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Quetiapine augmentation in treatment-resistant depression: a naturalistic study

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Running title: Quetiapine in treatment-resistant depression

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Abstract

Rationale Treatment resistant depression is a common clinical problem, often complicated with suicidal ideations and greater lifetime functional impairment, and represents a considerable challenge to management and treatment.

Objective The aim of a prospective, open-label, non-comparative, flexible-dosed 20-week study was to evaluate the effects of quetiapine, as an add-on therapy, in patients with treatment resistant depression who were refractory to previous treatments.

Method Fourteen patients with major depressive disorder (DSM-IV criteria) were treated for 20 weeks with quetiapine (mean dose 315 ± 109 mg/day). Patients were evaluated at baseline, and weekly from 1-9 week, and than after 12, 16 and 20 weeks of treatment, using Hamilton Rating Scale for Depression-17 items (HAMD) scale.

Results Fourteen patients with treatment resistant depression completed the 20-week open trial with quetiapine. The augmentation with quetiapine significantly reduced total scores and scores listed in the anxiety and insomnia subscales on the HAMD, and these effects were observed after the first week of treatment. Quetiapine add-on treatment significantly decreased the scores listed in the depressive mood on the HAMD subscale after fourth week of treatment.

Conclusions Our preliminary data indicate that quetiapine add-on therapy appears to have beneficial effects in the treatment of patients with treatment resistant depression, with the rapid and sustained improvement in insomnia and anxiety.

Key words: Treatment resistant depression, Quetiapine, Add-on therapy

Introduction

Treatment resistant depression is a common clinical problem, frequently associated with the greater suicidal ideation and attempts during the current episode, and the greater lifetime functional impairment (Malhi et al. 2005). Although there are many effective treatments for a depressive episode, the management of treatment resistant depression continues to represent a considerable challenge to the psychiatrists. There are a few comparative data regarding the treatment options for treatment resistant depression (Kennedy and Lam 2003), because treatment resistant depression represents an exclusion criteria for the most antidepressant clinical trials (Dodd et al. 2005).

Quetiapine is an atypical antipsychotic with a unique receptor binding profile: it has moderate affinity for 5-HT2A serotonergic, α1-adrenergic, muscarinic and histaminergic receptors, only a minor affinity for dopamine D2 and 5-HT1A receptor and a low affinity for 5-HT2C, α2-adrenergic and D1 receptors (DeVane and Nemeroff 2001). It possesses a positive effect on the depressive mood in patients with schizophrenia (Kasper 2004) and bipolar disorder (Calabrese et al. 2005). While atypical antipsychotics have been successfully applied in the treatment resistant depression (Nemeroff 2005), there are only a few data regarding the efficacy of quetiapine in treatment resistant depression. Since one study retrospectively investigated the efficacy of quetiapine in treatment resistant depression in 10 adolescents (Pathak et al. 2005), and the other study assessed the augmentation of quetiapine to sertraline in the naturalistic case series outcome in 6 patients with treatment resistant depression (Devarajan et al. 2006), the aim of our study was to evaluate the efficacy and safety of quetiapine augmentation in

the treatment resistant adult inpatients with major depressive disorder who were resistant to multiple antidepressant trials. We hypothesized that adding quetiapine to the current antidepressants would be a well-tolerated and effective treatment of treatment resistant depression.

Materials and methods

Subjects

This was a prospective, open-labelled, non-comparative, flexible-dosed study that lasted 20 weeks. Patients (N=18) with major depressive disorder (diagnosis was made using structured clinical interview for DSM-IV disorders (American Psychiatric Association 1994) were recruited **consecutively** from the inpatients from the Department of Psychiatry of the Clinical Hospital Centre Zagreb, and 14 patients finished the study. All patients have signed informed consent document, approved by the local Ethic Committee, prior to inclusion. The following inclusion criteria were used: a) age $\geq$ 18 years; b) patients with major depressive disorder, who have failed at least two antidepressant trials of different classes (Annath 1998), with a minimum HAMD-17 cut-off scores of 20; c) patients who have failed the mood stabilizer augmentation trial were also included. The exclusion criteria were: a) psychoactive use disorder within the previous 6 months; b) diagnosis of schizophrenia, schizoaffective disorder, dementia, posttraumatic stress disorder, bipolar I and bipolar II disorder using; c) presence of psychotic features (determined as the presence of either delusions or hallucinations in clinical interview, as specified in DSM-IV); d) treatment with any antipsychotics for the current depressive episode; e) pregnant or nursing women, or women in risk of becoming pregnant; f)

