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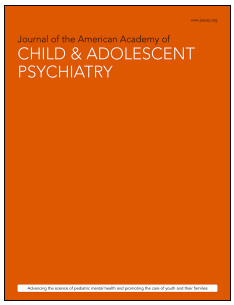

Systematic Review and Meta-Analysis: An Empirical Approach to Defining Treatment Response and Remission in Pediatric Obsessive-Compulsive Disorder

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RH = Response and Remission in Pediatric OCD

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Abstract

Objective: A lack of universal definitions for response and remission in pediatric obsessive-compulsive disorder (OCD) has hampered the comparability of results across trials. To address this problem, we conducted an individual participant data diagnostic test accuracy meta-analysis to evaluate the discriminative ability of the Children's Yale-Brown Obsessive-Compulsive Scale (CY-BOCS) in determining response and remission. We also aimed to generate empirically derived cutoffs on the CY-BOCS for these outcomes.

Method: A systematic review of PubMed, PsycINFO, Embase and CENTRAL identified 5,401 references, 42 randomized controlled clinical trials (RCTs) were considered eligible and 21 provided data for inclusion (N 1,234). A score ≤ 2 in the Clinical Global Impressions Improvement and Severity scales were chosen to define response and remission, respectively. A two-stage random-effects meta-analysis model was established. The area under the curve (AUC) and the Youden Index were computed to indicate the discriminative ability of the CY-BOCS and to guide for the optimal cutoff, respectively.

Results: The CY-BOCS had sufficient discriminative ability to determine response (AUC 0.89) and remission (AUC 0.92). The optimal cutoff for response was a ≥ 35% reduction from baseline to posttreatment (sensitivity [95% CI] 83.9 [83.7, 84.1]; specificity [95% CI] 81.7 [81.5, 81.9]). The optimal cutoff for remission was a posttreatment raw score ≤ 12 (sensitivity [95% CI] 82.0 [81.8, 82.2]; specificity [95% CI] 84.6 [84.4, 84.8]).

Conclusion: Meta-analysis identified empirically optimal cutoffs on the CY-BOCS to determine response and remission in pediatric OCD RCTs. Systematic adoption of standardized operational definitions for response and remission will improve comparability across trials for pediatric OCD.

Key words: obsessive-compulsive disorder, randomized controlled trials, meta-analysis, diagnostic test accuracy, cy-bocs

Introduction

Obsessive-compulsive disorder (OCD) is a common psychiatric condition among children and adolescents[1, 2] characterized by intrusive unwanted thoughts or urges (obsessions) and repetitive behaviors or mental acts (compulsions).[3] The Children's Yale-Brown Obsessive-Compulsive Scale (CY-BOCS) is a semi-structured clinician-rated instrument typically employed to evaluate the presence and severity of OCD symptoms over the past week in youth.[4] It contains two 5-item severity rating scales, one for obsessions and one for compulsions, which are then summed to obtain a total severity score. The CY-BOCS has good psychometric properties[4, 5] and has been widely adopted in randomized controlled trials (RCTs) of interventions for pediatric OCD as the instrument of choice to measure OCD symptom severity and change.

Pediatric OCD RCTs have typically determined the improvement in mean CY-BOCS scores from baseline to posttreatment in the active versus the control group as the primary outcome for efficacy. However, the clinical meaning of these average changes in CY-BOCS scores across treatment groups is debatable. It could be argued that reductions in mean CY-BOCS scores are less informative clinically than the likelihood of responding positively to treatment or achieving remission. Several pediatric OCD trials have reported positive treatment response, i.e., a substantial improvement in symptoms, and remission, i.e., the presence of no more than minimal symptoms, as secondary outcomes. Unfortunately, and similarly to adult OCD studies, definitions of positive treatment response and remission have not been consistent across RCTs for pediatric OCD. For instance, different thresholds of improvement – 25%,[6-8] 30%,[9] 40%,[10] or 50%[11] – and posttreatment severity – 11,[12] 14[13] – based on the CY-BOCS have been adopted to determine positive treatment response and remission, respectively. Additionally, a large proportion of clinical researchers in pediatric OCD have only adopted the Clinical Global

Impressions-Improvement (CGI-I) and Clinical Global Impression-Severity[12-15] (CGI-S) scales to define positive treatment response and remission, respectively. Solely relying on the CGI-I or CGI-S might be problematic as improvements in these scales may not be as rigorous as quantitative measures. For instance, improvements in commonly comorbid conditions such as depression, anxiety and tics may also be combined with improvement in OCD symptoms when using more general scales of improvement or severity.

