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Personalizing the Treatment of Pediatric Obsessive-Compulsive Disorder: Evidence for Predictors and Moderators of Treatment Outcomes

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Abstract Cognitive behavioral therapy (CBT), delivered alone or with a serotonin reuptake inhibitor (SRI), is efficacious for treating pediatric obsessive-compulsive disorder (OCD), but not all youth respond optimally. Research to understand for whom a given intervention is beneficial can inform efforts to personalize treatment or tailor it to specific youths to enhance outcomes. We review studies that examined potential predictors/moderators of response to CBT, medication, and multimodal treatment for pediatric OCD: demographics, disorder-specific characteristics, general illness characteristics, neuropsychological functioning, biomarkers, family factors, and non-specific therapy factors. Methodological differences across studies make it challenging to synthesize findings and more research with large samples is needed. However, family factors have emerged as relatively consistent and strong predictors of treatment outcomes and there is preliminary support for attention to the presence of tics in treatment selection. There is little evidence for age and other demographic differences in treatment response.

Keywords Obsessive-compulsive disorder · Treatment · Predictors · Moderators · Children

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Introduction

Approximately 1 % of children and adolescents are affected by obsessive-compulsive disorder (OCD) [1], which is chronic if left untreated [2] and associated with impairment across multiple domains of functioning [3]. Cognitive - behavioral therapy (CBT) with exposure and response prevention (E/RP), delivered alone or with a serotonin reuptake inhibitor (SRI), is the first-line intervention for youth with OCD [4, 5]. However, as many as 35 % of youth do not exhibit sufficient improvement with CBT or multimodal treatment, and many treatment responders have residual symptoms [5]. Thus, increased attention has been paid to identifying predictors and moderators of treatment response to inform ways to tailor, augment, and/or intensify interventions to optimize outcomes for individual patients.

A *predictor* is a variable that has a main effect on outcome; that is, its impact is not specific to a treatment condition. Predictors are often pretreatment characteristics, such as sociodemographic characteristics, clinical characteristics of the disorder, and biological markers (e.g., identified through neuroimaging) that provide prognostic information, indicating which individuals are likely to benefit from any of the treatments studied. The impact of a *moderator* on treatment outcome depends on which treatment condition is considered. Thus, moderators provide prescriptive information, answering the question of which patients in which treatment condition

are likely to benefit [6]. Moderators can inform inclusion and exclusion criteria for stratification in future randomized clinical trials (RCTs) to maximize statistical power. In clinical practice, moderators can facilitate matching individual patients to suitable treatments [6]. Efforts to identify predictors and moderators of treatment outcomes fall under the umbrella of *personalized medicine*, or the differential prediction of outcome as a function of treatment that is provided to the patient. Such attention to individual differences may enhance the value of treatment research for understanding psychopathology in addition to optimizing the outcomes of interventions and their uptake in clinical practice [7].

The current report is a review, synthesis, and critique of the available research on predictors and moderators of response to treatments for pediatric OCD. The review is organized by candidate variable classes: demographics, disorder-specific characteristics, general illness characteristics, neuropsychological functioning, biomarkers, family factors, and non-specific therapy factors. Relevant studies are further divided based on whether they sampled youth receiving CBT alone, medication alone, or combined CBT and medication (e.g., as part of an RCT of multimodal treatment or a naturalistic study of services provided in a clinic setting).

Demographics

Given that OCD has a bimodal age of onset by gender, with greater representation of males among individuals with early onset [8, 9], the impact of age and gender on treatment outcomes has been examined in many clinical trials. Additionally, it has been speculated that relative to children, adolescents may be less responsive to exposure-based treatment due to blunted regulation of fear extinction associated with lack of synaptic plasticity in prefrontal regions [10–12]. Few studies have investigated the impact of demographic variables other than age and gender.

Gender

CBT In a study of intensive family-based CBT ($N=78$ [13]), gender did not predict status as a treatment responder (=88.5 %) but uniquely predicted post-treatment OCD severity and remission status, with males showing greater improvement than females. Other studies that examined gender as a predictor of CBT response found no significant association [14–16, 17•].

Medication Although males showed a greater response to clomipramine than did females in an early pilot study [18], gender was not a significant predictor of outcomes in controlled medication-only trials of clomipramine [19], sertraline [20], or paroxetine [21] nor have uncontrolled trials shown an effect of gender on response to citalopram [22, 23], paroxetine [24], or fluvoxamine [25]. In a naturalistic follow-up of pharmacotherapy (SRI monotherapy for 50 % of the sample), gender was not related to outcomes [26].

CBT and Medication Gender did not significantly predict or moderate outcomes of the Pediatric OCD Treatment Study (POTS; $N=112$), which examined the relative efficacy of CBT with E/RP, sertraline, and their combination against pill placebo [5, 27]. A naturalistic study of youth receiving outpatient treatment ($N=82$) also found no significant gender effect [28].

