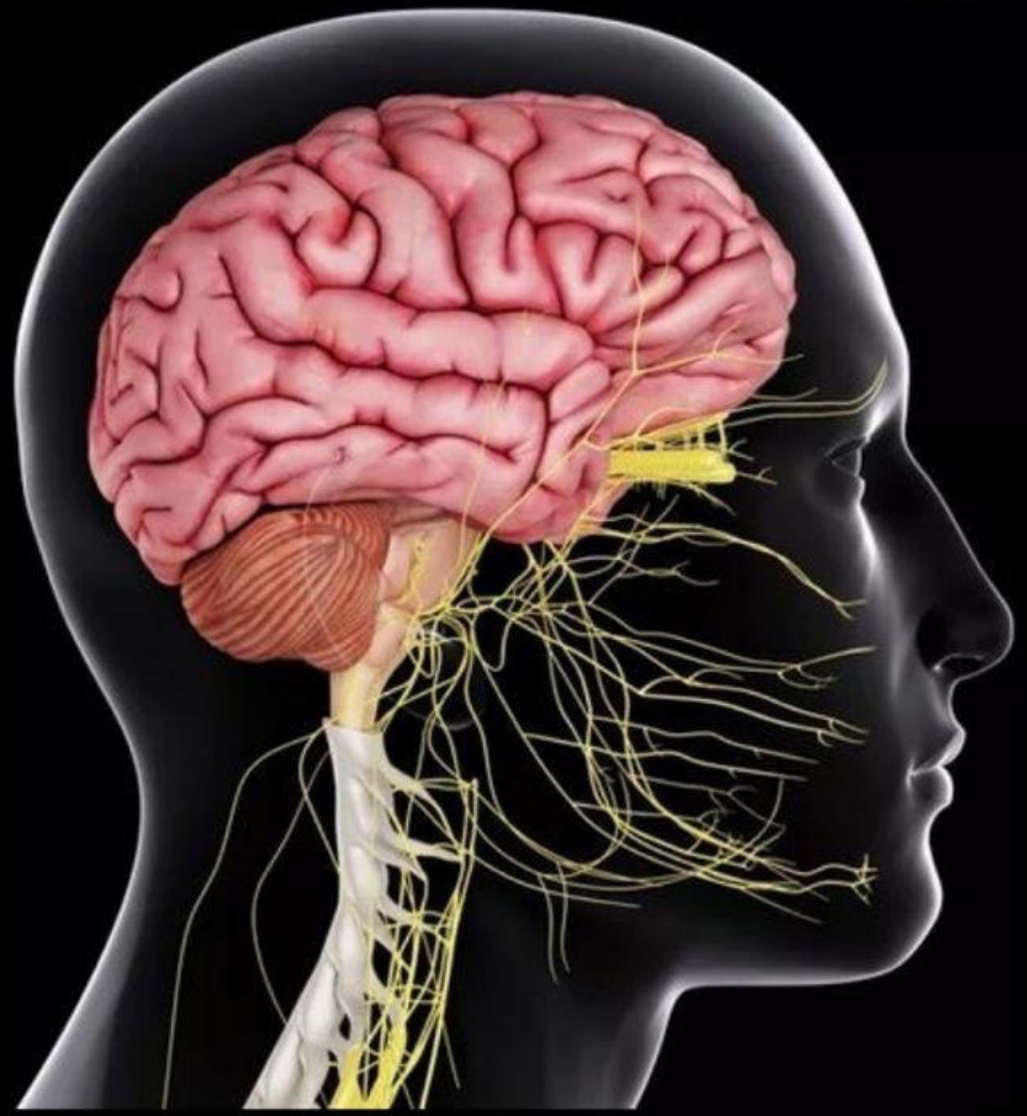
وَقُل رَّبِّ زِدْنِي عِلْمًا



النادي الطبي

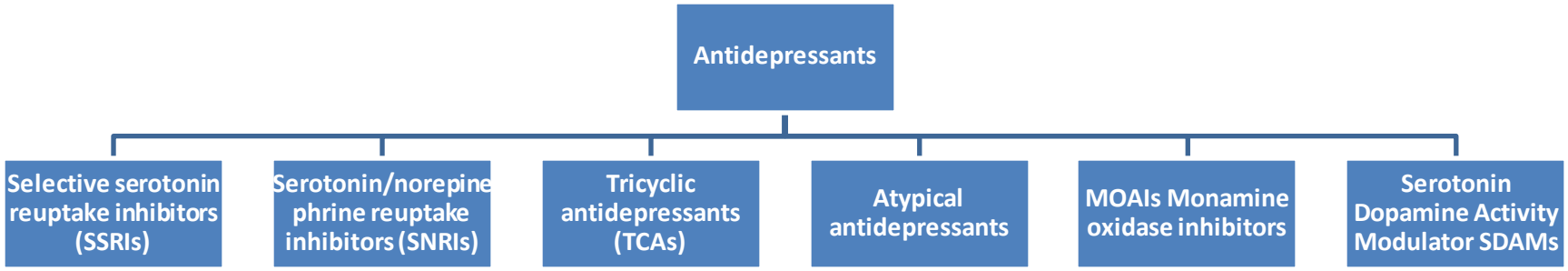
CENTRAL NERVOUS SYSTEM

SUBJECT : Pharma

LEC NO. : Lec 3 antidepressants

DONE BY : Enas wail hantash

Antidepressants



Pathophysiology of Depression

- NOT fully understood.

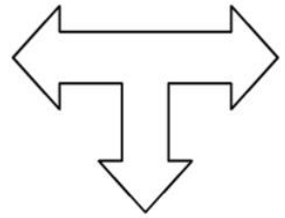
Monoamine Theory of Depression:

- 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.

Mood Disorders

Mood disorders



Others

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

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
  - 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

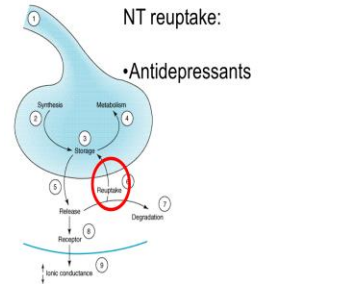
Antidepressants

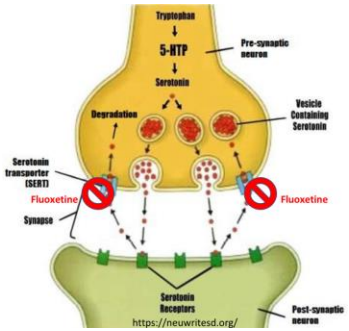
- Selective serotonin reuptake inhibitors (SSRIs)
- Serotonin/norepinephrine reuptake inhibitors (SNRIs)
- Tricyclic antidepressants (TCAs)
- Atypical antidepressants
- MOAIs Monamine oxidase inhibitors
- Serotonin Dopamine Activity Modulator SDAMs

SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIs)

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

Sites and Mechanisms of CNS Drug Action



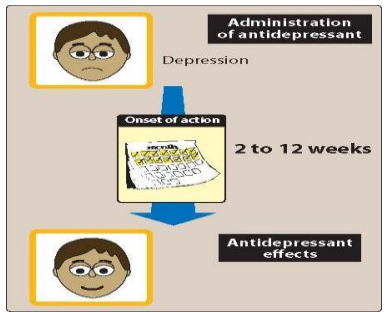


- Fluoxetine inhibits SERT and interferes with serotonin reuptake.
- This results in increased serotonin availability in the synaptic cleft.

Mechanism of action

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

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



Therapeutic uses

- **Depression** (The primary indication)
- Obsessive Compulsive disorder (OCD) ,Panic disorder , Generalized anxiety disorder , Social anxiety disorder , Post-traumatic stress disorder Premenstrual dysphoric disorder , Bulimia Nervosa (*Only fluoxetine*) , SSRIs require 2 weeks to establish a significant alteration in mood (up to 12 weeks and more).

