

**Review Article****Olanzapine in the Treatment of Schizophrenia and How Its Response is Modulated by Variations in Certain Genes**

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**Abstract**

Schizophrenia is a chronic disease with diverse psychopathology and multiple phases of illness. Consequently, numerous factors must be considered when assessing the benefits of a given treatment over short-and long-term periods. Olanzapine is a typical antipsychotic reported to be effective without producing many of the disabling extrapyramidal adverse effects associated with older, typical antipsychotic drugs. Even though olanzapine is still associated with a known risk of adverse metabolic effects such as weight gain, many clinicians continue to prescribe olanzapine for the treatment of Schizophrenia with the expectation of significant therapeutic efficacy relative to other first-line atypical antipsychotics. This review focuses on the epidemiology, pathogenesis, and treatment of Schizophrenia, with a particular emphasis on the role of olanzapine in its treatment. Genetic variants associated with the therapeutic efficacy and adverse effects of olanzapine are reviewed, and those with the potential to act as clinical predictors of therapeutic response and/or adverse effects are discussed. Finally, recommendations are made for the use of some of these genetic variants in clinical medicine.

**Keywords:** Schizophrenia, olanzapine, therapeutic response, adverse effects, genetic variants**Introduction**

Schizophrenia (Scz) is a complicated neuro-developmental psychiatric illness that is characterized by distortions in reality perception and expression, as well as substantial social and vocational dysfunction (Gottesman 1991). Its symptoms can be divided into four classes: positive symptoms, negative symptoms, cognitive impairment, and other mood complications, including hallucinations, delusions, formal thought disorder, speech derailments, and social and emotional withdrawal (Arango and Carpenter 2011; McGurk and Mueser 2004). Furthermore, speech content in individuals with Scz is frequently odd along with behavior, as they may sit for a long time without changing their posture or position or maintaining prolonged silence. Some may not show any evidence of disability

until they begin expressing their thoughts. Despite popular belief, Scz is quite different from learning disabilities, in which individuals demonstrate episodic dysfunction (Klein 2013). The International Classification of Diseases-10 (ICD-10) updated by the WHO in 1992, and the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) provide formal operational criteria for diagnosing Scz. According to ICD-10, which is extensively followed in Europe, manifestation should come about for the minimal duration of one month. However, DSM-5 criteria are typically utilized in the US, requiring the deterioration for about six months (Schultz, North, and Shields 2007). Despite this disparity, both systems of classification are highly acceptable.

## Epidemiology of Schizophrenia

Scz is among the leading diseases in the world responsible for functional impairment, impacting 1% of people (approximately 24 million people) (Murray, Lopez, and Organization 1996). Despite this, about half of these patients are not getting the treatment they need (Murray, Lopez, and Organization 1996). It has a severe socioeconomic impact on patients, their families, social circle, the hospitals, and the entire healthcare infrastructure of a country. Some of the reasons why it is one of the most crippling and financially draining conditions include its onset in early adulthood, the need for lifetime therapy, decreased social acceptance, and the devastating cerebral manifestations (Murray, Lopez, and Organization 1996). It commonly appears in the mid-teens up to 40, affecting both genders equally. However, in certain circumstances, the condition strikes women later in life than it does men (Goldner et al. 2002). There is some global variation in the incidence of Scz. However, there is no significant evidence of high variation between geographic regions, populations, and ethnic groupings (Torrey 1987). Approximately 90% of Scz patients are thought to live in low-and middle-income/third-world nations. According to some studies, Scz is spread unequally throughout society. Lower-income groups are more likely to experience it. According to a meta-analysis, males have a more significant lifetime chance of suffering from Scz than females (Aleman, Kahn, and Selten 2003).

The rate, pervasiveness, and mortality of Scz were summarized previously by McGrath and colleagues. In that report, they claimed that, contrary to previous assumptions, the incidence of Scz may vary depending on several factors. The median prevalence of Scz was 15.2/100,000 people, with a range of 7.7 to 43.0/100,000 people. Male are more likely than females by a ratio of 1.4 to 1. Scz had a lifetime morbidity rate of 72 per 10000 people (McGrath et al. 2008)

## Major Risk Factors of Schizophrenia

Several major risk factors for Scz have been identified. These include environmental, genetic, those related to pregnancies, infections, etc., among other factors (Modinos et al. 2013). These are described as follows (Figure1).

### *Environmental Factors*

The effect of the climate on the progression of Scz has been the subject of various epidemiological examinations. Psychotic illnesses might be misdiagnosed due to a lack of social integration. Even though heritability is regularly emphasized, onset is related to natural components such as birth complications, hardship in childhood, growing up in a dense population, being part of minority groups, and marijuana use. Studies reveal that psychological insecurity may lead to the development of more catastrophic psychopathology (Janoutová et al. 2016) in Scz patients. In a study of 100 patients (55 male, 45 female), several risk factors were found to be associated with Scz, such as gynecological problems, retarded motor and speech function, prolonged exposure to unfavorable conditions, and access to illegal drugs. It was also found that pregnancy complications and marijuana use are associated with Scz patients with non-familial origins (Scherr et al. 2012). Changes in specific environmental variables over time or space have been associated with Scz cases to variable degrees. In several etiopathogenetic investigations, environmental risk factors have been explored, putting the environment at the frontline of research into psychotic disorders. Urbanization, relocation, cannabis usage, childhood traumas, microbial attacks, obstetrical challenges, and psychosocial concerns escalate the risk of Scz. These hazards might be natural, physical, mental, or social and can develop at any age (neonatal, prepubescence, pubescence, and early adulthood)). Some of these environmental variables have a more significant impact than

others (Matheson et al. 2011). Many of these factors influence the development of Scz or may be indicators that should be perceived seriously for activating the responsible determinants.

### *Pregnancy and birth complications*

There is a possible connection between birth issues with Scz, which has provided evidence of early age growth and non-hereditary involvement in the illness (Dorrington et al. 2014). Fetal hypoxia is a commonly cited risk factor (Boydell 2001). Preeclampsia, abnormalities, and vacuum extraction are all birth problems that may increase the chance of developing Scz. Perinatal harm is more prominent among children of schizophrenic mothers (Vigod et al. 2014). They are a vulnerable and exposed group. Premature birth or children born with lower birth weights are also associated with developmental issues in neonates. These findings increase the possibility that unfavorable conditions during pregnancy can function as a trigger in individuals who are genetically prone to it. Problems during pregnancy and delivery are also regarded as a substantial risk factor for Scz development (Cannon, Jones, and Murray 2002). In these individuals, awareness of the hazards can be used to avoid disease through vigilant monitoring and early therapeutic interventions (Clarke, Harley, and Cannon 2006).

### *Infections*

Although the evidence suggesting an infectious origin of the disease is inconclusive, it can't be ignored. Bacterial, protozoan, and viral infections cause acute and subacute alterations (Flegr et al. 2014) (Konat 2016). Infection with the influenza virus during pregnancy has been linked to neurodevelopmental problems in children, including the risk of Scz (Landreau et al. 2012). In humans, this effect reaches to peak level at the end of the 2nd trimester. It is linked to infectious agents in the mother's blood (Mednick, Machon, and Huttunen 1990). Influenza infection A virus causes a brief spike in kynurenic acid content in

the brain during development, which may affect early brain development and lead to intellectual issues. Changes in tryptophan absorption caused by viral infections may likely lead to Scz manifestations later in adulthood. Measles presentation amid pregnancy has been connected to an expanded hazard of creating psychosis and Scz afterward in life (Yolken 2004)

### *Substance and drug abuse*

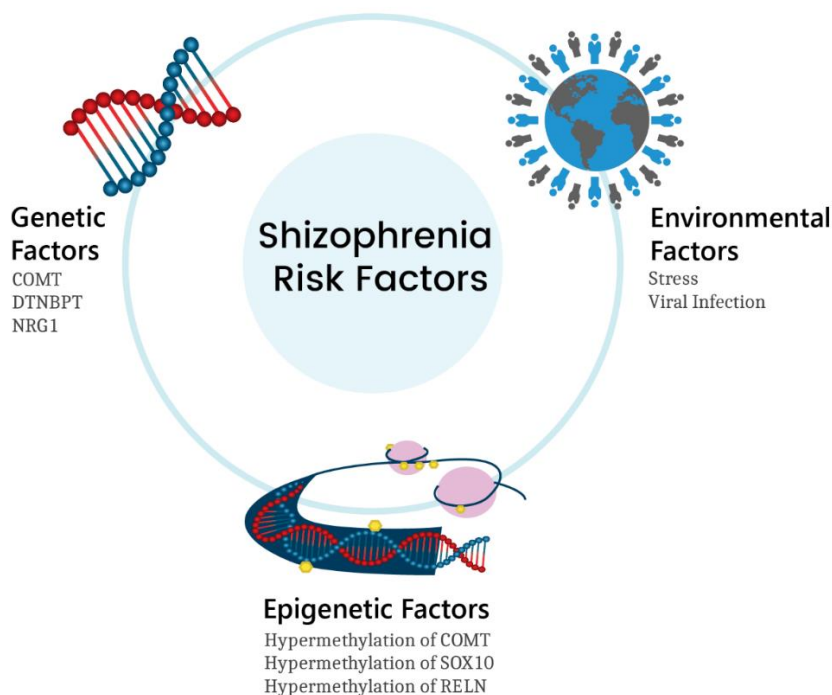
Perhaps the most widely recognized side effect of drug abuse is psychiatric issues. Lysergic acid diethylamide, phencyclidine, methamphetamine, cocaine, opiates, alcohol, tobacco, and cannabis are examples of these substances. People who already have a disturbed mental state or individuals who are inclined to these substances might develop psychosis because of the above substances. It may be difficult to differentiate between the symptoms developed due to natural causes or substance-induced. Cannabis, alcohol, and cigarettes are the drugs most abused (Pushpa-Rajah et al. 2015). Although it is implied that cannabis usage throughout adolescence is linked to an increased risk of Scz development, there is no unambiguous supporting evidence. Some researchers believe that cannabis usage can only cause Scz in those who are already mentally ill (Hickman et al. 2007) (Boydell 2001). Tobacco addiction is common among Scz patients (le Foll et al. 2015). Tobacco smoke contains ingredients that can help to alleviate a variety of Scz symptoms. For example, nicotine helps with concentration, information processing, and memory, all hampered by the disease. Alcohol misuse has been recorded in about 50 percent of Scz patients (Thoma and Daum 2013). These individuals are in danger of relapsing if they do not refrain from drugs and alcohol.

