King Saud University

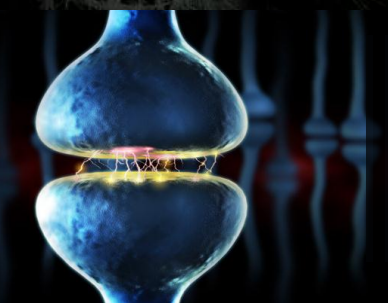
College of Medicine

2nd Year, 1st Block

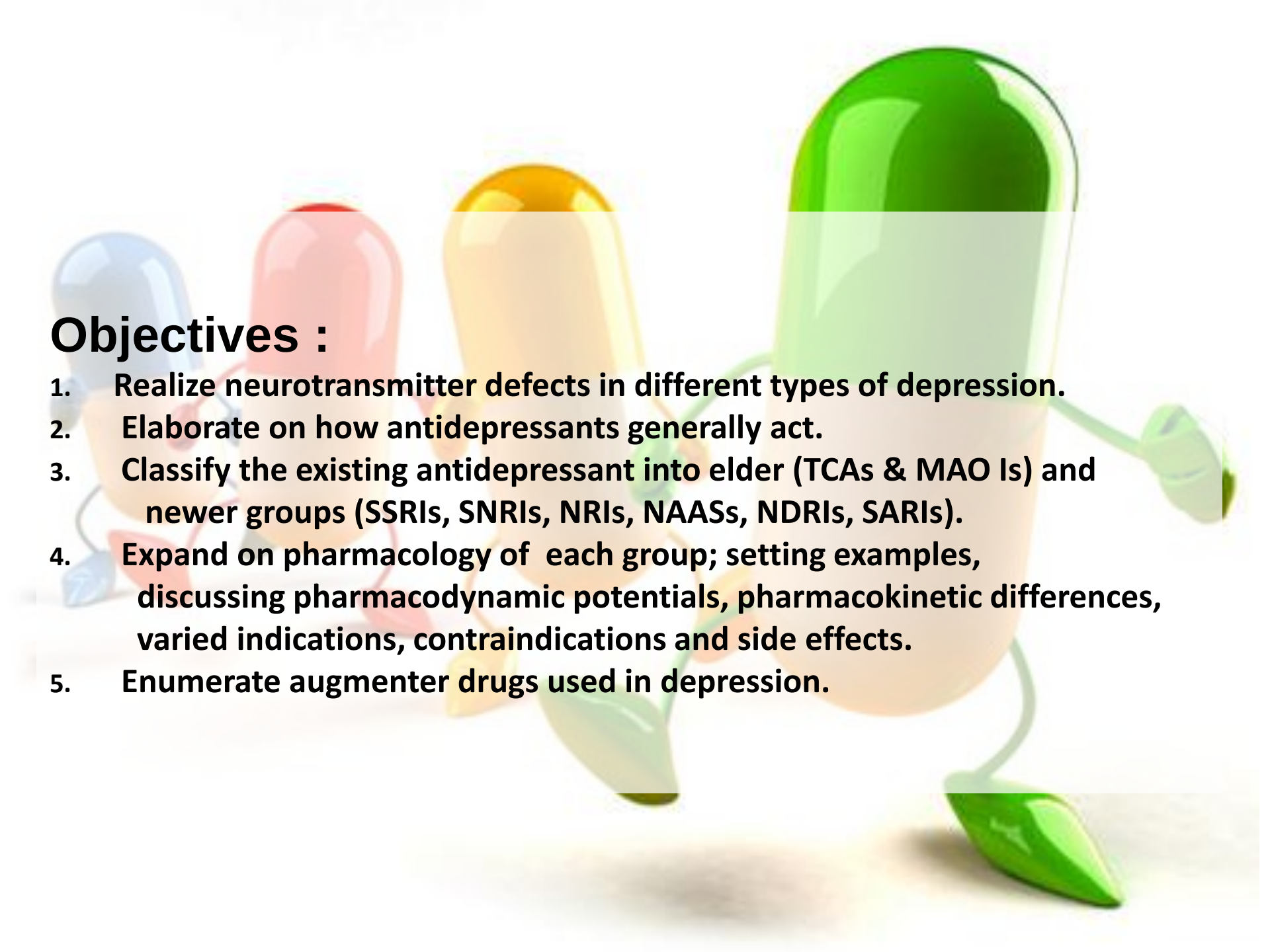
