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Quetiapine versus clomipramine in the augmentation of selective serotonin reuptake inhibitors for the treatment of obsessive-compulsive disorder: a randomized, open-label trial

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Abstract

After 12 weeks of selective serotonin reuptake inhibitor (SSRI) monotherapy with inadequate response, 10 patients received clomipramine and 11 received quetiapine as augmentation agents of the SSRI. The primary outcome measure was the difference between initial and final scores of the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS), rated in a blinded fashion, and the score of clinical global improvement (CGI-I). Statistical analyses were performed using nonparametric tests to evaluate treatment efficacy and the difference between treatment groups. Percentile plots were constructed with YBOCS scores from the clomipramine and quetiapine groups. Considering response a ≥35% reduction in the initial Y-BOCS score plus a rating of 'much improved' or 'very much improved' on CGI-I, four of eleven quetiapine patients and one out of ten clomipramine patients were classified as responders. The mean final Y-BOCS score was significantly lower than baseline in the quetiapine augmentation group ($P = 0.023$), but not in the clomipramine augmentation group ($P = 0.503$). The difference between groups showed a trend towards significance only at week 4, the mean Y-BOCS score being lower for those receiving quetiapine ($P = 0.052$). A difference between groups was also observed at week 4 according to percentile plots. These results corroborate previous findings of quetiapine augmentation efficacy in obsessive-compulsive disorder (OCD). Clomipramine augmentation did not produce a significant reduction in Y-BOCS scores. Higher target maximum dosages might have yielded different results.

Key words

clomipramine; obsessive compulsive disorder; psychiatry; quetiapine; serotonin reuptake inhibitors

Introduction

Obsessive-compulsive disorder (OCD) is considered a chronic illness that can negatively affect individual quality of life and functioning and is responsible for a significant portion of the global burden related to psychiatric disorders (Kastrup and Ramos, 2007).

Serotonin reuptake inhibitors (SRIs) and cognitive-behavioural therapy have been used to successfully treat OCD. However, a significant number of patients do not

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respond to these first-line treatments (Miguel, *et al*., 1997; March, *et al*., 1997; Abramowitz, 2006). Even patients who improve can continue to present severe residual symptoms (Pallanti, *et al*., 2004). Therefore, to increase treatment response rates, therapeutic alternatives are needed. There is no consensus regarding which treatment should be given after first-line treatments fail. The lack of well-established second-line treatments justifies the assessment of alternative therapeutic options for OCD.

The current literature suggests that adding medicines from other pharmacological classes is the most effective next step in treatment after an inadequate response to an SRI. Because SRIs can decrease the dysfunction associated with OCD but rarely produce complete remission of symptoms, the hypothesis that other neurotransmitters are involved in the pathophysiology of OCD symptoms has been raised. To date, combining first- or second-generation antipsychotics with an SRI has been the most successful form of pharmacological augmentation. However, data regarding this augmentation strategy are only preliminary because there have been few large, controlled clinical trials. Three recent systematic reviews on antipsychotic augmentation of SRIs (Keuneman, *et al*., 2005; Bloch, *et al*., 2006; Skapinakis, *et al*., 2007) suggested that antipsychotics are helpful as augmentation agents in OCD. However, only approximately one-third of patients show improvement after treatment with this combination (Bloch, *et al*., 2006). In addition, the current evidence regarding specific antipsychotics, such as quetiapine and olanzapine, is inconclusive.

Quetiapine has been tested in some open-label trials (Denys, *et al*., 2002; Mohr, *et al*., 2002; Sevincok and Topuz, 2003; Misri and Millis, 2004), in one single-blind, placebo-controlled trial (Atmaca, *et al*., 2002) and in three double-blind, placebo-controlled trials (Denys, *et al*., 2004a; Fineberg, *et al*., 2005; Carey, *et al*., 2005). The study by Denys, *et al*. (2004a) was the only placebo-controlled trial to show significant improvement after treatment with the quetiapine-SRI combination. However, a number of factors might explain the negative results obtained in the other trials. In the study conducted by Carey, *et al*. (2005), for example, the placebo group experienced a relatively high response rate. This finding might have stemmed from ongoing improvement resulting from the SRI in question.

Other pharmacological agents have been tested in combination with SRIs for the treatment of OCD. Rather than combining drugs with different pharmacological profiles, some investigators have tried to enhance serotonin reuptake blockade by combining two serotonergic agents. Clomipramine with an SSRI has yielded positive results in a number of open trials: fluoxetine (Simeon, *et al*., 1990; Browne, *et al*., 1993); sertraline (Ravizza, *et al*., 1996); fluvoxamine (Koran, 1999) and citalopram (Pallanti, *et al*., 1999). In the study conducted by Pallanti, *et al*. (1999), all nine patients randomized to clomipramine combined with citalopram were considered responders. No double-blind, placebo-controlled trials have evaluated this therapeutic strategy.

