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The impact of comorbid body dysmorphic disorder on the response to sequential pharmacological trials for obsessive-compulsive disorder

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Abstract

Our aim was to investigate the impact of comorbid body dysmorphic disorder (BDD) on the response to sequential pharmacological trials in adult obsessive-compulsive disorder (OCD) patients. The sequential trial initially involved fluoxetine monotherapy followed by one of three randomized, add-on strategies: placebo, clomipramine or quetiapine. We included 138 patients in the initial phase of fluoxetine, up to 80 mg or the maximum tolerated dosage, for 12 weeks. We invited 70 non-responders to participate in the add-on trial; as 54 accepted, we allocated 18 to each treatment group and followed them for an additional 12 weeks. To evaluate the combined effects of sex, age, age at onset, initial severity, type of augmentation and BDD on the response to sequential treatments, we constructed a model using generalized estimating equations (GEE). Of the 39 patients who completed the study (OCD-BDD, $n = 13$; OCD-non-BDD, $n = 26$), the OCD-BDD patients were less likely to be classified as responders than the OCD-non-BDD patients (Pearson Chi-Square = 4.4; $p = 0.036$). In the GEE model, BDD was not significantly associated with a worse response to sequential treatments (z -robust = 1.77; $p = 0.07$). The predictive potential of BDD regarding sequential treatment strategies for OCD did not survive when the analyses were controlled for other clinical characteristics.

Keywords

Body dysmorphic disorder, comorbidity, generalized estimating equations, obsessive-compulsive disorder, psychopharmacology, recruitment, sequential treatment, study design, study participation

Introduction

Obsessive-compulsive disorder (OCD) is characterized by persistent, intrusive, anxiety-provoking thoughts or images (obsessions) associated with repetitive physical or mental rituals (compulsions) aimed at relieving that discomfort. In OCD there are typical symptom dimensions, but there are no restrictions for the possible content of obsessions. Intrusive thoughts that are exclusively centered on concerns regarding appearance, accompanied by rituals aimed at checking, disguising or correcting imaginary or slight physical defects are classified in a clinical entity denominated body dysmorphic disorder (BDD) (Phillips et al., 1993). OCD and BDD frequently co-occur (Eisen et al., 2004) and both disorders lie under the umbrella of the chapter for OCD and related disorders, in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV).

The estimated prevalence of OCD in the general population ranges from 1.1 to 3.9% (Andrade et al., 2012; Kessler et al., 2012; Ruscio et al., 2010); whereas for BDD it is smaller, ranging from 0.7 to 1.1% (Bienvenu et al., 2000; Otto et al., 2001). In a clinical sample of 901 patients with a primary diagnosis of OCD, 12.1% also reported lifetime BDD (Costa et al., 2012). In a study conducted by Phillips and Stout (2006), 33% of patients with a primary diagnosis of BDD reported concurrent lifetime OCD, which was the third most common comorbid condition, after major depression and social anxiety disorder (SAD). One major study found a familial relationship between OCD and BDD, as

well as between OCD and “compulsive grooming behaviors,” suggesting that these disorders are part of the “familial OCD spectrum” (Bienvenu et al., 2000). Patients with OCD or BDD have a high chance of presenting a chronic course of symptoms, with low rates of full remission, even when adequately treated (Eisen et al., 2010; Jakubovski et al., 2012; Phillips et al., 2013), a poor quality of life, and impaired occupational and social functioning (Ishak et al., 2012; Rosa et al., 2012). These disorders generally require long-term treatment and share serotonin reuptake inhibitors (SRI) and cognitive behavior therapy (CBT) as their first-line treatment options (Bandelow et al., 2012; Neziroglu and Khemlani-Patel, 2002; Phillips and Hollander, 2008).

The combination of OCD and BDD (OCD-BDD) is associated with poorer insight of OCD symptoms (Costa et al., 2012; Eisen