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*

Adverse effects

- **Headache, sweating, nausea, vomiting and diarrhea**.
- **Sleep disturbances:** -*Paroxetine* and *fluvoxamine* are sedative
  -*Fluoxetine* and *sertraline* are more activating.
- **Sexual dysfunction**: loss of libido, delayed ejaculation, anorgasmia. ,,, Very common ,,, Could require switching to another family of antidepressants
- **Overdose**: "*serotonin syndrome*" especially when used with another MAOi (includes seizures, hyperthermia, muscle rigidity, sweating, myoclonus, …)
- **Discontinuation syndrome**: occurs due to abrupt withdrawal (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

Antidepressants

- Serotonin/norepinephrine reuptake inhibitors (SNRIs)
- Tricyclic antidepressants (TCAs)
- Atypical antidepressants
- MOAIs Monamine oxidase inhibitors
- Serotonin Dopamine Activity Modulator SDAMs

SEROTONIN/NOREPINEPHRINE REUPTAKE INHIBITORS (SNRIs)

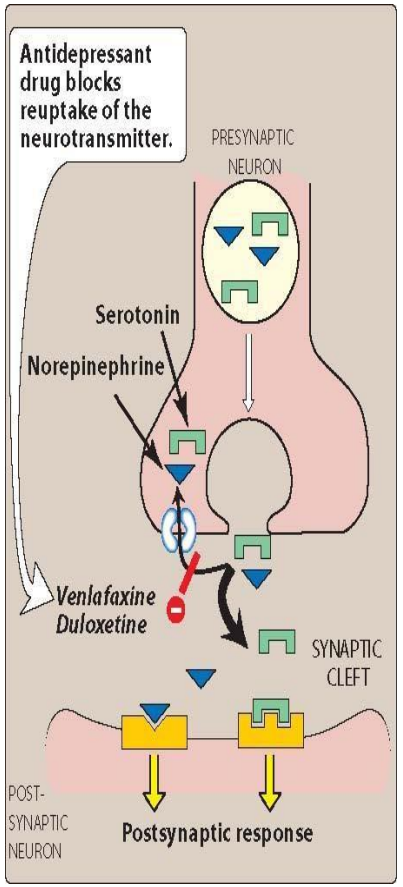
- *Desvenlafaxine* PRISTIQ
- *Duloxetine* CYMBALTA
- *Levomilnacipran* FETZIMA
- *Venlafaxine* EFFEXOR

Mechanism of action

- **SNRIs inhibit the reuptake of BOTH serotonin and norepinephrine**

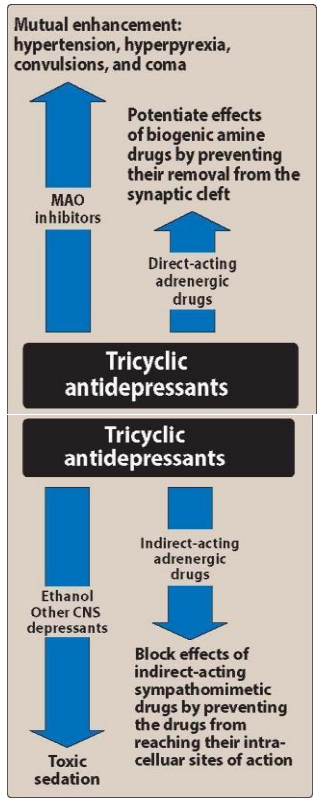
Therapeutic uses

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



TRICYCLIC ANTIDEPRESSANTS (TCAs)

- Tetracyclic: *Amitriptyline*
- Tetracyclic: *Amoxapine*
- *Clomipramine* ANAFRANIL
- *Desipramine* NORPRAMIN (the metabolite of imipramine)
- *Doxepin* SINEQUAN
- *Imipramine* TOFRANIL
- Tetracyclic: *Maprotiline* LUDIOMIL
- *Nortriptyline* PAMELOR (the metabolite of amitriptyline)
- *Protriptyline* VIVACTIL
- *Trimipramine* SURMONTIL



Mechanism of action

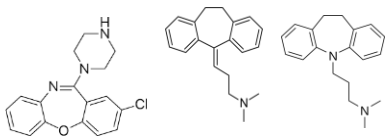
- **Inhibition of neurotransmitter** (NE and 5-HT) **reuptake**:
- **Receptor antagonism**:

- TCAs also block serotonergic, α-adrenergic, histaminic and muscarinic receptors.
  - Amoxapine also blocks 5-HT2 and dopamine D2 receptors

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

Therapeutic uses

- Moderate to severe depression
- Panic disorder
- Nocturnal enuresis (bedwetting): Imipramine (largely replaced by desmopressin).
- Migraine and chronic pain conditions: amitriptyline.
- Insomnia: doxepin.



