PHARMACOLOGY TEAM

Lecture 7

AntiDepressant "OLD"

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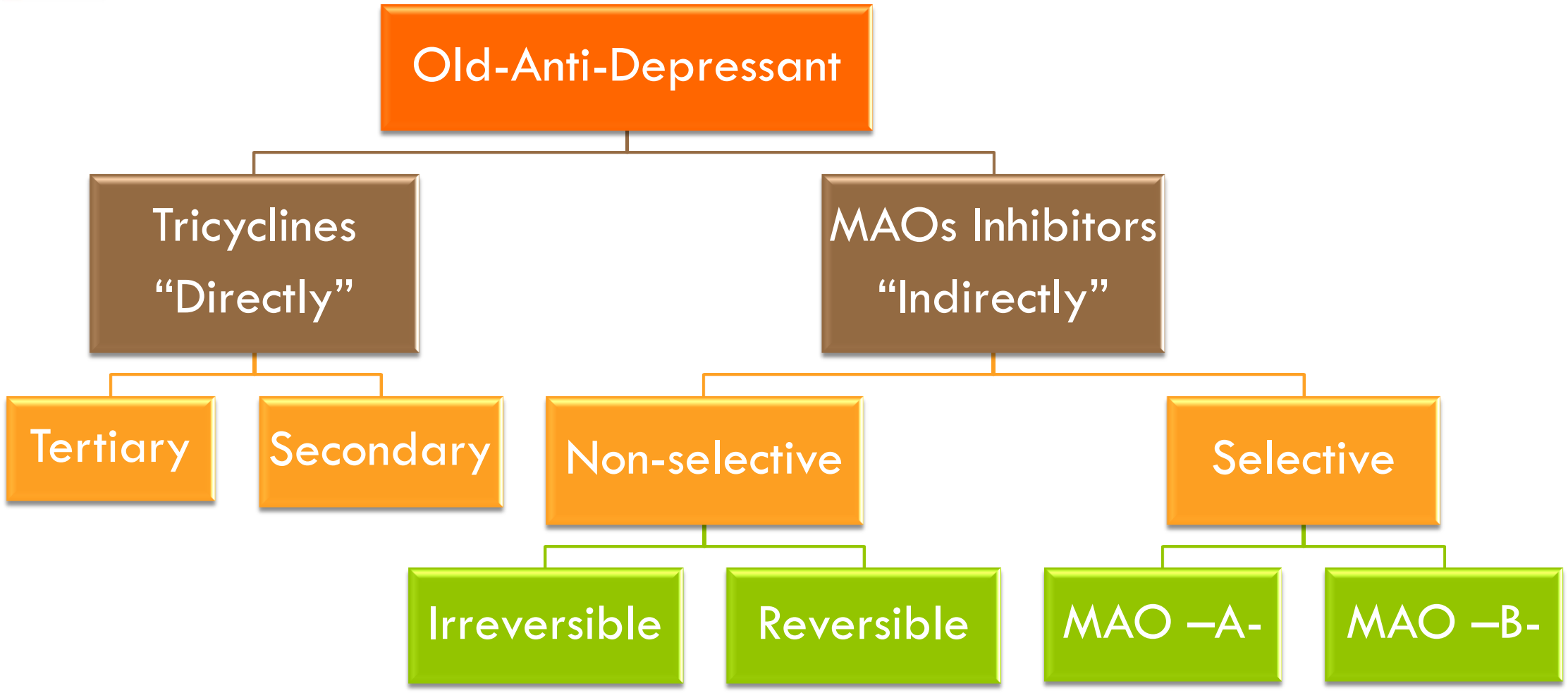
OBJECTIVES

- 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 pharmacodynamic potentials, pharmacokinetic differences,
  varied indications, contraindications and side effects
- Enumerate augmenter drugs used in depression

MIND MAP



Slides Important Doctor's Notes Explanation

Depression

- **Disturbance in MOOD rather than of thought or behavior**
- **CLASSIFICATION OF DEPRESSION :**

1) Unipolar Depression

Mood swings are always in the same direction,common,in elder /associated with stressful life effects ± symptoms of anxiety and agitation, the patient is usually inert

2) Bipolar Depression

Depression alternates & oscillates with mania develops early in life, runs in families, hereditary nature "related to genes" episodes can sometimes be provoked by stressful experience or physical illness

