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An evaluation of treatment response and remission definitions in adult obsessive-compulsive disorder: A systematic review and individual-patient data meta-analysis

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ABSTRACT

Introduction: Expert consensus operationalized treatment response and remission in obsessive-compulsive disorder (OCD) as a Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) reduction ≥35% and score ≤12 with ≤2 on Clinical Global Impressions Improvement (CGI-I) and Severity (CGI-S) scales, respectively. However, there has been scant empirical evidence supporting these definitions.

Methods: We conducted a systematic review and an individual participant data meta-analysis of randomized-controlled trials (RCTs) in adults with OCD to determine optimal Y-BOCS thresholds for response and remission. We estimated pooled sensitivity/specificity for each percent reduction threshold (response) or posttreatment score (remission) to determine response and remission defined by a CGI-I and CGI-S ≤ 2, respectively.

Results: Individual participant data from 25 of 94 eligible RCTs (1235 participants) were included. The optimal threshold for response was ≥30% Y-BOCS reduction and for remission was ≤15 posttreatment Y-BOCS. However, differences in sensitivity and specificity between the optimal and nearby thresholds for response and remission were small with some uncertainty demonstrated by the confidence ellipses.

Conclusion: While the empirically derived Y-BOCS thresholds in our meta-analysis differ from expert consensus, given the predominance of data from more recent trials of OCD, which involved more refractory participants and novel treatment modalities as opposed to first-line therapies, we recommend the continued use of the consensus definitions.

1. Introduction

Obsessive-Compulsive Disorder (OCD) is a psychiatric disorder characterized by recurrent, intrusive, and unwanted thoughts, images, or urges (obsessions) and repetitive actions, behaviors, or mental rituals (compulsions). The obsessions and compulsions often severely impair an individual's daily functionality without treatment (Skoog and Skoog, 1999). OCD is also associated with considerable morbidity and mortality, e.g., increased risk of suicide (Albert et al., 2019; Fernández de la Cruz et al., 2022). In fact, prior to the advancements in evidence-based treatments, OCD was listed by the World Health Organization as one of the top ten conditions associated with the greatest financial loss and decrease in quality of life in the 1990's (Bobes et al., 2001). Since then, the development and dissemination of effective treatments for OCD has decreased the morbidity substantially for many patients (Hirschtritt et al., 2017).

The current first-line treatment for OCD includes a combination of selective serotonin reuptake inhibitors (SSRIs) and cognitive behavioral therapy (CBT) (Bloch et al., 2013). However, even with evidence-based treatments, 40–60% of individuals still experience OCD symptoms that can significantly impair their quality of life (Bloch et al., 2013; Garnaat et al., 2015). Over the last couple of decades, there has been a considerable number of randomized clinical trials (RCTs) evaluating the efficacy of novel treatments for adults with OCD, including psychotherapeutic (Andersson et al., 2012, 2015; Lundström et al., 2022) and pharmacological interventions, such as antipsychotics (Bloch et al., 2006), N-methyl-D-aspartate (NMDA) receptor modulators (Pasquini and Biondi, 2006; Poyurovsky et al., 2005; Stewart et al., 2010), opioid agonists (Koran et al., 2005; Shapira et al., 1997), and ketamine (Rodriguez et al., 2013), and invasive/non-invasive neuromodulation, such as deep brain stimulation (DBS) (Abelson et al., 2005; Denys et al., 2010) repeated transcranial magnetic stimulation (rTMS) (Lusicic et al., 2018; Rehn et al., 2018), and transcranial direct current stimulation (tDCS) (Fineberg et al., 2023; Pinto et al., 2023; Silva et al., 2021).

In RCTs of adult OCD, the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) (Goodman et al., 1989a), a 10-item clinician-rated scale that measures the severity of obsessive-compulsive symptoms by characterizing the time, interference, distress, resistance, and control related to the OCD symptomatology, is typically used as the primary outcome to determine the comparative efficacy of interventions. In the Y-BOCS, each item is scored in a 5-point Likert scale ranging from 0 (no symptoms) to 4 (extreme symptoms). Separate scores for obsessions (obsession severity scale) and compulsions (compulsion severity scale), each ranging from 0 (no symptoms) to 20 (extreme symptoms), are calculated and can be summed to provide a total score. The Y-BOCS has sound psychometric properties, including high internal consistency (Cronbach's $\alpha = 0.89$) and interrater reliability (intraclass correlation coefficient = 0.98) (Goodman et al., 1989b; Storch et al., 2010). However, the precise clinical meaning of average changes in Y-BOCS scores during treatment remains unclear. While global measures of clinical judgment (very much/much improved; very much/much ill) may be less informative than Y-BOCS scores regarding specific OCD symptomatology, from a clinical perspective the dichotomized response and remission categories based on the CGI-I and CGI-S, respectively, may be at least as meaningful as previously discussed for schizophrenia (Leucht et al., 2005, 2006, 2019) and depression (Leucht et al., 2017). Dichotomous outcomes such as a treatment remission and response may be more important because they are more clinically interpretable than numeric change scores in the Y-BOCS. However, response and remission have been traditionally reported as secondary outcomes in OCD RCTs with varying definitions including different Y-BOCS percentage improvement cutoffs or auxiliary scales, e.g., Clinical Global Impressions-Improvement/Severity (CGI-I/S) (Busner and Targum, 2007), two global measures of improvement/severity that have been widely adopted in clinical research across psychiatric disorders, including OCD, depression and schizophrenia (Busner and Targum, 2007). The lack of consensus operational definitions of response and remission in OCD RCTs has impaired the standardization and comparability of OCD RCTs, e.g., in meta-analyses, creating difficulties for communication in the field (Kühne et al., 2020).

In response to these varied definitions, a web-based Delphi survey of OCD experts from around the world was conducted to determine consensus definitions of response and remission in OCD RCTs (Mataix-Cols et al., 2016). For response, the consensus determined an operational definition of a reduction of at least 35% in Y-BOCS score after treatment plus a CGI-I score of 1 ("very much improved") or 2 ("much improved") lasting for at least one week. For remission, the consensus determined an operational definition of a Y-BOCS score of at most 12 posttreatment plus a CGI-S score of 1 ("normal, not at all ill") or 2 ("borderline mentally ill") lasting for at least one week (Mataix-Cols et al., 2016).

