A Double-Blind, Randomized, Controlled Trial of Fluoxetine Plus Quetiapine or Clomipramine Versus Fluoxetine Plus Placebo for Obsessive-Compulsive Disorder

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Abstract: Obsessive-compulsive disorder patients who do not improve sufficiently after treatment with a selective serotonin reuptake inhibitor might improve further if other drugs were added to the treatment regimen. The authors present a double-blind, placebo-controlled trial comparing the efficacy of adding quetiapine or clomipramine to a treatment regimen consisting of fluoxetine. Between May 2007 and March 2010, a total of 54 patients with a primary diagnosis of obsessive-compulsive disorder, as defined by *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision*, and a current Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) score of at least 16, the score having dropped by less than 35% after fluoxetine monotherapy, were allocated to 1 of 3 arms (n = 18 per arm): quetiapine + fluoxetine (≤200 and ≤40 mg/d, respectively), clomipramine + fluoxetine (≤75 and ≤40 mg/d, respectively), or placebo + fluoxetine (≤80 mg/d of fluoxetine). Follow-up was 12 weeks. The Y-BOCS scores were the main outcome measure. No severe adverse events occurred during the trial, and 40 patients (74%) completed the 12-week protocol. The Y-BOCS scores (mean [SD]) were significantly better in the placebo + fluoxetine and clomipramine + fluoxetine groups than in the quetiapine + fluoxetine group (final: 18 [7] and 18 [7], respectively, vs 25 [6], $P < 0.001$) (reduction from baseline: −6.7 [confidence interval {CI}, −9.6 to −3.8; and −6.5 [CI, −9.0 to −3.9], respectively, vs −0.1 [CI, −2.9 to 2.7], $P < 0.001$; number needed to treat = 2.4). The clomipramine-fluoxetine combination is a safe and effective treatment for fluoxetine nonresponders, especially those who cannot tolerate high doses of fluoxetine. However, the period of monotherapy with the maximum dose of fluoxetine should be extended before a combination treatment strategy is applied.

Key Words: obsessive-compulsive disorder, clinical trial, combined therapy, antipsychotic agents, antidepressant agents

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Obsessive-compulsive disorder (OCD) often manifests as a chronic illness, even when appropriate treatment is available.[1,2] It is associated with functional losses, impaired quality of life, and a high family burden,[2–5] contributing significantly to the social costs related to anxiety disorders.[4]

First-line treatment options, which include serotonin reuptake inhibitors (SRIs), as well as cognitive behavioral therapy with exposure and response prevention techniques,[6–8] fail to provide a satisfactory response in up to 40% of patients. Even when there is improvement, the persistence of OCD symptoms is the rule rather than the exception.[9] Therefore, second-line treatment strategies are warranted.

The use of antipsychotics combined with SRIs is listed as a second-line treatment strategy in international treatment guidelines[10,11] and is the only such strategy that has proven effective according to meta-analyses.[12,13] The addition of an antipsychotic to the treatment regimen has been associated with meaningful improvement in approximately one third of SRI nonresponders.[12] However, most patients do not respond significantly to the addition of an antipsychotic, prompting the investigation of other treatment strategies.

Quetiapine is a second-generation antipsychotic with a favorable side effect profile regarding the risk of tardive dyskinesia and sexual dysfunction.[14] In 5 small placebo-controlled trials, quetiapine was evaluated as an augmenter for OCD patients under SRI treatment.[15–19] Two of those trials reported a better response to quetiapine than to the placebo.[16,18] Small sample sizes, short follow-up periods, limited dose ranges, and heterogeneous samples could explain the negative results obtained in the other 3 trials.[19,20] Because OCD patients are expected to require prolonged drug treatment,[21,22] the use of atypical antipsychotics, such as quetiapine, raises concerns related to the long-term adverse effects of these drugs, which include an increased risk of cardiovascular morbidity and mortality.[13] Therefore, the use of drugs with less potential for harmful long-term adverse effects should be investigated.

