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Review Article

A Review Article On Antipsychotic Drugs-Mechanism Of Action And Their Therapeutic Uses

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ABSTRACT

Antipsychotics, also termed neuroleptics or major tranquillizers have several chemical groups. The main two types are: Typical and Atypical antipsychotics. The various psychosis conditions are mutually seen in the older adults. Among the recently available atypical antipsychotics, Olanzapine, Risperidone, Clozapine, and Quetiapine have been the most widely studied in schizophrenia, bipolar disorder, and depression. Antipsychotics are often effective in treating troublesome mental health issues or various symptoms related to psychosis. The choice of atypical antipsychotic agent can be guided by the nature, severity of the target symptom, and the medication least likely to cause harm to the patient. The study of antipsychotics drugs is useful for the treatment of mental health disorders (such as schizophrenia, mania disorders, etc.). First generation antipsychotics (FGA) are older class of drugs compared to the second-generation antipsychotics (SGA). Antipsychotic drugs do not completely treat the psychosis conditions but helps to reduce the symptoms.

INTRODUCTION

Psychosis: Psychosis is a mental disorder which leads to cause an individual to lose contact with reality. [16] The term refers to various mental disorders characterized by one or more following symptoms: hallucinations, delusions, disorganized behavior, aggression or violence, incoherence, etc. [1]

Antipsychotic drugs: Antipsychotic drugs are the medications that are usually taken during the treatment of psychosis conditions. They are also called as neuroleptics or major tranquilizers. They are used for the treatment of acute psychosis conditions as well as the chronic psychosis conditions (i.e. condition of Schizophrenia).

These drugs lessen the symptoms such as hallucinations, aggression or violence, disorganized behavior, incoherence, etc. regardless of underlying cause or causes. These agents are prescribed for the treatment of mania,

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some movement disorder, etc. but are mostly prescribed for the therapy of Schizophrenia. [1] Antipsychotic drugs are not curative. [16]

Neuroleptics: Neuroleptics is a subtype of anti-psychotic drug that produces a high incidence of extra-pyramidal side effects (EPS) at clinically effective doses, or catalepsy in laboratory animals. [2]

Schizophrenia: Schizophrenia is the term for group of disorders marked by chronicity, impaired behavioral function and disturbances of thinking and affect. [1] It is one of the most common psychotic illness. The symptoms of this disorders are prevalent in the age of 16-20. [16] The symptoms are subcategorized into positive, negative and cognitive. It has prevalence of about 1% in the U.S. population. [16] The disorder is most commonly observed in late adolescences or early adulthood. [1]

History:

Reserpine and Chlorpromazine were the first drug found to be useful to reduce psychotic symptoms. [2] In 1949's, Henri-Marie Laborit, French army surgeon, used promethazine, a phenothiazine derivative. [3]

Chlorpromazine was synthesized by Paul Charpentier in the year 1951. [3]

Haloperidol belongs to Butyrophenones and was synthesized in 1958 at a Belgian laboratory by Paul Janssen. [3]

In 1990's the atypical drugs (Second generation antipsychotics) were discovered and are now recently used. [3]

Classification:

Antipsychotic Drugs are classified into major types:

- First Generation Antipsychotics.
- Second Generation Antipsychotics.

A. **First Generation Antipsychotics:** First generation antipsychotics are also called as 'Typical antipsychotics or Conventional antipsychotic drugs. [16] These drugs were initially developed in the 1950s for the treatment of psychosis. [4] These types of drugs were the first type of medications used for treating psychosis. These drugs are not most commonly prescribed now-a-days. They are dopamine- receptor antagonists (DRA). [4] These consists of high potency as well as low potency drugs.

