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Brief report

Efficacy, safety and tolerability of quetiapine augmentation in treatment resistant depression: An open-label, pilot study

I.M. Anderson [a,*], A. Sarsfield [a], P.M. Haddad [b]

[a] Manchester Mental Health and Social Care Trust/University of Manchester M13 9WL, United Kingdom
[b] Greater Manchester West Mental Health NHS Foundation Trust, Salford M30 0GT, United Kingdom

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ABSTRACT

Background: Atypical antipsychotics may have efficacy as augmentation therapy in treatment resistant depression (TRD) but evidence is limited.

Methods: An open label study of quetiapine augmentation in 24 patients (mean age: 46.3 years) with a DSM-IV major depressive episode resistant to at least 2 trials of antidepressant medication, and currently taking a monoamine reuptake inhibitor. An 8-week treatment phase was followed by an 18-week extension in patients who showed clinical benefit.

Results: Eighteen patients (75%) completed the 8-week treatment phase with seven patients (29%) being responders on the Montgomery Åsberg Depression Rating Scale and 13 (54%) on the CGI-I. Fewer patients responded if they had previously received olanzapine in the current episode but this was not statistically significant (0% v 37%, $p=0.27$). Of the eleven patients entering the extension phase, 3 patients (27%) experienced a significant worsening of mood. The most common adverse events were sedation (54%), dry mouth (38%) and dizziness (29%). Significant weight gain was found in 40% of patients treated for 26 weeks. Average quetiapine doses were 245 mg at 8 weeks and 346 mg at 26 weeks.

Conclusions: Quetiapine may be a helpful adjunctive agent for some patients with TRD but placebo-controlled trials are needed to establish its place in management.

Limitations: The trial was open-label and the numbers were small.

1. Introduction

As many as one-third of depressed patients fail to respond to two or more trials of antidepressants (Rush et al., 2006) making treatment resistant depression (TRD) a major clinical problem. Treatment options for non-responders include optimising the dose of existing medication, switching antidepressant or augmentating with other treatments (Anderson et al., 2008).

There is accumulating evidence to support the efficacy of augmentation with atypical antipsychotics but at the price of increased adverse events (Papakostas et al., 2007). The atypical antipsychotic quetiapine has been shown to be an effective treatment for bipolar depression (Calabrese et al., 2005; Thase et al., 2006) and recent short-term pilot studies suggest that quetiapine is effective in augmenting antidepressants in unipolar depression (McIntyre et al., 2007; Dorée et al., 2007). However little is known about whether efficacy is sustained or whether failure to respond to augmentation with another atypical antipsychotic will reduce subsequent response to quetiapine.

The current open study examined the clinical use of quetiapine augmentation in TRD with an emphasis on safety and tolerability, whether the effect was sustained in patients deriving initial benefit and whether prior treatment with another atypical antipsychotic in the current episode would reduce its efficacy.

* Corresponding author. Neuroscience and Psychiatry Unit, Room G809, Stopford Building, The University of Manchester, Oxford Road, Manchester, M13 7PT, United Kingdom. Tel./fax: +44 161 275 7428.
E-mail address: ian.anderson@manchester.ac.uk (I.M. Anderson).

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2. Methods

2.1. Patients

Inpatients and outpatients aged 18 to 65 years with a DSM-IV major depressive episode resistant to at least 2 adequate trials of medication and who were taking a monoamine reuptake inhibitor were recruited. A minimum Montgomery Åsberg Rating Scale (MADRS) (Montgomery and Åsberg, 1979) score of 20 was required and exclusion criteria included bipolar, non-affective psychotic or organic disorders, substance dependence, serious suicidal risk and significant medical illness or drugs that might interact with quetiapine.

The study was approved by a Local Research Ethics Committee and written informed consent was obtained.

2.2. Study design

This open study of adjunctive quetiapine consisted of a 2 week titration phase, a 6 week treatment phase and an 18 week extension phase for patients much/very much improved on the Clinical Global Impression (CGI) Improvement scale. The target quetiapine dose was 150 mg twice daily by day 14, but flexible dosing up to 300 mg bd was allowed.

The primary efficacy variable was the proportion of patients responding to treatment by week 8 (≥50% decrease in MADRS score from baseline). Other assessments included Clinical Global Impression (Guy, 1976) and the Clinical Anxiety Scale (CAS) (Snaith et al., 1982). Safety and tolerability were assessed by adverse events (AEs), dropouts due to AEs, weight change, random plasma glucose and serum prolactin.

