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Systematic Review and Meta-Analysis: Early Treatment Responses of Selective-Serotonin Reuptake Inhibitors and Clomipramine in Pediatric Obsessive-Compulsive Disorder

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Abstract

Objective—We conducted a meta-analysis to examine (1) the time-course of response to selective serotonin reuptake inhibitors (SSRIs) and clomipramine in pediatric obsessive-compulsive disorder (OCD), (2) whether higher doses of SSRIs are associated with an improved response in pediatric OCD, (3) differences in efficacy between SSRI agents; (4) differences in efficacy between SSRIs and clomipramine and (5) whether the time-course and magnitude of response to SSRIs are different in pediatric and adult patients with OCD.

Method—We searched PubMed and CENTRAL for randomized controlled trials comparing SSRIs (or clomipramine) to placebo for the treatment of pediatric OCD and using the Children's Yale-Brown Obsessive-Compulsive Scale as an outcome. We extracted weekly symptom data from trials in order to characterize the trajectory of pharmacological response to SSRIs. Pooled estimates of treatment effect were calculated based on weighted mean differences between treatment and placebo group.

Results—Nine trials involving 801 children with OCD were included in this meta-analysis. A logarithmic model indicating the greatest benefits occurred early in treatment best fit the longitudinal data for both clomipramine and SSRIs. Clomipramine was associated with a greater measured benefit compared to placebo than SSRIs. There was no evidence for a relationship between SSRI dosing and treatment effect, although data was limited. Adults and children with OCD demonstrated a similar degree and time-course of response to SSRIs in OCD.

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Conclusion—These results suggest that the greatest incremental treatment gains in pediatric OCD occur early in SSRI treatment (similar to adults with OCD and children and adults with major depression).

Keywords

Obsessive-compulsive disorder; meta-analysis; serotonin reuptake inhibitors; clomipramine

Introduction

Over the past three decades, we have made advances in the pharmacotherapy of obsessive-compulsive disorder (OCD) in both adult and pediatric populations. Meta-analyses of randomized, placebo-controlled trials in adults with OCD suggest the superiority of selective serotonin reuptake inhibitors (SSRIs) and clomipramine compared to placebo.¹⁻⁸ Clomipramine appears to have a larger effect size than SSRI medications when compared to placebo in meta-analyses of adults with OCD.¹⁻⁸ Nonetheless, clomipramine is not to be considered the first-line pharmacotherapy for OCD because of its poor side-effect profile compared to SSRIs.⁹⁻¹¹ Multiple randomized, placebo-controlled trials have been conducted in children with OCD. A landmark meta-analysis revealed similar efficacy regarding serotonin reuptake inhibitors in the pharmacotherapy of children with OCD compared to adults.¹² This meta-analysis found that SSRIs and clomipramine were significantly more effective than placebo in treating children with OCD and that clomipramine trials demonstrated a larger effect size than SSRI trials when compared to placebo.¹² SSRIs are currently a first-line treatment for OCD along with cognitive-behavioral therapy (CBT).¹³⁻¹⁵ CBT is currently recommended for children with mild to moderate OCD.¹³

Several aspects of current OCD pharmacological treatment guidelines have been well supported by data in adults with OCD: (1) high-dose SSRI treatment is marginally more effective than low-dose treatments (2) a proper trial of an SSRI medication is 2-3 months and (3) antipsychotic augmentation is effective in treatment-refractory OCD.^{16,17} However, these guidelines have largely been adopted for children with OCD without evidence specific to pediatric populations. The objective of this meta-analysis is to examine weekly treatment data in pediatric OCD pharmacotherapy trials in order to (1) examine the time frame and magnitude of treatment response to SSRIs and clomipramine in children; (2) clarify if high doses of SSRIs are more effective than low doses in children with OCD; (3) examine potential differences in efficacy between individual SSRI agents and (4) examine differences in measured efficacy between SSRIs and clomipramine. We will then compare the data in children and adults to determine if the pattern of response to SSRIs is indeed similar between the two age groups. A previous meta-analysis using a similar set of included trials has already demonstrated (1) a greater measured efficacy of clomipramine as compared to SSRIs in placebo-controlled trials and (2) no difference in measured efficacy between different SSRI agents in children with OCD. We will replicate and extend upon the findings in that meta-analysis by comparing these agents using longitudinal data from each trial.

