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www.elsevier.com/locate/psychres

PII: S0165-1781(17)31733-X
DOI: https://doi.org/10.1016/j.psychres.2017.12.034
Reference: PSY11070

To appear in: *Psychiatry Research*

Received date: 21 September 2017
Revised date: 29 November 2017
Accepted date: 13 December 2017

Cite this article as: Cynthia Turner, Beth O'Gorman, Archana Nair and Richard O'Kearney, Moderators and predictors of response to cognitive behaviour therapy for pediatric obsessive-compulsive disorder: A systematic review, *Psychiatry Research,* https://doi.org/10.1016/j.psychres.2017.12.034

Moderators and predictors of response to cognitive behaviour therapy for pediatric obsessive-compulsive disorder: A systematic review.[1]

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Abstract

We report a systematic review of moderators of CBT efficacy for pediatric OCD relative to other treatments. CENTRAL, MEDLINE, EMBASE, CINAHL, and PsycINFO were searched for RCTs reporting on effect moderation for CBT outcomes. Five studies (N = 365) examined 17 variables with three significant moderators identified. Compared to pill-placebo, CBT monotherapy was not effective for children with a family history of OCD but was for those without a family history. For children with a family history, CBT plus sertraline efficacy was attenuated but remained significant. For children with tics, CBT but not sertraline remained superior to pill-placebo. For non-responders to initial treatment with CBT, continuing CBT was inferior to commencing sertraline for those with tics but was not different for those without tics. A supplementary review identified older age, symptom and impairment severity, co-morbidity and family accommodation as consistent predictors of a

[1] Registered systematic review: PROSPERO 2014:CRD42014009386

poorer outcome to CBT. Current evidence for moderation effects is post-hoc, from single RCTs, has small Ns and requires replication. The review identifies family history of OCD and the presence of tics as factors requiring further examination in properly conducted trials and about which clinicians need to show care in their treatment recommendations.

Keywords: pediatric OCD; CBT; effect moderators; predictors.

1. Introduction

Obsessive-Compulsive Disorder (OCD) in children and youth is a serious mental disorder associated with significant distress and marked interpersonal, academic and occupational impairments (Piacentini et al., 2003), which over time can have major detrimental impacts on children's psychosocial development and on their families' ongoing well-being (Stewart et al., 2004*)*. While SSRI medication and cognitive behavioural therapy with exposure and response prevention (CBT), either combined or alone, have been identified as efficacious initial treatments (Ivarsson et al., 2015; March et al., 2004; O'Kearney et al., 2010), CBT is usually considered the treatment of choice when available because of its lower risk-to-benefit ratio compared to medication and higher acceptability by patients and their families.

There is significant variability in how well children and adolescents with OCD respond to CBT with a notable proportion showing limited clinically significant benefits. Less than half (39%) of those treated with CBT show adequate remission of their symptoms (De Haan, 2006; March et al., 2004). This compares to about 22% remission rates following monotherapy with an SSRI, and 54% when CBT is combined with an SSRI (March et al.,

2004). These rates of treatment response highlight the importance of improving the capability of clinicians to provide recommendations which optimise the initial treatment for a particular patient. Currently, practice guidelines recommend that CBT be offered as the first line treatment for patients with mild to moderate symptom severities and that combined CBT and SSRI be used as the initial treatment in more severe cases (American Academy of Child and Adolescent Psychiatry, AACAP, 2010), or that an SSRI be added when the patient has not shown an adequate response to CBT alone (National Institute for Health and Clinical Excellence [NICE], 2005). While the severity of the OCD symptoms may be one factor guiding treatment recommendation, the decision should be based primarily on evidence about which pre-treatment characteristics of the patient or his/her context moderate the chances of the patient responding better to one treatment compared to another in randomised controlled trials.

There are increasing calls for this question to become a central one in the design and analysis of controlled trials of treatments for mental disorders including those in children and adolescents (Bloch, 2014; Kraemer et al., 2006). Not only can evidence about factors which differentiate subgroups of children with OCD who respond better to one treatment compared to another optimise treatment outcomes, it can also prevent delivery of less or unhelpful, or even harmful treatments to individual patients. Despite these calls, empirical work in regard to outcomes for CBT for pediatric OCD has overwhelming focused on factors which are associated with the strength of the CBT treatment effect, i.e. predictors, with several reviews integrating the evidence about predictors of treatment outcome (Ginsburg et al., 2008; Torp et al., 2015). Only one study (McGuire et al., 2015) has previously attempted to bring together some of the evidence about moderators in a review and analyses of factors which predict the relative treatment efficacy of CBT compared to some comparators. This study used between study variability in the average value of possible moderators to estimate, using meta-

regression, the strength of the association between these factors and study effect size. It found a positive association between the percentage of children and adolescents in the study with co-occurring anxiety disorders and the effect of CBT relative to a waitlist control. The study also found a positive association between the percentage of children and adolescents in the study with co-morbid Tourette's or Tic disorder and the benefits of CBT relative to treatment with relaxation training. While informative, these results are limited because studies examining factors which may moderate the comparative efficacy of CBT compared to other treatments with demonstrated efficacy, particularly medication or combined CBT plus medication, were not included in the analysis. Choice of comparator is crucial for clinicians in weighing up the evidence about the initial treatment of a child with OCD. In addition, while McGuire et al., (2015) included some clinically useful potential moderators such as initial OCD severity and co-morbidity, it also considered factors such as study quality and number of sessions which are not outcome moderators and cannot contribute to clinical decisions about which children may respond better to CBT and which may not (Kraemer et al., 2006).

The approach we take here is to use systematic review methodology to identify all RCT trials of CBT compared to any comparator which reported on a pre-treatment characteristic of the participants, their illness, or the context, and tested this characteristic as a moderator of CBT efficacy relative to the comparator. We document these findings and pool them when appropriate. This method has advantages for clinical decision making over the use of meta-regression particularly when there may be only a small number of studies with relevant data as in the McGuire et al. (2015) review. First, it preserves the temporal connection of the moderators to the treatments and their outcomes and the control for individual-level confounds of comparative treatment effects provided by randomisation in the initial study design. Second, each study analysis provides an independent estimate of the

strength of the moderator effect as well as, for significant estimates, the strength of the association between the moderator and outcome for the CBT and comparator groups. This allows consideration of the consistency of any finding across studies as well as predictions about the size of the relative response to CBT for individual patients with the moderator characteristic. Our approach also avoids meta-regression's inherent limitations for drawing inferences about how individual children might response to CBT (Thompson & Higgins, 2002). These problems include little between-study variability in the moderator tested, over interpretation of very small sets of studies and invalid conclusions because the relationship between treatment response and the average level of a moderator across trials may not be the same as its relationship with between-individual variability in the moderator s within an RCT ('aggregation bias'; Aquinis et al., 2005; Higgins, 2001; Thompson & Higgins, 2002).

