REVIEW

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Systematic Review and Meta-Analysis: Cognitive-Behavioral Therapy for Obsessive-Compulsive Disorder in Children and Adolescents

Camilla Funch Uhre, MSc, Valdemar Funch Uhre, MSc, Nicole Nadine Lønfeldt, MSc, PhD, Linea Pretzmann, MSc, Signe Vangkilde, MSc, PhD, Kerstin Jessica Plessen, MD, PhD, Christian Gluud, MD, Dr Med Sci, Janus Christian Jakobsen, MD, PhD, Anne Katrine Pagsberg, MD, PhD

Ms. C.F. Uhre and Mr. V.F. Uhre are co-first authors of this article.

Objective: To assess benefits and harms of cognitive-behavioral therapy (CBT) versus no intervention or versus other interventions for pediatric obsessive-compulsive disorder (OCD).

Method: We searched for randomized clinical trials of CBT for pediatric OCD. Primary outcomes were OCD severity, serious adverse events, and level of functioning. Secondary outcomes were quality of life and adverse events. Remission from OCD was included as an exploratory outcome. We assessed risk of bias and evaluated the certainty of the evidence with the Grading of Recommendations Assessment, Development and Evaluation (GRADE).

Results: Nine trials (N = 645) were included comparing CBT with no intervention and 3 trials (N = 146) comparing CBT with selective serotonin reuptake inhibitors (SSRIs). Compared with no intervention, CBT decreased OCD severity (mean difference [MD] = −8.51, 95% CI = −10.84 to −6.18, $p < .00001$, low certainty), improved level of functioning (patient-rated: standardized MD [SMD] = −0.90, 95% CI = −1.19 to −0.62, $p < .00001$, very low certainty; parent-rated: SMD = −0.68, 95% CI = −1.12 to −0.23, $p = .003$, very low certainty), had similar proportions of participants with adverse events (risk ratio = 1.06, 95% CI = 0.93−1.22, $p = .39$, GRADE: low certainty), and was associated with reduced risk of still having OCD (risk ratio = 0.50, 95% CI = 0.37−0.67, $p < .00001$, very low certainty). We had insufficient data to assess the effect of CBT versus no intervention on serious adverse events and quality of life. Compared with SSRIs, CBT led to similar decreases in OCD severity (MD = −0.75, 95% CI = −3.79 to 2.29, $p = .63$, GRADE: very low certainty), and was associated with similar risk of still having OCD (risk ratio = 0.85, 95% CI = 0.66−1.09, $p = .20$, very low certainty). We had insufficient data to assess the effect of CBT versus SSRIs on serious adverse events, level of functioning, quality of life, and adverse events.

Conclusion: CBT may be more effective than no intervention and comparable to SSRIs for pediatric OCD, but we are very uncertain about the effect estimates.

Key words: cognitive-behavioral therapy, obsessive-compulsive disorder, systematic review

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Obsessive-compulsive disorder (OCD) is among the most common psychiatric disorders, with an estimated prevalence of 1% to 3% in children and adolescents.[1,2] Pediatric OCD is associated with reduced quality of life, as well as familial, social, and occupational impairment.[3-7]

The recommended first-line treatment for pediatric OCD is cognitive-behavioral therapy (CBT) including exposure and response prevention.[5,8] Previous reviews support the recommendation of CBT for pediatric OCD,[9-18] but limitations such as not assessing risk of bias in included trials,[9-13] pooling results from randomized trials and noncontrolled studies,[9,13,14] or including only symptom severity as an outcome measure[15-17] may have led to inaccurate conclusions regarding the efficacy of CBT.

In this systematic review, we assessed beneficial and harmful effects of CBT versus no intervention and versus other interventions, in terms of symptom severity, level of functioning, quality of life, lack of remission, and adverse events, for OCD in children and adolescents. We assessed risk of bias in included trials, controlled for random errors due to sparse data or multiple testing using trial sequential

analysis (TSA),[19] and evaluated the certainty of the evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.[20]

METHOD

Protocol and Registration

The protocol for this systematic review was registered with PROSPERO on November 28, 2017 (CRD42017079118).

Search Strategy

We systematically searched for eligible trials in Cochrane's CENTRAL, MEDLINE, PsycINFO, EMBASE, LILACS, Science Citation Index Expanded on Web of Science, SSCI, and BIOSIS. The search strategy for MEDLINE is provided in Supplement 1, available online. Details on the search are provided in the protocol.

Trial Selection

Three authors (CU, VU, and LP) independently screened titles and abstracts and retrieved and screened all relevant full-text articles for eligibility. A fourth author (NL) was consulted to solve any discrepancies. We included all randomized clinical trials of CBT for children and adolescents (as defined by trialists) with a primary diagnosis of OCD, according to a standard diagnostic system (ie, the *International Classification of Diseases* [*ICD*][21] or the *Diagnostic and Statistical Manual of Mental Disorders* [*DSM*][22]). We included trials irrespective of language, setting, publication status, and publication year. We accepted any type of CBT defined as CBT by trialists. We accepted any non-CBT control intervention. Trials comparing CBT plus a co-intervention with the co-intervention alone (eg, CBT + selective serotonin reuptake inhibitors [SSRIs] versus SSRI) were included if the co-intervention was delivered similarly in the experimental and control groups.

Data Extraction and Outcomes

Three reviewers (CU, VU, and LP) independently extracted the following information from full-text articles of each included trial: author names; publication year; trial location; participant characteristics; sample size; interventions (number of sessions/dosage, duration, and format); mean scores and SDs for each specified outcome at baseline, end of treatment, and maximum follow-up; and information for risk of bias assessment. Our primary outcomes were: (1) symptom severity assessed with the Children's Yale−Brown Obsessive-Compulsive Scale (CY-BOCS)[23]; (2) serious adverse events, defined as death, any life-threatening event, hospitalization, persistent or significant loss of function, or disability[24]; and (3) level of functioning measured on any validated scale. Our secondary outcomes were: (1) quality of life measured on any validated scale; and (2) adverse events, defined as any adverse event not classified as a serious adverse event. Our exploratory outcome was lack of remission from OCD diagnosis.

