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Is Dosage Adjustment for Olanzapine Really Necessary?

Kelvin N. Christie

School of Health Professions, Long Island University, New York, USA
Email: christiek123@gmail.com

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Abstract

Schizophrenia is a prevalent and disabling disorder, commonly treated with medications such as clozapine and olanzapine. However, long-term side effects and limitations of these drugs, coupled with treatment resistance in a significant proportion of patients, necessitate alternative strategies. Furthermore, individuals with schizophrenia are at an increased risk of developing kidney and liver diseases, which may be influenced by cardiovascular comorbidities and shared genetic markers. Considering the use of olanzapine in patients with severe liver or kidney diseases requires careful evaluation. Although these organs play crucial roles in olanzapine excretion and metabolism, current pharmacological research suggests that dosage adjustment may not be necessary even in the presence of severe organ disease. Olanzapine acts on D2 and 5HT2A receptors, alleviating both positive and negative symptoms of schizophrenia. However, the metabolism and clearance of olanzapine exhibit substantial inter-individual variability influenced by factors such as gender, age, ethnicity, smoking habits, and co-medication. Additionally, olanzapine may induce unwanted side effects, including prolactin release, metabolic dysregulation, and liver-related complications. The present study aims to investigate whether dosage adjustment of olanzapine is necessary for individuals with comorbid moderate liver and severe kidney disease. While the study remains ongoing, preliminary findings using a pharmacokinetic model predict that dosage adjustment may not be required in these patients. The expected olanzapine plasma concentration in individuals with both conditions is estimated to be 18.14ng/ml, which is considerably below the identified toxic dosage threshold of 100ng/ml. However, further investigations are warranted to validate the findings and establish definitive guidelines and personalize treatment strategies for individuals with both liver and kidney disease.

Keywords

Schizophrenia, Kidney, Liver, Olanzapine (OLZ)

1. Introduction

Schizophrenia, a severe and lifelong disorder affecting cognitive, behavioral, and emotional functioning, ranks among the top 25 causes of disability worldwide [1]. Despite the availability of several effective medications for schizophrenia, their limitations in tolerability necessitate the ongoing development of alternative treatment options [2]. Clozapine, the most effective treatment for treatment-resistant symptoms, is hindered by safety concerns such as agranulocytosis, preventing its use as a first-line antipsychotic [3]. Similarly, olanzapine, considered highly effective [4], is constrained by long-term metabolic consequences and weight gain [2]. With a global prevalence of more than 20 million people, schizophrenia affects approximately 0.7% to 1.0% of the world population [5]. Although over 60 antipsychotic treatments [6] targeting hyperdopaminergia through dopamine receptor blockade exist, 20% to 30% of patients with schizophrenia remain resistant to current therapies [7].

Kidney disease affects about 843.6 million people globally, roughly over ten percent of the population [8]. Cirrhosis of the liver increases the risk factor for kidney disease. Kaps *et al.* (2020) compared approximately 50,000 individuals with non-alcoholic fatty liver disease to about 50,000 individuals without non-alcoholic fatty liver disease [9]. They found that 17.6% of individuals with non-alcoholic fatty liver disease developed kidney disease compared to 11.6% of individuals without non-alcoholic fatty liver disease that developed kidney disease [9].

Schizophrenia is a risk factor for developing both kidney and liver disease. The reason why people with schizophrenia are more likely to develop kidney disease is due to their high rate of cardiovascular disease, and cardiovascular disease is a risk factor for kidney disease [10] [11]. Another reason people with schizophrenia develop liver disease is genetic alcohol predisposition. The shared loci of alcoholic and schizophrenic genes increase the likelihood of consumption of alcohol among people with schizophrenia, and the overconsumption of alcohol is a risk factor for liver disease [12] [13]. Kidney disease typically results in reduced excretion of olanzapine, while cirrhosis of the liver results in reduced metabolism of olanzapine.

The current paper studies schizophrenia diseases in patients with either severe liver or kidney diseases or both and the impact of dosage of olanzapine in treating these illnesses.

Established pharmacological research supports the notion that a psychiatrist does not need to adjust the dosage of olanzapine for someone with liver or kidney disease.

2. Kidney

2.1. Working Mechanisms of Kidney

The kidney transports water-soluble toxins or water-soluble medications from blood to urine via glomeruli filtration, passive diffusion at the distal tubules, and

active transport of toxins such as drugs [14]. High blood pressure within the kidney causes blood to flow through the afferent arteries at high pressure. Blood flows at high pressure through the afferent arteries to the glomerulus. The glomerulus has fenestrations in which unwanted toxins or water-soluble medications pass through. The fenestrations are small enough to filter out unwanted material but not large enough to filter out essential blood components like red blood cells and albumin. The glomerulus can filter the blood because it has higher hydrostatic pressure than the bowmen capsule. Due to less hydrostatic pressure in the bowmen capsule, fluid leaks out of the glomerulus into the bowmen capsule. The bowmen capsule eventually conveys the filtrate to the proximal convoluted tubule. The proximal convoluted tubule has efflux pumps that require ATP to transport toxins or drugs from the blood into the filtrate. These transporters are organic anion transporters, organic anion transporting polypeptides, organic cation transporters, multidrug resistance-associated protein, multidrug resistance protein, and multidrug and toxic compound extrusion [15] [16] [17]. Passive diffusion is a slow process in which fat-soluble medications or toxins leave the blood and enter the urine by crossing the lipid membrane of tubules and vice versa (e.g., 7% of olanzapine remains unchanged in urine).

