy

1. **Improve brain cholinergic transmission**
2. **Reduce glutamate-NMDA-induced excitotoxicity**

1. glutamate is the most predominant excitatory NT in the CNS
2. glutamate binds to two main receptors NMDA, AMPA
3. overstimulation with glutamate signaling can actualy produce cell death within the neurons WHY!
4. The NMDA receptors
   ↙
   ligand-gated ca^{+2} channel

   when glutamate binds to NMDA Receptors it facilitate the entry of ca^{+2} ions inside the cell
5. massive ca^{+2} influx inside any cell ⟶ lead to indiction of apoptosis

So we can oppose this action by using glutamate antagonist to decrease the neuronal destruction.

6. this called ⟶ antagonism of excitotoxicity

Drugs Used in Alzheimer's Disease

- Acetylcholinesterase inhibitors

❑Donepezil

❑Galantamine

❑Rivastigmine

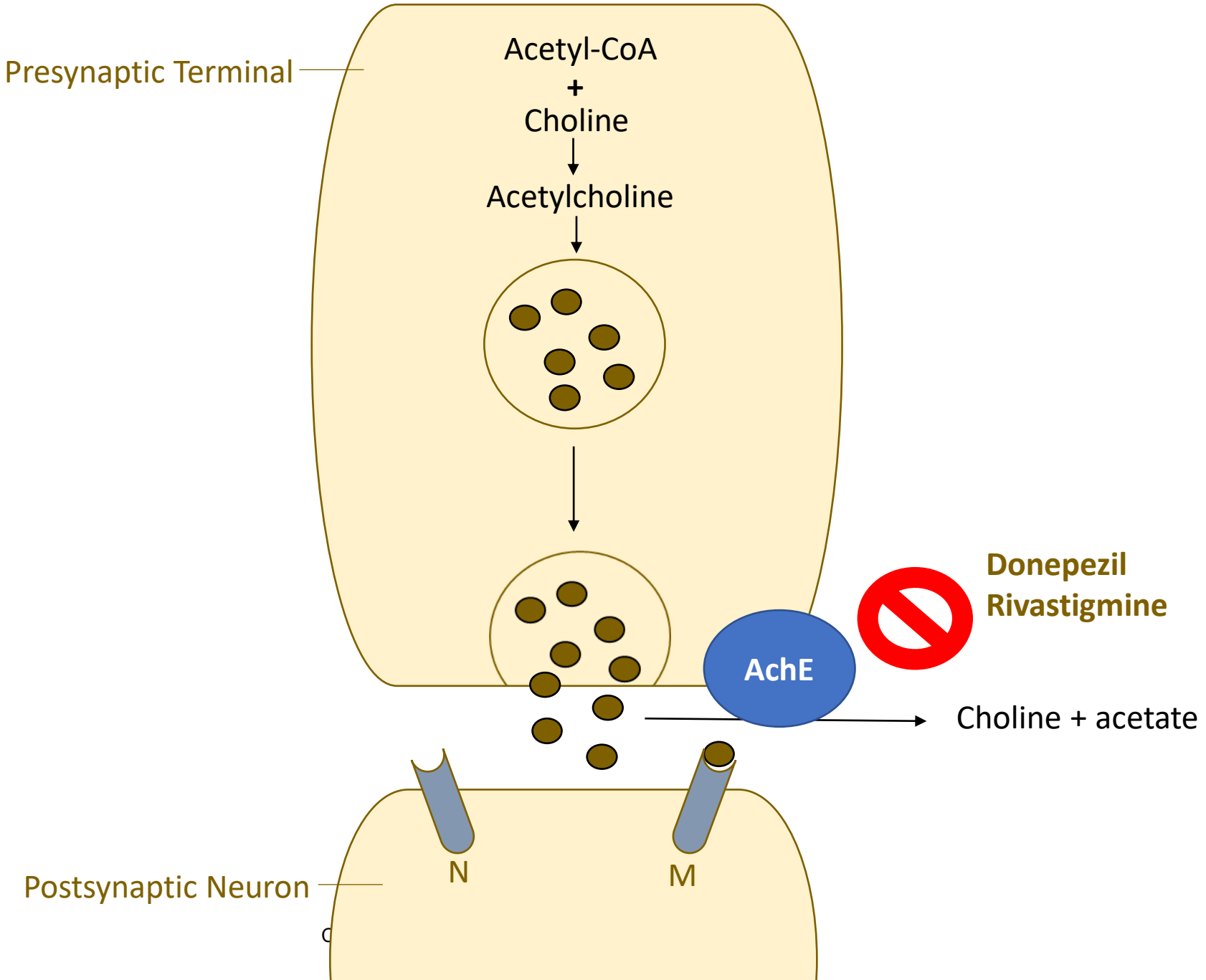
- NMDA receptor antagonists

❑Memantine

Acetylcholinesterase Inhibitors

Mechanism of action:

- hallmark of the disease: Progressive loss of cortical cholinergic transmission participates in Alzheimer's disease-associated dementia.
- Inhibition of acetylecholinesterase (AchE) → improve cholinergic transmission.



Acetylcholinesterase Inhibitors

* symptomatic treatment
* do not prevent the progression of the disease (the distruction of neurons will be continued

Therapeutic uses:

The reversible AchE inhibitors (Donepezil, galantamine and rivastigmine) are approved for the treatment of *mild* to *moderate* Alzheimer's disease.

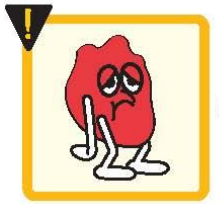
- These drugs provide a modest reduction in rate of loss of cognitive function in Alzheimer patients.
- Rivastigmine is the ONLY agent approved for the management of dementia associated with Parkinson's disease.
- Rivastigmine is the ONLY agent available as a transdermal patch.

Acetylcholinesterase Inhibitors

Adverse effects

1. Nausea
2. Diarrhea
3. Vomiting
4. Anorexia
5. Tremors
6. Bradycardia
7. Muscle cramps


Tremors


Bradycardia


Nausea


Diarrhea

Anorexia


Myalgia

2 NMDA Receptors Antagonists

Mechanism of action:

- Overstimulation of NMDA glutamate receptors in the brain→ increases intracellular calcium → neurodegenerative or apoptotic loss of neurons (excitotoxicity)

NMDA Receptors Antagonists

Therapeutic uses

- Memantine is an NMDA receptors antagonist approved for the treatment of *moderate* to *severe* Alzheimer's disease.
- Memantine is often given in combination with an AchE inhibitor to treat Alzheimer’s disease.

Treatment of Alzheimer's Disease

- Pharmacotherapy of Alzheimer's disease is symptomatic.
- The standard care includes AchE inhibitors + a NMDA antagonist.
- They both provide modest, short-term benefits but do NOT alter the underlying neurodegenerative process.

course of dz ← ما بغيروا الـ

Future alternatives for the treatment of Alzheimer's Disease

- **Cholesterol-lowering agents**: statins
- **Insulin sensitizers**: PPAR-γ agonists (Rosiglitazone) (it sensitizes tissue to insulin and alters apolipoprotein E gene expression → ↑ break-down of β-amyloid).
- **Intranasal insulin** (insulin crosses BBB from the nasal mucosa via transport from the olfactory receptor cells in the roof of the nasal cavity as patients with AD have lower insulin levels in CSF and higher plasma insulin levels)
- **NSAIDs**: low dose aspirin, celecoxib

Future alternatives for the treatment of Alzheimer's Disease

Experimental disease-modifying drugs:

1. • Amyloid lowering agents: Semagacestat
2. • Drugs interfering with amyloid-β deposition: Tramiprosate
3. • Drugs increasing amyloid-β clearance: anti-amyloid antibodies
4. • Drugs interfering with tau deposition: Li+ small dose, valproate, methylene blue

Antidepressants

→ mental health disorder

Pharmacology and Toxicology

Central Nervous System Module

Third Year Medical Students

Tareq Saleh

Faculty of Medicine

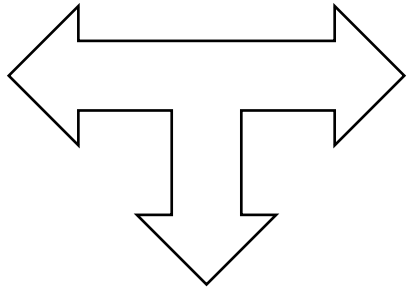
The Hashemite University

Mood Disorders

Mood disorders

1 Major depressive disorder

- 2 weeks of at least 5 of the following symptoms:
  - Depressed mood
  - *Anhedonia* (diminished interest or loss of pleasure in almost all activities)
  - Weight change or appetite disturbance
  - Sleep disturbance (insomnia or hypersomnia)
  - Psychomotor agitation
  - Fatigue or loss of energy,
  - Feelings of worthlessness, diminished ability to think or concentrate;
  - suicidal ideation or a suicide attempt



Others

2 Bipolar disorder

- periods of prolonged depression that alternate with periods of an excessively elevated mood (mania)
- Manic episodes: 1 week of at least 3 of the following symptoms:
  - Grandiosity الشعور بالعظمة .
  - Diminished need for sleep-excessive talking or pressured speech
  - Racing thoughts or flight of ideas-distractibility
  - Increased level of goal-focused activity at home, at work, or sexually
  - excessive pleasurable activities

Pathophysiology of Depression

- NOT fully understood.

