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Randomized, placebo-controlled trial of cognitive-behavioral therapy alone or combined with sertraline in the treatment of pediatric obsessive–compulsive disorder

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ABSTRACT

Background: To examine the efficacy of sequential sertraline and cognitive-behavioral therapy (CBT) treatment relative to CBT with pill placebo over 18 weeks in children and adolescents with obsessive–compulsive disorder (OCD).

Methods: Forty-seven children and adolescents with OCD (Range = 7–17 years) were randomized to 18-weeks of treatment in one of three arms: 1) sertraline at standard dosing + CBT (RegSert + CBT); 2) sertraline titrated slowly but achieving at least 8 weeks on the maximally tolerated daily dose + CBT (SloSert + CBT); or 3) pill placebo + CBT (PBO + CBT). Assessments were conducted at screening, baseline, weeks 1–9, 13, and 17, and post-treatment. Raters and clinicians were blinded to sertraline (but not CBT) randomization status. Primary outcomes included the Children's Yale-Brown Obsessive–Compulsive Scale, and response and remission status. Secondary outcomes included the Child Obsessive Compulsive Impact Scale–Parent/Child, Children's Depression Rating Scale-Revised, Multidimensional Anxiety Scale for Children, and Clinical-Global Impressions-Severity.

Results: All groups exhibited large within-group effects across outcomes. There was no group by time interaction across all outcomes suggesting that group changes over time were comparable.

Conclusions: Among youth with OCD, there was no evidence that sequentially provided sertraline with CBT differed from those receiving placebo with CBT.

ClinicalTrials.gov Identifier: NCT00382291.

Pediatric obsessive–compulsive disorder (OCD) affects ~1% of children and adolescents and is associated with marked functional impairment (Piacentini, Bergman, Keller, & McCracken, 2003) and a high probability of secondary diagnoses (Geller et al., 2003). Most affected individuals experience symptom onset during childhood with symptoms running a protracted course in the absence of appropriate intervention (Pauls, Alsobrook, Goodman, Rasmussen, & Leckman, 1995). Two treatments have demonstrated efficacy: cognitive-behavioral therapy (CBT) and serotonin reuptake inhibitor (SRI) medications. Current practice parameters recommend that clinicians begin with CBT alone for mild to moderate OCD presentations and use combined CBT–SRI treatment in moderate to severe presentations (AACAP, 2012). Yet, studies directly examining the efficacy of combining CBT and SRI medications have yielded unequivocal results. Among pediatric OCD samples, only one study has prospectively examined the efficacy of combined therapy relative to CBT alone finding that combined treatment was superior to CBT and sertraline alone (Cohen's $d = 1.40$ vs. .97 and .67; POTS, 2004). However, a site effect was present with CBT alone associated with a robust effect at one site ($d = 1.60$) and a modest effect at the other ($d = .51$), while sertraline yielded effects of moderate and large sizes at different sites ($d = .53$ and .80).

More information on the relative benefits of combined CBT and SRI therapy versus CBT alone has been reported in adults with OCD. Several studies have found positive results in support of combined

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treatment. Marks and colleagues (Marks et al., 1988; Marks, Stern, Mawson, Cobb, & McDonald, 1980) found an additive effect of combined clomipramine and CBT relative to placebo and CBT. Hohagen et al. (1998) compared CBT + fluvoxamine to CBT + placebo in 58 adults. More patients were classified as responders to CBT + fluvoxamine treatment versus CBT + placebo. Others have not found additional benefit with combined treatment. van Balkom et al. (1998) randomized 117 adult patients to one of five conditions: 1) cognitive therapy for 16 weeks; 2) CBT for 16 weeks; 3) fluvoxamine for 16 weeks plus cognitive therapy for weeks 9–16; 4) fluvoxamine for 16 weeks plus CBT for weeks 9–16; or 5) eight-week wait-list control. Active treatments did not differ and there was no benefit to the sequential combination of fluvoxamine with either therapy versus other conditions. Foa et al. (2005) examined the comparative efficacy of intensive CBT for four weeks followed by eight weekly maintenance sessions, clomipramine alone, their combination, or placebo for 12 weeks in 122 adults with OCD. All treatments were efficacious, with a distinct advantage for CBT alone or in combination with clomipramine, which did not differ. Cottraux et al. (1990) randomized 60 patients to one of three conditions lasting 24 weeks each: weekly CBT + fluvoxamine, weekly CBT + placebo, and fluvoxamine. No significant group differences were present at post-treatment.