2.2. Causes of Kidney Failure

Large, amphipathic, or fat-soluble molecules also reduce the kidneys' ability to excrete them by being too big to pass through the Glomerulus fenestration or binding to large proteins such as albumin [18]. Glomerulus fenestrations' diameters are between 60 nm - 70 nm. Therefore, molecules bigger than 70 nm or bound to a protein larger than 70 nm cannot pass through the glomerulus fenestration. Some medications or toxins are amphipathic, meaning half the molecule is water-soluble, and the other half is fat-soluble. If the toxin or medication is amphipathic, it will initially be filtered out. However, it can return to the blood at the distal convoluted tubule because of its fat-soluble properties. Its fat-soluble properties allow it to cross the lipid membrane at will. Active transport requires a steady supply of ATP to remove amphipathic and fat-soluble molecules from blood. When this steady supply of ATP is interrupted, it can result in the kidney being unable to get rid of potential toxins and medication that can cause cellular injury. A medical condition that can decrease ATP production is Neuropathy, ataxia, and retinitis pigmentosa (NARP) [19]. Individuals with NARP have a mutation in a gene that codes for a subunit in ATP synthase. The subunit is MT-ATP, which means mitochondrially encoded ATP synthase membrane subunit 6. MT-ATP6 is the subunit of ATP synthase that helps convert ADP into ATP via chemiosmosis.

Illness that causes a decrease in blood pressure that can lead to kidney failure is internal and external bleeding. Alcohol stimulates the release of nitric oxide, and nitric oxide causes blood vessels to dilate, resulting in a decrease in blood pressure [20]. Alcohol can also increase blood pressure due to its effect on the adrenal gland and prevent baroreceptors from detecting an increase in blood

pressure [20]. Baroreceptors signal blood vessels to widen or stretch when it senses increased blood pressure, but alcohol can prevent baroreceptors from doing their job. Alcohol can stimulate the adrenal glands to release adrenalin [21]. Adrenalin causes an increase in cardiac output that increases blood pressure. Researchers have confirmed that hypotension and hypertension can both lead to kidney failure. The reason is that the kidney cannot filter blood if the hydrostatic force in the glomerulus is not significant enough for fluid to escape into the bowmen capsule. In addition, if the blood pressure is too high, afferent arteries and glomerulus rupture. If they rupture, the nephron will lose the ability to filter toxins—the kidneys' inability to filter toxins and medication over time results in kidney disease progression and liver disease. The same can be true if the liver is not able to convert fat soluble molecules or toxins into water soluble molecules. The fat-soluble molecules build-up can cause kidney disease.

3. Liver

3.1. Working Mechanisms of Liver

The liver is a bilobed organ that instantaneously processes approximately 13 percent of the blood supply [14]. Each lobe has about eight segments, each with about 1000 lobules. Each lobule contains multiple hepatocytes. The hepatocytes create bile. The small ducts convey bile from the lobules to the left and right hepatic ducts. The common hepatic duct's function is to convey bile from the left and right hepatic ducts to the cystic duct. The cystic duct's function is to convey the bile to the gallbladder, where the gallbladder stores it for later usage. The function of bile is to transport fat-soluble nutrients and medication by creating micelles. In addition, bile can transport water-soluble medication by two pathways. The two pathways within the intestine are bile-forming pores within cell membranes and between cell junctions so that water-soluble medication can pass through. Medical researchers have taken advantage of bile's capability to form hydrophilic pores within the cell membrane and cell-to-cell junctions allowing hydrophilic molecules to cross the blood-brain barrier. Bile acids also regulate phase I cytochrome P450 Enzymes genes via nuclear receptors [22].

3.2. Liver Abnormalities

Another form of abnormality that can result in reduced liver function is hypertension. Hypertension within the portal venous system causes shunts in the liver. Shunt in the liver is associated with atrophy of the posterior cortex, elevated amount of unconjugated bilirubin in the blood, reduced glutamate neurotransmission, and elevated levels of S100β4 in serum. Shunts within the liver are known to cause psychotic symptoms in patients. These psychotic symptoms are visual hallucination and cognitive impairment [23]. The patient experience visual hallucinations because shunts cause atrophy of the posterior cortical cortex. The elevated amount of unconjugated bilirubin in the blood, reduced glutamate neurotransmission, and elevated levels of S100β4 in serum are associated with

schizophrenic positive symptoms [24].

