pharmacology
Team 438

MED438
KING SAUD UNIVERSITY

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Neuropsychiatry Block

Pharmacology Team 438

Drugs Used in Depression Old & New

Objectives

By the end of the lecture , you should know:

- Realize neurotransmitter defects in different types of depression
- Elaborate on how antidepressants generally act
- Classify the existing antidepressant into elder (TCAs & MAO Is) and newer groups (SSRIs, SNRIs, NRIs, NAASs, NDRIs, SARIs).
- Expand on pharmacology of each group; setting examples, discussing pharmacodynamics potentials, pharmacokinetic differences, varied indications, contraindications and side effects.
- Enumerate augmenter drugs used in depression

Color index:

Black : Main content
Red : Important
Blue: Males' slides only
Pink : Females' slides only
Grey: Extra info or explanation
Green : Dr. notes

Editing File

Depression

Depression is a very common psychiatric disorder that is related to the "mood" (Affective disorder).

Classification of Depression

According to severity of symptoms:

1. Mild depression:
Self-limiting.
2. Moderate depression:
difficulties at home and work.
3. Severe depression:
serious associated with **suicidal** thoughts.

According to Type:

1. Unipolar depression (Major depression):

- Mood swings are always in the same direction (depression).
- **About 75% of cases are non-familial.**
  ↳ Accompanied by symptoms of anxiety and agitation.
  ↳ Associated with stressful life events.
- **25% of cases are familial.**
  ↳ unrelated to external stresses.
  ↳ endogenous depression.

2. Bipolar depression (Manic-depressive):

- In which depression alternates with **mania**.
- It is mainly hereditary and appears in early adult life.

Other forms of depression:

1. Psychotic depression.
2. Postpartum depression.
3. Atypical depression.

Symptoms of:

Depression

1- Loss of energy and interest:
- Diminished ability to enjoy yourself.
- Decreased or increased sleeping or appetite.
- Difficulty in concentrating: indecisiveness; slowed or fuzzy thinking.
- Exaggerated feelings of sadness, hopelessness, or anxiety.

2-Feelings of worthlessness:
- Recurring thoughts about death and suicide.
- If most of these symptoms last for two weeks or more, the person probably has depressive illness.

Mania

Causes mood swings creating periods with the following symptoms:

1- A high energy level with decreased need for sleep.

2- Unwarranted or exaggerated belief in one's ability.

3- Extreme irritability.

4- Rapid, unpredictable emotional changes.

5- Impulsive, thoughtless activity, with a high risk of damaging consequences (i.e. stock speculations, sudden love affairs)

Biochemical Theory of Affective Disorders

Affective disorders leads to ↓ serotonin			Treatment
	⇧ NE	Mania	Drugs that ⇩ NE
	⇩ NE	Depression	Drugs that ⇧ NE

What is the evidence to support this theory?

- **Amphetamine** causes **Mania.**
- while, **Reserpine**[1] and **Methyldopa**[1] produce **Depression**
  (these drugs depletes **NE** and **Dopamine** storage).

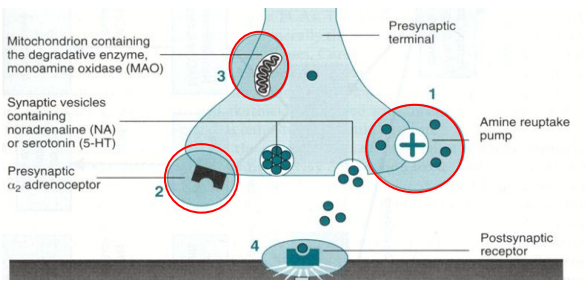
Pathophysiology of depression

5-HT Deficiency	May cause sleep problems , irritability and anxiety associated with depression.
Decreased level of **NE**	Which regulates mood, alertness, arousal, appetite, reward & drives, may contribute to the fatigue and depressed mood of the illness.
Dopamine	important for pleasure, sex & psychomotor activity.

What are the features of drugs that should be used for treatment of depression?

