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Author for correspondence:
*Arash Mowla, MD
Email: mowlaar@gmail.com

Is quetiapine effective for obsessive and compulsive symptoms in patients with bipolar disorder? A randomized, double-blind, placebo-controlled clinical trial

Ali Sahraian[1], Bahareh Ghahremanpouri[1] and Arash Mowla[2*]

[1]Research Center for Psychiatry and Behavioral Sciences, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran, and [2]Substance Abuse and Mental Health Research Center, Shiraz University of Medical Sciences, Shiraz, Iran

Abstract

Background. The aim of this study is to examine the effects of quetiapine as an adjuvant treatment for obsessive–compulsive (OC) symptoms in patients with bipolar disorder (BD) type I.

Methods. In this 8-week double-blind placebo-controlled randomized clinical trial, 47 patients with BD in euthymic phase that had OC symptoms were randomly allocated to receive either quetiapine or placebo plus their routine medications (lithium + clonazepam). Yale–Brown Obsessive–Compulsive Scale (YBOCS) was used to assess the outcomes. Adverse effects were also recorded.

Results. Of 47 BD patients with OC symptoms that were randomly allocated in two groups of quetiapine (n = 24) and placebo group (n = 23), 40 patients (20 in quetiapine group and 20 in placebo group) completed the trial. Throughout the trial, the mean score of YBOCS in the quetiapine group dropped from 24.37 ± 1.51 to 15.26 ± 1.16 ($P < .001$) and in the placebo group decreased from 24.21 ± 1.33 to 23.94 ± 1.66 ($P = 1.97$). At the end of the study, 12 (60%) patients in the quetiapine group and 1 (5%) patient in the placebo group had more than 34% decline in YBOCS score ($P < .001$). No serious adverse effects were reported in two groups.

Conclusions. Our double-blind placebo-controlled clinical trial showed that quetiapine may be an effective adjuvant agent for reducing OC symptoms in BD patients.

Introduction

Bipolar disorder (BD) is a chronic, multiphasic, and recurrent psychiatric condition characterized by oscillations in mood, energy, and functioning capacity.[1,2] Clinical and epidemiological studies have reported lifetime prevalence rates for comorbid obsessive–compulsive disorder (OCD) in BD to be between 3.2% and 35%.[3-6] The association of BD and OCD can complicate the course of these illnesses and increase the mortality and morbidity, as reflected in rise in suicide rate, substance abuse rate, total medical burden, economic cost, and quality of life.[7–10] It needs to be noted that the combination of the two symptomatic conditions (BD and OCD) may reflect common physiology rather than true comorbidity.[11,12]

Selective serotonin reuptake inhibitors (SSRIs) which currently are considered the first line treatment for OCD may shift euthymic BD patients toward manic episode.[13] There are reports that these medications even in combination with mood stabilizers may lead to treatment-emergent mania/hypomania in patients with BD.[14] In addition, up to 50% of OCD patients fail to respond to SSRIs,[15] and many others suffer from the side effects associated with SSRIs like sexual dysfunction.[16] Therefore, looking for alternative treatments is highly required for treating obsessive–compulsive (OC) symptoms in patients with BD.

Quetiapine is a second-generation atypical antipsychotic (SGA). It is distinguished from other SGAs (except clozapine) because of its low extrapyramidal side effects.[17] Quetiapine is a dibenzothiazepine with more potent serotonergic (5-HT2) than dopaminergic (D2) receptor-blocking properties.[18,19] The beneficial effects of quetiapine in the treatment of OCD have been reported in several studies.[20,21] Vulink et al, in their clinical trial of surveying the augmenting effects of quetiapine on OCD partiers, reported that quetiapine addition ($N = 22$, 69%) was associated with a significantly greater number of patients responding to treatment compared with placebo addition ($N = 15$, 41%; $P = .019$).[22] Quetiapine high serotonergic receptor affinity may justify its anti-OCD effects.

One of the main goals of pharmacological treatment for BD patients is the prevention of manic/hypomanic and depressive episodes by the administration of mood stabilizer drugs. There are several studies that have revealed quetiapine's mood stabilizing effects in BD patients.[23–25]

Due to quetiapine's mood stabilizing effects and anti-OCD properties, it may be a suitable remedy for patients with BD and OC symptoms. In this double-blind clinical trial, we would study its efficacy on OC symptoms in patients with BD.

