ORIGINAL ARTICLE

THE EFFICACY OF QUETIAPINE XR AS AN ADJUNCTIVE THERAPY TO DULOXETINE IN DEPRESSED PATIENTS WITH INADEQUATE RESPONSE TO MONOTHERAPY

THEODOR MOICA [1,2], IOSIF GABOS GRECU [1,2]*, DANIELA SABĂU [1,2], SIMONA SZASZ [2], MARIETA GABOS GRECU [1,2], SORINA MOICA [3], ALEXANDRA GROSAN [2], FLORIN BUICU [2]

[1]*Psychiatric Clinic I, Târgu Mureş, Romania*
[2]*University of Medicine and Pharmacy, Târgu Mureş, Romania*
[3]*"Petru Maior" University, Târgu Mureş, Romania*

**corresponding author: gabos@orizont.net*

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Abstract

The objective of the study was to demonstrate the efficacy of quetiapine XR (extended release) used as an augmentation treatment to duloxetine, in patients with major depressive disorder, with inadequate response to monotherapy. In this 8 weeks prospective study, the efficacy of quetiapine XR used as an augmentation treatment was evaluated using the Hamilton Rating Scale for Depression (HAM-D_{17}), on two groups of patients: group A - patients with incomplete response, that used quetiapine XR 150 mg daily as augmentation therapy in addition to duloxetine and group B - patients with incomplete response who continued the antidepressant monotherapy. We evaluated the levels of depression at baseline (week 0) and at the end of the study (8^{th} week) for 72 patients. According to HAM-D scores, the level of depression for group A at week 0 (baseline) was M = 22.17 ± 3.23 and after 8 weeks of treatment M = 8.58 ± 3.74. In group B at week 0 (baseline) the level of depression was M = 24.61 ± 4.19, and M = 18.22 ± 7.78 after 8 weeks of treatment. The patients' scores between the studied groups were significantly different after 8 weeks of treatment. Quetiapine XR 150 mg daily may be effective as an augmentation treatment to duloxetine in patients with major depressive disorder, major depressive episode, single or recurrent, without psychotic symptoms, with inadequate response to monotherapy.

Rezumat

Obiectivul studiului a fost de a demonstra eficacitatea quetiapinei XR (cu eliberare prelungită) utilizată ca terapie adjuvantă pentru duloxetină, la pacienții cu tulburare depresivă majoră, cu răspuns inadecvat la monoterapia cu acest antidepresiv. Am efectuat un studiu prospectiv, timp de 8 săptămâni, eficacitatea quetiapinei XR folosită ca terapie adjuvantă fiind evaluată comparativ, folosind Scala Hamilton pentru depresie (HAM-D_{17}). Pacienții au fost împărțiți în două grupuri: Grupul A - pacienți cu răspuns incomplet la monoterapie, care au primit quetiapina XR, 150 mg zilnic, ca terapie adjuvantă pentru duloxetină și grupul B - pacienți cu răspuns incomplet care au continuat monoterapia cu acest antidepresiv. În grupul A, nivelul depresiei inițial (săptămâna 0) pe scala HAM-D a arătat următoarele valori: M = 22,17 ± 3,23, iar după 8 săptămâni M = 8,58 ± 3,74. În grupul B, nivelul depresiei evidențiat pe scala HAM-D, inițial, a fost M = 24,61 ± 4,19, respectiv după 8 săptămâni M = 18,22 ± 7,78. Grupurile studiate au evidențiat diferențe semnificative în ceea ce privește nivelul depresiei la finalul studiului. Quetiapina XR 150 mg pe zi, poate fi eficientă ca terapie adjuvantă pentru duloxetină la pacienții cu tulburare depresivă majoră, episod depresiv major, fără simptome psihotice, cu răspuns inadecvat la monoterapia cu acest antidepresiv.

Keywords: depression, quetiapine XR, duloxetine, inadequate response, monotherapy

Introduction

In patients with major depressive disorder (MDD), even if monotherapy with an antidepressive treatment is correctly managed, only 1/3 of patients reach remission [1]. One of the strategies adopted for increasing the remission rates includes the use of atypical anti-psychotics as augmentation agents. Quetiapine XR seemed to be safe and effective as an augmentation agent to selective serotonin reuptake inhibitors (SSRIs) and serotonin and noradrenalin reuptake inhibitors (SNRI), in patients with an inadequate response to antidepressive monotherapy [2].

The objective of the study was to demonstrate the efficacy of quetiapine XR used as an augmentation therapy to the SNRI - duloxetine, in patients with major depressive disorder, major depressive episode, single or recurrent, without psychotic symptoms, with inadequate response to monotherapy with this SNRI.

