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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

fertile age. Patients were excluded if: a) IQ < 80; b) they were pregnant; c) suicidal ideation or intent, need of inpatient care were present.

No incentives were paid to participants, but refund for transportation was offered. A signed consent form was obtained from the parent or legal guardian of all participants, and the child's assent was obtained concomitantly. The project was approved by the local Ethics Committee (0361/09) and registered at clinicaltrials.gov (Registry name: Developing Adaptive Treatment Strategies for Children and Adolescents with Obsessive-compulsive Disorder; Identification number: NCT01148316; URL: https://goo.gl/HwkZEG).

### 2.3. Measures

Blind independent evaluators that took part in the "The Brazilian Research Consortium on Obsessive-Compulsive Spectrum Disorders" assessed the study outcomes (Euripedes Constantino Miguel et al., 2008). Evaluations occurred in a different setting than the study clinic to avoid contact with the clinicians and other subjects. The primary outcome was the total Y-BOCS score. The Y-BOCS is a 10-item instrument to assess the frequency, impairment, subjective discomfort, resistance, and control over obsessions and compulsions (Goodman et al., 1989). Both the Y-BOCS and the C-YBOCS have been translated and adapted to Brazilian Portuguese, but there are no validation studies of these scales published to date. The Brazilian Portuguese version of the Y-BOCS has been used instead of the Children's Yale-Brown Obsessive-Compulsive Scale (CY-BOCS) (Scahill et al., 1997) because we had already conducted a reliability training of our staff with the YBOCS for previous studies (e.g. Miguel et al., 2008). In addition, the YBOCS and C-YBOCS share the same overall structure, anchor points, and scoring. In the present sample the Y-BOCS presented good psychometric properties (Cronbach's Alpha = 0.83, McDonald's Omega = 0.85). In this study, all evaluators considered information from the parent/caregiver and the child when rating each item. Additionally, to assess the severity of OCD and comorbid disorders at baseline, the Clinical Global Impression Scale, Severity subscale (Guy, 1976) was used.

To verify the inclusion criteria and to assess for the presence of comorbidities, the Kiddie-Schizophrenia and Affective Disorders Scale-Present and Lifetime (K-SADS-PL) was used. The K-SADS-PL is a semi-structured interview for psychiatric disorders in children and adolescents based on DSM-IV diagnostic criteria (Brasil & Bordin, 2010). The Wechsler Abbreviated Scale of Intelligence (WASI) 4 subtests (vocabulary, similarities, matrix reasoning and block design) were used to assess the child's intelligence quotient at baseline (Heck et al., 2009). The Systematic Assessment for Treatment Emergent Effects (SAFTEE) was used to actively assess adverse events in the FLX groups (Levine & Schooler, 1986).

### 2.4. Randomization

Randomization occurred in real-time, by means of a sequential allocation method developed to minimize the possibility of differences between groups by balancing allocation via a computer algorithm using the Aitchison's compositional distance to calculate the smallest difference between treatment groups, based on the following prognostic factors: age, sex, years of education, parent's or main caregiver's years of education (highest between the mother and father), baseline Y-BOCS score, and baseline CGAS (Fossaluza, Diniz, de Bragança Pereira, Miguel, & de Bragança Pereira, 2009). This randomization procedure was implemented with success in previous studies (Costa et al., 2017; Diniz et al., 2011; Hoexter et al., 2012). The same randomization procedure occurred in both stages of the study and was performed by the study manager, who also allocated participants to treatments. All research staff but the study manager were unaware of the randomization and allocation procedures.

### 2.5. Treatments

Fluoxetine was the SSRI chosen based on the evidence of efficacy and safety for childhood OCD (Geller et al., 2003), due to its wide availability in public health services in Brazil and to a lower cost as compared to other alternatives (e.g., sertraline). In addition, the drops presentation available only for fluoxetine allowed for a very careful dose titration, which is desirable for children. As soon as the dose of 5 mg/day was reached, FLX presentation was switched to pills, to allow for pill counting.

Pharmacological treatment was conducted under the following conditions: (a) appointments with a study psychiatrist every 2 weeks; (b) a phone call by the research assistant in the week between appointments to reinforce compliance with the prescription and check for medication side effects; (c) FLX was administered in doses 10–60 mg/day, depending on clinical improvement and tolerability; (d) adverse events were actively analysed with use of the Systematic Assessment for Treatment Emergent Effects (SAFTEE) (Levine & Schooler, 1986); (e) weight/height were assessed at every appointment. The parent or caregiver was invited to participate in every medical appointment, when general issues regarding OCD diagnosis and treatment could be discussed, but no formal cognitive-behavioural techniques were employed. Concomitant psychotropic medications were permitted as required to treat attention-deficit hyperactivity disorder (ADHD). Subjects had to be stable on psychostimulants for at least 4 weeks before initiating treatment.