Summary A relatively large number of studies have shown that gender does not predict outcomes of CBT, medication, or their combination.

Age

CBT Studies of CBT for pediatric OCD have generally not found significant effects of age on treatment outcomes [15, 16, 29, 30]. An exception is the NordLOTS study ($N=269$ [17•]), which evaluated the effectiveness of 14 weeks of family-based CBT delivered in community outpatient clinics as the initial treatment in a stepped care model; preadolescent children benefited more from CBT than adolescents. The discrepancy with prior research was attributed to greater parental participation in the NordLOTS manual relative to previously studied treatment protocols.

Medication Post hoc analyses of the benefits of fluvoxamine revealed a higher response rate among children (8–12 years) versus adolescents (13–17 years) ($N=120$ [31]). Although age has been examined as a predictor of outcomes in medication-only trials of clomipramine [18], citalopram [22, 23], sertraline [20, 32], paroxetine [21, 24], and fluoxetine [33], results were non-significant. The first of two naturalistic follow-up studies found no effect of age [26]. However, Masi and colleagues ($N=257$ [34]) reported preliminary results, suggesting that among youth treated with SRI monotherapy or polypharmacy, responders were younger at the time of first medication consultation than non-responders.

CBT and Medication Age did not significantly predict or moderate outcomes in POTS [27], nor did it discriminate treatment responders from non-responders to medication (with or without CBT) in a sample of 60 outpatients [35]. In another outpatient sample of youth ($N=82$), the majority of whom received combined behavior therapy and medication, age was not related to treatment response [28].

Summary With the exception of one CBT study [17•] and one medication trial [31], in which children benefited more from

treatment than adolescents, studies have not supported age effects on treatment outcomes.

Other Demographics

CBT Socioeconomic status (SES) was not associated with CBT response in NordLOTS [17•]. In a study of intensive family-based CBT ($N=78$ [13]), post-treatment symptom severity scores did not differ by race/ethnicity. No medication-only studies have examined the impact of SES or race/ethnicity on treatment outcomes.

CBT and Medication In POTS [5], household income did not significantly predict or moderate treatment outcomes [27]. Neither SES nor living situation discriminated treatment responders from non-responders to medication (with or without CBT) in an outpatient sample of 60 youth [35].

Summary SES and race/ethnicity have not predicted or moderated treatment outcomes, although research with diverse samples is lacking.

Disorder-Specific Characteristics

OCD Severity

CBT Findings of CBT studies are mixed with regard to the impact of pretreatment OCD severity on outcomes. In the largest study of CBT monotherapy ($N=257$ youth), higher levels of OCD symptom severity and functional impairment at baseline were each associated with poorer response [17•]. In a recent study of intensive family-based CBT ($N=78$), greater pretreatment symptom severity but not impairment predicted greater post-treatment symptom severity; neither symptom severity nor impairment predicted responder status (which was positive for 88.5 % of the sample) or remission [13]. An open trial of CBT ($N=42$) found that pretreatment obsession severity and OCD-related impairment in school functioning only were associated with poorer outcome [16]. An early study found no effect of baseline OCD severity, although the sample was small ($N=15$ [30]). In three studies of CBT, duration of illness did not predict outcomes [16, 17•, 30].

Medication Duration of illness has not significantly predicted medication response [18, 19, 23, 24, 26, 32, 36]. In the majority of medication-only studies, baseline OCD severity did not predict outcomes [18–22, 30, 36]. An exception is a study conducted with youth ($N=132$) who participated in a 52-week sertraline continuation trial; baseline scores on the Children's Yale-Brown Obsessive-Compulsive Scale (CY-BOCS) [37] predicted full remission status, defined as a CY-BOCS score ≤ 8 [32]. Additionally, a naturalistic follow-up of youth ($N=257$) treated with SRIs found that symptom severity and functional impairment at baseline distinguished responders from non-responders; however, this study relied on single ratings, excluded youth who had responded to psychosocial treatment, and did not adjust the alpha level for multiple comparisons [34].

Two studies assessing the efficacy of SRI augmentation strategies found that non-responders showed greater functional impairment at baseline [38, 39]. In one of the studies, which assessed augmentation with risperidone or aripiprazole in youths with tic-related OCD who had not responded to selective serotonin reuptake inhibitor (SSRI) monotherapy ($N=120$), non-responders also had greater baseline OCD symptom severity than responders [39]. The other study, which evaluated aripiprazole augmentation in adolescents ($N=39$), found no differences in responder status by baseline clinical severity or insight [38]. A limitation of medication-only studies is that they have generally relied on single ratings of symptom severity and impairment.

