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Research report

Bipolar pharmacotherapy and suicidal behavior☆ Part 2. The impact of antidepressants

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Abstract

Antidepressant-induced mania and cycle acceleration is a potential risk in bipolar patients. Another serious risk of antidepressants, that of increasing suicidal behavior, has been identified in some affectively ill populations. However, there is a dearth of knowledge about the effects of antidepressants on suicidal behavior specifically in bipolar patients.

Methods: Retrospective chart review of 405 veterans with bipolar disorder followed for a mean of three years, with month by month systematic assessment of current pharmacotherapy and suicide completion, attempt or hospitalization for suicidality. Chi-squared comparison of (log) rates of suicidal events during mood stabilizer monotherapy, antidepressant monotherapy, and combination of mood stabilizer and antidepressant.

Results: Suicidal behavior event rates (per 100 patient years) were greatest during treatment with antidepressant monotherapy (25.92), least during mood stabilizer monotherapy (3.48), and intermediate during mood stabilizer + antidepressant combination treatment (9.75). These differences were statistically significant.

Limitations: In a clinical setting, antidepressants may have been prescribed because patients were deemed at greater risk of suicidality.

Conclusions: During treatment with antidepressants (even when coupled with mood stabilizers), patients with bipolar disorder have significantly higher rates of non-lethal suicidal behavior compared to those on mood stabilizers without antidepressants, and thus require careful monitoring.

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Keywords: Suicide; Suicide attempt; Antidepressants; Bipolar disorder; Veterans; Longitudinal study; Public health

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1. Introduction

The controversy over the issue of antidepressants contributing to suicidal behavior continues in the literature. Numerous epidemiologic and clinical reports (Rihmer and Akiskal, 2006; Baldessarini et al., 2006; Moller, 2006a) actually point to reduction of suicidal behaviors with antidepressant treatment over the long term. However, meta-analyses of short-term clinical trials of antidepressants have found evidence of increased suicidal ideation (Khan et al., 2003) and attempts (Fergusson et al., 2005) during the course of treatment of depressive disorders. Such findings have led the FDA to mandate warnings for all antidepressants (FDA, 9-14-04). Patients enrolled in clinical trials of antidepressant for major depression typically are assumed to be non-bipolar and recognized bipolars are explicitly excluded. The question of the effects of antidepressants on suicidality specifically in bipolar patients is controversial (Mc Elroy et al., 2006) and deserves further study. This is of particular importance in light of the emerging evidence that bipolarity – particularly bipolar II – plays a major role in suicide (Rihmer, 2002, 2007). Given that the course of bipolar disorder is dominated by depression (Judd et al., 2002, 2003) and that antidepressants prescribed to depressed patients could destabilize an unknown percentage of them towards suicidality (Akiskal and Mallya, 1987; Koukopoulos et al., 1992; Pompili et al., 2005), a systematic study of the effects of antidepressants in bipolar patients assumes great public health importance.

Parallel developments in the field of bipolar research have emphasized the importance of recognizing subtle bipolar conditions. The clinical characteristics of these "pseudo-unipolar" patients have been described (Akiskal et al., 2005; Dilsaver and Akiskal, 2005) and caution has been issued about the negative consequences of treating both overt and sub-clinical bipolar patients with antidepressants alone (Ghaemi et al., 2003). Antidepressant-induced mania/hypomania, induction of rapid cycling as well as mood instability have all been described and the high risk of mixed states for suicidality has been emphasized (Akiskal and Benazzi, 2005). Relatively little attention has been paid to the impact of antidepressants on suicidal behavior in recognized bipolar patients who are often prescribed antidepressants (Post et al., 2003; Simon et al., 2004).

In a recent study, Shi et al. (2004) found that unrecognized bipolar patients (who are more likely to be treated with antidepressant monotherapy compared to recognized bipolars) were significantly more likely to attempt suicide (0.9%) than recognized bipolar patients (0.3%) or non-bipolar patients (0.2%). In a cross sectional study of 1000 bipolar patients in the STEP-BD program, Goldberg et al. (2005) found that suicidal ideation was more prevalent in patients taking antidepressants compared to those who were not (25% *versus* 14%). In a prospective report from the STEP-BD program, Bauer et al. (2006) reported no association between new onset suicidality (n = 24/425) and increased antidepressant exposure or initiation of antidepressants. Aizenberg et al. (2006), in a case controlled chart review of elderly hospitalized bipolar patients found no increased rate of antidepressant use among 16 admitted after a suicide attempt compared with 16 matched controls without suicide attempt prior to admission. There are thus contradictory findings concerning the impact of antidepressants on suicidal behavior in bipolar patients.

In this retrospective study of a large group of bipolar veterans, we sought to answer the questions: Do antidepressants affect suicidal behavior in bipolar patients and if so how? To that end we compared the rates of suicidal behaviors in bipolar patients maintained on 1) monotherapy with mood stabilizers, 2) combination of mood stabilizer and antidepressant, or 3) antidepressant alone. The study was approved by the Institutional Review Board of the VA Greater Los Angeles Healthcare System.

2. Patients and methods

2.1. Clinical setting and patients

The study is a retrospective chart review analysis of bipolar patients seen in a large Veterans Administration healthcare system in Southern California (VA Greater Los Angeles Healthcare System or VAGLAHS). The Computerized Patient Record System (CPRS) in use at the facility since 1994 includes progress notes of 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. The period under study was January 1, 1994 to December 31, 2002. To identify patients with bipolar disorder within the system, we obtained pharmacy records of ALL lithium, divalproex, carbamazepine, gabapentin, topiramate, and lamotrigine prescriptions ever dispensed during that period of time. From this a list of 2650 patients was identified, and 405 patients met the following inclusion criteria:

1). A *chart* diagnosis of bipolar disorder, Type I, Type II, schizoaffective disorder bipolar type or bipolar NOS. For convenience, patients with cyclothymia, antidepressant-induced mania, or mania specified as secondary to other general