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Moderators of Internet-Delivered Cognitive-Behavioral Therapy for Adolescents With Chronic Pain: Who Benefits From Treatment at Long-Term Follow-Up?

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Abstract: **Cognitive behavioral therapy (CBT) is effective for pediatric chronic pain, but little is understood about which youth are most likely to benefit. The current study aimed to identify individual characteristics for which CBT yielded the greatest (and least) clinical benefit among adolescents with chronic pain participating in a multicenter randomized controlled trial of Internet-delivered CBT (WebMAP2). A total of 273 adolescents ages 11 to 17 with chronic pain (M age = 14.7; 75.1% female) were randomly assigned to Internet-delivered CBT or Internet-delivered pain education and evaluated at pretreatment, post-treatment, and 2 longer term follow-up periods (6 and 12 months). Multilevel growth models tested several adolescent- and parent-level moderators of change in pain-related disability including 1) adolescent age, sex, pain characteristics, distress, and sleep quality and 2) parent education level, distress, and protective parenting behavior. Younger adolescents (ages 11–14; vs older adolescents ages 15–17) and those whose parents experienced lower levels (vs higher levels) of emotional distress responded better to Internet CBT treatment, showing greater improvements in disability up to 12 months post-treatment. This study expands knowledge on who benefits most from Internet-delivered psychological treatment for youth with chronic pain in the context of a large multicenter randomized controlled trial, suggesting several avenues for maximizing treatment efficacy and durability in this population.**

Perspective: ***This study identified adolescent- and parent-level predictors of treatment response to Internet-based CBT for pediatric chronic pain up to 12 months later. Younger adolescents and those whose parents had lower levels of distress may particularly benefit from this intervention. Older adolescents and those whose parents exhibit higher distress may require alternative treatment approaches.***

Key words: *Treatment moderators, pediatric pain, adolescents, cognitive behavioral therapy, eHealth.*

Chronic pain affects 1 in 4 children and adolescents,[19,24] and is associated with disruption of physical activity, reduced school attendance, high health care utilization and costs, poor quality of life in youth, as well as emotional distress in youth and their parents.[16,31,49] Risk for ongoing pain, disability, and psychiatric disorders can extend into adulthood, making prevention and treatment of disabling pain in childhood a major public health priority.[31,51] Considerable progress has been made toward developing effective psychological interventions for chronic pediatric pain, with almost 60 randomized controlled trials (RCTs) completed using treatments delivered face-to-face or remotely (see Eccleston et al[7] and Fisher et al[14] for meta-analytic reviews). However, most trials demonstrate small effects for reducing pain and disability,[7] and there is large interindividual variability in treatment response. Unfortunately, most trials report only

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average, group-level effects and have not identified youth who benefit most from treatment. The experience of pain is influenced by a unique mosaic of demographic and psychosocial factors that may affect the extent to which youth benefit from treatment.[13]

Recently highlighted as a top research priority by the Federal Pain Research Strategy,[20] examining treatment moderators has been recognized as a promising pathway toward translating scientific data from trials to the treatment of individual patients in clinical practice.[8,25,26] Identification of treatment moderators not only allows researchers and clinicians to direct existing resources to patients most likely to benefit from them, but also facilitates identification of patients with poor responsiveness, highlighting the best targets for future tailored treatment.[9,25] To our knowledge, there have been no studies that have examined treatment moderators in RCTs of psychological treatments for pediatric chronic pain. This is a significant gap in knowledge that has hindered progress in matching specific treatments to patient subgroups.

Developmental models of pediatric pain impact can help guide the study of treatment response moderators. These models include sociodemographic factors (ie, adolescent age, sex, parent education), pain intensity, co-occurring symptoms (ie, mood and sleep deficiency), and parent factors (ie, parent distress, protective behaviors).[32,36] Sleep deficiency and parent distress have been identified as *general predictors* of post-treatment outcomes in youth with chronic pain, specifically predicting less improvement in pain-related disability.[11,28] However, associations have been examined *within a single treatment group.* Because similar associations may have also occurred within the control or placebo groups, these findings may reflect factors broadly associated with changes in youths' disability over time rather than those predictive of treatment response.[26] In contrast, treatment moderators are characteristics selectively associated with better (or worse) outcomes in the treatment condition relative to the control condition and are therefore much more conducive to isolating characteristics that predict response to treatment.[26]

Moreover, long-term treatment effects have been investigated in just a few previous RCTs of cognitive behavioral therapy (CBT) for pediatric chronic pain,[17,29,37,48] and much less is known about the long-term efficacy of remotely delivered CBT interventions. It is important to distinguish children who are at risk for unfavorable long-term treatment outcomes from those who maintain improvement after completing treatment in order to determine whether additional monitoring or tailoring of Internet-based CBT is needed to enhance long-term efficacy.

To address these gaps in the literature, the current study identified moderators of longer term treatment response in a RCT evaluating an Internet-delivered pain management program for adolescents with chronic pain: Web-based Management of Adolescent Pain (WebMAP2[35]). Remotely delivered psychological interventions are uniquely positioned to extend the reach of clinical services for pain management to families who experience significant geographical or financial barriers to receiving care. Thus, discovering ways to make even small improvements in the efficacy and efficiency of Internet-delivered interventions could translate to substantial positive effects at the population level. Guided by theoretical models of pediatric pain impact, we conducted a secondary data analysis examining several potential adolescent- and parent-level treatment moderators of WebMAP2 at 2 longer term follow-up periods (6 and 12 months). Individual adolescent moderators included age, sex, pain intensity, and co-occurring symptoms (ie, emotional distress, sleep quality). Parent-level moderators included education, emotional distress, and protective parenting behavior.