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.
- **H1 histamine blockade:** sedation.
- **Overdose:** can be associated with life-threatening cardiac arrhythmias.
- **Sexual dysfunction:** less than SSRIs.

Antidepressants

Selective serotonin ...itors | Serotonin/norepinephrine reuptake inhibitors (SNRIs) | Tricyclic antidepressants (TCAs) | Atypical antidepressants | MOAIs Monamine oxidase inhibitors

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 (MAOIs)

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

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

-Selective for MAO-B

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

Mechanism of action: The action of MAOi is delayed for several weeks.

- 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**

Therapeutic uses:

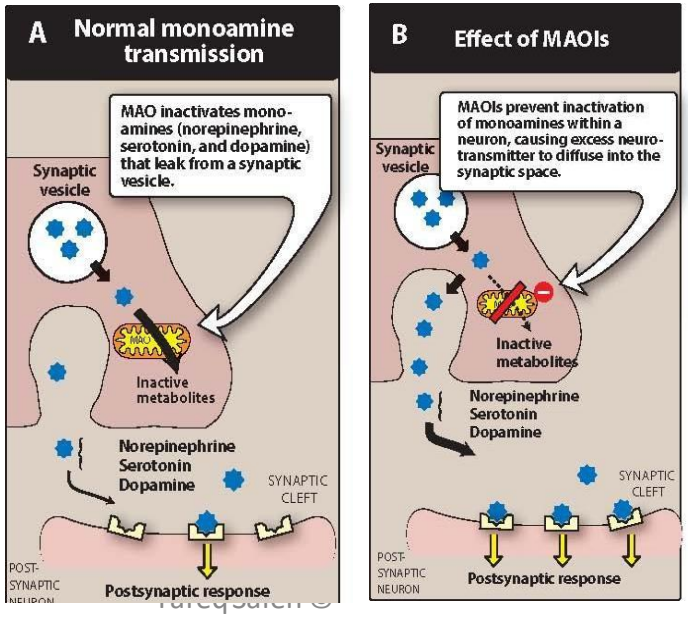
- **Last line for the treatment of depression:** for patients who are unresponsive to SSRIs or TCAs.
- **Atypical depression.**

Adverse effects:

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

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

MAOIs +				
1. Tyramine - rich food ↓ Hypertensive crisis **(Cheese reaction)**	**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
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.				

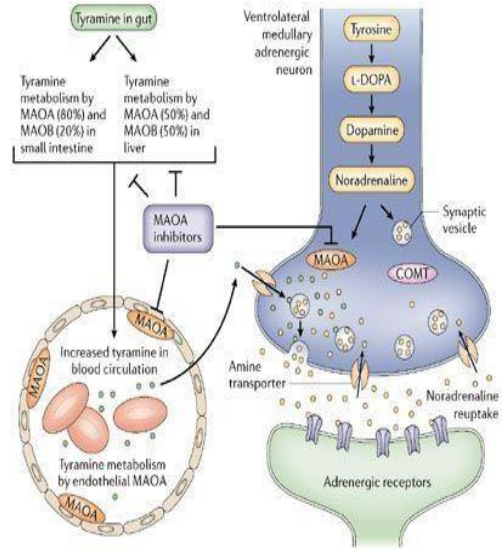


Tyramine-rich diet and MAOi

- 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!!!