CBT and Medication Across treatment conditions in POTS ($N=112$), youth with lower OCD symptom severity and less parent- but not child-rated OCD-related functional impairment showed greater improvement [27]. In a sample of 60 outpatients, non-responders endorsed more obsessions and compulsions as well as greater functional impairment at baseline than responders to medication (with or without CBT [35]). In a naturalistic study of the course of illness over three years, OCD symptom severity predicted time to remission (defined as no longer meeting OCD criteria for at least 8 weeks), but multivariate analyses showed that general psychosocial functioning was a better predictor of remitting course [40]. In this study, shorter latency to initial OCD treatment was also associated with faster onset of remission. Duration of illness did not predict outcomes of outpatient treatment (with behavior therapy and/or medication) in an early, naturalistic study [28].

In POTS ($N=112$), insight (the absence of which has been considered an indicator of OCD severity [41]) significantly predicted better treatment outcomes (across CBT, sertraline, their combination, and pill placebo [27]). In another study of 60 outpatients, responders to medication (with or without CBT) showed greater insight than non-responders [35].

Summary Findings regarding the impact of baseline severity and impairment on treatment outcomes are mixed; however, both emerged as significant predictors across CBT, sertraline, combination, and pill placebo conditions in a relatively large trial funded by the National Institute of Mental Health (NIMH) (POTS [27]). Duration of illness has not predicted treatment outcomes, while insight has been associated with greater symptom improvement in a couple of studies [27, 35].

Age of Onset

In a naturalistic retrospective follow-up of youth with OCD ($N=257$) who were treated with SRIs, responders and non-responders did not differ by age of onset [34]. This finding was held when analyses were repeated for youth whose SRIs were augmented with atypical antipsychotics. An analysis of records from a specialized OCD clinic ($N=109$) showed no differences in response to treatment (CBT or CBT with medication) between youth with very early onset (before 10 years old) and late onset (at least 10 years old) OCD [42]. In a naturalistic study of the course of illness in 50 treatment-seeking youth over three years, age of onset, early childhood onset (before 10 years old), and age at which the child first experienced minor symptoms did not distinguish youth with a chronic versus remitting course [40].

Summary Age of OCD onset has not predicted treatment outcomes; studies have generally relied on retrospective report or record review [34, 40, 42].

Symptom Type

CBT Among youth ($N=92$) who received 14 sessions of weekly or intensive family-based CBT, treatment response did not differ substantially by OCD subtype (based on symptom dimensions identified through factor analysis of the CY-BOCS [43]), although patients with checking rituals and harm obsessions showed greater treatment-related change according to one of three indicators [44]. This study was underpowered to detect an effect of hoarding on treatment outcomes.

Medication Symptom type did not significantly predict outcomes of clomipramine in early pilot studies [18, 19], nor has it discriminated responders and non-responders in studies of SRI augmentation with aripiprazole or risperidone [38, 39]. In a sample of 81 youth treated with SRIs and classified according to predominant obsessive-compulsive symptom type, hoarding was associated with relatively poor response and contamination symptoms were associated with relatively good response [26]. Also, a naturalistic follow-up of youth ($N=257$) treated with SRI monotherapy or polypharmacy showed that responders more frequently presented with contamination symptoms and less frequently presented with hoarding than non-responders, although the alpha level in this study was not adjusted for multiple tests [34].

CBT and Medication In a sample of 60 outpatients, there were no differences between treatment non-responders and responders to medication (with or without CBT) in subtypes of obsessions or compulsions except for repeating compulsions, which were more likely to be endorsed by the treatment-resistant group [35]. Findings are preliminary in that the impact of treatment type could not be evaluated and the alpha level was not adjusted for multiple tests. Finally, Mancebo et al. [40] examined the course of illness in 60 treatment-seeking youth over three years and found no differences by OCD symptom type, although no participants in this sample presented with primary hoarding.

Summary Relatively few studies have examined differences in treatment response by OCD symptom type, although some preliminary data suggest better treatment outcomes among youth with contamination symptoms and worse outcomes among youth with repeating or hoarding symptoms [34, 44]. It is possible that symptom types with greater genetic contribution are relatively treatment-resistant [45]. The distinction between "just right" and fear-based symptoms should be considered.

General Illness Characteristics

Comorbidity

CBT Greater parent- but not youth-reported anxiety symptoms have predicted poorer treatment outcomes [16, 17•]. A small open trial showed no effect of clinician-rated anxiety symptoms on treatment outcomes [14]. Only one study directly examined the impact of co-occurring anxiety at the disorder level; generalized anxiety disorder (GAD) was not related to treatment outcomes [46]. However, a meta-analysis showed that non-active comparison trials with greater incidence of co-occurring anxiety disorders among youth sampled were associated with greater CBT effects [47•]. Parent- but not youth-reported depressive symptoms have predicted worse treatment outcomes [17•, 48]. Among youth ($N=96$) who received weekly or intensive CBT, major depressive disorder was related to lower OCD remission rates [46]. Greater parent-reported internalizing symptoms (per the Child Behavior Checklist (CBCL) [49]) but not disorders predicted poorer treatment outcomes in NordLOTS ($N=257$ [17•]). Parent-reported internalizing symptoms did not predict outcomes of intensive family-based CBT ($N=78$ [13]).