Simply to **increase the levels of these amines.**

Site of Action for Antidepressants[2]



1. **Monoamine** (**NE** or / and **5-HT**) **reuptake** inhibitors.
2. Blockade of **presynaptic a_2** receptors.
3. inhibition of **MAO** enzyme.

Classification of antidepressants based on site of action:

Drugs that **block** the reuptake of **NE** and **5-HT.**	Drugs that **selectively Block reuptake of 5-HT (SSRIs).**	Drugs that **Block presynaptic a_2** adrenoceptors.	Drugs that **inhibit MonoAmine Oxidase (MAO).**
e.g. Most **Tricyclics** (Old Antidepressants)	e.g. **Fluoxetine**, **Paroxetine**, **Sertraline**, **Citalopram** (New Antidepressants).	e.g. **Mirtazapine, Mianserin.**	e.g. **MAOIs: Phenelzine, Tranylcypraine, Moclobemide** (Old depressants).

1- used as hypertensive, cause depression.
2- Questions from the Doctor:
Q1. what are **Monoamine** (**NE** or / and **5-HT**) **reuptake** pump inhibitors? Q2. what Blocks **presynaptic a_2** receptors?
Q3.what inhibit **MAO** enzyme?

Antidepressants available in the market (Worldwide)

Class	Drugs
1. Tricyclics (TCAs) and Tetracyclics	**Tetracyclics**: Amoxapine, Maprotiline **Tricyclics**: Imipramine, Nortriptyline, Clomipramine, Trimipramine, Protriptyline, Doxepin, Desipramine, Amitriptyline.
2. Monoamine Oxidase Inhibitors (MAOIs)	Tranylcypramine, Phenelzine, Moclobemide.
3. Selective Serotonin Reuptake Inhibitors (SSRIs)	Fluoxetine, Fluvoxamine, Citalopram, Sertraline, Paroxetine, Escitralopram.
4. Serotonin and Norepinephrine Reuptake Inhibitor (SNRI)	Venlafaxine, Duloxetine.
5. Serotonin-2 Antagonist and Reuptake Inhibitors (SARIs)	Nefazodone, Trazodone.
6. Norepinephrine and Dopamine Reuptake Inhibitor (NDRI)	Bupropion.
7. Noradrenaline Reuptake Inhibitor (NRI)	Reboxetine.
8. Noradrenergic and Specific Serotonergic Antidepressant (NaSSA)	Mirtazapine.
9. Serotonin Reuptake Enhancer	Tianeptine

Slow Onset of Action

Antidepressants do not act immediately (show clinical effects after 3 weeks)[1] indicating that secondary adaptive changes must occur before the benefit is gained.

The most consistent adaptive change seen with antidepressant drugs is the **downregulation of beta-, alpha-2 and 5-HT2 receptors.** These receptor mediate negative feedback on monoamine release in the brain

Desensitization (down-regulation) of β- adrenoceptors (decrease c-AMP) is very important and is related to clinical response.

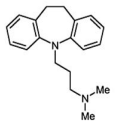
1- it is very important to alert the patient that the drug takes a minimum of 3 weeks, because the patient might stop using the drug thinking it doesn't work.

Old Antidepressants

1. Tricyclic antidepressant
2. Monoamine Oxidase inhibitors

Tricyclics (TCAs)

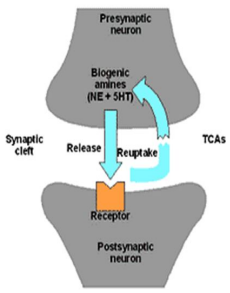
Drug



- TCAs are the oldest class of antidepressant drugs.
- **Tricyclic** (They have characteristic **three**-ring nucleus): Imipramine, Nortriptyline, Clomipramine, Desipramine, Amitriptyline, Trimipramine, Doxepin.
- **Tetracyclic Antidepressants** (They have **four**-ring nucleus): Amoxapine, Maprotiline.