Monoamine Theory of Depression:

- norepinephrine (NE), dopamine (DA) & serotonin (5-HT) are neurotransmitters responsible for mood.
- Depression is due to a deficiency in monoamines such as NE and 5-HT.

Very simplistic----fails to explain the long time course of most antidepressants.

Treatment of Depression

Classes of antidepressants

1. • Selective serotonin reuptake inhibitors (SSRIs)
2. • Serotonin/norepinephrine reuptake inhibitors (SNRIs)
3. • Tricyclic antidepressants (TCAs)
4. • Atypical antidepressants
5. • Monoamine oxidase inhibitors (MAOIs)
6. • Serotonin-Dopamine Activity Modulators (SDAMs)

1 Selective Serotonin Reuptake Inhibitors (SSRIs)

the most common

SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIs)
Citalopram CELEXA
Escitalopram LEXAPRO
Fluoxetine PROZAC
Fluvoxamine LUVOX CR
Paroxetine PAXIL
Sertraline ZOLOFT

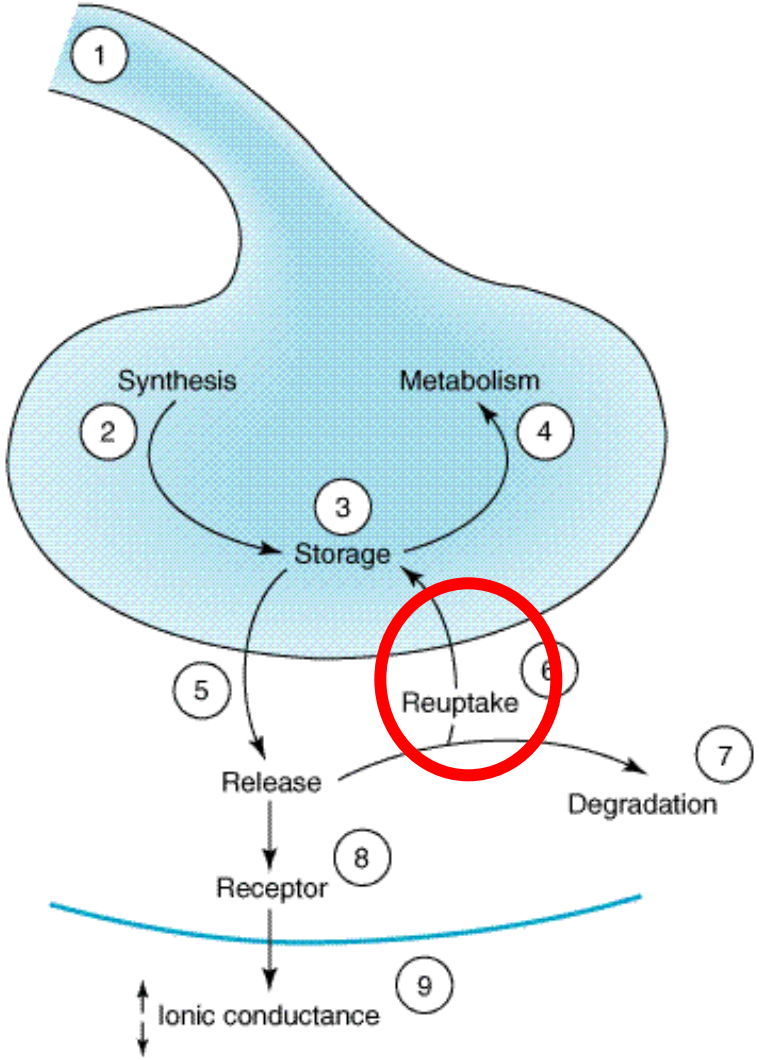
Selective Serotonin Reuptake Inhibitors (SSRIs)

Mechanism of action

- SSRIs block the reuptake of serotonin →increase its concentrations in the synaptic cleft.

	DRUG	UPTAKE INHIBITION	
		Nor-epinephrine	Serotonin
1.	Selective serotonin reuptake inhibitor	×	✓
	Fluoxetine	0	++++
2.	Selective serotonin/ norepinephrine reuptake inhibitors	✓	✓
	Venlafaxine	++*	++++
	Duloxetine	++++	++++
3.	Tricyclic antidepressants	<more>	
	Imipramine	++++	+++
	Nortriptyline	++++	++

Sites and Mechanisms of CNS Drug Action



NT reuptake:

•Antidepressants

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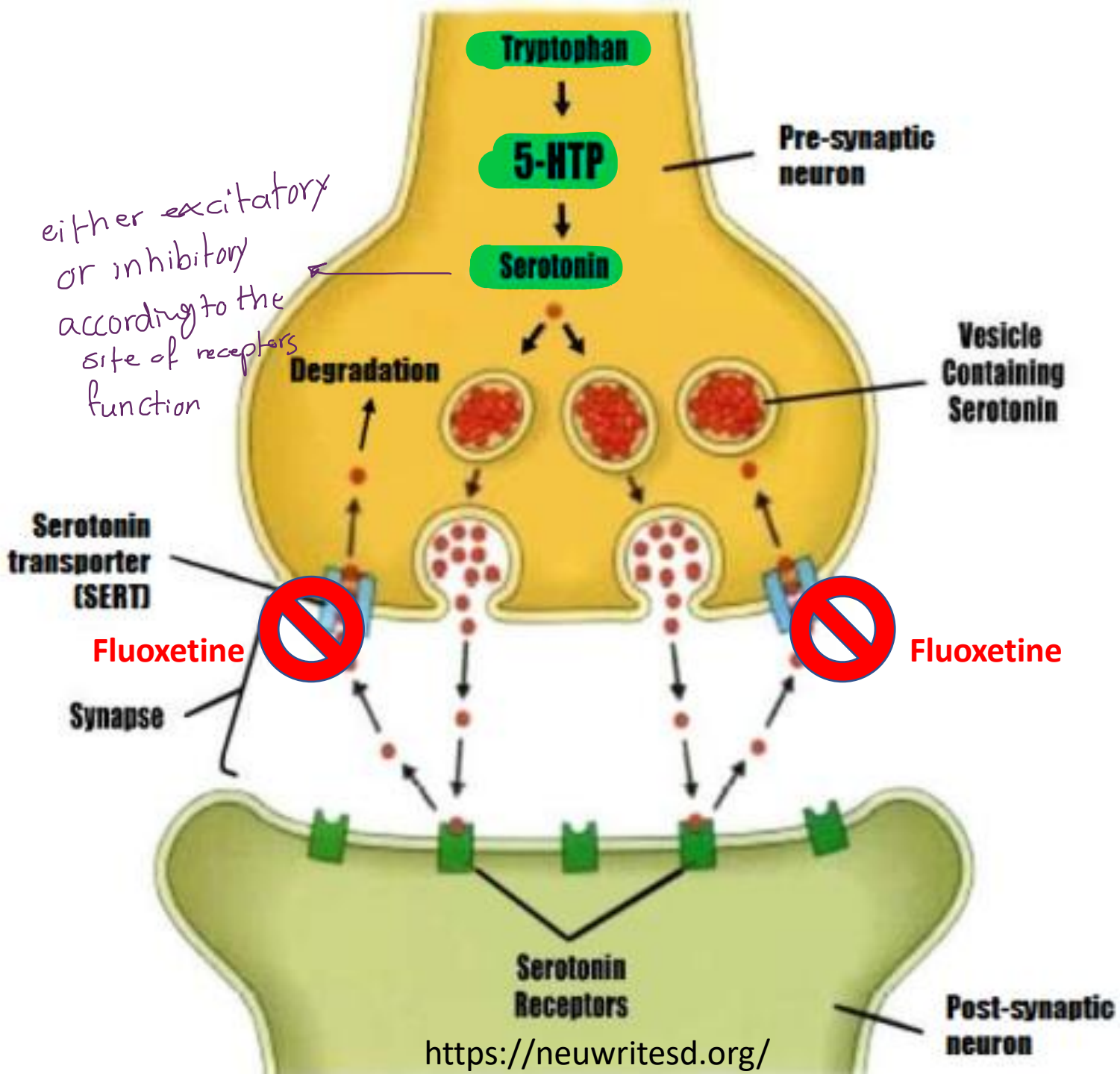
Selective Serotonin Reuptake Inhibitors (SSRIs)

- Fluoxetine inhibits SERT and interferes with serotonin reuptake.
- This results in increased serotonin availability in the synaptic cleft.