This type of medications involves:

1) Phenothiazines- Rifluoperazine, Perphenazine, Prochlorperazine, Acetophenazine, Triflupromazine, Mesoridazine
2) Butyrophenones- Haloperidol, Droperidol, Penfluridol.
3) Thioxanthenes-Thiothixene, Chlorprothixene. [4]

B. **Second Generation Antipsychotics:** Second generation antipsychotics are also called as 'Atypical antipsychotics. These drugs were developed during the 1980s. This type of antipsychotics has been approved by the FDA (Food and Drug Association) to manage and to treat psychosis. [4] These drugs are the main drugs prescribed now-a-days as they have lesser side effects. These drugs are Serotonin-Dopamine antagonists. [4] Clozapine is first FDA approved anti-suicidal drug.

This type of medications involves:

Isperidone, Olanzapine, Quetiapine, Ziprasidone, Aripiprazole, etc.

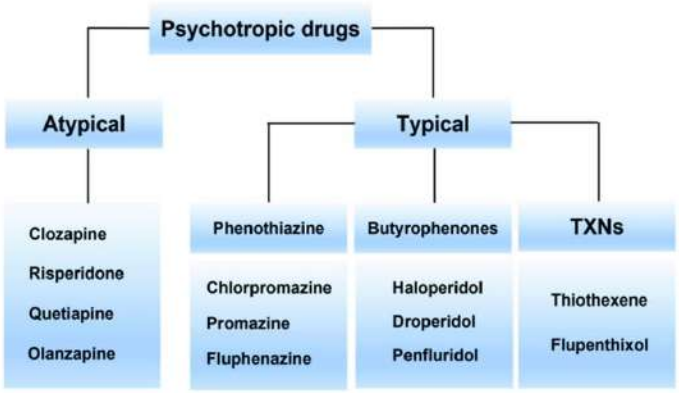

Fig. No 01 Psychotropic Drugs

Various Drugs Of First- And Second-Generation Antipsychotics Approved By Fda (Food And Drug Association): [5]

First Generation Antagonists	Second Generation Antagonists
Chlorpromazine	Aripiprazole
Droperidol	Asenapine
Fluphenazine	Clozapine
Haloperidol	Iloperidone
Loxapine	Olanzapine
Perphenazine	Paliperidone
Pimozide	Quetiapine
Prochlorperazine	Risperidone
Thiothixene	Ziprasidone
Thioridazine	
Trifluoperazine	

TABLE NO. 01 Various Drugs of First- And Second-Generation Antipsychotics Approved by FDA (Food and Drug Association)

Mechanism Of Action Of Antipsycotic Drugs:

The conventional antipsychotic drugs produce undesirable effects like Hyperprolactinemia, NMS and EPS these are associated with high doses. [16]

Many antipsychotic drugs strongly block post-synaptic D_2 receptors in CNS, especially in the mesolimbic-frontal limbic system and block the action of dopamine.

The most frequent uses of these agents are in manic disorders and the schizophrenias. In the manic disorders, the agents may block dopamine, (3,4-dihydroxyphenethylamine) at limbic D_2 and D_3receptors, reducing euphoria, delusional thinking and hyperactivity. In the chronic idiopathic psychoses (schizophrenias), both conventional (typical) and newer (atypical) antipsychotics appear to act to benefit positive symptoms by blocking dopamine at D_2 and D_3 limbic receptors. The activity of the atypical agents against negative symptoms may be due to blocking of serotonine$_{2A}$receptor (5-HT$_{2A}$). [6]

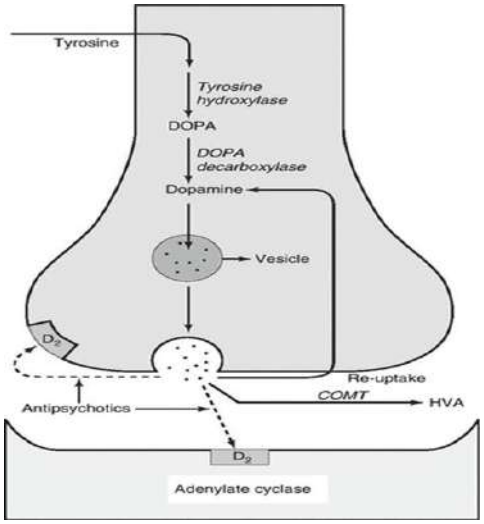

Fig. No.02 Mechanism Of Action Of Antipsychotic Drugs [7]

