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Research report

Efficacy and tolerability of extended release quetiapine fumarate (quetiapine XR) monotherapy in major depressive disorder: A placebo-controlled, randomized study ☆

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ABSTRACT

Background: Evaluate the efficacy and tolerability of extended release quetiapine fumarate (quetiapine XR) once-daily monotherapy for patients with major depressive disorder (MDD).
Methods: In this 10-week, (8-week active treatment phase and 2-week drug-discontinuation/tapering phase), multicenter, parallel-group, placebo-controlled, double-blind, randomized, Phase III study (D1448C00003: Opal), patients initially received quetiapine XR 150 mg/day or placebo. At Week 2, inadequate responders (<20% reduction in MADRS total score) were up-titrated to 300 mg/day quetiapine XR or matching placebo for the final 6 weeks. Primary endpoint: change from randomization to Week 8 in MADRS total score. Secondary endpoints included: MADRS response (≥50% reduction in total score from randomization) and changes from randomization to Week 8 in HAM-D and CGI-S.
Results: 310 patients were randomized. At Week 8, quetiapine XR significantly reduced mean MADRS total score versus placebo (−16.49 vs −13.10, respectively; $p<0.01$). Mean MADRS score was significantly reduced by quetiapine XR versus placebo at Week 1 ($p<0.05$). MADRS response rates were significantly greater at Week 8 for quetiapine XR versus placebo (61.9% vs 48.0%, respectively; $p<0.05$). Significant changes in HAM-D total score and CGI-S were seen at Week 8 for quetiapine XR versus placebo. Withdrawal rates due to AEs were 9.9% and 2.6% for quetiapine XR and placebo, respectively. Common AEs (>10% any group during the randomized phase) for quetiapine XR and placebo, respectively were dry mouth (32.9% and 6.5%), sedation (21.7% and 1.9%), somnolence (20.4% and 5.2%), and headache (10.5% and 10.3%).
Limitations: The study was not designed to compare quetiapine XR 150 mg/day and 300 mg/day; it was intended to reflect dose titration that might occur in clinical practice.
Conclusions: Quetiapine XR monotherapy is effective in patients with MDD, with symptom improvement seen as early as Week 1, and tolerability results consistent with the known profile of quetiapine.

☆ *Trial Registration:* clinicaltrials.gov Identifier: NCT00326144.

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1. Introduction

Major depressive disorder (MDD) is a common disorder, affecting more than 16% of adults at some point in their life (Kessler et al., 2003) and has high comorbidity with other psychiatric disorders and physical illness (Kessler et al., 1996).

In its most severe form, MDD may be accompanied by suicidal ideations, and it has been estimated that approximately 3–4% of patients with MDD commit suicide (Blair-West et al., 1997). As a result of the decreased physical functioning experienced by patients with MDD, many have decreased social, occupational, and educational functioning leading to a high level of reported disability (Ustun et al., 2004). A considerable societal and economic burden (Prince et al., 2007; Ustun et al., 2004) is posed by the direct and indirect costs of this associated disability and the treatment of patients with MDD.

Existing first-line pharmacotherapy for MDD includes the selective serotonin reuptake inhibitors (SSRIs), and selective serotonin norepinephrine reuptake inhibitors (SNRIs). Although both classes of antidepressants are efficacious (Anderson, 2000), 30–45% of patients show partial or no response to first-line antidepressant therapy of adequate dose and duration (Fava and Davidson, 1996). In addition, onset of symptom relief may not occur until after 2–3 weeks of treatment (Rush et al., 2003) with only 28% of patients achieving remission within 10–14 weeks (Trivedi et al., 2006). These findings indicate that existing treatments for MDD provide suboptimal therapy and that there is a clear need for additional treatment options.