Because no information is available from double-blind, placebo-controlled trials regarding pharmacological augmentation strategies other than those involving antipsychotics, studies investigating clomipramine augmentation are warranted.

To date, few clinical trials have compared two different agents in the augmentation of SSRIs for the treatment of OCD patients who are refractory to SSRI monotherapy. This trial sought to compare the efficacy of a quetiapine-SSRI combination with that of a clomipramine-SSRI combination in OCD patients having been treated unsuccessfully with SSRI monotherapy.

Methods

This was a randomized, open-label study conducted between January of 2006 and December of 2007 at the OCD Program of the Department & Institute of Psychiatry, Clinical Hospital, University of São Paulo Medical School, located in São Paulo, Brazil. The protocol was approved by the local ethics committee. The intervention and all potentially harmful effects were fully explained to the candidates, and all participating patients gave written informed consent.

Subjects

Prior to this augmentation trial, all of the candidates had participated in a trial comparing SSRI treatment versus group cognitive-behavioural therapy. Those completing the SSRI trial[a] and having not achieved adequate response were then invited to participate in the augmentation trial.

In the initial trial, patients who agreed to participate were sequentially allocated to receive an SSRI or group cognitive behavior therapy (CBT). The methodology used to sequentially allocate patients will be described elsewhere (Fossaluza, *et al*., unpublished observations). To simulate what occurs in naturalistic clinical settings, patients allocated to receive an SSRI were preferentially treated with fluoxetine, and medical appointments were scheduled every four weeks. Fluoxetine was chosen as the preferential antidepressant for various reasons: its efficacy is well established for both short- and long-term treatment (Greist, *et al*., 2003); it is among the recommended first-line treatments for OCD in international guidelines (Greist, *et al*., 2003; Math and Janardhan Reddy, 2007) and it is the mostly available and mostly used SSRI in our national setting (Andrade, *et al*., 2004). Patients were allowed full-time telephone access to a psychiatrist of the group. The potential side effects and the delayed onset of therapeutic effects were explained in detail at the first consultation. Patients were instructed to initiate the fluoxetine dosage by 20 mg per day

[a] Patients could receive SSRI treatment in two conditions: if they were randomize to the SSRI therapeutic arm or if they were not respondent to psychotherapy.

for the first week, then increase dosage by 20 mg per week, until reaching the maximum tolerated dosage or 80 mg/day. Intolerable side effects were managed by reducing the dosage and administering symptomatic medication. If side effects persisted at the subsequent consultation, a second SSRI (preferentially sertraline) was used (Belotto-Silva, *et al*., unpublished observations).

After completing 12 weeks of SSRI treatment, patients meeting all of the following criteria were invited to participate in the pharmacological augmentation trial: being 18–65 years of age; having been diagnosed with primary OCD according to the criteria set forth in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; current symptoms causing significant distress; having been previously treated for at least 12 weeks with an SSRI (at least 8 weeks at the maximum tolerated dosage) and having experienced treatment failure (SSRI treatment failed to produce satisfactory improvement of OCD accordingly to patients report-Clinical Global Impression (CGI) score of global improvement >2 and a final YBOCS score above 14). Exclusion criteria for the initial and the pharmacological augmentation trial were as follows: having a clinical or neurological disease that might be worsened by the medicines included in the treatment protocol; presenting current substance dependence or abuse; exhibiting current psychotic symptoms; being currently at risk for suicide; and being pregnant or having the intention to become pregnant prior to the end of the treatment protocol.

Of the 48 patients who completed the initial 12-week SSRI trial, 11 presented OCD symptom remission, four refused to participate in the augmentation trial and two were excluded for current suicide risk. Patients who dropped out during the first two weeks of the trial (mainly due to side effects - drowsiness for quetiapine and severe constipation for clomipramine) were excluded from the analysis ($n = 10$; five quetiapine patients and five clomipramine patients). The flow of this study is diagrammed in Figure 1.

Note that 31 patients were randomized but the final sample comprised only 21 patients. The reason for this difference was the exclusion of 10 patients (five from the clomipramine group and five from the quetiapine group) due to treatment discontinuation prior to the first consultation after treatment initiation. Three patients (two from the quetiapine group and one from the clomipramine group) who did not complete the 12-week period of treatment but who discontinued after that period were included in the analyses.

