Antipsychotic Agents & Lithium

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Antipsychotic drugs are able to reduce psychotic symptoms in a wide variety of conditions including

- Schizophrenia
- Bipolar disorder
- Psychotic depression
- Senile psychoses
- Various organic psychoses
- Drug-induced psychoses
- They are also able to improve mood and reduce anxiety and sleep disturbances

- **Typical antipsychotic (neuroleptic):**
  This antipsychotic drug produces a high incidence of
  - Extrapyramidal side effects
  - Hyperprolactinemia
- **Atypical antipsychotic drugs** are now the most widely used type of antipsychotic drug.

Drugs for Psychoses & Bipolar Disorders

Antipsychotics

- Classic drugs (D2 receptor affinity)
  Chlorpromazine, Fluphenazine, Haloperidol , Thioridazine, Trifluoperazine
- Newer agents (5HT2 receptor affinity)
  Clozapine Olanzapine, Quetiapine, Risperidone, Ziprasidone

Bipolar Drugs

- Classic drug: Lithium
- Newer agents: Carbamazepine, Clonazepam, Olanzapine and Valproic acid

Pharmacokinetics of The Antipsychotic Drugs

- Well absorbed orally
- Lipid soluble (enter CNS)
- Extensively Bounding to plasma proteins
- Metabolisd by liver enzymes before elimination
- Long plasma half-lives that permit once daily dosing.
- Parenteral forms of many agents (eg, fluphenazine, haloperidol) are available for both rapid initiation of therapy and depot treatment.

Mechanism of Action

The dopamine hypothesis of schizophrenia proposes that the disorder is caused by a relative excess of functional activity of the neurotransmitter dopamine in specific neuronal tracts in the brain.

- The therapeutic efficacy of the older antipsychotic drugs correlates with their relative affinity for the D2 receptor.
- Most of the newer atypical antipsychotic agents have higher affinities for other receptors than For the D2 receptor.
- α- Adrenoceptor-blocking action, histamine H1 receptors

- **Clozapine**, a drug with significant D4 and 5-HT2 receptor-blocking actions, has no affinity for D2 receptors.
- Most of the newer atypical drugs (eg, **olanzapine, quetiapine, and risperidone**) also have high affinity for 5-HT2A Receptors, although they may also interact with D2 and other receptors.
- **Ziprasidone** is an antagonist at the D2, 5-HT2A, And 5-HT1D receptors and an agonist at the 5-HT1A receptor.

Effects

- Dopamine receptor blockade is the major effect that correlates with Therapeutic benefit for older antipsychotic drugs.

Dopaminergic atracts in the brain include

- The mesocortical-mesolimbic pathways (regulating mentation and mood),
- Nigrostriatal tract (extrapyramidal function)
- Tuberoinfundibular pathways (control of prolactin release)
- Chemoreceptor trigger zone (emesis).

Note: Mesocorticalmesolimbic dopamine receptor blockade presumably underlies antipsychotic effects, and a similar action on the chemoreceptor trigger zone leads to the useful antiemetic properties of some antipsychotic drugs..

Clinical Use

1. Treatment of Schizophrenia

- Antipsychotic drugs reduce some of the positive symptoms of schizophrenia, including hyperactivity, , hallucinations, and delusions.
- Beneficial effects may take several weeks to develop
- Clozapine is effective in some schizophrenic patients resistant to treatment with other antipsychotic drugs

2. Other Psychiatric and Neurologic Indications

- Treatment of mania(newer antipsychotic drugs used with lithium), For acute mania ,several second-generation drugs .
- Maintenance treatment of bipolar Disorder. (Second-generation drugs : Aripiprazole & Olanzapine)
- Tourette's syndrome (Molindone)
- Alzheimer's disease and in parkinsonism(The newer atypical antipsychotics to allay psychotic symptoms)

3. Nonpsychiatric Indications

- Phenothiazines have Antiemetic actions (prochlorperazine)
- Side-chain phenothiazines (H1-receptor blockade), have Antipruritics, Sedatives & Antiemetic effects.

Toxicity

- **Reversible Neurologic Effects**
  - **1. Extrapyramidal Effects**
    - (Dose-dependent) (bradykinesia, rigidity, and tremor) which may be reversed by a decrease in dose & muscarinic blocking agents.
    - Extrapyramidal toxicity occurs most frequently with haloperidol & side-chain phenothiazines (eg, fluphenazine, trifluoperazine).
    - Parkinsonism occurs infrequently with clozapine

2. Tardive Dyskinesias

- Choreoathetoid movements of the muscles of the lips and buccal cavity (may be irreversible)
- There is no effective drug treatment for tardive dyskinesia, Switching to clozapine does not exacerbate the condition.
- Tardive dyskinesia may be attenuated temporarily by increasing neuroleptic dosage; this suggests that tardive dyskinesia may be caused by Dopamine receptor sensitization.

