ANTIDEPRESSANT AGENTS

Dr. kamlesh Patel

ASSOCIATE PROFESSOR
Department of Pharmacology
NHL MUNICIPAL MEDICAL COLLEGE

Psychiatric disorders

- Psychoses - schizophrenia
- Neuroses- anxiety disorders
- **Affective disorders of Mood**
- * **Unipolar Depression**
- * **Bipolar Depression** (Depression + Mania)
- { ↓ NA, ↓5-HT and ↓DA}
- * **Mania**
- { ↑NA, ↑ 5-HT and ↑ DA}

Affective Disorders of Mood

Depression

- Deficiency of NE,5-HT,DA in brain
- (A) Psychological/Reactive :-
  - * Sadness (Gloom)
  - * Unhappiness
  - * Tearfulness
  - * Blames the situation rather than himself
  - * Intense emotional feelings.

Ŗ Moral , spiritual, social support

Sedatives / anti - anxiety drugs

Mania

- Overproduction of monoamines (NE,5-HT,DA)
- Excessive enthusiasm
- Extreme self confidence
- Rapid Thought & Speech Pattern,Impaired judgement
- Excessive Physical activity, Restlessness , Irritability, Anger, Impatience, Brilliant ideas & outstanding work.
- Ŗ ECT, Anti– Manic Drug -à Lithium Carbonate

Affective Disorders of Mood

- **(B) Endogenous (Major depression)**
- * Dejection, Misery, Apathy, Hopelessness
- * Retardation of sleep, thought, speech, movement
- * Remains abstain, inferiority complex
- * Guilt, anxiety, inadequency, ugliness
- * Self – blaming, indecisiveness
- * Loss weight, Libido, appetite, self-esteem (confidence)
- * Tendency to commit suicide

Affective Disorders of Mood

- Monoamine Hypothesis:

- MANIA
- DEPRESSION

  - Modification- storage, release, uptake, degradation
  - ?concentration- postsynaptic receptors

CLASSIFICATION- ANTIDEPRESSANTS

- **(I) Drugs which Blocks Both NE and 5HT Re-Uptake :**
  Imipramine, Clomipramine, Amitriptiyine,Doxepin
- **(II) Drugs which Blocks NE– Re-Uptake :-**
  Desipramine, Nortryptiline, Amoxapine
- **(III) Selective Serotonin (5HT) Re-Uptake Inhibitors (SSRIs) :-**
  Fluoxetine, Sertraline, Fluvoxamine, Paroxetine, Citalopram
- **(IV) Atypical Antidepressants :-**
  Trazodone, Buspirone, Mirtazapine, Mianserin, Venlafaxine
- **(V) MAO- A Inhibitors :-**
  Moclobemide, Tranylcypromine
- **(VI) Antidepressant of Natural Origin :-**
  St. John's Wort (Hyperforin)

Antidepressant agents

(Psychoenaleptics or Mood Elevators)

(I) Limitations of Tricyclic Antidepressants (TCA) :-

- **S**low onset of action
- Effect achieved after 2-4 weeks of starting therapy
- Low margin of safety (< T.I.)
- Fatal in overdose
- Marked CVS, Neurological , Anticholinergic adverse effects
- Eg. Imipramine, Amitriptyline still used.

Antidepressant agents

(I) Limitations of MAO-A Inhibitors :-

* **Lower antidepressant effect than TCAs.**
* **Pronounced Hepatotoxicity**
* **Troublesome interactions with food (Cheese reactions) and drugs**
* **Not a drug of choice as an antidepressant**

BUT, may still be used in :

** **Major depression refractory to TCAs**
** **in whom ECT is C/I or refused**
** **In certain neurotic states like Phobias, Obsessive- Compulsive Disorders (OCDs)**
** **Narcolepsy by inhibiting REM sleep.**

Antidepressant agents

Newer Generations Antidepressants &Their Advantages:

** Better than TCAs
** Better S/Es& Acute Toxicity Profile
** Toxicity less than TCAs
** Short acting (Except – Maprotiline)
** Preferred in elderly
** Less CVS, neurological, anticholinergic S/Es

Eg. Doxepin, Dothiepin, Clomipramine, Trazodone.