Treatment received in the augmentation trial

Patients randomized to receive clomipramine initiated treatment at 25 mg/day and increased the daily dosage by 25 mg every week until reaching 75 mg/day, unless intolerable side effects occurred.

Patients randomized to receive quetiapine initiated treatment at 50 mg/day and increased the daily dosage by 50 mg every week until reaching 200 mg/day, unless intolerable side effects occurred.

At enrollment in the augmentation trial, 18 patients were taking fluoxetine (80 mg per day), two were taking sertraline (200 mg per day) and one was taking citalopram (60 mg per day). For safety reasons (risk of pharmacokinetic interaction leading to increased serum levels of quetiapine and clomipramine for those taking fluoxetine) (Zhou, *et al*., 2007), the maximum allowable dosage of fluoxetine was set at 40 mg/day. The two patients taking sertraline and the one taking citalopram were instructed to maintain the current dosage (200 mg/day for the patients taking sertraline and 60 mg/day for the patient taking citalopram) because the impact of these SSRIs on the cytochrome P450 system are less prominent (Preskorn, *et al*., 2007).

Security measures

Physical examination was performed at first consultation to exclude clinical disorders that could be worsened by the medications in this protocol. Blood tests (including thyroid hormone levels, blood glucose levels, blood cell count, liver and kidney function) and electrocardiograms were performed prior to enrollment, at week 2 and at week 12. No abnormalities were present at physical and blood exams for all patients recruited at all time intervals evaluated. One patient was taking thyroid hormone replacement for hypothyroidism and current hormone dosages were within normal ranges. Blood pressure and heart rate were measured in every consultation and no significant changes were observed. No patient showed a QT interval prolongation during this trial.

After informed consent was obtained for this specific augmentation trial, a simple randomization procedure was used.

Outcome measures

The Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) scores (Goodman, *et al*., 1989) and ratings of the Clinical Global Impression-Improvement (CGI-I) scale were obtained by a blinded researcher at baseline and at week 12. The primary outcome measure was the difference between the initial and final (week 12) Y-BOCS scores. In intermediate evaluations (at weeks 4 and 8), scores were obtained by the psychiatrist responsible for the treatment of each patient (not blinded).

Statistical analysis

Power calculation was not performed for two reasons. First, this study was a hypothesis-generating pilot study. Second, previous trials that evaluated clomipramine combined with SSRIs included a very small number of patients and generated rates of response that cannot be confidently compared to those found in the quetiapine augmentation trials. Therefore, any sample size calculation would have to rely on a great number of hypothesized results not supported by previous studies. For the same reasons, no non-inferiority limit was set.