Method

Search Strategy and Study Selection

Eligible trials were searched using the search terms “Serotonin Uptake Inhibitors”[Mesh] OR “Serotonin Uptake Inhibitors” [Pharmacological Action] AND “Obsessive-Compulsive Disorder” [Mesh] on PubMed on May 22, 2013. Results were limited to randomized controlled trials. The reference lists of relevant SSRI meta-analyses on adults were also searched for additional citations of potential trials.^{2,16} From this extensive list, trials were selected on the basis that they were done in children and adolescents. To be included in this meta-analysis, trials had to (1) be randomized; (2) be double-blinded; (3) compare SSRIs or clomipramine to placebo; (4) measure OCD using Children's Yale-Brown Obsessive-Compulsive Scale (CY-BOCS) or change in CY-BOCS over weekly time points¹⁸⁻²⁰ and (5) involve children and/or adolescents in the study population. Henceforth, clomipramine and SSRIs (otherwise known as serotonergic reuptake inhibitors) will be referred to SRIs. Trials were excluded if they (1) did not study OCD; (2) did not examine the efficacy of an SRI; (3) did not include a placebo comparison group; (4) did not use CY-BOCS scales; (5) included adults in the treatment population; (6) provided adjunctive behavioral therapy concurrently to pharmacological treatment; (7) were discontinuation trials. We used CY-BOCS as the exclusive outcome measure, as this measure has been routinely utilized as the primary outcome of SSRI trials in pediatric OCD, and limited longitudinal data was likely to be available for any other rating scale. Selection criteria for and characteristics of adult OCD trials used in comparison are similar and are described in depth elsewhere.²¹

Data Extraction

Included trials provided weekly data points reported in CY-BOCS or change in CY-BOCS with a given SRI.²²⁻³⁰ Some trials explicitly reported the weekly values in a table,^{24,27,30} while others provided a graph of CY-BOCS scores or change in CY-BOCS over time.^{22-26, 28-30} A computer program (Dexter; German Astrophysical Virtual Observatory, University of Heidelberg, Germany) was used to extract weekly data points from these graphs. Dexter is a computer program that allows for accurate data extraction from figures by defining length and scale of x- and y-axes and then assigning values to selected data points on this scale. In order to verify the inter-rater reliability of the extraction technique, we had two investigators blindly extract the data included in this meta-analysis. For the 400 data points included in this meta-analysis (weekly CY-BOCS scores for 8 included trials), only 3 out of the 400 values extracted (CY-BOCS ratings) differed by greater than 1%. The average % difference in CY-BOCS scores extracted between the two raters was 0.4%. Only 1% of all extracted values differed by greater than 0.2 of a CY-BOCS point between the two extractors.

Additional data was collected on type of medication utilized, maximum dosage of medication, duration of trial, number of recruitment sites, publication year, and year that recruitment was started. All medication doses were transformed into imipramine- (or clomipramine-) equivalent doses using previously described methodology.³¹

Data Analysis

The statistical analysis for this trial was adapted from a previously published meta-analysis examining the response curve of SSRIs for major depression and OCD.^{21,32} All analyses were conducted using the statistical software program SAS 9.2 and Microsoft Excel 2007. For each trial at each available weekly time point (up to week 12), we calculated weighted mean difference (WMD) for the difference in CY-BOCS improvement between the medication and placebo group. Weighted mean difference can be interpreted as the true treatment effect of SSRIs and is calculated as the difference (SSRI-placebo) in CY-BOCS score at a given time point.³³ We used generalized estimating equations to examine the effects of trial and treatment, modeling different forms of the treatment effect (see tested models below), accounting for different periods within trials as repeated measures, and defining a new covariance structure for each trial as a random effect (see reference³² for further details on methodology). Each trial's point estimate of WMD was weighted by the number of randomized patients in that trial.