Quetiapine and its major active human metabolite, norquetiapine, have a combination of effects on several central neuroreceptors. These include moderate to high antagonist affinity for serotonin $5HT_{2A}$ receptors and moderate affinity for dopamine D_2 and $5HT_{1A}$ receptors (Goldstein et al., 2008). Furthermore, norquetiapine has been shown to be a potent inhibitor of the norepinephrine transporter (NET) (Jensen et al., 2008). Inhibition of NET is a common mechanism of action for several antidepressants and may explain, at least in part, why quetiapine is effective against depressive symptoms.

Results from earlier small studies have suggested that quetiapine is effective as an adjunct treatment to antidepressants for the treatment of MDD with comorbid anxiety and in treatment-resistant depression (Adson et al., 2004; Doree et al., 2007; Mattingly et al., 2006; McIntyre et al., 2007; Yargic et al., 2004). Furthermore, several large, randomized, double-blind, parallel-group, placebo-controlled, studies from a large clinical trial program, have demonstrated that once-daily quetiapine XR is effective both as monotherapy in the treatment of patients with MDD (Cutler et al., 2009; Weisler et al., 2009) and also as adjunct therapy in patients with MDD with an inadequate response to antidepressant treatment (Bauer et al., 2009; El-Khalili et al., 2010). The results of a study investigating quetiapine XR monotherapy as a maintenance treatment for MDD demonstrate that the level of improvement in depressive and anxiety symptoms is maintained over the longer term (Liebowitz et al., 2010).

The aim of this flexible-dose study was to evaluate the efficacy and tolerability of quetiapine XR as once-daily monotherapy for MDD.

2. Methods

2.1. Study design

This was a 10-week multicenter, parallel-group, placebo-controlled, double-blind, double-dummy, randomized study (D1448C00003: Opal).

After withdrawal of previous protocol-mandated psychotropic medication during a 1- to 4-week enrollment/washout period, eligible patients entered an 8-week, randomized active treatment period followed by a 2-week follow-up period.

The study protocol was approved by Institutional Review Boards for each study site and performed in accordance with the Declaration of Helsinki and the International Conference on Harmonization/Good Clinical Practice guidelines. All patients provided written informed consent.

2.2. Patients

Male or female patients (aged 18–65 years), with a Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) (American Psychiatric Association, 1994) diagnosis of MDD (single episode or recurrent), were eligible for inclusion in the study. The diagnosis was confirmed by the Mini-International Neuropsychiatric Interview (Sheehan et al., 1998).

Patients were required to have a Hamilton Rating Scale for Depression (HAM-D; 17-item) total score $\geq$22 and a HAM-D Item 1 (depressed mood) score $\geq$2 at both enrollment and randomization (Hamilton, 1960).

Patients were excluded from the study if they had been diagnosed with any DSM-IV Axis I disorder other than MDD within 6 months prior to enrollment or any DSM-IV Axis II disorder that had a major impact on the patient's current psychiatric status, if the current episode of depression exceeded 12 months or had started less than 4 weeks prior to enrollment, or if they had an inadequate response to at least 6 weeks of treatment with two or more classes of antidepressants during the current episode. Additional exclusion criteria included substance or alcohol abuse within 6 months prior to enrollment, a current serious suicidal or homicidal risk, a HAM-D Item 3 score $\geq$3, or a suicide attempt within the past 6 months; a clinically significant medical illness; or any clinically significant findings on laboratory tests or electrocardiogram (ECG); or use of drugs that induce or inhibit the hepatic metabolizing cytochrome P450 3A4 enzymes within 2 weeks prior to randomization. Prior to randomization, patients could not have received any antipsychotic, mood stabilizer, or antidepressant medications within 7 days prior to randomization, monoamine oxidase inhibitors, anxiolytics, or hypnotics within 14 days, fluoxetine within 28 days, or use of a depot antipsychotic injection within two dosing intervals prior to randomization. Patients were permitted to receive psychotherapy during the study period if it had been ongoing for a minimum of 3 months prior to randomization.

2.3. Study medication and dosing schedule

Quetiapine XR and placebo were administered once daily, orally and in the evening. All patients randomized to quetiapine XR received 50 mg/day on Day 1 and were