duration of current depressive episode for less than 2 years, to exclude chronic depression. Comorbid chronic medical conditions were not the exclusion criteria, except the life-threatening conditions. Quetiapine was added to the current antidepressant treatment according to the usual dose-titration recommendation (the starting dosage was 50 mg at bedtime). The dosage was increased in 50 mg increments daily, up to the individual target dose. The target dose was determined according to the safety and tolerability. The mean quetiapine dose was 315 ± 109 mg/day. All patients have continued taking their current antidepressant treatment regimen within the current dose-range. Antidepressants given in combination with quetiapine were: reboxetine + paroxetine (3 patients), reboxetine + sertraline (1 patient), fluvoxamine (2 patients), sertraline (1 patient), paroxetine (2 patients), paroxetine + maprotiline (4 patients), moclobemide (1 patient). Symptomatic benzodiazepine treatment in flexible dose range was allowed. Depressive symptoms were measured by Hamilton Rating Scale for Depression-17 items (HAMD) (Hamilton 1960). Total HAMD scores and the scores in the depressive mood subscale (item 1), insomnia subscale (items 4, 5 and 6), anxiety subscale (items 10 and 11) on the HAMD scores were evaluated at baseline, weekly during first 9 weeks of treatment, and monthly thereafter (i.e. after 1, 2, 3, 4, 5, 6, 7, 8, 9, 12, 16 and 20 weeks of quetiapine treatment). Response was defined as a 50% or greater reduction of the baseline HAMD scores. In addition to antidepressants, 3 patients were currently treated with carbamazepine, and 2 patients received also lamotrigine. Concomitant medical conditions in patient treated quetiapine were: hyperlipidemia in 4 patients, arterial hypertension in 5 patients, ulcer disease in 2 patients, Parkinson's

disease in 2 patients, hypothyroids in 2 patients, and rheumatoid arthritis or coronary artery disease or psoriasis vulgaris in 1 patient.

Among responders, 3 patients had hypotension, and 2 patients had daytime sedation, which were transient and mild in all cases. There were no serious adverse events.

Statistical analysis

Statistical evaluation of the results, expressed as means ± standard deviations (SD), was performed using Friedman repeated measures one-way analysis of variance (RMANOVA) and Dunnett's test. The treatment effect was evaluated with RMANOVA, and Dunnett's test compared the treatment scores achieved after 1-20 weeks of treatment with the baseline scores.The significance was accepted when $p<0.05$. All calculations were made with the statistical program Sigmastat (Jandel, version 2, Jandel Corp., USA).

Results

Demographic and clinical characteristics of patients are presented in Table 1. From the 18 patients, 14 patients have responded to add-on quetiapine treatment. One patient has dropped out from the study due to the persistent hypotension and 3 patients have dropped out due to the lack of response to quetiapine.

Fourteen patients with treatment resistant depression completed the 20-week open trial with quetiapine. Quetiapine add-on treatment for 1-20 weeks significantly [χ^2 =161.4; df=12; $p<0.001$] reduced the total scores on the HAMD scale (Figure 1) in patients, and this rapid effect was observed from the first week of treatment in all 14

patients. However, the 50% reduction of the total HAMD scores was achieved after the sixth week of treatment (Table 1). Quetiapine significantly [χ^2 =136.0; df=12; p<0.001] decreased the scores on the HAMD-insomnia subscale (items 4, 5 and 6) after 1-20 weeks of treatment, and this fast effect was significant also from the first week of treatment (Figure 2). A significant [χ^2 =156.9;df=12; p<0.001] response to quetiapine was observed in the HAMD-depressive mood subscale (item 1) after 4-20 weeks of treatment, where depressed mood scores were significantly reduced after the fourth week of quetiapine treatment (Figure 3). The anxiety scores on the HAMD (items 10 and 11) were significantly [χ^2 =158.2; df=12; p<0.001] lower after the second week of treatment than at baseline (Figure 4), and stayed lower from 2-20 weeks of treatment.

Discussion

The add-on quetiapine treatment improved the clinical state in adult patients with treatment resistant depression. The study was performed in naturalistic setting with the wide inclusion criteria. Most of our patients, due to their substantial burden of medical comorbidity, past suicide attempts, multiple drug resistance and concomitant medical treatment, would not be able to fulfil the inclusion criteria in the typical randomized, double-blind clinical trials. It has been questioned recently (Tandon and Jibsen 2003) whether the results of the formal clinical randomized, double-blind clinical trials might be applied to these refractory patients, who are, in turn, frequently present in the clinical practice, and the most difficult to treat. The increasing body of evidence suggests that atypical antipsychotics are effective in treatment resistant depression (Hirose and Ashby

2002; Simon and Nemeroff 2005). The data from our study confirm this hypothesis (Nemeroff 2005), and extend it with the data showing beneficial effects of another atypical antipsychotic, quetiapine, as an add-on therapy, which showed promise as a safe and effective therapeutic strategy for patients with difficult-to-treat major depression.

