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Identifying treatment responders and predictors of improvement after cognitive-behavioral therapy for juvenile fibromyalgia

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ABSTRACT

The primary objective of this study was to estimate a clinically significant and quantifiable change in functional disability to identify treatment responders in a clinical trial of cognitive-behavioral therapy (CBT) for youth with juvenile fibromyalgia (JFM). The second objective was to examine whether baseline functional disability (Functional Disability Inventory), pain intensity, depressive symptoms (Children's Depression Inventory), coping self-efficacy (Pain Coping Questionnaire), and parental pain history predicted treatment response in disability at 6-month follow-up. Participants were 100 adolescents (11–18 years of age) with JFM enrolled in a recently published clinical trial comparing CBT to a fibromyalgia education (FE) intervention. Patients were identified as achieving a clinically significant change in disability (ie, were considered treatment responders) if they achieved both a reliable magnitude of change (estimated as a $\geqslant$7.8-point reduction on the FDI) using the Reliable Change Index, and a reduction in FDI disability grade based on established clinical reference points. Using this rigorous standard, 40% of patients who received CBT (20 of 50) were identified as treatment responders, compared to 28% who received FE (14 of 50). For CBT, patients with greater initial disability and higher coping efficacy were significantly more likely to achieve a clinically significant improvement in functioning. Pain intensity, depressive symptoms, and parent pain history did not significantly predict treatment response. Estimating clinically significant change for outcome measures in behavioral trials sets a high bar but is a potentially valuable approach to improve the quality of clinical trials, to enhance interpretability of treatment effects, and to challenge researchers to develop more potent and tailored interventions.

1. Introduction

Cognitive-behavioral therapy (CBT) is an effective treatment for pediatric chronic pain conditions that significantly reduces functional disability [11,35], with 1 study demonstrating maintenance of improvement in disability over 6 months for adolescents with juvenile fibromyalgia (JFM) [26]. Even with large and statistically significant overall treatment effects reported in clinical trials, there is variability in outcomes for individual patients, and not all patients achieve functional improvements that are clinically meaningful [13]. Clinically meaningful or significant improvements are considered worthwhile to patients and involve a noticeable reduction in symptomatology [2,7,18]. To distinguish patients who achieve clinically significant improvements from those who do not, it is important to determine cut-off scores for outcome measures that represent clinically meaningful change. Such empirically

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derived scores have the potential to significantly improve the interpretability of treatment effects across trials and to provide valuable information to clinicians who are seeking evidence to inform their practice [2,9,32,48].

Functional disability, as measured by the Functional Disability Inventory (FDI) [47], is a key outcome measure in trials of behavioral interventions for pediatric chronic pain [30]. Although published clinical reference points have been established for the FDI [21], there are no clear established guidelines for determining whether statistically significant changes in the FDI are of clinical significance in randomized controlled trials. Unfortunately, the process of determining clinical significance remains a challenge, particularly among functional health outcomes (eg, the FDI) [5,16] because of varying methods of defining clinical significance [16,48]. Estimating clinically meaningful differences has gained support as a new standard for determining clinical significance of treatment effectiveness [1,7,9,41]. Thus, estimating clinically significant changes of functional disability after treatment can be a helpful tool for use in identifying patients who respond to treatment and examining patient characteristics that predict treatment response.

A few studies in adults have identified patient characteristics that may predict positive response to treatment. In CBT studies of adults with chronic pain, predictors of positive treatment response included older age, higher levels of distress, depression, or disability, greater coping efficacy, and less solicitous spouse behaviors at baseline [3,43–45]. In children with chronic pain, parents play an integral role in the management of pain and functioning. Specifically, family history of chronic pain may be an additional factor to consider, given its known association with patients' greater disability [29,39,40]. To date, little is known about predictors of treatment success in pediatric chronic pain.

In the current study, secondary analyses of data from our published randomized controlled trial of CBT for JFM [26] were used as an exemplar to begin the process of evaluating clinical significance for the FDI (the primary outcome) in pediatric trials of chronic pain. The study objectives were as follows: to estimate clinically significant changes in functional disability to identify treatment responders versus nonresponders; and to test whether patient characteristics at baseline (functional disability, pain intensity, depressive symptoms, coping efficacy, parent pain history) would predict clinically significant treatment response in functional disability.

