# Concomitant Use of Multiple antipsychotics to treat Schizophrenia: Risk benefit analysis

By

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Bachelor of Pharmacy (Hons.)

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# Declaration

It is hereby declared that

1. The thesis submitted is my own original work while completing degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
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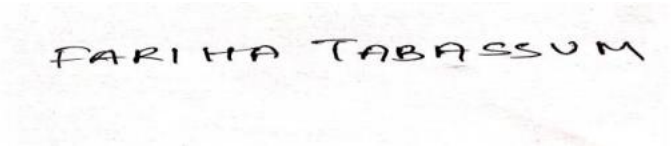


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# Approval

The thesis titled “Concomitant use of multiple antipsychotics to treat schizophrenia, risk and benefit analysis” submitted by Fariha Tabassum (18146054) spring 2018 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy.

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## Ethics Statement

This study does not involve any human and animal trial.

# Abstract

This article discusses about what schizophrenia and its symptoms are and what antipsychotics can be used to treat the disease. The main cause of schizophrenia is not found and some hypothesis and pathways for the disease is considered. The pathways and hypothesis shape the methods applied for the treatment of schizophrenia. Antipsychotics were introduced and these antipsychotics work by blocking some hyperactive receptors like that of dopamine, serotonin. Sometimes patients do not respond to monotherapy of antipsychotics therefore concomitant therapy of antipsychotics are given. This polypharmacy can be helpful in maintenance and treatment for resistant schizophrenia and for reducing side effects. Even though this seems beneficial, it comes with a lot of adverse effects and not all patients respond in the same way. There are not many studies available for the concomitant use of antipsychotics, so this article presents some of the benefits and side effects of the treatment.



**Keywords**: schizophrenia; antipsychotics; dopamine; serotonin; glutamate; extrapyramidal side effects.

# Dedication

This project is dedicated to my parents and my project supervisor, Dr. Md. Abul Kalam Azad.

## Acknowledgements

First, I would like to thank Almighty for his unlimited blessings in attempt to empower me with the strength and willingness to accomplish this project work.

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# List of Acronyms

EPS: extrapyramidal side effects

TD: Tardive dyskinesia

VTA: ventral tegmental area

D1/D2: dopamine receptor

5HT/5HT2A: serotonin receptor

H1: histamine receptor

M1: muscarinic receptor

ODT: oral disintegrating tablet

IM: intramuscular route

FGA: first generation antipsychotics

SGA: second generation antipsychotics

NMDA receptor: N-methyl-D-aspartate

# Chapter 1

# Introduction

## 1.1 Background

Schizophrenia is a common and severe mental health disorder in which individuals have distorted reality, difficulty to relate to others, control emotions and function normally, thus, affecting the persons' daily life activities. It is a complex and heterogenous (DeLisi, 1992; Ross et al., 2006a) debilitating illness, that has very devastating consequences on the individual and as well as the family (Walker et al., 2004). Schizophrenia affects about 1in every 300 people according to WHO worldwide. Schizophrenia has an early onset of the disease, and it is more noticeable from the 20 or 30 (DeLisi, 1992) and shows significant disability from its beginning although it can be diagnosed in early childhood and it reduces the life expectancy by 10-20 year(Owen et al., 2016) .It affects men more than it affects women (Bhugra, 2005). The treatment opportunities available for schizophrenia are partially successful and understanding the etiology and pathogenesis of schizophrenia is essential. Schizophrenia is a very highly heritable disease (Gottesman & Wolfgram, 1991)with a heritability score of 0.8 (Ross et al., 2006a)The treatment of schizophrenia for patients varies from an individual to another, the cost and the health, age, gender, family history, all plays an important role (Bhugra, 2005; Walker et al., 2004).

The specific cause of schizophrenia is yet to be identified. Although some research shows that factors like brain function or pathway deficit, genetics, drugs, environmental factors, can contribute to higher risk for schizophrenia. There is a high chance of increased danger of schizophrenia if a biologically related member is affected with this disease (Gottesman & Wolfgram, 1991).As well as the children that grew up in a disruptive environment, like adopted children with parents with mental disorder, children in abusive homes (Tienari et al., 1994) . For

neurotransmitters dysregulation like GABA, glutamate, dopamine also plays a role in schizophrenia. Mothers experiencing childbirth complications (like hypoxia) can affect the child's brain development, mothers getting infection during pregnancy (Owen et al., 2016; Stilo & Murray, 2019; Walker et al., 2004)

The disease itself is a burden on the patient as it can hamper the way of living, as well as on the family or the care giver. The symptoms of schizophrenia like delusions and hallucinations causes problems in everyday life, the patients need constant care, the cost of treatment/ medications, cost of health care providers and treatment/medications burdens the family members. Also affects the social life of the family members, they may become depressed trying to earn more (Panayiotopoulos et al., 2013) .

Genes may give valuable insight on the treatment of schizophrenia. Schizophrenia has symptoms like hallucinations, delusions, cognitive deficits, thought disorder, and these worsen as the condition progresses (Owen et al., 2016; Ross et al., 2006a; Walker et al., 2004) .These symptoms are classified as positive, negative, and cognitive symptoms. This review article hopes to clarify the use of antipsychotics to manage and treat these symptoms and provide a better-quality care to the affected individual as well as the limitations of these diseases.

## 1.2 Symptoms of schizophrenia

- **Positive System**: hallucinations, delusions, confusion, disorganized speech, concentration problem, muscle movement problems (Addington et al., 1991; Ross et al., 1994; Ross et al., 2006b; Walker & Lewine, 1988) .
- **Negative problems**: difficulty in showing emotions, lethargy, flattened emotions, unwillingness to do daily task, isolation from social relationship, etc. (Addington et al., 1991; Buchanan et al., 2007; Okasha et al., 2020; Walker & Lewine, 1988) .

- **Cognitive symptoms**: disorganized speech, impaired reasoning, confusion, trouble in focusing and paying attention (Addington et al., 1991; Buchanan et al., 2007; Okasha et al., 2020; Owen et al., 2016; Ross et al., 2006a).

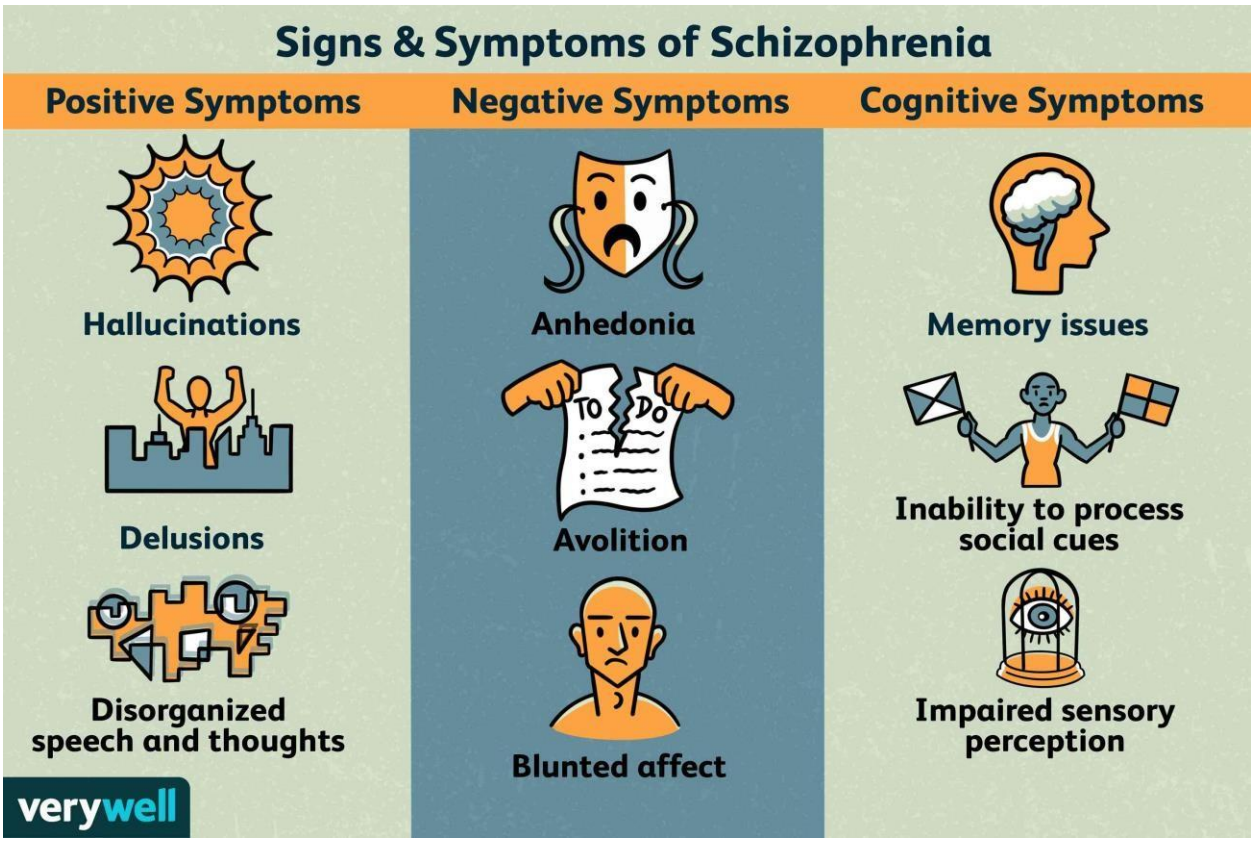


Figure 1: Signs and Symptoms of Schizophrenia (Addington et al., 1991; Buchanan et al., 2007; Okasha et al., 2020; Owen et al., 2016; Ross et al., 2006a)

