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Secondary outcomes from the pediatric obsessive compulsive disorder treatment study II

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ABSTRACT

The Pediatric Obsessive-Compulsive Disorder Treatment Study II (POTS II) investigated the benefit of serotonin reuptake inhibitor (SRI) augmentation with cognitive behavioral therapy (CBT). Primary outcomes focused on OCD symptom change and indicated benefit associated with a full course of CBT. Given that the majority of youth with OCD suffer from significant comorbid symptoms and impaired quality of life, the current study examined POTS II data for effects on secondary outcomes. Participants were 124 youth ages 7–17 years with a primary diagnosis of OCD who were partial responders to an adequate SRI trial. Participants were randomized to medication management, medication management plus instructions in cognitive behavioral therapy (CBT), or medication management plus full CBT. Acute effects on non-OCD anxiety, depression, inattention, hyperactivity, and quality of life were examined across treatment conditions. Improvement across treatment was observed for non-OCD anxiety, inattention, hyperactivity, and quality of life. Changes were generally significantly greater in the group receiving full CBT. Child-rated depression was not found to change. OCD-focused treatment lead to improvement in other areas of psychopathology and functioning. For youth who are partial responders to SRI monotherapy, augmentation with full CBT may yield the greatest benefit on these secondary outcomes.
Clinical trials registration: Treatment of Pediatric OCD for SRI Partial Responders, Clinicaltrials.gov Identifier: NCT00074815, http://clinicaltrials.gov/show/NCT00074815.

1. Introduction

Two primary forms of treatment, namely cognitive behavioral therapy (CBT) and pharmacological agents, effectively reduce symptoms of obsessive-compulsive disorder (OCD) in youth (Freeman et al., 2014; Watson and Rees, 2008), but less is known about the effect of these treatments on other domains of functioning. Empirical evidence suggests that CBT involving exposure with response prevention (ERP), either alone or in combination with a serotonin reuptake inhibitor (SRI), is the best choice for initial treatment of pediatric OCD (Pediatric, 2004). In community settings, however, pharmacotherapy with SRI alone is very commonly used as an initial and sole treatment due to limited dissemination of CBT (Rushton and Whitmire, 2001). Given that most patients with OCD who receive SRI alone continue to experience clinically significant residual symptoms after a full course of pharmacotherapy (March et al., 1998; Riddle et al., 2001), the Pediatric Obsessive-Compulsive Disorder Treatment Study II (POTS II) was conducted to investigate the effects of two CBT augmentation

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approaches in children who demonstrated partial response to pharmacotherapy with SRI (Franklin et al., 2011).

The overarching goal of POTS II was to examine the benefit of SRI augmentation using CBT strategies, including an instructional CBT protocol that could be easily disseminated by child psychiatrists (Freeman et al., 2009). To investigate this, participants in POTS II were randomized to one of three conditions: A) Medication Management (MM): medication management visits with a study psychiatrist; B) Medication Management plus OCD-specific CBT (MM + CBT): same medication management visits as in MM plus a full dose of CBT from a second provider (a study psychologist using established CBT manual); C) Medication Management plus Instruction in CBT skills (MM + iCBT): extended medication management visits in which the study psychiatrist provided instructions in CBT during the visit (Freeman et al., 2009). Primary outcomes, based on changes in the Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS; Scahill et al., 1997), indicated that those receiving MM + CBT had significantly greater symptom reduction compared with those receiving MM alone (ES = 0.85), whereas those receiving MM + iCBT did not show greater symptom reduction compared to MM alone (ES = 0.16; Franklin et al., 2011). Importantly, these results provided additional support for CBT augmentation in a sample of partial responders but only limited support for delivery of an abbreviated version of CBT skills over medication management alone. Authors postulated that lack of effect in the MM + iCBT group may have been due to lower intensity of treatment, less contact time with a provider, and/or omission of key treatment elements (i.e. in-session exposures, Franklin et al., 2011).