Importantly, the lack of consistency in reporting criteria of positive treatment response and remission in pediatric OCD RCTs has created challenges when comparing rates across trials, i.e., in meta-analyses, and as a result, the communication in the field has been stunted. In an attempt to address this issue, Mataix-Cols and colleagues[16] conducted a multi-round, web-based Delphi survey involving international experts to provide a consensus definition of positive treatment response and remission in OCD. The consensus determined as the operational definitions of (1) positive treatment response a ≥ 35% reduction in (C)-YBOCS scores plus a CGI-I ≤ 2 and of (2) remission a (C)-YBOCS score ≤ 12 plus a CGI-S ≤ 2; both were required to last for at least a week.

However, there have been few studies using empirical methods to validate such operational criteria. In pediatric populations, two studies have examined through signal detection analyses the optimal amount of symptom improvement and severity to classify an individual as 'positive responder' and 'remitter', but conflicting findings have been reported.[17, 18] Specifically, both 25% and 35% reductions have been identified as the minimal improvement required to determine positive treatment response; likewise, both 14 and 11 posttreatment scores have been identified as the maximum severity required to determine remission. These inconsistencies may be explained, at least in part, by limited statistical power, particularly for remission, a relatively rare outcome. Available evidence[19] indicates a sample size of at least 775 individuals would be required to perform diagnostic

accuracy analysis with a sufficient level of power (80%) and a low level of type I error (0.05). Because previous studies analyzed data from a considerably smaller set of participants (N = 109; 269), additional research with larger samples is currently warranted.

To address this gap, we conducted an individual participant data (IPD) diagnostic test accuracy (DTA) meta-analysis to determine the empirically optimal (1) percent and absolute reductions in CY-BOCS scores from baseline to posttreatment that correspond to positive treatment response and the (2) posttreatment CY-BOCS raw score that corresponds to remission. This article is in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). The PRISMA checklist[20, 21] can be found in Supplement 1, available online. A protocol was not established for this review. Our group is currently working on a similar effort for the Y-BOCS, the adult scale, but its data has not yet been published.

Method

Eligibility criteria.

References were considered eligible for inclusion in the meta-analysis if the study (a) included individuals aged ≤ 18 years old with a diagnosis of OCD as determined through formal diagnostic criteria (e.g., DSM-III, DSM-III-R, DSM-IV, DSM-IV-TR, DSM-5, ICD-9, ICD-10); (b) evaluated the efficacy of any pharmacological or psychotherapeutic interventions in comparison to any control condition in the short-term (~ 1 – 4 months) using random allocation procedures to determine the treatment group for participants. Studies including individuals who were considered 'treatment-resistant' or 'treatment-refractory' were considered eligible. Pharmacological interventions were required to be orally administered to be considered eligible. Add-on pharmacological and multimodal treatment studies, i.e., combinations of medication and psychotherapy such as

d-cycloserine augmented cognitive behavioral therapy or selective serotonin reuptake inhibitors combined with cognitive behavioral therapy, were considered eligible. Studies with passive control conditions, such as community treatment/treatment as usual and wait-list, were eligible for inclusion. Studies including individuals who had an abrupt onset of obsessive-compulsive symptoms, such as those fulfilling criteria for pediatric acute-onset neuropsychiatric syndrome (PANS), were not considered eligible. Cross-over studies were not eligible to avoid including two sets of observations for the same individual. Studies which randomized less than 10 participants were not considered eligible.

Study identification and selection process.

Selected electronic databases (PubMed, CENTRAL, EMBASE and PsycINFO) were searched from inception to March-July 2020 for relevant references. Search strategies were tailored for each database, and detailed descriptions can be found in Supplement 2, available online. The references section of review articles and meta-analyses were carefully read to identify additional eligible studies. No language restrictions were applied. No further efforts were made to search for unpublished research. Titles and abstracts of records were screened by two independent reviewers (LCF, DR) to identify those that were eligible for inclusion. Disagreements between the two reviewers was solved through discussing with a third independent reviewer (MHB). Risk of bias of individual studies was not assessed.

Data collection and data items.

An email was sent to either the first or last author of articles fulfilling the eligibility criteria for our meta-analysis. If authors failed to reply to our first email, follow-ups were

sent at least 1 week after the first email. We also tried to contact other study co-authors if we did not receive a reply from the initial email.

IPD was requested for the following: (1) CY-BOCS total score at baseline, (2) CY-BOCS total score at posttreatment, (3) CGI-I scores at posttreatment, (4) CGI-S scores at posttreatment and (5) treatment group to which the individual was allocated to.

Diagnostic test accuracy meta-analytical method.