Materials and Methods

Study design

The efficacy of quetiapine as augmentation therapy was evaluated during a prospective, randomized, opened study, on a number of 72 patients, hospitalized in Psychiatric Clinic I of Târgu Mureş, Romania, between

1st January 2014 and 1st July 2014. All patients had a diagnostic of major depressive disorder, major depressive episode, single or recurrent, without psychotic symptoms, and they had an inadequate response to the antidepressant therapy (the use of minimal doses accepted as effective for a period of at least 4 - 6 weeks), for the current depressive episode, meaning a score on Hamilton Rating Scale for Depression (HAM-D_{17}) ≥14. At the time of the enrolment, all patients were treated with duloxetine 60 mg *per* day. The dose of quetiapine XR was gradually increased, meaning that the dose was 50 mg for the first two days, then 150 mg *per* day until the end of the study.

The study was approved by the Institution Ethics Committee and the informed consent signed by patients voluntarily was obtained.

The efficacy was evaluated based on the mean changes of scores on the HAM-D_{17}, at 4 consecutive visits conducted at weeks 0, 2, 4 and 8. The assessment was performed between two groups of patients: the first group, the augmentation group, group A - 18 patients with incomplete response, that used quetiapine XR 150 mg daily as augmentation therapy in addition to duloxetine, and the second group, the monotherapy group, group B - 18 patients with incomplete response, who continued the monotherapy with duloxetine.

Statistical analyses

For the statistical analyses and interpretation of data we used SPSS 20 for Windows and GraphPad Prism version 6.

Results and Discussion

In group A (patients receiving augmentation) 36 patients were included in the study, 26 females and 10 males, with a mean age of 40.27. In group B we included 36 patients, with a mean age of 39.25, 28 of them being females and 8 males.

As showed in Figure 1, in group A at week 0 (baseline) the level of depression according to HAM-D_{17} scores, was M = 22.17 ± 3.23. At week 8, the level of depression was M = 8.58 ± 3.74, with a normal distribution of data.

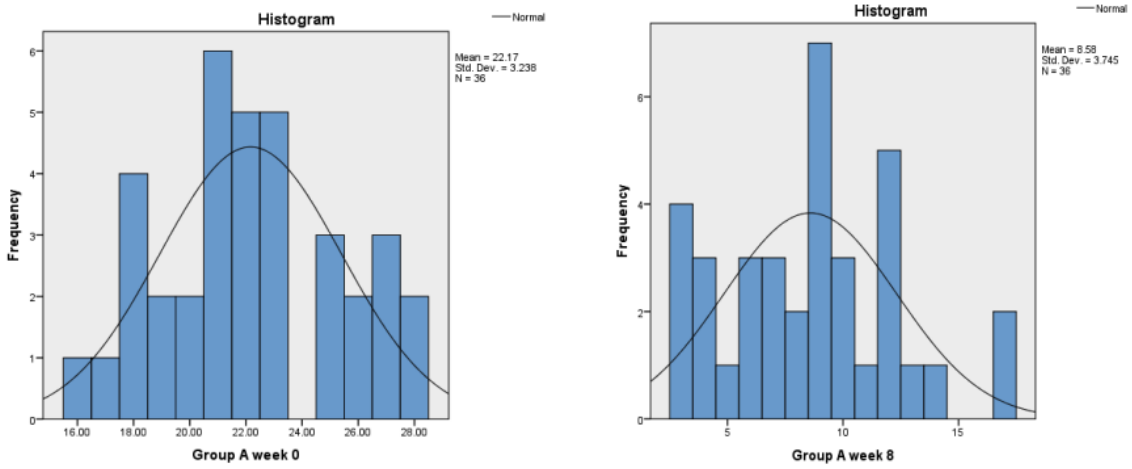

Figure 1.
The mean distribution of HAM-D scores in group A at baseline - week 0 and after 8 weeks of treatment

