

## A comparison of efficacy, mechanism, and side effects of clozapine and risperidone in patients with schizophrenia

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World Journal of Biology Pharmacy and Health Sciences, 2022, 12(01), 066–080

Publication history: Received on 02 September 2022, revised on 16 February 2021, accepted on 09 October 2022

Article DOI: <https://doi.org/10.30574/wjbphs.2022.12.1.0151>

### Abstract

Schizophrenia is a chronic psychotic disorder characterized by the presence of psychotic symptoms (hallucinations, delusions), negative symptoms (decreased expressiveness), and cognitive symptoms (lack of executive function). The exact etiology of schizophrenia is unknown, although it is thought to be linked to increased dopaminergic activity in the mesolimbic neuronal pathway and decreased dopaminergic activity in the prefrontal cortical pathway. Treatment of schizophrenia includes both pharmacological and psychosocial intervention. Nonpharmacological treatments are effective in treating the negative and cognitive symptoms of schizophrenia and increasing patient adherence to medications.

The first-generation “conventional” antipsychotic drugs are high-affinity antagonists of dopamine D2 receptors that are most effective against psychotic symptoms and atypical agents differ pharmacologically from previous antipsychotic agents in their lower affinity for dopamine D2 receptors

Clozapine and risperidone both are atypical antipsychotics. Clozapine has weak D2 blocking action. It mainly acts by blocking 5-HT<sub>2</sub>, alpha-adrenergic, and D4 receptors. Risperidone acts by blocking 5-HT, alpha-adrenergic and D2 receptors. It is a more potent D2 blocker than clozapine and can cause extrapyramidal symptoms at a high dose.

Aggravation of seizures more with olanzapine and fewer chances with risperidone. Clozapine is a high potential atypical antipsychotic to cause metabolic side effects, while risperidone is a low potential antipsychotic to cause metabolic side effects. Clozapine is used in the treatment of resistant schizophrenia and risperidone is the most potent atypical antipsychotic agent available in long-acting injectable form.

**Keywords:** Schizophrenia; Clozapine; Risperidone; Psychotherapy

### 1. Introduction

Schizophrenia is a chronic, remitting, and relapsing psychotic disorder with significant dysfunction and increased mortality (1). Schizophrenia is a highly prevalent disorder affecting approximately 1% of the world's population (2) Schizophrenia is increasingly viewed as a neurodevelopmental process caused by an interaction between genetic factors and environmental stressors. (3) The early onset of the disease and its chronic course make it a disabling disorder for many patients and their families. Negative symptoms (marked by loss or deficits) and cognitive symptoms, such as

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deficiencies in attention, working memory, or executive function, frequently combine to cause disability. (4) Due to the often-chronic course of illness, patients with schizophrenia have poor educational attainment, reduced quality of life, impairment in independent living, and major socio-occupational dysfunction (5).

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## 2. Epidemiology

Understanding the prevalence of schizophrenia has important implications for both health service planning and risk factor epidemiology (6). There is a lot of variation and intriguing gradients in the epidemiology of schizophrenia. The epidemiology of schizophrenia is far more fascinating than was previously thought. In contrast to earlier interpretations, there is a significant regional difference in the incidence of schizophrenia. The prevalence of schizophrenia was 15.2/100,000 people on average, while the middle 80% of estimates ranged from 7.7 to 43.1/100,000. Males outnumbered females by a ratio of 1.4:1. Estimates of prevalence also exhibit significant variation. The median chance of developing schizophrenia over one's lifetime was 7.2 per 1,000 people. According to the median standardized mortality ratio (5.26 for all-cause mortality), people with schizophrenia have a two- to threefold greater risk of dying. This disparity in mortality has grown over the past several decades. Migrants have a higher incidence and prevalence of schizophrenia than those who are native-born. There is also a relationship between some frequency metrics and exposures related to urbanity, economic status, and latitude. (7).

### 2.1. Etiology

The etiology of schizophrenia represents the involvement of environmental factors, the role of genes, social stressors, such as discrimination or economic hardship, relationships, childhood difficulty, use of cannabis in adolescence, maternal stress, nutritional deficiencies, maternal infections, intrauterine growth retardation, and complications of pregnancy, while pathophysiology represents dysfunctional neurotransmission of dopamine, stress-associated signaling cascades (GABAergic, glutamatergic, cholinergic, serotonin, and adrenergic signaling cascades) and enzymatic changes (acetylcholinesterase, catechol-o-methyl-transferase, monoamine oxidase, and phosphodiesterase). (8)