Greater parent-reported externalizing symptoms but not disorders predicted poorer outcomes of weekly CBT in NordLOTS [17•]. Parent-reported externalizing symptoms did not predict outcomes of intensive family-based CBT [13], although another study of youth ($N=96$) who received intensive or weekly CBT found lower response and remission rates among youth with comorbid disruptive behavior disorders and lower response rates among youth with comorbid attention-deficit/hyperactivity disorder (ADHD) [46]. In a pilot study of group CBT ($N=43$), youth with ADHD were less likely to be classified as responders and remitters at 6-month follow-up [48].

Two studies with modest sample sizes have evaluated the impact of a comorbid pervasive developmental disorder (PDD) or autism spectrum disorder (ASD). A case–control study suggested an attenuated response to individual CBT among youth with ASD ($N=22$ [50]). Outcomes of a pilot study of group CBT ($N=43$) did not differ by the presence of PDD [48].

Medication Anxiety disorders were not associated with treatment outcomes in a small open-label trial of paroxetine [24]. In a naturalistic study of youth ($N=81$) treated with SRIs (50 % monotherapy), responders presented with GAD and panic disorder more often than non-responders [34]. Medication studies have not found an effect of pretreatment depression, rated by clinicians using a single item [18] or a depression rating scale [20], on treatment outcomes. However, two naturalistic studies identified higher rates of bipolar disorder among non-responders than responders [26, 34]. Both studies also found that relative to treatment responders, non-responders had higher rates of oppositional defiant disorder and conduct disorder, while findings regarding ADHD were mixed [26, 34].

CBT and Medication Anxiety symptoms did not predict or moderate treatment outcomes in POTS [27]. A naturalistic study examined specific symptom-type outcomes of group CBT with youth, a subset of whom were taking medication, and found that having a comorbid anxiety disorder was associated with relatively slow reduction in harm obsessions but lower levels of sexual obsessions at post-treatment [15].

In a sample of 100 youth who received CBT, with or without medication, depressive symptoms and suspected depressive disorders were associated with worse OCD severity at post-treatment but not when controlling for pretreatment OCD severity; it appeared that depression severity decreased over the course of CBT and was not independently associated with worse outcomes [51]. Using multilevel modeling to examine weekly changes in OCD among youth randomized to CBT with either sertraline on a regular titration schedule, sertraline with slow titration, or pill placebo, Meyer and colleagues [52] found that higher average OCD severity was associated with greater depressive symptoms across conditions but that these symptoms decreased in line with reductions in OCD symptom severity regardless of initial depressive symptom severity. Among adolescents who received multimodal residential treatment ($N=126$), depression severity at admission was related to baseline OCD severity but not to treatment outcome or duration; controlling for baseline OCD severity, greater change in depressive symptoms predicted OCD severity at discharge [53]. Storch and colleagues [35] reported higher levels of self-reported depressive symptoms among treatment responders than non-responders to medication (with or without CBT) in a sample of 60 outpatients and speculated that youth receiving medication may have experienced improved insight, thereby increasing distress regarding their OCD. A growth curve modeling analysis of symptom change in group CBT, with or without medication, suggested that depressive symptoms were associated with relatively fast reductions in intrusive thoughts of harm; in this study, E/RP was associated with reductions in depressive symptoms but not anxiety [15].

In POTS, the presence of an internalizing disorder did not predict or moderate treatment outcomes [27]. However, a naturalistic study that followed treatment-seeking youth with OCD ($N=60$) over three years found that having a comorbid internalizing disorder distinguished youth with a chronic (vs. remitting) course [40]. Two studies examined the impact of internalizing symptoms on treatment response, with mixed results [28, 35].

Greater externalizing symptoms but not the presence of an externalizing disorder predicted poorer outcomes (across treatments) in POTS [27]. The presence of an externalizing or impulse control disorder did not distinguish treatment-seeking youth with a chronic versus remitting course of OCD over three years [40]. In an outpatient sample of youth ($N=82$), the majority of whom received multimodal treatment, CBCL aggression predicted poorer outcomes while CBCL delinquent behavior predicted better outcomes; the reason for these apparently discrepant findings is unclear [28]. Temper outbursts did not influence treatment response in a sample of 109 youth treated with CBT, with or without medication [54]. The CBCL dysregulation profile (which reflects impairments in self-regulation across affective, cognitive, and behavioral domains) predicted treatment discontinuation but not outcomes of CBT in a sample of 97 youth, many of whom also took SRI medication [55].