CBT was delivered in group format in order to optimize the delivery of the intervention with a small number of trained professionals treating a large number of subjects. Such format it is best suited for public health systems, where potentially cost-effective approaches should be prioritized. Evidence suggests the effectiveness of GCBT to treat childhood OCD (Asbahr et al., 2005; Barrett, Healy-Farrell, & March, 2004; Fischer, Himle, & Hanna, 1998; Martin & Thienemann, 2005; O'Leary, Barrett, & Fjermestad, 2009; Thienemann, Martin, Cregger, Thompson, & Dyer-Friedman, 2001). GCBT was delivered to two different age groups, 7–11 and 12–17-year-olds. Groups were formed by 2–5 subjects and consisted of 14, 100-minute, weekly sessions. Smaller groups (2–3 participants) were allowed along the study in order to reduce the unforeseen burden on those randomized to GCBT, who had to wait for the recruitment and randomization of new participants in order to start treatment. A standardized manual was adapted by the study team from an international reference manual (March & Friesen, 1998), adjusted to group format in a previous study (Asbahr et al., 2005). A second Brazilian CBT manual written in Portuguese by a senior therapist with extensive expertise in OCD (Cordioli, 2008) was used to support the adaptation of certain cultural and language (i.e., expressions and metaphors) aspects. One of the authors (F.R.A.) trained and supervised the therapists on a weekly basis. The main elements of the treatment manual included psychoeducation concerning OCD, cognitive training, exposure and response prevention (ERP) and family psychoeducation. Sessions were delivered in groups exactly as in individual treatment, but each subject had his/her own treatment plan tailored individually, which included symptom hierarchy, OCD mapping, fear thermometer ratings, and cognitive and ERP techniques. Homework tasks were determined for each subject individually at the end of the sessions, and completion of homework was verified at the beginning of the next session.

### 2.6. Statistical analysis

Our main outcome measure was the severity of obsessive-compulsive symptoms, as assessed by the Y-BOCS scores at five-time points (baseline, weeks 7, 14, 21, and 28). A modified intention-to-treat approach was used (Dossing et al., 2016). Patients for whom there were less than three observations available were excluded from the analysis (N = 11). Patients with three or four observations had their measures

completed by means of imputations based on linear regressions, following a regular regression modelling using available data. The proportion of missing values was around 8% and this falls into the standard recommendation of the statistical literature (Molenberghs et al., 2014; Verbeke, Molenberghs, & Beunckens, 2008). The final numbers and functions of our statistical analysis were obtained using data after imputation.

By taking longitudinally the measures for all patients, we have as many time series as the number of patients studied. For each time series, i.e. for each patient, a cubic polynomial function was adjusted (Neter, Kutner, Wasserman, & Nachtsheim, 1996). Having $n$ as our sample size, there are in fact $n$ of such functions in our study. Defining $t$ as the time, for the $i^{th}$ patient ($i$ = 1, 2, …, n) the following growth cubic function is to be adjusted:

$$y_i(t) = \alpha_i + \beta_{i1}t + \beta_{i2}t^2 + \beta_{i3}t^3$$

For each patient, we have one observation in each t = 0, 7, 14, 21 and 28. Hence, each patient across these 5 observations produces its corresponding vector of four coefficients. Then $(\alpha_i, \beta_{i1}, \beta_{i2}, \beta_{i3})$ is the statistic measured for the $i^{th}$ patient. That is, respectively to the four arms of adaptive treatments, AT1, AT2, AT3 and AT4, there should be respectively $n_1$, $n_2$, $n_3$, and $n_4$ of such vectors that are going to be the data used for arms comparison. As the statistic representation of each AT we consider the center of gravity of the set of vectors. Using now this statistic vector, we draw its corresponding cubic function as above. Analyzing the four cubic functions we compare the treatment arms.

The primary analysis compared the two arms formed by the first randomization: FLX x CGBT. In a secondary analysis we compared the four arms resulting from the second randomization of non-responders to initial FLX and GCBT.

