Antipsychotic Agents & Lithium

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مقرر فرع الادويه والعلاجيات

- The term **antipsychotic & neuroleptics** are used interchangeably to denote a group of drugs that have been used mainly **for treating schizophrenia.**
- But they are also effective in some other psychoses & agitated states. The term neuroleptic describes characteristic, emotional quieting & psychomotor slowing induced by the drug.

- **Classification :**
- **1.Phenothiazine derivatives :**
- a. **Aliphatic** derivative e.g. ***Chlorpromazine.***
- b. **Piperidine** derivative e.g. ***Thioridazine.***
- c. **Piperazine** derivative e.g. ***Fluphenazine & Trifluperazine***
- **2. Thioxanthine derivatives:** e.g. ***Thiothixene***
- **3. Butyrophenone derivatives :** e.g. ***Haloperidol***
- **4.Miscellaneous structures: (Atypical Antipsychotics)**
- a. Dibenzodizepine :e.g. ***Clozapine***
- b. Benzisoxazole : e.g. ***Risperidone***

- **Pharmacokinetics :**
- They are **readily but incompletely absorbed**, they undergo **significant 1st pass metabolism**, e.g. the oral dose of **Chlorpromazine & Thioridazine** have **systemic availability 25-35%** .
- Most antipsychotics **highly lipid soluble** & **protein bound**, tend to have a **large volume of distribution**, they are completely metabolized by a variety of processes, very little is excreted unchanged.

- **Dopamine hypothesis of Schizophrenia :**
- This proposed that this disorder is caused by **relative excess of functional activity** of the neurotransmitter **dopamine** in **specific neuronal tracts in the brain; Mesolimibic-mesocrtical pathway**:(**regulating creation**, **mentation & mood**).

- **Dopaminergic tracts in the brain :**
- 1. **Mesolimibic-mesocrtical pathway:(regulating creation, mentation & mood).**
- 2. **Nigrostraital tract** (**extrapyramidal** function).
- 3. **Tuberoinfundibular pathway (prolactin release).**
- 4. **Chemoreceptor trigger zone** (CTZ) (**emesis**).
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- ***Antipsychotic effect*** → D® block → Mesolimibic-mesocrtical pathway
- ***Extrapyramidal side effect*** → D® block → Nigrostraital tract
- ***Hyperprolactinemia*** ***(S.E.)***→ D® block → Tuberoinfundibular pathway
- ***Antiemetic effect*** → D® block → CTZ

- **Pharmacological effects of antipsychotics :**

- The 1st phenothiazine antipsychotic drug is **chlorpromazine** (the **prototype**) proved to have a **wide variety of CNS, autonomic & endocrine effects** .
- These action are due to blocking effect at a remarkable no. of receptors including: **dopamine, α-adrenoceptor, muscarinic ,histamine H1 & 5-HT receptors .**

Endocrine effect:

- **Amenorrhea, galactorrhea, false +ve pregnancy test** & **↑ libido in women. ↓ Libido & gynecomastia in men**.
- These effects are secondary to **blockade of dopamine affect prolactin secretion.**

Cardiovascular effect: (alpha1 blockage)

- **Orthostatic hypotension**

Typical antipsychotics:(chlorpromazine)

: Acts more on

Blockage of **D2 R** at mesolimbic and mesocortical pathway (treats +ve symptoms)

More extrapyramidal side effects

A Typical antipsychotics:(resperidone)

: Acts more on

Blockage of **5HT R** at mesolimbic and mesocortical pathway (treats -ve symptoms)

.Less or no extrapyramidal side effects

Chlorpromazine :

Typical antipsychotic drug **modify abnormal behavior in schizophrenia**, **control muscle spasm**, **reduces muscle spasticity** due to other neuralgic lesions.

It is an antiemetic, effective against both **drug & disease induced vomiting**, but **ineffective against motion sickness**.

. **Postural hypotension** may occur due to peripheral α-adrenoceptor blocking effect.

It's local anesthetic effect useful in intractable hiccup.

The trade name ***Largectil*** (come from **large action**)

- **Indications of antipsychotic agents**

1. **Schizophrenia.**
2. **Schizoaffective disorders.**
3. **Manic episode in bipolar affective disorder**
4. **Tourette's syndrome. (chronic multiple tics**
5. **Senile dementia of the Alzheimer's type.**
6. **Antiemetic effect**

7- H_1-receptor blocking action (relief of pruritis or sedative).

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- At present, use of **Clozapine** is limited to these patients who have **failed to respond to** substantial doses of **conventional antipsychotic** drugs