Risk of Bias Evaluation

We used the guidelines provided in the *Cochrane Handbook for Systematic Reviews of Interventions* to evaluate risk of bias in the included trials.[25] Three authors (CU, VU, and LP) independently classified the trials according to specific criteria (detailed in the protocol). Disagreements were resolved with a third author (JJ). We assessed selection bias (allocation sequence generation and allocation concealment), performance bias (blinding of trial participants and treatment providers), detection bias (blinding of outcome assessors), attrition bias (incomplete outcome data), reporting bias (selective outcome reporting), and other bias (eg, vested interest bias). Only trials assessed at low risk of bias within all assessed domains were classified as trials at overall low risk of bias.

Data Synthesis and Meta-analyses

We followed the recommendations of the *Cochrane Handbook for Systematic Reviews of Interventions,*[25] Keus *et al.*,[26] and the eight-step assessment for meta-analyses described by Jakobsen *et al.*[27] We used Cochrane's Review Manager 5[28] to analyze data.

For continuous outcomes, we calculated mean differences (MDs) with 95% CIs. When different scales were used to measure the same outcome type, we calculated standardized mean differences (SMDs) by dividing the MD between a CBT and control group by the pooled SD at end of treatment. To aid interpretation of the intervention effect, we re-expressed SMDs in the unit of the scale most commonly used in the included trials by multiplying the SMD with the pooled SD at end of treatment of the CBT and control groups that had scores on this scale.[29] We multiplied scores by −1 for scales on which increases represent beneficial outcomes, to ensure consistent directionality across scales. For dichotomous outcomes, we calculated risk ratios with 95% CIs. For all outcomes, the intervention effects were assessed with both random-effects[30] and fixed-effect[31] meta-analyses, and the most conservative estimate was reported as the main result.[27] If the two estimates were similar, we used the estimate with the widest CI. We planned to assess three primary and two secondary outcomes. Following the recommendations of Jakobsen *et al.*, we therefore considered a p value of $\leq .025$ for primary outcomes and of $\leq .033$ for secondary outcomes as thresholds for statistical significance.[27] We used the

conventional p value of .05 for the exploratory outcome. We inspected forest plots and trial characteristics to identify potential sources of heterogeneity. We assessed the presence and quantities of statistical heterogeneity by the I^2 statistic, with significance set at $p < .10$.[32,33] When multiple intervention groups were reported in a single trial, we included only the relevant groups. If two comparisons from the same trial were combined in the same meta-analysis, we halved the control group to avoid double counting.[25]

We contacted trial authors to obtain missing data for quantitative analyses and risk of bias assessment. For continuous outcomes, we calculated SDs using other reported data when necessary (eg, calculating SDs from reported CIs or standard errors).

Trial Sequential Analysis

Meta-analyses run the risk of random errors due to sparse data and repetitive testing of accumulating data when updating reviews.[19,34] We controlled for risks of false-positive results (type I errors) and false-negative results (type II errors), and estimated the information size required to detect or reject an anticipated minimal clinically relevant difference between comparison groups by performing TSA[19] on each outcome (details are provided in the protocol and the TSA manual[35]).

Planned Subgroup Analyses

We performed the following planned subgroup analyses for the primary outcomes (CY-BOCS score, serious adverse events, and level of functioning) when at least two trials or comparisons provided data for the analysis: type of control intervention, type of CBT assessed (ie, individual, group format, or Internet-based), and trials with blinded outcome assessors compared to trials without blinded outcome assessors. We had insufficient data for the following planned subgroup analyses for all primary outcomes: trials at low risk of bias versus trials at high risk of bias, children (<13 years of age) versus adolescents (≥13 years of age), severe OCD versus mild to moderate OCD, and OCD with one or more comorbid psychiatric disorders versus OCD without comorbidity. We used the test for subgroup differences in Review Manager.[28]

Sensitivity Analyses

We performed sensitivity analyses to assess the potential impact of missing data. A "best/worst" scenario was assessed for continuous outcomes by assuming that all patients lost to follow-up in CBT had a beneficial outcome (the group mean plus 2 SD) and that all patients lost to follow-up in the control group had a harmful outcome (the group mean minus 2 SD). A "best/worst" scenario was assessed for dichotomous outcomes by assuming that no patients lost to follow-up in CBT had an event and that patients lost to follow-up in the control group had an event. In addition, we assessed the reverse "worst/best" scenarios for all outcomes. As supplementary analyses, we repeated all analyses for continuous outcomes with 1 SD instead of 2 SD.[27]

Protocol Deviations

In our protocol, we defined remission as not meeting the criteria for OCD as assessed with a diagnostic interview or having a CY-BOCS score ≤12 in combination with a Clinical Global Impression–Severity (CGI-S) score of 1 (not at all ill) or 2 (borderline mentally ill).[36] However, as only three trials assessed remission in either of these ways, we accepted any reported measure of remission.