MOA

- All tricyclics **block reuptake pumps for both 5HT and NE** in nerve terminals by competing for binding site of the transport protein, so ↑ conc. of NE & serotonin in the synaptic cleft & at the receptor site.
- **Clomipramine, Imipramine, Amitriptyline** have more potency for inhibition of **5HT** uptake pump.
- **Nortriptyline, Desipramine** have more potency for inhibition of **NE** uptake pump.



Actions

- Elevate mood.
- Improve mental alertness.
- Increase physical activity.
- The antidepressant effect may develop after several weeks of continued treatment (2-3 weeks).
- In non-depressed patients: They cause sedation, confusion & motor incoordination. [1]

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- **Peak levels:** 2-6 hours post ingestion.
- They are **"lipophilic"** in nature, therefore they are well absorbed from the GIT and readily cross the blood brain barrier to penetrate CNS.
- **Elimination:** hepatic oxidation.
- ★ TCAs are metabolized in the liver by **demethylation** (**Imipramine** to **Desipramine**, **Amitriptyline** to **Nortriptyline**) and by hydroxylation into metabolites that **retain the biological activity of the parent compounds.**

ADR

TCAs block: 1- α1 adrenergic receptors 2- H1 histamines receptors 3- M1 cholinergic receptors 4- 5HT2 receptors.

Adverse effects of TCAs:

- **Anti-cholinergic:** Dry mouth, blurred vision, constipation & urine retention, aggravation of glaucoma.
- **Anti-histaminic:** Sedation, confusion. → **H1** receptor effects.
- **Anti-adrenergic:** Postural hypotension[2], arrhythmias, conduction defects.
- Weight gain, sexual dysfunction & impotence.
- Lower seizure threshold.
- ★ **TCAs have narrow therapeutic index:** toxicity can develop; excitement, Delirium, respiratory depression, convulsions, coma, atropine-like effects, cardiac arrhythmias, sudden death.[3]
  - TADs are highly protein bound and have a large volume of distribution →Therefore hemodialysis is not effective for treatment of TCA toxicity.

1- these effects show immediately(not after 3 weeks) and are not affected by the downregulation of the receptors. So it is again important to alert the patient of (1) the delayed onset of action (2) these ADRS which will show immediately.
2- the doctor need to tell the patient during consultation.
3- which is why TCAs are avoided with suicidal patients because an OD is much more dangerous than other antidepressants(there's no antidote & hemodialysis isn't effective)

Tricyclics (TCAs) cont…

Uses	• Endogenous (Major) Depression → moderate to severe. • Panic attack /acute episode of anxiety. ★ **Imipramine** because is used for treatment of nocturnal enuresis in children and geriatric patients because it constricts internal urethral sphincter (anti-muscarinic effect). • Generalized Anxiety Disorder (GAD). • Obsessive Compulsive Disorder (OCD). • Attention Deficit Hyperkinetic Disorder (ADHD). • Chronic neuropathic pains or unexplained body pains.
Drug inter-actions	• **TCA are strongly bound to plasma protein**, therefore their effect can be potentiated by drugs that **compete for their plasma protein binding site (Aspirin and Phenylbutazone)**. • **TCAs** are metabolized by **liver microsomal enzymes**, therefore their effect can be reduced by inducers of liver microsomal enzymes **(Barbiturates)**, or potentiated by inhibitors of liver microsomal enzymes **(Oral contraceptives, Antipsychotics, and SSRIs)**. • TCAs (Inhibitors of Monoamine reuptake) **should not be given with MAOIs** (Inhibitors of Monoamine degradation) → **cause hypertensive crisis.** • Additive to **anti-psychotics** and **anti-parkinsonisms** → **increase anti-cholinergic effects.**
C.I	• **TCAs** should not be used in patients with **Glaucoma** or with **enlarged prostate** because of their **atropine-like action.** • **TCAs (if given alone) are contraindicated in manic-depressive illness**, because they tend to "switch" the depressed patient to the "manic" phase, therefore, they should be combined with "lithium salts".[1] • **Seizure disorder.(TCAs increases NA level in brain)**

