Pyschosis

- Pyschosis is a mental health problem that causes people to perceive or interpret things differently from those around them.
- Psychosis is a loss of contact with reality typically including delusion and hallucination.

Symptoms

- Loss of touch with reality
- Hallucination (seeing, hearing, feeling or otherwise perceiving things are not there)
- Delusion (false beliefs) a person may believe that other people want to kill him, even when other people donot want to kill him)
- Illusion: mistaken perception or misinterpretation of stimulus arising from external objects.
- Loss of insight (person doesnot recognize that he is ill and feel his experiences an behaviour is normal)
- Disorganized thought or speech behavior
- Inappropriate mood (person is abnormally happy and talks too much or person may laugh or cry for no reason)

Antipsychotic / Neuroleptics Drugs

- These are the drugs having a salutary therapeutic effect in psychosis.
- All currently available antipsychotic drugs that alleviate symptoms of schizophrenia, decrease dopaminergic and/or serotonergic neurotransmission.

Classification
Typical Neuroleptic
Low potency- chlorpromazine, prochlorperazine, thioridazine
High potency- Flupenazine, Haloperidol, Pimozide, Thilothixene

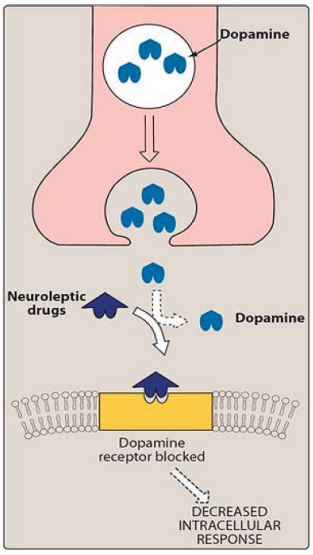
Atypical Neuroleptic- Clozapine, Olanzapine, Risperidone, Aripiprazole, Ziprasidone

Mechanism of action

Dopamine receptor blocking activity in the brain

- All antipsychotics (except clozapine-like atypical) have block dopamine (D2) receptors in the brain and the periphery.
- Antipsychotic potency has shown good correlation with their capacity to bind to D2 receptor in the mesolimbic system of the brain.

The actions are antagonized by agents that raise synaptic dopamine concentrations (levodopa, bromocriptine).



Serotonin receptor blocking activity in the brain
Most of the newer atypical agents appear to exert part of their unique action through inhibition of serotonin receptors (5-HT), particularly 5-HT_{2A} receptors.

Pharmacological Actions

1. Antipsychotic actions: All of the neuroleptic drugs can reduce the hallucinations and delusions associated with Schizophrenia by blocking dopamine receptors.

2. Extrapyramidal effects: Dystonias (sustained contraction of muscles leading to twisting distorted postures), parkinson-like symptoms, akathisia (motor restlessness), and tardive dyskinesia (involuntary movements of the tongue, lips, neck, trunk, and limbs) occur with chronic treatment.
Blocking of dopamine receptors probably causes these unwanted movement symptoms.
The atypical neuroleptics exhibit a lower incidence of these symptoms..

Actions

3. Antiemetic effects: Most of the neuroleptic drugs (except aripiprazole and thioridazine) have antiemetic effects that are mediated by blocking D2-dopaminergic receptors of the chemoreceptor trigger zone of the medulla. [Note: The atypical antipsychotic drugs are not used as antiemetics.]

4. Antimuscarinic effects: Some of the neuroleptics, particularly thioridazine, chlorpromazine, clozapine, and olanzapine produce anticholinergic effects, including blurred vision, dry mouth (exception: clozapine increase salivation), confusion, and inhibition of gastrointestinal and urinary tract smooth muscle, leading to constipation and urinary retention. This anticholinergic property may actually assist in reducing the risk of EPS with these agents.

Actions

5. Other effects:

- Blockade of alpha adrenergic receptors causes orthostatic hypotension and light- headedness.
- The neuroleptics also alter temperature-regulating mechanisms and can produce poikilothermia (body temperature varies with the environment).
- In the pituitary, neuroleptics block D2 receptors, leading to an increase in prolactin release. Atypical neuroleptics are less likely to produce prolactin elevations.
- Sedation occurs with those drugs that are potent antagonists of the H1-histamine receptor, including chlorpromazine, olanzapine, quetiapine, and clozapine.

