Treatment of Obsessive-Compulsive Disorder in Children and Youth: A Meta-Analysis

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abstract

CONTEXT: We examined treatments for obsessive-compulsive disorder (OCD) in children and adolescents.

OBJECTIVE: The objective was to evaluate the comparative efficacy of behavioral and pharmacologic treatments.

DATA SOURCES: Sources include 6 databases and the ClinicalTrials.gov registry; search was last updated on May 15, 2024.

STUDY SELECTION: Dual screening was augmented by Abstrackr machine learning algorithm.

DATA EXTRACTION: Data include participant characteristics, intervention details, and risk of bias.

RESULTS: Results are from 71 randomized controlled trials. In the random effects network meta-analysis of OCD symptom severity, assessed by the Children's Yale-Brown Obsessive-Compulsive Scale Total (CY-BOCS), exposure and response prevention therapy (ERP) is more effective than waitlist (net mean difference [NMD], −10.5; 95% CI, −12.6 to −8.4) and probably more effective vs behavioral control (NMD, −5.3; 95% CI, −8.0 to −2.7). Remote ERP is more effective than waitlist (NMD, −9.4; 95% CI, −11.9 to −7.0) and as effective as in-person ERP. Selective serotonin reuptake inhibitors (SSRIs) are more effective than placebo (NMD, −4.4; 95% CI, −6.1 to −2.6). Clomipramine is probably more effective than placebo (NMD, −4.5; 95% CI, −6.8 to −2.1). ERP is probably more effective than SSRI (NMD, −2.7; 95% CI, −5.4 to −0.0), and combined ERP and an SSRI are probably more effective than SSRI alone (NMD, −3.0; 95% CI, −5.1 to −1.0). Overall, treatments including ERP (ERP+SSRI, ERP, and remote ERP) comprise the 3 highest-ranked interventions.

LIMITATIONS: Non–CY-BOCS outcomes were sparsely reported.

CONCLUSIONS: ERP, delivered in-person or via telehealth, SSRIs, and clomipramine are all effective treatments. ERP, alone or in combination with an SSRI, is probably more effective than an SSRI alone.

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Dr Steele conceptualized and designed the review, designed data collection instruments and supervised data collection, performed data analysis and interpretation of data, drafted and revised the manuscript, and approved the final manuscript as submitted. Drs Caputo and Kanaan collected data including risk of bias assessments, critically reviewed the manuscript, and approved the final manuscript as submitted. Drs Freeman and Brannan assisted in conceptualization and design, helped categorize interventions and comparators, critically reviewed the manuscript, and approved the final manuscript as submitted. Dr Balk assisted in conceptualization and design, collected data including risk of bias assessments, critically reviewed the manuscript, and approved the final manuscript as submitted. Dr Trikalinos assisted in meta-analyses and with supplemental analyses and interpretation of data, critically reviewed and revised the (Continued)

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INTRODUCTION

Obsessive-compulsive disorder (OCD) is a common, chronic, and impairing psychiatric disorder, defined by 1 or both of 2 cardinal features—obsessions and compulsions. Obsessions are persistent thoughts, urges, or images that are experienced as intrusive and unwanted, generally related to 1 or more domains that can range from fear of illness or death to uncomfortable experiences of incompleteness or disgust.[1] People with OCD exhibit a wide range of compulsive rituals, avoidance behaviors, and other strategies to neutralize or avoid distress and obsessional triggers. For most people with OCD, symptoms begin in childhood or adolescence. An international study of patients with OCD reported that 21% had symptom onset in childhood (aged ≤12 years) and 36% had symptom onset during adolescence (aged 13–17 years).[2] Prevalence rates of pediatric OCD are generally found to be similar across youth from diverse racial and ethnic groups,[3–6] but youth from marginalized racial and ethnic groups may be less likely to receive treatment or experience a remission.[6–8]

Early identification and effective treatment of OCD is important to prevent a cascade of developmental disruptions lasting into adulthood that can affect both function and quality of life, particularly in academic and social domains.[9–11] Untreated OCD is associated with depression, substance abuse, and suicide attempts.[8,10,12–14]

Recommended treatments for OCD include exposure and response prevention (ERP) therapy and treatment with selective serotonin reuptake inhibitors (SSRIs).[15] ERP is a form of cognitive behavioral therapy (CBT) that involves gradually facing the content of one's obsessions while resisting associated rituals and avoidance behaviors. However, it remains unclear what treatments and combinations of treatments work best in specific populations and settings. In particular, the efficacy of new treatment modalities (ie, atypical antipsychotic medications and neuromodulation) has not been systematically assessed.

OBJECTIVE

We conducted a systematic review (SR) for the Agency for Healthcare Research and Quality (AHRQ) and the Patient-Centered Outcomes Research Institute (PCORI). The review protocol and the full comparative effectiveness review are available at https://effectivehealthcare.ahrq.gov/products/obsessive-compulsive-disorder/research.

This manuscript addresses the following 2 questions: what are the comparative effects and harms of treatment interventions, used alone or in combination, for OCD in children and adolescents? How do the effectiveness and harms vary with patient, family, social, or other characteristics? We report a SR of brief assessment tools for OCD in the full report[16], and in a concurrent paper.[17]

Data Sources

We searched for studies and existing SRs in PubMed, the Cochrane Register of Clinical Trials, the Cochrane Database of Systematic Reviews, Embase, CINAHL, PsycINFO, and Education Resources Information Center databases. The final searches were conducted on May 15, 2024. The reference lists of relevant existing SRs were also screened for additional eligible studies. The full peer-reviewed search strategy is available in the Supplemental Material.

Study Selection

We conducted double, independent screening of abstracts in Abstrackr (http://abstrackr.cebm.brown.edu/account/login), which incorporates machine learning. Based on empirical evaluations and experience with numerous SRs, we stopped double screening when the predicted relevance score of the remaining unscreened papers was below 0.40, and further 400 consecutive citations were rejected. Potentially relevant full-text articles were also screened in duplicate. Discrepancies were adjudicated in conference with the lead author.

Data Extraction

We extracted data into the Systematic Review Data Repository Plus database (https://srdrplus.ahrq.gov). Each eligible study was extracted and assessed for risk of bias (RoB) by 1 researcher. Extracted data, including RoB assessment, were confirmed by a second, independent researcher.

RoB

We evaluated each randomized controlled trial (RCT) for RoB using the Cochrane RoB tool,[18] which addresses confounding bias (through issues related to randomization and allocation concealment), information and measurement bias (through blinding of patients and outcomes assessors and outcome measurement), deviations from intended intervention, missing data, outcome measurement, and reporting biases. The following assessments were typical in this topic. If allocation or randomization problems suggested high risk of confounding bias, the overall RoB was often deemed high. If any other single bias domain was indicative of high RoB, the overall RoB was not automatically high but moderate. If 2 or more other domains were at high RoB, the overall RoB was typically high. If there was not enough information for assessing confounding and information and measurement biases (randomization, allocation concealment, and blinding items), the overall RoB was, at best, moderate. For information and measurement biases, we assigned higher importance to the blinding of the participants than the blinding of the outcome assessors.

