Aripiprazole versus quetiapine in treatment-resistant obsessive-compulsive disorder: a double-blind clinical trial

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Abstract

Introduction: Around 40–60% of the patients with obsessive-compulsive disorder (OCD) remain unimproved by serotonin reuptake inhibitors (SRIs). Goal of this study was to compare the efficiency and safety of aripiprazole *versus* quetiapine, in patients with OCD, who did not respond effectively to fluvoxamine.

Method: A total of 44 female inpatients with OCD, who did not respond successfully to fluvoxamine at maximum dose (300 mg/day) and duration (12 weeks), were assigned randomly, in a double-blind trial, to receive aripiprazole ($n = 22$) or quetiapine ($n = 22$), in addition to their SRI, for 12 weeks. Treatment response was assessed by the Yale–Brown Obsessive–Compulsive Scale (YBOCS), as primary outcome measure, and Clinical Global Impressions–Severity Scale (CGI-S), as a secondary outcome measure.

Results: A total of 27.27% of the cases in the aripiprazole group ($n = 6$) and 54.54% of them in the quetiapine cluster ($n = 12$) responded moderately to the aforesaid augmentation. The mean $\pm$ SD baseline YBOCS score of 33.27 ± 3.90 dropped to a mean of 30.72 ± 4.67 ($p = 0.06$) in the aripiprazole group, and from 31.18 ± 4.93 to 27.97 ± 3.71 ($p = 0.01$) in the quetiapine group, at the end of the evaluation. There was no significant change with respect to CGI-S in either of the aforesaid groups.

Conclusion: This study shows that treatment-resistant OCD patients may benefit more from addition of quetiapine in comparison with aripiprazole, to their ongoing SRI therapy.

Keywords: aripiprazole, obsessive-compulsive disorder, quetiapine.

Introduction

Obsessive-compulsive disorder (OCD) is a psychiatric disorder that affects 2–3.5% of people during their lifetimes [Sasson *et al.* 1997]. Poor response occurs in 40–60% of people that are prescribed first-line pharmaceutical treatments such as selective serotonin reuptake inhibitors (SSRIs), and moreover 20–40% do not respond adequately even after several prescriptions [Expert Consensus Panel for Obsessive–Compulsive Disorder, 1997; Catapano *et al.* 2006].

Therapeutic strategies in these resistant cases usually consist of augmentation therapies with a range of adjunctive drugs, including antipsychotics. Treatment with second-generation antipsychotics (SGAs) that show fewer extrapyramidal

symptoms, in comparison with typical antipsychotics, may be a useful alternative for treatment-refractory OCD patients. The broader range of effective treatment with the addition of atypical antipsychotics may be due to D2 blockade or a combined serotonergic–dopaminergic blockade, particularly a 5-HT_{2A} and D2 antagonism [Komossa *et al.* 2010]. However, according to Bloch and colleagues [Bloch *et al.* 2006], only one-third of treatment-refractory OCD patients show a meaningful treatment response to antipsychotic augmentation, along with sufficient evidence that demonstrates the efficacy of haloperidol and risperidone, and inconclusive data regarding quetiapine and olanzapine. In addition, patients with comorbid tics are likely to have a differential benefit to antipsychotic augmentation [Dold *et al.*

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2011]. This group also, according to a meta-analysis, declared risperidone more efficacious than other SGAs in treatment-resistant OCD [Dold *et al.* 2011]. In addition, with respect to newer SGAs, there are a number of clinical trials in the literature with different outcomes as regards the effectiveness of quetiapine [Kordon *et al.* 2008; Carey *et al.* 2005; Denys *et al.* 2004; Fineberg *et al.* 2006] and aripiprazole [Pessina *et al.* 2009; Muscatello *et al.* 2011; Delle Chiaie *et al.* 2011; Ak *et al.* 2011]. In this study, the efficacy and safety of aripiprazole has been compared with quetiapine in a group of patients suffering from treatment-resistant OCD.

Method

This study was approved by University's Medical Ethics Committee. A total of 44 female inpatients, as accessible sample in the chronic ward of the hospital, after full explanation of the procedure for them and obtaining signed informed consent, were entered into a 12-week parallel group, double-blind study for random assignment to adjunctive aripiprazole ($n = 22$ patients) or quetiapine ($n = 22$ patients), plus their regular prescription. Patients were diagnosed with OCD according to the criteria of Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Revision [APA, 2000].

Cases with identified comorbidity, such as substance misuse, mood, medical and neurological problems, had been excluded from the trial. Inclusion criteria in this study were as follows.