Selective Serotonin Reuptake Inhibitors (SSRIs)

Therapeutic uses

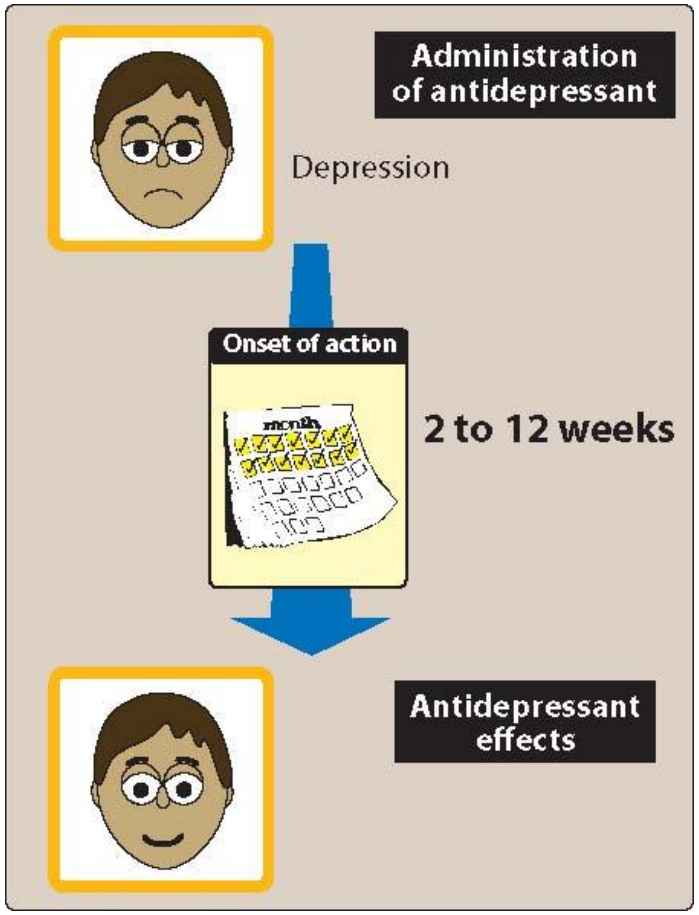
1. • **Depression** (The primary indication)
   - Obsessive Compulsive disorder (OCD)
   - Panic disorder
   - Generalized anxiety disorder
   - Social anxiety disorder
   - Post-traumatic stress disorder
   - Premenstrual dysphoric disorder

2. anxiety disorders.

3. • Bulimia Nervosa (*Only fluoxetine*)
   - ↳eating disorder

Therapeutic Effect

- SSRIs require 2 weeks to establish a significant alteration in mood (up to 12 weeks and more).



Selective Serotonin Reuptake Inhibitors (SSRIs)

Pharmacokinetics

- **Oral.**

  - Food has little impact on their absorption (*except for sertraline, for which food increases its absorption*).

- **Metabolized by CYP450 enzyme family**

  - fluoxetine differs from the other members of the family in that it has a much longer half life (~50 hours), and the half life of its metabolite can be longer than 10 days.

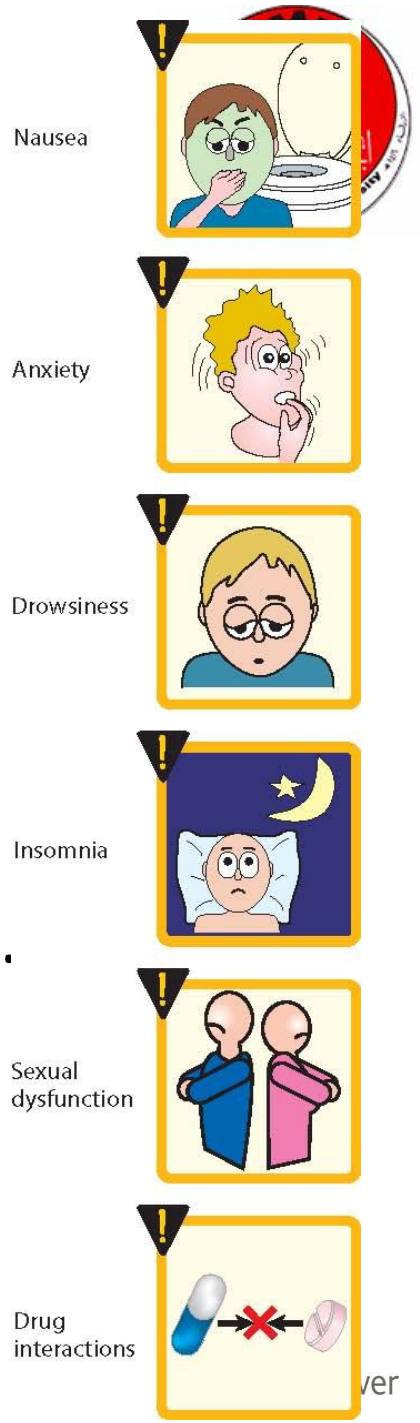
  - fluoxetine and paroxetine are a potent inhibitors of *CYP2D6*

↳ drug-drug interactions

Selective Serotonin Reuptake Inhibitors (SSRIs)

Adverse effects

- **Headache, sweating, nausea, vomiting and diarrhea**.
- **Sleep disturbances:** according to pt
  - -*Paroxetine* and *fluvoxamine* are sedative for (insomina)
  - -*Fluoxetine* and *sertraline* are more activating for (to hypersomnia)
- **Sexual dysfunction**: loss of libido, delayed ejaculation, anorgasmia.
  - Very common
  - Could require switching to another family of antidepressants



Selective Serotonin Reuptake Inhibitors (SSRIs)

Adverse effects

- **Overdose**: "*serotonin syndrome*" especially when used with another MAOi (includes seizures, hyperthermia, muscle rigidity, sweating, myoclonus, …)
- **Discontinuation syndrome**: occurs due to abrupt withdrawal (sudden stop of drug) (includes headache, malaise, flu-like symptoms, irritability, nervousness, sleep disturbances).

❑ Particularly by the agents with the shorter half-lives.

❑ SSRIs should be discontinued gradually.

Use of SSRIs in Children/Adolescents

- Used with caution.

[reports of suicidal ideation]

- ❑ Fluoxetine and escitalopram are approved to treat childhood depression.
- ❑ Fluoxetine, fluvoxamine and sertraline are approved to treat OCD in children

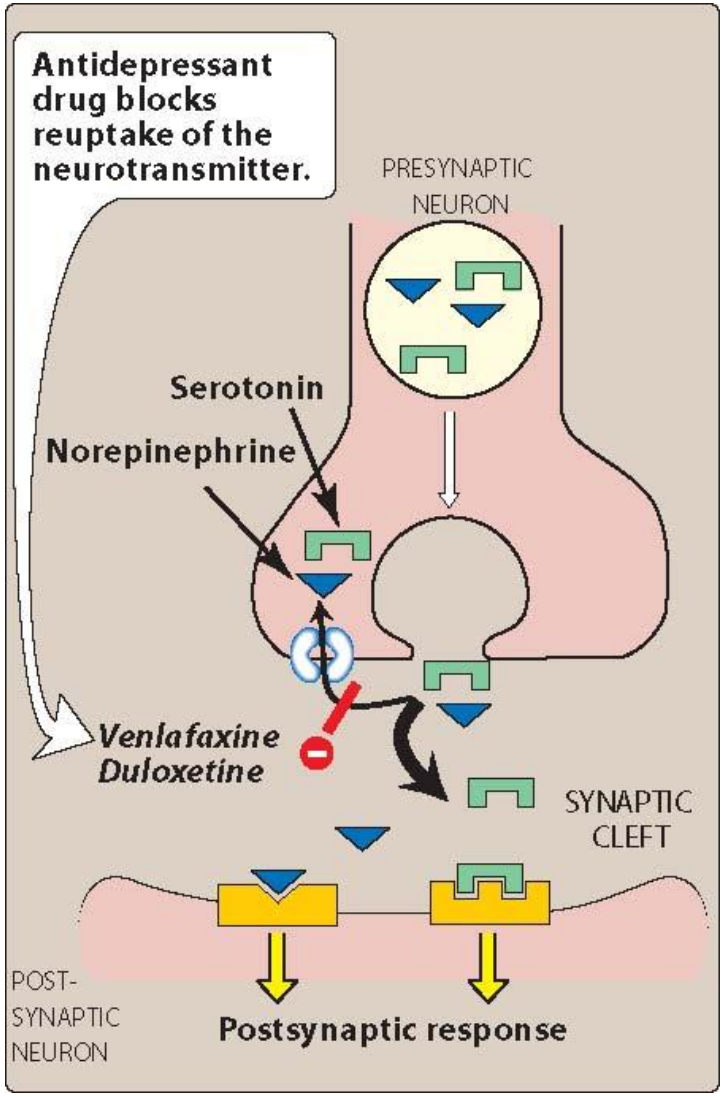
2 Serotonin/Norepinephrine Reuptake Inhibitors (SNRIs)

