Draft Systematic Review

Number XX

Diagnosis and Management of Obsessive Compulsive Disorders in Children

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None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of healthcare in the United States. The Patient-Centered Outcomes Research Institute (PCORI) requested this report from the EPC Program at AHRQ. AHRQ assigned this report to the EPC (to be included in the final version of the report) (Contract Number: to be included in the final version of the report).

AHRQ EPC reviews provide comprehensive, science-based information on common, costly medical conditions, and new healthcare technologies and strategies.

The Patient-Centered Outcomes Research Institute (PCORI) was established to fund research that helps patients and caregivers make better informed health care choices. To fulfill its authorizing mandate, PCORI partners with AHRQ to generate evidence synthesis products and make comparative effectiveness research more available to patients and providers.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews can help clarify whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about AHRQ EPC systematic reviews, go to https://effectivehealthcare.ahrq.gov/about/epc/evidence-synthesis.

AHRQ expects that the EPC evidence reports and technology assessments, when appropriate, will inform individual health plans, providers, and purchasers as well as the healthcare system as a whole by providing important information to help improve healthcare quality. Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the website (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an email list to learn about new program products and opportunities for input.

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The authors gratefully acknowledge the following individuals for their contributions to this project: To be included in the final version of the report.

Key Informants

In designing the study questions, the EPC consulted several Key Informants who represent the end-users of research. The EPC sought the Key Informant input on the priority areas for research and synthesis. Key Informants are not involved in the analysis of the evidence or the writing of the report. Therefore, in the end, study questions, design, methodological approaches, and/or conclusions do not necessarily represent the views of individual Key Informants.

Key Informants must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any conflicts of interest.

The list of Key Informants who provided input to this report follows: To be included in the final version of the report.

Technical Expert Panel

In designing the study questions and methodology at the outset of this report, the EPC consulted several technical and content experts. Broad expertise and perspectives were sought. Divergent and conflicted opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design, methodologic approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

Technical Experts must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

The list of Technical Experts who provided input to this report follows: To be included in the final version of the report.

Peer Reviewers

Prior to publication of the final evidence report, EPCs sought input from independent Peer Reviewers without financial conflicts of interest. However, the conclusions and synthesis of the scientific literature presented in this report do not necessarily represent the views of individual reviewers. AHRQ may also seek comments from other Federal agencies when appropriate.

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Diagnosis and Management of Obsessive Compulsive Disorders in Children

Abstract

Background. Obsessive-compulsive disorder (OCD) is a common, chronic, and impairing psychiatric disorder affecting about 3% of youth (children and adolescents). Early identification and treatment of OCD is important to prevent a cascade of developmental disruptions lasting into adulthood. The 2012 AACAP Practice Parameter recommends cognitive behavioral therapy that incorporates exposure and response prevention (ERP) as a first-line treatment for mild-to-moderate OCD in youth, and recommends combined treatment with ERP (if feasible) and a selective serotonin reuptake inhibitor (SSRI) for some patients, particularly those with more severe symptoms. Clinical uncertainty exists regarding the optimal treatment strategies (and treatment combinations) that work best for specific populations and settings. In this report, we seek to evaluate the accuracy of brief assessment tools to identify OCD in symptomatic youth (KQ1) and the effects and harms of treatment options for youth with OCD (KQ2).

Methods. We searched Medline®, Cochrane, Embase®, CINAHL®, and ClinicalTrials.gov from inception to July 6, 2023. After double screening, we extracted study data, risk of bias assessments, and conducted network and pairwise meta-analyses. We evaluated the strength of evidence (SoE) using standard methods. The protocol was registered in PROSPERO (registration number CRD42023461212).

Results. We found 115 studies (reported in 158 papers) that met inclusion criteria. Of these, 31 cross-sectional studies pertained to KQ1, diagnosis of OCD. For KQ 2, treatment of OCD, we included 69 randomized controlled trials (RCTs), 2 nonrandomized comparative studies (NRCSs), and 13 single-arm studies that reported potential treatment effect modifiers. For KQ1, there is insufficient evidence regarding most brief assessment tools. Based on nine studies, the Child Behavior Checklist-Obsessive Compulsive subscale (CBCL-OCS) may have sufficiently high sensitivity and specificity to identify patients for specialist referral and diagnostic evaluation (moderate SoE). For KQ2, meta-analyses indicate that in-person ERP is more effective than waitlist for OCD symptoms (high SoE; moderate SoE vs. behavioral control), for remission (moderate SoE), for global severity (high SoE), and for family accommodation (low SoE). ERP via telehealth is more effective than waitlist for OCD symptoms (high SoE), remission (moderate SoE), and family accommodation (low SoE). SSRI is more effective than placebo for OCD symptoms and global severity (high SoE). Clomipramine is probably more effective than placebo (moderate SoE). ERP and SSRI vs. SSRI is probably more effective than treatment with an SSRI alone for OCD symptoms (moderate SoE). The side effects of SSRIs and clomipramine were inconsistently reported, precluding graded conclusions. Augmentation of ERP with D-cycloserine is as effective as ERP alone to reduce OCD symptoms (high SoE) or global severity (moderate SoE). The evidence was insufficient regarding potential effect modifiers.

Conclusion. The diagnosis of OCD relies on expert clinical evaluation, sometimes augmented by semi-structured interviews. The CBCL-OCS, may be sufficiently accurate to indicate which youth should be further evaluated for OCD. ERP, delivered in-person or via

telehealth, is an effective treatment for OCD in children and adolescents. ERP, alone or in combination with an SSRI, is more effective than treatment with an SSRI alone.

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Main Points

- **Diagnosis of Obsessive Compulsive Disorder (OCD)**
  - Nine brief assessment tools were identified, but only one had sufficient evidence to draw conclusions. Thus, the available evidence is insufficient regarding the diagnostic accuracy of most brief assessment tools.
  - The 8-question version of the Child Behavior Checklist-Obsessive Compulsive subscale (CBCL-OCS) probably has sufficient diagnostic accuracy to identify symptomatic patients for specialist referral and comprehensive diagnostic evaluation of OCD, with a summary area-under-the-curve of 0.84 (moderate SoE).
- **Treatment of OCD**
  - Cognitive behavioral therapy with exposure and response prevention (ERP) is more effective than waitlist control (high SoE) and probably more effective compared to behavioral control for OCD symptoms, remission (moderate SoE), and more effective for global severity and family accommodation outcomes (high SoE)
  - Cognitive behavioral therapy with exposure and response prevention (ERP) provided via telehealth is more effective than waitlist for OCD symptoms (high SoE), remission (moderate SoE), and family accommodation outcomes (low SoE)
  - Cognitive behavioral therapy with exposure and response prevention (ERP) provided via telehealth is as effective as in-person ERP for OCD symptoms (high SoE), and may be as effective for global symptoms (low SoE)
  - Treatment with a selective serotonin reuptake inhibitor (SSRI) is more effective than placebo control for OCD symptoms and global severity outcomes (high SoE).
  - Treatment with ERP is probably more effective than treatment with an SSRI alone for OCD symptoms (moderate SoE)
  - Treatment with ERP and an SSRI is more effective than treatment with an SSRI alone for OCD symptoms (moderate SoE).
  - Treatment with ERP with an SSRI is probably equivalent to ERP alone for OCD symptoms (high SoE)
  - Treatment with the tricyclic antidepressant clomipramine may be more effective than placebo control for OCD symptoms (moderate SoE), but equivalent to treatment with an SSRI for OCD symptoms (high SoE).
  - The side effects of SSRIs and clomipramine were inconsistently reported, precluding graded conclusions.
  - Treatment with D-cycloserine to augment ERP is not more effective than ERP alone in reducing OCD symptoms (high SoE) and is probably not more effective in reducing global OCD severity (moderate SoE).
  - Studies were consistent in failing to find statistically significant associations between treatment effects and age, sex, baseline Child Obsessive Compulsive Impact Scale (COIS) score, baseline Family Accommodation Scale (FAS), or comorbid autism spectrum disorder or tics. Studies were inconsistent regarding the association between treatment effect and baseline OCD severity as assessed by CY-BOCS.

Background and Purpose

OCD is a common, chronic, and impairing psychiatric disorder affecting about 3% of youth (children and adolescents). OCD is defined by one or both of two cardinal features—obsessions and compulsions. Obsessions are persistent thoughts, urges, or images that are experienced as intrusive and unwanted, generally related to one or more domains that can range from fear of illness or death to uncomfortable experiences of incompleteness or disgust. People with OCD exhibit a wide range of compulsive rituals, avoidance behaviors, and other strategies to neutralize or avoid distress and obsessional triggers. Early identification and 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 functioning.

The 2012 American Academy of Child and Adolescent Psychiatry (AACAP) Practice Parameter recommends that for children and adolescents undergoing psychiatric assessment for any condition, (1) "The psychiatric assessment … should routinely screen for the presence of obsessions and/or compulsions or repetitive behaviors," even when not part of the presenting complaint; (2) "If screening suggests [obsessive compulsive] symptoms may be present, clinicians should fully evaluate the child using [Diagnostic and Statistical Manual of Mental Disorders (DSM)] criteria and scalar assessment"; (3) Clinicians should use information from all available sources; and (4) "A complete psychiatric evaluation should be performed, … with attention to commonly occurring comorbid psychiatric disorders".[1] The reference standard for an OCD diagnosis is a clinical interview by an expert assessing current DSM criteria, often augmented, with a clinician rated diagnostic tool, and in research settings, with a semi-structured diagnostic interview.

Because practitioners may not have the expertise or the time to do the full diagnostic interview required for diagnosis, they identify only about 10% of cases of childhood OCD.[2] Systemic barriers to accessing experts in assessing OCD may lead to late or missed diagnosis of OCD in children. To address these issues, this review focuses on the diagnostic accuracy of brief OCD assessment tools. In terms of treatment, the 2012 AACAP Practice Parameter recommends CBT that incorporates ERP as a first-line treatment for mild-to-moderate OCD in youth, and recommends combined treatment with ERP (if feasible) and a selective serotonin reuptake inhibitor (SSRI) for some children, particularly those with more severe symptoms. However, questions remain about what (combinations of) treatment strategies work best for specific populations and settings. In addition, new treatment modalities, such as neuromodulation and complementary interventions, have come into use since the 2012 Practice Parameter.

This comparative effectiveness review will summarize the findings from: (1) Studies related to the diagnostic accuracy of brief assessment tools compared to reference standard methods to identify OCD in symptomatic youth, and (2) Studies of psychological and/or pharmacological treatments of OCD.

Executive Summary

The systematic review addresses two Key Questions (KQs):

KQ 1: How accurate are brief assessment tools compared to reference standard methods to identify OCD in symptomatic children and adolescents?

> KQ 1.a: How does diagnostic accuracy of brief assessment tools vary by patient, family, social, or other characteristics, or by respondent type?

KQ 2: What are the comparative effects and harms of treatment interventions, used alone or in combination, for OCD in children and adolescents?

> KQ 2.a: How do the effectiveness and harms vary with patient, family, social, or other characteristics?

Methods

In this systematic review, we used methods consistent with those outlined in the Agency for Healthcare Research and Quality Evidence-based Practice Center Program Methods Guidance (https://effectivehealthcare.ahrq.gov/topics/cer-methods-guide/overview). Our searches targeted comparative studies (i.e., randomized controlled trials [RCTs] and nonrandomized comparative studies [NRCSs] with adjustment for potential confounders) for both KQs from database inception to July 6, 2023. For KQ 1 and for predictors of treatment response in KQ 2, we included single-arm studies. We extracted study data into the Systematic Review Data Repository Plus (SRDR+). With input from technical experts and key informants, we identified prioritized outcomes for each KQ. Where there was sufficient evidence, we conducted random effects network and pairwise meta-analyses. We assessed the risk of bias and evaluated the SoE using standard methods. The PROSPERO protocol registration number is CRD42023461212.

Results

We found 115 studies (reported in 158 papers or records) that met inclusion criteria. The studies were published between 1982 and 2022. Of these, 31 cross-sectional studies pertained to KQ1. For KQ 2, we included 69 randomized controlled trials (RCTs) and 2 nonrandomized comparative studies (NRCSs). Potential treatment effect modifiers were reported for 2 of the above RCTs and in 13 additional single-arm treatment studies.

Among the one-third of studies that reported data, more than 80% of children were White. Few studies reported on other potential social determinants of health, but among these, at least two-thirds of parents were living together with the child and about 60% to 90% of parents had at least a college degree.

Diagnosis: There are 31 studies that have evaluated tools that use either specific cut-points to classify an individual as having OCD or a prediction algorithm or model to predict the probability of OCD. Of these, 23 analyzed 9 brief assessment tools that determine whether a

child should be further evaluated for OCD and were included in the analysis. For most of the 9 **brief assessment tools**, the evidence was sparse and insufficient to draw any conclusions. However, for the 8-question version of the CBCL-OCS, based on 6 studies that provided sufficient data to include in meta-analysis), we found a summary area-under-the-curve (AUC) of 0.84 (95% CI 0.74 to 0.91) in 3,340 children, 11% of whom were diagnosed with OCD.

Treatment: We found 69 RCTs and 2 adjusted NRCSs evaluating OCD treatments. These included behavioral interventions in 31 studies, pharmacologic treatments in 24 studies, and combined behavioral and pharmacologic treatments in 16 studies. After removing small RCTs (N < 100 participants) that evaluated novel comparators, e.g., variations in ERP duration, intensity, location or medications other than SSRIs or clomipramine, we performed separate Network meta-analyses (NMA) by outcome, and concluded that each of these interventions (ERP, remote ERP, SSRI, and clomipramine) significantly reduces **OCD symptom severity** on the Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS) or Yale-Brown Obsessive Compulsive Scale (Y-BOCS). The relative rate of **remission** with ERP is 4.2-fold higher (95% CI 1.8 to 9.7) than in control. ERP and SSRI both result in a net reduction in **global severity** as measured by the Clinical Global Impressions-Severity (CGI-S) scale, and **family accommodation** on the FAS scale is significantly reduced with ERP compared to control. Network meta-analyses indicated that remote ERP is equivalent to in-person ERP for OCD symptoms and may be equivalent for global severity outcomes. Treatment with ERP is more effective than treatment with SSRI alone, and treatment with ERP plus SSRI is probably more effective than treatment with an SSRI alone. Treatment with clomipramine (a tricyclic antidepressant) is probably more effective than control, and equivalent to treatment with an SSRI. **Harms:** The side effects of SSRIs and clomipramine were inconsistently reported, precluding graded conclusions. No study collected or reported potential harms of behavioral interventions. In a pairwise meta-analysis of 5 studies evaluating D-cycloserine to augment ERP, we conclude that the combination of D-cycloserine and ERP is not more effective than ERP alone in reducing OCD symptom severity and is probably not more effective in reducing global OCD severity.

We found 15 studies (2 RCTs and 13 single-arm studies) that reported multivariable analyses of predictors of treatment response for ERP or a comparison of ERP with medication that was included in a multivariable model. The evidence was too sparse for any given predictor of treatment to form any conclusions. However, we found a consistent lack of association with treatment response for age (7 studies), sex (7 studies), baseline COIS (2 studies), baseline FAS (2 studies), comorbid autism spectrum disorder (3 studies), and comorbid tics (3 studies). For post-treatment CY-BOCS score, we found a consistent lack of association for age (6 studies), sex (5 studies), baseline functioning (2 studies), baseline FAS (3 studies), and comorbid tics (3 studies). Studies were inconsistent regarding the association between treatment effect and baseline OCD severity as assessed by CY-BOCS. There is some evidence that higher baseline scores mostly predicted higher post-treatment CY-BOCS scores (i.e., positive correlation between baseline and final scores), but also greater reduction in CY-BOCS scores.

Limitations

Multiple small studies reported novel comparisons sizes that did not support graded conclusions. Few studies reported on social determinants of health, but among those that did, study participants were mostly White with well-educated parents who lived together.

For the most robust CY-BOCS outcome network, various control conditions, waitlist, pill placebo, and behavioral control were treated as separate. To construct connected networks for remission and CGI-S, it was necessary to aggregate interventions into broader categories. Given the relatively sparse evidence within comparator-outcome categories, we did not perform subgroup analyses, or meta-regression of potential predictors and moderators of treatment effects.

Implications and Conclusions

The diagnosis of OCD relies on expert clinical evaluation, often augmented by semi-structured interviews. Brief assessment tools have been proposed to be used by primary care providers evaluating youth with symptoms of OCD to facilitate early identification and specialty referral for a comprehensive diagnostic evaluation and early initiation of treatment. The CBCL-OCS may be sufficiently accurate to indicate which youth should be further evaluated for OCD, but the available evidence is insufficient for other brief assessment tools.

We found evidence supporting the efficacy of ERP, delivered in-person or remotely, and for both SSRIs and clomipramine compared to placebo. ERP alone, or ERP in combination with an SSRI, is more effective than treatment with an SSRI alone.

The side effects of SSRIs and clomipramine were inconsistently reported in the included RCTs, precluding graded conclusions. However, based on evidence from other sources, the side effects of these drugs in children and adolescents are well known.[3] No study collected or reported potential harms of behavioral interventions.

Treatment with D-cycloserine to augment ERP is not more effective than ERP alone in reducing OCD symptom severity and is probably not more effective in reducing global OCD severity.

Future research efforts should focus on: 1) inclusion of study participants who are representative of all youth affected by OCD, including non-white, low socioeconomic status children, and of sufficient size to allow subgroup analyses to determine what works for whom; 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/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 (e.g., neuromodulation).

1. Introduction

1.1 Background

Obsessive-compulsive disorder (OCD) is a common, chronic, and impairing psychiatric disorder, defined by one or both of two cardinal features—obsessions and compulsions. Obsessions are persistent thoughts, urges, or images that are experienced as intrusive and unwanted, generally related to one or more domains that can range from fear of illness or death to uncomfortable experiences of incompleteness or disgust. People with OCD exhibit a wide range of compulsive rituals, avoidance behaviors, and other strategies to neutralize or avoid distress and obsessional triggers.[1] About 3% of youth (children and adolescents) experience OCD,[4] but 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 (≤12 years) and 36% had symptom onset during adolescence (13-17 years).[5]

Early identification and 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 functioning.[6-8] Untreated OCD is associated with depression, substance abuse, suicide attempts, and functional impairment in adulthood.[7, 9-12] Establishing an OCD diagnosis can be more challenging in children than in adults due to overlap with developmentally typical childhood fears and rituals, and, especially in young children, developmentally limited cognitive ability to describe their experiences.[1, 13, 14] Furthermore, OCD in children is often comorbid with depression, anxiety disorders, attention deficit hyperactivity disorder (ADHD), and eating disorders.[15] Individuals with OCD may exhibit behaviors similar to those seen in autism, tic disorders, and other anxiety-related disorders, which frequently co-occur with OCD, making differential diagnosis challenging.[14]

The 2012 American Academy of Child and Adolescent Psychiatry (AACAP) Practice Parameter recommends that for children and adolescents undergoing psychiatric assessment for any condition, (1) "The psychiatric assessment … should routinely screen for the presence of obsessions and/or compulsions or repetitive behaviors," even when not part of the presenting complaint; (2) "If screening suggests [obsessive compulsive] symptoms may be present, clinicians should fully evaluate the child using [Diagnostic and Statistical Manual of Mental Disorders (DSM)] criteria and scalar assessment"; (3) Clinicians should use information from all available sources; and (4) "A complete psychiatric evaluation should be performed, … with attention to commonly occurring comorbid psychiatric disorders".[1] The reference standard for an OCD diagnosis is a clinical interview by an expert assessing current DSM criteria, often augmented, with a clinician rated diagnostic tool (e.g., Children's Yale-Brown Obsessive Compulsive Scale [CY-BOCS]), and in research settings with a semi-structured diagnostic interview (e.g., Anxiety Disorders Interview Scale-Child Version [ADIS-C] or MINI-KID).[16]

Because practitioners may not have the expertise or the time to do the full diagnostic interview required for diagnosis, they identify only about 10% of cases of childhood OCD.[2] Systemic barriers to accessing experts in assessing OCD may lead to late or missed diagnosis of OCD in children. To address these issues, this review focuses on the diagnostic accuracy of brief OCD assessment tools. The diagnostic accuracy of a given index test is a cross-sectional question: it addresses the extent to which a classification, based on a specific index test result, corresponds to how an individual would be classified by the reference standard.[17] An index test with sufficiently high diagnostic accuracy might allow primary care providers to make a

provisional diagnosis of OCD, prompting expedited specialist referral for additional diagnostic assessment, and treatment.[18, 19] In the literature, these tools are sometimes referred to as "screeners". In this review, we avoid the use of the terms "screening" or "screener" to clearly indicate that our focus is on the accuracy of brief assessment tools for use with symptomatic children and adolescents (i.e., treatment seeking, or referred for clinical concern for a behavioral health concern).

In terms of treatment, the 2012 AACAP Practice Parameter recommends cognitive behavioral therapy that incorporates exposure and response prevention (ERP) as a first-line treatment for mild-to-moderate OCD in youth, and recommends combined treatment with ERP (if feasible) and a selective serotonin reuptake inhibitor (SSRI) for some patients, particularly those with more severe symptoms.[1] However, clinical uncertainty exists regarding the sequencing and combinations of treatment strategies that work best for specific populations and settings. Examples include individual versus family-focused versus parent-mediated, residential versus outpatient settings, through telemedicine as compared to in-person ERP, and ERP combined with medications or medication alone. In addition, new treatment modalities, such as neuromodulation and complementary interventions such as mindfulness, have come into use since the 2012 Practice Parameter.