For single-arm studies reporting predictors of treatment effect, we assessed the adequacy of adjustment for potential

confounders using 3 criteria: (1) whether all predictors in the model were described in the article, (2) whether results were given for all predictors in the model, and (3) whether the number of participants per variable was greater than 10. Where all 3 criteria were met, the analysis was considered to be adequate; otherwise, the analysis was considered inadequate.

Data synthesis

For treatment studies, we analyzed continuous effect metrics on the original reported scales. For continuous outcomes, we computed net mean differences (NMDs or difference in difference). For remission, a categorical outcome, we report effects as relative risks (RR).

For all networks, we assigned separate control groups—waitlist (WL), pill placebo (placebo), and behavioral control (behavCntrl)—to separate comparator nodes.

We conducted random-effects network meta-analysis (NMA) using the R package netmeta.[19] Restricted maximum likelihood was used to estimate the between study variance τ^2. The effect estimates for each treatment contrast derive from 2 sources—studies that directly compare 2 treatments (direct evidence)—and studies in a connected path via 1 or more intermediate comparators (indirect evidence).[19]

We report pooled-effect estimates (which combine direct and indirect evidence) only for those comparisons informed by direct evidence from at least 2 study arms. The transitivity assumption is supported when the direct and indirect estimates are similar. We compare direct and indirect evidence for each pairwise comparison using the separate indirect from direct evidence method.[20] To assess for global inconsistency, we report the P value for the between designs inconsistency statistic Q_B, based on a the full design-by-treatment interaction random effects model.[21] The prediction interval is the expected range of treatment effects in future similar studies and represents an indirect indicator of between study heterogeneity.[22]

For comparisons represented as "hanging branches" (nodes connected to the network by a single treatment only), we performed random-effects pairwise meta-analysis when there were 3 or more analyzable studies using the R package meta.[23]

Strength of Evidence (SoE) Assessment

We assessed SoE as per the AHRQ Methods Guide,[24] considering RoB, consistency, precision, directness, and sparsity of the evidence. For each prioritized outcome in Table 1, we assigned a SoE rating of high, moderate, low, or insufficient. High, moderate, and low grades indicate the degree of confidence we have that the estimate lies close to the true effect; an insufficient rating indicates the SoE does not warrant an estimation of the true effect. In accordance with AHRQ guidance for describing treatment effects,[15,25,26] we have incorporated qualifying language regarding SoE when communicating conclusions as follows: "probably" for conclusion statements with moderate SoE, and "may" for conclusion statements with low SoE. Conclusions with high SoE do not include any qualifiers.

TABLE 1. Prioritized Outcomes

OCD symptom severity • CY-BOCS • CGI-S
Treatment response and remission • Clinical remission (after treatment CY-BOCS total score ≤12 as defined by Farhat et al,[167] or as reported) • CGI-I
Functional impairment in school, social, and home and/or family domains • COIS-R
Family accommodation • FAS • HRQoL (validated scales only)
Acceptability of treatment
Adverse events related to treatment

Abbreviations: CGI-I, Clinical Global Impression-Improvement; CGI-S, Clinical Global Impression-Severity; COIS-R, The Child Obsessive-Compulsive Impact Scale-Revised; CY-BOCS, Children's Yale-Brown Obsessive-Compulsive Scale; FAS, Family Accommodation Scale; HRQoL, quality of life general and health related; OCD, obsessive-compulsive disorder.

Three noninferiority trials, 1 in adults with OCD[27] and 2 trials enrolling youth,[28,29] have considered a 4- or 5-point decrease in the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS), or Children's Y-BOCS (CY-BOCS) to represent a clinically important difference. When interpreting effects as NMDs on the (C)Y-BOCS scale, we refer to the interval from NMD of between −4 and 4 as the zone of indifference.

RESULTS

Our search for the full AHRQ SR yielded 12 907 records. We retrieved and screened the full-text publications for 443 citations or records. From these, we included primary reports of 71 RCTs[28–98] with additional information from 38 copublications,[99–136] for a total of 109 reports.

We extracted predictors and moderators of treatment reported in 21 papers (2 secondary analyses of included RCTs[102,119] and 19 single-arm studies[137–155]), representing 15 cohorts (see Supplemental Tables 2 and 3).

Of the 71 RCTs, 24 evaluated pharmacologic treatments, 31 were studies of behavioral interventions, and 16 studied combined behavioral and pharmacologic treatments. Thirty-two studies were conducted in the United States, 10 in Europe, 9 in China, 6 in the United Kingdom, 6 in Iran, 3 in Australia, 2 in Brazil, 2 in Canada, and 1 in Japan. Race and ethnicity were reported in 22 of the 32 US-based RCTs. Among these US studies, 84% of participants were described as white and 3% as Black. Across all 71 RCTs, few studies reported other social drivers of health. Across 6 studies, 55% to 78% of parents had at least a college education. Among 5 studies, the parents of about

75% of participants were married and living together in 4 studies (62% in one additional study).

We conducted an NMA for each of 4 outcomes. In order of decreasing network size and complexity, these included OCD severity (CY-BOCS or Y-BOCS), remission, global severity (Clinical Global Impressions-Severity [CGI-S] scale), and Family Accommodation Scale.

Separately, we report a pairwise meta-analysis of 5 trials[56,63,72,76,92] that evaluated whether D-cycloserine augments the effect of ERP and reported CY-BOCS and CGI-S outcomes.

Nineteen trials were excluded from the meta-analyses: 2 that enrolled participants based on their clinical response to a prior open-label intervention—responders to an SSRI (paroxetine)[42] and nonresponders to ERP in phase I of the 2-phase Nordic long-term OCD treatment study trial[75] were excluded from the NMA due to possible differences in treatment effects. The other 17 compared a novel treatment or treatment adjunct with a reference treatment (often ERP). These comparisons between nonreference treatments rely on indirect evidence, limiting the reliability of these estimates. Among these RCTs, 3 evaluated variations in ERP delivery,[48,70,90] 7 augmented ERP with another behavioral intervention,[55,64,65,74,81,91,98] 4 evaluated other behavioral interventions,[66,84,87,95] 7 evaluated additional medications,[31,53,62,69,79,86,94] and 1 evaluated transcranial direct current stimulation.[96]

CY-BOCS

Figure 1 displays the network of studies reporting the (C)Y-BOCS outcome. The plot graphically describes the network topology for the 41 RCTs[28,29,32–41,43–47,49–52,54,57–61,67,68,71,73,78,80,82,83,85,88,89,93,97] that enrolled 2651 participants and provides direct evidence for 12 (of 46 possible)