SEROTONIN/NOREPINEPHRINE REUPTAKE INHIBITORS (SNRIs)
Desvenlafaxine PRISTIQ
Duloxetine CYMBALTA
Levomilnacipran FETZIMA
Venlafaxine EFFEXOR

Serotonin/Norepinephrine Reuptake Inhibitors (SNRIs)

Mechanism of action

- SNRIs inhibit the reuptake of BOTH serotonin and norepinephrine



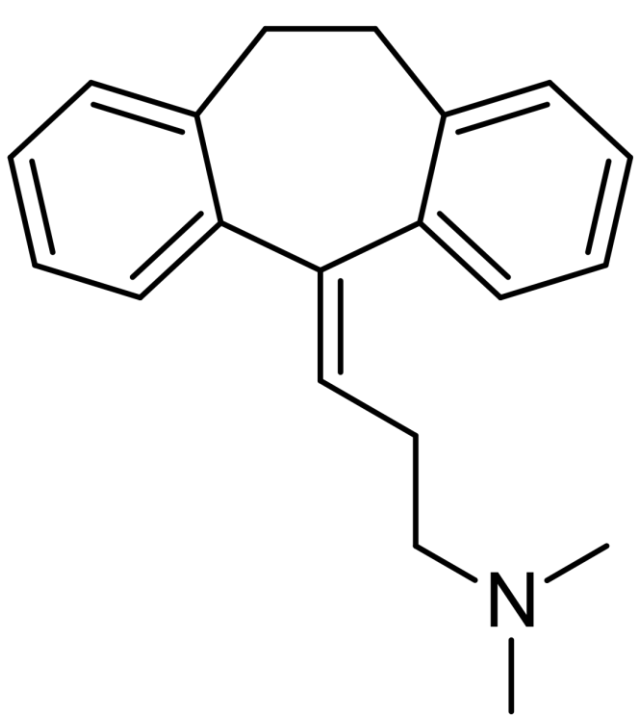
Serotonin/Norepinephrine Reuptake Inhibitors (SNRIs) 2nd line

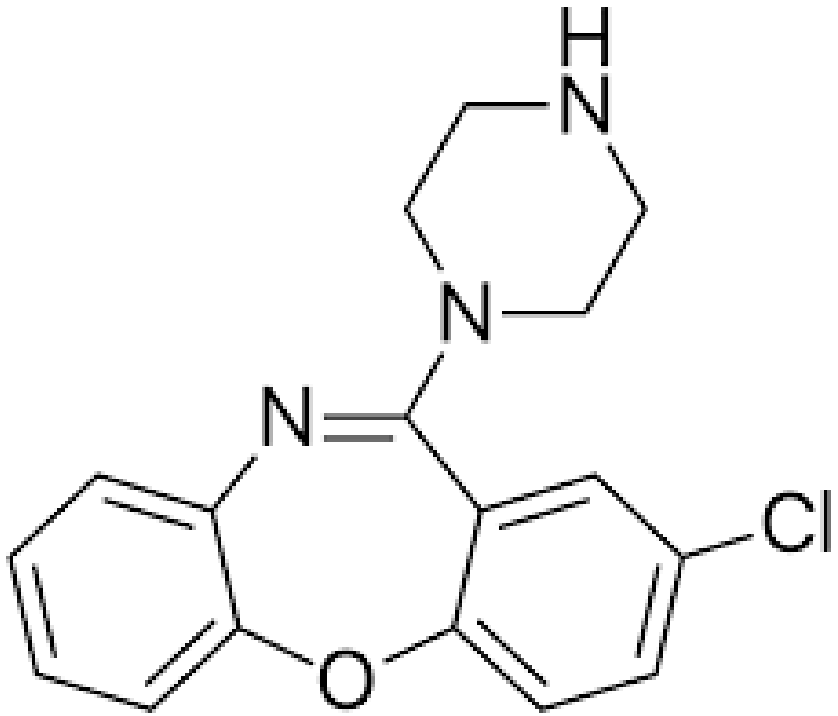
Therapeutic uses

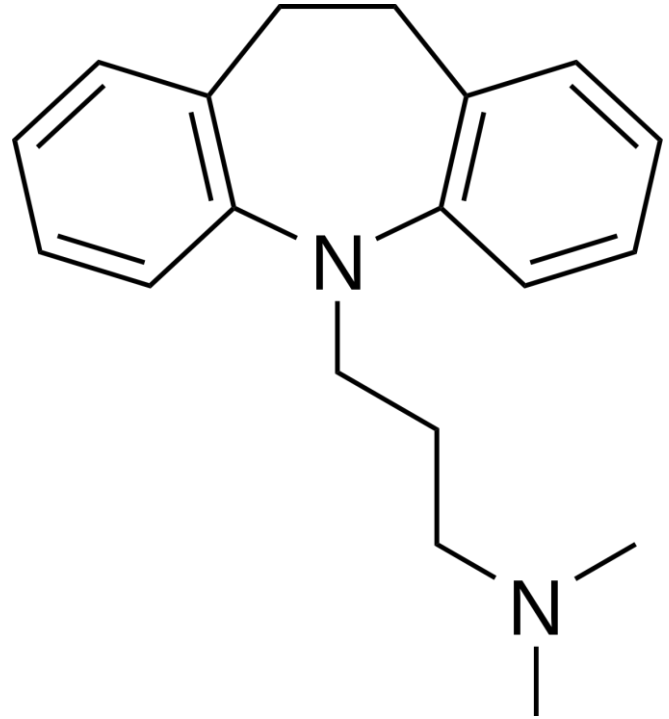
[first line]

1. **Depression** (when SSRIs are ineffective).
2. **Depression accompanied by a chronic painful condition.**
3. **Neuropathic Pain** (diabetic neuropathy, postherpetic neuralgia, fibromyalgia, etc.…)