Despite the important implications of POTS II results for improving OCD symptoms in children who have experienced partial response to SRI treatment, the impact of these treatments on secondary outcomes has yet to be explored. The majority of youth with OCD suffer from significant comorbid symptoms and experience considerable impairments in quality of life (Palermo et al., 2011; Piacentini et al., 2003; Selles et al., 2014; Valderhaug and Ivarsson, 2005). Common psychiatric comorbidities include non-OCD anxiety disorders (e.g., separation anxiety, specific phobia, social phobia, generalized anxiety disorder), depressive disorders, and externalizing disorders (e.g., attention deficit hyperactivity disorder, oppositional defiant disorder; Alvarenga et al., 2016). Although not the primary treatment target, comorbid symptoms and quality of life represent important measures of a child's functioning, and the impact of treatment on such “secondary outcomes” is of great relevance in determining a treatment's broader impact on patient's lives. Researchers have argued that reporting outcome only in terms of primary symptom change is overly simplistic and yields suboptimal clinical information about treatment effects (Westen and Morrison, 2001). For example, treatment effects may generalize to other clinically important outcomes, comorbidities may be related to treatment moderation or mediation (Eddy et al., 2004), and information on secondary factors improves the generalizability of clinical trials (Westen and Morrison, 2001). Some evidence already appears to support the positive impact of treatment, particularly CBT, on these domains in youth with OCD, including decreases in depressive and anxiety symptoms, as well as reductions in impairment/improvements in quality of life (Bolton et al., 2011; Storch et al., 2013).

CBT's effects on secondary outcomes have generally supported the broader impact of treatment (e.g., Saavedra et al., 2010; Suveg et al., 2009), and examining such effects in the POTS II trial is our overarching goal here. More specifically, our current study aimed to compare children receiving MM, MM + CBT, or MM + iCBT as part of POTS II for effects on secondary (i.e. non-OCD) outcomes including other psychiatric symptoms (e.g., anxiety, depression, and behavioral symptoms) and broad psychosocial functioning (e.g., impairment and quality of life). It was hypothesized, that similar to the primary outcomes, the MM + CBT condition would be associated with the greatest benefit in secondary outcomes when compared to both the MM and MM + iCBT conditions, which would not be hypothesized to differ from one another. As an exploratory aim, we also sought to understand whether changes in these secondary outcomes were related to change in OCD symptoms across the entire sample.

2. Methods

2.1. Study design

POTS II was a 12-week, randomized, parallel group, controlled trial examining the efficacy of CBT augmentation strategies for youth who were partial responders to an optimal SRI dosage. The study rationale, design, methods, and primary outcomes have been reported elsewhere (Franklin et al., 2011; Freeman et al., 2009). POTS II participants were recruited from three sites (University of Pennsylvania, Duke University, and Brown University) between 2004 and 2009 and randomized to one of three treatment strategies, briefly described below (for more detail see Freeman et al., 2009):

1) Medication Management (MM, n = 42): Participants received seven medication management visits with a study psychiatrist over 12 weeks focused on monitoring of clinical status. Pharmacotherapists offered general encouragement to resist OCD but did not instruct participants or parents in specific OCD-management strategies or provide other psychotherapeutic interventions (e.g., family therapy).
2) Medication Management plus OCD-specific CBT (MM + CBT, n = 42): Participants received the same medication management visits plus a full dose of CBT occurring in 14 hourly visits over 12 weeks from a second provider (a study psychologist using a previously established CBT manual; March and Mulle, 1998). CBT components included psychoeducation, cognitive training, detailed hierarchy development, therapist-assisted exposure practice in the office, and exposure homework. Parent training elements were incorporated into CBT sessions and focused on differential attention, exposure procedures, reducing family accommodation, reward systems to bolster compliance, and skills generalization.
3) Medication Management plus Instruction in CBT skills (MM + iCBT, n = 40): Participants received extended medication management visits in which the study psychiatrist provided instructions in CBT during the visit. iCBT included didactic information about the main psychoeducational and ERP components of the full CBT protocol, but did not include therapist-assisted exposure practice, cognitive training (except for bossing back metaphors and externalizing techniques), imaginal exposure instructions, reward system development, or dyadic parent sessions. Hierarchy development was comparatively simpler than full CBT and involved creation of a single ordinal hierarchy, rather than multiple hierarchies addressing different aspects of OCD.