We evaluated CY-BOCS percent and absolute reductions from baseline to posttreatment in relation to positive treatment response.[16] Cutoffs on the CY-BOCS were calculated at every 5%, from 5% to 70%, for percent reductions[17, 18] and at every 2-points, from 2 to 28, for absolute reductions. Positive treatment response was conceptually defined as a clinically meaningful reduction in symptoms relative to baseline severity. A CGI-I score of either 2 ('much improved') or 1 ('very much improved') was adopted as the primary operational definition of positive treatment response. A 10-point reduction on the CY-BOCS based on a Reliable Change Index (RCI) ≥ 1.96[22] – details on this metric and its calculation can be found in Supplement 2, available online – was employed as a secondary operational definition of positive treatment response for percent reductions as sensitivity analysis.

We evaluated CY-BOCS posttreatment raw scores in relation to remission.[16] Cutoffs on the CY-BOCS were calculated at every 1-point, from 5 to 20, for raw score severity.[17, 18] Remission was conceptually defined as an individual having no more than minimal symptoms. A CGI-S score of either 2 ('borderline mentally ill') or 1 ('normal, not at all ill') was adopted as the operational definition of remission.

Because each study contributed with multiple data points to the meta-analysis, we established a two-stage random effects meta-analysis model for multiple thresholds.[23] At

the study-level, 1-sensitivity values at all thresholds provide an estimate of the cumulative distribution function (cdf) of the CY-BOCS reductions /raw scores for positive responders/remitters. Likewise, specificity values at all thresholds provide an estimate of the cdf of the CY-BOCS reductions/raw scores for non-positive responders/non-remitters. At the meta-analytical level, the model fits the data for positive responders/remitters, non-positive responders/non-remitters and all available thresholds, providing estimates of the cdf for each group across all studies. A logit transformation to 1-sensitivity/specificity values is adopted to fit a linear model. We adopted a random intercept model to fit the data and assumed equal variances in the distribution of the CY-BOCS among positive responders/remitters and non-positive responders/non-remitters. Each data point was weighted by the inverse variance. All analyses were conducted in R using the package 'diagmeta'.[24] To increase the reproducibility of our research, we have made all code available online in OSF (DOI10.17605/OSF.IO/U5DRX).

We obtained pooled sensitivity and specificity with 95% confidence intervals for every CY-BOCS cutoff for response and remission. Pooled values of sensitivity and specificity were used to plot summary receiver operating characteristic (SROC) curves. The Area Under the SROC Curve (AUC) was computed to indicate the discriminative ability of the CY-BOCS in determining positive treatment response and remission; values range from 0.5, which indicate no discriminative ability, to 1, corresponding to perfect discrimination. We also used pooled values of accuracy measures to calculate the Youden Index (*J*), which was used to help inform the optimal cutoff. The *J* statistic is computed by the maximum value of the difference between sensitivity and 1 – specificity and represents the maximum vertical distance from the SROC curve to the chance line.[25]

The I^2 statistic typically employed to assess heterogeneity is not useful in DTA meta-analyses because it does not account for the correlation between sensitivity and specificity. Therefore, heterogeneity was evaluated by visual inspection of the confidence ellipse in the SROC curve, which indicates the uncertainty around the optimal cutoff.[26] We did not evaluate publication bias because this is not routinely recommended in DTA meta-analyses.[27]

Results

Study selection and IPD obtained.

Our search identified 5,401 references, of which 42 were considered eligible for inclusion.[6-15, 28-59] Figure 1 depicts the PRISMA flowchart for the inclusion/exclusion procedures with reasons of exclusion. Of the 42 potentially eligible trials, 4 authors replied they did not have the CGI-I/CGI-S in their assessments. Of the remaining 38 studies, we were able to obtain IPD for 21 (55.26%) studies.[6, 9, 11-14, 34, 38-44, 47, 51, 52, 54-57] Reasons we were unable to obtain IPD from trials were lack of access (9), refusal to share data due to IRB restrictions (2) and lack of response to our request (6).

Study characteristics.

Table 1 depicts the characteristics of the included studies. Of the 21 included studies, 14 (67%) recruited participants from North America, 4 (19%) from Europe, 2 (9%) from South America and 1 (5%) from Asia. Across the 21 RCTs, 1,234 participants whose mean age was 12 years (SD 4) were included; 716 (58%) were boys. Fifteen studies (71%) – including thirteen (93%) from the US – reported race/ethnicity of participants; of the 876 participants with race/ethnicity information, 764 (87%) self-identified as white. Select studies included between 1% and 3% of African-American/Black individuals; between 1% and 7% of Asian-American individuals; between 2% and 13% of Hispanic/Latino

individuals. In total, of the 1,234 participants, 223 (18%), 650 (53%) and 298 (24%) were enrolled in a pharmacological, psychotherapeutic and multimodal treatment arm, respectively. The remaining 63 (5%) participants were enrolled in passive control conditions. The mean study sample size was 59 (SD 36). The mean year of publication was 2013 (SD 4). None of the 21 studies was funded by pharmaceutical companies.