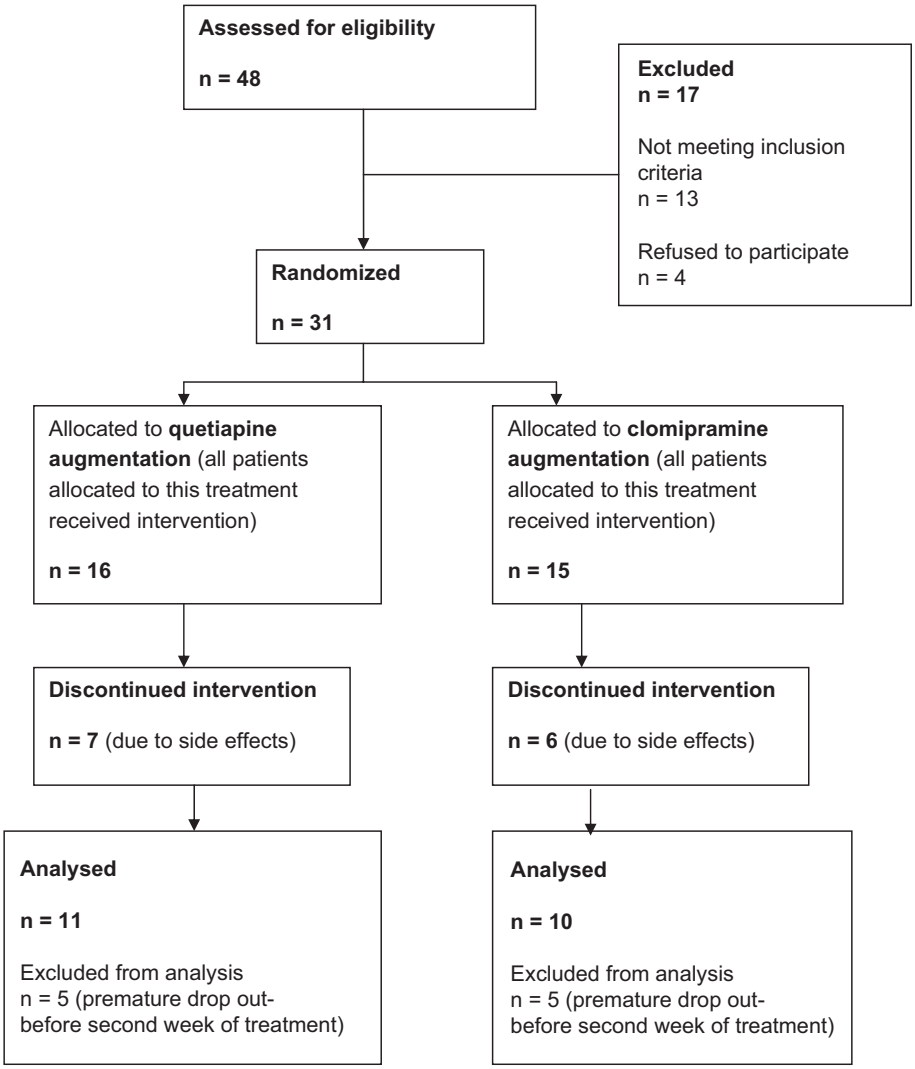

Figure 1 Flow diagram (Source: Altman, *et al.*, 2001).

A last observation carried forward (considering only the analyzed sample of 21 patients) was applied to the treatment efficacy measures. Only the data related to patients who completed the study were included in the analysis of differences between treatment groups.

The Wilcoxon test for related samples was used to determine the significance of the difference between the initial and final mean Y-BOCS scores. The Mann–Whitney *U*-test was used to analyse differences between treatment groups, in terms of mean Y-BOCS scores, at baseline and at weeks 4, 8 and 12.

Percentile plots (also known as p-p plots or q-q plots, where "q" stands for quantile) were constructed with YBOCS scores from the clomipramine and quetiapine groups. To produce a graphical comparison of these two independent samples' score frequency distributions, we estimated the percentiles for each sample. We chose, as percentiles, the quartile levels (0, 25, 50, 75 and 100%) and calculated the pairs of quartiles for all levels. For example, we obtained at week 4 the pairs of median (14.25; 18.25) at the percentile level 25% (or first quartile), (16.5; 24) at level 50% (second quartiles) and (21.75; 27.75) at level 75% (third quartiles). The graph was constructed with these pairs of medians for quartile levels. A diagonal line indicating the graph position of the identical pairs was drawn for interpretation. Hence a pair above (below) this line indicates that the second sample has that the quantile larger (smaller) than that of the first sample.

Results

A total of 11 subjects were randomly assigned to quetiapine augmentation and 10 to clomipramine augmentation. No

severe adverse side effects were reported. One patient (Table 1, clomipramine patient 8) was instructed to discontinue treatment at week 4, after reporting three symptoms of serotonergic syndrome (excessive sweating, tremors and motor agitation). These symptoms remitted one day after the cessation of treatment. Demographic characteristics and individual responses are described in Table 1.

The mean initial and final Y-BOCS scores for the total sample were 22.19 ± 4.9 and 19.61 ± 8.5, respectively. The difference between the initial and final Y-BOCS scores was significant ($P = 0.024$). Of the sample as a whole, 12 patients received 'much improved' or 'very much improved' CGI-I ratings at the end of treatment. Considering a response criterion of a ≥35% reduction from the initial Y-BOCS score plus a rating of 'much improved' or 'very much improved' on CGI-I, four of eleven quetiapine patients and one of ten clomipramine patients were classified as responders.

The difference between the initial and final Y-BOCS score was significant for the quetiapine group (22 ± 5.3 vs 18 ± 8.5; $P = 0.023$) but not for the clomipramine group (21.9 ± 4.1 vs 21.5 ± 7.7; $P = 0.503$).

Among the patients receiving quetiapine, 'much improved' or 'very much improved' final CGI-I ratings were given to eight quetiapine patients, compared with four patients receiving clomipramine. As can be seen in Figure 2, most patients presented lower Y-BOCS scores at week 12 than at baseline: nine patients in the quetiapine group and four patients in the clomipramine group.

The magnitude of the reduction in Y-BOCS scores was greater in the quetiapine group. However, no significant difference was found between the clomipramine group and the quetiapine group in terms of mean Y-BOCS scores at weeks 8 and 12. A trend towards significance ($P = 0.052$) was found at week 4 (Figure 3).

Percentile plots were constructed to represent the difference between groups in terms of Y-BOCS scores (Figure 4). The difference between groups was most pronounced at week 4 (Y-BOCS scores were lower in the quetiapine group than in the clomipramine group). A difference, albeit less evident, was also seen at week 12.