Materials and Methods

Patients

Patients were recruited from Ebnesina Psychiatry Hospital affiliated to the Shiraz University of Medical Sciences from August 2019 to September 2020. The patients were diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) criteria for BD type 1 by a board-certified psychiatrist through Structured Clinical Interview for DSM-V, Clinical Version. They were complaining from OC symptoms too. Inclusion criteria were diagnosis of BD type 1, euthymic phase according to DSM-V criteria, and Young Mania Rating Scale (YMRS) <11 and Hamilton Depression Rating Scale (HDRS) <7, being between 18 and 65 years of age, and obtaining scores of 17 or more in Yale–Brown Obsessive–Compulsive Scale (YBOCS).

Exclusion criteria were being in manic or depressive phase of BD, existence of any other axis I and II diagnosis, major medical problems (cardiovascular, pulmonary, renal, or gastrointestinal diseases), pregnancy, and substance or alcohol abuse. All patients completed a general medical examination and blood chemistry tests, including TSH, FT4, liver function test, renal function test, and complete blood count before the study.

Procedure

The patients were randomly allocated into two groups using a predetermined random numbers list. Both groups were receiving lithium and clonazepam in the euthymic phase of BD. In the placebo group, the mean dosages of the medications were: lithium 800 mg and clonazepam 0.5 mg; whereas in the quetiapine group, the mean dosage of lithium was 825 mg and clonazepam was 0.35 mg. There is no contraindication for adding quetiapine to the patients' current medications. In the quetiapine group, quetiapine was administered with the starting dose of 25 mg/d during the first week and tittered up to 50 mg weekly. The dosage of quetiapine was increased until the patient was symptom-free. The mean dosage of quetiapine was 325 mg/d. If any patient could not tolerate any more quetiapine dosage tittering up, increasing the dosage was stopped for him or her.

Measurements

To assess the outcome of two regimens, YBOCS was administered.[26] Assessments of efficacy of the two drug regimens were performed at weeks 4 and 8. There is no standard cutoff point for YBOCS. Decrease of more than 34% in YBOCS was considered as response rate in our study based on expiratory analysis of data in previous similar studies.[27,28] However, in one study on resistant OCD patients, more than 25% decrease in YBOCS was chosen as cutoff point for treatment response.[29] Adverse effects of the medications were also registered.

For assessing mania symptoms at weeks 0, 4, and 8, YMRS was administered.[30] This survey consists of 11 items; the score of each item of the questionnaire is scaled between 0 and 4. Our patients' scores were less than 12 in each session (not manic).

Depressive symptoms were assessed by HDRS[31] at weeks 0, 4, and 8. The patients' scores in each session were less than 7 (not depressed). All the patients provided informed consent, and the study protocol was approved by the ethic committee of the Shiraz University of Medical Sciences that adheres to the Declaration of Helsinki Ethical Principles for Medical Research involving human subjects. This clinical trial was registered on the Iranian Registry of Clinical Trial (IRCT) database with IRCT number: IRCT 20190307042963 N1.

Statistical analysis

Software IBM SPSS (version 17.0) was performed for all statistical analyses. The mean and the standard deviation were used to describe quantitative variables. Categorical variables were compared with chi-square test, and *t*-test was applied to compare YBOCS score between two groups. *P*-values of less than .05 were considered as statistically significant.

Results

At first, 79 BD patients in euthymic state with OC symptoms were screened, and 47 patients were eligible to enter the study. The patients were randomly allocated in two groups of quetiapine (n = 24) and placebo (n = 23). Forty patients completed the trial. There were 20 patients in the quetiapine group and 20 patients in the placebo group at the end of the study. Figure 1 demonstrates the flow chart of the patients of the two groups.

The demographic and clinical data of the patients are shown in Table 1. The findings of this study indicate a significant difference between the two groups regarding the number of patients with a decline of over 34% in total YBOCS score. Overall, in the quetiapine group, 12 (50%) patients showed more than 34% decrease in mean YBOCS score compared to 1 (5%) patient in the placebo group at the end of the trial (Figure 2). This ratio of improvement was statistically different between the two groups (X^2 = 5.0, df = 1, $P < .001$). The adverse events experienced by the patients of both groups are depicted in Table 2. The quetiapine group showed a good tolerability and safety.