### *Genetic Influence*

Several genes are known to be associated with Scz. It is well known that peoples with a positive family history of psychiatric illness are more

susceptible to Scz. Hereditary and ecological factors are considered to incline toward the onset of Scz. The genetic involvement is deemed to be significantly high. If one of the twins develops Scz, there is a 50% chance that the other will also be schizophrenic (Hosak 2013). A review of more than 70 candidate genes (such as *DISC1*, *DISC2*, *COMT*, *DTNBPT1*, and *NRG1*) revealed that the literature on candidate genes was ambiguous on the hereditary linkage of the disorder. Inadequate statistical data was likely to be one of the reasons why candidate gene research failed to accomplish its primary goals (Farrell 2015). The strong connections between Scz and the >100 susceptible loci, the discovered CNVs, and SNVs, appear encouraging on various levels. Furthermore, the hundreds of common alleles, each with just a minor impact, may have a significant association

with this psychiatric disorder that can't be neglected (Henriksen, Nordgaard, and Jansson 2017). Hopefully, these findings will open the gateway for really unique, practical scientific information. However, it is crucial to link the relationship between normal (SNPs) or unusual (CNVs, SNVs) genetic variants and Scz, which are statistically significant. These may not be real indicators of natural cause, as most of these variants have been associated with a hereditary susceptibility to multiple psychiatric problems. The complexity of Scz etiopathogenesis and genetic influence is generally unclear. Therefore, any significant genetic association between the Scz and the disease's etiology must be viewed with caution (Henriksen, Nordgaard, and Jansson 2017).



**Figure 1 Risk Factors for Schizophrenia**

## Pathophysiology of Scz

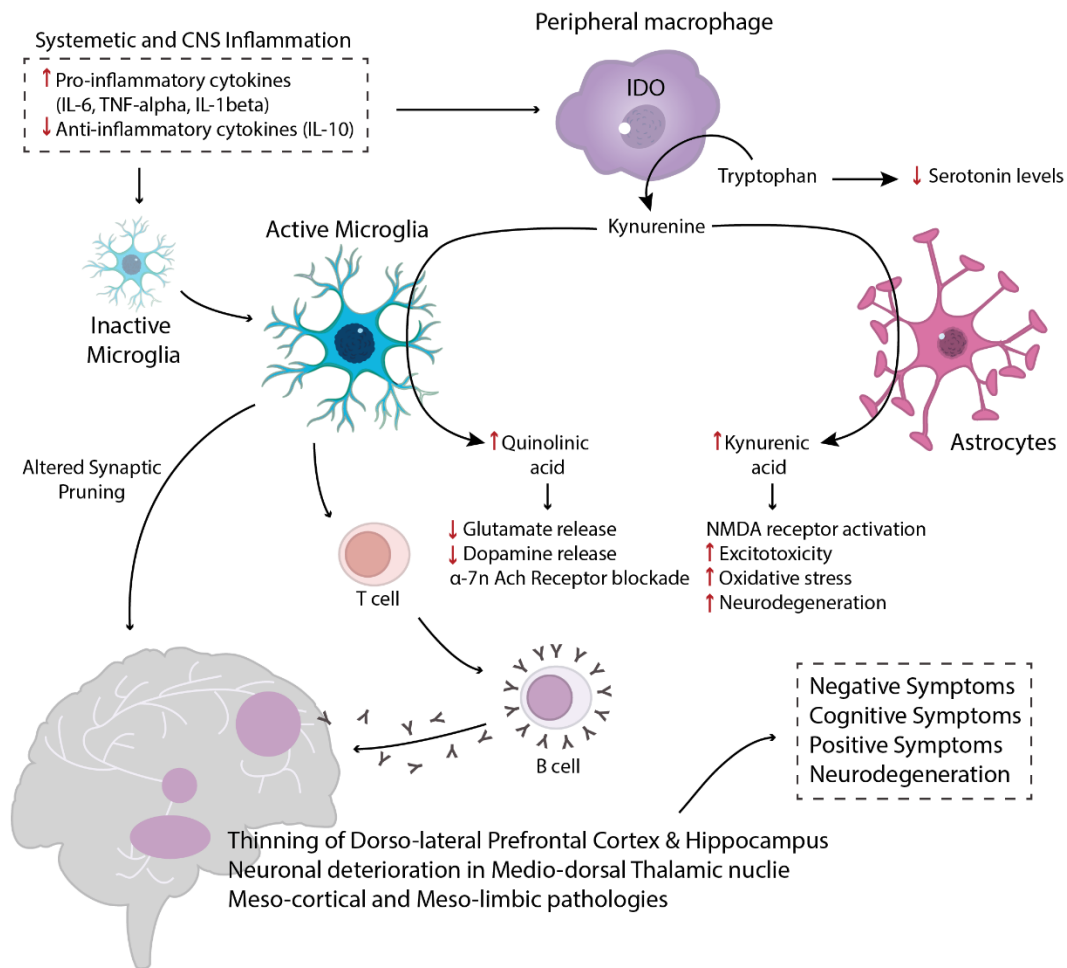
The pathogenesis of Scz is related to the idiosyncratic behavior of dopamine, serotonin, and glutamate. Some opinions propose the uneven effect of aspartate, glycine, and gamma-aminobutyric acid (GABA) as an abnormality in neurotransmission processes (Mueser and Jeste 2011). Most symptoms of Scz are considered to be due to the unusual release of dopamine (especially D2). Currently, four different theories, each dependent on dopamine release, have been proposed that point out that abnormal dopamine release can trigger the situation (Kandel et al. 2000) (Stahl et al. 2013). The development of extrapyramidal symptoms is linked with the dopamine release into the nigrostriatal route that flows from the substantia nigra to the caudate nucleus (Mueser and Jeste 2011). While hallucinations and delusions are linked with the overproduction of dopamine in the mesolimbic region that derives from the ventral tegmental area (VTA) (Mueser and Jeste 2011). Cognitive behavior and negative symptoms depend on a low dopamine concentration in the mesocortical pathway that moves from VTA to the cortex. Hormonal imbalance develops when the dopamine release from the tuberoinfundibular circuit is partly or completely blocked, which elevates prolactin concentration that, and leads to galactorrhea, amenorrhea, and lower sexual desires.

Similarly, the serotonin hypothesis for the onset of psychosis depends on the reports that lysergic acid diethylamide (LSD) enhances the level of serotonin in the frontal cortex (Mueser and Jeste 2011). Compared to earlier drugs that exclusively interact with dopaminergic receptors, recent synthetic compounds also act on serotonergic receptors along with the dopamine circuit to overcome the positive and negative symptoms (Mueser and Jeste 2011). It is also reported that phencyclidine and ketamine block the glutamate activity that leads to the development of psychosis (Jentsch and Roth 1999).

Because NMDA receptors are inactive during the routine activity of mesocortical neurons, this provides a potential clarification for its role in the development of negative symptoms along with mood and intellectual manifestation (Stahl et al. 2013). In schizophrenic patients, the central nervous system (Figure 02) undergoes physical alteration in different areas, including a reduction in the size of the medial temporal lobe while unusual enlargement in the third and lateral ventricles (Dipiro et al. 2014). The probability of an immune reaction as the causative agent for Scz and its subsequent inflammation, playing a role in the pathophysiology of Scz, also received little attention. The markers responsible for the exploration of similar elements are under consideration, including the involvement of proinflammatory cytokines, the effect of pro & anti-inflammatory cytokines on tryptophan/kynurenine consumption, the impacts of cytokines on glutamatergic neurotransmission, imaging examination, genetics, and the valuable impact of NSAIDs on Scz. However, many scientists believe that although Scz is a disorder caused by multiple underlying factors, the involvement of inflammation of the auto-immune system may be the most critical (N. Müller 2018).

## Treatment Options

The basic purpose of treating Scz is to manage the patient's symptoms such as delusions, hallucinations, and other symptoms of psychosis, to minimize the chances of recurrence, enhance functional activity so that the affected person can return to a premorbid level of functioning (Dipiro et al. 2014). Most patients can not attain a premorbid level of functioning, so they are treated with psychological therapies and medications for long periods, often for life (Dipiro et al. 2014). Treatment with medications is the main component of therapy to relieve symptoms, but sometimes psychological interventions are also helpful for persisting symptoms (Dickerson and Lehman 2011).