Summary Comorbidities have received much attention as candidate predictors/moderators of treatment response, with studies yielding inconsistent results. In a couple of studies [34, 47•], the presence of a comorbid disorder (i.e., anxiety) was even associated with better treatment response; potential mediators of this relationship (e.g., therapy/homework compliance and OCD symptom type) have not been examined. No comorbidity studies have distinguished symptoms/disorders that are secondary to OCD (e.g., oppositional behavior that is functional for securing the accommodation of OCD symptoms or escaping/avoiding their triggers) from those that could stand alone (e.g., oppositional behavior in the form of vindictiveness). Comorbid problems that are secondary to OCD-related impairment (e.g., depressed mood because OCD symptoms interfere with academic performance) may resolve when OCD is targeted, as suggested by treatment studies examining symptom trajectories [52].

Presence of Tics

Geller and colleagues [8, 9] proposed that the presence of a tic disorder is a defining characteristic of early-onset OCD in

youth. They attributed the co-occurrence of tics and OCD to shared etiology involving dysfunction of the dopamine system and basal ganglia-thalamocortical circuits.

CBT Individual studies of CBT have generally not supported the presence of a tic disorder as a predictor of attenuated treatment response [16, 17•, 46, 56]. A recent meta-analysis showed that active comparison trials of CBT in which a greater percentage of youth had Tourette's syndrome/chronic tic disorders exhibited *larger* effect sizes [47•].

Medication Lifetime history of a tic disorder predicted poor outcome of clomipramine (compared to desipramine in a crossover trial) at 2- to 7-year follow-up ($N=48$ [19]). Also, tic-related OCD has been associated with a lower rate of response to paroxetine [57]. In a placebo-controlled sertraline trial ($N=187$ [20]), the presence of a comorbid tic disorder did not predict response but rates of tic disorders were very low (5 % in sertraline and 3 % in placebo). In a small study of aripiprazole augmentation of SRI treatment in adolescents ($N=39$), there were no differences in responder status by the presence of a tic disorder [38]. In a study of SSRI augmentation with risperidone or aripiprazole in youths with tic-related OCD who were non-responders to SSRI monotherapy ($N=120$), pretreatment scores on a tic severity measure did not differ between responders and non-responders [39]. A meta-analysis showed that the rate of Tourette syndrome/chronic tic disorder among youth sampled in SRI trials (collapsing those with active and non-active comparisons) did not significantly moderate treatment efficacy, response, or remission [47•].

In a naturalistic study of youth ($N=81$) treated with SRIs (50 % monotherapy), the presence of a tic disorder was more common among non-responders [26]. A larger naturalistic retrospective follow-up of youth ($N=257$) treated with SRIs found that the presence of a tic disorder did not differ significantly by responder status; this was also true for the subsample that received augmentation with atypical antipsychotics [34].

CBT and Medication In POTS ($N=112$), 15 % of the sample had a comorbid tic disorder and sertraline was superior to pill placebo only in patients without tics [58]. Tic disorders did not adversely impact outcomes of CBT or combined CBT and sertraline. POTS II evaluated medication management alone, medication management with CBT, and medication management with CBT instructions (from the pharmacotherapist) among SRI partial responders ($N=124$ [59]); 53 % of the sample had tic-related OCD, which was not associated with differential treatment response (across conditions) or premature termination [60•]. In NordLOTS, youth identified as non-responders to a 14-week course of open-label CBT were randomized to continued CBT ($N=28$) or sertraline ($N=22$) for an additional 16 weeks; in patients with a comorbid tic disorder, average CY-BOCS scores were significantly lower among youth who received sertraline than among those who continued CBT [61]. In a naturalistic study conducted over three years ($N=60$ treatment-seeking youth), the presence of a tic disorder did not distinguish youth with a chronic versus remitting course [40].

Summary There appears to be converging evidence that CBT is preferable to medication for youth with comorbid tics [19, 26, 27, 47•], although more research is needed before making specific practice recommendations. Neurobiological differences by tic status might account for differential treatment response, as youth with non-tic-related OCD have shown larger error-related negativity than youth with tic-related OCD [62].

Sleep

Among youth who received CBT as the first-line intervention in NordLOTS stepped care, elevated sleep problems, measured using sleep items from the CBCL [49], as well as the presence of any sleep problem at baseline were associated with poorer outcomes based on the CY-BOCS [63]. As in a prior study [64], there were treatment-related decreases in most sleep problems. No medication studies have investigated the impact of sleep on treatment response.

Summary Limited data on sleep problems among youth with OCD suggest that they predict response to CBT. In addition to affecting anxiety/emotion regulation [65], sleep disturbances might affect motivation for treatment (e.g., due to altered reward-related brain function [66]).

Neuropsychological Functioning

Medication Neuropsychological and neurolinguistic functioning did not predict response to clomipramine in a small pediatric OCD sample ($N=19$ [18]). Among youth treated with clomipramine and desipramine in a double-blind crossover trial ($N=48$), fewer errors on one of two tests of spatial ability weakly but significantly predicted better response to clomipramine [19].