Treatment effects were described in models as (1) constant effect (2) ramp effect (3) square root effect (4) constant and ramp effect (5) logarithmic effect and (6) exponential effect. An autoregressive variance function was then used, and best-fitting models for clomipramine and SSRIs were selected separately using the Aikake information criterion.³² For the primary analysis, SSRI and clomipramine trials were analyzed separately. We also ran the same analyses examining the improvement from baseline in CY-BOCS in the placebo and SSRI treatment groups as outcomes. The shape of the response curve for the true treatment effect of SSRIs (SSRI improvement- placebo improvement) may differ from the actual improvement in the SSRI or placebo groups that includes other non-specific effects such as natural course and variation in the disease, regression towards the mean, other time effects and unidentified parallel interventions.³³

Once the best-fitting model of response trajectory was established for WMD, we examined several additional questions in secondary analyses to examine the effects of salient trial features on the response curves to SRIs in pediatric OCD. Specifically, we examined the effects of type of SSRI (e.g. fluoxetine, fluvoxamine, sertraline, paroxetine), SSRI dosage, year of trial publication, start date of trial recruitment, and number of trial recruitment sites. The measured efficacy of antidepressant medications in pediatric depression has been previously demonstrated to be associated with publication year and number of recruitment sites.^{34,35} Participants with OCD enrolling in later trials were also less likely to be treatment naïve and more likely to have greater diagnostic complexity. In these models we added both a main effect of the variable of interest and an interaction between the variable of interest and study week in the models. If main effects were non-significant, they were eliminated from the model (as the variables of interest were unlikely to cause significant differences between medication and placebo at baseline). When examining the effects of dose, we additionally examined models taking into account the possibility that the effect of dose would be delayed (as it typically takes 2-4 weeks to titrate to the maximum SSRI dose in OCD trials). We explored dose effects that started at baseline, week 2, week 4, or week 6 by adding a main effect of a dummy variable indicating whether the time point was greater than or equal to the week of interest and added that dummy variable to the interaction term to

indicate at what point that term would contribute to the model. We additionally examined the difference in response curves between (1) SSRIs and clomipramine in children and (2) SSRIs in children and adults using similar methodology. We compared to the efficacy of SSRIs in children to previously collected similar data in a recent meta-analysis of adults.²¹ Methodology for selection and analysis of adult SSRI OCD trials were nearly identical to that performed in this meta-analysis, except adult trials were included and trials involving children were excluded.²¹

Results

Included Trials

Figure 1 depicts the procedure for selection of trials. We identified 9 trials of SRIs involving 801 children and adolescents that were eligible for inclusion in this meta-analysis. Table 1 depicts the characteristics of included trials. Seven trials examined efficacy of SSRIs, and 2 trials examined the efficacy of clomipramine. Only 4 different SSRIs have been studied in placebo-controlled trials in children: fluvoxamine (k=1, n= 120), fluoxetine (k=3, n= 159), paroxetine (k=1, n=203), and sertraline (k=2, n=243). Table S1 (available online) describes the characteristics of trials of SSRIs utilized in the adult comparison group.²¹

Time Course of SSRI Response in Pediatric OCD compared to Placebo

Overall, seven trials with a total of 725 participants (placebo: n= 351 and SSRI: n=374) provided data for analysis across multiple weekly points to assess the trend of OCD symptom improvement (Table 1). The actual (pooled) weighted mean differences in CY-BOCS scores per week for all SSRI trials is shown in Figure 2A. A significant benefit of SSRI compared to placebo was observed as early as 2 weeks after the initiation of treatment in pediatric OCD. Over 85% of the improvement observed on SSRI compared to placebo in pediatric OCD trials was observed by week 2.

Based on the Akaike information criterion, the best fitting model for treatment response to SSRIs was a logarithmic model. A logarithmic model indicates that improvement in OCD symptoms compared to placebo was greatest initially, and the rate of improvement compared to placebo declined over successive weeks. The estimate of treatment effect for SSRIs compared to placebo in the best-fitting logarithmic model was 2.25 (95% CI: 1.79-2.72); $p < .001$. The best-fitting treatment response curve of SSRIs vs. placebo in pediatric OCD over time is shown in Figure 2B.

The logarithmic model was significantly better than the alternative models with a constant and ramp effect ($\chi^2=8.8$, $p < .001$), a constant effect ($\chi^2=23.2$, $p < .001$), a ramp effect ($\chi^2=30.5$, $p < .001$), and an exponential effect ($\chi^2=61.8$, $p < .001$). The logarithmic model had a better fit than model with a square root function ($\chi^2=1.7$, $p=.19$), but not to a statistically significant degree. A model using a square root transformation of week is associated with a similar decreasing treatment effect with time as the logarithmic model.

