ANTIDEPRESSANT AND ANTIANXIETY DRUGS

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Introduction

- Major depression: symptoms
  - ✓Sad mood
  - ✓Loss of interest
  - ✓Worthlessness
  - ✓Guilt
  - ✓Change in appetite
  - ✓Sleep
  - ✓Suicidal thoughts
- Either unipolar or bipolar disorder

Antidepressants

- Drugs which can elevate mood
- Main mode of action

1) Metabolism
2) Reuptake
3) Pre/post synaptic receptors

- Due to affecting more than one monoamine neurotransmitter, classified into

Classification

1. **Reversible inhibitors of mono amine oxidase (RIMAs)**:
   - Moclobemide, Clorgyline
2. **Tricyclic antidepressants (TCAs):**
   A. NA + 5-HT reuptake inhibitors: Imipramine, Amitriptyline, Doxepine
   B. Predominantly NA reuptake inhibitors: Desipramine, Nortriptyline, Amoxapine, Reboxetine
3. **Selective Serotonin Reuptake Inhibitors (SSRIs):**
   - Sertraline, Citalopram, Fluoxetine, Fluoxamine, Paroxetine, Dapoxetine
4. **Serotonin and Noradrenaline Reuptake Inhibitors (SNRIs):**
   - Venlafaxine, Duloxetine
5. **Atypical antidepressants:**
   - Trazodone, Mianserin, Mirtazapine, Bupropion, Tianeptine, Atomoxetine

❖MAO inhibitors: Moclobemide, Clorgyline

MAO-A deaminates 5-HT and NA

Initially non-selective MAO inhibitors were in use

*Cheese reaction

Similar reaction can occur with cough & cold remedies, TCAs, SSRIs, SNRIs

❖RIMAs: Moclobemide

Competitive, reversible, short duration of action

Clinically useful in elderly and cardiac patients; also in social phobia

Lacks anticholinergic, antihistaminic, cardiovascular adverse effects of TCAs

S/E: Nausea, headache, insomnia, excitement, liver damage

❖TCAs:

NA & 5-HT reuptake inhibition

Also have antiadrenergic, anticholinergic and antihistaminic property, known as ‘first generation antidepressants’.

Followed by second generation (SSRIs, SNRIs)

- Pharmacological actions:

1. CNS:

After 2-3 weeks of continuous treatment, mood is gradually elevated

REM sleep phase is suppressed and reduction in night awakenings

Different **sedative** property, more sedative for agitated patients

Lower **seizure** threshold: produce convulsions (e.g. Clomipramine & Bupropion)

- **Antidepressants**: Inhibit NA & 5-HT uptake

- **CNS stimulant drugs**: Inhibit DA uptake

- **Monoaminergic hypothesis**:

Deficiency of NA and 5-HT in limbic & cortical areas

Why delay of 2-3 weeks in antidepressant action?

- **Neurotrophic hypothesis of depression:**

Deficiency of BDNF improved by antidepressants leads to neural plasticity

Increase in monoaminergic transmission leads to neurotrophic changes

Therapeutic response is delayed due to time taken for neurogenesis to occur

2. ANS:

Anti adrenergic (α1):

Anti cholinergic action:

3. CVS: Prominent at therapeutic doses

Tachycardia, postural hypotension, arrhythmias

- Tolerance & dependence:

Tolerance develops to anticholinergic and hypotensive actions gradually

Physical dependence over long term high dose use

- P/K:

Absorption: good

Distribution: High tissue & PPB

Long t1/2 allows once daily dosing at bed time

Metabolism: CYP2D6, CYP3A4

Excretion: Urine

*Dose should be individualized due to narrow therapeutic window

- Adverse effects: more with this group of drug

1. **A**nticholinergic
2. **A**ntihistaminics
3. **A**ntiadrenergic
4. Increased **A**ppetite and weight gain
5. Cardiac **A**rrhythmias
6. Abrupt '**S**witch over'
7. **S**weating
8. **S**eizures: Clomipramine, Bupropione, Amoxapine
9. **S**exual distress

Drug	Sedation	Anti-muscarinic	Hypotension	Cardiac arrhythmia	Seizure precipitation	Daily dose (mg)
Tricyclic antidepressants (TCAs)						
1. Imipramine	+	++	++	+++	++	50–200
2. Amitriptyline	+++	+++	+++	+++	++	50–200
3. Trimipramine	+++	++	++	+++	++	50–150
4. Doxepin	+++	++	++	+++	++	50–150
5. Clomipramine	++	++	+	+++	+++	50–150
6. Dothiepin (Dosulepin)	++	++	++	++	++	50–150
7. Nortriptyline	+	++	+	++	+	50–150

- Acute Poisoning:

Excitement, delirium, anticholinergic manifestation followed by convulsions, coma

Treatment:

1. Gastric lavage
2. Respiratory assistance
3. Fluid infusion
4. Maintenance of vitals
5. Acidosis corrected by bicarbonate
6. Propranolol/lidocaine for arrhythmia

- Drug-drug interaction:

1. With sympathomimetic amines, MAO inhibitors
2. Replaced in PPB
3. SSRIs inhibit metabolism

- Major limitations:

1. Side effects profile

2. Low safety margin

3. Less response to therapy

❖SSRI:

-Higher efficacy than TCAs & RIMAs

-Improved tolerability and safety profile

-There are chances of non-responders to SSRI and SNRI

-First line drug for depression

-Can be useful in **neurosis** disorders; 1st choice drug for OCD, phobia, PTSD, kleptomania, premature ejaculation

-little or **no sedation, no anticholinergic or antiadrenergic side effects**

-no **seizure or arrhythmias**

- S/E:

Gastrointestinal

Interfere with ejaculation

Nervousness, restlessness, insomnia, headache, anorexia (milder form)

Epistaxis has been reported

- Drug-drug interaction:

Enzyme inhibition (CYP2D6, 3A4): TCAs, Warfarin

'Serotonin syndrome': MAOIs, Tramadol

*No significance difference in efficacy but P/K and S/E profile changes in individual SSRIs

Fluoxetine:

- Safe to use in children with depression and **OCD**, but preferred only after psychotherapy fails.
- Not suitable for patient of depression with agitation (its side effect)

Fluvoxamine:

-**OCD** and generalized anxiety disorder

-S/E: More nausea, dyspepsia, flatulence

Paroxetine:

-**Higher incidence of side effects**

Sertraline:

-Most commonly used

-Less side effect profile

-Less Drug-drug interaction

-Also effective in **juvenile depression**, **anxiety** and post traumatic stress disorder (**PTSD**)

Citalopram:

-**CVS**: Q-T prolongation and death

-Mood disorder in premenstrual dysphoric disorder

*Escitalopram : Improved safety profile

Dapoxetine:

Delaying premature ejaculation (1 hour before ejaculation), combined with behavioural therapy

Reference

Author	Outcomes	Journal	Level
Steven S cleavanger	Metanalysis Continuing SSRIs for 1 year appears to reduce risk of MDD and relapse.	Therapeutic advances in psychopharmacology	Level 1