See Table S1, available online, for the characteristics of the 21 studies which were eligible but did not provide IPD for inclusion in the meta-analysis. Although the majority of these studies recruited participants from North America (48%), a larger proportion recruited participants from Europe (33%), Oceania (9%) and Asia (10%). Across the 21 RCTs, 1,381 participants whose mean age was 12 years (SD 3) were included; 603 (53%) were boys. Most participants – 810 (59%) – were allocated to a pharmacological treatment arm, while substantially smaller proportions were allocated to a psychotherapeutic (300; 22%) or multimodal (124; 9%) treatment arm. The mean study sample size was 66 (SD 54). The mean year of publication was 2006 (SD 6). Six of the fifteen studies with funding information available (40%) were supported by pharmaceutical companies.

After excluding individuals who dropped out before the posttreatment assessment, 1,092 and 948 participants were retained for the meta-analysis for positive treatment response and remission, respectively.

FIGURE 1 HERE

TABLE 1 HERE

Positive treatment response

The meta-analysis indicated that percent reductions from baseline to posttreatment had sufficient discriminative ability (AUC = 0.89) to determine positive treatment response as defined by the CGI-I, our primary operational definition of positive treatment response. There was slight uncertainty regarding the confidence around the optimal cutoff because both the 35% and 40% reduction cutoffs were comprised by the ellipse according to visual inspection of the SROC curve (Figure 2 top panel). The Youden Index indicated a ≥ 35% reduction in CY-BOCS from baseline to posttreatment was optimal to determine positive treatment response as defined by the CGI-I (Figure 2 lower panels). The 35% reduction cutoff had a sensitivity of 83.9% (95% CI 83.7, 84.1) and a specificity of 81.7% (95% CI 81.5, 81.9) (Table 2A).

FIGURE 2 HERE

The meta-analysis also indicated that absolute reductions from baseline to posttreatment had sufficient discriminative ability (AUC = 0.83) to determine positive treatment response as defined by the CGI-I. There was slight uncertainty regarding the confidence around the optimal cutoff because both the 8-point and 10-point cutoffs were comprised by the ellipse according to visual inspection of the SROC curve (see Figure S1 top panel, available online). The Youden Index indicated a ≥ 10-point reduction in CY-BOCS from baseline to posttreatment was optimal to determine positive treatment response as defined by the CGI-I (see Figure S1 lower panels, available online). The 10-point reduction cutoff had a sensitivity of 75.8% (95% CI 75.5, 76.0) and a specificity of 77.8% (95% CI 77.6, 78.1) (see Table S2, available online).

The meta-analysis also indicated that percent reductions from baseline to posttreatment had sufficient discriminative ability (AUC = 0.92) to determine positive treatment response as defined by the RCI, our secondary operational definition of positive treatment response. There was more certainty regarding the confidence around the optimal cutoff because only the 40% reduction cutoff was comprised by the ellipse according to visual inspection of the SROC curve (see Figure S2 top panel, available online). The Youden Index indicated that a ≥ 40% reduction in CY-BOCS from baseline to posttreatment was optimal to determine positive treatment response as defined by the RCI (see Figure S2 lower panels, available online). The 40% reduction cutoff had a sensitivity of 86.0% (95% CI 85.8, 86.1) and a specificity of 86.1% (95% CI 85.9, 86.3) (see Table S3, available online).

Remission

The meta-analysis indicated that the posttreatment raw scores had sufficient discriminative ability (AUC = 0.90) to determine remission as defined by the CGI-S. There was some uncertainty regarding the confidence around the optimal cutoff because the 11, 12 and 13 raw score cutoffs were all comprised by the ellipse according to visual inspection of the SROC curve (Figure 3 top panel). The Youden Index indicated a posttreatment raw score ≤ 12 in CY-BOCS was optimal to determine remission as defined by the CGI-S (Figure 3 lower panels). The 12-point cutoff had a sensitivity of 82.0% (95% CI 81.8, 82.2) and a specificity of 84.6% (95% CI 84.4, 84.8) (Table 3).

