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Research Article

Clozapine Protective Effect on Suicide Behavior in Schizophrenics

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Abstract

Introduction: The World Health Organization estimates that, by 2020, about 1.5 million people will die of suicide, representing approximately 2.4% of all deaths worldwide. Suicide is highly associated with psychiatric disorders, including schizophrenia.

Objective: To investigate the protective effect of clozapine in a schizophrenic patient with suicidal behavior.

Method: Non-exhaustive narrative review highlighting the main works published since 2011, in the electronic database MEDLINE, by the use of the keywords, in English, "clozapine", "schizophrenia", "risk", "suicide".

Results: Studies have shown that clozapine is a psychopharmacological alternative of a protective effect on the risk of suicide in schizophrenics. Clozapine is the only atypical antipsychotic approved by the FDA with a prophylactic indication in these psychiatric settings.

Keywords: *Clozapine; Schizophrenia; Risk; Suicide*

Introduction

The World Health Organization estimates that in 2020, suicide will represent approximately 2.4% of the total obits in the world. The highest suicide rates are currently observed in developed countries. However, a large mortality increase in developing countries is estimated, due to the harsh socioeconomic and behavioral changes occurring in these countries. Coupled with this, there is another worrying trend: although suicide rates increase with age, currently younger commit suicide more frequently than elderly people, becoming suicide the main death cause among the 15 to 24 age group [1].

The suicide is intrinsically associated with psychiatric illnesses, particularly with the main affective and psychotic disorders [2].

Schizophrenic patients show a 9% to 13% risk of committing suicide [3]. It is believed that suicide among schizophrenia patients is an impulsive act, caused by a hallucinatory command of delusional thinking. The antipsychotics effect on suicide has been the subject of wide debate, due to the notorious complexity of the suicide risk in psychotic patients. Moreover, due to the inconsistencies among the most research works, which show that antipsychotics can prevent, induce or not have an impact on suicidal behavior [4].

Among the antipsychotic medications, clozapine has been studied coupled with its relation to suicidal behavior in psychotic and schizophrenia patients. The presented results diverge from each other. As an example, Meltzer., *et al.* [3] found studies that conclude a positive effect in clozapine employment to decrease suicidal behavior in schizophrenic patients. On the other hand, the authors also showed investigations that don't achieve such results due to insufficient effects of clozapine on this proposal.

However, some studies limitations such as methodological design and sample size could have affected many of these investigations. This assumption contributes to a better understanding of non-competing results in these studies.

Aim of the Study

In this context, this work aims the investigation of protective clozapine effect in the suicidal behavior in schizophrenic patients, through the conception of a narrative review about this topic.

Methods

The methodology of this paper consists of a narrative non-exhausted narrative, held in March 2020 in the database MEDLINE, where the main published works were investigated. To conceive the search in the database, the keywords were selected according to the classification of Health Sciences Descriptors. The words used for the search consisted of "schizophrenia", "clozapine", "risk" and "suicide". The initial screening resulted in 111 publications. Another screening was done, aiming to reduce the number of papers. For this, some criteria were including as textual modality of the article, study design, clinical trial in humans, full text of free access and write in English. Also, the search was limited between 01/01/2011 to 01/01/2020. Thus, search filtering resulted in 11 publications. After reading and analyzing of respective abstracts, 7 publications were excluded due to the subject deviation to this revision focus. For this reason, just 4 articles were eligible for this review.

The search and selection methodology adopted in this review is illustrated according to the flowchart shown in figure 1.