Nevertheless, data from empirical studies have been conflicting regarding whether the Y-BOCS percent reductions and absolute endpoint raw scores suggested by the expert consensus provide the optimal thresholds for response and remission, respectively. Several previous studies have examined the optimal thresholds in the Y-BOCS that correspond to response and remission using a signal detection analytic approach with the CGI-I and CGI-S scales as the reference

standards, respectively (Farris et al., 2013; Lewin et al., 2011; Tolin et al., 2005). The previous studies have suggested an optimal threshold between 30% and 45% reduction in Y-BOCS and a Y-BOCS endpoint score between 12 and 14 for treatment response and remission, respectively (Farris et al., 2013; Lewin et al., 2011; Tolin et al., 2005). However, these studies have been limited by only including a few hundred individuals at most. More recently, in children and adolescents, a meta-analysis of RCTs demonstrated a promising approach to investigate this problem by aggregating data across studies, therefore increasing sample sizes and statistical power. That study indicated that the thresholds proposed by the consensus study had the best discriminatory abilities for response and remission as defined by a CGI-I $\leq$ 2 and CGI-S $\leq$ 2, respectively (Farhat et al., 2022). However, at present a similar study has not been conducted for adult OCD.

To empirically validate the consensus Y-BOCS definitions, we conducted a large-scale individual participant data meta-analysis of adult OCD RCTs and used a novel multiple thresholds linear mixed effects model to find the optimal Y-BOCS threshold for response and remission defined as a CGI-I $\leq$ 2 and CGI-S $\leq$ 2, respectively.

2. Material and methods

This article is reported in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). This review followed the analytical plan conducted in our pediatric meta-analysis (Farhat et al., 2022). All review stages involving study selection, coding of data items, and statistical analyses were conducted by two independent reviewers (DR, LCF) and a third reviewer (MHB) resolved all disagreements between the two reviewers.

2.1. Eligibility criteria

Any RCT which investigated treatments for adults (age range of individuals $\geq$ 18 years) with OCD as the primary diagnosis and had a treatment duration of at least four weeks were considered eligible for inclusion. We restricted our analysis to RCTs since they are the most rigorously conducted studies. A duration of at least four weeks was set to exclude any challenge studies or RCTs with shorter treatments which may be insufficient to evaluate treatment outcomes. Individuals were required to have a formal diagnosis of OCD as determined by standardized diagnostic criteria. RCTs including individuals considered "treatment-refractory" or "treatment-resistant" were eligible for inclusion. No restrictions were made regarding interventions (i.e., pharmacological, psychotherapeutic, invasive/non-invasive neurostimulation treatments, or yoga were eligible), including controls (i.e., placebo, treatment as usual, any active or passive psychotherapeutic treatments were eligible). Both double-blind and single-blind studies were considered eligible. No language restrictions were adopted.

2.2. Data sources and study selection

We searched selected electronic databases (PubMed, EMBASE, and PsycINFO), in March 2020 for eligible RCTs to include in the meta-analysis. The detailed search strategy can be found in the supplementary file. Searches were tailored for each database. Titles/abstracts of the records were initially screened, and selected full texts were inspected to determine eligibility. The references section of review articles and meta-analyses were carefully read to identify additional eligible studies. No further efforts were made to search for unpublished research.

2.3. Data collection and data items

The following data were extracted for each study in an Excel spreadsheet: name of first and last author, email address of the corresponding author and year of publication; age range and number of study participants; treatment arms. We then sent an email to the corresponding author of each study requesting the following de-identified information for each study participant in an Excel spreadsheet: 1) pre-treatment Y-BOCS score, 2) post-treatment Y-BOCS score, 3) post-treatment CGI-I/CGI-S scores, and 4) assigned treatment arm. If we did not receive a reply from an author, we sent a follow-up email within three weeks after the initial email. If we still did not receive a reply from an author after the first follow-up email, we tried to contact other study co-authors. We sent no more than three total emails to any study author.

We evaluated Y-BOCS percent reductions from baseline to post-treatment in relation to treatment response. We computed 14 percentage reduction thresholds from 5% to 70% reduction with 5% intervals in accordance with our methods in pediatric OCD (Farhat et al., 2022). For each study, we categorized individuals as treatment responders if they had a CGI-I score of 1 or 2. Then, for each of the Y-BOCS percent reduction thresholds, we calculated the true positives (TP), true negatives (TN), false positives (FP), and false negatives (FN) in treatment response for each study.

We evaluated Y-BOCS posttreatment raw scores in relation to remission. We computed 16 posttreatment raw score thresholds from 5 to 20 with one-point intervals in accordance with our methods in pediatric OCD (Farhat et al., 2022) and previous studies in the field of adult OCD (Lewin et al., 2011; Tolin et al., 2005). For each study, we categorized individuals as treatment remitters if they had a CGI-S score of 1 or 2. Then, for each of the Y-BOCS posttreatment raw score thresholds, we calculated the true positives (TP), true negatives (TN), false positives (FP), and false negatives (FN) in treatment response for each study.

We chose to use the CGI-I and CGI-S scales as our reference standards for treatment response and remission, respectively, given that the CGI has been extensively used in psychiatry (Leucht et al., 2005, 2006, 2017, 2019) and in the context of OCD specifically (Farris et al., 2013; Lewin et al., 2011; Tolin et al., 2005; Farhat et al., 2022) although it may have poor operationalization of symptom improvement and remission. However, it is important to note that the CGI is a global judgment of treatment response by a single rater, and to the best of our knowledge its reliability and validity in the context of OCD have not been directly examined to date.

2.4. Meta-analytical method

Since each study contributed multiple thresholds in our meta-analysis, we applied a multiple thresholds linear mixed effects model (Steinhauser et al., 2016) previously used in our meta-analysis of pediatric OCD (Farhat et al., 2022). Using this approach, we focused on the cumulative distribution function of a negative result for response defined as scoring below the Y-BOCS percent reduction threshold in treatment non-responders (specificity) and treatment responders (1-sensitivity). Specificity and 1-sensitivity were both defined as functions of the Y-BOCS percent reduction threshold for non-responders and responders, respectively. For remission, we focused on the cumulative distribution function of a negative result defined as scoring above the Y-BOCS raw posttreatment score threshold in treatment non-remitters (specificity) and treatment remitters (1-sensitivity). Specificity and 1-sensitivity were both defined as functions of the Y-BOCS raw post-treatment score threshold for non-remitters and remitters, respectively. To apply a linear model to fit the individual participant data, we applied a logit transformation to the sensitivity and specificity. A random intercept model with study as the grouping factor was employed. We weighted each data point by its inverse variance. We assumed equal variances in the distribution of the Y-BOCS between treatment responders and non-responders. We obtained pooled sensitivity and specificity with 95% confidence intervals for every Y-BOCS cutoff for response and remission. Pooled values of sensitivity and specificity were used to plot summary receiver operating characteristics (SROC) curves. The Area Under SROC Curve (AUC) was computed to indicate the discriminative ability of the Y-BOCS in determining response and

