Antidepressant Drugs

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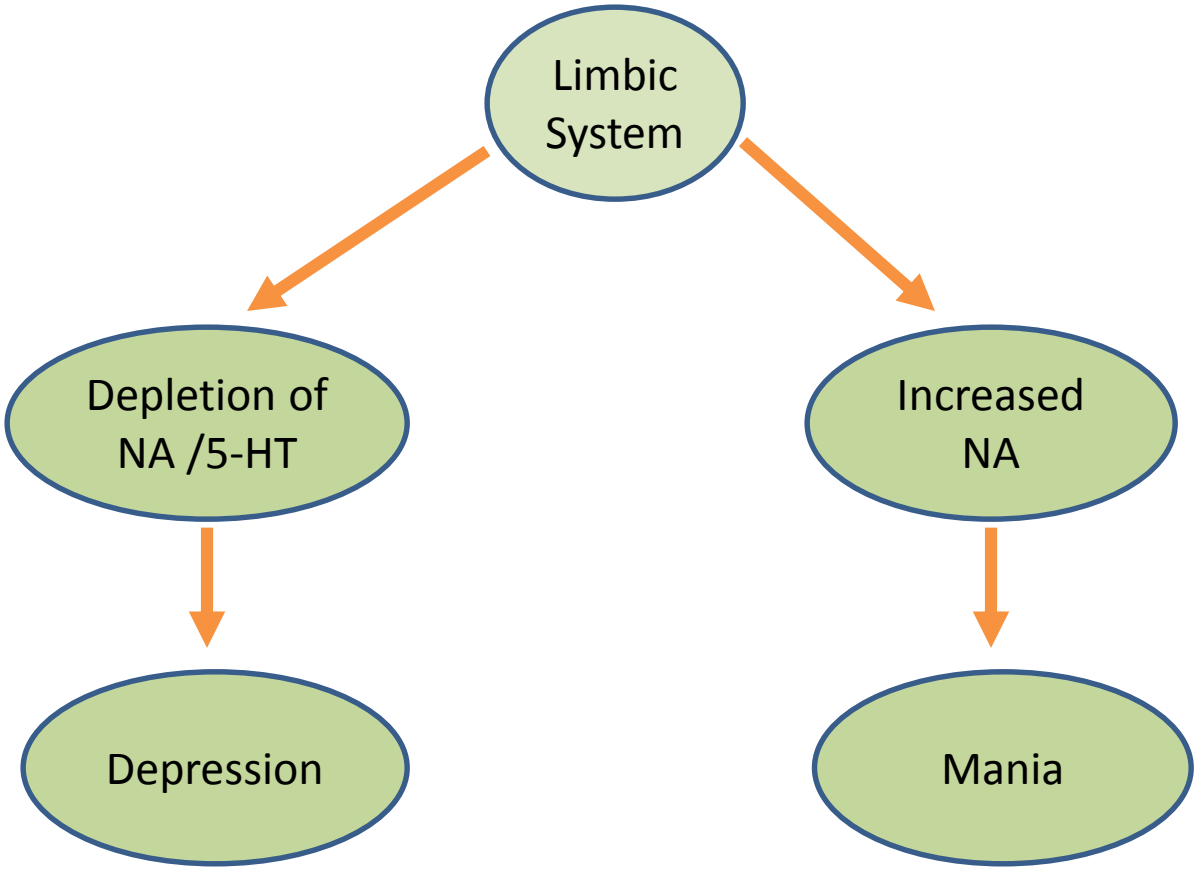
Limbic System
Depletion of NA /5-HT
Increased NA
Depression
Mania

Depression

- sadness
- hopelessness
- inability to experience pleasure
- changes in sleep patterns
- changes in appetite
- suicidal thoughts

Mania

- Enthusiasm
- anger
- rapid thought and speech patterns
- extreme self-confidence
- impaired judgment
- auditory hallucinations
- decrease need to sleep

NE System

NE pathways (originate in locus coereleus in midbrain) send their axons to

cortex	**mood, cognitive function**
Brainstem	**Drive and motivation**
limbic areas	
-hippocampus and amygdala	**Memory and emotion**
-hypothalamus	**Endocrine response**

Serotonin System

Serotonin neurons (raphe nuclei) located in the **pons and midbrain** send their projections to

cortex, hippocampus, amygdala, hypothalamus, thalamus

This system is also involved in:

- Anxiety
- Sleep
- Sexual behavior
- Temperature regulation

Serotonin receptors

- Divided into 1, 2, 3, and 4-7 family
- All are G-protein coupled receptors except 3
- 1- decreases cAMP while 4-7 increase cAMP
- 2- generation of IP_3/DAG
- 3- ligand gated cation channel