The efficacy of quetiapine was investigated using retrospectively evaluated charts of adolescents up to 18 years of age who have failed to respond to an 8-week treatment with selective serotonin reuptake inhibitors (SSRIs), and 7 out of 10 adolescents responded to quetiapine (Pathak et al. 2005). A clinical efficacy of quetiapine augmentation to sertraline has been shown, and quetiapine addition has improved the HAMD-21 rating scores and outcome in 6 patients with treatment resistant depression during 5-6 weeks (Devarajan et al. 2006). The results from our study, obtained on the larger group of patients, treated for the longer period (20 weeks) with add-on quetiapine, agree with these results. We have observed a rapid overall response of adult patients with treatment resistant depression to quetiapine augmentation. In our study, from 18 patients which were enrolled, 14 patients were responders, as shown in significantly reduced HAMD total and subscale scores. Other 4 patients dropped out due to the persistent hypotension and the lack of response to quetiapine, hence their data were excluded from the study. The response to quetiapine, defined as 50% reduction of the baseline HAMD-17 scores, was achieved in the majority of patients after 6 weeks (between 4 and 8 week) of treatment. In agreement with the clinically relevant reduction in depressive and anxiety symptoms in 11 patients with different anxiety disorders (Adson et al. 2004), quetiapine augmentation in our study significantly decreased total scores and scores listed in the anxiety and insomnia subscales on the HAMD, and these rapid effects were observed

after first week of treatment. In line with the reported beneficial effects of quetiapine on depressive symptomatology, aggression, hostility, mania, anxiety, delirium and posttraumatic stress disorder (PTSD) (Adityanjee and Schulz 2002, Nemeroff et al. 2002), anxiety disorders (Adson et al. 2004), and in treatment resistant depression (Devarajan et al. 2006), we have found that quetiapine, added to the current antidepressant treatment, significantly reduced the scores listed in the depressive mood on the HAMD subscale after fourth week of treatment.

Sleep disturbances are common and severe symptoms in depression. While the efficacy of SSRIs in the treatment of depression is beyond doubt, SSRIs are not so effective in the treatment of insomnia. Addition of quetiapine to a stable dose of a SSRI resulted in the significant reduction of early and middle insomnia in 11 patients with anxiety disorders after 2 weeks of quetiapine treatment (Adson et al. 2004). The mean quetiapine dose in that study was 180 mg/day (Adson et al. 2004), which is twice lower than the dose used in our study. Given the diagnoses of generalized anxiety disorders, and/or unipolar depression and dysthymia in the former study (Adson et al. 2004), it might be suggested that our patients with treatment resistant depression were more severely disabled, and therefore they required the higher doses of quetiapine to achieve a similar reduction of the symptoms. **of atypicals on sleep in depression, the papers of Sharpley et al (Journal of Clinical Psychiatry 66 (4), pp. 450-454 and Journal of Clinical Psychiatry 64 (2), pp. 192-196) Quetiapine, olanzapine and risperidone were found to improve subjective sleep quality in patients with schizophrenia (Yamashita et al. 2005), and quetiapine (Roberts et al. 2005; Kozaric-Kovacic and Pivac 2006) and olanzapine (Jakovljević et al. 2003) rapidly improved insomnia and nightmares**

in combat-related PTSD mijenjati. Atypical antipsychotic drugs possess sleep-improvement properties across the diagnoses. Low dose of quetiapine (25 to 100 mg) has improved sleep quality in healthy volunteers (Cohrs et al. 2004). Sleep-improving properties of quetiapine might be achieved by its antihistaminergic (H1 receptors), dopaminergic (D1 receptors) and the α1-adrenergic receptors blocking properties.

On the other hand, the mechanism by which quetiapine's addition into the current antidepressant treatment improved depressive symptoms in treatment resistant depression is still not clear, although quetiapine shows efficacy in treating depressive symptoms in different psychiatric illnesses (Kasper 2003). The well-established antipsychotic efficacy of quetiapine does not explain the improvement of depression observed in the present and previous (Pathak et al. 2005) study, because these patients were not psychotic. However, the combination of quetiapine and other antidepressant/s might have improved untreated residual psychopathology of these patients (Deverajan et al., 2006). Quetiapine targets different neurotransmitter receptors (DeVane and Nemeroff 2001)**,** that interact with each other and affect brain regions involved in the regulation of anxiety and mood. In addition, quetiapine was found to down-regulate the activity of the hypothalamic-pituitary-adrenal (HPA) axis in healthy male volunteers (Cohrs et al. 2006). An over-activity of HPA axis is a characteristic feature of major depression, and although we did not study the HPA axis activity in our treatment resistant depression patients, we might assume that they have a hyperactive HPA axis. Hence the beneficial antidepressant effect of quetiapine augmentation might be achieved via a down-regulation of the HPA axis.