First Generation Antipsychotics:

A] Haloperidol:

Haloperidol is extensively metabolized in the liver with only about 1% of the administered dose excreted unchanged Haloperidol, a first-generation typical antipsychotic, is commonly used worldwide to block dopamine D_2 receptors in the brain and exert its antipsychotic action. Use of the first-generation antipsychotics is considered highly effective for the management of the "positive" symptoms of schizophrenia. [8] The efficacy of haloperidol was first established in controlled trials in the 1960s. [15]

Mechanism Of Action:

While haloperidol has demonstrated pharmacologic activity at a number of receptors in the brain, it exerts its antipsychotic effect through its strong antagonism of the dopamine receptor (mainly D_2), particularly within the mesolimbic and mesocortical systems of the brain. Haloperidol is known to inhibit the effects of dopamine and increase its turnover. Haloperidol is used as dopamine-antagonizing medications that improve psychotic symptoms by halting the over-production of dopamine. [8] The effects of haloperidol are not limited to the D2 receptor, as it also exerts blocking action on noradrenergic, cholinergic, and histaminergic receptors. [15]

Pharmacokinetics-

- **Absorption-**

Haloperidol a highly lipophilic drug undergoes extensive metabolism. [8] Studies have found a wide variance in pharmacokinetic values for orally administered haloperidol with 1.7-6.1 hours reported for time to peak plasma concentration (t_{max}), 14.5-36.7 hours reported for half-life ($t^1/_2$), and 43.73 µg/L•h [range 14.89-120.96 µg/L•h] reported for AUC. Haloperidol is well-absorbed from the gastrointestinal tract when ingested orally, however, the first-pass hepatic metabolism decreases its oral bioavailability to 40 - 75%. [15]

- **Distribution-**

The apparent volume of distribution was found to range from 9.5-21.7 L/kg. This high volume of distribution is in accordance with its lipophilicity, which also suggests free movement through various tissues including the blood-brain barrier. [15]

- **Metabolism-**

In humans, haloperidol is bio transformed to various metabolites, including p-fluorobenzoylpropionic acid, 4-(4-chlorophenyl)-4-hydroxypiperidine, reduced haloperidol,

pyridinium metabolites, and haloperidol glucuronide. [15]

The drug is metabolized in the liver via Sulfoxidation and oxidation pathways with the involvement form CYP3A4, CYP2D6 and minor CYP1A2 enzymes. [8]

- **Excretion-**

In radio labeling studies, approximately 30% of the radioactivity is excreted in the urine following a single oral administration of 14C-labelled haloperidol, while 18% is excreted in the urine as haloperidol glucuronide, demonstrating that haloperidol glucuronide is a major metabolite in the urine as well as in plasma in humans. [15]

Therapeutic Uses-

1. Haloperidol is used treat severe behavioral problems (i.e. aggressive, impulsive, behavior). [17]
2. It is used to treat uncontrolled movements and outbursts of words/sounds related to Tourette's syndrome. [18]

Adverse Drug Effects-

Haloperidol being a typical antipsychotic medication they are associated with extrapyramidal symptoms due to their blockade of the Dopamine pathway in the brain.

Extrapyramidal adverse effects are as follows:

1. Acute dystonia
2. Akathisia
3. Neuroleptic malignant syndrome (NMS)
4. Parkinsonism
5. Tardive dyskinesia (TD)

Anticholinergic effect includes increased body temperature, dry mouth, drowsiness or sedation, constipation, and urinary retention.

Other common adverse effects of haloperidol include weight gain, erectile dysfunction in males, and oligomenorrhea or amenorrhea in females.