OCD is thought to be a heterogeneous disorder with multiple potential causes. Individuals with OCD often have comorbidities (or co-occurring symptoms) including ADHD and tics. There is a robust emerging literature describing the neurocircuitry underlying OCD which suggests that shared biological mechanisms may underly the frequent co-occurrence of OCD, ADHD, and tics.[20]

The concept of an "autoimmune OCD" subtype has been proposed. Among patients with OCD some have presentations consistent with proposed definitions of pediatric acute-onset neuropsychiatric syndrome (PANS) and pediatric autoimmune neuropsychiatric disorder associated with streptococcal infections (PANDAS).[21, 22] In one study from a subspeciality pediatric OCD clinic, 7 of 136 (5.1%) children with OCD met proposed diagnostic criteria for PANS/PANDAS.[23] Evidence relating to the diagnostic criteria for PANS/PANDAS, and treatment of these patients with antibiotics or anti-inflammatory medications is outside the scope of this review.

1.2 Purpose of the Review

This comparative effectiveness review will inform a planned update of the 2012 AACAP Practice Parameter.[1] AACAP nominated this topic to the Patient-Centered Outcomes Research Institute (PCORI), which contracted with the Agency for Healthcare Research and Quality (AHRQ) to conduct the review.

Specifically, the systematic review summarizes the findings from: (1) Studies related to the diagnostic accuracy of brief assessment tools compared to reference standard methods to identify OCD in symptomatic youth, and (2) Studies of behavioral interventions, pharmacological treatments, and combined behavioral and pharmacological interventions for the treatment of OCD.

The intended audience includes guideline developers, child psychiatrists and psychologists, pediatricians, family physicians, advanced practice providers, parents, and patients.

2. Methods

2.1 Review Approach

For all Key Questions (KQs), the systematic review (SR) followed Agency for Healthcare Research and Quality (AHRQ) Evidence-based Practice Center Program methodology, as laid out in its Methods Guide, particularly as it pertains to reviews of comparative effectiveness, and meta-analyses.[24, 25] Appendix A provides full details for the search strategies, protocol development process, detailed inclusion and exclusion criteria, abstract screening, and data management. We registered the protocol for this SR in PROSPERO (registration number CRD42023461212).

2.2 Key Questions

Key Question 1: How accurate are brief assessment tools compared to reference standard methods to identify OCD in symptomatic children and adolescents?

> **1.a**: How does diagnostic accuracy of brief assessment tools vary by patient, family, social, or other characteristics, or by respondent type?

Key Question 2: What are the comparative effects and harms of treatment interventions, used alone or in combination, for OCD in children and adolescents?

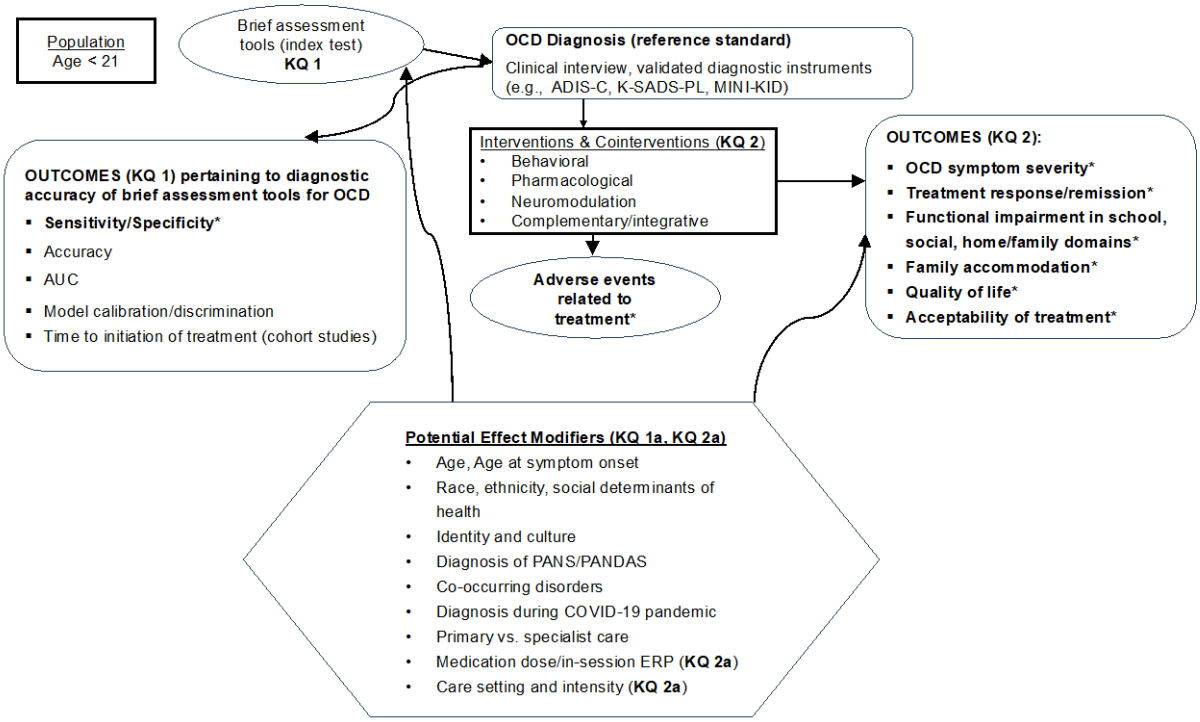
> **2.a**: How do the effectiveness and harms vary with patient, family, social, or other characteristics?

2.3 Logic Model

Based on discussions with Key Informants and Technical Expert Panel members, we developed a logic model for the two KQs (Figure 2.1).

Methods

Figure 1. Logic Model for Diagnosis and Management of Obsessive Compulsive Disorders in Children



Abbreviations: ADIS-C = Anxiety Disorders Interview Schedule for Diagnostic and Statistical Manual of Mental Disorders 5 (DSM-5), K-SADS-PL = Kiddie Schedule for Affective Disorders and Schizophrenia, Present and Lifetime version , MINI-KID = Mini-International Neuropsychiatric Interview for Children and Adolescents, AUC = Area under the receiver operating characteristic curve, KQ = Key question, OCD = Obsessive-compulsive disorder, PANS = pediatric acute-onset neuropsychiatric syndrome, PANDAS = pediatric autoimmune neuropsychiatric disorder associated with streptococcal infections

2.4 Study Selection

We searched for studies and existing systematic reviews in MEDLINE (via PubMed), the Cochrane Register of Clinical Trials, the Cochrane Database of Systematic Reviews, Embase, CINAHL and PsycINFO and Education Resources Information Center (ERIC) databases on July 6, 2023. Additional searches were conducted on September 1, 2023 in the ClinicalTrials.gov registry for ongoing and unpublished studies with study results. The reference lists of relevant existing systematic reviews were screened for additional eligible studies. Additional searches were conducted on September 1, 2023 in the ClinicalTrials.gov registry for ongoing and unpublished studies with study results. Additional articles suggested to us from any source were screened with the same eligibility criteria as the studies identified in the database searches.

We took advantage of the machine learning capacities of Abstrackr (http://abstrackr.cebm.brown.edu/) to limit resources spent on abstract screening. We stopped double screening when the predicted likelihood of the remaining unscreened papers was below 0.40 (this threshold is based on experience with several dozen screening projects and an analysis in preparation for publication) and we had rejected at least 400 consecutive citations.

For Key Question 1, we report studies that evaluate the diagnostic accuracy (predictive validity) of brief assessment tools for OCD in children and adolescents, compared to a reference standard (clinical interview by an expert assessing current DSM criteria, possibly augmented by

a semi-structured interview using a validated assessment instrument). Non-brief tools are reported in the Appendix.

For Key Question 2, we included randomized controlled trials (RCTs) and nonrandomized comparative studies (NRCSs) that compared psychological and pharmacological interventions for OCD, alone or in combination, compared to control conditions (i.e., waitlist, pill placebo, behavioral interventions that did not include ERP), or another active intervention or co-intervention(s) or delivery method. Eligible NRCSs had to adjust for potential confounders. We evaluated outcomes as listed in the Study Eligibility Criteria section, focusing on listed prioritized outcomes related to OCD symptom severity, treatment response and remission, functional impairment, family accommodation, quality of life, and acceptability of treatment and adverse events related to treatment. Prioritized outcomes are in bold font (with asterisks) in the Study Eligibility Criteria table.

We extracted reported predictors and moderators of treatment effect from the included RCTs, and in addition from adjusted single-arm studies that reported predictors of treatment response.

For all Key Questions, we identified predictors and moderators of treatment effect from the included RCTs (see potential effect modifiers/subgroups of interest), and in addition from adjusted single-arm studies that reported predictors of treatment response. Studies excluded in full text along with their exclusion reasons are listed in Appendix B.

2.5 Data Extraction and Data Management

We extracted data into the Systematic Review Data Repository Plus (SRDR+) database (https://srdrplus.ahrq.gov) and Google Sheets as appropriate. Data extracted in Google Sheets were imported into SRDR+ at the end of the project. Each eligible study was extracted and assessed for risk of bias (RoB)/quality by one researcher. Extracted data, including RoB assessment, were confirmed by a second, independent researcher.

2.6 Assessment of Risk of Bias and Methodologic Quality

We evaluated each comparative study (RCT and NRCS) for RoB. All overall RoB assessments were determined by discussion of the team.

For RCTs, including cluster randomized trials, we completed the Cochrane Risk of Bias tool,[26] which addresses issues related to randomization and allocation concealment; blinding; deviations from intended intervention; missing data; outcome measurement; and reporting biases.

For NRCSs, we added assessments of specific elements from ROBINS-I[27] (Risk Of Bias In Non-randomized Studies - of Interventions) related to selection bias (comparability of groups) and relevant concepts addressed for RCTs (i.e., related to missing data, outcome measurement, analysis plan).[27]

In developing a RoB rating for comparative studies, we used the following heuristic: If allocation or randomization RoB was high, the overall RoB was high. If any other single element was at high RoB, the overall RoB was moderate. If two other elements were at high RoB, the overall RoB was high. If allocation, randomization, and blinding were all unclear, the overall RoB was (at best) moderate. If blinding of outcome assessor was at low RoB and blinding of participants was at high RoB, overall blinding was determined to be at low RoB. If blinding of the outcome assessor was unclear and blinding of participants was at high RoB, overall blinding was at high RoB. For NRCSs, given lack of randomization, all were at best moderate RoB.

Those with other methodological issues that increased the likelihood of residual confounder were deemed high RoB.

For single-arm studies reporting predictors of treatment effect, we assessed the adequacy of adjustment for potential confounders using three criteria: (1) whether all predictors in the model were described in the article, (2) whether results were given for all predictors in model, and (3) whether the number of variables in the model divided by number of participants was greater than 10. Where all 3 criteria were met, the analysis was considered to be adequate; otherwise, the analysis was considered inadequate.

For single test diagnostic accuracy studies, we assessed specific elements from the QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies 2).[28-30] Overall RoB rating was determined in consensus among the group using the following heuristics: If the study was a single-arm study (with no control group) or a case control study that did not enroll a random or consecutive sample, and did not report using a reference standard on all participants, the study was determined to have high RoB. If the study was not a case-control study and reported using a reference standard on all participants, RoB was low. If the study was a case-control design, but all other criteria were low, RoB was moderate.

2.7 Data Synthesis

Each study is described in summary and evidence tables presenting study design features, study participant characteristics, descriptions of interventions, outcome results, and RoB/methodological quality in Appendix C.

For diagnostic test studies, we extracted all relevant outcome measures (e.g., sensitivity, specificity, area under the curve receiver operating characteristics curve [AUC ROC]) at all reported thresholds.

For KQ 1, we conducted random-effects model meta-analyses of comparative studies if at least 6 studies were sufficiently similar in population, interventions, outcomes, and study design. The diagnostic meta-analysis models estimate 5 parameters: mean sensitivity, mean specificity, the standard deviations of the random effects of sensitivity and specificity, and the correlation between the random effects of sensitivity and specificity. We created summary ROC curves for tools where there were at least 5 studies with sufficient data using the diagmeta[31] package in R,[32] which uses a hierarchical restricted maximum likelihood (REML) linear random effects model.

For KQ 2, we analyzed continuous effect metrics on the original reported scales, such as CY-BOCS. We focus on common scales reported across studies, and do not use standardized effect sizes such as Cohen's d. For continuous outcomes, we compute net mean differences (NMD; the difference between arms of the within-arm changes in outcome). For categorical outcomes such as remission, we report effects on the risk ratio (RR) scale.

In the network graphs, the circles (nodes) represent interventions. The diameter of the circles is proportional to the number of patients who received each intervention. The lines connecting nodes (edges) represent the direct comparisons between pairs of interventions. The width of the edges are proportional to the number (shown in text on each line/edge) of studies that directly compared each pair of treatments.

For the more robust CY-BOCS network, we assign separate control groups—wait list (WL), pill placebo (placebo) and behavioral control (behavCntrl)— to separate comparator nodes. In a sensitivity analysis, we combined these control group types into a common 'Control' node and performed a subgroup analysis by control group type.

For the other, less robust networks, remission, and CGI-S, we combined separate control groups into a common 'Control' node in order to create connected networks.

In each network, we found studies comparing a novel treatment or treatment adjunct with a reference treatment (often ERP). Comparisons between non-reference treatments rely on indirect evidence, limiting the reliability of these estimates. We removed these "hanging branches" during network construction. For those comparisons with fewer than 100 participants, we summarize narratively. When comprised of three or more studies, we synthesize these "hanging branches" via separate pairwise meta-analysis.

We conducted network meta-analysis (NMA), an extension of pairwise MA, that synthesizes direct and indirect evidence in a single analysis of multiple comparisons. We fit random effects models using the R package netmeta.[33] Restricted maximum likelihood (REML) was used to estimate the between study variance τ^2.

The effect estimates for each treatment contrast derive from two sources—studies that directly compare two treatments (direct evidence)—and also from studies in a connected path via one or more intermediate comparators (indirect evidence).[33] The Q statistic under the assumption of a full design-by-treatment interaction random effects model was used to test the null hypothesis of consistency.We report network effect estimates (which combine direct and indirect evidence) only for those comparisons informed by direct evidence from at least 2 study arms. For each comparison, the figures display separate direct and indirect estimates, the overall network estimate, and the predictive interval. The transitivity assumption is supported when the direct and indirect estimates are similar. To assess the global inconsistency of the random effects models, we report the Q_B statistic.[26]To compare direct and indirect evidence for each pairwise comparison using the separate indirect from direct evidence (SIDE) method.

The prediction interval is the expected range of treatment effects in future similar studies and represents an indirect indicator of between study heterogeneity.[34]

We performed random effects pairwise MA using the R[32] package meta[35] for comparisons represented as "hanging branches" (nodes connected to the network by a single edge) that are informed by direct comparisons in 3 or more studies.

For sparsely reported outcomes (i.e., outcomes reported by fewer than 3 studies for a given comparison), we summarize the number of studies reporting each outcome, and report study specific effects in the appendix evidence tables. We summarize but do not detail these results in the main report.

We narratively describe differences in effects and harms by different factors, subgroups, or predictors. This includes NRCSs with adjustment for potential confounders, and single-arm studies of over 50 participants that performed any type of adjusted analysis with at least three variables in the model.

2.8 Grading the Strength of Evidence for Prioritized Outcomes

Following AHRQ Methods guidance, we considered the number of studies, their designs, limitations (i.e., RoB and overall methodological quality), the directness of the evidence, the consistency of study results, the precision of any estimates of effect, the likelihood of reporting bias, other limitations, and the overall findings across studies, and assigned a consensus strength of evidence (SoE) rating of high, moderate, low, or insufficient to estimate an effect, addressing each prioritized outcome for each KQ.

Outcomes with highly imprecise estimates (with 95% confidence intervals that extend beyond both 0.5 and 2.0 for categorical outcomes, or a confidence interval greater than half the full range of the scale for continuous outcomes), highly inconsistent findings across studies (in terms of directions of effect), or with data from only one study were deemed to have insufficient evidence to allow for a conclusion. Data from a single study were deemed insufficient evidence to allow for a graded conclusion, with the exception that a relatively large (defined as N ≥100), well-conducted (defined as low RoB) study could provide low SoE.

This approach is consistent with the concept that for imprecise evidence "any estimate of effect is very uncertain," which is the definition of Very low-quality evidence per the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) approach.[36]

In accordance with AHRQ guidance for describing treatment effects,[1, 37, 38] we have incorporated qualifying language regarding SoE when communicating conclusions (e.g., in Key Points sections of the text) 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.

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3. Results

3.1 Literature Search Results

The literature search yielded 12,027 records after deduplication. Detailed search strategies, inclusion and exclusion criteria, and a list of excluded studies (with reasons for their exclusion) are in Appendixes A and B. Appendix C Figure C-1 summarizes the results of the search and screening processes.

We retrieved and screened the full-text publications for 436 citations or records. We extracted data from 158 papers or records that met our inclusion criteria. Of these, 31 cross-sectional studies pertained to KQ 1 (of which 22 evaluated brief assessment tools and were included in the analysis). For KQ 2, we included 69 randomized controlled trials (RCTs) and 2 nonrandomized comparative studies (NRCSs)) in 108 papers or records. Predictors of treatment effects were reported for 2 of the above RCTs and in 13 additional single-arm treatment studies (reported in 19 papers).

Appendix Tables C-1.1 to C-3.3 summarize the design, arm, and patient characteristics for each KQ. Appendix D Tables D-1.1 to D-1.3 summarize the risk of bias (RoB) for comparative studies for RCTs and NRCSs, and methodological quality for single arm studies. Detailed results are in Appendix E, Tables E–1.2 to E–3.1. References for all appendixes are in Appendix F.

3.2 Description of Included Evidence

Tables describing study designs, groups, and sample characteristics; RoB; and details of outcome data are in Appendix C, Results. We call attention to specific appendix table numbers in the relevant subsections.

3.3 Key Question 1

Key Question 1: How accurate are brief assessment tools compared to reference standard methods to identify OCD in symptomatic children and adolescents?

> **1.a**: How does diagnostic accuracy of brief assessment tools vary by patient, family, social, or other characteristics, or by respondent type?

3.3.1 Key Points

- Nine brief assessment tools were identified, but only one had sufficient evidence to draw conclusions. Thus, the available evidence is insufficient regarding the diagnostic accuracy of brief assessment tools other than CBCL-OCS.
- Brief assessment tools: The 8-question version of the Child Behavior Checklist-Obsessive Compulsive subscale (CBCL-OCS) probably has sufficient diagnostic accuracy to identify symptomatic patients for specialist referral and comprehensive diagnostic evaluation of OCD, with a summary area-under-the-curve of 0.84 (moderate SoE).

3.3.2 Evidence Identified

In the context of tools that use specific cut-points to classify an individual as having OCD or a prediction algorithm or model to predict the probability of OCD, 31 studies met eligibility criteria.[2, 18, 19, 39-66] Of these, 22 addressed brief assessment tools that determine whether a child should be further evaluated for OCD and were therefore included in this analysis. The nine studies that evaluated non-brief tools and are summarized in Appendix E. The rest of this section describes the results for brief assessment tools.

Descriptions of the brief tools evaluated are in Table 3.3.2. In all studies the reference standard was a clinical diagnosis by a doctoral-level evaluator. The studies enrolled between 50 and 2,512 children (between 8 and 489 with OCD). The mean ages ranged from 9 to 15 years, with most children in early adolescence. The cohorts were generally equally distributed between males and females but ranged from 32% to 71% male. Among the studies that reported data on race and/or ethnicity, participants were predominantly White (88% to 98%). In the OCD group, 82 percent of studies drew their participants from outpatient psychiatric clinics, 2 described as OCD-specific; 2 drew from intervention research study populations, 1 from an inpatient psychiatric clinic, and 1was not reported. In the control group, 50 percent of studies drew their participants from outpatient psychiatric clinics, one OCD-specific; 4 drew from nonclinical populations (e.g., schools), 2 drew from intervention research study populations, 1 from an inpatient psychiatric clinic, and 4 did not have a control group. Full details of study design and cohort characteristics are in Appendix Tables C1.1-C1.2. Most studies used a case-control design (91%), comparing a known group of children with OCD with a control group of either clinical controls or a mix of clinical and nonclinical controls. Studies that compared children with OCD only with nonclinical controls (i.e., children who were not being evaluated for OCD, such as general school children) and studies that had no controls were extracted for sensitivity only (i.e., evaluation only of the group of children with OCD). Overall risk of bias (RoB) is reported in the results tables for each study, full RoB data are in Appendix Table D1.1.