The study has several limitations such as the small number of patients, open-labelled design, and the fact that quetiapine concentration was not measured and therefore

the pharmacokinetic interaction with antidepressants cannot be ruled. However, its advantage was in a prolonged (20-week) treatment, an add-on therapy with quetiapine, and in inclusion of the treatment resistant patients with major depression.

In conclusion, the preliminary data on the quetiapine add-on therapy appear to have beneficial effects in patients with treatment resistant depression, and quetiapine augmentation showed rapid and sustained improvement in insomnia and anxiety.

Acknowledgements

Thanks are due to the staff of the Clinical Hospital Centre Zagreb, Department of Psychiatry, Zagreb, Croatia. The experiments comply with the current laws of Croatia. The research was supported by the Croatian Ministry of Sciences, Education and Health, grant number 0098088 and 0108106.

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Table 1. Demographic and clinical characteristics (means ± SD) in patients with treatment resistant depression

Age (years)	54.0 ± 11.7
Male: female ratio	10:4
Number of patients with at least 1 suicide attempt	9
Duration of current depressive episode (months)	11.1 ± 8.1
Number of antidepressants given to threat the current episode	3.77 ± 1.16
HAMD total score at baseline	39.14 ± 2.14
50% reduction of the HAMD total score	16.64 ± 1.50
Week when a 50% fall of HAMD was achieved	6.21 ± 0.98

Legend to the Figures:

Figure 1. Total scores (mean ± SD) in Hamilton Rating Scale for Depression (HAMD) in patients with treatment resistant depression at baseline, during and after 20 weeks of treatment with quetiapine.
*differences from the baseline scores, $p<0.05$.

Figure 2. Insomnia scores (mean ± SD) in Hamilton Rating Scale for Depression (HAMD: items 4, 5 and 6: insomnia early, middle and late) in patients with treatment resistant depression at baseline, during and after 20 weeks of treatment with quetiapine.
*differences from the baseline scores, $p<0.05$.

Figure 3. Depressed mood scores (mean ± SD) in Hamilton Rating Scale for Depression (HAMD: item 1) in patients with treatment resistant depression at baseline, during and after 20 weeks of treatment with quetiapine.
*differences from the baseline scores, $p<0.05$.

Figure 4. Anxiety scores (mean ± SD) in Hamilton Rating Scale for Depression (HAMD: items 10 and 11: anxiety psychosocial and somatic) in patients with treatment resistant depression at baseline, during and after 20 weeks of treatment with quetiapine.
*differences from the baseline scores, $p<0.05$.

Figure 1.