4. Enzyme Regulation and Functions

Genetic mutation and gene duplication can result in enzyme upregulation, enzyme downregulation, and isoenzymes (U.S. National Library of Medicine, n.d). Genetic upregulation results in an increase in plasma concentration of CYP1A2, CYP2D6, CYP3A4, or CYP2C19. An increase in enzyme concentration typically correlates with an increase in enzyme function because an excess number of enzymes are available to complete its function. However, the downregulation of CYP1A2, CYP2D6, CYP3A4, or CYP2C19 can result in a decrease in their concentration that also results in a decrease in their function. Polyploidy can result in the duplication of an enzyme's gene resulting in an isoenzyme. Another way isoenzyme can result is due to unequal crossing over between misaligned sequences [25]. The mechanism of action that causes the unequal crossing over is due to the homologous chromosomes sharing similar repeated sequences. The DNA polymerase crosses over to the sister chromosome and inserts or deletes one or more amino acid sequences that result in an isoenzyme, as in the case of truncated CYP2B6 (partial deletion).

Nuclear receptors activate phase I cytochrome P450 Enzymes [26]. The genetic expression of phase I cytochrome P450 Enzymes plays a role in metabolizing most pharmacological drugs via reduction, oxidation, or hydrolysis. Phase I cytochrome P450 Enzymes usually add a hydroxyl, carboxyl, or an amino group during reduction, oxidation, or hydrolysis. Phase I cytochrome P450 Enzymes refer to a collection of a family of enzymes. They are CYP1 Enzymes, CYP2A-E Enzymes, CYP3A Enzymes, and CYP4 Enzymes. Specific isoenzymes from these families of enzymes that are responsible for the metabolism of antipsychotics are CYP1A2, CYP2D6, CYP3A4, and CYP2C19 [27]. These isoenzymes are responsible for the reduction, oxidation, and hydrolysis of antipsychotics and drug-to-drug interactions. Such drug-to-drug interaction is one antipsychotic hindering an isoenzyme that reduces the clearance of another antipsychotic. For example, chlorpromazine, fluphenazine, haloperidol, levomepromazine, perphenazine, pimozide, and asenapine is antagonistic to CYP2D6, so the inhibition of CYP2D6 would result in decreased metabolism of aripiprazole, clozapine, olanzapine, quetiapine, risperidone, and zuclopenthixol [27]. Genetic mutation, such as gene duplication, can increase or decrease an enzyme's ability to metabolize antipsychotics.

After the phase I enzyme system has made the endogenous or exogenous xenobiotic water soluble, the phase II enzyme system, as the name implies, additionally modifies the xenobiotic so the kidney and fecal route can eliminate it [26]. Phase II enzymes refer to 6 classes of enzymes. The classes of enzymes are UDP-Glucuronosyltransferases, amino acid transferases, sulfotransferases, methyltransferases, glutathione S-Transferases, and N-Acetyl Transferases (NAT). Their names imply their function. For example, UDP-Glucuronosyltransferases are a class of enzymes that facilitate glucuronidation in the liver. Glucuronida-

tion is UDP-Glucuronosyltransferases facilitating the transfer of glucuronic acid from uridine diphosphate to a xenobiotic that had obtained a hydroxyl, phenol, carboxylic acid, thiol, or amine group. Amino acid transferases facilitate the transfers of an amino acid to a xenobiotic for elimination. An amino acid that can be transferred to the xenobiotic by amino acid transferases is glycine, taurine, glutamine, ornithine, or arginine. Sulfotransferases are a class of enzymes that facilitate sulfur transfer to a xenobiotic's hydroxyl or amine groups. Methyltransferases are enzymes capable of transferring a methyl group to a xenobiotic. Glutathione S-Transferases function is to transfer glutathione to the xenobiotics. N-Acetyl Transferases (NAT) catalyzes certain functional groups on xenobiotics to aromatic amides and hydrazides. The functional groups are aromatic amines or hydrazine.

Oxidative stress induces phase II enzyme production [26]. Oxidative stress activates the nuclear factor receptor, NFr2, by removing Keap 1. The binding of Keap 1 to NFr2 promotes its degradation. NFr2 that is not bound to Keap 1 promotes the transcription phase II enzymes DNA into mRNAs. RNA polymerase is an enzyme responsible for transcribing DNA information copied into a messenger RNA. RNA polymerase has an error rate of about one incorrect nucleotide for every 10,000 correct nucleotides [28]. The high mutation rate is because RNA polymerase cannot proofread. RNA polymerase inserts incorrect nucleotides in mRNA via insertion, deletion, or substitution that children cannot inherit from their parents. However, mRNA with mutations induced by RNA polymerase can affect the translated phase II enzyme. Sometimes this error can increase the enzyme's function, has no effect on the enzyme, and other times it negatively impacts the enzyme's function. It is important to note that breaking the enzyme is more effortless than improving it or giving it a new function. Other epigenetic factors that can affect the transcription of mRNA of phase II enzymes are all viral infections. For example, Hepatitis b viral infection can prevent the transcription of mRNA of phase II enzymes via the suppression of promoters. A promoter is the portion of a gene that transcription factors cling to initiate the DNA transcription into mRNA. Abiotic and biotic factors may contribute to non-alcoholic liver disease, and individuals with non-alcoholic fatty liver disease have reduced expression of CYP1A2, CYP2C19, CYP2D6, and CYP3A4 that metabolize antipsychotics [28] [29] [30] [31].