Side Effects:

They have various common side effects such as:

1. Feeling dizzy or low blood pressure
2. Constipation
3. Dry mouth
4. Blurred vision
5. Feeling sleepy or drowsy
6. Problems sleeping (insomnia)

[B] Prochlorperazine:

Prochlorperazine, also known as Compazine, is a piperazine phenothiazine and first-generation antipsychotic drug that is used for the treatment of severe nausea and vomiting. [15] Prochlorperazine was first developed in the 1950s and was first approved by the FDA in 1956. [15] Non-FDA Indications include migraine headaches. [9]

Mechanism Of Action-

As a first-generation antipsychotic, Prochlorperazine mainly blocks D2 dopamine receptors in the brain. It can also block histaminergic, cholinergic, and noradrenergic receptors. [9] One study found that Prochlorperazine also inhibits the P2X7 receptor in human macrophages but not in mouse cells, preventing a calcium ion influx. This mechanism was independent of dopamine antagonism. [9]

Pharmacokinetics-

- **Absorption-**

Prochlorperazine is well absorbed from the gastrointestinal tract. The onset of pharmacological action is about 30 to 40 minutes following oral administration and 10 to 20 minutes following intramuscular administration. The duration of action for all routes is about 3 to 4 hours. Following oral administration in healthy volunteers, the mean oral bioavailability was about 12.5%. In these patients, the time to reach the peak plasma concentrations was about 5 hours. Following multiple twice daily dosing, the steady state of Prochlorperazine was reached by 7 days. [15]

- **Distribution-**

In a preliminary pharmacokinetic study involving healthy volunteers, the mean apparent volume of distribution following intravenous administration

of 6.25 mg and 12.5 mg Prochlorperazine were approximately 1401 L and 1548 L, respectively. Prochlorperazine is reported to be distributed to most body tissues with high concentrations being distributed into liver and spleen. There is evidence that phenothiazine are excreted in the breast milk of nursing mothers. [15]

- **Metabolism-**

Prochlorperazine undergoes hepatic metabolism involving oxidation, hydroxylation, demethylation, sulfoxide formation and conjugation with glucuronic acid. The oxidation reaction is mediated by CYP2D6. N-dimethyl Prochlorperazine was detected in the plasma1, as well as Prochlorperazine sulfoxide, Prochlorperazine 7-hydroxide and Prochlorperazine sulfoxide 4'-N-oxide, following oral and buccal administration. [15]

- **Excretion-**

Prochlorperazine is mainly excreted via the feces and bile. Low quantities of unchanged Prochlorperazine and its metabolite were detectable in the urine. [15]

Therapeutic Uses-

1. Prochlorperazine is used to control severe vomiting and nausea. [19]
2. It works in balancing the levels of dopamine in your brain, a substance that helps regulate mood, behaviors and thoughts. [18]

Adverse Drug Effects-

Anticholinergic side effects include anorexia, blurred vision, constipation, dry mucosa, and urinary retention. Antihistaminic side effects (blockage of H1 receptor) includes sedation. Prochlorperazine can also lower the seizure threshold. It can also lead to prolonged QTc interval and cause other cardiac conduction abnormalities.

Side Effects-

Side effects of Prochlorperazines are usually mild and go away by themselves.

They are as follows:

1. Feeling sleepy or drowsy
2. Blurred vision
3. Dry mouth
4. Headaches
5. Stuffy nose

[C] Loxapine:

Loxapine is an antipsychotic used in psychiatry for over 40 years with a well-established profile. Loxapine is a dibenzoazepine tricyclic antipsychotic agent, available for oral, intramuscular and inhalatory administration. [10]

Mechanism Of Action:

Loxapine is a dopamine antagonist, and also a serotonin 5-HT_2 blocker. The exact mode of action of Loxapine has not been established, however changes in the level of excitability of sub-cortical inhibitory areas have been observed in several animal species in association with such manifestations of tranquilization as calming effects and suppression of aggressive behavior. [15]

Pharmacokinetics:

- **Absorption-**

Systemic bioavailability of the parent drug was only about one third that after an equivalent intramuscular dose (25 mg base) in male volunteers. [15]