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et al., 2004; Nakata et al., 2007; Phillips et al., 2012), higher frequency of suicidal behaviors (Costa et al., 2012; Phillips et al., 2007), higher prevalence of hoarding symptoms (Costa et al., 2012; Nakata et al., 2007) and a higher frequency of specific psychiatric comorbidities (Costa et al., 2012; Diniz et al., 2006; Frare et al., 2004; Nakata et al., 2007; Phillips et al., 1998; Veale et al., 1996) in comparison with OCD without comorbid BDD (OCD-non-BDD). Most of these characteristics were associated with worse prognosis, in previous studies (Belotto-Silva et al., 2012; Catapano et al., 2010; Erzegovesi et al., 2001; Mataix-Cols et al., 1999; Kishore et al., 2004; Shetti et al., 2005); nevertheless, in the only study that systematically investigated the impact of BDD on OCD treatment response, there were similar response patterns observed in OCD patients with and without comorbid BDD (Stewart et al., 2008). In that particular study, the sample comprised 275 patients with severe and treatment-refractory OCD (42 with comorbid BDD) and the treatment response was obtained for 403 individuals whom had participated in a previous clinical trial (Stewart et al., 2005) that evaluated the efficacy of intensive residential treatment for OCD. The OCD overall severity, as measured by the Yale-Brown Obsessive-Compulsive Scale (YBOCS), and the mean reduction in YBOCS scores with treatment were not significantly different between the OCD-BDD and OCD-non-BDD groups. Hantouche and Demonfaucon (2008), on the other hand, reported that "concerns about appearance" (which are the core symptoms of BDD) were one of the most important predictive factors of resistance to treatment, according to a survey performed with 360 patients from the French Association of OCD. Therefore, although it is likely that BDD may negatively interfere with outcome, prospective studies with non-refractory OCD patients are still required to establish whether comorbid BDD should be regarded as a predictive factor of non-response in OCD patients whom are initiating treatment with a SRI. Also, the frequent use of second-line treatment strategies for OCD patients makes it necessary to investigate the effect of BDD on such interventions. Moreover, given that BDD is associated with several other characteristics that might interfere with treatment outcome, researchers should try to disentangle the effects of BDD from other factors, such as their poor insight and hoarding.

To assess the impact of BDD on OCD treatment outcome within this context, we aimed to prospectively investigate the impact of BDD on the response to sequential pharmacological trials in adult patients whose primary diagnosis was OCD and whom were not treatment-resistant. To our knowledge, this is the first study to evaluate the impact of BDD on the response to OCD treatment with fluoxetine monotherapy and combined with pharmacological augmenters.

Methods and materials

Subjects

Patients were eligible for recruitment if aged 18 to 65 years old and if treated between May 2007 and March 2010 at the outpatient clinic of the OCD Spectrum Disorders Program of the Institute of Psychiatry, Clinical Hospital, University of São Paulo Medical School, located in São Paulo, Brazil. The study protocol was approved by the local Research Ethics Review Board, and all participants gave their written informed consent. We conducted all procedures in accordance with Good Clinical Practice guidelines.

We enrolled patients whom met DSM-IV-TR criteria for a primary diagnosis of OCD, had no prior resistance to adequate treatments, and had a current YBOCS score of at least 16. All patients had either never received a SRI prior to study initiation, or had received a SRI in low dosage and for an insufficient time according to current treatment guidelines (Bandelow et al., 2012). We excluded patients at risk of complications associated with the medications used in this trial, such as: those with an abnormal electrocardiogram (ECG), those whom presented with mania, were at imminent suicide risk, had a current untreated psychotic disorder, or had a current substance abuse/dependence, as well as those whom were pregnant or lactating. Only patients with current psychiatric comorbidities that could increase the risk of SRI use or that caused greater impairment than OCD itself were excluded; patients with comorbidities such as depression and other anxiety disorders were not excluded from the trial. As expected for a sample representative of patients seeking treatment in an academic outpatient clinic, our sample had a high frequency of comorbid psychiatric conditions.

Instruments

The interviewers were clinical psychologists or psychiatrists experienced in OCD. A better description of our methodology for data collection can be found elsewhere (Miguel et al., 2008). The YBOCS (Goodman et al., 1989) was chosen as the main measure of OCD severity and we used the Dimensional Yale-Brown Obsessive-Compulsive Scale (DY-BOCS) (Rosario-Campos et al., 2006) to assess OCD symptoms. We used the Brown Assessment of Beliefs Scale (BABS) (Eisen et al., 1998) to evaluate insight regarding only OCD-related beliefs. We chose the Structured Clinical Interview for DSM-IV Axis I Disorders, patient version (SCID-I/P) (Spitzer et al., 1992), and the Structured Clinical Interview for DSM-IV-TR module for Impulse Control Disorders (SCID-TCIm) as the main diagnostic interviews.

In addition to the BDD module from SCID, our BDD diagnoses were confirmed by an additional questionnaire, specifically designed by Phillips (Phillips et al., 1995) to assess BDD symptoms, based on DSM criteria. From this questionnaire, we also extracted the level of insight specifically for BDD-related beliefs. Both current and lifetime diagnoses were considered. All patients with lifetime BDD fulfilled criteria for current BDD. The main outcome of our study was defined as the percent reduction in initial YBOCS scores.

Study design

We conducted secondary analyses of the results of a sequential trial involving initial fluoxetine monotherapy, followed by three possibilities of randomized, add-on treatments: fluoxetine (up to 40 mg/day) plus clomipramine (up to 75 mg), fluoxetine (up to 40 mg/day) plus quetiapine (up to 200 mg), or fluoxetine (up to 80 mg/day) plus placebo. A complete description of the original clinical trial is found elsewhere (Diniz et al., 2011b). When we designed the original study, quetiapine was a promising augmenting for treating OCD. Since then, other augmentation strategies have been considered better options; therefore, our original study design does not reflect the most recent treatment guidelines. In addition, we used lower than recommended doses of fluoxetine,

clomipramine and quetiapine, due to the perceived risk of pharmacokinetic interactions between fluoxetine and clomipramine. This risk was later shown to be overestimated. The use of higher doses warrants investigation in future trials.