## 1.3 Hypothesis of schizophrenia

**Dopamine theory:**

This theory basically states that schizophrenia happens due to dopamine hyperactivity in mesolimbic dopamine pathway. The hyperactivity of dopamine gives rise to the positive symptoms in a schizophrenia patient. the high dopamine activity in the brain triggers psychosis. the

understanding of this theory contributes to the mechanism of action of antipsychotic drugs. Therefore, many antipsychotics act by blocking the D2 receptors (Brisch et al., 2014a; Kahn, 1997; Lyne et al., 2004.; Stahl, 2018a; Toda et al., 2007).

**Glutamate/NMDA theory:**

Glutamate or glutamic acid is an excitatory neurotransmitter in brain, if the regulation of the glutamic acid is not proper in the pre-frontal cortex, then it also affects the dopamine regulation as well. Competitive inhibitors like phencyclidine and ketamine inhibits the NMDA receptors and can worsen cognitive function and psychosis in schizophrenia patient. Abnormal glutamate transmission can reduce the function of NMDA receptors and can cause hallucinations, confusion, memory problems etc (Ishimaru & Toru, 1997; Lyne' et al., 2004; Stahl, 2018a)

**Serotonin theory:**

The serotonin theory says that schizophrenia is a result of hyperactive serotonin receptors. It is said that the increase in excessive serotonin receptor, excess serotonin binding to the receptors or an agonist of the 5HT2A receptor. It is understood that the 5HT2A and 5HT2C stimulation is mainly responsible for the hallucination because these receptors regulate the release of dopamine, norepinephrine, gamma aminobutyric acid, glutamate, acetylcholine in cortex, striatum, and the limbic region. The second-generation antipsychotics target the serotonin receptors to treat and maintain schizophrenia (Eggers, 2013; Geyer & Vollenweider, 2008; Lyne' et al., 2004; Stahl, 2018a) .

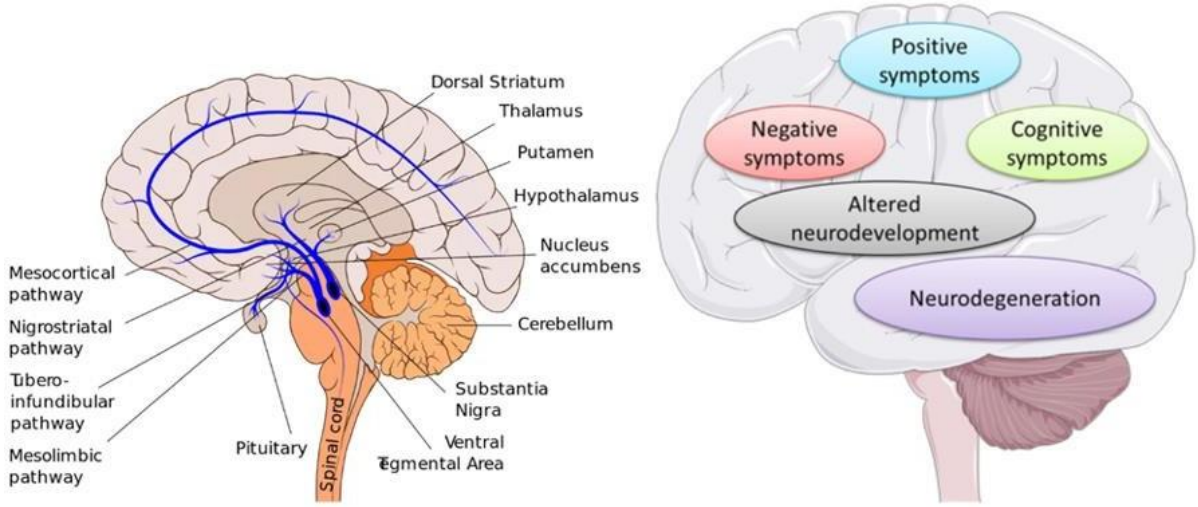


Figure 2: Different region of Brain (Eggers, 2013; Geyer & Vollenweider, 2008; Lyne' et al., 2004; Stahl, 2018a)

## 1.4 Neurochemical basis of schizophrenia: (dopamine pathways)

a) **Mesolimbic pathway:** This pathway gives the positive symptoms of the disease, it is located in the mid brain ventral tegmental area, and projects to parts of the limbic system. Since the mesolimbic pathway facilitates the feeling of euphoria and rewards, hyperactivity of dopamine can cause the positive symptoms (Stahl, 2018b; Weinstein et al., 2017).

b) **Mesocortical pathway:** This pathway is responsible for the negative symptoms. It extends from the ventral tegmental area to the per frontal cortex, where there is ample amount of dopamine receptors, especially D1, this controls cognition and emotions (Stahl, 2018b; Weinstein et al., 2017).

c) **Nigrostriatal pathway:** The neurons in this pathway extend from the substantia nigra to dorsal striatum, caudate and putamen. These parts of the brain are accountable for coordination and voluntary movement. This region is concentrated with dopamine neuron cell bodies in

substantia nigra, and axons in corpus striatum. The antagonism of D2 receptor in the brain cause the extrapyramidal and tardive dyskinesia(Brisch et al., 2014b; Weinstein et al., 2017).

d) **Tuberoinfundibular pathway:** This pathway consists of neurons from ventral hypothalamus to the median eminence and pituitary gland. The dopamine release from these neurons causes the inhibition of prolactin release from the pituitary and have other functions. Therefore, blocking these receptors with lead to prolactin release and sexual dysfunction, amenorrhea (absence of period) (Brisch et al., 2014b; Stahl, 2018b; Weinstein et al., 2017).

## 1.5 Diagnosis

Identification and diagnosis of schizophrenia has always been slow and long overdue. Patients suffer from hallucinations and delusions for a couple of years before they are diagnosed. Early symptoms like flattened emotions, social withdrawal, inability to maintain stable relationship, often goes unnoticed and the preclinical stages get more severe before getting a diagnosis. Early diagnosis and treatment can improve the quality of the patient's life. Identifying the risk factors, neuropsychology, brain imaging, help seeking behaviors, etc., these domains can help in early diagnosis (Riecher-Rössler et al., 2006). Diagnosis of psychosis is usually done according to the DSM-5 criteria as it is a syndromic concept, and it gives a dependable approach. Since the symptoms and signs vary a lot amongst individual patients, it's hard to detect and provide a diagnosis. On the contrary, most diagnosis have common symptoms (categorical method) and some these symptoms between schizophrenia and other psychiatric disorders coincide, therefore, leading to the dimensional approaches for a diagnosis(Owen et al., 2016; Riecher-Rössler et al., 2006).

## 1.6 Antipsychotics

During the second world war, the extended research on the antimalarial agents led to the discovery of an antihistaminic agent, chlorpheniramine. Further research by Rone-Poulene found that promethazine has a prominent sedating effect than other antihistamines. And in 1950, H. Laborit, French anesthesiologist, noticed that it heightens the effect of other anesthetics agents. And in 1950, S-Courvoisier verified a new compound Chlorpromazine extended sleep stimulated by barbiturates in mice. In 1951, Laborit and Hugnerd informed that patient stimulated with a concoction of chlorpromazine, promethazine and analgesic needed less anesthetics and performed better in enduring anxiety of surgery.