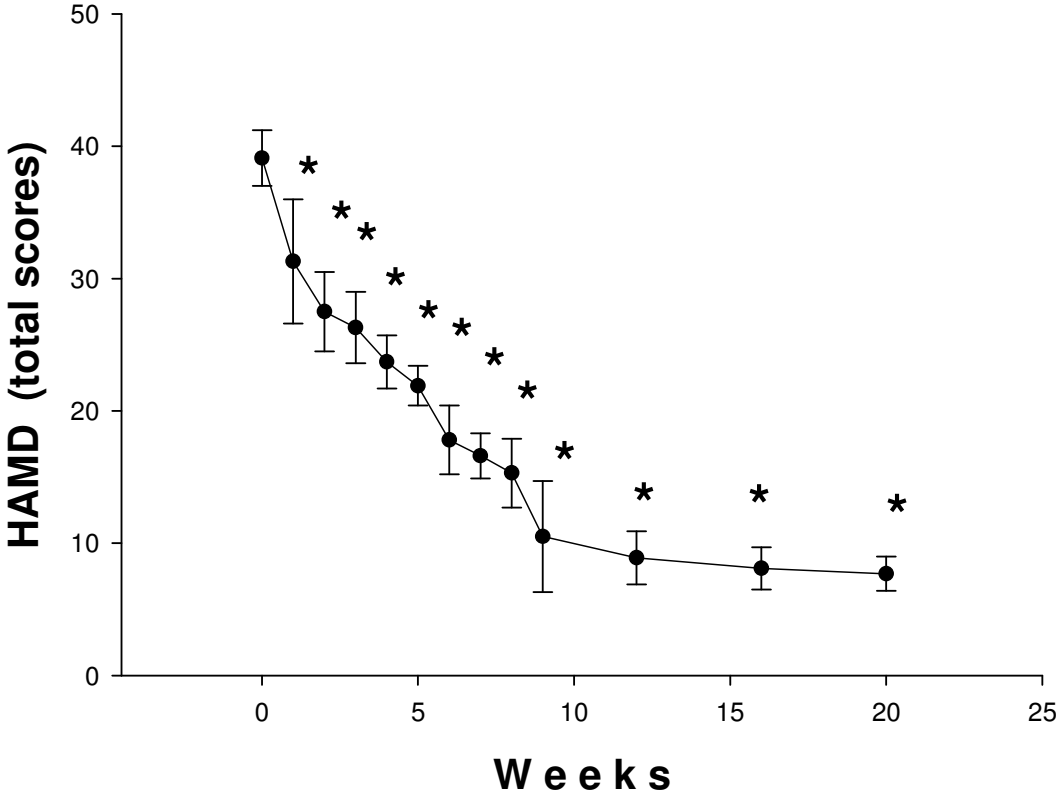


Figure 2.

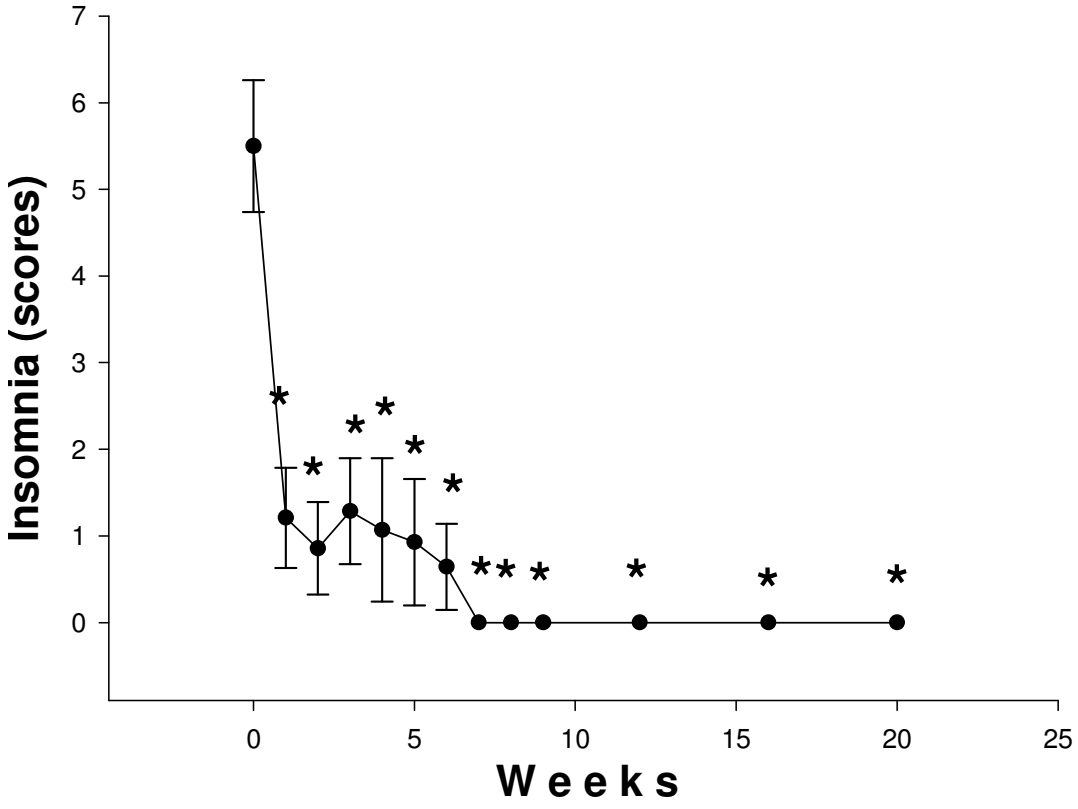


Figure 3.