The institutional review board at each site approved the study protocol, and informed consent/assent was obtained from all participants. The Consolidated Standards of Reporting Trials diagram was originally reported in Franklin et al. (2011). The current study focused on treatment-related change in secondary (i.e., non-OCD) psychiatric symptoms and psychosocial functioning as measured from baseline to week 12.

2.2. Participants

As reported in Franklin et al. (2011) and Freeman et al. (2009), POTS II participants included 124 children aged 7–17 years with a primary DSM-IV diagnosis of OCD who experienced partial response to an adequate SRI trial and had clinically relevant residual OCD symptoms (defined as a score of 16 or higher on the CY-BOCS). Partial response to SRI treatment was defined as: continued, stable OCD symptoms at an SRI dose equal to the recommended upper dose; a flat dose-response curve; or reported adverse effects with a higher dose than currently receiving. Exclusion criteria were: other primary or co-primary psychiatric disorder, suicidal ideation with intent, pervasive developmental disorder(s), mental retardation, thought disorder, pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS), pregnancy, previous failed trials of CBT for OCD, or taking more than 1 SRI concurrently. Sample characteristics are described in Freeman et al. (2011).

2.3. Measures

Multidimensional Anxiety Scale for Children (MASC; March, 1997; March et al., 1997). The MASC is a 39-item questionnaire assessing emotional, cognitive, physical and behavioral symptoms of non-OCD anxiety. The child (MASC-C) and parent-report (MASC-P) versions have demonstrated similar factor structure and predictive validity, and both have acceptable psychometric properties. Previous research in treatment-seeking samples suggests low parent-child agreement but high agreement between parent dyads (Villabø et al., 2012). T scores are available for the MASC-C; only raw scores are available for the MASC-P. T scores greater than 65 indicate clinically significant symptoms. Subscale scores are generated for the following domains: Anxious Coping, Harm Avoidance, Humiliation/Rejection, Perfectionism, Performance Fears, Physical Symptoms, Separation, Social Anxiety, Somatic/Autonomic, and Tense/Restless.

Conners' Parent Rating Scale-Revised—Long Version (CPRS-R-L; Conners, 1997; Conners et al., 1998). The CPRS-R-L is an 80-item parent-report measure of attention-deficit/hyperactivity disorder symptoms and oppositional behavior. It has shown good convergent and divergent validity and excellent test-retest reliability and internal consistency. Norms are derived from a large representative sample, and t scores greater than 60 indicate clinically relevant symptoms.

Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire (PQ-LES-Q; Endicott et al., 2006). The PQ-LES-Q is a 15-item child self-report scale assessing satisfaction with life across a variety of functional domains. Items are rated from 1 (very poor) to 5 (very good) and summed to generate a total score, such that higher scores indicate better quality of life. The PQ-LES-Q has demonstrated excellent internal consistency and sensitivity to change during treatment.

Children's Depression Inventory (CDI; Kovacs, 1992). The CDI is a 27-item child self-report measure of depressive symptomatology over the preceding two weeks. The CDI has shown adequate reliability and concurrent validity (Kovacs, 1992). T scores are age and gender-based; scores above 65 indicate clinically significant symptoms.

Children's Yale-Brown Obsessive-Compulsive Scale (CY-BOCS; Scahill et al., 1997). The CY-BOCS is a semi-structured clinician interview measuring the severity of OCD symptoms. The CY-BOCS Total Score ranges from 0 to 40, with higher scores representing greater OCD symptom severity. In the POTS II study, the CY-BOCS was administered by a trained clinician blind to participant treatment assignment.

2.4. Analytic plan

Treatment effect (MM vs. MM + CBT vs. MM + iCBT) from baseline to week 12 (post-treatment) was tested using generalized linear mixed modeling (GLIMMIX procedure in SAS 9.1). The model included fixed effects for treatment (3 levels), site (3 levels), and time (pre vs. post treatment). Classical Sandwich estimation was used to adjust for across-groups differences in variance and skewness. Family-wise alpha was maintained at 0.05 and adjusted with Holm's sequential Bonferroni correction for multiple comparisons.