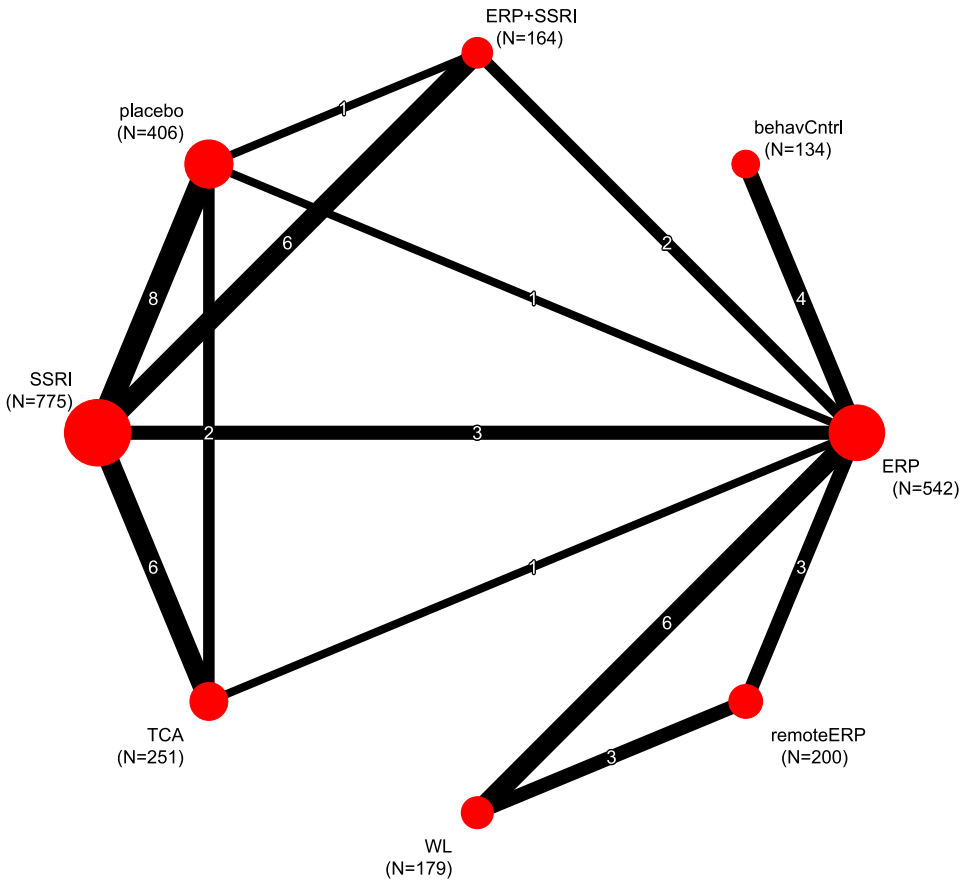

FIGURE 1.
Network plot: CY-BOCS. The network graphically describes the network topology for 41 RCTs. The plot represents all intervention categories (represented by red circles and/or nodes) that were compared with 1 or more other intervention categories. The diameter of the circles is proportional to the number of participants (in parentheses) who received the intervention of interest. The black lines connecting nodes (edges) represent the direct comparisons between pairs of interventions. The width of the edges is proportional to the number (shown in white text on each line and/or edge) of studies that directly compared each pair of treatments.
Abbreviations: behavCntrl, behavioral control; ERP, cognitive behavioral therapy with exposure and response prevention; placebo, pill placebo; remoteERP, synchronous or asynchronous ERP via telehealth; SSRI, selective serotonin reuptake inhibitor (various); TCA, tricyclic antidepressant (clomipramine); WL, waitlist.

pairwise comparisons between 5 interventions (SSRI, clomipramine, ERP, ERP via telehealth [remoteERP], and ERP+SSRI) and 3 control conditions—pill placebo (placebo), WL, and behavCntrl groups. The median end-of-treatment time was 12 weeks, with an IQR of 9 to 14 weeks. The overall RoB was low in 21 studies, moderate in 15 studies, and high in 5 studies. The most common concerns were lack of blinding of outcome assessor, dropouts resulting in incomplete outcome data, and unclear reporting. The omnibus test for consistency ($P = .029$) suggests some inconsistency between direct and indirect effect estimates across the network.

The NMD in CY-BOCS (with 95% CIs) for all pairwise contrasts are shown in Figure 2. Note that a negative NMD value indicates that the first listed intervention is more effective (reduces CY-BOCS score more) than the second intervention (or control). Figure 3 displays a histogram ranking each of 5 treatments and 3 control categories. Treatments including ERP (ERP+SSRI, ERP, and remote ERP) comprise the 3 highest-ranked interventions, suggesting these may be the most effective treatments. Medications (tricyclic antidepressant [TCA] and SSRI) are ranked in the middle, with the 3 control conditions (behavCntrl, pill placebo, and wait list) comprising the lowest ranks.

Figure 4 illustrates the comparisons of ERP vs various WL and behavCntrl comparators. For ERP vs behavCntrl, the NMD was −5.3 (95% CI, −8.0 to −2.7), which is statistically significant and compatible with effects ranging from clinically important to uncertain clinical importance. Four RCTs (with 298 participants) contributed direct evidence in this network. Among these, 2 studies enrolled children aged 5 to 8 years and compared family-based ERP with family-based relaxation treatment that included psychoeducation, affective education to identify negative and positive feelings, and relaxation training.[50,68] One study enrolled children aged 8 to 17 years and compared ERP plus a structured family intervention vs a behavCntrl that included psychoeducation and relaxation training.[60] Another study enrolled adolescents aged 12 to 18 years and compared ERP with stress management therapy.[97]

For ERP vs WL, the pooled NMD is −10.5 (95% CI, −12.6 to −8.4), with 6 RCTs (with 237 participants) contributing direct evidence.[41,43,49,57,58,77] This estimate is statistically significant, and the CI is entirely compatible with clinically

	ERP	remoteERP	ERP+SSRI	TCA	SSRI	behavCntrl	placebo	WL
ERP		-1.1 (-3.5, 1.3)	0.3 (-2.7, 3.3)	-2.6 (-5.8, 0.6)	-2.7 (-5.4, 0.0)	-5.3 (-8.0, -2.7)	-7.1 (-10.2, -4.0)	-10.5 (-12.6, -8.4)
remoteERP	1.1 (-1.3, 3.5)		1.4 (-2.4, 5.2)	-1.5 (-5.6, 2.5)	-1.6 (-5.3, 2.0)	-4.3 (-7.9, -0.7)	-6.0 (-9.9, -2.1)	-9.4 (-11.9, -7.0)
ERP+SSRI	-0.3 (-3.3, 2.7)	-1.4 (-5.2, 2.4)		-3.0 (-5.8, -0.2)	-3.0 (-5.1, -1.0)	-5.7 (-9.7, -1.7)	-7.4 (-10.0, -4.9)	-10.8 (-14.5, -7.2)
TCA	2.6 (-0.6, 5.8)	1.5 (-2.5, 5.6)	3.0 (0.2, 5.8)		-0.1 (-2.1, 1.9)	-2.7 (-6.9, 1.5)	-4.5 (-6.8, -2.1)	-7.9 (-11.7, -4.0)
SSRI	2.7 (0.0, 5.4)	1.6 (-2.0, 5.3)	3.0 (1.0, 5.1)	0.1 (-1.9, 2.1)		-2.6 (-6.4, 1.2)	-4.4 (-6.1, -2.6)	-7.8 (-11.2, -4.3)
behavCntrl	5.3 (2.7, 8.0)	4.3 (0.7, 7.9)	5.7 (1.7, 9.7)	2.7 (-1.5, 6.9)	2.6 (-1.2, 6.4)		-1.7 (-5.8, 2.3)	-5.1 (-8.5, -1.7)
placebo	7.1 (4.0, 10.2)	6.0 (2.1, 9.9)	7.4 (4.9, 10.0)	4.5 (2.1, 6.8)	4.4 (2.6, 6.1)	1.7 (-2.3, 5.8)		-3.4 (-7.1, 0.3)
WL	10.5 (8.4, 12.6)	9.4 (7.0, 11.9)	10.8 (7.2, 14.5)	7.9 (4.0, 11.7)	7.8 (4.3, 11.2)	5.1 (1.7, 8.5)	3.4 (-0.3, 7.1)	