Reversible inhibitor of MAO-A (RIMAs)-Moclobemide, Clorgyline

Tricyclic antidepressants (TCAs)

- NA + 5 HT reuptake inhibitor- Imipramine, Amitriptyline, Trimipramine, Doxepin, Clomipramine, Dothiepin

- Predominantly NA reuptake inhibitor

Desipramine, Nortriptyline, Amoxapine, Reboxetine

Selective serotonin reuptake inhibitors (SSRIs)-

Fluoxetine, Fluvoxamine, Paroxetine, Sertraline, Citalopram, Escitalopram

Atypical antidepressants-

Trazodone, Mianserine, Mirtazapine, Venlafaxine, Duloxetine, Tianeptine, Amineptine, Bupropion

MAO (monoamine oxidase)

In neuron, MAO functions as a “safety valve” - inactivate any excess neurotransmitters

- **MAO – A**
  - -adrenergic nerve endings
  - -Intestinal mucosa
  - -Human placenta
  - -Liver
  - -Deaminates
    - Serotonin , Noradrenalin and dopamine
  - -Inhibited by moclobemide and clorgyline
- **MAO-B**
  - -brain (basal ganglia)
  - -Platelets
  - -Liver
  - -Deaminates
    - dopamine
  - -Inhibeted by selegiline

Nonselective MAOIs not favorable

Cheese Reaction

- Cheese, beer, wine, meat, fish contain large amount of tyramine (tyramine is indirectly acting amine)
- Due to irreversible blockade of MAO tyramine escapes degradation in intestinal wall and liver
- Tyramine reaches to circulation and displace large amount of noradrenalin from loaded nerves
- Results in **Hypertensive crisis**
- Phentolamine, Prazosin are used to treat this condition

Reversible inhibitor of MAO-A (RIMAs)

- Moclobemide-
  - –Reversible and selective MAO-A inhibitor
  - –Competitive enzyme inhibition
  - –Tyramine is able to displace it
  - –Cheese reaction is less likely
  - –Devoid of anticholinergic, sedative, cognitive, cardiovascular effects
  - –Good for elderly with heart diseases

Tricyclic Antidepressants (TCAs)

- **Imipramine** represents the class (Prototype)
- Inhibit monoamine reuptake (serotonin and noradrenaline)
- Increase the concentration of **Serotonin and NA** at synapse and potentiate the action (therapeutic effects)

- Other receptors affected by TCAs
    - Muscarinic blockade- Anticholinergic side effects (dryness etc.)
    - Alpha receptor blockade- postural hypotension etc
    - Histamine blockade -sedation
    - Dopamine blockade- antipsychotic effect (amoxapine)

TCAs actions (CNS)

- In Normal person

- Tiredness
- Sleepiness
- Difficulty in concentration,
- Gait disturbances
- Provoke anxiety
- Unpleasant

- In Depressed

-Sedation immediately

-Elevation of mood

(2-4Weeks)

-Suppresses REM

-prolongs total sleep duration

Lower seizure threshold and produce convulsions in overdose

TCAs uptake blockade is *not* directly responsible for antidepressant action

- Uptake blockade occurs quickly but antidepressant action occurs after months
- Initially

  Pre synaptic alpha 2 and 5-HT1 auto receptors are activated by increased amount of NA and Serotonin in synaptic cleft

  -resulting in decreased firing
- But on long term

  -desensitize and down regulation of these auto-receptors induce –

  -enhanced NA and Serotonin transmission

  -antidepressant action appears

- Signaling via NE or 5-HT increases the expression of

  brain-derived neurotrophic factor (BDNF)
- BDNF- related to the ultimate mechanism of action of antidepressant drugs
- Increase in BDNF levels

increased **neurogenesis** in the hippocampus

TCAs Adverse effects

- ***Anticholinergic***- dry mouth, bad taste, constipation, epigastric fullness, urinary retention (more common in elderly male), blurred vision, palpitation
- **Sedation**, mental confusion, weakness
- Increased appetite and weight
- Sweating, fine tremors
- Precipitation of seizures
- **Postural hypotension**
- **Cardiac arrhythmias**
- Rashes and jaundice (mianserin)

TCAs (Acute Poisoning)

- Usually suicidal attempt
- Presents as
  - **Excitement**
  - delirium
  - Anticholinergic symptoms like atropine poisoning
  - Muscle spasm
  - **Convulsions**
  - **arrhythmias**
  - Respiratory depression
  - Coma