Discussion

In our sample, a significant decrease in Y-BOCS scores was found for the quetiapine group but not for the clomipramine group. Although there was no significant difference between the two groups at baseline or at weeks 8 and 12, a tendency towards a better response was observed in the quetiapine group at week 4. However, the week 4 ratings were not blinded. Nevertheless, for the quetiapine group, results at the week 4 and week 12 were quite comparable. In addition, for the clomipramine group, there was no significant difference between week 8 and week 12 results.

It is important to highlight that, as this trial is a pilot study, further investigation with double blind, head-to-head comparisons of augmentation strategies of SSRIs for OCD treatment are required to confirm these initial findings. Both efficacy results and safety issues were not definitely addressed in this trial, and before additional information is obtained from other studies, no change in current treatment practice is advisable, having only this trial results as the main source of information.

In accordance with the literature, patients in the quetiapine group presented an early response (observed at week 4), and their Y-BOCS scores remained at comparable levels at subsequent evaluations (Denys, *et al*., 2004a). In addition, our finding that approximately one-third of the quetiapine-treated population were classified as responders (a reduction in Y-BOCS score of ≥35%) replicates the response rate previously reported for the combination of atypical antipsychotics and SSRIs (Bloch, *et al*., 2006). Although one previous study involving a sample of similar size failed to identify a significant difference between quetiapine and placebo augmentation of SSRIs (Fineberg, *et al*., 2005), we did observe a significant reduction in Y-BOCS scores in the quetiapine group.

The pharmacodynamic effect responsible for anxiolytic augmentation produced by the association of serotonergic drugs and atypical antipsychotics is still unknown. The low dosages of antipsychotics required to produce this effect have generated the hypothesis that only partial occupancy of D_2 receptors would be necessary to augment the anxiolytic effect of antidepressants (Gefvert, *et al*., 2001; Rasmussen, 2006). Functionally, it is likely that the serotonergic system interacts with dopaminergic neurons to produce the final symptoms of OCD (Aouizerate, *et al*., 2005).

However, it has been argued that partial occupancy of D_2 is not sufficient to produce any therapeutic effect and, therefore, other receptors that are occupied with low dosages of atypical antipsychotics (such as 5-HT_{2A} receptors) might be important for the observed augmenting effect. Quetiapine has higher affinity for 5-HT_{2A} than D_2 receptors. Consequently, at low dosages such as the ones used in this trial, it is likely that occupancy of $5HT_{2A}$ receptors is higher than that of D_2 receptors (Rasmussen, 2006).

Previous attempts to enhance serotonergic activity to further improve OCD symptoms have been less successful than attempts to augment SSRIs with antipsychotics. Of four studies evaluating augmentation of SRIs with pindolol (Dannon, *et al*., 2000; Mundo, *et al*., 1998; Blier and Bergeron, 1996; Koran, *et al*., 1996), three produced negative results, as did one study evaluating clonazepam (Crockett, *et al*., 2004), one of two studies evaluating buspirone (Markovitz, *et al*., 1990; Pigott, *et al*., 1992), two studies evaluating lithium (McDougle, *et al*., 1991; Pigott, *et al*., 1991) and two studies evaluating inositol (Seedat and Stein, 1999; Fux, *et al*., 1999). These findings are consistent with the hypothesis that the better response associated with clomipramine augmentation of SSRIs is related to a pharmacodynamic effect involving noradrenaline reuptake or to a pharmacokinetic mechanism (drug-drug interaction).

The pharmacodynamic hypothesis, however, has not been corroborated by previous findings. Barr, *et al*. (1997) combined

