Can Atypical Antipsychotics Reduce Suicide Risk in Patients With Schizophrenia?

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By Eduardo J. Aguilar, MD, PhD [8], Samuel G. Siris, MD [9], and Carmen Leal, MD, PhD [10]

Suicide is a devastating, tragically frequent outcome for persons with varying psychiatric conditions, including schizophrenia. An estimated 5% to 10% of persons with schizophrenia commit suicide and 20% to 50% attempt suicide during their lifetime.\(^1\,^2\) Patients with schizophrenia have more than an 8-fold increased risk of completing suicide (based on the standardized mortality ratio) than the general population.\(^3\)

Atypical antipsychotics are now considered to be a first-line treatment for schizophrenia. It is therefore crucial that we have an evidence-based approach to minimizing suicidal thinking and behavior. We have recently reviewed the relationship between antipsychotic drugs and suicide in patients with schizophrenia, observing that many inconsistencies exist among the studies. This, in turn, prevents any definitive conclusions; the sole exception is clozapine, which should be considered when suicide risk is detected.\(^4\)

Evidence for the antisuicidal effect of atypicals In spite of the vast amount of literature on atypical antipsychotics, there is a dearth of studies evaluating their specific antisuicidal effect. The existing evidence is summarized in Table 1.

Clozapine has the strongest level of evidence for antisuicidal effect. A recent meta-analysis found a lower overall risk of both suicidal behaviors and completed suicide with clozapine as compared with other treatments.\(^5\) However, 3 major caveats merit attention. First, only 6 studies were included and only 1 of these was randomized. Moreover, its conclusions only referred to suicide attempts.\(^6\) Second, we still do not have a comprehensive understanding of this drug's mode of action in preventing suicide. Finally, the more recent the study, the smaller the relative benefit for clozapine was shown. In spite of this, clozapine was the first medical treatment approved by the FDA for reducing the risk of suicidal behaviors in patients with schizophrenia or schizoaffective illness.\(^7\)

Clinical guidelines also support the use of clozapine for reducing suicide risk in patients with schizophrenia. The most recent version of the Texas Medication Algorithm Project antipsychotic algorithm for schizophrenia recommends that persistent symptoms of suicidality should prompt earlier (ie, before the usual 2-trial failures) treatment with clozapine.\(^8\)

Risperidone and olanzapine have generated some evidence that permits their consideration as an
alternative to clozapine in clinical settings. Herings and Erkens\textsuperscript{15} demonstrated a 4-fold increase in suicide attempts for patients who interrupt or stop treatment with these drugs. Similarly, another study found a significant association between good versus poor adherence with these atypical antipsychotics and quetiapine, as well as a decreased risk of suicidal behaviors.\textsuperscript{16} In addition, risperidone and olanzapine have been reported to be safer in overdose than clozapine.\textsuperscript{17}

Although no meta-analysis or randomized study supports the use of risperidone for preventing suicide, an interesting study analyzing deaths due to poisoning involving antipsychotics in England and Wales (1993 through 2002) reported relevant data on deaths per million prescriptions for quetiapine (31.3 per million), amisulpride (17.0 per million), olanzapine (13.2 per million), flupentixol (3.3 per million), and risperidone (1.1 per million).\textsuperscript{18}

The strongest evidence for risperidone comes from retrospective studies that compare it with typical antipsychotics\textsuperscript{19} and olanzapine (nonsignificant differences).\textsuperscript{20} There is not enough information about the long-acting preparation of risperidone, but conclusions may differ. For example, in a subgroup analysis of the open-label Switch to Risperidone Microspheres trial, the authors reported a suicide attempt that was possibly related to this drug.\textsuperscript{21} On the other hand, 2 prospective, randomized, double-blind studies supported the superiority of olanzapine compared with haloperidol\textsuperscript{22} and risperidone\textsuperscript{23} in preventing suicide attempts.

There are not enough data on the rest of the atypical antipsychotics to suggest their effectiveness and, thus, potential use for treating suicidal tendencies in patients with schizophrenia. One review reported a potential antisuicidal effect of quetiapine,\textsuperscript{24} but the data are lacking for this drug if studies on affective disorders are excluded. Findings from a recent, multicenter, observational study involving 8608 patients showed that suicide mortality rates with sertindole in real-life practice are not higher than those found in clinical trials.\textsuperscript{25} Finally, while a case report recently suggested a suicide-potentiating effect with aripiprazole,\textsuperscript{26} another study reported a good safety profile in cases of overdose.\textsuperscript{27}