Table 3.3.2. Brief Assessment Tools

Tool Acronym	Tool Components/Items	Tool Description	Tool Range*	No. Studies
Children's Florida Obsessive Compulsive Inventory (C-FOCI)[67]	17 questions addressing obsessions and compulsions that are frequent among young people with OCD	OCD-specific, brief, focused instrument: Symptom Checklist is a dichotomous tool that evaluates the presence/absence of obsessions and compulsions.	Symptom checklist: 0 to 17 Severity scale: 0 to 85	2
Child Behavior Checklist-Obsessive Compulsive subscales (CBCL-OCS)[19]	8 questions addressing fears/worries, obsessions, and compulsions	OCD-specific subscale: A subset of the full CBCL. The most common CBCL-OCS subscale consists of a subset of 8 items determined to be most predictive in an analysis by Nelson et al.[19] OCS-R (revised) contains 6 items, which are a subset of the 8 established by Nelson et al..[18]	0 to 24	9
Obsessional Compulsive Inventory-Child (CHOCI)[57, 68]	19 questions addressing obsessions, compulsions, and impairment associated with both	OCD specific: Designed to assess the presence and severity of OCD in children and adolescents aged 7-17 years; derived from the CY-BOCS, but intended for self-report rather than clinician rating	Total impairment: 0 to 48 Total symptoms: 0 to 40	1

Results

Tool Acronym	Tool Components/Items	Tool Description	Tool Range*	No. Studies
Leyton Obsessional Inventory – Child Version (LOI-CV)[69]	44 items that assess obsessive symptoms. Short version consists of 20 items	OCD specific. Self-report questionnaire focused on obsessions.	1 to 44 (full version) 1 to 20 (short version)	3 (1 full version, 2 short version)
Obsessive Compulsive Inventory – Child Version (OCI-CV)[70]	21 items addressing six domains: washing/checking, obsession, ordering, doubting, neutralizing, and hoarding	OCD specific: Self-report severity scale for children aged 7-17 years old OCI-CV-R (revised) assesses all items except those related to hoarding (18 items) OCI-CV-5 assesses a five-item subset of the OCI-CV-R	OCI-CV: 0 to 63 OCI-CV-R: 0 to 35 OCI-CV-5: 0 to 15	4 (2 OCI-CV, 1 OCI-CV-R, 1 OCI-CV-5)
Spence Children's Anxiety Scale – OCD subscale (SCAS-OCD) [64]	6 items, assessing obsessions and compulsions	OCD specific subscale: Derived from the Spence Children's Anxiety Scale, assesses a subset of symptoms related to OCD for children ages 8 to 15 years	0 to 24	2
Short Obsessive-Compulsive Disorder Screener (SOCS)[63]	5 items that address common symptoms (e.g., checking, touching, cleanliness/washing, repeating, and exactness)	OCD specific: Includes the 5 most discriminant items of the 44-item LOI	0 to 14	2
Toronto Obsessive–Compulsive Scale (TOCS)[49]	21-item measure of obsessive and compulsive thoughts	OCD specific: designed to measure OCD traits in the general population; designed to be administered by clinicians for children and adolescents	-63 to 63†	1
Youth Self-Report OCD subscale (YSR OCD subscale)[59]	Addresses obsessions, and compulsions	OCD specific subscale: A subset of the YSR, which assesses internalizing and externalizing problems, designed for children ages 11 to 18 years.	0 to 11	1

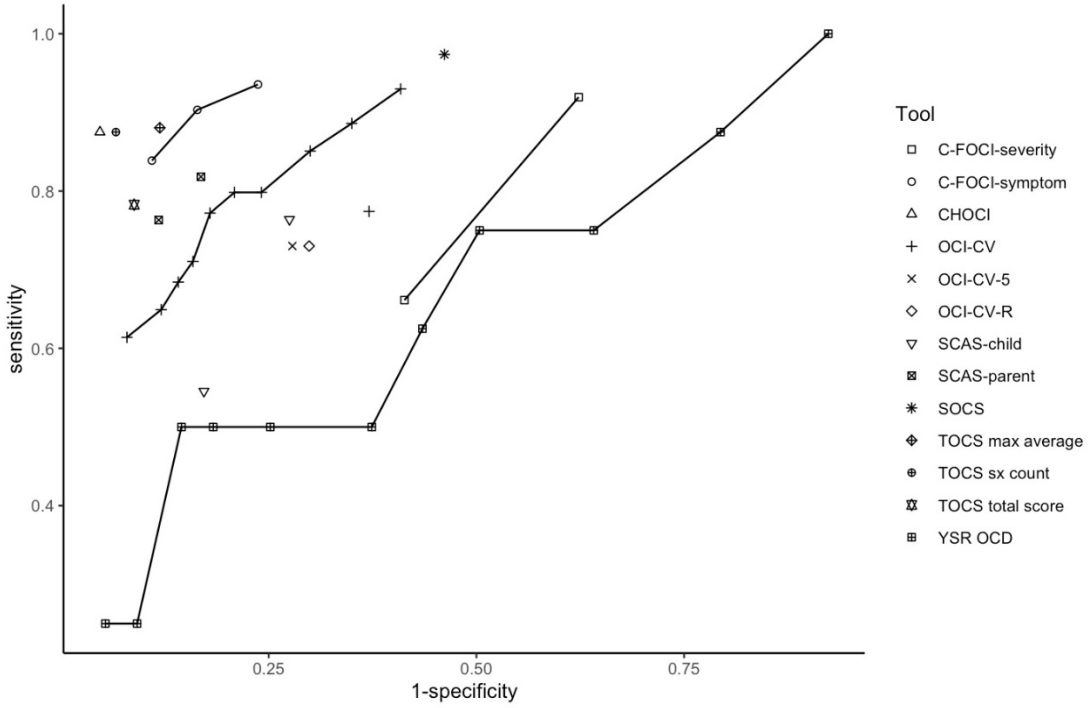
Tools are listed in alphabetical order based on their acronyms.
Abbreviations: CV = child version; DSM = Diagnostic and Statistical Manual of Mental Disorders; ICD = International Classification of Diseases; OCD = obsessive compulsive disorder; R = revised.

* higher scores reflect greater severity
† scores for each item range from −3 = far less often to 0 = average to +3 = far more often.

3.3.2.1 Brief Assessment Tools

Most of the brief assessment tools were evaluated in only one or two studies each, with the exception of the CBCL-OCD, which was evaluated in nine studies. The small number of studies and inconsistent control groups mostly precluded comparisons across studies. Sensitivity and specificity results for each study are presented by tool in Figure 3.3.3.2 and by study in Table 3.3.3.2. Information for the CBCL-OCD is below.

Figure 3.3.2.1-1. Observed ROC curves for other tools



Datapoints connected by lines are from the same studies. Studies that did not provide specificity data are omitted.
Abbreviations: C-FOCI = Children's Florida Obsessive Compulsive Inventory; CHOCI = Child Obsessional Compulsive Inventory; OCD = obsessive compulsive disorder; OCI-CV = Obsessive Compulsive Inventory – Child Version; SCAS = Spence Children's Anxiety Scale (OCD subscale); ROC = receiver operating characteristic; SOCS = Short Obsessive-Compulsive Disorder Screener; TOCS = Toronto Obsessive–Compulsive Scale; YSR-OCD = Youth Self-Report OCD subscale

Results

Table 3.3.2.1. Sensitivity and specificity for brief assessment tools

Tool	Study (N OCD/N control) RoB	Cutoff	Sensitivity, %	Specificity, %
C-FOCI Symptom	Piqueras 2017[52] (94/NA) high	9	37 (27, 48)	NA
C-FOCI Symptom (Persian)	Zemestani 2021[66] (62/NA) high	9	94 (84, 98)	76 (71, 81)
C-FOCI Severity (Persian)	Zemestani 2021[66] (62/NA) high	6	92 (82, 97)	59 (53, 64)
CHOCI	Shafran 2003[57] (24/64) high	17	88 (47, 100)	95 (87, 99)
LOI-CV 20 question version	Stewart 2005[60] (81/NA) moderate	25	28 (18, 39)	NA
LOI-CV 20 question version	Storch 2011[62] (50/NA) moderate	25	14 (6, 27)	NA
LOI-CV 20 question version, measured using symptom frequency	Bamber 2002[42] (9 OCD only/NA) high	5	78 (40, 97)	NA
LOI-CV 20 question version, measured using symptom frequency	Bamber 2002[42] (14 OCD + depression/NA) high	5	79 (49, 95)	NA
LOI-CV 44 question version	Stewart 2005[60] (81/NA) moderate	30	52 (40, 63)	NA
OCI-CV	Rough 2020[53] (114/641) high	11	77 (68, 85)	82 (78, 86)
OCI-CV (Persian)	Zemenstani 2022[65] (62/NA) high	17.5	77 (65, 87)	63 (57, 68)
OCI-CV-R	Abramovitch 2022[18] (489/298) moderate	8	73 (69, 77)	70 (65, 75)
OCI-CV-5	Abramovitch 2022[39] (489/298) moderate	2	73 (69, 77)	72 (67, 77)
SCAS-OCD parent	Whiteside 2012[64] (76/85) moderate	7	76 (65, 85)	88 (79, 94)
SCAS-OCD parent	Sattler 2018[55] (33/279) high	8	82 (65, 93)	83 (78, 87)
SCAS-OCD child	Whiteside 2012[64] (76/85) moderate	7	76 (65, 86)	72 (61, 82)
SCAS-OCD child	Sattler 2018[55] (33/279) high	8	55 (36, 72)	83 (78, 87)
SOCS	Uher 2007[63] (114/13) low	6	97 (93, 99)	54 (25, 81)
SOCS	Piqueras 2015[51] (94/NA) high	6	76 (66, 84)	NA
TOCS max average	Lambe 2021[49] (184/227) moderate	1	88 (82, 92)	88 (83, 92)
TOCS symptom count	Lambe 2021[49] (184/227) moderate	2	88 (82, 92)	93 (89, 96)
TOCS total score	Lambe 2021[49] (184/227) moderate	1	78 (72, 84)	91 (87, 95)
YSR-OCD subscale	Skarphedinsson 2021[59] (8/131) moderate	9	50 (16, 84)	85 (78, 91)

Abbreviations: C-FOCI = Children's Florida Obsessive Compulsive Inventory; CHOCI = Child Obsessional Compulsive Inventory; LOI-CV = Leyton Obsessional Inventory – Child Version; OCD = obsessive compulsive disorder; OCI-CV = Obsessive Compulsive Inventory – Child Version; RoB = risk of bias; SCAS-OCD = Spence Children's Anxiety Scale – OCD subscale; SOCS = Short Obsessive-Compulsive Disorder Screener; TOCS = Toronto Obsessive–Compulsive Scale; YSR-OCD = Youth Self-Report OCD subscale

The shading groups tools but does not provide any unique meaning.

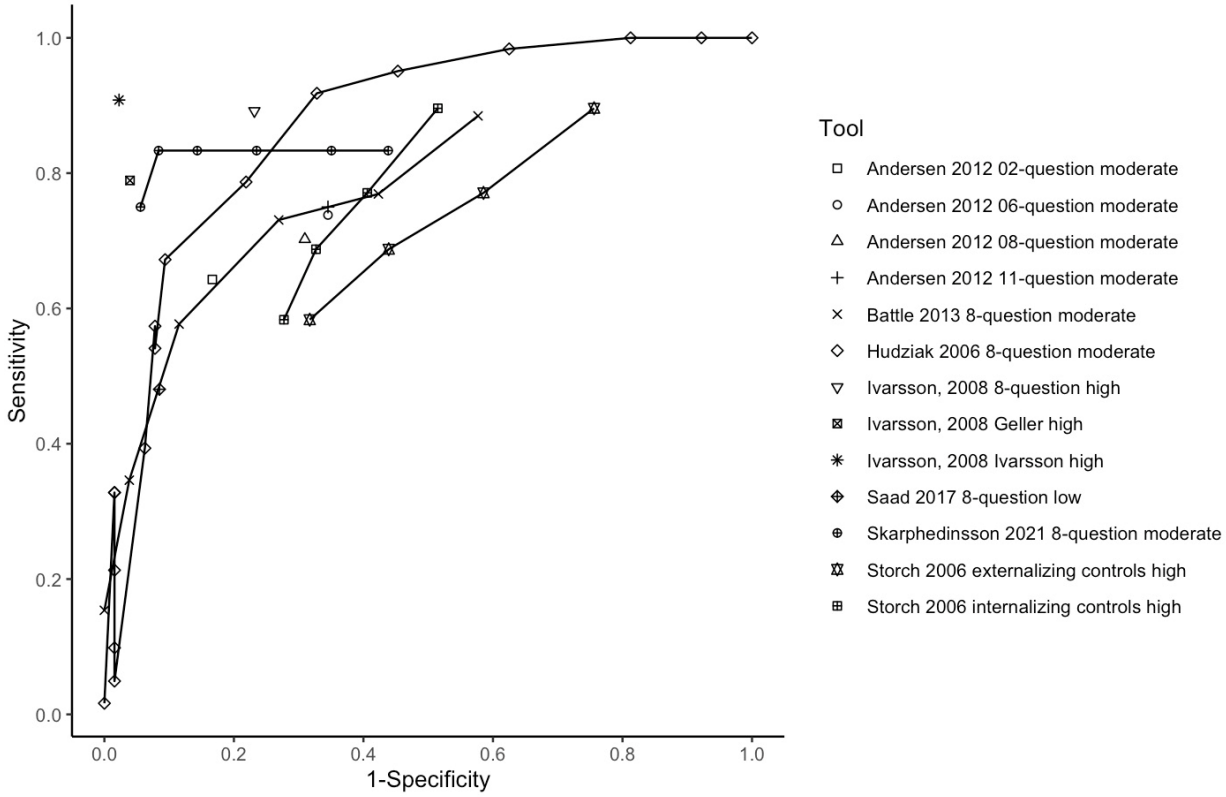
In terms of discriminating among OCD, attention-deficit/hyperactivity disorder (ADHD), and autism spectrum disorder (ASD), Lambe 2021 reported AUC analyses for the **TOCS** in a cohort of 350 children with OCD, 820 children with ADHD, and 794 children with ASD.[49] For OCD versus ADHD, the TOCS had an AUC of 0.86 (95% CI 0.84 to 0.89). For OCD versus ASD, the TOCS had an AUC of 0.81 (95% CI 0.78 to 0.84). These results suggest that the tool may be better at differentiating OCD from ADHD than OCD from ASD.

Nine studies evaluated the Child Behavior Checklist-Obsessive Compulsive subscale (CBCL-OCS; also called the CBCL-OCD), a subscale of the CBCL, in 3746 participants.[2, 19, 41, 43, 45, 47, 54, 59, 61] Only one study was rated as low RoB,[54] four were rated as of moderate RoB,[2, 41, 43, 59] and two were rated as of high RoB.[47, 61] Individual ratings are listed with the study name in Figure 3.3.3.1-1. Both Nelson 2001 and Geller 2006 reported data only by percentile; thus, their

data are not included in the figures.[19, 45] Both reported sensitivity and specificity for percentiles ranging from the 40th to the 90th. Sensitivities ranged from 98% in the 40th percentile to 30% in the 90th, and specificities ranged from 41% in the 40th percentile to 100% in the 90th. Six studies evaluated the 8-question subscale developed by Nelson et al. in 2001.[19] The other three evaluated subsets of these questions. The prevalence of OCD in the nine studies ranged from 3% to 54%, with a median of 49% (interquartile range [IQR] 33% to 49%) and a mean of 39% (standard deviation [SD] 17%).

Meta-analysis of the six studies[2, 41, 43, 47, 54, 59] that evaluated Nelson et al.'s 8-question subscale (in 3,340 children, 361 with OCD) showed a summary AUC of 0.84 (95% CI 0.74 to 0.91). The summary receiver operating (SROC) curve is shown in figure 3.3.2.1-2.

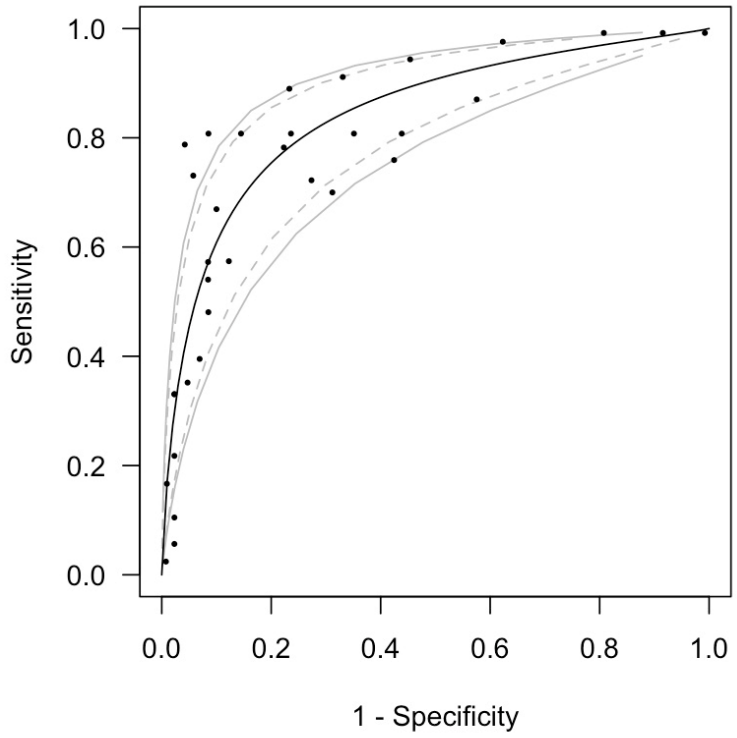
Figure 3.3.2.1-2. ROC curves for the CBCL-OCS scale



Listed studies present the study author, year, differentiating information as needed, and overall risk of bias rating.

Abbreviations: CBCL-OCS = Child Behavior Checklist-Obsessive Compulsive subscales, ROC = receiver operating characteristic, SROC = summary receiver operating characteristic.

Figure 3.3.2.1-3. SROC curve for the CBCL-OCS scale



The meta-analysis was done on only the 8-question version of the CBCL-OCS. The solid black line is the summary receiver operating curve (SROC); the solid gray line demarks the 95% confidence region for sensitivity given specificity and the dashed gray line demarks the 95% confidence region for specificity given sensitivity. The dots represent the reported sensitivity and 1-specificity points from each of the 6 studies. See figure 3.3.2.1-1 for details on the individual studies.

Several studies evaluated the CBCL-OCD scale for different subsets of questions, reporting generally very good AUCs, which ranged from 0.74 to 0.96. These were not included in the meta-analysis, as they were not directly comparable to the standard 8-question CBCL-OCS. Specifically, Andersen 2012 evaluated the CBCL-OCD scale for different subsets of questions (2, 6, 8, and 11) in 168 children (84 with OCD) and reported AUCs were between 0.74 and 0.79.[41] Ivarsson 2008 chose four CBCL-OCD scale items that, in a logistic regression, best predicted OCD.[47] In a cohort of 362 children (185 with OCD and 177 clinical controls, the AUC for these items was 0.96 (95% CI 0.94 to 0.98). They compared this with the 8-question scale developed by Nelson et al. in 2001 in the same cohort and reported an AUC for the 8-question scale of 0.91 (95% CI 0.87 to 0.94). Storch 2006 narrowed the criteria in the 8-question scale developed by Nelson et al. in 2001to 6 factors with the greatest predictive strength.[61] Then evaluated the 6-question CBCL-OCS subscale in participants with internalizing and externalizing disorders. As can be seen in Figure 3.3.3.1 left panel, the scale was poorer at differentiating OCD from other disorders than evaluations of CBCL-OCS in other studies. It is unclear if this is because the comparator groups had disorders more similar to OCD than the other studies' comparator groups or because the scale had fewer elements.

3.3.3 Evidence Profile for Key Question 1

Overall, the current evidence is insufficient to justify broad conclusions about the performance and utility of tools and tools used to diagnose OCD other than the CBCL-OCD. See Table 3.3.3.

Table 3.3.3. Evidence Profile for Key Question 1, diagnosis of OCD

Tool type	Tool	N Studies (Patients)	RoB	Consistency	Precision	Directness	SoE	Conclusions
Brief assessment tools	CBCL-OCD	9 (4021); 6 (3508) using Nelson's CBCL 8 question version	Moderate	Consistent	Precise	Direct	Moderate	Summary AUC0.84 (0.74 to 0.91)*

Tools with insufficient evidence are omitted.

*Based on the 6 studies evaluating the 8 question score

Abbreviations: CBCL-OCS = Child Behavior Checklist-Obsessive Compulsive subscales; AUC = area under the curve..

3.4 Key Question 2

Key Question 2: What are the comparative effects and harms of treatment interventions, used alone or in combination, for OCD in children and adolescents?

2.a: How do the effectiveness and harms vary with patient, family, social, or other characteristics?

3.4.1 Key Points

- Cognitive behavioral therapy with exposure and response prevention (ERP) is more effective than waitlist control (high SoE) and probably more effective compared to behavioral control for OCD symptoms, remission (moderate SoE), and more effective for global severity and family accommodation outcomes (high SoE)
- Cognitive behavioral therapy with exposure and response prevention (ERP) provided via telehealth is more effective than waitlist for OCD symptoms (high SoE), remission (moderate SoE) and family accommodation outcomes (low SoE)
- Cognitive behavioral therapy with exposure and response prevention (ERP) provide via telehealth is as effective as in-person ERP for OCD symptoms (high SoE), and may be as effective for global severity (low SoE)
- Treatment with a selective serotonin reuptake inhibitor (SSRI) is more effective than placebo control for OCD symptoms and global severity outcomes (high SoE).
- Treatment with ERP is probably more effective than treatment with an SSRI alone for OCD symptoms (moderate SoE)
- Treatment with ERP with an SSRI is probably equivalent to ERP alone for OCD symptoms (high SoE)
- Treatment with the tricyclic antidepressant clomipramine may be more effective than placebo control for OCD symptoms (moderate SoE), but equivalent to treatment with an SSRI for OCD symptoms (high SoE).
- The side effects of SSRIs and clomipramine were inconsistently reported, precluding graded conclusions.
- Treatment with D-cycloserine to augment ERP is not more effective than ERP alone in reducing OCD symptoms (high SoE) and is probably not more effective in reducing global OCD severity (moderate SoE).
- Studies were consistent in failing to find statistically significant associations between treatment effects and age, sex, baseline Child Obsessive Compulsive Impact Scale (COIS) score, baseline Family Accommodation Scale (FAS), or comorbid autism spectrum disorder or tics. Studies were inconsistent regarding the association between treatment effect and baseline OCD severity as assessed by CY-BOCS.

