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Research report

Safety and effectiveness of continuation antidepressant versus mood stabilizer monotherapy for relapse-prevention of bipolar II depression: A randomized, double-blind, parallel-group, prospective study

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ABSTRACT

Objective: Compare the safety and effectiveness of continuation antidepressant versus mood stabilizer monotherapy for preventing depressive relapse in bipolar II disorder.
Methods: Subjects ≥18 years old with bipolar II depression ($n=129$) were randomized to double-blind venlafaxine or lithium monotherapy for 12 weeks. Responders with a ≥50% reduction in depression score were continued for an additional 6 months of relapse-prevention monotherapy. Primary outcome was depressive relapse during continuation monotherapy. Secondary outcomes included sustained response rate from initiation of treatment to study end-point, relapse hazard, time to relapse, change in mania ratings, and frequency of treatment-emergent sub-syndromal hypomania and/or depressive episodes.
Results: Venlafaxine produced greater sustained response rate versus lithium ($p<0.0001$); however, there was no difference in relapse rate for venlafaxine (7.5%) versus lithium (26.7%) ($p=0.079$); relapse hazard ($p=0.073$), or time to relapse ($p=0.090$) between treatment conditions during continuation monotherapy. There were no group differences in mania rating scores over time and no difference in frequency or duration of syndromal or sub-syndromal hypomanic episodes. There were more sub-syndromal depressive episodes during lithium monotherapy ($p=0.03$).
Limitations: Sample size was limited by the lower sustained response rate for lithium versus venlafaxine; study was not specifically powered to detect differences in treatment-emergent hypomanic or depressive episodes between groups.
Conclusion: Results suggest that continuation venlafaxine monotherapy may provide similar prophylactic effectiveness relative to lithium, with no difference in treatment-emergent hypomanic episodes and without the need for frequent serum lithium level and metabolic monitoring. Larger, prospective trials are needed to confirm these observations.

1. Introduction

The use of antidepressant medication to treat bipolar type II disorder remains a controversial practice (Bond et al., 2008; Gitlin and Frye, 2012; Pacchiarotti et al., 2013; Parker, 2015; Parker et al., 2006). Practice guidelines for long-term therapy of bipolar II disorder generally recommend mood stabilizer monotherapy and the discontinuation of antidepressant medication within 12–20 weeks after recovery (American Psychiatric Association, 2006; Fountoulakis et al., 2005; Sachs et al., 2000; Yatham et al., 1997). This time frame for discontinuing prophylactic antidepressant therapy is considerably shorter than that recommended for unipolar depression (Reimherr et al., 1998). However, this recommendation is not based upon evidence that bipolar patients require less prophylactic antidepressant therapy than unipolar patients. Instead, the reluctance to use prophylactic antidepressant therapy for bipolar depression is primarily due to concerns over antidepressant-induced mania (Ghaemi et al., 2000; Goldberg and Nassir Ghaemi, 2005; Goldberg and Truman, 2003; Truman and Goldberg, 2007).

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Studies of mixed populations of bipolar I and II depressed patients have reported increases in manic symptoms and depressive relapse during antidepressant prophylaxis (Altshuler et al., 1995; Ghaemi et al., 2004; Leverich et al., 2006; Sachs et al., 2007). For example, one controlled trial reported adequate antidepressant effectiveness, but more treatment-emergent manic symptoms during venlafaxine versus sertraline or bupropion therapy (Leverich et al., 2006). Another study of continuation bupropion versus desipramine found only modest sustained antidepressant response with no difference between the two drugs, but a higher manic switch rate during desipramine treatment (Sachs et al., 1994). A retrospective study found that 44% of subjects with a history of prior mood conversion episodes had at least one manic switch episode during antidepressant therapy and that concurrent mood stabilizer therapy provided little or no protection against treatment-emergent manic switch episodes (Goldberg and Truman, 2003). A recent retrospective chart-review study of bipolar I and II patients found higher manic switch rates during antidepressant monotherapy versus combined antidepressant plus mood stabilizer therapy (Viktorin et al., 2014).

In contrast, controlled trials of long-term antidepressant monotherapy in recovered bipolar II depressed patients suggest good sustained efficacy during antidepressant therapy with a low manic switch rate (Altshuler et al., 2009; Amsterdam et al., 1998, 2013; Amsterdam and Shults, 2010b; Kupfer et al., 2001; Parker et al., 2006). For example, a 26-week continuation trial of fluoxetine monotherapy found a similar relapse rate in recovered bipolar II depressed (22%) versus recovered unipolar depressed (33%) subjects with similar hypomanic switch rates (Amsterdam et al., 1998). A subsequent randomized, double-blind, placebo-controlled, 50-week continuation study of fluoxetine versus lithium monotherapy found no difference in the proportion of subjects who relapsed on fluoxetine (32.1%), lithium (57.7%), or placebo (51.9%) ($p=0.14$) (Amsterdam and Shults, 2010b). A subsequent *post hoc* analysis of recovered rapid cycling versus non-rapid cycling bipolar II subjects also found no difference in relapse rate based on cycling status during continuation antidepressant or mood stabilizer monotherapy with similar rates of treatment-emergent hypomanic symptoms (Amsterdam et al., 2013).