Logarithmic models also provided the best fit for describing the improvement from baseline in CY-BOCS in the placebo and SSRI treatment groups. Figure 2C provides data from meta-

analysis of individual time point data in placebo and SSRI treatment groups, and Figure 2D depicts the best-fit model for improvement in CY-BOCS from baseline in each group.

Effects of Different SSRI Agents

Models failed to demonstrate any significant differences between individual SSRI agents, consistent with previous literature.¹² There was no significant difference between fluoxetine, fluvoxamine, sertraline, and paroxetine.

Effect of SSRI Dose

Meta-analysis demonstrated no effect of maximum SSRI dosing on therapeutic response in pediatric OCD. In the best fit model, there was neither a significant effect of time or of the interaction of dose with time ($\log[\text{week}+1]=0.40$ [95%CI: -3.48-2.67], $p=.79$; $\text{interaction}=0.005$ [95%CI: -0.007-0.017], $p=.38$). Figure S1 (available online) depicts the non-significant improvement in SSRI response with maximum titrated dosing in pediatric OCD. Models in which the effects of SSRI dose were delayed did not improve the overall fit of the model.

Effect of Publication Year

Later publication year was associated with significantly decreasing treatment effect of SSRI compared to placebo. There was a significant effect of time and interaction between time and publication year in the best fit model ($\text{interaction}=-0.22$ [95% CI: -0.41 to -0.03]; $p=.02$; $\log[\text{week}+1]=444$ [95% CI: 64-824] $p=.02$). Benefits of SSRIs compared to placebo became negligible in trials published towards the end of the date range of SSRI trials for pediatric OCD. Figure S2A (available online) depicts the declining measured efficacy of SSRIs compared to placebo by publication year.

Effect of Trial Start Date

Meta-analysis demonstrated no significant association between recruitment start date and measured efficacy of SSRI pharmacotherapy ($\text{interaction}=-0.12$ [95% CI: -0.24 to 0.01]; $p=.06$; $\log_e[\text{week}+1]=237$ [95%CI: -20 to 494], $p=.06$) (Figure S2B, available online). However, there was a trend towards trials with a later recruitment start date demonstrating smaller benefits of SSRIs ($p=.06$).

Effect of Number of Trial Sites

The number of recruitment sites in pediatric SSRI trials was not significantly associated with measured treatment effects of SSRIs compared to placebo ($\text{interaction} = 0.006$ [95% CI: -0.05 to 0.06]; $p = .8$; $\log[\text{week}+1] = 0.79$ [95% CI: -0.38 to 1.98]; $p = .17$).

Comparison of SSRI Response in Children Compared to Adults with OCD

Meta-analysis demonstrated no significant difference between SSRI response in children and adults with OCD. The best-fit model indicated a significant effect of time ($\log[\text{week}+1] = 1.33$ [95% CI: 1.13 to 1.54]; $p<.0001$) and children demonstrated a lesser response compared to adults, but not to a statistically significant degree ($\text{interaction}=-0.41$ [95% CI:

-0.93 to 0.1]; $p=.11$). Figure S3 (available online) depicts the SSRI response compared to placebo in adults and children with OCD.

Time Course of Clomipramine Response in Pediatric OCD Compared to Placebo

Overall, only 2 trials with a total of 76 participants (placebo $n=37$, clomipramine $n=39$) provided data for analysis across multiple weekly points to assess OCD symptom improvement using clomipramine. The actual (pooled) weighted mean differences in CY-BOCS scores per week for all clomipramine trials is shown in Figure 3A. Over 75% of the improvement in OCD symptoms observed with clomipramine compared to placebo in pediatric OCD trials was evident by 2 weeks.

Based on the Aikaike information criterion, the logarithmic model remained the best fit model. A logarithmic model indicates that improvement as measured by a change in CY-BOCS was greatest initially, followed by a declining rate of improvement in successive weeks. The root effect model, which also models a decreasing treatment effect with time, did not separate statistically from the logarithmic model ($\chi^2=1.6$, $p=.2$). A model with a constant and ramp effect ($\chi^2=1.8$, $p=.17$) also did not statistically separate from the logarithmic model. The logarithmic model had a significantly better fit than the constant effect ($\chi^2=3.8$, $p=.05$), the ramp effect ($\chi^2=15.6$, $p<.0001$), and an exponential effect ($\chi^2=32.5$, $p<.0001$) models. The best fitting treatment response curve comparing clomipramine to placebo over time is shown in Figure 3B ($\log[\text{week}+1]=3.03$ [95% CI: 1.94 to 4.13], $p<.0001$).

