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Brief report

Pooled analysis of sustained response rates for extended release quetiapine fumarate as monotherapy or adjunct to antidepressant therapy in patients with major depressive disorder

Eduard Vieta [a,*], Michael Bauer [b], Stuart Montgomery [c], Roger S. McIntyre [d], Johan Szamosi [e], Willie R. Earley [f], Hans Eriksson [e]

[a] Clinical Institute of Neuroscience, Hospital Clinic, University of Barcelona, IDIBAPS, CIBERSAM, Barcelona, Spain
[b] Department of Psychiatry and Psychotherapy, University Hospital Carl Gustav Carus, Dresden, Germany
[c] Emeritus Professor of Psychiatry, Imperial College, University of London, PO Box 8751, London, UK
[d] Psychopharmacology Unit, Department of Psychiatry, University Health Network, Toronto, Ontario, Canada
[e] Formerly AstraZeneca, Södertälje, Sweden
[f] Formerly AstraZeneca, Wilmington, Delaware, USA

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ABSTRACT

Background: Clinical trials are not generally powered to analyze outcomes such as sustained response. We evaluated sustained response rates for patients with major depressive disorder receiving quetiapine XR as monotherapy or adjunct therapy.

Method: Post hoc analyses of pooled data from four previously reported randomized, placebo-controlled studies of quetiapine XR 150 and 300 mg/day as monotherapy or adjunct therapy to ongoing antidepressant. Sustained response rates (≥50% reduction in MADRS total score at specific timepoint and each subsequent visit until Week 6) were calculated at Weeks 1, 2, and 4; rates were compared using a Cochran–Mantel–Haenszel analysis.

Results: In the monotherapy studies, the proportion of patients experiencing sustained response was greater with quetiapine XR 150 mg/day versus placebo at Week 2 (20.0% vs. 13.3%; $p<0.05$) and Week 4 (33.3% vs. 23.3%; $p<0.01$) (observed cases [OC]). The corresponding sustained response rates for quetiapine XR 300 mg/day were 18.0% ($p=0.104$) and 29.7% ($p=0.063$), respectively (OC).

The proportion of patients experiencing sustained response was greater in the adjunct studies versus placebo at Weeks 2 and 4 for quetiapine XR 150 (Week 2, 30.1% vs. 15.2%, $p<0.001$; Week 4, 40.1% vs. 32.0%, $p<0.05$) and 300 mg/day (Week 2, 29.0% vs. 15.2%, $p<0.001$; Week 4, 42.0% vs. 32.0%, $p<0.05$) (OC).

Limitations: Post hoc analyses, acute treatment period; no active comparator.

Conclusions: Quetiapine XR as monotherapy (150 mg/day at Weeks 2 and 4) or adjunct to ongoing antidepressant therapy (150 and 300 mg/day at Weeks 2 and 4) increased sustained response rates versus placebo.

1. Introduction

Current treatment options for major depressive disorder (MDD), including selective serotonin reuptake inhibitors (SSRIs) and serotonin–norepinephrine reuptake inhibitors (SNRIs), may be associated with a delay, typically of at least 2 weeks, between the initiation of therapy and onset of improvement in depressive symptoms (Machado-Vieira et al., 2008).

However, any medication that achieves an early clinical improvement is of little substantial therapeutic benefit if the response plateaus shortly after onset, or is followed quickly by relapse. Thus, obtaining a sustained improvement in depressive symptoms is a fundamental challenge in the development of new therapies for MDD (Brannan et al., 2005), and there is increasing interest in applying novel and more ecologically valid outcomes beyond the traditionally defined outcomes of response and remission in clinical trials for mood disorders (Miret et al., in press; Vieta and Colom, 2011).

Extended release quetiapine fumarate (quetiapine XR) has demonstrated efficacy in the acute treatment of MDD in adult patients both as monotherapy (Bortnick et al., 2011; Cutler et al.,

* Correspondence to: Department of Psychiatry, Clinical Institute of Neuroscience, Hospital Clinic, University of Barcelona, IDIBAPS, Villarroel 170/Rossello 140, 08036 Barcelona, Spain. Tel.: +34 932 275 401; fax: +34 932 275 477.
E-mail address: evieta@clinic.ub.es (E. Vieta).

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2009; Weisler et al., 2009) and as an adjunct therapy for patients with an inadequate response to antidepressant therapy, with improvements in severity rating scales scores seen as early as the first week of treatment (Bauer et al., 2009; El-Khalili et al., 2010). We present post hoc analyses, based on four acute studies, to assess the sustained response rates for quetiapine XR as monotherapy and adjunct therapy in patients with MDD. Sustained response rates may be more clinically meaningful than mere rating scales changes from baseline.

2. Methods

2.1. Study design and treatment

Pooled data from the quetiapine XR 150 mg/day and 300 mg/day groups in two monotherapy studies (Study 1 [Weisler et al., 2009]; Study 2 [Cutler et al., 2009]) and two adjunct therapy studies (Study 6 [El-Khalili et al., 2010]; Study 7 [Bauer et al., 2009]) were evaluated (Bauer et al., 2010; Weisler et al., 2012).