MonoAmine Oxidase Inhibitors (MAOIs)

MAO is a mitochondrial enzyme found in nearly all tissues, and they exist in **two** forms:

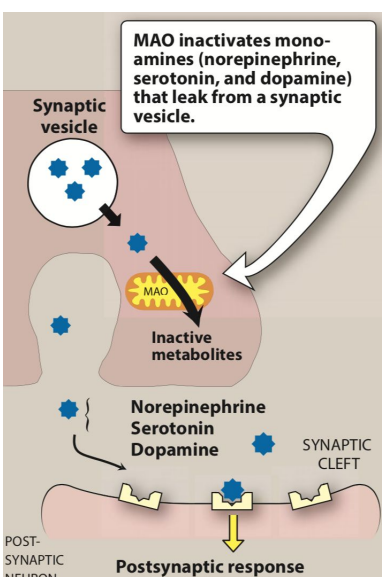
responsible for **NE, 5-HT** catabolism. It also metabolizes **tyramine** of ingested food.

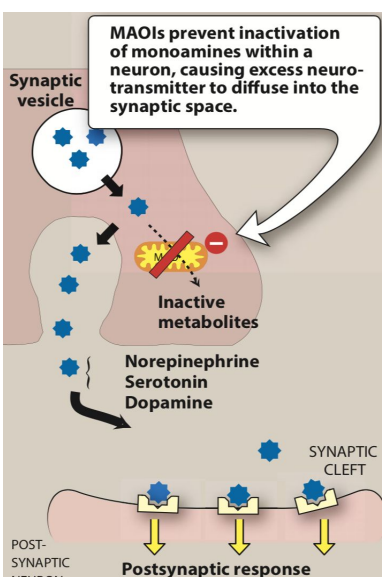
MAO-A

MAO-B

more selective for **dopamine** metabolism.

Mechanism of action of MAOIs:





1- lithium is a mood stabilizer.

MAO-A or MAO-B

1. Moclobemide: Antidepressant action, short acting **(MAO-A).**
2. Selegiline: used in treatment of **Parkinsonism (MAO-B).**