- **Distribution**– Not yet known. [15]
- **Metabolism–** Hepatic. [15]
- **Excretion-** Metabolites are excreted in the urine in the form of conjugates and in the feces unconjugated. [15]

Therapeutic Uses-

1. Loxapine is used to treat the symptoms of Schizophrenia.
2. It works to decrease abnormal excitements in the brain. [19]

Adverse Drug Effects-

1. Hypotension, Orthostatic Hypotension
2. Akathisia, Dizziness, Drug-Induced Tardive Dystonia, Dystonia, Extrapyramidal Disease, Parkinsonian, Somnolence, Tardive Dyskinesia

3. Diminished Sweating
4. Xerostomia

Side Effects-

1. Slowed movements
2. Stiffness of the arms and legs
3. Trembling and shaking of the fingers and hands
4. Uncontrolled chewing movements
5. Uncontrolled movements of the arms or legs.

Second Generation Antipsychotics

A] Clozapine:

Clozapine is an FDA-approved atypical antipsychotic drug for treatment-resistant schizophrenia. Clozapine is also approved by schizophrenia-associated suicide prevention. Clozapine was first synthesized in 1956 in many European countries. [11] . It is a high dose neuroleptics drug. [16]

Mechanism Of Action-

Clozapine is part of a group of drugs known as second-generation antipsychotics or atypical antipsychotics. As an atypical antipsychotic, Clozapine is an antagonist to dopamine and serotonin receptors. Clozapine binds to the dopamine D4 receptor with a higher affinity than the dopamine D2 receptor. It contributes to decreased adverse effects and extra pyramidal symptoms (EPS). Clozapine is a partial 5-HT1A agonist that reduces adverse and extra pyramidal symptoms and a muscarinic M1, M2, M3, M5, histamine, and alpha-1 adrenergic-receptor antagonist. [11]

Pharmacokinetics-

- **Absorption-**

Clozapine tablets are bioequivalent to a Clozapine solution. The peak plasma concentrations are attained at 2.5 hours (1 to 6 hours). Food does not seem to influence the bioavailability of Clozapine; Clozapine may be administered with or without food. [11]

- **Distribution-**

Clozapine exhibits approximately 97% plasma protein binding. Clozapine is transported across the blood-brain barrier. [11]

- **Metabolism-**

The uptake of Clozapine in the liver is mediated by SLC22A1, SLC22A2, and SLC22A3 (solute carrier (SLC) family). Clozapine is extensively metabolized in the liver by cytochrome P450 isozymes, particularly CYP1A2, CYP2D6, and CYP3A4. CYP3A4 and CYP1A2 are the major enzymes responsible for demethylation, with CYP2D6 playing a minor role. The desmethyl-norclozapine is an active metabolite of Clozapine. [11]

- **Excretion-**

The mean elimination half-life ranges from 8 to 12 hours; the elimination half-life increases after multiple dosing. Approximately 50% of Clozapine is excreted in the urine and 30% in the feces. [11]

Therapeutic Uses-

1. It works in changing the activity of certain natural substances in the brain. [10]
2. It is used to lower risks of suicidal behavior in patients with schizophrenia or schizoaffective disorders. [9]

Adverse Drug Effects:

There is various common adverse drug effect of Clozapine such as:

1. Agranulocytosis
2. Myocarditis
3. Metabolic syndrome
4. Seizures
5. Excessive salivation
6. Constipation
7. Neuroleptic malignant syndrome (NMS)

Side Effects:

Clozapine recommended as effective regarding negative symptoms of schizophrenia and treatment resistant schizophrenic patient.

Clinically relevant side effects occurred in 73% of all patients. Tachycardia (67%), the increase of

liver enzymes (36%), hypotension (29%) and sedation (27%) were most frequent.

The other side-effects (constipation, nausea and vertigo) were rare and transient.

