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A review on the impact of Clozapine on relapses in Substance abuse among Schizophrenia patients

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ABSTRACT

Schizophrenic patients often use alcohol and other drugs, contributing to their disorder's morbidity. In individuals with schizophrenia, the lifetime prevalence of substance use disorders (SUDs) is close to 50%. With a large proportion of poly-substance users, the most commonly used substances are cannabis, alcohol, and nicotine. The emotional and financial toll that schizophrenia has on individuals, families, and the mental health system as a whole is significantly increased by these comorbid diseases. Standard antipsychotic drugs do not limit substance use, but atypical antipsychotics like clozapine may decrease it. Clozapine's beneficial effect in patients with comorbid schizophrenia and substance use disorders may be due to its ability to ameliorate deficits in dopaminergic neuronal projections. The aim of the current article is to review clozapine's effectiveness in treating SUD in schizophrenia patients. Different studies were taken into account and reviewed. There is more evidence of clozapine's impact on SUD, particularly when comparing it to first-generation antipsychotics in polydrug users.

Key words: schizophrenia, substance use disorder (SUD), atypical antipsychotics, relapse, and clozapine.

INTRODUCTION

Schizophrenia is a mental illness marked by delusions, hallucinations, and abnormalities in behaviour [1]. About 24 million individuals, or 1 in 300 persons (0.32%) worldwide, suffer from schizophrenia, and among adults, the rate is 1 in 222 persons (0.45%) [2]. Substance abuse disorders are highly prevalent among patients diagnosed with schizophrenia. Compared to 16% of the general population, individuals with schizophrenia have significant issues related to drug or alcohol use during their lives. Specifically, substance use disorders related to tobacco, alcohol, cannabis, and cocaine are widespread in individuals with schizophrenia; lifetime prevalence rates for these substances range from 60–90% for cigarette smoking, 21–86% for alcohol, 17–83% for cannabis, and 15–50% for cocaine use. Interestingly, co-occurring disorders are problematic in this population because they have been linked to clinical exacerbations like violence, suicide, poor global functioning, non-compliance with treatment, relapse, and increased rates of hospitalization. Over the years, several theories have been put forth to explain the relationship between schizophrenia and substance use disorders. The diathesis-stress model suggests a neurobiological vulnerability, and environmental stressors, including substance use, contribute to schizophrenia. The cumulative risk factor hypothesis suggests poor cognitive, social, educational, and vocational functioning, poverty, victimization, and deviant environments increase the risk of substance use. The self-medication hypothesis suggests substance use in schizophrenia is a response to antipsychotic treatment [3, 4, 5]. There is a suggestion that schizophrenia may impact the brain circuitry responsible for mediating drug reward, making a person more susceptible to addiction. A number of neurotransmitters, including those of the glutamatergic and dopaminergic systems, are implicated in the development and progression of addiction. Neuronal and motivational alterations observed in chronic substance misuse may result from dysregulated neuronal integration of dopamine and glutamate in the nucleus accumbens. Substance abuse is influenced by both genetic and environmental factors, such as personality traits, trauma, and family. Research pertaining to demographic features consistently indicates that males who are younger and have less education are more likely to abuse drugs [6].

Treatment for substance abuse and antipsychotics should be considered together, as they may work in concert for individuals with dual conditions. Among antipsychotics, clozapine shows positive evidence in the literature. Several studies have revealed that among patients treated with clozapine, the expected rate of decrease in substance usage might be 70–80%. Clozapine's rapid dissociation of the D2 receptors and the blockade of 5-HT2A and noradrenergic receptors are actions that are possibly associated with a reduction in substance craving. According to a recent study, over 90% of clinicians administered this medicine to patients with resistant schizophrenia, but only about 30% would use it on dual-diagnosis patients. Despite the available data and scientific consensus, clozapine should be used as a first-line treatment for schizophrenia with a dual diagnosis [7]. In contrast to concerns that first-generation antipsychotic medications may exacerbate substance abuse, case reports and correlational studies indicate that the second-generation antipsychotic medication clozapine may reduce the use of nicotine, alcohol, or other drugs of abuse among schizophrenia patients [4, 8]. The aim of the present article is to provide a review of the efficacy of clozapine in improving SUD in schizophrenic patients.

DISCUSSION

Reza Rafizadeh *et al.*,[9](2023) conducted a descriptive-analytic retrospective cohort study on the association of clozapine treatment and the rate of methamphetamine (MA) relapses and abstinence among individuals with concurrent schizophrenia spectrum disorder and amphetamine use disorder. Data were collected using electronic health records. Out of 365 patients admitted to the program, 87 met inclusion criteria, of whom 29 were administered clozapine for 90 days; half of them were schizophrenia patients, and most were male. The study found that clozapine treatment increased the likelihood of maintaining abstinence from any substance use, with (51) 59% of patients experiencing at least one MA relapse ($p = 0.025$), and (65) 75% of patients having at least one relapse to any substance use ($p = 0.02$). Clozapine treatment significantly reduced the rate of MA relapses during observation ($p = 0.009$). Clozapine monotherapy, when compared to other antipsychotic medications, decreased MA relapse rates but did not significantly impact the likelihood of maintaining abstinence.