According to most experts, the most plausible assumption is that the majority of cases of schizophrenia are polygenetically determined. (9). Studies suggest that alleles of at least two genes, those encoding D3, and 5HT2A, confer a small rise in susceptibility to schizophrenia (10). Reduced brain volume was observed in people with a high hereditary risk of schizophrenia, but it was not observed in controls. As patients with schizophrenia matured, changes in brain structure were also linked to worsening psychotic symptom intensity. (11)

People with a schizotypal personality disorder may be protected against the psychosis and severe social and cognitive decline of chronic schizophrenia due to genetic or environmental variables that support increased frontal ability and less striatal dopaminergic responsiveness. (12)

### 2.2. Pathophysiology

The dopamine hypothesis has been the leading pathologic theory of schizophrenia for more than four decades. Two lines of data serve as the foundation for the dopamine hypothesis. First, it was proven by clinical investigations that dopaminergic agonists and stimulants might cause psychosis in healthy people and exacerbate it in people with schizophrenia. The second was learning that antipsychotic medications have an impact on the dopamine system. (13)

There are 3 interconnected pathways theoretically linked to hallucinations and delusions: dopamine hyperactivity at D2 dopamine receptors in the mesolimbic pathway, which extends from the VTA to the ventral striatum, NMDA receptor hypoactivity at GABAergic interneurons in the prefrontal cortex, and serotonin hyperactivity at 5-HT2A receptors on glutamate neurons in the cerebral cortex. All 3 neuronal networks and neurotransmitters are linked together, and both 5HT2A and NMDA receptor actions can result in hyperactivity of the downstream mesolimbic dopamine pathway. (14)

Schizophrenia frequently exhibits altered presynaptic striatal dopamine production and release. In the prodrome, this is also apparent to a lesser extent, and it gets worse as frank psychosis develops. Blunted cortical dopamine release has now been related to schizophrenia, and there is growing proof that in persons with prodromal symptoms, the altered cortical function is connected to striatal dopamine hyperactivity, suggesting a key role in corticosteroid dysregulation. Furthermore, by compromising the cortical regulation of midbrain dopamine neurons, it is now able to start comprehending how genetic and environmental risk factors may cause striatal dopamine dysregulation. Yet more research needs to be done on the prodrome's reduced cortical dopamine release and the precise biochemical mechanisms that underlie it. (15) In schizophrenia, a hyperdopaminergic state exists during the initial episode and subsequent relapses but not during times of remission (16). This emphasis on dopamine D2 receptors, however, also highlights how few therapeutic alternatives there are. (17)

Since D2 receptors are primarily found in the limbic system and STR, schizophrenia has important features including cognitive impairment and abnormalities in motivation and affect that is substantially seen in these regions. Dependent upon nonstriated mechanisms that are not directly targeted by D2 antagonists, it is clear that there should be more effective means to treat this complex syndrome. Atypical APDs may be able to boost DA release in the medial prefrontal cortex by blocking the 5-HT<sub>2A</sub> receptor in the presence of lesser D2 receptor antagonistic effects. Having a smaller effect on mesolimbic DA release.

This may contribute to their advantages for cognition, negative symptoms, and antipsychotic activity. Antagonism at 5-HT<sub>2C</sub> receptors may also be useful for improving cortical function. When combined with modest D2 receptor blockade, the use of 5-HT<sub>1A</sub> receptor agonists may replace 5-HT<sub>2A</sub> antagonism and produce many of the same benefits. Some new antipsychotic drugs are weak D2 antagonists or partial D2 receptor agonists, and 5-HT<sub>1A</sub> receptor partial agonists, aripiprazole may owe its efficacy and tolerability, which far exceeds that of other D2 partial agonists that have been tried in schizophrenia, to 5-HT<sub>1A</sub> receptor agonism, along with 5-HT<sub>2A</sub> receptor antagonism. To build more potent antipsychotic drugs that can be adjusted by more selective drugs, additional research is required to understand how to use this information. For most patients, more complex agents such as the atypical APDs have greater potential for interacting with various elements of the circuitry that underlies the multiple deficits of schizophrenia. (18)

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### 3. Diagnosis and Symptoms

Schizophrenia is a psychiatric syndrome characterized by psychotic symptoms of hallucinations, delusions, and disorganized speech, negative symptoms such as decreased motivation and diminished expressiveness, and cognitive deficits involving impaired executive functions, memory, and speed of mental processing (19) in patients in different cultures who could be diagnosed as suffering from schizophrenia shared many common symptomatologic features. (20)