remission; values range from 0.5, which indicates no discriminative ability, to 1, corresponding to perfect discrimination. We also used pooled values of accuracy measures to calculate the Youden Index (*J*), which was used to help inform the optimal cutoff. The *J* statistic is computed by the maximum value of the weighted sum of the sensitivity and specificity obtained: λ*sensitivity + (1- λ)*specificity, where λ corresponds to the weight attributed to sensitivity. We calculated the Youden Index attributing equal importance to sensitivity and specificity (λ = 0.5). We conducted analyses in R using the package 'diagmeta' (Steinhauser et al., 2016).

3. Results

3.1. Description of included trials in meta-analysis

Our search identified 3806 references of which 94 were considered eligible for inclusion (Supplemental A). Fig. 1 depicts the PRISMA flowchart that describes reasons for exclusion. We were able to include 25 of the 94 eligible studies in our final analysis. We were unable to include data from the other 69 eligible studies (Supplemental B). Out of these 69 studies, we did not receive a response from 39 study authors, and individual participant data was not available for the other 30 studies. Table 1 describes the characteristics of the final 25 studies included in the meta-analysis. Across the 25 RCTs, a total of 1235 participants were included. The mean age of participants was 36 years (SD = 3.4). Participants were recruited from North America in 7 (28%) RCTs, from South America in 4 (16%), from Europe in 8 (32%), from the Middle East in 5 (25%), from Asia in 2 (8%), and from Australia in 1 (4%). Of the 25 RCT's, 22 reported sex of the participants. Of the 1108 participants for whom sex was reported, 467 (42%) were male. The following is the breakdown of the treatment modality administered in the 25 RCT's: 10 (40%) pharmacotherapy, 5 (20%) psychotherapy, 5 (20%) neurostimulation, 4 (16%) multimodal (psychotherapy and pharmacotherapy), and 1 (4%) Kundalini yoga meditation. Of the 25 RCTs, 22 (962 participants) contributed data to calculate a response threshold while 20 (904 participants) contributed data to calculate a remission threshold.

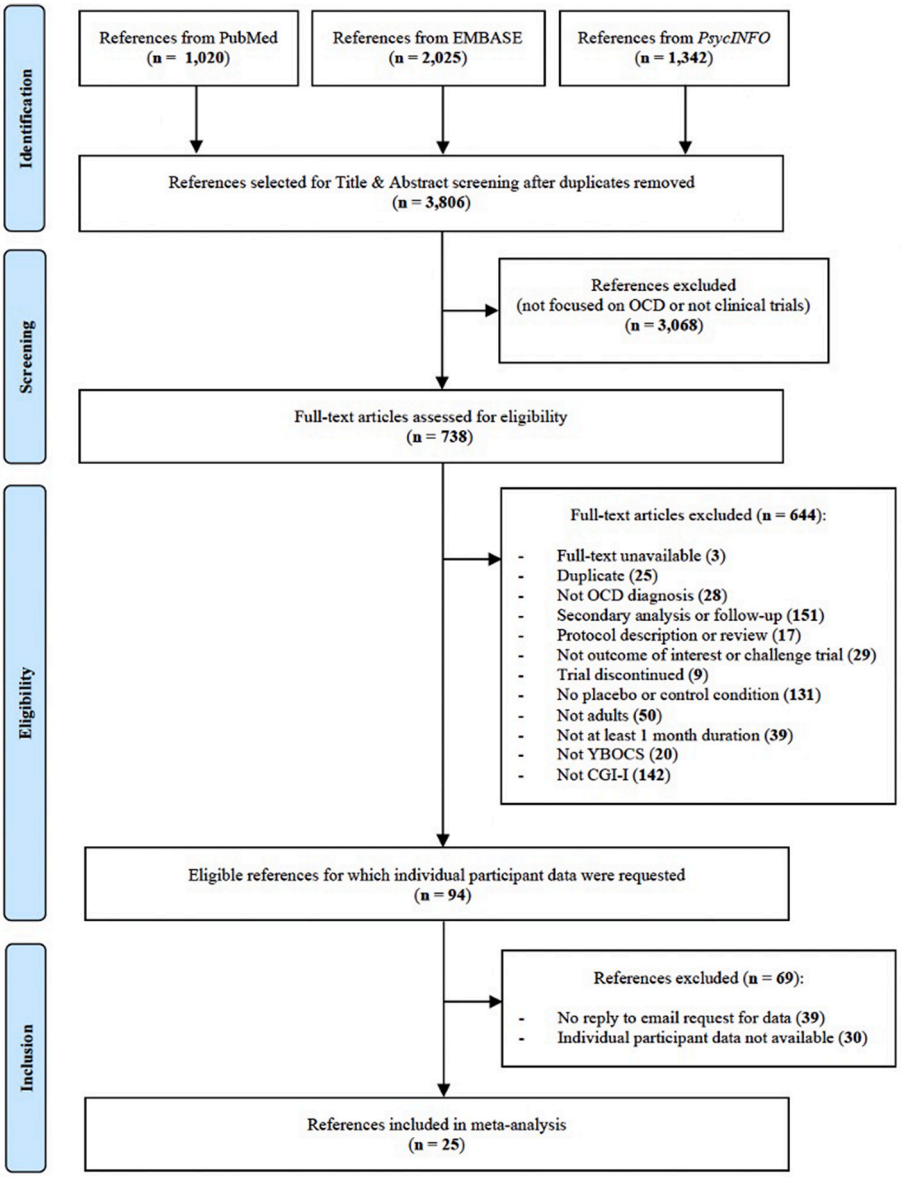

Fig. 1. PRISMA flowchart of study selection process.

Table 1
Study characteristics.

