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Journal of Affective Disorders 115 (2009) 376–385

Journal of Affective Disorders

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Research report

Randomized, placebo-controlled trial of risperidone for acute treatment of bipolar anxiety☆

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Received 18 March 2008; received in revised form 25 September 2008; accepted 3 October 2008
Available online 29 November 2008

Abstract

Background: The treatment of bipolar disorder is often complicated by the presence of a co-occuring anxiety disorder. Although second generation antipsychotics are being used with increasing frequency in bipolar patients, their anxiolytic effects have not been well studied in this population.
Methods: The anxiolytic effect of risperidone 0.5–4 mg/day was tested in an 8-week, double-blind, placebo-controlled, randomized clinical trial in 111 patients with bipolar disorder and a co-occuring panic disorder or generalized anxiety disorder (GAD). The primary outcome measure was the Clinician Global Improvement-21 Anxiety scale (CGI-21 Anxiety). Secondary measures included the Hamilton Anxiety Scale (HAM-A) and the Sheehan Panic Disorder Scale.
Results: On the last-observation-carried forward analysis of repeated measures analysis of variance (ANOVA), risperidone was not more effective than placebo for the CGI-21 Anxiety score or the other anxiety outcome measures. Risperidone was well tolerated, with only two patients withdrawing because of adverse events.
Limitations: The risperidone treated group had more patients with mixed states and lifetime panic disorder at randomization than the placebo group. The study was limited to 8 weeks and to individuals with bipolar and comorbid panic disorder or GAD. The results may not be applicable to risperidone as an add-on treatment to mood stabilizers, or to bipolar disorder comorbid with anxiety disorders other than panic disorder or GAD.
Conclusions: Risperidone monotherapy was not an effective anxiolytic for bipolar patients with comorbid panic disorder or GAD in doses of 0.5–4 mg/day over 8 weeks of treatment. The efficacy of other second generation antipsychotics and mood stabilizers on anxiety in patients with bipolar disorder and a co-occuring anxiety disorder should be investigated in double-blind, placebo-controlled studies.

Keywords: Bipolar disorder; Anxiety; Panic disorder; Placebo; Atypical antipsychotic; Second generation antipsychotic

☆ This study was supported by a grant from Janssen Pharmaceutica.
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doi:10.1016/j.jad.2008.10.005

1. Introduction

From 24–79% of patients with bipolar disorder present with at least one lifetime anxiety disorder (Pini et al., 1997; Feske et al., 2000; McElroy et al., 2001; Freeman et al., 2002, Henry et al., 2003; Kessler et al., 2005; Otto et al., 2006; Simon et al., 2007). Compared to patients without a comorbid anxiety disorder, those with comorbid anxiety have been shown to have an earlier age of illness onset (Schurhoff et al., 2000; Carter et al., 2003; Henry et al., 2003; Perlis et al., 2004) and higher rates of mixed states, depressive symptoms, alcohol abuse, and suicidal ideation (Young et al., 1993; Frank et al., 2002; Carter et al., 2003; Simon et al., 2004; Perlis et al., 2004). Bipolar patients with co-occurring anxiety have also been shown to have a poorer response to lithium or anticonvulsants and to experience more severe medication side effects (Young et al., 1993; Frank et al., 2002; Feske et al., 2000; Henry et al., 2003). These considerations have led to a growing recognition of the need to specifically target anxiety in the treatment of bipolar disorder.

The second generation antipsychotics aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone, when administered alone or in combination with mood stabilizers, 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, 2007). Olanzapine, with and without fluoxetine, and quetiapine alone have been shown to be effective in episodes of bipolar depression (Calabrese et al., 2005; Thase et al., 2006; Tohen et al., 2007). In addition, olanzapine and aripiprazole have indications for maintenance treatment in bipolar I disorder (Derry and Moore, 2007; Perlis, 2007). Since second generation antipsychotics are being used with growing frequency in patients with bipolar disorder (Kessler et al., 2005; Ghaemi et al., 2006a), their anxiolytic effects are a matter of growing interest.

Preliminary research has shown that adding risperidone, olanzapine, or quetiapine to a selective serotonin reuptake inhibitor (SSRI) produces results superior to placebo in the treatment of refractory obsessive–compulsive disorder (OCD), generalized anxiety disorder (GAD), and post-traumatic stress disorder (PTSD) in patients without bipolar disorder (Gao et al., 2006). In addition, the anxiolytic effects of olanzapine and quetiapine have been evaluated in three large double-blind, placebo-controlled studies of bipolar depression using the HAM-A as a secondary measure. In one study, Tohen et al. (2007) found that olanzapine alone and olanzapine combined with fluoxetine were both superior to placebo in reducing HAM-A scores after 8 weeks of treatment. In a pooled analysis of data from 2 studies, Hirschfeld et al. (2006) found that quetiapine at doses of 300 and of 600 mg/d significantly reduced total HAM-A scores compared to placebo after 8 weeks. For individual HAM-A items, these results were more robust among patients with bipolar I disorder than among those with bipolar II disorder.

In none of the latter studies, however, was it specified whether or not subjects had co-occurring syndromal anxiety disorders. Moreover, although second generation antipsychotics may be beneficial for anxiety symptoms in patients with bipolar depression, these agents have been reported to exacerbate the symptoms of panic disorder and OCD, possibly because of their serotonergic antagonistic properties (Baker et al., 1992; de Haan et al., 2002). There is therefore a need for systematic examination of the effects of second generation antipsychotics on the anxiety cluster of symptoms in patients with bipolar disorder and a co-occuring anxiety disorder.

2. Methods

2.1. Study design

This randomized, double-blind, parallel group, 8-week study compared risperidone monotherapy and placebo in adult outpatients with a lifetime bipolar I, II, or NOS disorder, a lifetime panic or generalized anxiety disorder, and current at least moderately severe anxiety symptoms. The institutional review board for each site approved the protocol and written informed consent was received from each participant after the study was fully explained. Following a 1–2 week screening, patients were randomized in a 1:1 ratio to receive risperidone or matching placebo in a flexible dose regimen of 0.5–4 mgs/day for 8 weeks.

2.2. Patients

Patients were recruited from three sites (University of South Florida, University of Cincinnati Medical Center, University of Texas Southwestern Medical Center) with advertisements requesting patients with a combination of mood swings and anxiety or anxiety attacks. Patients enrolled in the study had to be 18–65 years of age. All patients had to meet DSM-IV criteria for a lifetime bipolar I, II, or NOS disorder and a lifetime panic disorder or GAD. However, for the purpose of the study, the GAD Criterion F clause, "does not occur exclusively during a mood disorder," was suspended. DSM-IV diagnostic criteria were documented with the Mini