

GENERAL PSYCHIATRY

Key Words: neuroleptic, clozapine, suicide, depression, psychoses

Do Antipsychotic Drugs Influence Suicidal Behavior in Schizophrenia?

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ABSTRACT ~ The literature concerning the net effect of antipsychotic medication on suicidality in patients with schizophrenia is not consistent. This review assesses this problem in the light of relevant research. MEDLINE was used to search for articles written in English from 1964 to 2006. Articles were classified according to the following three orientations: positive, negative, or null effect on suicidality. Several inconsistencies among the studies and methodological difficulties appeared and a singular conclusion on this issue was not possible. Competing properties of various antipsychotic drugs may have differential effects on suicidality. Second-generation antipsychotic agents appear to have a better potential for preventing suicide in schizophrenia, but the relative profile of each drug is yet to be clarified. A good profile to treat hostility, impulsivity, and depression while not provoking extrapyramidal side effects is crucial when choosing an antipsychotic in the presence of suicide risk. The strongest and perhaps unique evidence has been shown for clozapine, which seems to have a clinically relevant advantage over both first- and second-generation antipsychotics for reducing suicidality. Although clozapine has not yet demonstrated a specific preventing effect on completed suicide in patients with schizophrenia, it should be considered when suicide risk is detected in a patient with schizophrenia. *Psychopharmacology Bulletin*. 2007;40(3):128-142.

INTRODUCTION

It is well known that suicidal behavior is a common concomitant of several psychiatric illnesses including schizophrenia. Suicide rates for this illness differ along the studies but the rate seems to be between 10%, which is the generally accepted modal rate,^{1,2} and 5%.³ Suicide-related costs include both financial losses, namely years of lost productivity and general hospital costs, and intangible costs. In this last sense, personal testimonies may do better than statistics when trying to understand this source of suffering and loss.⁴ Moreover, suicidality during life is not only a painful situation for the patient but also a powerful contributor to

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family burden.⁵ Although financial consequences are difficult to quantify in a comprehensive way, some studies have suggested a significant potentiality of second-generation antipsychotics (SGAs)⁶ and, particularly, clozapine,⁷ for ameliorating such costs. This article subjects these assertions to a critical review.

Since antipsychotic treatment is the mainstay of the treatment of schizophrenia, we should know whether and how these drugs influence suicidal behavior. Regrettably, these questions have remained elusive for almost half a century. It is a commonly held opinion that first-generation antipsychotics (FGAs)⁸ and SGAs⁹ have not reduced (or may have even increased) suicidality among schizophrenic patients. However, it is relevant to observe that the magnitude of suicidal risk is hard to establish because of the sporadic nature or the event and inconsistencies across the various studies. Therefore, attempted comparisons may not be reliable and firm conclusions may still be premature.

Soon after their introduction, some studies reported that antipsychotic medications might either have no effect¹⁰ or actually increase the risk of suicide.^{11,12} However, these early negative reports have not been replicated and several studies have not found differences in neuroleptic treatment between suicide and control groups.¹ Indeed, several controlled studies have rejected a negative influence on completed suicide¹³ and have even shown a preventing effect on suicide attempts.^{14,15} More recently, several other studies have indicated that both FGAs and SGAs probably reduce the risk of suicide and suicide attempts in schizophrenia.^{16,17}

One of the most intuitive ways of understanding this issue comes from analyzing the neuroleptic dose-suicide relationship. But again results have varied. One study did not find any association.¹⁸ Three studies have shown a relationship between lower doses and suicide,¹⁹⁻²¹ although the difference was not statistically significant in the second study.²⁰ Finally, one study found higher doses of antipsychotic medications to be associated with suicide,²² while another found this association only for those patients taking depot fluphenazine, probably through extrapyramidal side effects.²³ Therefore, we can conclude that there is not a linear relationship between suicide and neuroleptic dose (or blood level). An explanation for these findings has been suggested by Palmer et al.¹⁶ According to these authors, it would follow an inverted "U" in which very low doses would be ineffective and higher doses might also be associated with higher suicide rates through side effects or by an artifact of the studies, namely, more severe (and suicidal) schizophrenic patients being treated with higher doses of neuroleptics.

Literature suggests that SGAs might have a different effect on schizophrenic suicide than FGAs. Although this is probably true, this article

will not make an a priori assumption that there is a difference, but rather discuss this issue objectively as it has unfolded in the literature to date.

At this point, we can already realize we are facing a complex relationship. It seems that antipsychotic drugs influence suicidal behavior but do not have a net positive effect. Several possibilities can be mentioned:

- (a) Antipsychotic drugs might induce suicidal behavior but:
 - Each antipsychotic agent has a different profile in regard to this negative effect.
 - Other variables mitigate this consequence.
 - The relationship between antipsychotic drugs and suicidality depends on diagnosis.

- (b) Antipsychotic medication can prevent suicidal behavior but:
 - Not all antipsychotic drugs have the same potential for preventing suicide.
 - Other “external” factors interact with their effect.
 - The effect varies among different diagnoses.

As the result of possible combinations of these effects, a noninfluence status may appear as a net effect.

The aim of this review is to analyze whether and how antipsychotic drugs influence suicidal behavior in schizophrenia in the light of relevant research. A better knowledge on this issue is necessary to prevent suicidal risk in patients with schizophrenia.

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