Sertraline treatment of non-responders to extended cognitive-behavior therapy in pediatric obsessive-compulsive disorder

Running title: Sertraline treatment of CBT non-responders

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Abstract

Objective: To investigate the effect of sertraline (SRT) in children and adolescents with obsessive-compulsive disorder (OCD) who did not respond to two consecutive courses of cognitive-behavior therapy (CBT).

Methods: Observational study with 11 participants (males n=6), age 7-17 years with DSM-IV primary OCD. All had received 14+10 sessions of CBT over the course of 218-532 days (M=342.2, SD=85.5). Outcome measures were mean reduction of the Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS) total score and adequate clinical response (CY-BOCS < 16). All participants received SRT (maximum dose 200 mg/day). The study was a part of the Nordic Long-Term OCD Treatment Study (NordLOTS).

Results: Participants were treated with SRT over 72-300 days (M=164.2, SD=68.3). The mean CY-BOCS score was reduced from 21.5 (SD=2.6) to 17.5 (SD=3.3). Only three participants obtained adequate clinical response (27.2%), and only two obtained more than 25% CY-BOCS total score reduction (close to 50%).

Conclusion: A clinical response in about one third of the participants suggests that SRT treatment might be beneficial to a minority of patients that have consistently failed CBT.

Keywords: Cognitive behavior therapy, selective serotonin reuptake inhibitors, sertraline, obsessive-compulsive disorder, children and adolescents, treatment outcome, treatment-resistant

Introduction

Obsessive-compulsive disorder (OCD) is characterized by recurrent obsessions and compulsions. It is often a chronic and functionally impairing disorder (Rasmussen and Eisen 1992, Ruscio, et al. 2010, Stewart, et al. 2004, Valderhaug and Ivarsson 2005) with a prevalence rate between 1-3% (Flament, et al. 1988, Rapoport, et al. 2000, Ruscio, et al. 2010, Valleni-Basile, et al. 1994). One third to one half of adults with OCD reported onset of their symptoms in childhood (Rasmussen and Eisen 1990), and thus the development of effective treatments for treatment-resistant pediatric patients is important.

Expert guidelines recommend cognitive behavior therapy (CBT) as the first-line treatment for mild to moderate pediatric OCD and a combination of CBT and selective serotonin reuptake inhibitors (SSRI) for moderate to severe OCD (Geller and March 2012). A combination of CBT and SSRI is also recommended if a clinical response is not achieved after several months of CBT (Geller and March 2012). However, the sequence implicated in these guidelines is primarily based on expert consensus and not on empirical evidence. In addition, clinically useful details, for example how many sessions of CBT should be provided before it is considered failed, are lacking.

This gap in the literature was one of the reasons that led to the establishment of the Nordic Long-Term OCD Treatment Study (NordLOTS), which is based on a stepped care model with three consecutive steps (Thomsen, et al. 2013). In the first step 269 youths with OCD were included in weekly exposure-based CBT for 14 weeks (Torp, et al. 2015). In the second step those with inadequate response to the CBT,defined as a score of 16 or above on the Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS), were randomized to either continued CBT or sertraline (SRT). Because both treatments for non-responders were effective with high within-group effect, there was no between-group difference on the CY-BOCS at post-treatment (Skarphedinsson, et al. 2014). Participants who had been randomized to continued CBT without obtaining adequate response (CY-BOCS < 16) could be considered to be truly treatment refractory to CBT (e.g. (Krebs, et al. 2014) as CBT in the NordLOTS study was carefully monitored and high treatment fidelity observed (Torp, et al. 2015). To this group of CBT refractory young patients, SRT treatment was offered using the same drug treatment protocol as for patients randomized to SRT in Step 2.

The aim of this study was to assess SRT treatment response in CBT refractory patients who did not respond to two consecutive courses of CBT.

Methods

Design and participants

The NordLOTS is a multi-national, stepwise trial designed in part to evaluate the relative efficacy of continued CBT versus SRT among children and adolescents 7 - 17 years of age with OCD who were non-responders to an initial course of individual CBT. Participants were offered 14 sessions of weekly individual exposure-based CBT as the first step of clinical care (Step 1). Non-responders were randomized to two alternative treatments (Step 2): (1) continued CBT for an additional 16 weeks or (2) treatment with SRT. In our protocol, all patients that relapsed after an initial response to Step 1 were offered continued CBT (or SRT if they refused further CBT). All patients who did not respond adequately to continued CBT in Step 2 were offered SRT treatment. In addition, patients that relapsed after an initial response to Step 2 CBT were offered SRT.