- (1) OCD symptoms resistant to fluvoxamine at maximum dose (300 mg/day) and long enough duration (12 weeks).
- (2) A score on the YBOCS of at least 18. During the trial, whereas the patients, staff and assessor were unaware of the prescribed augmentation that were packed into identical capsules, all patients continued to take their current SRI (fluvoxamine) at the maximum dose (300 mg/day) during assessment. Aripiprazole addition was initiated at a dose of 2.5 mg/day and then increased by 2.5 mg increments in weekly meetings, to a maximum of 10 mg by week 4 and then this dose was held constant to the end of the study. Quetiapine (immediate-release formulation) as well was started by 25 mg bid, and then increased by 75 mg in weekly meetings, to

maximum of 300 mg by week 4 and that dose was held constant to the end of the study. No other psychotropic drug or psychosocial intervention, during the trial, was administrated for them.

The primary outcome measure was YBOCS [Goodman *et al.* 1998]. Clinical Global Impressions-Severity Scale (CGI-S) also was used as the secondary outcome [Guy, 1976]. Full response to treatment was defined of at least 50% decrease in YBOCS score and partial response as between 25% and <50% decrease in that score in comparison with the baseline. The study duration was 12 weeks, and the patients were assessed by means of YBOCS at baseline (week 0), and weeks 2, 4, 8, and 12. CGI-S was scored at the baseline and at the end of the assessment. Adverse events were assessed at each visit by means of patients' spontaneous reports and clinical examination by psychiatrist.

Statistical analysis

Patients were compared on baseline characteristics by means of *t* tests. Treatment efficacy also was analyzed by *t* test and repeated-measures analysis of variance (ANOVA) comparing both groups over 12 weeks. Statistical significance was defined as a two-sided *p* value ≤ 0.05 . MedCalc, version 9.4.1.0, was used as statistical software tool for analysis.

Results

Analysis for efficacy was based on data from an equal number of patients in both groups, which were initially comparable, and demographic and diagnostic variables were analogous (Table 1). According to the findings, there was no full response in any of the cases in either group. A total of 6 patients (27.27%) in the aripiprazole group and 12 patients in the quetiapine group (54.54%) showed partial response, with a decrease from 33.17 ± 3.90 to 30.72 ± 4.67 and 31.18 ± 4.93 to 27.97 ± 3.71 by aripiprazole and quetiapine, respectively (Tables 2 and 3).

Within-group analysis showed that although this improvement was significant in the quetiapine group ($t = 1.88$, $p = 0.01$) at the end of the trial, but it was not so with aripiprazole ($t = 2.44$, $p = 0.06$); see Table 3.

In addition, repeated-measures ANOVA regarding YBOCS, did not show any significant improvement

Table 1. Demographic characteristics of patients participating in the quetiapine and aripiprazole groups.

Groups variables	Aripiprazole	Quetiapine	Degrees of freedom	<i>t</i>	<i>p</i>
Gender (female)	22	22		–	–
Age (years)	38.45 ± 8.47 (SD), 1.81 (SE)	39.27 ± 9.08 (SD), 1.94 (SE)	42	0.21	0.82
Duration of illness (years)	10.36 ± 6.54 (SD), 1.39 (SE)	9.90 ± 7.51 (SD), 1.60 (SE)	42	0.15	0.87
YBOCS - baseline	33.17 ± 3.90 (SD), 0.83 (SE)	31.18 ± 4.93 (SD), 1.05 (SE)	42	1.55	0.12
CGI-S - baseline	3.29 ± 0.33 (SD), 0.07 (SE)	3.38 ± 0.08 (SD), 0.02 (SE)	42	1.32	0.19
Abbreviations: YBOCS, Yale–Brown Obsessive–Compulsive Scale; CGI-S, Clinical Global Impressions–Severity Scale; SD, standard deviation; SE, standard error.					

Table 2. Percentage of positive response on the YBOCS, in the aripiprazole and quetiapine groups.

Patient number	Quetiapine YBOCS (baseline)	Quetiapine YBOCS (endpoint)	Quetiapine % change	Aripiprazole YBOCS (baseline)	Aripiprazole YBOCS (endpoint)	Aripiprazole % change
1	38	25	34.21	31	23	25.80
2	29	21	27.58	40	29	27.51
3	35	23	34.28	32	23	28.12
4	31	23	25.80	42	31	26.19
5	30	22	26.66	29	21	27.58
6	37	26	29.72	31	23	25.80
7	35	24	31.42			
8	38	27	28.94			
9	29	22	24.13			
10	31	23	25.80			
11	30	22	26.66			
12	36	25	30.55			

by aripiprazole [$F(4,84) = 0.636$, $p < 0.63$, $SS = 1058.00$, $MSe = 416.07$], whereas a remarkable improvement was evident by quetiapine [$F(4,84) = 10.8$, $p < 0.04$, $SS = 286.64$, $MSe = 8.45$] at the end of the assessment, and also in comparison with aripiprazole [$F(1,105) = 3.71$, $p < 0.05$, $SS = 4.09$, $MSe = 1.10$], in a split-plot (mixed) design ANOVA. In addition, while head-to-head analysis could not illustrate any important difference between quetiapine and aripiprazole in weeks 2, 4 and 8, it was significant in week 12 (Table 3 and Figure 1).