For measures with available t scores (CDI, MASC-C, CPRS), all t score values were based on participant age at baseline. An ideographic approach was taken in analyses of MASC-C and MASC-P measures, as we were most interested in examining whether treatment-related changes occurred in each child's most elevated non-OCD anxiety symptom cluster. Therefore, baseline MASC scores represent each child's maximum MASC subscale score at baseline, and post-treatment scores are the value of this particular subscale at week 12. CPRS subscales measuring hyperactivity and inattention symptoms were examined separately.

In order to understand whether changes in secondary outcomes were related to change in OCD symptoms, relationships between pre-to post treatment change in CY-BOCS Total Score and change in each secondary outcome measure Pearson correlation coefficients were calculated.

3. Results

Correlations between CY-BOCS Total Score change and secondary outcome measure change are presented in Table 1. Results of main effects tests for three-way (site by time by treatment) and two-way (time by treatment) interactions for all measures are presented in Table 2. Results of post-hoc tests for measures showing significant three-way (site by time by treatment interactions are presented in Table 3. Table 4 includes results of post-hoc tests for measures showing significant 2 way (time by treatment) interactions. Supplemental figures depict pre-post treatment scores by treatment condition by site for each secondary outcome measure.

3.1. Comorbid symptoms

3.1.1. Parent-report measures

MASC-P. The three way interaction for site, time, and treatment was non-significant, $F(4, 91) = 1.17$, $p = 0.33$, but there was a significant interaction effect between time and treatment, $F(2, 91) = 4.97$, $p = 0.009$. Post-hoc pairwise comparisons indicated that MM + CBT was associated with significantly greater improvement in non-anxiety OCD symptoms than both MM ($t = 2.59$, $p = 0.022$) and MM + iCBT ($t = 3.09$, $p = 0.008$). MM and MM + iCBT were not significantly different from each other ($t = 0.33$, $p = 0.74$). Across the whole POTS II whole sample, change in MASC-P was not significantly correlated with change in CY-BOCS score ($r = 0.11$, $p = 0.34$), suggesting that improvements in OCD and non-OCD anxiety were not related to each other.

CPRS. On the hyperactivity subscale, the three way interaction for site, time, and treatment was non-significant, $F(4, 53) = 1.96$, $p = 0.11$, but there was a significant interaction effect between time and treatment, $F(2, 53) = 6.91$, $p = 0.002$. MM + CBT was associated with significantly greater improvement in hyperactivity than MM ($t = 3.60$, $p = 0.001$), and MM + iCBT produced better hyperactivity outcomes than MM ($t = 2.33$, $p = 0.04$). Hyperactivity outcomes did not differ between MM + CBT and MM + iCBT ($t = 0.46$, $p = 0.64$). In terms of clinical significance, mean scores shifted from the clinical

to the nonclinical range in MM + CBT and MM + iCBT but not in MM. Across the whole study sample, change in hyperactivity was significantly and positively correlated with CY-BOCS change ($r = 0.26$, $p = 0.04$), suggesting that improvement in hyperactivity co-occurred with OCD improvement.

On the inattention subscale of the CPRS, the three way interaction for site, time, and treatment was non-significant, $F(4, 53) = 1.37$, $p = 0.25$, but there was a significant interaction effect between time and treatment, $F(2, 53) = 6.68$, $p = 0.002$. In particular, MM + CBT was associated with better improvement than MM ($t = 3.37$, $p = 0.004$). MM + CBT was significantly better than MM + iCBT when the uncorrected p value was examined ($t = 2.25$, $p = 0.02$) but lost significance with the adjusted p value ($p = 0.056$). MM and MM + iCBT did not differ in terms of inattention outcomes ($t = 0.21$, $p = 0.83$). Clinical significance paralleled findings from hyperactivity, such that mean inattention scores shifted from the clinical to the nonclinical range in MM + CBT and MM + iCBT but not in MM. Across the entire sample, change in inattention was significantly and positively correlated with CY-BOCS change ($r = 0.34$, $p = 0.005$), indicating that improvement in inattention was associated with improvement in OCD symptoms.

