Antidepressant Drugs

Disclaimer: This presentation is meant for educational purposes only and not for any commercial activity
Limbic System

Depletion of NA / 5-HT
- Depression

Increased NA
- 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
- Inhibited 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 (2-4 Weeks)
  - 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

• Fluvoxamine
  – Short acting
  – Sedating SSRI
  – Commonly used in indoor patients

• Sertraline
  – Activating SSRIs
  – Less chances of drug interactions due to low potency to cause cytochrome enzyme depression

• 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 prominent 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 urethral 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