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Research report

Divalproex in the treatment of bipolar depression: A placebo-controlled study

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Abstract

Background: The treatment of bipolar disorder in the depressed phase is complicated by a tendency for conventional antidepressant drugs to worsen the course of the illness by precipitating a manic episode or increasing cycle frequency. Thus, the potential antidepressant efficacy of mood stabilizers, such as divalproex, which is an effective treatment for the manic phase of bipolar disorder, is of considerable interest.
Methods: The clinical efficacy of divalproex (valproate, Depakote®) was tested in an 8-week, double-blind, placebo-controlled, randomized clinical trial in 25 outpatients with bipolar I depression. The primary outcome measure was the 17-item Hamilton Rating Scale for Depression, and secondary measures included the Hamilton Rating Scale for Anxiety, the Clinician Administered Rating Scale for Mania, and the Clinical Global Impression scale.
Results: Using repeated measures ANOVA with last observation carried forward, divalproex was more effective than placebo in improving symptoms of depression (p=0.0002) and symptoms of anxiety (p=0.0001) than placebo.
Limitations: The sample size was small, and most patients were male.
Conclusions: These pilot results indicate that divalproex is effective in reducing the symptoms of depression and anxiety in bipolar I, depressed phase. These positive results support the need to perform a larger, multisite study of divalproex treatment for bipolar depression.

Keywords: Divalproex; Valproate; Bipolar disorder; Depression; Mood stabilizers; Anticonvulsants

1. Introduction

The lifetime prevalence of bipolar disorder ranges from 3% to 6.5%, depending on the specific diagnostic definition of bipolar used (Hirschfeld et al., 2002a;

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Akiskal et al., 2000; Lewinsohn et al., 1995; Weissman et al., 1996). As part of the natural course of illness, patients with bipolar disorder often suffer from episodes of depression more frequently and for longer durations than mania (Judd et al., 2002; Judd et al., 2003). Although, perhaps, less overtly disruptive than the manic phase of the illness, bipolar depression is a significant cause of psychiatric morbidity and mortality, and thus a major public health concern. A major challenge in the treatment of bipolar depression is the tendency for antidepressant medications, particularly tricyclic antidepressants, to precipitate episodes of mania, or to increase cycle frequency or symptom intensity (Boerlin et al., 1998; Bottlender et al., 1998; Peet, 1994). Thus, exploring the utility of mood stabilizers as monotherapy for bipolar depression is important. Divalproex (Depakote®) has become the most widely prescribed mood stabilizer in the United States but has not been extensively tested for its potential antidepressant characteristics (Davis et al., 2000).

We have previously reported an open label treatment trial of divalproex in unipolar major depressive disorder with positive results (Davis et al., 1996). Also, data from the double-blind study of treatment for acute mania in bipolar disorder, which compared divalproex, lithium, and placebo (Bowden et al., 1994), suggests that those patient with pretreatment depressive symptoms responded preferentially to divalproex compared to lithium or placebo (Swann et al., 1997). These promising results encouraged us to perform a double-blind, randomized, placebo-controlled clinical trial to test the efficacy of divalproex in the treatment of patients with bipolar depression.

2. Methods

2.1. Subjects

Subjects were recruited from the Mental Heath Clinic at the Dallas Veterans Affairs Medical Center. The study was approved by the Dallas VA Subcommittee on Human Studies (Institutional Review Board). After providing signed informed consent, patients received a standard laboratory, medical, and psychiatric examination. Diagnoses were confirmed by the Structured Clinical Interview for DSM-IV (SCID) and the borderline and antisocial personality disorder modules of the Structured Clinical Interview for DSM-IV Personality Disorders (SCID-II). Criteria for entry into the study included a diagnosis of bipolar I disorder, currently in the depressed phase of the illness, a score $\geq$16 on the 17-item Hamilton Rating Scale for Depression (HRSD; Hamilton, 1960), and stable general medical condition with no clinically significant abnormal laboratory values. A minimum 2-week (6 weeks for fluoxetine) washout for psychotropic medications was required. Exclusion criteria included a diagnosis of an active Axis I disorder other than bipolar I, diagnosis of borderline or antisocial personality disorder, previous history of intolerance to divalproex, or significant suicidality. Prior to study entry, psychoactive substance use disorders were required to be in remission for at least 3 months.

2.2. Assessments

Symptom severity was rated at baseline and at weekly clinic visits using the 17-item HRSD, the Hamilton Rating Scale for Anxiety (HRSA; Hamilton, 1959), the Clinical Global Impression (CGI), as well as the Clinician Administered Rating Scaled for Mania (CARS-M). The HRSD served as the primary outcome measure. Adverse events were recorded during weekly visits. Serum levels of valproic acid and liver function tests were obtained at week 4 and 8 during the study. Remission of depression was defined apriori as >50% improvement and total score <9 in HRSD. Relapse into mania was defined apriori as meeting criteria for mania as defined by the DSM-IV.

2.3. Medication

At baseline, patients were started on 500 mg per day of divalproex or look-alike placebo, divided into two doses. The medication was rapidly titrated up to 2500 mg/day, as tolerated, to a target serum level of 50–100 μg/dl. The study blind was maintained by having the laboratory report valproic levels as either low, in the therapeutic range, or high, with fictitious levels reported for patients treated with placebo. Patients returned to the clinic on a weekly basis for monitoring of clinical status with the rating scales and possible adverse effects. Patients were allowed to use diphenhydramine or hydroxyzine (25 to 50 mg/day)