FIGURE 2.
League table: CY-BOCS. Table cells summarize the net mean difference in (C)Y-BOCS, with 95% CIs, for each row by column treatment contrast (intervention in the row vs the intervention in the column). For example, the right-most upper cell displays the NMA estimate, which represents the ERP vs WL comparison. Larger negative NMDs represent greater treatment effect. Shading is added to emphasize larger effects.
Abbreviations: behavCntrl, behavioral control; CY-BOCS, Children's Yale-Brown Obsessive-Compulsive Scale; ERP, cognitive behavioral therapy with exposure and response prevention; NMA, network meta-analysis; NMD, net mean difference; placebo, pill placebo; remoteERP, synchronous or asynchronous ERP via telehealth; SSRI, selective serotonin reuptake inhibitor (various); TCA, tricyclic antidepressant (clomipramine); WL, waitlist; Y-BOCS, Yale-Brown Obsessive-Compulsive Scale.

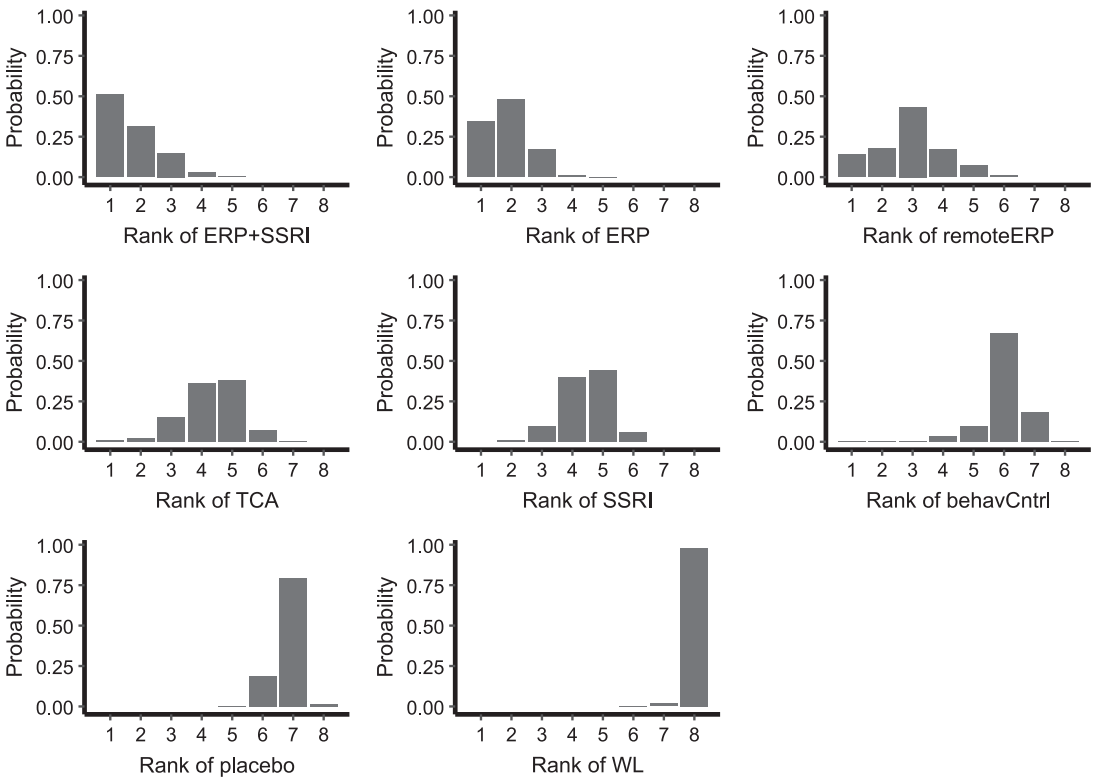

FIGURE 3.
Distribution of ranking probabilities. The height of each bar represents the probability that each treatment is the best, the worst, or in between. Abbreviations: behavCntrl, behavioral control; ERP, cognitive behavioral therapy with exposure and response prevention; placebo, pill placebo; remoteERP, synchronous or asynchronous ERP via telehealth; SSRI, selective serotonin reuptake inhibitor (various); TCA, tricyclic antidepressant (clomipramine); WL, waitlist.

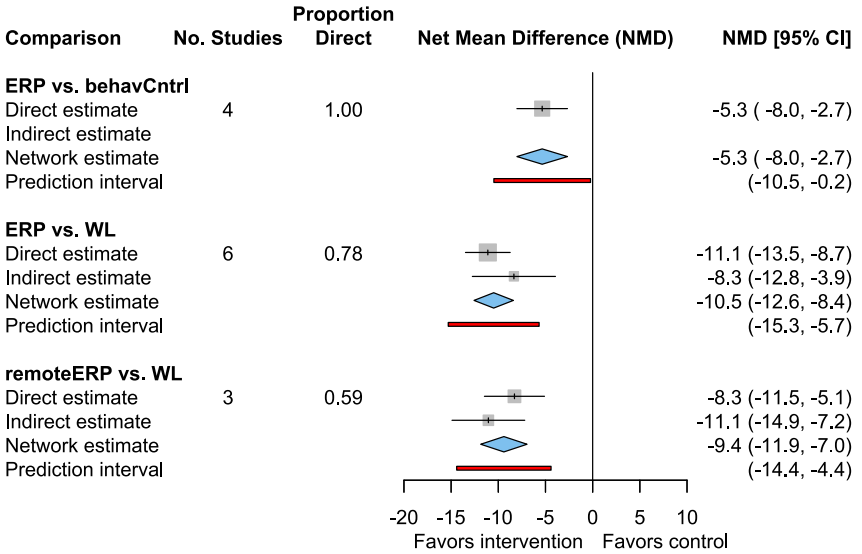

FIGURE 4.
Effects of behavioral interventions: (C)Y-BOCS. A *P* value for the null hypothesis of local coherence for ERP vs behavCntrl cannot be calculated due to the absence of indirect evidence. For ERP vs WL, $P = .279$. For remote ERP vs WL, $P = .279$.
Abbreviations: behavCntrl, behavioral control; (C)Y-BOCS, (Children's) Yale-Brown Obsessive-Compulsive Scale; ERP, cognitive behavioral therapy with exposure and response prevention; No., number of studies that contributed direct evidence for a comparison; NMD, net mean difference; remoteERP, synchronous or asynchronous ERP delivered via telehealth; WL, waitlist.

important effects. Three RCTs[61,80,93] compared remote ERP vs WL control in 158 participants. The NMD was −9.4 (95% CI, −11.9 to −7.0). This estimate is statistically significant, and the 95% CI is entirely compatible with clinically important effects.

Figure 5 illustrates the comparative effect of remote ERP vs in-person ERP. The NMD was 1.1 (95% CI, −1.3 to 3.5). Three RCTs[28,29,78] compared remote ERP with ERP in 246 participants. The 95% CI overlaps the null effect and includes effects of uncertain clinical importance only.