Study	Country	Age[a]	Sex[b]	Ethnicity[c]	Treatment arms	Blinding/Rater Independence	N	Duration[d]	Outcomes	Funding
Afshar et al. (2014)	IR	34.5 (8.6)	5	N.R.	Topiramate + SRI; placebo + SRI	Double-blind	38	12	CGI-S; CGI-I	IUMS
Amiaz et al. (2008)	IL	34.6 (10.5)	50	N.R.	Naltrexone; placebo	Double-blind	10	5	CGI-S; CGI-I	None
Andersson et al. (2012)	SE	34.0 (13.0)	34	N.R.	ICBT; online non-directive supportive therapy	Independent rater	101	10	CGI-S; CGI-I	SRC/SSM
Andersson et al. (2015)	SE	34.8 (12.3)	42	N.R.	DCS + ICBT; placebo + ICBT	Double-blind	128	12	CGI-S; CGI-I	SRC
Baruah et al. (2018)	IN	30.5 (7.8)	39	N.R.	BFBI + SRI;RE + SRI	Independent rater	64	4	CGI-S; CGI-I	DBT, Govt of India
Carmi et al. (2018)	IL	33.9 (2.9)	53	N.R.	HF dTMS;LF dTMS; sham dTMS of mPFC and ACC	Double-blind	38	5	CGI-S	Brainsway Ltd.
Carmi et al. (2019)	US/IL/CA	38.8 (11.9)	41	N.R.	HF dTMS; sham dTMS of mPFC & ACC	Double-blind	94	6	CGI-S	Brainsway Ltd.
Costa et al. (2017)	BR	38.0 (10.8)	52	69	NAC; placebo	Double-blind	40	16	CGI-S; CGI-I	FAPESP
Diniz et al. (2011)	BR	33.8 (10.6)	N.R.	N.R.	Quetiapine + fluoxetine; clomipramine + fluoxetine; placebo + fluoxetine	Double-blind	54	12	CGI-S; CGI-I	Janssen Pharma
Erzegovesi et al. (2005)	IT	36.5 (11.3)	N.R.	N.R.	Risperidone + fluvoxamine; placebo + fluvoxamine	Double-blind	39	6	CGI-I	None
Greenberg et al. (2009)	US	40.1 (13.7)	38	100	Glycine; placebo	Double-blind	24	12	CGI-S; CGI-I	OCF
Hawken et al. (2016)	TR/BG	33.5 (12.4)	50	N.R.	LF rTMS; sham rTMS of SMA	Double-blind	22	6	CGI-S; CGI-I	None
Kobak et al. (2005)	US	37.7 (11.2)	55	77	St John's wort; placebo	Double-blind	60	12	CGI-S; CGI-I	NCCAM
Kobayashi et al. (2019)	JP	30.1 (9.0)	53	N.R.	FERP; treatment as usual	Independent rater	17	16	CGI-S; CGI-I	JSPS/MEXT
Maina et al. (2010)	IT	31.5 (7.5)	44	N.R.	BDT + SSRI; SSRI	Independent rater	54	16	CGI-S; CGI-I	N.R.
Mallet et al. (2008)	FR	43.1 (7.9)	59	N.R.	Active stimulation; sham stimulation of STN	Double-blind	17	12	CGI-I	ANRP
Meyer et al. (2010)	BR	38.6 (12.5)	25	N.R.	MI + TM + CBGT; information-only session + CBGT	Independent rater	93	12	CGI-I	CNPQ/ FAPESP
Pelissolo et al. (2016)	FR	40.5 (10.5)	39	N.R.	Active rTMS; sham rTMS of pre-SMA	Single-blind and independent rater	36	4	CGI-S; CGI-I	PHRP
Sarris et al. (2015)	AU	37.0 (12.1)	55	N.R.	NAC; placebo	Double-blind	44	16	CGI-S; CGI-I	None
Shannahoff-Khalsa et al. (2019)	BR	41.7 (12.9)	35	83	Kundalini yoga meditation; RR	Independent rater	48	15	CGI-S	FAPESP/ INPD
Storch et al. (2007)	US	29.0 (9.9)	50	N.R.	DCS + E/RP therapy; placebo + E/RP therapy	Double-blind	34	12	CGI-S; CGI-I	OCF
Storch et al. (2013)	US	43.7 (11.4)	N.R.	94	Paliperidone + SRI; placebo + SRI	Double-blind	34	8	CGI-S; CGI-I	JSA
Tolin et al. (2007)	US	38.2 (13.1)	37	N.R.	Therapist administered E/RP; self-administered E/RP	Independent rater	41	7.5	CGI-I	N.R.
Vulink et al. (2009)	NL	34.5 (11.5)	49	N.R.	Quetiapine + citalopram; placebo + citalopram	Double-blind	76	10	CGI-S; CGI-I	AstraZeneca
Wilhelm et al. (2009)	US	33.4 (11.2)	48	N.R.	CT; wait list	Independent rater	29	12	CGI-I	NIMH

ACC = anterior cingulate cortex; ANRP = Agence Nationale de la Recherche Program; BDT = brief dynamic therapy; BFBI = brief family-based intervention; CBGT = cognitive behavioral group therapy; CNPQ = Conselho Nacional de Desenvolvimento Científico e Tecnologico; CT: cognitive therapy; DB = double-blind; DCS = d-cycloserine; DBT = Department of Biotechnology; dTMS = deep transcranial magnetic stimulation; E/RP = exposure and response prevention; FAPESP = Foundation for Research Support in the State of São Paulo; FERP = family-based exposure and response prevention; HF = high-frequency; ICBT = internet-based cognitive behavioral therapy; INPD = National Institute of Developmental Psychiatry for Children and Adolescents; IUMS = Isfahan University of Medical Sciences; JSA = Janssen Scientific Affairs; KY = Kundalini yoga; LF = low-frequency; JSPS = Japan Society for the Promotion of Science/MEXT = The Ministry of Education, Cultures, Sports, Science and Technology; MI + TM = motivational interviewing + thought mapping; mPFC = medial prefrontal cortex; NAC = N-acetylcysteine; NCCAM = National Center for Complementary and Alternative Medicine; NIMH = National Institute of Mental Health; OCF = Obsessive Compulsive Foundation; PHRP = Programme Hospitalier de la Recherche Clinique; pre-SMA = presupplementary motor area; rDLPFC = right dorsolateral prefrontal cortex; RE = relaxation exercises; RR = relaxation response; rTMS = repetitive transcranial magnetic stimulation; SMA = sensory motor area; SRC = Swedish Research Council; SRI = serotonin reuptake inhibitor; SSM = Swedish Society of Medicine; SSRI = selective serotonin reuptake inhibitor; STN = subthalamic nucleus.

[a] Mean and standard deviation.
[b] Percentage of male participants.
[c] Percentage of individuals who self-identified as white.
[d] Weeks.

