

Quetiapine or haloperidol as monotherapy for bipolar mania—a 12-week, double-blind, randomised, parallel-group, placebo-controlled trial[☆]

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Abstract

Methods: Patients ($n=302$) with bipolar I disorder (manic episode) were randomised to 12 weeks' double-blind treatment with quetiapine (flexibly dosed up to 800 mg/day), placebo, or haloperidol (up to 8 mg/day). The primary efficacy outcome variable was change from baseline to Day 21 in Young Mania Rating Scale (YMRS) score. **Results:** YMRS score improved with quetiapine at Day 21 (-12.29 versus -8.32 for placebo; $P<0.01$). The difference in favor of quetiapine increased by Day 84 (-17.52 versus -9.48 ; $P<0.001$). Haloperidol also showed an advantage over placebo at Days 21 and 84 ($P<0.001$). There was no significant difference in efficacy measures between quetiapine and haloperidol groups at any assessment except Day 21. The only common adverse event with quetiapine was somnolence (12.7%). Extrapyramidal symptoms (EPS), including akathisia, occurred at 59.6% with haloperidol, 12.7% with quetiapine, 15.8% with placebo. Most quetiapine responders (84%) received a dose of 400–800 mg/day. **Conclusion:** Quetiapine was effective and well tolerated. The efficacy and tolerability profile of haloperidol (including its propensity for EPS) supported study validity.

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1. Introduction

Bipolar disorder is a devastating illness that is usually chronic, recurring, and associated with considerable morbidity, mortality, and caregiver burden. While pharmacotherapy can substantially reduce morbidity, many patients do not fully respond to standard treatments and have poor long-term outcomes following hospitalisation for a manic episode (Dittmann et al., 2002; Keck et al., 1998).

First-line options for the treatment of mania include monotherapy with lithium, divalproex, or an antipsychotic.

When choosing an antipsychotic, treatment guidelines generally recommend the use of atypical antipsychotics over conventional (typical) antipsychotics based on their equivalent efficacy and more favorable tolerability profile (American Psychiatric Association, 2002; Goodwin, 2003; Grunze et al., 2003).

The general effectiveness of atypical antipsychotics offers an improvement over their therapeutic predecessors, the conventional antipsychotics. The atypical agents, however, are not without adverse events. For example, some atypical agents are associated with clinically significant weight gain, QTc prolongation, and extrapyramidal symptoms (EPS) within their therapeutic dose range. Moreover, patients with bipolar disorder often receive polypharmacotherapy with a potentially additive effect on the overall adverse event burden. Studies that can identify specific atypical antipsychotics that combine broad efficacy with favorable tolerability are warranted, particularly

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as adherence to pharmacotherapy is influenced by these factors.

Several atypical antipsychotics have been shown to be effective as monotherapy and combination therapy in the treatment of mania, in large, randomized, placebo-controlled clinical studies (Tohen et al., 1999, 2000, 2002; Keck et al., 2003; Segal et al., 1998; Hirschfeld et al., 2004; Yatham et al., 2003; Sachs et al., 2002).

Quetiapine fumarate (Seroquel[®]) has demonstrated efficacy as monotherapy in the treatment of schizophrenia. The safety profile of quetiapine in populations with schizophrenia is favorable relative to placebo and active comparators (Kasper et al., 2001; Arvanitis and Miller, 1997; Copolov et al., 2000; Emsley et al., 2000; Small et al., 1997). Specifically, placebo-level EPS and serum prolactin concentration, as well as moderate weight gain, have been noted with quetiapine.

Results from several preliminary clinical studies suggested that quetiapine is effective and well tolerated in the treatment of mania associated with bipolar disorder (Del-Bello et al., 2002; Vieta et al., 2002; Ghaemi et al., 2003; Chisholm et al., 2001; Dunayevich et al., 2001; Sajatovic et al., 2001; Zarate et al., 2000; Kasper et al., 2001). The present study was undertaken to further characterize the effectiveness of quetiapine when used as monotherapy for the treatment of bipolar mania for up to 12 weeks of double-blind, parallel-group treatment.

2. Patients and methods

This international, multicenter, double-blind, randomised, parallel-group, controlled trial compared the efficacy and safety of quetiapine with placebo for 12 weeks in patients hospitalised for the treatment of mania associated with bipolar I disorder.

The study was conducted at sites in South America, Asia, and Europe in accordance with the standards and guidelines established in the current amendment of the Declaration of Helsinki, and consistent with Good Clinical Practice (GCP) guidelines and applicable regulatory requirements. All subjects were inpatients at the start of the study. Patients screened as outpatients who subsequently required hospitalization for treatment of an acute manic episode were also eligible. Written informed consent was obtained from all patients prior to any study-related activities and the study protocol was reviewed and approved by the appropriate institutional review boards.

2.1. Inclusion and exclusion criteria

Eligible patients were aged 18 years and older and hospitalised with a *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV) diagnosis of bipolar I disorder, current episode manic, with or without

psychotic features. All patients had at least one prior, reliably documented, manic or mixed episode.

Subjects were required to have a minimum score of 20 on the Young Mania Rating Scale (YMRS), plus a score of at least 4 on two of the core YMRS items of Irritability, Speech, Content, and Disruptive/Aggressive Behaviour at screening and at randomisation. A score of at least 4 was also required on the Severity of Illness item of the Clinical Global Impressions–Bipolar (CGI–BP) assessment tool, ensuring that patients were at least moderately ill (or worse) at entry.

Patients were excluded if they had received treatment with clozapine within 28 days of the start of the trial; had an index manic episode judged to be the direct physiological consequence of a medical condition, treatment, or substance abuse; or had been hospitalised for 3 weeks or longer for the index manic episode. Patients were excluded who met DSM-IV criteria for rapid cycling or a current mixed episode, as were those with known intolerance or lack of response to quetiapine or clozapine.

Use of the following medications was a criterion for excluding patients: antihypertensive agents if a stable dose had not been administered for at least 1 month before randomisation; antidepressants in the week (or a period of 5 half-lives of the drug) before randomisation; continuous daily use of benzodiazepines in excess of 4 mg/day of lorazepam, or the equivalent, during the month preceding screening (the week prior to randomisation); potent cytochrome P450 inducers, potent cytochrome P450 3A4 inhibitors, or thioridazine in the 14 days prior to randomisation; and depot antipsychotic medication within one dosing interval prior to randomisation.

Other exclusion criteria were clinically significant electrocardiographic (ECG) or laboratory abnormalities, e.g., thyroid-stimulating hormone (TSH) concentration more than 10% above the upper limit of the normal range. Patients with an unstable medical disorder, history of seizure disorder (except febrile convulsions), substance or alcohol dependence within a month of randomisation, electroconvulsive therapy in the 30 days prior to randomisation, and participation in another clinical study or compassionate use program within 4 weeks of randomisation also were excluded, as were pregnant or lactating women.

2.2. Patient population and study medication

Subjects were recruited at 49 centers in South America, Asia, and Europe between 7 January 2001 and 25 April 2002. Patients were screened within 7 days of randomisation and those who met enrollment criteria were randomly assigned to one of three groups (quetiapine, placebo, or haloperidol) to achieve a target ratio of 1:1:1 in each group.

All study medications were flexibly dosed and administered in double-blind fashion twice daily in identical number, form, and color, throughout the 3-month study

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