**Figure 1 Pathophysiology of Schizophrenia**

### Non-Pharmacological Therapy

The classical psychological interventions can be divided into three sections: personal, group-based, and psycho-education-based (Dipiro et al. 2014). However, newer non-conventional psychotherapies, including meta-cognitive coaching, talking therapy, and meditation strategies are becoming more popular (Dickerson and Lehman 2011). Non-Pharmacological interventions should also be considered as a help in the recovery of the patient being treated by medicines (Dipiro et al. 2014). Non-pharmacological therapies not only cover the deficiencies associated with medicine but also

enhances patient compliance (Lindenmayer et al. 2009). According to available data, non-compliance to medications in Scz fluctuates between 37% to 74% (Morken, Widen, and Grawe 2008). The reason behind this high level of non-compliance among psychiatric patients depends upon several factors, including unpleasant adverse effects of medicines or sometimes they feel medications are not helping in relieving their symptoms (Dipiro et al. 2014). The majority of the patients who presented with recurrent psychotic episodes had poor medication compliance (Lindenmayer et al. 2009). Subsequently, it is necessary to counsel patients about sickness along

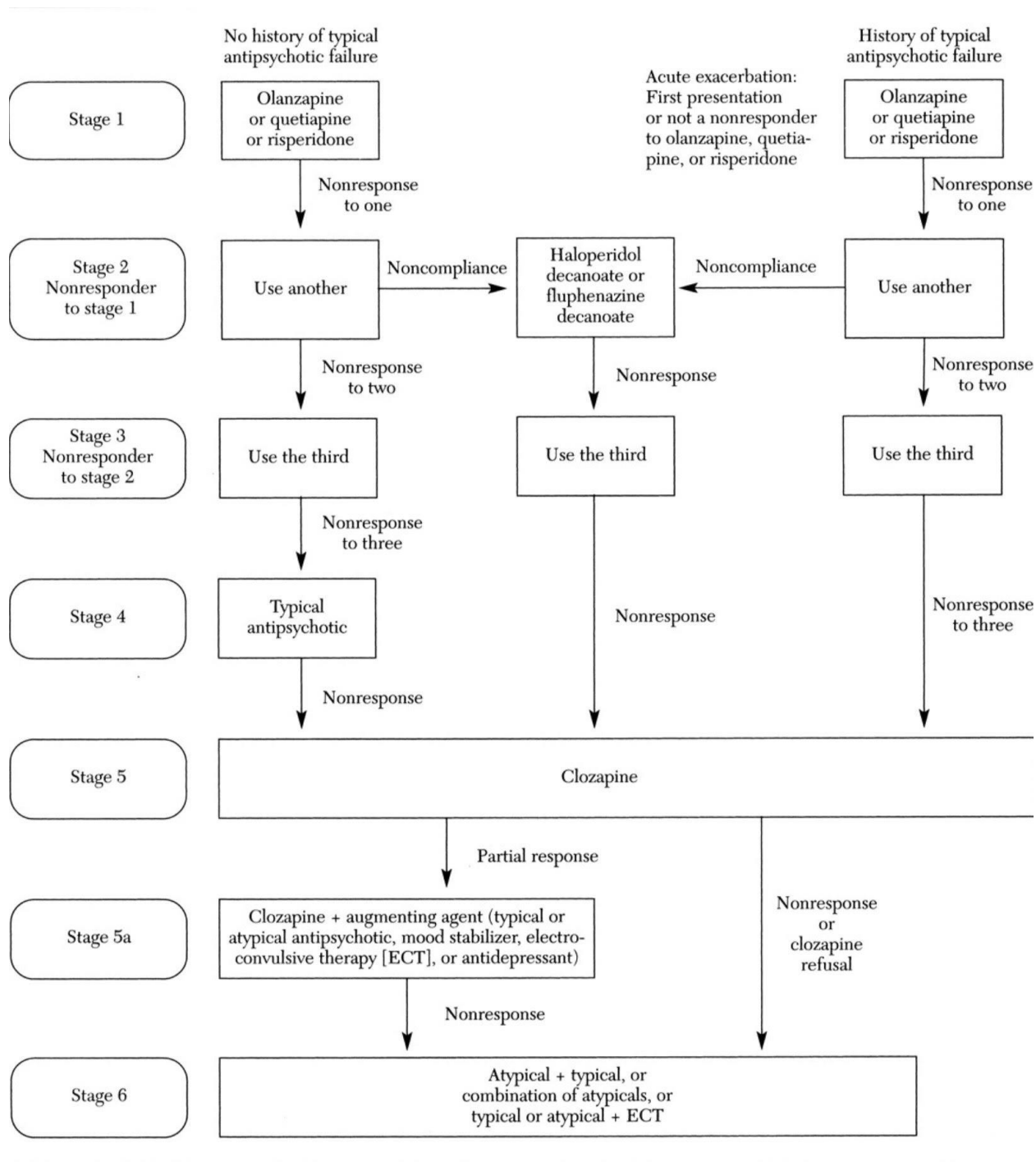
with the positive and negative effects of medication compliance (Rummel-Kluge and Kissling 2008). Some psychological interventions, including *Cognitive behavior therapy* (CBT), personalized therapy, and compliance therapy, can change the patient attitude toward their medications (Dickerson and Lehman 2011).

Along with medication therapy, it is also observed that patients who receive support from their families during treatment have high levels of functional recovery and have low chances of relapse (Dipiro et al. 2014). Attendants and guardians should also be counseled to keep an eye on small changes in their behavior and functional condition and report to clinicians immediately when things become uncontrollable (Rummel-Kluge and Kissling 2008). The majority of the interventions are unsuccessful without family support (Dickerson and Lehman 2011).

### Pharmacological Therapy

For the successful management of psychotic features, 1st or 2nd generation antipsychotic agents must be incorporated into the therapy. Clinical treatment should be initiated as soon as possible after the onset of illness because of higher chances of physiological changes in the brain due to chemical imbalance (Buckley et al. 2009). The use of organic substances along with medications reduces its effect because of chemical interaction. Medicinal interventions are necessary for early episodes to make sure that the patient is not aggressive and has normal sleep and appetite. Treatment should be initiated with a low dose, gradually increasing to the required dose depending upon the condition. Therapy during severe episodes is continued for a long time by maintenance dose to minimize the probability of recurrence and to attain the required level of functioning and personal care (Dipiro et al. 2014). Patients who receive maintenance therapy have a recurrence rate of 20-30% compared to those patients who did not receive maintenance treatment and who have 60% to 80%

recurrence (Stefan Leucht et al. 2003). In early psychosis, medicine should be used for one year (Lehman 2004) (Argo, Crimson, and Miller 2014). Second-generation antipsychotics (SGA) are commonly used drugs of choice for the treatment of Scz (Moore et al. 2007), except clozapine which affects granulocytes negatively (Dipiro et al. 2014). Due to less side, SGAs are more commonly used than first-generation antipsychotics (FGA). But SGAs are responsible for metabolic side effects, including an unplanned increase in weight, high cholesterol, and high level of blood glucose, that may lead to death due to cardiac issues in patients with Scz (Raedler 2010). Texas Medication Algorithm Project (TMAP) has devised a step-wise intervention mechanism for the treatment of Scz (Figure 03). In step one, a single agent atypical antipsychotic is used. If the response is poor, the patient should move on to step 2, which is again a single-agent treatment with another atypical or typical antipsychotic. Failing again, the plan should be switched to step 3, which includes initiation of Clozapine and observing the risk of agranulocytosis (Argo, Crimson, and Miller 2014). In case of any moderate to severe changes in WBC count, step 4 should be adopted, which includes the addition of atypical or typical antipsychotics with Clozapine or electroconvulsive therapy (ECT) (Suehs et al. 2008). In case of the still non-responsive condition, step 5 should use a previously unused single agent from atypical or typical antipsychotics (Argo, Crimson, and Miller 2014). Step 6 therapy includes a composition of atypical or typical antipsychotics, ECT, and/or a mood stabilizer (Suehs et al. 2008). Due to the failure of possible medical interventions, combination therapy is adopted, but the use of multiple antipsychotics simultaneously enhances the possibility of drug-drug interactions that may lead to unpleasant side effects (Stefan Leucht et al. 2003). Past medical records should be reviewed to avoid failure response before starting a new antipsychotic drug (Dipiro et al. 2014).



**Figure 2 Texas Medication Algorithm Project for Schizophrenia Treatment.**

**Long-Acting Antipsychotic Injectables**

When oral antipsychotics are unable to show the required response, the patient may be switched to long-acting injectable (LAI) antipsychotic medicines. However, it must be ensured that the

response is independent of significant adverse effects. If there is an exaggerated untoward response, the patient should be switched to an oral treatment plan with minimum possible adverse effects. Similarly, for initiating any LAI, tolerance

and response should be checked by its oral analog (Dipiro et al. 2014).

### *Treatment-Resistant Schizophrenia (TRS)*

In some pilot studies with typical antipsychotics, it was observed that approximately 30% of the patients showed no response to treatment, while even more patients (30%-60%) developed moderate to severe adverse events associated with the antipsychotic regime (Lehman et al. 2004). Clozapine is the drug of choice but is approximately 30% successful in treating psychotic episodes in TRS. On the other hand, the combined effect of chlorpromazine and benztropine is less than 5% (Kane et al. 1988). Individuals with polydipsia and hyponatremia have reported high a level of sodium in blood after clozapine use (Spears, Leadbetter, and Shutty Jr 1996). Clozapine may cause orthostatic hypotension, which requires close clinical surveillance (Dipiro et al. 2014). Seizures are also reported among individuals receiving the maximum therapeutic dose of clozapine.

### *Augmentation and Combination Therapy*

When clozapine fails to work, patients may be considered for an augmented treatment (with electroconvulsive therapy or a mood stabilizer) or combination therapy (with antipsychotics). When delivering augmentation therapy, clinicians should observe the following guidelines: The treatment should only be used in patients who have had a poor response to previous treatments (Argo, Crimson, and Miller 2014). When taken alone, augmenting drugs are rarely effective for Scz symptoms. Mood stabilizers are a popular form of augmentation. In some patients, lithium, for example, improves mood and behavior without having an antipsychotic impact (Stefan Leucht et al. 2003). In combination therapy, either two atypical or one typical & other atypical antipsychotics are used (Dipiro et al. 2014). Numerous antipsychotics taken combined, however, increase the chance of major adverse

events (Moore et al. 2007) (Lieberman et al. 2005). The majority of patients who respond to augmentation treatment improve quickly. If an augmentation method fails to reduce the patient's symptoms, the substance should be stopped.