In order to be able to provide effect sizes between-groups and within-groups (and respective p-values through the Mann-Whitney and Wilcoxon tests), we performed end-point analyses considering baseline and week 28 as follows: as a measure of improvement we consider $(y_{baseline} + 0.5)/(y_{baseline} + y_{week28} + 1)$, where $y_{baseline}$ and $y_{week28}$ are the corresponding YBOCS observations at baseline and week 28, respectively (Cohen, 1988). Thus, for each patient we have a constant for this measure. The interpretation of this measure is as follows: if it is equal to 0.5, then $y_{baseline} = y_{week28}$ (no change); if it is greater than 0.5, then $y_{baseline} > y_{week28}$ (improvement); or if it is lower than 0.5, then $y_{baseline <} y_{week28}$ (worsening of symptoms).

## 3. Results

### 3.1. Recruitment and retention

A hundred and forty-four subjects were assessed for eligibility and 83 were enrolled in the study and randomized to FLX (n = 43) or GCBT (n = 40). Seventy-two participants completed stage 1, and 63 participants completed stage 2. Dropout rate (lost to follow-up and discontinued intervention) was 13.2% (n = 11) at stage 1, and 14.3% (n = 9) at stage 2. Total dropout rate was 24.1% (n = 20). The only variable associated with dropout status was the presence of comorbid depressive disorder (p = 0.003). First and second randomization and other baseline characteristics did not differ by dropout status. Fig. 1 shows the study flowchart.

### 3.2. Sample characteristics

From August 2010 to December 2013, 144 children were screened and 83 children were included in the study. Forty subjects (48.2%) were male, with a mean age of 11.8 (SD = 3.2) years. Twenty-one patients (25.9%) belonged to the upper socioeconomic class, 44 (54.3%) to the upper-middle and 16 (19.8%) to the lower-middle class. Regarding race, 76 (91.6%) were white, 5 (6.0%) were mixed-race (white/black), 1 (1.2%) was Asian and 1 (1.2%) was black. Prior to study enrolment, 27 patients (67.1%) had received psychiatric treatment, 28 (34.1%) had received psychotherapy treatment, and 3 (3.8%) had received psychiatric inpatient care. The mean number of psychiatric comorbidities in this sample was 2.51 (SD = 1.62). Table 2 describes the baseline socio-demographical and clinical characteristics of the 83 randomized children.

### 3.3. Data on treatment adherence and compliance

In each treatment stage, the number of scheduled GCBT sessions was 16 (including the booster sessions) and the number of in person medical appointments was 8, every other week, with follow-up phone calls in the week between appointments (total of weekly contacts = 16). In the first stage, the mean (standard deviation, range) number of attended GCBT sessions and medical appointments was 11.5 (4.5, 0–14) and 6.6 (2.6, 0–8), respectively. In the second stage, the mean (SD, range) number of attended GCBT sessions and medical appointments was 6.4 (6.3, 0–14) and 4.3 (3.5, 0–8), respectively. The overall frequency of the attended GCBT and medical appointments along the study was 78.6%.

Pill counting was used as an estimate of compliance with the prescribed medication among subjects allocated to pharmacological treatment. All subjects and caregivers were instructed to return the blister cards at every appointment, either empty or containing untaken pills. The number of pills was delivered in the exact amount needed until the next scheduled visit. FLX was prescribed to 53 subjects at some point in the study. Twenty patients returned their blister cards containing untaken pills, corresponding to 1.8% of the prescribed amount.

### 3.4. Clinical response

Among the 40 children randomized to FLX who completed the first stage, 15 (41.7%) responded to treatment (50% reduction in the baseline Y-BOCS criterion) and 21 non-responders were randomized to switch to (n = 9) or add GCBT (n = 12). Among the 43 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).

Table 3 presents, for each treatment group, the descriptive measures of the respective vector of coefficients ($\alpha$, $\beta_1$, $\beta_2$, $\beta_3$). Considering the interquartile interval, [p25%; p75%], there is an intersection between these intervals for each suitable group comparison, indicating no significant difference among FLX and GCBT groups (p = 0.67). In the secondary analysis, no ATS showed superiority in reducing OCD symptoms. Fig. 2 illustrates the substantial reduction of OCD symptoms across the FLX and GCBT groups over time.

Table 4 presents the descriptive statistics of YBOCS severity for all treatment groups. It is also possible to note similarities among the ATSs through time looking at the measures. More importantly, there is a significant clinical reduction of YBOCS score through time irrespective of treatment group.

For end-point analysis: i) between-groups comparisons – the Mann-Whitney p-values are p = 0.67 for FLX x CGBT, p = 0.56 for AT1 x AT3, p = 0.45 for AT1 x AT4, p = 0.42 for AT2 x AT3, p = 0.36 for AT2 x AT4; ii) within-group comparisons – the Wilcoxon p-values are all less than 0.001, showing a statistically significant reduction of Y-BOCS score through time. Table 5 presents the effect sizes between and within-groups and the respective p-values.