Data on the relative long-term efficacy of antidepressant versus mood stabilizer monotherapy in bipolar II are limited. We present data from the first randomized, double-blind, parallel-group, 6-month relapse-prevention study of the safety and effectiveness of continuation antidepressant versus mood stabilizer monotherapy in bipolar II subjects recovered from acute depression (Trial Registration number NCT00602537). Based upon preliminary open-label observations (Amsterdam et al., 1998, 2010; Amsterdam and Shults, 2008), we hypothesized that venlafaxine monotherapy would be superior to lithium monotherapy in preventing depressive relapse and the two treatments would be associated with similar levels of treatment-emergent manic and/or depressive symptoms.

2. Methods

2.1. Subjects

This study contained a new cohort of subjects distinct from that of all prior bipolar II depression studies conducted by our group (ClinicalTrials.gov identifier: NCT00602537). Outpatients ≥ 18 years old with a DSM-IV-TR Axis I diagnosis of bipolar II disorder and current major depressive episode with a 17-item Hamilton Rating Scale for Depression (HRSD) (Williams, 1988) score ≥ 16 were recruited. Exclusion criteria were prior mania or psychosis, substance abuse or dependence within the preceding 3 months, non-response to venlafaxine or lithium within the current episode, sensitivity to venlafaxine or lithium, presence of unstable medical condition, pregnancy or nursing, renal or hepatic insufficiency, dementia, malignancy, or concurrent use of antidepressant or mood stabilizer medication.

2.2. Procedures

Informed consent was obtained in accordance with the ethical standards of the Institutional Review Board. The study was conducted using Good Clinical Practice guidelines (International Conference on Harmonisation Working Group, 1996) with oversight by the local Office of Human Research and an independent Data and Safety Monitoring Board. Psychiatric history was verified using the *Structured Clinical Interview for DSM-IV* (SCID) Axis I disorders (First et al., 2002). Medical history, physical examination, and laboratory tests (including renal and thyroid panels, pregnancy test in women, drug screen, and electrocardiogram) were performed. Best estimates of the number of prior major depressive and hypomanic episodes (as defined by DSM IV criteria) that occurred since the onset of the disorder were obtained from subjects at their initial interview using SCID interview format.

Structured 17-item HRSD and Young Mania Rating Scale (YMRS) (Young et al., 1978) measures were obtained by a study clinician blind to treatment condition. Symptom ratings were obtained with attribution as to the origin of the symptom. For example, insomnia could be recorded on the HRSD scale as a depressive symptom, or recorded on the YMRS as a hypomanic symptom, or simultaneously recorded on both rating scales as a mixed hypomanic and depressive symptom. This rating method sometimes resulted in baseline YMRS scores above zero. The procedure has been employed as a 'real world' means of distinguishing mood conversion episodes from depressive symptom (Amsterdam and Shults, 2008, 2010a, 2010b; Amsterdam et al., 2010).

2.3. Randomization

Blocked randomization was performed with randomly selected block sizes containing group numbers randomly permuted within each block using the random number generator in Stata statistical software. All study subjects, treating clinicians, research coordinators, and data managers were blinded to the treatment condition. Treatment allocation codes for emergency un-blinding were maintained on the Investigational Drug Service at the medical center.

2.4. Treatment

Venlafaxine was initiated at 37.5 mg daily and increased to 75 mg daily during week 1 of treatment. The dose was then titrated upward in 37.5 mg or 75 mg increments every week to a maximum of 375 mg daily by week 4 of treatment. This dose was then maintained for an additional 8 weeks of therapy. Venlafaxine could be reduced to a minimum of 75 mg daily based upon tolerability and response. Subjects unable to tolerate a minimum venlafaxine dose of 75 mg daily were discontinued from the trial without un-blinding the study clinician (and treated as clinically warranted).

Lithium was initiated at 300 mg daily and increased to 600 mg daily during week 1 of treatment; and a serum lithium level was obtained. Based upon clinical response, tolerability and a serum lithium level of 0.8–1.5 mEq/L, the dose of lithium could be increased to 900 mg daily during week 2 of therapy. Another lithium level was obtained, and the dose increased to 1200 mg daily during week three of therapy based upon clinical response and serum