Although not yet tested in placebo-controlled trials, the use of clomipramine, a nonselective SRI, in combination with a selective serotonin reuptake inhibitor (SSRI) has been investigated in case series and open-label trials. In an open-label trial, the quetiapine-SSRI combination provided responses that were slightly better and faster than those obtained with the clomipramine-SSRI combination. However, the lack of a placebo arm and the small sample size (n = 21) prevented the drawing of any definite conclusions regarding the comparative efficacy.[23]

In this article, we compare the use of quetiapine and clomipramine as add-ons to treatment with the SSRI fluoxetine.

MATERIALS AND METHODS

Patients were eligible for recruitment if they were aged 18 to 65 years and were treated between May 2007 and March 2010 at the outpatient clinic of the OCD Spectrum Disorders

Program of the Institute of Psychiatry, Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (University of São Paulo School of Medicine), located in São Paulo, Brazil. The study protocol was approved by the Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo ethics review board, and all participating patients gave written informed consent. All procedures were carried out in accordance with the Good Clinical Practice guidelines.[24]

We enrolled patients who met the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* (*DSM-IV-TR*) criteria for a primary diagnosis of OCD, had been consistently taking the highest recommended or tolerated dose of fluoxetine for at least 8 weeks, and had a current Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) score of at least 16, the score having dropped by less than 35% over the course of their treatment with fluoxetine. Patients at risk for complications associated with the medications used in this trial—such as those with an abnormal electrocardiogram (ECG), those who presented with mania, imminent suicide risk, psychotic symptoms, or substance abuse/dependence, as well as those who were pregnant or lactating—were not included.

This was a 12-week, randomized, double-blind trial involving quetiapine (Seroquel; Astra Zeneca, São Paulo, SP, Brazil), clomipramine (Anafranil; Novartis Pharmaceuticals, São Paulo, SP, Brazil), and fluoxetine (Daforin; EMS Pharma, São Paulo, SP, Brazil). Patients were randomized into 3 groups: quetiapine + fluoxetine (≤200 and ≤40 mg/d, respectively), clomipramine + fluoxetine (≤75 and ≤40 mg/d, respectively), and placebo + fluoxetine (sustained maximum or tolerated dose of fluoxetine, ≤80 mg/d).

All medications were administered orally and once per day. Quetiapine was started at 50 mg/d and increased weekly by 50 mg/d, up to a maximum of 200 mg/d. Clomipramine was started at 25 mg/d and increased weekly by 25 mg/d, up to a maximum of 75 mg/d. The maximum fluoxetine dose was 40 mg/d in the quetiapine + fluoxetine and clomipramine + fluoxetine groups and 80 mg/d in the placebo + fluoxetine group. Therefore, the daily dose of fluoxetine was actually reduced for some patients (those taking >40 mg/d at enrollment and assigned to the quetiapine + fluoxetine or clomipramine + fluoxetine group).

The rationale for establishing the maximum dose of fluoxetine at 40 mg/d in the augmentation groups was the fact that this dose is associated with 80% occupancy of the serotonin transporter,[25] the estimated limit for a therapeutic response. In addition, increasing the fluoxetine dose to greater than 40 mg/d is associated with only a small increase in transporter occupancy.[25] Because of the pharmacokinetic interactions between fluoxetine and clomipramine, a 40-mg/d dose of fluoxetine should still result in a significant increase in plasma clomipramine levels, although a gain in safety and tolerability is expected.[26,27] No loss in efficacy was expected as a previous study has shown that patients who reported the greatest benefits from the addition of quetiapine were those who were taking the lowest SRI doses.[28]

Clinicians, raters, and patients were blinded to the augmenter being used and to the current fluoxetine dose. Patients were seen by the study clinician once a week for weeks 1 through 4 and once a month for weeks 5 through 12. Additional appointments were scheduled as necessary.

At the initial evaluation, patients were interviewed by researchers trained in the application of the following instruments: Y-BOCS[29,30]; Clinical Global Impression of Improvement (CGI-I) scale[31]; Beck Depression Inventory (BDI)[32]; Beck Anxiety Inventory (BAI)[33]; Social Adjustment Scale-Self Report (SAS-SR)[34]; Medical Outcomes Study 36-item Short-Form Survey, version 2 (SF-36)[35]; Structured Clinical Interview for *DSM-IV* Axis I Disorders–Patient Version[36]; Structured Clinical Interview for *DSM-IV-TR* Impulse Control Disorders[37]; and Brown Assessment of Beliefs Scale.[38] The Y-BOCS, CGI-I, BDI, BAI, SF-36, and SAS-SR were reapplied at week 12. The Y-BOCS scores were also obtained at weeks 1, 2, 3, 4, and 8. Blinded raters, not involved in the care of the patients, obtained Y-BOCS scores at weeks 0 and 12. Intermediate measures (at weeks 1, 2, 3, 4, and 8) were taken by the study clinician during routine consultations. The primary outcome measures were the Y-BOCS scores.