FIGURE 3 HERE

TABLE 2 and 3 HERE

Discussion

We performed an IPD meta-analysis to evaluate the discriminative ability of the CY-BOCS in determining positive treatment response and remission in RCTs for pediatric OCD. We also determined the empirically optimal cutoffs corresponding to both of these outcomes. Meta-analyses indicated the percent (AUC = 0.89) and absolute (AUC = 0.83) reductions from baseline to posttreatment had sufficient discriminative ability to determine positive treatment response as defined by the CGI-I ≤ 2; the percent reductions also had sufficient discriminative ability (AUC = 0.92) to determine positive treatment response as defined by the RCI ≥ 1.96. For percent reductions, both ≥ 35% (CGI-I) and ≥ 40% (RCI) reductions were identified as optimal; for absolute reductions, a ≥ 10-point reduction was identified as optimal. Meta-analysis indicated the posttreatment raw scores had sufficient discriminative ability (AUC = 0.90) to determine remission as defined by the CGI-S ≤ 2. A posttreatment raw score ≤ 12 was identified as optimal.

Meta-analyses suggested percent reductions have slightly larger discriminative ability than absolute reductions in determining positive treatment response, and therefore, the former should be preferred in detriment of the latter. Regarding the optimal threshold for percent reductions, both ≥ 35% (CGI-I) and ≥ 40% (RCI) reductions have been found optimal depending on the criterion adopted to define positive treatment response. Given that the CGI-I represents the clinician's judgment of overall improvement while the RCI simply indicates that the reliable change is unlikely to be attributed to measurement error alone, we believe the available evidence provides a more compelling case to adopt the 35%

reduction cutoff, a strong indicator of positive treatment response, in future RCTs for pediatric OCD. Besides, the percent reductions are intertwined with scale-standardized metrics like the RCI; for instance, for every participant with a baseline score ≤ 25, a 10-point reduction always corresponds to a ≥ 40% reduction in the CY-BOCS. This could have artificially inflated the accuracy measures of the CY-BOCS and of certain cutoffs when the RCI was adopted to define positive treatment response.

Because, strikingly, our empirically-derived findings are nearly identical to the expert-based guidelines,[16] we recommend future RCTs adopt a ≥ 35% reduction from baseline to posttreatment to determine positive treatment response and a posttreatment raw score ≤ 12 to determine remission. Although adopting the CY-BOCS to determine positive treatment response and remission requires dichotomization of a continuous variable, which decreases power,[60, 61] from a statistical perspective it eliminates the need for the linearity assumption and makes data summarization more efficient.[62] Adopting a clear definition of positive treatment response and remission in pediatric OCD through the CY-BOCS also aids in clinical practice by making dichotomous outcome results interpretable with regard to a specific magnitude of improvement on the CY-BOCS in individual patients.

Although the present study is able to confirm the adequate discriminative ability of the CY-BOCS in determining positive treatment response and remission and to identify empirically optimal cutoffs for these outcomes, there are potential limitations of the CY-BOCS in measuring these outcomes which have to be disclosed. Exclusively relying on percent reductions and raw scores to determine positive treatment response and remission may be problematic as those do not take into account the clinician's judgment regarding global improvement or severity.[63] For instance, children with greater OCD severity may have more room for improvement in the CY-BOCS and therefore might meet a 35% reduction in CY-BOCS during treatment without achieving a clinically meaningful

reduction in symptom levels. Similarly, children with lower OCD severity may have less room to improve in the CY-BOCS and might meet a 12-point posttreatment CY-BOCS score without showing minimal symptoms in comparison to the baseline assessment. Indeed, the expert-based guideline[16] further recommends the CGI-I/CGI-S should be employed as necessary auxiliary measures beside the established CY-BOCS cutoffs to determine positive treatment response/remission in pediatric OCD.

Moreover, the CY-BOCS is anchored in the past week. Therefore, adopting this scale to determine positive treatment response/remission corresponds to defining these outcomes based on the severity of OCD symptoms over a one-week period. Given OCD typically presents with a 'wax and wane' course of symptoms, it seems advisable that larger periods of sustained improvement (~ 1 month) should be experienced before declaring an individual as a 'positive responder' or 'remitter'. Indeed, in the expert-based guideline,[16] the majority of experts (56% for positive response, 58% for remission) considered one month as the required period to determine positive treatment response and remission among individuals with OCD. However, because the CY-BOCS was developed and validated to measure OCD symptoms over the past week, clinical-researchers would ideally be required to extend follow-up periods for an additional month after the posttreatment assessment to measure OCD symptoms for four consecutive weeks. Alternatives to this approach would be to evaluate the validity and stability of the 'positive responders' and 'remitters' as based on one single posttreatment CY-BOCS score over a longer period of follow-up (e.g. 1 month), or to develop and validate a version of the scale which would measure OCD symptoms over one month instead of one week. To date, this important problem has yet to be adequately explored and additional research is required.