Therapeutic uses

- Schizophrenia
- Anxiety
- Antiemetic
- Other uses
  - To potentiate hypnotics, analgesics and anaesthetics
  - Intractable hiccups (Chlorpromazine)

Adverse effect

CNS: Drowsiness, lethargy, mental confusion
CVS: Postural hypotension, palpitation
Anticholinergic: Dry mouth, blurring of vision, constipation, urinary retention
Extrapyramidal Effect
Endocrine: Hyperprolactinemia

Neuroleptic malignant syndrome (NMS) is a possibly fatal syndrome that can be caused by chlorpromazine. Symptoms may include fever; stiff muscles; confusion; abnormal thinking; fast or irregular heartbeat; and sweating

Difference between Typical Antipsychotics and Atypical Antipsychotics

1. The side effects of atypical anti psychotics are much less than the typical anti psychotics.
2. The efficacy of atypical anti psychotics is much more than the typical anti psychotics in the treatment of psychosis.
3. Atypical anti psychotics are less likely to cause extra pyramidal motor control and tardive dyskinesia disabilities when compared to typical anti psychotics.
4. Atypical anti psychotics are easier to discontinue and are less addictive than the typical anti psychotics.
5. Withdrawal symptoms are less likely with atypical anti psychotic drugs as the physical dependency of this drug is less when compared to typical anti psychotics.

Drugs Used in Mood Disorders

- Mood disorders are a group of mental disorders characterized by extreme exaggerations and disturbances of mood and affect.
- Mood disorders can be classified as depression (unipolar disorder) and mania; alternating episodes of mania and depression (manic depression) are termed bipolar disorder.
- Drugs used to treat these conditions may be grouped into

1 Antidepressants
2 Antimanic (Mood stabilizer)

Drugs used in depression

Depressive illness is characterized by feelings of intense sadness and despair, dysphoric mood, attempts at suicide, hopelessness, worthlessness, feeling of guilt and shame, mental slowing and loss of concentration, pessimistic worry, social withdrawal, anhedonia (lack of pleasure in things previously enjoyed), self-deprecation, and variable agitation.

Theories of Depression

The Monoamine Theory

The main biochemical theory of depression is the *monoamine hypothesis* which states that depression is caused by a functional deficit of monoamine transmitters at certain sites in the brain, while mania results from a functional excess.

noradrenaline (norepinephrine) and 5-hydroxy tryptamine (5-HT) being the key mediator.

Classification of Antidepressants

1. Reversible inhibitors of MAO A (RIMAs)- Moclobemide, Clorgyline
2. Tricyclic Antidepressants (TCAs)

i. *NA + 5-HT reuptake inhibitors*- Imipramine, Amitryptyline, Trimipramine, Doxepin, Dothiepin, Clomipramine

ii. *Predominantly NA reuptake inhibitors*- Despiramine, Nortriptyline, Amoxapine

3. Selelective serotonin reuptake inhibitors (SSRIs)- Fluoxetine, Fluvoxamine, Paroxetine, Sertaline, Citalopram
4. Atypical antidepressants- Trazodone, Mianserin, Mirtazapine, Venlafaxine, Tianeptine, Amineptine, Bupropion

Reversible inhibitors of MAO-A

- MAO is a enzyme localized in mitochondrial membranes found in nerve terminals, the liver, intestinal mucosa and other organs. It regulates the metabolic degradation of catecholamines and serotonin in the CNS or peripheral tissues.
- Two isoenzyme forms of MAO have been identified. MAO-A deaminates 5-HT and NA, and is inhibited by clorgyline, moclobemide.
- MAO-B deaminates epinephrine, norepinephrine and dopamine and inhibited by selegiline.
- Selective inhibitors of MAO-A are more effective in treating major depression than are type B inhibitors.