3.4.2 Evidence Identified

We found 71 comparative studies. Of these, 69 were RCTs,[71-139] and 2 were NRCSs with adjustment for confounding.[140, 141] Additional information 37 co-publications,[142-178] for a total of 108 reports.

Of these comparative studies, 24 evaluated pharmacologic treatments, 31 were studies of behavioral interventions, and 16 studied combined behavioral and pharmacologic treatments. Among comparative studies, 32 were conducted in the U.S., 10 in Europe, 9 in China, 6 in the U.K., 6 in Iran, 3 in Australia, 2 in Brazil, 2 in Canada and 1 in Japan. The median end-of-treatment time for analyzed outcomes was 10 months (IQR: 8 to 13.8 months).

Fifty-eight percent (42/73) of the studies reported (or implied) race or other social determinants of health. Nine studies were conducted in China. Among studies not conducted in East Asia, between 60% and 100% of participants were White, with a median of 88% across studies and only 8 of 29 relevant studies (28%) including more than 20% children who were categorized as other than White. With the exception of one study with 20 participants, 2 of whom were categorized as Black, fewer than 7% of participants were Black.

Few studies reported other social determinants 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). In 3 studies that reported data related to income, 94% of parents were employed in one study, socioeconomic status was described as high in one study, and mean family income (in approximately 2005) was $96,055 in one study (about $150,000 in 2023 dollars).

3.4.2.1 Evidence Not Included in Network Meta-Analyses

Two RCTs compared medications belonging to the same drug class and would therefore be assigned to the same pharmacological treatment node in our meta-analysis. These included a randomized cross-over study[142] that compared two TCAs (desipramine versus clomipramine) and an RCT[71] that compared two SSRIs (citalopram versus fluoxetine).

One RCT[97] randomized 31 young children (ages 3 to 8 years) to ERP compared to treatment as usual (TAU). The TAU group received a variety of active behavioral and pharmacological interventions that were not well characterized.

A single RCT[109] evaluated treatment with an herbal syrup and fluvoxamine, compared to fluvoxamine and placebo syrup. They reported Y-BOCS (and no other outcomes) using undefined categorical summaries and median differences, precluding calculation of NMA.

There were 15 RCTs (12 two-arm and 3 three-arm), each enrolling fewer than 100 participants, that evaluated novel behavioral interventions or variations in ERP delivery.

Among these, 8 studies tested behavioral interventions—one RCT that enrolled 24 participants evaluated the efficacy of an attachment-based intervention versus waitlist.[116] Four RCTs evaluated variations in provision of ERP— duration (brief ERP vs. ERP and brief ERP versus waitlist),[77] intensity (daily sessions for 3 weeks vs. weekly sessions for 14 weeks),[125] location of ERP delivery (home versus clinic)[121] and treatment provider (mother as treatment provider versus parent(s) and child).[119] Three RCTs evaluated behavioral augmentations added to ERP compared with ERP without augmentation (Cognitive Bias Modification of Interpretation (CMB-I),[120, 134] or use of an app to create and push tailored assignments to patients on their mobile devices.[130]

Four studies evaluated the efficacy of glutamate inhibitors (riluzole and N-acetylcysteine [NAC]) versus placebo,[91, 98] and the comparative efficacy of augmenting SSRI with NAC,[90] or the atypical antipsychotic risperidone,[100] compared to SSRI alone.

One 3-arm study (POTS II) assigned one group of participants to instruction in CBT by their psychiatrist in the context of medication management,[84]. Another 3-arm study studied the

combination of acceptance and commitment therapy (ACT) with SSRI, compared to ERP+SSRI and SSRI alone.[122] Further details are provided in Appendix Table E-2.

Two RCTs randomized participants based on their clinical response to an open-label intervention—responders to an SSRI (paraoxetine), [88] and nonresponders to ERP in phase I of the two phase Nordic long-term OCD treatment study (NordLOTS) trial.[124] described in section 3.4.5

The two NRCSs are described narratively in section 3.4.5.

Five RCTs[80, 81, 104, 126, 129] evaluated whether D-cycloserine augments the effect of ERP and reported CY-BOCS and CGI-S outcomes. We report pairwise meta-analyses of these studies in sections 3.4.3.1.4.1 (CY-BOCS outcome) and 3.4.3.3.2 CGI-S outcomes (reported in 3 of 5 RCTs).

Three studies[111, 112] with 132 participants provided supplemental family interventions in addition to ERP with ERP and compared to ERP alone. These studies are described in section 3.4.3.1.4.2, but not meta-analyzed.

3.4.3 Network Meta-Analyses of RCTs—OCD Severity, Clinical Remission, Functional Impairment, and Family Accommodation Outcomes

We performed separate network meta-analyses (NMAs) for each prioritized outcome, resulting in four networks. In order of decreasing network size and complexity, these included: OCD severity (Children's Yale-Brown Obsessive Compulsive Scale [CY-BOCS] or Yale-Brown Obsessive Compulsive scale [Y-BOCS])—12 direct comparisons (designs), remission—7 designs, global severity (Clinical Global Impressions-Severity [CGI-S] scale)—7 designs, and family accommodation scale (FAS)—2 designs.

To enable organization of the interventions across studies and for the purpose of the NMAs, similar treatment interventions were categorized. (see Appendix Table C-2.2: Arm Details). In the network graphs (Figures 3.4.3.1.1-1, 3.4.3.2.1), these intervention categories are represented by the nodes (circles).

For each outcome network, we report treatment effects and make a graded determination for strength of evidence (SoE) for those comparisons that are informed by direct evidence from at least two studies.

Treatment effects for possible comparisons (many informed by indirect evidence only) are presented in a league table.

For "hanging branches" excluded from the network, we report pairwise meta-analyses when three or more studies contribute direct evidence.

Study-specific effects for all studies, including studies not included in the meta-analyses, are detailed in Appendix E. Evidence Tables, E-1 to E-40.

3.4.3.1 OCD Symptom Severity: (C)Y-BOCS

Sixty of the 69 RCTs that evaluated OCD symptom severity reported the CY-BOCS or the Y-BOCS as a measure of overall OCD symptom severity. Both scales are clinician-rated, 10-item scales, with each item rated from 0 (no symptoms) to 4 (extreme symptoms), for a total range from 0 to 40.[179-181] A threshold score of 16 or greater is most commonly used as a study inclusion criteria. No study reported results on the CY-BOCS-II (Second Edition), which has an expanded scoring range with a ceiling of 50.[182]

Results

Three non-inferiority trials, one in adults with OCD[183] and two trials enrolling youth,[73, 131] have considered a 4 or 5 point decrease in (C)Y-BOCS to represent a clinically important difference. When interpreting effects as net means differences (NMD) on the (C)Y-BOCS scale, we refer to the interval from NMD of less than −4 to 4 as the zone of indifference.

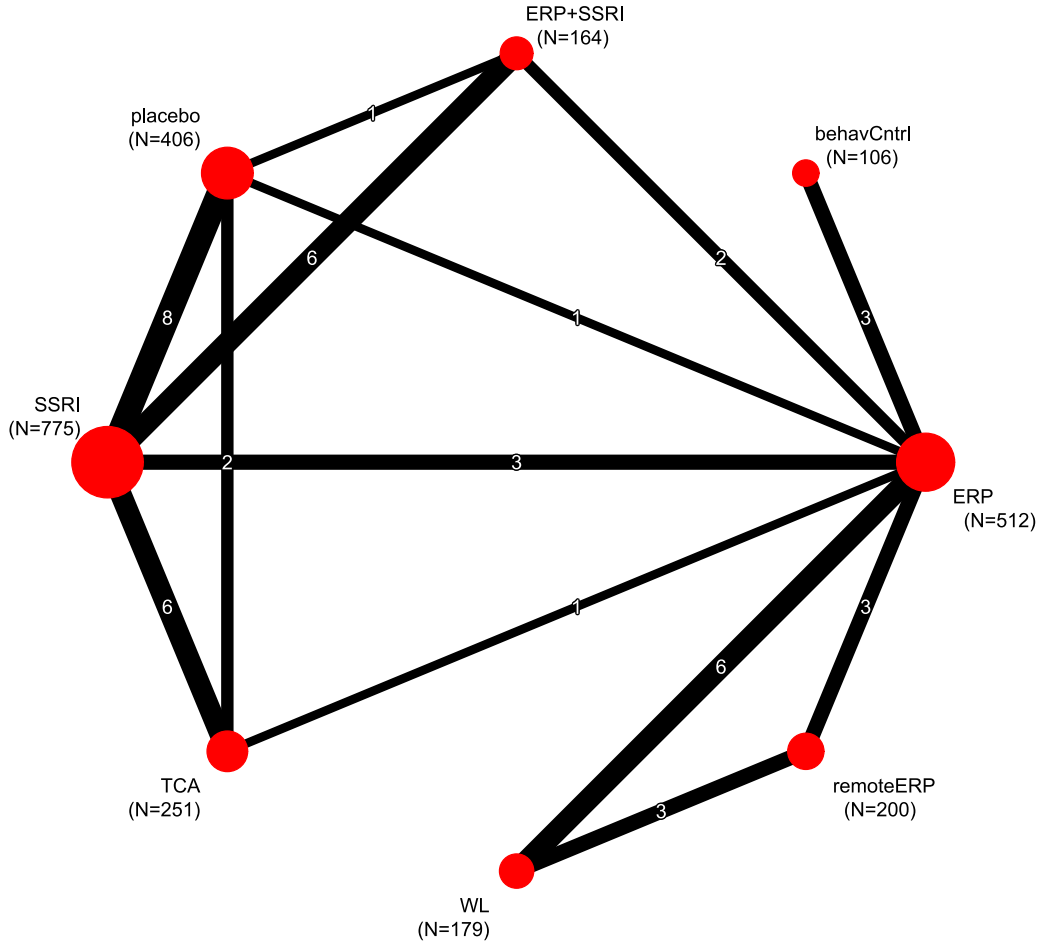
Among the 6 included studies that evaluated OCD severity, two reported an alternative severity scale,[83, 107] one summarized median change (with interquartile range) in Y-BOCS only, precluding calculation of NMD,[109] two evaluated medications belonging to the same treatment category (i.e., citalopram versus fluoxetine[71] [both SSRIs] and desipramine versus clomipramine[96] [both tricyclic antidepressants]) and one reported a treatment as usual (TAU) comparator that could not be classified[120].

3.4.3.1.1 Network Meta-Analyses: (C)Y-BOCS

Figure 3.4.3.1.1-1 displays the network plot for studies (C)Y-BOCS outcome. The plot graphically describes the network topology for the 41 RCTs that enrolled 2624 participants and provide direct evidence for 12 (of 46 possible) pairwise comparisons between 5 interventions (SSRI, TCA, ERP, remoteERP, ERP+SSRI) and 3 separate control conditions—pill placebo (placebo), waitlist (WL), and behavioral control groups (behavCntrl). The median end-of-treatment time was 12 weeks, with an interquartile range from 9 to 14 weeks.

Among the 41 studies included in the (C)Y-BOCS network, we assessed the overall risk of bias (RoB) as low in 20, moderate in 16 and high in 5 studies.

Figure 3.4.3.1.1-1. Network plot — CY-BOCS



The network presents all intervention categories (represented by red circles/nodes) that were compared with one 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 are proportional to the number (shown in white text on each line/edge) of studies that directly compared each pair of treatments.

Abbreviations: behavCntrol = behavioral control; ERP = CBT with exposure and response prevention; N = number of participants; placebo = pill placebo; remoteERP = synchronous or asynchronous ERP via telehealth; SSRI = selective serotonin reuptake inhibitors (various); TCA = tricyclic antidepressant (clomipramine); WL = waitlist

The omnibus null hypothesis of consistency was not rejected (P = 0.763).

The net mean difference in (C)Y-BOCS (with 95 percent confidence intervals) for all pairwise contrasts are shown in Figure 3.4.3.1.1-2.

Results

Figure 3.4.3.1.1-2. League table: (C)Y-BOCS — all possible pairwise comparisons

	ERP	remoteERP	ERP+SSRI	TCA	SSRI	behavCntrl	placebo	WL
ERP		-1.1 (-3.5, 1.4)	0.3 (-2.7, 3.3)	-2.6 (-5.9, 0.6)	-2.7 (-5.5, 0.0)	-4.9 (-8.0, -1.9)	-7.1 (-10.2, -4.0)	-10.5 (-12.6, -8.4)
remoteERP	1.1 (-1.4, 3.5)		1.4 (-2.5, 5.3)	-1.6 (-5.6, 2.5)	-1.6 (-5.3, 2.0)	-3.9 (-7.8, 0.1)	-6.0 (-10.0, -2.1)	-9.4 (-11.9, -6.9)
ERP+SSRI	-0.3 (-3.3, 2.7)	-1.4 (-5.3, 2.5)		-3.0 (-5.8, -0.1)	-3.1 (-5.1, -1.0)	-5.3 (-9.6, -1.0)	-7.4 (-10.0, -4.9)	-10.8 (-14.5, -7.2)
TCA	2.6 (-0.6, 5.9)	1.6 (-2.5, 5.6)	3.0 (0.1, 5.8)		-0.1 (-2.1, 1.9)	-2.3 (-6.8, 2.2)	-4.5 (-6.9, -2.1)	-7.9 (-11.7, -4.0)
SSRI	2.7 (0.0, 5.5)	1.6 (-2.0, 5.3)	3.1 (1.0, 5.1)	0.1 (-1.9, 2.1)		-2.2 (-6.3, 1.9)	-4.4 (-6.1, -2.6)	-7.8 (-11.2, -4.3)
behavCntrl	4.9 (1.9, 8.0)	3.9 (-0.1, 7.8)	5.3 (1.0, 9.6)	2.3 (-2.2, 6.8)	2.2 (-1.9, 6.3)		-2.2 (-6.5, 2.2)	-5.6 (-9.3, -1.8)
placebo	7.1 (4.0, 10.2)	6.0 (2.1, 10.0)	7.4 (4.9, 10.0)	4.5 (2.1, 6.9)	4.4 (2.6, 6.1)	2.2 (-2.2, 6.5)		-3.4 (-7.1, 0.3)
WL	10.5 (8.4, 12.6)	9.4 (6.9, 11.9)	10.8 (7.2, 14.5)	7.9 (4.0, 11.7)	7.8 (4.3, 11.2)	5.6 (1.8, 9.3)	3.4 (-0.3, 7.1)	

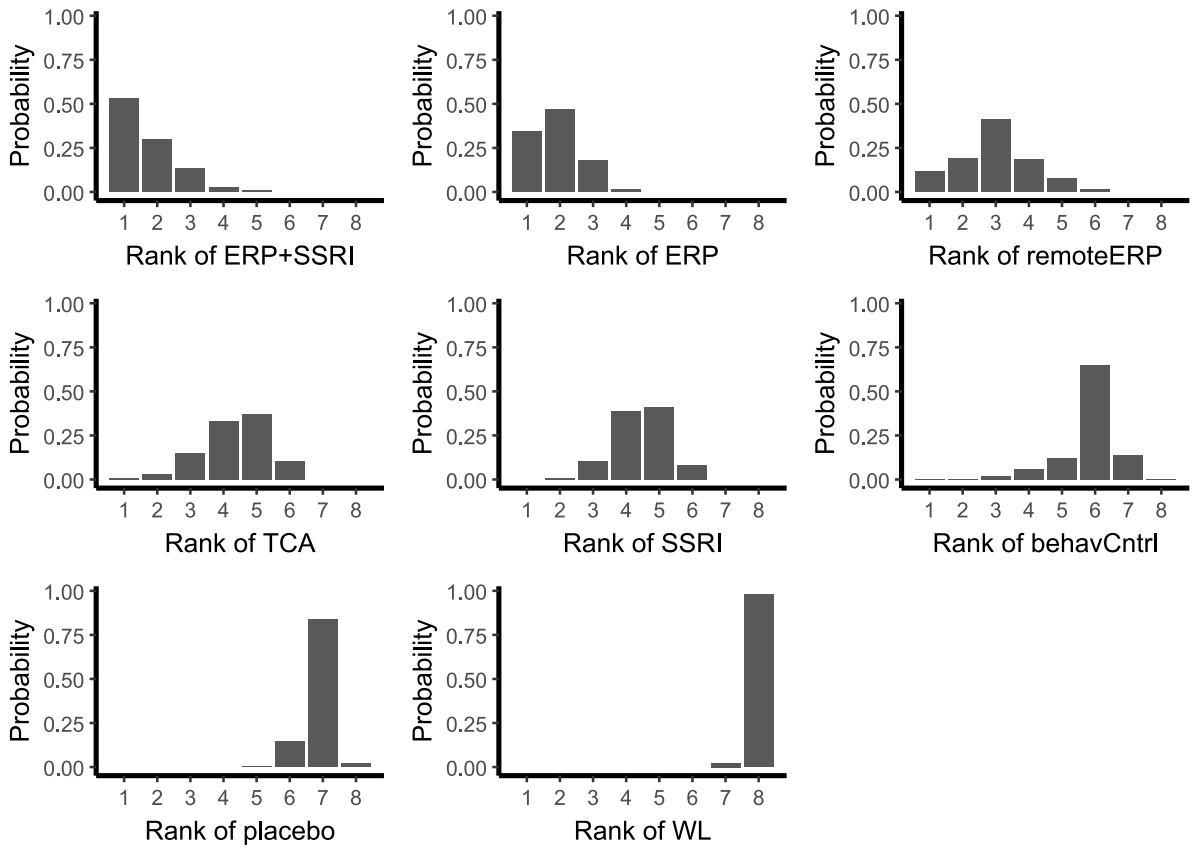
Table cells summarize the net mean difference in (C)Y-BOCS, with 95 percent confidence intervals, for each row by column treatment contrast. For example, the right-most upper cell displays the NMA estimate represents the ERP vs. WL comparison. Larger negative NMDs represent greater treatment effect. Shading is added to emphasize larger effects.

Abbreviations: behavCntrol = behavioral control; ERP = CBT with exposure and response prevention; N = number of participants; placebo = pill placebo; remoteERP = synchronous or asynchronous ERP via telehealth; SSRI = selective serotonin reuptake inhibitors (various); TCA = tricyclic antidepressant (clomipramine); WL = waitlist

We used the network meta-analysis methods to rank the 5 behavioral, pharmacological and combination treatments and 3 control conditions (behavioral control, pill placebo and waitlist).. Figure 3.4.3.1.1-3 below, is a rank-o-gram, with histogram for each of 5 treatments and 3 control categories The height of each bar represents the probability given treatment is the best, the worst and all positions in between, based on the effect metric of decrease in total CY-BOCS NMD as the relative treatment effect metric.[184]

Treatments including ERP (ERP+SSRI, ERP and remoteERP) comprise the 3 highest ranked interventions, medications (TCA, SSRI) the mid-ranked interventions, with the 3 control conditions (behavioral control, pill placebo, wait list) with the lowest ranks.

Figure 3.4.3.1.1-3. Rank-o-gram



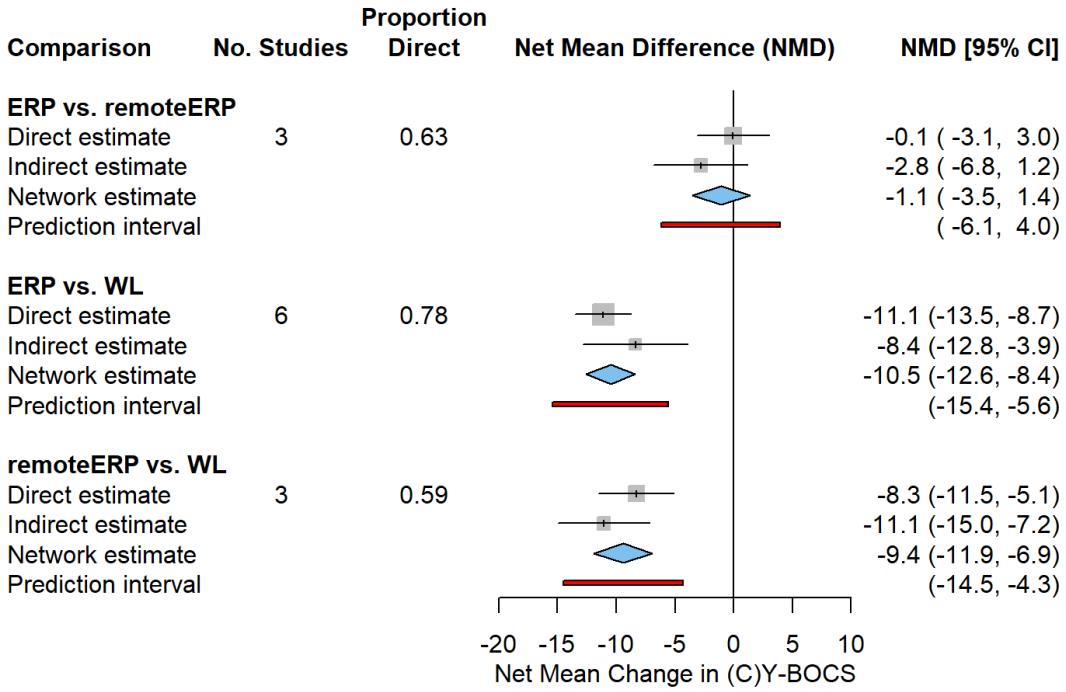
3.4.3.1.2 Estimates of Effects and Comparative Effects from NMA: (C)Y-BOCS

For each comparison with at least two studies contributing direct evidence, we provide figures illustrating these effects. The figures provide the number of studies contributing direct evidence, and the proportion of direct evidence, and display row-wise point estimates with 95 percent confidence intervals for the direct, indirect, and pooled effect estimates, to facilitate a visual comparison of the degree of similarity between direct and indirect estimates, i.e., local coherence. The P values associated with the null hypothesis of local coherence are provided in each figure note. The red bar represents the range of effect estimates that would be expected in a future study.