Table 1 Demographic characteristics and individual treatment response

Patient	Age	Gender	Previous treatment history	Percentage of Y-BOCS reduction with last SSRI (%)[a]	Initial Y-BOCS score	Final Y-BOCS score	Percentage of Y-BOCS reduction after augmentation[a]	Clinical Global Impression	Week of last observation carried forward	SSRI (drug/mg/day)	Quetiapine maximum dosage (mg/day)
Quetiapine group											
1	41	Female	Not responding to one previous appropriate course of treatment	−11	30	26	13	Improved	4	Fluoxetine/40	50
2	25	Male	No previous appropriate treatment	21	26	15	42	Very much improved	12	Fluoxetine/40	150
3	35	Female	Not responding to one previous appropriate course of treatment	9	21	22	−5	Much improved	12	Fluoxetine/40	200
4	35	Male	No previous appropriate treatment	0	19	13	32	Much improved	8	Fluoxetine/40	50
5	20	Male	Not responding to one previous adequate treatment	32	15	4	73	Much improved	12	Citalopram/60	100
6	32	Female	No previous appropriate treatment	14	25	23	8	Much improved	12	Fluoxetine/40	75
7	46	Male	No previous appropriate treatment	−8	32	28	13	Improved	12	Fluoxetine/40	200
8	45	Female	No previous appropriate treatment	10	18	14	22	Much improved	12	Fluoxetine/40	100
9	32	Female	Not responding to one previous appropriate course of treatment	33	16	6	63	Very much improved	12	Sertraline/200	200
10	37	Male	Not responding to one previous appropriate course of treatment	31	25	31	−24	Improved	12	Fluoxetine/40	200
11	28	Female	Not responding to one previous appropriate course of treatment	36	20	13	35	Very much improved	12	Fluoxetine/40	25
Clomipramine group											
1	27	Male	Not responding to one previous appropriate course of treatment	13	20	17	15	Much improved	12	Fluoxetine/40	50
2	49	Male	Not responding to one previous appropriate course of treatment	31	20	9	55	Very much improved	12	Fluoxetine/40	75
3	27	Male	Not responding to one previous appropriate course of treatment	30	22	20	9	Improved	12	Fluoxetine/40	75
4	42	Female	No previous appropriate treatment	31	22	24	−9	Improved	12	Sertraline/200	75
5	23	Male	No previous appropriate treatment	5	20	18	10	Much improved	12	Fluoxetine/40	50

(continued)

Table 1 *(continued)*

Patient	Age	Gender	Previous treatment history	Percentage of Y-BOCS reduction with last SSRI (%)[a]	Initial Y-BOCS score	Final Y-BOCS score	Percentage of Y-BOCS reduction after augmentation[a]	Clinical Global Impression	Week of last observation carried forward	SSRI (drug/mg/day)	Quetiapine maximum dosage (mg/day)
6	33	Female	Not responding to one previous appropriate course of treatment	19	25	26	−4	Not improved	12	Fluoxetine/40	75
7	35	Male	No previous appropriate treatment	6	15	16	−7	Much improved	12	Fluoxetine/40	75
8	62	Male	No previous appropriate treatment	30	19	17	11	Not improved	4	Fluoxetine/40	50
9	24	Female	Not responding to one previous appropriate course of treatment	19	25	36	−44	Not improved	12	Fluoxetine/40	75
10	53	Male	Not responding to one previous appropriate course of treatment	−7	31	32	−3	Not improved	12	Fluoxetine/40	75

Y-BOCS, Yale-Brown Obsessive-Compulsive Scale; SSRI, selective serotonin reuptake inhibitor.
[a]Negative results represent worsening of Y-BOCS score after treatment.

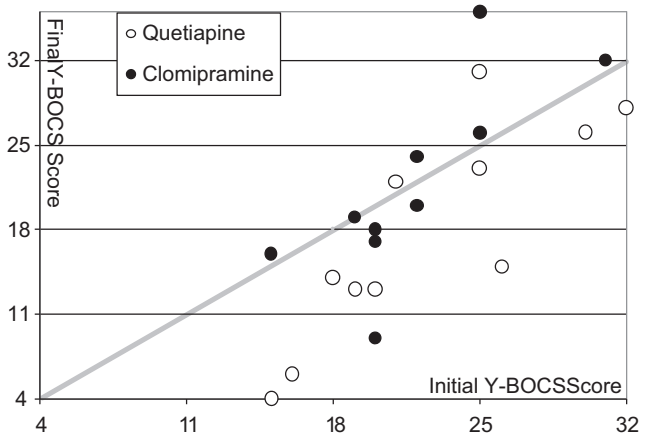

Figure 2 Dispersion Diagram of Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) scores at baseline (initial) and at week 12 (final) for each patient by treatment. Each dot represents a patient. Dots below the grey line represent patients who had a final YBOCS score lower than the initial score. The distance between the dot and the grey line represents the magnitude of the difference between the initial and final score.