The hypothetically central symptoms required for the basic diagnosis of the condition include (a) delusions, (b) hallucinations, (c) disorganized speech (frequent derailment or incoherence), (d) grossly disorganized or catatonic behavior, and (e) negative symptoms (affective flattening, alogia). Accompanying symptoms in schizophrenia include depression and anxiety, cognitive and attentional problems, and belligerent or aggressive behavior. The diversity of the central and accompanying symptoms has been difficult to explain, particularly from an etiological perspective. (21)

The diagnosis of schizophrenia is based on a clinical assessment. While more recent descriptions emphasize positive symptoms, earlier conceptualizations saw negative symptoms as core features of the disorder, and negative and cognitive symptoms contribute substantially to the long-term burden associated with the disorder. The disorder typically appears in early adulthood, and a prodromal period frequently precedes the first psychotic episode. (22)

#### 3.1. DSM-5 Criteria for Schizophrenia

Other sources of symptoms must be ruled out along with satisfying criteria A, B, and C.

Two or more of the following symptoms must be present for 1 month or longer, and at least 1 of them must be item 1, 2, or 3:

- Delusions
- Hallucinations
- Disorganized speech
- Grossly disorganized or catatonic behavior
- Negative symptoms, such as diminished emotional expression
  - Impairment in 1 of the major areas of functioning (work, interpersonal relations, or self-care) for a substantial period since the onset of the disturbance.
  - At least six months must pass without any remission of some of the disorder's symptoms.
  - This 6-month period may include periods of residual symptoms but must contain at least 1 month of symptoms that fulfill criterion A (Active-phase symptoms) or less (if treated).
  - There may be no positive symptoms during residual periods.

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### 4. Prodromal Phase

Recognizing schizophrenia's prodromal symptoms may allow for early intervention to prevent relapse and re-hospitalization. A standard monitoring system was developed involving the completion of a new early signs scale (ESS)

measuring changes in key symptoms phenomenologically (self-report) and behaviourally (observer report). The ESS offers itself as a reliable, valid, and administratively feasible measure and demonstrates considerable potential as a cost-effective procedure for secondary prevention. (23) Relapse in schizophrenia remains common and cannot be eliminated even by the best combination of biological and psychosocial interventions. Relapse prevention is crucial as each relapse may result in the growth of residual symptoms and accelerating social disablement. (24)

#### 4.1. Managing the early warning signs of schizophrenia

- Engagement and education
- Identification of the relapse signature
- Development of a relapse drill
- Rehearsal and monitoring
- Clarification of the relapse signature and drill

Clinical and functional recovery is usually achieved after treatment for the first episode of psychosis (FEP). Unfortunately, subsequent relapse remains common, occurring within a year for approximately 30% of individuals and up to 80% over five years. Relapse risk factors for each given person are still poorly understood. Clinical and functional recovery is usually achieved after treatment for the first episode of psychosis (FEP). Unfortunately, subsequent relapse remains common, occurring within a year for approximately 30% of individuals and up to 80% over five years. Factors that make relapse more likely in any given individual remain poorly understood. (25)

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## 5. Symptoms in Menstruation

- Symptoms in women suffering from schizophrenia frequently vary with the different phases of the menstrual cycle.
- The positive symptoms improved significantly only during the progesterone phase and negative symptoms showed improvement in estrogen phases of the menstrual cycle.
- There is also improvement of affective and other behavioral symptoms which is evident from improvement in general psychopathology subscale improvement on estrogen phases of the menstrual cycle.
- Estrogen or combined estrogen/progesterone supplementation might be particularly effective in women suffering from schizophrenia but keeping the long-term side effects of estrogen in mind, selective estrogen receptor modulators specific to the brain may be considered. (26)

### 5.1. Catatonia

Catatonia remains a poorly understood syndrome of abnormal volition and motor behavior in several psychiatric and medical conditions. The syndrome is a disorder of cerebral motor network dysfunction (27)

### 5.2. Imaging Studies

Global abnormalities of cerebral and ventricular volumes have regularly been seen in imaging examinations of people with schizophrenia. Anatomical abnormalities in these schizophrenic patients with marked negative symptoms were most evident in left hemispheric neocortical and limbic regions and related white matter tract (28)

It appears that brain structural change is detectable in both Gray and white matter before illness onset, that active progression of the changes may also begin before the onset of clinical symptoms, and that progressive brain changes may account for the brain structural anomalies seen in chronic schizophrenia, and that the structures involved in language processing are affected (29)

### 5.3. Management

Numerous evidence-based recommendations can assist in guiding clinical decision-making related to the pharmacological treatment of schizophrenia in adults. (30) Early intervention is aimed at improving prodromal symptoms, avoiding functional deterioration, and suppressing or delaying the transition to psychosis. (31)