3.4.3.1.2.1 Effects of Behavioral Interventions: (C)Y-BOCS

Figure 3.4.3.1.2-1 displays 3 relative effect estimates—ERP versus remote ERP, ERP versus WL, and remote ERP versus WL.

Figure 3.4.3.1.2.1-1. ERP and remoteERP versus WL: CY-BOCS



The P values for the null hypothesis of local coherence are ERP vs. remoteERP, P = 0.287; ERP vs. WL; P = 0.287; remoteERP vs. WL, P = 0.287.

Abbreviations: CI = confidence interval; ERP = CBT 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 control

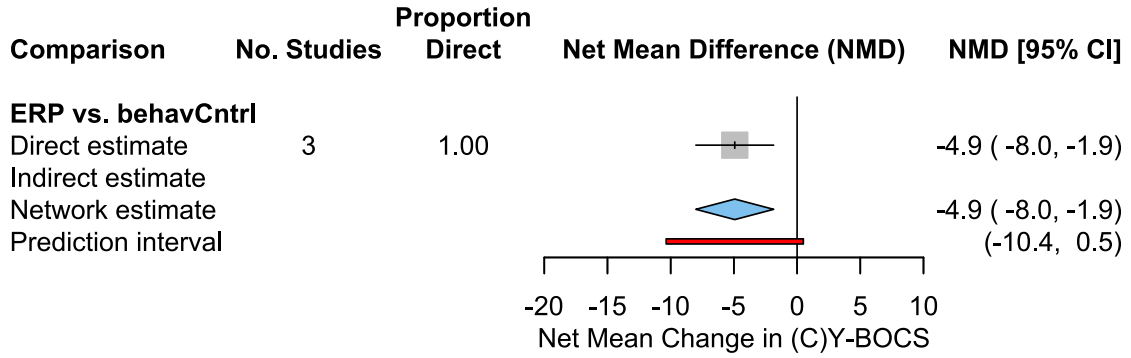
For ERP versus remoteERP, the NMD was −1.1 (95% CI −3.5 to 1.3). Three RCTs[73, 78, 131] directly compared ERP with remote ERP in 246 participants. This estimate overlaps the null effect, and the confidence interval spans effects of uncertain clinical importance.

For ERP versus WL, the pooled NMD is −10.6 (95% CI −12.6 to −8.6). There were 7 RCTs (with 268 participants) that contributed direct evidence.[74-77, 97, 132, 133] This estimate is statistically significant, and the confidence interval is entirely compatible with clinically important effects.

For remoteERP versus WL, the NMD was −9.5 (95% CI −11.9 to −7.0). Three RCTs[94, 95, 127] compared remote ERP versus waitlist control in 158 participants. This estimate is statistically significant, and the 95% confidence interval is entirely compatible with clinically important effects.

Figure 3.4.3.1.2-2 displays the relative effect estimate for ERP versus behavioral control.

Figure 3.4.3.1.2.1-2. ERP versus behavCntrl: CY-BOCS



A P value for the null hypothesis of local coherence for ERP vs. behavControl cannot be calculated due to absence of indirect evidence.

Abbreviations: behavCntrl = behavioral control; CI = confidence interval; ERP = CBT with Exposure and Response Prevention; No. = number of; NMD = net mean difference; remoteERP = remote synchronous or asynchronous ERP

This estimate is statistically significant and compatible with effects ranging from clinically important, to effects of uncertain clinical importance. Three RCTs (with 240 participants) contributed direct evidence. Two studies enrolled children 5 to 8 years-of-age and compared family-based ERP with family-based relaxation treatment that included psychoeducation, affective education to identify negative and positive feelings, and relaxation training [85, 86] The other study enrolled children 8 to 17 years-of-age and compared ERP plus a structured family intervention versus a behavioral control including psychoeducation and relaxation training.[113]

3.4.3.1.2.2 Effects of Pharmacological Interventions: (C)Y-BOCS

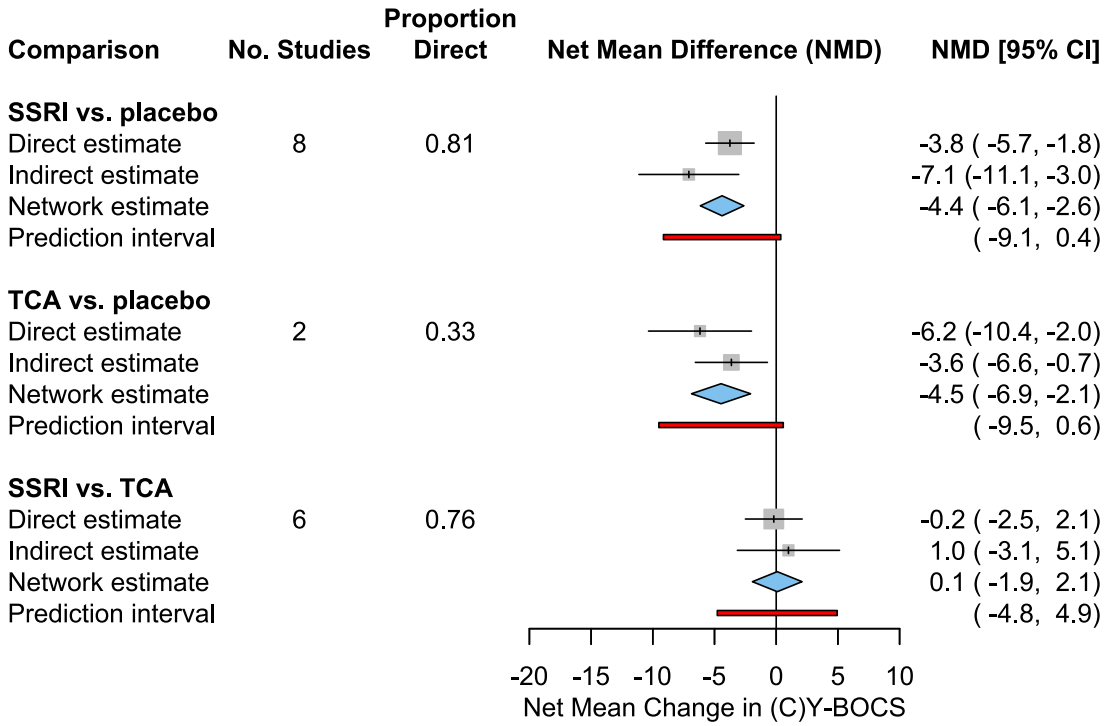
Figure 3.4.3.1.2.2-1 illustrates the effects and comparative effects of pharmacological therapies, compared to placebo and each other. For each comparison, the figure shows the number of studies contributing direct evidence and the proportion of direct evidence. The direct, indirect, and pooled estimates of NMD associated 95 percent confidence intervals are displayed to visually compare the degree of similarity between direct and indirect estimates, i.e., local coherence. The red bar represents the range of effect estimates that would be expected in a future study.

For SSRI versus placebo the pooled NMD −4.4 (95% CI −6.1 to −2.6) on the (C)Y-BOCS scale. This estimate is statistically significant and compatible with effects ranging from clinically important, to effects of uncertain clinical importance.

Treatment with the TCA clomipramine was more effective than placebo, with a NMD of −4.5 (95% CI −6.8 to −2.1). This estimate is statistically significant, and the confidence interval is compatible with a range of effects from clinically important, to effects of uncertain clinical importance.

For SSRI versus TCA, the NMD in CY-BOCS was 0.1 (95% CI −1.9 to 2.1). This comparative effect estimate overlaps the null effect, and the confidence interval includes effects of uncertain clinical importance only.

Figure 3.4.3.1.2.2-1: 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 = 0.147; TCA vs. placebo; P = 0.328; SSRI vs. TCA, P = 0.623.

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

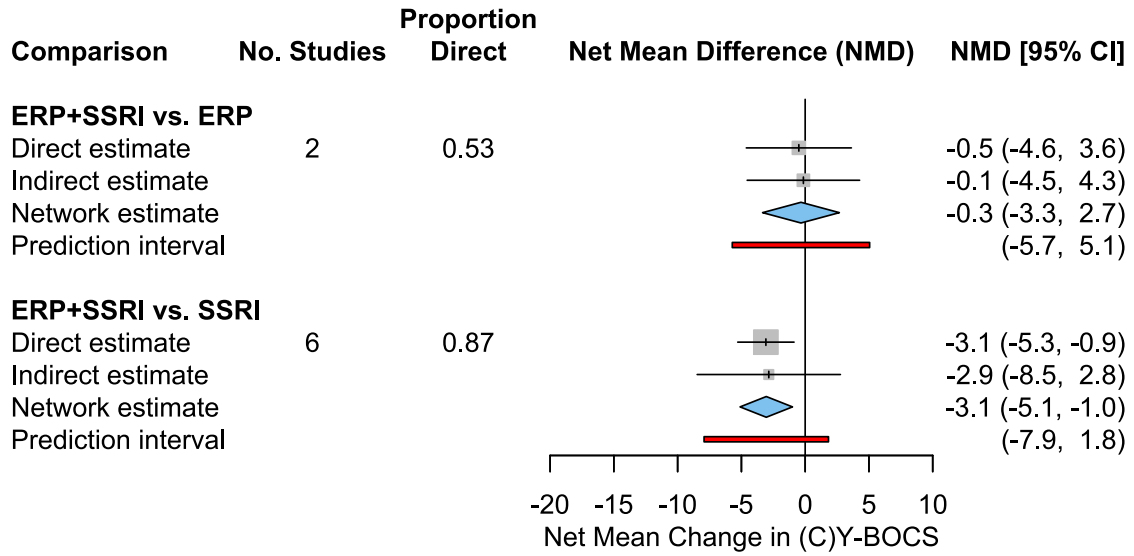
3.4.3.1.2.3 Effects of Combinations of Behavioral and Pharmacological Interventions: (C)Y-BOCS

Figure 3.4.3.1.2.3-1 displays the relative effects for ERP+SSRI versus ERP, and for ERP+SSRI vs. SSRI.

For ERP+SSRI versus ERP, the pooled NMD is −0.3 (95% CI −3.3 to 2.7). There were 2 RCTs[110, 128, 166] (with 103 participants) that contributed direct evidence. This estimate overlaps the null effect, and the confidence interval is compatible with small effects of uncertain clinical importance only.

For ERP+SSRI versus SSRI, the pooled NMD is −3.0 (95% CI −5.1 to 1.0). There were 6 RCTs[110, 128] (with 273 participants) that contributed direct evidence. This estimate is statistically significant, and the confidence interval is compatible with both clinically important effects, and with effects of uncertain clinical importance.

Figure 3.4.3.1.2.3-1: ERP+SSRI vs. ERP, ERP+SSRI vs. SSRI



P values for null hypothesis of local coherence: ERP+SSRI vs. ERP, P = 0.908; ERP+SSRI vs. SSRI; P = 0.941.

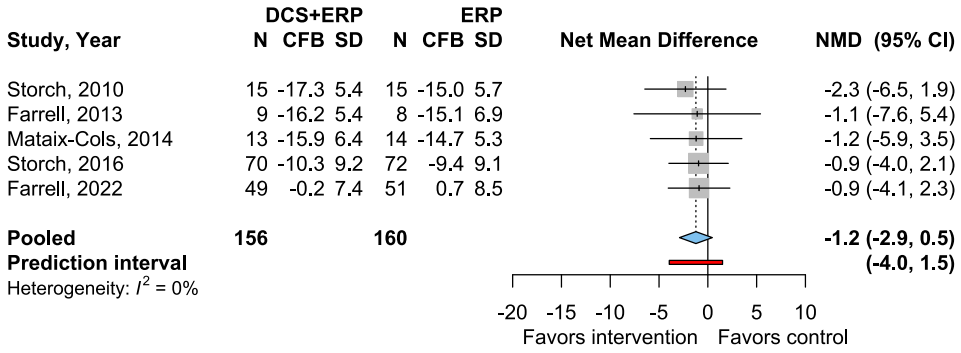
Abbreviations: CI = confidence interval; (C)Y-BOCS = (Children's)Yale-Brown Obsessive Compulsive Disorder Scale; ERP = CBT with Exposure and Response Prevention; SSRI = selective serotonin reuptake inhibitor (various); No. Studies = number of studies directly comparing; NMD = net mean difference; "+" = indicates a combination of interventions

3.4.3.1.4 Pairwise Meta-Analyses

3.4.3.1.4.1 Augmentation of ERP With D-Cycloserine Versus ERP—CY-BOCS

Five studies with 316 participants evaluated whether D-cycloserine augments the effect of ERP on symptom severity as assessed by the total CY-BOCS score. The summary NMD was −1.2 (95% CI −2.9 to 0.5). This comparative effect estimate overlaps the null effect, and the confidence interval includes effects of uncertain clinical importance only. See Figure 3.4.3.1.4.2.

Figure 3.4.3.1.4-1: D-cycloserine with ERP versus ERP—CY-BOCS

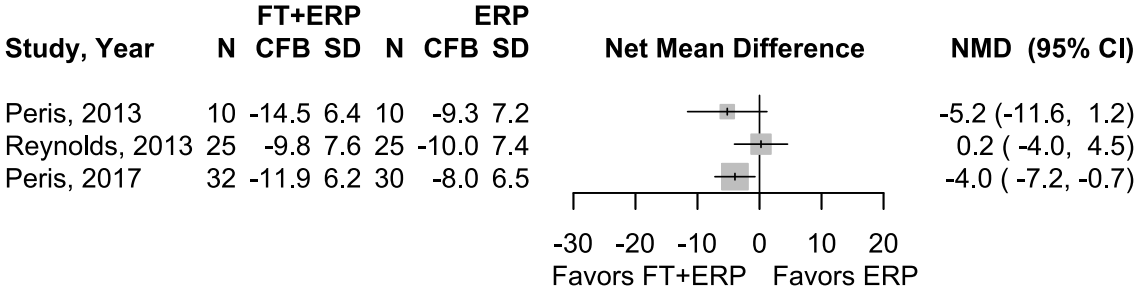


Abbreviations: CFB = change from baseline; CI = confidence interval; DCS = D-cycloserine; ERP = exposure and response prevention; N = number of patients in arm; NMD = net mean difference; SD = sample standard deviation

3.4.3.1.4.2 Family Interventions Added to ERP Versus ERP—CY-BOCS

Three studies[111, 112] with 132 participants combined a supplemental family with ERP and compared to ERP alone. Two studies used Positive Family Interaction Therapy (PFIT) in addition to individual child CBT. Another trial, Reynolds 2013, evaluated the effect of parent-enhanced CBT, which emphasized parent and family factors, including accommodation.[115] Overall RoB was rated as low in 2 studies and moderate in one study. Given clinical and statistical heterogeneity, we do not report summary effect.

Figure 3.4.3.1.4-2: Additional parent/family therapy with ERP versus ERP—CY-BOCS



Abbreviations: CFB = change from baseline; CI = confidence interval; Control = control condition (placebo, waitlist, behavioral intervention without ERP); ERP = exposure and response prevention; FT = family therapy, N = number of patients in arm; NMD = net mean difference; SD = sample standard deviation

3.4.3.2 OCD Remission

There were 16 studies that reported the number of participants whose OCD remitted (by end of treatment in 11 to 18 weeks). Among these studies, remission was variably defined as subjective "clinical remission" or using CY-BOCS cutoffs ranging from ≤10 to ≤14.

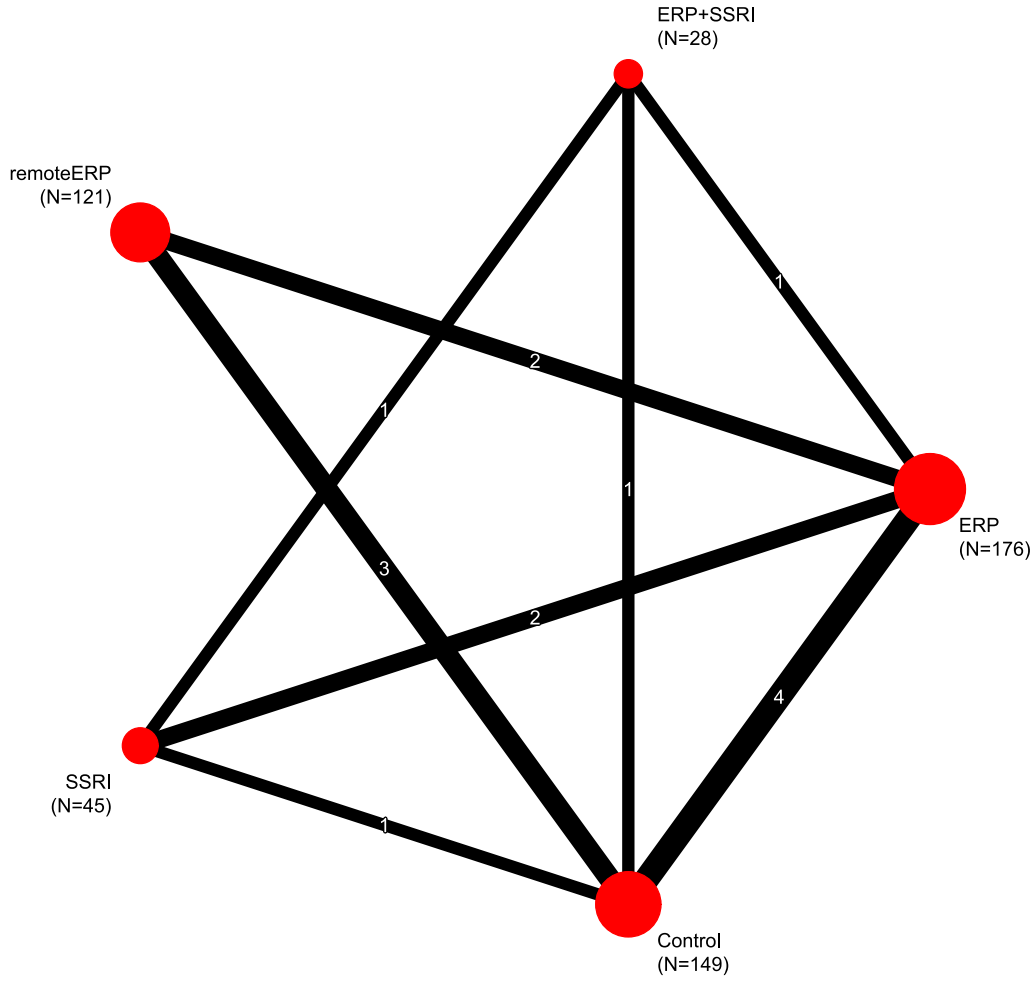
3.4.3.1.1 Network Meta-Analyses: Remission

Figure 3.4.3.1.1 displays the network topology for the 10 RCTs included in the NMA that enrolled 519 participants, that provided direct evidence for 5 out of 15 possible pairwise comparisons between 5 interventions (ERP, remote ERP, ERP+SSRI) and a combined Control node (combining waitlist, placebo and behavCntrl conditions). A combined Control node was chosen due to network sparsity, resulting in improved consistency.

Among the 10 studies included in the remission network, we deemed overall RoB to be low in 8, and high in 2 studies.

The omnibus null hypothesis of consistency was not rejected (P = 0.210).

Figure 3.4.3.1.1: Network of comparators — Remission



The network presents all intervention categories (represented by red circles/nodes) that were compared with one or more other intervention categories across studies. The diameter of the circles is proportional to the number of patients who received the intervention of interest. The black lines connecting nodes (edges) represent the direct comparisons between pairs of interventions made by eligible studies. The width of the edges are proportional to the number (shown in white text on each line/edge) of studies that directly compared each pair of treatments.

Abbreviations: Control = control condition (combines placebo, waitlist, or behavioral control groups); ERP = CBT with exposure and response prevention; '+' = combined interventions; remoteERP = remote synchronous or asynchronous ERP; SSRI = selective serotonin reuptake inhibitors (various)

3.4.3.1.2 ERP and Remote ERP Versus Control — Remission

Figure 3.4.3.1.2 displays the relative effects for comparisons informed by direct evidence from at least two studies— ERP+SSRI versus Control, remoteERP versus Control, ERP vs. remoteERP and ERP vs. SSRI.