Of the 269 participants included in the NordLOTS, the 11 participants who had not obtained an adequate response (CY-BOCS < 16) after Steps 1 and 2 (14+10 sessions CBT) or relapsed during follow-up were included in this study (see Fig. 1). Further details of the NordLOTS are described elsewhere (Thomsen, et al. 2013, Torp, et al. 2015).

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Measures

The Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime (K-SADS-PL) (Kaufman, et al. 1997) is a semi-structured diagnostic interview that assesses a variety of childhood psychopathologies and demonstrates favorable psychometric properties as detailed below. The K-SADS-PL has shown an excellent inter-rater reliability of 98% and a 1 to 5 week test-retest kappa of .80 for any anxiety disorder diagnosis (Kaufman, et al. 1997). Symptoms can be classified as "not present," "possible," "in remission," or "certain". In this study, OCD diagnoses and comorbidity were based on symptoms classified as "certain" only. The K-SADS-PL was used for diagnostic assessment at the baseline of Step 1. All interviews were conducted by experienced clinicians, trained by the NordLOTS research group.

The CY-BOCS (Goodman, et al. 1989) is a widely used clinician-rated, semi-structured interview assessing OCD symptomatology. It evaluates the severity of obsessions and compulsions using 10 items across five dimensions (time occupied by symptoms, interference, distress, resistance, and degree of control over symptoms). The total severity score can range from 0 to 40. The CY-BOCS shows reasonable reliability and

validity (Gallant, et al. 2008, Scahill, et al. 1997, Storch, et al. 2004), and in particular high internal consistency (.87) for the total score and good to excellent inter-rater agreement (.84, .91 and .68 for total score, obsessions, and compulsions, respectively) have been reported (Scahill, et al. 1997). In the NordLOTS sample, the inter-rater agreement was .92 (95%CI 0.78-0.97), .94 (95% CI 0.85-0.97), and .87 (95% CI 0.67-0.93) for total score, obsessions, and compulsions, respectively.

Parental psychopathology was assessed by asking parents about their psychiatric symptoms and diagnosed psychiatric disorders.

Procedure

SRT was chosen because it is the only approved SSRI for OCD treatment in adolescents and children as young as six years of age in all three countries (Denmark, Sweden, and Norway) (Thomsen, et al. 2013) and it has proved to be equally effective as the other SSRIs (Geller and March 2012). The pharmacotherapy treatment manual was adapted to Nordic conditions from the manual used in the POTS study (2004). A starting dose of 25 mg per day was titrated up to 100 mg per day by week 4; children below 10 years of age with low weight could be started on a lower dose if deemed necessary. If response was considered inadequate at a dose of 100 mg, the dose was increased gradually up to a maximum of 200 mg per day by week 8. Treatment response and adverse events were monitored at every visit and the dose reduced if necessary. The manual included guidelines for clinical support where participants were encouraged to practice exposure tasks learned during Step 1. However, introducing new exposure tasks by the therapist was not allowed. The rationale for this component was to reduce the variability of treatment effects unrelated to SRT. Pharmacotherapists were required to use a standardized script and were instructed to ask child and parent(s) (1) about resistance to compulsions; (2) about activities the child will engage in once he or she improves; (3) whether the child actively uses treatment techniques learned during Step 1; (4) whether the child has engaged in exposures and the resulting outcome; (5) to encourage the child to continue to do exposures and to not engage in avoidance or rituals; and (6) to inquire and address any concerns related to the medication the family may have.

Statistics

All descriptive statistical procedures were performed with SPSS, version 22.0.

Results

Patient characteristics

Eleven patients participated in the study, with eight having received 14 and 10 sessions of CBT in Steps 1 and 2, respectively, without achieving adequate response. Consequently, they were offered SRT treatment according to the protocol. Although one participant achieved adequate symptom reduction after Step 2 CBT, a 12 month follow-up revealed that he had experienced relapse. He was then offered SRT treatment as well. Two Step 1 CBT responders experienced relapse at 6 months follow-up. Consequently they received a second course of 10 CBT sessions according to Step 2 protocol, but did not show adequate response and were therefore switched to SRT (see Fig. 1).