RESULTS

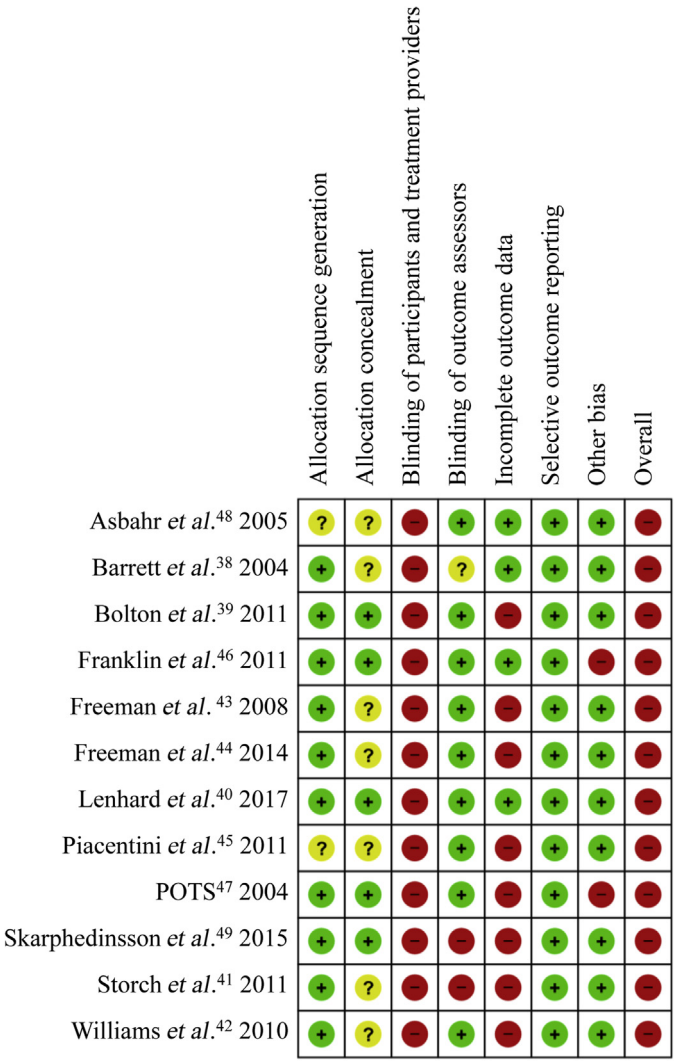
Study Selection and Characteristics

We completed the primary search on July 27, 2017, and the latest search on November 21, 2018 (see the PRISMA flow diagram[37] in Figure S1, available online). Study characteristics are presented in Table S1, available online. Twelve randomized clinical trials were eligible for inclusion in the review ($n_{analyzed} = 819$; age range 4−18 years; 52% female patients; 65% patients with ≥1 comorbid disorder; baseline mean CY-BOCS score = 23.9; 5−14 planned CBT sessions delivered over 12−14 weeks). Five trials[38-42] compared CBT with waitlist. Three trials[43-45] compared CBT with a control intervention including psychoeducation and relaxation training, defined as placebo psychotherapy in all three trials. Two trials[46,47] compared CBT with "no intervention" with SSRI co-intervention delivered similarly in both groups (ie, CBT+SSRI versus SSRI); one of these trials[47] also included an active control comparison of CBT versus pill-placebo. In total, three eligible trials[47-49] compared CBT with SSRI. Based on the trials identified, we did two comparisons: (1) CBT versus "no intervention" (including waitlist, placebo, and no intervention, with a co-intervention delivered similarly in the experimental and control groups); and (2) CBT versus SSRIs. We calculated effects of interventions only at end of treatment, as we had insufficient data to evaluate long-term effects. We found no substantial discrepancies between effect estimates from random-effects and fixed-effect meta-analyses (see Table S2, available online).

Risk of Bias Assessment

Details on the assessment of risk of bias are presented in Figure 1. All trials and all meta-analysis results were rated at overall high risk of bias. Given the nature of psychotherapeutic interventions, no trial had adequate blinding of

FIGURE 1 Risk of Bias in the Included Randomized Clinical Trials



Note: Random allocation sequence generation was adequate in 10 of 12 trials (83%); allocation concealment was adequate in 5 of 12 trials (42%); blinding of trial participants and treatment providers was adequate in 0 of 12 trials (0%); blinding of outcome assessors was adequate in 9 of 12 trials (75%); there was low risk of bias for "incomplete outcome data" in 4 of 12 trials (33%); there was low risk of bias for "selective outcome reporting" in 12 of 12 trials (100%); and the "other bias" domain (eg, vested interest) was adequate in 10 of 12 trials (83%). Green (+) = low risk of bias; yellow (?) = unclear risk of bias; red (–) = high risk of bias. Please note color figures are available online.

participants and treatment providers. Only one trial[40] had low risk of bias in the remaining bias domains and was therefore potentially less affected by bias.

Comparison 1: CBT Versus "No Intervention"

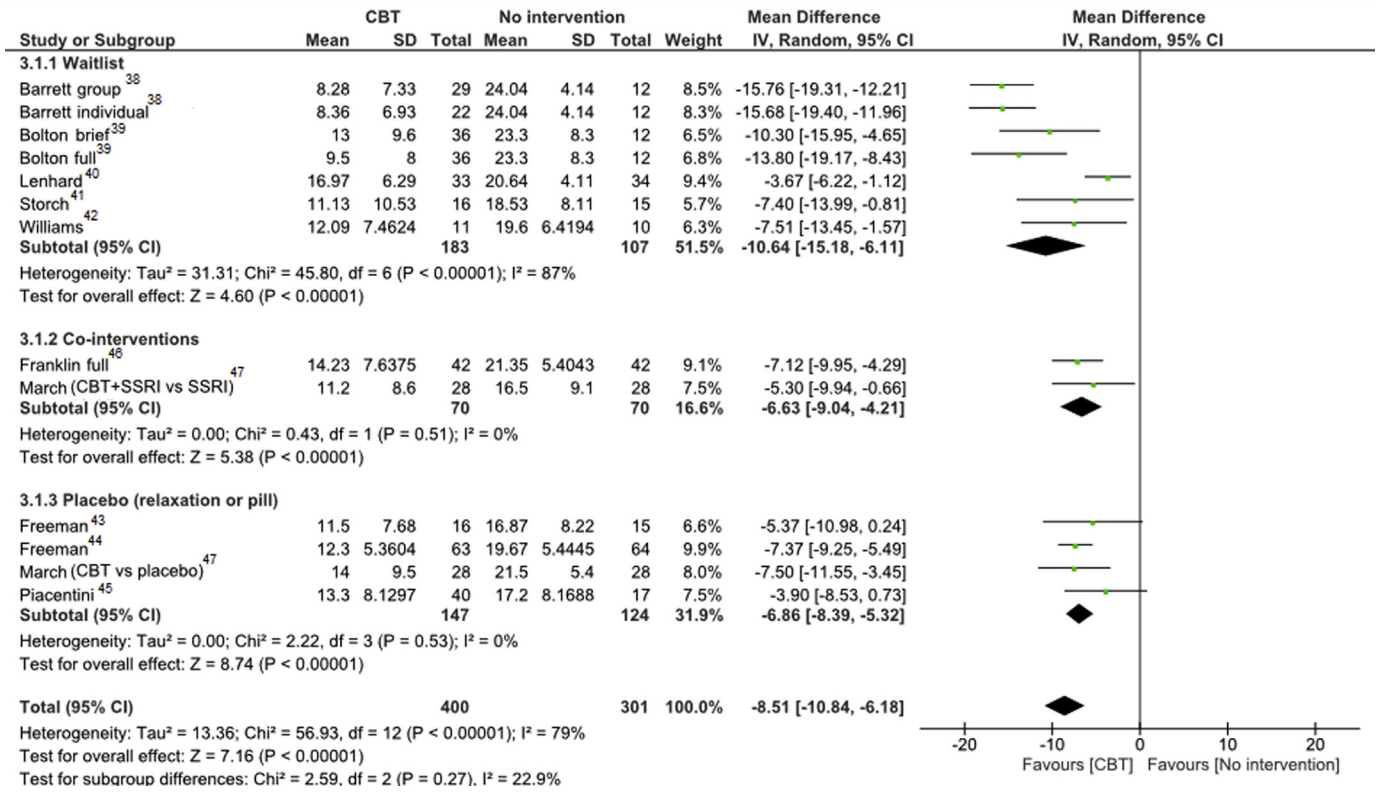
Primary Outcome: Children's Yale–Brown Obsessive-Compulsive Scale. Ten trials[38-47] ($n_{analyzed}$ = 701; 13 comparisons) tested the efficacy of CBT in reducing OCD symptom severity on the CY-BOCS scale versus a control condition considered ineffective for OCD. Five trials[38-42] used waitlist control; two trials[46,47] used "no intervention" with an SSRI co-intervention applied equally in both comparison groups (one of these trials[47] also included a control condition with pill-placebo); and three trials[43-45] used placebo psychotherapy. Random-effects meta-analysis showed evidence of a difference in favor of CBT versus "no intervention" (MD = −8.51, 95% CI = −10.84 to −6.18, $p < .00001$) (Figure 2). TSA showed that this finding is unlikely to be a random finding due to lack of power or multiple testing (Figure S2, available online). Missing outcome analysis showed that the finding is unlikely to have been caused by missing outcome data bias (Table S3, available online).