The Schizophrenia Patient Outcomes Research Team (PORT) that the psychopharmacological treatment recommendations provide a comprehensive summary of current evidence-based pharmacological treatment practices. To ensure that all people with schizophrenia receive the highest quality pharmacological treatment, providers of mental

health services should strive to ensure that each of these evidence-based practices is readily available for those patients for whom the treatments are indicated. (32)

#### 5.4. Relapse

The majority of people with schizophrenia undergo many episodes of psychotic aggravation and relapse. Schizophrenia is a chronic, burdensome condition. Relapse in schizophrenia can be associated with progressive functional deterioration, declining treatment response, worsening clinical outcomes, escalating caregiver burden, and an increased economic burden for families and society. Therefore, a key therapy objective for the effective long-term management of schizophrenia is the avoidance of relapse. Patients with a longer duration of illness (i.e., particularly >10 years) have a higher risk of relapse (33)

Relapse rates are very high when treatment is discontinued, even after a single psychotic episode, a longer treatment period before discontinuation does not reduce the risk of relapse, many patients relapse soon after treatment reduction and discontinuation, the transition from remission to relapse may be abrupt and with few or no early warning signs, once illness recurrence occurs symptoms rapidly return to levels similar to the initial psychotic episode, while most patients respond promptly to re-introduction of antipsychotic treatment after relapse, the response time is variable and notably, treatment failure appears to emerge in about 1 in 6 patients. These observations are consistent with contemporary thinking on the dopamine hypothesis, including the aberrant salience hypothesis. (34)

Overall, the currently available data suggest that new-generation antipsychotics have the potential to reduce relapse rates (35)

#### 5.5. Drugs

Antipsychotics were first introduced into clinical practice in the 1950s and revolutionized the treatment of psychosis. (36) The breakthrough in the treatment of schizophrenia with the introduction of chlorpromazine, followed by many other first-generation antipsychotics (FGAs). Starting in the 1990s, several second-generation antipsychotics (SGAs) were introduced. They were developed based on the receptor binding profile of clozapine, after it was recognized that clozapine was substantially different from other available antipsychotics at the time, with clearcut advantages in terms of efficacy in refractory patients and a virtual absence of motor side effects. While the SGAs have become widely regarded as the first-choice treatment for schizophrenia in countries that can afford them, they have not lived up to earlier high expectations regarding superior efficacy. SGAs have been inconsistently found to be modestly more efficacious than FGAs in treating negative, cognitive, and depressive symptoms, and have a lower risk of causing tardive dyskinesia (TD) (37).

The first-generation “conventional” antipsychotic drugs are high-affinity antagonists of dopamine D2 receptors that are most effective against psychotic symptoms but have high rates of neurologic side effects, such as extrapyramidal signs and tardive dyskinesia. The introduction of second-generation, or “atypical,” antipsychotic drugs promised enhanced efficacy and safety. The atypical antipsychotic drugs are pharmacologically distinct from earlier antipsychotic drugs in that they have higher affinities for serotonin receptors and less affinity for dopamine D2 receptors. (5-hydroxytryptamine<sub>1A</sub>, 2A, 2C, 3, 6, and 7) and norepinephrine ( $\alpha_1$  and  $\alpha_2$ ) (38)

Medication that targets dynamic modulation of DA presynaptic function more subtly than D2 blockade might be helpful for the prevention of the first episode and maybe maintenance of the therapeutic response. The imaging data also suggest that sparing the mesolimbic DA system might be beneficial to minimize the impact of medications on negative symptoms. (39)

That LAIs (with their intrinsically better adherence) would be more effective than OAPs in preventing relapse, this was not evident in a synthesis of the available RCTs. (40)

The antipsychotic medications are helping—but the improvement is less than 100% due to medication nonadherence (41)

#### 5.6. Side Effects

Antipsychotic medications can have side effects that range from being tolerable (like mild sedation or dry mouth) to being extremely unpleasant (like constipation, akathisia, or sexual dysfunction), painful (like acute dystonia), disfiguring (like weight gain, tardive dyskinesia), or even life-threatening (e.g., myocarditis, agranulocytosis). Some

adverse effects have little short-term clinical implications (e.g., increased prolactin or serum lipid levels), but may involve long-term risk of medical complications (42)

The use of antipsychotic agents has been associated with hyperprolactinemia or elevated prolactin levels. Hyperprolactinemia is more than an abnormal laboratory value, elevated prolactin levels can interfere with the functioning of reproductive, endocrine, and metabolic systems. First-generation antipsychotics are most recognized for causing hyperprolactinemia (43)