Table 1 reports descriptive data for each patient. Six participants (55%) were boys. Mean age of the sample was 13.4 (SD=3.0). The current sample had a slightly higher mean age compared with the Step 1 sample (N=269, M=12.8, SD=2.7). Only three patients (27%) lacked a comorbid disorder in comparison with 59.5% (n=160) in the Step 1 sample (n=160, 59.5%). Of the remaining eight patients, four had comorbid anxiety disorder, three had tic disorder, two had ADHD, and one had comorbid major depressive disorder (MDD). The most common OCD symptoms were cleaning compulsions and contamination obsessions (n=9).

- Insert table 1 around here-

Treatment outcome

All CY-BOCS total scores before and after CBT and SRT are reported in Table 2. For the CBT effect the mean within change of the CY-BOCS total score was 6.2 and the within-group uncontrolled effect size of CBT was 0.89, adjusted for the fact that the two means were not independent (Morris and DeShon 2002). Patients 9 and 10 were initially Step 1 responders with a CY-BOCS total score of 4 and 12, respectively. However, they experienced relapse and showed a CY-BOCS total score of 26 and 22, respectively, six months after treatment. Therefore, they were treated with the 10 additional sessions of CBT according to Step 2 protocol without achieving adequate symptom reduction. Patient 8 had been randomized to Step 2 CBT and was a responder at post-treatment assessment. However, the patient relapsed during follow-up and was treated with SRT. Most of the patients started SRT treatment within four weeks after CBT termination. Four patients started SRT after more than four weeks and were reassessed with the CY-BOCS before SRT treatment. The mean within change of the

CY-BOCS total score during the SRT treatment was 4.0 and the within-group uncontrolled effect size was 1.07. Only three participants (27.2%) obtained a score below 16 on the CY-BOCS, with two of them (6 and 9) achieving almost 50% symptom reduction during SRT treatment. However, most of the remaining patients achieved little or no symptom reduction.

The most frequent adverse events were cognitive/psychiatric effects (n=4) and gastrointestinal effects (n=3). No serious adverse events were reported. One patient experienced moderate suicidal ideation in the starting phase of the SRT treatment which he reported in one visit only. The same patient also reported behavioral activation, which caused extensive problems. Consequently, the dose of SRT was increased very carefully to a final dose of only 125 mg per day. The final mean dose of SRT for the full sample was 150 (SD=41.5) mg per day.

-Insert table 2 around here-

Discussion

Current guidelines recommend adding a SSRI (Geller and March 2012) or switching to SSRI (National Institute for Heath and Clinical Excellence 2005), if CBT does not work. However, these recommendations are based on clinical experience and not on empirical research. In general, very little has been published about CBT treatment-resistant patients. Although the current study is limited in terms of sample size and the observational design, it is the first study that reports on the effect of SSRI in patients that have failed two consecutive CBT trials. Our main results show that switching to SRT caused a mean improvement of 4 points on the CY-BOCS that corresponds to a high within-group effect size (1.07). Although the uncontrolled total effect size of the SRT treatment was large, it was predominantly attributed to the two patients with close to 50% symptom reduction. Only these two and one additional patients with 18% symptom reduction achieved a score below our pre-defined cut-off of 16 points on the CY-BOCS. The remaining patients achieved a mean reduction of 10% with none experiencing more than 25% reduction. This indicates that SRT treatment might be beneficial to a small minority of patients that have consistently failed CBT. However, a larger randomized controlled trial is needed in order to generalize the results and to predict which therapy will lead to good treatment outcomes for certain patients.

The two patients (6 and 9) that achieved the highest symptom reduction had severeal common features. Both had a relatively low pre-CBT CY-BOCS total score of 21 and achieved no symptom reduction after CBT. During the SRT treatment both had gastrointestinal adverse events. The patients that responded poorest to SRT (1, 2, 4, and 8) all had severe OCD at CBT baseline and some improvement after CBT, leading to moderate OCD at SRT-baseline. All had a comorbid disorder (anxiety or ADHD), contamination fear, and were titrated up to mean or maximum daily doses of SRT.

Our data, suggesting that some non-responders of two CBT trials may benefit from SSRI, are in line with current guidelines (Geller and March 2012). SSRI should be offered to all pediatric patients that have failed CBT, although it is not clear how many sessions of CBT are needed before it is necessary to add SSRI. The only trial on CBT non-responders is the NordLOTS Step 2 trial which indicated that patients with inadequate response (after 14 weeks) that still had moderate to severe OCD could expect some improvement whether they would continue their CBT with 10 additional sessions or switch to SRT (Skarphedinsson, et al. 2014). One possible interpretation is that patients, who despite compliance and a certain treatment progress have not responded adequately after 14 sessions of CBT, should be given more CBT sessions before adding or switching to SSRI.