**Affective symptoms**

Hopelessness and other affective symptoms such as depression or low self-esteem are probably the most common contributors to suicide in patients who have chronic schizophrenia.\textsuperscript{1,28} This is the case even when psychotic motivations predominate (Table 2).\textsuperscript{29} There is good evidence about the potential antidepressant properties of atypical antipsychotics, but we should not forget that depression from antipsychotic adverse effects can also occur.\textsuperscript{7} In fact, dysphoric responses to both typical and atypical antipsychotics may, and often do, occur with high individual variability. Dynamic interactions between the state of the dopamine receptor and the pharmacological properties of conventional antipsychotics may be responsible for the variability in dysphoric responses.\textsuperscript{30}

Recommendations to use atypical antipsychotics for the treatment of depressive symptoms are complicated because most of them (except clozapine) can potentially induce mania, an effect that has not been reported for typical antipsychotics.\textsuperscript{31} This phenomenon seems to be particularly relevant for ziprasidone,\textsuperscript{31} which, curiously, can also induce depression in patients with schizophrenia.\textsuperscript{32} This paradoxical finding is not unique to ziprasidone among the atypical antipsychotics, since depression associated with quetiapine has also been reported in patients with schizophrenia.\textsuperscript{33}

**Active psychosis**

Some patients with schizophrenia attempt and/or complete suicide in response to psychotic experiences.\textsuperscript{34,35} The strongest evidence among these symptoms resides in command auditory hallucinations.\textsuperscript{28}

With the possible exception of clozapine, atypical antipsychotics are usually believed to have similar effectiveness in treating the positive symptoms of schizophrenia.\textsuperscript{36}

**Agitation-hostility**
Agitation and motor restlessness have been linked to suicidal behaviors.\(^2\) A recent study by McGirr and Turecki\(^3\) used the psychological autopsy method to examine 527 consecutive suicides, 43 of whom met criteria for schizophrenia and schizoaffective disorder. Elevated levels of impulsive-aggressive personality traits, considered an indicator of an elevated risk of suicide in other diagnostic categories, were found in these patients.

The effect of atypical antipsychotics on improving agitation states and hostility may be used to reduce the risk of suicidal behavior. Again, the strongest level of evidence lies with clozapine. A double-blind, randomized clinical trial has demonstrated the relative advantage of clozapine over other antipsychotics (at least haloperidol and risperidone) as a specific antihostility agent.\(^3\) Not surprisingly, clozapine is recommended by the American Psychiatric Association's practice guidelines for both persistent suicidal ideation or behavior and persistent hostility and aggressive behavior.\(^3\)

Medications such as olanzapine and quetiapine could also be considered when treating agitation or hostility; the former may be particularly helpful in the emergency department, where intramuscular olanzapine is frequently used for these purposes.

**Parkinsonism and akathisia**

There is no strong evidence linking extrapyramidal symptoms and suicidal behaviors. An international prospective study showed that both the severity of depression and the severity of parkinsonism were among the most predictive variables for suicidal behaviors.\(^3\) These conclusions deserve a note of caution, however, since akinesia (which, along with rigidity and tremor, is part of parkinsonism) may not necessarily be related to suicide. In fact, it could be that it might even be a protective factor against suicidal behavior, although not against suicidal thinking.

On the other hand, another study failed to find any association between either akathisia or parkinsonism and suicidality in a study of patients with treatment-resistant schizophrenia.\(^4\) A previous review also concluded that akathisia could neither be excluded as a causal factor for suicidal behaviors nor could it be unequivocally linked to it.\(^4\)

**Evidence for the antidepressant effect of atypical antipsychotics**

Since treatment of depressive symptoms gathers the highest level of evidence, the specific profile of each atypical antipsychotic has been reviewed and summarized in Table 3. Flupentixol and amisulpride are included in this section since some interesting data have appeared on these drugs and some authors consider them as partial atypicals.

Many clinicians would agree that olanzapine should be considered when treating depressive symptoms in patients with schizophrenia or with an affective psychosis. The evidence for this assertion comes from 2 empowered, randomized, double-blind studies. In the first study, improvements were found in depressive symptoms with both haloperidol and olanzapine; patients treated with the latter showed significantly greater reductions in depressive symptoms.\(^2\) A second, more recent study in patients with schizophrenia or schizoaffective disorder found that patients treated with olanzapine and ziprasidone showed significant improvement in prominent depressive symptoms. Although group differences were not statistically significant, a significantly higher proportion of patients who received olanzapine completed the study and continued taking the medication longer, compared with patients who received ziprasidone.\(^3\)