PHARMACOLOGY 433

MED 433 Teams

L6&7:Drugs used in depression

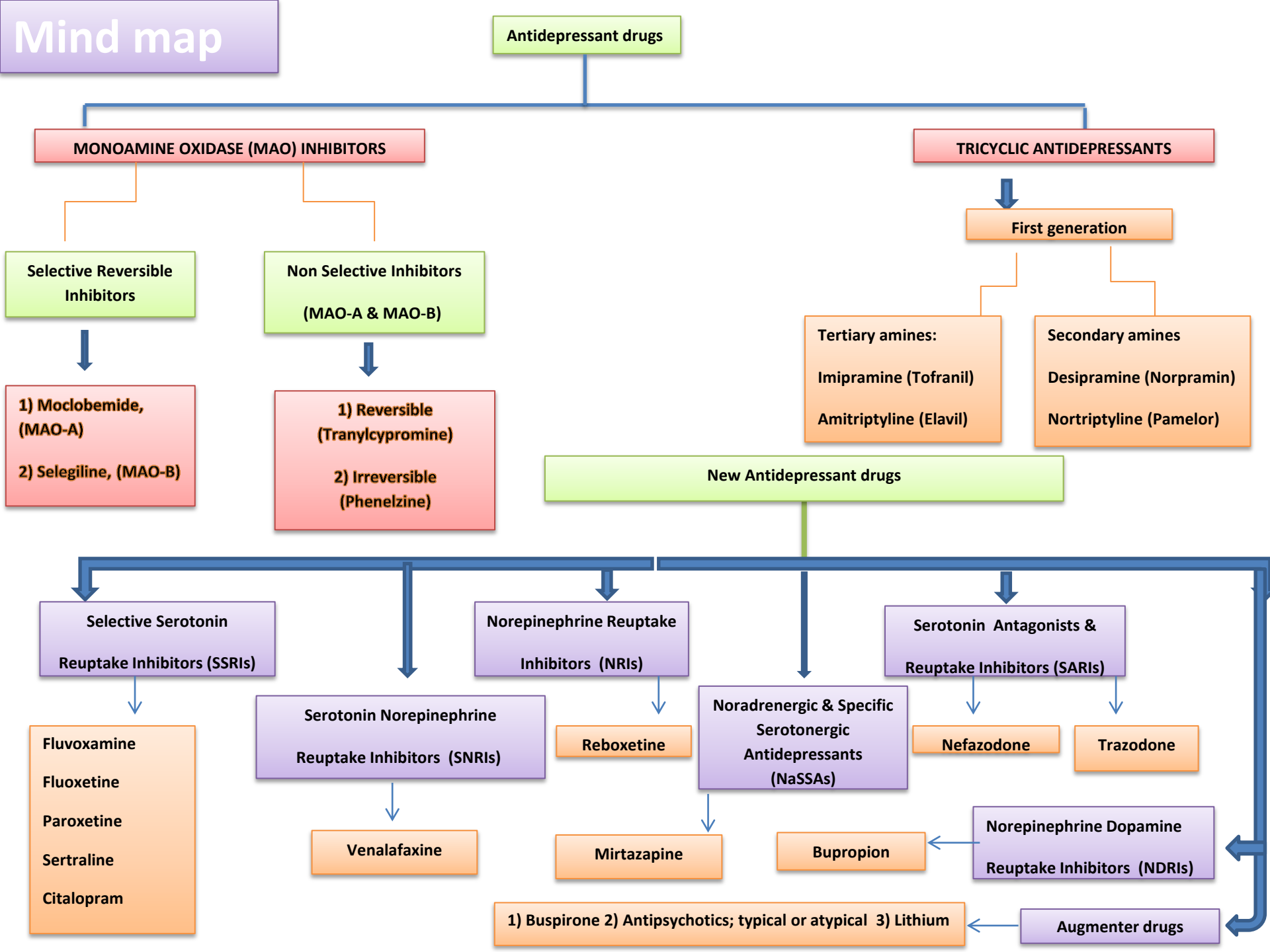


CNS Block



Objectives :