The relative rate (RR) of remission with ERP was significantly higher, RR 4.2 (95% CI 1.8 to 9.7) compared to Control, albeit with a wide confidence interval.

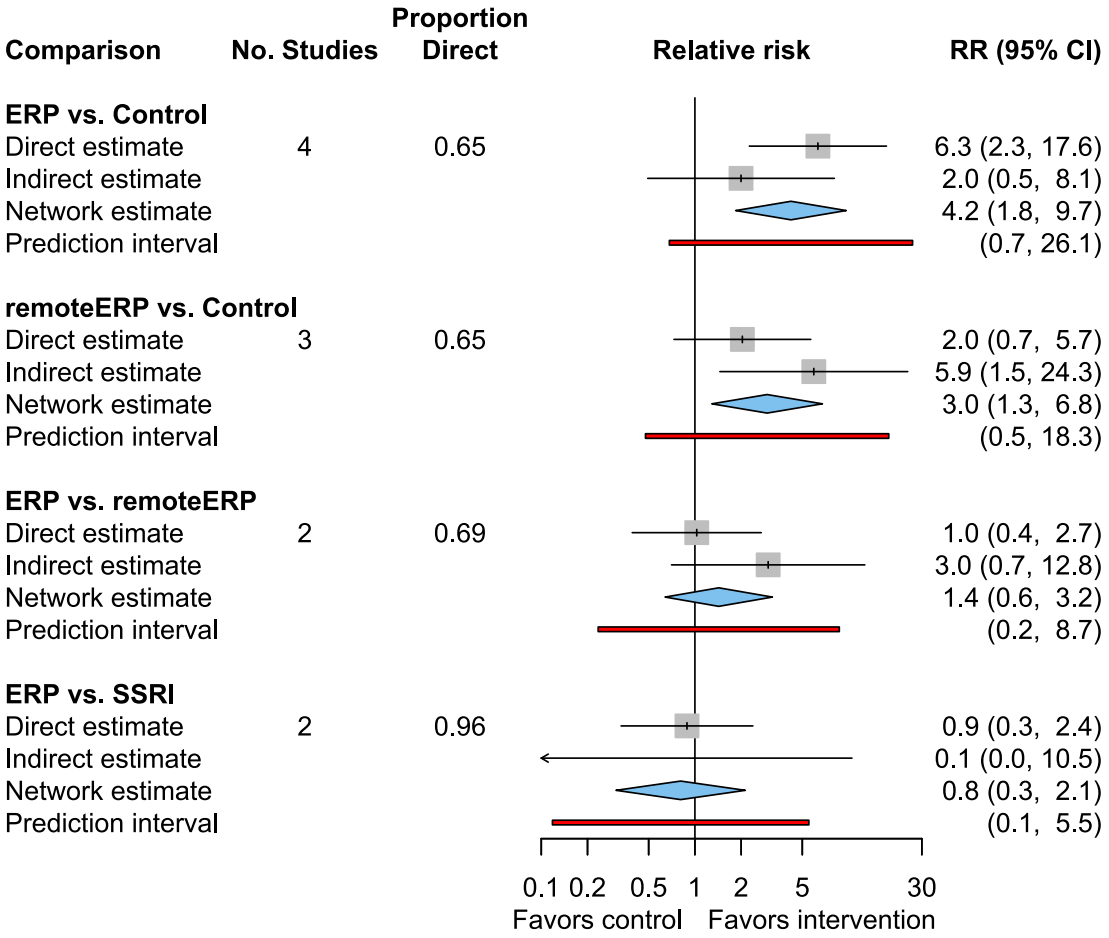
In participants receiving ERP remotely, the rate of remission was significantly greater, RR 3.0 (95% CI 1.3 to 6.8) greater compared to Control, albeit with a wide confidence interval.

In participants receiving ERP versus remoteERP, the rate of remission was similar, RR 1.4 (95% CI 0.6 to 3.2), with a wide confidence interval.

Results

In participants receiving ERP versus SSRI, the rate of remission were similar, albeit with a wide confidence interval, RR 0.8 (95% CI 0.3 to 2.1).

Figure 3.4.3.1.2-1: ERP vs. Control, remote ERP vs. Control, ERP vs. remoteERP and ERP vs. SSRI—Remission



P values for null hypothesis of local coherence: ERP vs. Control, P = 0.193; remoteERP vs. Control, P = 0.228; ERP vs. remoteERP, P = 0.228; ERP vs. SSRI, P = 0.326.

Abbreviations: CI = confidence interval; Control = combined waitlist, placebo or behavioral controls; ERP = CBT with Exposure and Response Prevention; SSRI = selective serotonin reuptake inhibitors (various); RR = relative rate; No. = number of; remoteERP = remote synchronous or asynchronous ERP; vs. = versus

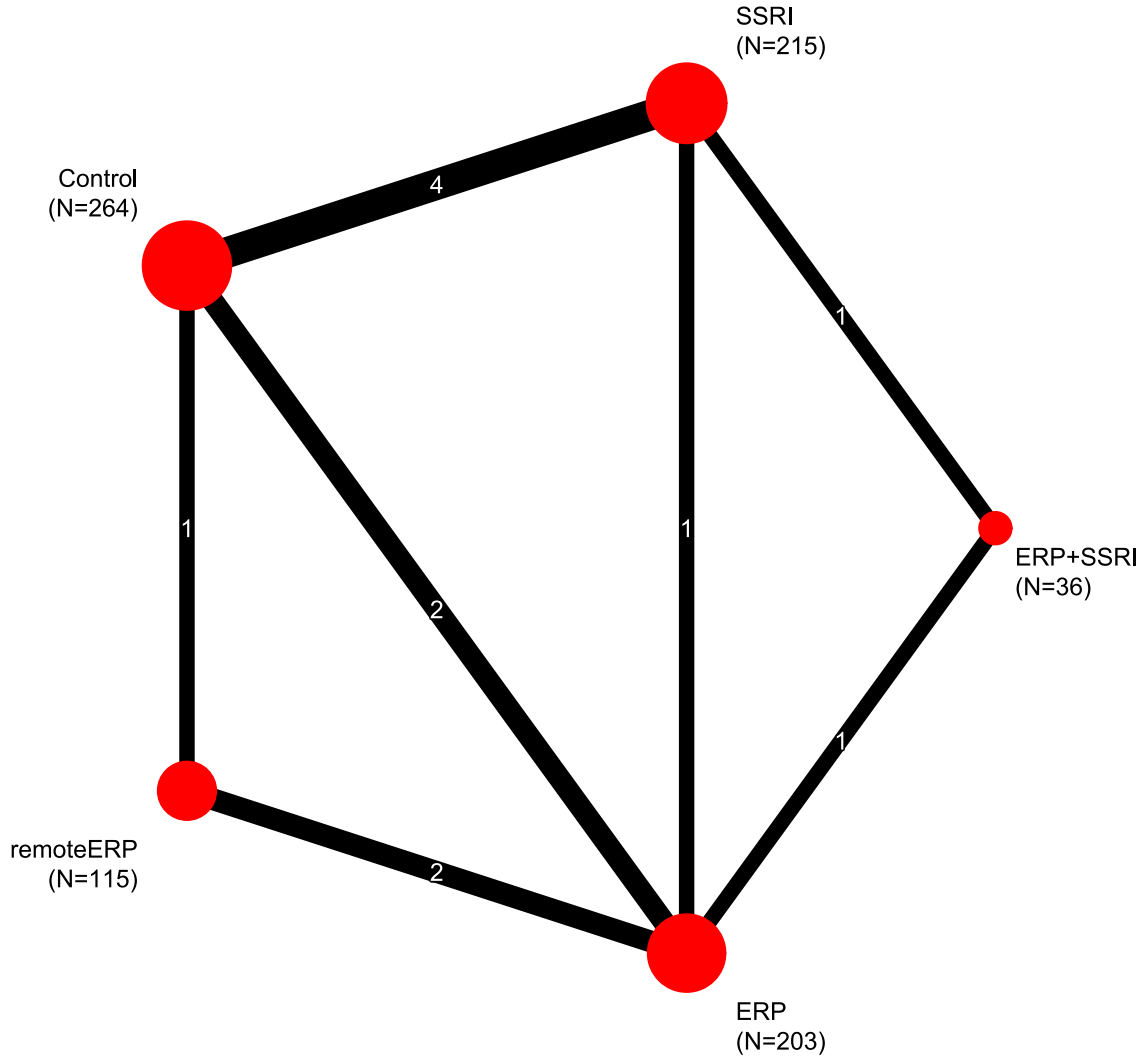
3.4.3.2 OCD Symptom Severity—CGI-S

Clinical Global Impressions-Severity (CGI-S) is a global assessment of overall OCD illness severity, with 7 severity categories: 1 = normal, 2 = borderline, 3 = mild, 4 = moderate, 5 = marked, 6 = severe, and 7 = extremely severe.[185]

Figure 3.4.3.2.-1 displays the network topology for the 12 RCTs included in the NMA that enrolled 833 participants, that provided direct evidence for 7 out of 12 possible pairwise comparisons between 5 interventions (ERP, remoteERP, ERP+SSRI, SSRI) and a combined Control node (combining waitlist, placebo and behavCntrl conditions). A combined Control node

was chosen due to network sparsity. Among the 12 studies included in the GGI-S network, the overall RoB was low in 8, moderate in 2, and high in 2 studies.

Figure 3.4.3.2-1: Network of comparators—CGI-S



The network presents all intervention categories (represented by red circles/nodes) that were compared with one or more other intervention categories across studies. The diameter of the circles is proportional to the number of patients who received the intervention of interest. The black lines connecting nodes (edges) represent the direct comparisons between pairs of interventions made by eligible studies. The width of the edges are proportional to the number (shown in white text on each line/edge) of studies that directly compared each pair of treatments.

Abbreviations: Control = control condition (placebo, waitlist, or behavioral control); ERP = CBT with Exposure and Response Prevention; '+' = combined interventions; remoteERP = remote synchronous or asynchronous ERP; SSRI = selective serotonin reuptake inhibitors (various)

3.4.3.3.1 Network Meta-analysis CGI-S

Figure 3.4.3.3.1-2 displays the comparisons informed by direct evidence from at least two studies—ERP vs. Control, SSRI versus Control, and ERP vs. remoteERP. The omnibus null hypothesis of consistency was not rejected (P = 0.337).

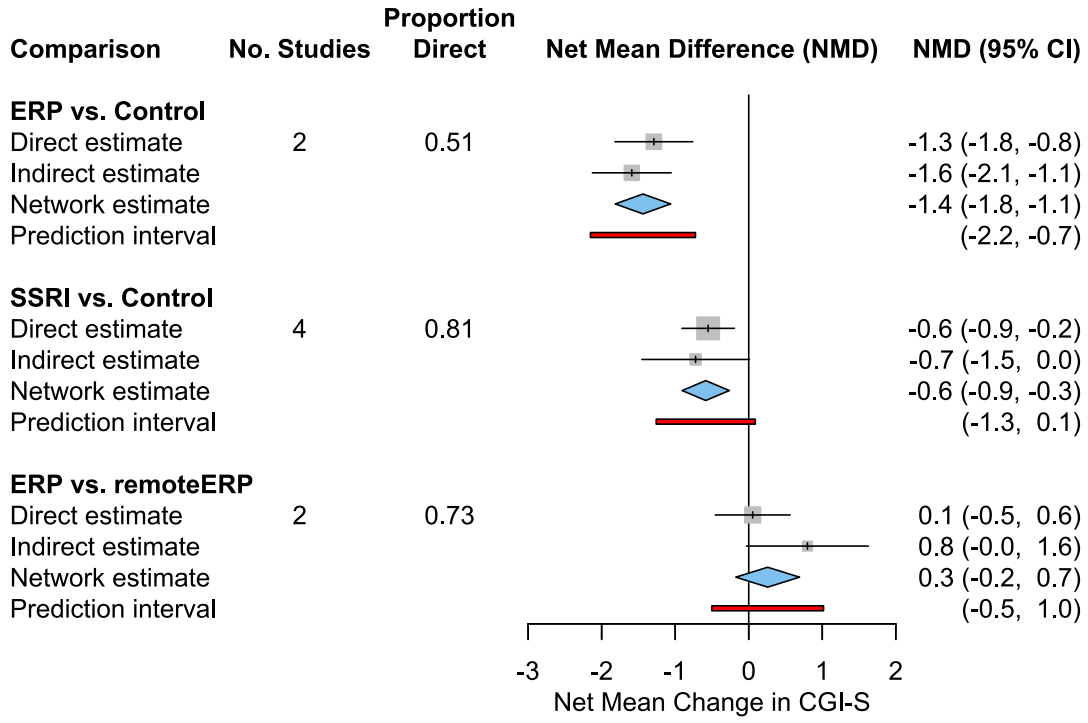
Results

The pooled estimate for ERP versus Control comparison is a NMD in CGI-S score of −1.4 (95% CI −1.8 to −1.1)

The pooled estimate for the SSRI versus Control comparison is a NMD in CGI-S score of −0.6 (95% CI −0.9 to −0.3).

The pooled estimate for the ERP versus remoteERP comparison is a NMD in CGI-S score of 0.3 (95% CI −0.5 to 1.0). This effect overlaps the null.

Figure 3.4.3.3.1-2: ERP vs. Control, SSRI vs. Control, and ERP vs. remoteERP—CGI-S

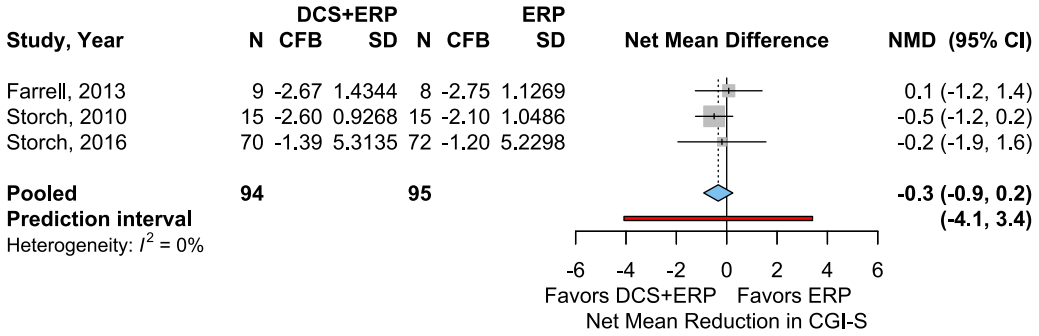


Abbreviations: CI = confidence interval; ERP = CBT with Exposure and Response Prevention; No. = number of; NMD = net mean difference; SSRI = selective serotonin reuptake inhibitor (various); vs. = versus

3.4.3.3.2 Pairwise Meta-Analyses: Augmentation of ERP with D-cycloserine Versus ERP—CGI-S

Figure 3.4.3.3.2-1 presents the pairwise MA for the 3 trials that enrolled 189 participants[80, 126, 129] that compared augmentation of ERP with D-cycloserine and reported a CGI-S outcome. The summary NMD in CGI-S is −0.3 (95% CI −0.9 to 0.2). The prediction interval is very wide.

Figure 3.4.3.3.2-1. D-cycloserine Augmented ERP versus ERP—CGI-S



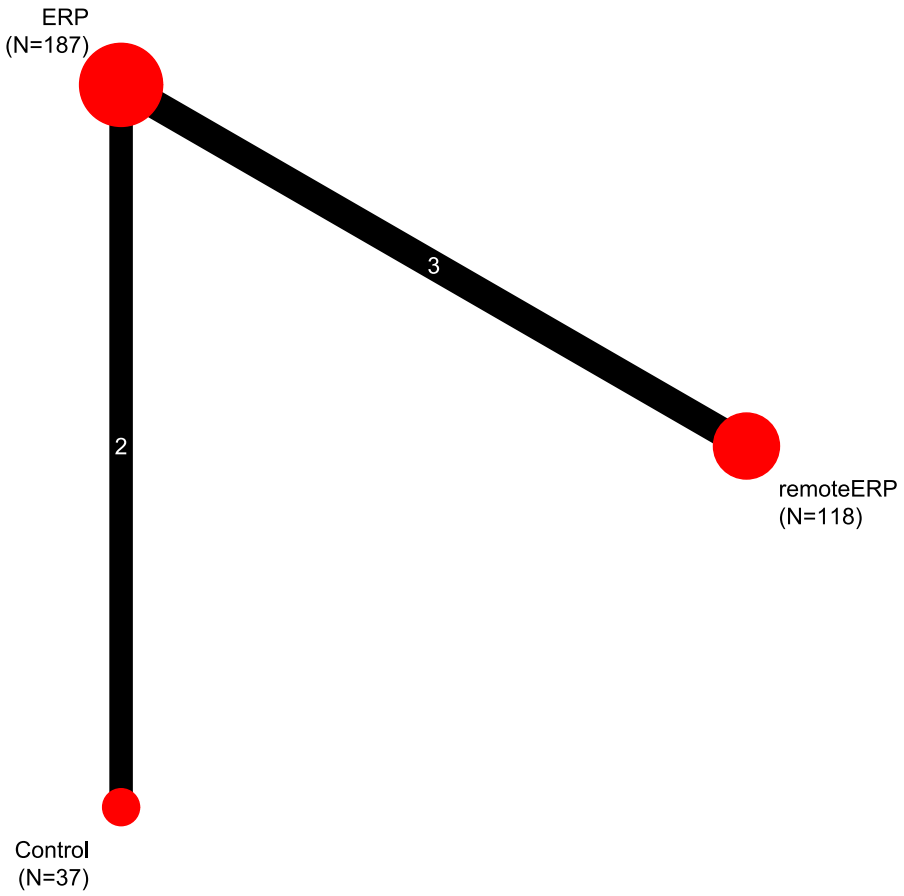
Abbreviations: CI = confidence interval; DCS = D-cycloserine; ERP = CBT with Exposure and Response Prevention; No. = number of; NMD = net mean difference; remoteERP = remote synchronous or asynchronous ERP; SSRI = selective serotonin reuptake inhibitor (various); vs. = versus

3.4.3.4 Family Accommodation—FAS

The Family Accommodation Scale (FAS) is a 12-item clinician-rated semi-structured interview designed to assess the family's accommodation to the child's OCD symptoms.[186] Accommodation is a change in the family's behavior with the goal of reducing distress in children with OCD. Greater family accommodation is associated with more severe OCD symptoms[187] and may decrease in response to treatment.[188, 189]

We included 5 studies with 342 participants reported FAS outcomes that directed compared 2 of 5 possible pairwise comparisons of 3 interventions (ERP, remoteERP and Control).[73, 78, 95, 113, 127] The network topology is shown in Figure 3.4.3.4.

Figure 3.4.3.4: Network of Comparators—FAS



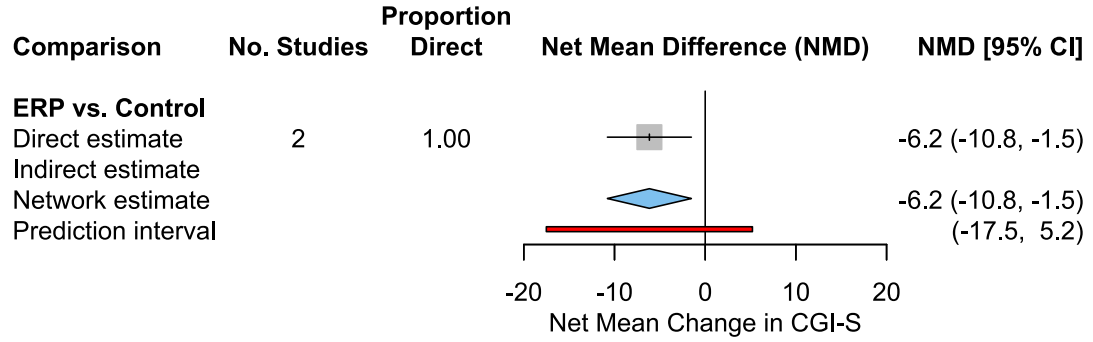
The network presents all intervention categories (represented by red circles/nodes) that were compared with one or more other intervention categories across studies. The diameter of the circles is proportional to the number of patients who received the intervention of interest. The black lines connecting nodes (edges) represent the direct comparisons between pairs of interventions made by eligible studies. The width of the edges are proportional to the number (shown in white text on each line/edge) of studies that directly compared each pair of treatments.

Abbreviations: Control = control condition (placebo, waitlist, or relaxation therapy); ERP = Cognitive behavioral therapy with exposure and response prevention; remoteERP = remote synchronous or asynchronous ERP

3.4.3.4.1 Pairwise Meta-Analyses: ERP Versus Control and remoteERP Versus ERP—FAS

Figure 3.4.3.4.1-1 is a forest plot the shows the individual study effects and the summary estimate of the effect of in-person ERP versus Control on family accommodation, as measured by FAS. For this comparison, family accommodation is significantly reduced, with a pooled NMD −6.2 (95% CI −10.8 to −1.5).