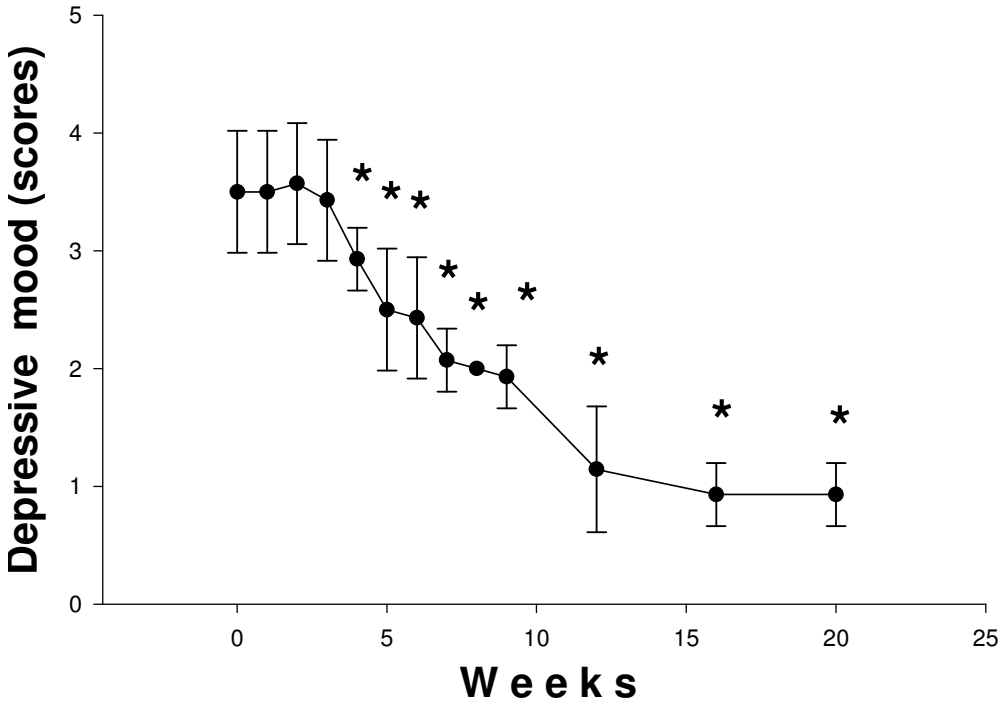
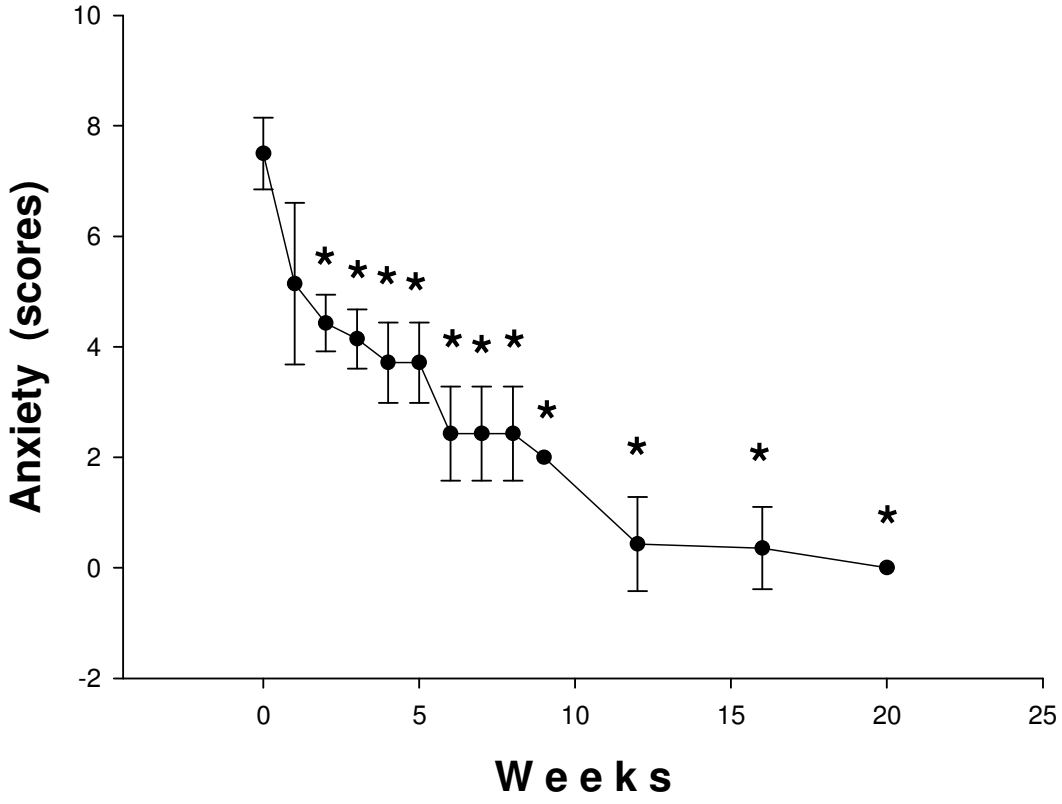


Figure 4.



