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Research report

Subtypes of antipsychotics and suicidal behavior in bipolar disorder

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ABSTRACT

Objective: Antipsychotics are commonly used in bipolar disorder, with newer (SGA) agents increasingly replacing FGA antipsychotics, particularly in bipolar depression. There are few data on differences between FGA and SGA antipsychotics in terms of their relationship to suicidal behavior in bipolar disorder.
Method: This was a retrospective chart review of 161 bipolar veterans treated naturalistically with antipsychotics at a university-affiliated VA hospital and clinics for up to 8 years. Charts were reviewed to determine monthly antipsychotic use and occurrence of suicidal behavior: completed suicide, attempted suicide or hospitalization to prevent suicide. Suicidal behavior events were compared across patients during treatment with individual antipsychotics and FGAs or SGAs as a class.
Results: Non-lethal suicide events were more common during FGA than SGA monotherapy (9 events/110 months of exposure vs. 6 events/381 months of exposure; $\chi^2=9.65$, $p=0.002$). Suicide event rates did not differ between FGAs and SGAs when used in conjunction with mood stabilizers. Event rates were lower with lithium than anticonvulsants when used in conjunction with antipsychotics. No differences were found between olanzapine, risperidone and quetiapine.
Limitations: The retrospective chart review methodology may have led to confounding by indication and diagnostic inaccuracy. No completed suicides occurred. Study participants were primarily male veterans. Results may not be generalizable to SGAs marketed since 2003.
Conclusions: FGA antipsychotic monotherapy may be associated with higher suicidal behavior risk than SGA antipsychotic monotherapy. Antipsychotics used in conjunction with mood stabilizers, particularly lithium, are associated with lower rates, independent of antipsychotic subtype.
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1. Introduction

Antipsychotics are commonly prescribed for bipolar patients, and in recent years, second generation (SGA) antipsychotics have largely replaced first generation/conventional (FGA) agents (Sankaranarayanan and Puumala, 2007). These agents are also replacing traditional mood stabilizers such as lithium, divalproex and carbamazepine (Depp et al., 2008; Pillarella et al., 2012), not only for mania and mixed states, but also for the treatment of bipolar depression (Keck, 2005). Risperidone, olanzapine, quetiapine, ziprazidone, aripiprazole and asenapine have been approved by the US FDA for treatment of acute mania or mixed states; aripiprazole, olanzapine, long-acting injectable risperidone, asenapine and both quetiapine and ziprasidone adjunctively with lithium or divalproex for maintenance treatment; and quetiapine and olanzapine+fluoxetine for acute bipolar depression (3). Recent treatment guidelines include SGAs as first line agents in their recommendations for treatment of acute mania and bipolar depression, and as second line for maintenance treatment (Connolly and Thase, 2011; Nivoli, 2011).

Despite these developments, there is little known about the impact of this group of medications on suicidal behavior, among the most serious outcomes in bipolar illness. Clozapine is indicated for treatment of suicidality in either schizophrenia or schizoaffective disorder (presumably including bipolar type), and this drug outperformed olanzapine in reducing suicide attempts and hospitalizations for suicidality in the studies that led to its approval for this indication (Meltzer et al., 2003; Hennen and Baldessarini, 2005; Modestin et al., 2005). Clozapine, but not olanzapine, risperidone or quetiapine, was found to reduce risk of

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suicide in schizophrenia in one cohort study using the Federal Register database in Finland (Haukka et al., 2008). However, another study on a smaller cohort from the same database did not find such differences (Tiihonen et al., 2006). Clozapine is not used often in bipolar disorder, and its possibly anti-suicidal properties have not been specifically studied in this condition.

For SGAs other than clozapine, some investigators have found benefit, or at least neutral effect on non-lethal suicidal behavior in bipolar disorder. In a long-term prospective study in bipolar patients, Vieta et al. (2008) did not find an effect of long-acting injectable risperidone on suicide events, although the number was small ($N=28$). Houston et al. (2006) found a greater reduction in mean Hamilton Depression Rating Scale (Hamilton, 1967) Suicidality Item 3 score 1–2 weeks after addition of olanzapine, compared with placebo, to mood stabilizer in 58 bipolar mixed patients. In the Tohen et al. (2005) randomized, double blind comparison of lithium to olanzapine as maintenance treatment in bipolar I patients who remitted following 12 weeks of open label combination treatment with both agents, 1/214 patients on lithium committed suicide, and 0/217 patients on olanzapine, although other suicidal behavior outcomes were not reported. In a short-term, controlled trial for bipolar depression, Calabrese et al. (2005) found greater reduction in suicidality ratings in quetiapine, compared with placebo treated patients. In a case control study of a large group of schizophrenic and schizoaffective patients admitted to hospital, Barak et al. (2004) reported that patients who had attempted suicide had a lower rate of exposure to SGA antipsychotics than a group who had not attempted suicide, suggesting the possibility of a protective effect. Adherence with antipsychotics appears to be associated with reduced risk for suicide in patients with schizophrenia (Tiihonen et al., 2006; Ward et al., 2006). In contrast to the possible protective findings for SGAs, Goldberg et al. (2005) reported from STEP-BD that at baseline, suicidal ideation was more prevalent among patients who were taking a second generation antipsychotic than among those who were not (26% vs. 17%).