A total of 138 patients received fluoxetine up to 80 mg or the maximum tolerated dosage, and 102 of those completed the 12-week protocol. We invited 70 patients whom were non-responders to fluoxetine monotherapy (less than 35% reduction in their initial YBOCS scores) to participate in the randomized augmentation trial: 54 patients agreed to participate and were followed for an additional 12 weeks. We allocated 18 patients to each treatment group by a minimization procedure that is better described elsewhere (Fossaluza et al., 2009). At the endpoint, patients were considered responders to augmentation treatment if they showed an additional reduction of at least 25% in their YBOCS scores, following the add-on treatment phase. In the augmentation trial, clinicians, raters and patients were blinded to the augmenting being used and to the patient's current fluoxetine dose.

Statistical analyses

For descriptive analyses, we used the Pearson Chi Square test for categorical variables, the Student *t* test for continuous variables with normal distribution and the Mann-Whitney test for continuous variables with non-normal distribution. In order to test the normality of the continuous or discrete variables, we performed the Kolmogorov-Smirnov test. The significance level was set at $\alpha = 5\%$.

We performed additional analyses comparing the groups with BDD and comorbid SAD (BDD-SAD), BDD alone, SAD alone, and neither BDD nor SAD, using an analysis of variance (ANOVA) for the four groups, or the Student *t* test for each group against the BDD-SAD group. Although beyond the scope of this paper, comparison of these four groups was included to assess whether there was interference of SAD in the BDD-OCD comorbidity, since SAD is highly associated with both OCD (Assunção et al., 2012) and BDD (Gunstad and Phillips, 2003), and is also associated with a worse prognosis in OCD (Belotto-Silva et al., 2012).

Likewise, given that OCD, BDD and tic disorder frequently occur in individuals from the same family and that the presence of tic disorder might be a confounder, in regards to the treatment response, we performed an analysis comparing the groups with BDD and comorbid tic disorder, BDD only, tic disorder only and neither BDD nor tic disorder, using the same tests described above.

To evaluate the combined effect of sex, age, age at onset, initial severity, type of augmentation and BDD on the response to sequential treatments, we constructed a model using generalized estimating equations (GEE), assuming a Poisson distribution, a logarithmic link function and unstructured correlation between measures. The GEE method is an extension of the use of quasi-likelihood functions for repeated or longitudinal measures, especially when they are binary or discrete (such as YBOCS scores) and it accounts for the dependency between variables (Liang and Zeger, 1986). Given that we had three time points for samples that were related, but not identical (due to the loss of subjects between time points), the GEE is fit to analyze this study's type of data. In the GEE model, the variables were selected backward, i.e. all variables were included in the model and one variable was removed prior to each analysis. We included the YBOCS scores obtained before initiating pharmacological treatment, after 12 weeks of

fluoxetine monotherapy and after an additional 12 weeks of add-on treatment as the within-subject variables in these analyses.

Results

The number of patients included in each treatment phase and the number of patients whom completed each treatment are presented in Figure 1.

Response to fluoxetine monotherapy

A total of 102 patients (OCD-BDD, $n = 24$; OCD-non-BDD, $n = 78$) completed the fluoxetine monotherapy protocol. Table 1 presents the demographic and clinical characteristics of this sample. The co-occurrence of BDD with SAD, other OCD spectrum disorders (trichotillomania and skin picking), tic disorder and impulse control disorders was higher than expected by chance. Groups did not differ regarding sex, age, age at onset and initial severity. As our group reported in a previous study, OCD-BDD patients presented higher frequencies and scores for most OCD symptom dimensions than OCD-non-BDD patients; however, these differences were not statistically significant in the current sample, except for the miscellaneous dimension, which includes concerns about appearance.

The overall mean percentage reduction in the initial YBOCS scores was 26% (SE = 2.5) and 32 patients showed a reduction in their initial YBOCS equal to or greater than 35% (Figure 1). The OCD-BDD patients had a lower mean reduction (18%; SE = 5.1) compared with OCD-non-BDD patients (28%; SE = 2.9) (Table 1); however, this difference did not achieve the required level of significance ($p = 0.06$; Mann-Whitney). Likewise, the frequency of responders according to the 35% reduction cut-off point was higher among those without BDD ($n = 27$ or 35% versus $n = 5$ or 21%; $p = 0.203$), but this difference did not reach statistical significance.

