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Corrigendum

Corrigendum to "Effectiveness of the Extended Release Formulation of Quetiapine as Monotherapy for the Treatment of Acute Bipolar Depression" [J. Affect. Disord. 121 (1–2) (2010) 106–115]

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ABSTRACT

Background: To evaluate the effectiveness of quetiapine extended release once daily in bipolar depression.
Methods: Double-blind, placebo-controlled study in acutely depressed adults with bipolar I or II disorder, with or without rapid cycling. Patients were randomized to 8 weeks of quetiapine extended release (XR) 300 mg daily monotherapy or placebo. The primary outcome measure was changed from baseline to Week 8 in MADRS total score.
Results: Quetiapine XR 300 mg once daily ($N=133$) showed significantly greater improvement in depressive symptoms compared with placebo ($N=137$) from Week 1 ($p<0.001$) through to Week 8 ($p<0.001$). Mean change in MADRS total score at Week 8 was −17.4 in the quetiapine XR group and −11.9 in the placebo group ($p<0.001$). Response ($\geq 50\%$ reduction in MADRS total score) and remission (MADRS total score ≤ 12) rates at Week 8 were significantly higher with quetiapine XR compared with placebo ($p<0.001$ and $p<0.05$, respectively). Quetiapine XR improved core symptoms of depression. The most common adverse events associated with quetiapine XR were dry mouth, somnolence, and sedation. Greater weight gain was observed in patients on quetiapine XR relative to placebo.
Limitations: Fewer patients with bipolar II disorder included, only one fixed dose tested and the lack of an active comparator.
Conclusions: Quetiapine XR (300 mg) once daily monotherapy was significantly more effective than placebo for treating episodes of depression in bipolar I disorder, throughout the 8-week study, with significance observed as early as Day 7. Adverse events were consistent with the known effects of quetiapine.
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1. Introduction

Approximately 1.0% of adults are diagnosed with bipolar I disorder at some point in their lifetime. An additional 1.1% are diagnosed with bipolar II disorder (Merikangas et al., 2007). The course of bipolar disorder is lifelong and chronic, with depressive symptoms dominating (Judd et al., 2002, 2003, 2005; Calabrese et al., 2004; Kupka et al., 2007). Despite the availability of varied treatment options, bipolar disorder, and bipolar depression in particular, continues to remain a public health concern (Post et al., 2003). Even with treatment, bipolar disorder is associated with significant functional and occupational impairment (Kessler et al., 2006; Calabrese et al., 2004; Judd et al., 2005).

A recent study has demonstrated the efficacy of the selective serotonin reuptake inhibitor (SSRI), fluoxetine, in combination with the second-generation antipsychotic, olanzapine, in the treatment of bipolar depression. The olanzapine–fluoxetine combination (OFC) was significantly more efficacious than olanzapine monotherapy, and was associated with higher response and remission rates, and lower discontinuation rates due to adverse events (Tohen et al., 2003). The need to use more than one medication to manage

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bipolar disorder – even those medications packaged together as in the case of the OFC – can increase the risk of adverse events and drug–drug interactions. In the study by Tohen and colleagues noted above, patients receiving OFC reported additional side effects than those who received olanzapine monotherapy.

Adverse events may negatively impact patient compliance, which also tends to decrease with increased complexity or inconvenience of the dose regimen (Burton, 2005; Fincke et al., 1998; Baldessarini et al., 2008). Well-controlled trials of other novel treatments for bipolar depression have yielded mixed results. Despite established efficacy and Food and Drug Administration (FDA) approval for use in the prevention of new depressive episodes in bipolar disorder, lamotrigine monotherapy has proved relatively ineffective in the treatment of acute bipolar depression (Calabrese et al., 2008). Two double-blind, placebo-controlled trials of aripiprazole for the treatment of bipolar depression in bipolar I patients failed to show significant differences in the change in MADRS score following 8 weeks of treatment (Thase et al., 2008).

The immediate release formulation of quetiapine has been available for the treatment of schizophrenia for several years and is now also indicated for the treatment of bipolar disorder. A once daily extended release (XR) formulation of quetiapine that provides similar 24-h coverage may represent a useful treatment option for patients with bipolar disorder. The efficacy and safety of the extended release formulation in the treatment of bipolar mania has been demonstrated in another study, the results of which will be published separately (Cutler et al., 2008). Quetiapine XR once-daily is now FDA-approved for the acute treatment of the depressive episodes associated with bipolar disorder, the manic and mixed episodes associated with bipolar I disorder, and the maintenance treatment of bipolar I disorder as adjunctive therapy to lithium or divalproex. This manuscript presents the results from the only study conducted in acute bipolar depression with the quetiapine extended release formulation.