Figure 6 illustrates the effects and comparative effects of pharmacologic therapies compared with placebo and each other. Eight RCTs compared SSRI vs placebo in 762 participants.[34,35,38–40,44,45,82] The pooled NMD was −4.4 (95% CI, −6.1 to −2. 6), which is statistically significant and compatible with effects ranging from clinically important to uncertain clinical importance. This figure also shows that treatment with the TCA clomipramine was statistically significantly more effective than placebo, with a pooled NMD of −4.5 (95% CI, −6.8 to −2.1), with direct evidence from 2 studies.[32,33] The CI includes effects ranging from clinically important to uncertain clinical importance. Finally, 6 RCTs[47,51,52,54,88,89] enrolling 509 participants compared SSRI vs TCA. The pooled NMD was 0.1 (95% CI, −1.9 to 2.1), which overlaps the null effect, including effects of uncertain clinical importance only.

Figure 7 also shows results for ERP vs SSRI. The pooled NMD is −2.7 (95% CI, −5.4 to 0). There were 3 RCTs[45,46,83]

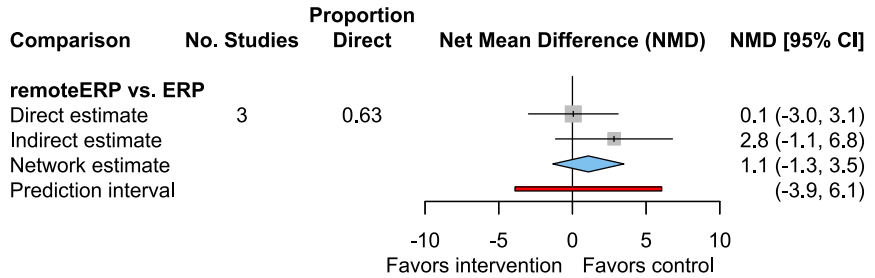

FIGURE 5.

Remote ERP vs ERP: CY-BOCS. For remoteERP vs ERP, the *P* value for the null hypothesis of local coherence is .279.

Abbreviations: behavCntrl, behavioral control; CY-BOCS, Children's Yale-Brown Obsessive-Compulsive Scale; ERP, cognitive behavioral therapy with exposure and response prevention; NMD, net mean difference; remoteERP, remote synchronous or asynchronous ERP.

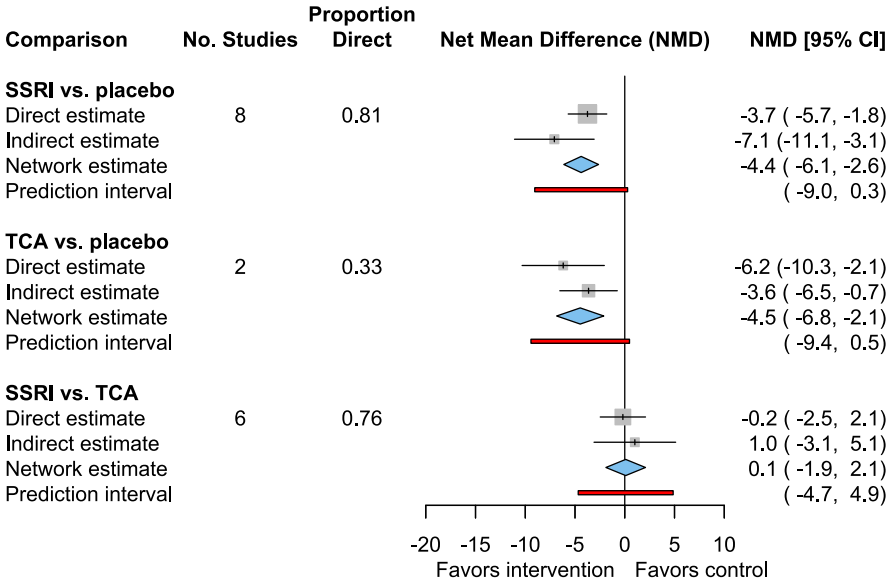

FIGURE 6.

SSRI vs placebo, TCA vs placebo, and SSRI vs TCA: (C)Y-BOCS. *P* values for null hypothesis of local coherence: SSRI vs placebo, $P = .142$; TCA vs placebo, $P = .322$; and SSRI vs TCA, $P = .615$.

Abbreviations: (C)Y-BOCS, (Children's) Yale-Brown Obsessive Compulsive Disorder Scale; No. Studies, number of studies directly comparing; NMD, net mean difference; SSRI, selective serotonin reuptake inhibitor (various); TCA, tricyclic antidepressant (all clomipramine).

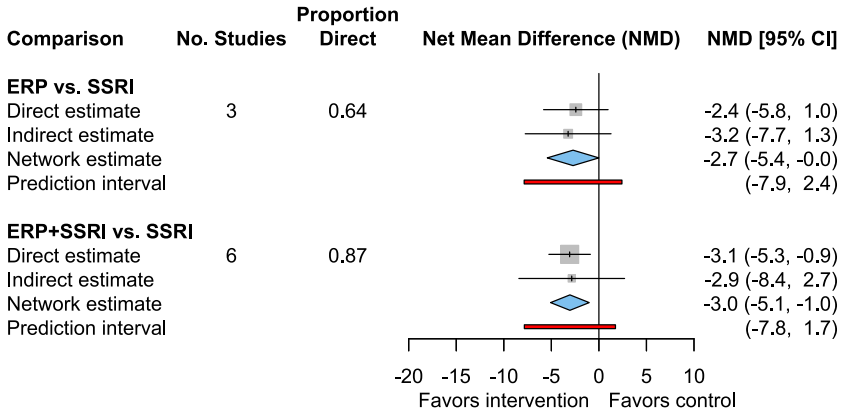

FIGURE 7.

ERP vs SSRI, ERP+SSRI, vs SSRI. *P* values for null hypothesis of local coherence: ERP vs SSRI, $P = .778$; and ERP+SSRI vs SSRI; $P = .942$. + indicates a combination of interventions.

Abbreviations: (C)Y-BOCS, (Children's) Yale-Brown Obsessive Compulsive Disorder Scale; ERP, cognitive behavioral therapy with exposure and response prevention; No. Studies, number of studies directly comparing; NMD, net mean difference; SSRI, selective serotonin reuptake inhibitor (various).

with 179 participants that contributed direct evidence for this analysis. This estimate is statistically significant, and the CI is compatible with both clinically important effects and effects of uncertain clinical importance. Figure 7 also illustrates the ERP vs SSRI and ERP+SSRI vs SSRI comparisons. For ERP+SSRI vs SSRI, the pooled NMD is −3.0 (95% CI, −5.1 to −1.0). There were 6 RCTs[37,45,59,71,73,85] with 273 participants who contributed direct evidence. This estimate is statistically significant, and the CI is compatible with both clinically important effects and with effects of uncertain clinical importance.

Figure 8 shows results for ERP+SSRI vs ERP. The pooled NMD is −0.3 (95% CI, −3.3 to 2.7). There were 2 RCTs[45,67] with 103 participants that contributed direct evidence. This estimate overlaps the null effect, and the CI is compatible with small effects of uncertain clinical importance only. Five studies[56,63,72,76,92] with 316 participants evaluated ERP+D-cycloserine vs ERP. As shown in Figure 9, the summary NMD was −1.2 (95% CI, −2.9 to 0.5), which overlaps the null effect, including effects of uncertain clinical importance only.