Upon releasing the interpretations of the effect of chlorpromazine on the central nervous system, Laborit and Hugnerd offered chlorpromazine to 2 groups of psychiatrists. The first group reported that a patient with erratic behavior, impulsive manners, aggressive conduct became a lot calmer within 1 day of treatment with chlorpromazine. After one week the patient was seen interacting happily with the medical stuff and three weeks into the treatment the patient seemed normal and was discharged(Shen, 1999).

Chlorpromazine, used to give calming effects, less psychotic behavior, fewer delusions, and hallucinations. Then these were introduced to the United States in 1955 and is still used as a treatment to maintain psychosis. Once the effects of the drug were well known for its activity, mental health facilities were cut down, housing for psychotic patients were lowered and this was a chance to cut costs. After this pharmaceutical companies started creating versions of antipsychotic drugs(Carpenter & Davis, 2012).

Antipsychotics are known as neuroleptics and tranquilizers, these drugs help in treating psychosis in schizophrenia patients, Alzheimer's, bipolar disorder, agitation etc. these drugs are taken to

control the symptoms of the disease by blocking the overactivity of the brain's dopamine receptors(Sykes et al., 2017).There are different types of antipsychotics, and they work on different symptoms and exhibits some side effects as well. (EPS) These side effects are increased with dose increments and physicians may prescribe other medications to mitigate the effects(Thomson et al., 2017).

There are about two generation of antipsychotics: first generation, second generation. And they maintain the symptoms of psychosis via various receptor mechanism.

## 1.7 Aim of the study

Schizophrenia is a very common disorder and treatment resistance is increasing day by day. This study is done to determine the risk and benefits analysis by reviewing articles and journals to find the best possible combination of antipsychotic drugs to treat schizophrenia resistance and reduce side effects.

# Chapter 2

# Methodology

This review paper is done on relevance research papers, article and journals. A complete search has been achieved with peer review article, reports, and articles. Supplementary information is also included to improve the paper. Search engines are also used to help with writing this paper, NCBI, Google Scholar, ResearchGate, PubMed, Elsevier, Science direct, Nature, drug bank, et cetera to cover the important points of this subject. Articles were searched using the key words schizophrenia, antipsychotics, side effects, names of drugs used for schizophrenia treatment, neurodevelopmental disease, etc. Recent and relevant articles were finalized to make a standard characteristic review on the concomitant use of antipsychotics of antipsychotic drugs use for treating schizophrenia. About 75 articles were selected and collected relevant data regarding the pathophysiology, symptoms, treatment, side effects and benefits. Then the paper is written with proper citation and reference for the used articles and journals.

# Chapter 3

# Antipsychotic Drugs Classifications

### 3.1.1 First Generation antipsychotics: (FGA)

FGAs are recognized as typical antipsychotics, dopamine antagonists, neuroleptics, and classic antipsychotics. these are usually used for treatment of schizophrenia and can be cost effective, although their use has declined since the new antipsychotics.

### 3.1.2 Mechanism

First generation antipsychotics work by blocking the dopamine receptors in postsynaptic(Stone et al., 2009). Data shows that this mechanism consists of high antagonism of the dopamine (D2) receptors in the cortical and the striatal region of the brain. Records show that there is a high correlation between the binding of dopamine receptors with the antipsychotics and pharmacological potency and stable requirement of about 65% (Kapur et al., 2000)D2 receptor saturation for antipsychotics to be effective(Kapur et al., 2000) .Since the receptor binding in non-specific all over the central nervous system these can have side effects like movement disorder and prolactinemia. Apart from the frequent activity of dopamine antagonist, every first-generation antipsychotic has some effects on neural serotonin (5HT2a), alpha-1, histaminic and muscarinic receptors.

### 3.1.3 High and low potency first generation anti psychotics

**High potency:** These antipsychotics are associated with No activity at histaminic and muscarinic receptors, low sedation, weight gain, anti-cholinergic activity but they have very high risk of extra pyramidal side effects.

Examples: fluphenazine, haloperidol, loxapine, perphenazine, pimozide, thiothixene, trifluoperazine.

**Low potency:**

these psychotics have high histaminic and muscarinic activity, highly sedating and shows anticholinergic effect nonetheless has low danger of extra pyramidal side effects. These are also associated with blurry vision, ophthalmic toxicity, orthostatic hypotension, QTc elongation and urinary retention.

Examples: Chlorpromazine and Thioridazine (Bryan, 2015)

### 3.1.4 Absorption and bioavailability

Some FGAs are prone to undergo first pass metabolism by the liver, causing reduced bioavailability. These drugs are lipophilic in nature and have a larger volume of distribution and tend to strongly bind to tissue and proteins. The absorption and bioavailability depend on and fluctuates from one person to another even with the same dose. Even the most frequent studied drug, haloperidol, its guidelines for therapeutic drug levels are difficult to understand (Odou et al., 1996). Loxapine and perphenazine are easily absorbed and can reach maximum concentration within 3 hours (orally). Intramuscularly Loxapine takes about 5 hours. It has the maximum bioavailability compared to other FGAs .and with aerosol Loxapine takes about 10 minutes to show therapeutic effects. (About 2mins to be absorbed)(Kwentus et al., 2012; Lesem et al., 2011).

### 3.1.5 Clearance and metabolic activation

Some FGAs use glucuronidation pathway and all FGAs undergo metabolism by cytochrome system. Chlorpromazine has a half-life of 30hrs and uses the CYP2D6, UGT-glucuronidation for metabolism. Fluphenazine consists of a 33-hour half-life and is metabolised by CYP2D6 system.

Haloperidol consists of a half-life of about 20 hours and is metabolised by CYP2D6, CYP3A4, UGT-glucuronidation (Dahl, 2002; Zhou, 2009).Loxapine has a half-life of about 6-8hours (parent drug) and about 12hours for (active metabolites) and is metabolised by CYPs 1A2, CYP2D6, and UGT-glucuronidation. Perphenazine has a half-life of 9-12 and metabolized by CYP2D6, CYP3A4 and others. Pimozide has a half-life of 55 hours(adults), 66 hours (children) and is metabolised by CYP1A2, CYP2D6, CYP3A4. Thiothixene has a half-life of 4-10 hours (parent drug), 21-25 hours (active metabolite) and is metabolised by the CYP2D6 and other CYPs. Trifluoperazine has a half-life of 3-12 hours (parent drug) and is metabolised by CYP1A2 and other CYPs.

### 3.1.6 Drug interaction

The first-generation antipsychotics can interact with drugs that affects the CYP system like fluoxetine, paroxetine, bupropion they have an inhibitory effect on the CYP2D6 system and Carbamazepine induces CYP1A4 and CYP3A4. The influence of cytochrome system stimulation or deactivation on plasma concentrations of most first-generation antipsychotic is controlled to some extent in the antipsychotic drugs that have several pathways for clearance, as well as chlorpromazine, haloperidol, etc. Since Fluphenazine is more prone to interactions with inhibitors of this system then other drugs due to its only primary pathway via CYP2D6, therefore it is not suggested to be used with other drugs that inhibit the CYP2D6. some studies reported that there is a risk of QT prolongation associated with the use of pimozide since it also inhibits the CYP2D6 system (DESTA et al., 1999). Chlorpromazine is metabolised by the CYP1A2 system, and the stimulation of these enzymes will cause serum levels of these drug to drop. Smoking induces this CYP1A2 system and therefore it is recommended to increase the dose for patients that smoke (ERESHEFSKY et al., 1991; Pantuck et al., 1982).

### 3.1.7 Administration

Oral dosing is favoured by majority of patients when taking first generation antipsychotics. Most of the FGAs require one a daily dosing although repeated administration can reduce side effects. Generally, the dosing is done recommended during sleep time due to its sedating effect, but the drugs work well regardless the time of the day. Some antipsychotics are administered via dosage forms like intramuscular, aerosol and long acting injectables. These routes of administration do also affect absorption and bioavailability (Spyker et al., 2010).

Example: Loxapine found in aerosol formulation and liquid formulation.