Non-selective

Selective

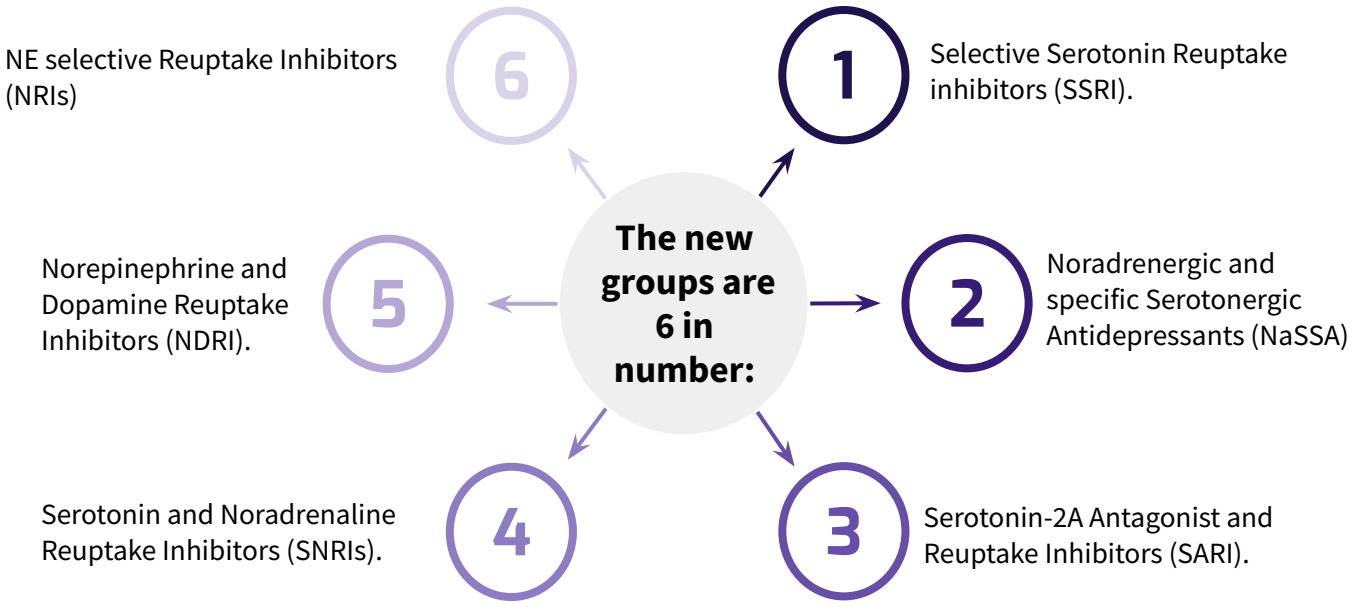
MAO-A & MOA-B

1. Tranylcypromine (Irreversible).
2. Phenelzine (Irreversible) long acting.
*The effect of irreversible MAOIs persists for period of 2-3 weeks after stopping treatment, time needed by the body to synthesize new enzyme.

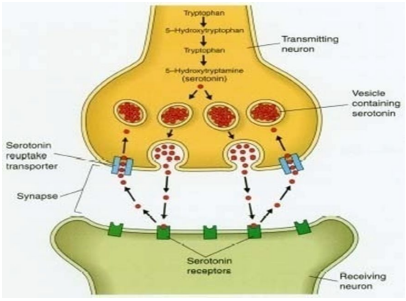
Drugs	Phenelzine	Tranylcypromine	Moclobemide[1]	Selegiline
Type	Non-selective (act on MAO A & B).		★ Selective & Reversible.	Selective & Irreversible
	Irreversible long acting (2-3 weeks).	Irreversible.	- Act on MAO-A. - Anti-depressant action. - Short acting.	- Act on MAO-B. - Used in the treatment of Parkinsonism.
Uses	• Only used for **refractory cases** and in atypical depression where phobia and anxiety are prominent symptoms. • **limited uses because: 1**.ADRs **2**.food and drug interactions. **3.**low antidepressant efficacy = Low Benefit/ risk ratio.			
ADRs	1. Antimuscarinic effects 2. Postural hypotension. 3. Sedation. 4. sleep disturbance. 5. Weight gain.		**Specific ADRs for (Phenelzine):** **1. Sexual dysfunction.** **2. Hepatotoxicity.**	
Drug inter-actions	• **Pethidine:** MAOIs interact with the **opioid receptor agonist (pethidine)** which may **cause severe hyperpyrexia, restlessness, coma, hypotension.** The mechanism still unclear – but it is likely that an abnormal pethidine metabolite is produced because of inhibition of normal demethylation pathway. • **Levodopa:** Precursor of dopamine can interact with MAOIs leading to **mania** and **hypertensive crisis**. • **Amphetamine and Ephedrine:** Indirectly acting **sympathomimetic** can interact with MAOIs causing the liberation of accumulated monoamines in neuronal terminals leading to **hypertensive crisis.** • **TCAs:** (inhibitors of monoamine reuptake) can interact with MAOIs (inhibitors of monoamine degradation) leading to **hypertensive crisis.** • **MAOIs & SSRIs: Serotonin syndrome.** (give 1-2 weeks gap before initiating SSRIs)			
Inter-action with tyramine (Cheese reaction)	• This occurs when **Tyramine** are taken with **MAOIs.** • Tyramine rich foods include old cheese, concentrated yeast products, Pickled or smoked fish, Red beans, Red Wine, Chicken liver, Sausages. • Tyramine in food is normally degraded in the in the gut by **MAO-A**. • Since the enzyme is inhibited by MAOIs, tyramine from ingested food is absorbed, and then taken up into adrenergic neurons where it is converted into **octopamine** (a false transmitter) which causes massive release of **(NE)** and may result in **hypertensive crisis**(severe hypertension, severe headache and fatal intracranial hemorrhage). ★ **The special advantage claimed for Moclobemide is that, No cheese reaction occurs with its use.**			