In addition to its value in treatment planning, evidence about moderators of treatment response can assist researchers in gaining further understanding of possible causal models of the different mechanisms of action of treatments for pediatric OCD. Contemporary models of the mechanism by which the key component of CBT (exposure with response prevention) has its effect propose that inhibitory learning processes are critical in the development of non-threat associations during exposure (Craske et al., 2014). Identifying factors which moderate these processes relative to medication or combined CBT plus medication could provide important clues regarding how certain child characteristics relate to fear acquisition and new non-threat learning, and how to adapt and integrate psychological and pharmacological treatments for OCD to produce lasting benefits. It also allows hypotheses about mechanisms to be tested in RCTs with children and adolescents selected for the potential moderators.

Another source of information about possible moderators is the evidence about pre-treatment factors which are consistently associated with treatment outcome (i.e. predictors). While evidence about non-specific predictors has less relevance to evidence-based clinical

decision-making about the choice of initial treatment, identifying predictors of treatment response can provide a focus for subsequent research on possible moderators, and on components of CBT which require further development or adaption for specific groups of patients in order to optimise outcomes (Kraemer, et al., 2006). We therefore include a supplementary review of the evidence of pre-treatment factors which predict CBT outcome to ensure that recommendations for future work on moderators of CBT outcome include all potential factors, and not only those which have been investigated in moderator studies.

1.1 Aims

The current study provides the first synthesis of evidence in a systemic review addressing the question: For children and youth under 18 years of age with OCD, which factors moderate treatment outcome for CBT relative to a comparator in RCTs? The review was supplemented by a systematic review of the evidence about pre-treatment factors which are associated with response to CBT. , 2 Method

2.1 Study design and protocol

The review was undertaken using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (PRISMA; Moher et al., 2009). A review protocol was registered with the Prospero International prospective register of systematic reviews (O'Gorman et al., 2014; Prospero 2014:CRD42014009386).

2.2 Eligibility criteria

Type of studies.

Two types of studies were included. 1) To address questions related to the moderation of CBT efficacy, eligible studies had to be RCTs or controlled trials of CBT with quasi-randomised allocation of participants which included an individual CBT arm. Eligible studies had to report on measures of moderators at baseline (prior to randomisation) and

examine these statistically as moderators of the effect of CBT relative to a comparator. 2) To address questions related to factors which predict CBT treatment effects, non-controlled trials of CBT were also included. Eligible studies had to measure the predictor at baseline (prior to randomisation) and report the association of these measures with the size of CBT effect post-treatment, at follow-up or across time.

Types of participants.

Participants in eligible studies for both moderator and predictor analyses had to be children or youth aged 18 years of age or less at time of study entry, who were diagnosed with OCD using explicit criteria described in the study. Studies had to include an intervention nominated as CBT monotherapy which included ERP as a component. RCTs were included regardless of type of comparator (active medication, combined CBT plus medication, pill placebo, other psychotherapy, wait list or treatment-as-usual). Studies of efficacy of medication were included, as well as studies which combined CBT and medications, as long as there was a CBT monotherapy arm.

2.3 Measures

Moderator or predictor variables were any study-defined characteristics of patients, their disorder or their environment (family or community) measured at base-line that was examined statistically in regard to the following. For moderators, how they interacted with the between group intervention effect on a primary OCD outcome, or how they influenced the effect size between CBT and a comparator (standardised mean difference or relative risk for the primary outcome). For predictors, how strongly they were associated with the primary outcome for the CBT group.

Primary outcome measures included: a) post and follow-up total OCD severity measured by the gold standard CY-BOCS; and b) percentage reductions on total CY-BOCS severity prior to post-treatment or prior to follow-up.

2.4 Search Methods for identification of studies

Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, CINAHL, and PsycINFO were searched until June 2017 using search terms: "Obsessive compulsive disorder"; "child" (including the terms "adolescent", "pediatric", and variants thereof); and "cognitive behaviour therapy" (including psychotherapy, behaviour therapy, exposure therapy, and cognitive therapy). Hand-searching identified theses, registered trials and conference proceedings which were accessed by contacting the study author or the clinical trial databases.

The search results were merged using reference management software and duplicate records of the same report were removed. Two reviewers examined titles and abstracts to remove obviously irrelevant reports. The full text of the potentially relevant reports were retrieved and multiple reports of the same study linked. Two reviewers separately examined the full-text reports for eligibility and conferred to make a final decision on study inclusion.

2.5 Assessment of risk of bias

Moderator studies.

The check-list of methodological criteria proposed by Pincus (Pincus, Miles, Froud, Underwood, Carnes & Taylor, 2011) for assessment of studies of moderators of treatment effects was used to assess risk of bias in moderator studies. Two reviewers examined the included studies for these criteria: were the moderator analyses planned; was the potential factor measured prior to randomisation; was a valid measure of the factor used; was there a test of the interaction; were subgroup outcomes reported; and, was the sample size adequate.

Predictor studies.

While there is no consensus criteria for assessing risk of bias in predictor studies, some similar criteria to the moderator studies can be applied. We report on the type of study

(control; open); type of participant (recruited; referred for treatment); numbers of predictors in each study; the sample size, and the pre- to post duration.

2.6 Data extraction and management

Data extraction was completed by two reviewers independently. Data were extracted for the following variables: study sample size, age details of participants, proportion of females, diagnostic criteria used, type of comparator, primary OCD outcome (CY-BOCS total), reported statistics, length of follow-up, number of participants in the analysis and numbers in each subgroup for significant interaction (moderation) effects, effect sizes, *p* values and confidence intervals.