5. What Is Schizophrenia?

The term "schizophrenia" is often used as a unitary diagnostic term for a state/illness which is highly heterogeneous in its presentation, etiology, trajectory, and pathophysiology [32]. It is one of the most severe mental disorders that influences the way a person feels, behave, and thinks. Ones suffering from this disorder often lose touch with reality and live in their own world, causing distressing feelings among friends and family.
(https://www.nimh.nih.gov/health/topics/schizophrenia)

5.1. Causes of Schizophrenia

Schizophrenia is caused by inheriting multiple predisposing alleles and environmental triggers [33]. Twin studies have allowed researchers to determine that the polygenetic inheritance of schizophrenia is due mainly to genetic inheritance. A monozygotic sibling is more likely to develop schizophrenia than a dizygotic sibling if their sibling has schizophrenia. Many genes are responsible for developing schizophrenia and alcohol use disorder. One is the polymorphic variant BDNF [33]—the BDNF gene codes for brain-derived neurotrophic factor (BDNF) protein. The cytogenetic location of the gene is 11p14.1. The reason is that variant brain-derived neurotrophic factor (BDNF) proteins can cause schizophrenia and alcohol use disorder. The variant BDNF gene by itself does not cause alcohol use disorder; however, if a person has schizophrenia and they have inherited a variant BDNF gene, there is a high genetic liability of developing an alcohol use disorder.

Some researchers believe that drugs and alcohol contribute to schizophrenia, and others believe in the latter [33]. However, all researchers agree that substance use disorder and schizophrenia are linked. The most excepted reason for the co-development of schizophrenia is the diathesis-stress model. The diathesis-stress model theorizes that the reason why people develop schizophrenia is neurobiological and environmental factors. For instance, someone may be more prone than the general population of developing schizophrenia and alcohol use disorder due to having one or more genetic risk factors for developing schizophrenia and drinking alcohol at a very young age [33]. Studies have refuted that drinking alcohol as a child contributes to developing psychosis later in life [33]. Neurodevelopment theory believes that neonatal ventral hippocampal lesions can result in both schizophrenia and alcohol use disorder [33]. In animal studies, researchers induce neonatal ventral hippocampal lesions in rats. The rats had similar neurological symptoms as schizophrenia and heavy alcohol drinking. Another explanation for the cooccurrence of schizophrenia and alcohol use disorder is the self-medication hypothesis. Under this hypothesis, the symptom of schizophrenia is intrusive to the person's life, and alcohol is a sedative, so they use it for tranquility. The problem with using alcohol is that alcohol can make the symptoms of schizophrenia worse due to stimulating the release of dopamine and the dopamine hypothesis. The revised dopamine hypothesis explains the cause of schizophrenia. The cause of schizophrenia is due to overexcited D2 receptors within the mesolimbic and prefrontal cortex. Drinking alcohol can increase the severity of positive symptoms in people with schizophrenia because it increases dopamine concentration. Increased dopamine outcompetes olanzapine binding to D2 receptors in the prefrontal cortex and mesolimbic pathway.

5.2. Symptoms of Schizophrenia

It is pivotal to recognize the early signs and symptoms of schizophrenia as early as possible and seek help accordingly. Generally, people aged between 16 and 30

are diagnosed for schizophrenia after the first episode of psychosis. It is quite rare in younger children. Starting the treatment as early as possible after the first episode of psychosis is an essential step toward the recovery of a person. Research does indicate gradual changes in thinking patterns, social engagements, and mood changes before the first episode of psychosis.

People with schizophrenia vary in their symptoms [34]. The client can experience severe and mild negative symptoms during the prodromal and residual phases. People with schizophrenia may experience a mood disorder. The way to differentia schizophrenia mood disorder and other psychotic disorders from schizophrenia is the presence of hallucinations or delusions.

Though the symptoms vary from one person to another but generally, they fall under three categories as discussed below:

5.2.1. Psychotic Symptoms

People exhibiting such symptoms in which they lose the shared sense of reality with others and experience the world in a twisted distorted way fall under this category. The symptoms entirely change the way person perceives things, observes, acts and think about the world. For some of patients these symptoms may come and go but for others they might become stable with passage of time. The psychotic symptoms include:

- **Hallucination:** usually when a person feels, perceives, hears, smells, tastes, or see a thing that is actually not there, one of most symptoms. For people suffering from schizophrenia, hearing voices is one of the most common symptoms. Patients normally start hearing voices even before a family member or a friend notices any unusual behavior in them.
- **Delusion:** In this condition, a person exhibits firm beliefs regarding things that are not present or true or may seem irrational to others. For instance, a patient may believe that people on television and radio are sending over special coded messages that require a certain response from them. They may also believe that others are always trying to hurt them or they are constantly in danger.
- **Movement disorder:** When a person shows out of normal body movements, have such disorder. The person with this disorder may repeat some gestures, movements, and motions repeatedly.
- **Thought disorder:** When a person's thoughts are all over the place, their thinking is illogical or unusual, representing this kind of disorder. Such people have difficulty organizing their speech and thoughts. They make up meaningless words, jump from one topic to another, and sometime will stop talking in the middle of thought altogether.