### *Mechanism of Action*

The specific mechanism of action of antipsychotic medications is unknown, while it has been suggested that they fall into three groups:

- 1) Classic antipsychotics, which have strong dopamine (D2) antagonism but low serotonin (5-HT2A) antagonism
- 2) Atypical antipsychotics with moderate-to-high D2 antagonism but low 5-HT2A antagonism.
- 3) Atypical antipsychotics with decreased D2 antagonism along with increased 5-HT2A antagonism (Dipiro et al. 2014) (Kapur and Mamo 2003) (Meltzer et al. 2003)

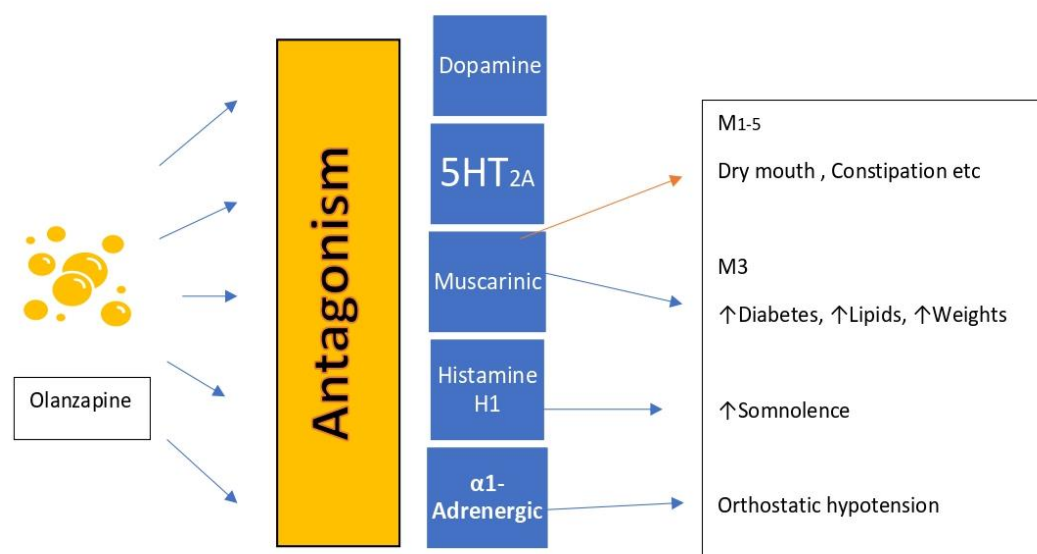
To minimize the hallucination and delusional symptoms in Scz, at least 57% to 62% of D2 receptors should be occupied, whereas 75% of D2 receptor occupancy has been linked to extrapyramidal symptoms (Kapur and Mamo 2003) (Nyberg et al. 1999). The influx of dopamine into the prefrontal cortex as a result of 5-HT2A antagonism combined with D2 blocking leads to the improvement of negative and cognitive symptoms in atypical (Dipiro et al. 2014). However, there are no standardized therapies for these indications, despite the fact that atypical antipsychotics emerged to relieve the negative symptoms.

### *Olanzapine*

Olanzapine is an SGA that was first approved by the US Food and Drug Administration (FDA) in September 1996 for the treatment of Scz (Lilly 2007). The emergence of olanzapine and the atypical class presented psychiatrists with therapeutic choices that are less likely to cause motor side effects (Komossa et al. 2010). A few meta-investigations have reported the efficacy and low extrapyramidal symptoms with olanzapine in

the treatment of Scz when compared to standard atypical antipsychotics (S Leucht et al. 1999; Davis, Chen, and Glick 2003). Due to the risk of metabolic instability and body weight, most guidelines list olanzapine as a 2nd chemotherapeutic choice for Scz (Buchanan et al. 2010; Osser, Roudsari, and Manschreck 2013). It is an analog of clozapine, which is ranked last due to safety concerns despite its proven effectiveness for treatment-resistant symptoms (Lehman et al. 2004) (Agid et al. 2010).

Nevertheless, many experienced clinicians believe that olanzapine has the best effectiveness profile of all the antipsychotic medicines now available (S Leucht et al. 1999; Davis, Chen, and Glick 2003) and continue to prescribe it to patients with Scz. Olanzapine is a thienobenzodiazepine derivative that inhibits D1-4 dopaminergic receptors, 5-HT<sub>2A</sub> and 5HT<sub>2C</sub> serotonergic receptors, α<sub>1</sub>-adrenergic, muscarinic, and H<sub>1</sub> histamine receptors (Figure 04).



**Figure 3 Mechanism of Action of Olanzapine.**

It has a 33-hour half-life and takes seven days to achieve a steady state. Olanzapine is absorbed intensively by hepatic cells through CYP1A2 but also by CYP2D6, CYP3A4, flavin-containing monooxygenase, & glucuronidation. Although the CYP1A2 isoenzyme metabolizes more than half the quantity of olanzapine, the CYP2D6 isoenzyme plays a limited role in 2-hydroxymethyl-olanzapine metabolism (Kassahun et al. 1997). The main metabolite is olanzapine 10-N-glucuronide, although there are

also olanzapine-4-N-oxide and 4-N-desmethyl-olanzapine, both of which are present in lesser quantities. None of these are clinically active (Ring et al. 1996). Patients may respond better to olanzapine at 10-15 mg/day (which may be reduced among nonsmoking females), But the dose can be increased to 15 mg if patients do not respond and blood concentration is below 20 ng/ml. The dosage and concentration of olanzapine appear to have a clear linear relationship. However, when compared among

different patients, certain types of patients may have a lot of variation in their olanzapine concentration. Patient demographics such as age, ethnicity, gender, and lifestyle are the factors that should be considered while administering olanzapine (Bishara et al. 2013). Although there appears a consensus on the lowest effective concentration of olanzapine (20 ng/mL), the highest non-toxic, effective level (40 ng/mL) remains a point of disagreement. Patients who are deemed resistant but are receiving 15 mg or higher per day and have not attained remission may benefit from therapeutic drug monitoring (TDM) of olanzapine (Bishara et al. 2013). Olanzapine's safety profile has been well investigated elsewhere (Komossa et al. 2010).

In short, SGA is more effective than FGA in antipsychotic-induced movement problems (Volavka and Citrome 2009). On the other hand, some of these drugs are responsible for clinically significant metabolic issues such as hyperglycemia, cholesterol, and increased weight (de Hert et al. 2012). Among patients using SGA, the possibility of insulin resistance increases with long-term use of Olanzapine in high doses (American Diabetes Association et al. 2004). One of its adverse effects, hypertriglyceridemia, a condition that leads to weight gain and is a serious health concern for diabetes, is a significant marker of insulin sensitivity (Meyer and Stahl 2009). Olanzapine also exacerbated atherosclerosis by altering hepatocellular lipid profile and elevating hypercholesterolemia and aortic inflammation in an experimental animal study (Chen et al. 2018). As we know, olanzapine's antagonistic actions at 5-HT<sub>2c</sub>, histaminergic H<sub>1</sub>, and muscarinic M<sub>3</sub> receptors are associated with increased weight. Despite the fact that a 2010 meta-analysis (Maayan and Correll 2010) found that adding metformin, fenfluramine, sibutramine, topiramate, or reboxetine in combination with olanzapine causes a reduction in weight gain versus placebo (Robert C Smith et al. 2018), but statistical data is not supportive in long term use of any of these

medications to relieve adverse metabolic effect (Maayan and Correll 2010; Robert C Smith et al. 2018) Olanzapine has significant adverse effects on muscle mass, which must be maintained constantly, in addition to its effects on lipid and glucose metabolism, and bodyweight (Citrome et al. 2011). In a meta-analysis of 13 short-term, placebo-controlled olanzapine single drug studies (duration six weeks), the minimum increase in weight with olanzapine was 2.6 kg (5.7lb), while weight reduction of 0.6lb was observed in patients exposed to placebo. The number of individuals who added at least 7 percent overall of their normal weight climbed to 22% with olanzapine, compared to 3% with placebo (Lilly 2007). In long-term studies (12 months), 64% of patients gained 7% of their initial body weight, while 32% had 15%, and about 12% had a 25% increase in weight (Lilly 2007). Shifts in plasma glucose or lipid variables from normal/borderline to abnormal have also been documented (Citrome et al. 2011). Numerous frameworks and reports have recommended solutions to reduce such adverse reactions, for example, using metformin with Olanzapine, a favorable diet, and improvements in physical activity (de Hert et al. 2012). However, there are presently no FDA-approved therapies to treat atypical antipsychotics-related metabolic dysregulation, including weight gain (Figure 05). Despite its well-known metabolic side effects, olanzapine has certain safety benefits over other antipsychotics. Extrapyramidal symptoms, a common cause of noncompliance and treatment cessation, are less common with olanzapine than with conventional and some atypical antipsychotics (Tran et al. 1997). Furthermore, none of the more than 2000 patients who received olanzapine in the four critical effectiveness and safety trials experienced agranulocytosis, a potentially deadly side event that restricts the use of clozapine (Beasley Jr et al. 1997). In comparison to several standard and atypical antipsychotics, olanzapine has little effect on prolactin (Volavka and Citrome 2009). When compared to

haloperidol (Beasley Jr et al. 1997) or risperidone, olanzapine therapy resulted in a considerably reduced number of individuals with prolactin elevations (Tran et al. 1997). Although olanzapine's effect on prolactin levels is presumably dose-related, elevations in prolactin linked with olanzapine were usually tolerable, short term, and of smaller quantity than haloperidol and risperidone (Beasley Jr et al. 1997). Several investigations have now established that olanzapine has a positive effect on prolactin levels

(Costa et al. 2007). As a result, as compared to other antipsychotics, individuals using olanzapine has a decreased probability of hyperprolactinemia symptoms such as gynecomastia, galactorrhea, menstruation problem, and a decreased libido (Tewksbury and Olander 2016). Finally, during premarketing trials, olanzapine therapy was related to a modest incidence of seizures (0.9 percent) (Lilly 2007).