Figure 3.4.3.4.1-1. ERP versus control — FAS

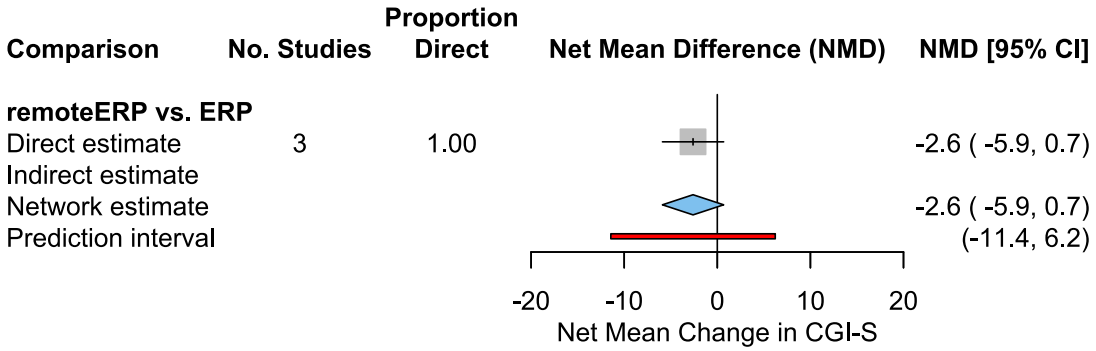


A P value for the null hypothesis of local coherence for ERP vs. Control cannot be calculated due to absence of indirect evidence.

Abbreviations: CI = confidence interval; Control = combined control group; ERP = CBT with Exposure and Response Prevention; No. Studies = number of studies; NMD = net mean difference

For remote ERP versus Control, Figure 3.4.3.4.1-2, the summary NMD in the FAS is −2.6 (95% CI −5.9 to 0.7). There is small reduction in FAS for ERP versus remote ERP, however plausible estimates overlap the null.

Figure 3.4.3.4.1-2. ERP versus Remote ERP—FAS



A P value for the null hypothesis of local coherence for ERP vs. Control cannot be calculated due to absence of indirect evidence.

Abbreviations: CFB = change from baseline; CI = confidence interval; ERP = CBT with Exposure and Response Prevention; N = number of participants in each arm; NMD = net mean difference; SD = sample standard deviation

3.4.4 Other Outcomes

Other outcome domains include functional impairment, quality of life, satisfaction, and adverse events. These were more sparsely reported, used different scales, were assessed by variable respondents (i.e., child versus parent), and were reported across different comparators, precluding meta-analysis and graded conclusions. We summarize studies reporting these outcomes and the scales used briefly below and in detail in Appendix E.

3.4.4.1 Functional Impairment—Child Obsessive-Compulsive Impact Scale (COIS)

Twelve studies, all RCTs,[77, 81, 86, 94, 99, 112, 113, 121, 125, 127-129] enrolling a total of 844 participants, assessed functional impairment using the Child Obsessive–Compulsive Impact Scale (COIS). The COIS is a 56-item, parent- or child-report measuring the degree to which the child experiences OCD-related impairment across several domains of functioning: school, social, and home/family activities.[127] The COIS-R (the revised version) is a 33-item of the scale, where responses are rated from 0 (not at all) to 3 (very much).[113]

Eight studies assessed the comparative effectiveness of ERP alone or as a combination, and 4 studies assessed a medication as a primary intervention or in combination. Studies which delivered ERP alone differed in setting (remote versus in-person, home versus hospital), and intensity (daily versus weekly). Seven studies compared **ERP with Control**, or another form of ERP.[77, 86, 94, 113, 121, 125, 127] In all studies, the net mean difference favored ERP over control, with the difference reaching statistical significance in all but one (Appendix tables E-14, E-15). Two studies reported nonsignificant differences between **home- and clinic-based ERP and intensive versus non-intensive ERP** (Appendix table E-17). One study reported a statistically significant improvement with an **family intervention plus ERP versus ERP** alone[112] (Appendix table E-19); one study reported a statistically significant improvement with **SSRI versus placebo** (Appendix table E-20).[99] Three studies compared of **pharmacological agents (e.g., DSC, SSRI) plus ERP to placebo** plus ERP and reported no significant differences (Appendix tables E-21, E-22).[81, 128, 129]

3.4.4.1 Quality of Life

Six RCTs[73, 77, 86, 90, 95, 121] and one NRCS,[140] enrolling a total of 1642 participants, and measured quality of life using a variety of instruments; Child Health Utility 9D (CHU9D), Manchester Short Assessment of Quality of Life (MANSA), Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire (PQ-LES-Q), Pediatric Quality of life Inventory (PEDSQL) and the EQ-5D.

CHU9D is a self-reported measure of quality of life with 9 items rated from 1 to 5, yielding a total score of 9-45, with higher scores indicating greater quality of life.[73] MANSA a brief and modified version of LQLP (Lancashire Quality of Life Profile). As in the LQLP, satisfaction is rated on 7-point rating scales (1 = negative extreme, 7 = positive extreme); PQ-LES-Q is a 15-item rating scale with items scored from 1 (very poor) to (very good); the first 14 items are summed based on the original Q-LES-Q, with higher scores reflecting greater enjoyment and satisfaction.[140, 190] The PedsQLTM 4.0 Generic Core Scales with two subscales, physical functioning, and emotional and social functioning. Higher scores reflect lower domain specific quality of life. The EQ-5D is a widely used measure in health economic evaluations and consists of five dimensions measuring health-related functioning and quality of life—pain/discomfort,

anxiety/depression, self-care, mobility, and usual activities. It also consists of a 0–100 visual analogue scale (VAS) used to measure subjective ratings of health. Results are in Appendix tables E-24 to E-30. Across scales and comparisons (ERP vs. control, ERP vs. remote ERP, N-Acetylcysteine vs. SSRI), only a single study reported a statistically significant difference: Ghanizadeh 2017 reported that in 29 children, those taking N-Acetylcysteine plus a SSRI had a statistically significant net mean improvement on the PedsQL (Table E-31).[90]

3.4.4.2 Parent Satisfaction with Services

Three RCTs[73, 78, 111]enrolling a total of 192 participants measured parent satisfaction with services using The Client Satisfaction Questionnaire (CSQ-8) or the 7-Item inventory at the end of intervention. CSQ-8 is an 8-item scale that is used to measure satisfaction with the treatment, each item is rated from 1 to 4, yielding a total score of 9-36 where higher scores indicate greater satisfaction.[73] The 7-item inventory includes items such as, “To what extent has this program met your needs?” and “If a friend's child were in similar need, would you recommend the program?” Items were rated on a 4-point Likert scale with 0=not at all and 4=very much (maximum score= 28).[111] Across scales and comparisons (ERP vs. remote ERP, ERP vs. ERP+Family focused intervention), no study reported a statistically significant difference. Results are in Appendix tables E-31 to E-34.

3.4.4.3 Adverse Events

3.4.4.3.1 Serious or Leading to Withdrawal or Discontinuation

Seven studies reported on adverse events leading to withdrawal or discontinuation.[72, 84, 88, 89, 96, 103, 110] Three studies compared clomipramine with placebo,[88, 89, 103] 2 studies compared ERP with SSRI,[84, 110] one study compared different TCAs,[96] and one compared ERP with clomipramine.[72]

Among these, 2 RCTs reported a significantly greater risk of adverse events leading to withdrawal—3.6-fold greater in a placebo controlled study of paroxetine,[89] and 4.1-fold higher for a similar study comparing sertraline with placebo.[103] Full results in Appendix table E-37.

Four studies reported on serious/severe adverse events.[84, 88, 128, 129] One study reported on the comparison of TCA versus Placebo,[88] one on NMDA versus CBT,[129] one on CBT versus SSRI,[84] and one on standard dosing versus slowly titrated SSRI.[128] No significant differences in risk of serious/severe adverse events were reported (Appendix table E-38).

3.4.4.3.1 Adverse events—Total

Ten studies reported on total adverse events (Appendix table E-39).[73, 84, 87, 93, 100, 104, 106, 126, 139, 191] One study reported on the comparison of different TCAs,[93] two on NMDA versus placebo,[104, 126] one on CBM-I versus waitlist,[191] one on TCA versus placebo,[139] one on antipsychotic drug versus TCA,[100] one on SSRI versus placebo,[87] one on SSRI versus CBT,[84] one on internet CBT versus in-person CBT,[73] and one on SSRI versus TCA.[106]

One study reported a reduced risk of total adverse events using fluvoxamine versus clomipramine (RR 0.48, 95%CI 0.27-0.83).[93] Another study comparing SSRI and TCA reported that participants treated with sertraline reported fewer adverse events than those treated with clomipramine (RR 0.42, 95% CI 0.24-0.72).[106] Full results in Appendix Table E-39.

3.4.4.3.2 Adverse Events—Suicidal Thoughts and Behavior

One study reported on suicidal thoughts and behavior using a questionnaire developed by the researchers.[89] No cases were reported in both regular sertraline plus CBT and slow sertraline plus CBT groups (Appendix table E-40).

3.4.4.4 Withdrawals/Discontinuation

Eleven studies reported on withdrawals and discontinuation not only due to adverse events.[56, 84, 87-89, 91, 95, 103, 124, 128, 129] One study reported on the comparison of CBT versus SSRI,[84] one on different TCAs,[88] two on TCA versus placebo,[89, 103] one on iCBT versus placebo,[95] one on CBT versus TCA,[124] one on ACT versus CBT,[56] one on SSRI versus placebo,[87] and one on different SSRIs.[128] No study reported a significant effect of any intervention on the risk of withdrawal or discontinuation (Appendix table E-41).

3.4.5 Nonrandomized Comparative Studies

Two NRCSs that adjusted for potential confounders (and were, thus, eligible) evaluated the comparative effectiveness of treatments for OCD.

Franklin 2024[140] reported outcomes from 1,286 youth, ages 7 to 17, who received intensive CBT with exposure and response therapy in intensive outpatient and partial hospitalization settings. This study evaluated the comparative effectiveness of CBT delivered via telehealth during the COVID-19 pandemic with a propensity-matched sample of patients treated in-person prior to the pandemic. At discharge, patients treated in-person had significantly lower CY-BOCS-SR (self-report) scores, corresponding to an effect size (Cohen's d, P=0.0004) interpreted as a small comparative benefit for in-person CBT. The authors reported no significant difference in quality of life, assessed using the Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire (PQ-LES-Q), or in treatment response (defined as a reduction of 35% in CY-BOCS-SR). In the in-person group, 218 of 643 patients (33.9%) achieved remission (defined as CY-BOCS-SR ≤12) compared to 187 of 643 (29.1%) in the telehealth group. This corresponded to a risk difference of 0.048 (95% CI −0.002 to 0.099, P = 0.062) and a risk ratio of 1.17 (95% CI 0.99, 1.37, P = 0.063).

Schuberth 2023[141] evaluated the comparative effectiveness of group parent management training (PMT) in addition to ERP, compared to ERP alone. Inverse probability of treatment weighting (IPTW) was used to account for differences in measured confounders. The adjusted 95% confidence intervals for the post-treatment between-group means for the following scales: CY-BOCS, the Coercive Disruptive Behavior Scale (CD-POC), Child OCD Impact Scale-Revised (COIS-R), OCD Family Functioning Scale (OFF) and FAS—all overlapping the null—providing no evidence that PMT+ERP improved OCD severity or family functioning.

3.4.5 Randomized, Phase II Trials Following Single Arm Phase I Interventions

Geller 2003[88] enrolled 335 participants in a phase I (open label) trial of paroxetine. They reported that 238 of 335 patients evaluated in phase I achieved a reduction of ≥25% in baseline CY-BOCS and a CGI-I score of 1 or 2 ("very much improved or much improved"). In phase II, 193 of the patients who were responsive to paroxetine were randomized to continued paroxetine versus placebo. Relapse was defined as any of the following: an increase in CGI-I of 2 or more points between two visits or 5 points ("much worse") compared to baseline. In the paroxetine

group, 33/95 (34.7%) experienced relapse compared to 43/98 (43.9%) in the placebo group [unadjusted risk ratio 0.79, 95% CI 0.56 to 1.12, P=0.197].

The Nordic Long-Term OCD Treatment Study (NordLOTS) enrolled 269 participants in a phase I (single arm) trial of ERP delivered in community outpatient mental clinics.[192] Among 66 step I completers who were did not respond to ERP, defined as CY-BOCS <16 after ERP, 54 were randomized to continued ERP or sertraline for 16 weeks. The authors reported no significant between group difference in CY-BOCS total score or the proportion of responders, suggesting that continued ERP and adding sertraline have similar effectiveness.[124]

3.4.6 Predictors of Treatment Response

There were 21 papers (2 secondary analyses of included RCTs[145, 161] and 19 single-arm studies[191, 193-210]). representing 15 cohorts, that reported multivariable analyses of predictors of treatment response for CBT or a comparison of CBT with medication that was included in a multivariable model. The RCTs included two studies that reported on three outcomes. The RCTs were generally at low RoB across all domains, and none were industry funded. Both had CBT with Psychoeducation, Cognitive Restructuring, and ERP in both arms. The 19 single-arm articles represented 13 unique cohorts. In no instance did two different articles report the same outcome and predictor combination for the same cohort at the same time point. Most articles evaluated outcomes immediately post-treatment, but two also had evaluations at 6 months after treatment,[205, 210] and one reported an interim analysis at 7 weeks.[193] All studies evaluated predictors of treatment success with CBT; in 17 articles CBT included ERP, while in two the CBT type was not specified and may or may not have included ERP. Study sizes ranged from 63 to 573 children.

We concluded that regressions were adequate in 12 articles and not adequate in the other 7. Details of interventions, regression quality, baseline data, and summaries of each study's predictors by outcome are in Appendix Tables E-40 and E-41; full data are in OCD_KQ2 predictor_studies appendix.xslx.

OCD treatment (i.e., CBT) response and final CY-BOCS score were the only outcomes assessed by more than one study. Across studies, the strongest predictor of both CBT response (Table 3.4.6-1) and final CY-BOCS score (Table 3.4.6-2) was baseline CY-BOCS score. Higher baseline scores mostly predicted higher post-treatment CY-BOCS scores (i.e., positive correlation between baseline and final scores), but also greater reduction in CY-BOCS scores. However, four of the six studies that evaluated treatment effect (change in score) found a nonsignificant association, and one study (of 63 children in a hospital cohort in Norway) found a nonsignificant association with CY-BOCS score at the end of treatment but a statistically significant negative association after 6 months (higher baseline scores were associated with lower 6-month scores), after controlling for baseline functional impairment.

One of three analyses found a significant association between comorbid ASD and a poorer treatment response to CBT. Jassi 2023 reported that having comorbid ASD predicted less reduction in CY-BOCS score.[209] A mediator analysis of this association found that it was partially explained by the higher functional impairment of children with ASD and their being on prescribed medication for OCD, primarily SSRIs.

Age, sex, baseline COIS, baseline family accommodation, and other comorbidities, including anxiety, depression, and tics, were not predictors of CBT response across studies.

Results

Table 3.4.6-1. Predictors of treatment response to ERP (net change, remission, or response) in two or more studies

Predictor	Comparison	+ Association N (n)	– Association N (n)	NS Association N (n)	Total Studies N (n)	Consistency	Association
Age	Younger vs. older	1 (573) cohort§[193, 207]	0	5 (699) cohorts[191, 194, 198, 206, 210] 2 (219) RCTs[145, 161]	5 (1272) cohorts 2 (219) RCTs	Consistent	No association found
Sex	Male vs. female	0	0	5 (905) cohorts[191, 193, 194, 198, 204, 206] 1 (142) RCT[161]	6 (968) cohorts* 1 (142) RCT	Consistent	No association found
Baseline COIS score	Higher vs. lower score	0	0	2 (347) cohorts[193, 198, 204]	2 (347) cohorts	Consistent	No association found
Baseline CY-BOCS score	Higher vs. lower score	2 (758) cohorts‡[194, 207] 1 (77) RCT‡[145]	0	4 (536) cohorts[191, 198, 203, 206]	6 (1294) cohorts 1 (77) RCT	Inconsistent	Variable association
Baseline FAS	Higher vs. lower score	0	0	2 (413) cohorts[193, 197, 204]	2 (413) cohorts	Consistent	No association found
Comorbid ASD	ASD vs. no ASD	0	1 (323) cohort†[209]	2 (248) cohort[193, 197, 206]	3 (571) cohorts	Consistent	No association found
Comorbid tics	Tics vs. no tics	0	0	2 (248) cohorts[193, 197, 206] 1 (142) RCT[161]	2 (248) cohorts 1 (142) RCT	Consistent	No association found

Cell coloring applied for visual emphasis only; it does not provide unique information.
Abbreviations: +, positive association (first comparator, e.g., younger, is associated with larger treatment response/improvement); – negative association; ASD = autism spectrum disorder; COIS = Child Obsessive Compulsive Impact Scale; CY-BOCS = Children's Yale-Brown Obsessive Compulsive Scale; FAS = Family Accommodation Scale; N, studies; n, participants; NS, no significant association; RCT, randomized controlled trial

* Includes one study that reported a significant predictor but did not specify direction.
† Significant predictor in logistic regression but mediation analysis noted this was partially explained by the higher functional impairment of children with ASD and their being on prescribed medication.
‡ Higher baseline CY−BOCS score may predict greater response to ERP.
§ Based on two analyses of the same cohort, one at 7 weeks and one at the end of treatment

Table 3.4.6-2. Predictors of final CY-BOCS score after ERP treatment in two or more studies

Predictor	Comparison	+ Association N (n)	– Association N (n)	NS Association N (n)	Total Studies N (n)	Consistency	Association
Age	younger vs older	1 (269)[201]	0	3 (490) cohorts[198, 199, 206] 2 (219) RCTs[145, 161]	4 (759) cohorts 2 (219) RCTs	Consistent	No association found
Age at onset	younger vs older	0	0	2 (378)[196, 201]	2 (378)	Consistent	No association found
Sex	Male vs Female	0	0	4 (770) cohorts[196, 199, 201, 206] 1 (142) RCT[161]	4 (770) cohorts 1 (142) RCT	Consistent	No association found
Baseline Functioning	higher vs lower score	0	0	2 (141) cohorts[198, 205]	2 (141) cohorts	Consistent	No association found
Baseline CY-BOCS score	higher vs lower score	1 (63) cohort‡[205]	4 (599) cohorts[196, 198, 199, 206]		5 (662) cohorts	Inconsistent	Variable association
Baseline FAS	higher vs lower score	0	0	3 (410) cohorts[198, 201, 205]	3 (410) cohorts	Consistent	No association found
Comorbid Tics	Tics vs no Tics	0	0	2 (378) cohorts[196, 201] 1 (142) RCT[161]	2 (378) cohorts 1 (142) RCT	Consistent	No association found

+ Assn. Positive Association, N studies (n participants); – Assn. Positive Association, N studies (n participants); NS Assn. No Significant Association, single arm + RCT, N studies (n participants); SPE = Strength of evidence for association; ASD = Autism Spectrum Disorder; FAS = family accommodation scale; COIS = Child Obsessive Compulsive Impact Scale; CY-BOCS = Children's Yale-Brown Obsessive Compulsive Scale

* Includes 1 study that gave a significant p value, but did not report direction; ‡ at end of treatment, no significant association found, but after 6 months lower baseline CY-BOCS predicted higher CY-BOCS

3.4.7 Evidence Profile for Key Question 2

Table 3.4.4. Evidence Profile for Key Question 2, treatment of OCD

Comparison: Overall Conclusion	Outcomes	Control	N Studies (Participants)	RoB L/M/H	Consistency	Precision	Directness	Other	SoE	Conclusions
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, −8.4)**
	CY-BOCS	Behavioral	3 (240)	3/0/0	Consistent	Imprecise	Direct (NMA)	None	Moderate	CY-BOCS NMD **−4.9 (−8.0, −1.9)**
	Remission	Combined	4 (103)	3/0/0	Consistent	Precise	Direct (NMA)	None	Moderate	Remission RR **4.2 (1.8, 9.7)**
	CGI-S	Combined	2 (188)	1/1/0	Consistent	Precise	Direct (NMA)	None	High	CGI-S NMD **−1.4 (−1.8, −1.1)**
	FAS	Combined	2 (101)	1/0/1	Consistent	Precise	Direct (NMA)	None	Low	FAS NMD **−6.2 (−10.8, −1.5)**
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, −6.9)**
	Remission	Combined	3 (145)	2/0/1	Consistent	Precise	Direct (NMA)	None	Moderate	Remission RR **3.0 (1.3, 6.8)**
	CGI-S	Combined	1 (60)	1/0/0	Consistent	Precise	Direct (no MA)	Sparse	Insufficient	Single study (N ≤100) NMD **−2.1 (−2.6, −1.6)**
	FAS	NA	0 (NA)	0/0/0	Consistent	Imprecise	NA	None	Insufficient	No evidence
ERP vs remote 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 (−3.5, 1.4)
	Remission	NA	2 (88)	2/0/0	Consistent	Imprecise	Direct (NMA)	Sparse	Insufficient	Remission RR 1.4 (0.6, 3.2)
	CGI-S	NA	2 (174)	2/0/0	Consistent	Precise	Direct (NMA)	Sparse	Low	CGI-S NMD −0.3 (−0.2, 0.7)
	FAS	NA	3 (241)	3/0/0	Consistent	Imprecise	Direct (NMA)	None	Low	FAS NMD −2.6 (−5.9, 0.7)
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, −2.6**)
	Remission	Combined	1 (56)	1/0/0	Consistent	Imprecise	Direct (no MA)	Sparse	Insufficient	No conclusion
	CGI-S	Combined	4 (346)	3/1/0	Consistent	Precise	Direct (NMA)	None	High	CGI-S NMD: **−0.6 (−0.9, −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 (−6.9, −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

Results

Comparison: Overall Conclusion	Outcomes	Control	N Studies (Participants)	RoB L/M/H	Consistency	Precision	Directness	Other	SoE	Conclusions
	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: **−4.1 (−6.2, −2.1)**
	Remission	NA	2 (33)	0/0/1	NA	Imprecise	Direct (no MA)	Sparse	Insufficient	Remission RR: 0.8 (0.3, 2.1)
	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
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, 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)	1/3/1	Consistent	Imprecise	Direct (NMA)	None	Moderate	CY-BOCS NMD: **−3.0 (−5.1, −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: **TCA is as effective as SSRI**	CY-BOCS	NA	6 (409)	0/5/1	Consistent	Precise	Direct (NMA)	None	High	CY-BOCS NMD 0.1 (−1.9, 2.1)
	Remission	NA	2 (149)	0/2/0	Consistent	Imprecise	Direct (no MA)	Sparse	Insufficient	No conclusion
	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, 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, 0.2)
	FAS	NA	0 (NA)	NA	NA	NA	NA	NA	Insufficient	No evidence

Prioritized outcomes with insufficient evidence across all listed comparisons are omitted. Cell coloring and bold font applied for visual emphasis only; it does not provide unique information.