Methods

Participants and Recruitment

Participants included 273 adolescents ages 11 to 17 years (M = 14.7, SD = 1.6) with chronic pain (including headache, abdominal, or musculoskeletal pain) and their parents, who were randomly assigned to either the active intervention (Internet-delivered CBT) or the active control condition (Internet-delivered Pain Education) of a multicenter RCT.[35] The clinical trial is registered (Web-based Management of Adolescent Pain, Web-MAP2; ClinicalTrials.gov Identifier NCT13165471). Adolescents were referred by a health care provider from 1 of 15 participating interdisciplinary pain clinics across the United States and Canada. Inclusion criteria for the adolescents were: 1) age 11 to 17 years, 2) chronic idiopathic pain present over the previous 3 months, 3) pain at least once per week, 4) parent report of pain interfering with at least 1 area of daily functioning, and 5) received a new patient evaluation in one of the participating interdisciplinary pain clinics. Participants were excluded if they: 1) had a serious comorbid psychiatric or chronic medical condition (eg, cancer), 2) had a developmental disability, 3) were non-English speaking, 4) did not have regular access to the Internet on a desktop, tablet, phone, or laptop computer, or 5) were not residing at home (eg, were enrolled in an intensive inpatient pain rehabilitation program). Study staff screened potential participants by telephone. Written informed consent and assent were obtained from parents and adolescents. The study was approved by the primary site's Institutional Review Board and the Institutional Review Boards at each referring center. Participants were compensated with gift cards for completion of each assessment.

Procedures

This study is a secondary analysis of data collected as part of the WebMAP2 RCT.[35] This RCT used a double-blinded, multicenter balanced (1:1) parallel group design. Assessments were completed online through a secure, password-protected website at pretreatment (prior to randomization), after completion of the 8- to

10-week intervention (immediately post-treatment) and at 2 longer term follow-up periods (6 and 12 months). Our research group has published articles reporting treatment efficacy on primary and secondary outcomes of WebMAP2 up to 6 months,[35] but this is the first study to analyze treatment moderators and to present 12-month follow-up results on the primary outcome: adolescent pain-related disability.

After the pretreatment assessment, participants were randomly assigned to either the Internet-delivered CBT arm (n = 138) or the Internet-delivered Pain Education (control) arm (n = 135) of the trial. The groups were provided with access to 2 different versions of the web program that presented either CBT or Pain Education (described below). Both interventions were adjunctive to the usual care provided by the interdisciplinary pain clinics. The flow of participants through the trial is shown in Fig 1. Nine participants (n = 8 Internet CBT; n = 1 Internet Pain Education) did not complete post-intervention or follow-up study assessments but were retained in analyses. Four participants were excluded from analyses due to major life events that occurred during the trial (eg, death in the family; n = 4 Internet CBT). Thus, final our analytic

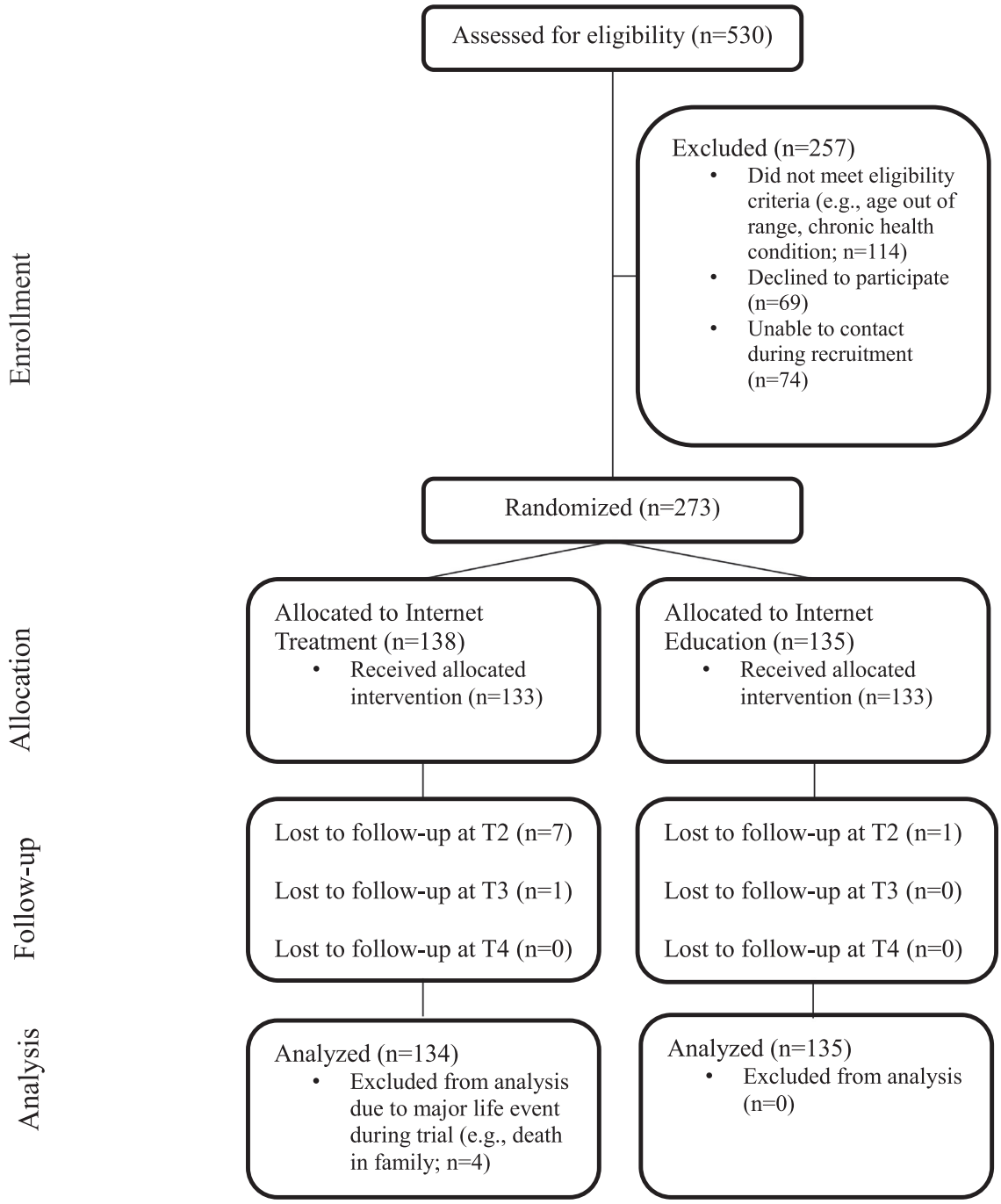

Figure 1. CONSORT flow diagram.

sample consisted of 269 participants (n = 134 Internet CBT; n = 135 Internet Pain Education).

Internet CBT

As described in Palermo et al,[35] adolescents and parents in the Internet CBT condition received access to the full version of WebMAP2, which included education about chronic pain, training in behavioral and cognitive coping skills, and parent operant and communication strategies using an engaging interactive format.