[B] Olanzapine:

Olanzapine is a thienobenzodiazepine classified as an atypical or second-generation antipsychotic agent. It was discovered by scientists at Eli Lilly and approved to be marketed in the US in 1996. [15] The FDA has recently approved Olanzapine in combination with Sami orphan to attenuate Olanzapine-induced weight gain for schizophrenia and bipolar I disorder. [12] it is a derivative of thienobenzodiazepine. [16]

Mechanism Of Action-

Olanzapine is an atypical (second-generation) antipsychotic that exerts its action primarily on dopamine and serotonin receptors. It works on dopamine D2 receptors in the mesolimbic pathway as an antagonist, blocking dopamine from potential action at the post-synaptic receptor. [12] The activity of Olanzapine is achieved by the antagonism of multiple neuronal receptors including the dopamine receptor D1, D2, D3 and D4 in the brain, the serotonin receptors 5HT2A, 5HT2C, 5HT3 and 5HT6, the alpha-1 adrenergic receptor, the histamine receptor H1 and multiple muscarinic receptors. [15] The effect on the D2 receptors leads to a decrease in positive symptoms in patients, including hallucinations, delusions, and disorganized speech, thought, and behavior. Olanzapine works similarly on serotonin 5HT2A receptors in the frontal cortex as an antagonist. [12]

Pharmacokinetics-

- **Absorption-**

Daily administration of Olanzapine leads to reaching the steady-state plasma concentration in about one week. The time to peak concentration is 6 hours for oral formulation and 15-45 minutes for IM Formulation. Olanzapine has a half-life of 21 to 5-4 hours, with an average of 30 hours. [12] Absorption of Olanzapine is not affected by the concomitant administration of food. [15]

- **Distribution-**

The volume of distribution is approximately 1000 liters, and the medication is distributed widely throughout the body. It is 93% bound to plasma proteins, primarily albumin and alpha-1 acid glycoprotein. [12]

- **Metabolism-**

Olanzapine is extensively metabolized by the liver by glucuronide enzyme and the cytochrome P450 system. [12] From the CYP system, the main metabolic enzymes are CYP1A2 and CYP2D6. As part of the phase I metabolism, the major circulating metabolites of Olanzapine, accounting for approximate 50-60% of this phase, are the 10-N-glucuronide and the 4'-N-desmethyl Olanzapine which are clinically inactive and formed by the activity of CYP1A2. On the other hand, CYP2D6 catalyzes the formation of 2-OH Olanzapine and the flavin-containing monooxygenase (FMO3) is responsible for N-oxide Olanzapine. [15]

- **Excretion-**

The half-life of Olanzapine is approximately 30 hours (varies between 21 to 34 hours). Olanzapine is excreted primarily via the renal route (57%) and feces (30%). [12]

Therapeutic Uses-

1. It helps in balancing the levels of serotonin and dopamine in the brain and also helps to manage symptoms of mental health conditions. [18]
2. This medication may cause heat stroke that is may make sweat loss and may cause overheat. [18]

Adverse Drug Effects:

Olanzapine treatment is associated with adverse drug effect such as:

1. Increase in appetite
2. Weight gain
3. Hyperglycemia
4. Onset of diabetes

5. Dry mouth

Side Effects:

1. Following side effects may affects up to 1 in 10 people:
2. Feeling sleepy in the day
3. Putting on weight or an increase in your appetite
4. Feeling dizzy (especially when getting up from a sitting or lying position)
5. Rash
6. Constipation

Serious side effects are rare and happen in less than 1 in 1,000 people.

[C] Quetiapine:

Initially approved by the FDA in 1997, Quetiapine is a second-generation atypical antipsychotic used in schizophrenia, major depression, and bipolar disorder. [15] Quetiapine is available in both as extended-release or immediate-release. [13]

Mechanism Of Action-

Quetiapine has a strong affinity for the 5-HT2 receptor. Although Quetiapine has many complex mechanisms, it mediates its pharmacological effect mainly via its 5HT2 antagonistic action. It also acts on dopaminergic D1 and D2 receptors. Quetiapine is an antagonist for D2 receptors and 5-HT2 receptors. [13] In bipolar depression and major depression, quetiapine's actions may be attributed to the binding of this drug. [15]

