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Research report

Rates of remission/euthymia with quetiapine monotherapy compared with placebo in patients with acute mania

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Abstract

Objective: To evaluate the effects of quetiapine monotherapy compared with placebo on acute (3-week) and more sustained (12-week) rates of response and remission/euthymia in bipolar disorder patients with acute mania.
Methods: Two similar 12-week multicenter, double-blind, placebo-controlled, parallel-group studies were conducted, with an *a priori* decision to combine the data and analyze response and remission rates. Response was measured as a decrease of at least 50% in Young Mania Rating Scale (YMRS) scores from baseline to Day 21 and Day 84. Five remission/euthymia criteria were employed to determine efficacy at Day 21 and Day 84: (i) YMRS score ≤ 12; (ii) YMRS score ≤ 12 and Montgomery–Asberg Depression Rating Scale (MADRS) score ≤ 10; (iii) YMRS score ≤ 12 and MADRS score ≤ 8; (iv) YMRS score ≤ 8; and (v) YMRS score ≤ 8 plus a score ≤ 2 for the YMRS core items of Irritability, Speech, Content, and Disruptive/Aggressive Behavior.
Results: Patients treated with quetiapine ($n=208$) and placebo ($n=195$) had mean YMRS scores at entry of 33.3 ± 6.3 and 33.5 ± 6.7, respectively. Significantly higher response rates were observed with quetiapine compared with placebo, at Days 21 (48.1% versus 31.3%; $p<0.001$) and 84 (66.8% versus 40.0%; $p<0.001$). At Day 21, remission/euthymia rates with quetiapine monotherapy versus placebo were: 37.5% versus 23.1% (YMRS ≤ 12), 35.6% versus 21.5% (YMRS ≤ 12 + MADRS ≤ 10), 35.1% versus 20.0% (YMRS ≤ 12 + MADRS ≤ 8), 25.0% versus 14.4% (YMRS ≤ 8), and 21.6% versus 14.4% (YMRS ≤ 8 plus core items ≤ 2) ($p<0.01$ for all comparisons except YMRS ≤ 8 plus core items ≤ 2: $p=0.06$). By Day 84, these had increased to: 65.4% versus 35.9% (YMRS ≤ 12), 60.1% versus 30.8% (YMRS ≤ 12 + MADRS ≤ 10), 58.7% versus 29.7% (YMRS ≤ 12 + MADRS ≤ 8), 60.1% versus 30.3% (YMRS ≤ 8), and 56.7% versus 29.7% (YMRS ≤ 8 plus core items ≤ 2) ($p<0.001$ for all comparisons). The average daily dose of quetiapine in responders was 575 mg/day at Day 21 and 598 mg/day at Day 84. Quetiapine was generally well tolerated.
Conclusions: Quetiapine was associated with significantly higher response and remission/euthymia rates compared with placebo with most criteria used, in patients with acute mania at the end of both 3 and 12 weeks.

Keywords: Quetiapine; Bipolar disorder; Mania; Remission; Euthymia

1. Introduction

The degree of achievable clinical improvement is an important factor to consider when assessing treatments for bipolar disorders, particularly when considering a monotherapy treatment regimen. The most commonly

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reported threshold for degree of improvement in acute monotherapy studies in bipolar disorders is a minimum of 50% improvement from baseline in symptoms of the index episode, and is referred to as "response" (Keck et al., 2003a,b; Tohen et al., 2000, 1999). This degree of symptom attenuation, although generally considered to reflect clinically significant improvement, can still permit (particularly in patients with severe illness) substantive ongoing problematic affective symptoms and associated functional impairment. Thus, investigators and clinicians have displayed increasing interest in assessing rates of more robust improvement, which reflect minimal residual symptoms of the index episode, and putatively greater capacity to return to premorbid function (Canuso et al., 2003; Chengappa et al., 2003). The term "remission" has been employed to reflect this greater degree of improvement.