The I^2 was 79% ($\chi^2 = 56.93$, $p < .00001$), suggesting substantial heterogeneity. Visual inspection of the forest plot indicated heterogeneity primarily in the CBT versus waitlist comparison. In 2[38,41] of the 5 trials comparing CBT with waitlist, the waitlist duration was considerably shorter than the CBT duration (eg, 12 weeks of CBT versus 4 weeks of waitlist). Excluding these trials from the analysis reduced I^2 to 45% but did not substantially alter the meta-analysis result (MD = −6.81, 95% CI = −8.45 to −5.18, $p < .00001$). Subgroup analyses showed no evidence of differences between the types of control conditions, but did show evidence of a difference in favor of conventional CBT versus Internet-delivered CBT (see Supplement 2, available online).

Primary Outcome: Serious Adverse Events. Three trials[40,44,46] assessed serious adverse events for CBT versus a control considered ineffective for OCD. One trial[40] used waitlist control, one trial[46] used "no intervention" with an SSRI co-intervention, and one trial[44] used placebo psychotherapy. None of the 137 patients in CBT experienced a serious adverse event compared with one of 138 patients (0.7%) in the "no intervention" group. The reported event was a suicide attempt by a participant with comorbid depression in a "no intervention" with SSRI in the co-intervention group. We did not perform meta-analysis, missing outcome analysis, or TSA for serious adverse events, because no events were observed for CBT and only one event was observed for "no intervention."

Primary Outcome: Level of Functioning. Five trials[39-41,44,45] ($n_{analyzed}$ = 377, 6 comparisons) assessed the effect of CBT on level of functioning versus a control considered ineffective for OCD. Three trials[39-41] used a waitlist control, and two trials[44,45] used placebo psychotherapy. Three trials[39,41,45] used the Child Obsessive-Compulsive Impact Scale–child rated (COIS-C) and –parent rated (COIS-P); one trial[40] used the Education, Work and

FIGURE 2 Effect of Cognitive-Behavioral Therapy Versus "No Intervention" on Severity of Obsessive-Compulsive Disorder Measured on the Children's Yale–Brown Obsessive-Compulsive Scale



Note: *CBT = cognitive behavioral therapy; SSRI = selective serotonin reuptake inhibitors. Please note color figures are available online.*

Social Adjustment Scale–child rated (EWSAS-C) and –parent rated (EWSAS-P); and one trial[44] used only COIS-P.

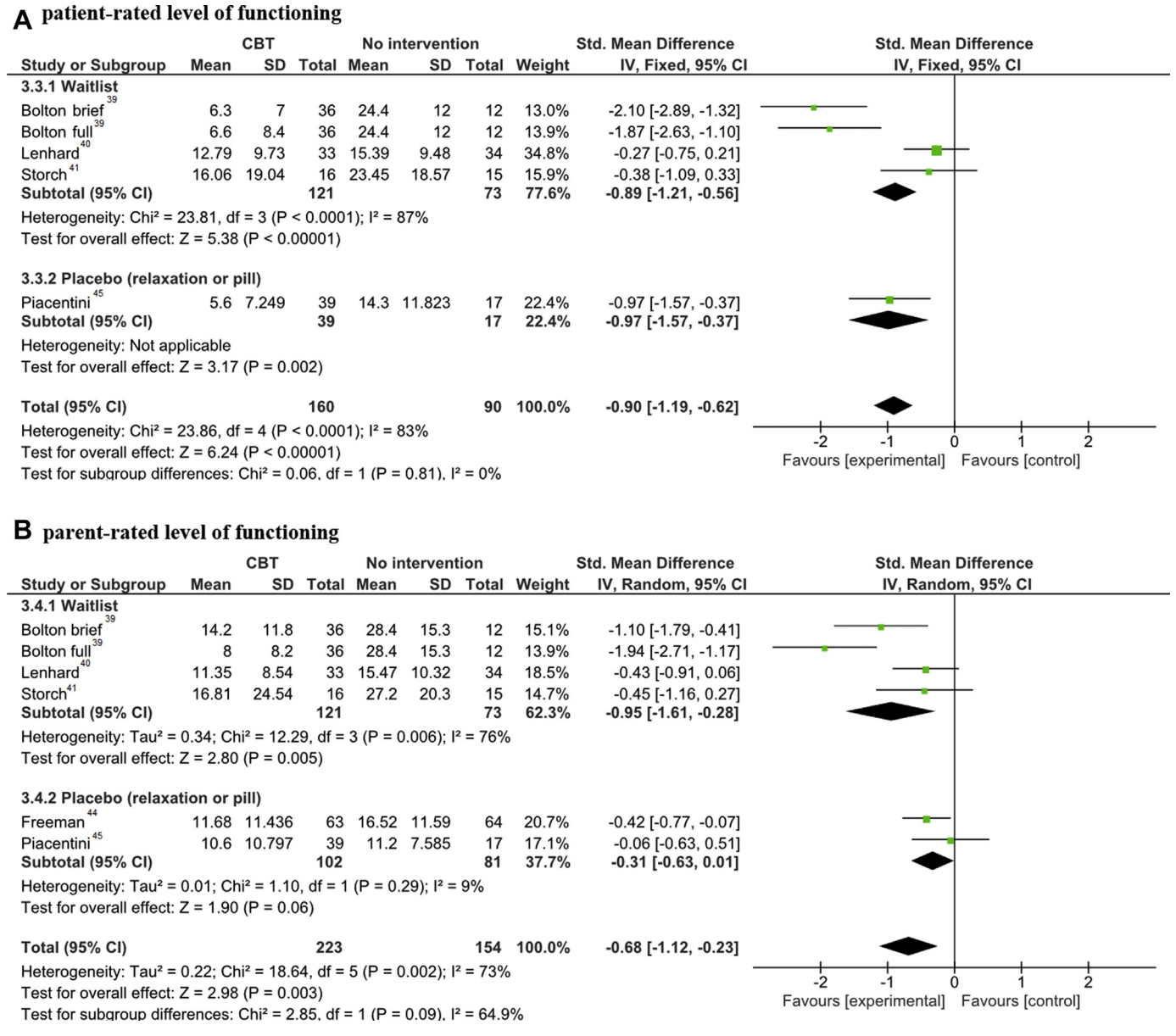
Patient-Rated Level of Functioning. Fixed-effect meta-analysis on patient-rated level of functioning showed evidence of a difference in favor of CBT versus "no intervention" (SMD = –0.90, 95% CI = –1.19 to –0.62, $p <$ .00001) (Figure 3a). Missing outcome analysis showed that this finding is unlikely to have been caused by missing outcome data bias (Table S3, available online). Restricting the analysis to the three trials reporting results from COIS-C did not substantially alter the meta-analysis result. TSA restricted to the trials reporting results from COIS-C showed that this finding is unlikely to be a random finding due to lack of power or multiple testing (Figure S3, available online).

