Journal of Affective Disorders 145 (2013) 83–94

Contents lists available at SciVerse ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research report

Randomized, placebo-controlled trial of quetiapine XR and divalproex ER monotherapies in the treatment of the anxious bipolar patient ☆

David V. Sheehan [a,*], Kathy Harnett-Sheehan [a], Rosario B. Hidalgo [a], Juris Janavs [a], Susan L. McElroy [b], Darlene Amado [a], Trisha Suppes [c]

[a] Clinical and Translational Science Institute, University of South Florida, College of Medicine, 3515 East Fletcher Ave., Tampa, FL 33613, USA
[b] Department of Psychiatry, University of Cincinnati College of Medicine, University of Cincinnatti, Lindner Center of Hope, 4075 Old Western Row Rd., Mason, OH 45040, USA
[c] Department of Psychiatry & Behavioral Science, Stanford University School of Medicine, VA Palo Alto Health Care System, 3801 Miranda Ave. (151T), Palo Alto, CA 94304, USA

ARTICLE INFO

Article history:
Received 18 April 2012
Received in revised form
8 July 2012
Accepted 17 July 2012
Available online 21 August 2012

Keywords:
Bipolar disorder
Anxiety
Panic disorder
Placebo
Atypical antipsychotic
Generalized anxiety disorder

ABSTRACT

Background: Anxiety disorders complicate the treatment of bipolar disorder but are seldom the focus of bipolar treatment studies.
Methods: The anxiolytic effect of quetiapine XR 50–300 mg/day compared to divalproex ER (500–3000 mg/day) was tested in an 8-week, double-blind, placebo-controlled, randomized clinical trial in 149 patients with bipolar disorder and a co-occurring panic disorder or GAD. The primary efficacy measure was the Clinician Global Improvement-21 Anxiety Scale (CGI-21). Secondary measures included the Hamilton Anxiety Scale (HAM-A) and Sheehan Panic Disorder Scale (SPS).
Results: Repeated measures last-observation-carried-forward (LOCF) analyses of variance demonstrated significant treatment-by-time interaction effects on 3 of the 4 anxiety measures. Quetiapine XR at a mean endpoint dose of 186 mg/day produced rapid sustained improvements relative to baseline, divalproex ER and placebo on anxiety. Mean baseline-to-endpoint improvement was significantly greater for quetiapine XR compared to divalproex ER and placebo on the HAM-A and SPS. Both active medications were well tolerated, but weight gain was higher on quetiapine XR.
Limitations: The study was limited to 8 weeks and to patients with bipolar disorder and comorbid panic disorder or GAD. The results may not be applicable to quetiapine XR as an add-on treatment to mood stabilizers or to bipolar disorder comorbid with other anxiety disorders.
Conclusions: Quetiapine XR in a dose range of 50–300 mg/day appears to reduce anxiety in bipolar patients with comorbid panic disorder or GAD treated for 8 weeks. The efficacy of other second-generation antipsychotics and mood stabilizers in patients with bipolar disorder and a co-occurring anxiety disorder should be investigated in double-blind, placebo-controlled studies.

1. Introduction

Anxiety disorders and anxious symptoms are common in bipolar disorder (Pini et al., 1997; Kessler et al., 1997; Feske, et al., 2000; Freeman et al., 2002; Boylan, et al., 2004). Indeed, in one study, Boylan et al. (2004) found that 55.8% of bipolar outpatients had at least one comorbid anxiety disorder and within this population 57% had more than two anxiety disorders. This comorbidity poses challenges for the treating physician. Compared to patients without an anxiety disorder, anxious bipolar patients have an earlier age of onset of illness (Schurhoff et al., 2000; McElroy et al., 2001; Carter et al., 2003; Henry et al., 2003; Perlis et al., 2004), higher rates of mixed states (Boylan et al., 2004), more depressive episodes, alcohol abuse and suicidal ideation (Young et al., 1993; Frank et al., 2002; Carter et al., 2003; Simon et al., 2004; Frye et al., 2003; Perlis et al., 2004) and a poorer response to lithium-based treatment (Freeman et al., 2002; McElroy et al., 2001; Frank et al., 2002). These observations, together with growing evidence that bipolar disorder with panic disorder may be a genetic subtype within the bipolar disorder spectrum (MacKinnon et al., 1997, 2003; Rotondo et al., 2002; Dilsaver et al., 2006; Nardi et al., 2007), have led to increasing interest in finding pharmacologic treatments that specifically target anxiety in bipolar disorder.