## OLANZAPINE

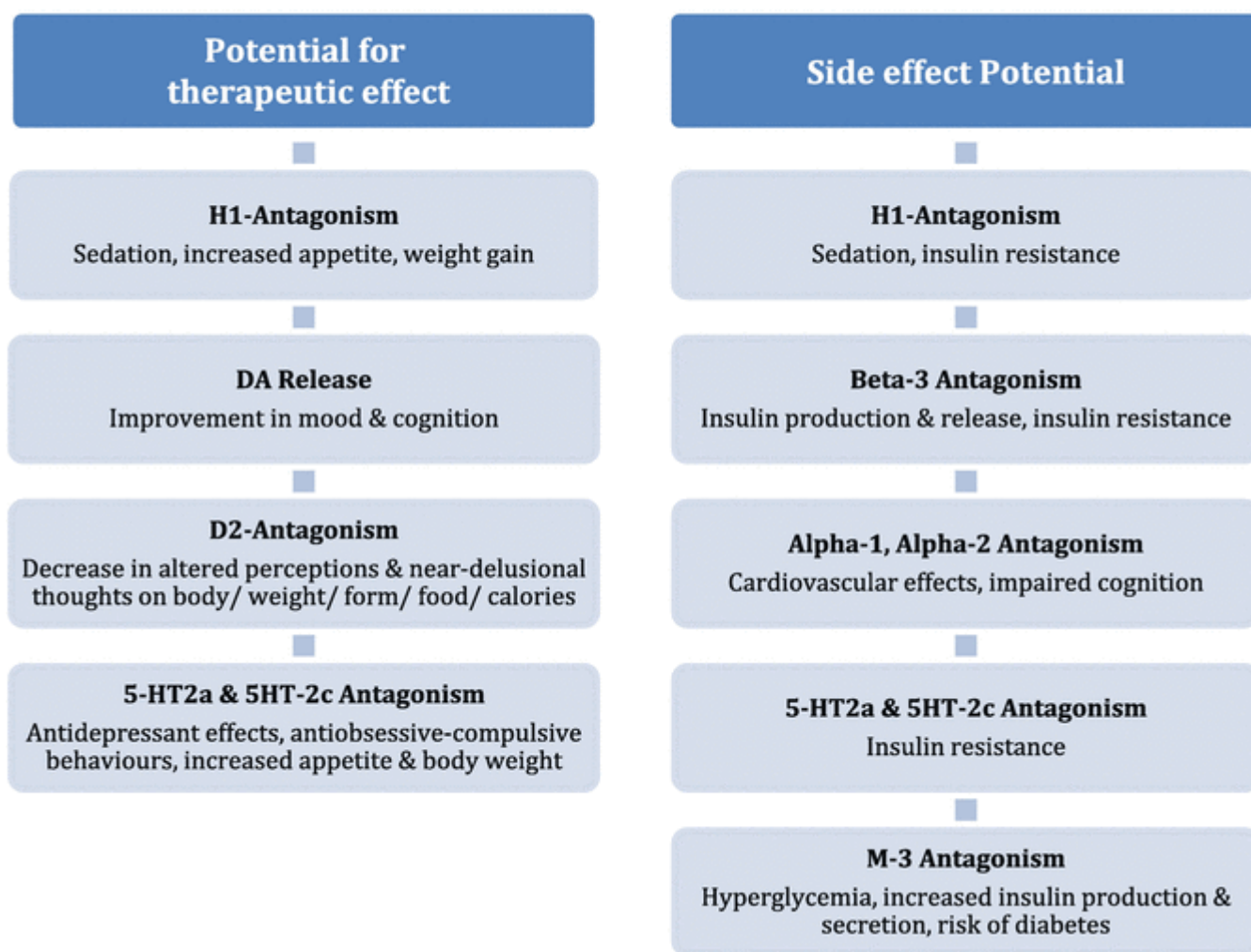


Figure 5 Olanzapine induced Side effects.

## Genetic factors affecting efficacy and adverse effects of Olanzapine in Schizophrenia

Plasma concentration of olanzapine exhibited a significant phenotypic diversity. The most flexible is CYP1A2 behavior, including the particular healthcare setting, which provides credible solutions through its comprehensive strategy with different medications and difficulties. CYP1A2 function is stimulated by tobacco smoking, processed meat, fruits, and vegetables, or pharmaceuticals like omeprazole, which is inhibited by fluvoxamine, ciprofloxacin, and oral hormone replacement therapy and contraceptives. Olanzapine binds to dopamine and serotonin receptors, especially 5-HTR2A, 5-HTR2C, and 5-

HTR1A. Numerous mutations were already recognized as promising correlations with therapeutic responses after antipsychotic treatment.

Some unexpected significant connections have also been discovered, including 5HTR2A, T102C; however, there are too many studies to make any predictions. The effects on treatment response are often described as small and unlikely to be clinically significant. As a result, in the experimental research paradigm, no associations between dopaminergic and serotonergic genotypes were discovered (Laika et al. 2010). Genes that affect the efficacy and adverse of Olanzapine are presented in Table 1.

**Table 1 Selected studies showing the association of genetic variants with adverse effects/efficacy of olanzapine**

Gene	Sample Size	Location	Study Design	Main findings	Reference
<i>CYP1A1</i>	342	Norway	Influence of <i>CYP1A1/CYP1A2</i> and <i>AHR</i> polymorphisms on systemic olanzapine exposure.	rs2472297 When olanzapine is used to treat persons with psychotic disorders, allele T is related to a 25% higher mean 4'-desmethyl OLA/olanzapine (OLA) ratio than genotype CC.	(Söderberg et al. 2013)
<i>CYP1A2</i>	124	Germany	Pharmacogenetics and olanzapine treatment: <i>CYP1A2*1F</i> and serotonergic polymorphisms influence therapeutic outcome	The <i>CYP1A2*1F</i> genotype is being used as a correct standard for <i>CYP1A2</i> performance along with olanzapine levels. The clinical significance of the concentration-response relationship discovered in patients with schizophrenia illnesses is highlighted.	(Laika et al. 2010)
<i>GRM3</i>	42	USA	Association between the polymorphic <i>GRM3</i> gene and negative symptom improvement during olanzapine treatment	In persons receiving olanzapine for Schizophrenia, genetic variations in the <i>GRM3</i> gene may be helpful indications of negative symptom relief.	(Bishop et al. 2005a)
<i>ABCB1</i>	233	Japan	Effects of <i>ABCB1</i> gene polymorphisms on autonomic nervous system activity during atypical antipsychotic treatment in Schizophrenia	<i>ABCB1</i> genetic polymorphisms affect aripiprazole-related ANS dysfunction but do not affect risperidone-, olanzapine-, or quetiapine-related ANS dysfunction	(S. Hattori et al. 2018)

<i>CYP1A2*1F</i>	214	Germany	Pharmacogenetics and olanzapine treatment: <i>CYP1A2*1F</i> and serotonergic polymorphisms influence therapeutic outcome	As investigated in patients with the *1/*1F and *1/*1 genotypes, *1F/*1F subjects exhibited substantially lower dose-normalized olanzapine ratios and small quantities/dose/ body weight.	(Laika et al. 2010)
<i>CYP1A2*1D and *1F</i>	241	China	Association of the genetic polymorphisms of metabolizing enzymes, transporters, target receptors and their interactions with treatment response to olanzapine in Chinese han schizophrenia patients	When evaluated to *1/*1 individuals, *1F allele carriers had substantially lower dose-corrected olanzapine blood concentrations and a worse outcome (both homozygous and heterozygous *1F allele carriers) (PANSS). The alleles *1D and *1F were more common in the poor response group (PANSS).	(Yan et al. 2020)
<i>DRD2</i>	66	Italy	<i>DRD2/AKT1</i> interaction on D2 c-AMP independent signaling, attentional processing, and response to olanzapine treatment in Schizophrenia	The relationship between the T allele of <i>DRD2</i> rs1076560 and the A allele of <i>AKT1</i> rs1130233 was linked to lower levels of <i>AKT1</i> protein, and <i>GSK-3</i> phosphorylation and, therefore, a changed cingulate reflex and decreased psychosocial correctness throughout cognitive processing.	(Blasi et al. 2011)
<i>ApoC3</i>	189	USA	Allelic variation in <i>ApoC3</i> , <i>ApoA5</i> and <i>LPL</i> genes and first- and second-generation antipsychotic effects on serum lipids in patients with Schizophrenia.	Allelic variation in <i>APOC3</i> gene is related to effects on lipid metabolism. <i>APOC3</i> rs5128 G/G carriers showed lower t1/2 than C allele carriers. The rs5128 G allele seems to be related to the underexposure of the drug.	(R C Smith et al. 2008)
<i>ApoA5</i>	189	USA	Allelic variation in <i>ApoC3</i> , <i>ApoA5</i> , and <i>LPL</i> genes and first- and second-generation antipsychotic effects on serum lipids in patients with Schizophrenia.	the <i>ApoA5_1131</i> (T/C) SNP is associated with lower cholesterol levels in patients treated with olanzapine.	(R C Smith et al. 2008)
<i>CPY3A4</i>	153	USA	Genetic variation in <i>CYP3A43</i> explains the racial difference in olanzapine clearance.	<i>Cyp3A4</i> rs472660 in Schizophrenic patients with AA genotype have increased clearance of olanzapine as compared to patients with the AG or GG genotype.	(Bigos et al. 2011)
<i>Cyp3A4</i>	152	Austria	Genetic variation in <i>CYP3A43</i> is associated with	rs680055 genotype CG is associated with increased	(Brandl et al. 2015)