For all studies, Institutional Review Board or Independent Ethics Committee approval was obtained at each study center. In accordance with the Declaration of Helsinki, International Conference of Harmonisation, Good Clinical Practice guidelines, and applicable regulatory requirements were adhered to. All patients provided written informed consent.

2.1.1. Monotherapy (Studies 1 and 2)

Full details of the designs of the two monotherapy studies presented here have been reported previously (Study 1 [Weisler et al., 2009]; Study 2 [Cutler et al., 2009]; pooled analysis of Studies 1 and 2 [Weisler et al., 2012]). For the present post hoc analysis, data were pooled and evaluated from the quetiapine XR 150 mg/day and 300 mg/day groups only. Results from the quetiapine XR 50 mg/day and duloxetine arm have been reported previously (Cutler et al., 2009; Weisler et al., 2009).

In both studies, quetiapine XR was initiated at 50 mg/day on Days 1–2, and increased to 150 mg/day on Days 3–4, and to 300 mg/day on Day 5.

2.1.2. Adjunct therapy (Studies 6 and 7)

The methodology employed in the two adjunct therapy studies described here have been reported in detail previously (Study 6 [El-Khalili et al., 2010]; Study 7 [Bauer et al., 2009]; pooled analysis of Studies 6 and 7 [Bauer et al., 2010]). Patients were randomized to receive quetiapine XR (150 or 300 mg/day) or placebo as adjunct to ongoing antidepressant therapy. Quetiapine XR was initiated at a dose of 50 mg/day on Days 1–2, 150 mg/day on Days 3–4, and 300 mg/day on Day 5.

2.2. Patients

In brief, male and female outpatients (aged 18–65 years) with a Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV; Studies 1, 2, and 6) or DSM-IV-Text Revision (DSM-IV-TR; Study 7) diagnosis of MDD (single episode or recurrent), as confirmed by the Mini-International Neuropsychiatric Interview (Sheehan et al., 1998), were eligible for inclusion in these studies.

Full details of the inclusion and exclusion criteria for the individual studies have been reported previously (Study 1 [Weisler et al., 2009]; Study 2 [Cutler et al., 2009]; Study 6 [El-Khalili et al., 2010]; Study 7 [Bauer et al., 2009]).

2.3. MADRS response rates and sustained response

This post hoc analysis assessed the proportion of patients experiencing a sustained response at each week. Sustained response was defined as $\geq$50% reduction in MADRS total score from randomization at the specific visit assessed and at all subsequent visits until Week 6. MADRS response rates ($\geq$50% decrease in MADRS total score from randomization) are also reported at Weeks 2 and 4 (Weeks 1 and 6 have been reported previously).

Using a conservative approach, analysis of sustained response was performed for observed cases (OC), assuming that patients withdrawing early from treatment are treatment failures. To enable comparisons with previously reported studies, an analysis was also performed using the last observation carried forward (LOCF) method.

2.4. Statistical analysis

Analyses of pooled data were performed on the modified intent-to-treat (MITT) populations (all randomized patients who received study medication and had randomization and $\geq$1 post-randomization MADRS assessments) of Studies 1 and 2 (monotherapy studies) and Studies 6 and 7 (adjunct therapy studies).

MADRS response rates at Weeks 2 and 4 were analyzed using a logistic regression model; p-values reported are nominal with no adjustment for multiplicity.

Analysis of sustained response rate was performed using the Cochran–Mantel–Haenszel (CMH) test. The control variable used in the present analysis was 'study'. The comparison between quetiapine XR and placebo is reported as relative risk together with the 95% confidence interval.

All statistical analyses were two-sided with 5% used as evidence of a difference given the post hoc nature of the analyses.

3. Results

3.1. Patient population

For the monotherapy studies, data were pooled from 1002 patients who received randomized treatment in the two studies. The pooled MITT population comprised 968 patients (quetiapine XR 150 mg/day, n=315; 300 mg/day, n=323; or placebo, n=330), (Weisler et al., 2012).

Across the two adjunct therapy studies, a total of 939 patients were randomized. The pooled MITT population consisted of 919 patients (quetiapine XR 150 mg/day, n=309; 300 mg/day, n=307; placebo, n=303) (Bauer et al., 2010).

Baseline demographic and clinical characteristics for both the monotherapy and the adjunct therapy studies were generally well matched across the treatment groups (Table 1).

3.2. MADRS response rates and sustained response

3.2.1. Monotherapy (Studies 1 and 2)

MADRS response rates at Weeks 1 and 6 have been reported previously (Weisler et al., 2012). At Week 2, response rates were greater for quetiapine XR 150 mg/day (33.0%, $p<0.001$) and 300 mg/day (33.9%, $p<0.001$) versus placebo (21.2%). Response rates at Week 4 were also greater for quetiapine XR 150 mg/day (43.2%, $p<0.01$) and 300 mg/day (42.4%, $p<0.01$) versus placebo (30.9%).

In the quetiapine XR 150 mg/day group, a greater proportion of patients experienced a sustained response at Weeks 2 and 4 compared with placebo (OC: Week 2, $p<0.05$; Week 4, $p<0.01$;