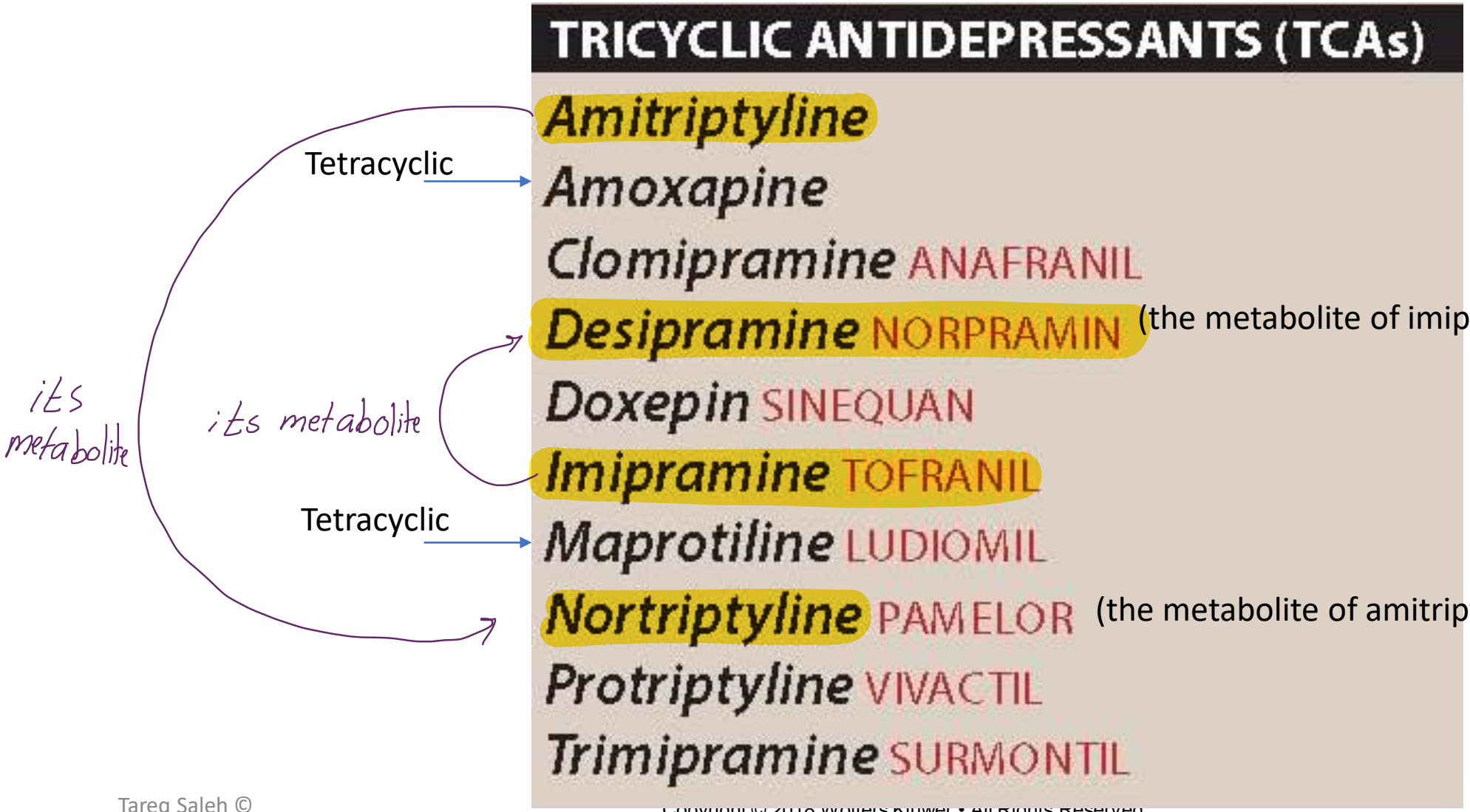
8 Tricyclic Antidepressants (TCAs)







Tricyclic Antidepressants (TCAs)



*all are tricyclic except amoxapine and maprotiline are tetracyclic

Tricyclic Antidepressants (TCAs)

Mechanism of action

- **Inhibition of neurotransmitter** (NE and 5-HT) **reuptake**:
- **Receptor antagonism**:

- TCAs also block serotonergic, α-adrenergic, histaminic and muscarinic receptors.

- Amoxapine also blocks 5-HT_2 and dopamine D_2 receptors.

many of the side effects of TCAs result from this non-selective receptor antagonism.

لذلك تم استبدالهم بـ SSRI

Tricyclic Antidepressants (TCAs)

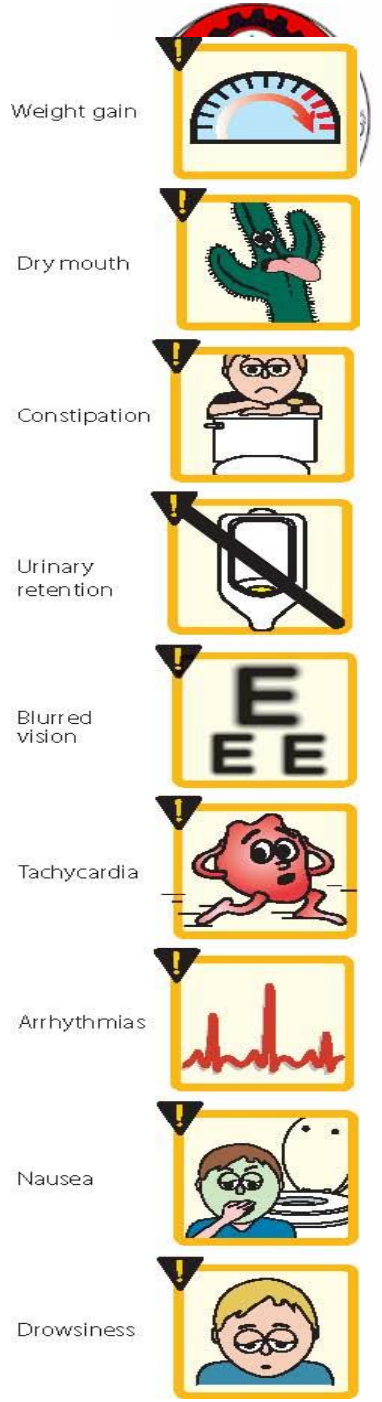
Therapeutic uses

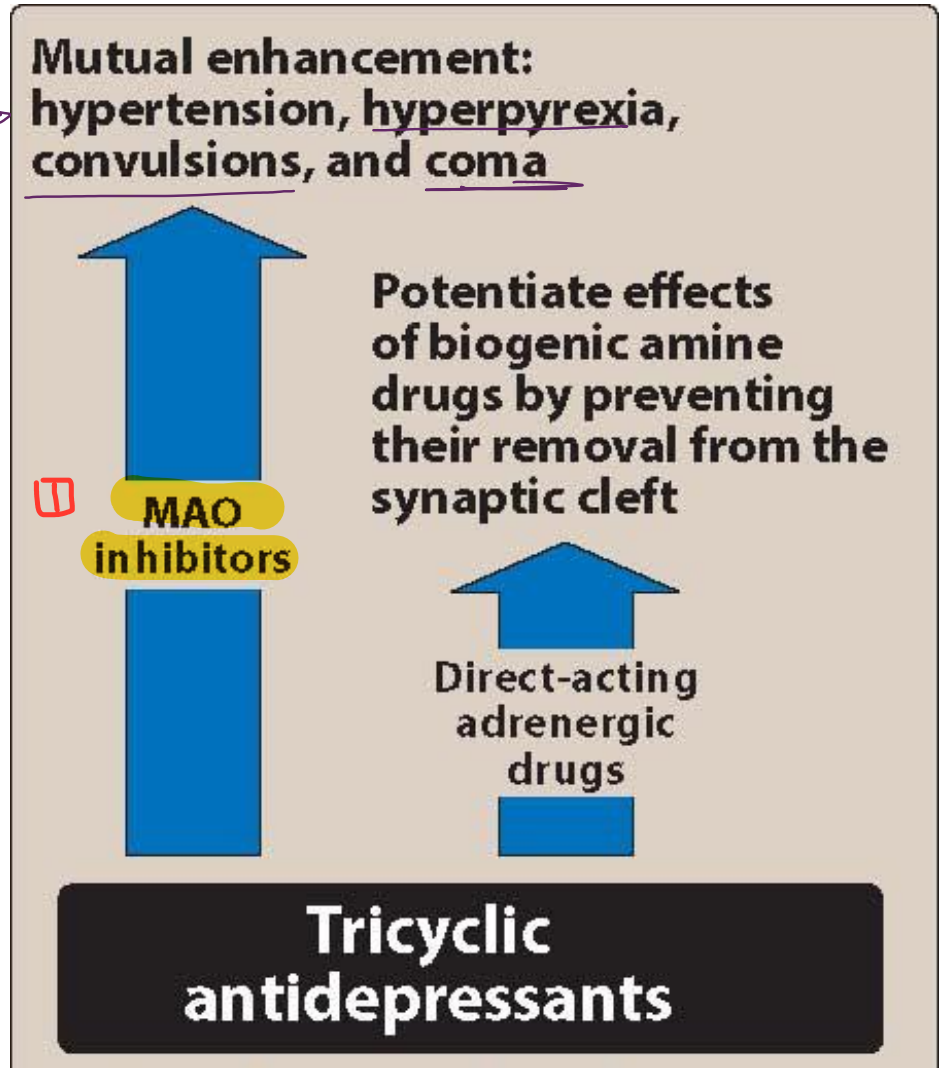
1. • **Moderate to severe depression**
2. • Panic disorder
3. • Nocturnal enuresis (bedwetting): Imipramine (largely replaced by desmopressin).
4. • Migraine and chronic pain conditions: amitriptyline.
5. • Insomnia: doxepin.