			response to antipsychotic medication.	response to olanzapine in Schizophrenia compared to genotype CC.	
<i>CYP2D6</i>	11	USA	<i>CYP2D6</i> polymorphisms and atypical antipsychotic weight gain.	<i>CYP2D6</i> *1/*3 + *1/*4 are associated with increased Weight gain when treated with olanzapine in men with Schizophrenia compared to <i>CYP2D6</i> *1/*1.	(Ellingrod et al. 2002)
<i>ADRB3</i>	164	Japan	Multiple genetic factors in olanzapine-induced weight gain in schizophrenia patients: a cohort study.	<i>rs4994</i> genotype GG is associated with an increased risk of Weight gain when treated with olanzapine in people with Schizophrenia as compared to genotypes AA + AG.	(Ujike et al. 2008)
<i>CYP2C9</i>	63	Spain	Polymorphisms influencing olanzapine metabolism and adverse effects in healthy subjects.	<i>CYP2C9</i> *1/*3 + *2/*3 + *3/*6 is associated with increased likelihood of Hypotension when exposed to olanzapine in healthy individuals as compared to <i>CYP2C9</i> *1/*1 + *1/*2 + *2/*2.	(Cabaleiro et al. 2013)
<i>SLC22A1</i>	80	Spain	Impact of polymorphisms in transporter and metabolizing enzyme genes on olanzapine pharmacokinetics and safety in healthy volunteers.	<i>rs34059508</i> genotype AG is associated with increased exposure to olanzapine in healthy individuals compared to genotype GG.	(Zubiaur et al. 2021)
<i>GLP1R</i>	86	Canada	Genetic variation in the <i>GCG</i> and in the <i>GLP1R</i> genes and antipsychotic-induced weight gain.	<i>rs2268639</i> Allele T is associated with increased Weight gain when treated with clozapine or olanzapine in people with Schizophrenia.	(Brandl et al. 2014)
<i>HTR1A</i>	221	S. Korea	Case-control association study for ten genes in patients with Schizophrenia: influence of <i>5HTR1A</i> variation <i>rs10042486</i> on Schizophrenia and response to antipsychotics.	<i>rs10042486</i> genotype TT is associated with increased response to olanzapine in patients with Schizophrenia as compared to genotypes CC + CT.	(Crisafulli et al. 2012a)
<i>HTR2A</i>	164	Japan	Multiple genetic factors in olanzapine-induced weight gain in schizophrenia patients: a cohort study.	<i>rs6313</i> genotype GG is associated with decreased risk of Weight gain when treated with olanzapine in people with Schizophrenia as compared to genotypes AA + AG.	(Ujike et al. 2008)
<i>HTR2C</i>	200	Thailand	Genetic polymorphisms of <i>HTR2C</i> , <i>LEP</i> and <i>LEPR</i> on metabolic syndromes in	<i>rs518147</i> genotype CC is associated with an increased likelihood of Metabolic	(Puangpetch et al. 2018)

			patients treated with atypical antipsychotic drugs.	Syndrome when treated with olanzapine in patients with Schizophrenia as compared to genotypes CG + GG.	
COMT	30	Italy	Interaction of COMT Val108/158 Met Genotype and Olanzapine Treatment on Prefrontal Cortical Function in Patients with Schizophrenia.	COMT genotype (Met Alleles) contributes to variation in the cognitive and negative symptom response to olanzapine in patients with Schizophrenia.	(Bertolino et al. 2004a)
DTNBP	205	USA	A Comparison of Clozapine and Haloperidol in Hospitalized Patients with Refractory Schizophrenia	Patients with diplotype ACCCTC/GTTGCC, genotypes T/T + T/C, or allele T of marker rs742105 (P1333) have a better response to clozapine	(Rosenheck et al. 1997)
BDNF	216	China	Association analysis of the dopamine D3 receptor gene ser9gly and brain-derived neurotrophic factor gene val66met polymorphisms with antipsychotic-induced persistent tardive dyskinesia and clinical expression in Chinese schizophrenic patients	Val66Met genotypes had higher TD occurrence than Met/Met or Val/Val genotype patients in Chinese.	(Liou et al. 2004a)
BDNF	214	Croatia	Association between the brain-derived neurotrophic factor Val66Met polymorphism and therapeutic response to olanzapine in schizophrenia patients.	rs6265 genotype CC is associated with increased response to olanzapine in people with Schizophrenia as compared to genotypes CT + TT.	(Nikolac Perkovic et al. 2014)
GNB3	164	Japan	Multiple genetic factors in olanzapine-induced weight gain in schizophrenia patients: a cohort study	rs5443 Allele T is associated with an increased risk of Weight gain when treated with olanzapine in people with Schizophrenia as compared to genotype CC.	(Ujike et al. 2008)
MTHFR	218	Canada	Methylenetetrahydrofolate reductase gene variants and antipsychotic-induced weight gain and metabolic disturbances	rs1801131 genotype GG is associated with increased Weight gain when treated with olanzapine in people with Schizophrenia as compared to genotype GT.	(Kao et al. 2014)
DRD2	206	Canada	Systematic analysis of dopamine receptor genes (DRD1-DRD5) in antipsychotic-induced weight gain.	rs1079598 Allele G is associated with an increased likelihood of weight gain when treated with clozapine or olanzapine in people with Schizophrenia as compared to allele A.	(D. J. Müller et al. 2012)
DRD2	98	USA	Association of DRD2 and ANKK1 polymorphisms	rs2734842 Allele A is associated with increased	(Houston et al. 2011)

			with prolactin increase in olanzapine-treated women.	prolactin when treated with olanzapine in women as compared to allele G.	
RGS4	198	USA	Ethnic stratification of the association of RGS4 variants with antipsychotic treatment response in Schizophrenia.	rs951439 genotype CT is associated with an increased likelihood of response when treated with olanzapine in people with Schizophrenia.	(Campbell et al. 2008)

### CYP1A2

The *CYP1A2* gene comprises seven exons, the first of which is non-coding and is found in the long arm of chromosome 15, in region 15q24. The *CYP1A2* enzyme makes up about 15% of all CYP enzymes. Haloperidol, perphenazine, thioridazine, olanzapine, clozapine, and chlorpromazine are all antipsychotics that use this enzyme for metabolic transformation. On chromosome 15, the *CYP1A2* gene is highly polymorphic. Several common *CYP1A2* polymorphisms have been thoroughly investigated. The effect of these polymorphisms on enzyme activity, however, is still unknown. Caffeine reduces *CYP1A2* activity, but smoking stimulates it, particularly in variations with the -3860G/A (*CYP1A2\*1C*) and -3860G/A (*CYP1A2\*1C*) alleles. The impact of the -2467delT (*CYP1A2\*1D*) polymorphism on enzyme activity is still unknown. In non-smoker volunteers, the *CYP1A2\*1K* (-163A, -739G, -729T) haplotype is linked to lower *CYP1A2* activity than the *CYP1A2\*1A* (wild type) and *CYP1A2\*1F* (-163A) or *CYP1A2\*1J* (-163A, -739G) haplotypes. External influences on *CYP1A2* activity are relevant since co-administration of antipsychotics that compete for the same enzyme inhibits it, resulting in reduced therapeutic response and higher adverse effects. Because the *CYP1A2* enzyme is responsible for up to 70% of clozapine metabolism, its variation has been linked to medication clearance. Olanzapine's main

metabolites are formed using around 60% of the *CYP1A2* pathway. Given these circumstances, *CYP1A2* pharmacogenetic testing is more than appropriate.

### CYP2D6

Cytochrome *CYP2D6* is the first polymorphism metabolizing enzyme to be discovered. *CYP2D6* is a highly polymorphic gene with nine exons on the long arm of chromosome 22 in region 22q13 (Ellingrod et al. 2002). About 90 mutations have been identified, with some having up to 13 subtypes. Aripiprazole, chlorpromazine, haloperidol, perphenazine, quetiapine, risperidone, and olanzapine are all metabolically transformed by *CYP2D6*. Unlike *CYP1A2*, the activity of *CYP2D6* is not induced. The metabolic activity of enzymes as extensive (EM), intermediate (IM), poor (PM), and ultra-rapid (UM) phenotypic metabolizers is determined by several functional genetic variations (Ellingrod et al. 2002). Standard, moderate, diminished, and amplified efficiency in metabolizing the enzyme's substrates are the characteristics of each. *CYP2D6\*3*, *CYP2D6\*4*, *CYP2D6\*5*, and *CYP2D6\*6* variations are linked to a complete lack of enzyme activity, resulting in a PM phenotype, whereas *CYP2D6\*1XN*, *\*2XN*, and *\*35XN*, the replication or amplification of a functional *CYP2D6* gene, produces exceptionally high *CYP2D6* function, resulting in comparison to EMs, poor metabolizers (PMs) have a 10–200 slower

metabolism of *CYP2D6* substrates. Extensive metabolizers (EMs) make up 55.71 percent of healthy people, whereas intermediate metabolizers (IMs) make up 34.7 percent, poor metabolizers (PMs) make up 2.28 percent, and ultra-rapid metabolizers (UMs) make up 7.31 percent. According to reports, UM frequency of UMs may be as low as 1% in Sweden and 5% to 10% in Southern Europe (Ellingrod et al. 2002). This percentage refers to those who have *CYP2D6* replication, but some of the overlapped alleles of *CYP2D6* may have little or low activity (Ellingrod et al. 2002). When UMs are precisely defined as people with at least three active alleles, the frequency drops to around 1.5 percent. The incidence of PM and UM phenotypes differs significantly between ethnic groups, which could explain the disparities in treatment response reported. Poor metabolizers account for 6.28 percent of the global population (Ellingrod et al. 2002). Geographic differences in PM frequencies exist, with 7–10% PMs in Caucasians and 1–2% in Asians. There are various phenotypes. (Ellingrod et al. 2002) Poor metabolizers given antipsychotics with limited dose ranges are more prone to adverse effects, while ultra-rapid inducers will not respond to normal antipsychotic doses. Several research studies have looked into the significance of *CYP2D6* genetic polymorphism in developing side effects, particularly EPS, following antipsychotic medication (Takashi et al. 2002). PMs on risperidone have a three-fold higher chance of having harmful effects than EM or IM patients. On the other hand, PMs have a six-fold higher chance of multidrug resistance than EMs (Mouaffak et al. 2011). *CYP2D6* is found in both the brain and the liver and is known to be involved in the metabolism of biological molecules and neurotransmitters such as dopamine. In the Japanese

population, the link between *CYP2D6* and neuroleptic malignant syndrome (NMS) has been investigated, and it has been demonstrated that carriers of *CYP2D6*\*5 have a greater risk of getting NMS (Mouaffak et al. 2011). External factors can influence *CYP2D6* metabolic activity, such as concurrent usage of popular drugs with the inhibitory potential to the gene, such as fluoxetine and paroxetine.