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


Mind map
Antidepressant drugs
MONOAMINE OXIDASE (MAO) INHIBITORS
TRICYCLIC ANTIDEPRESSANTS
Selective Reversible Inhibitors
Non Selective Inhibitors (MAO-A & MAO-B)
First generation
1) Moclobemide, (MAO-A)
2) Selegiline, (MAO-B)
1) Reversible (Tranylcypromine)
2) Irreversible (Phenelzine)
Tertiary amines:
Imipramine (Tofranil)
Amitriptyline (Elavil)
Secondary amines
Desipramine (Norpramin)
Nortriptyline (Pamelor)
New Antidepressant drugs
Selective Serotonin Reuptake Inhibitors (SSRIs)
Serotonin Norepinephrine Reuptake Inhibitors (SNRIs)
Norepinephrine Reuptake Inhibitors (NRIs)
Noradrenergic & Specific Serotonergic Antidepressants (NaSSAs)
Serotonin Antagonists & Reuptake Inhibitors (SARIs)
Norepinephrine Dopamine Reuptake Inhibitors (NDRIs)
Fluvoxamine
Fluoxetine
Paroxetine
Sertraline
Citalopram
Venalafaxine
Reboxetine
Mirtazapine
Nefazodone
Trazodone
Bupropion
1) Buspirone 2) Antipsychotics; typical or atypical 3) Lithium
Augmenter drugs

introduction

Depression

Disturbance in MOOD, biological changes, though changes & behavioral changes.

Classification of depression

Unipolar Depression

Mood swings are always in the same direction

common in elder /associated with stressful life effects

↓5HT & NE

Bipolar Depression

Depression alternates & oscillates with mania

common develops early in life.

↑5HT & NE

Antidepressants

All drugs take weeks to manifest their clinical effect ➔indicating that secondary adaptive changes must occur before the benefit is gained

The delay presents ➔ (down regulated) synthesis & release of transmitter at synaptic cleft with enhanced signaling at postsynaptic serotonergic & adrenergic

Treatment should continue 6 months at full therapeutic doses before withdrawal.

Withdrawal of drugs must be very gradual otherwise

withdrawal symptoms

	Classification of antidepressant drugs
OLD Group	Tricyclic Antidepressants (TCAs)
	Monoamine oxidase inhibitor (MAOI)
NEW Group	Selective serotonin reuptake inhibitor (SSRI)
	Noradrenergic & Specific Serotonergic Antidepressants (NaSSAs)
	Serotonin Antagonists & Reuptake Inhibitors (SARIs)
	Serotonin and Norepinephrine reuptake Inhibitors (SNRIs)
	Norepinephrine Dopamine Reuptake Inhibitors (NDRIs)
	Norepinephrine Reuptake Inhibitors (NRIs)

Augmenter drugs

Some antidepressants work better in some patients when used in combination with another drug.

The Most imp augmenter drugs: Buspirone

NOTE: Some drugs can cause depression like; Clonidine and methyldopa. While amphetamine cause mania.

A) OLD GROUP

1. Tricyclic Antidepressants (TCAs)*:

NAME	Imipramine	Amitriptyline	Desipramine
M.O.A	It blocks NE & serotonin reuptake into the neuron		
Pharmacokinetic	Lipophilic with High plasma protein binding , Some of them give active metabolites: Imipramine ➔ Desipramine - Amitriptyline ➔ Nortriptyline		
Clinical use	1- Severe depression.* 2- Panic disorder 3- Nocturnal Enuresis in children*	1- Severe depression 2- Chronic pain. 3- anxiety. 4- IBS*.5-Migraine. 6- Anorexia nervosa. 7-Obsessive-compulsive disorders (OCD).	Severe depression
Adverse effect	They're drugs with broad spectrum of pharmacological effects at many receptors 1- Sedation (Because of histamine receptor) 2- Cardiovascular effects (Tachycardia and hypotension) 3- Anticholinergic effects (Dry mouth, constipation, urinary retention) 4- Weight gain 5- Seizure 6- Hypomania 7- sexual dysfunction & impotence Early in use ➔ aggravate suicidal thoughts specially in young aged During use ➔ narrow therapeutic index ➔ toxicity can develop stopage of use ➔ Withdrawal Symptoms; characterized by cholinergic rebound Flu-like symptoms.		
Antidote of TCAs	1- NaCO3 (To protect the heart & increase the binding) 2- Diazepam (For seizure) 3- Gastric lavage plus charcoal فحم (For absorption of organic compound)		

*NOT used for elderly people. * التبول الليلي *Irritable bowel syndrome

*Elevate mood, Improve mental alertness & Increase physical activity

2. Monoamine oxidase inhibitor (MAOI)

- MAO inhibitors increase level of NE & Serotonin :

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

-MAO-B is more selective for dopamine metabolism

- USED in Patient resistant to other therapy, atypical depression* & In treatment of social anxiety (agrophobia)
- RARLEY used, because food-drug, and drug-drug interactions = Low benefit/risk ratio
- Has anticholinergic effect like; (Tachycardia, dry mouth, constipation etc..)

