Pharmacology Team 431

(CNS BLOCK)

Antidepressants Old Group

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Depression:

Disturbance in MOOD rather than of thought or behavior Yet it affects the way one feels about himself … (emotional changes), the way he person eats, sleeps,… (Biological changes), the way one thinks about things….(though changes) & The way he reacts….(behavioral changes). It can be **Unipolar:** Mood swings are always in the same direction. Or **Bipolar:** Depression alternates & oscillates with mania.

Antidepressants:

- 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 effect [to control depressive manifestations], even though their pharmacological actions starts immediately ➔ indicating that secondary adaptive changes must occur before the benefit is gained
- Raphe nuclei are inhibited by Serotonin + Raphe Nuclei inhibit NE release. In depression, Raphe Nuclei are stimulated (Indicates low serotonin), and thus, NE is inhibited, this is why we need to increase serotonin and NE.
- Treatment should continue 6 months at full therapeutic doses before withdrawal.
- Withdrawal of drugs must be very gradual otherwise **withdrawal symptoms** Agitation Worsening of the disease Withdrawal manifestation

Classification of Anti-Depressants:

A) Drugs that Block the RE-uptake of NE and 5-HT (e.g.: Most tricyclics) (old Antidepressants).
B) Drugs that Selectively Block Re-Uptake of 5-HT (SSRIs) (Fluoxetine; Paroxetine; Sertraline; Citalopram).
C) Drugs that Block Presynaptic α2-adrenoceptors (e.g.: Mirtazapine, Mianserin). (They inhibit alpha 2 receptors which inhibit the release of NE, Thus, it causes the release of NE by inhibiting the inhibition).
D) Drugs that Inhibit MonoAminoOxidase (MAOIs, Phenelzine, Tranylcypraine, Moclobemide).

Monoamine Oxidase:

- MAO is a mitochondrial enzyme found in nearly all tissues
- Two forms of monoamine oxidase exist:

MAO-A responsible for NE, 5-HT catabolism. It also metabolizes tyramine of ingested food
MAO-B is more selective for dopamine metabolism

Monoamine Oxidase Inhibitors:

Types	Non-Selective (MAO-A & MAO-B): • **Reversible ➔ Tranylcypromine, [persists 7 days after stop** • **Irreversible ➔ Phenelzine, long acting [persists 2w after stop]**	Selective: • **Reversible ➔ Moclobemide, *(MAO-A)* *this is mostly used from MAOIs*** • **Irreversible ➔ Selegiline, *(MAO-B) anti Parkinson's drug*** Both types are rarely used now
Mechanism of action	MAOIs ➔↓ activity of MAO ➔ preventing monamine break down ➔↑ availability indirectly Possess both α Adrenoceptor & mAch blocking effects	
Indications	Now only reserved in atypical depression and depression resistant to other therapy (last drug to use) In treatment of social anxiety (agrophobia)	
ADR	1. Antimuscarinic effects. 2- Postural hypotension. 3- Sexual dysfunction mainly with phenelzine. 4- Sedation, sleep disturbance. 5- Weight gain 6- Hepatotoxicity (phenelzine)	
Food interaction	Many foods containing **tyramine** are normally degraded in the gut by **MAO-A** *Aged cheese, liver, sausages, fish, some meat & yeast extracts.* Levodopa; *Broad beans, FAVA beans.* Cause hypertensive crisis	
Drug interaction	1. **Hypertensive crisis** → with (sympathometic, flu medication, local Anesthtics, &TCA) 2. **Fatal Serotonin Syndrome** → with SSRI [hyperthermia, muscle rigidity, cardiovascular collapse] keep 6 weeks space between their use 3. **Toxicity** → Pethidine	

Drug interactions of MAOIs are IMPORTANT

Tricyclic Antidepressants:

