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Functional Disability in Adolescents with Chronic Pain: Comparing an Interdisciplinary Exposure Program to Usual Care

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Abstract: (1) Background: Chronic musculoskeletal pain (CMP) in adolescents can negatively affect physical, psychological and social functioning, resulting in functional disability. This study aims to evaluate the effectiveness of an outpatient rehabilitation program based on graded exposure in vivo (EP) compared with care as usual (CAU) in a RCT. The aim of the interventions (EP and CAU) is to improve functional ability in adolescents with CMP, CAU is interdisciplinary outpatient rehabilitation care, based on graded activity. **(2) Methods:** A pragmatic multicenter randomized clinical trial with a 12-month follow-up was used. Adolescents (12-21 years) with musculoskeletal pain were invited to participate. Primary outcome was functional disability (Functional Disability Inventory). Most important secondary measures: perceived harmfulness, pain catastrophizing and intensity. Data analysis was performed by intention-to-treat linear mixed model analysis. **(3) Results:** Sixty adolescents were randomized to EP or CAU and data of 53 adolescents (93% female) could be analyzed (25 EP, 28 CAU). Mean age was 16.0 years ($SD=1.87$). Adolescents in EP showed a clinically relevant and statistically significant decrease in functional disability (estimated mean difference at least $-8.81, p\text{-values}\leq 0.01$) compared with CAU at all time points. Significant differences in favor of EP were found for perceived harmfulness at all time points ($p\text{-values}\leq 0.002$), for pain catastrophizing (PCS) at 2 months follow-up ($p\text{-value}=0.039$) and for pain intensity at 4 and 10 months follow-up ($p\text{-values}\leq 0.028$). **(4) Conclusion:** The effectiveness of the trial is in favor of the EP and leads to a significant and clinically relevant decrease in functional disability compared to usual care.

Keywords: Chronic musculoskeletal pain; Adolescents; functional disability; multidisciplinary rehabilitation.

1. Introduction

Chronic pain in children and adolescents is a major health concern [1, 2]. Chronic musculoskeletal pain (CMP) is one of the most reported pain complaints next to chronic headache and abdominal pain [1, 2]. Internationally, prevalence rates for CMP vary between 4 and 40% and appear to be increasing [1, 2]. Pain during adolescence increases the risk of pain in adulthood [3, 4].

Evidence about treatment effects of interdisciplinary treatments for adolescent chronic pain is relatively scarce. Psychologically-based treatments, including cognitive behavioral therapy, for adolescent chronic pain appear to be effective in reducing pain, and the quality of studies has improved over the years [5, 6]. However, most studies focus on adolescents with headache and use pain reduction as the primary outcome of interest. Evidence of treatment effectiveness on disability and emotional distress in adolescents with CMP is rare [5-7].

Pain-related fear can contribute to the development and maintenance of chronic pain and, in adults, there is evidence that cognitive behavioral graded exposure in vivo decreases functional disability by reducing pain-related fear [8-10]. The fear-avoidance model of chronic pain is the theoretical model underlying exposure therapy [11]. According to this model, in the event of pain, both fear of pain/movement and catastrophic thinking about pain can lead to the development and maintenance of chronic pain problems [11]. By exposing patients to movements and activities previously avoided due to pain-related fear, patients find that normal functioning is possible despite pain [8-10].

Recently, more evidence was found on the negative consequences of pain-related fear in children and adolescents with chronic pain [12-14]. Furthermore, the fear-avoidance model was expanded into an interpersonal fear avoidance model, accounting for the interaction between adolescents and parents, the social context in which adolescent pain problem arises [15]. These progresses led to the development of an interdisciplinary graded exposure program (EP), specifically for adolescents with CMP.

The primary objective of this study is evaluating the effectiveness of the EP in reducing functional disability, compared with care as usual (CAU), in adolescents of 12-21 years with CMP reporting pain-related fear. Secondary objectives are evaluating the effectiveness of the EP in reducing fear of pain, perceived harmfulness, pain catastrophizing, depressive symptoms, pain intensity, and improving health related quality of life. Explorative health care utilization and school support and school absenteeism of adolescents until 12 months after treatment in both groups are compared.