Name of drug	Phenelzine	Tranylcypromine	Selegiline	Moclobemide
	Non –selective		Selective reversible	
Type	irreversible	Reversible	MAO-B	MAO-A
ADRS	Antimuscarinic effects, Postural hypotension, Sedation, sleep disturbance, Weight gain			
Specific ADRS	Sexual Dysfunction Hepatotoxicity	----------	--------	----------
Interaction	1- Food contain tyramine* (like meat), flue medications, local anesthetics & TCA lead to hypertensive crisis. 2-pethidine lead to hypotension and coma. 3- MAOIs taken together with SSRIs, lead to serotonin syndrome*			

* hyperthermia, muscle rigidity, cardiovascular collapse

*Tyramine is normally inactivated by MAO in gut, individuals receiving MAOI are unable to degrade tyramine obtain from the diet. Tyramine causes the releases of large amount of catecholamines.= Mainly NE leads to **hypertensive crisis**

B) NEW GROUP

1. Selective serotonin reuptake inhibitor (SSRI)

Name	Fluoxetine	Fluvoxamine	Citalopram	Sertraline	Paroxetine
M.O.A	Block the reuptake of serotonin				
Pharmacokinetic	*They have long half live (Fluoxetine 3-11 days), Moderate length (~24hr): Sertraline, Paroxetine, Citalopram. *metabolize in liver, Strong inhibitors > Fluoxetine, Paroxetine → ↓ metabolism of TCA, neuroleptic, some antiarrhythmic, β-blockers.				
Clinical use	1- Best drugs for depression (few side effect). 2- Used in premature ejaculation 3- Panic disorder. 4- OCD*. 5- Anorexia nervosa*. 6- Bulimia nervosa*				
Side effect	1- Nausea and vomiting (Act on 5-HT_3 receptor). 2- ↓Appetite. 3- Impotence* in both gender. 4- Insomnia (except Paroxetine, cause sedative)				
Interaction	Serotonin Syndrome →if combined with MAOIs				
NOTES	They're the best group of drugs of antidepressant Good for elderly people and cardiac patients				

* Obsessive Compulsive Disorders

*Anorexia nervosa: an eating disorder characterized by a fear of becoming fat (self-imposed starvation). SSRI relive depression and fear, so patient will eat normally

*Bulimia nervosa: eating disorder characterized by consuming a large amount of food in a short time followed by an attempt to rid oneself of the food consumed (purging),

* ضعف جنسي

2. Noradrenergic & Specific Serotonergic Antidepressants (NaSSAs) (α_2 adrenoceptors antagonists)

NAME	Mirtazapine
M.O.A	Block presynaptic a_2 adrenoceptors → ↑ NE & 5-HT (Serotonin)
Clinical use	Depressed patient having sleeping problems
Adverse effect	1- Sedation. 2- Weight gain. 3- ↑Appetite (Block 5-HT_3)
NOTES	Best drug for cancer patient*

3. Serotonin Antagonists & Reuptake Inhibitors (SARIs)

NAME	Trazodone	Nefazodone
M.O.A	1-Selective blocker of 5-HT reuptake 2-significant α- blocking effect	
Adverse Effect	1-Hypotension 2- Sedation. 3-Blocks 5-HT2 receptors (Priapism*)	Less sedative effect

*Priapism: is a potentially painful medical condition, in which the erect penis does not return to its flaccid state.

*Improves appetite, ↓nausea & vomiting (5-HT_3 blocking), ↑ body weight, Sedation (potent antihistaminic), Less sexual dysfunction (5-HT_2 blocking) & Has no anti-muscarinic effect .

4. Serotonin and Norepinephrine reuptake Inhibitors (SNRIs)

NAME	Venlafaxine
M.O.A	Blocking 5-HT and NE uptake
Clinical use	1- Patient not respond to SSRI. 2- Neuropathic pain (EX. Diabetic neuropathy)
Adverse Effect	Similar to SSRI but may be withdrawal manifestations on discontinuation. + 1-seizure 2- Constipation

5. Norepinephrine Dopamine Reuptake Inhibitors (NDRIs)

NAME	Bupropion
M.O.A	Weak NE & Dopamine reuptake inhibitor
Adverse effect	Seizures
Clinical use	1- Depression and bipolar disorder. 2- Used for smoking cessation (Main use).
Advantages	No sexual dysfunction ➔given in young

6. Norepinephrine Reuptake Inhibitors (NRIs)

NAME	Reboxetine
M.O.A	Only blocking NE uptake
Clinical use	Depression
Adverse effect	1- Tremor 2- Tachycardia 3- urinary hesitancy*
NOTE	Safe to combine with SSRIs

*Difficulty in beginning the flow of urine

Summary

Antidepressants receptors include mainly:

Histaminergic antagonism has been associated with sedation and drowsiness. Can contribute to increased appetite & weight gain.