Moclobemide

- This is a short-acting, reversible, selective MAO-A inhibitor with moderate grade of antidepressant effect.
- *Indications*: depressive illness, social phobia
- *Adverse effects*: orthostatic hypotension, nausea, dizziness, drowsinees, headache, insomnia, rarely excitement and liver damage.
- *Contraindication*: hepatic impairment or abnormal liver function tests, cerebrovascular disease, pheochromocytoma,
- *Dose*: 150 mg BDS-TDS (max 600 mg/day)

Tricyclic Antidepressant: Amitryptyline

- These drugs are popularly known as tricyclic antidepressants because of the characteristic three-ring nucleus and act by nonselective blockade of the reuptake of both norepinephrine and serotonin.
- except venlafaxine also have significant level of muscarinic cholinergic-, alpha-adrenergic- and H1-receptors blocking properties and so produce sedative and autonomic effects.

Adverse effects: sleepiness, weakness, fatigue, seizures, convulsion; dry mouth, sour or metallic taste, epigastric distress, constipation, dizziness, tachycardia, palpitations, blurred vision, urinary retention; orthostatic hypotension, sinus tachycardia, tremor, cardiac arrhythmias; weight gain,

Tricyclic Antidepressant

Contraindication: pregnancy, hepatic dysfunction, cardiac disease, history of urinary retention.

Dose:
Amitryptyline: 50-200mg/d

- The major limitations of conventional TCAs are:
- ✓ Frequent anticholinergic, cardiovascular and neurological side effects.
- ✓ Relatively low safety margin, hazardous in overdose; fatalities common.

Selelective serotonin reuptake inhibitors (SSRIs): Fluoxetine

- These drugs block neuronal transport of serotonin immediately and apparently indefinitely, leading to complex secondary responses.
- SSRIs have fewer antimuscarinic side effects than the older tricyclics and they are also less cardiotoxic in over dosage.
- Adverse effects: dose-related, fairly common gastrointestinal effects include nausea, vomiting, dyspepsia, abdominal pain, diarrhea, constipation, anorexia and weight loss; paradoxically may be increased appetite and weight gain; sexual dysfunction
- *Contra-indications:* hepatic and renal impairment; pregnancy and breast-feeding; epilepsy
- Fluoxetine: 20-50 mg/d Sertaline: 50-200 mg/d

Atypical anti depressants

Atypical anti depressants have actions at several different sites. They are not SSRIs or SNRIs. They have different mechanisms of actions. They are different in side effects profile and have additional beneficial effects and indications. However they are more efficacious than TCAs (tricyclic antidepressants)

Bupropion

- It often is described as norepinephrine dopamine reuptake inhibitor (NDRI) and is also a nicotinic antagonist.
- primarily used as an antidepressant and smoking cessation aid.
- Side Effect: *Dry mouth, Sweating, Nervousness, Tremor, Increase risk of seizures at high doses*

Nefazodone

- This drug is weak inhibitor of serotonin reuptake. It blocks post synaptic 5HT 2A receptors and hence, enhances neurotransmission.
- Nefazodone is hepatotoxic

Mirtazapine

- It blocks presynaptic alpha 2 receptors and enhance the neurotransmission of serotonin and nor epinephrine. (Stimulation of alpha 2 receptors blocks further release of epinephrine or serotonin. Inhibition of alpha 2 receptors enhances the neurotransmission.)
- It also blocks 5 HT2 receptors. (5HT 2 receptors Inhibit neurotransmission. Therefore, inhibition of these receptors will enhance transmission.)
- It has antihistaminic activity and has sedative activity; hence it can be used In depressed patients having difficulty in sleeping.

Side effect: Increased appetite, Weight gain, Sedation.

Antimanic (Mood stabilizer)

- Bipolar affective (manic-depressive) disorder is characterized by cyclic attacks of mania with many symptoms of paranoid schizophrenia.
- The episodes of mood swings characteristic of this condition are generally unrelated to life events.
- Although exact biologic disturbance has not been identified, a preponderance of catecholamine-related activity is thought to be present.
- Acetylcholine or glutamate may also be involved. However, the nature of abrupt switch from mania to depression experienced by some patients is uncertain.

Lithium: Antimanic or mood stabiliser

- The antimania drug lithium is a small monovalent cation and commonly referred as a "mood-stabilizing" agent.
- Lithium salts have a narrow therapeutic/ toxic ratio and should only be prescribed if there are facilities for monitoring serum lithium concentrations.
- It is not a sedative, depressant, or euphoriant, and this characteristic differentiates Li+ from other psychotropic agents.

