



Research report

Suicide attempts in veterans with bipolar disorder during treatment with lithium, divalproex, and atypical antipsychotics



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ABSTRACT

Suicide attempt rates were assessed in 1306 subjects in this 6 year retrospective study of Bipolar disorder. Participants were Veterans from 5 different Veterans Administration Hospitals who met criteria for bipolar type 1 or 2 and who had at least one prescription for lithium or divalproex or both during the study period. This study focused on the impact of atypical antipsychotics on the suicide attempt rate when used in addition to or in place of lithium or divalproex. Medication exposure was calculated using computerized pharmacy records. Suicide attempts were established through chart review including emergency room records, inpatient records, and outpatient records. There were a total of 117 suicide attempts and 2 suicide completions during the study period. Most attempts (59%) occurred when patients were on no medications. Nearly 90% of subjects spent an average of 45 months during the 6 year period on none of the aforementioned medications. The lowest percentage of suicide attempts (15%) occurred while on lithium, 21% while on divalproex and 24% while on atypical antipsychotics. When total months of exposure were taken into account, the lowest attempt rate occurred on lithium plus divalproex (6.3 attempts per 10,000 months of exposure), followed by divalproex alone (7.0 attempts/10,000 months of exposure), and lithium alone (7.7 attempts per 10,000 months of exposure). Patients on atypical antipsychotics alone had an attempt rate of 26.1 attempts per 10,000 months of exposure. In this study, lithium and divalproex provided protection against suicide attempts. Results need to be replicated in future prospective studies and clearly strategies for improving medication compliance among veterans are warranted.

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1. Introduction

Bipolar disorder can be a debilitating illness with significant morbidity and mortality risk due to suicide. The risk of suicide attempts is 3.9% annually with a corresponding rate of completions of 1% annually (Baldessarini and Pompili, 2006). This high lethality ratio, defined as the ratio of suicide attempts to completions, reflects the seriousness of all suicide attempts in bipolar disorder (Baldessarini and Pompili, 2006).

Studies have focused on understanding the factors that increase suicide risk in an effort to curb the excessive mortality rate. Those results suggest that delayed or misdiagnosis, co-morbid substance abuse, and poor medication compliance contribute to less than optimal treatment (Goodwin and Jamison, 2007). Also, the misconception that bipolar type II is a less malignant form of bipolar illness may have led to an underestimation of suicide risk with this subtype (Novick et al., 2010). Studies of the clinical state of bipolar disorder have identified agitated depression or mixed affective states as being particularly high risk situations for suicide attempts and completions (McElroy et al., 2006).

An important area of research has been the impact of medications on suicide risk. Controlled, open-label, and retrospective studies have convincingly demonstrated that long term lithium treatment prevents suicide in bipolar disorder (both types I and II).

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Baldessarini et al. (2006) conducted a meta-analysis of all studies which provided information on suicidal behaviors during lithium treatment. Both open label and controlled trials, with and without a comparator treatment were included in this analysis. In 31 studies of lithium treatment in subjects with affective illness, the risk of attempted or completed suicide was 5-fold lower during treatment with lithium (RR=4.91, 95% CI 3.82–6.31, $p < 0.0001$). The results were sustained when the groups were divided into diagnostic groups (bipolar versus other affective illness). He also found a reduction in the lethality index with lithium, with the ratio of attempts to suicides increasing 2.5 fold (6.94%/year versus 2.79%/year). A second meta-analysis (Cipriani et al., 2005) of 32 randomized controlled trials of lithium for mood disorders also demonstrated a significant reduction in both suicide (60% decrease) and in deliberate self harm (70% decrease) with lithium.

How do other medications used to treat bipolar disorder compared to lithium in terms of suicidal behavior? In a large retrospective study, Goodwin et al. (2003) found lithium to be more protective against suicide attempts and completion than divalproex in bipolar disorder. In a retrospective naturalistic study, Yerevanian et al. (2007a) found no difference in attempted suicide rates between carbamazepine, divalproex, and lithium. A study of 372 patients by Bowden (2000) in a one year maintenance treatment study showed no statistical difference in suicide attempts between lithium and divalproex, with a trend toward a lower rate of attempt with divalproex. The data on carbamazepine are mixed. One study of patients with affective disorders or schizophrenia, showed a superior protective effect of lithium relative to carbamazepine in both attempts and completions (Thies-Flechtner et al., 1996), while Yerevanian's study showed no difference as noted previously. Collins' study of 12,662 Medicaid patients demonstrated a protective effect of lithium for suicide attempts relative to anticonvulsants (Collins and McFarland, 2008). Baldessarini and Tondo (2009) reviewed 6 studies of suicide risk during long term treatment with lithium or anticonvulsants. Rates of suicidal acts were 2.86 times higher in the anticonvulsant treated group compared with the lithium group. Overall, it appears that lithium provides more protection against suicide attempts than anticonvulsants, but reports have shown mixed results.