We hypothesize that an exposure based program will be more effective in reducing (pain related) disability measured with the Functional Disability Inventory in adolescents with CMP who report pain related fear as compared to usual care. Explorative, we hypothesize that adolescents in the EP program will utilize less health care and school support and will be less absent from school and schoolwork in the year after the treatment, compared to usual care.

2. Materials and Methods

2.1 Study design

The design was a multicenter pragmatic randomized controlled clinical trial (RCT) to evaluate whether EP is superior to CAU in reducing functional disability, the primary outcome measure. A study protocol is published elsewhere [16]. A pragmatic approach was chosen in line with our clinical focus. With the outcomes of the study we intend to support clinicians in their decision process between different options for care [17]. Ethical approval was granted for this trial (Project identification number NL47323.068.13) from the Medical Ethical Committee of the Maastricht

University Medical Centre. The study was conducted in accordance with the Declaration of Helsinki. All participants in the study gave their informed consent before they participated in the study. For the adolescents younger than 18, both the adolescent as well as the parents gave their informed consent.

2.2 Sample and procedure

Adolescents were recruited by consultants in rehabilitation medicine in four Dutch rehabilitation centers between August 2014 and September 2016. Patients and their parents were recruited after a pre-treatment screening and after eligibility criteria were checked. Adolescents referred to outpatient rehabilitation treatment for CMP, reporting pain-related fear according to the professional opinion of the interdisciplinary treatment team, aged 12-21 years, and with adequate Dutch literacy, were eligible for inclusion. Their opinion was based on their clinical experience. The decision-making process in the evaluation of the presence of pain related fear was supported by the outcome of Fear of Pain Questionnaire. Exclusion followed in case of any suspicion of a medical (orthopedic, rheumatic or neurological) disease that could fully explain their current level of severity of pain complaints, or any suspicion of an underlying psychiatric disease that would hamper rehabilitation treatment, or pregnancy.

Two of the four rehabilitation centers were rehabilitation departments of hospitals offering specialized outpatient rehabilitation care. All centers offered EP and CAU. A coordinator was appointed in each center to support the treatment teams with the study procedures during the trial.

2.3 Interventions

The EP consisted of active treatment sessions for both the adolescents and their parents. This program aims to restore the adolescents' age-appropriate functional abilities by systematically reducing pain-related fear and catastrophic thinking through gradually exposing adolescents to fear-provoking daily activities and movements. For adolescents, the treatment entailed an intake session with a consultant in rehabilitation medicine, screening, and 14 program sessions of 60 minutes each, during a 7 week period. The program sessions comprised an interdisciplinary intake session, an education session, and twelve graded exposure in vivo sessions. For parents, three parent meetings were offered in parallel with their adolescents' program, in a group or individually. Parent sessions were delivered in a group of 3-6 parent-couples to stimulate interaction between participants within the group. In case there were no additional parent-couples to join, the parent module was delivered individually (for a pair of parents), to restrict waiting time before starting the program.

For adolescents with hypermobility syndrome, physical training [18, 19] was added to the to prevent hypermobility problems hindering the graded exposure [6].

For adolescents diagnosed with joint hypermobility syndrome, the program incorporated 16 physical training sessions of 120 minutes each. Training was offered prior to the graded exposure in vivo sessions, expanding program duration to 15 weeks. The modules of the program are presented in the addendum. In addition, a detailed description of EP is provided in the design-article and highlights are again presented in table 1 [16, 20].