### 3.5. Adverse events

The frequency of at least one adverse event among FLX treated participants is presented in table 8. The most common adverse events were: insomnia (40.4%), other sleeping problems (42.3%), sedation (46.1%), and headache (40.4%).

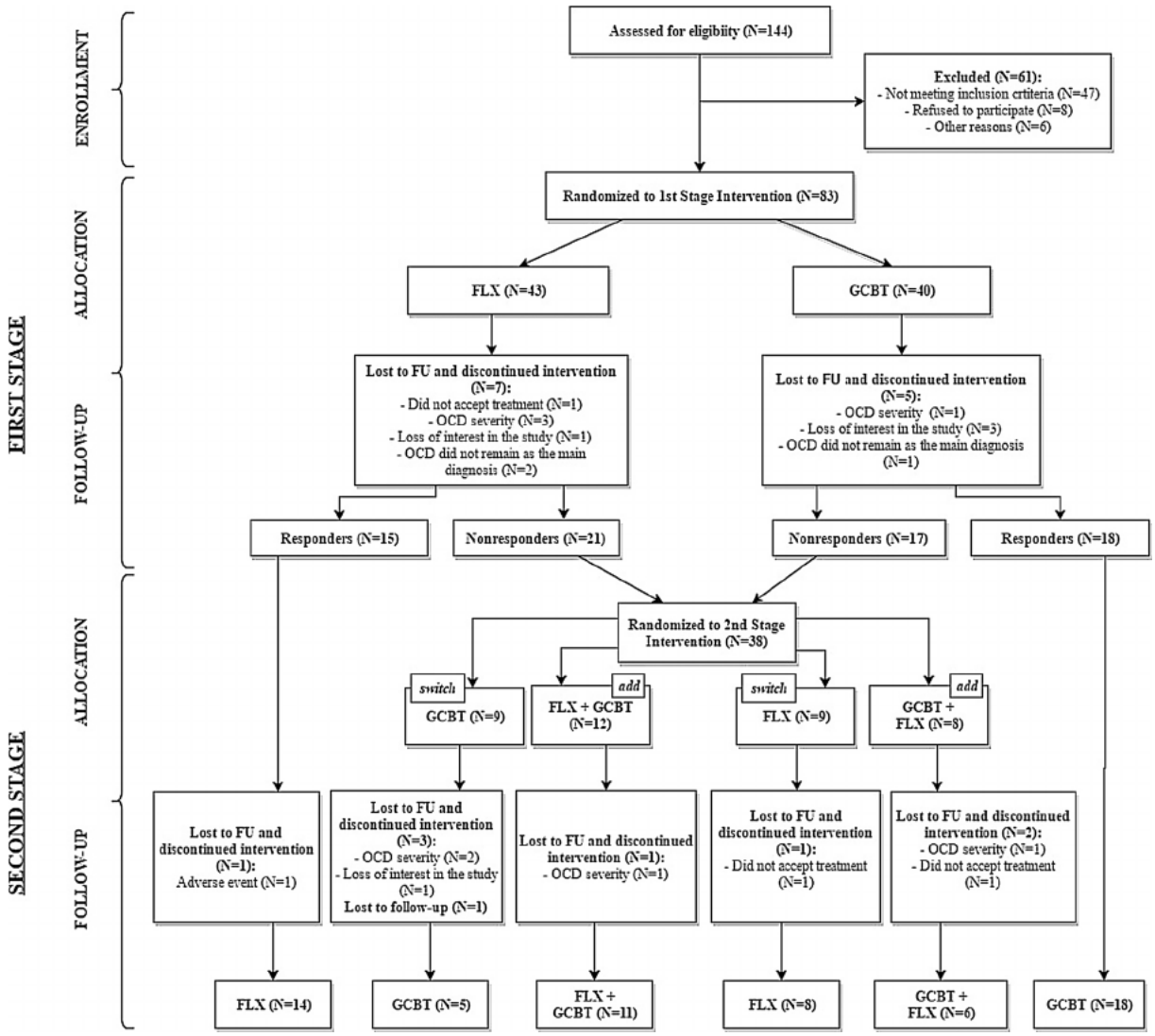


**Fig. 1.** CONSORT diagram.

## 4. Discussion

This study tested the effect of beginning treatment for childhood OCD with fluoxetine or GCBT considering treatment failures over time. Significant reduction of symptoms was observed across both groups, with no significant statistical difference between them. We also compared four adaptive treatment interventions defined by initial treatment and treatment response over time, showing no statistical differences between them. Finally, our data showed that the severity of obsessive-compulsive symptoms, as measured by the YBOCS, continued to decrease after 14 weeks of treatment, suggesting that maintaining treatment over time is key when treating childhood OCD.

