ANTIPSYCHOTICS: A EXHAUSTIVE REVIEW OF FIRST AND SECOND GENERATION DRUGS

Abstract- **Antipsychotic medications play a crucial role in the management of various psychiatric disorders, offering relief from a wide range of symptoms. This comprehensive review provides an overview of both first-generation (typical) and second-generation (atypical) antipsychotic drugs, shedding light on their mechanisms of action, indications, dosages, and adverse effects.**

First-generation antipsychotics, exemplified by haloperidol and chlorpromazine, primarily act as dopamine receptor antagonists in the central nervous system, effectively targeting positive symptoms of schizophrenia and related conditions. Haloperidol, in particular, finds application in the treatment of schizophrenia, Tourette syndrome, and severe behavioural disturbances in children. However, the use of these drugs is associated with the risk of extrapyramidal symptoms (EPS) and other adverse effects, including anticholinergic effects, sedation, and metabolic changes.

Second-generation antipsychotics, known as atypical antipsychotics, exhibit a different mechanism of action. These drugs, such as risperidone and olanzapine, combine dopamine receptor antagonism with serotonin receptor modulation, providing a broader therapeutic spectrum and a reduced risk of EPS. Risperidone has been approved for the treatment of schizophrenia, bipolar disorder, and irritability associated with autism, while olanzapine has indications for schizophrenia, bipolar disorder, and treatment-resistant depression.

This review emphasises the importance of tailoring antipsychotic therapy to individual patient needs, taking into account factors like age, specific psychiatric conditions, and potential adverse effects. It also underscores the significance of ongoing research to better understand the molecular mechanisms behind antipsychotic action and the development of novel treatments with improved efficacy and tolerability.

Keywords- **Antipsychotics, First Generation Antipsychotics , Second Generation Antipsychotics, Mechanism Of Action, Adverse Effects**

INTRODUCTION

Antipsychotic drugs are used to treat and manage the symptoms of numerous psychiatric diseases. **They can be divided into first-generation or "typical" antipsychotics and second-generation or "atypical" antipsychotics.** Different psychiatric conditions are treated with first- and second-generation antipsychotics. These include attention-deficit hyperactivity disorder (ADHD), behavioural changes in dementia, geriatric agitation, depression, eating disorders, personality disorders, insomnia, generalised anxiety disorder, obsessive-compulsive disorder, post-traumatic stress disorder (PTSD), and substance use and dependence disorders. The evidence supporting their usage is questionable for several of these disorders. **(1)**

TYPICAL ANTIPSYCHOTICS

Typical antipsychotics are first-generation antipsychotics which act as dopamine receptor antagonists (DRA). Butyrophenones (haloperidol), Chlorpromazine (conventional antipsychotics) , thioxanthenes (thiothixene, chlorprothixene), dibenzoxazepines (loxapine), dihydroindoles (molindone), and diphenylbutylpiperidines (pimozide) are a few of them. **(2)**

MECHANISM OF ACTION

The mechanism of action of first-generation antipsychotic medicines is postsynaptic blockage of dopamine D2 receptors in the CNS's mesolimbic system. Evidence indicates that D2 receptors are strongly antagonistic in both striatal and cortical areas, there is a greater correlation between D2 receptor binding and potency, and 65% D2-receptor occupancy is required for antipsychotic efficacy in functional imaging investigations. The nonspecific distribution of dopamine binding throughout the central nervous system (CNS) correlates with the risk of Parkinson's disease and prolactinemia. **(3)**

A) HALOPERIDOL

Haloperidol is a first-generation (typical) antipsychotic that is utilised extensively around the world. Haloperidol is used to treat positive schizophrenia symptoms such as hallucinations and delusions. It is licenced by the Food and Drug Administration to treat schizophrenia, Tourette syndrome, severe behavioural conditions in children (combative and explosive hyperexcitability), and hyperactivity in children .**(4)**

MECHANISM OF ACTION

Haloperidol is a first-generation (typical antipsychotic) drug that functions by inhibiting dopamine D2 receptors in the brain. This drug has the greatest effect when 72% of dopamine receptors are inhibited. **(5)** Haloperidol does not target the D2 receptor. It also inhibits noradrenergic, cholinergic, and histaminergic conduction. The inhibition of these receptors is linked to a variety of undesirable medication responses. **(6)**

ADMINISTRATION

Haloperidol is frequently used in multiple nations. It can be bought in an array of formulations. It is available for oral administration in the form of tablets (0.5 mg, 1 mg, 2 mg, 5 mg, and 10 mg) and oral concentration (2 mg/mL). It is also accessible in nasal spray form. Haloperidol lactate is injected intramuscularly as a short-acting parenteral solution (5 mg/mL). Long-acting intramuscular haloperidol decanoate formulations are available. **(7)**

- Psychosis - In this case, both the oral and intramuscular variations can be used. For moderate symptomology, rely on 0.5 to 2 mg orally 2 to 3 times per day. In certain cases of resistance, up to 30 mg/day may be required. An intramuscular injection of 2 to 5 mg every 4 to 8 hours can be given to manage acute agitation. The daily maximum intramuscular dose is 20 mg. **(8)**

- Schizophrenia - The dosage for moderately severe patients is 0.5 to 2 mg haloperidol orally 2 to 3 times per day. In serious circumstances, it should not exceed 30 mg daily. Dose 2 to 5 mg haloperidol intramuscularly every 4 to 8 hours to control acute agitation in a schizophrenic patient.