3.1.2. Child-report measures

MASC-C. A significant three-way interaction between site, time, and treatment was found $F(4, 59) = 3.65$, $p = 0.01$. At the Penn site, anxiety symptoms did not differentially change across time or treatment condition, $F(5,59) = 0.55$, $p = 0.74$. In comparison, a treatment effect was found for the Brown site, $F(5,59) = 176.00$, $p < 0.001$, and the Duke site, $F(5,59) = 8.74$, $p < 0.001$. Significant reductions in primary non-OCD anxiety from pre to post treatment occurred in all treatment conditions for both Brown (MM: $t = -3.59$, $p = 0.004$; MM + iCBT: $t = -15.18$, $p < 0.001$; MM + CBT: $t = -3.79$, $p = 0.003$) and Duke (MM: $t = -2.21$, $p = 0.12$; MM + iCBT: $t = -2.74$, $p = 0.04$; MM + CBT: $t = -5.25$, $p < 0.001$). Of note, mean scores were in the nonclinical range for all groups at post-treatment. In regards to between-group comparisons, at the Brown site, MM + CBT was superior to MM + iCBT ($t = 3.78$, $p = 0.003$), but anxiety outcomes did not differ between MM + CBT and MM ($t = 0.63$, p = 1.00) or between MM + iCBT and MM ($t = -2.27$, $p = 0.21$). At the Duke site there were not any differential outcomes across treatments (MM + CBT vs. MM + iCBT: $t = -0.63$, $p = 1.00$; MM + CBT vs MM: $t = -0.22$, $p = 1.00$; MM + iCBT vs. MM: $t = 0.24$, $p = 1.00$). Across the entire study sample, change in MASC-C scores was not significantly correlated with change in CY-BOCS scores, further supporting the finding on the MASC-P that improvements in OCD and non-OCD anxiety were not related to each other.

CDI. Depression symptoms did not differentially change across treatments as indicated by a non-significant three-way interaction between site, time, and treatment, $F(4, 56) = 2.17$, $p = 0.08$ and non-significant two-way interaction between time and treatment, $F(2, 91) = 4.97$, $p = 0.009$. Mean scores fell in the nonclinical range at both pre- and post-treatment in all groups across all sites. Across the whole study sample, change in CDI was significantly and positively correlated with CY-BOCS change ($r = 0.32$, $p = 0.007$), suggesting a relationship between improvement in depression and improvement in OCD.

Table 2
Results of main effects tests for 3 way (site by time by treatment) and 2 way (time by treatment) interactions.

Measure	GLM Results	
	Site x Time x Treatment	Time x Treatment
MASC-P	$F(4, 91) = 1.17$, $p = 0.33$	$F(2, 91) = 4.97$, $p = 0.009$
CPRS Hyperactivity	$F(4, 53) = 1.96$, $p = 0.11$	$F(4, 53) = 6.91$, $p = 0.002$
CPRS Inattention	$F(4, 53) = 1.37$, $p = 0.25$	$F(4, 53) = 6.68$, $p = 0.002$
PQ-LES	$F(4, 68) = 2.69$, $p = 0.03$	$F(2, 68) = 2.67$, $p = 0.07$
MASC-C	$F(4, 59) = 3.65$, $p = 0.01$	$F(2, 59) = 0.21$, $p = 0.81$
CDI	$F(4, 56) = 2.17$, $p = 0.08$	$F(2, 56) = 0.58$, $p = 0.56$

CDI: Children's Depression Inventory; CPRS: Conners' Parent Rating Scale-Revised—Long Version; MASC-C: Multidimensional Anxiety Scale for Children, Child-Report; MASC-P: Multidimensional Anxiety Scale for Children, Parent-Report; PQ-LES: Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire.

3.2. Impairment/quality of life

3.2.1. PQ-LES-Q

The three-way interaction between time, site, and treatment was significant, $F(4, 68) = 2.69$, $p = 0.03$. Post-hoc comparisons of treatments at each site indicated that MM + CBT was associated with significantly greater improvements in quality of life than MM ($t = 3.57$, $p = 0.005$) and MM + iCBT ($t = 3.90$, $p = 0.002$) only at the Penn site. No other significant treatment effects were found on the PQ-LES-Q. Across the whole sample, change in PQ-LES-Q scores was significantly and negatively correlated with CY-BOCS change ($r = -0.29$, $p = 0.02$), indicating that decreases in OCD symptoms were related to improvements in quality of life.

