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Adaptive treatment strategies for children and adolescents with Obsessive-Compulsive Disorder: A sequential multiple assignment randomized trial

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ABSTRACT

Objective: This sequential multiple assignment randomized trial (SMART) tested the effect of beginning treatment of childhood OCD with fluoxetine (FLX) or group cognitive-behavioral therapy (GCBT) accounting for treatment failures over time.

Methods: A two-stage, 28-week SMART was conducted with 83 children and adolescents with OCD. Participants were randomly allocated to GCBT or FLX for 14 weeks. Responders to the initial treatment remained in the same regimen for additional 14 weeks. Non-responders, defined by less than 50% reduction in baseline Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) scores, were re-randomized to either switch to or add the other treatment. Assessments were performed at baseline, 7, 14, 21, and 28 weeks.

Results: Among the 43 children randomized to FLX who completed the first stage, 15 (41.7%) responded to treatment and 21 non-responders were randomized to switch to (N = 9) or add GCBT (N = 12). Among the 40 children randomized to GCBT who completed the first stage, 18 (51.4%) responded to treatment and 17 non-responders were randomized to switch to (N = 9) or add FLX (N = 8). Primary analysis showed that significant improvement occurred in children initially treated with either FLX or GCBT. Each time point was statistically significant, showing a linear trend of symptom reduction. Effect sizes were large within (0.76–0.78) and small between (-0.05) groups.

Conclusions: Fluoxetine and GCBT are similarly effective initial treatments for childhood OCD considering treatment failures over time. Consequently, provision of treatment for childhood OCD could be tailored according to the availability of local resources.

1. Introduction

Obsessive-compulsive disorder (OCD) is relatively common in children and adolescents, with a prevalence of 2.7% (Rapoport et al., 2000). Evidence suggests that OCD usually begin early in life (Kessler et al., 2005) and tend to persist through adulthood (Micali et al., 2010). When unrecognized and untreated, OCD may impair the child's functioning, with a significant impact on social, affective and academic development, and potential lifelong negative consequences (Piacentini, Bergman, Keller, & McCracken, 2003).

In the last decades, several clinical trials advanced our knowledge on childhood OCD treatment. Pharmacotherapy (clomipramine and selective serotonin reuptake inhibitor, SSRI) and cognitive behavioral therapy (CBT), alone or in combination, have been proved to be effective in reducing OCD symptoms in children and adolescents (Geller et al., 2003; Watson & Rees, 2008). Based on expert consensus, current guidelines recommend CBT as the first-line treatment for children and adolescents with mild to moderate OCD. In moderate to severe cases, or for youths who do not sufficiently respond to CBT monotherapy, the association of a SSRI is recommended (Alvarenga, Mastrorosa, & do Rosário, 2015; Geller & March, 2012).

However, recent evidence from a meta-analysis (Sánchez-Meca,

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Rosa-Alcázar, Iniesta-Sepúlveda, & Rosa-Alcázar, 2014) and a clinical trial (Storch et al., 2013) demonstrate that the combination of a SSRI and CBT shows similar effect sizes when compared to CBT alone. Furthermore, about one third of children with OCD do not respond satisfactorily to first choice treatments (Geller et al., 2003; POTS Team, 2004), with no strong evidence indicating the best option in terms of the sequence of treatments for partial responders or non-responders to monotherapy or combination of treatments (Ivarsson et al., 2015). Thus, the question "what to do next" often accompanies mental health professionals, whereas the question "what to do first" seems relevant to policy makers.

One way of answering the question of the best treatment sequence is by developing adaptive treatment strategies (ATS). In the context of a chronic disorder with large heterogeneity in response to treatment and where full symptom remission is not the rule, a dynamic approach is needed. Thus, an ATS consists of a set of decision rules based on clinical characteristics and time sensitive outcomes to inform a sequence of evidence-based treatments (Almirall, Nahum-Shani, Sherwood, & Murphy, 2014). A sequential multiple assignment randomized trial (SMART) constitutes an experimental design that facilitates the development of ATSs (Collins, Murphy, & Strecher, 2007). The SMART approach considers the order in which treatments are presented. One possible outcome of a SMART is to suggest the most appropriate moment when the type of treatment should be changed based on clinical characteristics (i.e., symptom severity, comorbidities) or degree of improvement (Murphy, Lynch, Oslin, McKay, & TenHave, 2007). Thus, a SMART could help to address questions relevant to both clinical practice and mental health policy making. In the field of child and adolescent mental health, SMART studies have been used in the context of autism (Kasari et al., 2014), conduct disorder (August, Piehler, & Bloomquist, 2014), and attention deficit disorder and hyperactivity (ADHD) (Jr et al., 2016).

To our knowledge, the best initial treatment to treat childhood OCD considering treatment failure over time has not been investigated so far using the SMART methodology. Such studies are timely, given the high rate of children and adolescents with OCD that may not achieve clinical remission. Therefore, the primary aim of this study was to test the effect of beginning treatment for childhood OCD with fluoxetine (FLX, a SSRI), or group cognitive behavioural therapy (GCBT) across two stages, accounting for non-response to treatment over time. A secondary aim was to compare the outcomes of switching to or adding the other treatment in case of non-response to the first treatment.