Remission

Thirteen studies[29,41,45–47,58,60,61,78,80,88,93,97] reported the number of participants whose OCD remitted by end of treatment in 11 to 17 weeks. Among these studies, remission was variably defined as subjective "clinical remission" or using CY-BOCS cutoffs ranging from 10 or less to 12 or less. An NMA (shown in Supplemental Figure 2) of 739 participants provided direct evidence for 11 out of 27 possible pairwise comparisons between 5 interventions (ERP, remote ERP, SSRI, TCA, and ERP+SSRI) and 3 separate control conditions—pill placebo (placebo), WL, and behavCntrl. We deemed overall RoB to be low in 9, moderate in 2, and high in 2 studies. The omnibus null hypothesis of consistency was not rejected ($P = .126$). As shown in Supplemental Figure 3, the RR of remission for ERP vs behavCntrl was significantly higher (RR, 2.7; 95% CI, 1.2–6.0), as was the RR of remission with ERP vs wait list (RR, 8.2; 95% CI, 3.7–18.5) and the rate of remission in participants receiving ERP remotely vs wait list (RR, 7.9; 95% CI, 3.5–17.5). As shown in Supplemental Figure 4, remission rates were similar in

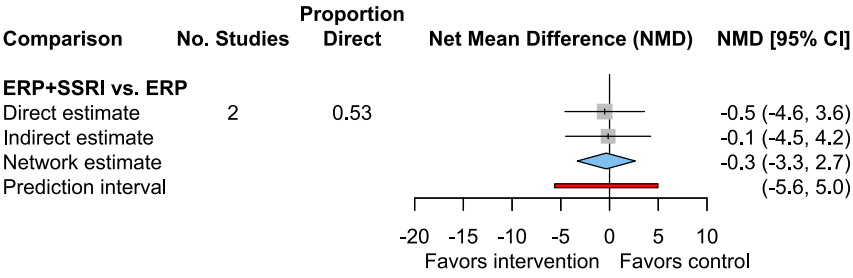

FIGURE 8.

ERP+SSRI vs ERP. *P* values for null hypothesis of local coherence: ERP+SSRI vs ERP, $P = .907$. + indicates a combination of interventions.

Abbreviations: (C)Y-BOCS, (Children's) Yale-Brown Obsessive Compulsive Disorder Scale; ERP, cognitive behavioral therapy with exposure and response prevention; No. Studies, number of studies directly comparing; NMD, net mean difference; SSRI, selective serotonin reuptake inhibitor (various).

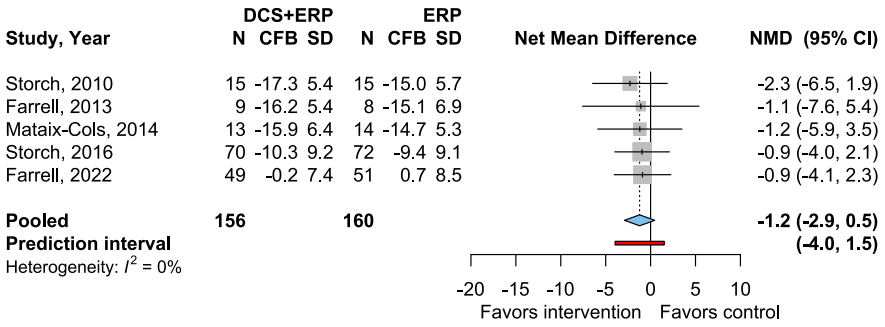

FIGURE 9.
D-cycloserine with ERP vs ERP: CY-BOCS.
Abbreviations: CY-BOCS, Children's Yale-Brown Obsessive Compulsive Disorder Scale; CFB, change from baseline; DCS, D-cycloserine; ERP, exposure and response prevention; NMD, net mean difference.

participants receiving remote ERP vs in-person ERP (RR, 1.0; 95% CI, 0.7–1.3).

Remission rates were similar in participants receiving ERP vs SSRI (RR, 0.9; 95% CI, 0.6–1.4) and in participants receiving SSRI vs TCA (RR, 1.1; 95% CI, 0.9–1.3), as shown in Supplemental Figure 5.

OCD Symptom Severity—CGI-S

CGI-S is a global assessment of overall OCD illness severity, with 6 severity categories: 0 to 1 is transient (no functional impairment) to 6, which is extremely severe (functions mainly with assistance).[156] The NMA for this score included 12 RCTs[28,34,35,37,38,40,46,61,67,68,78,93] that enrolled 833 participants, providing direct evidence for 8 out of 12 possible pairwise comparisons among 4 interventions (ERP, remoteERP, ERP+SSRI, and SSRI) and 3 control conditions (WL, placebo, and behavCntrl). Twelve studies were included in the CGI-S network (illustrated in Supplemental Figure 2). Overall, RoB was low in 8, moderate in 2, and high in 2 studies. The omnibus null hypothesis of consistency was not rejected ($P = .826$). The pooled estimate (shown in Supplemental Figure 7) for remote ERP vs in-person ERP is an NMD in CGI-S score of −0.0 (95% CI, −0.3 to 0.3). The pooled estimate (shown in Supplemental Figure 8) for SSRI vs pill placebo is an NMD in CGI-S score of −0.5 (95% CI, −0.8 to −0.3).

Supplemental Figure 9 illustrates the pairwise meta-analysis of the 3 studies that compared D-cycloserine augmentation of ERP with ERP alone. The pooled estimate of −0.3 (95% CI, −0.9 to 0.2) overlaps the null.

Family Accommodation Scale

The Family Accommodation Scale (FAS) is a 12-item, clinician-rated, semistructured interview designed to assess the family's accommodation to the child's OCD symptoms.[157] Accommodation is a change in the family's behavior with the goal of reducing distress in youth with OCD. Greater family accommodation is associated with more severe OCD symptoms[158] and may decrease in response to treatment.[159,160] Five studies[28,60,61,78,80] with 342 participants reported FAS outcomes that directly compared 3 of 5 possible comparisons of 2 interventions (ERP and remote ERP) and 2 control comparators (WL and behavCntrl). The network topology is shown in Supplemental Figure 10. The comparison of remote ERP vs in-person ERP was informed by direct evidence from 3 studies.[28,78,80] For remote ERP vs in-person ERP (Supplemental Figure 11), the NMD in the FAS score was −2.7 (95% CI, −6.4 to 1.0), but this estimate has high heterogeneity and overlaps the null.

Other Outcomes

Other outcomes, including functional impairment, quality of life, and parent satisfaction with services, were sparsely reported. Adverse events were reported only for pharmacologic studies. Among these, 2 RCTs reported a significantly greater risk of adverse events leading to withdrawal—3.6-fold greater than placebo in a controlled study of paroxetine[44] and 4.1-fold higher for sertraline than placebo in a similar study.[35]

Predictors of Treatment Response

There were 21 papers (2 secondary analyses of included RCTs[102,119] and 19 single-arm studies[137–155]) representing 15 cohorts that reported multivariable analyses of predictors of treatment response for CBT. These studies are summarized in Supplemental Tables 2 and 3. We found that age, sex, baseline Child Obsessive Compulsive Impact Scale, baseline family accommodation, and other comorbidities, including anxiety, depression, and tics, were not consistent predictors of response to CBT with ERP across studies.