Cardiometabolic effects of second-generation antipsychotic medications are concerning but the benefits of second-generation antipsychotic medications must be balanced against their cardiometabolic risks through a careful assessment of the indications for their use, consideration of lower-risk alternatives, and proactive adverse effect monitoring and management (44). Young patients are more sensitive to body image and self-esteem issues, thus transforming weight gain into social discrimination and stigma. (45)

EPS can be categorized as acute (dystonia, akathisia, and Parkinsonism) and tardive (tardive dyskinesia and tardive dystonia) syndromes (46) Extrapyramidal symptoms (EPS) are less frequent with atypical than with conventional antipsychotics but remain common in clinical practice partly due to lack of screening by health professionals. Severe muscle rigidity, pyrexia, a shift in consciousness level, and autonomic dysfunction make up the Neuroleptic Malignant Syndrome (NMS), however, there are also partial versions. NMS is particularly associated with the initiation and rapid increase in the dose of high-potency antipsychotics but it has been reported with all the atypical antipsychotics and rarely with other drugs including antidepressants (47) DIP and TD prevalence estimates range from approximately 20 to 35% among antipsychotic users (48)

Neurocognitive impairment in schizophrenia is severe and is an important predictor of functional outcomes. The relative effect of the second-generation (atypical) antipsychotic drugs and older agents on neurocognition has not been comprehensively determined. There were no differences between any pair of agents (49)

### **5.7. Comorbidity**

People with schizophrenia have a wide range of comorbid and multiple physical-health conditions but are less likely than people without schizophrenia to have a primary care record of cardiovascular disease. (50)

Patients with medical comorbidity who were treated with antipsychotic medications were as likely to receive doses within the PORT guidelines as schizophrenic patients without medical comorbidity (51)

Comorbid psychiatric disorders, such as substance use disorder, often have a deleterious effect on the course of schizophrenia, and comorbid medical conditions, such as diabetes, may contribute to a decreased life span in patients with schizophrenia.

Some comorbid conditions may have a genetic link to schizophrenia itself, and establishing whether patients with schizophrenia are at increased risk for certain genetic disorders may further understanding of psychosis. Preliminary evidence indicates an increased prevalence of schizophrenia and bipolar disorder in adults with velocardiofacial syndrome, a condition associated with small deletions of chromosome 22q11.

Obsessive-compulsive symptoms may make the prognosis worse, alcohol and substance use problems are linked to a poor outcome, depression is linked to suicide, the main cause of premature death in persons with schizophrenia, and comorbid medical conditions, including cardiac and pulmonary disease, infectious diseases, diabetes, hyperlipidemia, hypogonadism, and osteoporosis, are often underrecognized and undertreated.

The new generation of antipsychotic medications has improved the potential outcome for patients with schizophrenia. Providing optimal treatment for patients and fully realizing the potential of these new agents require focused attention on the detection, recognition, and treatment of comorbid psychiatric and medical conditions in patients with schizophrenia (52)

### **5.8. Suicide**

Suicide risk assessment in schizophrenia is recognized to be challenging. Prevention of suicide in schizophrenia will rely on identifying those individuals at risk, treating comorbid depression and substance misuse, as well as providing the best available treatment for psychotic symptoms (53)

### 5.9. Drug Abuse

Drug use and mental health are connected (54) Cannabis use is observationally associated with an increased risk of schizophrenia, but whether the relationship is causal is not known. (55)

Schizophrenic patients who abuse drugs may represent a subgroup of patients with better prognoses and less severe clinical characteristics of schizophrenia, but their drug abuse may adversely affect the global outcome. It has been reported that drug-abusing schizophrenic patients who require more hospitalization have lower compliance with treatment regimens and are at greater risk for suicide. data show that despite decreased scores on measures of positive and negative symptoms at discharge, drug-abusing patients function no better than patients without drug abuse during the stabilization phase, suggesting that the combination of drug abuse and Schizophrenia may complicate an otherwise less severe case of schizophrenia. (56)

### 5.10. Resistance

The treatment of schizophrenic patients who fail to respond to adequate trials of neuroleptics is a major challenge. (57)

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## 6. Definitions of Treatment Resistance

- Active and persistent symptoms for 12 weeks with impaired functioning More robust if measured by well-validated scales More robust if distinct symptom domains are elicited
- Well-documented measurement of previous treatment failures More robust with multiple measures, including pill use review
- At least 6 weeks of treatment at appropriate, effective use of an antipsychotic at doses equivalent to 600 mg chlorpromazine daily