Discussion

Our double-blind placebo-controlled clinical trial revealed that quetiapine adjuvant may be effective in reducing OC symptoms in BD patients. Moreover, this adjunction was well tolerated and showed no significant adverse effects. The response rate in the quetiapine group was 50% compared to 5% in the placebo group.

Several studies have revealed that quetiapine has improved OC symptoms in inpatients or outpatients suffering from OCDs.[20–22] All of these studies have reported good tolerability and benefits. No dangerous adverse effect has been reported after adding quetiapine to routine anti-obsessive medications. The results of our research support these studies. We did not detect any serious adverse effects too.

The risk of deterioration of manic symptoms or shift of stable BD patients toward hypomania/mania phases hinders the use of antidepressant SSRIs in BD patients.[13,14] Therefore, treatment of OC symptoms in BD patients is a challenge. Recently, antipsychotics have been surveyed as an alternative in treatment of OC symptoms in BD patients. Amerio et al in their systemic review revealed that Aripiprazole augmentation to mood stabilizers

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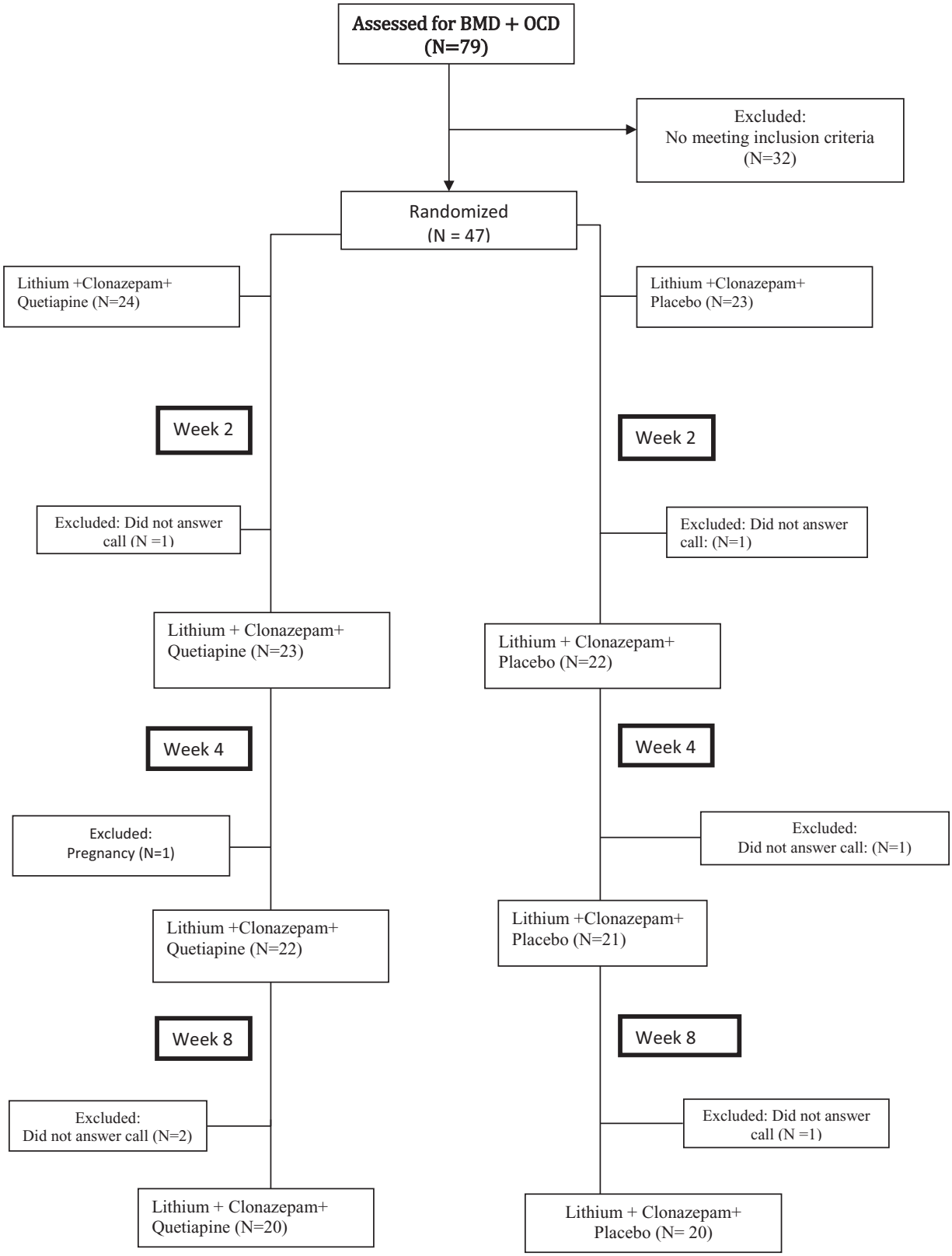