3.2. Response

The meta-analysis indicated that percent reductions from baseline to posttreatment had sufficient discriminative ability (AUC = 0.89) to determine response as defined by the CGI-I. Accuracy measures are described in Table 2, and Fig. 2 illustrates the SROC curve for response. The Youden index was optimal for a threshold ≥30% reduction from baseline to posttreatment to determine response as defined by the CGI-I. The 30% reduction cutoff had a sensitivity of 80.5% (95% CI 80.2, 80.7) and a specificity of 83.4% (95% CI 83.2, 83.6). However, both the 25% reduction and 35% reduction cutoffs were included in the confidence ellipse. The 25% reduction cutoff had a sensitivity of 85.8% (95% CI 85.6, 86.0) and a specificity of 77.3% (95% CI 77.1, 77.6). The 35% reduction had a sensitivity of 73.7% (95% CI 73.4, 74.0) and a specificity of 88.0% (95% CI 87.9, 88.2).

3.3. Remission

The meta-analysis indicated that posttreatment raw score on the Y-BOCS had sufficient discriminative ability (AUC = 0.87) to determine remission as defined by the CGI-S. Accuracy measures are described in Table 3, and Fig. 3 illustrates the SROC curve for remission. The Youden index was optimal for a threshold of ≤15 posttreatment raw score to determine remission as defined by the CGI-S. The 15-point cutoff had a sensitivity of 78.9% (95% CI 78.6, 79.3) and a specificity of 80.3% (95% CI 80.1, 80.5). However, the 14-point and 16-point cutoffs were included in the confidence ellipse. The 14-point cutoff had a sensitivity of 74.4% (95% CI 74.0, 74.8) and a specificity of 84.0% (95% CI 83.9, 84.2). The 16-point cutoff had a sensitivity of 82.9% (95% CI 82.6, 83.2) and a specificity of 76.0% (95% CI 75.8, 76.2).

4. Discussion

We conducted an individual-participant data meta-analysis to investigate the optimal cut point on the Y-BOCS to determine response and remission as defined by the CGI in data from RCTs of adults with OCD. Our findings indicated that there was sufficient discrimination to determine treatment response by percent reduction in Y-BOCS score (AUC = 0.89) and remission by posttreatment raw Y-BOCS score (AUC = 0.87). We found that the combination of sensitivity and specificity as defined by the Youden index was greatest for a percent reduction threshold of ≥30% in defining treatment response. However, there was some uncertainty in the data, and the confidence ellipse also included the ≥25% and ≥35% reduction cutoffs, the cutoff recommended by expert consensus. We also found that the combination of sensitivity and specificity as defined by the Youden index was greatest for a posttreatment Y-BOCS raw score threshold of ≤15 in defining remission; however, there was some uncertainty in the data as the confidence ellipse also included the 14-point and 16-point cutoffs (Mataix-Cols et al., 2016). The confidence ellipse for defining remission using Y-BOCS score did not include the cutoff recommended by expert consensus. Therefore, our findings did not support the consensus definition, particularly for remission.

Table 2
Accuracy measures of Yale-Brown Obsessive-Compulsive Scale percent reductions for response according to a Clinical Global Impressions - Improvement score ≤ 2. The Y-BOCS percent reduction cutoff with optimal Youden index is highlighted in boldface.

Cutoffs	Sens % (95% CI)	Spec % (95% CI)	Youden (95% CI)
5%	96.6 (96.5–96.6)	42.2 (41.9–42.6)	0.388 (0.384–0.392)
10%	95.1 (95.0–95.1)	51.8 (51.4–52.1)	0.468 (0.464–0.473)
15%	92.9 (92.8–93.0)	61.2 (60.9–61.6)	0.541 (0.537–0.546)
20%	89.9 (89.7–90.0)	69.9 (69.6–70.2)	0.598 (0.593–0.602)
25%	85.8 (85.6–86.0)	77.3 (77.1–77.6)	0.632 (0.627–0.636)
30%	**80.5 (80.2–80.7)**	**83.4 (83.2–83.6)**	**0.638 (0.634–0.643)**
35%	73.7 (73.4–74.0)	88.0 (87.9–88.2)	0.618 (0.613–0.622)
40%	65.6 (65.2–66.0)	91.5 (91.4–91.7)	0.571 (0.567–0.576)
45%	56.5 (56.1–56.9)	94.1 (94.0–94.2)	0.506 (0.501–0.510)
50%	46.9 (46.5–47.3)	95.9 (95.8–96.0)	0.428 (0.423–0.433)
55%	37.5 (37.1–37.9)	97.2 (97.1–97.2)	0.347 (0.343–0.351)
60%	29.0 (28.7–29.3)	98.1 (98.0–98.1)	0.271 (0.267–0.274)
65%	21.7 (21.5–22.0)	98.7 (98.6–98.7)	0.204 (0.201–0.207)
70%	15.9 (15.7–16.1)	99.1 (99.1–99.1)	0.150 (0.148–0.152)

It is important to consider that our study included individual participant data from only 27% of the eligible RCTs. Therefore, it is possible that our findings may have been influenced by relatively small availability of data. It is also possible that the RCTs that contributed data were not representative of the RCTs in the field. Indeed, a considerable proportion (44%) of the included trials primarily recruited treatment-refractory participants defined as participants with inadequate symptom reduction after an adequate trial of one or more first-line treatments, such as SRIs and CBT. We hypothesize that treatment-refractory participants may be classified as "responders" or "remitters" based on clinical observation (i.e., with the CGI-I/S) while experiencing smaller percent reductions or higher posttreatment raw scores on the Y-BOCS, which could lead to a lower optimal percent reduction and higher raw score threshold for response and remission, respectively. Future studies should test this hypothesis directly.

It is also important to note that there was some uncertainty among the optimal threshold as represented by the surrounding confidence ellipse. Indeed, the differences in sensitivity and specificity across the optimal and nearby thresholds were small. It is possible that relative indices of treatment effects (e.g., odds ratio) may be generally constant across percent reduction thresholds and may not influence comparative outcomes across treatments, e.g., in meta-analyses (Furukawa et al., 2011). Future research should examine this hypothesis directly. On the other hand, evidence from longitudinal studies seem to indicate individuals who are classified as responders may have better prognosis across time. For instance, a recent study based on Swedish data (RCTs and cohort studies) found that the consensus definitions of treatment response and remission captured meaningful improvements in everyday life of individuals with OCD, as determined by patient-reported symptoms/quality of life and clinician-rated functioning. However, individuals with smaller improvements in OCD symptoms (e.g., partial response, ≥25% but <35% reduction in Y-BOCS) had similar outcomes as non-responders (Mataix-Cols et al., 2022). Similarly, the consensus Y-BOCS definition for remission was also found to have a high predictive ability for symptom deterioration versus stability at one year follow-up posttreatment (Elsner et al., 2020). Additional studies examining treatment outcomes in real-world settings are also warranted to further clarify this important point.