Limitations

There were limitations in the evidence base that challenged our quantitative synthesis and may limit applicability.

First, although the CY-BOCS was almost always reported, fewer studies reported other priority outcomes, resulting in progressively sparser networks for remission, CGI-S, and FAS. For all networks, control conditions were categorized as WL, pill placebo, or behavioral and treated as separate comparators. Given the relatively sparse evidence within comparator-outcome categories, we did not perform subgroup analyses or metaregression of potential predictors and moderators of treatment effects across RCTs.

Second, few studies reported on social drivers of health other than race, but among those that did, study participants were mostly white and living in 2-caregiver households whose caregivers have high educational attainment. We found no studies that included participants with OCD who had concurrent features of pediatric acute-onset neuropsychiatric syndrome or pediatric autoimmune neuropsychiatric disorder associated with streptococcal infections, precluding any direct conclusions about intervention effects in this subgroup. All included RCTs enrolled adolescents younger than 18 years of age, precluding conclusions specific to treatment of OCD in older youth (aged 18 to 20 years).

CONCLUSIONS

Table 2 summarizes our detailed conclusions, by comparison, across all outcomes. CBT with ERP, provided in-person or via telehealth, is an effective treatment for OCD. SSRIs and clomipramine (a TCA) are both more effective than pill placebo.

The evidence was insufficient regarding potential effect modifiers. No study collected or reported potential harms of behavioral interventions. The side effects of SSRIs and clomipramine were inconsistently reported in the included RCTs, precluding graded conclusions specific to youth with OCD. However, based on evidence from other sources, the side effects of these drugs in children and adolescents are well known and include insomnia, restlessness, gastrointestinal distress, and dry mouth.[161]

It is inherently challenging to synthesize treatment effects in networks of trials that enroll different control comparators (primarily pill placebo in pharmacologic trials and waitlist or behavioral controls in trials of ERP). We found the largest effects in studies comparing ERP with a waitlist control group. The pooled effect estimate for the 4 RCTs that compared ERP with active control interventions (eg, psychoeducation and relaxation therapy) is smaller than the effect for ERP vs WL. Indirect evidence (Figure 2) suggests that participants in behavioral control arms, and possibly in placebo arms, have greater improvement in CY-BOCS than those on waiting lists. Overall, based on the NMA ranking, interventions that include ERP (ERP+ SSRI, ERP, and remote ERP) are most effective, followed by medications.

Clinical Implications

Our findings support ERP as a first-line treatment, alone or in combination with an SSRI, for children with OCD. Treatment with an SSRI may be useful in certain patients, including those with more severe impairment, patients unable to engage in ERP because of their degree of distress, those awaiting referral to or lacking access to ERP, and those with an incomplete response to ERP. ERP delivered via telehealth is more effective than WL control, with effects similar to those seen with in-person ERP, supporting consideration of telehealth as a means to increase access to care, particularly in locations with a shortage of trained ERP providers. Although robust telehealth services have been helpful for some youth, use of telehealth may not eliminate disparities in treatment access. Recent data suggest differential rates of telehealth care use by race, with minoritized youth receiving less care than nonminoritized youth.[162]

There has been a longstanding failure to include youth who have been historically underrepresented (eg, based on race, ethnicity, or income) in pediatric OCD treatment studies.[163] Past studies often underrecruited marginalized youth, in part because the settings (academic settings) and treatment models (once weekly in an office) perpetuate barriers to equitable access and acceptability. Consequently, there is a need to prioritize the inclusion of youth who have been historically underrepresented in treatment trials[164] and underserved in clinical practice.[165] This is imperative for research that addresses tailoring treatment to better address barriers to access, quality, and clinical improvement for these groups of youth.[166]

Our review found very sparse published evidence to inform how to treat individuals who fail to respond to treatment. One proposed treatment, augmentation of ERP with the glutamate inhibitor D-cycloserine, is not more effective than ERP alone.

Future research efforts should focus on (1) the inclusion of study participants who are representative of all youth affected by OCD, including children who are nonwhite and of low socioeconomic status; (2) increased transparency in study reporting around dose of exposure, as well as therapist training and quality monitoring; (3) implementation research around the when, where, who, and how of OCD treatment to be sure it is reaching everyone who needs it; and (4) development and evaluation of both pharmacologic and behavioral augmentation to ERP and novel interventions (eg, neuromodulation).

ERP, delivered in-person or remotely, is an effective treatment for OCD in children and youth. SSRIs and clomipramine are both effective compared with placebo. ERP alone, or ERP in combination with an SSRI, is more effective than treatment with an SSRI alone.