2. Methods

This study is part of the National Institute of Developmental Psychiatry (INPD), a Brazilian multicentre research initiative dedicated to improving mental health of children and adolescents (Miguel, Mercadante, Grisi, & Rohde, 2009).

2.1. Design

This is a two-stage, 14-week each, SMART, conducted at the Institute & Department of Psychiatry, University of Sao Paulo Medical School, Brazil. In the first stage, all children and adolescents were randomized to fluoxetine (FLX) or group CBT (GCBT). At the end of 14 weeks, responders maintained the initial treatment for 14 weeks. Non-responders were re-randomized to switch or add the other treatment (those who began with FLX could (1) switch to GCBT or (2) add GCBT; those who started with GCBT could (3) switch to FLX or (4) add FLX). Response was defined as at least 50% reduction in baseline Yale-Brown Obsessive-Compulsive Scale scores (Y-BOCS) (Goodman et al., 1989). Table 1 describes the ATSs embedded in this SMART.

Up to three absences were accepted for each stage of treatment. Patients who did not complete one of the assigned treatments, but from whom the research staff managed to take at least partial follow-up measures, were considered treatment dropouts (these subjects did not complete the assigned treatment but were invited for subsequent evaluations). Patients who interrupted their assigned treatment and were not available to follow-up measures after the last appointment were considered study dropouts.

Table 1
Clinical and socio-demographic characteristics of participants by first randomization.

		FLX (N = 43)	GCBT (N = 40)	Total (N = 83)
Gender, No. %	**Male**	18 (41.9%)	22 (55.0%)	40 (48.2%)
Age, Mean (SD)		121 (3.1)	11.4 (3.2)	11.8 (3.2)
SES, No. %	**Upper class**	9 (21.4%)	12 (30.8%)	21 (25.9%)
	Upper-middle	24 (57.1%)	20 (51.3%)	44 (54.3%)
	Lower-middle	9 (21.4%)	7 (17.9%)	16 (19.8%)
Race, No. %	**White**	40 (93.0%)	36 (90%)	76 (91.6%)
	Black	1 (2.3%)	0	1 (1.2%)
	Asian	1 (2.3%)	0	1 (1.2%)
	Mixed	1 (2.3%)	4 (10.0%)	5 (6.0%)
Previous psychiatric treatment, No. %		13 (31.0%)	14 (35.0%)	27 (32.9%)
Previous psychotherapy, No. %		27 (64.3%)	27 (67.5%)	28 (34.1%)
Previous psychiatric inpatient, No. %		2 (4.9%)	1 (2.6%)	3 (3.8%)
OCS onset (years), Mean (SD)		6.55 (2.74)	6.24 (2.80)	6.40 (2.75)
Any comorbidity, No. %		39 (92.9%)	35 (89.7%)	74 (91.4%)
No. of comorbidities, Mean (SD)		2.68 (1.72)	2.33 (1.51)	2.51 (1.62)
Depressive disorders, No. %		11 (26.2%)	5 (12.8%)	16 (19.8%)
Anxiety disorders, No. %		35 (83.3%)	30 (76.9%)	65 (80.2%)
Disruptive disorders, No. %		11 (26.2%)	12 (30.8%)	23 (28.4%)
Tics disorders, No. %		7 (16.7%)	10 (25.6%)	17 (21.0%)
YBOCS (total score), Mean (SD)		25.9 (6.9)	27.3 (4.9)	26.6 (6.0)

Abbreviations: FLX = fluoxetine, GCBT = group cognitive-behaviour therapy, SD = standard deviation, OCS = obsessive-compulsive symptoms, YBOCS = Yale-Brown Obsessive-Compulsive Scale, SES = Socioeconomic Status.

2.2. Participants

Announcements of the study were published in the media, community, and at health facilities. Eligibility criteria were assessed via a multiple-stage procedure. First, participants were screened by a telephone interview with the primary caregiver, using a brief structured interview to verify the age and OCD symptoms. For those eligible at this screening stage, an in-person screening interview was conducted with the child/adolescent and the primary caregiver by a child psychiatrist, comprising a structured questionnaire developed by the research team (socio-demographic data, clinical characteristics and history of psychiatric symptoms), the Y-BOCS and the Children's Global Assessment Scale (C-GAS). A trained child and adolescent psychologist also evaluated the child's intelligence quotient (IQ) with the Wechsler Abbreviated Scale of Intelligence (WASI). Finally, patients who met full criteria underwent a thorough assessment of baseline measures.

The inclusion criteria for this study were: a) to have an OCD diagnosis according to DSM-IV criteria as the main reason for seeking treatment; b) age between 7–17 years; c) parent or legal guardian provided consent for the subject to participate in the study; d) absence of physical or mental conditions that prevented active participation in the study; e) baseline Y-BOCS score $\geq$ 16; f) weight $\geq$ percentile 10; g) barrier contraceptive method use in case of female adolescents in