Date: 18-Apr-2006

Manuscript No. Psych-2006-00182
Title : Quetiapine augmentation in treatment-resistant depression: a naturalistic study
Corresponding author : Dr. Nela Pivac

Dear Dr. Pivac,

We have now received the reviewers' comments on your above-mentioned paper. We kindly ask you to give the comments below your careful consideration and that you submit a thoroughly revised version of your manuscript.

We kindly ask that you submit your revised manuscript as follows:
- The text, including tables and figure legends, in one file, compatible with MS Word.
- If high resolution Figures are necessary please submit each figure in a separate file without the figure legend.

Please respond in a detailed and itemized fashion to each of the comments of the Referees and Editor.

Please also try and make the paper more concise. One reviewer recomended resubmission as a letter to the editor but I think we can take it as research communication if you cut the length by at least 25%.

We request that you revise your manuscript as quickly as possible, but within three months of receipt of this letter.

To submit your revision please log in your author center at https://mc.manuscriptcentral.com/psychopharmacology , click on 'Manuscripts with decision'. Please follow the instructions when the 'Submit a revision' window opens.

Please check your " Author Center" for the complete comments from the reviewers. These comments may include important attached files that are not listed in the present letter but should be addressed if you decide to send in a revision.

We look forward to the receipt of your revised manuscript.
Sincerely,

Prof. P. J. Cowen

Principal Editor
Psychopharmacology

Answers to the Reviewer No. 1
Thank you very much for your comments.

1. It may be useful to note in the methods whether patients were consecutive patients or randomized to the study?
Patients were consequently enrolled into the study. We have stated that in the Methods…"This was a prospective, open-labelled, non-comparative, flexible-dosed study that lasted 20 weeks….". However, we have accepted your comment and added…".. Patients (N=18) with major depressive disorder (diagnosis was made using structured clinical interview for DSM-IV disorders (American Psychiatric Association 1994) were recruited **consecutively….**

2. It is important to note that whether patients predominantly with sleep disturbances (insomnia) and high anxiety scores were selected to the study?

Patients with sleep disturbances and high anxiety scores were not predominantly selected for the study. However, these symptoms were pronounced in our sample.

3. It remains unclear from the discussions whether the authors suggest that predictors of positive response to quetiapine are insomnia and highly anxious patients? Does the rapid onset of improvement correlate with improvement of insomnia?

We can only hypothesize that insomnia and high anxiety scores might be used as predictors of the positive response to quetiapine in patients with TRD. However, small number of patients, an open studyy design, and the fact that we did not correlate baseline insomnia and anxiety scores with the treatment response, do not allow us to draw any conclusion regarding their value as the potential predictors of response.

4. Has any of the patients been on any antipsychotic in the past (not current episode)?

No patient has, according to our knowledge, ever received any antipychotic for their previous depressive episode-except for low-dose sulpiride (up to 200 mg daily), which has been prescribed as an antidepressant drug (. Ref?? Sulpirid i efikasnost u depresiji dodati)

5. How was psychosis assessed? BPRS or PANSS? (Exclusion criteria)
Psychosis was determined as the presence of either delusions or hallucinations in clinical interview, as specified in DSM-IV. No BPRS and PANSS were applied. We have added this into Method section...»..presence of psychotic features (determined as the presence of either delusions or hallucinations in clinical interview, as specified in DSM-IV);"

6. It is important to note that possible pharmacokinetic interactions have been ruled out?

Since quetiapine concentration was not measured, pharmacokinetic interaction with antidepressants cannot be ruled-out. We have changed the Limitatations of the study and added this comment... «.The study has several limitations such as the small number of patients, open-labelled design, and the fact that quetiapine concentration was not measured and therefore the pharmacokinetic interaction with antidepressants cannot be ruled-out.»..

Answers to the Reviewer No. 2:

1. The MS does not seem very well organised. For example, we are told in the Methods section about drop-outs and rate of response when this should be in the Results section. The MS needs to be better structured. In addition the Introduction and Discussion should be made much more concise. The open design means that the information we can take from the study is limited. MIJENJATI TEKST SKRATITI ZA 25 %
We have accepted your comment and reduced the MS. We have also included the drop-outs and rate of response into Results. MIJENJATI REZULTATE SKRATITI

2. I am unclear what the target dose was. Was it decided individually? Escalating the dose of QTP by 50mg each night seems too rapid. What clinical or pharmacological data guided the identification of the initial target dose?