Table 1. Summary of contents of the Exposure program and treatment as usual program

Exposure program	Treatment as usual (GA)
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Underlying paradigm	Classical conditioning, Cognitive behavioural	Operant learning principles
Main treatment aim	Restore adolescents age-appropriate functional abilities by reducing pain related fear through gradually exposure to fear-provoking activities	Increase adolescents age appropriate functional abilities healthy behaviour by encouraging desired behaviour and time-contingent stepwise increase in activity levels
Therapists	Consultant in rehabilitation medicine, psychologist, physiotherapist or occupational therapist	Consultant in rehabilitation medicine, psychologist, physiotherapist or occupational therapist
Number of sessions	1 intake with consultant in rehabilitation medicine + 14 sessions of 1 hour. 3 sessions for parents	Varied van 9-16 sessions
Treatment overview in phases	Phase 1: intake + PHODA-youth (1 hour): cognitive behavioural analysis of complaints and consequences Phase 2: education (1 hour) about treatment rationale, personal fear avoidance model Phase 3: Exposure with behavioural experiments (12 x 1 hour), exposure to fear provoking activities and movements, generalisation and relapse prevention	Phase 1: inventory of the problem Phase 2: problem analyses Phase 3: education Phase 4: choosing activities Phase 5: determining baseline (pain contingent functioning) Phase 6: determining goal and scheme to increase activity Phase 7: executing scheme, time contingent increase of activities, encouraging of successful behaviour Phase 8 generalisation and evaluation
Parent module	3 sessions of 2 hours; medical education and treatment rationale, the role of pain in the family system, generalisation and relapse prevention	No separate parent program
Additional Physical training + alternative treatment schedule	Adolescents with pain complaints related to hypermobility receive 16 (x2 hours) physical training focusing on aerobic capacity, muscle strength, core stability, proprioception	No separate program for adolescents with pain complaints related to hypermobility.

The CAU, predominantly interdisciplinary cognitive behavioral graded activity treatment. In graded activity treatment, the aim is to restore the adolescents' age-appropriate functional abilities by encouraging desired behaviors, and a time-contingent, stepwise increase in activity levels. For the control intervention, centers followed their own CAU protocol (usual care), which is based on a consensus document of the Dutch working group for youth with chronic pain and fatigue. Due to each center's practical and logistic differences, CAU treatment duration varied between 9-16 weeks.

Both interventions were specialized rehabilitation care offered by interdisciplinary treatment teams consisting of a consultant in rehabilitation medicine, a psychologist, and a physiotherapist or occupational therapist. In CAU, a social worker might be involved as well. In both interventions, adolescents were asked to refrain from other (co-)interventions, and medication use was reduced or terminated if possible. In both interventions, an individual treatment plan was proposed to adolescents and parents, the teams evaluated progress regularly, the consultant in rehabilitation medicine evaluating progress with the adolescents on their treatment. A detailed description of all elements (differences and similarities) included in both treatment programs, is presented in the design article of this study, published in 2016 [6].

2.4 Measurement points, describing baseline and outcome measures for treatment effectiveness

Measurements were at baseline and at 2, 4, 10 and 12 months after start of EP, by digital questionnaires, accessible through a personalized link sent by email. Monthly diaries to assess health care utilization, school support and school absenteeism were used after the end of the treatment till a period of 12 months. Description of the measures and details of their psychometric properties are published in the design article of this study [16].

The primary outcome was functional disability, measured with the Functional Disability Inventory (FDI, 15 items, scored on a 0-4 point Likert scale: total score range 0-60, higher scores indicating more severe disability) [21, 22]. Secondary outcomes were fear of pain (Fear of Pain Questionnaire) [23, 24], perceived harmfulness (Photograph Series of Daily Activities for adolescents) [25], pain catastrophizing (Pain Catastrophizing Scale) [26], depressive symptoms (Children's Depression Inventory) [27], pain intensity (Visual Analogue Scale) [28], and pain-specific quality of life (Quality of Life Questionnaire for Adolescents with Chronic Pain) [29].

2.5 Protocol adherence and contamination check

An adapted Method of Assessing Treatment Delivery (MATD) was used [20, 30] to measure protocol adherence in EP and verify that neither intervention was contaminated with elements of the other intervention. Protocol adherence was measured as the degree to which essential treatment elements of EP were offered by the treatment teams [30, 31]. Treatment teams recorded their own program sessions. A random sample of 36 audio- and video-recorded sessions (14% of 262 recorded sessions) was drawn for analysis by one of the researchers (CD). Outcomes were reported as percentages for protocol adherence and contamination.