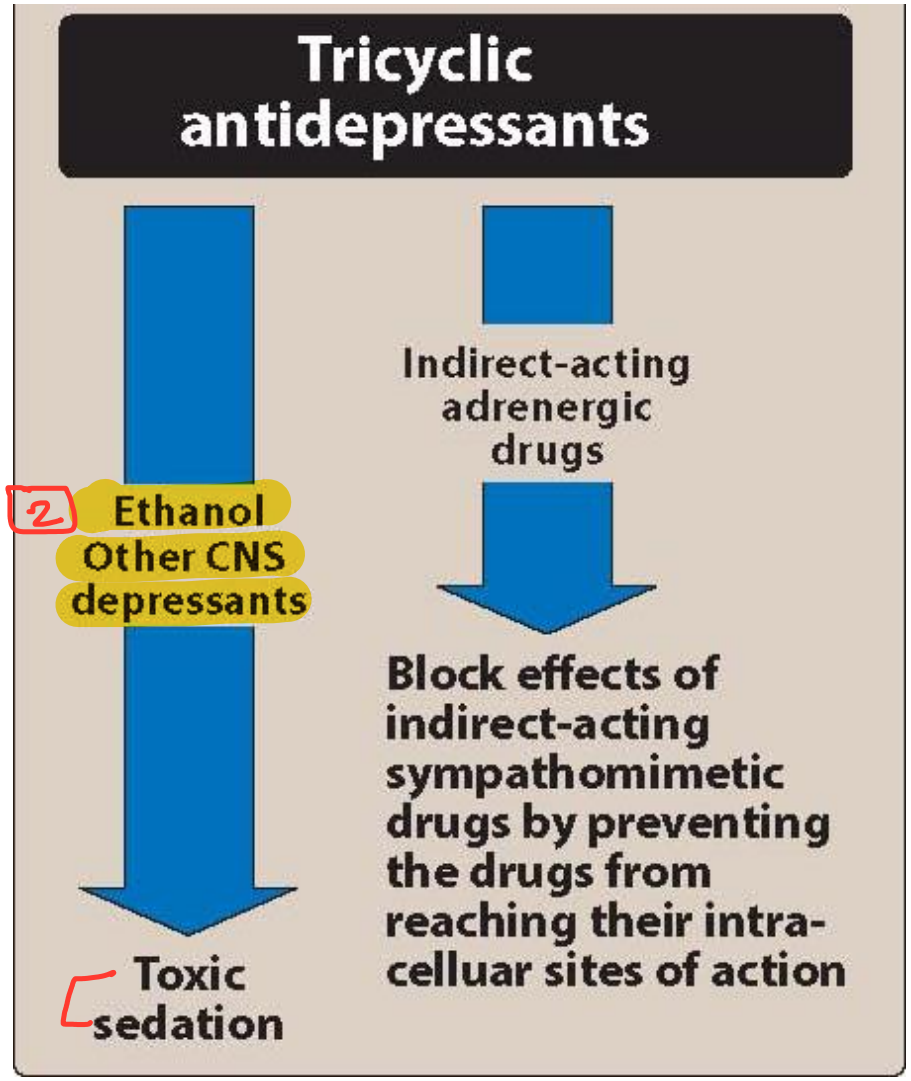
Tricyclic Antidepressants (TCAs)

Adverse effects

- **Muscarinic blockade:** blurred vision, xerostomia, urinary retention, sinus tachycardia, constipation and aggravation of angle-closure glaucoma.
- **α-adrenergic blockade:** orthostatic hypotension (imipramine), dizziness and reflex tachycardia.
- **H_1 histamine blockade:** sedation.
- **Overdose:** can be associated with life-threatening cardiac arrhythmias.
- **Sexual dysfunction:** less than SSRIs.







4 Monoamine Oxidase Inhibitors (MAOi)

MONOAMINE OXIDASE INHIBITORS (MAOIs)	
Isocarboxazid	MARPLAN
Phenelzine	NARDIL
Selegiline	EMSAM
Tranylcypromine	PARNATE

1 Non-selective (inhibit both MAO-A and MAO-B)

2 -Selective for MAO-B

-also used for the treatment of Parkinson's disease.

Monoamine Oxidase Inhibitors (MAOi)

The use of MAOi is limited (last line) due to the dietary restrictions required while taking these agents, toxicity and drug-drug interaction.

Monoamine Oxidase Inhibitors (MAOi)

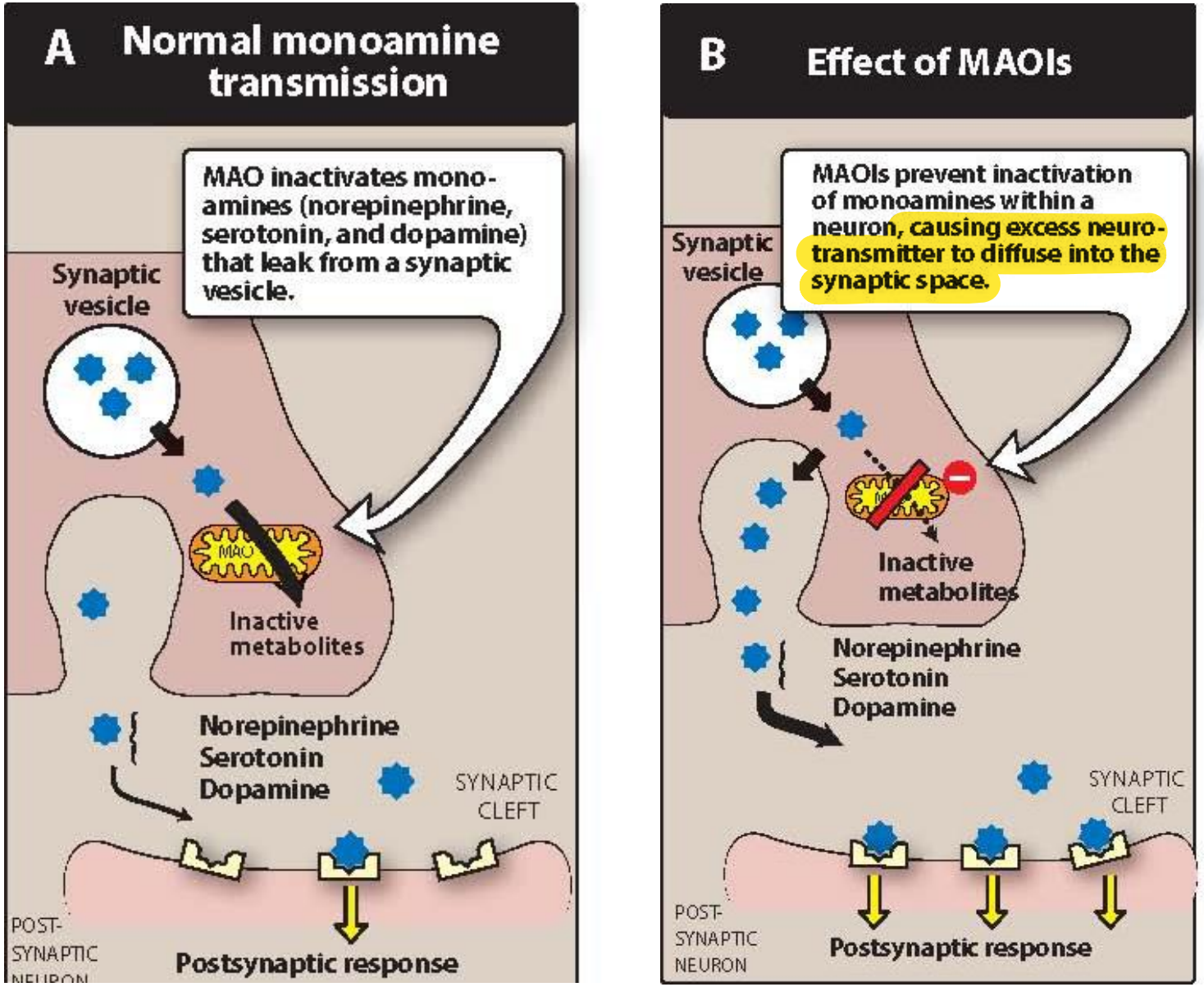
Mechanism of action:

- MAO enzyme exists in 2 forms:

1- MAO-A: responsible for metabolism of NE and 5-HT.

2- MAO-B: more selective for dopamine (DA) metabolism.

- Most MAOis form stable complexes with the enzyme causing irreversible inactivation.
- **Inhibition of MAO results in ↑ NE + 5-HT + DA**



Monoamine Oxidase Inhibitors (MAOi)

Mechanism of action:

- The action of MAOi is delayed for several weeks.

MAOi also interfere with hepatic and intestinal isoforms of the enzyme which accounts for their high drug-drug and food-drug interactions.