Implications of the extant combination trials are that CBT and SRIs are effective acute treatments for pediatric and adult OCD when administered alone and in conjunction. It remains unclear, however, if a combined approach has incremental benefits over CBT monotherapy. This holds relevance because although safe, pharmacological interventions involving serotonergic medications may be accompanied by side effects (Murphy, Segarra, Storch, & Goodman, 2008) and may not be an acceptable intervention to some parents. On balance, the majority of the studies reviewed above conducted combined treatment simultaneously. An adequate trial of an SRI is 10–12 weeks with some data suggesting that optimal response cannot be determined until after 18–20 weeks of treatment (Walsh & McDougle, 2004). Thus, trials that combine treatments simultaneously may not provide the best test of combined pharmacological and psychosocial approaches. Intuitively, the effects of combined treatment would be optimized using sequential rather than simultaneous study designs, with an adequate medication trial initiated first. Use of this methodology prior to initiating CBT may facilitate exposure to feared situations vis-à-vis reductions in baseline levels of anxiety or treatment complicating factors (e.g., depression). Yet, the majority of studies have initiated psychosocial and pharmacological treatment regimens simultaneously usually for 12 weeks, preventing the optimal dose from being reached by the end of the trial. Further, since dissemination of CBT for OCD is fairly limited, the sequential addition of CBT to patients who have been treated with SRI medications may parallel the real world and provide insight into treatment options for those who do not respond to initial efforts.

To date, several sequential trials in adults with OCD and one in children with OCD have been conducted. Franklin et al. (2011) randomized 124 youth with OCD who remained symptomatic following an adequate SRI trial to CBT + continued SRI, a brief version of CBT + continued SRI, or continued SRI therapy alone. The CBT + SRI arm was superior to the other groups on all outcomes. As noted, van Balkom et al. (1998) indicated no benefit to the sequential combination of fluvoxamine with either therapy versus other conditions. Tenneij, van Megen, Denys, and Westenberg (2005) examined the addition of CBT to venlafaxine (300 mg/day) or paroxetine (60 mg/day) responders ($N = 96$). Medication responders were randomly assigned to either receive the addition of CBT (18 45-min sessions) or continue drug treatment for an additional six-months. Those who received CBT augmentation showed a greater improvement in symptoms and remission rates than those who continued on medication treatment alone.

In the present study, we had a unique opportunity to examine the efficacy of sequential sertraline and CBT treatment relative to CBT alone. The study design involved children and adolescents with OCD being randomized to 18-weeks of sertraline or placebo with CBT being initiated four weeks after pharmacotherapy onset: 1) sertraline at standard dosing + CBT (RegSert + CBT); 2) sertraline titrated slowly but achieving at least 8 weeks on the maximally tolerated daily dose + CBT (SloSert + CBT); or 3) pill placebo + CBT (PBO + CBT). We were interested in determining if symptom reduction and response/remission rates differed as a function of both group and medication status (i.e., sertraline arms collapsed versus PBO + CBT). Secondary analyses examined group differences in child-reported anxiety and depressive symptoms and parent- and child-rated impairment.

Method

Participants

Forty-seven youth ages 7–17 years with a principal diagnosis of OCD were recruited between February 2009 and January 2011 across two study sites with expertise in pediatric OCD treatment.[1] Inclusion criteria consisted of: 1) Current DSM-IV-TR diagnosis of OCD established via expert clinician assessment and the Schedule for Affective Disorders and Schizophrenia for School-Age Children (K-SADS-PL; Kaufman et al., 1997); 2) Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS) $\geq$ 18 (Scahill et al., 1997); 3) English speaking and able to read. Exclusion criteria included: 1) Prior adequate trial of (AACAP, 2012) or allergy to sertraline. 2) History of rheumatic fever, serious autoimmune disorder, or generally poor physical health. 3) Inability to swallow study medication. 4) Presence of active suicidality or suicide attempt in the past 12 months. 5) Pregnancy or having unprotected sex [in females]. 6) Concomitant psychotropic medications other than medication for attention deficit hyperactivity disorder or PRN sedative/hypnotics for insomnia. 7) Presence of comorbid psychosis, bipolar disorder, autism, anorexia, or substance abuse/dependence.

Procedures

Appropriate institutional review board permissions from both sites were obtained. After obtaining written parent consent and child assent, participants completed study measures, were administered a physical examination by a board certified child psychiatrist, and had lab values assayed (e.g., CBC, metabolic panel, urine toxicology, and pregnancy test [for post-pubescent females]). Thereafter, eligible participants were randomized by a computer-generated randomization program in a double-blinded fashion (for sertraline/placebo but not CBT) to one of the three study arms: 1) RegSert + CBT; 2) SloSert + CBT; or 3) PBO + CBT. Assessments were conducted by trained raters at screening, baseline, weeks 1–9, 13, and 17, and post-treatment,

[1] During the conduct of the study, a pharmacy-related medication error occurred, which affected 9 of 56 initially randomized study participants and resulted in a temporary study suspension. After full root-cause analysis was completed and the study was reopened, the DSMB advised to conduct analyses including the 47 unaffected subjects (the treatment of 4 of these subjects was terminated early due to the study suspension).