5. Discussion

Pediatric OCD pharmacological and psychological treatments have demonstrated efficacy in improving symptom severity both alone and in combination. While improvement in OC-symptoms remains the core intention of these treatments for youth with OCD, comorbid symptoms and ratings of quality of life are important markers of a youth's overall clinical functioning and should also be examined for their response to treatment. Therefore, while the POTS II primary outcome study examined the efficacy of varying levels of CBT treatment application on improving OCD symptom severity (Franklin et al., 2011), the present study focused on the

Table 1
Correlations between pre-post treatment change in CY-BOCS Total Score and change in secondary outcome measures across entire sample.

Secondary Outcome Measure	Change Score	Correlation with CY-YBOCS Change
	$\bar{\chi}$ (SD)	r, p
MASC-P	−0.07 (0.24)	0.11, $p = 0.34$
CPRS Hyperactivity	−5.87 (13.34)	0.26, $p = 0.04$
CPRS Inattention	−6.49 (8.38)	0.34, $p = 0.005$
PQ-LES-Q	3.31 (9.12)	-0.29, $p = 0.02$
MASC-C	−0.15 (0.24)	0.08, $p = 0.47$
CDI	−2.96 (8.39)	0.32, $p = 0.007$

CDI: Children's Depression Inventory; CPRS: Conners' Parent Rating Scale-Revised—Long Version; MASC-C: Multidimensional Anxiety Scale for Children, Child-Report; MASC-P: Multidimensional Anxiety Scale for Children, Parent-Report; PQ-LES-Q: Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire.

Table 3
Post-hoc tests for measures showing significant 3 way (site by time by treatment) interaction.

		Site		
		Penn	Brown	Duke
Measure	Group	$\overline{\chi}_{\Delta}$ (SE); p	$\overline{\chi}_{\Delta}$ (SE); p	$\overline{\chi}_{\Delta}$ (SE); p
PQ-LES	MM	−1.39 (1.50); $p = 0.35$	−1.84 (3.37); $p = 0.58$	5.07 (2.65); $p = 0.6$
	MM + iCBT	−1.62 (0.97); $p = 0.10$	4.75 (2.99); $p = 0.11$	5.44 (2.52); $p = 0.03$
	MM + CBT	10.07 (2.83); $p = 0.0007$	2.80 (2.39); $p = 0.24$	4.6 (3.41); $p = 0.05$
MASC-C	MM	−1.10 (3.39); $p = 1.00$	−12.78 (3.55); $p = 0.004$	−9.74 (4.40); $p = 0.12$
	MM + iCBT	1.23 (2.68); $p = 1.00$	−21.48 (1.41); $p < 0.0001$	−8.45 (3.08); $p = 0.04$
	MM + CBT	−6.34 (5.10); $p = 0.65$	−9.74 (2.69); $p = 0.0034$	−10.79 (2.05); $p < 0.001$
CDI	MM	−0.48 (2.56); $p = 0.85$	2.95 (1.86); $p = 0.12$	−9.70 (3.73); $p = 0.01$
	MM + iCBT	−1.40 (2.40); $p = 0.55$	0.38 (2.73); $p = 0.88$	−3.57 (2.67); $p = 0.18$
	MM + CBT	−5.95 (2.33); $p = 0.13$	−3.03 (0.86); $p = 0.0009$	−1.62 (2.44); $p = 0.51$

CDI: Children's Depression Inventory; CPRS: Conners' Parent Rating Scale-Revised—Long Version; MM: medication management; MM + CBT: medication management plus cognitive behavioral therapy; MM + iCBT: medication management plus instructions in cognitive behavioral therapy; MASC-C: Multidimensional Anxiety Scale for Children, Child-Report; PQ-LES: Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire.

Table 4
Post-hoc tests for measures showing significant 2 way (time by treatment) interactions.