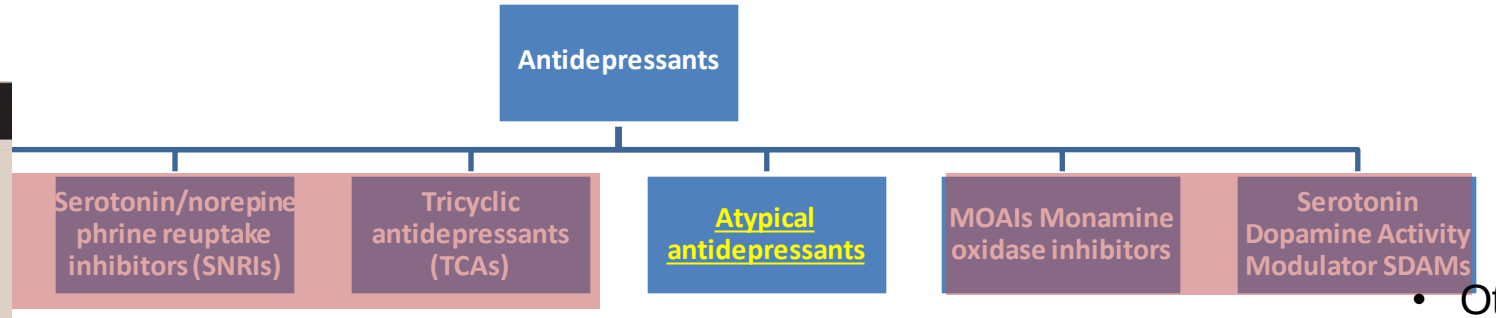
Precautions with MAOi

- 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

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



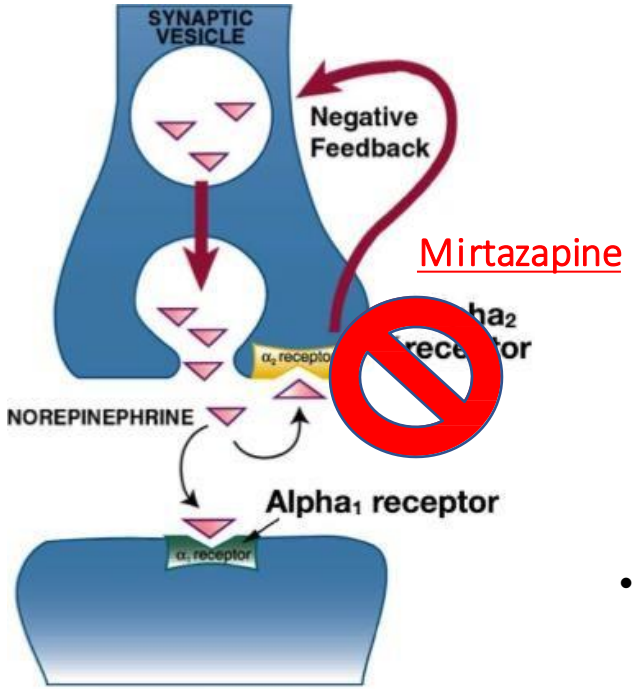
- **Bupropion**
- **Mechanism of action**: Weak DA and NE reuptake inhibitor
- **Therapeutic uses:** Depression and smoking cessation (reduces cravings and attenuates nicotine withdrawal symptoms.
- **Adverse effects:** associated with a dose-dependent increased risk for seizures.

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

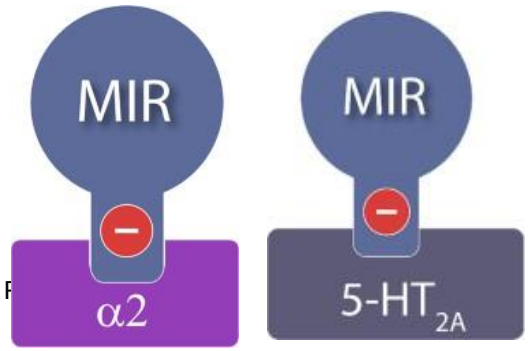
- **Mirtazapine**
- **Mechanism of action**: presynaptic α2 antagonist and partially due to 5-HT2 antagonism (enhances serotonin and norepinephrine neurotransmission)
- **Therapeutic uses:**

  -patients intolerant to TCAs or SSRIs.

  -sedating antidepressant improve insomnia
- **Advantages:** No sexual dysfunction, nausea, anxiety of SSRIs.



Mirtazapine



- 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

- Esketamine

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	**Members**	**Members**
1. TCAs **2. TTAD**	**Tranylcypromine**	**Mirtazapine**
3. SSRI **4. NSRI**	**Phenelzine**	
5. Bupropion	**Moclobemide**	

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

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

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.

Drugs Used to Manage Bipolar Disorder

- Lithium
- 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**.**

Other drugs

- **Antiepileptics:** Carbamazepine, valproic acid and lamotrigine.
- **Antipsychotics:** Chlorpromazine, haloperidol, risperidone, olanzapine, aripiprazole.

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