5.2.2. Negative Symptoms

People with such symptoms lose the sense of enjoyment or interest in everyday activities, lose motivation to do and achieve anything, have difficulty in expressing emotions, withdrawal from social life, etc.some of the symptoms are listed below:

- Exhibiting limited facial expression and interacting in a dull voice.
- Low on energy and spend plenty of time in passive activities. In extreme scenarios a person may experience a rare condition called catatonia, in which the person may stop talking or moving for a while.
- Difficult to plan and stick to achieve daily goals and activities e.g., grocery shopping.
- Awkward social interaction or avoiding such social gatherings altogether.
- Trouble experiencing the everyday pleasure of life and anticipating.
- These symptoms are often mistaken for depression or other mental illnesses as well.

5.2.3. Cognitive Symptoms

A person may experience difficulty in concentrating, memorizing, or giving attention. These symptoms make it hard for a person to learn new things, memorize appointments or dates or to follow up a conversation. The health care workers evaluate the cognitive functions of a person using specific tests. As it is one of the best predictors of a person's cognitive functioning required for performing daily chores. Some of the cognitive symptoms include:

- Trouble in paying attention or focusing;
- Difficulty in processing information to make decision;
- After learning new information having trouble implementing and using that.

5.3. Diagnostic Criteria of Schizophrenia

The diagnostic criteria to diagnose someone with schizophrenia is that a patient must exhibit either delusion, hallucination, or disorganized speech for one month, concurrently with grossly disorganized or catatonic behavior or negative symptoms [34]. If the patient is a child, there must be significant disruption in the child's "interpersonal, academic, or occupational functioning" [34]. If the patient is an adult, the patient must be experiencing problems at "work, interpersonal relationship, or self-care" [34]. The disturbances in their interpersonal, occupational, and academic functioning and experience in some combination of delusions, hallucination, disorganized thinking (speech disorganized), abnormal motor behavior (including catatonia), and negative symptoms must persist for six months or due to medical treatment efficacy at least one month or less of symptoms. The schizophrenic symptoms must not be due to ingesting medication, drug use, or other medical illness. During the six months, some people may experience avolition, anhedonia, "anxiety, depression, mood swings, sleep disturbances, irritability, anger, and suicidal ideas" [35]. Thus, it is crucial to distinguish schizophrenia from schizoaffective disorder, depressive disorder, and dual diagnosis of bipolar disorder and another psychotic disorder. The patient has schizophrenia if, during the active phase, the patient does not experience little to no major depressive and manic episodes. If there is a childhood diagnosis of a communication disorder or autism, a diagnosis of schizophrenia can only be made when symptoms of delusion or hallucination are present for at least one

month and considering if the patient meets other schizophrenic diagnostic criteria.

The new definition of schizophrenia suggests a thorough and complex method of diagnosing and treating the condition. It considers time characteristics, risk factors that can affect or cause symptoms, the most common symptoms, and treatment outcomes. Temporal descriptors describe the beginning, duration, and different stages of the sickness, as well as the timing and advancement of the disease. The patient's history and potential causes of the disease, such as trauma, affective dysthymia, substance abuse, and traumatic brain damage, are taken into account when determining the moderating or causative risk factors.

The patient's predominant symptoms, which might include a wide range of manifestations like hallucinations, disarray, cognitive decline, mood problems, and suicidality, paint a clear picture of the patient's clinical presentation. Creating individualized treatment plans is made easier by categorizing treatment outcomes as D2-antagonist responsive or nonresponsive, clozapine responsive, mood stabilizer responsive, or treatment-resistant/refractory. The proposed nomenclature's application is demonstrated by four cases that each fulfill the DSM's criteria for schizophrenia. The cases demonstrate the variety of schizophrenia's manifestations, from chronic PSI with sneaky beginnings to remitting/relapsing PSI during adolescence. They stress how crucial it is to consider individual symptom profiles, histories, and treatment outcomes while managing schizophrenia.

Specifiers are what clinicians use to give people with schizophrenia an exact diagnosis if they have been experiencing the disorder for one year and do not falsify the schizophrenia diagnostic criteria [34]. They are first episodes, multiple episodes, continuous, and unspecified. A person can experience the first episode concurrently with an acute episode. The first episode is when the person first experiences the symptoms associated with schizophrenia, and the acute episode refers to a narrow window of time in which they may be experiencing the symptoms. The first episode can also be concurrent with partial remission. Partial remission is when they get better and display fewer diagnostic criteria than they initially encounter. A person can also experience the first episode with complete remission. Full remission is when the person shows no symptoms of the diagnostic criteria they had. Multiple episodes are having two or more episodes of once-experienced symptoms. As with the first episode, multiple episodes can be concurrent with the acute episode, partial remission, and full remission. The patient can experience the symptoms of schizophrenia continually with also little to no interruption of not having symptoms. Schizophrenic symptoms can also be unspecified, and clinicians can rate the magnitude of the symptoms on a five-point Likert scale. Zero means symptoms are not present, and five meaning symptoms is present and is the most severe.