Figure 1. Flow chart of the patients in the two groups.

(lithium carbonate and valproate), even at low doses (10-15 mg/d), helped to achieve significant remission in affective and OC symptoms.[32] A 8-week, randomized, double-blind, placebo-controlled trial also demonstrated that aripiprazole can be used as an effective adjuvant agent for the treatment of OC symptoms during manic episodes. In particular, aripiprazole augmentation to lithium carbonate and clonazepam decreased the YBOCS scores more than the combination of lithium carbonate and clonazepam (91.30% vs

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Table 1. Demographic and Clinical Characteristics of the Patients

	Quetiapine Group	Placebo Group	*P*-Value
Age (years)	36.45 ± 13.83	38.45 ± 14.60	.462
Female (%)	10(50.00%)	9(45.00%)	.752
Weight (kg)	70.75 ± 17.67	67.81 ± 10.90	.753
Height (cm)	166.95 ± 12.25	158.45 ± 35.36	.584
Age of diagnosis	23.54 ± 11.3	25.6 ± 7.1	.301
YBOCS score			
Baseline	24.37 ± 1.51	24.21 ± 1.33	.263
Week 4	18.84 ± 1.18	23.89 ± 1.29	.000
Week 8	15.26 ± 1.16	23.94 ± 1.66	.000

Abbreviation: YBOCS, Yale–Brown Obsessive–Compulsive Scale.

Table 2. Adverse Effects in the Quetiapine and Placebo Groups

Adverse Effects	Quetiapine Group	Placebo Group
Increase appetite	2	1
Day drowsiness	3	1
Dry month	3	0
Constipation	5	2
Orthostatic hypotension	1	0
Nausea	2	2
Nasal congestion	0	1

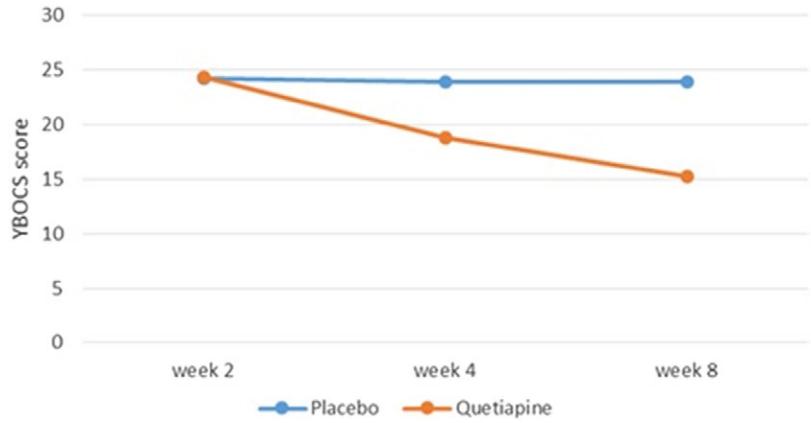

Figure 2. Response to treatment in quetiapine and placebo groups.
Abbreviation: YBOCS, Yale–Brown Obsessive–Compulsive Scale.

4.34%).[27] Our results demonstrate that quetiapine, another second-generation antipsychotic, can be considered as a treatment for OC symptoms in bipolar manic patients.

Topiramate and memantine augmentation to routine mood stabilizers was more effective than placebo in decreasing OC symptoms in BD patients in two separate clinical trials. These novel medications were well tolerated and safe.[33,34] Our study of quetiapine for OC symptoms in BD patients is in line with these researches to find novel treatments for OC symptoms in bipolar patients.