2.6 Randomization, allocation concealment and blinding

Minimization was used. Minimization factors chosen were age, sex and treatment center. In each center, the first adolescent had a 50% probability of being allocated to EP or CAU. In case of an unbalance in minimization factors, the probability of allocation to a particular group was adjusted to 90% for each following adolescent, to better ensure balance. The procedure was executed by a validated electronic randomization system (ALEA, offered by the Clinical Trial Center Maastricht). After written informed consent, the site coordinator was able to insert participant data: the system then randomized the adolescent and arranged a blinded treatment allocation. The randomisation and concealed allocation process included blinding of all relevant caregivers, statisticians during the trial. Patients were kept naïve about the preference of the researcher regarding the interventions. The data-collection and analysis remained blinded until results were analyzed.

2.7 Sample size

Sample size was calculated for the primary outcome measure FDI. A mean of 23 points (SD=9.2) (own unpublished clinical data) and expected mean difference of 5 points (approximately 25% difference) between groups on the total average FDI score at the end of treatment were used. Given $\alpha=0.05$, two sided testing, a power of 80%, and anticipating 15% loss to follow-up, a sample size of 62 participants per trial arm, 124 participants in total was calculated.

2.8 Statistical analysis

Descriptive statistics were used to explore the data, check for outliers and summarize baseline characteristics (number, % or observed mean, *SD*) for adolescents. Analyses were performed in IBM SPSS Statistics for Windows, version 25 (Armonk, NY: IBM Corp.).

2.9 Analysis of treatment effectiveness

To evaluate effectiveness, intention-to-treat linear mixed model analysis was used. This analysis accounts for correlation between repeated measures, uses all available data, assumes missing values to be random (missing at random, MAR), and corrects for baseline differences. Since it uses a likelihood approach, no imputation strategy was used. The primary and secondary outcome measures were used as dependent variables, while time (categorical: 0, 2, 4, 10, and 12 months), group (intervention vs control), interaction between time and group, and minimization variables (age, sex, and center) were included as fixed factors. If necessary, variables related to missing outcome values were included in the fixed part of the model to ensure MAR. As for the random part of the model, several options were considered, including an unstructured (UN) covariance structure for repeated measures, or a random intercept and/or random slope model (unstructured or variance components). The model with the smallest Bayesian Information Criterion (BIC) was chosen to be the best fitting model. Effect sizes are reported as estimated mean differences with 95% confidence interval between intervention and control. Two-sided *p*-values ≤ 0.05 were considered statistically significant.