More robust if the duration also includes 6 weeks of treatment with a long-acting injectable (LAI) antipsychotic requires two antipsychotics from different drug profiles

Adherence is ensured by achieving documented 80% compliance with oral medications, LAI antipsychotic trial, antipsychotic blood levels, or any combination of these. (58)

### 6.1. Recommendations Regarding Clozapine Treatment for Treatment-Resistant Schizophrenia

- Clozapine should be the first choice of treatment for patients with schizophrenia whose illness has shown a poor response to sequential trials of two (or more) different antipsychotic medications that have been suitable in terms of quantity and time.
- Poor medication adherence and comorbid substance use should be excluded as causes of the apparent poor response to antipsychotic medication.
- Where a patient's illness meets the criteria for treatment-resistant schizophrenia, a trial of clozapine should be considered with minimal delay.
- The treatment plan for individual patients should ensure adherence to the recommended starting dose titration schedule and the requirements for laboratory investigations and side-effect monitoring, as well as meeting the patient's requirement for assistance from the medical staff, family, and caregivers.
- For an adequate trial, clozapine monotherapy should be prescribed for at least 6 months.
- Treatment-emergent side effects should be monitored, preferably using a self-report instrument such as the GASS-C
- Adverse effects should be managed proactively, to maximize tolerability and reduce the risk of discontinuation.
- Consideration should be given to the use of clozapine plasma concentration to guide dosage and check adherence where there is a sub-optimal response, or where adverse effects are problematic.
- If possible, when a patient's clozapine is to be discontinued, the dose should be gradually tapered over at least 1–2 weeks.
- After stopping clozapine, particularly if stopped abruptly (e.g., because of agranulocytosis), a patient's physical and mental state should be monitored for symptoms reflecting cholinergic rebound or rapid re-emergence of psychosis, particularly in the first week.
- If clozapine therapy is temporarily interrupted for more than 48 h, it must be restarted at a dose of 12.5– 25 mg/day. It may be reasonable to titrate the dosage if this dose is well tolerated, there are no signs of

cardiovascular disease or respiratory distress, and prior usual dosage titrations have gone smoothly. Dose to the therapeutic level more rapidly than is recommended for initial treatment. If a patient previously experienced adverse effects with initial dosing, even if a therapeutic dose was subsequently successfully relieved, rapid titration should be avoided.

- Augmentation strategies with clozapine should only be considered after optimized clozapine treatment has been administered for an adequate period of not less than 3 months.
- Clozapine augmentation with a second antipsychotic: an adequate trial of clozapine augmentation with another antipsychotic medication may need to be at least 10 weeks in duration.
- When choosing an augmenting antipsychotic medication, consideration should be given to medications with a complementary receptor profile to clozapine, and a side-effect profile that minimizes compounding recognized problems with sedation, weight gain, and adverse metabolic consequences of clozapine.
- Augmentation strategies should always be prescribed as an individual patient treatment trial, with review and discontinuation if any gains achieved fail to outweigh the side effects. (59).

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## 7. Switching Of Therapy

Despite decades of research, our many treatments for schizophrenia remain only partially effective in ameliorating the symptoms of this disease. The CATIE trials, primarily designed to compare currently available agents to each other regarding the efficacy and side effects, are perhaps most remarkable for their high discontinuation rates. These rates are reflected in the high proportion of patients switching or not adhering to their medication. The availability of the many atypical antipsychotics with varying clinical and side effect profiles allows for increased choice for the patient and clinician. In evaluating the ACD, the clinician must be aware of the multiple factors in drug discontinuation or desire to switch. For example, changes in functional levels interplay with a patient's symptoms and may secondarily result in a drug termination or change. We won't be able to have a complete picture of all the aspects of how a person with schizophrenia functions and behaves unless we have this broader background. Thereby maximizing our treatments.

### 7.1. Components of ACD (All-cause discontinuation)

- Efficacy
- Tolerability
- Clinician input
- Patient input. (60)

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## 8. Psychotherapy

Psychotherapy is frequently used to treat the psychological distress that many schizophrenias patients experience. Numerous various psychotherapeutic strategies for schizophrenia have been created and researched. Of these approaches, cognitive behavior therapy (CBT) has the strongest evidence base and has shown benefits for symptom reduction in outpatients with residual symptoms.

In addition to CBT, other modalities include supportive treatment, acceptance and commitment therapy, compliance therapy, and personal therapy. Finally, primary prevention of disease or early course alteration of disease must be the long-term therapeutic goal (secondary prevention). The role that psychotherapeutic approaches may play in these early stages of prevention and treatment remains quite unclear.

