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Research Report

First controlled treatment trial of bipolar II hypomania with mixed symptoms: Quetiapine versus placebo ☆

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ABSTRACT

Objectives: To compare the efficacy and safety of adjunctive quetiapine (QTP) versus placebo (PBO) for patients with bipolar II disorder (BDII) currently experiencing mixed hypomanic symptoms in a 2-site, randomized, placebo-controlled, double-blind, 8-week investigation.
Methods: Participants included 55 adults (age 18–65 years) who met criteria for BDII on the Structured Clinical Interview for DSM-IV-TR (SCID). Entrance criteria included a stable medication regimen for $\geq$2 weeks and hypomania with mixed symptoms ($\geq$12 on the Young Mania Rating Scale [YMRS] and $\geq$15 on the Montgomery Asberg Depression Rating Scale [MADRS] at two consecutive visits 1–3 days apart). Participants were randomly assigned to receive adjunctive quetiapine (n=30) or placebo (n=25).
Results: Adjunctive quetiapine demonstrated significantly greater improvement than placebo in Clinical Global Impression for Bipolar Disorder Overall Severity scores ($F(1)=10.12$, $p=.002$) and MADRS scores ($F(1)=6.93$, $p=.0138$), but no significant differences were observed for YMRS scores ($F(1)=3.68$, $p=.069$). Side effects of quetiapine were consistent with those observed in previous clinical trials, with sedation/somnolence being the most common, occurring in 53.3% with QTP and 20.0% with PBO.
Conclusions: While QTP was significantly more effective than PBO for overall and depressive symptoms of BDII, there was no significant difference between groups in reducing symptoms of hypomania. Hypomania improved across both groups throughout the study.

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1. Introduction

While the lifetime prevalence of DSM-IV-TR defined bipolar II disorder (BDII) is estimated at about 1% (Merikangas et al., 2007), the prevalence may increase to 3% or more when broader diagnostic criteria are applied (Akiskal, 1996; Benazzi, 1999; Angst, 1998; Cassano et al., 1999; Angst et al., 2010; Merikangas et al., 2011; Angst et al., 2011). Patients with BDII experience similar levels of disability as those with BDI (MacQueen and Young, 2001; Coryell et al., 1989; Judd and Akiskal, 2003; Kupka et al., 2007; Suppes and Dennehy, 2002).

Mixed states, in which manic or hypomanic and depressive symptoms occur concurrently or in close temporal proximity, were recognized and described historically (Angst and Marneros, 2001; Marneros, 2001; Salvatore et al., 2002). The DSM-IV-TR nosology does not include mixed symptoms occurring during hypomania or subsyndromal mixed episodes, but includes only mixed episodes, which require individuals to meet full criteria for a major depressive episode and manic episode simultaneously.

We recently characterized prevalence of hypomania with mixed symptoms in over 900 patients with bipolar disorders in a naturalistic prospective study (Suppes et al., 2005). Hypomania

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with mixed symptoms was defined at a minimum as mild depressive symptoms, of inadequate number or intensity to qualify for a fully depressive episode, accompanying hypomanic symptoms. In the subsample with BDII disorder ($n=187$), depressive symptoms were present in 76% of hypomanic visits (Suppes et al., 2005). While hypomanic symptoms were less likely to occur in patients with BDII versus BDI, once hypomanic symptoms occurred they were equally likely to be mixed regardless of BDI or BDII diagnosis.

Benazzi (2007) described the prevalence of dysphoric, or mixed, hypomania in a cohort of 441 patients with BDII disorder. In this study, hypomania with mixed symptoms was defined as the co-occurrence of DSM-IV-TR irritable mood hypomania and a major depressive episode (MDE). Hypomania with mixed symptoms was present in 17% of those with a current MDE. Compared to classic euphoric hypomanic symptoms recalled by 275 remitted patients with BDII, hypomania with mixed symptoms was characterized by more racing thoughts, smaller increase in goal directed behavior, and greater loss of function. Dilsaver and Akiskal (2009) found a severe diurnal variation in bipolar children and adolescents such that they awoke feeling depressed and lethargic and became hypomanic in the evening, often with spikes of euphoria. Patients presenting with mixed symptoms often represent more complex presentations of bipolar disorder (Bauer et al., 1994; McElroy et al., 1992). In acute treatment, patients with mixed symptoms may have poorer outcomes with lithium or antidepressants than those with more classic presentations (McElroy et al., 1992; Swann et al., 1997). To our knowledge, there have been no controlled clinical trials assessing treatment options for patients with BDII experiencing hypomania with mixed symptoms. The current study presents findings from a small clinical trial assessing the efficacy and safety of adjunctive quetiapine versus placebo in this understudied patient population.