- **Adverse reactions:**
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- 1.**Neurological effect:**
- A- **Dose dependant *extrapyramidal effect*** including:
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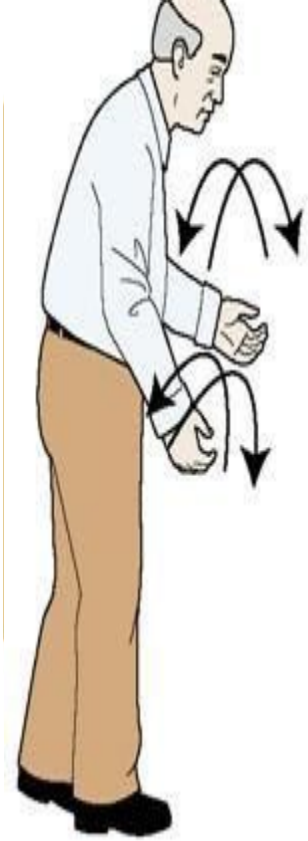
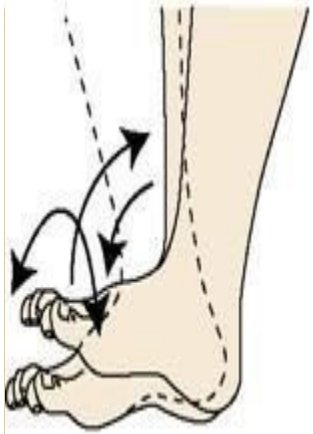
- (1) **Parkinson like syndrome** (**akinesia, rigidity & tremor**) this can be **reversed with decreasing the dose** & can be **antagonized by centrally acting atropine like drugs**. Extrapyramidal toxicity occurs more frequently with **Haloperidol, Fluphenazine .**
- (2) **Akathisia** (uncontrollable restlessness) & **dystonia** (spastic torticollis) which usually **responds to treatment with Diphenhydramine.**
- B. ***Tardive Dyskinesia*** (**choreoathetoid movements of lips, tongue, face, jaws & buccal cavity**) may develop **late in therapy after 6 months to several years** of treatment & **may be irreversible**.

- The first step in treatment is to switch to one of the newer agents.



Pseudo-parkinsonism
- Stooped posture
- Shuffling gait
- Rigidity
- Bradykinesia
- Tremors at rest
- Pill-rolling motion of the hand

Acute dystonia
- Facial grimacing
- Involuntary upward eye movement
- Muscle spasms of tongue, face, neck, and back (back muscle spasms cause trunk to arch forward)
- Laryngeal spasms



Akathisia
- Restless
- Trouble standing still
- Paces the floor
- Feet in constant motion, rocking back and forth

Tardive dyskinesia
- Protrusion and rolling the tongue
- Sucking and smacking movements of the lips
- Chewing motion
- Facial dyskinesia
- Involuntary movements of the body and extremities

- **2. Autonomic effect:**
- They includes blockage of peripheral muscarinic receptors &α –adrenoceptors.
- **Muscarinic receptors blockade :** dry mouth, constipation, urine retention, visual problems & confusion (S.E. of atropine)

α–adrenoceptors blockade: postural hypotension & failure of ejaculation.

- **3. Endocrine & metabolic effect:** weight gain, gynecomastia, amenorrhea, galactorrhea & infertility.
- **4.Toxic & allergic reactions:** **agranulocytosis** (with **Clozapine**), **cholestatic-jaundice** (**Chlorpromazine)**
- **5.Ocular complication:** visual impairment caused by **retinal deposits** has occurred with **Thioridazine**.
- **6. Cardiac toxicity :** at high doses, **Thioridazine** may cause sever conduction defects that result in fatal ventricular **arrhythmias.**
- **7.Neurolepitic malignant syndrome:** patients who are particularly **sensitive to the extrapyramidal effect** of antipsychotic drugs, may develop **muscles rigidity, impairment of sweating, hyperpyrexia & autonomic instability**. Drug treatment involves the use of **: dantrolene or diazepam**

- **Lithium**
- It's referred to as **anti manic drug or mood stabilizing agent**, because of the primary action is preventing mood swings in patients with bipolar affective (manic depressive) psychosis (MDS).
- ***Pharmacokinetics:***
- Lithium is a small monovalent cation, completely absorbed within (6-8 hrs), **distributed in total body water** with entry into the intracellular compartment, not metabolized & entirely excreted in urine. The therapeutic plasma concentration is close to the toxic concentration (it has **low therapeutic index**). Lithium is easily dialyzable from the blood but the intracellular concentration falls slowly. Lithium ions are filtered in the glomeruli & **reabsorbed in the renal tubules at the same site of sodium.**
- **In sodium deficiency, lithium is retained in the body**, leads to **Lithium toxicity is treated by giving NaCl**. The $t_{1/2}$ of lithium is about 20 hr. Plasma level should be monitored, especially during the 1^{st} week of therapy.

- ***Pharmacodynamics:***
- **IP3 levels are elevated in patients with mania**
- Lithium, by **inhibiting the recycling of inositol substrates**, may cause depletion of the 2nd messenger source (phosphatidyl inositol biphosphate or PIP_2) & therefore reduces the release of inositol trisphosphate (IP3) & diacyl glycerol (DAG), both IP3 & DAG are important 2nd messengers for both α-adrenergic & muscarinic transmission.

- ***Clinical uses:***

Bipolar affective disorder: lithium carbonate is preferred for the treatment, especially in mania.

- ***Drug interactions:***

- Diuretics ↓ clearance of lithium
- Non-steroidal anti-inflammatory drugs ↓ clearance of lithium.
- Neuroleptics are potentiated.

- ***Adverse effects*** :

1. **tremor**
2. On the **thyroid**: it **decreases thyroid function**. It causes" Frank thyroid enlargement ".
3. **Renal**: it produces **polyuria & polydypsia, nephrogenic diabetes insipidus**
4. **Cardiac depression** at SA node.
5. Pregnancy: it increases the incidence of cardiac anomalies (**teratogenic effect**).

- **Other mood stabilizers:**
  - Carbamazepine
  - Valproaic acid
  - Lamotrigine

Thank you