If 5HT fall, is not properly modulating NE, so that it becomes abnormally high, the patient becomes MANIC.
If 5HT fall, is not properly modulating NE and NE also falls to abnormally low levels, the patient becomes DEPRESSED

Pathophysiology Of Depression

- **NEUROTROPHIC REGULATION**
- **SIGNAL TRANSDUCTION >>** Abnormal 2nd messenger cascade ➔ gene expression
- **RECEPTORS >>** Alteration in rssion eceptor density
- **TRANSMITTERS >>** Too little monoaminergic activity

*All of these pathophysiological causes of depression are theories < which means that they might change any classification of the drugs or the depression itself in later years

Antidepressants

The terget in the therapy is “MOOD”
By increasing Serotonin levels

Normally	Depressant drugs
The nuerotransmitters are released to the post-synaptic and bind to the receptors, then uptaken by the transporters , afterthat , they are degraded partially by the MAO enzyme	**The concept of action of all drugs relay on ↟↟extracellular biogenic amines in the brain indirectly by blocking their catabolism or directly by preventing their uptake ± altering receptor firing**

All drugs take weeks to manifest their clinical effects even though their pharmacological actions starts immediately

Secondary Adaptive mechanism

Time needed for down regulation of the receptors

Cont…

The delay presents➔time needed for inhibitory somatodendritic autoregulatory $5HT_{1A}$ receptors or axonal autoregulatory $5HT_{1D}$ to be sensitized [down regulated] to permit more synthesis & release of transmitter at synaptic cleft with enhanced signaling at postsynaptic serotonergic & adrenergic > (b) neurones → therapeutic effect.

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When I give a drug "either direct acting or indirect" it will increase the serotonin level in the synapse,,

But the inhibitory receptors are up regulated >> so it will inhibit the secretion of serotonin in response to this increasing level because of the drug ..

And this adaptation mechanism takes weeks to be overcome by the drug

Anti depressant (old)

Class of Antidepressant	MAO Inhibitors				Tricyclic Antidepressants	
Pharmacological Actions	1- Inhibit the action of MAO in mitochondria which prevents monoamine breakdown and increases its availability. 2- Blocks mAch receptors (Atropine-like action) 3- Blocks α-adrenoceptors				**Blocks:** 1- 5HT and NE reuptake 2- α_1-adrenoceptors 3- m_1Ach 4- Histamin H_1 receptors Elevates mood, improves mental alertness, increases physical activity. (Long duration, no loss of effectiveness, better than MAOI)	
	Selective		**Non-Selective**		**Tertiary Amines**	**Secondary Amines**
	MAO-A: NE, Serotonin, and Tyramin metabolism **Moclobemide**	MAO-B: Dopamine metabolism **Selegiline**	Reversible: **Tranylcypromine** (persists 7 days after stop)	Irreversible: **Phenelzine** (persists 2 weeks after stop)	Not selective to NE (More side effects) 1- **Imipramine** (Tofranil) → Gives Desipramine (Active metabolite) 2- **Amitriptyline** (Elavil) → Gives Nortiptyline (Active metabolite)	More selective to NE (Less side effects) 1- **Desipramine** (Norpramin) 2- **Nortriptyline** (Pamelor)
Indications	1- Atypical depression 2- Resistance to other therapy 3- Social Anxiety	Not used in depression.	Seldom used (low benefit/risk ration)		**1- Depression:** - + Lithium in Depressed phase of Bipolar depression - + Antipsychotics in Depressed Psychotic patients - Resistance to other therapy **2- Other Psychiatric Disorder:** - OCD - Generalized Anxiety Disorders - Panic Disorders - Anorexia Nervosa **3- Other Disorders:** - Control Bed-wetting in children (Imipramine/**Desmopressin**): ↑ Contraction of internal sphincter of the bladder, it's gradually withdrawn and should not be given for more than 3 months. - Neuropathic pain: **Tertiary amines** are better because they modulate	

Cont...

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Cont...

Adverse Effects	1- Atropine-like action causes Antimuscarinic effects 2- α- adrenoceptors blockage causes Postural hypotension 3- Effects on 2A receptor causes: -Sexual dysfunction (especially in Phenelzine) -Sedation -Weight gain	1- Anticholinergic: (Dry mouth, blurred vision, constipation and urine retention, aggravation of glaucoma) 2- Antihistaminic: (Sedation, confusion, stop sedatives 1-2 weeks before use) 3- Antiadrenergic (α): (Postural hypotension, arrhythmias, conduction defects such as prolonged Q-T intervals and heart block) 4- Weight gain, sexual dysfunction, and impotence 5- Lower seizure threshold → Contraindicated in Seizure disorder. 6- Aggravation of psychosis

Con...