During the augmentation phase, patients were periodically submitted to ECG and determination of plasma fluoxetine levels (24 hours after the most recent dose) and clomipramine levels (12 hours after the most recent dose). At each evaluation, the clinician actively questioned patients about adverse effects. Unusual or potentially severe adverse events were reported to an independent, nonblinded committee, which decided whether to withdraw the affected patient from the study. Patients were sequentially allocated to treatment arms according to a minimization procedure developed specifically for this trial and described elsewhere.[39]

With a difference of 5 points in the mean Y-BOCS scores between the active and placebo groups considered clinically significant, the estimated sample size required to produce a power of 80% was 60 patients.

Interim analyses (to determine the effect of the sample size) were scheduled at 50% and 90% of data collection. The interim analysis at 50% (sample size, n = 30) did not show any statistically significant differences between groups. The interim analysis at 90% (sample size, n = 54) showed a significant difference between groups. The distribution of probabilities showed a 98% chance that response rates would be higher in 2 groups (at the time kept blind) compared with the additional one. At this point, the study was interrupted to avoid exposure of additional patients to a procedure that appeared inefficient (addition of quetiapine to fluoxetine).

We used intention-to-treat analysis and hot-deck imputation of missing data. To evaluate whether the imputation method used interfered significantly with the statistical results, we performed sensitivity analyses.

To evaluate the ordinal categorical variables group, time, and interaction effects for Y-BOCS scores at all time points, we used Wald statistics from nonparametric analysis of covariance (ANCOVA) with repeated measures,[40] the initial Y-BOCS score being a covariate. Number needed to treat was calculated with bases on the risk of less than 25% reduction in initial Y-BOCS scores.

To evaluate the secondary outcome measures (BDI, BAI, SF-36, and SAS-SR) between weeks 0 and 12 (for the sample as a whole, for each group, and between groups), we used nonparametric ANCOVA, the covariates being the initial values. We used the χ^2 test to evaluate CGI-I scores at week 12 and thus classify individuals as responders (much improved or very much improved) or nonresponders (slightly improved, not improved, or worse). We used the Student *t* tests to compare responders and nonresponders by mean plasma levels of fluoxetine and clomipramine. Data are expressed as mean (SD) except where noted.

RESULTS

We assessed 138 eligible patients, and 59 failed to meet the inclusion criteria, 30 of those 59 because they were fluoxetine responders. Therefore, the final sample is composed of 54 patients (Fig. 1). Demographic and clinical characteristics of the sample are available as supplemental digital material to this manuscript (Supplemental Table 1, Supplemental Digital Content 1, http://links.lww.com/JCP/A99).