There is a similar level of evidence for risperidone, but there have been more studies of this medication. Double-blind, randomized studies that compared this drug with olanzapine have found superiority of olanzapine,\(^4\) nonsignificant differences,\(^5\) and superiority of risperidone.\(^6\) Peuskens and colleagues\(^7\) analyzed pooled data (N = 1294) from 6 double-blind trials and found risperidone to be superior in comparison to haloperidol or placebo in reducing the Positive and Negative Syndrome Scale anxious/depressive factor. Myers and Thase\(^8\) reviewed 7 randomized, controlled trials of risperidone (vs haloperidol, olanzapine, and clozapine) in patients with schizophrenia or schizoaffective disorders and concluded that risperidone was efficacious in the treatment of depressive symptoms in these pathologies; the greatest support came from the haloperidol studies. More recently, a study that reanalyzed data from the North American risperidone trial showed similar
Examining the only long-acting atypical antipsychotics (risperidone microspheres) is relevant at this point, since poor adherence to treatment has also been linked with suicidal risk. Several open-label, uncontrolled studies have demonstrated that long-acting risperidone improves anxiety and depression symptoms in stable patients with schizophrenia and/or schizoaffective disorder.

Amisulpride also has a fairly good level of evidence for treating depressive symptoms in schizophrenia. Peusken and colleagues compiled data from 3 short-term, double-blind, randomized studies. They found a greater improvement in the anxious/depressive factor for amisulpride compared with haloperidol and risperidone in patients with acute exacerbations of schizophrenia. Eighty-five adults fulfilling DSM-IV criteria for schizophrenia and presenting with a depressive episode were randomized to amisulpride or olanzapine for 8 weeks. There were no significant differences in depressive symptom improvements between the 2 drugs. A multicenter, double-blind, randomized study that evaluated patients with chronic schizophrenia (DSM-IV) showed that amisulpride was not inferior to risperidone in improving symptoms of depression. Finally, findings from an open-label, 12-week study of patients who were initially treated with risperidone and were randomized to a risperidone-continuation group or an amisulpride-switch group showed that improvements in depressive symptoms were significantly greater in the amisulpride-switch group than in the risperidone-continuation group.

Quetiapine is superior to placebo in reducing anxiety, depression, and hostility but, to the best of our knowledge, it has not yet been compared with another atypical antipsychotic for its antidepressant effect in schizophrenia. This efficacy for treatment of affective symptoms is maintained in long-term treatment. Additional evidence comes from a multicenter, double-blind, randomized trial of quetiapine compared with high doses of haloperidol (20 mg/d). The study demonstrated superiority of quetiapine in reducing depressive symptoms in patients with refractory schizophrenia. Haloperidol dosage is a strong limitation of this study, since higher doses of antipsychotics could be associated with worsening of depressive symptoms.

Somewhat surprisingly, scarce attention has been paid to the effect of clozapine on depressive symptoms. Indirect data come from the study by Meltzer and colleagues. These investigators reported that patients who received clozapine required less concomitant treatment with antidepressants than the patients who were treated with olanzapine.

For the rest of the compounds, the highest level of evidence corresponds to flupentixol and ziprasidone, although very little information is available. In a randomized, double-blind, multicenter study of patients with predominant negative symptoms, flupentixol demonstrated noninferiority compared with risperidone. Similarly, in a 6-week, multicenter, double-blind, parallel-design, flexible-dose trial, ziprasidone and olanzapine showed comparable efficacy in reducing depressive symptoms of acutely ill inpatients with schizophrenia or schizoaffective disorder.

Aripiprazole is also a potentially good choice for treating depressive symptoms in patients with schizophrenia, but there are no comparisons with other atypical antipsychotics. Relevant indirect data come from a recent study of aripiprazole augmentation in a group of outpatients who had chronic schizophrenia and were treated with clozapine. The researchers found that the augmentation led to a substantial improvement in depressive symptoms. Furthermore, analysis of data from 2 randomized, double-blind, multicenter studies of 1294 patients with chronic schizophrenia in acute relapse who had previously responded to antipsychotic medications suggests that aripiprazole is superior to haloperidol in improving depressive symptoms.

Conclusion
Although clozapine is the only strictly evidence-based treatment for reducing the risk of suicide in schizophrenia, several other atypical antipsychotics may be reasonable options when treating specific symptoms associated with suicide risk, such as depressive symptoms. Olanzapine, risperidone, and amisulpride also may be helpful. These and the other atypical antipsychotics need to be compared in head-to-head randomized and, preferably, independent studies. Further reviews and meta-analyses will confirm the steps for preventing suicide through evidence-based use of these drugs.
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