The I^2 was 83% ($\chi^2 = 23.86$, $p < .0001$), suggesting substantial heterogeneity. Visual inspection of the forest plot indicated that one trial[39] had a markedly larger intervention effect estimate. Excluding this trial from the analysis reduced I^2 to 40% but did not substantially alter the meta-analysis result. Subgroup analyses showed no evidence of differences between the types of control conditions, but did show evidence of a difference in favor of conventional CBT versus Internet-delivered CBT (Supplement 2, available online).

Parent-Rated Level of Functioning. Random-effects meta-analysis on parent-rated level of functioning showed evidence of a difference in favor of CBT versus "no intervention" (SMD = –0.68, 95% CI = –1.12 to –0.23, $p = .003$) (Figure 3b). Missing outcome analysis showed that this finding is sensitive to missing outcome data bias (Table S3, available online). TSA restricted to the trials reporting results from COIS-P showed that this finding may be a random finding due to lack of power or multiple testing (Figure S4, available online).

The I^2 was 73% ($\chi^2 = 18.64$, $p = .002$), suggesting substantial heterogeneity. Visual inspection of the forest plot indicated that one trial[39] had a markedly larger intervention effect estimate. Excluding this trial from the analysis reduced I^2 to 0% but did not substantially alter the meta-analysis result. Subgroup analyses showed no evidence

FIGURE 3 Effect of Cognitive-Behavioral Therapy Versus "No Intervention" on Patient-Rated Level of Functioning (a) and Parent-Rated Level of Functioning (b)



Note: *CBT = cognitive-behavioral therapy. Please note color figures are available online.*

of differences between the types of control conditions (Supplement 2, available online).

Secondary Outcome: Quality of Life. Two trials[39,44] ($n_{analyzed}$ = 223, 3 comparisons) assessed the effect of CBT on quality of life versus a control considered ineffective for OCD. One trial[39] used waitlist control and assessed quality of life with the Manchester Short Assessment of Quality of Life (MANSA). One trial[44] used placebo psychotherapy and assessed quality of life with the Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire (PQ-LES-Q). Random-effects meta-analysis suggested a difference in favor of CBT versus "no intervention" (SMD = –0.39, 95% CI = –0.77 to –0.02, p = .04) (Figure S5, available online), although this effect did not meet our predefined significance threshold of $p \leq 0.025$. Missing outcome analysis showed that this finding is sensitive to missing outcome data bias (Table S3, available online). The I^2 was 33% (χ^2 = 2.98, p = .23), suggesting negligible heterogeneity. We had insufficient data for TSA.

Secondary Outcome: Adverse Events. Three trials[40,44,46] ($n_{analyzed}$ = 275, 3 comparisons) assessed adverse events for CBT versus a control considered ineffective for OCD. One trial[40] used waitlist control, one trial[46] used "no intervention" with an SSRI co-intervention, and one trial[44] used placebo psychotherapy. A total of 49 of 137 patients (35.8%) in CBT experienced an adverse event compared with 44 of 138 patients (31.9%) in the "no intervention." Two of the trials[40,44] reported the types of adverse events. In one trial,[40] the events recorded were mood problems (9%), OCD-related symptoms (6%), anxiety (4%), and sleep problems (1%). The overall occurrence was similar between the groups, and no type of event was more common in either group. The other trial[44] recorded a single event of aggressive impulsive behavior in the CBT group. Random-effects meta-analysis showed no evidence of a difference between CBT and "no intervention" in the risk of experiencing an adverse event (RR = 1.06, 95% CI 0.93–1.22, $p = 0.39$) (Figure S6, available online). TSA showed that this finding may be a random finding due to lack of power or multiple testing (Figure S7, available online). Missing outcome analysis showed that the finding is unlikely to have been caused by missing outcome data bias (Table S3, available online). The I^2 was 0% ($\chi^2 = 1.08$, $p = .58$), suggesting negligible heterogeneity.