Among those who completed the fluoxetine monotherapy trial, there were 16 (15.7%) OCD patients with BDD-SAD. Following fluoxetine treatment, there was a persistence of higher mean YBOCS scores (mean = 25.7; SE = 1.4; $p = 0.021$, one-way ANOVA) and less improvement (mean = 0.1%; SE = 5.2; $p = 0.011$) among these patients more often than among those with BDD alone (mean YBOCS = 16.2; SE = 3.4; mean improvement = 37.3%; SE = 12.3; $n = 8$), SAD alone (mean YBOCS = 19.2; SE = 1.4; mean improvement = 25.4%; SE = 5.1; $n = 32$) or neither BDD nor SAD (mean YBOCS = 19.9; SE = 1.2; mean improvement = 27.6%; SE = 3.9; $n = 46$).

Response to pharmacological augmentation

Among the 54 patients who agreed to participate in the add-on trial, 39 completed this phase (OCD-BDD, $n = 13$; OCD-non-BDD, $n = 26$). The demographic and clinical characteristics of these patients are presented in Table 2. The previous finding of high comorbidity between BDD, other OCD spectrum disorders, SAD, tic disorder and impulse control disorders was also evident in this subsample. Groups did not differ regarding sex, age, age at onset and initial severity. The frequencies and scores of OCD symptoms dimensions were not statistically different between groups (except for the miscellaneous dimension); and patients

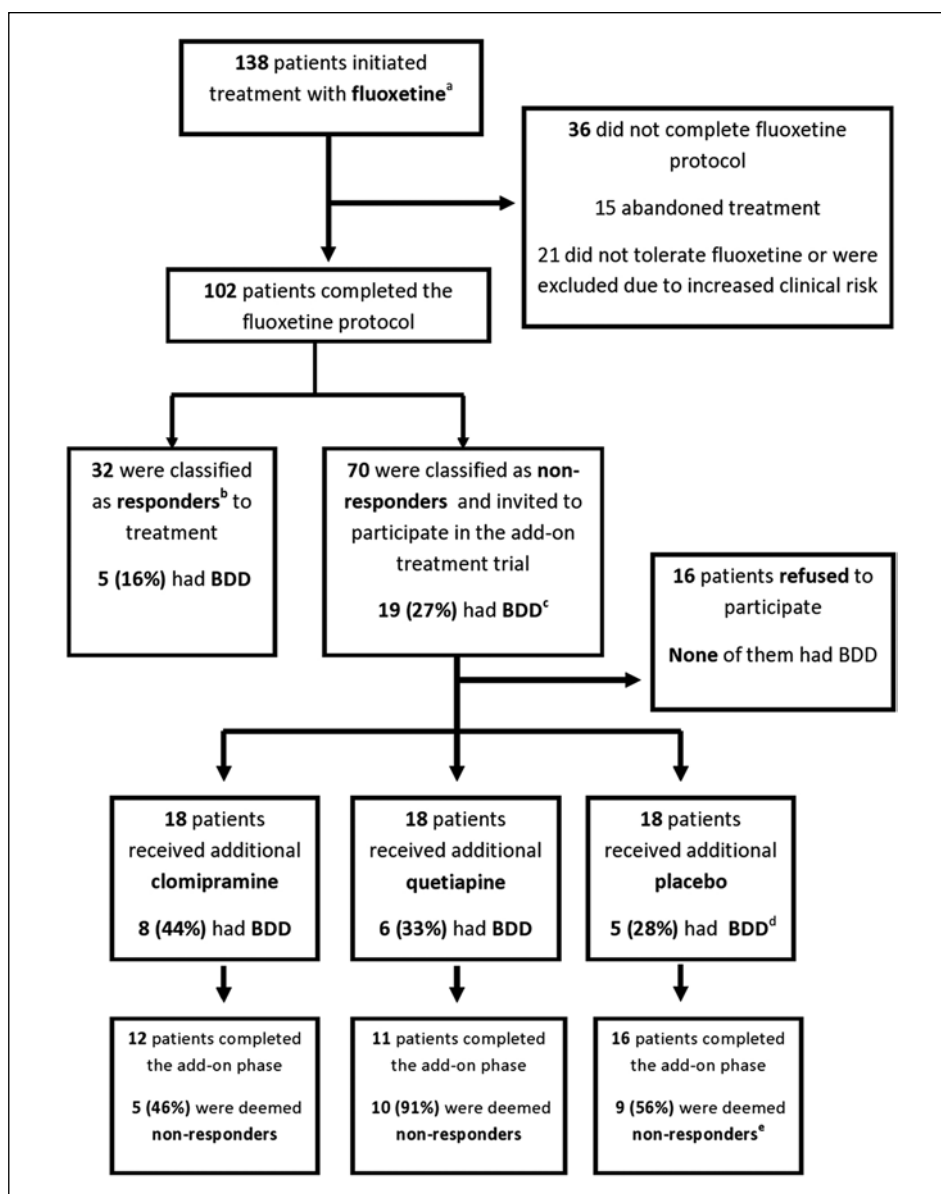


Figure 1. Flow chart of sequential treatments for OCD patients.