However, there are some limitations to this clinical study. Small sample of patients and short duration of the study are pitfalls of this trial. In addition, the study was conducted only in a single center. Larger clinical trials with longer duration are needed to confirm our results.

In conclusion, quetiapine, as an adjuvant medication, was more effective than placebo in decreasing OC symptoms in patients with BD. No serious side effects also were reported in patients taking quetiapine.

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Disclosure. The authors declare no conflicts of interest.

References

1. Kessing LV, Andersen PK, Vinberg M. Risk of recurrence after a single manic or mixed episode—a systematic review and meta-analysis. *Bipolar Disord*. 2018;**20**(1):9–17.
2. Radua J, Grunze H, Amann BL. Meta-analysis of the risk of subsequent mood episodes in bipolar disorder. *Psychother Psychosom*. 2017;**86**(2):90–98.
3. Chen YW, Dilsaver SC. Comorbidity for obsessive–compulsive disorder in bipolar and unipolar disorders. *Psychiatry Res*. 1995;**59**(1–2):57–64.
4. Merikangas KR, Akiskal HS, Angst J, *et al.* Lifetime and 12-month prevalence of bipolar spectrum disorder in the National Comorbidity Survey replication. *Arch Gen Psychiatry*. 2007;**64**(5):543–552.
5. Amerio A, Maina G, Ghaemi SN. Updates in treating comorbid bipolar disorder and obsessive–compulsive disorder: a systematic review. *J Affect Dis*. 2019;**256**:433–440.
6. Faravelli C, Abrardi L, Bartolozzi D, *et al.* The Sesto Fiorentino study: background, methods and preliminary results. Lifetime prevalence of psychiatric disorders in an Italian community sample using clinical interviewers. *Psychother Psychosom*. 2004;**73**(4):216–225.
7. Henry C, Van den Bulke D, Bellivier F, *et al.* Anxiety disorders in 318 bipolar patients: prevalence and impact on illness severity and response to mood stabilizer. *J Clin Psychiatry*. 2003;**64**(3):331–335.
8. Koyuncu A, Tükel R, Ozyildirim I, *et al.* Impact of obsessive–compulsive disorder comorbidity on the sociodemographic and clinical features of patients with bipolar disorder. *Compr Psychiatry*. 2010;**51**(3):293–297.
9. Shashidhara M, Sushma BR, Viswanath B, *et al.* Comorbid obsessive compulsive disorder in patients with bipolar-I disorder. *J Affect Disord*. 2015;**174**:367–371.