If the clinician is from a different background than the patient, he must take extra precautions in diagnosing schizophrenia [34]. The reason is that some cultures may engage in normative practices that can be mistaken for disorga-

nized speech or delusion. For example, speaking in tongues is an example of a normative practice that can be mistaken for disorganized speech. People may speak in their tongue due to religious experiences unique to their culture. An example of normative behavior that can be mistaken for delusion is believing the way someone looks at their child can curse their child, also known as the evil eye. Another cultural factor to consider is that clinician is likely to misdiagnose African American and Hispanics that have schizophrenia with schizoaffective disorder.

5.4. Influence of Comorbid Diseases on Schizophrenia Patients

As compared to the general population, gastrointestinal, cardiovascular, and endocrinal diseases are more prevalent in people suffering from schizophrenia, which may contribute to enhance mortality in serious cases. Studies conducted by Ewusi-Mensah *et al.* (1983) [36] suggest that a person who is alcoholic is more likely to develop severe liver diseases and, thus other psychic illnesses, especially schizophrenia. Another study conducted by Tzeng *et al.* (2015) [37] shows 25% more chances of developing chronic kidney disease among schizophrenia patients.

Several studies suggest that major comorbidities may be responsible to put additional stress on a person already living under stressful conditions like schizophrenia, thus increasing the chances of premature death [38].

5.5. Treatment of Schizophrenia

With continuous progress in medicine, it is a somewhat treatable and manageable disorder, which when controlled can help patients to pursue their normal everyday life activities. One of the most important ways to manage this illness is through antipsychotic medications that are given either in the form of pills or liquid/fluid injections once or twice a month, depending on the requirement. One of the most commonly prescribed drugs among the others is clozapine. These drugs may have side effects that are either short-term or stay on with patients.

Alongside drugs psychosocial treatment also helps patients to successfully perform their everyday life activities. Some of the types of psychotherapy can also be helpful that includes cognitive remediation interventions, behavioral therapy, supported employment, behavioral skills, etc.

Other ways to manage this illness involve education, support, and awareness regarding schizophrenia. Coordinated specialty care (CSC) programs are recovery-focused programs for people with first-episode psychosis, an early stage of schizophrenia, that are very effective. Assertive community treatment ACT is usually delivered by a team of healthcare providers who work together to provide care to patients in the community. A treatment program that includes treatment for both schizophrenia and substance use is important for recovery because substance use can interfere with treatment for schizophrenia.

However, the current paper focuses on the use of antipsychotic drugs i.e.,

olanzapine, on schizophrenia, particularly among patients that have either severe kidney or liver diseases or both. It focuses on how the dosage alternation of drugs impacts the patients and their diseases.

6. What Is Olanzapine?

Olanzapine (OLZ) is one of the most prescribed antipsychotic drugs with large inter-individual variability in pharmacokinetics (*i.e.* up to 10-fold). The intrinsic and extrinsic factors that play a part in its variability involve gender, status, age, co-medication, ethnicity, and smoking habits. The patients that are either African-American or black remove OLZ more quickly than the patients that belong to another ethnic background. It is observed that systemic clearance of OLZ is also around two-fold higher in regular smokers than the non-smokers. With respect to gender and age, the clearance of OLZ seems to be lower in women and in elderly. The inducers of CYP1A2, such as carbamazepine, decrease exposure by approximately half, while Fluvoxamine, a strong cytochrome P450 (CYP) 1A2 inhibitor, can double the systemic exposure of OLZ [39].

6.1. Olanzapine Mechanisms of Action

Drinking alcohol can increase the severity of positive symptoms in people with schizophrenia because it increases dopamine concentration. Increased dopamine outcompetes olanzapine binding to D2 receptors in the prefrontal cortex and mesolimbic pathway.

Olanzapine achieves its therapeutic effect by antagonizing dopamine neuron's D2 and serotonin 5HT2A receptors by preventing too much serotonin or dopamine from being able to bind to them and causing excessive action potentials within the prefrontal cortex; similarly, it also antagonizes D2 dopamine receptors from binding to dopamine within the mesolimbic pathway [40]. Blocking D2 receptors reduces the severity of positive symptoms associated with schizophrenia while inhibiting 5HT2A receptors decreases the severity of negative symptoms associated with schizophrenia.

6.2. Olanzapine Metabolism in Body

Olanzapine digest via oral route must go through first-pass metabolism. Enzymes that metabolize olanzapine during the first pass metabolism produce 10-N-glucuronide and the 4'-N-desmethyl-olanzapine [41]. 10-N-glucuronide and the 4'-N-desmethyl-olanzapine constitute around 50% - 60% of olanzapine metabolite. CYP1A2 plays a significant role in the metabolism of olanzapine during first-pass metabolism, and CYP2D plays a minor role. CYP1A2 catalyzes olanzapine to 4'-N-desmethyl-olanzapine, while glucuronosyltransferase family one-member A4 metabolizes olanzapine to 10-N-glucuronide. The human body excretes 30 percent of olanzapine by feces, meaning only 70 percent makes it to portal circulation. Of the 70 percent that make it to the liver, only 28% make it to system circulation because the liver metabolizes 40%.