Primary analysis was intention-to-treat (ITT) over 8 weeks with those benefiting from treatment followed to 26 weeks. Statistical analysis (2-sided) consisted of *t*-tests and, to examine differences in subgroups, univariate analysis of week 8 values covaried for baseline and Fisher's exact test for proportions of responders. Results are shown as mean ± SD.

3. Results

3.1. Patient demographics

Twenty four patients (15 females, 9 males), mean age 46.3 years (range 25 to 62 years) were enrolled into the study. Eighteen patients completed the treatment phase. Thirteen patients showed clinical benefit at the end of the first 8 weeks of whom 11 (46%) entered the extension phase, all of whom completed the 26-weeks treatment.

The patients were moderate to markedly ill on average at baseline (mean MADRS score 28.1, mean CGI-Severity score 4.3). Twelve patients were being treated with a selective serotonin reuptake inhibitor (SSRI), eleven with a serotonin and noradrenaline reuptake inhibitor (SNRI), 2 patients with a TCA and one with reboxetine. Five patients had received an atypical antipsychotic (all olanzapine) in the current episode and 3 patients were also on lithium. The mean number of previous antidepressant treatment trials in the current episode was 2.4 ± 0.7.

The mean daily dose of quetiapine taken was 245 ± 68 mg at the end of the 8-week treatment phase and 346 ± 53 mg at the end of the 18-week extension phase.

3.2. Efficacy

After 8 weeks 7 patients (29%) were MADRS responders, 13 patients (54%) were CGI responders and 4 patients (17%) achieved remission (MADRS total score < 12). There was a 32% reduction in MADRS score over the 8 weeks of the acute treatment phase (28.1 ± 5.7 to 19.1 ± 8.2, $p<0.001$) and a 27% reduction in CAS Anxiety score at week 8 (9.9 ± 3.1 to 7.5 ± 2.8, $p<0.001$). Fig. 1 shows the change in MADRS scores over time in the acute treatment phase.

There was no difference in efficacy between those treated with an SSRI compared with an SNRI/TCA/reboxetine in MADRS response (27% v 31%, $p=1.0$) or other efficacy endpoints (data not shown).

For the 11 patients who entered the extension phase their MADRS dropped from 27.5 ± 5.2 at baseline to 15.1 ± 3.9 (−45%) at 8 weeks and 15.8 ± 5.2 (−43%) at 26 weeks ($p<0.001$). However 3 patients (27%) experienced a significant relapse (defined as an increase of ≥5 points above their MADRS score at 8 weeks) by 26 weeks.

3.3. Effect of previous olanzapine treatment

The 5 patients previously treated with olanzapine had non-significantly lower initial MADRS scores ($p=0.22$, Table 1). There was no significant difference in responders or changes in rating scale scores between patients who had received olanzapine in their current episode and those who had not although numerically the results mostly favoured those who had not received olanzapine.

3.4. Safety and tolerability

Six patients discontinued during the acute treatment phase, 2 due to adverse events including one who experienced increased suicidal ideation after the first 2 weeks. The most common AEs reported were sedation (13 patients), dry mouth (9 patients) and dizziness (7 patients). Overall, drug-

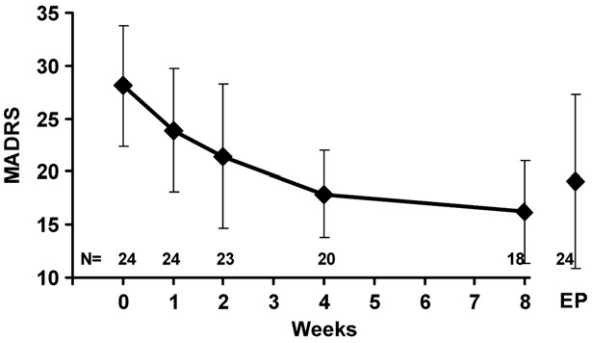

Fig. 1. Acute treatment phase Montgomery–Åsberg Depression Rating Scale (MADRS) score over time in patients on treatment and at week 8 endpoint (EP) in the Intention-to-Treat-Analysis set (ITT). There was a significant reduction in MADRS score at each assessment point ($p<0.001$ at all time points).