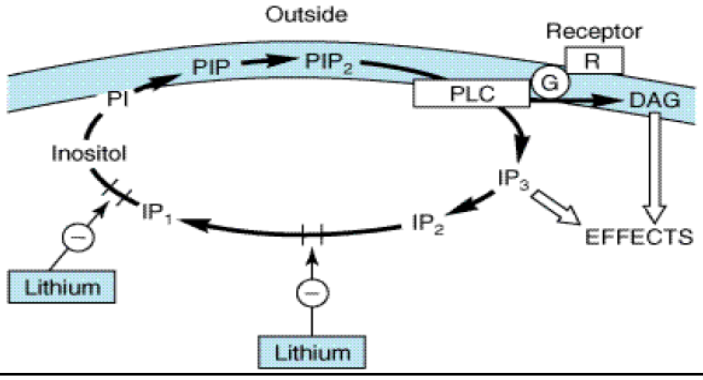
MOA

- The precise mechanism of action of Li+ as a mood-stabilizing agent remains unknown. Several speculations have been made including

1. **<u>Effects on Electrolytes and Ion Transport</u>:** Li^+ is being closely related to Na^+, replaces Na+ but being inadequate as substrate for Na+ pump, cannot maintain membrane potentials and thus resulting in neuronal inhibition;
2. **<u>Effect on Neurotransmitter:</u>** Its inhibitory effects on the depolarization-provoked and Ca2+-dependent reduces release of norepinephrine and dopamine and lastly

MOA

<u>3. Effects on second messengers:</u> its inhibitory effects on several enzymes in the normal recycling of membrane phosphoinositides leading to depletion of phosphoinositol-4,5 bisphosphate (PIP2), the membrane precursor of the second-messengers inositol triphosphate (IP3) and diacylglycerol (DAG).



Adverse effects

- Side effects are common, but are mostly tolerable. Toxicity occurs at levels only marginally higher than therapeutic levels.
- **Nausea, vomiting and mild diarrhoea** occur initially, can be minimized by starting at lower doses.
- **Thirst and polyuria** are experienced by most, some **fluid retention** may occur initially, but clears later.
- **Fine tremors and rarely seizures** are seen even at therapeutic concentrations.
- CNS toxicity manifests as plasma concentration rises-tremors, ataxia, motor incoordination, mental confusion, slurred speech → require withdrawal of treatment with severe overdosage (plasma concentration above 2 mEq/L).
- Treatment: It is symptomatic. There is no specific antidote. Osmotic diuretics and sod. bicarbonate infusion promote Li+ excretion. Haemodialysis is indicated if serum levels are > 4 mEq/L.

Other mood stabilizing agent

- Carbamazepine
- Sodium valproate
- Lamotrigine
- Atypical antipsychotics (olanzapine)

Parkinson's Disease

- is a progressive degenerative disorder, mostly affecting older people, first described by James Parkinson in 1817.
- is a progressive neurological disorder of muscle movement as a clinical syndrome consisting of 4 cardinal features:

1. Bradykinesia (slowness and poverty of movement)
2. Muscular rigidity (involves increased muscular resistance to passive range of motion. Postural instability may lead to falls).
3. Resting tremor (Tremor is present most commonly in the hands, often begins unilaterally. The resting tremor is absent during sleep)
4. Impairment of postural balance leading to disturbances of gait (walking, stepping, or running) and falling.

Cause of disorder

- In our brain there is a chemical named dopamine (causes relaxation) & acetylcholine (causes contraction) which have opposite action to each other and hence maintaining body movement & other activities. But if there is decrease in dopamine content and increase in acetylcholine, the Parkinson will appear.

Anti-Parkinsonism Drugs

CLASSIFICATION

I. *Drugs affecting brain dopaminergic system*
   (a) *Dopamine precursor* : Levodopa (l-dopa)
   (b) *Peripheral decarboxylase inhibitors* : Carbidopa, Benserazide.
   (c) *Dopaminergic agonists*: Bromocriptine, Ropinirole, Pramipexole
   (d) *MAO-B inhibitor:* Selegiline
   (e) *COMT inhibitors:* Entacapone, Tolcapone
   (f) *Dopamine facilitator:* Amantadine.

II. *Drugs affecting brain cholinergic system*
   (a) *Central anticholinergics:* Trihexyphenidyl (Benzhexol), Procyclidine, Biperiden.
   (b) *Antihistaminics :* Orphenadrine, Promethazine.