### 3.1.8 Side effects/ Adverse effects

All antipsychotics have some side effects even though they can be contrasted between their efficacies. These antipsychotics have unique side effect profiles within their class and compared to the second-generation antipsychotics as well. The type of antipsychotic drug, regimen and dose are dependent on the patient's medical condition, needs and susceptibilities. For instance, a sedating antipsychotic drug can be prescribed for a person with insomnia and a drug with low metabolic syndrome threat can be advised to someone with diabetes or obese. There are more side effects linked with antipsychotics such as EPS (dystonia, dyskinesia, akinesia, akathisia, etc), hyperprolactinaemia, neuroleptic malignant syndrome, QT prolongation, sudden death, increased risk of mortality in patients with dementia in adults(Savitt & Jankovic, 2018; Strassnig et al., 2018).

### 3.1.9 Extrapyramidal side effects

First generation antipsychotics has a higher tendency towards restlessness, stiffness, bradykinesia, tremor, and involuntary muscle movement that comprise of EPS than second generation antipsychotics. These drugs are dopamine antagonists and interferes with the dopamine pathway

that regulates and controls muscle movement and thus causes symptoms like Parkinson's disease. High potency drugs from first generation antipsychotics like haloperidol, fluphenazine, loxapine, thiothixene are linked to higher extrapyramidal symptoms. In a review it is found that 21%-31% patients suffered from extrapyramidal symptoms after treating with haloperidol for about three to eight weeks (Gao et al., 2008) . In some studies, Chlorpromazine and Thioridazine are low potency drugs and have less extrapyramidal symptoms and less risk compared to moderate/high doses of second-generation antipsychotic risperidone. In another study perphenazine is found to have lowers EPS than haloperidol (Coley et al., 1995). Therefore, patients' clinical conditions need to be assessed regularly about restlessness, motility, tremor, muscle rigidity, especially during dose increments(Peluso et al., 2012; Sykes et al., 2017b).

### 3.1.10 Tardive dyskinesia

tardive dyskinesia is a type of movement disorder that triggers a range of recurring uncontrolled muscle movements in the neck, tongue, including lip smacking, jaw movements and others. The threat of tardive dyskinesia adds with age, length of time of patient taking the antipsychotic drugs and development prior of extrapyramidal symptoms. Even though the symptoms may be benign at first to the patient, they sometimes progress and develop into restricting and immobilizing.

A report shows that there has been an added 5% risk in older population of tardive dyskinesia due to the first-generation antipsychotics (Morgenstern, 1993); Tarsy & Baldessarini, 2006) . The major reason that newer second-generation antipsychotics are preferred is due to fewer risk than the first-generation antipsychotics(Correll et al., 2004). It's uncertain if the lower potency FGAs like chlorpromazine and thioridazine carry fewer threat due to EPS. Higher potent drugs like fluphenazine, pimozide, thiothixene are connected to higher risk and patients on these medications

requires to be officially reviewed every 3-6weeks. And patients that more prone and older needs to be assessed at shorter intervals.

### 3.1.11 Metabolic syndrome

First generation antipsychotics have fewer risk of weight gain, ketoacidosis, diabetes, and cardiovascular diseases. These risks are generally associated with second generation antipsychotics. Even though first-generation antipsychotics have very low chance of weight gain and there are some changes in the metabolic control and appetite, (Roerig et al., 2011) correlated metabolic effects, chlorpromazine happens to keep elevated risk while fluphenazine, haloperidol, pimozide, show low risk subsequently loxapine. the possible harm of these symptoms has led to suggestions for standard monitoring of weight gain or weight loss, blood pressure, glucose level in blood while fasting, and lipid profile of patients taking any of the antipsychotics (Dossenbach et al., 2007a; Kane et al., 2002; Meyer & Koro, 2004)

### 3.1.12 Anticholinergic effects

Chlorpromazine and thioridazine possess antimuscarinic activity as they are low potency antipsychotics and causes patients to usually have dry mouth, constipation and sometimes about blurred vision and urinary retention. The symptoms are not seen that frequently with high potency first generation antipsychotics and doesn’t insist on special monitoring, but patient’s comments may be addressed with adjusting the dose, changing the drug/medication and suitable clinical intervention (Mintzer et al., 2000)

### 3.1.13 QT prolongation

QT prolongation risk is increases during the use of chlorpromazine, intravenous haloperidol and especially with pimozide and thioridazine. The active metabolite of thioridazine, mesoridazine, has the highest risk of QT prolongation amongst first and second-generation antipsychotics(Salih

et al., 2007) and was terminated due to this side effect in 2004. Thioridazine are not recommended as first line treatment for psychosis. Patients are advised to get an ECG and serum potassium level before starting treatment, and regularly during treatment, before dose adjustment and any changes in their heart condition. Patients with a limit of more than 450 millisecond QT interval should not be given this medication and if a patient's QT interval increases 60 milliseconds or reaches 500 milliseconds it implies a greater risk of ventricular tachycardia/fast heart rhythm (Moss, 1993; Shah et al., 2014). Drugs inhibiting the CYP2D6 should be avoided as this can cause QT prolongation along with thioridazine.

Haloperidol given intravenously above 35mg/day has a greater chance of QT prolongation than the other dosage forms (Shah et al., 2014) and continuous cardiac monitoring invite during the intravenous administration, especially with patients who are medically ill, have a history of cardiac illness, old age, or patients taking medications that will promote QT prolongation.

### 3.1.14 Orthostatic Hypotension

It is a drop in pressure when a person is standing up from sitting or lying down. Thioridazine and chlorpromazine have more orthostatic hypotension than olanzapine and loxapine("Cardiovascular Effects of Psychotropic Drugs," 2002; Dossenbach et al., 2007b) . Hypotension is reported with chlorpromazine where it is given parenterally. there is no report of such hypotension with fluphenazine, perphenazine, haloperidol. This is most likely caused due to the alpha-adrenergic blockade by the first-generation antipsychotic. During the first few days of exposure or during the dose increment of these drugs can also cause orthostatic tachycardia. Slow increment of dosage and low dose can help.

### 3.1.15 Increased risk of mortality

Treating adults with dementia for behavioural symptoms with FGAs can have heightened risk of stroke, myocardial infarction and sometimes even death (Schneider et al., 2005).

Risk of stroke, myocardial infarction and even death rate increases when FGAs are used to treat behavioural problems in adult patients with dementia. Cardiac and metabolic problems in patients' needs to be carefully monitored and if possible, alternatives other than antipsychotics may be advised.

### 3.1.16 Ocular

Some reports mentioned that first generation runs the risk of progressive retina photoreceptor damage. This is a disease of the eye as the light sensitive cells of retina becomes damaged progressively. First generation antipsychotics like phenothiazines brings the maximum threat of ocular issues like occur. If these first-generation antipsychotics are used in treatment, it is suggested that patients are queried about any eye problems and ocular check-up especially older patients. Drugs of FGAs like, thioridazine, perphenazine runs a high risk of ocular problems(Richa & Yazbek, 2010).

### 3.1.17 Prolactin increase, sexual dysfunction, sedation

Tuberoinfundibular pathway blocks the release of prolactin from pituitary, and FGAs blocks the tuberoinfundibular dopamine, and this stops the inhibition of prolactin. FGA cause the rise in prolactin levels in both male and females about 2-3 times the normal range. Even though some patients may be tolerant, most of them develop raised levels of prolactin. Now this surplus of prolactin causes infertility, menstruation irregularity, galactorrhoea (nipple discharge), loss of libido, erectile dysfunction. Even if the FGAs that don't cause prolactin elevation, may cause loss of sexual dysfunction. So, it is advised that patients are regularly monitored and asked about sexual

dysfunction and abnormal lactation. FGAs that are less potent like chlorpromazine and thioridazine are Histaminic H1 receptor antagonist, therefore, are highly sedating, which can sometimes be useful for patients that are agitated. It is suggested that patients are wary and vigilant during driving and operating heavy machinery. the high potent drugs do not have high sedation(la Torre et al., 2013; Peuskens et al., 2014) .

### 3.1.18 Cost

First generation drugs are cheaper than second generation drugs, since the patients need to take antipsychotics for quite some time, these are more within their means.

### 3.1.19 Name of Some First-Generation Antipsychotic Drugs

- **Chlorpromazine:** This is a first-generation antipsychotic, and it acts on the adrenergic receptors by blocking its activity (blocks post-synaptic dopamine receptors in the cortical and limbic areas of the brain), slight antagonism at the cholinergic, histamine and serotonin receptors. This drug treats the positive symptoms of schizophrenia and when it binds to these receptors promotes sedation and anti-emetic actions, reduces psychosis, hallucinations, and delusion by preventing the binding of dopamine with the receptors.