Monoamine Oxidase Inhibitors (MAOi)

Therapeutic uses:

- **Last line for the treatment of depression:** for patients who are unresponsive to SSRIs or TCAs.
- **Atypical depression.**

Monoamine Oxidase Inhibitors (MAOi)

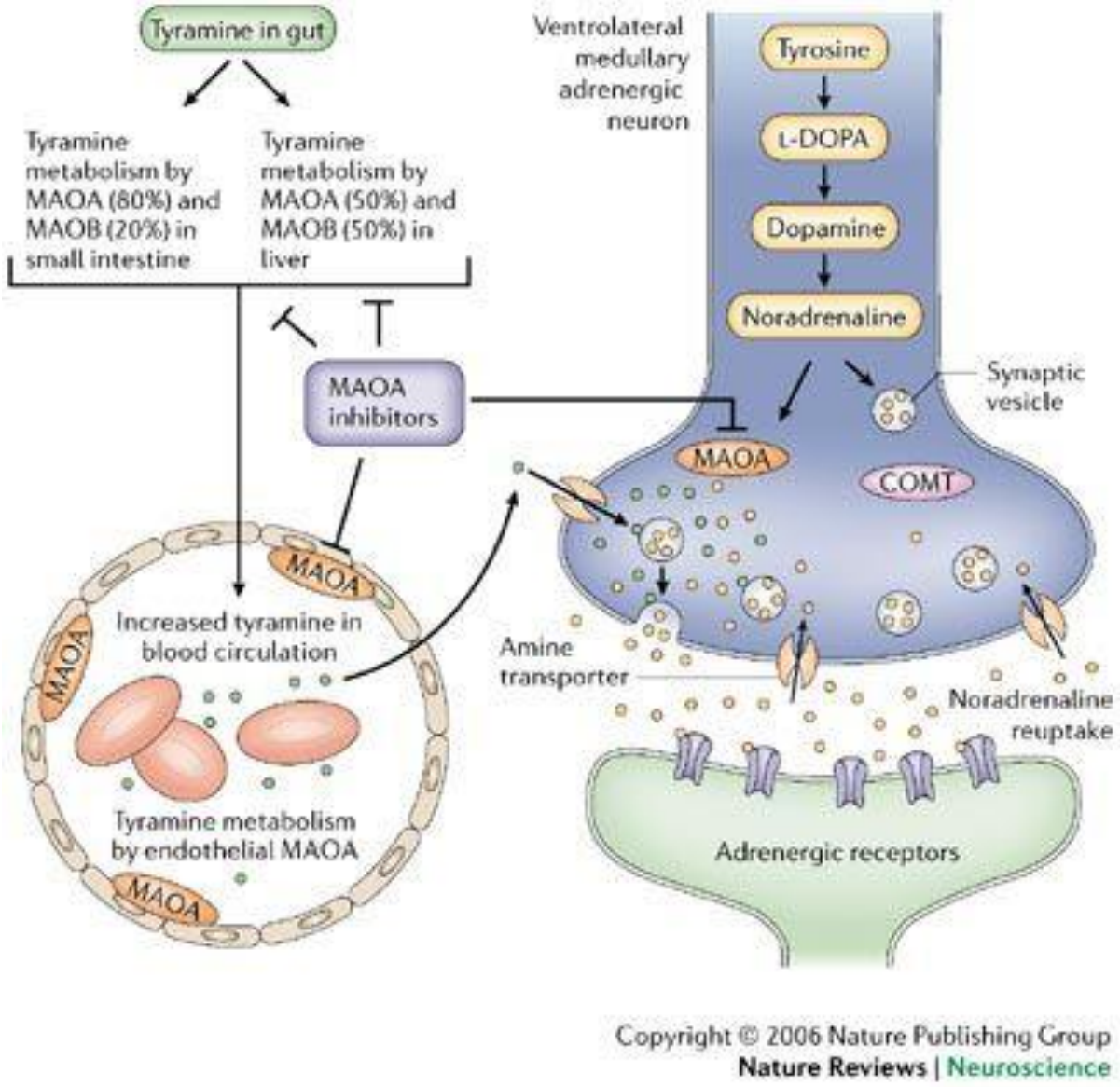
Adverse effects:

- Orthostatic hypotension, insomnia and convulsions.
- Hepatotoxicity (Phenelzine).
- **Serious food (tyramine-rich) and drug interactions.**

Monoamine Oxidase Inhibitors (MAOi)

Tyramine-rich diet and MAOi

- Tyramine is contained in foods such as aged cheese, meats, chicken liver, smoked fish and red wine.
- Tyramine is inactivated by hepatic and intestinal MAOs.
- MAOi interfere with the degradation of dietary tyramine.
- Tyramine accumulation results in the release of large amounts of stored catecholamines→ Hypertensive crisis!!!



Youdim et al, 2006

MAOIs +				
1. Tyramine - rich food ↓ Hypertensive crisis **(Cheese reaction)** *Tyramine in food is metabolized in GIT by MAO-A & MAO-B. MAOIs allow tyramine in tyramine-rich food (old cheese, chicken liver, chocolate) to escape metabolism & release ↑ ↑ ↑ amounts of catecholamines from neurons → hypertensive crisis.*	**2. Cold Remedies** (sympathomimetic) ↓ Hypertensive Crisis.	**3. TCAs** (↑ CA) ↓ -Hypertension -Hyperthermia -Convulsions	**4. Pethidine** ↓ -Respiratory depression -Hyperthermia -Convulsions	**5. SSRIs** (↑ 5HT) ↓ **"Serotonin syndrome":** -Hyperthermia -Convulsions

Monoamine Oxidase Inhibitors (MAOi)

Precautions with MAOi

- Patients on nonselective MAOIs should be warned against serious drug interactions and should be given a list of the foods they should avoid.
- Patients on MAOIs should not receive TCAs or SSRIs except after 2 weeks from stopping MAOIs (effect persists for 2 weeks or 6 for fluoxetine).
- Avoid in the elderly because of postural hypotension.

Atypical antidepressants

ATYPICAL ANTIDEPRESSANTS	
Bupropion	WELLBUTRIN, ZYBAN
Mirtazapine	REMERON
Nefazodone	
Trazodone	DESYREL
Vilazodone	VIIBRYD
Vortioxetine	BRINTELLIX

Bupropion

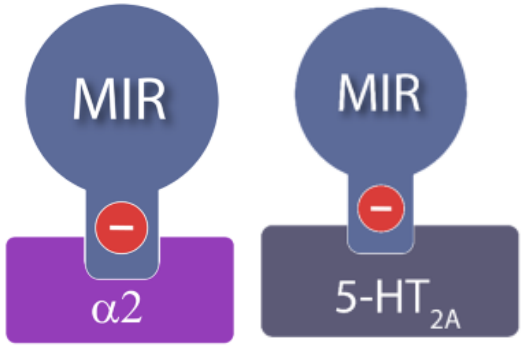
- **Mechanism of action**: Weak DA and NE reuptake inhibitor
- **Therapeutic uses:** Depression and smoking cessation (reduces cravings and attenuates nicotine withdrawal symptoms.
- **Adverse effects:** associated with a dose-dependent increased risk for seizures.