BDD: Body dysmorphic disorder; OCD: obsessive compulsive disorder; YBOCS: Yale Brown Obsessive Compulsive Scale

^aOf the 134 patients who received fluoxetine as the first treatment option, only four patients received group cognitive behavior therapy and were considered non-responders before entering fluoxetine treatment.

^bPatients were classified as responders, if they reported a reduction of their initial YBOCS score of at least 35% or a final YBOCS score below 16 (range 0–40).

^cPrevalence of BDD was not significantly different between responders and non-responders ($n = 102$; $p = 0.20$; Pearson Chi-square). Those with BDD presented a trend toward less reduction of initial YBOCS scores than those without, after fluoxetine monotherapy ($n = 102$; $p = 0.060$; Mann-Whitney).

^dPrevalence of BDD was not significantly different between groups in the add-on phase ($n = 54$; $p = 0.57$; Pearson Chi-square).

^eThere was a reduction on YBOCS scores, albeit < than 25%, with augmentation.

with and without BDD were equally distributed in the three types of augmentation (clomipramine, quetiapine and placebo).

Overall, at the end of the sequential treatments, the final mean YBOCS score of the patients whom completed the protocol ($n = 39$) was 20.0 (SE = 1.3), with a mean additional YBOCS reduction of 24% (SE = 4.1) following add-on pharmacotherapy. OCD-BDD patients improved less than those without BDD (mean percent reduction = 12%, SE = 3.2 and 30%, SE = 5.6, respectively, with p

= 0.015, Mann-Whitney test). The OCD-BDD patients were also more likely to be classified as non-responders ($n = 11$; 84.6%) than the OCD-non-BDD patients ($n = 13$; 50%; Pearson Chi Square = 4.4; $p = 0.036$). Only two patients with BDD, both from the clomipramine augmentation group, were classified as responders. In the original augmentation trial, add-on treatment with both clomipramine and placebo were effective at reducing OCD symptoms, while add-on treatment with quetiapine was not.

Table 1. Demographic and clinical characteristics of those OCD patients with and without comorbid BDD whom completed the 12-week fluoxetine monotherapy trial ($n = 102$).

	OCD with BDD ($n = 24$)	OCD without BDD ($n = 78$)	p value ^k
Current age, mean (SE)	32 (2.0)	34 (1.2)	NS
Sex, male, n (%)	13 (54%)	33 (42%)	NS
Age at onset, mean (SE)	10 (0.8)	12 (0.9)	NS
Initial severity ^a , mean (SE)	26 (1.0)	27 (0.6)	NS
Unipolar mood disorder ^b , n (%)	17 (71%)	40 (51%)	NS
Bipolar mood disorder, n (%)	2 (8%)	3 (4%)	NS
Social phobia, n (%)	16 (67%)	32 (41%)	0.028
Other anxiety disorders ^c , n (%)	20 (83%)	57 (73%)	NS
Other OCD spectrum disorders^d, n (%)	12 (50%)	15 (19%)	0.003
Tic disorders^e, n (%)	10 (43%)	14 (18%)	0.010
Impulse control disorders^f, n (%)	19 (79%)	28 (36%)	< 0.001
Aggression symptom dimension ^g , n (%)	18 (75%)	44 (58%)	NS
Aggression dimension score ^g , mean (SE)	6.6 (1.0)	5.6 (0.6)	NS
Sexual/religious dimension, n (%)	14 (58%)	36 (47%)	NS
Sexual/religious score, mean (SE)	6.0 (1.1)	4.2 (0.6)	NS
Symmetry dimension, n (%)	22 (92%)	59 (78%)	NS
Symmetry score, mean (SE)	8.2 (0.8)	7.1 (0.6)	NS
Contamination/cleaning dimension, n (%)	16 (67%)	57 (75%)	NS
Contamination/cleaning score, mean (SE)	6.1 (1.0)	7.7 (0.6)	NS
Hoarding dimension, n (%)	9 (37%)	29 (38%)	NS
Hoarding score, mean (SE)	2.2 (0.7)	2.7 (0.5)	NS
Miscellaneous dimension, n (%)	24 (100%)	53 (70%)	0.002
Miscellaneous score, mean (SE)	9.9 (0.9)	6.5 (0.6)	0.003
OCD insight ^h about self, mean (SE)	7.1 (0.9)	5.4 (0.6)	NS
BDD insight ⁱ			
good, n (%)	7 (29%)		
fair, n (%)	9 (37%)		
poor, n (%)	8 (33%)		
delusional, n (%)	0 (0%)	NA	NA
Response to fluoxetine ^j , mean (SE)	18% (5)	28% (3)	0.060
Patients classified as non-responders ^l , n (%)	19 (79%)	51 (65%)	NS

Significant differences ($p < 0.05$) are marked in bold.

^aYBOCS

^bIncludes lifetime major depressive episode or dysthymia.

^cLifetime generalized anxiety disorder, post-traumatic stress, panic or agoraphobia.

^dLifetime trichotillomania or skin picking.

^eChronic motor tic disorder or Tourette syndrome.