  These drugs are easily absorbed in the gastrointestinal tract, but it undergoes first pass metabolism by the liver altering the bioavailability. So, dose should be adjusted accordingly. The half-life of chlorpromazine is about 8-30hours and it is excreted by the kidneys in urine. The drugs are found in tablets and injectables (IM/IV) starting dose is 30-75mg/day and then gradually increased to 200mg/day or 800mg/day for maintenance(Javaid, 1994).

  **side effects:** dizziness, akathisia, anxiety, tardive dyskinesia, elevated prolactin, dry mouth, slight QT prolongation.

- **Fluphenazine:** This drug is highly potent and acts on the postsynaptic D2 receptors in the brain's neural pathways, (mesolimbic, nigrostriatal, tuberoinfundibular pathways), also acts as an antagonist on the alpha-1 adrenergic receptors, muscarinic 1 and histamine 1receptors. The inhibition of dopamine receptor treats the positive symptoms of schizophrenia.

  This drug is available in oral tablets and liquids, long acting injectables (IM, subcutaneous). Starting dose is 2.5-10mg/day, then gradually increased to maintain 1-5mg/day and the dose should not exceed 40mg/day. The drug has an elimination half-life of 14-16hours, and it is excreted in urine and faeces. Patients with renal impairment should have their dose adjusted to avoid toxicity and avoid drugs that inhibit CYP450 and CYP2D6 (metabolic system for fluphenazine). Examples of inhibitors of CYP2D6 are fluoxetine, paroxetine, bupropion, etc (Correll et al., 2021).

  **Side effects:** Since the drug acts on multiple receptors, dry mouth, sedation, orthostatic hypotension, extrapyramidal side effects, tachycardia, tremor, involuntary muscle movement, sexual dysfunction, hyperprolactinaemia, etc.

- **Haloperidol:** This drug competitively blocks the dopamine receptors specially the D2 receptors in the mesolimbic and mesocortical pathways in brain. It is a very potent drug that treats the positive symptoms of schizophrenia as it inhibits the excess dopamine production and prevents psychosis, hallucinations, and delusions. It also has very small effects on the serotonin and adrenergic alpha 1 receptors.

  The drug is found in tablets and injectables and is usually used in patients with acute agitation. The long-term use of this drug or a large dose is not recommended due to its high

risk of extrapyramidal side effects. This drug has a high half-life of 36 hours and is metabolised by CYP3A4 (Correll et al., 2021; Froemming et al., 1989)

**Side effects:** extrapyramidal side effects, muscle movement disorder, parkinsonism, tardive dyskinesia, acute dystonia, dry mouth, sedation, erectile dysfunction, etc.

- **Loxapine:** It acts on the dopamine and serotonin receptor by blocking its activity and reducing hyperactivity of dopaminergic neurotransmitter. It is found in capsules and starting dose is usually about 10mg two times per day up to 50mg/day. The dose is gradually increased over the next 5-7 days and maintaining up to 60-100mg/day. Dose exceeding 250mg/day is not advised (Selim et al., 2017).

  **Side effects:** Dry mouth, drowsiness, agitation, etc.

- **Perphenazine:** This is a highly potent (10-15 time more potent than chlorpromazine) first generation antipsychotic drug that acts on the D1 and D2 receptors in the mesolimbic pathway. This reduces the hyperactivity of dopamine and balances the excess dopamine in brain and alleviates hallucinations, psychosis, agitation, and anti-emetic actions. It also has small antagonistic effect on the cholinergic receptors.

  It is available in oral tablets; and the half-life of this drug is about 9-12 hours and is metabolised by the CYP2D6 system. Dosing for in patient is 8-16mg and should not exceed 64mg/day. Patients with hepatic impairment may need reduced dose and inhibitors of CYP3A4 and CYP2D6 (Jin et al., 2010) .

  **Side effects:** dry mouth, sedation, akathisia, muscle stiffness, parkinsonism, TD, dystonia, Eps, erectly dysfunction, orthostatic hypotension.

### 3.2.1 Second generation Antipsychotics

These are known as atypical antipsychotics/ conventional antipsychotics. These were introduced in the 1970s, to help treat schizophrenia, Parkinson's, agitation in autism. These are more commonly used since the first-generation antipsychotics have more debilitating side effects.

### 3.2.2 Mechanism

Second generation antipsychotics block dopamine (D2) receptors and antagonist serotonin receptors (Seeman, 1987) This also helps with the lowering risk of extrapyramidal side effects as well. The SGAs and the FGAs have different binding affinity.

### 3.2.3 Side effects

Side effects do involve weight gain, hyperlipidaemia, extrapyramidal and tardive dyskinesia, discontinuation syndrome etc. but these comes with very low risk compared to first generation antipsychotics. The side effects of SGAs are weight gain, metabolic disorders, dry mouth, orthostatic hypotension but it costs more than the first-generation antipsychotics(Hirsch et al., 2018).

### 3.2.4 Formulations

Intravenous, oral, rapid disintegrating tablets, etc. this allows a variety of options to treat patients according to their needs.

### 3.2.5 Risperidone

These are found in oral, parenteral, rapid disintegrating tablets, etc but oral formulations are not absorbed in the oral mucosa. It consists of a half-life of 20 hours and reaches peak concentration within an hour. It is absorbed readily and has a little muscarinic activity and no activity at anticholinergic. There is very rare case of drug-drug interaction, but the serum concentration of

the drug decreases when taken with carbamazepine since it induces the CYP450 system, and the serum concentration increases when the system is inhibited by fluoxetine and ketoconazole. Physicians may recommend a different regimen when concurrent medications are used. Physicians usually prescribe this drug once a day, dosed as 1-2mg/day when starting, 2-6mg/day for maintenance and doses above 6-8mg/day can increase the risk of Extrapyramidal side effects. For the elderly people dosage is usually 0.25-1mg/day and must not exceed 2mg/day as this could lead to build-up and cause toxicity. People with liver disease or problems have increased blood concentration and activity about 35% of the free drug and renal damage in patients can decrease the excretion of drug by 60% (Wang et al., 2010)

**Side effects** of the drugs include mild sedation, hypotension, akathisia, prolactin elevation, weight gain, pituitary adenoma (non-cancerous tumour)

### 3.2.6 Olanzapine

It is found in rapid disintegrating tablet, coated tablet, both long and short acting injectables. Orally is it slowly absorbed with a 30-hour elimination half-life. This drug is recommended once a day and taken immediately after taking is out of packaging since it oxidizes rapidly. This drug acts on the muscarinic and histamine receptors. Levels of olanzapine are possibly decreased by smoking and patients are advised to discontinue smoking while on the drug as this could affect serum concentration of drug and give less therapeutic effect.

Dose requirement: adult- Starting dose- 5-10mg/day, maintenance dose-15-30mg/day, in some cases 40mg/day. But it is highly advised not to exceed 20mg/day for patients that respond well to treatment as higher doses brings tolerance to the drug. In 18-month effectiveness study stable patients with schizophrenia were given an average dose of 20mg/daily. For elderly patients the starting dose was 1.25-2.5mg/day and could be increased up to 10mg/day. And for acute agitation

the dose is 5-10mg in intervals of 30-120min up to 20mg/day. Oral absorption of olanzapine is very slow therefore this is given intramuscularly and causes less drowsiness compared to haloperidol and benzodiazepines. Combination of olanzapine with diazepine can cause some problems in the heart and may even prove to be fatal in some cases(Callaghan et al., 1999).

**Side effects:** weight gain, akathisia, dry mouth, constipation hyperglycaemia, hyperlipidaemia, are greater in olanzapine compared to other SGAs.

### 3.2.7 Quetiapine

Available in both immediate and extended-release tablets with an elimination half-life and clearance about 6-7hours. Their active metabolite nor quetiapine has an elimination rate of 12 hours. Both the formulations are recommended once daily.

This drug acts on the histaminic, cholinergic, and alpha-1 receptors and give high sedating effects, anticholinergic, and orthostatic hypotension. Even though there are no significant drug-drug interactions, but serum levels of this drug can vary depending on the inducers or inhibitors of the CYP450 system.

The dosing starts at 25-30mg/day and then gradual titration of 25-50mg/day up to a 300-600mg/day if needed. The introduction of gradual increase in dose can be slowed down if the patient complains about excessive sedation and hypotension. Patient that are elderly or young may have different starting doses and renal impairment also demands a dose adjustment (DeVane & Nemeroff, 2001).