Food Interactions	1- Tyramin **(in aged cheese, liver, sausages, some meats, and yeast extracts)** 2- Levodopa **(in broad and FAVA beans)** **Those compounds are normally degraded by MAO. MAOI inhibits the process of degrading Tyramin which results in Tyramin being absorbed and taken up by adrenergic neurons and converted into false transmitter that replaces NE in the vesicles.** **Net result: HYPERTENSIVE CRISIS.**	1- Enhanced toxicity by: - Hepatic microsomal enzymes inhibitors because it is metabolized by liver enzymes. → Contraindicated in liver disease. - Plasma-bound drugs such as **Asprin** and **Phenylbutazone** because TCA is strongly bound to plasma proteins and other plasma-bound drugs decrease it binding and enhance its toxicity. 2- Hypertensive Crisis: with **SSRI**, **MAOI**, and any **Sympathomimetics**. → Contraindicated in heart disease and pheyochromocytoma. 3- Respiratory Depression: with **Sedatives** or **CNS depressants**. → Contraindicated in Chronic bronchitis. 4- Increased Anticholinergic effects: with **Antipsychotics** and **Antiparkinsonisms**. → Contraindicated in Glaucoma and prostate hypertrophy ***Contraindications:** Thyroid disease.
Drug Interactions	1- Drugs degraded by MAO: cause sever hypertension → hypertensive crisis. (**Indirect sympathomimetics**, **flu medication**, **local anesthetics**) 2- Drugs that increase Serotonin: cause Fatal Serotonin Syndrome → Hyperthermia, muscle rigidity, cardiovascular collapse (**SSRI**; must keep at least 6 weeks between giving MAOI and SSRI) 3- **Pethidine**: MAOI inhibit its metabolism which results in the increase of its levels → ↑ action (Hyperpyrexia, irritability, hypotension, and coma).	

Notes on TCA:

EARLY IN USE ➔ During 1st month ➔ aggravate suicidal thoughts specially in young aged. Can happen less upon change of dose.

DURING USE ➔ narrow therapeutic index ➔ toxicity can develop

Excitement, delirium , convulsions, respiratory depression , coma, atropine like- effects, cardiac arrhythmias, sudden death.

STOPAGE OF USE ➔ Withdrawal Symptoms; characterized by cholinergic rebound, flu-like symptoms.

SUMMARY

- Anti-depressant drugs :
- 1-MAO inhibitors
- 2-Tricyclin inhibitors
- **Indication of MAOI >> atypical depression + social phobia
- **Indication of Tricyclin inhibitors >> depression , psycatric , bed-sweatting , Nueropathic and prophylaxis of migrain
- ^^MAOI >> have anti-muscaranic effect
- ^^Tricyclin >> have anti-cholinergic, anti-histaminic and anti-adrenergic effects
- $$ MAOI : if given with (indirect acting sympathmimetic, flue medications, local anesthetics & TCA) severe hypertension
- While if it is given with Pethedin : hypotension
- $$ TRICYCLIC : With MAOIs, SSRIs or any sympathomimetic drugs >> sever hypertenstion

QUESTIONS

- Why there is a latency in getting the clinical effects of anti-depressant-drugs?

Secondary Adaptive mechanism

- Depressed patient come with hyperthermia, muscle rigidity, cardiovascular collapse .. What is this condition and how it happened ?

serotonin syndrome, If MAOs inhibitors are given with SSRI

- 1- A 51-year-old woman with the symptoms of major depression also has narrow-angle glaucoma. Which of the following antidepressants should be avoided in this patient?

  a. Amitriptyline

  b. Sertaline

  c. Bupropion

  d. Mirtazepine

QUESTIONS

- 2- In which of the following drugs you should avoid foods containing tyramine ?

  a- Imipramine

  b- Amitriptyline

  c- Desipramine

  d- Phenelzine

- 3- Which of the following drugs is contraindicated in case of Pheochromocytoma ?

  a. Desipramine

  b. Sertaline

  c. Bupropion

  d. Mirtazepine

- ANSWERS: 1-A , 2-D , 3-A

THE END

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