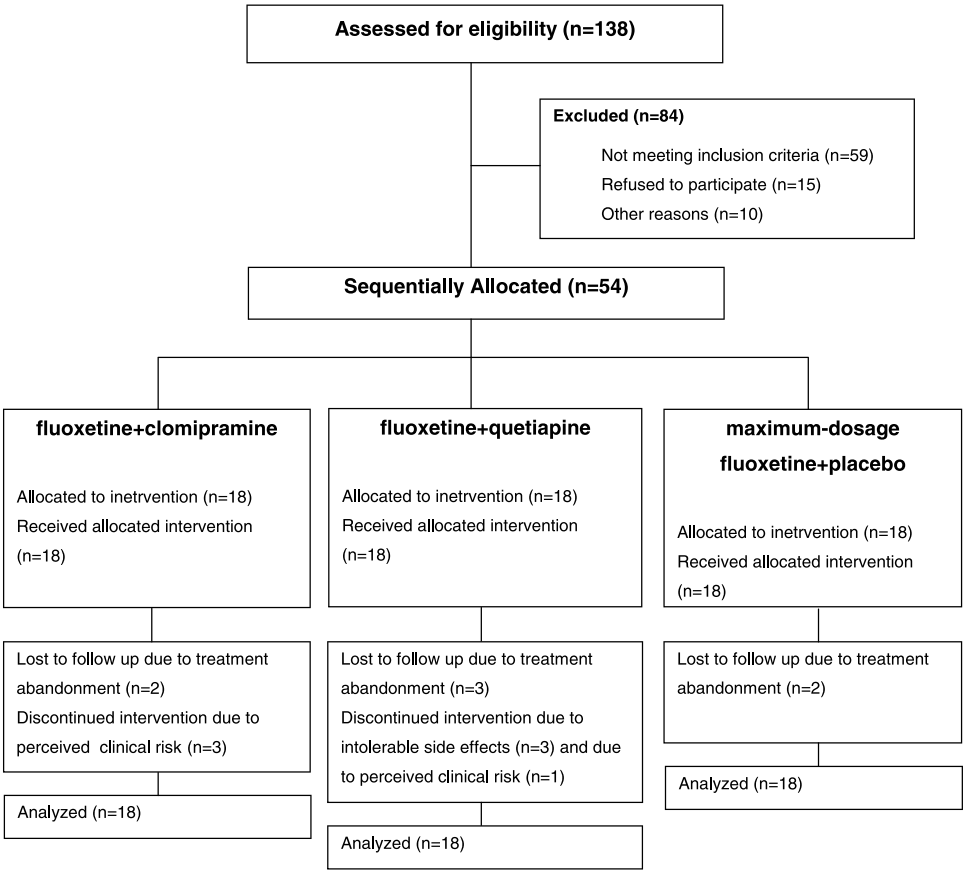

FIGURE 1. CONSORT diagram.

Of the 18 patients in the clomipramine + fluoxetine group, 12 (67%) were taking 80 mg/d of fluoxetine at enrollment, compared with 60 mg/d in 1 (6%), 40 mg/d in 4 (22%), and 20 mg/d in 1 (6%). The maximum dose of clomipramine (75 mg/d) was attained in 8 patients (44%), whereas 6 (33%) tolerated only 50 mg/d, and 4 (22%) tolerated only 25 mg/d. Intolerance manifested as adverse effects such as constipation and postural hypotension without syncope. The mean (SD) clomipramine dose for the group was 55 (20) mg/d.

Of the 18 patients in the quetiapine + fluoxetine group, 16 (89%) were taking 80 mg/d of fluoxetine at enrollment, compared with 60 mg/d in 1 (6%) and 40 mg/d in 1 patient (6%). Eight patients (44%) reached the maximum dose of quetiapine (200 mg/d) (44%), whereas 4 (22%) tolerated only 150 mg/d, 1 (6%) tolerated only 100 mg/d, and 5 (28%) tolerated only 50 mg/d. The main adverse effects associated with intolerance were drowsiness and sedation. The mean (SD) quetiapine dose was 142 (65) mg/d.

Of the 18 patients in the placebo + fluoxetine group, 15 (83%) were taking 80 mg/d of fluoxetine at enrollment, compared with 60 mg/d in 2 (11%) and 40 mg/d in 1 (6%).

In the ECG evaluation at week 2, 3 of the clomipramine + fluoxetine group patients had QTc intervals that were prolonged in comparison with the baseline value. The increases were small, reaching borderline limits with no clinical repercussions, except in 1 case, in which the patient also presented tachycardia (140 beats/min). The augmentation treatment was discontinued in those 3 patients, and they were excluded from the study. One patient in the quetiapine + fluoxetine group complained of orthostatic hypotension leading to an episode of syncope. That patient was also instructed to discontinue the treatment and was excluded from the study. No severe adverse events were reported by any of the patients in the sample.

Primary Outcome Measures

The total Y-BOCS scores are shown in Figure 2. The most pronounced differences between groups were seen at week 12.