	Treatment	$\overline{\chi}_{\Delta}$ (SE); p
MASC-P	MM + CBT vs. MM	−3.35 (1.29); $p = 0.02$
	MM + iCBT vs. MM	0.32 (0.97); $p = 0.74$
	MM + CBT vs. MM + iCBT	−3.67 (1.18); $p = 0.008$
CPRS Hyperactivity	MM + CBT vs. MM	−11.16 (3.02); $p = 0.001$
	MM + iCBT vs. MM	−9.50 (4.08); $p = 0.04$
	MM + CBT vs. MM + iCBT	−1.65 (3.57); $p = 0.64$
CPRS Inattention	MM + CBT vs. MM	−6.78 (2.01); $p = 0.004$
	MM + iCBT vs. MM	−0.62 (2.93); $p = 0.83$
	MM + CBT vs. MM + iCBT	−6.16 (2.73); $p = 0.056$

CPRS: Conners' Parent Rating Scale-Revised—Long Version; MM: medication management; MM + CBT: medication management plus cognitive behavioral therapy; MM + iCBT: medication management plus instructions in cognitive behavioral therapy; MASC-P: Multidimensional Anxiety Scale for Children, Parent-Report.

varying effect of these treatments on secondary outcomes. Although specific relationships varied by outcome, in general the secondary outcomes mirrored those of the primary outcomes, suggesting that many of these secondary outcomes improve with treatment. Here again, full combination treatment was the most likely to be associated with the largest improvement.

Improvement across treatment types at all sites was observed for parent-rated anxiety, inattention, hyperactivity, and quality of life, and was observed for two of the three sites in regards to child-rated anxiety symptoms. Child-rated depression was the only comorbid symptom domain consistently found to not change over the course of treatment; however, it should be noted that average depression scores were in the sub-clinical range, and as a result the lack of significant improvement may indicate a floor effect. Overall, the results suggest that treatment of OCD leads to improvement in other areas of psychopathology and functioning, and at the very least, in regards to depression, does not lead to worsening comorbid symptoms.

Exploratory correlational analyses examining the relationship between change in OCD severity and change in these secondary outcomes across the whole sample indicated that improvements in OCD were associated with improvements in hyperactivity, inattention, depression, and quality of life. These results suggest that improvement in OCD is likely to co-occur with improvement in these domains regardless of the specific treatment modality in which improvement occurred. Whether OCD change precedes change in these other domains remains unknown, as only pre-post data were available in the current study. Interestingly, although improvements in non-OCD anxiety were observed to be superior in MM + CBT, change in anxiety severity across the whole sample was not significantly correlated with change in OCD severity on both the parent- and child-report anxiety measures. This finding suggests that non-OCD anxiety may not change simply when OCD symptoms are the treatment target. Rather, it may be the case that anxiety only improves when the treatment modality includes interventions that generalize to anxiety symptoms (e.g., the use of in-vivo exposure in MM + CBT).

In general, the improvements in secondary outcomes observed in the present study are consistent with previous pediatric OCD treatment trials. Given the often complex presentation of patients in community settings, these outcomes further support the use of OCD-focused treatments as means of improving a child's OC-symptoms, comorbid symptoms, and overall functioning. Notably, POTS II treatments did not directly target these secondary domains; thus, the mechanism through which youth experience improvement is unclear. However, some hypotheses can be proposed: first, it is possible that the treatments have a direct or generalized benefit on these other areas. For example, CBT also has empirical support for other anxiety disorders in youth (Walkup et al., 2008). By learning how to effectively face OCD-related fears through exposure, youth may learn to reduce avoidance and face fears in other domains. Similarly, parent-led behavioral skills taught to address OCD and family accommodation (e.g., behavioral reward systems, limit setting, differential attention) are also supported for treatment of behavioral disorders (Jones et al., 2007). Parents may learn to translate and apply these skills to their child's ADHD symptoms.

On the other hand, the improvement in these domains may simply be a reflection of reduced OCD-related impairment, particularly in those domains found to be correlated with change in OCD severity (i.e., hyperactivity, inattention, depression, quality of life). Improvements in comorbid symptoms could also be a reflection of improved OCD symptom severity. For example, a child who is no longer experiencing frequent and distressing obsessions would likely appear less inattentive and agitated than prior to treatment. Given the general difficulty in differentiating anxiety/OC-symptoms and ADHD symptoms, these results might suggest that if significant ADHD symptoms persist at post-treatment, additional measures to diagnosis and treat ADHD symptoms may be indicated.