SRIs and a norepinephrine reuptake inhibitor (desipramine) in SRI-resistant OCD patients and found no significant differences between the adjunctive desipramine and placebo groups. In a study evaluating venlafaxine, which is a selective serotonin-noradrenaline reuptake inhibitor, the response observed was comparable to that obtained using an SSRI (Denys, *et al.*, 2004b). However, some authors have questioned whether the power of noradrenaline reuptake inhibition induced by venlafaxine is equal to that induced by clomipramine (Gillman, 2007). In addition, although noradrenaline reuptake inhibition alone does not seem to promote OCD symptom improvement (Hoehn-Saric,

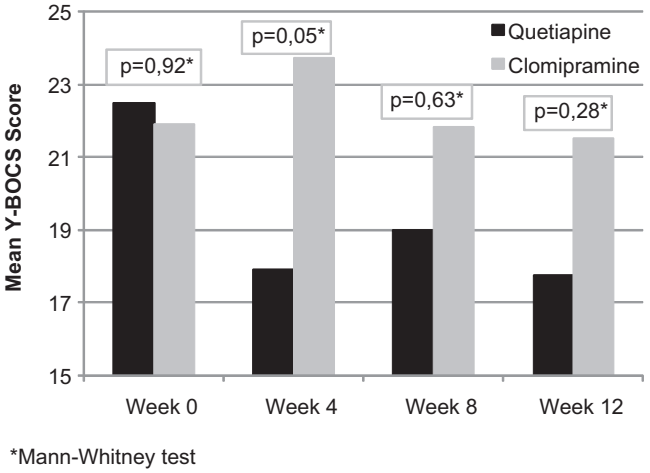

Figure 3 Mean Yale-Brown Obsessive-Compulsive Scale scores at baseline (week 0), week 4, week 8 and week 12 by treatment.

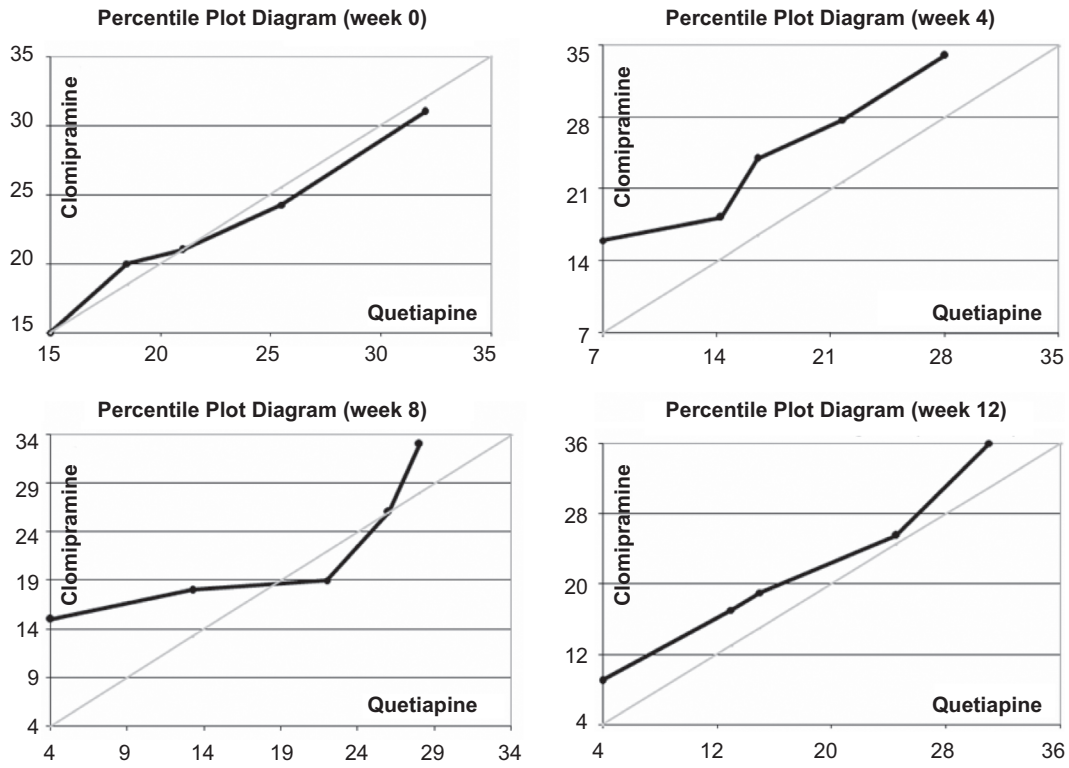

Figure 4 Percentile plots representing the relationships between the two treatment groups in terms of the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) scores. Grey lines represent the point of equality. The distance between the black line and the grey line represents the magnitude of the difference between groups. The black line appears above the grey line when Y-BOCS scores for the clomipramine group are higher than Y-BOCS scores for the quetiapine group.

et al., 2000), it remains possible, albeit unproven, that the combination of noradrenaline reuptake inhibition and serotonin reuptake inhibition has a synergistic effect (Noorbala, *et al*., 1998; Fontenelle, *et al*., 2005).