To our knowledge, this is the first SMART to address sequential treatments for childhood OCD, with no equivalent studies to which ours could be compared. Nevertheless, there are studies examining the effect of additional strategies for children who did not respond initially to CBT. A randomized trial conducted in Europe comparing sertraline to continued CBT among children and adolescents (N = 54, age range 7–17 years) that did not respond after 14 weeks of CBT found no difference between groups, but large within-group effect sizes (Skarphedinsson et al., 2014). Another study examined the efficacy of combined sertraline and sequential CBT relative to CBT with placebo over 18 weeks in youth with OCD. There were large within-group effects across outcomes for all groups, suggesting no benefit for the combination of sertraline to CBT as compared to placebo (Storch et al., 2013). Our findings are in accordance with these two studies.

### 4.1. Limitations

Our study should be understood in the context of its limitations. Recruitment represented a challenge, despite the high demand for the treatment of mental disorders in Brazil. The absence of other centres to work collaboratively and with homogeneous methodology towards a larger sample also has contributed to this limitation. Second, the treatment dropout rate of 24.1% was higher than that reported in previous trials for childhood OCD (Franklin et al., 2011; POTS Team, 2004) and lower than that reported by Geller et al. (2001). Several reasons may explain the dropout rate, such as the longer duration of our study, and the high rates of comorbid depressive disorder. This association suggests that additional, specific CBT components to treat depressive symptoms may be needed, potentially increasing treatment adherence. Although current evidence does not show depression as a moderator of childhood OCD treatment (Garcia et al., 2010; McGuire et al., 2015), additional studies should further clarify the role of comorbid depression in the treatment of childhood OCD. Lastly, an alternative explanation for the absence of differences among treatments could be related to the limited sample size of our study, since sample size represents a central challenge for SMART studies, where typically

**Table 2**
Estimates and 95% confidence intervals for the parameters (α; β1; β2; β3).

| Coefficients | Groups | min | 2.5% | 25% | median | 75% | 97.5% | max | mean | SD |
|---|---|---|---|---|---|---|---|---|---|---|
| **α** | **FLX** | 14.74 | 16.84 | 24.20 | 25.93 | 29.46 | 35.45 | 36.58 | 26.60 | 4.91 |
| | **CGBT** | 16.46 | 19.66 | 24.94 | 28.15 | 30.06 | 35.34 | 35.71 | 27.53 | 4.□9 |
| | **ATS1** | 14.74 | 16.14 | 23.89 | 25.61 | 29.46 | 35.83 | 36.58 | 25.96 | 5.24 |
| | **ATS2** | 14.74 | 16.14 | 23.89 | 25.61 | 29.46 | 35.83 | 36.58 | 25.96 | 5.24 |
| | **ATS3** | 16.46 | 18.91 | 24.59 | 27.00 | 29.58 | 32.07 | 32.59 | 26.56 | 3.87 |
| | **ATS4** | 21.64 | 21.87 | 25.26 | 27.91 | 29.88 | 35.44 | 35.71 | 27.80 | 3.77 |
| **β1** | **FLX** | −9.31 | −6.86 | −1.96 | −1.23 | 0.11 | 1.91 | 3.01 | −1.31 | 2.17 |
| | **CGBT** | −5.24 | −4.84 | −1.94 | −1.37 | −0.63 | 1.31 | 1.59 | −1.42 | 1.53 |
| | **ATS1** | −9.31 | −7.67 | −2.30 | −1.37 | −0.04 | 2.28 | 3.01 | −1.52 | 2.51 |
| | **ATS2** | −9.31 | −7.54 | −2.18 | −1.26 | 0.03 | 0.70 | 0.89 | −1.63 | 2.27 |
| | **ATS3** | −5.24 | −4.94 | −1.91 | −1.24 | −0.63 | 1.37 | 1.59 | −1.36 | 1.65 |
| | **ATS4** | −5.24 | −4.95 | −2.37 | −1.51 | −0.74 | 0.01 | 0.16 | −1.77 | 1.37 |
| **β2** | **FLX** | −0.25 | −0.25 | −0.04 | 0.04 | 0.12 | 0.46 | 0.78 | 0.06 | 0.18 |
| | **CGBT** | −0.22 | −0.18 | −0.02 | 0.05 | 0.12 | 0.34 | 0.36 | 0.06 | 0.14 |
| | **ATS1** | −0.25 | −0.25 | −0.04 | 0.05 | 0.12 | 0.57 | 0.78 | 0.07 | 0.21 |
| | **ATS2** | −0.11 | −0.09 | −0.03 | 0.04 | 0.11 | 0.55 | 0.78 | 0.08 | 0.18 |
| | **ATS3** | −0.22 | −0.19 | −0.05 | 0.02 | 0.07 | 0.35 | 0.36 | 0.04 | 0.14 |
| | **ATS4** | −0.13 | −0.10 | −0.01 | 0.06 | 0.15 | 0.35 | 0.36 | 0.08 | 0.13 |
| **β3** | **FLX** | −0.02 | −0.01 | 0.00 | 0.00 | 0.00 | 0.01 | 0.01 | 0.00 | 0.00 |
| | **CGBT** | −0.01 | −0.01 | 0.00 | 0.00 | 0.00 | 0.00 | 0.01 | 0.00 | 0.00 |
| | **ATS1** | −0.02 | −0.01 | 0.00 | 0.00 | 0.00 | 0.01 | 0.01 | 0.00 | 0.00 |
| | **ATS2** | −0.02 | −0.01 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| | **ATS3** | −0.01 | −0.01 | 0.00 | 0.00 | 0.00 | 0.00 | 0.01 | 0.00 | 0.00 |
| | **ATS4** | −0.01 | −0.01 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |

FLX = fluoxetine, GCBT = group cognitive-behavioral therapy, ATS = adaptive treatment strategy, ATS1 = start with fluoxetine, if responds remains on fluoxetine, if does not respond switch to GCBT; ATS2 = start with fluoxetine, if responds remains on fluoxetine, if does not respond add GCBT; ATS3 = start with GCBT, if responds remains on GCBT, if does not respond switch to FLX; ATS4 = start with GCBT, if responds remains on GCBT, if does not respond add FLX; min = minimum value, max = maximum value, SD = standard deviation.

**Table 3**
Descriptive analysis of the YBOCS scores at five time points for the primary (FLX X GCBT) and secondary analyses of this SMART.

| Group | Time | min | 2.5% | 25% | median | 75% | 97.5% | max | mean | SD |
|---|---|---|---|---|---|---|---|---|---|---|
| **FLX** | **0** | 15.00 | 15.00 | 24.00 | 26.00 | 29.00 | 35.20 | 37.00 | 26.51 | 5.18 |
| | **7** | 0.00 | 0.90 | 17.00 | 22.00 | 25.00 | 34.50 | 39.00 | 20.41 | 8.26 |
| | **14** | 0.00 | 0.00 | 6.00 | 19.00 | 26.00 | 32.10 | 33.00 | 16.43 | 10.71 |
| | **21** | 0.00 | 0.00 | 8.00 | 15.74 | 21.00 | 29.20 | 31.00 | 14.78 | 8.58 |
| | **28** | 0.00 | 0.00 | 2.00 | 9.00 | 15.06 | 26.20 | 28.00 | 9.77 | 8.22 |
| **GCBT** | **0** | 16.00 | 19.40 | 25.00 | 28.00 | 30.00 | 35.15 | 36.00 | 27.49 | 4.34 |
| | **7** | 3.00 | 6.40 | 17.00 | 21.00 | 24.50 | 27.60 | 31.00 | 20.23 | 6.04 |
| | **14** | 0.00 | 2.55 | 7.50 | 15.00 | 25.00 | 30.00 | 30.00 | 15.83 | 9.33 |
| | **21** | 0.00 | 2.55 | 7.00 | 12.03 | 19.43 | 29.00 | 29.00 | 13.92 | 8.20 |
| | **28** | 0.00 | 0.00 | 5.00 | 10.00 | 15.38 | 26.10 | 38.00 | 10.78 | 8.57 |
| **ATS1** | **0** | 15.00 | 15.00 | 24.00 | 25.00 | 29.00 | 35.80 | 37.00 | 25.80 | 5.45 |
| | **7** | 0.00 | 0.60 | 15.00 | 20.00 | 25.00 | 36.00 | 39.00 | 18.80 | 9.35 |
| | **14** | 0.00 | 0.00 | 3.00 | 13.00 | 25.00 | 29.60 | 32.00 | 13.36 | 11.01 |
| | **21** | 0.00 | 0.00 | 6.00 | 15.00 | 19.39 | 27.80 | 29.00 | 12.67 | 8.67 |
| | **28** | 0.00 | 0.00 | 1.00 | 6.40 | 13.55 | 26.20 | 28.00 | 8.49 | 7.99 |