Side effects of olanzapine are sedation, orthostatic hypotension, akathisia, dry mouth, and weight gain. Sedation may decrease after some days even if the dose is gradually increased.

### 3.2.8 Ziprasidone

Dosage forms are in capsules and intramuscular solutions. The drug is poorly absorbed in oral dosage form especially when taken without food and increasing the oral dose doesn't necessarily increase the drug concentration of plasma. Patients need to be taught about taking the drug with a meal. Interactions between the drug and inducers/ inhibitors of the CYP450 system and causes mild QT prolongation.

Starting dose recommended for adults are 2 times (20-40mg)/day, gradually increasing it to 80mg/day over 2-5 days and up to 120mg/day for efficient blocking of the dopamine. Renal impairment may be incompatible with the intramuscular formulation since the drug is excreted through kidneys, and hepatic impairment may increase serum level and lead to toxicity, so dose adjustment is advised for acute agitation, FDA has approved injectable ziprasidone of 20mg/4hrs or 10mg/2hr to maximum of 40mg/day.

**Side effects:** mild sedation in early treatment, nausea, weakness, nasal congestion, QT prolongation low weight gain, hyperglycaemia, hyperlipidaemia it is advised to use concurrent medications with caution that can prolong the QT intervals. Patients with cardiac diseases are informed to get regular check-ups(Miceli et al., 2000; Preskorn, 2005)

### 3.2.9 Aripiprazole

This drug acts differently than other second-generation antipsychotics but gives similar clinical effects. Generally, antipsychotics are antagonists of the dopamine receptors, but Aripiprazole acts as a partial dopamine receptor agonist. This drug works like dopamine but stimulates a smaller response than dopamine (neurotransmitter). It also partially acts on the serotonin in 5HT1a receptors as an agonist, but for the receptors 5HT2a, H1 and alpha-1-adrennergic receptors it gives antagonistic effects.

It is found as an oral disintegrating tablet, parenteral (intramuscular). The drug is slowly absorbed orally and has 75-hour elimination half-life. The injectable preparation gives a quicker response and clinical efficacy in just 45 minutes and reaches a peak concentration within 3 hours. The long half-life of the drug helps in maintaining steady serum levels even with random missed doses but delays transition to a different medication or dose modification.

The drug is metabolised by the CYP450 system, so interactions with drug that interferes with the CYP450 system. It is recommended to increase the dose in presence of the CYP450 inducers (example: carbamazepine) since the metabolism increases and reduce the dose in presence of inhibitors (example: fluoxetine, quinidine, etc) to prevent overdose.

Starting doses of adults recommended by experts is 10-15mg/day in one unit d(DeLeon et al., 2004; Mallikaarjun et al., 2013; DeLisi, 1992; Ross et al., 2006a) debilitating illness, (DeLeon et al., 2004; Mallikaarjun et al., 2013). But can be increased up to 30mg/day for patients that do not respond well with pervious dose.

**Side effects** include headache, nausea, vomiting, insomnia, tremor, constipation, weight gain. Compared to other antipsychotics this drug has lower risk of EPS, prolactin levels, sedation and does not cause QT prolongation. This drug does increase akathisia(restlessness) in patients with bipolar disorder and depression compared to patients receiving medications only for schizophrenia Transition to this drug from other medication should be done slowly since the drug has very high affinity for dopamine receptor and acts as partial agonist.

### 3.2.10 Paliperidone

It is available in capsules and should be taken with a meal to increase its bioavailability. After absorption the drug, has an elimination half-life of 23 hours, and the drug needs a couple of days

to reach a steady sate kinetics. Almost 60% of the unchanged drug is eliminated via the kidneys and the rest metabolised by the CYP450 system. Since the excretion of the unmetabolized paliperidone is so high, the drug doesn't require hepatic function for clearance and no dose requirement needed for patients with hepatic impairment

Patients that are not adult can have a starting dose of 3mg/day and if needed can be increased with an increment of 3mg/day at five-day intervals.

**Side effects:** EPS, parkinsonism (symptoms like Parkinson disease, muscle movement impairment, slurred speech, slow movement), QT prolongation, dystonia (involuntary muscle movement), akathisia (restlessness), weight gain, tachycardia, increase in prolactin level. These symptoms vary according to the dose, so higher the dose higher the chances of these symptoms (de Leon et al., 2010).

### 3.2.11 Iloperidone

It is an antagonist at the dopamine and serotonin 5HT2a receptors and works well at 12-24mg/day. since the drug tends to cause orthostatic hypotension starting dose is 1mg twice a day where it is gradually increased to 6mg twice a day with in the fourth day. Elimination half-life is about 18-33 hours, and the plasma level increases in the presence of drugs that inhibits the CYP2D6 and CYP3A4 (ex: fluoxetine interferes with the metabolism of iloperidone)

**Side effects:** QT prolongation, dizziness, orthostatic hypotension, tachycardia weight gain, dry mouth, sedation. Cardiac monitoring is recommended for patients with heart problems and manufacturer advise use of drug against patients with hepatic impairment (Citrome, 2010)

### 3.2.12. Asenapine

This drug works on a variety of receptors. Acts as an antagonist at the dopamine receptor, serotonin, adrenergic, histamine and have very little effect on the muscarinic receptor. It has a rapid absorption rate in the sublingual route since poor absorption in the GI tract, metabolised by the CYP 1A2 system and can have an elimination half-life of 24 hours. Starting doses are 5-10mg twice per day and maximum dose up to 10mg twice per day. Patient is advised not to take any food or drink within 10 minutes of administration (Citrome, 2014).

**Side effects:** sedation, weight gain, dizziness, EPS, akathisia, oral hypoesthesia (loss of sensation in mouth). Weight gain is the most common in the use of secondary generation antipsychotics. In one study it shows that Asenapine contributed to an average weight gain of 1.2 kg compared to a 0.1-0.2kg with a placebo. Over the period of 52-week treatment it is found that the average gain was 0.9kg. not many clinical trials on the elderly patients but caution is advised due to increased risk of orthostatic hypotension. Serious hepatic dysfunction can raise serum concentration of the drug to 7 folds, therefore the use of this drug in such patients is not advised. Renal impairment doesn't have significant effect on the drugs clearance(Citrome, 2014).

### 3.2.13 Lurasidone

This drug has the most affinity for the D2 and 5HT2A receptors, moderate affinity for 5HT2A, this drug takes about 1-3 hours to be absorbed and as a clearance time of about 18 hours. The bioavailability is enhanced 3-fold when taken with a high calorie food. The drug is metabolised by the CYP3A4 system and any drug that inhibits this system is found to interact with lurasidone. For example, ketoconazole inhibits the CYP3A4 system and can increase the lurasidone concentration in serum by 9-fold. Also, CYP3A4 inducer drugs like Rifampin decreases the serum concentration level by 5-7-fold. Therefore, these drugs are recommended against coadministration. Starting dose is 40-80mg/day, found in tablet formulations (Greenberg & Citrome, 2017).

**Side effects:** drowsiness, akathisia, nausea, parkinsonism less common side effects include acute dystonia, agitation, anxiety, dizziness, weight gain. In one study it is found that fasting glucose levels are increased with lurasidone (10-14%) compared to a placebo (8.6%), prolactin elevation increased in 8.3% of women and 1.9% of men compare to 0.6-1% in placebo.

### 3.2.14 Clozapine

Clozapine is very effective in treating the positive symptoms of schizophrenia, but it runs a very high risk of fatal agranulocytosis (body doesn't make enough WBC ex: neutrophils). This drug acts on a wide number of receptors such as the antagonism of D4, H1, alpha-1-adrenergic, muscarinic receptors. The serum level is increased by CYP450 inducers like carbamazepine, smoking and inhibitors like ketoconazole, fluoxetine. Found in oral disintegrating tablets they are moderately absorbed and has an elimination half-life of 12 hours.

Starting dose is gradually increased to 12.5-25mg twice daily. Orthostatic hypotension can occur when the dose titrated. Maintenance dose is between 300-600mg/day and doses higher than 900mg/day is not advised. In elderly and medically ill patients the titration is done more slowly, and the drug maintenance dose is 100-150mg/day(Jann et al., 1993).