The WebMAP2 intervention consisted of 2 separate, password-protected web programs, one for adolescent access and the other for parent access. There are 8 adolescent modules: 1) education about chronic pain, 2) recognizing stress and negative emotions, 3) deep breathing and relaxation, 4) implementing coping skills at school, 5) cognitive skills (eg, reducing negative thoughts), 6) sleep hygiene and lifestyle, 7) staying active (eg, activity pacing, pleasant activity scheduling), and 8) relapse prevention. The 8 parent modules included: 1) education about chronic pain, 2) recognizing stress and negative emotions, 3) operant strategies I (using attention and praise to increase positive coping), 4) operant strategies II (using rewards to increase positive coping; strategies to support school goals), 5) modeling, 6) sleep hygiene and lifestyle, 7) communication, and 8) relapse prevention.

Adolescents and parents were asked to complete 1 module per week. For 6 of the 8 modules, youth and parents spent time practicing skills and completed weekly behavioral assignments (eg, scheduling time to practice the skills, identifying stressors, writing thoughts down), which were reviewed by an online coach. More detailed information on the design and treatment content of WebMAP is included in our main outcomes paper.[35]

Internet Pain Education

The Internet-delivered Pain Education group served as an attention control condition for the purposes of equalizing time, attention, and computer usage. The control version of the WebMAP2 website contained 8 modules with educational material compiled from publicly available websites about chronic pain management (eg, the National Headache Foundation). Participants in this condition were instructed to log into the control version of the website at the same frequency as the CBT group (at least once per week).

Measures

Outcome

The present analysis focused on the primary outcome of the RCT: adolescent pain-related disability measured at 4 time points: pretreatment, post-treatment, 6-month, and 12-month follow-up.

Pain-Related Disability

To assess the primary outcome of adolescent's disability due to pain, the Child Activity Limitations (CALI) Diary Version was administered via a 1-week (ie, 7 days) online diary.[35] At study enrollment, adolescents chose 8 activities from a list of 21 activities that they perceived as most difficult to complete due to pain and important in their daily lives (eg, going to school, spending time with friends). At each assessment, youth rated the difficulty of these 8 activities once daily over a 7-day monitoring period on a 5-point scale (0 = "no difficulty," 4 = "extreme difficulty"). Daily total scores ranged from 0 to 32, with higher scores indicating greater disability due to pain. For each time point, daily total scores were averaged across the total number of diary entries completed over the 7-day assessment period. Reliability and validity of the CALI have been demonstrated in school-age children and adolescents with chronic pain recruited through pain clinics and specialty clinics.[35]

Moderator and General Predictor Variables

All potential moderator/general predictor variables were assessed at pretreatment prior to randomization. Per our analytic method described below, variables were grouped into 2 domains representing potential adolescent- and parent-level predictors/moderators.

Adolescent-Level Moderators/General Predictors

Adolescent-level moderators/predictors included adolescent demographics, pain characteristics, emotional distress, and sleep quality:

Demographics. Adolescent age and sex were collected through a background form completed by a parent.

Pain intensity. Pain intensity was assessed using the WebMAP diary, which was completed prospectively over a 7-day assessment period prior to the treatment as part of the intervention and control websites. Pain intensity was assessed using an 11-point numerical rating scale (NRS-11) (0 = "no pain," 10 = "worst pain"), averaged across the 7-day period. The NRS-11 has been recommended for assessment of pain intensity in adolescents with chronic pain.[50]

Emotional distress. Adolescents' emotional distress was measured using the Bath Adolescent Pain Questionnaire (BAPQ).[6] For the purposes of this study, we used a composite (average) of 3 subscales measuring distress-related symptoms including adolescents' depression (6 items, eg, "I feel hopeless about the future"), general anxiety (7 items, eg, "I worry about the future"), and pain-specific anxiety (7 items, eg, "I worry that I will do something to make my pain worse") over the past 2 weeks. Response options ranged from 0 = "never" to 4 = "always." Items were summed to create total scores of each subscale, with higher scores indicating greater adolescent emotional distress. Creation of

composite scores has been recommended as a useful data management technique to reduce the number of analyses,[18] particularly when scales of the same construct are highly correlated as was the case in this study (rs = .51−.79). The BAPQ was developed for use in clinical populations of youth with chronic pain and has demonstrated good validity and test-retest reliability in outpatient pain samples.[6] Cronbach's alphas for the three subscale scores in this sample ranged from .83 to .84.

Sleep quality was measured using the 10-item short form version of the Adolescent Sleep Wake Scale (ASWS[10]). Adolescents report on a 6-point Likert scale (1 = "always," 6 = "never"), with higher scores indicating better sleep quality. Scores are summed to create a total score. The ASWS has been previously validated in youth with chronic pain[10] and has acceptable reliability and validity. Cronbach's alpha for the 10-item total score in this sample was adequate (α = .79).

Parent-Level Moderators/Predictors

Parent-level moderators/predictors included parent education, distress, and protective parenting behavior.

Education. Parents reported their own and their spouses' highest level of education achieved (ie, less than high school, high school, some college, college degree, or higher). Parent education was coded as either parent's highest level of education.

Emotional distress was measured using the Bath Adolescent Pain—Parental Impact Questionnaire (BAPPIQ[22]). For the purposes of this study, we used a composite (average) of parent distress composed of 3 subscales measuring parent depression (9 items, eg, "I have felt sad"), general anxiety (6 items, eg, "I have not been able to get my mind off my worries"), and catastrophizing about their child's pain (6 items, eg, "I have been concerned that my child will always experience pain") over the past 2 weeks. This procedure has been followed in a previous study[28] indicating that the 3 scales loaded on a single construct (parent distress). Response options ranged from 0 = "never" to 4 = "always," with higher scores indicating greater parental emotional distress. In this sample, the 3 subscales were highly correlated (rs = .58−.80) and Cronbach's alphas ranged from .83 to .90.

Protective parenting behavior. Protective parenting behaviors were assessed using the Protect subscale from the Adult Responses to Children's Symptoms (ARCS[52]). The subscale comprises 15 items identifying protective parenting behavior in response to child pain. For example, specific behaviors measured on this scale include limiting children's activities, relieving their responsibilities, or granting special privileges. Items are measured with a 5-point Likert scale, ranging from 0 = "never" to 4 = "always." Responses were averaged to provide the subscale score, which ranged from 0 to 3.47. Higher scores indicate more frequent engagement in protective parenting behaviors. Cronbach's alpha for this subscale was adequate (α = .86).