In terms of the mean (SD) final Y-BOCS scores and the mean (SD) reduction in Y-BOCS score, the patients in the placebo + fluoxetine and clomipramine + fluoxetine groups showed significantly greater improvement than did those in the quetiapine + fluoxetine group (final total Y-BOCS score: 18 [7] and 18 [7], respectively, vs 25 [6], $P < 0.001$; reduction from baseline: −6.7 [confidence interval {CI}, −9.6 to −3.8] and −6.5 [CI, −9.0 to −3.9], respectively, vs −0.1 [CI, −2.9 to 2.7], $P < 0.001$; number needed to treat = 2.4).

In all ANCOVA comparisons, a temporal effect was evident, initial scores being significantly higher than final scores for the sample as a whole. No interaction effects (of group or time) were observed between the clomipramine + fluoxetine and placebo + fluoxetine groups. However, we observed an interaction effect of time and group among the 3 groups, as well as between the pooled group of clomipramine + fluoxetine plus placebo + fluoxetine and the quetiapine + fluoxetine group. The final Y-BOCS scores were significantly higher in the quetiapine + fluoxetine

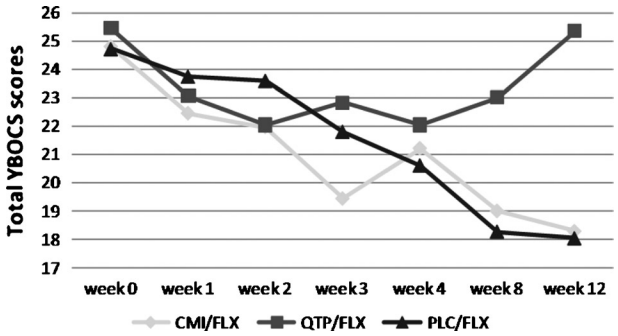

FIGURE 2. Total (obsessions plus compulsions) Y-BOCS scores by group and by time point. CMI/FLX indicates clomipramine ≤75 mg/d plus reduced-dose fluoxetine; QTP/FLX, quetiapine ≤200 mg/d plus reduced-dose fluoxetine; PLC/FLX, placebo plus sustained-dose fluoxetine.

group than in the clomipramine + fluoxetine and placebo + fluoxetine groups ($P < 0.001$).

Secondary Outcome Measures

Nonparametric ANCOVA did not show any statistical differences between groups regarding the secondary outcome measures (BDI, BAI, SF-36, and SAS-SR). Responders accounted for 8 (44%) of the clomipramine + fluoxetine group patients, 6 (33%) of the quetiapine + fluoxetine group patients, and 10 (56%) of the placebo + fluoxetine group patients. The differences between these proportions were not statistically significant across groups.

At week 2, plasma clomipramine levels were 11 to 180 ng/mL (mean [SD], 38 [43] ng/mL), whereas plasma desmethylclomipramine levels were 34 to 105 ng/mL (mean [SD], 65 [22] ng/mL), and the desmethylclomipramine/clomipramine ratio was 0.6 to 4.6 (mean [SD], 2.5 [1.1]). None of the patients showed levels approaching the near toxic limits that would require dose reduction.

At week 2, plasma fluoxetine levels were 127 to 1100 ng/mL (mean [SD], 475 [251] ng/mL). At week 12, plasma fluoxetine levels were 126 to 1090 (mean [SD], 455 [286] ng/mL). At weeks 2 and 12, norfluoxetine levels were 93 to 638 ng/mL (mean [SD], 309 [127] ng/mL) and 20 to 508 ng/mL (mean [SD], 286 [122] ng/mL), respectively (Supplemental Fig. A, Supplemental Digital Content 2, http://links.lww.com/JCP/A100).

There was no significant difference between responders and nonresponders regarding plasma levels of clomipramine and fluoxetine. The use of imputation strategies for missing data, such as last observation carried forward and worst case scenario, did not alter the statistical significance of the results.

DISCUSSION

Only a few open-label trials and case series have evaluated the efficacy of clomipramine as an SSRI augmenter.[41–45] Those trials have used different SSRIs (mainly citalopram) and higher doses of clomipramine (≤150 mg/d). In the present trial, we used low doses of clomipramine (≤75 mg/d) and found plasma clomipramine to be far below the toxic levels. Safety issues regarding the use of clomipramine together with cytochrome P450 2D6/3A4 inhibitors might be less of a concern then initially thought.[46] Although ECG data, blood pressure, and plasma clomipramine levels should be monitored, severe adverse events have rarely been reported in patients treated with a clomipramine-SSRI combination.[47] Compared with the use of atypical antipsychotics, clomipramine has the advantage of being less expensive[48] and potentially safer in the long term.[13]

Previous trials have obtained inconsistent results regarding treatment response after the addition of quetiapine,[15–19] although 1 study demonstrated better responses to quetiapine addition among patients receiving lower SSRI doses,[28] which was not confirmed in the present study.