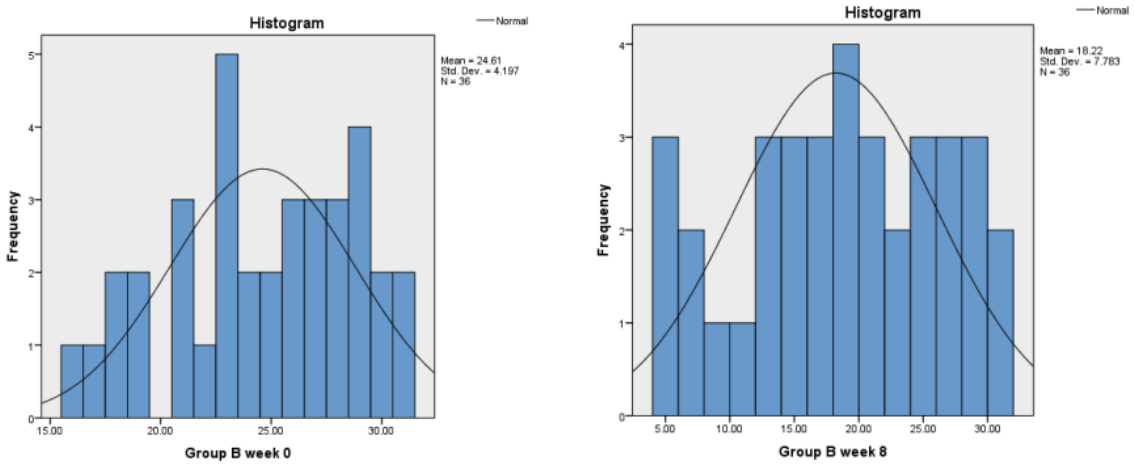

Figure 2.
The mean distribution of HAM-D scores in group B at baseline - week 0 and after 8 weeks of treatment

In group B at week 0 (baseline) the level of depression was revealed on HAM-D_{17}, was M = 24.61 ± 4.19, and at week 8, M = 18.22 ± 7.78, with a normal distribution of data.

The paired t-test analyses revealed that results in group A and group B at week 8 were significantly different, $p < 0.05$ [14]. This means that at week 8 there is a statistically significant difference between the level of depression in group A - patients with incomplete response that used quetiapine XR 150 mg daily as augmentation therapy in addition to duloxetine and the level of depression in group B - patients with incomplete response who continued antidepressant monotherapy with this SNRI.

It is considered that by 2020 depression will be the second leading cause of morbidity worldwide after the cardiovascular diseases. After one depressive episode, the risk of re-experiencing another one at some point in the future is very high, around 85% [15]. Depression is a public health issue, because even if there are a lot of available classes of antidepressive treatments, still the remission rates after the first antidepressant treatment are low (less than 30%) and incomplete or suboptimal response is frequently encountered [20].

Strategies adopted for patients with incomplete response to antidepressant treatment, may include: optimizing the dose, switching to another antidepressant, combinations of antidepressants, augmentation with carbamazepine, lithium, buspirone, thyroid hormones or an atypical antipsychotic, pharmacotherapy combined with psychotherapy, electroconvulsive therapy (ECT), vagus nerve stimulation, transcranial magnetic stimulation and deep brain stimulation, deprivation of sleep, light therapy [3, 8].

Recent studies have shown that switching to another antidepressant or the combination of antidepressants did not showed supplementary benefices and were not validated by clinical researches, in double blind, randomized control trials [4, 18]. Numerous studies have shown that atypical antipsychotics, in addition to their antipsychotic effect, have also an anti-depressive effect [1, 6, 7], which was initially observed in patients with schizophrenia [9, 10] and schizo-affective disorders [11, 19]. Also, in a series of randomized, placebo-controlled trials, the authors concluded that the use of atypical antipsychotics [2, 12] as an adjunct to antidepressant monotherapy may be a viable option in major depressive disorder for treatment-resistant patients [16, 17]. Our study revealed that quetiapine XR used as augmentation therapy was effective as an augmentation therapy to the SNRI duloxetine. Our data are consistent with the literature which supports the use of this drug in patients with MDD with an inadequate response to SNRI monotherapy. We previously showed the efficacy and tolerability of quetiapine XR, used as an augmentation therapy to 3 SSRIs, namely paroxetine, sertraline and escitalopram, in MDD patients, with an inadequate response to monotherapy with one of these 3 SSRIs [13]. In a meta-analysis, Bauer *et al*. also showed the efficacy and safety of quetiapine XR as adjunctive therapy in patients with MDD, with incomplete response to antidepressant monotherapy [5].

In the study we have conducted, quetiapine XR used as augmentation therapy at a dose of 150 mg daily, resulted in improvement of most of MDD symptoms between week 0 and week 8. The efficacy, evaluated by the HAM-D_{17} scale, showed a significant improvement in depressive symptoms in patients with adjunctive therapy, compared to patients who continued the monotherapy. Changes in HAM-D_{17} scores were significantly higher after 8 weeks of treatment in patients who received augmentation therapy compared to patients who continued the monotherapy with duloxetine.