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 = CBT with exposure and response prevention; FAS = Family Accommodation Scale; L, M, H = low, medium and high strength of evidence; N = number of studies (number of participants); NMD = net mean

difference; NMA = network meta-analysis; placebo = pill placebo; pwMA = pairwise meta-analysis; RoB = risk of bias (L= low, M=moderate, H=high); SSRI = selective serotonin reuptake inhibitors; TCA = tricyclic antidepressant; Waitlist = wait list control.

4. Discussion

4.1 Findings in Relation to the Decisional Dilemmas

KQ1: Diagnosis of Obsessive Compulsive Disorder

Brief Assessment Tools. Brief assessment tools can be used to determine whether a child should be further evaluated for obsessive compulsive disorder (OCD). Across 22 studies, 9 different scales were evaluated for multiple cutoffs. For only one tool was there evidence from a sufficient number of studies to draw any conclusions across studies. There is moderate strength of evidence (SoE) that the 8-question version of the Child Behavior Checklist-Obsessive Compulsive subscale (CBCL-OCS) is sufficiently sensitive and specific (summary area under the curve of 0.84, 95% CI 0.74 to 0.91) to prompt specialist referral for additional diagnostic assessment. Overall, the current evidence is insufficient to justify broad conclusions about the performance of the other 8 brief assessment tools. However, assessment tools need not have perfect diagnostic accuracy, only acceptable sensitivity and specificity as screens to prompt referral or further inquiry. Based on the current evidence the CBCL-OCS has good enough performance for use, and more studies should be done on the other eight scales to verify their usefulness in this way.

KQ2: Treatment of Obsessive Compulsive Disorder

CBT with Exposure and Response Prevention (ERP) is consistently effective for the treatment of OCD across multiple outcomes, including symptoms, remission, global severity, and reduction in family accommodation. Large effects are consistently reported in studies that compare ERP with a waitlist control. In a pooled estimate from 3 recent RCTs that compare ERP with active control interventions (e.g., psychoeducation and relaxation therapy, but not ERP), the magnitude of the ERP effect is somewhat attenuated.

ERP delivered via telehealth is more effective than waitlist 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 rural areas, and in locations with a shortage trained ERP providers.

Pharmacological treatment and combination of ERP and Medication. Selective serotonin reuptake inhibitors (SSRI) and clomipramine (a tricyclic antidepressant) are both more effective than pill placebo. ERP is probably more effective than SSRI, and the combination of ERP and an SSRI are probably more effective than SSRI alone. These conclusions argue for early referral for ERP, and treatment with medications in patients who have more severe illness, are not able to engage in ERP whether because of degree of distress/impairment or logistical/access barriers, have an incomplete response to ERP, or have been referred but are not yet receiving ERP. Our review found very sparse evidence to inform recommendations relating to how to treat individuals who fail to respond to ERP alone, or combined treatment with ERP and an SSRI or TCA. In the patients enrolled in clinical trials, augmentation of ERP with the glutamate inhibitor D-cycloserine is not more effective than ERP alone.

4.2 Strengths and Limitations

4.2.1 Strengths and Limitations of the Evidence Base

KQ 1: Strengths— multiple scales (with multiple informants) have been developed which have face validity as brief assessment tools, providing an opportunity for future research.

KQ 1: Limitations—While we found 22 studies that evaluated the diagnostic accuracy of brief assessment tools, almost all used a case-control design or had other critical methodologic limitations, including inclusion of only patients with OCD and inclusion of nonclinical controls, potentially overestimating both sensitivity and specificity due to the spectrum effect (or bias).[211] Few tools were assessed by more than 2 or 3 studies, and we found no studies designed to evaluate potential clinical effects, such as resource use or time to treatment, or potential effect modifiers, such as race or comorbidity status.

KQ 2: Strengths—The evidence base was large (69 randomized controlled trials [RCTs] and 2 nonrandomized comparative studies [NRCSs]). Meta-analysis was facilitated by the near universal use of a common outcome metric (C)Y-BOCS to assess changes in overall clinical severity.

KQ 2: Limitations—Many RCTs enrolled a small number of participants, and conclusions may be influenced by "small-study effects", a term for observation that small studies sometimes show different, often larger, treatment effects than large studies.[212] Reporting of outcome measures was variable, and effects were often reported in the form of regression parameters with significance tests, or as standardized effects (i.e., Cohen's d rather than mean within- and between-group mean and standard deviation of total CY-BOCS score). Across studies, there was a lack of consistent definitions regarding what constituted clinical remission or relapse. Trials often reported last observation carried forward analyses to account for missing data due to dropouts, potentially increasing bias and resulting in overly precise estimates. Treatment durations were relatively short, and somewhat variable, and durability of treatment effects remains unclear. Across all interventions, inclusion and exclusion criteria varied, as did treatment intensity. Providers and participants in trials of behavioral interventions cannot be masked, thus the potential for investigator bias is more easily controlled in pharmacological trials.

Few individual studies were adequately powered to evaluate predictors and moderators of intervention effectiveness.

Given the small sample size of included RCTs and the inconsistent reporting of medication side effects, there was insufficient evidence for graded conclusions regarding the harms and comparative harms of pharmacological treatments. However, based on evidence from other sources, the side effects of these drugs in children and adolescents are well known.[3] None of the included studies systematically collected or reported potential adverse events related to psychotherapy

We included no studies that identified participants with OCD who had concurrent features of pediatric acute-onset neuropsychiatric syndrome or pediatric autoimmune neuropsychiatric disorder associated with streptococcal infections (PANS/PANDAS), 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 youth aged 18 to 20 years inclusive.

4.2.2 Strengths and Limitations of the Systematic Review Process

Visualization of the network of treatment comparisons provides a visual overview of the available intervention comparisons. For the CY-BOCS outcome in particular, this resulted in a robust connected network, allowing for pooled effect estimates to include both direct and indirect information for key intervention comparisons, and opportunities to assess whether consistency assumption was tenable. Our findings were, thus, more robust than conclusions we could have made from pairwise (direct) comparisons only.

To construct the connected networks, it was necessary to aggregate interventions into broader categories. For example, waitlist, active treatment with relaxation therapy and pill placebo were aggregated in Control nodes. This aggregation allows high level comparisons, but likely widens the confidence intervals for estimated effects. We found some evidence that the effectiveness of CBT, for example, versus control varied based on what type of control was used (waitlist, placebo, relaxation therapy).

Given the large number of intervention comparisons with limited direct evidence, we report combined effects (indirect and direct evidence) from the network meta-analyses where two or more study arms contributed direct evidence. Effect estimates for comparisons with fewer than two (or no) direct comparisons (particularly for small studies) are much less likely to be robust.

Given the relatively sparse evidence within comparator-outcome categories, we did not perform subgroup analyses or meta-regression of potential predictors and moderators of treatment effects. Potential predictors and moderators are described narratively.

We followed contemporary standards for conducting systematic reviews, including engaging multiple stakeholders in Key Question development and refinement and careful adherence to recommended methods for literature searching, screening, data extraction, risk of bias assessment, qualitative synthesis, quantitative synthesis, and SoE assessment. During protocol development, we prioritized interventions in consultation with panels of Key Informants and Technical Experts. However, due to the multiple comparisons reported across studies, small sample size, many of the potential comparison-outcome combinations were reported in an insufficient number of studies to allow conclusions (or to support either pairwise or network meta-analyses).

4.3 Applicability

Studies of brief assessment tools primarily relied on case-control designs, and therefore may not be representative of symptomatic patients in primary settings for whom OCD is a consideration. Thus, existing studies may overestimate both sensitivity and specificity, limiting the applicability of recommended thresholds for diagnostic referral.

Across both KQs, studies performed in the U.S. enrolled primarily White, middle class, socially advantaged participants (more than about 90% of study participants were White, about two-thirds their parents were living together, and about two-thirds of their parents were college educated), with a major underrepresentation of marginalized or socially disadvantaged youth. For both behavioral and pharmacological interventions, prior experiences of stigmatization and discrimination may contribute to negative perceptions of diagnostic assessments and treatment. The majority of RCTs evaluating the efficacy of ERP are done specialty care settings by therapists providing provide high fidelity, within-session CBT with ERP. This may not translate into all clinical settings.[213] A poor fit with providers may impede treatment quality by reducing

engagement and retention. Clinical outcomes may be attenuated if families feel misunderstood or not believed, or if clinicians fail to adapt to the cultural context (e.g., by not involving community members such as faith leaders or extended family). Inequities in access to CBT with ERP may contribute to overuse of psychotropic medications.[214] In those receiving ERP, exposure quality and clinical outcomes may be attenuated for such reasons as families feeling misunderstood or not believing in the treatment, or if clinicians fail to adapt for cultural context.[215-217]

4.4 Implications for Clinical Practice

KQ 1: Across the 9 brief assessment tools, only the CBCL-OCS 8-question version was evaluated by a sufficient number of studies to draw conclusions, and probably has sufficiently diagnostic accuracy to help identify symptomatic patients for specialist referral and comprehensive diagnostic evaluation of OCD.

KQ 2: There is strong evidence that CBT with ERP is effective, and probably more effective than SSRIs alone. Remote ERP appears to have similar efficacy compared to in-person ERP.

These findings support widespread dissemination of CBT with ERP as a first-line treatment in children and adolescents with OCD. Provision of ERP via telehealth may facilitate wider dissemination. The evidence suggests that treatment with an SSRI cannot replace ERP, though pharmacological treatments could be useful in selected patients to facilitate engagement in ERP, or when ERP is not available.

Only a minority of youth with OCD receive minimally acceptable care,[213] and average wait times exceed 6 to 12 months. Even when able to access CBT, these youth rarely receive ERP,[218] due in part to low rates of exposure training and comfort among providers.[219] Marginalized youth face even greater barriers to accessing high-quality care. Barriers to access include limited availability of services, transportation difficulties, being less aware of the illness and/or treatment options, and experiences of stigmatization and discrimination. Health equity initiatives to increase access and quality must focus on settings that serve a majority of marginalized youth and promote culturally responsive interventions.[217, 220]

4.5 Implications for Research

KQ 1: All of the brief assessment tools should be evaluated in further studies to assess their sensitivity and specificity. These studies should ideally be prospective cohorts, enrolling a consecutive sample of patients for whom there is clinical concern for OCD. Comparative accuracy is best assessed by directly comparing two or more index tests in the same study, rather than across studies.[221] In addition, future studies should evaluate diagnostic accuracy across important effect modifiers, such as race and comorbidity status.

The same reference standard should be applied to all patients, ideally using a Longitudinal Expert All Data (LEAD) process that incorporates an expert clinical assessment, semi-structured interviews (e.g., K-SADS-PL, ADIS-C), multiple informants, assessment of level of impairment (e.g., CY-BOCS, CY-BOCS-II), and longitudinal response to treatment.[59, 222] Diagnostic evaluations should include assessment for common comorbid diagnoses (e.g., autism spectrum disorders, tic disorders, and presentations that raise concern for PANS/PANDAS). Once reliable tools are developed and validated, trials that evaluate the impact diagnostic strategies on clinical outcomes, such as time to treatment and improved functional outcomes, should be performed.

Discussion

KQ 2: Selective serotonin reuptake inhibitors (SSRIs) are widely used in pharmacotherapy for children and adolescents with anxiety and depressive disorders.[3] A recent meta-analysis[223] of placebo controlled trials of pediatric patients with OCD and other anxiety disorders (generalized, separation or social anxiety disorders) concluded that SSRIs are associated with distinct adverse events (AE), including activation, abdominal pain, and drowsiness. They found higher rates of AE-related discontinuation compared to placebo, but no association with suicidality. Future studies should assess for a standardized set of potential side-effects and assess the potential role of pharmacogenetic testing.

Future studies should evaluate interventions for which we have found no evidence, or insufficient evidence, including, neuromodulation, identification of patients for whom SSRI+ERP improves outcomes compared to ERP, and interventions in patients resistant to standard therapy (i.e., atypical antipsychotic mediations, and novel therapies based on advances in the understanding of the underlying pathophysiology of OCD. None of the included studies provide direct evidence for the magnitude of the placebo effect. Assuming participants in waitlist are otherwise similar to participants receiving pill placebo, an estimate (based on indirect evidence only) for the placebo effect[224] (placebo versus waitlist comparison) is a NMD in CY-BOCS of −3.1 with a 95 percent confidence interval ranging from −7.1 to 0.3. Future pharmacological studies should consider assigning patients to active intervention and both waitlist and placebo arms.

Given the overall strong evidence for efficacy, future studies should prioritize the evaluation of treatment strategies tailored to OCD and co-occurring mental health disorders. Implementation trials are needed to evaluate what works best for whom. Studies should address the comparative benefits alternative settings (e.g., remote, home, clinic, partial hospitalization), and intensities. Predictors studies should be adequately powered to detect effect modifiers and should more fully report the model specifications and results. Individual participant data meta-analysis of existing trials may also be useful to evaluate predictors and moderators.[225]

There has been a longstanding failure to include youth who have been historically underrepresented (e.g., based on race, ethnicity, or income) in pediatric OCD treatment studies.[216] Past studies often under recruit 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 resounding call from patients, families, clinicians, researchers, and advocacy groups to prioritize the inclusion of youth who have been historically underrepresented in clinical science and underserved in clinical practice. This is imperative for research that addresses tailoring treatment to better address barriers to access, quality, and clinical improvement for these groups.[226]

KQ 2 Research planned or in progress. We surveyed ongoing studies registered in ClinicalTrials.gov and found 8 trials (See Appendix Table C-2.1.3) whose design would meet the inclusion criteria for KQ 2. Of these, one is an effectiveness trial (the TECTO trial) comparing family based cognitive behavioral therapy with psychoeducation/relaxation training. The TECTO trial plans to gather qualitative and quantitative information related to potential adverse events associated with ERP.[227] Other ongoing trial addresses the comparative effectiveness of different delivery methods and styles of CBT, comparing patient-centered home-based CBT versus patient-centered-telehealth versus traditional office-based CBT; three registered trials will evaluate transcranial magnetic stimulation; two trials evaluate pharmacological strategies,

including a trial of celecoxib as an adjunct to treatment as usual, and a trial enrolling both adolescents and adults, comparing fluvoxamine and sertraline versus aripiprazole and sertraline. Finally, a two-phase trial is seeking to determine whether participants who benefit from CBT augmentation of their SSRI treatment can successfully discontinue SSRI treatment without relapse.

4.6 Conclusions

The diagnosis of OCD relies on expert clinical evaluation, often augmented by semi-structured interviews. Brief assessment tools have been proposed to be used by primary care providers evaluating youth with symptoms of OCD to facilitate early identification and specialty referral for a comprehensive diagnostic evaluation and early initiation of treatment. The CBCL-OCS may be sufficiently accurate to indicate which youth should be further evaluated for OCD, but the available evidence is insufficient for other brief assessment tools.

We found evidence supporting the efficacy of ERP, delivered in-person or remotely, and for both SSRIs and clomipramine compared to placebo. ERP alone, or ERP in combination with an SSRI, is more effective than treatment with an SSRI alone.

The side effects of SSRIs and clomipramine were inconsistently reported in the included RCTs, precluding graded conclusions. However, based on evidence from other sources, the side effects of these drugs in children and adolescents are well known.[3] No study collected or reported potential harms of behavioral interventions.

Treatment with D-cycloserine to augment ERP is not more effective than ERP alone in reducing OCD symptom severity and is probably not more effective in reducing global OCD severity.

Future research efforts should focus on: 1) inclusion of study participants who are representative of all youth affected by OCD, including non-white, low socioeconomic status children, and of sufficient size to allow subgroup analyses to determine what works for whom; 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/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 (e.g., neuromodulation)

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Abbreviations and Acronyms

AACAP	American Academy of Child and Adolescent Psychiatry
ACT	Acceptance and commitment therapy
ADIS-C	Anxiety Disorders Interview Scale-Child Version
AHRQ	Agency for Healthcare Research and Quality
ANOVA	analysis of variance
ASD	Autism spectrum disorder
AUC ROC	Area Under the receiver operating characteristics curve
briefERP	Brief duration exposure and response therapy
CBCL-OCS	Child Behavior Checklist-Obsessive Compulsive subscale
CBT	Cognitive Behavioral Therapy
CD-POC	Coercive Disruptive Behavior Scale
CFB	Change from baseline
C-FOCI	Children's Florida Obsessive Compulsive Inventory
CGI-S	Clinical Global Impressions-Severity Severity
CHOCI	Obsessional Compulsive Inventory-Child
CMB-I	Cognitive bias modification-interpretation
COIS, COIS-R	Child Obsessive Compulsive Impact Scale-Revised
CY-BOCS	Children’s Yale-Brown Obsessive Compulsive Scale
CI	confidence interval
CINAHL	Cumulative Index to Nursing and Allied Health Literature
Cohen’s d	a standardized effect size
COI	conflicts of interest
COIS	Child Obsessive Compulsive Impact Scale
DABWA	The Development and Well-Being Assessment
DISC-2.1	Sensitivity of the Diagnostic Interview Schedule for Children, 2nd edition
DSM	Diagnostic and Statistical Manual of Mental Disorders
DCS	D-cycloserine
EPC	Evidence-based Practice Center
ERP	Cognitive behavioral therapy with exposure and response prevention
FAS	Family Accommodation Scale
FI	Family Intervention
GRADE	Grading of Recommendations, Assessment, Development, and Evaluations
I^2	Perecnet of total variability that is due to between-study variability
intensiveERP	Intensive delivery of exposure and response prevention
IPTW	Inverse probability of treatment weighting

Abbreviations and Acronyms

K-SADS-PL	Kiddie Schedule for Affective Disorders and Schizophrenia, Present and Lifetime version
KI	Key Informant
KQ	Key Question
LEAD	Longitudinal Expert All Data
LOI-CV	Leyton Obsessional Inventory – Child Version
MD	mean difference
MINI-KID	Mini International Neuropsychiatric Interview for Children and Adolescents
N, n	number of (studies, participants)
MA	meta-analysis
N/A	not applicable
NMA	network meta-analysis
NMD	Net Mean Difference
NordLOTS	Nordic long-term OCD treatment study
NR	not reported
NRCS	nonrandomized comparative study
NS	not significant, defined as $P < 0.05$
OCI-CV	Obsessive Compulsive Inventory – Child Version
OCD	Obsessive-Compulsive Disorder
OFF	OCD Family Functioning Scale
OR	odds ratio
aOR	adjusted odds ratio
PANDAS	Pediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcal infections
PANS	Pediatric Acute-onset Neuropsychiatric Syndrome
PCORI	Patient-Centered Outcomes Research Institute
PFIT	Positive Family Interaction Therapy
PMT	Parent Management Training
PQ-LES-Q	Pediatric Quality of Life Enjoyment and Satisfaction Questionnaire
PROSPERO	International Prospective register of systematic reviews
pwMA	pairwise meta-analysis
QoL	Quality of Life
QUADAS-2	Quality Assessment of Diagnostic Accuracy Studies 2
RCT	randomized controlled trial
RD	risk difference
REML	restricted maximum likelihood
RoB	risk of bias
ROBINS-I	Risk of Bias in Nonrandomized Studies of Interventions

Abbreviations and Acronyms

RR	relative risk
aRR	adjusted relative risk
remoteERP	Remotely delivered ERP
rTMS	repetitive transcranial magnetic stimulation
SD	sample standard deviation
SoE	strength of evidence
SCAS-OCD	Spence Children's Anxiety Scale – OCD subscale
SOCS	Short Obsessive-Compulsive Disorder Screener
SPE	Strength of evidence for association
SR	systematic review
SROC	Summary receiver operating characteristics
SRDR+	Systematic Review Data Repository Plus
SSRI	Selective Serotonin Reuptake Inhibitor
TAU	Treatment As Usual
TCA	Tricyclic antidepressant
TEP	Technical Expert Panel
TOCS	Toronto Obsessive–Compulsive Scale
TOO	Task Order Officer
U.S.	United States
U.K.	United Kingdom
vs	versus
Y-BOCS	Yale-Brown Obsessive Compulsive Scale
CY-BOCS-SR	Children’s Yale-Brown Obsessive Compulsive Scale -Self Report
YSR OCD	Youth Self-Report OCD subscale