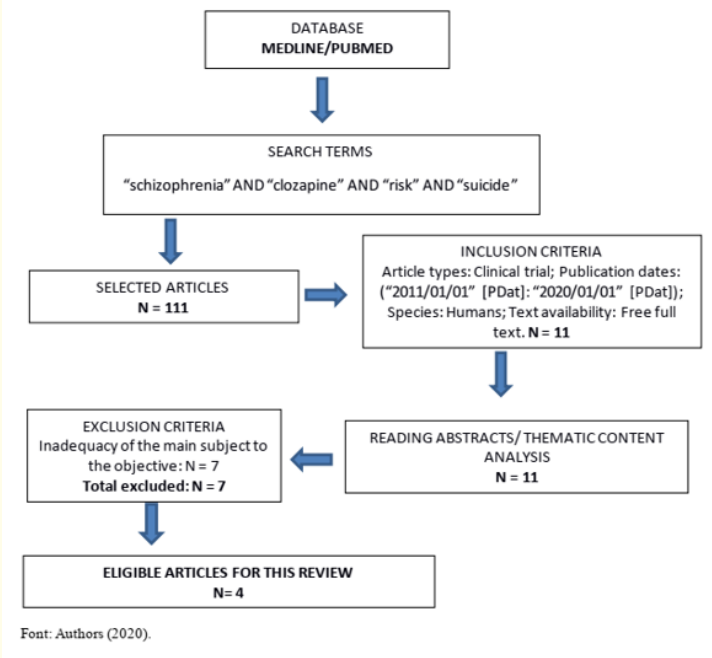


Figure 1: *Search and selection methodology.*

Results

Kasckow., *et al.* [5] performed a bibliographic review to study the therapeutic management of patients with schizophrenia at risk. The evidence seems more favorable to second-generation antipsychotics, especially the clozapine, which is the only approved drug by the US

FDA to prevent suicide in schizophrenic patients. Besides, the treatment of depressive symptoms in these patients also seems to mitigate suicidal thoughts.

Warnez., *et al*. [6] aimed, through its publication, provide information about the role of therapy using clozapine, and discuss the prescription tendency for clozapine since the publication of the latest schizophrenia clinical practice guidelines. In conclusion, clozapine was noted as more effective than first and second-generation antipsychotics in reducing schizophrenia symptoms, including olanzapine. The evidence supports a clear advantage of the clozapine in terms of mortality reduction over other antipsychotics, including the typical ones, as risperidone and quetiapine. In the last 20 years, clinical practice guidelines and algorithms have confirmed that clozapine is the gold standard treatment to schizophrenia resistant against treatment. In Canada and Europe, the low adhesion of clozapine is formalized by the practices of polypharmacy and high prescript drug doses. In contrast, Australia presents a percentage greater than 50% of clozapine use.

Patchan., *et al*. [7] described 3 patient cases with a history of suicide idea and previous attempt, who achieved success in the treatment and did not maintain the suicide idea while submitted to clozapine use. All of them committed suicide after the interruption of the treatment drug. Therefore, it can be concluded the importance of minimizing the risk of abrupt clozapine discontinuation. Coupled with this, further evaluation of ideation and suicidal attempts when the drug is discontinued is recommended.

Pompili., *et al.* [2] collected and critically evaluated the available research, relevant to the topic "treating suicide risk with atypical antipsychotics". The aim of this work was formulating a hypothesis to be tested with further research. As a conclusion, the authors noted that clozapine is the only treatment with regulatory approbation, to decrease the suicide risk in schizophrenic patients. Moreover, the hypothesis that olanzapine, quetiapine, ziprasidone, aripiprazole and asenapine could reduce the suicide risk was supported, even among people with major affective or psychotic disorders. Lastly, it is emphasized that these indications require further studies.

Discussion and Conclusion

Clozapine is an atypical antipsychotic employed in psychotic refractory disorders to other drugs, and its action mechanism as an anti-suicide is unknown. There is a hypothesis that clozapine would normalize serotonin function, whose relation with suicidal acts is better established. Its antidepressant effect, as well as its specificity in suicidal behavior, can be triggered by an increase in the central availability of norepinephrine and dopamine, together with serotonin. This occurs especially in the prefrontal cortex, due to the low regulation of central 5-HT2A receptors, associated with the increase in central serotonin. The negative regulation of 5-HT2A receptors would be common to antipsychotics and antidepressants [4].