SGAs have undergone trials in unipolar depression as adjuncts to antidepressants. Reports on trials with risperidone (Reeves et al., 2008), extended-release quetiapine (Bauer et al., 2009), and aripiprazole (Berman et al., 2007; Marcus et al., 2008) for this indication have found no increases in various measures of suicidality, although these short-term, industry-sponsored trials have excluded patients with significant suicide risk.

Prior to the advent of SGAs, FGAs were widely used in bipolar disorder as adjuncts to lithium or in patients intolerant of lithium. Chlorpromazine and haloperidol have FDA indications for acute mania. Soon after their entry into the market, SGAs were widely used in preference to FGAs for schizophrenia because of their reduced risks of EPS. Later studies purported advantages in terms of antipsychotic and antimanic efficacy as well. With respect to their use in schizophrenia, however, two large, randomized naturalistic effectiveness studies failed to find reliable differences between SGAs and FGAs, and confirmed clinicians' experiences of the greater metabolic syndrome risk burden with several of the newer drugs (Lewis and Lieberman, 2008). Thus, most recently, the "pendulum" may be swinging back to the use of FGAs for many patients for whom there are clinical indications for an antipsychotic (Pringsheim et al., 2011).

There have been few comparisons of suicidal behavior during treatment with FGAs versus SGAs in schizophrenia, and none in bipolar disorder. Altamura et al. (2003) conducted a retrospective chart review of 103 outpatients with schizophrenia and compared antipsychotic use histories between those with and without a history of suicide attempt. Patients with suicide attempt histories were more likely to be using an FGA currently and those without suicide attempt history, an SGA, including clozapine. Lieberman et al. (2003) and Tollefson et al. (1998) found more improvement in depressive symptoms in patients with schizophrenia or schizoaffective disorder treated with olanzapine, compared with those treated with haloperidol. Suicidality was not assessed in these trials.

In bipolar disorder, antipsychotic use is common, although patterns of use vary widely in the USA and Europe. In a survey of prescriptions for bipolar patients in the USA, Baldessarini et al. (2008) found that 63% were prescribed an antipsychotic. This was the case for only 10% of bipolar patients in Germany during a similar time period (Quante et al., 2010). In another study, bipolar outpatients in the US were more commonly prescribed SGAs than those in Germany and the Netherlands (51% vs. 33%), and less commonly prescribed FGAs (11% vs. 19%) (Post et al., 2011). Perhaps most notably, FGAs are still used frequently in bipolar disorder in both the US and in Europe.

To our knowledge, there are no published data on the effect of FGA antipsychotics on suicidal behavior specifically in bipolar patients, the comparative effect of FGAs vs. SGAs, nor the relative effect of different SGAs aside from the studies quoted above. There have been findings from antipsychotic studies in bipolar disorder suggesting differential effects on depressive symptoms with different antipsychotic subtypes, however. In the EMBLEM Study, Novick et al. (2010) found greater improvement in the HAMD-5 during 6 weeks of treatment for acute mania for olanzapine-treated ($N=209$), compared with risperidone-treated ($N=36$) patients.

In our retrospective review of records of 405 longitudinally treated bipolar veterans, we found that the rate of non-lethal suicidal behavior (attempts and hospitalizations for suicide potential) was lowest during mood stabilizer monotherapy (lithium, valproate/divalproex, or carbamazepine), intermediate during mood stabilizer in combination with antipsychotic, and highest during antipsychotic monotherapy (Yerevanian et al., 2007a). In that report, we considered only antipsychotics as a class, and did not assess differences between antipsychotic subtypes.

The aims of the present study are thus to compare rates of suicidal behavior during treatment of bipolar patients with FGA vs. SGA antipsychotics, and assess differences in these rates during treatment with individual SGAs. Rates during both antipsychotic monotherapy and during antipsychotic+mood stabilizer combination therapy were considered. Since there were no completed suicides in our patients during treatment with any antipsychotic, only the relationships between antipsychotics and non-lethal suicidal behavior are described.

2. Material and methods

The study was a retrospective chart review analysis of bipolar patients treated naturalistically at the Veterans Administration Greater Los Angeles Healthcare System (VAGLAHS). The Computerized Patient Record System (CPRS) in use at the facility since 1994 includes progress notes by all treating personnel, discharge summaries of any hospitalizations, laboratory tests, records of medications dispensed including refills with dates, patient problem lists, demographic and other data. "Remote data" from other VA medical centers where patients may have received care were also available. The research was approved by the VAGLAHS Human Subjects Research Committee, and the methodology detailed previously (Yerevanian et al., 2007b).

Briefly, the period studied was 1994 to December 31, 2002. Included patients had a chart diagnosis of Bipolar Disorder Type I or II, Schizoaffective Disorder Bipolar type or Bipolar NOS. Patients with cyclothymia, antidepressant-induced mania, or mania specified as