This study has several strengths. We were able to collect IPD from multiple sites across the world, demonstrating the importance of collaborative cross-site research; to

include a sample size at least 4-times bigger than those included by the two previous studies on the topic, increasing the statistical power of our analyses[19]; to adopt a rigorous systematic review and DTA meta-analysis methodology; and to provide open access to our scripts, hopefully aiding future replication/follow-up studies on the topic. The limitations of this study should also be noted. We only included IPD for 50% of the RCTs for pediatric OCD which were considered eligible in our systematic review of the literature. Although there were not large discrepancies in sociodemographic characteristics of participants from included versus non-included studies, non-included RCTs more frequently recruited participants from continents other than the Americas, enrolled participants to pharmacological treatment arms, had larger sample sizes, were older and received funding from pharmaceutical companies. Multiple factors can help explain why data acquisition for pharmacological trials was suboptimal, but perhaps most important is the fact that the pharmacological RCTs for pediatric OCD date about 15-20 years ago[7, 8, 10, 64]; of note, it is also difficult to acquire individual level participant information from industry given the bureaucracy and obstacles towards obtaining these data. Regardless, we cannot discard the hypothesis that results could have been modified if a larger proportion of data from eligible studies were included.[65] The samples included in each RCT were predominantly composed of white individuals, indicating additional efforts are required to increase race/ethnicity diversity among participants in RCTs for pediatric OCD; as a consequence, it is possible, although unlikely, that the findings from this study are not generalizable to race/ethnicity minorities such as African-American/Black, Asian-American and Hispanic/Latino individuals. Although our study was adequately powered, the sample size was still not large enough to enable the estimation of multiple models with a larger number of parameters; it is possible more complex models (e.g. random intercepts, random slopes) would provide a better fit to the data.

In conclusion, this study provides strong empirical support for the discriminative ability of the CY-BOCS in determining positive treatment response and remission in pediatric OCD RCTs. Empirically derived cutoffs for these outcomes have also been determined. Specifically, a ≥ 35% reduction from baseline to posttreatment and a posttreatment raw score ≤ 12 should be adopted by future RCTs of interventions for youth with OCD to determine positive treatment response and remission, respectively. Considering percent reductions and raw scores do not consider the clinician's judgment regarding global improvement or severity, in instances when CGI data is also available from the same participants, we further suggest that a combination of CY-BOCS and CGI scores be used. Also, additional research is required to investigate the validity and stability of 'positive responders' and 'remitters' as based on one single posttreatment CY-BOCS score over a longer period of follow-up (e.g. 1 month) considering the 'wax and wane' pattern of OCD symptoms.

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Table 1. Characteristics of Included Studies

Study	Country	Age[a]	Gender[b]	Race/ethnicity[c]	Treatment arms	N	Endpoint[d]	Outcomes	Funding
Asbahr_2005[6]	BR	13.1 (2.6)	65	Not reported	SSRI; GCBT	40	12	CGI-S	FAPESP
Comer_2017[34]	US	6.7 (1.3)	59	91	FB-CBT; VTC-FB-CBT	22	14	CGI-S; CGI-I	IOCDF/NIH
Fatori_2018[11]	BR	11.8 (3.2)	48	92	SSRI; GCBT	83	14	CGI-I	FAPESP
Franklin_2011[38]	US	13.6 (2.8)	47	93	SRI; SRI + CBT; SRI + iCBT	124	12	CGI-S; CGI-I	NIMH
Freeman_2008[39]	US	7.1 (1.3)	43	80	FB-CBT; FB-RT	42	14	CGI-I	NIMH
Freeman_2014[40]	US	7.2 (1.2)	47	90	FB-CBT; FB-RT	127	14	CGI-S; CGI-I	NIMH
Grant_2014[41]	US	14.5 (2.4)	73	Not reported	Riluzole; placebo	60	12	CGI-S; CGI-I	IP-NIMH
Lenhard_2017[42]	SE	14.6 (1.7)	54	Not reported	Internet-based CBT; WL	67	12	CGI-S; CGI-I	SRC/SCC
Lewin_2014[43]	US	5.8 (1.6)	71	87	CBT; Treatment as usual	31	6	CGI-S; CGI-I	USFRC
Li_2020[44]	US	11.9 (2.9)	73	100	N-acetyl cysteine; placebo	11	6	CGI-S; CGI-I	BBRF
Merlo_2010[47]	US	13.3 (3.0)	63	81	MI + CBT; PE + CBT	16	3	CGI-S; CGI-I	Not reported
Peris_2017[13]	US	13.1 (2.7)	56	65	PFIT + CBT; ST + CBT	62	12	CGI-I	BBRF/NIMH
Piacentini_2011[12]	US	12.2 (2.5)	37	78	FCBT; PRT	71	14	CGI-S; CGI-I	NIMH
Rosa-Álcazar_2019[51]	ES	6.6 (0.7)	75	100	Parent CBT; parent + child CBT	44	12	CGI-S; CGI-I	MEC
Shabani_2019[52]	IR	15.0 (1.5)	55	Not reported	SSRI + ACT; SSRI + CBT; SSRI	69	10/ 12	CGI-S; CGI-I	KUMS