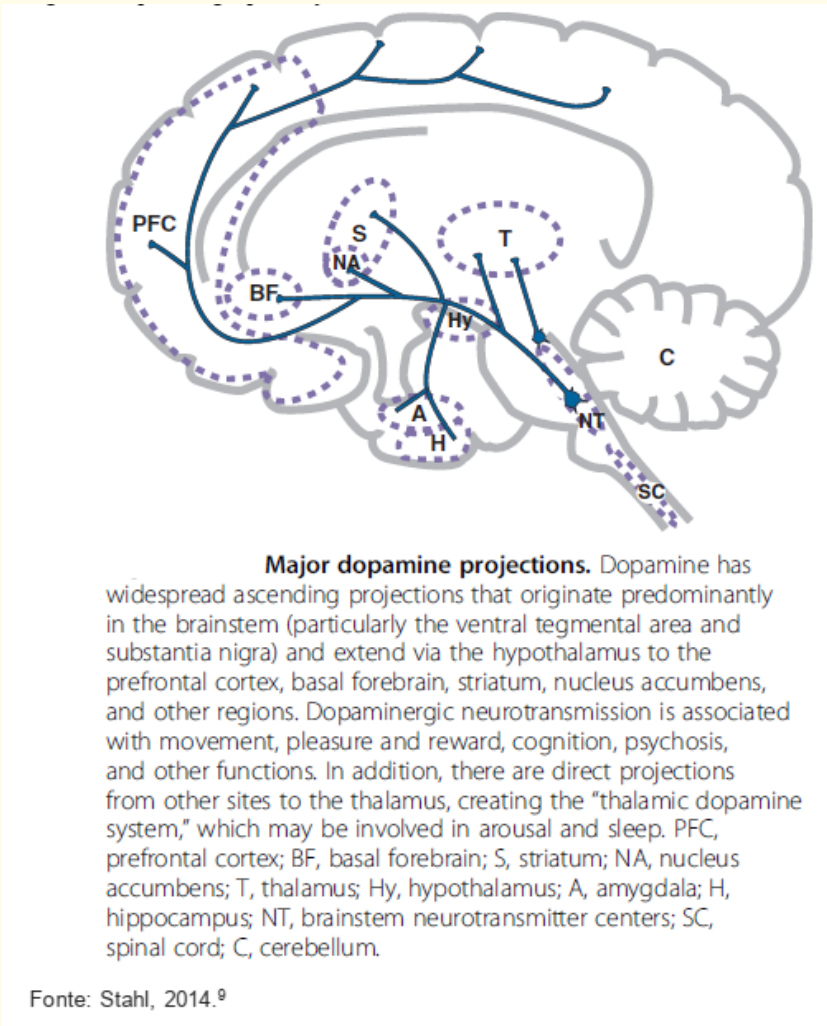
Cordioli., *et al.* [8] point out that clozapine presents low D2 affinity, occupying them only between 40 and 50%, and also blocks other receptors such as D1, D3, D4, cholinergic, serotoninergic, especially 5-HT2A and 5-HT2c. In this way, a different profile from other atypical is demonstrated, contributing to this discussion. Among the most common adverse reactions, constipation, weight gain, hypotension, sialorrhea, drowsiness, dizziness and tachycardia are included. Agranulocytosis is the most worrying adverse reaction, but it comes as a less common reaction (around 1 - 2%), as corroborates Warnez., *et al* (2014). The use of clozapine is contraindicated to uncontrolled epilepsies when leukocyte levels are less than 3,500/mm^3 and/or neutrophils are less than 2,000/mm^3; if agranulocytosis (neutrophils less than 500/mm^3) and myocarditis, as well as the QTc interval, are greater than 500ms. The contraindication of its use is also extended to comatose states, CSN depression, severe liver or heart disease and drug hypersensitivity.

Clozapine is a 5HT2A serotonin - dopamine D2 receptor antagonist or serotonin and dopamine antagonist. This fact attributes to the drug one of the most complex pharmacological profiles of these agents. Clozapine was the first antipsychotic characterized as "atypical",

which presents little or no extrapyramidal side effect. It is characterized by not causing tardive dyskinesia or increased prolactin. In the nigrostriatal dopaminergic pathway and the tuber infundibular dopaminergic pathway, enough dopamine is released to causes partial reversion of the unwanted actions of extra-pyramidal symptoms and hyperprolactinemia. This behavior seems doesn't happen in the mesolimbic dopaminergic pathway, because the antipsychotic actions are exactly effective as conventional antipsychotics [9].

Stahl [9] emphasized the prefrontal cortex as the key point of the dysfunctional brain circuits responsible for the remaining schizophrenia symptoms: The ventromedial prefrontal cortex with negative and affective symptoms; the dorsolateral prefrontal cortex with cognitive symptoms; and the orbitofrontal cortex and its amygdala connections, with aggressive and impulsive symptoms.