TABLE 2. Evidence Profile

Comparison: Overall Conclusion	Outcomes	Control	N Studies (Participants)	RoB, L/M/H	Consistency	Precision	Directness	Other	SoE	Conclusions (95% CI)
ERP vs control: ERP is more effective than control	CY-BOCS	Waitlist	6 (237)	3/3/0	Consistent	Precise	Direct (NMA)	None	High	CY-BOCS NMD **−10.5 (−12.6 to −8.4)**
	CY-BOCS	Behavioral	3 (240)	3/0/0	Consistent	Imprecise	Direct (NMA)	None	Moderate	CY-BOCS NMD **−5.3 (−8.0 to −2.7)**
	Remission	Waitlist	2 (84)	2/0/0	Consistent	Precise	Direct (NMA)	None	High	Remission RR **8.2 (3.7–18.5)**
	Remission	Behavioral	2 (115)	2/0/0	Consistent	Precise	Direct (NMA)	None	Moderate	Remission RR **2.7 (1.2–6.0)**
	CGI-S	Waitlist	1 (31)	0/0/1	NA	Precise	Direct (NMA)	Sparse	Insufficient	No conclusion
	CGI-S	Behavioral	1 (126)	1/0/0	NA	Precise	Direct (NMA)	Sparse	Insufficient	No conclusion
	FAS	Behavioral	1 (70)	1/0/0	NA	Imprecise	Direct (NMA)	Sparse	Insufficient	No conclusion
	FAS	Waitlist	1 (31)	0/0/1	NA	Imprecise	Direct (NMA)	Sparse	Insufficient	No conclusion
Remote ERP vs control: remote ERP is more effective than control	CY-BOCS	Waitlist	3 (158)	2/0/1	Consistent	Precise	Direct (NMA)	None	High	CY-BOCS NMD **−9.4 (−11.9 to −7.0)**
	Remission	Waitlist	3 (145)	2/0/1	Consistent	Precise	Direct (NMA)	None	High	Remission RR **7.9 (3.5–17.5)**
	CGI-S	Waitlist	1 (60)	1/0/0	NA	Imprecise	Direct (no MA)	Sparse	Insufficient	No conclusion
	FAS	NA	0 (NA)	NA	NA	Imprecise	NA	Sparse	Insufficient	No evidence
Remote ERP vs ERP: remote ERP is as effective as in-person ERP	CY-BOCS	NA	3 (246)	3/0/0	Consistent	Precise	Direct	None	High	CY-BOCS NMD 1.1 (−1.3 to 3.5)
	Remission	NA	2 (88)	2/0/0	Consistent	Precise	Direct (NMA)	Sparse	High	Remission RR 1.0 (0.7–1.3)
	CGI-S	NA	2 (174)	2/0/0	Consistent	Precise	Direct (NMA)	Sparse	Moderate	CGI-S NMD −0.0 (−0.3 to 0.3)
	FAS	NA	3 (241)	3/0/0	Inconsistent	Imprecise	Direct (NMA)	None	Low	FAS NMD −2.7 (−6.4 to 1.0)
SSRI vs control: SSRI is more effective than control	CY-BOCS	Placebo	8 (762)	5/3/0	Consistent	Precise	Direct (NMA)	None	High	CY-BOCS NMD **−4.4 (−6.1 to −2.6)**
	Remission	Placebo	1 (56)	1/0/0	NA	Imprecise	Direct (no MA)	Sparse	Insufficient	No conclusion
	CGI-S	Placebo	4 (346)	3/1/0	Consistent	Precise	Direct (NMA)	None	High	CGI-S NMD **−0.5 (−0.8 to −0.3)**
	FAS	NA	0 (NA)	NA	NA	NA	NA	NA	Insufficient	No evidence
TCA vs control: treatment with TCA is more effective than placebo	CY-BOCS	Placebo	2 (76)	1/1/0	Consistent	Imprecise	Direct (NMA)	Sparse	Moderate	NMD **−4.5 (−6.8 to −2.1)**
	Remission	NA	0 (NA)	NA	NA	NA	NA	NA	Insufficient	No evidence
	CGI-S	NA	0 (NA)	NA	NA	NA	NA	NA	Insufficient	No evidence
	FAS	NA	0 (NA)	NA	NA	NA	NA	NA	Insufficient	No evidence
ERP vs SSRI: ERP is more effective than SSRI	CY-BOCS	NA	3 (179)	2/0/1	Consistent	Precise	Direct (NMA)	None	Moderate	CY-BOCS NMD **−2.7 (−5.4 to −0.0)**
	Remission	NA	2 (89)	1/0/1	NA	Imprecise	Direct (no MA)	Sparse	Moderate[†]	Remission RR 0.9 (0.6–1.4)
	CGI-S	NA	1 (39)	0/0/1	NA	Imprecise	Direct (no MA)	Sparse	Insufficient	No conclusion
	FAS	NA	0 (NA)	NA	NA	NA	NA	NA	Insufficient	No evidence

(Continued on next page)

TABLE 2. Evidence Profile (Continued)

Comparison: Overall Conclusion	Outcomes	Control	N Studies (Participants)	RoB, L/M/H	Consistency	Precision	Directness	Other	SoE	Conclusions (95% CI)
ERP+SSRI vs ERP: ERP+SSRI is as effective as ERP alone	CY-BOCS	NA	2 (103)	2/0/0	Consistent	Precise	Direct (NMA)	None	High	CY-BOCS NMD −0.3 (−3.3 to 2.7)
	Remission	NA	1 (56)	1/0/0	NA	Imprecise	Direct (no MA)	Sparse	Insufficient	No conclusion
	CGI-S	NA	1 (47)	1/0/0	NA	Imprecise	Direct (no MA)	Sparse	Insufficient	No conclusion
	FAS	NA	0 (NA)	NA	NA	NA	NA	NA	Insufficient	No evidence
ERP+SSRI vs SSRI: ERP+SSRI is more effective than SSRI	CY-BOCS	NA	6 (273)	2/3/1	Consistent	Imprecise	Direct (NMA)	None	Moderate	CY-BOCS NMD **−3.0 (−5.1 to −1.0)**
	Remission	NA	1 (56)	1/0/0	NA	Imprecise	Direct (no MA)	Sparse	Insufficient	No conclusion
	CGI-S	NA	1 (10)	0/1/0	NA	Imprecise	Direct (no MA)	Sparse	Insufficient	No conclusion
	FAS		0 (NA)	NA	NA	NA	NA	NA	Insufficient	No evidence
SSRI vs TCA: SSRI is as effective as TCA	CY-BOCS	NA	6 (409)	0/5/1	Consistent	Precise	Direct (NMA)	None	High	CY-BOCS NMD 0.1 (−1.9 to 2.1)
	Remission	NA	2 (149)	0/2/0	Consistent	Precise	Direct (NMA)	Sparse	High	Remission RR 1.1 (0.9–1.3)
	CGI-S	NA	0 (NA)	NA	NA	NA	NA	NA	Insufficient	No evidence
	FAS	NA	0 (NA)	NA	NA	NA	NA	NA	Insufficient	No evidence
DCS+ERP vs ERP: DCS+ERP is as effective as ERP	CY-BOCS	NA	5 (316)	5/0/0	Consistent	Precise	Direct (pwMA)	None	High	CY-BOCS NMD −1.2 (−2.9 to 0.5)
	Remission	NA	2 (242)	2/0/0	Consistent	Highly Imprecise	Direct (no MA)	Sparse	Insufficient	No conclusion
	CGI-S	NA	3 (189)	3/0/0	Consistent	Precise	Direct (pwMA)	None	Moderate	CGI-S NMD −0.3 (−0.9 to 0.2)
	FAS	NA	0 (NA)	NA	NA	NA	NA	NA	Insufficient	No evidence

Abbreviations: Behavioral, behavioral control; CGI-S, Clinical Global Impressions Scale-Severity; Control, one of granular control groups (placebo or behavioral) or combined (all control groups combined); CY-BOCS, Children's Yale-Brown Obsessive-Compulsive Scale; DCS, D-cycloserine; ERP, cognitive behavioral therapy with exposure and response prevention; FAS, Family Accommodation Scale; H, high strength of evidence; L, low strength of evidence; M, medium strength of evidence; MA, meta-analysis; NA, not applicable; NMA, network meta-analysis; NMD, net mean difference; placebo, pill placebo; pwMA, pairwise meta-analysis; RoB, risk of bias; RR, relative risk; SoE, strength of evidence; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

Prioritized outcomes with insufficient evidence across all listed comparisons are omitted.

Bold text indicates an effect with a 95% confidence interval that excludes the null value.

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ABBREVIATIONS

AHRQ: Agency for Healthcare Research and Quality
behavCntr: behavioral control
CBT: cognitive behavioral therapy
CGI-S: Clinical Global Impressions-Severity
CY-BOCS: Children's Yale-Brown Obsessive-Compulsive Scale
ERP: exposure and response prevention
FAS: Family Accommodation Scale
NMA: net meta-analysis
NMD: net mean difference
OCD: obsessive-compulsive disorder
PCORI: Patient-Centered Outcomes Research Institute
RCT: randomized controlled trial
RoB: risk of bias
RR: relative risk
SoE: strength of evidence
SR: systematic review
SSRI: selective serotonin reuptake inhibitor
TCA: tricyclic antidepressant
WL: waitlist
Y-BOCS: Yale-Brown Obsessive-Compulsive Scale

manuscript, and approved the final manuscript as submitted. Dr Adam assisted in conceptualization and design, performed the literature search, participated in data collection and interpretation of data, critically reviewed the manuscript, and approved the final manuscript as submitted. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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