2.7 Data analysis

For moderators, we report the value of the test of the interaction, its significance and for any significant interactions, the effect size for the subgroup comparisons (Cohen's *d*; 95% CIs; *p* value). For predictors, we report first order correlation coefficients (*r*) between the pre-treatment factor and OCD outcome. When a study reported another estimate of association (χ^2, *B*) or a test of difference for participants categorised by level of predictor (*t, F*), we used standard methods (Lipsey & Wilson, 2001; Rosenthal, 1994) to convert the effect size to a correlation coefficient (*r*). Meta-analysis was conducted using MedCalc for windows (MedCalc, 2017) with random effects models. Pooled effect sizes were estimated using the Hedges-Olkin method (Hedges & Olkin, 1985) when three or more independent effect sizes for the same factor were extracted and statistical heterogeneity between the effect sizes was no more than moderate ($I^{2<}$=60%).

2. Results

3.1 Search Results

Figure 1 outlines the flow of studies through the study's inclusion and exclusion processes. Full texts of 69 articles were reviewed with 34 rejected at this point. Most of the

rejected studies (n=26) did not present statistical analyses of moderation or tests of association for predictors. Other reasons for exclusion were that studies did not measure putative moderators at baseline, presented associations with a non-OCD outcome or only with an OCD subcomponent, did not include a CBT monotherapy arm or did not disaggregate results for the CBT monotherapy arm. The 35 included studies consisted of 4 which presented results for a moderator interaction, 30 which reported on predictor associations, and one which reported on both moderator and predictor effects.

3.2 Study characteristics

Moderator studies.

Table 1 provides the characteristics of the studies for the moderator analyses (Barrett et al., 2004; Bolton et al., 2011; Garcia et al., 2010; March, et al., 2007; Skarphedinsson et al., 2015). The studies report results from 4 RCTs with a total of 365 participants conducted in Australia, Norway, UK and USA. Two (Barrett et al., 2004; Bolton et al., 2011) report moderator effects as part of the RCT outcome report, while two (March et al., 2007; Garcia et al., 2010) provide reports of subsequent analyses of data from a single RCT (POTS, March et al., 2004). One study (Skarphedinsson, et al., 2015) reports moderation outcomes for continuing CBT compared to switching to sertraline for children who failed to respond to an initial course of CBT. Details of the risk of bias assessment of the studies are presented in Table 2. The main risks are the lack of power analysis; very small numbers in the sub-groups; lack of a-priori predictions, and inadequate reporting of the statistics for non-significant interactions and sub-group effects.

Predictor studies.

The characteristics of the 31 studies identified as reporting predictors of outcome of CBT are presented in Appendix A of the supplementary material. Thirty-three different predictors across 7 domains (demographic; OCD related; concurrent treatment; co-morbidity;

family functioning; neuropsychological performance; pathophysiology) were identified. Most studies were of children referred for treatment rather than selected children who met specified inclusion criteria, and most were un-controlled studies. Several reports contained evidence on different predictors from single RCTs. Duration of study through to post treatment ranged from 4 weeks to 18 weeks. The total number of participants for the predictor analyses could not be calculated because many of the studies report on different predictors from the same sample of participants or from open trials with accumulating numbers presented in different reports. Study sample size for estimating individual effects ranged from 12 to 269.

3.3. Moderator outcomes

Table 3 summaries the results of the studies for the moderator analyses. No pooling was possible because of the small number of studies for each moderator. Three significant moderator by treatment interactions were identified. Using data from the POTS trial, March et al. (2007) reported that the presence of tics was an effect moderator for treatment outcomes. The analyses of subgroups indicated that the presence of tics most strongly impacted on the efficacy of sertraline compared to pill placebo, but not on the efficacy of CBT monotherapy or of CBT combined with sertraline relative to a pill placebo control. Numbers in the sub-groups are very small, but only the sertraline versus placebo comparison for children with tics showed no treatment effect. Skarphedinsson et al. (2015) also reported a significant moderation effect for the presence of tics. In this study of children who did not respond to an adequate initial trial of CBT, continuing CBT monotherapy was inferior to sertraline monotherapy for those with tics, but was not different from sertraline in those without tics.

Using data from the POTS study, Garcia et al., (2010) reported that a history of OCD in first degree relatives moderated the efficacy of CBT. Compared to a pill placebo, CBT

monotherapy had a non-significant effect in children with a family history but was effective in children without a family history. Family history had no impact on the efficacy of sertraline monotherapy compared to the placebo. While the combined treatment was effective in both groups of children relative to the placebo, the size of its effect for children with a family history was attenuated relative to the effect size for children without a family history. Age by treatment effects were not significant (Barrett et al., 2004; Bolton et al., 2011; Garcia et al., 2010). All other factors investigated were not significant as interactions with treatment group (Garcia et al., 2010).

3.4. Predictor outcomes

Table 4 presents the results for the predictors, organised into predictor type and specific predictors. There were significant pooled effects showing poorer responsiveness to CBT was predicted by older age, higher OCD symptom severity, higher level of OCD-related impairment, higher level of depressive symptoms, the presence of any co-morbid mental disorder, and higher family accommodation of the child's symptoms. The pooled effect for the presence of medication at pre-treatment was not significant.

3. Discussion

4.1. Main findings

The available best evidence about factors which may influence the relative efficacy of CBT for pediatric OCD compared to other efficacious treatments is still preliminary and requires replication. This systematic review, however, allows several tentative conclusions and suggestions for further exploration. First, children with a family history of OCD may not benefit from CBT alone relative to a pill placebo. Second, children with tics may do better with CBT than with medication alone. Third, the co-occurrence of a Tic disorder in children and adolescents who fail to respond to an initial course of CBT may be associated with an inferior response to continued CBT as compared to switching to sertraline. Fourth, there is no

evidence from RCTs to conclude that higher initial severity of OCD symptoms moderates the response that a patient will have to CBT monotherapy compared to response to medication. Fifth, severity of OCD symptoms, along with higher initial levels of impairment, depressive symptoms, presence of co-morbidity with another mental disorder, and how the child's OCD is responded to within the family, all predict a higher level of OCD symptoms after CBT.