Data Analysis Plan

We performed all analyses using IBM SPSS (Version 19 for Windows). To address our aim of identifying predictors and moderators of change in pain-related disability, we constructed hierarchical linear models using multilevel modeling (MLM) with full maximum likelihood. MLM is an intent-to-treat approach that uses all data from the full sample to estimate both the slope of change and the intercept for each individual.

We were guided by the conceptual and data analytic approach advocated by Kraemer et al[26] and Fournier et al[15] to simultaneously assess whether an individual characteristic was a *moderator* or *general predictor* of changes in disability. Within this framework, individual characteristics are considered *moderators* if they predict a better (or worse) response to the treatment condition compared to the control condition, whereas *general predictors* are individual characteristics associated with treatment outcome irrespective of study condition (ie, across both conditions). Accordingly, a moderator variable requires evidence of a significant interaction between the predictor (individual characteristic), study treatment condition (dichotomized: 0 = Internet CBT; 1 = Internet Pain Education), and time (ie, Individual characteristic X Treatment X Time point). General predictors require evidence of a significant interaction with time point (ie, Individual characteristic X Time) *and* no evidence of a significant moderation effect (no interaction with treatment condition).

As recommended for testing treatment moderators,[53] we restricted analyses to the primary outcome used in the RCT (ie, pain-related disability). The time variable was treated as a categorical variable in the MLM models, with pretreatment values specified as the reference point for the change in pain-related disability from pretreatment to post-treatment, pretreatment to 6-month follow-up, and pretreatment to 12-month follow-up (ie, slope terms). While estimated slope terms representing the rate change in pain-related disability from pretreatment to post-treatment were necessarily included in all MLM models as stated, any main and interactive effects involving pretreatment to immediately post-treatment slope are not explicitly presented within the text or tables due to our focus on longer term 6- and 12-month outcomes. These data are available upon request from the corresponding author. MLM models comprised the following variables: 1) intercept and Time (ie, the slope terms); 2) individual characteristics that were used to predict the intercept (pretreatment score) and slopes of improvement (ie, Predictor X Time); and 3) potential predictor/moderator variables, treatment condition, and their interaction (ie, Predictor X Treatment X Time).

We were guided by the commonly used statistical approach known as the Fournier Approach[15,44,55] to identify significant moderators and general predictors. Due to the relatively large number of candidate predictors/moderators, we first grouped putative moderators/general predictors into 2 separate domains: 1) adolescent-level characteristics (adolescent moderators/predictors) and 2) parent-level characteristics (parent

moderators/predictors; see Measures section). For each of the 2 domains, a larger prediction model containing all potential predictors in that domain was compared to a smaller, nested model. This smaller, simple model contained the terms implemented in the original article reporting the main outcomes up to 6 months[35] (ie, main effects of treatment, time, as well as the treatment X time interaction and adolescent race as a covariate). The relative fit of the prediction model was compared to that of the simple model by means of evaluating the difference in the −2 log likelihood (−2LL) between the models (Singer & Willett),[43] which follow a chi-squared distribution. The specific effects of individual predictors/moderators were tested further using the steps below if the prediction model proved statistically superior to the simple model at $P < .05$.

As recommended,[15] for each domain, a separate multilevel model was developed in a stepwise manner where variables were successively evaluated as to whether they significantly had an effect on the rate of symptomatic improvement. For example, in the first step (Step 1), a model which included all candidate moderators/predictors for the adolescent domain (ie, adolescent age), and their interaction with time (predictor × time), was tested. Only those variables that had an interaction with time at the $P < .20$ level were included in a new model (Step 2). In Step 3, those variables that met the $P < .10$ level were kept and finally assessed in Step 4, at the $P < .05$ level. This procedure was repeated for the parent domain. Finally, each term that was significant at $P < .05$ in Step 4 of the adolescent and parent domain models were included together in a final model, allowing the testing of significant adolescent-level moderators/general predictors while accounting for significant parent-level moderators/general predictors (and vice versa).

The Fournier approach is the preferred method[26] for maximizing moderator identification while maintaining an acceptable likelihood of chance capitalization, thus balancing risk for type I and type II errors. Specifically, Type I error (false positive) is minimized because multiple predictor/moderator variables are examined in groups rather than separately (one variable at a time), reducing the total number of models run and helping to identify those variables that are predictive over and above others in their domain, and over and above significant variables in other domains. Type II error (false negative) is also minimized because the moderation analysis does not include all potential predictors/moderators in a single, very large model but rather in stepwise, domain-specific fashion.

As required for testing interactions, variables coding Treatment Condition and the interactions of Treatment Condition and Time were included in the MLM models regardless of their significance level. Subcomponents of significant interactions were also necessarily retained in the models. Per recommendations,[26] adolescent race was not tested as a potential moderator due to pretreatment differences between the Internet CBT and Internet Pain Education groups as reported in the main study.[35] Instead, race was included as a covariate (dichotomized: 0 = "Caucasian"; 1 = "All other racial categories") in the models. Continuous variables were converted to z-scores to center them at their means for interactions.

A significant Predictor X Treatment X Time interaction indicates that the trajectory of treatment response differs across the treatment conditions and depends on the level of the moderator variable. To understand the nature of the moderator interactions that were significant, we followed the approach developed by Aiken & West[42] calculating the effect of the treatments at high and low levels of the moderator (usually defined as 1 SD above and 1 SD below the mean, respectively). This technique, which uses all data in the MLM model to calculate model predicted parameters for different levels of the moderator, allows one to understand how the relationship between treatment and outcome varies for high and low values of the moderator.

We calculated effect sizes (Cohen's ds) to elucidate the magnitude of treatment effects and moderator effects (ie, treatment effect sizes for levels of the moderator). By convention, d = .20, d = .50, and d = .80 are interpreted as small, moderate, and large effects, respectively. In addition to effect sizes, we calculated clinically significant changes in main treatment effects according to Jacobson and Traux.[21] This approach suggests a 2-pronged approach to determining clinically relevant change: 1) achieving a magnitude of change that is statistically reliable tested by use of the Reliable Change Index (RCI) and 2) demonstrating movement from a dysfunctional to a functional level. The RCI calculates a critical change score for reliable improvement, based on the baseline SD and test-retest reliability of the outcome measure. Individual RCI values that exceeded the cut-point of 1.96 were unlikely to occur by chance and reflected a reliable change in scores with 90% confidence. Adolescents exceeding this cutoff were classified as "improved." If, in addition to this, adolescents' level of disability was no longer in the 90% range of the patient population (mean before treatment ± 1.64 SD[17]) they were classified as "recovered."