Our study has many strengths. Perhaps the most important one is that it includes individual participant data from several OCD trials across different countries and many participants. Our meta-analysis is also unique in that it employed an approach to meta-analysis that enabled aggregating multiple thresholds simultaneously. Unlike the standard bivariate models for meta-analysis, the multiple thresholds model uses all the data from individual studies instead of only relying on one pair of sensitivity and specificity per study, which may minimize bias typically present when analyzing data from each study individually (Rücker and Schumacher, 2010; Steinhauser et al., 2016).

However, our study also has limitations. First, the patient demographic from the included studies were primarily white individuals from the US, which may affect generalizability of our results across different race/ethnic groups. Second, the Y-BOCS considers OCD symptoms over one week. Since OCD is a disorder with periodic exacerbations of symptoms over time, tracking the change in Y-BOCS score over a span of several weeks might better reflect treatment response and remission. Third, although the CGI scores represent global impressions of the treating physician and have been widely used to determine response/remission in previous studies in OCD (Farris et al., 2013; Lewin et al., 2011; Tolin et al., 2005; Farhat et al., 2022) and other

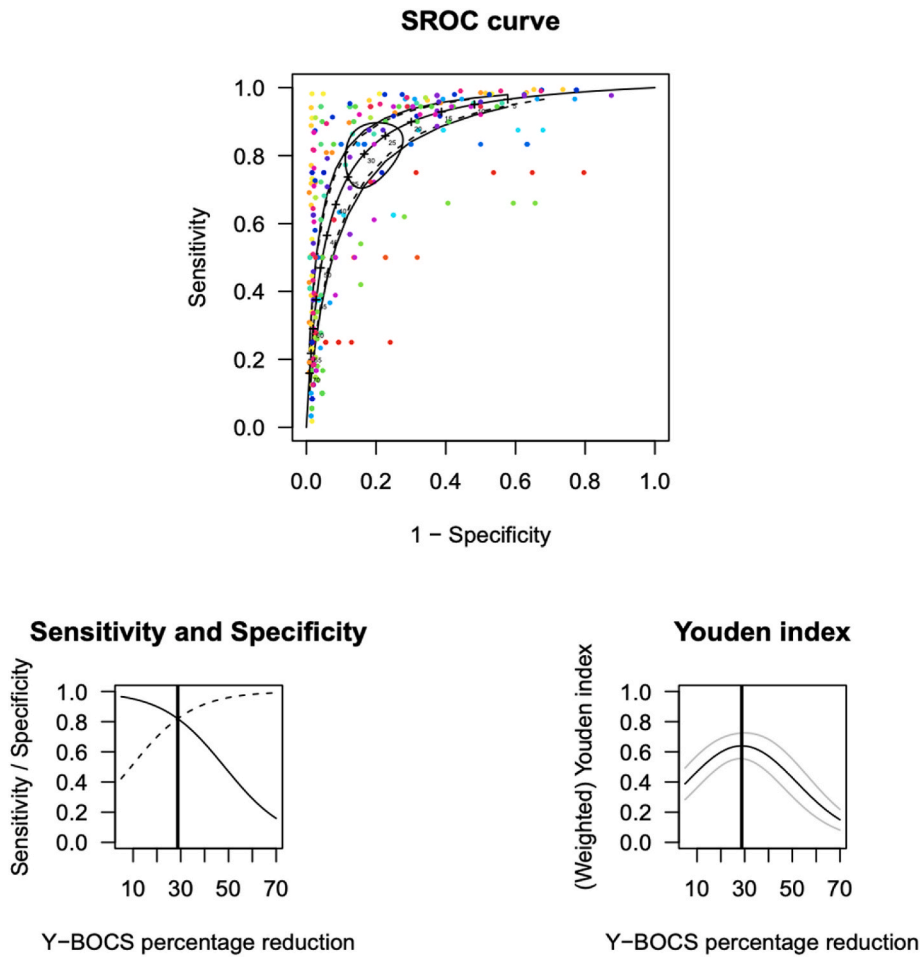

Fig. 2. Receiver Operating Characteristic (ROC) Analysis for Yale-Brown Obsessive-Compulsive Scale Percent Reduction Thresholds and Treatment Response as Defined by a Clinical Global Impressions – Improvement Scale Score of ≤2. The top panel shows the summary receiver operating characteristic (SROC) curve for overall discriminative performance of the percentage reduction in Y-BOCS in determining CGI-I defined treatment response with individual points color coded by study. Confidence intervals for pooled sensitivity (solid line) and specificity (dashed line) are shown. A threshold of 30% reduction on the Y-BOCS scale had the optimal Youden index. However, the confidence ellipse around the 30% cutoff includes both 25% and 35% thresholds, highlighting the uncertainty in the data. The lower left panel shows tradeoffs in sensitivity (solid line) and specificity (dashed line) at each Y-BOCS percentage threshold. A threshold of 30% had the optimal balance between sensitivity and specificity as shown by the intersection of the solid and dashed lines. The lower right panel shows the Youden indices (black line) with 95% confidence interval (gray lines) for different Y-BOCS percentage thresholds. The optimal Youden index occurred at a 30% threshold.

Table 3
Accuracy measures of Yale-Brown Obsessive-Compulsive Scale raw scores for remission according to a Clinical Global Impressions - Severity score ≤ 2. The Y-BOCS posttreatment raw score with optimal Youden index is highlighted in boldface.