6.3. Olanzapine Pharmacokinetic

The bioavailability of olanzapine in people with liver or kidney disease is higher than in those without either condition due to reduced clearance or metabolism. Using pharmacokinetic modeling, [42] Sun *et al.* (2019) predicted that a client with moderate liver or severe kidney impairment would not need dosage adjustment because an individual with moderate or severe liver or severe renal disease c max value for plasm olanzapine level would be one-and-a-half-fold the control. As they predicted, the c-max value for people with liver impairment was 10.65 ng/ml, and for those with renal disease was 7.36 ng/ml [42]. The c-max value for individuals with liver disease was 2.17 greater than the control group, and the c-max value for people with severe renal disease was 1.4-fold greater than the control group. Assuming pharmacokinetic modeling is correct, individuals with moderate liver and severe kidney disease will have a c-max value of 3.57-fold greater than the control group. There were two control groups within Sun *et al.*'s experiment. The two-control group's c-max value was 4.91 ng/ml and 5.25 ng/ml; the average c-max value for both control groups was 5.08 ng/ml. Chue and Singer (2003) reported that 100 ng/ml of olanzapine is toxic, about 19.69-fold greater than the control group [43].

6.4. Olanzapine Unwanted Side Effects

Olanzapine causes unwanted side effects due to its inhibitory role on the dopamine D2 receptor in the pituitary gland [44]. Dopamine D2 receptors have a dual role in releasing and preventing prolactin release. If dopamine concentration is low, the pituitary gland will release prolactin. However, if the dopamine level is high, the pituitary gland will not release prolactin. Because dopamine D2 receptors play stimulatory and inhibitory roles in prolactin release, olanzapine can cause unwanted side effects. If olanzapine binds to D2 receptors within the pituitary gland, it prevents or reduces the amount of dopamine that can bind to activate the dopamine D2 receptors. As a result, the pituitary gland releases prolactin. The excessive release of prolactin contributes to gynecomastia and inhibits the release of gonadotropin-releasing hormone. Gonadotropin-releasing hormone (GnRH) is responsible for the stimulation of testosterone production within Leydig cells. Low production of testosterone is associated with erectile dysfunction.

An unwanted side effect of olanzapine is the induction of apolipoprotein A5 and sortilin [45]. Apolipoprotein A5 and sortilin can cause non-alcoholic liver disease. Li *et al.*, (2021) demonstrated that inhibiting apolipoprotein A5 and sortilin prevented and reversed the adverse effects of olanzapine-induced non-alcoholic liver disease [45]. Apolipoprotein A5 siRNA and sortilinsiRNA inhibited apolipoprotein A5 and sortilin. Apolipoprotein A5 siRNA and sortilinsiRNA bind to complementary messenger RNA of apolipoprotein A5 or sortilin, preventing the ribosome from binding to each respective mRNA and translating apolipoprotein A5 and sortilin. The presence of siRNA for apolipoprotein A5 and sortilin can

reverse the unwanted side effect of increasing the level of apolipoprotein A5 and sortilin in the human body.

Another side effect of olanzapine is metabolic dysregulation. Olanzapine causes an increase in kappa opioid receptor in the paraventricular nucleus of the hypothalamus and an increase in mu opioid receptor in the paraventricular nucleus of the hypothalamus, arcuate nucleus of the hypothalamus, and ventromedial nucleus of the hypothalamus [46]. The arcuate nuclei do not produce neuropeptide Y and agouti-related proteins if the person has eaten enough fatty food. However, if the person has not eaten enough fatty food, the parasympathetic nervous system is activated due to the arcuate nuclei releasing neuropeptide Y and agouti-related proteins. Neuropeptide Y and agouti-related proteins trigger the feeding behavior via the lateral hypothalamus, ventromedial hypothalamus, and paraventricular nucleus [47]. Researchers knocking out kappa opioid receptors and mu-opioid receptors in mice resulted in weight gain. In human studies, samidorphan is antagonistic to mu-opioid receptors and is an agonist to kappa and delta opioid receptors [48]. Therefore, olanzapine causes metabolic dysregulation via action on mu-opioid receptors since samidorphan reverses metabolic dysregulation by blocking mu receptors.

Olanzapine can cause metabolic dysregulation by blocking serotonin 2C receptors on proopiomelanocortin neurons located within the arcuate nucleus of the hypothalamus [49] [50]. Serotonin is a neurotransmitter that can suppress appetite due to its ability to activate the sympathetic nervous system. The sympathetic nervous system is responsible for the fight-or-flight response. Once serotonin activates the sympathetic nervous system, the body's metabolic rate increases, the body does not digest food or store food, and satiety is triggered. Olanzapine contributes to weight gain by preventing the body from activating the sympathetic nervous system [51]. Olanzapine can also indirectly affect the sympathetic nervous system through gut microbiota. The gut microbiome can respond to neurotransmitters and produce neurotransmitters such as serotonin [52]. Serotonin increases bacterial growth rate, while norepinephrine and epinephrine activate pathogenic phenotypes in some bacteria [53] [54]. Like how olanzapine binds to serotonin receptors in humans, olanzapine competes with serotonin to bind to bacterial serotonin receptors and plays a role in quorum sensing. Olanzapine has antibiotic properties and affects gut microbiota composition. Because bacterial receptor competes with human receptors for neurotransmitters, bacteria reduce neurotransmitters' availability. The killing of bacteria with antibiotics reverses olanzapine-induced metabolic dysregulation [55]. Similarly, researchers have also increased the bioavailability of olanzapine by killing bacteria with antibiotics.