1. Maclobemide has the least sedation, anticholinergic, hypotension effect (Least toxic).

New Antidepressant



1. Selective Serotonin Reuptake Inhibitors (SSRIs)

Drugs	**Fluoxetine, Fluvoxamine, Sertraline, Paroxetine, Citalopram, Escitalopram.**
General Idea	• The most widely utilized class of antidepressants in clinical practice. • **This group act** by increasing the level of serotonin (5-HT) in the synaptic gap by inhibiting its re-uptake within the brain. • They are **selective** Because they affect only the reuptake pumps responsible for Serotonin only.
MOA	• **Selective serotonin reuptake inhibitors (SSRI)**: Binds to SERT ➔ Block 5HT transport ➔ increase 5-HT levels in synapse. • They have No effect on **NET** (norepinephrine transporter) and they do not block **mAch**, **H**, or **a1 Adrenoceptor** ➔ so no antimuscarinic nor sedative effects Except **Paroxetine**. • They are nearly of comparable efficacy but of preferential response in each individual. 
Advantages	• The Most commonly prescribed antidepressants • Lacks cardiovascular and anticholinergic side effects compared to **TCAs** • In contrast to **MAOIs**, they do not cause 'cheese' reaction. • **Safer** (low risk of overdose). • **Acute toxicity is less than that of MAOIs or TCAs**.

SSRIs Cont...

P.K

- **T1/2 :**
  → **Too long** (3-11 days): **Fluoxetine (Prozac)**.
  → **Moderate length** (~24hr): **Sertraline, Paroxetine, Citalopram**.
- **Metabolized by P450 then conjugation.**
  → **They are enzyme inhibitors.**
  → **Weak inhibitors** → **Sertraline, Citalopram** → ↓ interaction
  → **Strong inhibitors** → **Fluoxetine, Paroxetine** → ↓ metabolism of TCAs, neuroleptics, some antiarrhythmics, β-blockers

Uses

Same as for TCA, but it is effective in the following conditions:
1) Depression. 2) Anxiety Disorder.
3) Eating disorders:
- bulimia nervosa **(fluoxetine)**.
- Anorexia nervosa (restricting eating).
4) Post traumatic stress disorder.(PTSD)
5) Premenstrual dysphoric disorder.
6) Attention Deficit Hyperkinetic Disorder.(ADHD)
7) Treatment of premature ejaculation[1] → by stimulation of 5-HT2A.

ADRs

- **Adverse effects of SSRIs:**
  1) GIT symptoms: Nausea, vomiting (due to 5-HT3 stimulation) and diarrhea[2]
  2) Changes in appetite weight loss/gain (5-HT3 stimulation).
  3) Sleep disturbances: Drowsiness with Fluvoxamine.
  4) Anxiety & Tremors (if combined with other antidepressants).
  5) Sexual dysfunction: Loss of libido, delayed ejaculation (5-HT2A stimulation).

- **Discontinuation syndrome:**[3]
  Symptoms are headache, malaise & flu-like symptoms, agitation, irritability & nervousness .

- **Side effects:**

Drug	Cardiotoxicity	Nausea	Anticholinergics	Sedation
Fluoxetine	-	++	-	-
fluvoxamine	-	+++	-	+
paroxetine	-	++	+	+
Sertraline	-	++	-	-

Drug inter-actions

- **SSRIs** are **potent inhibitors of liver microsomal enzymes.** Therefore they **should not** be used in combination with **TCAs** because they can inhibit their metabolism increasing their toxicity.
- **SSRIs** should not be used in combination with **MAOIs** because of the risk of **life threatening "serotonin syndrome"** :
  (tremors, hyperthermia, cardiovascular collapse and death).
  Both drugs require a "washout" period of **6 weeks** before the administration of the other

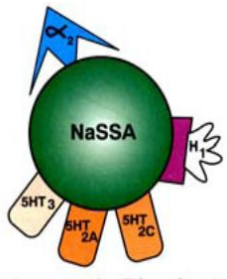
Fluoxetine

Info:

- It is a Strong inhibitor, it differs from other members of this class in:
  - It has a longer t1/2 (50 hrs).
  - Available as sustained release preparations → once weekly.
  - Its Metabolite norfluoxetine = potent as parent drug t1/2 (10 days).
  - Indicated in bulimia nervosa.