Cutoffs	Sens % (95% CI)	Spec % (95% CI)	Youden (95% CI)
5	22.9 (22.5–23.2)	98.1 (98.1–98.1)	0.210 (0.206–0.214)
6	27.6 (27.2–28.1)	97.6 (97.5–97.6)	0.252 (0.248–0.257)
7	33.0 (32.5–33.5)	96.9 (96.8–96.9)	0.299 (0.294–0.304)
8	38.8 (38.3–39.3)	96.0 (96.0–96.1)	0.348 (0.343–0.354)
9	45.0 (44.5–45.5)	94.9 (94.9–95.0)	0.399 (0.393–0.405)
10	51.3 (50.8–51.9)	93.6 (93.5–93.6)	0.449 (0.443–0.455)
11	57.6 (57.1–58.1)	91.8 (91.7–91.9)	0.495 (0.488–0.501)
12	63.7 (63.2–64.1)	89.7 (89.6–89.8)	0.534 (0.528–0.540)
13	69.3 (68.8–69.7)	87.1 (87.0–87.3)	0.564 (0.559–0.570)
14	74.4 (74.0–74.8)	84.0 (83.9–84.2)	0.584 (0.579–0.590)
15	**78.9 (78.6–79.3)**	**80.3 (80.1–80.5)**	**0.593 (0.587–0.598)**
16	82.9 (82.5–83.2)	76.0 (75.8–76.2)	0.589 (0.583–0.594)
17	86.2 (85.9–86.4)	71.1 (70.8–71.3)	0.572 (0.567–0.578)
18	88.9 (88.7–89.1)	65.6 (65.3–65.9)	0.545 (0.540–0.550)
19	91.2 (91.0–91.4)	59.7 (59.4–60.0)	0.509 (0.504–0.513)
20	93.0 (92.9–93.2)	53.4 (53.1–53.8)	0.465 (0.460–0.469)

psychiatric disorders (Leucht et al., 2005, 2006, 2017, 2019), it is important to note that it is a global judgment of change by a single rater. There are other approaches to determine response and remission that could have been used. For response, the reliable change index (RCI) (Jacobson and Truax, 1991) has been previously described, and there is evidence indicating that the RCI may correlate with the Y-BOCS threshold suggested by the expert consensus (Kathmann et al., 2022). Nevertheless, the RCI simply indicates that the change is unlikely to be attributable to measurement error alone, and, therefore, may not translate to clinically meaningful outcomes directly. For remission, evaluation of long-term stability could be relevant (Elsner et al., 2020), but most RCTs were conducted in the short-term. Fourth, despite our best efforts to include studies, we cannot rule out having missed out relevant literature. Finally, it is important to note that our meta-analysis was restricted to RCTs. While this restricted eligibility ensures that only the most rigorously conducted studies are included (Cuijpers et al., 2017), the selection criteria of RCTs may limit ecological validity.

In conclusion, our study used meta-analysis of RCTs in adults with OCD to investigate the optimal cut point on the Y-BOCS to determine response and remission as defined by the CGI. Our findings indicated that a 30% reduction and a 15-point score would be optimal to determine response and remission, respectively, which is not in agreement

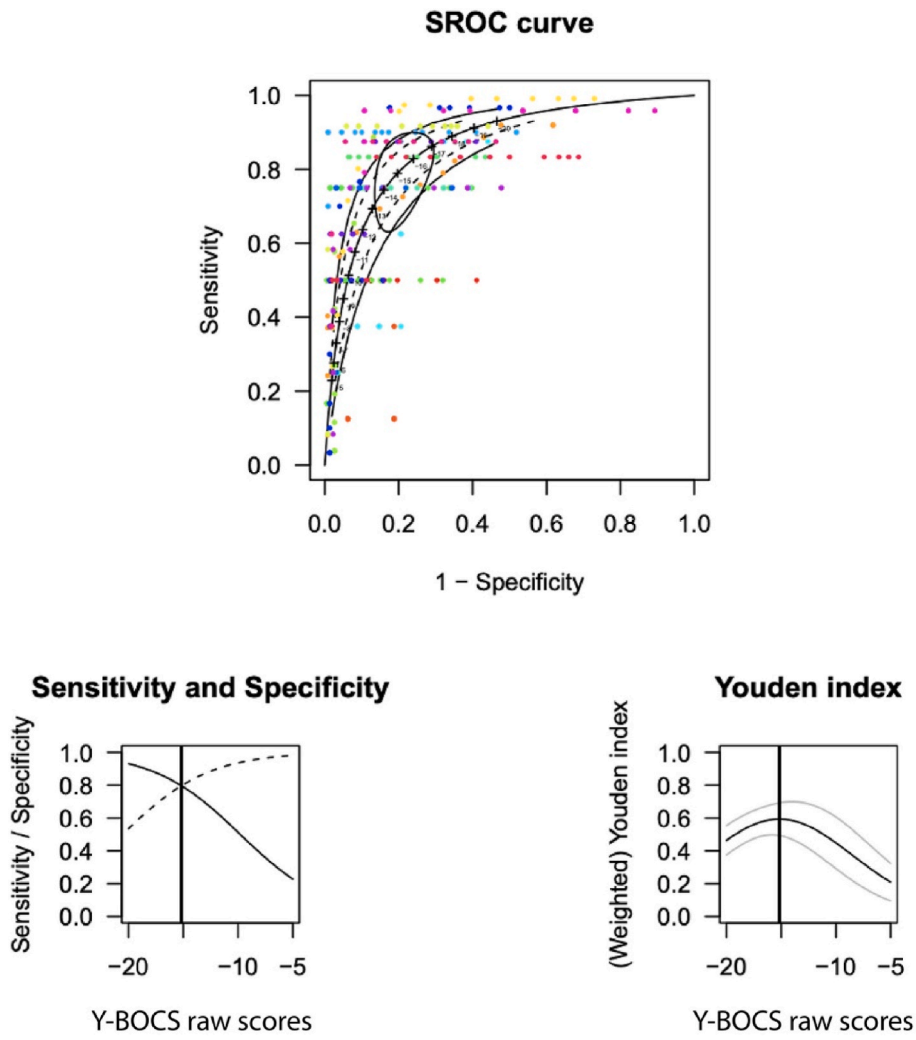

Fig. 3. Receiver Operating Characteristic (ROC) Analysis for Yale-Brown Obsessive-Compulsive Scale Posttreatment Raw Score and Posttreatment Remission as Defined by a Clinical Global Impressions – Severity Scale Score of ≤2. The top panel shows the summary receiver operating characteristic (SROC) curve for overall discriminative performance of the posttreatment raw Y-BOCS score in determining CGI-S defined treatment remission with individual points color coded by study. Confidence intervals for pooled sensitivity (solid line) and specificity (dashed line) are shown. A threshold of 15 on the Y-BOCS scale had the optimal Youden index. However, the confidence ellipse around the 15-point cutoff includes both 14 and 16, highlighting the uncertainty in the data. The lower left panel shows tradeoffs in sensitivity (solid line) and specificity (dashed line) at each Y-BOCS raw score. A threshold of 15 had the optimal balance between sensitivity and specificity as shown by the intersection of the solid and dashed lines. The lower right panel shows the Youden indices (black line) with 95% confidence interval (gray lines) for different Y-BOCS raw score thresholds. The optimal Youden index occurred at a posttreatment raw score of 15.

with the consensus thresholds on the Y-BOCS scale. However, differences in sensitivity/specificity across cut points were small and our findings were limited by small availability (27%) of RCTs, most of which recruited participants with treatment-resistant/previous failed trials with first-line treatments. In summary, while the empirically derived Y-BOCS thresholds in our meta-analysis differ from expert consensus (Mataix-Cols et al., 2016), given the predominance of data from more recent trials of OCD, which involved more refractory participants and novel treatment modalities as opposed to first-line therapies, we recommend the continued use of the consensus definitions.