Leckman et al. (2009) have suggested a negative influence of family history of OCD on CBT efficacy and our systematic review of the literature identified one study (Garcia et al., 2010) which reported evidence that confirmed a robust moderation effect of family history. This evidence indicated that despite CBT being effective for children and adolescents without a first degree relative with OCD, for those with a family history, CBT did not show benefits over a pill placebo. The efficacy of CBT when combined with an SSRI was attenuated for children and youth with a family history of OCD, compared to its efficacy for those without a family history. Nevertheless, combined treatment remained efficacious for patients with a family history and not less so than SSRI monotherapy. The findings suggest that while CBT alone may not be the appropriate initial treatment for children with a family history of OCD, even for these children, CBT may provide benefits when combined with an SSRI compared to using an SSRI by itself.

There is no evidence that the presence of a co-morbid Tic disorder in pediatric OCD is associated with reduced benefits for CBT alone or for combined treatment. Evidence from one RCT (March et al., 2007) showed that using SSRI monotherapy as an initial treatment for children with co-morbid Tic Disorder has no benefit. There was some evidence, nevertheless, that the presence of tics may differentiate a group of non-responders to an initial course of CBT monotherapy who benefit from switching to an SSRI more than they benefit from continued CBT (Sharphedinsson et al., 2015). The explanation for this latter finding is unclear. It may reflect the impact on the initial response to CBT of other co-morbidities

which are associated with Tic disorders, such as ADHD or disruptive behavior disorders. Alternatively, it might indicate that there is a subgroup of CBT non-responders who have a specific pattern or blend of OCD and tic symptoms that requires a wider array of treatment approaches than CBT. Unfortunately, there is very little evidence about the factors which predict outcomes for either continuing CBT or adding an SSRI for children who do not respond to initial treatment with CBT. Taken together, the current evidence suggests that for non-responders to CBT, adding an SSRI while continuing CBT, rather than switching to SSRI monotherapy may be the best option to optimise outcomes regardless of the presence of a co-morbid Tic disorder.

While the recommendation of some practice guidelines (AACAP, 2012) is that CBT combined with an SSRI is the preferred initial treatment in more severe cases, our review did not find any evidence for a difference in relative efficacy between CBT monotherapy and combined treatment that was related to the severity of the patient's OCD. There was suggestive evidence (March et al., 2007) that degree of pre-treatment OCD-related psychosocial impairment may moderate the relative efficacy of CBT, SSRI and combined treatment. However, as this effect only trended towards significance, that study did not report on the direction or strength of any potential moderation effect on CBT for level of OCD impairment. Our finding regarding severity of OCD symptoms is consistent with the equivocal findings of studies directly examining the relative efficacy of CBT plus medication compared to CBT alone. While the influential POTS trial (POTS, 2004) reported that combined treatment was superior to CBT monotherapy this finding was not uniform across the two sites which conducted that trial. A recent RCT (Storch et al., 2013) did not find a significant difference between combined CBT plus SRI treatment compared to CBT monotherapy while recent meta-analytic studies of treatments for pediatric OCD (Ivarrson et al., 2015; Öst et al., 2016) concluded that there was no evidence to infer that combination

treatment was superior to CBT monotherapy. As pre-treatment symptom severity is a non-specific predictor of a poorer response to SSRI monotherapy (Geller et al., 2003) as well as to CBT, the findings taken together indicate that currently there is no evidence about their relative efficacy to support any preference for combination treatment or CBT monotherapy as an initial treatment when symptoms are more severe.

We did not find any evidence that the presence of another mental disorder or high levels of symptoms of anxiety, depression or disruptive behavior problems moderated response to CBT compared to another treatment. These factors were predictors of a poorer CBT response. However, they are also associated adversely with response to SSRI treatments (Geller et al., 2003). We know that levels of depression are correlated with OCD symptom severity and this interrelationship may explain their association with treatment outcome. Studies (Storch et al., 2007; Torp et al., 2015) which examined OCD-specific and general psychological distress concurrently found that level of general psychological distress did not predict outcome of CBT after controlling for pre-treatment OCD-specific severity. These findings strongly suggest that other strategies to enhance CBT's efficacy for severe OCD need to be developed and evaluated. Tentatively, the evidence from the predictor studies summarised here confirm that strategies to enhance the child's capacity to self-regulate emotional distress and to improve the parent's abilities to manage the child's general anxiety and disruptive behaviours may be worthwhile adjunct treatments to develop and evaluate. Family accommodation is already recognised as a key factor in maintaining symptoms and increasingly it is being targeted for change in current versions of CBT (Peris & Piacentini, 2013).

4.2 Limitations

The findings about moderation effects of CBT need to be considered in the context of significant limitations and risks to bias in the review arising from three sources. First, there

were only a small number of studies which examined specific moderators and these individual studies have small sample sizes. Because the numbers needed to detect interactions are significantly higher than for between treatment differences (Aquinis 2005; Pincus et al., 2001) moderator analyses were underpowered. The non-significant results reported, therefore, are not able to be validly interpreted. Given this, it is important not to exclude factors such as degree of OCD-related impairment and parental psychopathology from continued exploration as potential moderators. In addition, because of the small number of participants in each treatment, the unpacking of significant interactions resulted in numbers in the subgroups stratified by level of the moderator which were well below the numbers recommended for valid inferences from subgroup differences (Pincus et al., 2011). For example, there were only 12 children in the subgroup with a family history who received CBT (Garcia et al., 2010) and only 3 in the subgroup with tics who received CBT (March et al., 2007). Caution is also needed in interpreting findings from single studies (Barrett et al., 2004; Garcia et al., 2010) where multiple comparisons are undertaken without consideration of inflated false positives.

The second source of bias is the substantial clinical and methodological variability particularly in the predictor studies arising from difference in the nature of the CBT treatment such as its components, delivery, duration and intensity, recruitment and assessment of the participants. While we included statistical variability in the decision to pool individual estimates and used random-effect models to reduce effects of methodological heterogeneity, clinical heterogeneity limits the ability to generalise from the pooled estimates to expectations about the delivery of CBT in clinical practice.

The third area of bias is that many studies examined multiple outcomes without adjusting the experiment-wise error rates reducing the confidence in the result for CY-BOCS. We used CY-BOCS total as the primary outcome to reduce the risk of reporting on false

positives and to better allow comparability between studies. Other limitations of the individual predictor studies include non-reporting of values of estimates for non-significant results; lack of clarity in number of participants in specific analyses; lack of clarity in multiple reports of open trials with accumulating numbers, and failing to report first-order associations when using partial or multiple regressions.