Power analysis. We performed post hoc power analyses for the largest/most complex model (Step 1 adolescent-level predictor model outlined above) using the program PinT 2.12 (Power in Two-Level Models[45]). This model included a total of 24 terms (ie, including Predictor X Time X Treatment interaction terms and all interaction subcomponents), using 1,092 data points from 273 participants across 4 time points. PintT indicated greater than a .95 power to detect a medium effect size for a moderator or predictor.

Results

Descriptive Statistics of the Study Sample

Demographic and clinical characteristics of the study sample are provided in Table 1. As reported in the main study, the 2 groups (Internet CBT and Internet Pain Education) were similar on demographic and baseline clinical characteristics (ie, adolescent age, sex, pain condition, and parent education) except for adolescent

Table 1. Sociodemographic Characteristics of the Study Sample

Characteristic	Total (n = 273)	CBT (n = 138)	Education (n = 135)	Group Differences
Adolescent sex (% female)	75.1	78.3	71.9	$\chi^2(1) = 1.50^{NS}$
Adolescent age (mean, SD)	14.71 (1.62)	14.63 (1.62)	14.70 (1.72)	$t(271) = .35^{NS}$
Adolescent race/ethnicity (%)				
White	85.0	92.0	77.8	$\chi^2(1) = 9.81$*
Black or African American	4.8	1.4	8.1	
Hispanic/Latino	3.7	1.4	5.9	
Other	5.0	4.5	6.0	
Not reported	1.5	.7	2.2	
Primary pain location (%)				
Head	7.0	8.0	5.9	$\chi^2(3) = 2.06^{NS}$
Abdomen	11.4	12.3	10.4	
Musculoskeletal	41.8	37.7	45.9	
Multiple	39.9	42.0	37.8	
Parent education (%)†				
High school or less	12.1	9.4	14.8	$\chi^2(3) = 3.97^{NS}$
Vocational school/some college	25.6	25.4	25.9	
College	39.6	38.4	40.7	
Graduate/professional school	21.2	25.4	17.0	
Not reported	1.5	1.4	1.5	
Household annual income (%)				
<$10,000	2.6	2.2	3.0	$\chi^2(5) = 7.85^{NS}$
$10,000–$29,999	10.6	6.5	14.8	
$30,000–$49,999	12.5	14.5	10.4	
$50,000–$69,999	32.2	30.4	34.1	
$70,000–$100,000	10.3	13.0	7.4	
>$100,000	27.5	27.5	27.4	
Not reported	4.4	5.8	3.0	

Abbreviation: CBT, cognitive behavioral therapy; NS, nonsignificant.
*$P < .05$.
†Education attainment of the primary participating parent.

race. Adolescents in the Internet CBT group were more likely to be Caucasian when compared to adolescents in the Internet Pain Education group. Participants who dropped out of the study and those who completed the study did not significantly differ on any demographic or baseline clinical variables ($P > .05$).

Overall Treatment Effects

Results of overall treatment (Treatment X Time) effects indicated small statistically significant effects for Internet CBT in reducing disability up to 6 months post-treatment compared to Internet Pain Education, but effects attenuated at 12-month follow-up. Specifically, youth receiving Internet CBT achieved statistically greater reductions in pain-related disability than did the Internet education group from pretreatment (CBT: M = 7.4, SD = 4.4; Education: M = 7.0; SD = 4.6) to 6-month follow-up (CBT: M = 5.5, SD = 4.3; Education: M = 6.2, SD = 5.0; b = 2.29, $P = .002$, d = −.25, but not from pretreatment to 12-month follow-up (CBT: M = 5.0, SD = 4.3; Education: M = 5.3, SD = 4.5; b = 1.40, $P = .054$, d = −.16; Table 2). In terms of clinical significance, 27.2% of the CBT group demonstrated recovery or improvement in pain-related disability at 6-month follow-up (14.0% recovered; 13.2% improved) compared to 21.8% of the Education group (12.9% recovered; 8.9% improved), $\chi 2$ [2] = 1.36, $P = .507$. These percentages increased slightly at 12-month follow-up to 35.0% for the CBT group (19.2% recovered; 15.8% improved) and 27.3% (17.4% recovered, 9.9% improved) for the Education group, $\chi 2$ [2] = 2.27, $P = .321$.

Moderators of Treatment Effects and General Predictors

Omnibus Tests of Adolescent and Parent Predictor Models

Results revealed that the adolescent-level and parent-level models fit the data better than the simple model, as indicated by significant likelihood ratio chi-squared tests (Adolescent: $\Delta\chi 2$ [40] 388.8, $P < .001$; Parent: $\Delta\chi 2$ [24] 2,182.1, $P < .001$). Thus, both adolescent and parent prediction models proved statistically superior to the simple model at $P < .001$.

Adolescent-Level Treatment Moderators

The majority of adolescent-level variables including sex, pain intensity, sleep quality, and emotional distress did not emerge as significant moderators of treatment effects (ps > .05). However, adolescent age significantly interacted with group and time to moderate pain-related disability (ie, significant Adolescent Age X

Table 2. General Predictors and Moderators of Change in Pain-Related Disability: Baseline to 6-Month and 12-Month Follow-Up Slope Effects