2. Methods

2.1. Patients

Participants were 100 children and adolescents aged 11 to 18 years with JFM, recruited from 4 pediatric rheumatology centers, who had completed a randomized clinical trial comparing CBT to an educational intervention (fibromyalgia education [FE]) [26]. Children and adolescents were eligible to participate if they met the following inclusion criteria: met the Yunus and Masi [49] JFM classification; 2) had been on stable medications for 8 weeks; 3) reported average pain intensity $\geqslant$4 on a visual analogue scale of 0 to 10 cm based on 1 week of daily pain diaries; and reported at least mild disruption in daily activities because of JFM symptoms (ie, score >7 on the FDI). Exclusion criteria included the following: diagnosis of any other chronic rheumatic disease; documented developmental delay; current symptoms of bipolar disorder, major depressive disorder, panic disorder, or psychosis; or active use of opioid medications.

Institutional review board approval was obtained at each site. Parents of the participants provided written informed consent, and children and adolescents provided written assent.

2.2. Study procedures

After completing a comprehensive medical and psychosocial baseline assessment that included a battery of questionnaires, eligible participants were randomized to receive either CBT or FE. In each treatment arm, participants met individually with a trained, doctoral-level therapist for 8 weekly treatment sessions in which the interventions were delivered using manualized protocols. CBT focused on training in active and adaptive behavioral and cognitive coping strategies in pain management. FE was designed to provide educational information about fibromyalgia, its treatment, and healthy lifestyle habits with no active training or instruction for behavior change. Sessions were well attended and the study had a high retention rate (88%) without any differential drop-out in the 2 treatment arms. The trial results published by Kashikar-Zuck [26] provides further details on the study treatments, study procedure, and primary outcomes.

2.3. Measures

The following measures were administered as part of the comprehensive baseline assessment. Functional disability, pain intensity, depressive symptoms, coping self-efficacy, and parent pain history were selected for the analyses based on evidence of their prediction of treatment response in studies of adults with various chronic pain conditions. Additional factors of potential interest (eg, age, medication use, duration since pain onset) were considered, but were not included in the analyses because of inconsistent predictive value based on the adult pain literature as well as limited statistical power [3,43–45].

2.3.1. Functional disability—primary outcome

The FDI is a well-validated, 15-item self-report instrument that assesses children's and adolescents' perceived difficulty in performing daily activities because of their pain symptoms in home, school, recreational, and social settings [47]. This measure was the primary outcome used in our trial, defined as change in FDI from baseline to end of study (6-month follow-up), and was used to assess clinically significant changes in functional disability outcomes in this secondary analysis [26]. Baseline FDI scores also were used as a predictor of achieving clinically significant changes in functioning. Participants rated how much difficulty they have performing each of the activities on a 5-point Likert scale (0 = no trouble to 4 = impossible). Total scores on the FDI ranged from 0 to 60, with higher scores indicating greater disability. For children with chronic pain, the clinical reference points include the following: 0 to 12 = no/minimal disability, 13 to 29 = moderate disability, and 30 to 60 = severe disability. These clinical cut-offs were based on a published study of the validity of the FDI in a large (n = 1300) multicenter clinical sample of youth with chronic pain [21]. The FDI has been found to have high internal consistency, moderate to high test–retest reliability, moderate cross-informant (parent–child) reliability, and good predictive validity [4,47].

2.3.2. Average pain intensity

Participants rated their average pain intensity on a 0- to 10-cm visual analog scale (0 "No pain" to 10 "Pain as bad as you can imagine") daily for 1 week. Average ratings were calculated for 1 week at baseline and used for analyses.

2.3.3. Depressive symptoms

The Children's Depression Inventory (CDI) is a 27-item self-report measure used to assess baseline levels of depressive symptoms. It has been well validated for use in children and adolescents [27]. The CDI has strong psychometric properties and is frequently used in pediatric pain research [6,10,22]. Participants select 1 of 3

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