1-fluvoxamine
2- b/c of increased serotonergic activity in the gut.
3- different than withdrawal syndrome.

2. Noradrenergic and specific Serotonergic Antidepressants (NaSSA)

Drug	Mirtazapine
Action	• **α2 receptor antagonist.** • Increase NE and 5HT levels. ★ **Blocks 5HT2A , 5HT3** and thus reduces side effects of sexual dysfunction[1] and anxiety. • Blocking **5HT2C**, and **H1** receptors cause side effects: **- Sedation** → **(H1 blocking effect).** **- weight gain** → **(5-HT2C blocking effect).** 
Uses	★ **Preferred in cancer patients because:** 1- It improves appetite. 2- ↓ nausea & vomiting (by **5-HT3 blocking**). 3- **↑ body weight (5-HT2C blocking effect).** 4- Sedation (**H1 blocking effect**). 5- Less sexual dysfunction (by **5-HT2 blocking**). 6- **Has no anti-muscarinic effect.**

3. Serotonin-2A Antagonist and Reuptake Inhibitors (SARI)

Drugs	Trazodone, Nefazodone
MOA	• **Blocks 5HT uptake selectively** but in a less potent manner than TCAs. **This reduces depression.** • However, they are powerful **5HT2A antagonists**, blockade of 5HT2A receptors **stimulates 5HT1A receptors**, which may help reduce depression. • **5HT2A antagonism** also reduces the **risk of anxiety, sedation or sexual dysfunction** which is normally associated with SSRIs. • **Nefazodone:** Structurally related to **trazodone** but has less sedative effect and **does not block α- adrenoceptors** , however; it likes most SSRIs inhibit **P450 3A4 isoenzyme.**

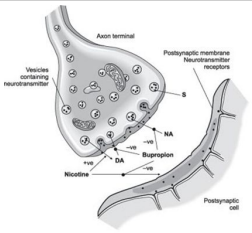
4. Serotonin and Noradrenaline Reuptake Inhibitors (SNRIs)

Drugs	Venlafaxine (Effexor)

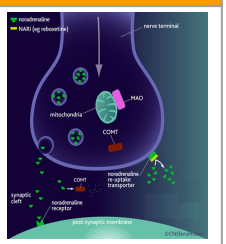
MOA	• It is used primarily for the treatment of:
	  ○ **Depression**.
	  ○ generalized anxiety disorder in adults.
	  ○ social anxiety disorder in adults.
	• **Venlafaxine is the first and most commonly used SNRI**.
	• Selective **5HT** and **NE uptake blockers** combines the action of **SSRIs** and **NRI**, but without α1, M1 cholinergic or H receptor blocking properties.
	• **Desvenlafaxine** is a metabolite of **Venlafaxine.**

1. If the patient have primary premature ejuclation it will be worse, but if the patient is normal the drug will have no effect on premature ejuclation.

5. Norepinephrine and Dopamine Reuptake Inhibitors (NDRI)

Drug	Bupropion
MOA	• It Is **unique** in possessing significant potency as **NE (Norepinephrine)** and **DA (Dopamine) reuptake inhibitor** **with no direct action on 5HT.** 
Uses	• Treatment of major **depression and Bipolar disorder**[1]**.** ★ **Can be used for smoking cessation** → As it reduces the severity of **nicotine craving** & withdrawal symptoms.
Advantages	• **No sexual dysfunction** → (b/c no 5- HT blocking effect) given in young. (combination with SSRIs to avoid sexual dysfunction). [2] • **No weight gain [No 5HT effect].** • **No orthostatic hypotension.**
ADRs	• **Seizures** → **it ↓ threshold of neuronal firing.** (increases the stimulating NT) → Similar to TCAs.