Pharmacokinetics-

- **Absorption-**

Quetiapine is rapidly and well absorbed after administration of an oral dose. Steady-state is achieved within 48 hours15 Peak plasma concentrations are achieved within 1.5 hours. The bioavailability of a tablet is 100%. The steady-state C_{max} of Quetiapine in Han Chinese patients with schizophrenia after a 300 mg oral dose of the extended released formulation was approximately 467 ng/mL and the AUC at steady-state was 5094 ng·h/mL.17 Absorption of Quetiapine is affected by food, with C_{max} increased by 25% and AUC increased by 15%. [15]

- **Distribution-**

Quetiapine distributes throughout body tissues. The apparent volume of distribution of this drug is about 10±4 L/kg. [15]

- **Metabolism-**

The metabolism of Quetiapine occurs mainly in the liver. Sulfoxidation and oxidation are the main metabolic pathways of this drug. According to in vitro studies, cytochrome P450 3A4 metabolizes Quetiapine to an inactive sulfoxide metabolite and also participates in the metabolism of its active metabolite, N-desalkylquetiapine. CYP2D6 also regulates the metabolism of Quetiapine. In one study, three metabolites of N-desalkylquetiapine were identified. Two of the metabolites were identified as N-desalkylquetiapine sulfoxide and 7-hydroxy-N-desalkylquetiapine. CYP2D6 has been found to be responsible for metabolism of Quetiapine to 7-hydroxy-N-desalkylquetiapine, a pharmacologically active metabolite. [15]

- **Excretion-**

After an oral dose of radio labeled Quetiapine, less than 1% of unchanged drug was detected in the urine8, suggesting that Quetiapine is heavily metabolized. About 73% of a dose was detected in the urine, and about 20% in the feces. [15]

Therapeutic Uses-

1. They are used to treat the episodes of mania or depression in patients with bipolar disorders. [19]
2. It helps to balance serotonin and dopamine levels in the patients to treatment various mental health conditions. [8]

Adverse Drug Effects:

Various adverse effects can be observed in patient, such as:

1. Hyperprolactinemia
2. Hypothyroidism
3. Tachycardia
4. Hallucinations

Side Effects:

The common side effects are seen in more than 1 to 10 people, such as:

1. Feeling sleepy during the day
2. Putting on weight
3. Feeling dizzy
4. Constipation
5. Swollen breasts
6. Fast heartbeat

[D] Risperidone:

Risperidone is a second-generation antipsychotic (SGA) medication used in the treatment of a number of mood and mental health conditions including schizophrenia and bipolar disorder.16 It is one of the most widely used SGAs. [15] It is associated the chemical class named Benzoxazole derivative. [16] Risperidone is an atypical antipsychotic medication, first approved for use in the USA by the Food and Drug Administration (FDA) in 1993. [14]

Mechanism Of Action-

All antipsychotics have some degree of antagonism at D2 receptors. First-generation antipsychotics (FGAs) produce antipsychotic effects at 60% to 80% D2 occupancy. Second-generation antipsychotics (SGAs) like Risperidone exhibit their therapeutic effects through some D2 blockade, but more from the blockade of serotonin receptors like 5HT2A. [14]

Risperidone has also been said to be an antagonist of alpha-1 (α1), alpha-2 (α2), and histamine (H1) receptors. [15] Risperidone can be used as an alternative for Clozapine. [16]

Pharmacokinetics-

- **Absorption –**

Well absorbed. The absolute oral bioavailability of Risperidone is 70% (CV-25%). The relative oral bioavailability of Risperidone from a tablet is 94% (CV-10%) when compared to a solution. [15]

- **Distribution-**

The volume of distribution of Risperidone is approximately 1 to 2 L/kg. [15]

- **Metabolism-**

Extensively metabolized by hepatic cytochrome P450 2D6 isozymes to 9-hydroxyrisperidone (i.e. Paliperidone), which has approximately the same receptor binding affinity as Risperidone. Hydroxylation is dependent on debrisoquine 4-hydroxylase and metabolism is sensitive to genetic polymorphisms in debrisoquine 4-hydroxylase. Risperidone also undergoes N-dealkylation to a lesser extent. [15]