The target dose was determined individually, as it was already mentioned in the text, in the «Materials and methods». Escalation of the dose od QTP by 50 mg daily was done in accordance with the QTP package insert. The target dose was determined according to the individual safety and tolerability, and this was also already pointed out in the text, in the «Materials and methods». The initial QTP target dose was not determned in advance. ...» . Quetiapine was added to the current antidepressant treatment according to the usual dose-titration recommendation (the starting dosage was 50 mg at bedtime). The dosage was increased in 50 mg increments daily, up to the individual target dose. The target dose was determined according to the safety and tolerability. The mean quetiapine dose was 315 ± 109 mg/day…"

3. As expected the effects of QTP on sleep and anxiety were fairly rapid. However, the effect on depressed mood seems substantially delayed. This is in contrast to most augmentation studies with atypicals where the majority of the antidepressant effect is seen in the first week of treatment. This needs discussion. Is it because the effect of QTP is less specific, perhaps due to natural remission?
We have accepted

We agree with your comment. While the QTP effects on sleep and anxiety were fairy rapid, the effect on depressed mood was substantially delayed. Therefore, the improvement of the depressed mood could also be contributed to the natural remission. We did not discuss that since only randomized, placebo-controlled, QTP add-on study, could determine whether QTP has a delayed antidepressant efficacy.

4. The plotted graphs presumably reflect study completers. I think that these data will be more clinically meaningful if all subjects are included with a last observation carried forward (LOCF) analysis. It would also be helpful to know how many subjects met criteria for remission (HAM-D <8).
In the article with

Friedman repeated measures one-way analysis of variance (RMANOVA) and Dunnett's test. The treatment effect was evaluated with RMANOVA, and Dunnett's test compared the treatment scores achieved after 1-20 weeks of treatment with the baseline scores.
Treba izracunati

5. When discussing the effects of atypicals on sleep in depression, the papers of Sharpley et al (Journal of Clinical Psychiatry 66 (4), pp. 450-454 and Journal of Clinical Psychiatry 64 (2), pp. 192-196) seem more relevant than the publications on schizophrenia and should be cited.

6. I think Table 1 should contain the data for all 18 subjects. Why is there an excess of male subjects? This seems unusual. The HAM-D scores look very high (with a small SD). I don't think we need the 50% HAM-D score.
We accepted your comment and included all data from 18 patients and used LOCF, and therefore had to change all statistics and consequently the results.

The excess of male subjects is simply due to the structure of our Department of Biological Psychiatry, where two thirds of hospital beds are occupied with males.

Reviewer: 3
Comments of Reviewer for the attention of authors.
This paper presents novel findings on the use of quetiapine augmentation in treatment-resistant depression. The study is well-designed and appropriately conducted. The findings are novel and relevant.
Minor:
1. In the inclusion criteria, indicate the cut-off minimum score on HAMD-17.
The minimum cut off scores on HAMD 17 was 20.

2. In the exclusion criteria, change “psychoactive use disorder” to “drugs of abuse disorder”.
3. On page 9, it is stated that out of 4 drop-outs, 3 were due to “the lack of response to quetiapine”. How was this taken in account in data analysis?
We have now included all 18 patients into analysis, using LOCF, and therefore had to change the results and statistical evaluation of the data.

Reviewer 2.
Pomaknuti drop-outs u sekciju metoda
Podaci za non-respondere i drop-outs (za LOCF) za 4 pacijenta (3 nonsrepondera N1 N2 i N3 I i 1 droppout jer je imao hypotension kao nuspojavu lijeka i zato je ispao=

	N-1	N-2	N-3	Drop-out
Gender	F	M	F	M
No of patients with at least 1 suicide attempt	0	0	1	1
Duration of current depressive episode (months)	14	12	7	8
Number of antidepressants given to threat the current episode	4	4	3	3
HAMD score on baseline	38	36	37	40
50% reduction of the HAMD total score	Not achieved			
Week when a 50% fall of HAMD was achieved	Not achieved			

	N-1	N-2	N-3	Drop out
Insomnia scores at baseline and on w-1, w-2, w-3, w-4	6,5,5-nakon w-2 prekinuo	5,5,4,3-nakon w-3 prekinuo	6,4,4-nakon w-2 prekinuo	6,4-nakn w-1 prekinuo
Depressed mood scores	4,4,4	3,3,4,4	4,3,4	4,4
Anxiety scores	6,5,5	6,5,6,5	7,5,6	6,5

5. U redu je.
6. Reviewer 3
    1) The cut-off minimal HAMD-17 score was 20.
    2) We change „psychoactive use disorder“ to „drugs of abuse disorder“.
    3) It was added to analysis