We report an outcome after mean=164 (SD=68) days in SRT treatment. It is possible that some of the children may experience additional improvement with longer SRT treatment. It does not seem to be effective to discontinue SSRI treatment after the acute treatment phase as one can expect a high relapse rate [50% in one study (Asbahr, et al. 2005)]. SSRI treatment has been documented to be increasingly effective up to one year. One study showed substantially better response (55% remitters) in those who completed SRT treatment up to one year. However, as many dropped out (53%) and many others had serious adverse events, it is still not clear whether the benefit of long-term SRT treatment outweighs the risks (Cook, et al. 2001, Wagner, et al. 2003). In addition, no known predictors of outcome exist that can assist clinicians in evaluating which group will benefit from medication in the long term.

It is difficult to generate hypotheses based on our limited data. However, future studies may focus on neurochemical or pharmacodynamic differences among patients (Hanna, et al. 1993, Rosenberg, et al. 2000). Investigating genetic variation may also be beneficial. For instance, allelic variation of the serotonin transporter gene and concomitant morphological changes may moderate individual response to SSRI [e.g., (Serretti, et al. 2005)]. Furthermore, the synergistic effects between CBT and SSRI need to be investigated. According to the

medication protocol patients were encouraged to engage in exposure exercises they had previously learned during CBT sessions (but no new exposures were initiated by the therapists). SSRI may have mediated better CBT outcomes at least in some patients by improving their tolerance for exposure and response prevention. An important goal is to develop assessment procedures identifying the likelihood of one or the other treatment response, allowing individualized treatment choices based on patient characteristics including relevant genetic variations .

Strengths and limitations

The strength of our study is the stepped care design. We have followed all patients for more than one year since their inclusion in Step 1 and evaluated their OCD symptoms regularly. In addition, state of the art measures were used to evaluate OCD symptoms and comorbidity. Thus, this is the first study that reports the effect of SSRI after two thorough CBT trials. However, the limitation is the small number of patients and the observational design used to evaluate the effect. Thus, it is necessary to conduct a larger randomized controlled trial to generalize the results. However, that will require large funding and the cooperation of a plethora of sites in many countries.

Clinical significance

The data suggest that SSRI may be effective for a minority of patients that still have moderate to severe OCD after 24 sessions of CBT. However, further studies are needed to generalize the results.

References

Asbahr FR, Castillo AR, Ito LM, Latorre MRDdO, Moreira MN and Lotufo-Neto F. Group cognitive-behavioral therapy versus sertraline for the treatment of children and adolescents with obsessive-compulsive disorder. J. Am. Acad. Child Adolesc. Psychiatry. 44:1128-1136, 2005.

Cook EH, Wagner KD, March JS, Biederman J, Landau P, Wolkow R and Messig M. Long-term sertraline treatment of children and adolescents with obsessive-compulsive disorder. J. Am. Acad. Child Adolesc. Psychiatry. 40:1175-1181, 2001.

Flament MF, Whitaker A, Rapoport JL, Davies M, Berg CZ, Kalikow K, Sceery W and Shaffer D. Obsessive compulsive disorder in adolescence: an epidemiological study. J. Am. Acad. Child Adolesc. Psychiatry. 27:764-771, 1988.

Gallant J, Storch EA, Merlo LJ, Ricketts ED, Geffken GR, Goodman WK and Murphy TK. Convergent and discriminant validity of the Children's Yale-Brown Obsessive Compulsive Scale-Symptom Checklist. Journal of Anxiety Disorders. 22:1369-1376, 2008.

Geller D and March J. Practice parameter for the assessment and treatment of children and adolescents with obsessive-compulsive disorder. J. Am. Acad. Child Adolesc. Psychiatry. 51:98-113, 2012.

Goodman WK, Price LH, Rasmussen SA, Mazure C, Fleischmann RL, Hill CL, Heninger GR and Charney DS. The Yale-Brown Obsessive Compulsive Scale. I. Development, use, and reliability. Arch. Gen. Psychiatry. 46:1006-1011, 1989.

Hanna GL, Yuwiler A and Cantwell DP. Whole-blood serotonin during clomipramine treatment of juvenile obsessive-compulsive disorder. J. Child Adolesc. Psychopharmacol. 3:223-229, 1993.

Kaufman J, Birmaher B, Brent D, Rao U and et al. Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime version (K-SADS-PL): Initial reliability and validity data. J. Am. Acad. Child Adolesc. Psychiatry. 36:980-988, 1997.