CBT and Medication A subset of participants in POTS ([5]; $N=63$) completed the Rey-Osterrieth Complex Figure (ROCF) test [67] and specific IQ subtests. Covarying ADHD symptoms, treatment responders performed significantly better than non-responders on 5-min recall accuracy (raw score) and percent recall from the ROCF [68]. In a sample of 56 youth, 7–17 years old, subscales of the Behavior Rating Inventory of Executive Function (BRIEF) [69] were tested as predictors of outcomes in an RCT of weekly CBT with one of the following three drug arms: sertraline with regular titration, sertraline with slow titration, and pill placebo

[70]. Multilevel modeling revealed that deficits in BRIEF Emotional Control but not Inhibition and Planning/Organizing predicted a relatively shallow trajectory of obsessive-compulsive symptom reduction, as measured by the CY-BOCS at baseline, weeks 1–9, 13, and 17 (or upon treatment completion).

Summary A small number of studies [18, 19, 68, 70] have examined neuropsychological predictors of treatment outcomes; they have been limited by small samples and/or have collapsed across treatment conditions. Deficits in recall [68], spatial ability [19], and emotional control [70] might interfere with positive treatment response.

Biomarkers

Neuroimaging

In line with the glutamatergic hypothesis of pediatric OCD [71], results of a pilot study using proton magnetic resonance spectroscopic imaging ($N=5$ pediatric OCD patients and $N=9$ controls) indicate that multiple metabolites in the cingulo-striato-thalamic brain structures may predict or change with clinical response to CBT [72•].

Summary Research on neuroimaging predictors of treatment response is in its infancy but findings implicating glutamate are promising [72•].

Psychophysiological Factors

In a small sample of youth treated with clomipramine ($N=19$), plasma levels were not consistently associated with change in OCD symptoms nor were brain ratios, electroencephalogram parameters, or results of a dexamethasone suppression test [18]. Also, a larger RCT ($N=187$) showed no relationship between response to 12 weeks of sertraline and plasma levels of sertraline and its primary active metabolite, desmethylsertraline [20]. Among youth treated with clomipramine over 5 weeks ($N=48$), skin conductance response but not spontaneous electrodermal fluctuations or heart rate predicted treatment response [19].

Summary With the exception of skin conductance response [19], medication studies [18–20] have not identified psychophysiological predictors of treatment response and they have not been studied in the context of CBT or multimodal treatment.

Family Factors

Family Accommodation

CBT In an open trial of family-based CBT ($N=50$), decreases in parent-rated family accommodation of OCD symptoms (e.g., participation in rituals [73]) during treatment predicted outcome, even when controlling for pretreatment OCD severity/impairment [74]. In a controlled comparison of family CBT and psychoeducation/relaxation training ($N=71$), reduction in family accommodation temporally preceded improvement in CY-BOCS scores for both groups and child-rated functional impairment for the family CBT group only [75]. Also, in a study of intensive family-based CBT ($N=78$ [13]), family accommodation significantly predicted post-treatment symptom severity and remission status (but not responder status, which was positive for 88.5 % of the sample). In NordLOTS ($N=269$), family accommodation predicted post-treatment CY-BOCS scores but not after accounting for the influence of demographic, illness severity, and comorbidity variables; the treatment had a high level of parental involvement and may have effectively addressed accommodation [17•].

CBT and Medication No medication-only trials have examined the impact of family accommodation on treatment outcomes. However, lower levels of parent-reported family accommodation predicted greater improvement across conditions (CBT, sertraline, their combination, and pill placebo) in POTS ($N=112$ [27]). In a sample of 60 outpatients who received medication (with or without CBT), greater baseline levels of parental stress related to family accommodation were reported among non-responders than responders [35].

Summary CBT and multimodal treatment studies [27, 35, 74, 75] have provided compelling evidence that family accommodation is associated with relatively poor treatment outcomes. It has not been studied in medication-only trials. Family accommodation might interfere with exposure that would otherwise occur between treatment sessions, limiting symptom reduction.

Expressed Emotion

High maternal expressed emotion (i.e., attitudes of high criticism, hostility, and/or emotional over-involvement [76]) at baseline significantly predicted poor treatment outcome in youth ($N=58$) who participated in a larger RCT testing the efficacy of family-focused CBT for pediatric OCD [77]. Among a subset of POTS participants ($N=62$), rates of high maternal expressed emotion and high child expressed emotion were relatively low and associations with treatment outcome were not consistent across informants or measures [78].

Summary Only a couple of studies [77, 78] have examined expressed emotion in relation to treatment outcomes. High maternal expressed emotion, rates of which differed across the samples, emerged as a significant predictor of poor outcome in the CBT [77] but not the multimodal treatment study [78]. The extent to which discrepant findings can be attributed to age differences in the relevance of the construct is unclear [79].