Antidepressants

- **Advantages of SSRIs over TCAs :-**
- **Lack of cholinergic, CVS, neurological S/Es**
- **No weight gain**
- **Low acute toxicity**
- **Low risk of overdose (T.I. >)**
- **No interactions with food containing tyramine – Hence, no 'Cheese Reaction'.**

- **Eg. Fluoxetine, Fluvoxamine, Sertraline**

Tricyclic Antidepressants (TCA)

- Examples
  - **First Generation**
    - Imipramine (Tofranil)
    - Desipramine (Norpramin)
    - Amitriptyline (Elavil)
  - **Second Generation**
    - Doxipen (Sinequan)
    - Maprotiline (Ludiomil)
    - Amoxapine (Asendin)

Tricyclic Antidepressants (TCA)

- Prototype -à Imipramine
- Inhibits NE & 5-HT Uptake, Has α2 Adrenergic, Central Muscarinic inhibitory action

CNS:

Imipramine, desipramine :- Less sedation , anxiety, and unplesant --à Suitable for withdrawn & retarded patients.

Amitriptyline,Doxepin,Clomipramine,Trazodone :- Suitable for depressed pts with anxiety & agitation.

TCAs

- **CNS :-** * Elevation of mood (2-3 weeks)
- * Communicable, amenable & speaks
- * Start taking interest in surroundings
- * Awakenings during night reduced.

- **ANS:-** * Potent Anti - cholinergic effects :-
  * Dryness of mouth, palpitation, constipation
  * Blurred vision, urinary incontinence
  * Block NE uptake (Potent NE action)
  * Weak alpha-1 adrenergic blocking action
  * Antihistaminic (H-1) action (Amitriptyline, Mianserin)

TCAs

- **CVS: -** * Postural hypotension(α1 –Blockade)
  * Tachycardia (Anticholinergic, NE stimulation)
  * ECG Changes, Cardiac Arrhythmias (Old pts)
  (NE + Ach blockade, direct myocardium suppresion)

Tolerance & dependance :

- * Physical dependence à Prolong use
- * Withdrawal symptoms
- * No abuse potential

TCAs – Mechanism of Actions

- **(I) Blocks Re-uptake of Monoamines at nerve terminals :**
- 5-HT --à Mood Improvement (Trazodone)
- NE ---à Motor activity improvement (Imipramine, Nortryptiline, Desipramine)
- DA --à Mood elevation (Nomifesine)
- 5-HT + NE -à Amitriptyline

- **(II) Blocks Receptors :**
- H-1 -à Sedation
- Muscarinic -à Blurred vision, Dry mouth, Urinary retention
- 5-HT à Sedation, Antiemetic
- Ailpha adrenoceptors-à Postural Hypotension.

TCAs – Mechanism of Actions

- (III) Down regulation of Beta and 5-HT receptors
- (IV) Mianserin à More seizures (NE release – alpha -2 presynaptic antagonist action)
- (V) Amoxapine -à More seizures (Inhibits NE uptake, Blocks DA2 receptors **(Antidepressant + Neuraleptic à** Psychotic depression
- (VI) Trazodone -à Blocks 5-HT uptake selectively.
- No DA2 receptors activity.

Adverse effects

- Relatively common
  - Antimuscarinic – e.g., dry mouth, constipation, blurred vision, Intensity varies with different drugs (amitriptyline strongest).
  - CNS – sedation, weakness, fatigue; may switch depressed patient to manic phase; tremor;seizures
  - Cardiovascular – orthostatic hypotension (a_1 block), tachycardia, myocardial infarction, congestive heart failure, arrhythmias. May be less likely or less severe with 2nd generation drugs

Adverse Effects

- Cholestatic jaundice, allergy,agranulocytosis
- Acute poisoning – life threatening; excitement and restlessness
  - Seizures ? coma ? death.
  - Must support vital functions.
  - Physostigmine can reverse antimuscarinic, cardiotoxic, and neurotoxic effects.