Also, with respect to CGI-S, no significant change was evident by aripiprazole (3.29 ± 0.33 to 3.17 ± 1.02 ; $t = 0.52$, $p = 0.60$) or quetiapine (3.38 ± 0.08 to 3.32 ± 0.14 ; $t = 1.74$, $p = 0.08$), though perhaps a better response was noticeable with the latter one.

As the sample size was small, the effect size (ES) was analyzed for changes on the YBOCS and

CGI-S at the end of the assessment. Outcome indicated a medium improvement of YBOCS by both quetiapine ($d = 0.7$, $r = 0.3$) and aripiprazole ($d = 0.5$, $r = 0.2$). Also, there was small and medium improvements of CGI-S by aripiprazole ($d = 0.15$, $r = 0.07$) and quetiapine ($d = 0.5$, $r = 0.2$), respectively.

Post hoc analysis showed power = 0.49 on behalf of this trial, which turned to power = 0.79 in compromise power analysis. The most common adverse effects of aripiprazole and quetiapine in our samples, during the trial, were somnolence (27.77% and 45.55%, respectively), dizziness (18.18% and 54.54%, respectively) and weight gain (27.27% in the quetiapine group only, with a mean increase of 0.36 ± 0.11 kg) and inner unrest (18.18% in the aripiprazole group). Since the side effects were mild and well tolerated, then no one dropped out owing to medication intolerance.

Table 3. Between-group analysis of primary outcome measure at baseline (week 0) and weeks 2, 4, 8 and 12.

Primary outcome measure	Aripiprazole N = 22	Quetiapine N = 22	t	p	Degrees of freedom	95% confidence interval
YBOCS – baseline	33.17 ± 3.90 (SD), 0.83 (SE)	31.18 ± 0.93 (SD), 1.05 (SE)	1.48	0.14	42	–0.71, 4.69
YBOCS –week 2	32.36 ± 4.81 (SD), 1.03 (SE)	30.02 ± 0.51 (SD), 0.75 (SE)	1.84	0.07	42	–0.22, 4.90
YBOCS – week 4	31.19 ± 3.75 (SD), 0.80 (SE)	29.43 ± 0.26 (SD), 0.70 (SE)	1.66	0.10	42	–0.38, 3.90
YBOCS – week 8	30.53 ± 4.11 (SD), 0.88 (SE)	27.68 ± 0.95 (SD), 1.27 (SE)	1.84	0.08	42	–0.26, 5.96
YBOCS – week 12	30.72 ± 4.67 (SD), 1.00 (SE)	27.97 ± 0.71 (SD), 0.79 (SE)	2.163	0.03	42	0.18, 5.32

Abbreviations: YBOCS, Yale–Brown Obsessive–Compulsive Scale; OCD, obsessive–compulsive disorder; SD, standard deviation; SE, standard error.

Figure 1. Changes of mean YBOCS between week 0 (baseline) and 12.

Discussion

According to the result of this study, the addition of aripiprazole and quetiapine to ongoing SRI treatment may be efficacious for treatment-refractory OCD patients, a finding that was significant only in the quetiapine group. Perhaps a longer duration of trial or higher dosage could result in significant outcomes in the aripiprazole group and better results in the quetiapine cluster. In this regard, although the baselines were generally comparable, the severity of the primary outcome measure in the aripiprazole group was greater than the secondary. This may have influenced the end result of our appraisal. The same issue is also applicable to the doses of these drugs, which only could be roughly considered as comparable. It is mentionable that in a somewhat similar approach, Selvi and colleagues, in a single-blind, randomized study, had also found risperidone more effective

than aripiprazole for improvement of YBOCS [Selvi *et al.* 2011].

