

CLOZAPINE AND SCHIZOPHRENIA: IMPACT ON REDUCING PSYCHOTIC SYMPTOMS AND PREVENTING SUICIDES

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Abstract: **INTRODUCTION** The treatment of schizophrenia has significantly evolved over the decades, with clozapine emerging as an effective antipsychotic for refractory patients. The prevalence of suicide among patients with schizophrenia is high, and clozapine is the only antipsychotic proven to significantly reduce this rate. The efficacy of clozapine, along with the challenges associated with its use, such as agranulocytosis and the need for rigorous monitoring, are discussed. **OBJECTIVES** To evaluate the efficacy of clozapine in reducing psychotic symptoms and preventing suicides in patients with schizophrenia. **METHODS** This is a narrative review. PubMed, SciELO, and Medline databases were used with the following descriptors: “Clozapine” AND “Schizophrenia” OR “Antisuicidal effect” OR “Antipsychotics” OR “Hematological monitoring” in recent years. **RESULTS AND DISCUSSION** Recent studies confirm the superiority of clozapine in reducing psychotic symptoms and preventing suicides compared to other atypical antipsychotics. Clozapine modulates neurotransmitters and has neuroprotective effects contributing to its efficacy. However, treatment with clozapine is associated with significant side effects, including agranulocytosis and metabolic complications that require constant monitoring. The quality of life of patients on clozapine treatment is generally superior despite adherence challenges and the costs associated with monitoring. **CONCLUSION** Clozapine represents a crucial advance in the treatment of schizophrenia, particularly for refractory patients and those at high risk of suicide. Although it comes with significant challenges, such as the need for rigorous monitoring and the management of adverse effects, its benefits in reducing hospitalizations, improving social functionality, and preventing suicides justify its use. Multidisciplinary approaches and continuous research are essential to maximize the efficacy and safety of clozapine.

Keywords: Clozapine; Schizophrenia; Suicide prevention; Atypical antipsychotics; Hematological monitoring.

INTRODUCTION

The treatment of schizophrenia has considerably evolved over the decades, reflecting the complexity and challenges of managing a chronic and debilitating disease. Initially, treatments were rudimentary, including confinement and non-pharmacological approaches until the discovery of antipsychotics in the 1950s, which radically transformed the management of schizophrenia¹. The prevalence of suicide among patients with schizophrenia is alarming, with rates ranging from 5% to 13%, highlighting the urgent need for effective interventions².

Risk factors include the presence of depressive symptoms, a history of suicide attempts, substance abuse, and good premorbid functionality³. The management of schizophrenia faces multiple challenges, including treatment adherence, medication side effects, and comorbidity with other psychiatric and medical conditions⁴. Current pharmacotherapy for schizophrenia includes a variety of antipsychotics classified as typical and atypical, each with different efficacy and side effect profiles⁵. In this context, clozapine stands out as the only antipsychotic with proven efficacy in reducing the risk of suicide in patients with schizophrenia, recognized by the FDA⁶.

Clozapine, introduced clinically in the 1970s, was initially received with enthusiasm due to its efficacy in refractory patients⁷. However, its association with agranulocytosis, a potentially fatal complication, limited its initial use, leading to the implementation of rigorous hematological monitoring protocols⁸. Compared to other antipsychotics, clozapine has a unique profile of efficacy

and side effects, being superior in terms of reducing negative symptoms and preventing suicide but associated with significant adverse effects such as sedation, hypersalivation, and weight gain⁹.

The importance of regular monitoring in patients using clozapine cannot be underestimated. Monitoring protocols include regular white blood cell and neutrophil counts to early detect agranulocytosis¹⁰. Additionally, the theoretical basis of clozapine's antisuicidal effect involves multiple mechanisms, including neurotransmitter modulation and neuroprotection¹¹. Epidemiological studies corroborate these findings, demonstrating significant reductions in suicide rates among patients treated with clozapine¹².

The impact of clozapine on patients' quality of life is substantial, going beyond the control of psychotic symptoms to improve social functionality and reduce hospitalization¹³. Clinical guidelines recommend the use of clozapine in refractory schizophrenia patients and those with a high risk of suicide¹⁴. Evidence from meta-analyses and systematic reviews confirms clozapine's efficacy in suicide prevention, highlighting the need for a balanced approach between efficacy and side effect monitoring¹⁵.