<table>
<tr><td>Types</td><td colspan="3">1st Generation Tricyclic Antidepressants ➔ have three-ring nucleus structure
Tertiary amines: Block 5HT& NE reuptake More side effects
*Imipramine (Tofranil) *Amitriptyline (Elavil)
Secondary amines: More selective to NE Less side effects
*Desipramine (Norpramin) *Nortriptyline (Pamelor)
➢ Block ADR (α_1), Histamine (H_1) & Ach (M_1) receptors.</td></tr>
<tr><td>Pharmacokinetics</td><td colspan="3">• Given once daily Most are incompletely absorbed Undergo first-pass metabolism.
• Highly bound to plasma proteins. Some of them give active metabolites:
*Imipramine ➔ Desipramine * Amitriptyline ➔Nortriptyline</td></tr>
<tr><td>Clinical Indication</td><td>1- Treatment of depression:
Used for long duration without loss of effectiveness [preferable to MAOIs] > In resistant depression if others fail
➢ Elevate mood
➢ Improve mental alertness.
➢ Increase physical activity
❖ With lithium in depressed phase of bipolar depression
❖ With antipsychotics in depressed psychotic patients.</td><td>2-Other psychiatric disorders
• Obsessive-compulsive disorders (OCD)(OCD; ↓ DA & NE in the brain's prefrontal cortex.)
• Generalized anxiety disorders
• Panic disorders
• Anorexia nervosa</td><td>3-Other disorders: (IMP)!!
• Control bed-wetting in children; Imipramine ➔↟ contraction of internal sphincter of bladder . Better desmopressin Gradually withdrawn/Treatment period do not exceed 3 months.
• Neuropathic pain; better Tertiary amines > → modulate endorphins given at doses < that prescribed for depression.
• Prophylaxis of migraine</td></tr>
<tr><td>ADR</td><td colspan="3">• Anti-cholinergic: Dry mouth, blurred vision, constipation & urine retention, aggravation of glaucoma
• Anti-histaminic: Sedation, confusion. Stop sedatives 1-2 w before use
• Anti-adrenergic (>α) ➔ C.V.S; Postural hypotension, arrhythmias conduction defects (prolonged Q-T interval - heart block)
• Weight gain, sexual dysfunction * Lower seizure threshold *Aggravation of psychosis</td></tr>
<tr><td></td><td colspan="3">Early in use → Suicidal thoughts</td></tr>
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Precaution in use	**During use** → toxicity **Stoppage of use** → withdrawal symptoms
Interactions	• Being strongly **bound to plasma proteins** → toxicity enhanced by aspirin, phenylbutazone, *(e.g. Pt w/ arthritis)* • Being metabolized by **hepatic microsomal enzymes** → toxicity by enzyme inhibitors. • With **MAOIs, SSRIs** or any sympathomimetic drugs → cause **hypertensive crisis** • Additive to sedatives or other CNS depressants → ↓respiration • Additive to antipsychotics & anti parkinsonisms → ↑ anti-cholinergic effects
Contradictions	• **Glaucoma** • **Seizure disorder** • **Thyroid disease** • **Pheochromocytoma** • **Prostate hypertrophy** • **Chronic bronchitis** • **Liver disease** • **Heart disease** *Anti-cholinergic* Sympathetic

Summary:

1- Desipramine is the most potent tricyclic in inhibiting the reuptake of NE.
2- Tertiary Amine tricyclic antidepressants has more side effects than secondary amines.
3- Tricyclic antidepressants in general are not commonly used for depression, but it is still used in other conditions. E.g. Amitriptyline is used in migraine and anxiety.
4- Mono amino oxidase inhibitors are only used in refractory cases (don't respond to other treatments).
5- MAO inhibitors have many drug and food interactions, It can react with foods containing **Tyramine** and cause **hypertensive Crisis** (Cheese Reaction).
6- Combining SSRIs with MAOIs will Result in **Serotonin Crisis** (Muscle Rigidity, Hyperthermia and CVS Collapse.

Questions:

1) Imipramine causes tachycardia by all of the following Except:
    a. Increase NE.
    b. Anticholinergic Effect.
    c. Increase Serotonin.
    d. Reflex Tachycardia Caused By postural Hypotension.

2) The irreversible MAO inhibitors have a very high risk of developing:
    a. Respiratory depression.
    b. Cardiovascular collapse and CNS depression.
    c. Hypertensive reactions to tyramine ingested in food.
    d. Potentially fatal agranulocytosis.

3) Indicate the antidepressant, which blocks the reuptake pumps for serotonin and norepinephrine:
    a. Amitriptyline
    b. Fluoxetine
    c. Maprotiline
    d. Phenelzine

4) Which of the following agents is related to tricyclic antidepressants?
    a. Nefazodon
    b. Amitriptyline
    c. Fluoxetine
    d. Isocarboxazid

5) Indicate the irreversible MAO inhibitor, which is a hydrazide derivative:
    a. Moclobemide
    b. Selegiline
    c. Tranylcypramine
    d. Phenelzine

6) Which of the following is NOT contraindication for using Tricyclic antidepressants:
    a. Pheochromocytoma.
    b. Heart Disease.
    c. Glaucoma.
    d. Diarrhea.

7) Combination of SSRI with MAOIs will result in:
    a. Hypertensive Crisis.
    b. Muscle Rigidity, Hyperthermia and CVS collapse.
    c. Respiratory Distress.
    d. Renal Failure.

8) Which of the following antidepressants is a selective short-acting MAO-A inhibitor?
    a. Maprotiline
    b. Amitriptyline
    c. Moclobemide
    d. Selegiline

Answers: C – C – A – B – D – D – B – C