In general and with respect to quetiapine, in contrast to Kordon and colleagues [Kordon *et al.* 2008] and Carey and colleagues [Carey *et al.* 2005], the result of our study was comparable with the findings of Denys and colleagues [Denys *et al.* 2004] and Fineberg and colleagues [Fineberg *et al.* 2006], while in connection with aripiprazole, it was not in concord with Pessina and colleagues [Pessina *et al.* 2009], Muscatello and colleagues [Muscatello *et al.* 2011], Delle Chiaie and colleagues [Delle Chiaie *et al.* 2011] and Ak and colleagues [Ak *et al.* 2011]. The primary outcome measure of all of the above trials was YBOCS, except than the last two, who used YBOCS plus CGI-S.

Nonetheless this diversity could be the outcome of dissimilarities between intervening factors, such as the kind of prescribed SRI, duration of study, patient's gender, and, in particular, the criteria of response. The main problem here is that there is some inconsistency in the definition of treatment refractoriness and there is not yet any universal agreement on the definition of responsiveness or resistance in the realm of OCD. Therefore, first of all, clear criteria for no response need to be agreed upon because frequently the standards for response rates differ to a large extent. For example, Weiss and colleagues [Weiss *et al.* 1999] used a cutoff of 50% decrease in YBOCS score as responders, while Francobandiera [Francobandiera, 2001] chose a cutoff of 25%.

On the other hand, McDougle and colleagues [McDougle *et al.* 2000] used a more restrictive criterion with a cutoff of 35% for YBOCS decrease and a final score of 16 on the YBOCS in combination with a final CGI-S rating of much improved or very much improved. Such differences invalidate the comparison of effect sizes between studies.

As regards quetiapine, Komossa and colleagues [Komossa *et al.* 2010] found that although quetiapine combined with antidepressants was no more efficacious than placebo combined with antidepressants in terms of response of patients with OCD to treatment, but it showed a significant superiority in comparison with olanzapine and risperidone in improvement of the mean YBOCS score. In addition, some beneficial effects of quetiapine, in terms of anxiety or depressive symptoms, were observable.

Alternatively and according to Denys and colleagues [Denys *et al.* 2004], not only quetiapine was superior to placebo regarding improvement of YBOCS in treatment-resistant OCD, but the best response was visible by means of its combination with clomipramine, fluoxetine, and fluvoxamine and with the lowest SRI doses.

Indeed, specific sociodemographic factors, including pharmacogenetic and clinical characteristics of the patients, and in addition, different treatments received by them in the past, could also have contributed to the modest responses in the current measurement.

Unlike other studies by olanzapine and risperidone, in this one, weight gain and extrapyramidal symptoms were not the most common side effects and also complaints such as somnolence, dizziness, and weight gain were mild to moderate and did not cause serious problems for the patients. Better tolerance and side-effect profiles, particularly in long term, may perhaps put quetiapine in a better position in comparison with the aforesaid SGAs. Small sample size, short duration of study, gender-based sampling and lack of placebo arm, which may have significant impact on the assay sensitivity of the study and artificially inflate results in an active comparator trial, were among the weak points of this trial. Surely, intermediary power of current assessment implies necessity of larger samples for verification of the outcome of this experiment.

Further analogous trials in future possibly will improve our knowledge in this regard.

Conclusion

This study shows that treatment-resistant OCD patients may benefit more from the addition of quetiapine, in comparison with aripiprazole, to their ongoing SRI therapy.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

References

- Ak, M., Bulut, S., Bozkurt, A. and Ozsahin, A. (2011) Aripiprazole augmentation of serotonin reuptake inhibitors in treatment-resistant obsessive-compulsive disorder: a 10-week open-label study. *Adv Ther* 28: 341–348.
- APA (2000) *American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders*, 4th edn, Text Revision. Washington, DC: American Psychiatric Association.
- Bloch, MH1., Landeros-Weisenberger, A., Kelmendi, B., Coric, V., Bracken, MB. and Leckman, JF. (2006) A systematic review: antipsychotic augmentation with treatment refractory obsessive-compulsive disorder. *Mol Psychiatry* 11(7): 622–632.
- Carey, PD., Vythilingum, B., Seedat, S., Muller, JE., Ameringen, van M. and Stein DJ. (2005) Quetiapine augmentation of SRIs in treatment refractory obsessive-compulsive disorder: a double-blind, randomised, placebo-controlled study. *BMC Psychiatry* 5: 44. doi: 10.1186/1471-244X-5-44
- Catapano, F., Perris, F., Masella, M., Rossano, F., Cigliano, M., Magliano, L., *et al.* (2006) Obsessive-compulsive disorder: a 3-year prospective follow-up study of patients treated with serotonin reuptake inhibitors OCD follow-up study. *J Psychiatr Res* 40: 502–510.