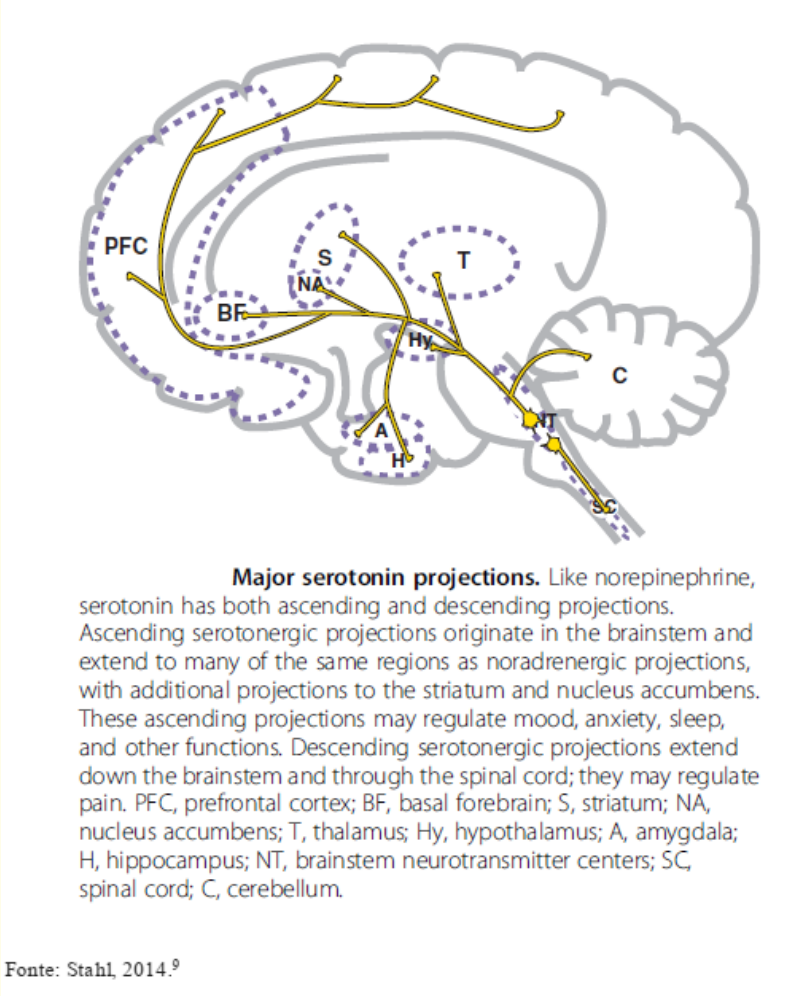
The dopaminergic and serotonergic pathways on the brain are schematically illustrated by figure 2 and 3.



Major dopamine projections. Dopamine has widespread ascending projections that originate predominantly in the brainstem (particularly the ventral tegmental area and substantia nigra) and extend via the hypothalamus to the prefrontal cortex, basal forebrain, striatum, nucleus accumbens, and other regions. Dopaminergic neurotransmission is associated with movement, pleasure and reward, cognition, psychosis, and other functions. In addition, there are direct projections from other sites to the thalamus, creating the "thalamic dopamine system," which may be involved in arousal and sleep. PFC, prefrontal cortex; BF, basal forebrain; S, striatum; NA, nucleus accumbens; T, thalamus; Hy, hypothalamus; A, amygdala; H, hippocampus; NT, brainstem neurotransmitter centers; SC, spinal cord; C, cerebellum.

Fonte: Stahl, 2014.[9]

Figure 2: *Dopaminergic pathway on the brain.*



Major serotonin projections. Like norepinephrine, serotonin has both ascending and descending projections. Ascending serotonergic projections originate in the brainstem and extend to many of the same regions as noradrenergic projections, with additional projections to the striatum and nucleus accumbens. These ascending projections may regulate mood, anxiety, sleep, and other functions. Descending serotonergic projections extend down the brainstem and through the spinal cord; they may regulate pain. PFC, prefrontal cortex; BF, basal forebrain; S, striatum; NA, nucleus accumbens; T, thalamus; Hy, hypothalamus; A, amygdala; H, hippocampus; NT, brainstem neurotransmitter centers; SC, spinal cord; C, cerebellum.