To date, there has not been a generally accepted or standard definition of remission. In general, definitions have employed an absolute final threshold (rather than a relative improvement threshold) for symptom ratings, for example having a final Young Mania Rating Scale (YMRS) (Young et al., 1978) score of 12 or less (Chengappa et al., 2003; Tohen et al., 2000) or 8 or less (Gopal et al., 2005). While this may allow a more stringent assessment of the degree of residual symptoms of the index episode, it does not account for the possibility of persistence, exacerbation, or emergence of symptoms from the opposite pole, and thus does not necessarily reflect a return to euthymia. For example, some patients with acute mania experience resolution of manic symptoms, but switch into a post-mania depression and thus remain clinically ill and functionally impaired (Maj et al., 2002). Arguably, definitions of remission that include not only a threshold for symptoms of the index episode, but also for those of the opposite pole, could be more clinically meaningful and better predict capacity for return to premorbid function. In addition to looking at symptom improvements, measures of patient functioning and quality of life can provide further insights into the patient's status following treatment.

Another important factor to consider when assessing a monotherapy treatment for bipolar disorder is the durability of improvement. Most acute studies in bipolar disorder have been designed for regulatory approval in the United States and are thus brief, lasting 3–4 weeks for acute mania (Bowden et al., 2005, 1994; Hirschfeld et al., 2004; Keck et al., 2003a,b; Tohen et al., 1999; Weisler et al., 2004; Potkin et al, 2005) and 7–8 weeks for acute bipolar depression (Calabrese et al., 1999, 2005; Tohen et al., 2003b; Thase et al., 2006). In contrast, European regulatory approval requires that efficacy is demonstrated during 12 weeks, as maintenance of effect during the episode has to be shown; thus, such studies are generally longer (Bowden et al., 2005; McIntyre et al., 2005; Smulevich et al., 2005; Tohen et al., 2003a; Vieta et al., 2005). This longer duration allows assessment of efficacy not only in the acute phase of treatment, when symptoms need to be brought under control, but also into the continuation phase of treatment, when symptomatic control is sustained for the putative duration of the index episode.

The ultimate treatment goal is sustained remission of symptoms that permits return to premorbid function. Therefore, the assessment of remission (rather than response) rates for longer durations than those reported in acute studies could provide important insights into the clinical use of therapies, and the concomitant assessment of functional status may provide a clearer picture of treatment benefits. Attainment of these goals with an effective monotherapy regimen would be a significant advance to current treatment. Monotherapy with lithium, divalproex, or an antipsychotic (preferably an atypical) is a recommended treatment approach for acute mania (American Psychiatric Association, 2002). Patients with particularly acute or severe mania or those who do not respond to monotherapy should receive a combination regimen. However, a single treatment that could provide sustained response and remission (euthymia) as monotherapy would provide a significant treatment advantage to patients with acute mania. Quetiapine is approved for the treatment of patients with acute mania associated with bipolar disorder, either as monotherapy or in combination with lithium (Li) or divalproex (DVP).

This paper reports response and remission rates from a pooled analysis of two large international, multicenter, randomized, double-blind, placebo-controlled studies (Study 104 and Study 105) that evaluated the effects of quetiapine monotherapy in patients with acute mania. The primary results of these studies have been published (Bowden et al., 2005; McIntyre et al., 2005). *A priori*, it was decided that the two studies would be conducted according to pre-defined, similar protocols to allow the 3-week and 12-week data from the quetiapine and placebo groups from each study to be combined (Bowden et al., 2005; McIntyre et al., 2005), thus increasing the statistical power of the current analysis and allowing better estimation of the effects of quetiapine monotherapy *vs* placebo on remission/euthymia rates in patients with acute mania.

Five different remission/euthymia criteria were defined to explore the effects of quetiapine on acute mania. Other measures assessed were the Clinical Global Impression—Bipolar Version (CGI-BP) Severity