7. Discussion

Schizophrenia is often complicated by physical health comorbidities such as kidney and liver diseases. The prevalence of these diseases in schizophrenia patients

can be attributed to shared genetic factors, lifestyle choices, and side effects from antipsychotic medications like olanzapine. Kidney disease is more likely in schizophrenia patients due to factors like cardiovascular disease, which is common in this population, and potential kidney damage from antipsychotic medications. Liver disease is also prevalent, especially in patients who misuse alcohol or substances, a common behavior among people with schizophrenia. Certain antipsychotic drugs can further exacerbate liver toxicity. Olanzapine and similar antipsychotic drugs, crucial in managing schizophrenia, pose challenges in patients with kidney or liver diseases. As these organs play a vital role in the metabolism and excretion of the drug, any dysfunction can affect pharmacokinetics, potentially causing toxic levels or reducing therapeutic efficacy. While current research suggests that olanzapine dosage might not require adjustments in patients with liver or kidney diseases, a more in-depth study is needed to understand its safety and efficacy in this group fully. The presence of liver or kidney diseases complicates schizophrenia management. However, treating these comorbidities can potentially improve both physical and psychiatric symptoms. Therefore, an integrated care approach addressing mental and physical health is essential. Moreover, research is ongoing to develop safer and more tolerable treatment alternatives.

The findings of our study indicated that dosage adjustment of olanzapine may not be necessary for schizophrenic individuals with liver and kidney disease. According to our predictions, the expected olanzapine plasma concentration for these patients is 18.14 ng/ml, which is significantly lower than the identified toxic dosage threshold of 100 ng/ml. This result suggests that the standard dosage of olanzapine may be safe and effective for individuals with both conditions, without the need for dose adjustment. However, it is crucial to note that further studies and personalized considerations are necessary to confirm these findings and ensure optimal treatment outcomes. Several factors should be taken into account when evaluating the need for dose adjustment. Firstly, individual variations in pharmacokinetics and pharmacodynamics may influence the response to olanzapine. Factors such as age, sex, body weight, liver function, and genetic variability can affect drug metabolism and clearance rates. Therefore, a personalized approach is essential to consider these factors and determine the appropriate dosage for each patient.

Additionally, co-administration of other medications may interact with olanzapine, affecting its plasma concentration and efficacy. Drug-drug interactions can lead to altered metabolism or enhanced adverse effects. Therefore, a thorough assessment of the patient's medication regimen is necessary to identify potential interactions and adjust the olanzapine dosage accordingly.

Moreover, the presence of specific comorbidities or medical conditions may warrant dose adjustments. For instance, patients with severe hepatic impairment may experience altered drug metabolism, requiring lower dosages to avoid potential toxicity. Similarly, individuals with compromised renal function may require dosage modifications due to changes in drug elimination. Furthermore,

monitoring Olanzapine plasma concentrations may be beneficial to ensure therapeutic levels are maintained. Therapeutic drug monitoring can help assess individual response and guide dose adjustments if needed, particularly in cases where patients exhibit suboptimal response or adverse effects.

8. Conclusions

In conclusion, schizophrenia is a severe and disabling disorder that ranks among the top causes of disability worldwide. While there are effective medications available, their limitations in tolerability necessitate the development of alternative treatment options. Clozapine, the most effective treatment for treatment-resistant symptoms, is hindered by safety concerns, and olanzapine, another effective option, is constrained by long-term metabolic consequences and weight gain. Additionally, a significant percentage of patients with schizophrenia remain resistant to current therapies. The prevalence of schizophrenia is high, affecting a substantial number of people globally. Patients with schizophrenia are at an increased risk of developing kidney and liver diseases. Cardiovascular disease, which is common among individuals with schizophrenia, is a risk factor for kidney disease. Genetic alcohol predisposition and the shared loci of alcoholic and schizophrenic genes contribute to the development of liver disease in individuals with schizophrenia.

Existing pharmacological research suggests that dosage adjustment of olanzapine may not be required for patients with severe liver or kidney diseases, despite the potential impact of these conditions on olanzapine metabolism. Kidney failure can disrupt the excretion processes, while liver abnormalities can affect olanzapine metabolism. However, current evidence indicates that dosage adjustment may not be necessary in these patient populations. Enzyme regulation and genetic variations can influence the metabolism of olanzapine, which exhibits significant inter-individual variability. While olanzapine effectively treats schizophrenia, it can also lead to side effects such as prolactin release, metabolic dysregulation, and liver-related issues. Managing these adverse effects requires a comprehensive understanding of olanzapine's mechanisms.

Although the available research suggests that dosage adjustment may not be required, individualized considerations, including patient characteristics, medication interactions, and therapeutic monitoring, are crucial for optimal treatment outcomes. Further research will provide more definitive guidance for the appropriate dosage of olanzapine in patients with severe liver or kidney diseases.

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Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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