4.3 Directions for future research

The significant limitations of the existing studies highlight the challenges that future work will need to address in order to avoid flawed conclusions from individual RCTs or systematic reviews and to limit the adoption of inaccurate clinical practices. While small subgroup sample sizes are ubiquitous in post-hoc moderator analyses from RCTs (Pincus et al, 2011) it is very important to confirm the moderation effects of an OCD family history and presence of Tic disorder. The limitations due to low power could be reduced in future meta-analysis by merging and analysing individual patient level data across existing studies (Bloch, 2014). A stronger confirmation would be future RCTs in which participants are stratified according to levels of the moderator of interest (e.g., family history; presence of tics) and randomised to receive CBT, medication or combined treatment (Kraemer et al., 2006). . Future prospective evaluations of possible moderators also need to focus more on factors where there are specified theoretical mechanisms to account for the differential treatment effects. Given that CBT, unlike medication, deliberatively seeks via exposure and response prevention to enhance new learning by inhibiting existing emotional associations, these considerations could, for example, include the psychological and neurobiological mechanisms which underpin theses learning processes. Possible candidates for examination might be variability in children's temperamental features such as behavioural inhibition as well as in neurophysiological variables such as brain-derived neurotropic factors which have been shown to facilitate inhibitory learning and also to predict poorer response to exposure

treatment in PTSD when identified by different genetic polymorphisms (Felmingham et al., 2013). The recent finding that aspects of brain glutamate, a neurophysiological factor involved in fear extinction, is a predictor of s CBT outcome for pediatric OCD (O'Neil et al., 2017) has the potential to move the area in important and productive new directions. Finally, pediatric OCD researchers are in a unique position of having almost universal agreement regarding the use of the CY-BOCS severity score as the gold-standard outcome measure. When researchers use this tool as a primary outcome, and report it as such, outcome comparisons are facilitated across different research groups.

4.4. Conclusions

In summary, this review provides the first systematic integration of the best evidence about the factors which differentiate treatment outcomes between CBT and other treatments for pediatric OCD. This evidence is very preliminary and more consistent findings across studies or further meta-analytic results combining sufficient individual patient data are required before firmer conclusions can be drawn. Tentatively, the review's results suggest that having a first-degree family member with OCD and the presence of tics may be important considerations for initial choice of treatment and that the presence of tics may also be important when considering options for children who not respond to an initial course of CBT. For researchers, findings of the review identify factors which could be further explored in order to better understand the mechanism by which CBT has its benefits and to improve treatment outcomes for a larger number of children and youth with OCD. The review also highlights the need for major methodological improvements in the design, implementation and reporting of future studies. International cooperation via the establishment of a Pediatric OCD Consortium would be one way to enhance sharing and pooling of trial outcomes and facilitate appropriately sized studies so as to better answer questions regarding treatment moderators.

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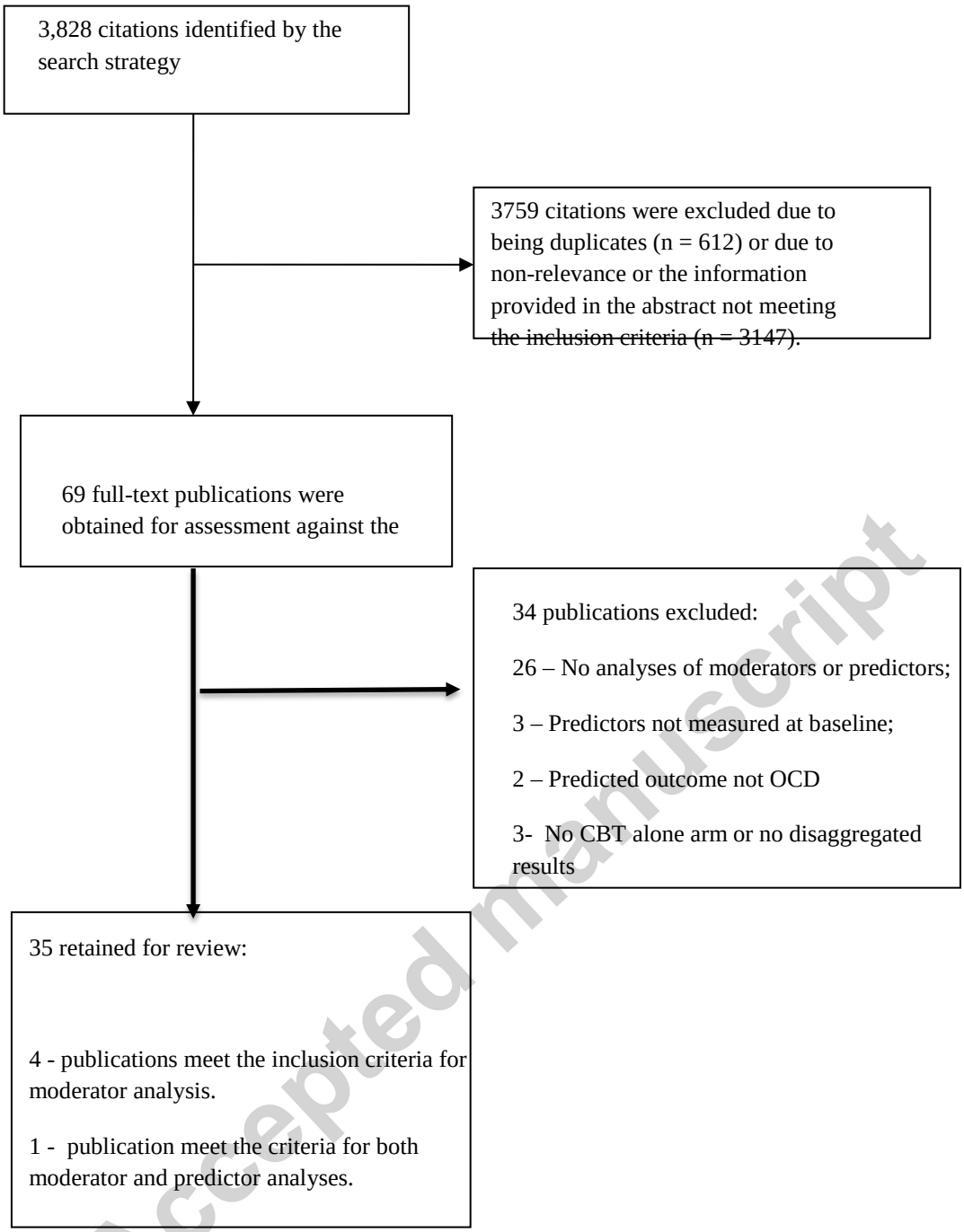