Predictors	Baseline to 6-Month Follow-Up Slope Effects			Baseline to 12-Month Follow-Up Slope Effects		
	b†	t	P	b†	t	P
Child-level model (significant slope terms from Step 4)						
Treatment X Time	2.29	3.13	.002*	1.36	1.86	.063
Pain Intensity X Time	−1.16	−4.41	<.001*	−1.73	−6.62	<.001*
Sleep Quality X Time	−.52	−1.94	.052	−.83	−3.12	<.002*
Adolescent Age X Time	1.55	2.15	.032*	1.75	2.42	.016*
Adolescent Age X Treatment X Time	−2.82	2.81	.005*	−2.13	−2.06	.040*
Parent-level model (significant slope terms from Step 4)						
Treatment X Time	1.16	2.18	.030*	.90	1.69	.092
Parent Distress X Time	.79	1.71	.087	1.47	3.19	.001*
Parent Distress X Treatment X Time	−.69	2.18	.261	−1.25	−2.02	.044*
Final (combined) model (significant slope terms from child and parent models)						
Treatment X Time	2.29	3.13	.002*	1.40	1.93	.054
Pain Intensity X Time	−1.22	−4.65	<.001*	−1.84	−7.04	<.001*
Sleep Quality X Time	−.46	−1.76	.079	−.76	−2.86	.004*
Adolescent Age X Time	1.39	1.94	.053	1.60	2.20	.028*
Parent Distress X Time	.79	1.79	.074	1.57	3.53	<.001*
Adolescent Age X Treatment X Time	−2.85	2.77	.006*	−2.07	−2.02	.044*
Parent Distress X Treatment X Time	−.42	−.70	.486	−1.20	−2.00	.046*

NOTE. Adolescent race was included as a covariate in each MLM model but not reported here; these effects were nonsignificant ($P > .05$). "Treatment" refers to the dummy variable coding the contrast between those in the Internet CBT condition (= 0) and those in Internet Pain Education condition (= 1). Table includes 6-month and 12-month slope terms that reached significance in Step 4 only; nonsignificant slope terms were omitted. Models included all lower order interactions but are not presented here. Full results are available upon request from the corresponding author. Supplementary Table 1 includes significant and nonsignificant slope terms in Steps 1 to 3.

†Interaction terms involving time only represent the slope effect of the predictor variable on pain-related disability. Interaction terms involving both treatment and time represent the difference in slopes between treatment groups with respect to the magnitude of the effect.

* $p < .05$.

Treatment X Time interaction) in Step 4 of the adolescent model, and this interaction remained significant in the final model (combining adolescent- and parent-level moderators/predictors). Specifically, adolescent age at pretreatment predicted a differential effect of treatment on change in pain-related disability from pretreatment to 6-month follow-up (b = −2.85, t = 2.77, $P = .006$) and from pretreatment to 12-month follow-up (b = −2.07, t = 2.02, $P = .044$; see final model in Table 2).

Fig 2 depicts the results of post hoc analyses (ie, tests of simple slopes) determining the nature of the moderating effect of adolescent age on change in pain-related disability following treatment. These analyses found that the simple slopes (ie, change in disability) of the treatment groups significantly differed from one another for younger (age 11−14) and older (ages 15−17) adolescent age groups. Post hoc analyses estimating simple effects of the lower order variables on

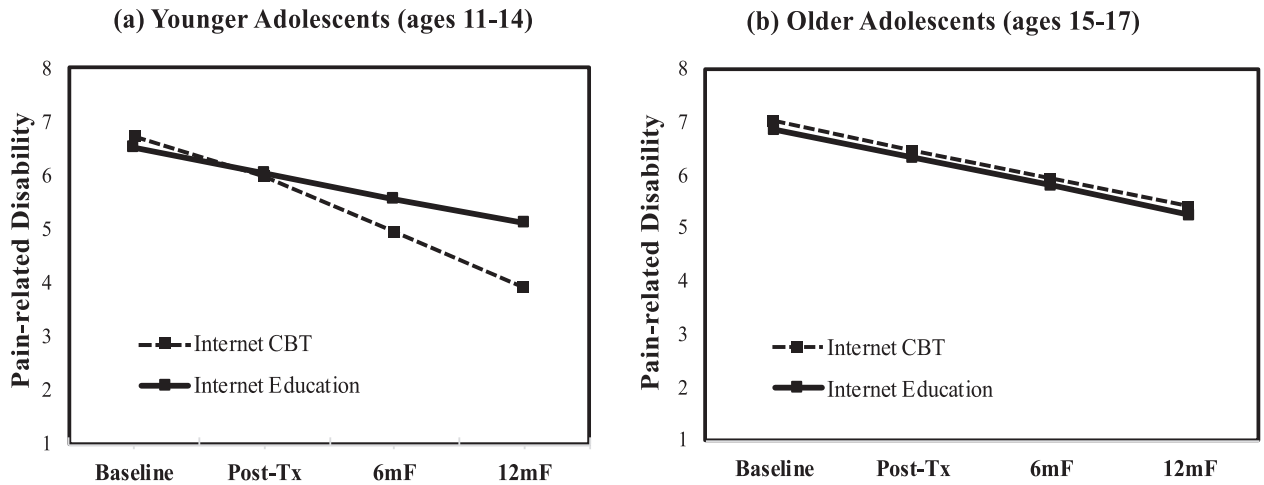

Figure 2. Adolescent age moderates the efficacy of Internet-delivered CBT.

Note. Figure 2 displays estimated marginal means of pain-related disability of the treatment and control group across each assessment occasion for (a) younger adolescents (ages 11−14) and (b) older adolescents (ages 15−17) to visually depict significant differences in treatment response according to level of the moderator (adolescent age).

reduced regression models found that the moderating effect of adolescent age remained significant. As depicted in Fig 2, predicted outcomes were calculated for younger (ages 11−14) and older (ages 15−17) adolescent age groups. Specifically, younger adolescents in the Internet CBT group demonstrated significantly greater improvement in pain-related disability relative to the Internet Pain Education group from pretreatment to 6-month follow-up (CBT: b = −2.92, SE = .51, $P < .00001$; Education: b = −.46, SE = .53, $P = .388$) and 12-month follow-up (CBT: b = −3.34, SE = .51 $P < .001$; Education: b = −1.81, SE = .53, $P = .001$). Treatment effect sizes (Cohen's ds) confirmed that for younger adolescents, Internet CBT was associated with superior outcomes relative to Internet Pain Education: Effects were medium from pre-treatment to 6 months (t[755] = −4.84, $P < .001$; Cohen's d = −.50) and small from pretreatment to 12 months (t[755] = −3.10, $P = .001$; Cohen's d = −.20). However, for older adolescents, changes in pain-related disability were similar between Internet CBT and Internet Pain Education conditions (pretreatment to 6 months: t[755] = −.73, $P = .234$, Cohen's d = .01; pretreatment to 12 months: t[755] = −.47, $P = .320$, Cohen's d = .04). In sum, these findings indicate that Internet CBT was associated with improvements in pain-related disability relative to Internet Pain Education up to 12 months post-treatment only for younger adolescents with chronic pain.