It is difficult to imagine psychotherapy that prevents the illness, but psychotherapeutic techniques, combined with other treatments that target underlying brain processes, are not entirely farfetched, especially when monitored by evolving neuroimaging technologies as have recently been shown to predict responsiveness to CBT in individuals with schizophrenia. Psychotherapy that changes behaviors to manage disease risks, analogous to medical counseling to enhance treatment compliance and thwart negative health habits in persons such as those at risk for diabetes, would fall within this realm of inquiry (61).

### 8.1. Mortality

Patients with schizophrenia have two-fold to three-fold higher mortality rates compared with the general population, corresponding to a 10–25-year reduction in life expectancy. Despite the high suicide mortality rate, natural causes of death are responsible for a larger portion of the decline in life expectancy. The studies that have been analyzed point to four key causes of increased mortality and decreased life expectancy. First, persons with schizophrenia tend to have



suboptimal lifestyles including unhealthy diets, excessive smoking and alcohol use, and lack of exercise. Second, antipsychotic drugs may have adverse effects. Third, physical ailments are common in people with schizophrenia, but they are often recognized too late and are not adequately treated. Lastly, the risk of suicide and accidents among schizophrenic patients is high. (62)

## 8.2. Clozapine Vs Risperidone

Antipsychotic drugs' clinical effectiveness has historically been correlated with the antagonistic effects they have on dopamine D2 receptors. However, clozapine's broader spectrum of therapeutic efficacy with minimum extrapyramidal side effects led to the notion that interaction with several receptors other than dopamine D2 was necessary for atypical antipsychotic action. As a result, most new antipsychotics introduced into the market in the past two decades (e.g., risperidone) have been multi-receptor acting agents, especially having concomitant 5-HT<sub>2</sub> receptor antagonism (63)

In clinical practice as well as in experimental studies, the association between CLZ and other antipsychotics is the most frequently employed and tested strategy for the management of SRS, particularly the combination of CLZ with risperidone. (64)

## 8.3. Clozapine

Clozapine was first discovered in 1959 by scientists at Wander Laboratories, who were screening tricyclic compounds for antidepressant activity and were surprised to discover drugs with a chemical structure comparable to the tricyclic antidepressants but with antipsychotic properties (65)

The clinical advantages and adverse effects of the first “atypical” antipsychotic, clozapine, are now well established. The advantages include clozapine's efficacy, compared to first-generation antipsychotics (FGAs) and other second-generation antipsychotics (SGAs), for individuals who are resistant or refractory to conventional treatment for schizophrenia, and the fact that it produces minimal extrapyramidal side effects (66)

Clozapine was significantly more efficacious than all the other antipsychotics (67) clozapine remains the gold standard for treatment-resistant schizophrenia, and its impressive efficacy has been demonstrated in several clinical trials and a meta-analysis. In addition to its unique efficacy in patients with treatment-resistant schizophrenia, clozapine possesses antisuicidal and anti-aggressive properties (68)

## 8.4. Risperidone

Risperidone was the first novel second-generation antipsychotic (SGA). It was introduced to the market at the beginning of the 1990s, many years after the advent of the prototype of the SGA, clozapine, which was licensed in Europe in the 1970s. (69)

Risperidone has a usually reduced risk of extrapyramidal symptoms than traditional antipsychotics at dosages of 8 mg/day and may have a better impact on cognitive function and quality of life. (70)

The striatal D<sub>2</sub> receptor occupancy is linked to antipsychotic efficacy. D<sub>2</sub> receptors can be measured in humans by using either positron emission tomography (PET) or single photon emission computerized tomography (SPECT). S. Kasper et al, data are indicative that antipsychotic efficacy is not associated with a high degree of striatal D<sub>2</sub> receptor occupancy in schizophrenic patients. (71)

Igor Elman, M.D et al, suggest that both risperidone and clozapine elevate plasma NE (norepinephrine) levels via enhanced neurotransmitter spill over, with risperidone producing a smaller effect. (72)

Zachary R. Stoecker found that patients taking clozapine before admission, but not risperidone, were more likely to be admitted with a diagnosis of pneumonia compared with the general population of those not taking antipsychotic medications. (73)

Clozapine and risperidone are used in treatment-resistant schizophrenia. W. Flynn et al found that Clozapine had better efficacy in subjects with treatment-resistant schizophrenia compared to risperidone. although risperidone appears to yield better response rates than those previously reported for typical antipsychotics. (74)