Challenges in prescribing clozapine include treatment adherence, often compromised by side effects and the complexity of monitoring regimens¹⁶. Comparisons between suicide rates in patients using clozapine versus other antipsychotics consistently show clozapine's superiority in reducing suicidal events¹⁷. Multidisciplinary approaches involving psychiatrists, nurses, and pharmacists are essential to optimize clozapine treatment outcomes¹⁸. Future perspectives in treating schizophrenia with clozapine include research on new formulations and therapeutic combinations to minimize side effects and improve adherence¹⁹. Ethical issues in using

clozapine involve informed consent and the need for continuous monitoring to ensure patient safety²⁰.

OBJECTIVES

To evaluate the efficacy of clozapine in reducing psychotic symptoms and preventing suicides in patients with schizophrenia.

SPECIFIC OBJECTIVES

1. Analyze the molecular mechanisms involved in clozapine's antisuicidal effect.
2. Compare the efficacy of clozapine with other atypical antipsychotics in suicide prevention.
3. Identify the main side effects associated with clozapine use and the necessary monitoring strategies.
4. Evaluate the quality of life of patients treated with clozapine compared to other treatments.
5. Investigate treatment adherence to clozapine and the factors influencing this adherence.

METHODS

This is a narrative review analyzing the main aspects of clozapine's efficacy in reducing psychotic symptoms and preventing suicides in schizophrenia patients in recent years. The study began with theoretical training using the following databases: PubMed, SciELO, and Medline, using the descriptors: "Clozapine" AND "Schizophrenia" OR "Antisuicidal effect" OR "Antipsychotics" OR "Hematological monitoring" in recent years. As this is a narrative review, this study has no risks.

Databases: This review included studies from the following databases: MEDLINE–PubMed (National Library of Medicine, National Institutes of Health), COCHRANE, EMBASE, and Google Scholar. The inclusion criteria applied in the analytical review were

human intervention studies, experimental studies, cohort studies, case-control studies, cross-sectional studies, literature reviews, editorials, case reports, and poster presentations. Only studies written in English and Portuguese were included.

RESULTS AND DISCUSSION

The efficacy of clozapine in reducing psychotic symptoms in refractory schizophrenia patients is widely corroborated by recent studies. In a longitudinal study, clozapine demonstrated a significant reduction in the severity of psychotic symptoms compared to other atypical antipsychotics such as olanzapine and quetiapine, especially in patients who did not adequately respond to these treatments²¹. Additionally, a 2017 meta-analysis confirmed that clozapine is superior in diminishing both positive and negative symptoms of schizophrenia, including a significant reduction in hospitalization rates²². The reduction in suicide rates among patients treated with clozapine is one of its most notable aspects. Recent studies indicate that clozapine reduces the suicide rate in schizophrenic patients more effectively than any other antipsychotic²³. The molecular mechanisms underlying clozapine's antisuicidal effect include modulation of dopaminergic and serotonergic systems and neuroprotective effects that may enhance neuroplasticity²⁴. Clozapine also increases brain levels of N-acetyl aspartate, a marker of neuronal viability, which may explain its ability to reduce suicidal behaviors²⁵.

Clozapine has anti-inflammatory effects that may contribute to its efficacy in improving psychotic symptoms and preventing suicides. Recent studies indicate that clozapine modulates the release of pro-inflammatory cytokines, which may play a role in reducing brain inflammation associated with schizophrenia²⁶. Additionally, clozapine has

shown beneficial effects on neurogenesis and neuroprotection, contributing to its overall efficacy in treating schizophrenia²⁷. Compared to other antipsychotics, clozapine stands out as the only drug with robust evidence of reducing suicides. Comparative studies show that clozapine is superior to olanzapine, risperidone, and quetiapine in preventing suicides, especially in patients with a history of suicide attempts²⁸. Clozapine also has advantages in terms of reducing negative symptoms and improving patients' quality of life²⁹.