**Side effects:** orthostatic hypotension, tachycardia, weight gain, the metabolic syndrome, sedation, constipation, increased risk of seizure with the increase of dose. The most dangerous one is the agranulocytosis, this reduction in white blood cells is monitored carefully. US FDA demands weekly observing for the first 6 months then every two weeks for the next 6 months, after that every four weeks for the length of treatment. To prevent accidental repetition of Clozapine with patients who have developed agranulocytosis in the past, it is essential for the patients and the prescribing physicians to be entered into a database prior to treatment. Pharmacies must record

the current WBC count prior to dispensing clozapine and register it into the database and won't be permitted to dispense any more medication until the next monitoring is due.

# Chapter 4

# Comparative Analysis of Concomitant uses of drugs

## 4.1 Concomitant use of antipsychotic drugs

Treatment of schizophrenia is usually done with monotherapy of antipsychotics. Starting with low doses antipsychotics and then moving towards higher doses and more potent antipsychotics as required by the patient. But sometimes, because of the seriousness of this disease patients do not improve with one antipsychotic drugs, therefore, physicians sometimes recommend combinations of different antipsychotics. Since both antipsychotics are known to cause side effects like EPS, cognitive and emotional flattening, weight gain and metabolic syndrome, they should be very carefully used (Bergendal et al., 2015; Miller & Craig, 2002)

Concomitant antipsychotics are used in schizophrenia treatment resistant patients, to reduce the side effects of other antipsychotics.

Treatment Resistance in schizophrenia means that the patients' symptoms of the disease is still persistent despite taking adequate treatments. About 30% people suffer from treatment resistant schizophrenia and may demonstrate inadequate reaction to therapy due to the intolerance of medication, irregular medication intake, unsuitable dosing as well as the resistance to the antipsychotic drug therapy. Treatment resistance is dependent on a few factors like, long duration of medication intake, several episodes (manic, delusions, hallucinations), left untreated for a long period of time (Pandarakalam, 2019).

Clozapine is a second-generation antipsychotic that is very potent, generally used in treatment resistant schizophrenia. Clozapine acts on a various receptor and exhibits some side effects. The

side effects are dependent dose dependent. Therefore, to reduce the dose but to make sure that the patient gets the same therapeutic effect combination drugs are used.

## 4.2 Combination of clozapine and other drugs

1. **Clozapine with Aripiprazole:** In current investigation, ariprapazole has frequently been examined as an adjunct with clozapine likely because of its less metabolic side effects. Statistics for this approach runs inconsistent outcomes. In a 2013 a study (Cipriani et al., 2013) there was a considerable variation between haloperidol and aripiprazole, where the tolerable score for aripiprazole were better even though both had the same efficacy. In another study (Barbui et al., 2011) aripirazole showed favolurable changes in the adverse effects profile. From these two studies it is apparent that combination therapy of clozapine and aripiprazole maybe a good choice for treatment in terms of good side effect profile.

   One study found improvements in the symptomology, functions, metabolic profile after six weeks, reported 4 cases in whom the negative and positive symptoms improved(de Risio et al., 2011; Mossaheb et al., 2010). All these would be beneficial in treating patients that are resistant to the mono therapy of clozapine, since clozapine has side effects like agranulocytosis, sedation, weight gain, involuntary urination. Dose reduction of clozapine from 476.7mg/day to 425.1 mg/day and mean dose of aripiprazole of about 20.5mg/day in the concomitant treatment has promising improvements in patients(Englisch & Zink, 2008; Mossaheb & Kaufmann, 2012)

   Clozapine is very potent antipsychotic, but it is kept for resistant treatment because of its activities n the other receptors. It has a strong blocking activity on the 5HT2C, H1 receptors, releases leptin(Jeon & Kim, 2017) aripiprazole doesn’t block H1 receptors and has a slight

agonistic action on the 5HT2C receptor and at 5HT1A receptors and lowers blood glucose level.

Even though the combination seems to be beneficial, they do have some side effects like akathisia, hypersalivation etc. also how patients can tolerate this treatment long term isn't still clear and requires further investigation.

2. **Clozapine with Amisulpride:** Amisulpride has high affinity for D3 and D2 receptor and combined with clozapine. Some studies shows that it has improved symptoms and reduced some side effects(Report et al., 2004). In this study it was mentioned that 6 cases of patients were suffering from weight gain, sedation during the monotherapy with clozapine, after the addition of Amisulpride, clozapine dose was reduced. This led to fewer side effects(Zink et al., 2004). In another study, the side effects did not increase other than an increase in serum prolactin level but there were no clinical manifestations (Murno et al., 2004)

   A current study shows that the combination of amisulpride and clozapine has far more benefits than just reducing side effects and symptoms. The study of (Hotham et al., 2013) observed 6 aggressive patients with schizophrenia that didn't react very well to clozapine, behave more calmly and less agitated.

   These studies indicate that combination therapy can have a positive impact on the patients' symptoms and as well as reduction is clozapine dose. Nevertheless, there isn't any proper evidence for the reduced metabolic side effects are due to clozapine dose reductions.

3. **Clozapine with Sulpiride:** Sulpiride is a D2 and D3 antagonist and it enhances the blocking activity of D2 receptor of clozapine. A study of 28 people found major progress in the positive and negative symptoms contrasted to placebo groups (Shiloh et al., 1997).

Unfortunately, the number of studies done or the patients that volunteered aren't adequate to build a side effects profile, or conclusion(Christy et al., 2014).

### 4.3 Combination of non-clozapine drugs

1. **Amisulpride with Olanzapine:** In a study of 15 people that are resistant to monotherapy of antipsychotics, 5 were given olanzapine and amisulpride combination. all except one showed improvement and none of the patients experienced any side effects(Lerner et al., 2005). In another report case seven patients with resistant symptoms were noticed to have improved according to the global assessment of functioning scale(Zink, Henn, et al., 2004). Side effects were also minimized due to dose reduction.
2. **Olanzapine with Risperidone:** In a study of 5 patients on this combination of olanzapine and risperidone(Lerner et al., 2000) all participants displayed betterment in positive symptoms and one presented improvement in negative symptoms as well. Another case stated the case of a woman (middle aged) that she developed agitation when she was changed from haloperidol to olanzapine monotherapy. But once she was introduced to the combination of olanzapine and risperidone, her symptoms reduced.
3. **Quetiapine and Reserpine:** In this study of quetiapine and reserpine combination a 46-year-old person with chronic schizophrenia experiencing serious tardive dyskinesia while being treated with risperidone monotherapy. Quetiapine monotherapy only maintained the abnormal muscle movements, but the positive symptoms exacerbated. So, when a quetiapine and reserpine combination therapy was given, it alleviated both the positive and tardive dyskinesia symptoms(Nelson et al., 2003). In another case (Bozaikas et al., 2003) mentioned that a patient with schizophrenia was given reserpine and quetiapine and his brief psychiatric reading scale moved from 57 to 36 to 33 after a week and then after a month of treatment his violence and

hostility faded away. There have been more cases where patients resistant to monotherapy were given this combination of antipsychotics and their symptoms have improved after treatment for a few months.

However, there were cases that show up that combination of these drugs influence priapism (Seger & Lamberti, 2001)**.** A man with schizophrenia and OCD was treated with this combo including fluvoxamine, gabapentin and oxazepam. There was evident improvement in the beginning but then the man developed priapism after three months of treatment. It is suggested that the alpha-adrenergic receptor antagonism may have caused this as level of these drugs increase because of fluvoxamine.

4. **Amisulpride and Quetiapine:** In some studies, this combination has proved to be beneficial, however there has been reports of adverse effects associated with this combination. In this case (O'Shea et al.,2003) (Jonnalagada & Norton, 1997) reported that a 67-year-old female uncooperative with clozapine. So, she was then put on amisulpride but then no change for three weeks. After that quetiapine was added, but on day three, an irregular heart rate was observed. The patient had no prior heart conditions. ECG presented ventricular ectopic and normal QTc of 404ms when she was on 150mg of amisulpride and quetiapine 100mg. so, amisulpride was stopped and the dose of quetiapine was decreased to 50mg. Ventricular ectopic and QTc elongation up to 465ms on day three and these symptoms were fixed by day 6.
5. **Olanzapine and Quetiapine:** A 35-year-old-woman with resistant schizophrenia and pituitary adenoma in the prolactin secreting region. 30mg/day clozapine didn't improve the patient's restlessness, positive symptoms. After the addition of quetiapine about 750mg/day to olanzapine reduced to 20mg/day she started to feel better, her psychotic symptoms were managed except for a quiet background commentary (Dunkley & Reveley, 2005).

