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Second-Generation Antipsychotics and Suicide: A Commentary

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More than 48,000 people in the United States die of suicide per year.[1] Suicide rates are progressively rising,[2] and recent research has identified that suicide rates are consistently underreported,[3] further highlighting the need for interventions to reduce suicide. There are robust data showing the potential suicide reducing properties of lithium[4] and clozapine,[5] the latter being the only medication with an FDA indication for reducing suicidal behaviors; however, literature on the suicide reducing effects of other pharmacologic agents is less clear. Second-generation antipsychotics (SGAs) are of particular interest, as early research showed promising results for potential associations with decreased suicide. However, further research on the effects of non-clozapine SGAs on suicidality has shown mixed results. Additionally, due to methodological difficulties, prospective controlled trials directly examining the effects of medications on suicidality are limited, and thus much of the data on the effects of SGAs on suicide has been obtained from retrospective cohort studies and epidemiologic data such as population based cross-sectional studies. The results of such research can be difficult for clinicians to interpret for implementation into clinical practice. Thus, a targeted literature review was conducted, and a summarizing commentary is presented in an effort to clarify the effects of non-clozapine SGAs on suicide, including both suicidal ideations and suicidal behaviors.

Initial studies examining SGAs showed promising results for suicide reducing effects, including an early randomized controlled trial (RCT) of the SGA olanzapine compared to the first-generation antipsychotic haloperidol, which found a 2.3-fold decrease in suicide attempts in individuals on olanzapine.[6] Since that time, a number of retrospective case control and population based cross-sectional studies have shown evidence for an association between SGAs and decreased suicidality. These include a retrospective case control cohort which found that SGAs were associated with a 3.54 times reduction in attempted suicide[7]; an epidemiologic study that showed individuals with schizophrenia who discontinued/interrupted treatment with an SGA were 4 times more likely to attempt suicide than those who remained on SGAs[8]; a retrospective cohort study which found that individuals prescribed SGAs were less likely to attempt suicide than those on first-generation antipsychotics[9]; and a large case-control study which found that individuals treated with an SGA had a 71% lower risk of death by suicide than individuals not treated with SGAs.[10]

However, not all studies examining the effects of antipsychotics on suicide have shown efficacy in reducing suicidality, particularly when examining their use in disorders other than schizophrenia/schizoaffective disorder. One study of veterans with bipolar affective disorder showed that those treated with antipsychotics had higher suicide rates when compared to individuals on monotherapy mood stabilizers and compared to individuals on mood stabilizers plus antipsychotics.[11] Another retrospective study looking at the effects of lithium, divalproex, and atypical antipsychotics on veterans with bipolar disorder found that individuals on antipsychotics had higher rates of suicide attempts compared to individuals on lithium or divalproex.[12] It is of note, however, that neither of these studies accounted for illness severity.

The above studies focused on antipsychotics as a class, and much of the literature supporting the SGA classwide suicide reducing effects includes clozapine. The inclusion of clozapine with other SGAs is problematic, as the known suicide-reducing properties of clozapine may bias classwide results in favor of suicide reducing properties that may not exist with other SGAs. When examining non-clozapine SGAs, data are mixed and are drug specific. Quetiapine appears to have the most evidence for beneficial effects in relation to suicide, although data remain limited. Multiple RCTs have shown a decrease in suicidal ideations in individuals on quetiapine, as evidenced by reductions on suicide items of rating scales, including for the treatment of bipolar disorder[13,14] and in major depressive disorder (MDD).[15] However, a pooled analysis of RCTs of patients with MDD treated with quetiapine found no statistically significant differences in suicidal *behaviors*.[16] These results suggest that quetiapine may have beneficial effects on decreasing suicidal ideations, yet supporting evidence for a reduction in suicide attempts or completed suicides is lacking. However, it is of note that rates of emergent suicidal behaviors in the quetiapine trials were low, and a lack of sufficient power for meaningful analysis of suicidal behaviors must be considered when interpreting the data.