The pharmacokinetic hypothesis would suggest that efficacy is associated with increased serum levels of clomipramine in relation to its metabolite (N-desmethylclomipramine) due to cytochrome P450 saturation induced by some SSRI. Such saturation is mainly promoted by fluvoxamine and only modestly by fluoxetine (Zhou, *et al*., 2007; Preskorn, *et al*., 2007). However, high dosages of sertraline and possibly citalopram can generate the same phenomenon (Preskorn, *et al*., 2007; Gillman, 2007; Mandrioli, *et al*., 2006). Still, no consistent relationship between magnitude or probability of therapeutic response in OCD and plasma concentrations of clomipramine or its metabolite or their sum has been found (Koran, *et al*., 2006).

Higher serum levels of clomipramine can increase cardiac risk and increase the risk of serotonergic syndrome (Gillman, 2007). In general, SSRIs are less likely than tricyclic antidepressants to induce cardiac side effects, although SSRIs have occasionally produced first-degree atrioventricular block, prolonged corrected QT interval and orthostatic hypotension (Rodriguez de la Torre, *et al*., 2001). Nevertheless, no serious complications were observed in our sample, for which the maximum dosages of both SSRI and clomipramine were set according to potential pharmacological interactions. Higher dosages of clomipramine might still be related to clinical risk and might also be associated with greater therapeutic effects.

Antipsychotics have also been reported to induce prolongation of heart rate-corrected QT interval (Haddad and Sharma, 2007), although no specific association has been found with quetiapine use. In our sample, use of the quetiapine-SSRI combination was not significantly associated with short-term clinical risk, which is in agreement with previous findings (Denys, *et al*., 2004a; Fineberg, *et al*., 2005; Carey, *et al*., 2005). Other side effects associated with increased cardiovascular risk in the long term could not be evaluated due to the short duration of this trial. Our safety results should be evaluated with caution, due to the small sample size, open label format and limited increases in dosage.

The reduction in the SSRI dosage among the fluoxetine users evaluated may have influenced the initial response. The response curve for patients in the clomipramine group shows an initial worsening of OCD symptoms (increase of Y-BOCS scores) with a trend towards a significant difference in relation

to the quetiapine group scores. However, this did not happen in the quetiapine group, in which patients were also instructed to reduce their fluoxetine dosage. These findings might be a consequence of the different times required to achieve the maximum effect of each type of pharmacological combination. Studies involving longer observational periods are needed to determine whether the apparent difference between these two therapeutic strategies is an artifact of the short evaluation period, which may have favoured the quetiapine response.

Interestingly, a previous study has found an association between lower dosages of SSRI and greater response to quetiapine augmentation (Denys, *et al*., 2007). In the studies revised by Denys, *et al*. (2007), SSRI lower dosage was maintained steady through the SSRI monotherapy trial. Differently, in our trial, we had the measurement of response for the greatest possible dosage of SSRI and only then reduced the SSRI dosage. Therefore, it would be premature to state that lower dosages of fluoxetine favoured the response to quetiapine augmentation. However, it is an important issue that should be evaluated in future studies.

Early dropout led to the exclusion of a significant number of patients from the final analysis and this may have influenced the trial results. These patients discontinued treatment due to side effects (primarily drowsiness for quetiapine and severe constipation for clomipramine) and refused to take the same drug again, even at lower dosages or together with symptomatic medication. However, seven of these patients were monitored through follow-up evaluation, and additional treatment resulted in a good response for three of them. Therefore, there was no specific profile among the excluded patients (either refractory or good responders to treatment). But it is important to have in mind that the decision to exclude those patients may have inflated the response rate of this trial if it is to be compared with other augmentation trials using intention-to-treat analyses.

Other limitations of our study include the small sample size, the absence of a placebo control and no controlling for serum level of the drugs used. As a consequence of the small number of patients, no clinical or sociodemographic prognostic factors could be evaluated. Tic disorders, for example, were reported by only two of the patients studied. In addition, the small sample size might explain why the apparent differences between groups seen in the percentile plots did not reach statistical significance. Also, although no severe side effects were reported in this trial, there are safety issues regarding clomipramine augmentation of SSRIs that have to be carefully evaluated in future trials.

The effect of the lack of a placebo group in this study should not be underestimated because previous studies have shown a greater than expected placebo response in OCD patients taking SRIs (Carey, *et al*., 2005; Fineberg, *et al*., 2006). Also, if clomipramine, quetiapine and fluoxetine serum levels had been available, higher dosages of augmenters could have been safely reached and better responses could have been shown.

Double-blind, placebo-controlled trials with active comparators are needed before a definite second-line treatment can be established for SRI-resistant OCD. So far, the best evidence of efficacy lies on antipsychotic augmentation of SSRIs.

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