The hypothesized results of MM + CBT outperforming MM + iCBT and MM were consistently supported in regards to parent-rated non-OCD anxiety as well as symptoms of inattention, but not for other domains. For hyperactivity symptoms, both MM + CBT and MM + iCBT outperformed MM but did not

significantly differ from each other. In contrast, for child-rated anxiety symptoms, Brown found MM + CBT to be superior to MM + iCBT but not MM, while Duke and Penn found no differences between treatments. It is slightly surprising that MM + CBT did not consistently outperform the other treatments across domains given that the MM + CBT arm received a considerably increased total time in treatment. Additionally, CBT is empirically supported for depression and non-OCD anxiety (Compton et al., 2004) and might be expected to generalize to a greater extent than observed. Despite these inconsistencies, MM + CBT was not outperformed in any domain and thus the overall results are supportive of MM + CBT as the best treatment option.

From a training and dissemination perspective, the current findings highlight the importance of training OCD treatment providers in the principles and techniques of in-session/in-vivo exposure delivery. A growing body of evidence indicates that in-session exposure is a necessary ingredient of CBT for pediatric OCD and anxiety disorders. For example, a recent meta-analysis found that more effective treatments for child anxiety disorders involve more sessions of exposure initiated earlier in the treatment course (Ale et al., 2015). Emerging neuroscience research also supports the importance of contextually based fear extinction learning, particularly for adolescents (Pattwell et al., 2016). However, many therapists report not using exposure-focused CBT due to beliefs that exposure may exacerbate patient anxiety, cause undue harm, or be otherwise unsafe or intolerable (Whiteside et al., 2016). Our findings indicate that exposure-based CBT at best improves secondary outcomes and, at a minimum, does not likely lead to worsening of the psychiatric symptoms we measured.

It is of note that site differences were more frequently observed than expected. Differences across sites suggest that improvements in these secondary outcomes may be particularly susceptible to additional non-measured factors that could vary across sites, such as geographical location, patient characteristics, clinician/rater characteristics, and treatment preference/delivery, amongst others. It is also possible that non-measured variation in treatment delivery impacted outcomes, as procedural variations can emerge even when providers are adherent to the same treatment manual (e.g., number of minutes spent doing exposure, provider responses to family questions, stylistic variations that influence alliance or patient adherence, motivation, etc.). This lack of consistency across sites further illustrates the importance of examining these secondary outcomes in studies of treatments for OCD– a clear picture of how secondary targets are impacted by OCD-specific treatment is still lacking.

The outcomes of the present study should be interpreted within the context of its limitations. First, comorbid symptom change was examined in all youth, regardless of baseline severity or diagnosis. As a result, our results indicate that these symptoms generally improve with OCD treatment but do not specify differences in individual symptom trajectories (e.g., clinical vs. subclinical symptoms). Second, secondary outcome measures were all parent- or child self-report forms and did not include ratings from clinicians blind to treatment assignment, as was done for primary OCD-related outcomes. Not all domains were rated by both the child and parent in parallel, and some discrepancies emerged in parent vs. child reporting of anxiety. Although discrepancies in parent and child report are common in psychiatric research, it is possible that levels of agreement are relevant in terms of treatment outcome (Becker-Haimes et al., 2017). Third, the collection of data only at pre- and post-treatment limits our ability to examine the trajectory of change across symptom domains. Thus, it is unclear whether change in secondary outcomes followed change in OCD symptoms. Fourth, the durability of observed gains is unclear given that results reflect changes observed only across acute treatment (12 weeks).

In conclusion, results of the present study support the generalizability of empirically supported treatments for pediatric OCD to comorbid symptoms and quality of life. Although not found across every measure, evidence suggested that MM + CBT treatment, which included medication management and a full course of CBT, was most likely to be associated with the largest improvements in these secondary outcomes. These results support the currently available treatment for youth with OCD, suggesting that those who receive treatment experience a more global benefit than simply OCD symptom improvement. Future research should attempt to examine predictors, individual differences, and mechanisms of improvement for secondary outcomes in the treatment of pediatric OCD.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jpsychires.2017.04.001.

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