Muscarinic-receptor antagonism is responsible for gastrointestinal disturbances; constipation, dry mouth, tachycardia, blurred vision, urine retention

a_1-adrenergic receptor may be responsible for dizziness and orthostatic hypotension

Antidepressants increase variably the availability of 5HT & NE at synapes

- ↑NE transmission → tremors, insomnia
- ↑5HT transmission → sedation, and a decrease in sexual drive.

Antidepressants

safe combinations

- Bupropion + Desipramine
- SSRIs + Mertazepine, Reboxetine or any other NRIs or SNRIs

age

- approved for use in children; fluoxetine
- Antidepressants good for elderly are SSRIs

dangerous combinations

- MAOIs + SSRIs → Serotonin syndrome
- Paroxetine, Fluoxetine, Nefazodone + Desipramine, Nortryptiline → severe sedation or toxicity

Summary

Antidepressants

sexual dysfunction

- $5HT_2$ blocking action as mirtazipine, has minimal action on sexual dysfunction
- more NE as Bupropion, have minimal sexual side effects
- Trazodone, nafazodone, With dual action are better than SSRIs with respect to sexual side effects

Sedation

- Sedating ADDs are; Amitryptyline, Paroxiteine, Sertraline, Mirtazapine, Trazadone, So better given near bed time
- Less Sedating ADDs are; Bupropion, Venalafoxine, MOA, So can be given in the morning as some cause insomnia as side effect.

appetite

- Most TCAs ↑ weight gain
- SSRIs → could suppress appetite. At least no weight gain with SSRIs.
- Mirtazepine ↑ weight gain

Nausa & Vomiting

- SSRIs → nausea & vomiting

Summary of clinical uses

I. Endogenous Depression (SSRIs “first Choice”, New generation and Tricyclics)

II. Panic Disorders (Imipramine or SSRIs)

III. Obsessive Compulsive Disorders (SSRIs and Clomipramine)

IV. Chronic pain (Amitriptyline)

V. Anorexia nervosa and Bulimia (SSRIs)

VI. Schizo-Afective Disorders (Amoxapine or SSRI + Haloperidol)

VII. Premature ejaculation (SSRI)

VIII. Anxiety disorders (Amitriptyline)

IX. Migraine and Anxiety & IBS (Amitriptyline)

X. Nocturnal Enuresis in children (Imipramine)

XI. Neuropathic Pain (SNRIs)

XII. Depression in Adolescence and young adults (Bupropion)

XIII. Depression in cancer patient (Mirtazapine)

Quiz yourself

Q1/ Which of the following drugs not given for prostatic hypertrophy patient?

A. Amitriptyline
B. Fluoxetine
C. Bupropion

Q2/ Which of the following drugs given for someone want to quite smoking?

A. Mirtazapine
B. Bupropion
C. Imipramine

Q3/ which of following given for epileptic patient?

A. Nefazodone
B. SSRI
C. Amitriptyline

Q4/Which of following is best for cancer patients?

A. Trazodone
B. Fluoxetine
C. Mirtazapine

Q5/ which of the following drugs not for elderly?

A. Tricyclic
B. Monoamine oxidase
C. Phenelzine

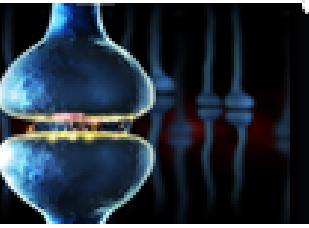
Q6/ Which one can causes hypertensive crisis?

A. Imipramine
B. Tranylcypromine
C. Amitriptyline

Q7/ which methods NOT used in antidote of TCAs?

A. Hemodialysis
B. Gastric lavage
C. Naco3

Answers: 1- A 2- B 3- B 4- C 5- A 6- B 7- A



CNS Block

PHARMACOLOGY 433

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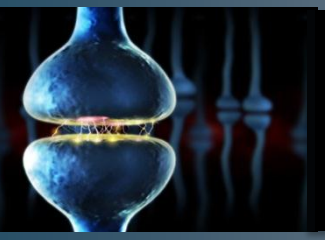
We hope that we made this lecture easier for you
Good Luck !



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