^fIncludes intermittent explosive disorder, compulsive buying, pathological gambling, disorders of sexual impulse control, internet addiction and kleptomania.

^gDimensional Yale-Brown Obsessive-Compulsive Disorder Scale.

^hBrown Assessment of Beliefs Scale, total score. Higher scores indicate worse insight.

ⁱInsight item from the BDD Questionnaire.

^jPercentage reduction in initial YBOCS.

^kPearson Chi Square for categorical variables, Student t test for continuous variables with normal distribution and Mann-Whitney test for continuous variables not normally distributed, $\alpha = 5\%$.

^l35% Reduction criteria.

BDD: Body Dysmorphic Disorder; OCD: obsessive-compulsive disorder; YBOCS: Yale-Brown Obsessive-Compulsive Total Score; NA: not applicable; NS: not significant.

Additional analysis with social anxiety disorder and tic disorders

At the end of the add-on phase, despite presenting a higher YBOCS score ($p = 0.017$, Student t test) and smaller percentage reduction ($p = 0.033$) than patients with neither BDD nor SAD (mean YBOCS = 17.8; SE = 1.2; mean improvement = 31.6%; SE = 7.0; $n = 15$), the BDD-SAD patients (mean YBOCS = 24.9; SE

= 1.9; mean improvement = 12.5%; SE = 3.4; $n = 12$) showed no difference from the BDD only patient (YBOCS = 22.0; improvement = 4.3%; $n = 1$) and the SAD only group (mean YBOCS = 18.9; SE = 2.7; mean improvement = 27.3%; SE = 9.4; $n = 11$).

Ten (43%) of the OCD-BDD patients who completed the fluoxetine phase and five (46%) of the OCD-non-BDD patients who completed the add-on trial also had a current or past tic disorder (BDD-tic disorder). At the end of the fluoxetine phase, in

Table 2. Demographic and clinical characteristics of OCD patients with and without comorbid BDD, whom completed the 12-week augmentation trial ($n = 39$).

	OCD with BDD ($n = 13$)	OCD without BDD ($n = 26$)	p value ^k
Current age, mean (SE)	35 (2.6)	33 (1.9)	NS
Sex, male, n (%)	9 (69%)	11 (42%)	NS
Age at onset, mean (SE)	10 (1.0)	12 (1.0)	NS
Initial severity ^a , mean (SE)	25 (1.5)	28 (1.0)	NS
Unipolar mood disorder ^b , n (%)	9 (69%)	15 (58%)	NS
Bipolar mood disorder, n (%)	1 (8%)	0 (0%)	NS
Social phobia, n (%)	12 (92%)	11 (42%)	0.003
Other anxiety disorders ^c , n (%)	13 (100%)	23 (88%)	NS
Other OCD spectrum disorders^d, n (%)	6 (46%)	4 (15%)	0.038
Tic disorders^e, n (%)	5 (38%)	1 (4%)	0.005
Impulse control disorders^f, n (%)	10 (77%)	11 (42%)	0.041
Aggression symptom dimension ^g , n (%)	11 (85%)	15 (58%)	NS
Aggression dimension score ^g , mean (SE)	8.2 (1.4)	5.3 (1.0)	NS
Sexual/religious dimension, n (%)	9 (69%)	14 (54%)	NS
Sexual/religious score, mean (SE)	7.2 (1.5)	4.6 (1.0)	NS
Symmetry dimension, n (%)	11 (85%)	21 (81%)	NS
Symmetry score, mean (SE)	8.4 (1.2)	6.5 (0.9)	NS
Contamination/cleaning dimension, n (%)	9 (69%)	19 (73%)	NS
Contamination/cleaning score, mean (SE)	6.7 (1.4)	7.6 (1.0)	NS
Hoarding dimension, n (%)	4 (31%)	9 (35%)	NS
Hoarding score, mean (SE)	2.2 (1.1)	2.4 (0.8)	NS
Miscellaneous dimension, n (%)	13 (100%)	14 (56%)	0.005
Miscellaneous score, mean (SE)	10.1 (1.4)	4.8 (1.1)	0.006
OCD insight ^h , mean SE	6.7 (1.3)	6.1 (1.3)	NS
BDD insight ⁱ			
good, n (%)	4 (31%)		
fair, n (%)	5 (38%)		
poor, n (%)	4 (31%)		
delusional, n (%)	0 (0%)	NA	NA
Type of add-on therapy			NS
Clomipramine, n (%)	5 (38%)	7 (27%)	
Quetiapine, n (%)	5 (38%)	6 (23%)	
Placebo, n (%)	3 (23%)	13 (50%)	
Response to add-on therapy^j, mean (SE)	12% (3.2)	30% (5.6)	0.015
Patients classified as non-responders^l, n (%)	11 (85%)	13 (50%)	0.036

Significant differences ($p < 0.05$) are marked in bold.

^aYBOCS.