2. Methods

2.1. Study design

This study (NCT00186043) was a two-site, 8-week, randomized, double-blind, placebo-controlled investigation of adjunctive quetiapine (QTP) versus placebo (PBO) for the treatment of patients diagnosed with BDII disorder experiencing hypomania with mixed symptoms defined as scores of $\geq$12 on the Young Mania Rating Scale (YMRS) (Young et al., 1978) and $\geq$15 on the Montgomery Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979).

Physicians, raters, and patients were blind to group assignment (QTP or PBO). Dosing of quetiapine was flexible to allow consideration of individual patient symptoms and tolerability, with each participant required to reach a minimum dose of 100 mg/day for at least 2 days by end of week 1, and after reaching this minimum, it was allowed to decrease QTP due to side effects to 50 mg/day. The maximum daily dose was 800 mg/day. Low dose, time-limited, adjunctive use of benzodiazepine (lorazepam) was allowed in the first 2 weeks of the study for the management of acute agitation (maximum 10 mg/day allowed).

The study was approved by institutional review boards from both sites (UT Southwestern Medical Center [Suppes] and Stanford University [Ketter]), and all patients provided verbal and written informed consent prior to participation.

2.2. Participants

Fifty-five subjects were consented across two sites: (1) UT Southwestern Medical Center and (2) Stanford University. Subjects were required to be 18–65 years of age (inclusive), have a diagnosis of BDII disorder verified by Structured Clinical Interview for DSM-IV-TR (SCID) (First et al., 2002) mood disorders module interview, already have been prescribed a stable medication regimen (including the possibility of no psychotropic medications) for at least 2 weeks prior to study entry, and use of a reliable method of contraception for women of child bearing potential. Additionally, potential participants were required to meet the entry criteria for hypomania with mixed symptoms at two consecutive visits 1–3 days apart. Potential participants who met DSM-IV-TR criteria for substance abuse or dependence within the last month were excluded.

Scores on the YMRS and MADRS obtained on the same day were used to define those individuals experiencing hypomania with mixed symptoms. For purposes of this analysis, the definitions for hypomania (YMRS) and depression (MADRS) were intentionally broad. A YMRS score of 12 or higher is considered reflective of at least mild hypomania (symptoms adequate to meet DSM-IV-TR hypomania criteria). We required scores on the MADRS to be greater than or equal to 15, which is considered reflective of at least mild to moderate depression.

2.3. Statistics

At each visit, participants completed assessment interviews including the YMRS, MADRS, Inventory of Depressive Symptomatology-Clinician-Rated (IDS-C) (Rush et al., 1996; Trivedi et al., 2004), Clinical Global Impression-Bipolar Disorder (CGI-BD) (Spearing et al., 1997), Global Assessment of Functioning (GAF) (Endicott et al., 1976), and the Positive Syndrome subscale of the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). The primary outcome measure was improvement on the CGI-BD Overall Severity (considering both depressive and mood elevation components). Changes in YMRS, MADRS, and GAF scores were key secondary outcome measures.

The *a priori* primary outcome of the study was the change in the CGI-BD Overall Severity. To understand the trajectory of change over study duration, Hierarchical Linear Modeling (HLM) was conducted on all outcome measures with predictor variables defined for group (QTP or PBO), time in study (in weeks), baseline symptoms, and group-by-time interaction. This interaction term was used to determine if, over time, participants in the QTP group improved at a different rate than participants in the PBO group. The natural log of weeks from baseline was used to give a more nearly linear relationship of outcomes to time in the study. To account for baseline severity, baseline scores on outcome measures were included in each model as a covariate. Outcome scores were modeled starting at the first visit after baseline (study week 1). For each outcome variable, effect size was calculated using Cohen's *d* and a continuous Number Needed to Treat (NNT). Improvement from baseline to final visit was calculated and continuous NNT was estimated at 1/(2AUC-1) where AUC is the area under the Receiver Operating Characteristic (ROC) curve (Kraemer and Kupfer, 2006).

Response and remission rates were also compared between the treatment groups with response defined as an improvement of 50% or more and remission defined as scores of 7 or less on the MADRS and YMRS, and 2 or less on the CGI-BD Overall Severity item. The way NNT is often calculated evaluating psychiatric studies is to set a specific symptom measure cut point as the variable of interest to determine NNT (Ketter et al., 2011). We refer to this here as dichotomous NNT (in contrast to continuous NNT discussed above) which we calculated for response and remission by dichotomizing outcome variables into "successes" and "failures" at the cut points described above and calculating the Success Rate Difference (SRD) by subtracting the success rates