- **Excretion-**

Risperidone is extensively metabolized in the liver. In healthy elderly subjects, renal clearance of both Risperidone and 9-hydroxyrisperidone was decreased, and elimination half-lives are prolonged compared to young healthy subjects. [15]

Therapeutic Uses-

1. It helps to restore the balance of certain natural substances in the brain. [18]
2. It is used to treat behavioral problems such as aggression, self-injury, and sudden mood changes in teenagers. [19]

Adverse Drug Effects:

Risperidone induced extrapyramidal symptoms (EPSs) which were seen in 36.7%. The most common symptom was tremors in 31.8%, among them.

Other effects can be as:

1. Weight gain
2. Hyperprolactinemia
3. Amenorrhea
4. Tardive dyskinesia
5. Sedation
6. GIT problems
7. Blurred vision
8. Excessive salivation

Side Effects:

Risperidone can cause side effects, although not everyone gets them, they can be:

1. Difficulty in falling asleep during night
2. Changes in appetite
3. Headaches

4. Stiff muscle movements
5. Nausea/vomiting
6. Diarrhea

Serious side effects can be seen rarely and are observed in less than 1 in 1000 people.

CONCLUSION:

It covers the information of some common antipsychotic's drugs (Clozapine, Haloperidol, Risperidone, Olanzapine, Quetiapine, Loxapine, and Prochlorperazine) in neuropsychiatric disorder. The various mechanism of action and its therapeutic uses are discussed. The antipsychotic drugs medications are frequently being prescribed for the treatment of mental health disorders. These drugs help to treat various psychosis disorders (mental health disorders) like schizophrenia, Parkinson's disease, Tourette's syndrome.

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REFERENCE

1. Reference book by Bertram G. Katzung and Todd W. Vanderah, of 'Basic and clinical Pharmacology', 15th edition, Page No.397-404.
2. Reference book by Charles R. Craig and Robert E. Stitzel of Modern Pharmacology, Page No.529-542.
3. Article by Chaitra T. Ramachandraiah, 'The story of antipsychotics-Past and present', from Indian Journal of Psychiatry, 2009 Oct-Dec.
4. Article by Krutika Chokhawala on 'Antipsychotic Medications' from Statpearls-Bookshelf (NIH), Feb.26,2023.
5. Article from 'National Library of Medicine' by Christian R. , 'FDA-Approved Indications For First and Second Generation Antipsychotics'.
6. A Book by Dr. Sanjay G. Walode of Medicinal Chemistry-1, Second edition, Jan-2020, Page No. 4.24-4.25.
7. Diagram from Springer link.
8. Article by Sajedur Rahman on Haloperidol from 'Statpearls-Bookshelf (NIH)', Sept.1,2023.
9. Article by Lennox Din on 'Prochlorperazine' from 'Statpearls-Bookshelf (NIH)', Aug.14,2023.
10. Article by Ann Gen Psychiatry,2015 on 'Revisiting Loxapine' on Annals of General Psychiatry, Apr.1,2015.
11. Article by Habib A. Halidary on 'Clozapine' from 'Statpearls-Bookshelf (NIH)', Nov.10,2023.
12. Article by Kristina Thomas on 'Olanzapine' from 'Statpearls-Bookshelf (NIH)', Aug.28,2023.
13. Article by Jasdave S. Mann on 'Quetiapine' from 'Statpearls-Bookshelf (NIH)', Aug.28,2023.
14. Article by Shawn E. McNeil on 'Risperidone' from 'Statpearls-Bookshelf (NIH)', Jan.16,2023
15. Articles from Go Drug Bank.
16. Article by Harleen Kaur on 'Antipsychotic Drugs' from 'Research Gate', Chap. No.13, Page. No. 293-312.
17. Website of Mayo clinic.
18. Website of Web MD.
19. Website of Medline Plus.

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