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10. Magalhães PV, Kapczinski NS, Kapczinski F. Correlates and impact of obsessive–compulsive comorbidity in bipolar disorder. *Compr Psychiatry*. 2010;**51**(4):353–356.
11. Maj M. "Psychiatric comorbidity": an artefact of current diagnostic systems? *Br J Psychiatry*. 2005;**186**:182–184.
12. Jeon S, Baek JH, Yang SY, *et al.* Exploration of comorbid obsessive–compulsive disorder in patients with bipolar disorder: the clinic-based prevalence rate, symptoms nature and clinical correlates. *J Affect Disord*. 2018;**225**:227–233.
13. Eddy KT, Dutra L, Bradley R, Westen D. A multi-dimensional meta-analysis of psychotherapy and pharmacotherapy for obsessive–compulsive disorder. *Clin Psychol Rev*. 2004;**24**(8):1011–1030.
14. Gao K, Kemp DE, Ganocy SJ, *et al.* Treatment-emergent mania/hypomania during antidepressant monotherapy in patients with rapid cycling bipolar disorder. *Bipolar Disord*. 2008;**10**(8):907–915.
15 Pittenger C, Bloch M. Pharmacological treatment of obsessive–compulsive disorder. *Psychiatr Clin North Am*. 2014;**37**(3):375–391.
16. Barth M, Kriston L, Klostermann S, *et al.* Efficacy of selective serotonin reuptake inhibitors and adverse events: meta-regression and mediation analysis of placebo-controlled trials. *Br J Psychiatry*. 2016;**208**(2):114–119.
17. Srisurapanont M, Maneeton B, Maneeton N, *et al.* Quetiapine for schizophrenia. *Cochrane Database Syst Rev*. 2004;**2004**(2):CD000967
18. Riedel M, Muller N, Strassnig M, *et al.* Quetiapine in the treatment of schizophrenia and related disorders. *Neuropsychiatr Dis Treat*. 2007;**3**(2):219–235.
19. Nemeroff CB, Kinkead B, Goldstein J. Quetiapine: preclinical studies, pharmacokinetics, drug interactions, and dosing. *J Clin Psychiatry*. 2002; **63**(suppl 13):5–11.
20. Kordon A, Wahl K, Koch N, *et al.* Quetiapine addition to serotonin reuptake inhibitors in patients with severe obsessive–compulsive disorder: a double-blind, randomized, placebo-controlled study. *J Clin Psychopharmacol*. 2008;**28**(5):550–554.
21. Diniz JB, Shavitt RG, Fossaluza V, *et al.* A double-blind, randomized, controlled trial of fluoxetine plus quetiapine or clomipramine versus fluoxetine plus placebo for obsessive–compulsive disorder. *J Clin Psychopharmacol*. 2011;**31**(6):763–768.
22. Vulink NC, Denys D, Fluitman SB, *et al.* Quetiapine augments the effect of citalopram in non-refractory obsessive–compulsive disorder: a randomized, double-blind, placebo-controlled study of 76 patients. *J Clin Psychiatry*. 2009;**70**(7):1001–1008.
23. Kishi T, Ikuta T, Matsuda Y, *et al.* Mood stabilizers and/or antipsychotics for bipolar disorder in the maintenance phase: a systematic review and network meta-analysis of randomized controlled trials. *Mol Psychiatry*. 2020. doi:10.1038/s41380-020-00946-6
24. Poyurovsky M, Braverman L, Weizman A. Beneficial effect of quetiapine monotherapy in patients with bipolar depression and comorbid obsessive–compulsive disorder. *Int Clin Psychopharmacol*. 2021;**36**(1):50–53.
25. Escudero MAG, Gutiérrez-Rojas L, Lahera G. Second-generation antipsychotics monotherapy as maintenance treatment for bipolar disorder: a systematic review of long-term studies. *Psychiatr Q*. 2020;**91**(4): 1047–1060.
26. Goodman WK, Price LH, Rasmussen SA, *et al.* The Yale–Brown Obsessive–Compulsive Scale: I. Development, use, and reliability. *Arch Gen Psychiatry*. 1989;**46**(11):1006–1011.
27. Sahraian A, Ehsaei Z, Mowla A. Aripiprazole as an adjuvant treatment for obsessive and compulsive symptoms in manic phase of bipolar disorder: a randomized, double-blind, placebo-controlled clinical trial. *Prog Neuropsychopharmacol Biol Psychiatry*. 2018;**84**(Pt A):267–271.
28. Mowla A, Ghaedsharaf M. Pregabalin augmentation for resistant obsessive–compulsive disorder: a double-blind placebo-controlled clinical trial. *CNS Spectr*. 2020;**25**(4):552–556.
29. Mowla A, Khajeian AM, Sahraian A, *et al.* Topiramate augmentation in resistant OCD: a double-blind placebo-controlled clinical trial. *CNS Spectr*. 2010;**15**(11):613–617.
30. Young RC, Biggs JT, Ziegler VE, Meyer DA. A rating scale for mania: reliability, validity and sensitivity. *Br J Psychiatry*. 1978;**133**:429–435.
31. Hamilton M. Development of a rating scale for primary depressive illness. *Br J Soc Clin Psychol*. 1967;**6**:278–296.
32. Amerio A, Odone A, Ghaemi SN. Aripiprazole augmentation in treating comorbid bipolar disorder and obsessive–compulsive disorder: a systematic review. *J Affect Disord*. 2019;**249**:15–19.
33. Sahraian A, Bigdeli M, Ghanizadeh A, *et al.* Topiramate as an adjuvant treatment for obsessive compulsive symptoms in patients with bipolar disorder: a randomized double-blind placebo-controlled clinical trial. *J Affect Disord*. 2014;**166**:201–205.
34. Sahraian A, Jahromi LR, Ghanizadeh A, *et al.* Memantine as an adjuvant treatment for obsessive–compulsive symptoms in manic phase of bipolar disorder: a randomized, double-blind, placebo-controlled clinical trial. *J Clin Psychopharmacol*. 2017;**37**(2):246–249.