- Tourette syndrome - In moderately symptomatic situations, 0.5 to 2 mg orally, 2 to 3 times per day; in severe cases, 3 to 5 mg, 2 to 3 times per day. **(9)**

ADVERSE EFFECTS

EXTRAPYRAMIDAL SYMPTOMS

- Acute Dystonia - (Develops within hours to days of onset. Muscle spasms, stiffness, and oculogyric crisis are among the potential signs.
- Akathisia - (This syndrome develops among days to months after taking haloperidol and is marked by restlessness.)
- Neuroleptic malignant syndrome (NMS) is a rare but life-threatening disease. Temperatures that are elevated and muscular rigidity are possible symptoms.)
- Parkinsonism - (Develops after a few days to a month of haloperidol use)
- Tardive dyskinesia - (Develops over a period of time and shows as a chore, particularly in the orofacial region)

OTHERS

- (Elevated temperature, dry mouth, drowsiness or sedation, constipation, urine retention) Anticholinergic effects
- Sedation
- increasing weight
- Male erectile dysfunction
- Oligomenorrhea or amenorrhea in females. **(10)**

B) CHLORPROMAZINE

Chlorpromazine is an antipsychotic drug that is used to control and treat schizophrenia, bipolar disorder, and acute psychosis. It falls in The category of antipsychotics or neuroleptic drugs known as first-generation antipsychotics. **(11).** Chlorpromazine's efficacy in bipolar disorder was initially shown to control the manic period of bipolar illness, such as excessive energy, decreased need for sleep, increased excitability and impulsivity, and grandiose ideations. Chlorpromazine is a drug that is approved by the FDA for persistent singultus, an illness in which hiccupping may continue for more than 48 hours. In instances of acute psychosis, research has indicated that chlorpromazine is an effective short-term treatment for combative and aggressive behaviour in children.**(12)**

MECHANISM OF ACTION

Chlorpromazine comes into the category of antipsychotic or neuroleptic drugs class, which is sometimes known as first-generation antipsychotics (FGAs). Its specific mechanism of action is uncertain, though it is thought to produce its antipsychotic effect by blocking post-synaptic D2 receptors in the mesolimbic pathway. The reduced activity of D2 receptors in the nigrostriatal pathway, on the other hand, is responsible for its extrapyramidal side effects. **(13).** Chlorpromazine's antiemetic action is caused by the concurrent blockage of histamine H1, dopamine D2, and muscarinic M1 receptors in the vomiting area. The liver significantly metabolises chlorpromazine (CYP450 enzymes A12 and 2D6; it is a CYP3A4 substrate). It additionally breaks into pieces in the kidneys and the GI tract. It gets eliminated by the urine, bile, and faeces. The parent drugs have a half-life of between 23 and 37 hours, and their active metabolite has a half-life of 10 to 40 hours. **(14)**

ADMINISTRATION

For the treatment of schizophrenia, the patient starts off on 25 to 75 mg/day orally twice a day and gradually raised to 200 mg/day. However, the maximum oral dose is 800 mg/day. If administered
intramuscularly or intravenously, the recommended dosage is initially 25 mg, followed by 25 to 50 mg every 1 to 4 hours as needed. The usual daily dose varies between 300 to 800 mg.

For relief from nausea and vomiting, administer 10 to 25 mg orally every 4 to 6 hours as needed. If used as an intramuscular or intravenous injection, the dose may vary from 25 to 50 mg every 4 to 6 hours as needed.Singultus can be managed with 25 to 50 mg of chlorpromazine administered orally every 6 to 8 hours. If hiccups stay after 2 to 3 days of oral treatment, chlorpromazine is administered intramuscularly or intravenously.Chlorpromazine dosages may vary from 25 to 50 mg orally and 12.5 to 25 mg

intramuscularly administered 2 to 3 hours before surgery to control preoperative anxiety.There is no demand for renal dosage modifications and no supplement is required for dialysis patients. Caution is advised for people with hepatic impairment. **(15)**