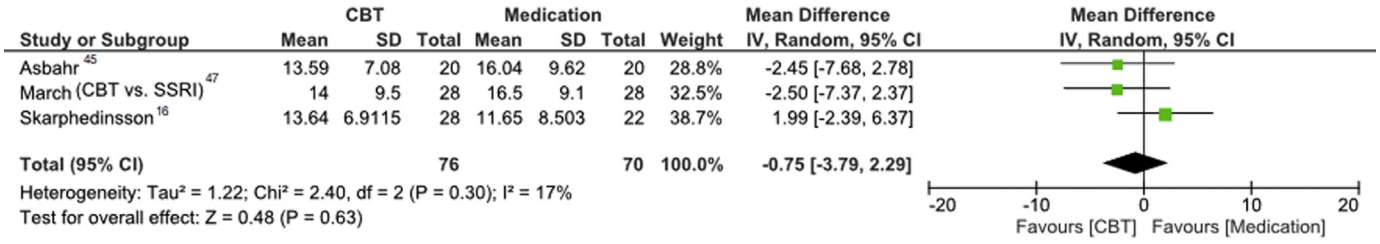
Exploratory Outcome: Lack of Remission. Seven trials[38-41,43,45,47] ($n_{analyzed}$ = 480, 10 comparisons) assessed the risk of still having OCD at end of CBT compared with a control considered ineffective for OCD. Four trials[38-41] used waitlist control; one trial[47] used "no intervention" with an SSRI co-intervention and included an additional control condition with pill-placebo; and two trials[43,45] used placebo psychotherapy. Two trials[38,39] used the Anxiety Disorders Interview Schedule–parent version (ADIS-P) clinical interview to assess remission; one trial[40] used a combination of CY-BOCS score ≤12 and CGI-S score ≤2; one trial[41] used a combination of ADIS-P severity rating ≤3 and CY-BOCS score ≤10; one trial[47] used CY-BOCS score ≤10, one trial[45] used CY-BOCS score ≤11; and one trial[43] used CY-BOCS score ≤12. A total of 141 of 295 patients (47.8%) in CBT compared with 171 of 185 patients (92.4%) in the "no intervention" group still had OCD at the end of treatment. Random-effects meta-analysis showed that patients were less likely to still have OCD at the end of treatment in the CBT versus "no intervention" group (RR = 0.50, 95% CI = 0.37–0.67, $p < .00001$) (Figure S8, available online). TSA showed that this finding is unlikely to be a random finding due to lack of power or multiple testing (Figure S9, available online). Missing outcome analysis showed that the finding is unlikely to have been caused by missing outcome data bias (Table S3, available online).

The I^2 was 82% ($\chi^2 = 50.34$, $p < .00001$), suggesting substantial heterogeneity. Visual inspection of the forest plot indicated that one trial[40] had a smaller intervention effect estimate and markedly smaller CI. Excluding this trial from the analysis reduced I^2 to 58% but did not substantially alter the meta-analysis result.

Comparison 2: CBT Versus Pharmacological Intervention

Primary Outcome: Children's Yale–Brown Obsessive-Compulsive Scale. Three trials[47-49] ($n_{analyzed}$ = 146, 3 comparisons) tested the efficacy of CBT in reducing OCD symptom severity assessed with CY-BOCS versus an SSRI intervention. One trial[48] did not report end-of-treatment CY-BOCS scores and SDs. As we were unable to obtain these data from the trial authors, we used values retrieved by authors of a previous review.[50] Random-effects meta-analysis showed no evidence of a difference between CBT and SSRI (MD = –0.75, 95% CI = –3.79 to 2.29, $p = .63$) (Figure 4). TSA showed that this finding is unlikely to be a random finding due to lack of power or multiple testing (Figure S10, available online). Missing outcome analysis showed that the finding is unlikely to have been caused by missing outcome data bias (Table S4, available online). The

FIGURE 4 Effect of Cognitive-Behavioral Therapy Versus Selective Serotonin Reuptake Inhibitors on Severity of Obsessive-Compulsive Disorder Measured on the Children's Yale–Brown Obsessive-Compulsive Scale



Note: *CBT = cognitive behavioral therapy; SSRI = selective serotonin reuptake inhibitors. Please note color figures are available online.*

I^2 was 17% ($\chi^2 = 2.40$, $p = .30$), suggesting negligible heterogeneity.

Primary Outcome: Serious Adverse Events. Three trials[47-49] assessed serious adverse events for CBT versus an SSRI intervention. However, two of these trials[47,49] assessed only SSRI-related serious adverse events. The remaining trial[48] reported having assessed serious adverse events in both comparison groups but did not report numbers of events or participants affected.

Primary Outcome: Level of Functioning. One trial[49] ($n_{analyzed} = 50$, one comparison) assessed the effect of CBT on level of functioning versus an SSRI intervention. This trial assessed patient-rated level of functioning with COIS-C and parent-rated level of functioning with COIS-P. There was no evidence of a difference between CBT and SSRI on parent-rated level of functioning (MD = 1.70, 95% CI = –6.45 to 9.85, $p = .68$) or patient-rated level of functioning (MD = 6.95, 95% CI = 0.15–13.75, $p = .05$).

Secondary Outcome: Quality of Life. No trials assessed the effect of CBT on quality of life versus an SSRI intervention.

Secondary Outcome: Adverse Events. Three trials[47-49] assessed adverse events for CBT versus an SSRI intervention. However, two of these trials[47,49] assessed only SSRI-related adverse events. The remaining trial[48] assessed adverse events in both comparison groups. This trial reported more weight loss in the SSRI group and more nausea and abdominal discomfort in the CBT group, but did not report numbers of events or participants affected.

Exploratory Outcome: Lack of Remission. Two trials[47,49] ($n_{analyzed} = 106$, 2 comparisons) assessed the risk of still having OCD at end of CBT compared with an SSRI intervention. Both trials defined remission as CY-BOCS score ≤ 10. A total of 36 of 56 patients (64.3%) in CBT compared with 38 of 50 patients (76.0%) in the SSRI intervention still had OCD at the end of treatment. Random-effects meta-analysis showed no evidence of a difference between CBT and SSRI intervention in the likelihood of still having OCD (RR = 0.85, 95% CI = 0.66–1.09, $p = .20$) (Figure S11, available online). TSA showed that this finding may be a random finding due to lack of power or multiple testing (Figure S12, available online). Missing outcome analysis showed that the finding is unlikely to have been caused by missing outcome data bias (Table S4, available online). The I^2 was 0% ($\chi^2 = 0.53$, $p = .47$), suggesting negligible heterogeneity.

Publication Bias

We did not have enough trials, and the clinical heterogeneity was too substantial, to perform any of the assessments of publication bias specified in our protocol.

GRADE Assessment

The GRADE assessments are presented in Table 1. The certainty of evidence was low or very low for all outcomes.