Joana Teixeira *et al.*,[7](2022) conducted a retrospective inpatient analysis on impact of clozapine as the mainstay therapeutical approach to schizophrenia and substance use disorder. A total of 536 patients were admitted for psychiatric inpatient treatment, with 17.5% having dual diagnoses at discharge, with schizophrenia ($n = 47$; 50%) being the most common diagnosis associated with substance use disorder, of 100%, at least one antipsychotic was prescribed, 21 (44.7%) had at least two prescribed, and 4 (8.5%) had at least three prescribed. In 20 patients (42.6%) with a primary diagnosis of schizophrenia, clozapine was prescribed; in 27 patients (57.4%), another antipsychotic medication was prescribed. A long-acting antipsychotic was prescribed for 33 patients (70.2%). Among these, clozapine and a long-acting antipsychotic had an association in 14 individuals (42.4%), found no correlation between the prescription of clozapine and other antipsychotics in preventing relapse of substance abuse (Fisher exact test p-value = 0.282). For people with dual diagnoses, clozapine appears to be very effective at preventing substance use relapses.

Reza Rafizadeh *et al.*,[10](2022) conducted a study on the effects of clozapine treatment on the improvement of substance use disorders other than nicotine in individuals with schizophrenia spectrum disorders. This review aimed to identify the relationship between clozapine and substance use (SUD) in human subjects. The review was conducted using PRESS guidelines and a web-based citation chaser. The literature was categorized into clinical trials, observational studies, cross-sectional studies, case reports, and abstracts of presentations. The search identified 2797 studies on substance use disorders (SUDs), with most being male, with abstinence being the most common outcome. The study involved 13 poly-drug users, mostly alcohol, cannabis, and cocaine, who maintained abstinence or reduced use through augmentation strategies of clozapine, with one case involving treatment-resistant substance use disorder. Four observational studies found that clozapine treatment was associated with greater odds of remaining abstinent ($p < 0.00001$) in individuals with concurrent SUDs compared to other antipsychotics. Clozapine treatment has been shown to reduce cannabis cravings in patients compared to risperidone and olanzapine and may improve brain reward system function in individuals with concurrent psychotic disorders and SUDs. The study's findings are limited by broad inclusion criteria, heterogeneity in studies, and a lack of reporting on antipsychotic discontinuation rates.

Marc Krause *et al.*,[11](2019) conducted a systematic review and meta-analysis on the efficacy, acceptability, and tolerability of antipsychotics in patients with schizophrenia and comorbid substance use. 19 blinded randomised control trials included 1742 participants; of the 910 patients, 88% were men. The trial duration ranged from 4 to 72 weeks. Eight antipsychotics were included in the meta-analysis: olanzapine, risperidone, haloperidol, clozapine, ziprasidone, aripiprazole, perphenazine, and quetiapine. Most patients had comorbidities of cannabis or cocaine use disorder or dependence, followed by alcohol. Outcome results showed no significant differences between clozapine, ziprasidone, or olanzapine in terms of drug use or craving. Nevertheless, in a small single study (n = 31), clozapine was better than a control group composed of 'any other antipsychotic'.

Arranz, B., *et al.*,[12](2018) conducted a systematic review on clozapine use in patients with schizophrenia and a comorbid substance use disorder, in which there were 685 studies. 52 studies were considered eligible for further evaluation, and fourteen studies constitute the final selection. The studies were divided into two categories: I) clozapine for reducing nicotine use or abstinence in schizophrenia patients; and II) clozapine for reducing substance use in patients with schizophrenia. The review of 15 studies on clozapine's effectiveness in improving nicotine use found only five met inclusion criteria, involving 727 patients. FGAs and non-clozapine SGAs were used as clozapine comparators in two studies, and none used placebo as a comparator. Three randomised control trials compared clozapine dosages, finding two decreases in smoking after 12 weeks of 200–600 mg/d clozapine compared to 50–150 mg/d. The study analysed clozapine efficacy in substance use, involving 999 patients with schizophrenic spectrum disorder and comorbid SUD. The main clozapine comparators were FGA, risperidone, olanzapine, and ziprasidone. The study indicates that high doses of clozapine (200–600 mg/d) provide more benefits than lower doses (50–150 mg/d). The review reveals limited evidence on clozapine's efficacy on nicotine use in schizophrenic patients, but stronger evidence is found in substance use disorder (SUD) treatment. Clozapine has shown superiority over FGA or risperidone but not over olanzapine or ziprasidone.