Adolescent-Level General Predictors

Although not identified as significant treatment moderators, pain intensity and sleep quality emerged as significant general predictors of changes in pain-related disability (ie, significant Predictor X Time interactions only) in Step 4 of the adolescent-level model and in the final model. Worse sleep quality at pretreatment predicted less improvement in (ie, higher) pain-related disability from pretreatment to 12-month follow-up (b = −.76, SE = .26, $P < .004$) irrespective of treatment condition (ie, across all youth randomized to either Internet CBT or Internet Pain Education conditions). Higher pretreatment pain intensity predicted greater improvement in (ie, lower) pain-related disability from pretreatment to 6-month follow-up (b = −1.22, SE = .26, $P < .001$) and pretreatment to 12-month follow-up (b = −1.84, SE = .26, $P < .001$) for youth across both treatment conditions.

Parent-Level Treatment Moderators

Parent education and protective parenting behaviors did not emerge as significant moderators (ps > .05). However, parent emotional distress significantly interacted with group and time to moderate pain-related disability (ie, significant Parent Distress X Time and Parent Distress X Treatment X Time interactions) in Step 4 and this interaction remained significant in the final model. Specifically, pretreatment parent distress predicted a differential effect of treatment on change in pain-related disability from pretreatment to 12-month follow-up (b = −1.20, t = −2.00, $P = .046$). This moderation effect was not present from pretreatment to 6 months (see final model in Table 2).

Fig 3 depicts the results of post hoc analyses (tests of simple effects) determining the nature of the moderating effect of pretreatment parent distress on change in pain-related disability following treatment. These analyses revealed that the simple slopes (ie, change in disability) of the treatment groups significantly differed from one another at high (+1 SD above mean) and low (−1 SD below mean) values of pretreatment parent distress. Specifically, relative to the Internet Pain Education group, Internet CBT was more effective in improving adolescents' pain-related disability (ie, rate of change was significantly greater) from pretreatment to 12-month follow-up for parents reporting *low* distress (CBT: b = −4.15, SE = .62, $P < .001$ Education: b = −2.07, SE = .47, $P = .001$); treatment effects were small (t[755] = 2.79, $P = .003$, Cohen's d = −.45). By contrast, rate of change in adolescents' pain-related disability from pretreatment to 12 months was similar between the treatment groups for

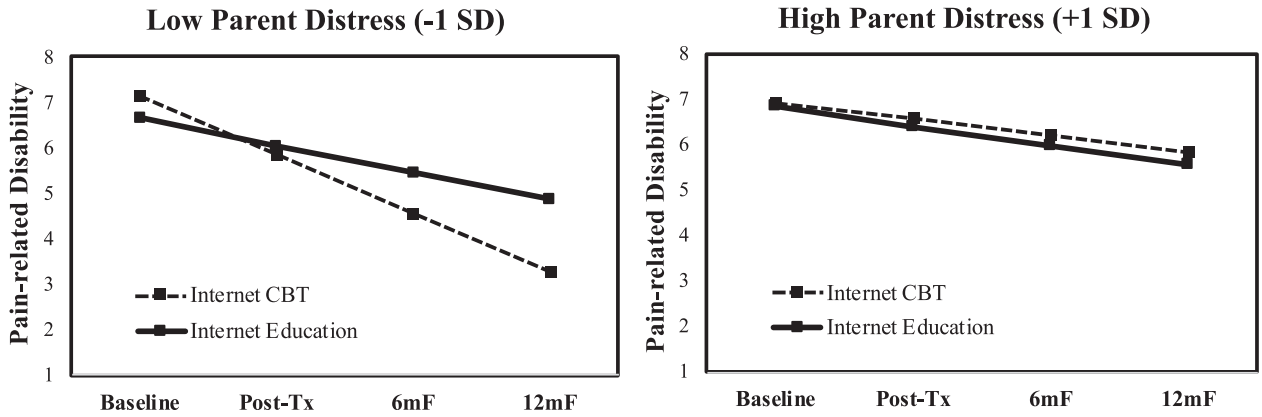

Figure 3. Pretreatment parent distress moderates efficacy of Internet-delivered CBT.
Note. Figure 3 displays estimated marginal means of pain-related disability of the treatment and control group across each assessment occasion for parents with (a) low distress and (b) high distress to visually depict significant differences in treatment response according to level of the moderator (parent distress).

parents reporting *high* pretreatment levels of distress (t [755] = .78, P = .219, Cohen's d = −.09). In sum, these findings indicate that Internet CBT was associated with long-term improvements in disability relative to Internet Education, but only in families with low parental distress prior to treatment.

Parent-Level General Predictors

Parent education and protective parenting behaviors did not emerge as significant general predictors of pain-related disability (ps > .05). Parent distress was identified as a moderator versus general predictor because both Distress X Time and Distress X Treatment X Time interactions were significant (see above).

Discussion

This study presents several key findings: first, as reported in Palermo et al,[35] small effect sizes were found for Internet CBT in reducing disability up to 6 months post-treatment compared to Internet Pain Education. We present new 12-month follow-up data indicating that mean levels of pain-related disability continued to improve, although the between-group treatment effects were attenuated. Finally, we evaluated adolescent and parent moderator variables and found that adolescent age predicted a differential effect of treatment on change in disability at both 6 and 12 months, while parent emotional distress emerged as a significant moderator of 12-month disability outcomes. A few general predictors also emerged, such that better sleep quality and higher pain intensity at pretreatment predicted greater improvements in disability across treatment conditions. These findings support the importance of moving beyond the singular investigation of average treatment effects to identify youth with chronic pain who may require tailored treatment approaches to enhance long-term outcomes.

Few studies have reported on the long-term efficacy of remotely delivered CBT interventions. Although some have demonstrated effects at 6 months post-treatment,[2,35,47] to our knowledge, this study is the first to report on effects at 1-year post-treatment. Our findings suggest that improvements in disability that were observed at 6 months were attenuated at 12-month follow-up. Considering ways to maximize long-term effects, such as by extending the duration of treatment and/or adding booster sessions, may be beneficial. Moreover, the current study's findings regarding treatment moderators at 12-month follow-up, discussed in detail below, suggest several promising avenues for identifying at-risk individuals and strengthening treatment durability.