| **ATS2** | **0** | 15.00 | 15.00 | 24.00 | 26.00 | 28.50 | 35.00 | 35.00 | 25.74 | 5.16 |
| | **7** | 0.00 | 0.65 | 15.00 | 21.00 | 25.00 | 28.35 | 29.00 | 18.52 | 8.23 |
| | **14** | 0.00 | 0.00 | 3.50 | 13.00 | 21.50 | 32.35 | 33.00 | 13.78 | 10.65 |
| | **21** | 0.00 | 0.00 | 6.50 | 12.00 | 20.00 | 26.62 | 31.00 | 13.00 | 8.69 |
| | **28** | 0.00 | 0.00 | 0.00 | 6.00 | 12.00 | 22.75 | 26.00 | 7.63 | 7.64 |
| **ATS3** | **0** | 16.00 | 18.60 | 24.50 | 27.00 | 29.00 | 32.35 | 33.00 | 26.41 | 4.00 |
| | **7** | 3.00 | 5.60 | 16.50 | 21.00 | 23.50 | 26.00 | 26.00 | 19.37 | 5.96 |
| | **14** | 0.00 | 1.95 | 6.50 | 12.00 | 19.50 | 27.70 | 29.00 | 13.00 | 8.54 |
| | **21** | 0.00 | 1.95 | 5.97 | 10.69 | 16.50 | 29.00 | 29.00 | 11.78 | 7.81 |
| | **28** | 0.00 | 0.00 | 4.00 | 9.00 | 14.00 | 26.95 | 38.00 | 9.66 | 8.53 |
| **ATS4** | **0** | 21.00 | 21.63 | 25.00 | 27.50 | 30.00 | 35.38 | 36.00 | 27.62 | 3.89 |
| | **7** | 3.00 | 5.50 | 15.50 | 20.00 | 24.50 | 28.50 | 31.00 | 19.42 | 6.60 |
| | **14** | 0.00 | 1.88 | 6.25 | 10.50 | 19.75 | 30.00 | 30.00 | 13.31 | 9.26 |
| | **21** | 3.00 | 3.00 | 8.00 | 11.87 | 18.75 | 27.38 | 28.00 | 13.07 | 7.25 |
| | **28** | 0.00 | 0.00 | 5.00 | 9.50 | 13.45 | 24.00 | 24.00 | 9.75 | 7.16 |

FLX = fluoxetine; GCBT = group cognitive-behavioral therapy; ATS = adaptive treatment strategy; ATS1 = start with fluoxetine, if responds remains on fluoxetine, if does not respond switch to GCBT; ATS2 = start with fluoxetine, if responds remains on fluoxetine, if does not respond adds GCBT; ATS3 = start with GCBT, if responds remains on GCBT, if does not respond switch to FLX; ATS4 = start with GCBT, if responds remains on GCBT, if does not respond adds FLX; min = minimum value; max = maximum value; SD = standard deviation.

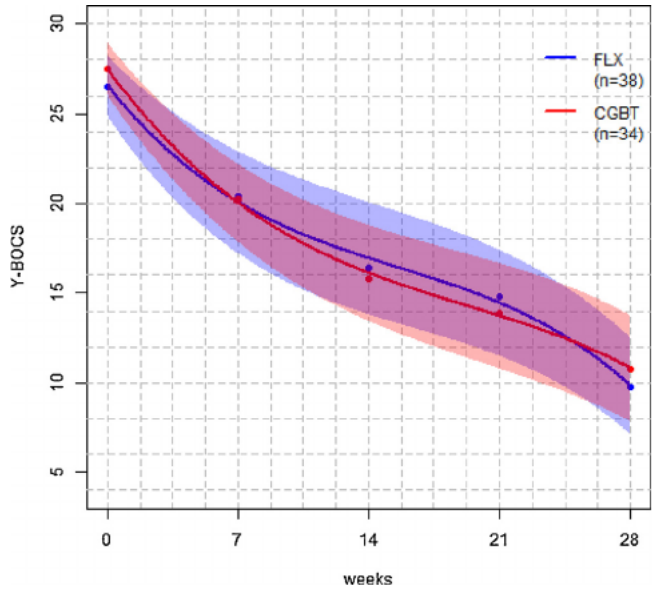


**Fig. 2.** Polynomials of order 3 with respective 95% confidence limits for the initial treatment with fluoxetine (FLX) and group cognitive behavioral therapy (GCBT).

there are multiple comparisons to be made.