TCA

Clinical Use

- Severe Major Depression
- Obscessive compulsive disorder & anxiety disorders
- Nocturnal enuresis (imipramine)
- ADHD-Desipramine,nortriptyline
- Acute Panic Disorder
- Irritable Bowel Syndrome (IBS)
- Bulimia, Anorexia Nervosa
- Phobic anxiety state (school phobia)
- Alcoholism, sleep apnoea.

Antidepressants

- **Specific serotonin reuptake inhibitors (SSRIs)**
  - **relatively new , drugs of first choice**
- Fluoxetine
- Paroxetine
- Fluvoxamine
- Sertraline
- Citalopram
- Escitalopram

SSRIs

- Pharmacological properties:
  - **block the reuptake of serotonin (5HT) - CNS potentiating - 5HT**
  - little or no effect on other neurotransmitter systems.

- CNS – not general stimulants but
  do elevate mood in depressed patients

- ANS – no significant effects in the ANS
- CVS – no significant effects in the CVS

SSRIs (cont.)

- Pharmacokinetics
  - Well absorbed orally
  - Hepatic metabolism – fluoxetine metabolized to active metabolite with long half-life
  - Long $t^{1/2}$ allows single daily dose
- **USES**

  Depression ,OCD, generalized anxiety disorder

SSRIs (cont.)

- Adverse effects
  - Nausea, headache, diarrhea are most common (stimulation of 5HT3 receptors)
  - Fluoxetine, and to a lesser extent, sertraline anxiety and motor restlessness, insomnia (stimulation of $5HT_{2C}$ receptors)

SSRIs (cont.)

- less common side effects - sexual dysfunction, dizziness, tremor, rash (Fluoxetine), hyponatremia (fluoxetine, venlafaxine).
- Current concern about paroxetine and suicide in children
- SSRIs lack the autonomic and cardiovascular side effects
- there is concern about **increased bleeding (platelet inhibition)**

SSRIs (cont.)

- Can “unmask” mania in patients with bipolar disorder
- Paroxetine may induce birth defects
- Drug interactions
  - Serotonin syndrome – potentially fatal
  - mix with other serotonin drugs (e.g., TCA, MAOI
  - symptoms include mental status changes, disorders of motor activity, and autonomic disturbances

Monoamine Oxidase Inhibitors

Irreverssible,	reverssible
nonselective	selective(MAO-A)
Tranylcypromine Phenelzine iproniazid	moclobemide

Monoamine Oxidase Inhibitors

- Pharmacological properties
  - **inhibition of monoamine oxidase**
    - CNS – stimulation,agitation,restlessness
    - Cardiovascular system – interference with postural reflexes, changes in cardiac conduction
    - Potentiate- pressor amines-HT crisis

Monoamine Oxidase Inhibitors

- Adverse effects
  - Central stimulation – tremors, insomnia
  - Overdose – agitation, hallucinations, convulsions, hypertensive crisis
  - Constipation, weakness, fatigue, skin rash, difficulty in urination, inhibition of ejaculation, headache
  - hepatotoxicity

Monoamine Oxidase Inhibitors

- Drug interactions
  - Potentiate sympathomimetic amines
  - Dangerous interaction with tyramine (found in food)
  - Prolong the effects of tricyclics, central depressants, analgesics, anticholinergic agents

Atypical Antidepressants

- chemically and pharmacologically different from SSRI, Tricyclics, and MAO inhibitors
  - Ø Trazodone **blocks** 5HT2A- Antianxiety,antidepressant
  - a -adrenergic-postural hypotension and priapism
  - H_1 receptors -sedation
  - Ø Nefazodone blocks 5HT2A - Antianxiety , antidepressant
  - 5HT1 Autoreceptors-? 5HT,NA release-antidepressant
  - ***Weak inhibition-5HT reuptake***

Atypicals (cont.)

- Mirtazapine- blocks H_1 receptors,
  - presynaptic a_2-adrenergic receptors, increases NE and 5HT release
  - blocks $5HT_2$ and $5HT_3$ receptors
    - Sedation

- Mianserine-same
  -Aplastic anemia