In our moderation analyses, we found that younger adolescents (ages 11−14) benefited significantly more from Internet-delivered CBT relative to older adolescents (ages 15−17) at both 6 and 12 months post-treatment. Age has rarely been examined in pediatric treatment studies; however, one RCT of CBT for adolescents undergoing spinal fusion surgery found that younger adolescents had greater reductions in postsurgical pain and anxiety than older adolescents.[27] Another study identified older adolescents (ages 15−17) as the largest proportion of treatment nonresponders 12 months after discharge from an intensive pediatric pain rehabilitation setting.[41]

Several theoretical reasons may explain why older adolescents evidence attenuated treatment response. First, adolescents may represent a difficult to treat population because they often experience debilitating pain for a longer period before entering tertiary care,[56] resulting in more ingrained cognitions and behaviors that perpetuate pain and disability. Indeed, observational research has shown increasing pediatric age is associated with more frequent use of maladaptive coping (eg, avoidance,[40] catastrophizing[4]) and these processes may have a stronger negative impact on disability as children grow older.[12,40] In addition, our CBT treatment incorporates active parental involvement to promote adolescent functioning, but this approach may be at odds with older adolescents' increased drive for independence from parents. In fact, studies of other pediatric conditions (eg, diabetes and cystic fibrosis) have found that older adolescents are at greater risk for poor adherence to self-management tasks, with corresponding declines in parental involvement and monitoring.[30] Altogether, this finding underscores the importance of further research to understand how best to tailor CBT treatment to the unique needs of older adolescents with chronic pain.

We also found that pretreatment parent distress moderated long-term treatment effects. High levels of parent distress have been commonly reported among parents caring for adolescents with chronic pain[5,23,33] and recent work shows longitudinal associations between changes in parental distress and changes in adolescent pain and disability.[3] Our research group previously published an analysis of only the CBT treatment condition, indicating greater parent distress at pretreatment predicted increases in adolescent disability over 12 months.[28] The present study extends these observations by demonstrating that parent distress also impacts the effectiveness of CBT at 12-month follow-up, such that CBT was more efficacious than pain education for adolescents whose parents displayed lower levels of pretreatment distress. It has often been noted that parents of youth with chronic pain may serve as important therapeutic agents of change.[5,34] Screening for and treating parental distress may have important downstream effects on adolescents' treatment outcome, as high distress may prevent a parent from effectively implementing pain management strategies or supporting their adolescent's use of self-management skills.

Notably, while parental distress emerged as a treatment moderator, adolescents' own distress was not linked to treatment benefit. This pattern of results may be related to the specific targets and content of our CBT treatment. The Internet CBT program included separate programs for adolescents and their parents, and only the adolescent program included a model directed at improving emotional coping while the parent program

emphasized operant strategies. Recent trials have highlighted significant improvement in distress and maladaptive parenting behaviors following interventions aimed at reducing parent distress[34] and mindfulness strategies.[38] This suggests potential value in screening for parent distress and using more targeted interventions to reduce distress.

Finally, this study also identified 2 general predictors across treatment conditions. First, higher pain intensity predicted greater improvement in disability. Other researchers have noted that elevated levels of active symptoms at baseline may provide greater impetus for change, facilitating the engagement and application of CBT skills and pain educational material to improve functioning.[39] Second, co-morbid sleep difficulties predicted less improvement in disability. Sleep deficiency is one of the most debilitating co-occurring symptoms in children with chronic pain (see reviews by Tang[46] and Allen et al[1]) and often results in impairments in cognitive-affective and neurobiological processes (eg, executive functioning, motivation) that might broadly effect adolescents' ability to learn and apply skills or knowledge-based information. Future studies may consider measuring sleep quantity as well as sleep quality to provide a more comprehensive understanding of the role of sleep deficiency.

This study has several notable strengths. Our study analyzed a relatively large sample of treatment-seeking youth recruited from tertiary pain clinics across North America and included a long-term follow-up at 12 months post-treatment. Like most RCTs, our trial was originally powered to detect main treatment effects and not smaller interaction effects; a priori designs that identify treatment moderators using well-powered multicenter pediatric trials are critically needed. Nevertheless, we adopted a balanced, conservative statistical approach by testing moderators simultaneously and requiring them to be significant in Step 4 and the final models, thus reducing the likelihood of Type I error.

Several questions remain that may be addressed in future research. First, we did not identify moderators a priori, thus a broader range of potential moderators may be tested in future work. A number of psychophysical, genetic, or cognitive-affective processes (eg, readiness to change, perceived self-efficacy have been found to moderate outcomes in CBT trials of adults with chronic pain; see Ehde, Dillworth, & Turner[9] for a review) and will be important to incorporate in future pediatric pain trials. While we chose to evaluate the primary outcome (pain-related disability) to limit the number of potential analyses, it is possible that different patterns of treatment response may be found for other key outcomes (ie, pain intensity, adolescent depression). Moreover, an important future development will be the provision of clear guidelines on the theoretical selection, measurement, and analysis of treatment moderators in the context of pediatric pain trials. Similar guidelines have been set forth by the IMMPACT group[8] to stimulate work on treatment moderators in adult trials. In addition, future work is needed on innovative assessment approaches given the complex, dynamic interaction of child and parent functioning and responses to pain. Exploratory statistical approaches that simultaneously combine treatment moderators have recently emerged in the adult treatment field,[54,57] and could lead to novel and powerful methods for matching youth to treatment based on multiple pretreatment characteristics. Finally, regarding sociodemographic characteristics of the study sample, the majority of the participants in the sample were non-Hispanic White females from middle-income households. While these characteristics are representative of youth presenting to tertiary pain clinics, the lower percentage of males, ethnic minorities, and low-income youth likely limited our ability to detect moderation effects and generalize findings to populations with different sociodemographic backgrounds. Relatedly, although baseline analyses found that groups were well balanced across a number of demographic covariates, there was a slightly higher proportion of non-Hispanic White participants in the treatment condition (vs the education condition); adolescent race was included as a covariate in analyses to reduce any potential bias resulting from racial/ethnicity imbalance.

In conclusion, this study presents important information on who benefits most (and least) from a RCT of a psychological intervention for pediatric chronic pain. Future investigations should replicate and extend these findings by testing additional theory-based moderators of treatment efficacy. Pediatric pain trials designed to capture this information can direct the next wave of personalized pediatric pain interventions.

Supplementary data

Supplementary data related to this article can be found at doi:https://doi.org/10.1016/j.jpain.2019.10.001.

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