The relationship between typical or first generation antipsychotics and suicide is complicated. Kerwin (2003) noted that the 13-fold increase in suicide rates in schizophrenia was unaffected by the development of first generation antipsychotic medications. While the conventional antipsychotics did improve symptoms of schizophrenia, they also had the potential to cause depression and had side effect problems such as akathisia and akinesia that led to increased suicide attempts in some cases. Other studies have supported this finding (Drake and Ehrlich, 1985; Shear et al., 1983).

Atypical antipsychotics may help lower suicide risk in patients with schizophrenia. Altamura et al. (2003) reported that the relative suicide risk was lower for atypical antipsychotics compared to typical antipsychotics in schizophrenia. Clozapine has demonstrated a reduction in suicide attempts and completion in schizophrenia (Meltzer and Okayli, 1995), and is the only atypical that is FDA labeled for lowering suicide risk in schizophrenia. A large multicenter prospective 2 year study in which schizophrenic subjects were randomized to clozapine or olanzapine (Meltzer et al., 2003) demonstrated lower suicidal behavior in clozapine subjects (hazard ratio=0.76) but no difference in completed suicides between the two groups. A small study comparing 44 chronic schizophrenic patients receiving either clozapine or haloperidol decanoate demonstrated a reduction of suicidality, impulsivity, and aggression in the clozapine group (Spivak et al., 2003). In a twenty eight week study comparing olanzapine and risperidone for schizophrenia and schizoaffective disorder (Tran et al., 1997), subjects on olanzapine had

significantly lower suicide attempt rates. Two other studies compared olanzapine to haloperidol in the treatment of schizophrenia. Glazer (1998) found a 2.3 fold reduced risk of suicide in schizophrenic patients on olanzapine relative to haloperidol in a 1 year study, while Beasley et al. (1998) found no outcome difference in suicidal behavior between olanzapine and haldoperidol, but a decrease in suicidal thoughts in olanzapine subjects. In a six week study, Muller-Siecheneder et al. (1998) compared risperidone to the combination of haldoperidol and amitriptyline in schizophrenic, schizoaffective, or psychotically depressed patients. There was no difference in suicidal ideation between the treatment groups. In a retrospective study, Barak et al. (2004) reviewed patient records from 1998–2002. The index group for the study was schizophrenic patients with a previous suicide attempt and the control group was comprised of patients with schizophrenia with no previous suicide attempt, matched for gender and age. The protective effect (odds ratio) of treatment by second generation antipsychotics was significant at 3.54.

While used frequently to treat bipolar disorder as monotherapy or in combination with other mood stabilizers, the effect of atypical or second generation antipsychotics on suicide risk has been understudied. Several case reports of clozapine use in affective disorders note a possible anti-suicide benefit (Vangala et al., 1999; Ranjan and Meltzer, 1996; Suppes et al., 1999). There have been reports of a decrease on the suicide item on the Montgomery Asberg Depression Rating Scale in a bipolar depression study of quetiapine as well as a decrease on the suicidality item on the Hamilton Depression Scale with olanzapine (Houston et al., 2006). In contrast to the aforementioned reports, other studies have indicated an increase in suicidality in bipolar patients on atypical antipsychotics. In a retrospective study by Yerevanian et al. (2007b), 405 veterans were followed naturalistically over a 3 year period. The rate of suicide attempts were 9.4 times greater during antipsychotic monotherapy compared with mood stabilizer (lithium, carbamazepine, divalproex) monotherapy. In addition the rate of suicide attempts during mood stabilizer plus antipsychotic treatment alone was 3.5 times greater than the rate on mood stabilizer monotherapy. Antipsychotic treatment was associated with a markedly increased rate of suicide attempts. Both first and second generation antipsychotics were used in this analysis and the study was limited by its retrospective design. In addition, clinical severity was not assessed, and patients on combinations of mood stabilizers and antipsychotics may have been more severely ill.

The purpose of this study was to extend the work of Goodwin et al. (2003) and Yerevanian et al. (2007b), by retrospectively analyzing whether atypical antipsychotics when used alone or in combination with lithium or divalproex affect the suicide attempt rate. Given the high frequency of their use in bipolar disorder and the high lethality associated with this illness, it is important to understand the impact of atypical antipsychotics on suicide potential. Every treatment that is used in bipolar disorder ought to be tested not only for its ability to quell mania or ameliorate depression, but also for its ability to prevent suicide. The main hypothesis of this study was that the use of atypical antipsychotics in combination with lithium or divalproex may provide additional protection against suicide in bipolar patients.

2. Methods

Five VA hospitals (Milwaukee, Durham, Minneapolis, Cleveland, and Madison) participated in this study. Institutional Review boards at all sites approved all study procedures. The William S. Middleton VA (Madison) served as the coordinating center for data. We reviewed data on detailed treatments, suicide events and other study variables between Jan 1, 1999 and December 31,

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