ADVERSE EFFECTS

Despite its relatively low potency, chlorpromazine is capable of causing extrapyramidal side effects (EPS), particularly acute dystonia, akathisia, parkinsonism, and tardive dyskinesia (TD). The onset of EPS side effects may range from hours to days. Acute dystonia is a condition characterised by muscle stiffness or convulsions of the head, neck, and eye muscles that may start hours after the drug is administered. Restlessness and frequent pacing are symptoms of akathisia. Parkinsonism is marked by bradykinesia, "cogwheel" stiffness, and and stumbling gait. TD is triggered by long-term antipsychotic drug use and consists of involuntary, repeated unusual movements of the face and extremities. **(16)**

2.) ATYPICAL ANTIPSYCHOTICS

Second-generation antipsychotics, frequently referred to as atypical antipsychotics, are serotonin-dopamine antagonists. As of 2016, the Food and Drug Administration (FDA) granted approval for 12 atypical antipsychotics. Risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole, paliperidone, asenapine, lurasidone, iloperidone, cariprazine, brexpiprazole, and clozapine are drugs included in this class. **(17)**

MECHANISM OF ACTION

Second-generation antipsychotics differ from first-generation antipsychotics because They occupy D2 receptors for a brief duration of time before immediately dissociating, letting normal dopamine neurotransmission. They also show quick D2 dissociation, antagonistic 5HT2A receptor attributes, and 5HT1A agonism. Second-generation antipsychotics have fewer adverse effects and are typically considered to be safe in adults and the elderly. Such variations account for normal prolactin levels, reduced cognitive deficits, and the absence of extrapyramidal symptoms. **(18)**

A) RISPERIDONE

Risperidone is an atypical antipsychotic drug that was approved by the Food and Drug Administration (FDA) in the US in 1993. Oral risperidone (tablets, oral solution, and M-TABs) have FDA-approved indications for the treatment of:

- Schizophrenia (in adults and children above the age of 13)
- Monotherapy for bipolar I acute manic or mixed episodes (in adults and children aged 10 and up)
- In adults, bipolar I acute manic or mixed episodes are managed with lithium or valproate.
- Irritability associated with autism (in children aged five and up)

The FDA has approved long-acting risperidone injectables for the treatment of schizophrenia and the maintenance of bipolar disorder in adults (as monotherapy or in combination with valproate or lithium). Risperidone has a wide range of non-FDA-approved applications. When psychotic symptoms are evident, it is utilised to treat them. It has also been used in the treatment of borderline personality disorder, delusional disorder, delirium, depression, brain damage, paedophilia, PTSD, bipolar disorder, conduct disorder, Lesch-Nyhan syndrome, Tourette syndrome, trichotillomania, stuttering, movement disorders, and developmental disorders. **(19)**

Risperidone serves a purpose in treating aggression and agitation in dementia patients, in addition to psychotic symptoms. Risperidone has also been used in the treatment of non-psychotic unipolar depression in addition to antidepressants. Risperidone has been used for the treatment of social impairment, categorised behaviours, cognitive impairments, and hyperactivity in autism, in addition to irritability. **(20)**

MECHANISM OF ACTION

D2 receptors were opposed by all antipsychotics to a certain degree. At 60% to 80% D2 occupancy, first-generation antipsychotics (FGAs) generate antipsychotic effects. Second-generation antipsychotics (SGAs) like risperidone show their therapeutic effects by inhibiting confident D2 receptors, but mainly through blocking serotonin receptors like 5HT2A. Second-generation antipsychotics bind to D2 receptors loosely and dissociate fast, which may account for their lower risk of eliciting extrapyramidal symptoms (EPS). **(21)**

Second-generation antipsychotics additionally trigger agonism at the 5HT1A receptor. Risperidone's antidepressant effects are believed to be caused by reduction of serotonin and norepinephrine reuptake. Positive symptoms have been suggested to be improved by inhibiting D2 receptors, especially those in the mesolimbic pathway. Antipsychotics' capacity to block D2 receptors in the prefrontal cortex and nucleus accumbens plays a role in relieving certain psychiatric symptoms. It is important to note because risperidone has no anticholinergic effects, which may benefit patients in some statistics, such as the elderly with dementia.

ADMINISTRATION

This drug is available in tablet, solution, or dissolvable M-TAB form, in addition to as a long-acting injectable. The orally disintegrating tablet formulation should not be sliced or swallowed by patients. It is also available as an injectable.

DOSING BASED ON INDICATIONS AS FOLLOWS

1). SCHIZOPHRENIA

- For the first episode, consume 1 to 3 mg/day orally divided into one or two doses if you are under the age of 65. Begin with 1 mg daily, then gradually work up to 2 mg daily by 0.5 mg every six to seven days. The highest daily dose is 16 mg, however, doses higher than 4 mg is rarely beneficial.
- Maintenance dosage for individuals under the age of 65: 1 to 4 mg/day taken orally in one or two doses. Begin with 1 to 2 mg daily, then gradually move up to 4 mg daily by 0.5 mg every three to seven days. The highest daily dose is 16 mg, however, doses higher than 4 mg is rarely beneficial.
- Age 65 and higher: 1 to 4 mg/day, divided into one or two doses. Beginning with 0.25 to 0.5 mg daily, then gradually increase to 2 mg daily by 0.5 mg every six to seven days. The recommended maximum daily dose is 16 mg, however, doses higher than 4 mg per day is rarely more beneficial.