Figure 1: Selection of studies. Note: OCD = Obsessive-compulsive Disorder; CBT – Cognitive-behavioral therapy

Table 1: Characteristics of studies included in CBT effect moderator review

	Study: first author, year (total no. of subjects)	Participant type	Diagnosis	Outcome measures	Moderator (Baseline measure - continuous unless stated otherwise)	Comparisons	Mean age, years (SD) Range	Female (%)
1	Barrett et al., 2004 (n = 77)	Recruited from community (Australia)	ADIS-P	CY-BOCS	Child age Taking medication (yes/no)	CBT(Ind.) v CBT (Group) v WL	10.75 (2.54) 7 to 17 years	50.7
2	March et al., 2007 (n = 112)	Recruited from community (USA) POTS	ADIS-C CY-BOCS>16	CY-BOCS	Presence of tics (yes/no)	CBT v Sertraline v Combined (CBT+ Sertaline) v PBO	11.7 (2.7) 10 to 18 years	50
3	Garcia et al., 2010 (n = 112)	Recruited from community (USA) POTS	ADIS-C CY-BOCS>16	CY-BCOS	Age Gender (Male/Female) Household income Severity Impairment Insight Co-morbid Internalizing (yes/no) Co-morbid Externalizing (yes/no) Anxiety symptoms Externalizing symptoms Parental psychopathology (yes/no) OCD Family History (1st degree relative)(yes/no) Family functioning Family accommodation	CBT v Sertraline v Combined (CBT + Sertraline) v PBO	11.7 (2.7) 10 to 18 years	50

4	Bolton et al., 2011 (n = 96)	Recruited from community (UK)	ADIS-C/P	CY-BCOS	Child age (Continuous and Binary: Younger < 13 years; Older >= 13 years)	Standard CBT v Brief CBT v WL	14.4 (2.4) 10 to 18 years	59.4
5	Skarphenedinson et al., 2015 (n = 50)	Recruited from community (Norway) Non-responders to initial CBT(post-treatment CY-BOCS >= 15) from NordLOTS	K-SADS-PL CY-BOCS>16	CY-BCOS	Presence of tics (yes/no)	Continued CBT v Sertraline	12.8 (2.7) 7 to 17 years	51.3

Note. ADIS-Anxiety Disorder Interview Schedule C – Child version; P- Parent version. K-SADS – Schedule of Affective Disorders and Schizophrenia for School-aged Children - Present and Lifetime version; CY-BOCS Child Yale-Brown Obsessive-Compulsive Scale; PBO- pill placebo; POTS – Pediatric Obsessive-compulsive Treatment Study; NordLOTS- Nordic Long-term OCD Treatment Study; WL-Waitlist

Table 2: Risk of bias assessment of studies (Criteria from Pincus at al., 2011)

Study (total no. of subjects) Moderator(s)	a-priori/post-hoc Plausible/ exploratory	Measured prior to randomization	Power analysis (yes/no) Adequate N (smallest n)	Valid baseline measures	Test Pooled effect size and 95% CIs (no/yes)	Difference for each group (Yes/No)	Replicated (Yes/no)
Barrett et al., 2004 (n = 77) Age;	Post-hoc Exploratory	Yes	Not reported N=6 (smallest	Yes	Yes – no statistics reported	Not required	Yes (Bolton, Garcia for age)

medication status			group)				
March et al., 2007 (n = 112) Presence of tics	Post-hoc Plausible (evidence-based)	Yes	Not reported N= 3 (smallest group)	Yes	Yes No effect size	Yes	No
Garcia et al., 2010 (n = 112) Family history; age; various	Post-hoc Exploratory	Yes	Not-reported N = 11 (smallest group)	Yes	Yes No effect size	Yes – for significant interaction	Yes (Barrett, Bolton for age); No otherwise
Bolton et al., 2011 (n = 96) Age	Post-hoc Exploratory	Yes	Not reported N= 15 (smallest group)	Yes	Yes No effect size	Not required	Yes (Barrett, Garcia for age)
Skarphedinson et al., 2015 (n = 50) Presence of tics	A-priori Plausible (evidence-based)	Yes	Not reported N= 5 (smallest group)	Yes	Yes No effect size	Yes	No

Table 3. Results of moderator analysis review with total CY-BOCS as outcome; moderator; Study; test of interaction; significance of test; for subgroup comparisons n, effect sizes (95% CI).

Moderator	**Study**	**Test of interaction**	***p* value**	**Sub-group analysis for significant interaction**
Age (continuous)	Barrett et al., 2004	Not reported	ns	
	Bolton et al., 2011	F (2, 89) = 0.08	p = 0.45	
	Garcia et al., 2010	F (3,104) = 0.11	p > .1	
Age (*young v old*)#	Barrett et al., 2004	Not reported	ns	
	Bolton et al., 2011	F (1,70) =0.52	p = 0.48	
OCD medication (*Yes/No*)	Barrett et al., 2004	Not reported	ns	