CRediT authorship contribution statement

Divya Ramakrishnan: Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Luis C. Farhat:** Writing – review & editing, Visualization, Validation, Supervision, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Edoardo F. Q. Vattimo:** Writing – review & editing, Data curation. **Jessica L.S. Levine:** Writing – review & editing, Data curation. **Jessica A. Johnson:** Writing – review & editing, Data curation. **Bekir B. Artukoglu:** Writing – review & editing, Data curation. **Angeli Landeros-Weisenberger:** Writing – review & editing, Data curation. **Abraham Zangen:** Writing – review & editing, Data curation. **Antoine Pelissolo:** Writing – review & editing, Data curation. **Carlos A. de B. Pereira:** Writing – review & editing, Data curation. **Christian Rück:** Writing – review & editing, Data curation. **Daniel L.C. Costa:** Writing – review & editing, Data curation. **David Mataix-Cols:** Writing – review & editing, Data curation. **David Shannahoff-Khalsa:** Writing – review & editing, Data curation. **David F. Tolin:** Writing – review & editing, Data curation. **Elham Zarean:** Writing – review & editing, Data curation. **Elisabeth Meyer:** Writing – review & editing, Data curation. **Emily R. Hawken:** Writing – review & editing, Data curation. **Eric A. Storch:** Writing – review & editing, Data curation. **Erik Andersson:** Writing – review & editing, Data curation. **Euripedes C. Miguel:** Writing – review & editing, Data curation. **Giuseppe Maina:** Writing – review & editing, Data curation. **James F. Leckman:** Writing – review & editing, Data curation. **Jerome Sarris:** Writing – review & editing, Data curation. **John S. March:**

Writing – review & editing, Data curation. **Juliana B. Diniz:** Writing – review & editing, Data curation. **Kenneth Kobak:** Writing – review & editing, Data curation. **Luc Mallet:** Writing – review & editing, Data curation. **Nienke C.C. Vulink:** Writing – review & editing, Data curation. **Revital Amiaz:** Writing – review & editing, Data curation. **Rodrigo Yacubian Fernandes:** Writing – review & editing, Data curation. **Roseli G. Shavitt:** Writing – review & editing, Data curation. **Sabine Wilhelm:** Writing – review & editing, Data curation. **Shahrokh Golshan:** Writing – review & editing, Data curation. **Sophie Tezenas du Montcel:** Writing – review & editing, Data curation. **Stefano Erzegovesi:** Writing – review & editing, Data curation. **Upasana Baruah:** Writing – review & editing, Data curation. **William M. Greenberg:** Writing – review & editing, Data curation. **Yuki Kobayashi:** Writing – review & editing, Data curation. **Michael H. Bloch:** Writing – review & editing, Validation, Supervision, Resources, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization.

Declaration of competing interest

Abraham Zangen is an inventor of Deep TMS coils developed to study and treat neurological and psychiatric disorders and has financial interest in BrainsWay which produces and markets these coils.

Daniel L.C. Costa received honoraria from Janssen, Lundbeck and Schwabe pharmaceuticals.

David Mataix-Cols receives royalties for contributing articles to UpToDate, Inc.

David Shannahoff-Khalsa reports royalties from two books published by W.W. Norton & Co, Inc. that includes the Kundalini Yoga meditation protocol, personal sales for a DVD for the protocol, and OCD patient fees.

Eric A. Storch receives research funding for his institution from the Ream Foundation, International OCD Foundation, and NIH. He is a consultant for Brainsway and Biohaven Pharmaceuticals. He owns stock less than $5000 in NView (for distribution of the Y-BOCS and CY-BOCS) and Limbix. He receives book royalties from Elsevier, Wiley, Oxford, American Psychological Association, Guildford, Springer, Routledge, and Jessica Kingsley.

Juliana B. Diniz has received speaker's fees from Lundbeck and Janssen Cilag for lectures.

Michael H. Bloch has received grant/research support from Therapix Biosciences, Emalex Biosciences, Janssen Pharmaceuticals, Biohaven Pharmaceuticals, NIH, Lesbian Health Fund, Yale Foundation for Lesbian and Gay Studies (FLAGS), and Patterson Foundation, has served on the advisory board/data monitoring and safety board of Therapix Biosciences, and serves as associate editor of Journal of Child Psychology and Psychiatry and on the editorial boards of Journal of Child and Adolescent Psychopharmacology and Depression & Anxiety. He has received royalties from Wolters Kluwer for Lewis's Child and Adolescent Psychiatry: A Comprehensive Textbook, Fifth Edition and moonlighting pay from the VA.

Roseli G. Shavitt has received consultancy honoraria from Lundbeck and research grants from Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) in the past three years.

Sabine Wilhelm is a presenter for the Massachusetts General Hospital Psychiatry Academy in educational programs supported through independent medical education grants from pharmaceutical companies. She has received royalties from Elsevier Publications, Guilford Publications, New Harbinger Publications, Springer, and Oxford University Press, speaking honoraria from various academic institutions and foundations, including the International Obsessive Compulsive Disorder Foundation, the Tourette Association of America, and the Centers for Disease Control and Prevention, and payment from the Association for Behavioral and Cognitive Therapies for her role as Associate Editor of the Behavior Therapy journal and John Wiley & Sons, Inc. as Associate Editor of the journal Depression & Anxiety. She has also received honoraria for her role on the Scientific Advisory Board for One-Mind (PsyberGuide), Koa Health, Inc, and Noom, Inc. She has received research and salary support from Koa Health, Inc.

None of the remaining co-authors have any conflicts of interest to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2024.03.044.

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