DISCUSSION

We included 12 randomized clinical trials in the present systematic review of CBT for pediatric OCD. First, we compared CBT with "no intervention." Our primary analyses showed that CBT may substantially reduce OCD symptom severity and may moderately improve level of functioning when compared with "no intervention", whereas we were unable to assess the effect on serious adverse events due to sparse data. Our secondary analyses showed that CBT and "no intervention" may have similar effects on quality of life, and may lead to similar proportions of participants experiencing adverse events, although TSA analysis suggested that the latter may be a random finding due to lack of power or multiple testing. Our exploratory analysis showed that CBT may have a substantial beneficial effect on remission when compared with "no intervention", although approximately one-half of patients in CBT were classified as nonremitters at the end of treatment.

It is possible that the relatively high proportion of participants affected by adverse events in the CBT and "no intervention" groups (35.8% and 31.9%, respectively) is partly related to high rates of concomitant use of SSRI in the 2 groups (36.2% and 34.3%, respectively). Indeed, some overlap exists between the adverse events reported here and known SSRI side effects in children and adolescents,[51] and the trial[44] reporting the lowest proportions of participants experiencing adverse events (1 of 63 participants in CBT and 0 of 64 participants in the "no intervention" group) also had the lowest rate of concomitant use of SSRI (2%). Nevertheless, as we do not have data to disentangle CBT-related adverse events and adverse events related to concomitant use of SSRI, the main finding is that knowledge about harmful effects of CBT is lacking.

Next, we compared CBT with SSRI interventions. Our primary analyses showed that CBT and SSRIs may have comparable effects on OCD symptom severity, whereas we were unable to assess the effect on serious adverse events and level of functioning due to sparse data. Secondary analyses on quality of life and adverse events were not possible. Our exploratory analysis showed that CBT and SSRI may have comparable beneficial effects on remission, although TSA

TABLE 1 Summary of Findings Tables for Cognitive-Behavioral Therapy Versus "No Intervention" and Versus Selective Serotonin Reuptake Inhibitors

CBT vs. "No Intervention" for OCD in Children and Adolescents

Outcomes	Anticipated Absolute Effects (95% CI)		Relative Effect (95% CI)	No. of Participants (Trials)	Certainty of the Evidence (GRADE)	Comments
	Risk With "No intervention"	Risk With CBT				
Severity of OCD		Mean severity of OCD was 8.51 lower in CBT (10.84 lower to 6.18 lower)	—	701 (10)	⊕⊕◯◯ LOW [a,b]	CBT may result in a large reduction in severity of OCD.
Serious adverse events	7 per 1,000	2 per 1,000 (0—58)	RR 0.33 (0.01— 7.96)	275 (3)	⊕◯◯◯ Very low [a,c,d]	We are very uncertain about the effect of CBT on serious adverse events.
Level of functioning (patient-rated)	—	SMD 0.90 lower (1.19 lower to 0.62 lower)	—	250 (4)	⊕◯◯◯ Very low [a,b,c,e]	CBT may improve level of functioning (patient-rated) but we are very uncertain. Note: lower scores represent higher level of functioning.
Level of functioning (parent-rated)	—	SMD 0.68 lower (1.12 lower to 0.23 lower)	—	377 (5)	⊕◯◯◯ Very low [a,b,c,e,f]	CBT may improve level of functioning (parent-rated) but we are very uncertain. Note: lower scores represent higher level of functioning.
Quality of life	—	SMD 0.39 higher (0.02 higher to 0.77 higher)	—	223 (2)	⊕◯◯◯ Very low [a,c,f]	We are very uncertain about the effect of CBT on quality of life.
Adverse events	319 per 1,000	338 per 1,000 (297—389)	RR 1.06 (0.93— 1.22)	275 (3)	⊕⊕◯◯ LOW [a,c]	CBT appears to result in little to no difference in adverse events.
Lack of remission	924 per 1,000	462 per 1,000 (342—619)	RR 0.50 (0.37— 0.67)	480 (7)	⊕◯◯◯ Very low [a,b,e,g]	CBT may reduce lack of remission, but we are very uncertain.

(continued)

TABLE 1 Continued

CBT vs. SSRI for OCD in Children and Adolescents

Outcomes	Anticipated Absolute Effects (95% CI)		Relative Effect (95% CI)	No. of Participants (Trials)	Certainty of the Evidence (GRADE)	Comments
	Risk With SSRI	Risk With CBT				
Severity of OCD		The mean severity of OCD was 0.75 lower in CBT (3.79 lower to 2.29 higher)	—	146 (3)	⊕◯◯◯ Very low [a,c]	CBT appears comparable to SSRI in reducing severity of obsessive-compulsive disorder, but we are very uncertain.
Serious adverse events	0 per 1,000	0 per 1,000 (0—0)	Not estimable	40 (1)	-	There was insufficient data to evaluate the effect on serious adverse events.
Level of functioning (patient-rated)	-	MD 6.95 lower (0.15 lower to 13.75 lower)	—	50 (1)	⊕◯◯◯ Very low [a,c,f]	We are uncertain about the effect of CBT compared to SSRI on level of functioning (patient-rated). Note: lower scores represent higher level of functioning.
Level of functioning (parent-rated)	-	MD 1.70 lower (9.85 lower to 6.45 higher)	—	50 (1)	⊕◯◯◯ Very low [a,c,d]	We are uncertain about the effect of CBT compared to SSRI on level of functioning (parent-rated). Note: lower scores represent higher level of functioning.
Quality of life	Not estimable	Not estimable	Not estimable	0	-	There were no available data to evaluate the effect on quality of life.
Adverse events	Not estimable	Not estimable	Not estimable	0	-	There were no available data to evaluate the effect on adverse events.

(continued)

TABLE 1 Continued

CBT vs. SSRI for OCD in Children and Adolescents

Outcomes	Anticipated Absolute Effects (95% CI)		Relative Effect (95% CI)	No. of Participants (Trials)	Certainty of the Evidence (GRADE)	Comments
	Risk With SSRI	Risk With CBT				
Lack of remission	760 per 1,000	646 per 1,000 (502−828)	RR 0.85 (0.66− 1.09)	106 (2)	⊕◯◯◯ Very low[a,c,d,g]	We are uncertain about the effect of CBT compared to SSRI on remission.

Note: The risk with CBT (and the 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). The Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group grades of evidence are as follows: High certainty = We are very confident that the true effect lies close to that of the estimate of the effect; Moderate certainty = We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different; Low certainty = Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect; Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect. CBT = cognitive-behavioral therapy; MD = mean difference; OCD = obsessive-compulsive disorder; RR = risk ratio; SMD = standardized mean difference; SSRI = selective serotonin reuptake inhibitors.