The primary objective of this study was to evaluate the efficacy and safety of quetiapine XR at a dose of 300 mg once daily, compared with placebo, in patients with acute bipolar depression. The 300 mg dose of quetiapine was selected on the basis of previous bipolar depression studies using the IR quetiapine formulation in which quetiapine demonstrated efficacy at 300 mg/day (Calabrese et al., 2005; Thase et al., 2006).

2. Methods

2.1. Study design

This was an 8-week, multicenter, randomized, double-blind, parallel-group, placebo-controlled, Phase III study (D144CC00002) conducted in 61 centers in the United States from December 2006 to June 2007. The screening and enrollment phase lasted for up to 35 days and included an initial screening eligibility period (up to 7 days) followed by a washout period (up to 28 days). Following enrollment, eligible patients were randomized in a 1:1 ratio to receive either quetiapine XR 300 mg once daily or placebo for 8 weeks. The study was conducted in accordance with the ethical principles in the Declaration of Helsinki and the International Committee on Harmonisation and signed informed consent was obtained from all patients prior to participation.

2.2. Patient population

Male and female outpatients, between the ages of 18 and 65 years, with a documented clinical diagnosis of bipolar I or II disorder, most recent episode depressed, as defined by DSM-IV criteria (American Psychiatric Association, 2000) were enrolled into this study. Patients with or without a rapid-cycling disease course (rapid cycling defined as ≥ 4 but ≤ 8 episodes of mood disturbance in the previous 12 months) were eligible for participation. To qualify for enrollment, patients were required to have a total score on the 17-item Hamilton Rating Scale for Depression (HAM-D_{17}) of ≥ 20, (Hamilton, 1960), a HAM-D_{17} Item 1 (depressed mood) score of ≥ 2, and a Young Mania Rating Scale (YMRS) total score of ≤ 12 (Young et al., 1978).

Patients were excluded from the study if they had a DSM-IV diagnosis of another Axis I disorder that was symptomatic or had required treatment 6 months prior to enrollment. Additional exclusion criteria included a history of current substance abuse, a history of nonresponse to an adequate trial (6 weeks) of more than two classes of antidepressants during the current episode of depression, a current episode of depression lasting for more than 12 months or commencing less than 4 weeks prior to enrollment, and clinically significant comorbid disease such as uncontrolled diabetes mellitus, renal or hepatic impairment, or coronary artery disease. Patients were excluded from the study if in the investigator's judgment they posed a current serious suicidal or homicidal risk, had a HAM-D_{17} item 3 score of ≥ 3, or had attempted suicide within the past 6 months. Female patients were excluded if they were nursing, pregnant, or were of childbearing potential and not using a reliable method of birth control.

2.3. Study medication

The quetiapine XR dose was titrated from 50 mg on Day 1 to 100 mg on Day 2, 200 mg on Day 3, and to a maximum of 300 mg on Day 4. From Day 4 to the end of the study, a fixed dose of quetiapine XR 300 mg was administered once daily in the evening.

2.4. Prior and concomitant medications

The use of nonpsychoactive medications, including over-the-counter medications for the treatment of nonpsychiatric concurrent conditions or illnesses was permitted. Concomitant use of psychoactive drugs was restricted, with the exception of the following: lorazepam (up to 2 mg/day) as rescue medication for severe anxiety; zolpidem tartrate (up to 10 mg/day), zaleplon (up to 20 mg/day), zopiclone (up to 7.5 mg/day), or chloral hydrate (up to 1 g/day) for the treatment of insomnia in instances where treatment was ongoing 28 days prior to enrollment; and anticholinergics for the treatment (but not the prevention) of extrapyramidal symptoms (EPS).

2.5. Efficacy evaluations

Clinical assessments of efficacy were conducted at baseline and at weekly intervals thereafter. The primary outcome measure was the change from baseline to Week 8 in Montgomery–Åsberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979) total score compared with placebo.

Secondary outcome measures included the change from baseline to Week 8 in MADRS total score in subgroups of patients based on diagnosis (bipolar I or bipolar II disorder) and disease course (with or without rapid-cycling disease); and MADRS individual item scores. Additional secondary outcome measures included the rates of response ($\geq 50\%$ reduction in MADRS total score) and remission (MADRS total score ≤ 12) at Week 8; Clinical Global Impression-Bipolar-Change (CGI-BP-C) at Week 8; the proportion of patients achieving CGI-BP-C of “much improved” or “very much improved” for overall bipolar illness at Week 8 (Spearing et al., 1997), and the change from baseline to Week 8 in Clinical Global Impression-Bipolar-Severity of Illness (CGI-BP-S) for overall bipolar illness (Spearing et al., 1997).