Krebs G, Isomura K, Lang K, Jassi A, Heyman I, Diamond H, Advani J, Turner C and Mataix-Cols D. How resistant is 'treatment-resistant' obsessive-compulsive disorder in youth? Br. J. Clin. Psychol., 2014.

Morris SB and DeShon RP. Combining effect size estimates in meta-analysis with repeated measures and independent-groups designs. Psychol Methods. 7:105-125, 2002.

National Institute for Heath and Clinical Excellence. Obsessive compulsive disorder (OCD) and body dysmorphic disorder (BDD). Edited by Excellence NIfHaC. London, National Institute for Health and Clinical Excellence; 2005, pp. National Institute for Health and Clinical Excellence.

POTS Study Team. Cognitive-behavior therapy, sertraline, and their combination for children and adolescents with obsessive-compulsive disorder: the Pediatric OCD Treatment Study (POTS) randomized controlled trial. JAMA. 292:1969-1976, 2004.

Rapoport JL, Inoff-Germain G, Weissman MM, Greenwald S, Narrow WE, Jensen PS, Lahey BB and Canino G. Childhood obsessive-compulsive disorder in the NIMH MECA study: parent versus child identification of cases. Methods for the Epidemiology of Child and Adolescent Mental Disorders. Journal of Anxiety Disorders. 14:535-548, 2000.

Rasmussen SA and Eisen JL. Epidemiology of obsessive compulsive disorder. Journal of Clinical Psychiatry. 51 Suppl:10-13, 1990.

Rasmussen SA and Eisen JL. The epidemiology and clinical features of obsessive compulsive disorder. Psychiatr. Clin. North Am. 15:743-758, 1992.

Rosenberg DR, MacMaster FP, Keshavan MS, Fitzgerald KD, Stewart CM and Moore GJ. Decrease in caudate glutamatergic concentrations in pediatric obsessive-compulsive disorder patients taking paroxetine. J Am Acad Child Adolesc Psychiatry. 39:1096-1103, 2000.

Ruscio AM, Stein DJ, Chiu WT and Kessler RC. The epidemiology of obsessive-compulsive disorder in the National Comorbidity Survey Replication. Mol. Psychiatry. 15:53-63, 2010.

Scahill L, Riddle MA, McSwiggin-Hardin M and Ort SI. Children's Yale-Brown Obsessive Compulsive Scale: Reliability and validity. J. Am. Acad. Child Adolesc. Psychiatry. 36:844-852, 1997.

Serretti A, Benedetti F, Zanardi R and Smeraldi E. The influence of Serotonin Transporter Promoter Polymorphism (SERTPR) and other polymorphisms of the serotonin pathway on the efficacy of antidepressant treatments. Prog. Neuropsychopharmacol. Bol. Psychiatry. 29:1074-1084, 2005.

Skarphedinsson G, Weidle B, Thomsen PH, Dahl K, Torp NC, Nissen JB, Melin KH, Hybel K, Valderhaug R, Wentzel-Larsen T, Compton SN and Ivarsson T. Continued cognitive-behavior therapy versus sertraline for children and adolescents with obsessive-compulsive disorder that were non-responders to cognitive-behavior therapy: A randomized controlled trial. Eur. Child Adolesc. Psychiatry. 2014.

Stewart SE, Geller DA, Jenike M, Pauls D, Shaw D, Mullin B and Faraone SV. Long-term outcome of pediatric obsessive-compulsive disorder: a meta-analysis and qualitative review of the literature. Acta Psychiatr. Scand. 110:4-13, 2004.

Storch EA, Murphy TK, Geffken GR, Soto O, Sajid M, Allen P, Roberti JW, Killiany EM and Goodman WK. Psychometric evaluation of the Children's Yale-Brown Obsessive-Compulsive Scale. Psychiatry Res. 129:91-98, 2004.

Thomsen PH, Torp NC, Dahl K, Christensen K, Englyst I, Melin KH, Nissen JB, Hybel KA, Valderhaug R, Weidle B, Skarphedinsson G, von Bahr PL and Ivarsson T. The Nordic long-term OCD

treatment study (NordLOTS): rationale, design, and methods. Child & Adolescent Psychiatry & Mental Health. 7:41, 2013.