Psychopathology in Family

CBT In an early pilot study ($N=15$), parent's psychological maladjustment was not related to long-term treatment outcome [30]. In NordLOTS ($N=269$), neither family history of OCD (defined as current or past diagnosis of OCD in first- or second-degree family members) nor parental psychopathology (i.e., at least one parent diagnosed with any psychiatric disorder, by parent report) at baseline predicted CY-BOCS scores following 14 sessions of CBT [17•].

Medication Among youth treated with clomipramine ($N=54$), having a parent with a DSM-III-R axis I disorder [80] was associated with relatively poor long-term outcome [36]. In a 10-week crossover trial of clomipramine ($N=48$), family history of OCD was not related to treatment response [19]. Having a parent with OCD appeared to benefit youth in a small, open trial of fluvoxamine ($N=11$ [25]).

CBT and Medication Parental psychopathology did not predict treatment outcomes in POTS [27]. However, family history of OCD—defined as the diagnosis of OCD among first-degree relatives—moderated treatment outcomes and was associated with a sixfold decrease in the effect size for CBT monotherapy [27]. Family history of OCD did not distinguish youth with a chronic versus remitting course in a naturalistic study of 60 treatment-seeking youth [40].

Summary Research has generally not supported a link between parental psychopathology (broadly defined) and acute outcomes of pediatric OCD treatment [17•, 19, 27, 30], although there is preliminary evidence that the presence of a mental disorder in at least one parent is associated with long-term outcomes of medication [36]. Findings regarding the impact of family history of OCD have been mixed [17•, 19, 25, 27, 40]; it moderated outcomes in an NIMH-funded multimodal treatment study such that it was associated with a decrease in the effect of CBT monotherapy [27].

Family Functioning

CBT In an 18-month follow-up of individual and group cognitive behavioral family therapy, higher levels of family dysfunction—measured using the Family Assessment Device [81]—predicted poorer outcomes on the NIMH Global OCD Scale [82, 83]. In another study ($N=49$), families with lower levels of parental blame and family conflict and higher levels of family cohesion were more likely to have a child who responded to family-focused CBT, even after adjusting for baseline symptom severity [84•]. Among families with relatively high levels of functioning on all three indicators, youth had a 93 % response rate. Among families with relatively poor functioning on all three indicators, youth had a 10 % response rate.

CBT and Medication In POTS, family functioning—measured using the Family Assessment Measure III [85]—did not predict treatment outcomes [27]. In a study of 82 youth presenting to an outpatient clinic for CBT and/or medication, family environment—assessed using medical records to complete the Global Family Environment Scale [86]—did not differentiate responders from non-responders at 6-month follow-up [28].

Summary Family functioning has predicted outcomes in CBT [80, 84•] but not multimodal treatment studies [27, 28], although measures have varied. The extent to which family dysfunction has been linked to diminished CBT response [84•] underscores the value of refining the assessment of family characteristics and testing novel family-based treatment approaches.

Non-Specific Therapy Factors

The influence of therapy process or non-specific factors have been examined in the context of CBT only. In family-based CBT ($N=25$), therapist-rated alliances with child and parent at session 1 each significantly predicted post-treatment OCD symptom severity (controlling for pretreatment OCD symptom severity). At mid-treatment, all ratings of the therapeutic alliance (with child and parent) significantly predicted treatment outcome, with a stronger alliance associated with greater symptom reduction [87].

Among youth ($N=71$) who received exposure-based treatment as part of a larger RCT, greater child and therapist, but not parent, expectancies of benefit from CBT were associated with the child's post-treatment symptom severity, level of OCD symptom reduction, and independent clinician ratings of improvement [88]. In a pilot study ($N=30$) comparing CBT enhanced with d-cycloserine to standard CBT, clinician-rated homework compliance predicted outcomes across conditions [89].

In light of revisions to prevailing models of exposure therapy [90, 91], there has been recent attention to the impact of exposure process on treatment outcomes. Among youth ($N=35$) who received family-focused CBT as part of a pilot RCT, greater variability of distress during ERP and greater proportion of combined exposures (i.e., targeting more than one symptom simultaneously) predicted better outcomes [92]. Within- and between-session decreases in distress during ERP did not consistently predict

outcomes nor did the number of exposure tasks completed and the amount of time spent on exposure per session.

Summary There is preliminary evidence that a range of non-specific therapy factors (therapeutic alliance, treatment expectancies, homework compliance, and exposure characteristics) significantly predict CBT outcomes [87–89, 92]. These factors might affect treatment response by acting on the "dose" of exposure within and between sessions.