Comparison of Treatment Effect of Clomipramine to SSRIs in Children with OCD

Meta-analysis demonstrated a large and statistically significant difference favoring clomipramine compared to SSRIs. In the model there was a significant effect of time on the improvement in OCD symptoms experienced on both medications compared to placebo ($\log[\text{week}+1]=0.90$ [95% CI: 0.38-1.41], $p=.001$) and a significantly larger effect of clomipramine compared to SSRI (interaction=2.22 [95% CI: 0.4-4.03], $p=.01$). Figure 4A depicts the actual improvement of pediatric participants with OCD on clomipramine and SSRIs relative to placebo. Figure 4B depicts the best fit model of the comparative efficacy of clomipramine and SSRIs relative to placebo.

Discussion

Our meta-analysis demonstrated several important findings in the pharmacotherapy of pediatric OCD: (1) benefit from SSRIs and clomipramine was greatest in the first few weeks of treatment in pediatric OCD and was minimal after the 6th week of treatment similar to the SSRI response pattern observed in depression^{32,36}; (2) there were no significant differences in magnitude of response to serotonergic medications between children and adults with OCD; (3) there were no significant differences in treatment responses between SSRI agents; but (4) clomipramine demonstrated a significantly greater response when compared to placebo than SSRIs; and (5) there is no evidence for increased benefit with higher maximum dosages of SSRIs as compared to lower maximum dosages in the pediatric OCD trials.

Previous meta-analyses of SSRIs in adults with OCD demonstrated a significant dosing effect of SSRIs, demonstrating that higher doses of SSRIs were associated with a significantly greater therapeutic response.^{16,21} We did not replicate this finding in children. Higher doses of SSRIs were associated with a marginally and not statistically significantly increased SSRI response in pediatric OCD. We believe that the lack of dosing effect seen in children with OCD may be attributable to the design of trials and the paucity of trials in pediatric OCD. Pediatric OCD studies, in contrast to adult OCD trials, were performed to demonstrate a treatment benefit at the maximum tolerated dose of SSRIs rather than being fixed-dose finding trials that examined the efficacy of agents across multiple different dosing regimens. Six out of seven pediatric OCD trials examining SSRIs used near maximally recommended doses of SSRI medications. These six trials involved 98% of participants included in our meta-analysis examining SSRI efficacy. Also, there are very few pediatric OCD trials compared to the adult literature. Therefore, our meta-analysis had limited power to replicate the SSRI dosing effect observed in adult OCD trials in pediatric OCD. Another possibility is that there exists no dose response relationship for SSRIs in pediatric OCD. We similarly did not demonstrate a dose response relationship in pediatric depression.³⁷ Reduced tolerability of high dose SSRI pharmacotherapy in children due to side-effects (possibly behavioral activation, irritability, anxiety, insomnia etc.) could explain the absence of a dosing effect.

Our meta-analysis also demonstrated a larger benefit of clomipramine than SSRIs when both agents were compared to placebo. Our finding of increased measured efficacy of clomipramine compared to SSRIs is consistent with several previous meta-analyses in children and adults with OCD.^{1,5,7,12} These results are not surprising given that the list of included trials in this meta-analysis is nearly identical to a previous meta-analysis in pediatric OCD with similar findings using endpoint data only.¹² Despite this finding, there are several reasons to be skeptical that clomipramine is more effective than SSRIs for OCD. Specifically, clomipramine trials were performed earlier on likely less refractory pediatric patients with OCD, and this could account for much of the increased efficacy. When meta-analysis was restricted to examining SSRI agents, there was a significant relationship between measured efficacy of SSRIs and publication year (and a trend towards a significant association with trial start date), suggesting that there may be diminishing measured effects of serotonergic agents with time. This result suggests that children enrolled in later pediatric OCD trials were more refractory to these medications. This result is not surprising considering that many families enrolled in later SSRI placebo-controlled trials would have previously failed to achieve symptom relief on other similar medications available by prescription. Clomipramine, by contrast, was the first effective agent available for OCD, and trials of this agent would have thus enrolled a study population completely naïve to serotonergic agents. Arguing against these explanations is that the benefit of clomipramine over SSRIs was still significant when publication year and/or dose were controlled for in the meta-analysis. Additionally, there is a more significant side-effect burden with clomipramine: weight gain, anticholinergic side effects, and arrhythmias.⁹⁻¹¹ These side effects not only affect compliance but also decrease the effectiveness of blinding in trials (e.g. if the child has side-effects on the pill, both the family and the study investigator may be more likely to believe that the participant is on active medication). This additional bias in