  -----*it has a very low incidence of sexual dysfunction.*

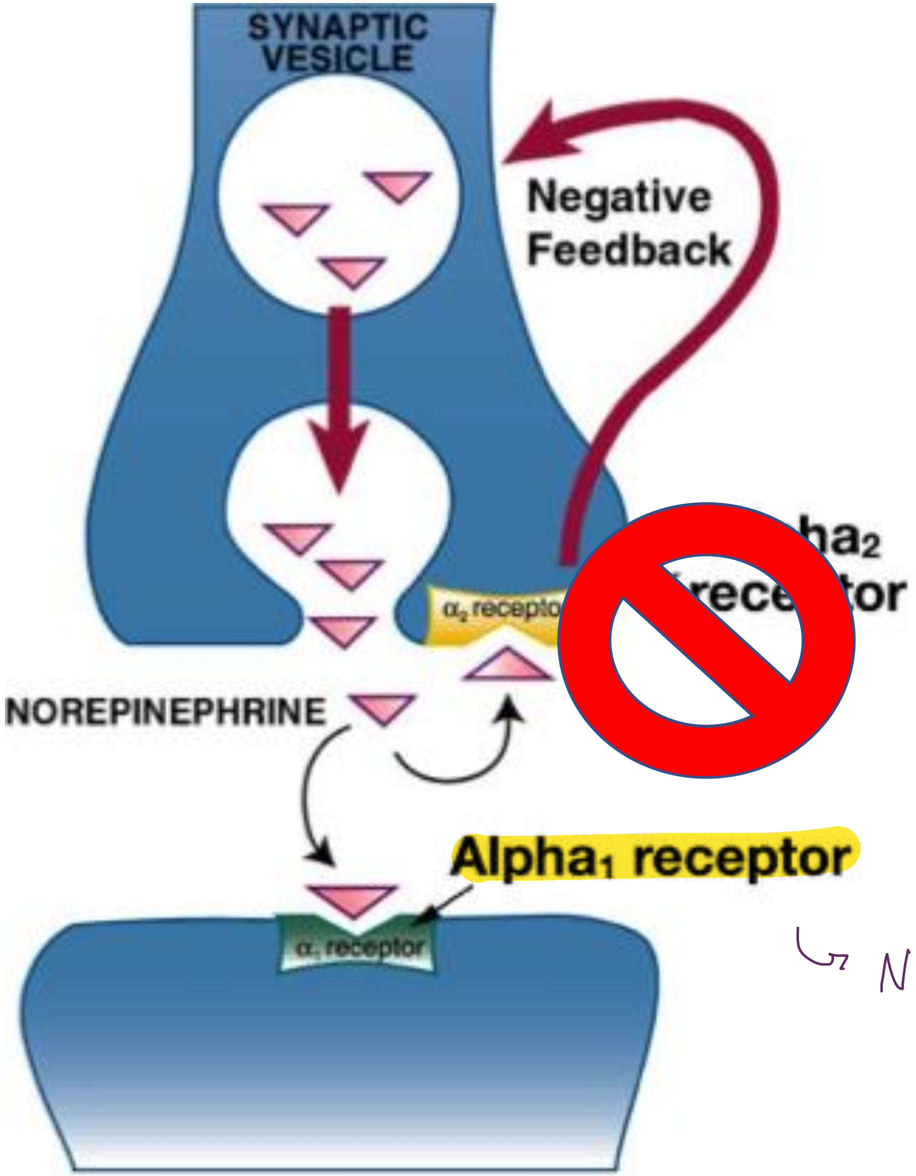
used as alternative to SSRI

Mirtazapine

- **Mechanism of action**: presynaptic α_2 antagonist and partially due to 5-HT_2 antagonism (enhances serotonin and norepinephrine neurotransmission)



- **Therapeutic uses:**
  1) -patients intolerant to TCAs or SSRIs.
  2) -sedating antidepressant improve insomnia
- **Advantages:** No sexual dysfunction, nausea, anxiety of SSRIs.



Mirtazapine

↩ NE يرتبط فيه ال

Other atypical antidepressants

- **Nefazodone and trazodone**: weak serotonin reuptake inhibitors + 5-HT_{2a} antagonists + H_1-blocking + α_1 antagonism
- **Vilazodone**: serotonin reuptake inhibitor + 5-HT_{1a} partial agonism
- **Vortioxetine**: serotonin reuptake inhibitor + 5-HT_{1a} agonism + 5-HT_3 and 5-HT_7 antagonism

Novel therapies

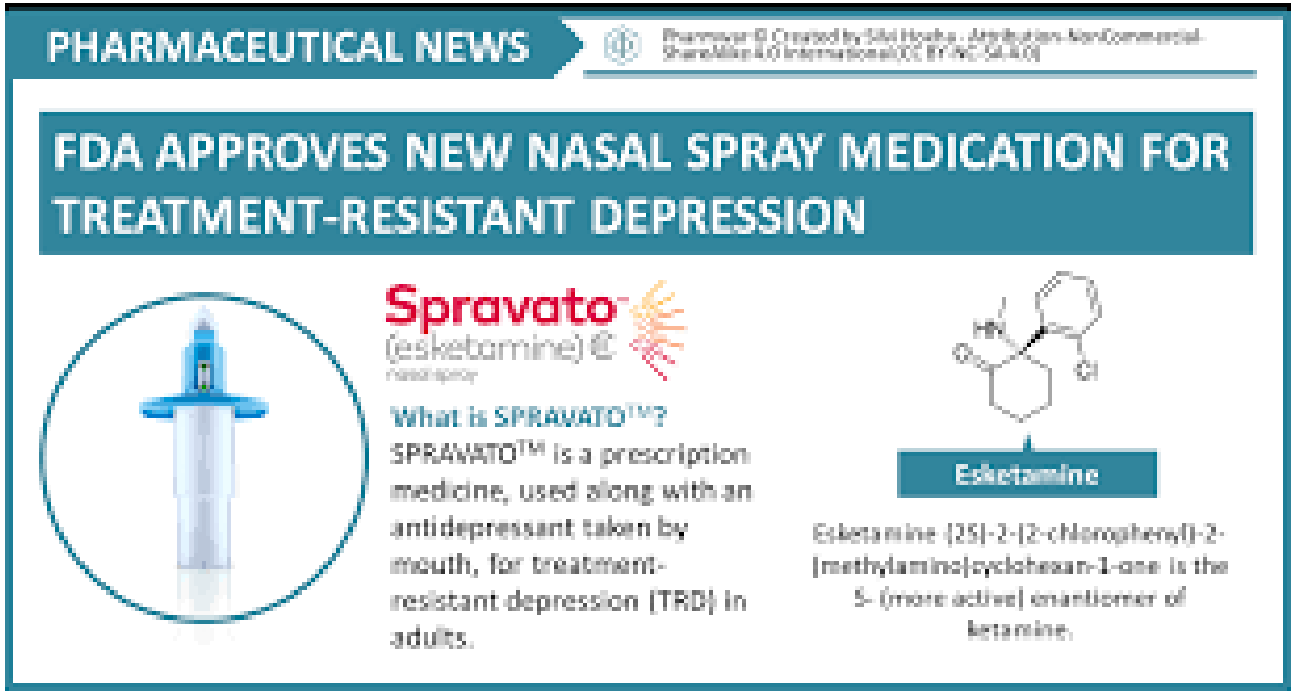
- Brexpiprazole.
- Serotonin-dopamine activity modulator.
- Reading assignment:

https://www.ncbi.nlm.nih.gov/pubmed/26849053

Good news?

NMDA receptor antagonists (glutamate antagonist)

- Esketamine (intranasal)



Summary of antidepressants mechanisms of action

Mechanisms of Increase of Biogenic Amines by Antidepressants

Amine Pump Inhibitors	**MAO Inhibitors**	**Presynaptic α_2 Blockers**
Inhibit uptake-I of biogenic amines into neurons resulting in their accumulation in synaptic cleft, potentiating their action at post synaptic receptors.	Inhibit metabolism of biogenic amines by MAO enzyme inside nerve endings → ↑stores available for release.	↑ NA release into synaptic cleft by preventing α_2 auto-inhibition.
Members **1. TCAs** **2. TTAD** **3. SSRI** **4. NSRI** **5. Bupropion**	**Members** **Tranylcypromine** **Phenelzine** **Moclobemide**	**Members** **Mirtazapine**

TCAs: Tricyclic antidepressants **NSRI:** Norepinephrine Serotonin Reuptake Inhibitor

TTADs: Tetracyclic antidepressants **SSRIs:** Selective Serotonin Reuptake Inhibitor.

Drug class used as first-line therapy of major depressive disorder is SSRIs

Consuming aged cheese and meat is contraindicated while on MAOis for the treatment of depression

The antidepressant that interferes with negative feedback inhibition of norepinephrine release is Mirtazapine

How can you manage major depression in patients on SSRI that are suffering from persistent sexual dysfunction?

Switch to atypical antidepressants

Overall Therapeutic Strategy

- The **goal** of initial treatment for depression is symptom remission and restoring baseline functioning.
- The treatment strategy includes *combination of pharmacotherapy and psychotherapy* (based upon randomized trials that found combination treatment was more effective than either of these treatments alone).
- **First line treatment**: SSRIs
- **Alternatives**: second generation antidepressants: SNRIs, atypical antidepressants and serotonin modulators.
- TCAs and MAOis are typically **not** used as initial treatment because of concerns about safety and adverse effects.

Treatment of Bipolar Disorder

Drugs Used to Manage Bipolar Disorder

1 Lithium 1st line

- Used acutely and prophylactically for managing bipolar patients. (effective in 60-80% of patients).
- **Mechanism of action**: Unknown.
- **Pharmacokinetics**:

  - very narrow therapeutic window (highly toxic).

  - entirely eliminated by renal clearance (best choice in patients with hepatic dysfunction)

- **Adverse effects:** headache, xerostomia, polyuria, polydipsia, polyphagia, dermatologic reactions and sedation.
- **Toxicity:** ataxia, slurred speech, confusion, seizures and thyroid dysfunction.

Treatment of Bipolar Disorder

Other drugs

2 • **Antiepileptics:** Carbamazepine, valproic acid and lamotrigine.
(mood stabilizers)

3 • **Antipsychotics:** Chlorpromazine, haloperidol, risperidone, olanzapine, aripiprazole.

- Thank you

- Questions?

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