^bIncludes lifetime major depressive episode or dysthymia.

^cLifetime generalized anxiety disorder, post-traumatic stress, panic or agoraphobia.

^dLifetime trichotillomania or skin picking.

^eChronic motor tic disorder or Tourette syndrome.

^fIncludes intermittent explosive disorder, compulsive buying, pathological gambling, disorders of sexual impulse control, internet addiction and kleptomania.

^gDimensional Yale-Brown Obsessive-Compulsive Disorder Scale.

^hBrown Assessment of Beliefs Scale, total score.

ⁱInsight item from the Diagnostic Scale for BDD.

^jPercentage reduction in initial YBOCS.

^kPearson Chi Square for categorical variables, Student t test for continuous variables and Mann-Whitney test for discrete variables, $\alpha = 5\%$.

^l25% Reduction criteria.

BDD: Body dysmorphic disorder; OCD: obsessive-compulsive disorder; YBOCS: Yale-Brown Obsessive-Compulsive Total Score; NA: not applicable; NS: not significant.

comparison with the BDD only (mean final YBOCS = 23.6; SE = 1.3; mean improvement = 9.0%; SE = 7.0; $n = 13$), tic disorder only (mean final YBOCS = 18.8; SE = 2.0; mean improvement = 25.0%; SE = 7.1; $n = 14$), and neither BDD nor tics (mean final YBOCS = 20.2; SE = 1.0; mean improvement = 25.9%; SE = 3.4;

$n = 65$) groups, the combination of BDD-tic disorder patients (mean YBOCS = 22.0; SE = 3.6; mean improvement = 14.4%; SE = 12.2; $n = 10$) did not differ regarding the mean final YBOCS score, nor the percentage reduction in the initial score. Likewise, these groups did not differ in regard to the final YBOCS score and

the percent reduction at the end of the add-on phase (BDD only, mean final YBOCS = 22.2; SE = 2.0; mean improvement = 13.1%; SE = 4.5; $n = 8$; tic disorder only, mean YBOCS = 19.0; SE = NA; mean improvement = 34.5%; SE = NA; $n = 1$; BDD-tic disorder, mean YBOCS = 28.6; SE = 2.6; mean improvement = 9.8%; SE = 4.6; $n = 5$, and neither BDD nor tic disorder, mean YBOCS = 18.2; SE = 1.6; mean improvement = 29.6%; SE = 5.8; $n = 25$).

Response to pharmacological sequential treatments. In the GEE model, BDD did not remain significantly associated with a worse response to sequential treatments after controlling for the effects of sex, age, age at OCD onset, initial severity and type of augmentation (z -robust = 1.77; $p = 0.07$).

Discussion

BDD appeared in this study as a potential predictor of worse response to sequential treatment strategies for OCD; however, the predictive potential of BDD did not remain significant when analyses were controlled for other clinical characteristics. Both BDD and OCD are chronic conditions (Phillips et al., 2007; Skoog and Skoog, 1999) with comparable long-term treatment responses. In OCD, the cumulative probability of full response at the 2-year follow-up was shown to range from 24–47% for a partial remission, and 6–12% for a full remission (Eisen et al., 1999; Eisen et al., 2010). In one study that followed BDD patients with a similar methodology for 4 years, the cumulative probability was determined to be 55% for a partial remission and 20% for a full remission (Phillips et al., 2013). In a sample with primary BDD, improvement in OCD was shown to significantly increase the likelihood of subsequent remission of BDD, even though BDD persisted in one-half of the patients whose OCD had already remitted (Phillips and Stout, 2006). These findings suggest that, when they co-occur, BDD symptoms are more resistant to treatment than OCD symptoms. On the other hand, comorbid BDD does not seem to preclude the improvement of OCD.

Results from several previous studies indicate that OCD-BDD is a more severe OCD variant, with poorer patient insight regarding OCD symptoms and a higher rate of comorbidity with SAD, impulse control disorders and other obsessive-compulsive spectrum disorders (Costa et al., 2012; Eisen et al., 2004; Nakata et al., 2007). Poorer insight in OCD has been associated with a worse OCD prognosis and treatment response, in several studies (Catapano et al., 2010; Erzegovesi et al., 2001; Kishore et al., 2004; Shetti et al., 2005), though these findings have not always been replicated (Alonso et al., 2008; Eisen et al., 2001). Specifically regarding our sample, insight was worse among patients with comorbid BDD, but this difference was not statistically significant. Given our sample size, it was not possible to disentangle the effects of BDD comorbidity and insight. In addition, our inclusion criteria (which required a primary diagnosis of OCD) and the fact that our patients were admitted to an OCD specialty clinic, may have biased patient selection toward less severe forms of BDD and may also explain the absence of delusional BDD patients in our sample. In addition, because we used the insight scale within the BDD diagnostic module by Phillips et al. in the present study, and not the Brown Assessment of Beliefs Scale (Eisen et al., 1998), any assessment issues may relate to these findings. If poor insight mediates worsening

outcome in OCD-BDD patients, a study with different inclusion criteria that assesses patients with a broader range of levels of severity and insight would be required to confirm this association.