Torp NC, Dahl K, Skarphedinsson G, Thomsen P, Valderhaug R, Weidle B, Melin K, Hybel K, Nissen JB, Lenhard F, Wentzel-Larsen T, Franklin M and Ivarsson T. Effectiveness of cognitive behavior treatment for pediatric obsessive-compulsive disorder: Acute outcomes from The Nordic Long-term OCD Treatment Study (NordLOTS). Behav. Res. Ther. 64:15-23, 2015.

Valderhaug R and Ivarsson T. Functional impairment in clinical samples of Norwegian and Swedish children and adolescents with obsessive-compulsive disorder. Eur. Child Adolesc. Psychiatry. 14:164-173, 2005.

Valleni-Basile LA, Garrison CZ, Jackson KL, Waller JL, McKeown RE, Addy CL and Cuffe SP. Frequency of obsessive-compulsive disorder in a community sample of young adolescents.[Erratum appears in J Am Acad Child Adolesc Psychiatry. 1995 Feb;34(2):128-9; PMID: 7896644]. J. Am. Acad. Child Adolesc. Psychiatry. 33:782-791, 1994.

Wagner KD, Cook EH, Chung H and Messig M. Remission status after long-term sertraline treatment of pediatric obsessive-compulsive disorder. J. Child Adolesc. Psychopharmacol. 13 Suppl 1:S53-60, 2003.

Table 1. Patient characteristics

Case no	Gender	Age	Comorbid diagnoses[a]	Main OC symptoms	Age of OCD onset	Parents psychopathology
1	Girl	15	Anxiety	Cleaning and contamination	7	
2	Boy	10	Anxiety	Cleaning and contamination	9	PTSD, other anxiety disorder, depressive disorder
3	Girl	17	Anxiety	symmetry	5	
4	Girl	13	Anxiety, depressive	contamination; symmetry	3	
5	Boy	16	Anxiety, tics	Cleaning and contamination; aggressive obsessions and checking	11	Mother PTSD
6	Boy	16	Tics	Hoarding, repeating compulsions	9	Anxiety and depressive disorders
7	Boy	9	ADHD, Tics	Cleaning and contamination, symmetry	4	Depressive disorder
8	Boy	13	ADHD	Cleaning and contamination	10	
9	Girl	10	None	Cleaning and contamination; aggressive obsessions and checking	9	Depressive disorder
10	Boy	17	None	Cleaning and contamination	16	
11	Girl	11	None	Cleaning and contamination	10	

[a] Based on the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime (K-SADS-PL)

Table 2. CY-BOCS total score measured at baseline, post-CBT, SRT-baseline, and post-SRT with adverse events and final daily dose of SRT.

Case no	CY-BOCS score		Symptom-reduction %	Days in CBT	Days between CBT and SRT	CY-BOCS score		Symptom-reduction %	Days in SRT	Adverse events (moderate or severe)	Final daily dose of SRT
	Baseline CBT	Post CBT				Baseline SRT	Post SRT				
1	23	25	-9	344	47	20[a]	20	0	112	Anxiety/tension, reduced concentration	200
2	31	22	29	310	<28	22	20	9	149		150
3	24	21	13	305	30	21[a]	16	24	132	Nausea, stomach ache, increased appetite, Anxiety/tension	100
4	28	16	43	312	61	19	18	5	131		150
5	29	17	41	338	<28	17	14	18	217	Restlessness, tiredness, headaches	125
6	21	21	0	532	143[c]	21[a]	11	48	265	Little appetite, diarrhea	200
7	24	24	0	218	<28	24[a]	21	13	72	Tension, restlessness, tiredness, impulsivity/ behavioral activation, suicidal ideation	125
8	26	14	46	303	235[c]	20	19	5	300	Hand tremor	200
9	21	26	-24	425	<28	26[a]	14	46	157	Dry mouth, diarrhea	175
10	38	23	39	427	<28	23	20	13	132		200
11	36	24	33	250	<28	24[a]	20	17	139	Nausea	100
Mean	27,4	21,2	19,3	342,2	103,2[b]	21,5	17,5	17,9	164,2		150
SD	5,7	3,9	24,3	88,8	85,5[b]	2,6	3,3	15,8	68,3		41,5

CY-BOCS = Child Yale-Brown Obsessive Compulsive Scale; CBT = Cognitive-behavior therapy; SRT = Sertraline

[a] SRT baseline score same as post CBT,

[b] Based on ≥28 days only,

[c] SSRI treatment was offered immediately after failure of the second CBT course, delay due to patients reluctance to start with medication or due to time before relapse after initial response to CBT.