Low quetiapine doses are associated with higher affinity for 5-HT_2 receptor blockade than for D_2 receptor blockade.[49] According to meta-analyses,[12] the antipsychotic associated with the most consistent results was risperidone, which is among the atypical antipsychotics with the highest potential of D_2 blocking.[50,51] If dopamine blockade were a necessary mechanism for the addition of an antipsychotic to an SSRI, quetiapine doses higher than 200 mg/d would be needed to produce a significant effect. In previous studies, positive results were obtained with quetiapine doses of 300 to 450 mg/d.[16,18] However, Carey et al[15] and Kordon et al[19] used doses of 300 mg/d or less and 600 mg/d or less, respectively, and found no evidence that adding quetiapine to an SSRI was efficacious, even at higher doses. These findings weakened the hypothesis that higher doses of quetiapine could achieve a positive response through D_2 blockade.

Kordon et al[19] stated that sample heterogeneity (high comorbidity due to the use of broad inclusion criteria) might have a negative impact on treatment response. Because we applied broad inclusion criteria, our study sample presented high comorbidity, which might have made our patients less likely to improve with the addition of quetiapine. Therefore, inconsistent results regarding the use of quetiapine as an augmenter might be attributable to differential responses of the various OCD subtypes. Less comorbid subtypes might show higher response rates and gain the most benefit from this strategy, as evidenced by the positive results obtained in quetiapine trials using rigid inclusion criteria.[16,18]

Similarly to our results, in 2 previous controlled trials that evaluated the combination of quetiapine with SSRIs, high rates of response were found among patients allocated in the placebo arm.[15,19] Indeed, the highest rates of response to placebo were observed in the study with only 6 weeks of follow-up with a SSRI before enrollment for augmentation with quetiapine.[15] Also, for OCD patients, some authors advocate aiming for the highest well-tolerated dose of an SSRI, up to the conventional limit.[52] Although delayed response is a common phenomenon in OCD,[53] our results raise the question of at which point pharmacological intervention (use of an augmenter) should be considered. According to our findings and to those of several long-term, double-blind studies,[54,55] longer periods of observation (>3 months) might be required before considering such an intervention

The minimization procedure used for treatment allocation is expected to have had a minor effect on the power of the study, because it reduces the risk of an imbalance between groups according to prognostic factors.[39] However, it is probably not a meaningful effect in a trial as small as ours. Despite the small sample size, the results related to our primary outcome measure were robust enough not to be affected by different analytical methods.

One limitation of our trial is that we used low doses of both augmenters. In fact, plasma clomipramine levels were quite low, providing a broad safety gap to be explored in future studies. Although plasma quetiapine levels were unavailable, previous trials have used higher quetiapine doses without raising any safety concerns. It is also possible that differential dropout rates for each treatment arm affected our results. In the quetiapine + fluoxetine group, dropouts due to adverse effects (mainly complaints of feeling sedated) occurred early (before week 2). The use of extended-release quetiapine could overcome this limitation.[56] In addition, a longer period of fluoxetine monotherapy would have been needed

to differentiate the effect of the augmenters from ongoing improvement associated with SSRI maintenance.

Despite these limitations, our results support the use of clomipramine as an effective alternative pharmacological augmentation for patients who do not tolerate high doses of fluoxetine (and perhaps high doses of other SSRIs). We can conclude that the period of fluoxetine (and perhaps other SSRIs) monotherapy should be extended, that is, to 12 weeks, at the maximum recommended dose if possible, before the use of an additional drug is considered. Finally, our findings shed light on important issues regarding the study of SSRI-resistant patients, such as dose ranges, optimal trial duration, and sample selection, all of which are of great consequence for the design of future trials evaluating the efficacy of such pharmacological interventions in OCD patients who do not respond to SSRI monotherapy.

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