- Delle Chiaie, R., Scarciglia, P., Pasquini, M., Caredda, M. and Biondi, M. (2011) Aripiprazole augmentation in patients with resistant obsessive compulsive disorder: a pilot study. *Clin Pract Epidemiol Ment Health* 7: 107–111.
- Denys, D., de Geus, F., van Megen, HJ. and Westenberg HG. (2004) A double-blind, randomized, placebo-controlled trial of quetiapine addition in patients with obsessive-compulsive disorder refractory to serotonin reuptake inhibitors. *J Clin Psychiatry* 65: 1040–1048.
- Dold, M., Aigner, M., Lanzenberger, R. and Kasper, S. (2011) Efficacy of antipsychotic augmentation therapy in treatment-resistant obsessive-compulsive disorder: a meta-analysis of double-blind, randomised, placebo-controlled trials. *Fortschr Neurol Psychiatr* 79: 453–466.
- Expert Consensus Panel for Obsessive–Compulsive Disorder (1997) Treatment of obsessive–compulsive disorder. *J Clin Psychiatry* 58(Suppl. 4): 2–725.
- Fineberg, NA., Stein, DJ., Premkumar, P., Carey, P., Sivakumaran, T., Vythilingum, B. *et al.* (2006) Adjunctive quetiapine for serotonin reuptake inhibitor-resistant obsessive–compulsive disorder: a meta-analysis of randomized controlled treatment trials. *Int Clin Psychopharmacol* 21: 337–343.
- Francobandiera, G. (2001) Olanzapine augmentation of serotonin uptake inhibitors in obsessive–compulsive disorder: an open study. *Can J Psychiatry* 46: 356–358.
- Goodman, WK., Price, LH., Rasmussen, SA., Mazure, C., Fleischmann, RL., Hill, CL. *et al.* (1998) The Yale–Brown Obsessive Compulsive Scale, 1: development, use, and reliability. *Arch Gen Psychiatry* 46: 1006–1011.
- Guy W. (ed.) (1976) *Clinical Global Impressions, ECDEU Assessment manual for psychopharmacology*. DHEW Publication No. (ADM) 76-338, US Department of Health, Education, and Welfare, Rockville, MD.
- Komossa, K., Depping, AM., Meyer, M., Kissling, W. and Leucht, S. (2010) Second-generation antipsychotics for obsessive compulsive disorder. *Cochrane Database Syst Rev* 12: CD008141. doi:10.1002/14651858.CD008141.pub2
- Kordon, A., Wahl, K., Koch, N., Zurowski, B., Anlauf, M., Vielhaber, K. *et al.* (2008) Quetiapine addition to serotonin reuptake inhibitors in patients with severe obsessive-compulsive disorder: a double-blind, randomized, placebo-controlled study. *J Clin Psychopharmacol* 28: 550–554.
- McDougle, CJ., Epperson, CN., Pelton, GH., Wasylink, S. and Price, LH. (2000) A double-blind, placebo-controlled study of risperidone addition in serotonin reuptake inhibitor-refractory obsessive-compulsive disorder. *Arch Gen Psychiatry* 57: 794–801.
- Muscatello, MR., Bruno, A., Pandolfo, G., Micò, U., Scimeca, G., Romeo, VM. *et al.* (2011) Effect of aripiprazole augmentation of serotonin reuptake inhibitors or clomipramine in treatment-resistant obsessive-compulsive disorder: a double-blind, placebo-controlled study. *J Clin Psychopharmacol* 31: 174–179.
- Pessina, E., Albert, U., Bogetto, F. and Maina, G. (2009) Aripiprazole augmentation of serotonin reuptake inhibitors in treatment-resistant obsessive-compulsive disorder: a 12-week open-label preliminary study. *Int Clin Psychopharmacol* 24: 265–269.
- Sasson, Y., Zohar, J., Chopra, M., Lustig, M., Iancu, I. and Hendler, T. (1997) Epidemiology of obsessive compulsive disorder: a world view. *J Clin Psychiatry* 58(Suppl. 12): 7–10.
- Selvi, Y., Atli, A., Aydin, A., Besiroglu, L., Ozdemir, P. and Ozdemir, O. (2011) The comparison of aripiprazole and risperidone augmentation in selective serotonin reuptake inhibitor-refractory obsessive-compulsive disorder: a single-blind, randomised study. *Hum Psychopharmacol* 26: 51–57.
- Weiss, EL., Potenza, MN., McDougle, CJ. and Epperson, CN. (1999) Olanzapine addition in obsessive-compulsive disorder refractory to selective serotonin reuptake inhibitors; an open-label case series. *J Clin Psychiatry* 60: 524–527.

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