Conclusions

The results of the study showed that after 8 weeks, there is a significant difference between the mean scores obtained by patients regarding the level of depression, for the group that used quetiapine XR for augmentation, compared to the group that continued the antidepressive monotherapy. This indicates that quetiapine XR 150 mg daily may be effective as an augmentation treatment to duloxetine in patients with major depressive disorder, major depressive episode, single or recurrent, without psychotic symptoms, with inadequate response to monotherapy with this SNRI.

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References

1. Babinkostova Z, Stefanovski B, Forms of anti-psychotic therapy: improved individual outcomes under personalised treatment of schizophrenia focused on depression. *EPMA J.*, 2011; 2(4): 391-402.
2. Barbee J, Conrad E, Jamhour N, The effectiveness of olanzapine, risperidone, quetiapine, and ziprasidone as augmentation agents in treatment-resistant major depressive disorder. *J Clin Psychiatry*, 2004; 65(7): 975-981.
3. Bauer M, World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Unipolar Depressive Disorders in Primary Care. *World J Biol Psychiatry*, 2007; 8: 67-104.
4. Bschor T, Baethge C, No evidence for switching the antidepressant: systematic review and meta-analysis of RCTs of a common therapeutic strategy. *Acta Psychiatr Scand.*, 2010; 121(3): 174-179.
5. Bauer M, El-Khalili N, Datto C, Szamosi J, Eriksson H, A pooled analysis of two randomised, placebo-

controlled studies of extended release quetiapine fumarate adjunctive to antidepressant therapy in patients with major depressive disorder. *J Affect Disord.*, 2010; 127(1-3): 19-30.
6. Cheer S, Wagstaff A, Quetiapine. A review of its use in the management of schizophrenia. *CNS Drugs*, 2004; 18(3): 173-199.
7. Emsley RA, Buckley P, Jones AM, Greenwood MR, Differential effect of quetiapine on depressive symptoms in patients with partially responsive schizophrenia. *J Psychopharmacol.*, 2003; 17(2): 210-215.
8. Gabos-Grecu I, Actualities in depression therapy. University Press Publishing House, Târgu Mureş, 2007, (available in Romanian).
9. Keck PEJr, Strakowski SM, McElroy SL, The efficacy of atypical antipsychotics in the treatment of depressive symptoms, hostility, and suicidality in patients with schizophrenia. *J Clin Psychiatry*, 2000; 61(Suppl 3): 4-9.
10. Khouzam H, Treatment of depressive mood in schizophrenia with the atypical antipsychotic quetiapine. *Depress Anxiety*, 200; 11(2): 80-82.
11. Levinson D, Umapathy C, Musthaq M, Treatment of schizoaffective disorder and schizophrenia with mood symptoms. *Am J Psychiatry*, 1999; 156(8): 1138-1148.
12. Matthews JD, Bottonari KA, Polania LM, Mischoulon D, Dording CM, Irvin R, Fava M, An open study of olanzapine and fluoxetine for psychotic major depressive disorder: interim analyses. *J Clin Psychiatry*, 2002; 63(12): 1164-1170.
13. Moica Th, Gabos Grecu I, Gabos Grecu C, Buicu G, Popa OC, Sebesi S, Gabos Grecu M, Quetiapine XR as an adjunctive therapy in patients with MDD with inadequate response to SSRI. *Rom J Psychopharmacol.*, 2013; 13(3): 136-145.
14. Moica S, Introduction to statistics and practical applications. "Petru Maior" University Publishing House, Târgu Mureş, 2013, (available in Romanian).
15. Mueller T, Leon A, Keller M, Solomon D, Endicott J, Recurrence after recovery from major depressive disorder during 15 years of observational follow-up. *Am J Psychiatry*, 1999; 156(7): 1000-1006.
16. Papakostas G, Shelton R, Use of atypical anti-psychotics for treatment-resistant major depressive disorder. *Curr Psychiatry Rep.*, 2008; 10(6): 481-486.
17. Ravindran A, Bradbury C, McKay M, Da Silva T, Novel uses for risperidone: focus on depressive, anxiety and behavioral disorders. *Exp Opin Pharmacother.*, 2007; 8(11): 1693-1710.
18. Thase M, Antidepressant combinations: widely used, but far from empirically validated. *Can J Psychiatry*, 2011; 56(6): 317-323.
19. Tollefson G, Sanger T, Lu Y, Thieme M, Depressive signs and symptoms in schizophrenia: a prospective blinded trial of olanzapine and haloperidol. *Arch Gen Psychiatry*, 1998; 55(3): 250-258.
20. Trivedi M, Rush A, Wisniewski S, Nierenberg A, Warden D, Ritz L, Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: Implications for clinical practice. *Am J Psychiatry*, 2006; 163: 28-40.