the clomipramine trials may inflate their estimates of efficacy. The definitive way to examine the relative efficacy of clomipramine and SSRIs would be through head-to-head trials, and thus far none of the few trials examining this issue demonstrated superiority of clomipramine.¹² Nonetheless, regardless of the actual superiority of clomipramine over SSRIs in pediatric OCD, we would not recommend it as the first-line pharmacological treatment for OCD because of its poor tolerability. Additionally, current practice guidelines recommend using CBT monotherapy in mild-to-moderate pediatric OCD cases and combined (SSRI and CBT) treatment for more severe pediatric cases.¹³

There were several limitations to our meta-analysis, including the small number of placebo-controlled trials in OCD, which limited our ability or power to conduct some comparisons, especially when examining clomipramine. Furthermore, it is possible that the shape of response curve for SSRIs and clomipramine over time is in some way determined by the design of the trials that contributed the data. In particular, the user of last observation carried forward analysis to account for missing data, which has become standard in trials of pharmaceutical treatments for depression and was used in some of the trials in this study, could make a constant effect appear logarithmic. Also, the shape of the response curve was likely influenced by the varying titration schedules of included trials. Nonetheless, this limitation would not detract from the observation that the greatest incremental treatment gains were observed early in SRI pharmacotherapy. We also had limited ability to examine the dose effects of SSRI within pediatric populations due to the paucity of trials and the absence of fixed-dose ranging studies in the pediatric population. Many participants also did not receive the maximal possible dose administered in the trials. Additionally, the generalizability of the pediatric OCD clinical population (with exclusion for several psychiatric comorbidities) to the clinical population of pediatric OCD is unclear. Increased psychiatric comorbidity has been previously associated with poor treatment response to SSRIs in pediatric OCD.³⁸ Lastly, uncontrolled, open-label extension phases of SSRIs for pediatric OCD have suggested that there may be continued long-term benefits of medication beyond the initial timeframe observed in randomized controlled trials.³⁹ Using data from this meta-analysis, we cannot rule out the possibility that children with OCD may be some additional improvement in symptoms that occurs beyond the timeframe of the acute treatment trials.

This meta-analysis establishes that in pediatric OCD, SSRI treatment gains are greatest early in treatment and detectable statistically within 2 weeks after the initiation of medication. This logarithmic pattern of SSRI response is similar to that of children and adults with major depressive disorder^{32,37} and OCD.²¹ Current American Academy of Child and Adolescent Psychiatry (AACAP) Practice Parameters in pediatric OCD define an adequate SRI trial as a minimum of 10 weeks in duration with at least 3 weeks at a maximum tolerated dose.¹⁵ The AACAP Practice Parameters are similar to the American Psychiatric Association guidelines and indicate that pharmacotherapy with SSRIs is first line (along with CBT) and should be continued for 8-12 weeks, including 4-6 weeks at a maximum tolerable dose.¹⁵ CBT is the preferred initial treatment option in children with mild to moderate OCD.¹⁵ The meta-analysis may possibly suggest that pharmacotherapy trials of 8-12 weeks may not be necessary and that if a child shows no improvement with SRI treatment, trial durations could potentially be shorter. However, before a change in guidelines is considered, there needs to

be more OCD pharmacological research that focuses on the prognostic utility of early SSRI response data on individual patient outcomes. Previous adult studies have suggested that early improvement with SSRIs and clomipramine is associated with response in short-term trials.^{40,41} Additionally, more effective, evidence-based treatments for SRI-refractory pediatric patients with OCD are needed, as there is limited guidance for further treatments once SRIs and CBT prove unhelpful.¹⁴ Further research is needed to identify these novel agents.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Selection of studies. Note: OCD = obsessive-compulsive disorder; RCT = randomized controlled trial; SSRI = selective serotonin reuptake inhibitor.