General Mechanism Of Action Of Drug

- **Levodopa**: precursor of Dopamine; Prevent dopamine deficiency, dopamine does not cross Blood Brain Barrier
- **Carbidopa**: Diminish metabolism of levodopa in GIT and Increase availability to CNS
- **Seligiline**: Inhibit MAO-B, reduces dopamine metabolism
- **Entacapone**: Inhibit COMT; COMT metabolizes both levodopa and dopamine
- **Amantadine**: Amantadine appears to act by promoting presynaptic synthesis and release of Dopamine in brain; blockage of cholinergic receptor.
- **Dopaminergic agonist**: bind with dopamine receptor

Levo Dopa

- It is inactive by itself, but is the immediate precursor of the transmitter Dopamine (DA).
- More than 95% of an oral dose is decarboxylated in the peripheral tissues (mainly gut and liver). DA thus formed acts on heart, blood vessels, other peripheral organs and on CTZ.
- About 1-2% of administered levodopa crosses to the brain, is taken up by the surviving dopaminergic neurones, converted to DA which is stored and released as a transmitter.
- Levodopa decreases the rigidity, tremors, and other symptoms of parkinsonism

A/E

- Anorexia, nausea, vomiting
- Orthostatic hypotension, arrhythmias
- Vivid dreams (seeming like real life) or insomnia, delusions, hallucination, confusion
- Serious effect: on/off oscillation; dyskinesia (movement disorders that are characterized by involuntary muscle movements)

- **Cautious** use is needed in elderly; patients with ischaemic heart disease; cerebrovascular, psychiatric, hepatic and renal disease; peptic ulcer; glaucoma, gout.

CARBIDOPA

- are extracerebral dopa decarboxylase inhibitors; they do not penetrate blood-brain barrier and do not inhibit conversion of levodopa to DA in the brain.
- Carbidopa diminishes the metabolism of levodopa in the gastrointestinal tract and peripheral tissues; thus, it increases the availability of levodopa to the CNS.
- The addition of carbidopa lowers the dose of levodopa needed by four- to five-fold and, consequently, decreases the severity of the side effects arising from peripherally formed dopamine.

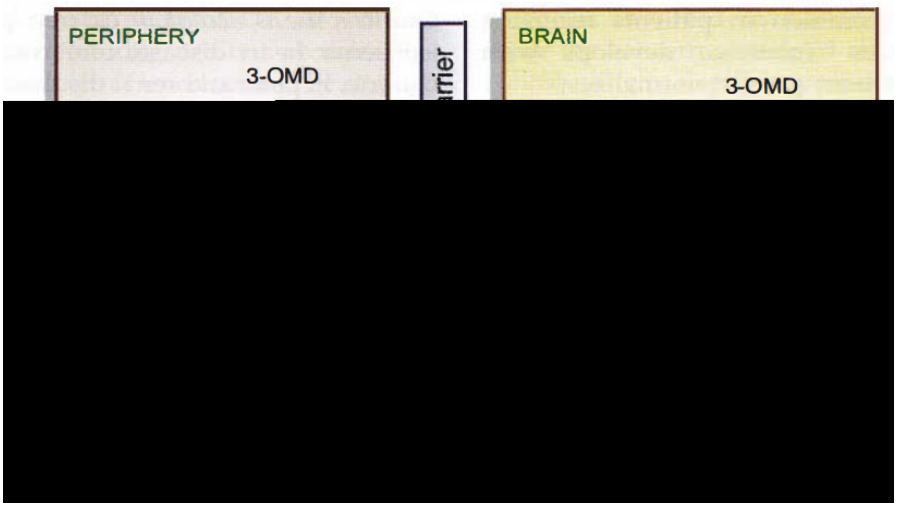


Fig. 31.2: Metabolic pathways of levodopa in the periphery and the brain.
3-OMD—3-O-methyldopa; COMT—Catechol-O-methyl transferase; MAO—monoamine oxidase; 3-MT—3-methoxytyramine; DOPAC—3,4 dihydroxy phenylacetic acid; HVA—Homovanillic acid (3-methoxy-4-hydroxy phenylacetic acid), DDC—Dopa decarboxylase