2) ACUTE MANIC/ MIXED BIPOLAR DISORDER

1 to 6 mg/day administered orally in one or two doses. Beginning with 2 to 3 mg daily, gradually increasing the dose by 1 mg per day no more frequently than every 24 hours until you achieve 2 mg daily. The maximum daily dose is 6 mg.

3.) TOURETTE SYNDROME

0.2 to 3 mg used orally once or twice daily. The maximum daily dosage is 6 mg. **(22)**

ADVERSE EFFECTS

Risperidone causes substantial weight gain, abnormalities in metabolism, and sleepiness. Extrapyramidal symptoms (EPS) such as acute dystonia, akathisia, tardive dyskinesia (TD), and Parkinsonian attributes can be caused by risperidone. Acute/early EPS can happen at the start of treatment or when the dose is increased. Late-onset EPS (tardive dyskinesia) is usually the result of ongoing therapy. Akathisia is a restless feeling which can show up as the patient paces. Acute dystonia is defined by muscle spasms that cause aberrant postures and typically affect the head and neck. Skeletal muscular rigidity (also known as "cogwheel rigidity"), tremors, shuffling gait, and bradykinesia are all signs of Parkinson's disease. Tardive dyskinesia is characterised by movements of the limbs, torso, neck, and head (often affecting the tongue and lips). This can manifest as facial grimacing or an oculogyric crisis. **(23)**

B) OLANZAPINE

Olanzapine is an atypical (second-generation) antipsychotic drug. The FDA has approved the drug for schizophrenia and bipolar disorder, including mixed or manic episodes, for individuals over the age of 13. Olanzapine is also authorised for use in a combination with fluoxetine, a selective serotonin reuptake inhibitor (SSRI), in patients with bipolar disorder type 1 and treatment-resistant depression. It should be mentioned that olanzapine is not approved by the FDA for patients under the age of 13. Likewise, the combination of olanzapine as well as fluoxetine is not approved to treat kids under the age of 10. **(24)**

MECHANISM OF ACTION

Olanzapine is a second-generation atypical antipsychotic which acts mostly on dopamine and serotonin receptors. It operates as an antagonist on dopamine D2 receptors in the mesolimbic pathway, inhibiting dopamine from activating at the post-synaptic receptor. Olanzapine binds to the receptor loosely and easily dissociates, allowing normal dopamine neurotransmission.Positive symptoms like hallucinations, delusions, unorganised speech, mental processes, and behaviour are mitigated as a result of the action on D2 receptors. Olanzapine functions as an antagonist on serotonin 5HT2A receptors in the frontal brain.Olanzapine's activity on serotonin lowers negative symptoms such as anhedonia, flat affect, alogia, avolition, and difficulty concentrating. **(25)**

ADMINISTRATION

A important positive aspect of olanzapine has numerous routes of administration, enabling it to be used in a wide range of patients. It exists in tablet form, which is helpful to obedient individuals who can take prescriptions orally. The tablet dosages include 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, and 20 mg. Additionally, olanzapine is readily available as a disintegrating tablet. This form is particularly beneficial for people who cannot swallow pills but desire an oral form, patients who avoid receiving the prescriptions by not swallowing the tablet, and those who are agitated. Orodispersible mixtures have been noticed to have significantly greater bioavailability than typical dose forms.

ADVERSE EFFECTS

Being susceptible towards gaining weight is one of the most common adverse reactions of olanzapine. Olanzapine produces an increase in hunger, which leads to hyperphagia or weight gain. **(26).** While the exact cause for these deleterious consequences was unidentified, studies indicate that the WNT signalling pathway effector TCF7L2 is important in glucose homeostasis. TCF7L2 expression is enhanced in the liver and skeletal muscle as a result of olanzapine-induced weight gain and compromised insulin sensitivity. TCF7L2 expression in adipose tissue increases when insulin levels rise. This elevated expression of TCF7L2 in several bodily organs, all of which play a role in glucose metabolism, provides a mechanism for olanzapine-induced metabolic dysfunction. The discovery also points to an intriguing therapeutic target for preventing or treating olanzapine's harmful metabolic consequences.**(27)**

SUMMARY

In summary, antipsychotic medications remain pivotal in the management of psychiatric disorders, offering a range of options to address the diverse needs of patients. However, their use should be guided by a thorough understanding of their mechanisms and potential side effects, ensuring optimal outcomes for individuals with these challenging conditions.

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