Presence of tics (*Yes/No*)	March et al., 2007	$\chi^2 = 12.32$	$p <$ .006	*Yes* CBT (n = 3) v PBO (n=5) (ES=1.63; 0.005 to 3.27)* *No* CBT (n=25) v PBO (n =23) (ES=2.59; 1.82 to 3.36)* *Yes* Comb.(n=4) v PBO (n=5) (ES=3.94; 1.69 to 6.18)* *No* Comb.(n=24) v PBO (n =23) (ES=3.95; 2.97 to 4.94)* *Yes* Sert.(n=5) v PBO (n=5) (ES=-0.20; – 1.44 to 1.04) *No* Sert.(n =23) v PBO (n =23) (ES=1.99; 1.29 to 2.70)*
	Skarphedinson et al., 2015	β= 0.06(0.023)	$p < .05$	*Yes* Sert. (n=7) v cont. CBT (n=7) (ES= -2.62;-4.25 to -1.11)* *No* Sert (n=17) v cont. CBT (n=21) (ES= 0.16; -0.47 to 0.79)
Family History (*Yes/No*)	Garcia et al., 2010	F (3,104) = 2.70	$p < .05$	*Yes* CBT (n = 12) v PBO (n=11) (ES=0.25; -0.58 to 1.07) *No* CBT (n=17) v PBO (n =16) (ES=1.63; 0.83 to 2.41)* *Yes* Comb (n=11) v PBO (n=11) (ES=1.11; 0.21 to 2.01)* *No* Comb.(n=16) v PBO (n =16) (ES=2.82; 1.85 to 3.77)* *Yes* Sert. (n=11) v PBO (n=11) (ES=0.74;-0.12 to 1.61) *No* Sert. (n= 16) v PBO (n=16) (ES= 0.81; 0.09 to 1.50)*
Gender	Garcia et al., 2010	F (3,104) = 0.73	ns	
Household income	``	F (6,90) = 0.57	ns	
OCD severity	``	F (3,104) = 1.01	ns	
COIS-P	``	F (3,96) = 1.94	ns^	
COIS-C	``	F (3,89) =	ns	

		2.06	
Insight	``	*F* (8,79) = 0.69	ns
ADIS-C internal	``	*F* (3,100) = 0.52	ns
ADIS-C external	``	*F* (3,100) = 0.70	ns
Anxiety symptoms	``	*F* (3,91) = 0.88	ns
External symptoms	``	*F* (3,88) = 0.99	ns
BSI	``	*F* (3,92) = 2.04	ns
FAM-III	``	*F* (3,96) = 0.12	ns
FAS-PR	``	*F* (3,88) = 1.32	ns

Note: ns – not significant p > .05; # cutoff for young group < 13 years; * p < .05; ^ reported as *p* < .05 in Garcia et al., 2010; Sert = sertraline group; PBO = pill placebo control; Comb = Combined CBT plus sertraline group; COIS-P = Child Obsessive-Compulsive Impact Scale–Parent Report; COIS-C = Child Obsessive- Compulsive Impact Scale–Child Report; ADIS-C =Anxiety Disorder Interview Schedule-Child version; BSI = Brief Symptom Inventory; FAM-111= Family Assessment Measure-III; FAS-PR = Family Accommodation Scale–Parent Report.

Table 4. Outcomes for predictors: Domain of predictor, predictor; study; statistical test; effect size *r* (95% CI), significance, number of participants, and for Pooled estimates: test, pooled effect size *r* (95%CIs), significance, total N and number of studies (k)

Predictor (Domain)	**Study**	**Test**	**Effect size *r* (95% CIs)**	***p* value**	**n**
Demographic					
Age	Piacentini, et al., 2002	not reported		ns	42
	Farrell, et al., 2010	*F* = 2.50	*r* = .14 (-.17 to .42)	*p* > .05	33
	Rudy, et al., 2014	*r* = .10	*r* = .10 (-.13 to .32)	*p* > .05	78

		Torp, et al., 2015	*t* = 2.84	*r* = .17 (.05 to .29)	*p* < .05	269
		Pooled (random effects)	***z* = 2.08**	***r* = .15 (.05 to .25)**	***p* = .003**	**380 (k=3)**	**I^2 = 0%**
	Sex	Piacentini, et al., 2002	not reported		ns	42
		Farrell, et al., 2010	*F* = .063	*r* = .04 (-.27 to .36)	*p* > .05	35
		Rudy, et al., 2014	*r* = .33	*r* = .33 (.12 to .52)	*p* < .05	78
		Torp, et al., 2015	*t* = 0.55	*r* = .03 (-.09 to .15)	*p* = .58	269
		Not pooled					**I^2 = 65.7%**
	SES	Torp, et al., 2015	*t* = 0.19	*r* = .01 (-.11 to .13)	*p* = .85	269
OCD-related variables						
	OCD severity	Lewin, et al., 2011	β = .33	*r* = .33 (.03 to .58)	*p* = .04	41
		Piacentini, et al., 2002	*r* = .34	*r* = .34 (.04 to .58)	*p* = .029	42
		Rudy, et al., 2014	*r* = .29	*r* = .29 (.07 to .48)	*p* < .05	78
		Torp, et al., 2015	*t* = 3.07	*r* = .19 (.07 to .30)	*p* < .002	269
		Wolters, et al., 2016	*F* = 0.29	not able to estimated	*p* = .75	58
		Pooled (random effects)	***z* = 4.91**	***r* = .24 (.14 to .32)**	***p* < .001**	**430 (k=4)**	**I^2 = 0%**
	Impairment	Piacentini, et al., 2002	*r* =-.44	*r* = .44 (.15 to 0.66)	*p* = .007	42

		Ruby, et al., 2014	r = .17	r = .17 (-.06 to .38) p < .05 78
		Torp, et al., 2015	t = 3.71	r = .15 (.03 to .26) p = .16 269
	(Social)	Piacentini, et al., 2002	r = .49	r = .49 (.22 to 0.69) p = .008 42
	(Academic)	Piacentini, et al., 2002	r = .42	r = .42 (.13 to 0.64) p = .025 42
		Pooled (random effects)	***z* = 2.70**	***r* = .21 (.06 to .36)** ***p* = .007** **389 (k=3)**
		I^2 = 43.38%		
	Age of onset	Nakatani, et al., 2011	F = 1.64	r = .12 (-.07 to .31) p = .21 109
	Duration of illness	Torp, et al., 2015	t = 1.36	r = .08 (-.04 to .20) p = .18 269
	Type			
	(Somatic)	Storch, et al., 2008	F = 1.06	r = .13 (-.12 to .36) p > .05 62
	(Sexual)	Fernandez, et al., 2013	F = 0.123	r = .03 (-.14 to .20) p = .73 153
	(Aggressive)	Storch, et al., 2008	χ^2 = 3.4	r = .19 (-.02 to .38) p = .06 92
	(Transformation)	Monzani et al., 2015	F = 0.858	not able to estimated p = .36 189
Concurrent Treatment				
	Medication	Piacentini, et al., 2002	χ^2 = 0.35	r = .09 (-.21 to 0.38) p = .6 42
		Himle, et al., 2003	t = 0.291	r = .07 (-.41 to 0.52) p = .77 18
		Storch, et al., 2007	F = 0.8	r = .14 (-.17 to .42) p = .38 39
		Farrell, et al., 2010	F= 0.68	r = .18 (-.25 to .53) p > .05 33