Fonte: Stahl, 2014.[9]

Figure 3: *Serotonergic pathway on the brain.*

Clozapine stands out for achieving favorable results in the suicidal behavior approach, which gave to this drug the indication as "prophylactic" in schizophrenic patients at high risk of committing suicide, granted by Food and Drug Administration (FDA), US [1]. Kasckow., *et al.* [5] and Stahl [9] corroborate this fact through the report of clozapine employment in aggression and violence treatment to psychotic patients.

Kasckow., *et al.* [5] suggest that schizophrenic patients require a thorough assessment of the nature of their suicidal ideation or suicidal behavior, their risk of suicide and what factors are contributing to suicidal symptoms.

Patchan., *et al.* [7] claim that the suicide risk in schizophrenia individuals is 8 to 13 times higher than individuals without psychotic disorders. Also, is pointed a clear need for further studies and clarity in some aspects of the clozapine use to protect against suicidal behavior. According to the authors, schizophrenia is a strong factor risk to suicide; it is estimated that 50% of schizophrenia patients may try suicide and 5 - 10% of them will commit suicide.

Furthermore, Pompili., *et al.* [2] pointed out the other risk factors to suicide. Among them, it can emphasize the poor therapeutic adherence, the association of an affective disorder, the use of psychoactive substances, high intellectual coefficient, high socioeconomic level, severe Parkinsonism, obsessive symptoms, pseudo hallucinations and/or auditory hallucinations. Concerning the inpatients, other risk factors appear, like bad relationships with the medical team and difficulty adapting to the ward environment [5].

According to Kasckow., *et al.* [5] the main treatment objectives are: (i) decrease psychotic symptoms; (ii) reducing depressive symptoms; (iii) relieving the patient's feeling of demoralization and despair; (iv) instill hope, and (v) solve any troubles like substance abuse and anxiety disorders. After hospitalization discharge, it is important to establish psychosocial programs as part of the aftercare plan, to increase the pharmacological treatment.

In dealing with drug treatment with antipsychotics, the clear relation between doses-effect is still unknown. In the use of typical antipsychotics, there are reports of prospective case-control studies, which are focus on the consequences of drug discontinuation. The deposit antipsychotics discontinuation at 18 months presented more self-injurious behavior than patients who were maintained under medication [5].

Some advantages in the use of clozapine over other first-generation antipsychotics, risperidone and quetiapine are reported by studies as Warnez., *et al* [6].

Until now, the action mechanism of atypical antipsychotics has not been elucidated. However, there is a hypothesis that this drug could reduce impulsivity and aggression [2].

Alphs., *et al*. [10] compared the use of clozapine and olanzapine in patients diagnosed with schizophrenia and schizoaffective disorder through a prospective, random and multicenter study, for 2 years. As a rule, typical antipsychotics were not used, once no reduction in the suicidal behavior is demonstrated. Besides, the increase in the risk of the patient presenting akathisia associated with secondary depression was considered. In this study, 980 schizophrenic or schizoaffective disorder patients were evaluated aiming to compare: 1) hospitalization rates for imminent suicide risk; 2) attempted suicides in high-risk patients (previous suicide attempt or hospitalization to prevent the attempt in the last 36 months; moderate or severe suicidal ideation with depressive symptoms; auditory hallucinations ordering self-harm in the last week); 3) suicidal ideation; 4) complete suicides. The patients were medicated for 2 years and randomly distributed, using clozapine or olanzapine. The suicidal reduction risk was preliminarily estimated at up to 85%. As a consequence, the results demonstrated clozapine as a relevant drug to alter the suicidal behavior.

Concerning the use of olanzapine, Pompili., *et al*. (2016) accentuate that it was not possible to rule out benefits associated with this drug, even if they were lower than those observed for clozapine.

Therefore, the reviewed works in this study showed the suicide as the main cause of death in schizophrenic patients. It deserves a highlight to the need of individual evaluation of each case to better define the pharmacologic prescription. In this context, clozapine appears as an alternative to treat schizophrenic patients with suicidal behavior.

Clozapine discontinuation can lead to dramatic and non-intentional consequences. The health improvement of patients under clozapine treatment shows the importance of the drug and how its discontinuation can have catastrophic effects [7].

To contain the increase in suicidal behavior in the human population, especially among those with mental disorders as schizophrenia, and to overcome the limitations of therapeutic approaches, studies are needed to prove the efficacy of different drugs, including antipsychotics. In this way, patient protection could be guaranteed [5].

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