Marise WJ Machielsen *et al.*,[13](2014) conducted a study on the effect of clozapine and risperidone on attentional bias in patients with schizophrenia and a cannabis use disorder. The study recruited 46 patients with schizophrenia, 35 with cannabis abuse, and 11 with a negative history of substance use disorders except smoking. The study included males aged 18–30 with a DSM-IV diagnosis of schizophrenia and excluded those with previous unsuccessful treatment or contraindications for the use of risperidone or clozapine. The control group had a history of substance use. Patients treated with clozapine (n = 12) showed a larger decrease in subjective craving compared to those treated with risperidone (n = 16). Clozapine and risperidone have distinct effects on brain activation and craving during cannabis use, with clozapine showing a larger reduction in craving.

Sarah C. Akerman *et al.*,[5](2014) conducted a study on pharmacotherapy of co-occurring schizophrenia and substance use disorders. A study of 151 patients with schizophrenia and substance use disorder found that clozapine versus those taking another atypical antipsychotic treatment led to a higher proportion of remission from drugs (64% vs. 30%) or alcohol use disorder (79% vs. 34%). Over the next year, clozapine had lower rates of relapse to substance use (8%) than those treated with other antipsychotics (40%). A prospective study found that clozapine treatment reduced cigarette smoking by lowering expired carbon monoxide, with an effect size of approximately 0.8. Two randomized controlled trials showed that clozapine significantly reduced cannabis

craving and bilateral insula activation in patients with schizophrenia and cannabis use disorder compared to risperidone.

Mary F. Brunette, MD *et al.,*[14](2011) conducted a randomized trial of clozapine versus other antipsychotics for cannabis use disorder in patients with Schizophrenia. The study recruited participants based on DSM-IV diagnoses of schizophrenia, schizoaffective disorder, and cannabis use disorder. The participants were outpatients and had current antipsychotic medication other than clozapine. Out of 50 people screened, 31 met the eligibility criteria; they are males and aged 35 years and older. They had cannabis dependence, had been hospitalized several times, and had mild symptoms. Most remained on study medication for 12 weeks but reported side effects like somnolence, hypersalivation, and weight gain. Clozapine treatment significantly decreased cannabis use compared to the continuation of the current antipsychotic. However, the small sample did not reach statistical significance. The study suggests that clozapine may limit cannabis use more than other antipsychotics in patients with schizophrenia and co-occurring cannabis use disorders.

Marise Machielsen *et al.,*[15](2011) conducted a study on the differences in craving for cannabis between schizophrenia patients using risperidone, olanzapine or clozapine. The study involved 503 patients using risperidone, olanzapine, or clozapine. The majority were male, with a higher rate of abuse of nicotine, alcohol, and other illicit substances. Of these, 187 used risperidone, 234 used olanzapine, and 82 used clozapine. The effect of clozapine (n = 27, mean dosage 350 mg), risperidone (n = 54, mean dosage 3.46 mg) and olanzapine (n = 60, mean dosage 13.78 mg) on subjective craving for cannabis was compared in patients with cannabis dependence and schizophrenia. Individuals receiving risperidone reported a notably higher level of desire than those receiving clozapine (p =.001) or olanzapine (p =.025).

Mary F. Brunette *et al.,*[8](2006) conducted a study on clozapine use and relapses of substance use disorder among patients with co-occurring schizophrenia and substance use disorders. Out of 223 outpatients with co-occurring severe mental and substance use disorders, focusing on schizophrenia and schizoaffective disorder, 72.8% of participants experienced a 6-month remission from substance use disorder during the 10-year follow-up. 115 patients were followed up a year later, with 95 taking one or more antipsychotic medications at the time of the first 6-month remission. The mean clozapine dose over the 3 months prior to the interview corresponding to the first remission was 417 mg. Patients with comorbid alcohol or drug disorders who were taking clozapine were less likely to experience substance abuse relapse at 1 year following remission (p =.003). Patients prescribed clozapine also experienced better 1-year post-remission outcomes. They were also assessed for remission at the 2nd and 3rd years following remission, where the clozapine group (n = 16) maintained a significantly lower rate of relapse than the patients on other antipsychotic medications (p =.05).

CONCLUSION

Schizophrenia patients frequently abuse alcohol and other substances, which adds to the overall morbidity of the illness. Conventional antipsychotic medications do not restrict the use of such substances and may potentially make it more. Atypical antipsychotic, clozapine significantly enhances substance use abstinence and prevents relapses in dual diagnoses. It reduces cannabis cravings in patients compared to risperidone and olanzapine.

Clozapine has superior effects over first generation antipsychotics or risperidone, but not olanzapine or ziprasidone. The effectiveness of antipsychotic medications in people with schizophrenia may be impacted by co-occurring substance misuse. Clozapine may also be helpful for these people, according to data from a small number of studies. The quality of life for people with schizophrenia will be enhanced if their cravings for alcohol or illegal drugs decrease, enabling them to live in the community and reducing the strain on the healthcare system.

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CONFLICTS OF INTEREST

According to the writers, there are no conflicts of interest in the article's content.

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