		Fernandez, et al., 2012	*F* = 1.27	*r* = .09 (-.07 to .26)	*p* = .27
153					
		Pooled (random effects)	***z* = 1.74**	***r* = .11 (-.01 to .22)**	***p* = .081**
285 (k=5)					
		I^2 = 0%			
Co-morbidity					
	Depression (disorder)	Brown, et al., 2014	β = 0.19	*r* = .19 (-.07 to .42)	*p* < .05
61					
		Farrell, et al., 2012	not reported		
ns	28				
	Depression severity	Piacentini, et al., 2002	not reported		
ns	nr				
		Brown, et al., 2014	β = .26	*r* = .26 (.07 to .44)	*p* < .05
98					
		Leonard, et al., 2014	*F* = 1.07	*r* = .16 (not able to estimated)	ns
126					
		Torp, et al., 2015	*t* = 2.82	*r* = .17 (.05 to .28)	*p* < .005
269					
		Lewin, et al., 2011	not able to estimated		
		Pooled (random effects)	***z* = 4.13**	***r* = .19 (.10 to .27)**	***p* < .001**
493 (k=4)					
		I^2 = 0%			
	Tics/Tourette's	Piacentini, et al., 2002	not reported		
ns	42				
		Himle, et al., 2003	*F* = 1.32	*r* = .26 (-.19 to .59)	*p* > .05
19					
		Bennett, et al., 2015	*F* = 1.24	*r* = .14 (-.11 to .38)	p = .22
58					
		Torp, et al., 2015	*t* = 1.81	*r* = .11 (-.01 to .23)	*p* =.07
269					
		Hojgaard, et al., 2017	*t* = 1.02	*r* = .06 (-.06 to .19)	*p* = .309
269					

		Pooled (random effects)		***z* = 2.263**	***r* = .09 (-.07 to .24)**	***p* = .267**
615 (k=4)						
		I^2 = 0%				
	ASD	Farrell, et al., 2012		not reported		
		ns	38			
		Wolters, et al., 2016		*F* = 2.09	not able to estimated	
		p =.15	58			
	Anxiety	Piacentini, et al., 2002		*r* = .38	*r* = .38 (.09 to .61)	
		p =.043	42			
		Torp, et al., 2015		*t* = 2.33	*r* = .14 (.02 to .26)	
		p = .02	269			
	ADHD	Farrell, et al., 2012		χ^2 = 3.99	*r* = .35 (.01 to .63)	
		p = .06	31			
	Temper outbursts	Krebs, et al., 2012		B = 1.15	*r* = .50 (-.51 to .87)	
		p = .329	109			
	Any disorder	Storch, et al., 2008		*r* = .39	*r* = .39 (.20 to .55)	
		p < .001	96			
		Farrell, et al., 2012		not reported (post-treatment)		
		ns	43			
		Farrell, et al., 2012	(f/up)	*r* = .37	*r* = .37 (.07 to .60)	
		p < .005	43			
		Rudy, et al., 2014		*r* =.12	*r* = .12 (- .11 to .33)	
		p > .05	78			
		Pooled (random effects)		***z* = 3.04**	***r* = .29 (.11 to .46)**	***p* = .002**
217 (k=3)						
		I^2 = 48.57%				
	Internalizing severity	Rudy, et al., 2014		*r* = .30	*r* = .30 (.08 to .49)	
		p < .05	78			
		Torp. et al., 2015		*t* = 3.33	*r* = .20 (.08 to .31)	
		p < .001	269			
	Int disorder	Torp, et al., 2015		*t* = 1.48	*r* = .09 (- .03 to .21)	
		p =.139	269			

Externalizing severity	Rudy, et al., 2014	r = .11	r = .11 (-.12 to .33)	p < .05
	78			
	Torp, et al., 2015	t = 2.37	r = .14 (.02 to .26)	p = .017
	269			
Ext. disorder	Torp, et al., 2015	t = 0.10	r = .01 (- .11 to .13)	p = .917
	269			
Sleep problems	Ivarsson,et al., 2016	g = .32	r = .15 (.03 to .27)	p < .001
	269			
Family functioning				
Family Climate	Perris, et al., 2012a (binary)	χ^2 = 17.45	r = .60 (.35 to.77)	p = .001
	49			
	Perris, et al., 2012a (number)	χ^2 = 19.74	r = .63 (.40 to .79)	p < .0001
	49			
Expressed Emotion	Perris, et al., 2012b	not reported		ns
	41			
Family accommod.	Rudy, et al., 2014	r = .25	r = .25 (.03 to .45)	p < .05
	78			
	Torp, et al., 2015	t = 1.99	r = .12 (.01 to .24)	p = .047
	269			
	Merlo, et al., 2011	r = .32	r = .32 (.03 to .56)	p < .05
	45			
	Pooled (random effects)	***z* = 3.07**	***r* = .19 (.07 to .29)**	***p* = .002**
	392 (k=3)			
	I^2 = 12.82%			
Parental psy. disorder	Torp, et al., 2015	t = 1.00	r = .06 (- .06 to .18)	p = .32
	269			
Family OCD history	Torp, et al., 2015	t = 1.09	r = .07 (- .05 to.19)	p = .28
	269			
Neuropsychology functioning				
Memory (recall)	Flessner, et al., 2010	F = 6.68	r = .60 (.10 to .82)	p = .29
	12			
Emotional control	McNamara, et al., 2014	β = .207	r = .21 (-.06 to .45)	p < .05
	56			

Pathophysiology

Glutamate (vPCC)	O'Neil et al., (2017)	$p < 0.001$	$r = .81$	$r = .81$ (.57 to .92) 20

Highlights

- Individual treatment response to CBT for pediatric OCD is considerably variable
- The first systemic review of moderators of CBT outcomes against other treatments
- Evidence is post-hoc, from single RCTs, has small Ns and requires replication
- Co-morbid tics and a family OCD history may moderate CBT outcomes against sertraline
- Studies with larger Ns and testing a-priori and plausible hypotheses are required