### *CYP3A*

Overall, 45–60% of all known medicines are metabolized by the *CYP3A* family of enzymes. Aripiprazole, haloperidol, perphenazine, and risperidone are antipsychotic medications that require metabolic transformation (Kirchheiner et al. 2004). The oral bioavailability and systemic clearance of its substrates are influenced by interindividual variability in *CYP3A* enzyme expression. There are four genes in the *CYP3A* gene family (*CYP3A4*, *CYP3A5*, *CYP3A7*, and *CYP3A43*). They are found in the 220kb tandem structure of chromosome 7's long arm, in the region q21-q22.1 (Kirchheiner et al. 2004). *CYP3A4* and *CYP3A5* are the most important isoforms in adulthood. The predominant cytochrome P450 isoform in embryonic, fetal, and newborn is *CYP3A7*, which is also found in small amounts in the adult liver and intestine (Kirchheiner et al. 2004). Although *CYP3A4* is the most common hepatic variant, *CYP3A5* contributes significantly to total *CYP3A* activity in the liver. *CYP3A4* is the most prevalent *CYP* isoform in the human liver, with a wide range of expression between individuals. In the *CYP3A4* (*CYP3A4*\*1A: wild type), there are around 347 SNPs, 25 clinically significant. With decreased or increased activity, only *CYP3A4*\*17 and \*18A show functional variability (Bigos et al. 2011). There has been no evidence of a link between these SNPs and

antipsychotic responsiveness. Because *CYP3A5* expression is low in the population (it is present in 33 percent of North American Caucasians and 60 percent of Afro-Americans), most studies on Caucasians believe the *CYP3A4* isoenzyme to be the primary one in the human liver (Bigos et al. 2011). The *CYP3A5* protein is only expressed in those with at least one functioning *CYP3A5\*1* allele. However, it has been shown that in people with *CYP3A5* expression, it has almost the same metabolic activity as *CYP3A4*. The promoter region of the gene, *CYP3A4\*1B*, influences transcription efficiency and hence *CYP3A4*'s total enzymatic activity (Bigos et al. 2011). Because of a *Met445Thr* change at the enzyme's active region, the *CYP3A4\*3* variant has a different substrate selectivity (Brandl et al. 2015). The *Ile118Val* mutation in the *CYP3A4\*4* variation causes lower enzyme activity. So far, several allele variants in the wild-type allele (*CYP3A5\*1*) have been identified. *CYP3A5* accounts for about half of the total *CYP3A* protein in wild-type allele carriers. The *CYP3A5\*3C* mutant allele is the most common faulty variant, causing alternative splicing and protein truncation, resulting in reduced enzyme activity and *CYP3A5* expression in more than 70% of Caucasians (Bigos et al. 2011). The enzymes *CYP3A5\*2* and *CYP3A5\*6* have no activity (Brandl et al. 2015). EMs account for 87.75 percent of the Caucasian population. (*CYP3A5\*3/\*3*), 15.88% are IMs (*CYP3A5\*1/\*3*) and 1.37% are UMs (*CYP3A5\*1/\*1*) (Wojnowski 2004).

### **ABCB1**

P-glycoprotein (P-gp) is a member of the adenosine triphosphate-binding cassette (ABC) superfamily of transporters and is widely expressed in normal tissue such as the intestine, liver, kidney, and brain. Its

physiological role is to act as an efflux pump and to serve as a barrier to the entry of xenobiotics and cellular metabolites (S. Hattori et al. 2018), but it also influences intestinal drug absorption and elimination and influences drug bioavailability (S. Hattori et al. 2018).]. In therapeutic concentrations, many SGA i.e., amisulpride, aripiprazole, olanzapine, perospirone, risperidone, and paliperidone, are P-gp substrates. Although clozapine and quetiapine are unlikely to be P-gp substrates, most antipsychotics function as P-gp inhibitors, influencing plasma and brain concentrations of other substrates. Taking this into account, this transporter plays a vital role in their pharmacokinetics (S. Hattori et al. 2018). The *C3435T* SNP in exon 26 and the *G2677T>A* SNP in the *ABCB1* gene have been demonstrated to change the amount of duodenal *ABCB1* expression, presumably due to a reduction in mRNA stability (Brambila-Tapia 2013), as well as the absorption and distribution of numerous medications that are their substrates (Zubiaur et al. 2021). The *C1236T* silent polymorphism in exon 12 is thought to be in close linkage disequilibrium with these two alterations (S. Hattori et al. 2018). The *2677A* mutation is found in 2% of white people, whereas the other variants, *1236T*, *2677T*, and *3435T* are fairly frequent (41–56%) (Tang et al. 2002). Kimchi-Sarfaty et al. found that wild-type and variant proteins have equal mRNA and protein concentrations but that the variant protein's conformation is changed, changing the shape of substrate and inhibitor interaction sites. Although polymorphism variants in *ABCB1* have been investigated extensively in relation to antipsychotic treatment response, further research is needed to validate their biological significance. The *ABCB1 2677T/T* and *3435T/T* genotypes in drug-naive first-episode

schizophrenia patients have been postulated (Sauna and Kimchi-Sarfaty 2011). According to recent research, those who carry the 3435T allele or the 2677T/3435-T haplotype have a superior reaction to risperidone and experience fewer extrapyramidal symptoms (S. Hattori et al. 2018). This pharmacogenetic profile may have protective properties against EPS symptoms in risperidone therapy. Polydipsia-hyponatremia has also been linked to the *ABCB1* C3435T polymorphism (S. Hattori et al. 2018). The 1236TT genotype has been linked to a greater behavioral anchored rating scale (BARS) score improvement in the Japanese population (Y. Suzuki et al. 2013) recently found that risperidone, 9-OH-RIS, and total active moiety levels were all substantially linked with *ABCB1* 3435C>T genotypes, but that the *ABCB1* 2677G>T/A genotypes had no effect on plasma RIS, 9-OH-RIS, or the number of active constituent quantities. Patients with the *ABCB1* 1236T/2677T/3435T haplotype exhibited greater olanzapine concentrations in their blood and cerebral fluid than those who did not. The P-gp C3435T genotype has been recommended as a way to assess favorable symptomatic relief from olanzapine clinically, but these findings need to be repeated on a larger sample of people (Alemayehu et al. 2019). Women with the T allele of the 2677G/T/A polymorphism had a greater response to olanzapine therapy have speculated that the *ABCB1* G2677T and C3435T *MDR1* genetic polymorphisms may impact the development of metabolic problems in female patients on olanzapine and risperidone (Kuzman et al. 2011).

### *Dopamine D2*

Dopamine D2 receptors are G-protein coupled receptors mostly expressed in the striatum, brain, and limbic system. The

occupancy of 65 percent of brain dopamine receptors is required for therapeutic effectiveness, whereas occupancy of more than 72 percent causes prolactin rise, and 77 percent or more causes EPS (Kiss, Krámos, and Laszlovszky 2022). Second-generation antipsychotics have a moderate to high affinity for D2, D3, and D4 receptors, whereas first-generation antipsychotics have a significant dopamine affinity (Li, L Snyder, and E Vanover 2016). Neuroleptics primarily impact positive symptoms of Schizophrenia by blocking D2 receptors. The emergence of Parkinsonian-like side effects is due to this antagonistic action mechanism. *DRD2*, the dopamine D2 receptor gene, is found on chromosome 11 and has many SNPs. The 141Cdel mutation in the *DRD2* promoter gene, which is responsible for reduced protein production, is the most important polymorphism related to worse antipsychotic treatment response (A. Suzuki et al. 2001).

In patients with the 141Cdel allele, significant weight gain is verified following six weeks of risperidone or olanzapine therapy (Zubiaur et al. 2021). Positive symptoms have improved in Japanese schizophrenia patients with the -141Cins genotype treated with risperidone. Patients with the 141-C del have a greater risk of developing neuroleptic malignant syndrome (NMS), characterized by severe dopaminergic system hypofunction. In vitro, the -141C del allele is linked to decreased D2 receptor protein expression. *Ser311Cys* is another polymorphism on the dopamine D2 receptor that has been demonstrated to predict pharmacological response. This polymorphism variation is thought to change receptor function via modulating receptor G protein interaction. Patients with the *Ser311* allele have a better prognosis for positive, negative, and cognitive symptoms, as well as a stronger antipsychotic response (Lane et al.

2004). During therapy with antipsychotics and selective serotonin reuptake inhibitors, a D2 restriction polymorphism known as Taq-IA has been linked to an increased risk of tardive dyskinesia and EPS (Güzey et al. 2007). The A1 allele was associated with a stronger sensitivity to dopamine antagonists. This mutation has also been linked to reduced receptor density and function. Taq1A has been linked to a reduction in striatal D2 receptor binding (Ye et al. 2019) A241G is associated with risperidone and olanzapine treatment response. Patients with the A allele had a stronger reaction to risperidone and have improved more, whereas G carriers have a slower response time (Ye et al. 2019).

### Dopamine D3

In the mesolimbic region of the brain, D3 receptors are located that deal with cognitive, emotional, and motor functions. The high affinity of several antipsychotics for the D3 receptor justifies pharmacogenetic studies on this receptor. The *Gly9Ser* SNP in the *DRD3* gene is the most fascinating and well-studied gene. In terms of positive symptoms, the 9Gly variant has a greater binding affinity and antipsychotic response, but it also increases the risk of tardive dyskinesia (Lencz and Malhotra 2022). Multiple psychiatric diseases are linked to polymorphisms in exon 3 of the dopamine D4 receptor (*DRD4*) gene with variable numbers of tandem repeats (*VNTR*). The Asian population (Japanese 0.5 %) has a smaller allele size of 7R than Caucasians, 20 %. The 4R variation is the most frequent and ancestral haplotype. Although there is no clear link between *VNTR* and *TD*, certain four Taq polymorphism haplotype study shows that *DRD4* may have a role in *TD* in Caucasians (E. Hattori et al. 2009).