SAD is also mentioned as a predictor of worse response to both pharmacotherapy and psychotherapy for OCD in a sample that overlaps with ours (Belotto-Silva et al., 2012) and as a factor associated with early treatment abandonment (Diniz et al., 2011a). In a recent study by Kelly et al. (Kelly et al., 2012), patients with comorbid BDD and SAD showed greater functional impairment than the BDD only and SAD only groups. Similarly, in our study, after fluoxetine treatment, BDD-SAD patients persisted with higher mean YBOCS scores and less improvement than patients with BDD alone, SAD alone, or neither BDD nor SAD. In addition to the negative impact of BDD comorbidity, these results highlight the close association between OCD, SAD and BDD.

Previous studies describe the high rate of co-occurrence between tic disorder and BDD in OCD patients (Coffey et al., 1998; Costa et al., 2012; Diniz et al., 2006). Studies that assessed tic disorder have yielded controversial results regarding its impact on outcome. In a pediatric sample, comorbid tic disorder was reported to adversely impact the outcome with sertraline treatment (March et al., 2007). In adult samples, tic disorder was not shown to interfere with first-line pharmacological treatment response (Shavitt et al., 2006); notwithstanding, comorbid tics significantly increase the probability of response to augmentation of SRI with antipsychotics (Bloch et al., 2006). Tic disorder was less likely a moderator of outcome with the fluoxetine treatment of OCD than BDD or SAD; however, larger trials are required to clarify its effects on augmentation with antipsychotics when comorbid with BDD.

Based on our results, we were unable to conclude whether our non-response results were more likely to occur in patients with a specific combination of comorbid conditions or with larger numbers of comorbid conditions. The latter is a proven condition, i.e. the number of comorbidities is shown to impact outcome in a previous study, with a sample that overlaps ours (Belotto-Silva et al., 2012). Many co-occurring factors seem to be associated with outcome; therefore, from a clinical standpoint, our results suggest that comorbid BDD alone should not be regarded as a predictive factor of non-response to SRI or to the combination of a selective serotonin reuptake inhibitor (SSRI) with clomipramine. In addition, the augmentation with low doses of quetiapine did not specifically improve the prognosis of OCD associated with BDD, despite the association of the latter with poorer insight. In summary, there is no evidence that comorbid BDD alone would hamper the expected efficacy of current treatment guidelines for OCD.

The lack of an association between BDD and worse outcome when controlled for other variables suggests that other co-occurring factors could be more relevant than BDD for predicting response to treatment. In the study conducted by Hantouche and Demonfaucon (2008), the association of “concerns about appearance” with resistance to OCD treatment was accompanied by higher rates of cyclothymic, depressive or irritable temperament. We did not assess soft signs of mood disorders nor affective temperaments. This limitation needs to be addressed in future trials.

BDD might interfere differently with the responses to pharmacotherapy and psychotherapy; therefore, the controversial results regarding the effect of BDD as a predictive factor of worse treatment response to pharmacotherapy do not exclude the possibility that BDD could play a more important role in the response to

psychotherapy. The only previous study that investigated this in a systematic manner (Stewart et al., 2008) evaluated patients with severe, treatment-refractory OCD. Further investigation of non-treatment-refractory OCD patients is still warranted.

The limitations of this study include the post-hoc design and the absence of an a priori power calculation for this specific analysis, the short period of follow-up and the inability to control for the effects of co-occurrence of BDD with SAD, tic disorders and other OCD spectrum disorders. Other characteristics previously associated with OCD-BDD, such as worse insight, higher frequency of hoarding symptoms, single marital status and worse social functioning are also limiting factors. In addition, concerning each individual augmentation treatment strategy, the results should be viewed with caution, due to the small number of observations. To our knowledge, no previous studies investigated the impact of BDD in the outcome of pharmacological sequential trials for OCD in a prospective trial. Sequential treatment trials are frequently necessary for those OCD patients whom do not sufficiently respond to SRI. Antipsychotics and clomipramine are possible pharmacological augmenters of SRI, yet no previous studies have investigated the role of comorbid BDD in regards to treatment responses to such augmenters.

Conclusion

In conclusion, in our study BDD did not remain as a predictive factor of worse treatment response to pharmacological sequential trials with OCD patients; however, several characteristics that are also associated with comorbid BDD, such as poor insight, comorbid SAD and tic disorders, could not be excluded as potential confounders. Studies with a larger number of observations are required to elucidate the individual impact of these variables. Our results cannot be generalized for response to psychotherapeutic interventions in OCD.

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Conflict of interest

Diniz was the principal investigator of the trial that originated the data reported in this study, which was partially funded by Novartis. Shavitt recently received a travel grant from Lundbeck. The remaining authors received no personal financial support from private companies within the last year.

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