Unfortunately, first line treatments for anxiety disorders (selective serotonin reuptake inhibitors [SSRIs] and selective-norepinephrine reuptake serotonin reuptake inhibitors [SNRIS]) are not recommended, at least as monotherapies, in bipolar patients with anxiety disorders because of their potential to induce rapid cycling and manic, hypomanic or depressive episodes (Ghaemi et al., 2003; Salvi et al., 2008; Young and Seim, 2009).

☆This study was supported by a grant from Astra Zeneca.
* Corresponding author. Tel.: +1 813 956 8437; fax: +1 813 974 4575.
E-mail address: dsheehan@health.usf.edu (D.V. Sheehan).

0165-0327/$ - see front matter © 2012 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.jad.2012.07.016

Moreover, the presence of anxiety is associated with a poorer response to lithium (Boylan et al., 2004, Henry et al., 2003).

Based on its demonstrated efficacy in panic disorder (Lum et al., 1990; Keck et al., 1993), the mood stabilizer divalproex has been postulated to have anxiolytic effects in bipolar disorder. To date, however, no double-blind, placebo-controlled studies have examined its potential effects in reducing anxiety in bipolar patients with a co-occurring anxiety disorder and only one small double-blind placebo-controlled study has been published demonstrating its superiority to placebo in reducing anxious symptoms in a bipolar population (Davis et al., 2005).

Several second generation antipsychotics have been shown to be effective and well tolerated in the treatment of manic and mixed episodes of bipolar I disorder (Derry and Moore, 2007; Perlis, 2005) and are increasingly being used as mood stabilizers in bipolar disorders (Kessler et al., 2005; Ghaemi et al., 2006). Their potential anxiolytic efficacy in bipolar disorder is therefore receiving growing attention.

Early reports indicated that adding quetiapine, risperidone, or olanzapine to an SSRI produced results superior to placebo in the treatment of anxiety disorders such as refractory obsessive compulsive disorder (OCD), generalized anxiety disorder (GAD) and post-traumatic stress disorder (PTSD) in patients without bipolar disorder (McIntyre and Katzman, 2003). However, the sample sizes of these studies were small (Gao et al., 2006). More recently, 2 large double-blind, placebo controlled studies, have demonstrated the anxiolytic efficacy of an extended-release formulation of quetiapine fumarate (quetiapine XR) in reducing anxiety in patients with a diagnosis of generalized anxiety disorder (GAD) (Khan et al., 2008; Bandelow et al., 2010) without bipolar disorder.

In addition, 3 large double-blind placebo-controlled studies have investigated the effects of atypical antipsychotics on anxious symptoms in patients with bipolar depression using the HAM-A as a secondary measure. In one study, Tohen et al. (2007) found that olanzapine alone and together with fluoxetine were superior to placebo in reducing HAM-A scores after 8 weeks of treatment. In a pooled analysis of data from two other studies, Hirschfeld et al. (2006) found that immediate release quetiapine at doses of 300 mg/day and 600 mg/day significantly reduced total HAM-A scores compared to placebo in 351 patients after 8 weeks of treatment. These results held up in a more recent secondary analysis of this data using a larger sample ($n=978$) (Lydiard et al., 2009).

Unfortunately none of the above three studies specified whether or not the subjects had co-occurring syndromal anxiety disorders. Such specification may matter because, while second generation antipsychotics may reduce anxiety symptoms in bipolar depression, these medications have been identified as exacerbating symptoms in panic disorder and OCD, possibly because of their serotonergic antagonistic properties (Baker et al., 1992, de Haan et al., 2002).