### 4.2. Conclusions

Our findings suggest that provision of treatment for childhood OCD could be tailored according to the availability of local resources. Currently, SSRI medications (either alone or in combination with psychotherapy) are frequently used as the initial intervention in youth with OCD despite a more modest efficacy (but greater dissemination) relative to CBT and the potential risk of side effects. Considering the scarcity of mental health services, especially in low and middle-income countries (WHO, 2015), flexibility in the provision of treatment for childhood OCD seems relevant to clinicians and policy makers dealing with limited financial and human resources. Also, in terms of health policy and service planning, our study provides evidence supporting the delivery of GCBT as a valuable low-cost choice for treating OCD in youth. To conclude, in this sample of youth with OCD, beginning treatment with either FLX or GCBT and switching to or adding the other treatment for nonresponders revealed to be equally effective

**Table 5**
Proportion of fluoxetine-treated participants who experienced at least one adverse event during the study (N = 53).

| Adverse event | N (%) |
|---|---|
| **Psychological** | |
| Insomnia | 21 (40.4%)[a] |
| Other sleeping problems | 22 (42.3%)[a] |
| Sedation | 24 (46.1%)[a] |
| Agitation | 20 (38.5%)[a] |
| Fatigue | 15 (28.8%)[a] |
| Malaise | 8 (15.4%)[a] |
| Irritability | 14 (27.0%)[a] |
| Memory problems | 10 (19.2%)[a] |
| Cognitive impairment | 7 (13.5%)[a] |
| **Head** | |
| Dizziness | 9 (17.0%) |
| Headache | 21 (40.4%)[a] |
| Hearing problems | 3 (5.8%)[a] |
| Nasal congestion | 10 (19.2%)[a] |
| Dry mouth | 9 (17.3%)[a] |
| Hypersalivation | 4 (7.7%)[a] |
| **Neuromuscular** | |
| Tics | 7 (13.2%) |
| Tremors | 16 (30.2%) |
| **Gastrointestinal** | |
| Nausea | 12 (22.6%) |
| Stomach/abdominal discomfort | 14 (26.4%) |
| Obstipation | 6 (11.3%) |
| Diarrhea | 8 (15.1%) |
| **Others** | |
| Increased sweating | 12 (22.6%) |
| Increased appetite | 15 (28.3%) |
| Decreased appetite | 20 (40.0%) |
| Weight gain | 20 (40.0%) |
| Weight loss | 20 (40.0%) |
| Dermatitis/allergy | 5 (9.4%) |
| Others | 6 (11.3%) |

[a] 52 valid cases.

**Table 4**
Effect sizes between and within groups considering the first randomization (primary analysis) and the four ATSs embedded in this SMART (baseline to endpoint).

| Between-groups (% reduction of Y-BOCS scores) | | | |
|---|---|---|---|
| Mann-Whitney test | Z | p-value | Effect size |
| FLX x GCBT | −0.43 | 0.67 | −0.05 |
| ATS1 x ATS3 | −0.59 | 0.56 | −0.08 |
| ATS1 x ATS4 | −0.76 | 0.45 | −0.06 |
| ATS2 x ATS3 | −0.82 | 0.42 | −0.11 |
| ATS2 x ATS4 | −0.93 | 0.36 | −0.13 |
| **Within-groups (baseline x end-point)** | | | |
| Wilcoxon test | Z | p-value | Effect size |
| FLX | 6.58 | < 0.001 | 0.76 |
| GCBT | 6.52 | < 0.001 | 0.78 |
| ATS1 | 5.39 | < 0.001 | 0.76 |
| ATS2 | 5.85 | < 0.001 | 0.80 |
| ATS3 | 5.75 | < 0.001 | 0.78 |
| ATS4 | 5.98 | < 0.001 | 0.83 |

FLX = fluoxetine; GCBT = group cognitive-behavioral therapy; ATS = adaptive treatment strategy; ATS1 = start with fluoxetine, if responds remains on fluoxetine, if does not respond switch to GCBT; ATS2 = start with fluoxetine, if responds remains on fluoxetine, if does not respond adds GCBT; ATS3 = start with GCBT, if responds remains on GCBT, if does not respond switch to FLX; ATS4 = start with GCBT, if responds remains on GCBT, if does not respond adds FLX.

treatments.

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