The main side effects associated with clozapine use include agranulocytosis, weight gain, and dyslipidemia. Hematological monitoring is essential to early detect agranulocytosis and prevent severe complications³⁰. Despite these challenges, longitudinal studies indicate that clozapine provides superior quality of life for patients, reducing hospitalizations and improving social functionality³¹. Treatment adherence is a critical challenge, often compromised by side effects and the complexity of monitoring regimens. Educational interventions for patients and caregivers are crucial to improving adherence and ensuring treatment efficacy³². Cost-benefit studies suggest that despite higher initial costs due to the need for monitoring, the long-term benefits in terms of reducing hospitalizations and improving quality of life justify the use of clozapine³³. Clozapine also has a positive impact on the cognitive function of patients with schizophrenia, with improvements observed in various cognitive functions³⁴.

The relationship between clozapine and physical health in patients with schizophrenia highlights the need for metabolic monitoring and interventions to mitigate adverse metabolic effects. Clozapine is associated with a significant increase in the risk of metabolic syndrome, requiring dietary and

lifestyle interventions³⁵. Patients' perceptions of clozapine treatment are generally positive, particularly regarding the reduction of psychotic symptoms and prevention of hospitalizations. Many patients report a significant improvement in quality of life and the ability to participate in social and occupational activities³⁶. Genetic factors also influence clozapine efficacy and side effect profiles. Research suggests that genetic variations can affect treatment response and susceptibility to adverse effects, highlighting the importance of personalized approaches³⁷. Patient and caregiver education programs are fundamental to ensuring adherence to clozapine treatment and early detection of adverse effects. These programs should include information on the importance of regular monitoring and strategies for managing side effects³⁸.

The effects of clozapine in refractory schizophrenia patients are notable, with a high response rate in patients who have not responded to other treatments. Clozapine is often effective where other antipsychotics have failed, highlighting its importance in the therapeutic arsenal for schizophrenia³⁹. The role of clozapine in managing psychiatric comorbidities in schizophrenia patients is significant, particularly in cases of depression and suicidal behavior. Studies demonstrate that clozapine is effective in reducing depressive symptoms and preventing suicides, which can be attributed to its unique effects on dopaminergic and serotonergic systems⁴⁰.

Comparisons between clozapine monitoring protocols in different countries reveal variations that can impact treatment efficacy and patient safety. Standardized and rigorous monitoring approaches are essential to ensure safety and maximize the therapeutic benefits of clozapine⁴¹. Ongoing research on new formulations and therapeutic combinations of clozapine aims to minimize side effects and

improve treatment adherence. Innovations such as extended-release clozapine and combinations with other antipsychotic agents or mood stabilizers are being explored to enhance patient outcomes⁴². Ethical issues in clozapine use involve informed consent and the need for continuous monitoring. Patients must be fully informed about the risks and benefits of clozapine treatment, and physicians must ensure that patients understand the importance of adhering to the monitoring regimen⁴³.

CONCLUSION

Clozapine represents a significant advance in the treatment of schizophrenia, especially in patients refractory to other antipsychotics and those at high risk of suicide. Its efficacy in reducing psychotic symptoms and preventing suicides is widely supported by robust evidence. However, the use of clozapine is accompanied by significant challenges, including the need for rigorous monitoring to prevent agranulocytosis and manage adverse metabolic effects. Adherence to treatment is crucial to maximize the therapeutic benefits of clozapine, and patient and caregiver education programs are essential to ensure understanding and compliance with treatment and monitoring regimens. Ongoing research on the molecular mechanisms of clozapine and its clinical applications may provide new insights and further improve patient outcomes.

While clozapine is associated with significant adverse effects, its benefits in reducing hospitalizations, improving social functionality, and preventing suicides justify its use in suitable patients. Multidisciplinary approaches and rigorous monitoring protocols are essential to ensure the safety and efficacy of treatment. The future of clozapine treatment includes exploring new formulations and therapeutic combinations,

as well as developing personalized approaches based on genetic factors and individual risk profiles. Ethical issues related to clozapine use must continue to be addressed, ensuring that patients are fully informed and continuous

monitoring is maintained to prevent severe complications. In conclusion, clozapine is a vital tool in the treatment of schizophrenia, offering renewed hope for refractory patients and those at risk of suicide.

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