6. NE Selective Reuptake inhibitors (NRIs)

Drugs	Reboxetine
MOA	• **Block only NET (norepinephrine transporter).** • No affinity for **5HT, DA, ADR**[2]**, H, mAch** receptors, So, has positive effects on the concentration and motivation in particular. 
Advantages	★ **Safe to combine with SSRIs** → **Minimal side effects** only related to activation of ADR system as tremor, tachycardia, and urinary hesitancy.

1- the male's doctor said its Contraindicated
2- Q: newlywed depressed patient which antidepressant would you recommend? A: bupropion
3-adrenergic receptor

Clinical uses of Anti-depressants Drugs

It's only examples not the only answer!

1. **Endogenous depression** → **SSRIs (first choice),** new generation and tricyclics can be used.
2. **Panic disorders (imipramine or SSRIs)**.
3. Obsessive Compulsive Disorders **(SSRIs and Clomipramine)** & Chronic pain **(Amitriptyline)**.[1]
4. **Anorexia nervosa and Bulimia (SSRIs).**
5. **Schizo-Affective Disorders (Amoxapine or SSRI + Haloperidol).**
6. Anxiety disorders **(Amitriptyline)**.[1]
7. Migraine and Anxiety & IBS **(Amitriptyline)**[1]
8. **Nocturnal Enuresis in children e.g. Imipramine.**
9. **Premature ejaculation (SSRI)**.
10. Neuropathic Pain **(Dual NE and 5-HT reuptake Blockers)**.

1- amitriptyline has the least side effects out of all TCAs.

Quiz

MCQ

Q1: Tricyclics antidepressants increase which of the following neurotransmitters?
A. Serotonin and Dopamine.
B. Dopamine and Norepinephrine.
C. Serotonin and Norepinephrine.
D. Dopamine.
Q2: Which of the following of has no cheese reaction with its use:
A. Phenelzine.
B. Tranylcypromine.
C. Moclobemide.
D. Selegiline.
Q3: 74 A 21-year-old man complains of depressed mood, lack of pleasure in activities he previously enjoyed, and lack of energy. This has been going on for .5 years now. His physician prescribes fluoxetine. Which of the following side effects is most likely to occur in this patient?
A. Peptic ulcer.
B. Delayed ejaculation.
C. Loss of taste.
D. Pancreatitis.
Q4: A 43-year-old woman with a history of breast cancer and depression presents to her physician for treatment. She complains of feeling sad and worthless. Which of the following treatments would be best for this patient?
A. Phenelzine.
B. Reboxetine.
C. Venfelzxine.
D. Mirtazapine.

SAQ

Q1: What are the sites of Action for antidepressants?

Q2: A 53-year-old man comes to clinic for depression. He has had decreased interest and a depressed mood for the past 6 months. He also smokes half a pack of cigarettes a day and thinks that if he could quit, that would help his mood as well. What is the most appropriate treatment for his depression and cessation of smoking?

Q3: What is the mechanism of action of the drug in Q2?

Q4: What is the mechanism of Action of fluoxetine?
Q5: Give 3 ADRs of fluoxetine.

Answers:

MCQ

Q1	C
Q2	C
Q3	B
Q4	D
Q5	

SAQ

Q1	1. Monoamine reuptake pump inhibitors 2. Blockade of presynaptic a2 receptors. 3.Inhibition of MAO
Q2	Bupropion
Q3	Norepinephrine and Dopamine Reuptake inhibitor (NDRI)
Q4	Selective Serotonin Reuptake inhibitor
Q5	1. Weight loss 2. Sexual dysfunction 3. Nausea

pharmacology

Team 438

Good Luck , Future Doctors!

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Share with us your ideas !