Conclusion

Since this literature was last reviewed [93, 94], there has been a sharp increase in the number of studies to identify

Table 1 Predictors and moderators of treatment outcomes in multisite studies of medication, manual-based CBT, and/or their combination with $N > 100$

Predictor/moderator	CBT	Medication				Multimodal treatment	
	NordLOTS step 1 [17•, 62] ($N = 269$)	Geller et al. [33] ($N = 103$)	Geller et al. [56] ($N = 335$)	Geller et al. [21] ($N = 207$)	March et al. [20, 32] ($N = 187$)	POTS [27, 58] ($N = 112$)	POTS II [60•] ($N = 124$)
Demographics							
Age	S	NS	–	NS	NS	NS	–
Gender	NS	–	–	NS	NS	NS	–
SES/income	NS	–	–	–	–	NS	–
Disorder-specific characteristics							
OCD severity	S	–	–	–	S[a]	S	–
Functional impairment, parent rated	S	–	–	–	–	S	–
Functional impairment, child rated	S	–	–	–	–	NS	–
Insight	–	–	–	–	–	S	–
Duration of illness	NS	–	–	–	–	–	–
General illness characteristics							
Externalizing disorder	NS	–	–	–	–	NS	–
Externalizing symptoms, parent report	S	–	–	–	–	S	–
Internalizing disorder	NS	–	–	–	–	NS	–
Internalizing symptoms, parent report	S	–	–	–	–	–	–
Anxiety symptoms, child report	NS	–	–	–	–	NS	–
Anxiety symptoms, parent report	S	–	–	–	–	–	–
Depressive symptoms, child report	NS	–	–	–	–	–	–
Depressive symptoms, parent report	S	–	–	–	–	–	–
Depressive symptoms, clinician rating	–	–	–	–	NS	–	–
Motor and/or vocal tics	–	–	–	–	–	–	NS
Tic disorder	NS	–	S	–	S	S[b]	–
Sleep problems	S	–	–	–	–	–	–
Biomarkers							
Plasma levels of medication	–	–	–	–	NS	–	–
Family factors							
Family accommodation	NS	–	–	–	–	S	–
Family functioning	–	–	–	–	–	NS	–
Family history of OCD	NS	–	–	–	–	S[b]	–
Parental psychopathology	NS	–	–	–	–	NS	–

POTS II sampled SRI partial responders

NordLOTS Nordic Long-term Obsessive-compulsive disorder Treatment Study, *POTS* Pediatric OCD Treatment Study, *S* statistically significant association between predictor/moderator and outcome, *NS* non-significant association between predictor/moderator and outcome, – predictor/moderator was not examined statistically

[a] OCD severity following the acute phase of the trial predicted outcome of sertraline continuation

[b] Moderator (vs. predictor)

predictors/moderators of response to the treatment of pediatric OCD. However, few studies have been adequately powered to test multiple predictors simultaneously while adjusting the alpha level to prevent type I error. (Table 1 summarizes the results of multisite studies of medication, manual-based CBT, and/or their combination that sampled over 100 youth.) Due to the paucity of multimodal treatment studies, analyses to identify moderators of response to CBT and medication have been limited, and synthesizing findings across monotherapy trials is challenging due to differences in measurement and treatment modalities (e.g., standard vs. intensive). Given the relatively low prevalence rate of OCD [1], collaborative research networks are needed to facilitate studies with large samples. At a minimum, consensus definitions of treatment response and remission [95] should be considered to allow for cross-trial comparisons.

Future studies should attend to emerging formats of treatment delivery (e.g., webcamera [96]) and augmentation strategies (e.g., d-cycloserine [97]) in addition to examining predictors of premature termination of treatment (especially in routine clinical care settings). Also, efforts to predict relapse among treatment responders are needed [98]. As the field moves toward disseminating well-established treatments, it will be important to examine the impact of therapist characteristics on outcomes; reservations about exposure, for example, have been linked to its underutilization [99] and suboptimal delivery [100].

Advances in research aimed at personalizing the treatment of other disorders may also inform an agenda for research on pediatric OCD. For example, research to uncover genetic profiles that predict preferential fit with psychosocial interventions is underway. Eley and colleagues [101] reported preliminary data suggesting that youth with a short-short genotype for the GHTTLPR serotonin transporter gene are more likely to benefit from CBT for anxiety than from medication. Also, efforts to identify a neuroimaging biomarker that guides treatment selection (CBT or medication) for adult depression have been promising [102].

Future research should make use of statistical innovations (e.g., latent class analysis and growth mixture modeling) to isolate clusters of non-responders and to test moderators for non-linear relationships with outcomes [103]. Also, statistical advances may allow for prescriptive findings to be translated into concrete recommendations for individual patients [104]. For example, Lindhiem et al. [105] developed a probabilistic individualized metric for determining the benefit of a given treatment for individuals with various baseline characteristics, which has been extended to anxious youth [106]. Kapelner et al. [107] introduced a framework that exploits RCT data using Bayesian regression models to guide treatment allocation; pretreatment characteristics are used estimate the expected difference in an individual client's symptom reduction based on which treatment is provided [104]. Finally, efforts to personalize the treatment of pediatric OCD should capitalize on advances in experimental designs for testing adaptive treatment strategies [108].

Compliance with Ethical Standards

Conflict of Interest Dr. Caporino declares that she has no conflict of interest.

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