To date there is only one published double-blind, placebo-controlled trial investigating the anxiolytic efficacy of a second generation antipsychotic on anxiety as the primary target of treatment in patients with bipolar disorder and a co-occurring *syndromal* anxiety disorder. That study (Sheehan et al., 2009) did not find risperidone monotherapy (0.5–4 mg/day) to be any more effective than placebo in reducing anxiety or other symptoms in 111 patients with bipolar disorder (I, II or NOS) and a co-occurring panic disorder or generalized anxiety disorder (GAD). The results, however, may have been unique to risperidone and not apply to other second generation antipsychotics.

Current treatment guidelines for bipolar disorder recommend treating anxiety disorders concurrently with bipolar disorder (Suppes et al., 2005; Perlis, 2005), but evidence based options for bipolar patients with a co-occurring anxiety disorder are still limited and treatment in this population is all too often based on anecdotal reports and open clinical experience (Perugi and Toni, 2004; Singh and Zarate, 2006). Given preliminary evidence that the mood stabilizer divalproex and at least 2 of the second generation antipsychotics (quetiapine and olanzapine) are effective in reducing anxiety symptoms in patients with bipolar disorder, an important question is how effective these types of treatments are, compared to each other and to placebo, in bipolar patients with a co-occurring syndromal anxiety disorder.

2. Method

2.1. Study design

This randomized, double-blind, parallel-group, multicenter study compared the anxiolytic efficacy of the second generation antipsychotic quetiapine XR as monotherapy with the mood stabilizer divalproex ER as monotherapy and placebo in adult outpatients with a lifetime bipolar I, II or NOS disorder, a lifetime panic or generalized anxiety disorder and at least moderately severe anxiety symptoms. The study was conducted between July of 2007 and April of 2010 at three sites in the United States (University of South Florida, University of Cincinnati, University of Texas Southwestern Medical Center). The institutional review board for each site approved the protocol and written informed consent was received from each participant before any study-related procedures were performed. Following a 2-day to 4-week screening, patients were randomized in a 1:1:1 ratio to receive quetiapine XR, divalproex ER or placebo in a flexible dose regimen of 50–300 mg/day quetiapine XR or 500–3000 mg/day divalproex ER for 8 weeks.

2.2. Patients

Eligible patients included men and women aged 18–65 years of age who met *Diagnostic and Statistical Manual*, 4th edition (DSM-IV) criteria for a lifetime bipolar I, II, or NOS disorder and a lifetime panic disorder (PD) or generalized anxiety disorder (GAD). Diagnoses had to be documented on the Mini International Neuropsychiatric Interview (MINI; Sheehan et al., 1998). However, for the purpose of the study, the GAD Criterion F clause, "does not occur exclusively during a mood disorder," was suspended. Each patient's bipolar symptoms could be no more than moderately severe, defined as a score of ≤ 4 on the Clinical Global Impressions Scale for use in Bipolar Illness (CGI-BP; Spearing et al., 1997) and his or her anxiety symptoms had to be at least moderately severe (defined as a score of ≥ 4 on the Clinician Global Impression Severity Scale (CGI-S; Guy, 1976)). Patients were not required to be in a euthymic state (i.e. without mood elevation or depression) at baseline. Patients were excluded if they had an acute, serious or unstable medical illness or clinical abnormality, were currently receiving an antimanic or mood stabilizing medication, met DSM-IV substance dependence criteria within the past 6 months, had current psychotic symptoms or a lifetime psychotic disorder (e.g. schizoaffective disorder or schizophrenia), or were judged clinically to be at a serious risk for suicide. All patients had to discontinue psychotropic drugs 7 days before baseline or 4 weeks in the case of fluoxetine and depot antipsychotics.

2.3. Assessments

Efficacy assessments were conducted at baseline and at weeks 1 to 8. All assessments were conducted by raters blind to treatment assignment. The Clinical Global Improvement Scale for