Skarphedinsson_2015[9]	DE/NO/SE	14.0 (2.7)	48	Not reported	SSRI; CBT	50	16	CGI-S; CGI-I	Multiple
Storch_2007[55]	US	13.3 (2.7)	45	92	Intensive CBT; weekly CBT	40	3/ 14	CGI-S; CGI-I	Not reported
Storch_2010[56]	US	12.2 (2.8)	63	97	DCS + CBT; placebo + CBT	30	8	CGI-S; CGI-I	BBRF/NIMH
Storch_2011[54]	US	11.1 (2.6)	61	74	CBT via web-camera; WL	31	12	CGI-S; CGI-I	FMHI
Storch_2016[14]	US	12.8 (3.0)	46	88	DCS + CBT; placebo + CBT	142	8	CGI-S; CGI-I	NIMH
Turner_2014[57]	GB	14.3 (2.1)	54	Not reported	Telephone-based CBT; CBT	72	17	CGI-S; CGI-I	NIHR

Note: ACT = acceptance-commitment therapy; BBRF = Brain & Behavior Research Foundation; CBT = cognitive-behavioral therapy; DCS = d-cycloserine; FAPESP = Fundação de Amparo à Pesquisa do Estado de São Paulo; FB-CBT = family-based cognitive behavioral therapy; FB-RT = family-based relaxation training; FCBT = child CBT plus family intervention; FMHI = Florida Mental Health Institute; GCBT = group cognitive behavioral therapy; iCBT = instructions in CBT; IOCDF = International Obsessive-Compulsive Disorder Foundation; IP-NIMH = Intramural program of the National Institute of Mental Health; KUMS = Kashan University of Medical Science; MEC = Ministerio de Economía y Competividad del Gobierno de España; MI = motivational interviewing; Multiple = TrygFonden, the Danish Council for Strategic Research, Pulje til styrkelse af psykiatrisk Forskning i Region Midtjylland, The Center for Child and Adolescent Mental Health, Eastern and Southern Norway (RBUP), Stiftelsen Clas Groschinskys Minnesfond, Stiftelsen Clas Groschinskys Minnesfond; NIH = National Institute of Healh; NIHR = National Institute for Health Research; NIMH = National Institute of Mental Health; PE = psychoeducation; PFIT = positive family interaction therapy; PRT = psychoeducation/ relaxation training; SCC = Stockholm County Council; SRC = Swedish Research Council; SRI = serotonin reuptake inhibitor; ST = standard treatment; SSRI = selective serotonin reuptake inhibitor; USFRC = University of South Florida Research Counsel; VTC-FB-CBT = videoteleconferencing family-based cognitive-behavioral therapy

[a] mean and standard deviation

[b] percentage of male participants

[c] percentage of individuals who self-identified as white

[d] weeks

Table 2. Accuracy Measures of Children's Yale-Brown Obsessive-Compulsive Scale Percent Reductions for Response According to a Clinical Global Impressions - Improvement score ≤ 2

Cutoffs %	Sens (%)	95% CI (%)	Spec (%)	95% CI (%)	*J* [a]	95% CI
5	98.0	97.9 – 98.0	32.7	32.4 – 33.0	30.6	30.3 – 30.9
10	97.1	97.0 – 97.1	41.3	40.9 – 41.6	38.3	38.0 – 38.7
15	95.8	95.8 – 95.9	50.4	50.1 – 50.7	46.2	45.9 – 46.6
20	94.1	94.0 – 94.1	59.6	59.2 – 59.9	53.6	53.2 – 54.0
25	91.6	91.5 – 91.7	68.1	67.8 – 68.4	59.7	59.3 – 60.1
30	88.3	88.2 – 88.4	75.5	75.3 – 75.8	63.8	63.5 – 64.2
35	**83.9**	**83.7 – 84.1**	**81.7**	**81.5 – 81.9**	**65.6**	**65.3 – 66.0**
40	78.3	78.0 – 78.5	86.6	86.5 – 86.8	64.9	64.5 – 65.3
45	71.3	71.1 – 71.6	90.4	90.2 – 90.5	61.7	61.3 – 62.0
50	63.2	62.9 – 63.5	93.1	93.0 – 93.2	56.3	55.9 – 56.7
55	54.2	53.9 – 54.6	95.2	95.1 – 95.2	49.4	49.0 – 49.8
60	45.0	44.7 – 45.3	96.6	96.6 – 96.7	41.6	41.3 – 42.0
65	36.1	35.8 – 36.4	97.6	97.6 – 97.7	33.7	33.4 – 34.1
70	28.1	27.8 – 28.4	98.4	98.3 – 98.4	26.4	26.2 – 26.7