[a]*All trials were at an overall high risk of bias.*

[b]*Substantial statistical heterogeneity was present and was not explained by planned or post hoc subgroup analyses.*

[c]*The sample size was insufficient to calculate a precise effect estimate.*

[d]*The CI around the effect estimate included both meaningful benefit and harm.*

[e]*There was wide variation in effect estimates across trials.*

[f]*The CI around the effect estimate included both meaningful benefit and no effect.*

[g]*Remission was assessed in nonstandardized and potentially invalid manners.*

analysis suggested that this may be a random finding due to lack of power or multiple testing.

All included trials were assessed at high risk of bias, and the certainty of the evidence was rated as low or very low for all outcomes for both comparisons. Trials evaluating effects of psychotherapy are inherently more prone to performance bias compared to trials evaluating effects of medication,[52-54] as it is not feasible to blind psychotherapists to the treatment they are providing. However, issues remained that could have been avoided. Several trials used unblinded outcome assessors or had unclear allocation concealment. Intervention effects on subjectively assessed outcomes (eg, CY-BOCS score) have been shown to be exaggerated by 25% in trials with inadequate or unclear blinding compared to trials with adequate blinding, and by 31% in trials with inadequate or unclear allocation concealment compared to trials with adequate allocation concealment.[52] Allocation concealment is always feasible, and the use of credible control interventions (eg, placebo psychotherapy) can limit performance bias.[18] Only one of the included trials[40] was assessed at low risk of bias on all other domains than the performance bias domain, highlighting a need for additional rigorous trials.

This review updates and extends findings from previous reviews. To our knowledge, this is the first review to assess the effects of CBT on adverse events, level of functioning, and quality of life in children and adolescents with OCD. In addition, we performed sensitivity analyses to assess the potential impact of missing data, and used TSA to control for risks of false-positive and false-negative results. This allowed us to determine whether a clinically meaningful and statistically significant difference, or lack of a difference, between CBT and a control intervention was likely to be a random finding due to missing outcome data bias, lack of power, or multiple testing.

Our review revealed an overall lack of data on beneficial and harmful effects of CBT beyond OCD symptom severity. All included trials assessed symptom severity measured on the CY-BOCS as a primary outcome. Most trials also included a measure of remission, but methodological limitations, such as dichotomizing a continuous outcome (CY-BOCS) and using varying arbitrary definitions of remission instead of assessing remission with a standardized diagnostic interview, raises serious concerns about both the reliability and validity of this outcome.[55] Few trials

assessed adverse events, level of functioning, and quality of life. Although symptom reduction is arguably an important outcome, a comprehensive and more complete evaluation of CBT efficacy should also include assessment of potential harmful effects (ie, adverse events), quality of life, and level of functioning.[56] Psychotherapy is often assumed to be associated with minimal harm, but adverse events are rarely systematically monitored in psychotherapy trials.[57] Differences in the frequency or severity of harmful effects could be decisive factors for clinicians and patients when choosing between CBT and SSRIs, especially considering our finding of comparable beneficial effects. Moreover, symptom reduction may have little relevance to patients if not accompanied by noticeable improvements in daily life well-being and functioning.

A potential methodological issue with the assessment of OCD symptom severity in all included trials is that 4 of the 10 items that comprise the CY-BOCS total score specifically address the patient's ability to resist and control obsessions and compulsions, which is a major focus of exposure and response prevention in CBT. Although inability to resist and control obsessions and compulsions are core features of OCD symptomatology, the heavy emphasis on items addressing these features might inflate estimates of the effect of CBT when CBT is compared with interventions that do not include exposure and response prevention (eg, psychoeducation and relaxation training or SSRI interventions). This potential issue may be circumvented by testing whether group differences persist when scores on these items are excluded from the total CY-BOCS score, or by including additional measures of benefits in future trials and reviews.

In conclusion, CBT may be more effective than no intervention and comparable to SSRI for pediatric OCD, but high risk of bias in included trials and low certainty of the evidence prevent firm conclusions regarding the efficacy of CBT. In addition, we had insufficient data to adequately explore potential reasons behind statistical heterogeneity in the meta-analyses. For all outcomes, we were unable to perform planned subgroup analyses based on overall risk of bias, participant age, OCD severity, and comorbidity status.

Based on the data reviewed, we have four recommendations for future trials in this field. First, future trials should be designed in accordance with the standard protocol items: recommendations for interventional trials (SPIRIT) guidelines[58] and reported according to the consolidated standards for reporting of trials (CONSORT) guidelines.[59] Second, we recommend that future trials define remission from OCD as not fulfilling the diagnostic criteria according to *ICD* or *DSM* and determine remission with a blinded standardized diagnostic interview. Third, we encourage trialists to include additional outcomes pertaining to treatment effects beyond symptom reduction, such as measures of quality of life and level of functioning. Fourth, we urge authors of future trials to systematically monitor and report adverse events for all comparison groups.

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Drs. Lønfeldt and Vangkilde, and Mss. C.F. Uhre, Pretzmann, and Pagsberg, and Mr. V.F. Uhre are with the Child and Adolescent Mental Health Centre, Mental Health Services, Capital Region, Denmark. Mss. C.F. Uhre and Pagsberg, and Mr. V.F. Uhre are also with the Faculty of Health Sciences, University of Copenhagen, Denmark. Mr. V.F. Uhre is also with the Danish Research Centre for Magnetic Resonance, Hvidovre Hospital, Denmark. Dr. Vangkilde is also with the University of Copenhagen, Denmark. Dr. Plessen is with Lausanne University Hospital, Faculty of Biology and Medicine, Lausanne, Switzerland. Drs. Gluud and Jakobsen are with Copenhagen Trial Unit, Centre for Clinical Intervention Research, Copenhagen University Hospital, Copenhagen, Denmark. Dr. Gluud is also with The Cochrane Hepato-Biliary Group, Copenhagen Trial Unit, Centre for Clinical Intervention Research, Copenhagen University Hospital, Copenhagen, Denmark. Dr. Jakobsen is also with Holbæk Hospital, Denmark.

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Correspondence to Camilla Funch Uhre, MSc, Child and Adolescent Mental Health Centre, Capital Region, Kildegårdsvej 28, 2900 Hellerup, Denmark; e-mail: Camilla.funch.staugaard@regionh.dk

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