Clozapine treatment remains the gold standard for treatment-resistant schizophrenia, but treatment with clozapine is associated with several side effects that complicate the use of the drug. J. Nielsen et al, Treatment with clozapine should

be optimized to increase the rate of response and to minimize side effects, thus diminishing the risk of discontinuation and psychotic relapse. (75)

Clozapine is regarded as the go-to medication for schizophrenia that has resisted therapy. However, clozapine use has restrictions owing to its many adverse effects. Myrto T. Samara, MD et al, found Insufficient evidence exists on which antipsychotic is more efficacious for patients with treatment-resistant schizophrenia, and blinded RCTs—in contrast to unblinded, randomized effectiveness studies—provide little evidence of the superiority of clozapine compared with other second-generation antipsychotics (76)

Ching-Hua Lin et al, the study demonstrated that atypical antipsychotics did not lengthen the time to rehospitalization. The earlier the age at onset of schizophrenia, the shorter the time to rehospitalization (77)

Ana Paula Werneck de Castro et al, study suggests that the rehospitalization rates of patients taking clozapine are lower than the rate for patients treated with risperidone. However, confounding variables such as gender distribution and age of onset represent limitations that should be taken into account for the interpretation of the results (78)

The enormous proportion of patients who only partially respond to clozapine poses a significant treatment problem. Regrettably, there is no conclusive evidence to support the most effective care for these patients. Elaine Weiner et al, study results suggest that adjunctive risperidone may have a modest benefit for treatment-resistant clozapine patients. (79)

Schizophrenia is a devastating mental illness that afflicts nearly 1% of the world's population. Currently available antipsychotics treat positive symptoms but are largely ineffective at addressing negative symptoms and cognitive dysfunction (80).

Antipsychotic medication is the cornerstone of schizophrenia treatment. (81) Long-term treatment is necessary for all patients with schizophrenia. If the patient has shown improvements with a particular medication regimen, continuation of that regimen with further monitoring is recommended for at least 6 months in the stabilization phase (82) additive effect of psychosocial treatment is needed in treating schizophrenia patients. (83)

Managing patients with schizophrenia can be challenging, even for the most experienced of clinicians. (84)

Psychiatrists should be aware that comorbid depression, suicidality, and substance use disorder further increase the already high mortality of schizophrenia. Therefore, these conditions need to be diagnosed correctly and treated quickly and with utmost care. (85) Most people with schizophrenia can achieve long and meaningful periods of recovery. (86) A large percentage of patients with schizophrenia or schizoaffective disorder did not adhere to their treatment in the post-discharge follow-up period. The profile identified may enable better prevention of this problem. Specific reasons for nonadherence should also be explored to provide individualized strategies. (87)

The overall outcome of schizophrenia is generally poor, and typically its course is characterized by frequent relapses, rehospitalizations, prominent impairment in social and occupational functioning, and suicidality.

Measurements of dopamine D2 receptor occupancy is a reliable indicator of prolactin rise, extrapyramidal side effects, and antipsychotic responsiveness. The new antipsychotics clozapine and risperidone, with few extrapyramidal side effects and little prolactin elevation. Clozapine, at doses known to be effective in routine clinical settings, showed a D2 occupancy lower than that of typical antipsychotics, while risperidone in usual clinical doses gave the same level of D2 occupancy as low-dose typical antipsychotics (88)

Clozapine use in patients with severe mental illness was associated with a significantly increased risk of death compared with that of the general population. (89)

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## 9. Conclusion

In patients with schizophrenia who prospectively failed to improve with an atypical antipsychotic, clozapine was more effective than switching to another newer atypical antipsychotic. Safety monitoring is necessary to detect and manage clozapine's serious side effects.

Clozapine and risperidone both are atypical antipsychotics. Clozapine has weak D2 blocking action. It mainly acts by blocking 5-HT<sub>2</sub>, alpha-adrenergic, and D<sub>4</sub> receptors. Risperidone acts by blocking 5-HT, alpha-adrenergic, and D<sub>2</sub> receptors. It is a more potent D<sub>2</sub> blocker than clozapine and can cause extrapyramidal symptoms at high doses. Aggravation of seizures more with olanzapine and fewer chances with risperidone. Clozapine is a high potential atypical antipsychotic to cause metabolic side effects, while risperidone is a low potential antipsychotic to cause metabolic side effects. Clozapine is used in the treatment of resistant schizophrenia and risperidone is the most potent atypical antipsychotic agent available in long-acting injectable form.

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## Compliance with ethical standards

### *Acknowledgments*

The authors appreciate Prof. E. TamilJothi sir's support and ongoing encouragement for the article.

### *Disclosure of conflict of interest*

No conflict of interest.

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