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Other SGAs with previously reported antisuicidal properties include olanzapine, which has shown an association with a reduced risk of suicidal behaviors when compared to both haloperidol[6] and risperidone,[17] and aripiprazole, which has shown an association with decreased suicidal ideation in individuals with MDD[18] as well as a decrease in completed suicide in individuals with schizophrenia.[19] Pompili et al conducted a systematic review examining individual SGAs and suicidal behaviors and found some degree of evidence for a potential suicide risk reducing effect of olanzapine, quetiapine, ziprasidone, and aripiprazole (asenapine was also included in this report; however, the cited studies did not specifically address suicide).[20] Further data on asenapine are limited, and a large meta-analysis of 22 ziprasidone studies found no significant difference in suicidal ideation or suicide attempts between individuals treated with ziprasidone vs placebo.[21]

There is a paucity of literature regarding the effects on suicide with the newer SGAs, defined for this purpose as SGAs that have been US FDA approved from 2009 to present. MEDLINE searches for publications with titles including the terms *suicide* plus the following "newer" SGAs all failed to yield a single result: brexpiprazole, cariprazine, iloperidone, lurasidone, and paliperidone, with the exception of 1 manuscript reporting on a suicide attempt by ingestion of paliperidone. As such, information on the potential suicide reducing effects of these agents is particularly limited.

Although individual studies have shown positive results for SGAs decreasing suicidal ideations and behaviors, meta-analyses and systematic reviews have not yielded as promising results when looking at suicidal behaviors, particularly when excluding clozapine. A meta-analysis of FDA databases looking at over 10,000 patients showed no significant difference between drug and placebo for rates of completed suicide or suicide attempts with olanzapine, risperidone, or quetiapine,[22] and a recent comparative analysis of a population based cohort from 2 nationwide registries evaluating 10 different antipsychotics across greater than 90,000 individuals with schizophrenia found clozapine to be the only antipsychotic associated with decreased attempted or completed suicide.[23]

The above studies identified in this targeted review have often yielded mixed results, and a further analysis of the methodologies suggests that these contradictions arise due to multiple confounders. The first is through the examination of varying outcome measures of interest. The often-used term *suicidality* has a broad definition and may consist of symptom severity ranging from suicidal ideations (which may be inclusive of merely passive death wishes) up to and including completed suicides. Second, the specific psychopharmacologic agent appears to be more important than a classwide effect. Since it is known that SGAs have notably different chemical, pharmacokinetic, and pharmacodynamic properties, this finding is not surprising as it is likely that different SGAs may have markedly different effects on suicidal thoughts and behaviors. Third, the specific mental health disorder appears to have a notable influence on the potential suicide reducing properties of the agents in question. SGAs are commonly used both on and "off label" for a number of conditions including psychotic disorders such as schizophrenia, unipolar depressive disorders, and bipolar disorder. The current literature suggests that the effects of SGAs on suicidal ideation and suicidal behaviors may be distinctly different based on the underlying psychiatric diagnoses of the cohort receiving treatment.

Thus, when reporting on the effects of SGAs on suicidality, it is prudent to differentiate the specific study populations and the specific outcome measure examined. Non-clozapine SGAs, as a class, appear to have the strongest association with a reduction in *suicidal ideation* in individuals with schizophrenia and schizoaffective disorder and a smaller degree of evidence for reducing *suicide attempts* and *completed suicides* in this population. Olanzapine, quetiapine, and aripiprazole may have particularly beneficial suicidality reducing properties over other non-clozapine SGAs, although the degree of evidence is modest. Alternatively, some studies suggest that SGAs as a class may be associated with increased suicidality when used for the treatment of bipolar disorder, particularly when used as monotherapy, although future studies must account for illness severity, a potential confounder that has been omitted from previous reports. Specific SGAs, particularly quetiapine and aripiprazole, may have suicide reducing properties for individuals with MDD, with a stronger degree of evidence showing an association with decreased *suicidal ideations* than with decreased *suicidal behaviors*; more studies are needed.

Perhaps the most notable finding from this targeted literature review is the striking lack of prospective RCTs directly examining suicidal ideations and suicidal behaviors as a primary outcome measure. Apart from clozapine, not a single SGA has adequate, prospective controlled trials examining the effects of the pharmacologic agent on suicide. Although methodological challenges are indeed significant, rising national suicide rates coupled with discrepancies in the current medical literature make the need for long-term prospective controlled trials examining interventions to reduce suicide imperative. In the absence of such data, clozapine remains the only SGA with data robust enough to support its use specifically for the purpose of decreasing suicidal behaviors and as such remains the preferred agent for individuals with psychotic disorders deemed high risk for suicide. However, for individuals who are not appropriate clozapine candidates, the literature suggests that olanzapine, quetiapine, or aripiprazole may be preferred over other SGAs, although the degree of evidence is modest and lacks the support of prospective clinical trials.

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