Figure 2.

Selective serotonin reuptake inhibitor (SSRI) response in obsessive-compulsive disorder (OCD). Note: Differences in CY-BOCS ratings across time between patients treated with SSRIs and placebo. A) Weighted mean difference in CY-BOCS between SSRIs and placebo at time points. Error bars represent standard error. B) Best-fit model (logarithmically decreasing treatment response) for the weighted mean difference between groups. Dotted lines represent 95% CIs.

Figure 3.

Clomipramine response in obsessive-compulsive disorder (OCD). Note: Differences in Children's Yale-Brown Obsessive-Compulsive Scale (CY-BOCS) ratings across time between patients treated with clomipramine and placebo. A) Weighted mean difference in CY-BOCS between clomipramine and placebo at time points. Error bars represent standard error. B) Best-fit model (logarithmically decreasing treatment response) for the weighted mean difference between groups. Dotted lines represent 95% CIs. These figures are based on data from 2 studies involving 76 participants.

Figure 4.

Comparison of clomipramine and selective serotonin reuptake inhibitor (SSRI) response in obsessive-compulsive disorder (OCD). Note: A) Comparison of weighted mean difference in Children's Yale-Brown Obsessive-Compulsive Scale (CY-BOCS) of clomipramine and SSRIs when compared to placebo at time points. Error bars represent standard error. Clomipramine response is depicted with a solid line. SSRI response is depicted with a dotted line. B) Best-fit model (logarithmically decreasing treatment response) for the weighted mean difference between SSRIs and clomipramine compared to placebo. Clomipramine was associated with a significantly greater treatment effect than SSRIs.

Table 1
Characteristics of 9 Randomized, Controlled Trials Used in a Meta-Analysis of Pharmacotherapy Responses Over Time for Pediatric Obsessive-Compulsive Disorder

Author	Year	N ^a	Medication	Dose ^b	Imipramine Dose Equivalent (mg)	Duration	Titration schedule	Number of Sites	Industry (I) or Publically Funded (P)	Recruitment start year
March ²⁹	1990	16	Clomipramine	200	240	10	Initial dose 25mg for 4 days then 25mg BID for 3 days then flexible titration	1	I	Not reported
Riddle ³⁰	1992	13	Fluoxetine	20	100	8	Fixed 20mg dose	1	P	1988
DeVeau-Geiss ²³	1992	60	Clomipramine	200	200	8	Initial dose 25mg for 4 days titrated to 75-100mg by end of week 2 then flexible titration	5	I	1991
March ²⁸	1998	187	Setraline	200	240	12	Minimum starting dose was 25 mg. Increased by 50 mg weekly to maximum daily dose by week 4	12	I	1991
Riddle ²²	2001	120	Fluvoxamine	200	200	10	Starting dose 25 mg. Increased by 25 mg every 3 or 4 days to maximum daily dose of 200 mg by week 3	17	I	1991
Geller ²⁵	2001	103	Fluoxetine	60	300	13	Initial dose 10 mg daily, increased to 20 mg daily by week 3. Flexible dosing thereafter.	21	I	1999
Liebowitz ²⁷	2002	43	Fluoxetine	80	400	16	Initial dose 20 mg, increased to 40 mg daily at week 3 and 60mg daily at week 5, possible further titration to 80mg after week 6.	2	I/P	1991
Geller ²⁶	2004	203	Paroxetine	50	250	10	Initial dose 10mg daily, increased in 10mg increments every week to maximal dose.	36	I	2000
POTS study ²⁴	2004	56	Setraline	200	240	12	Initial dose 25 mg/daily, increased in 25mg increments to maximum dose by week 6	3	P	1997

Note: CY-BOCS = Children's Yale-Brown Obsessive Compulsive Disorder Scale; SSRI = Selective Serotonin Reuptake Inhibitor.

^aMaximum number of participants randomized to either an SSRI or placebo group in the respective study. Participants randomized to non-SSRI treatment groups were not included in this total estimate.

^bRepresents the fixed dose or maximum dose to which a study medication was titrated if study had flexible dosing regimen.