- Treatment
  - Gastric lavage
  - I.V. line
  - Oxygen
  - Maintenance of BP and Temperature
  - Diazepam iv
  - Propranolol / lignocaine

Miscellaneous

- Amoxapine
  - Blocks D2 + inhibition of NA reuptake
  - Has mixed antidepressant and neuroleptic effects
  - Good for psychotic depression
- Reboxetine
  - Selective NA reuptake blocker
  - Weak action on 5-HT mechanism
  - Anticholinergic effects are minimal

TCA Vs SSRI

Limitations of TCA

- Anticholinergic effects
- Alpha blocking action
- Cardio toxicity
- Sedation, seizures ppt
- Weight gain
- Overdose poisoning common
- Incomplete response to Tt

Benefits of SSRI

- More tolerability and better acceptability
- No sedation, No seizure ppt
- No alpha blocking action
- Less chances of arrhythmia
- No weight gain
- Used in depression as well as in OCD, phobias
- Now 1st choice for OCD, Panic disorders, Social Phobia, Eating disorders, Premenstrual syndrome, Post traumatic stress

Individual compounds

- Fluoxetine
  - Prototype of SSRIs
  - Longest acting
  - activating SSRI
- Sertraline
  - activating SSRIs
  - Less chances of drug interactions due to low potency to cause cytochrome enzyme depression
- Fluvoxamine
  - Short acting
  - Sedating SSRI
  - Commonly used in indoor patients
- Paroxetine
  - Short acting
  - Sedating SSRI
  - More GI side effects

SSRIs

- **Side effects**
  - **Gastric upset**
  - **Nausea**
  - **Diarrhea**
  - **Anorexia**
  - **Interfere with ejaculation**
  - **Nervousness**
  - **Restlessness**
  - **Insomnia**
  - **Headache**
  - **Epistaxis**
  - **Ecchymosis**
- **Others**
  - ***Inhibit*** **cytochrome enzymes** and elevate the plasma level of other drugs
  - If other serotonergic drug (MAOIs) is taken simultaneously, may precipitate **Serotonin Syndrome** manifesting as agitation, restlessness, sweating, twitching, convulsions

Atypical Antidepressants

- Trazodone
  - Blocks 5-HT uptake
  - Has prominenent alpha blocking
  - potent 5-HT_2 antagonist
  - No anticholinergic effect
  - **Prolonged and painful penile erection (priapism)**
- Mianserin
  - **Blocks pre-synaptic alpha 2 receptors** increases release and turnover of NA
  - Antagonist at serotonin 2, 1c, and H1 receptors
  - Has sedative effect
  - Damages liver and bone marrow (Reserve drug)

Atypical Antidepressants

- Tianeptine / and Amineptine
  - Increases rather inhibiting 5-HT uptake
- Bupropion
  - Inhibits DA and NA uptake has excitant effect
  - Used to reduce smoking
- Duloxetine
  - Duloxetine increases uretheral tone, used in urinary incontinence (over active bladder)
  - Used in panic attacks, diabetic neuropathic pain

Antidepressant uses

- Depression -(ECT may be needed in severely depressed and patients having suicidal tendency)
- Bipolar affective disorders- TCAs and lithium or SSRIs with lithium or valporate/ lamotrigine
- Psychotic depression - SSRIs with atypical antipsychotic
- Obsessive compulsive disorders -(SSRI and Clomipramine)
- Eating disorders (fluoxetine)

- Neuropathic pain (Amitriptyline)
- Attention deficit hyperactivity disorder in children (bupropion)
- Enuresis- (Imipramine 25mg at night)
- Overactive bladder (stress incontinence)- Duloxetine
- Migraine prophylaxis-(Amitriptyline)
- Pruritus -(Topical doxepin)

Mania and MDI

Treatment

- Lithium
- Carbamazepine
- Sodium Valproate
- Lamotrigine
- Topiramate
- Gabapentin
- Olanzapine, aripiprazole, quetiapine

Lithium

- inhibition of inositol monophosphatase
- decreased cerebral inositol concentrations
- suppresses inositol signaling

- inhibits glycogen synthase kinase-3 (GSK-3), a multifunctional protein kinase.
- GSK-3 is a component of diverse intracellular signaling pathways.

Dec NA and DA, Without affecting 5-HT release

S/E of Lithium

- Tremors
- seizures
- Diabetes incipidus
- Goiter, Hypothyroidism
- C/I during pregnancy- may cause congenital abnormalities (cardiac)

- TDM is required

  (maintained level 0.5 - 0.8mEq/L)

Toxicity appears when serum level exceeds 1.5 mEq/L

Thanks