Even though this case seems to have benefited from this combination of antipsychotics, (Hedges & Jeppson, 2002) mentioned about a 27-year-old female on stable dose of olanzapine and clonazepam and sertraline. After one day of the addition of quetiapine and stopping clonazepam 2 days prior, the woman started having a seizure while talking to another person. After some screening, quetiapine was discontinued and then there was no recurrence of seizure.

6. **Olanzapine and Aripiprazole:** A 47-year-old female of schizophrenia was presented with psychomotor retardation, speech disturbances, delusions, loosening of association. She scored 46 on positive symptoms and 25 on negative symptoms. So, she was put on olanzapine, and it improved her positive symptoms but no progress on the negative symptoms. Since olanzapine helped with the positive symptoms, aripiprazole was added in combination with olanzapine. Withing two weeks of the treatment, there were significant changes in her symptomology. The score on the positive, negative scale and psychosis score dropped by 50%, 69%, 45% correspondingly (Duggal, 2004).
7. **Ziprasidone and Amisulpride:** In this study, a 59-year-old man with resistant schizophrenia displaying agitation, positive symptoms (delusions, auditory hallucinations), insomnia were treated with a combination of amisulpride and ziprasidone. No adverse effects were reported but progress was seen in sleep, behaviour, and positive symptoms. ( Lerner et al., 2005)

## 4.4 Advantages and disadvantages

Using two drugs as combinations there are a few problems like drug-drug interactions, patient adherence to two drugs, cost, higher risk of EPS/side effects, drug-drug interactions. Since there are issues with the studies regarding the polypharmacy of antipsychotics, physicians have difficulty knowing what combinations of antipsychotics would be good for patients and what does of drug will be effective. Other that clozapine there are very less studies regarding the other

antipsychotics. And every patient is different along with different physiological problems. Determining which drugs mechanism is giving the pharmacological effect isn't very clear. There has been even less studies concerning the long-term treatment of this combination concerning the safety and tolerability.

However, if a combination recommended by the physician is helpful for the patient who is resistant to other medications, that person may lead a normal life/better life. Before adding any new drug, a physician must counsel the patient about the changes in the regimen. After starting the patient on the combination therapy, strict monitoring should be maintained. Any adverse effects should be noted, and the new drug should be stopped.

## 4.5 concomitant antipsychotic study on patients

19 studies were conducted on 1216 participants where sample sizes varied from study to study widely. The chart of some studies are given below (Correll et al., 2008):

| Study | Blinding timing of cotreatment- Dosing setting | Comments |
|---|---|---|
| Antipsychotics combinations including clozapine. Clozapine+ FGA | Double blind costart-reduced dose combination- in patients | Combination with these drugs were done at different doses of (clozapine + chlorpromazine) and monotherapy of clozapine and monotherapy of chlorpromazine. The result found for Brief Psychiatric rating Scale of 4 was not shown, but the depressive symptoms were improved in each use of clozapine arm compared to chlorpromazine monotherapy. |
| Clozapine + SGA | Double blind - augmentation- comparative dose combination- outpatients | Monotherapy of clozapine and combination therapy of (clozapine + risperidone). In this case 14.3% patients removed because of not meeting the symptom severity criteria. |
| | Double blind augmentation comparative dose combination - | Monotherapy of clozapine and combination therapy of (clozapine and risperidone). Assessment of the positive and negative syndrome scale after 7 days of single blind placebo augmentation run in phase. |

| | | |
|---|---|---|
| | inpatients and outpatients | More males and higher doses of clozapine in the combination treatment than monotherapy. Clinical Global Impression of severity is not shown. |
| | Double blind augmentation comparative dose combination-inpatients and outpatients | Monotherapy of clozapine and sulpiride and combination therapy (clozapine + sulpride). No information/data found for patients that left.<br>Combination of risperidone and clozapine, given flexible dosing. |
| | | Monotherapy of olanzepine and risperidone and combination of (olanzepine and risperidone).<br>Relatively low body mass index and after about 3 years the body mass index increased. |

# Chapter 5

# Discussion

After the diagnosis of schizophrenia, patients may need treatment for life. Treatments with medication and psychosocial therapy. Clinicians check the patient's conditions and prescribe antipsychotic medications; the doses are titrated gradually and patient counselling to set reasonable beliefs that the side effects of antipsychotics will decrease with time. Physicians observe the patient's response to the drugs and adjust the dose accordingly. When monotherapy isn't working the physician may prescribe the combination of non-clozapine antipsychotics are used. If polypharmacy therapy doesn't work anymore then the physicians may prescribe clozapine. This drug is a highly potent drug and has some side effects. So, this drug is titrated gradually, and the patient is monitored carefully as this drug has high risk of agranulocytosis. If the response from the patient on clozapine is not helping the patient due to increased side effect or the patient is resistant, then combination therapy with clozapine is used.

In this paper the recent studies on clozapine and non-clozapine antipsychotics rug combinations are encapsulated. It is observed that there are insufficient number of studies, case reports and the general reports are difficult to clarify.

It is likely that the unsuccessful use of the combination of antipsychotics have unpublicized and the drug companies are asked to make available both positive and negative data about the use of antipsychotic combination use, so to diminish the bias in the direction of positive results. Most studies do not define the type of schizophrenia the patient. The combinations of drug doses given to patients vary and there is very less evidence to know which dose works best. In some cases, it is not fully established that the patient has tried all the monotherapies at the effective dosage.

Also, it is not clear that the combination is responsible for the change in the symptoms in the patient is due to the addition of new drug. It is possible that the previous monotherapy was used long enough to start having therapeutic effects.

There are not many trials for these probably because of how costly it would be, and the number of participants is very small, so not enough to build a safety and tolerability profile. The patients may not be able to cooperate with the processes for the study and these would further compromise the study.

Despite the limitations, there are some findings of benefits of the combination therapy, and this review paper has reported some of the case studies that benefited from the combination therapy especially the olanzapine-risperidone and quetiapine-risperidone.

# Chapter 6

# Conclusion

Schizophrenia can be treated with antipsychotics, however there is no known cure. The antipsychotics maintains the symptoms. The etiology of schizophrenia is still unknown. Some hypotheses like the glutamate, dopamine, serotonin elucidate some symptoms of schizophrenia, and the pathways explain how the receptors work and what they control.

In the occasions where schizophrenic patients are resistant to all types of monotherapies and demands to reduce the side effects of antipsychotic therapy, these combination treatment approaches merits attention. Even with the inadequate data obtainable, the combinations of these drugs with olanzapine, clozapine, amisulpride, risperidone theoretically works on various receptors have displayed progress in symptoms.

While prescribing polypharmacy, physicians need to customize every combination for individual patient, bearing in mind the patient's preference, prior reactions or side effects, physical heath.

There needs to be well thought out and properly designed studies with the target of precisely exploring the impacts and effects of combination therapy to facilitate the medical practitioner to better balance the risks and benefits for the treatment.

Based on these hypothesis and pathways, the antipsychotics work by acting on the serotonergic, glutamate, dopaminergic pathways to reduce the hyperactivity or hypoactivity. By altering the receptor activity, the symptoms can be managed.

Drug selection is very important for the patient. This is because every patient has specific physiology, symptoms, and underlying diseases. The physician should council with patient and check medical history before prescribing him antipsychotics. The physician must monitor the

patient’s response to medication, check the patient’s lifestyle, underlying diseases and prescribe drug properly. The second-generation antipsychotic drugs nowadays are more popular due to the less extrapyramidal side effects. But it depends on what works best for the patient.

The patient taking antipsychotics needs constant monitoring thorough out the treatment to observe any changes in the patient, (Changes in behaviour, complaints from patients about more symptoms rising or decreasing, new diseases) so that the physician can then adjust the dose accordingly.

The antipsychotic drugs also come with side effects and drug interaction. So concomitant use of the antipsychotics is usually not recommended.

## Future Work

These antipsychotics drugs are useful in treating and maintaining psychosis but comes with a wide range of side effects. So, in future if these structures can be modified to increase their potency and possible side effects. Also understanding more about how schizophrenia affects the physiology of the patient and the etiology, more drugs can be developed, or existing drugs can be used to alleviate symptoms and maintain by focusing on the pathways, gene, neurotransmitters etc. Although combination therapy is a very common practise, there is very less research on it. More research on combination therapy with adequate number of volunteers, specific combinations of drugs versus placebo, drug versus drugs, properly designed study. Then more information about the side effects and the benefits of combination therapy would be available to make a better side effect, tolerability, efficacy profile.

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