Table 3. Accuracy measures of Children's Yale-Brown Obsessive-Compulsive Scale raw scores for remission according to a Clinical Global Impressions – Severity score ≤ 2

Cutoffs	Sens (%)	95% CI (%)	Spec (%)	95% CI (%)	*J* [a]	95% CI
5	34.4	34.0 – 34.7	98.0	97.9 – 98.0	32.3	31.9 – 32.7
6	41.6	41.2 – 42.0	97.2	97.2 – 97.3	38.9	38.4 – 39.3
7	49.3	48.9 – 49.7	96.3	96.2 – 96.3	45.5	45.1 – 46.0
8	57.0	56.6 – 57.3	95.0	94.9 – 95.1	51.9	51.5 – 52.4
9	64.3	64.0 – 64.7	93.3	93.2 – 93.4	57.6	57.2 – 58.1
10	71.1	70.7 – 71.4	91.1	91.0 – 91.2	62.1	61.7 – 62.6
11	77.0	76.7 – 77.3	88.2	88.1 – 88.4	65.2	64.8 – 65.6
12	**82.0**	**81.8 – 82.2**	**84.6**	**84.4 – 84.8**	**66.6**	**66.2 – 67.1**
13	86.1	85.9 – 86.3	80.2	79.9 – 80.4	66.3	65.9 – 66.7
14	89.4	89.3 – 89.6	74.8	74.5 – 75.1	64.2	63.8 – 64.6
15	92.0	91.9 – 92.1	68.5	68.2 – 68.9	60.5	60.1 – 61.0
16	94.0	93.9 – 94.1	61.5	61.2 – 61.9	55.5	55.1 – 56.0

17	95.5	95.5 – 95.6	54.0	53.6 – 54.4	49.5	49.1 – 50.0
18	96.7	96.6 – 96.7	46.3	45.9 – 46.6	43.0	42.5 – 43.4
19	97.5	97.5 – 97.6	38.7	38.4 – 39.1	36.3	35.9 – 36.7
20	98.2	98.2 – 98.2	31.7	31.4 – 32.0	29.9	29.5 – 30.2

Note: Bold indicates optimal cutoff. Sens = sensitivity; Spec = specificity
a – Youden Index

FIGURES

Figure 1. PRISMA Flowchart.

Figure 2. Children's Yale Brown Obsessive-Compulsive Scale percent reduction cutoffs and positive treatment response as defined by the Clinical Global Impressions-Improvement scale ≤ 2. The top panel shows the summary receiver operating characteristics (SROC) curve, which demonstrates the overall performance of the Children's Yale-Brown Obsessive-Compulsive Scale. Points were colored at the study-level. Confidence intervals for pooled sensitivity (solid) and specificity (dash) estimates are also illustrated. Both 35% and 40% reduction cutoffs were comprised by the ellipse, which indicates the uncertainty around the optimal cutoff. The lower left panel shows the trade-offs between pooled sensitivity (solid) and specificity (dash) estimates for each percent reduction cutoff. The 35% reduction cutoff displayed adequate sensitivity and specificity. The lower right panel shows the Youden Index, a statistic that maximizes both sensitivity and specificity, for each cutoff. The 35% reduction cutoff was found to maximize accuracy measures according to the Youden Index.

Figure 3. **Children's Yale Brown Obsessive-Compulsive Scale raw score cutoffs and remission as defined by the Clinical Global Impressions-Severity scale ≤ 2.** The top panel shows the summary receiver operating characteristics (SROC) curve, which demonstrates the overall performance of the Children's Yale-Brown Obsessive-Compulsive Scale. Points were colored at the study-level. Confidence intervals for pooled sensitivity (solid) and specificity (dash) estimates are also illustrated. The 11, 12 and 13 raw score cutoffs were comprised by the ellipse, which indicates the uncertainty around the optimal cutoff. The lower left panel shows the trade-offs between pooled sensitivity (solid) and specificity (dash) estimates for each raw score cutoff. The 12-point cutoff displayed adequate sensitivity and specificity. The lower right panel shows the Youden Index, a statistic that maximizes both sensitivity and specificity, for each cutoff. The 12-point cutoff was found to maximize accuracy measures according to the Youden Index.