3. Autonomic Effects

- Block of peripheral muscarinic receptors atropine-like effects (dry mouth, constipation, urinary retention, and visual problems) & α adrenoceptors
- Muscarinic receptor blockade, are often pronounced with the use of thioridazine and phenothiazines
- α-receptor blockade, postural hypotension caused by α blockade is a common manifestation of many of the older drugs, especially phenothiazines.
- The atypical drugs, especially clozapine and ziprasidone, also block α receptors and can cause orthostatic hypotension.
- Failure to ejaculate is common in men treated with the phenothiazines

4. Endocrine and Metabolic Dffects

- Endocrine and metabolic effects include hyperprolactinemia, gynecomastia, the amenorrhea-galactorrhea syndrome, and infertility.
- Most of these side effects are predictable manifestations of dopamine D2 receptor
- Blockade in the pituitary; dopamine is the normal inhibitory regulator of prolactin secretion.
- Elevated prolactin with risperidone (because dopamine is the normal inhibitory regulator of prolactin secretion dopamin)
- Diabetogenic action (clozapine and olanzapine)

5. Neuroleptic Malignant Syndrome

- The symptoms include muscle rigidity, impairment of sweating, hyperpyrexia & autonomic instability
- Drug treatment involves the prompt use of dantrolene, Diazepam, and dopamine agonists.

6. Sedation

- Phenothiazines (especially chlorpromazine)

- **Miscellaneous Toxicities**
  - Visual impairment (high doses of thioridazine)
  - Ventricular arrhythmias (thioridazine), quetiapine and ziprasidone, prolong the QT interval of the electrocardiogram (ECG& cause cardiac arrhythmias
  - Clozapine causes agranulocytosis (1–2%) & at high doses has caused seizures.

Lithium

- Lithium is effective in treatment of the manic phase of bipolar(manic-depressive) disorder
- Used for acute-phase illness & for Prevention of recurrent manic and depressive episodes.

Pharmacokinetics of Lithium

- Lithium is absorbed rapidly and completely from the gut.
- The drug is distributed throughout the body
- The half-life of lithium is about 20 h.
- levels should be monitored, to establish an effective and safe dosage
- Plasma levels of the drug may be altered by changes in body water
- Dehydration, or treatment with thiazides, nonsteroidal anti-inflammatory drugs (NSAIDs), angiotensin- Converting enzyme inhibitors (ACEIs), and loop diuretics, may result in an increase of lithium in the blood to toxic levels.
- Caffeine and theophylline increase the renal clearance of lithium

Mechanism of Action

- The Drug inhibits several enzymes involved in the recycling of neuronal Membrane phosphoinositides.
- This action may result in depletion of the second messenger source which are important in amine neurotransmission, including that mediated by central adrenoceptors and muscarinic receptors

Clinical Use

- Lithium carbonate used for the treatment of bipolar disorder (manic-depressive disease)

  Note :valproic acid and carbamazepine are equally effective
- Maintenance therapy with lithium decreases manic behavior and reduces both the frequency and the magnitude of mood swings.
- Antipsychotic agents and/or benzodiazepines are commonly required at the initiation of treatment because both lithium and valproic acid have a slow onset of action.

Toxicity of Lithium

1. Tremor, sedation, ataxia, and aphasia.
2. Thyroid enlargement & hypothyroidism
3. Reversible nephrogenic diabetes insipidus (at therapeutic drug levels).
4. Edema
5. Acneiform skin eruptions ,leukocytosis.
6. Contraindicated in pregnancy (increase the incidence of congenital cardiac anomalies)
7. Contraindicated in nursing mothers.

Other Drugs Used in Bipolar Disorder

- Antipsychotic drugs, (olanzapine and quetiapine as monotherapy) for the manic phase
- Antiseizure drugs (Valproic acid has antimanic effects equivalent to those of lithium it is used as a First choice in acute illness.
  - Valproic acid may be effective in patients who fail to respond to lithium,
  - In some instances it has been used in combination with lithium.
  - Carbamazepine and lamotrigine (for acute mania and for prophylaxis in the depressive phase)