### 5-HT1A

Another possible target for predicting treatment response with atypical antipsychotic medications is the 5-HT1A receptor. The most researched polymorphism is the -1019C/G SNP, which is found in the upstream regulatory area and modulates gene transcription. Elevated levels of 5HT1A define G allele carriers. The -1019C/G variation may influence cortical dopamine release since 5HT1A is involved in modulating dopaminergic activity. While higher dopamine levels in the cortical area are necessary for improving negative symptoms of Schizophrenia, this polymorphism might be useful for predicting antipsychotic medication treatment response. It was verified in two recent investigations on risperidone-treated Chinese and Caucasian schizophrenia patients. CC genotype carriers improved their unpleasant symptoms in both tests (Crisafulli et al. 2012b).

### 5-HT2A

In addition to the hypothalamus, limbic system, and striatum, 5-HT2A receptors are abundantly distributed in cortical brain locations. Clozapine, risperidone, and olanzapine have a high affinity for this postsynaptic G-protein receptor. *HTR2A*, the coding gene for the 5-HT2A receptor, is found on chromosome 13q14-21. The most important polymorphisms are the 1438A/G promoter polymorphism, which is linked to lower promoter activity and receptor protein expression (Yan et al. 2022), the 102T/C silent polymorphism within the coding region, which is in complete linkage disequilibrium with the previous one, and the *His452Tyr* (1354C/T) polymorphism, which is linked to an amino acid substitution within the receptor's cytoplasmic C-terminal. (Yan et al. 2022). This alteration has no effect on expression or substrate binding to the

receptor, but it does render it useless. The *452Tyr* allele is more common in schizophrenia individuals who do not respond to clozapine therapy. This variation inhibits platelet calcium mobilization mediated by serotonin. In Caucasians, the *102C* allele is linked to reduced protein expression, an increased incidence of Schizophrenia and EPS, and worse treatment response. Among clozapine non-responders and schizophrenia patients with established TD, this allele is considerably overexpressed. Because this is a quiet polymorphism, an epigenetic process like methylation is thought to be responsible for *102C>T* SNP functioning (Yan et al. 2022).

### 5-HT<sub>2C</sub>

The 5-HT<sub>2C</sub> receptors are involved in the control of eating behavior, anxiety, and motor activities and are linked to stimulatory G-protein. The choroid plexus, prefrontal cortex, basal ganglia, and limbic areas of the brain all express these receptors (Puangpetch et al. 2018). *HTR2C*, the coding gene for the 5-HT<sub>2C</sub> receptor, is found on the Xq24 chromosome and is a good candidate for pharmacogenetic testing and confirmation of its relationship with illness and therapy response. The promoter region polymorphism *997G/A* is in full linkage disequilibrium with the *-759C/T* polymorphism (Puangpetch et al. 2018). Reduced promoter activity is caused by a C to T mutation in the gene's promoter region. In individuals on clozapine, olanzapine, risperidone, or chlorpromazine, the *759T* allele protects against antipsychotic-induced weight gain (Miron et al. 2014). The *-759C/T* polymorphism has a protective effect on weight gain in drug-naïve individuals on short-term therapy. This link has been repeatedly verified in the European

population but is less studied in the Asian population (Campbell et al. 2008). Another promoter polymorphism, *697G/C*, has been linked to lower promoter activity and the start of chronic tardive dyskinesia (Liou et al. 2004b). The protective function of the C allele in a 10% increase in BMI and weight gain was validated in research in the European population, whereas the other showed no link (Tang et al. 2002). In vitro, the *Cys23Ser* (*68G/C*) polymorphism causes the *23Ser* variation to have greater constitutive activity than the *23Cys* version (Wallace et al. 2011). This discovery could not be replicated in mammalian cells producing the mRNA-edited 5-HT<sub>2C</sub> isoforms. The *HTR2C 23Ser* allele has been linked to a greater response to clozapine therapy and a higher likelihood of tardive dyskinesia. The functional haplotype investigations suggested that higher *HTR2C* transcription, which leads to a more active 5-HT<sub>2C</sub> pathway, might protect against antipsychotic-induced weight gain by making patients less susceptible to the metabolic alterations produced by medication (Wallace et al. 2011).

### COMT

The catechol-O-methyltransferase (*COMT*) gene is found on chromosome 22q11.21-23. Because of its function in catecholamine breakdown, which includes dopamine, it was considered the primary gene for Schizophrenia and an essential biomarker. The human *COMT* gene has three common variants (*A22S*, *A52T*, and *V108M*). The *A22S* and *V108M* mutations make the protein more susceptible to heat and oxidation, but the *A52T* mutation does not affect the protein structure. The *V108M* mutation rearranges the active site residues, whereas the *A22S* mutation shifts the essential residues away from the substrate-binding pocket (Bertolino

et al. 2004b). The reduced activity of *A22S* and *V108M* is linked to a higher risk of Schizophrenia. The *108M* variation is linked to improved antipsychotic medication responsiveness and fewer adverse effects (Bertolino et al. 2004b). The Met variation is linked to lower enzyme activity and dopamine buildup; hence these findings are perplexing. Two distinct sets of researchers also provide contradictory findings. Although a study of Japanese patients found no link between risperidone and *COMT*, recent research of Chinese Han patients found that risperidone medication is linked to the *V108M COMT* variation (Gupta et al. 2011). The Met allele is also linked to improved cognitive improvement in clozapine-treated individuals, as well as improvement in total schizophrenia symptoms in olanzapine-treated patients

### **GRM3**

The pathophysiology of Scz has been linked to polymorphisms in the type-three metabotropic glutamate receptor gene (*GRM3*). In addition, apical antipsychotics like olanzapine and clozapine have been demonstrated to influence *GRM3* expression as assessed by mRNA levels, and continuous treatment of these drugs raises serum glutamate levels (Bishop et al. 2005b).

### **BDNF**

Long-term potentiation, a cellular mechanism of learning and memory, is aided by the brain-derived neurotrophic factor (*BDNF*). Several genetic investigations have found a link between specific polymorphism mutations in the *BDNF* gene and mental illnesses. Other neurotransmitter systems involved in Schizophrenia, including as dopamine, glutamate, serotonin, and GABA, interact with *BDNF*. Dinucleotide repeat

polymorphism (GT) in the promoter region, *Val166Met* (196G/A) polymorphism, the -270C/T substitution, and the -256G/A polymorph are the most investigated polymorphic variations (Fu et al. 2020). The first two polymorphisms are linked to the amount of *BDNF* expression, but the *Val66Met* polymorphism influences *BDNF* intracellular activity and activity-dependent secretion. Although there is rising evidence that *BDNF* has a role in antipsychotic treatment response and the pathophysiology of TD, the data is conflicting. Compared to healthy volunteers, patients with schizoaffective disorder are considerably more likely to be carriers of the most prevalent haplotype (carrying the valine allele of the *Val66Met* SNP) (Fu et al. 2020). According to a recent study, the *Val/Val* genotype was found more frequently in olanzapine treatment responders, and this genotype was linked to a reduction in clinical symptoms. Responders to risperidone therapy have a greater frequency of the 230-bp allele of the (GT)<sub>n</sub> dinucleotide repeat polymorphism than non-responders, according to another recent study (Fu et al. 2020). Patients with the 230-bp allele (GT)<sub>n</sub> dinucleotide repeat polymorphism and the *230bp/C270/rs6265G* haplotype show a greater Risperidone response than those with the 234-bp allele and the *234-bp/C270/rs6265A* haplotype (Fu et al. 2020).

### **RGS4**

*RGS4* has been connected to antipsychotic response variability and adverse medication responses. Lane HY et al. verified in their study that *RGS4* variations impact clinical symptoms of Schizophrenia and risperidone treatment responsiveness, indicating that *RGS4* plays a role in disease pathogenesis. *A/A* genotype at SNP1 was related to greater

improvement in social function, but *A/A* genotype at SNP-18 has a favorable influence on PANSS total score and greater improvement in social function (Campbell et al. 2008).

### Concluding Remarks

Conventional treatments for Scz provide symptomatic relief attained through multiple strategies. The effectual options include olanzapine and several other drugs. Despite the substantial effectiveness of olanzapine, the anticipated therapeutic outcome is not always achieved in all patients, while several of them experience adverse effects. So far, there is no reliable way to predict treatment response in patients; hence pharmaceutical companies are restricted to a 'one size fits all' approach while developing therapeutic agents. However, this perspective for drug development in Scz does not benefit all patients.

Moreover, the studies stated above show that this approach may lead to detrimental effects in many other Scz. Despite many environmental and pharmacokinetic factors fostering this heterogeneity, a major contributor, 'genetic variation,' is often ignored. In order to reduce risk of such adverse events, incorporation of pharmacogenomics into clinical practice would be a prudent choice. The main goal of pharmacogenomics is to identify the genetic factors accountable for variable drug efficacy among individuals, consequently predicting drug response and facilitating personalized medicine. This approach ultimately lowers the cost of health care, patient's treatment duration, and drug-induced complications, thus enhancing treatment safety. Besides, it can also lower the risk of failures and cost in clinical trials by selecting only those patients who are eligible to respond to drug therapy.

In this manuscript, we reviewed important studies conducted to identify the influence of genetic variations on variable responses to Scz treatments. However, the data obtained so far are mostly erratic, and the functional role of genetic variants is generally ambiguous as these were underpowered and small-scale studies. There is a need to upgrade these researches in order to reap benefits from them by adding to clinical practice. Furthermore, novel disease-modifying drugs for the treatment of Scz are also needed to have more treatment options for personalized medicines based on the pharmacogenomic signature of individuals.

### Conflict of Interest

The authors declare that they have no competing interests.

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### Study Approval

NA

### Consent Forms

NA.

### Authors Contribution

SS conceptualized the study and wrote the initial manuscript, SS, SMAH, and IK did the literature search, collection of studies, and analysis and wrote the final manuscript.

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