2.10 Analysis of treatment delivery

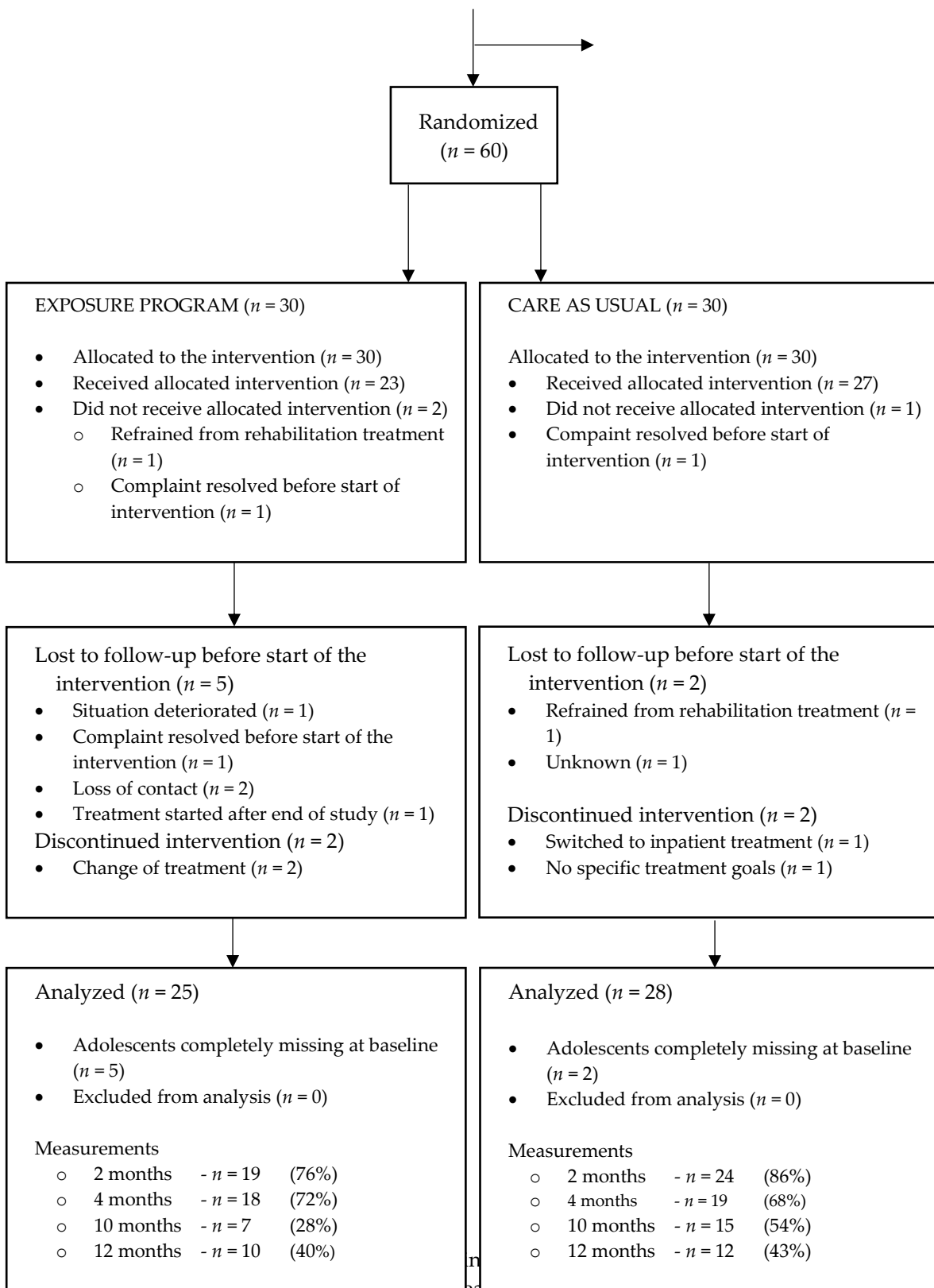
The recordings of treatment sessions were scored by two independent raters. De independent raters are: a master student in developmental psychology and a health scientist. These raters were trained to analyze the recordings for protocol adherence. In case of sufficient inter-rater reliability (Cohen's Kappa ≥ 0.61)[32], mean scores of both raters were used for subsequent analysis. Following the criteria of Leeuw and colleagues[30], for the EP, the proportion of essential treatment elements present in three different program phases (preparation, education, treatment) should exceed 70% for sufficient protocol adherence. Contamination was considered absent when less than 10% of prohibited treatment elements were scored in both treatments. Furthermore, more than 90% of the recorded sessions should be classified correctly as belonging to either EP or CAU.

3. Results

3.1 Description of the study population

Seventy-seven eligible adolescents were invited to participate. Seventeen participants declined participation for different reasons. Sixty adolescents were randomized and, because of seven completely missing cases, 53 were analyzed (Figure 1).

<p>Invited to participate after eligibility assessment (<i>n</i> = 77)</p>	<p>Declined to participate (<i>n</i> = 17)</p> <ul style="list-style-type: none"> • Unwilling to participate in study (<i>n</i> = 4) • Too busy with school (<i>n</i> = 3) • Unwilling to be randomized (<i>n</i> = 2) • Traveling distance to the center is
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there were no meaningful differences between the groups. A total number of 10 adolescents were identified as having a hypermobile syndrome: 6 were randomized to EP and received an additional physical training-program as part of the new treatment and 4 were randomized to CAU and

received usual care. Since the number of participants did not progress as planned, the recruitment period was extended by 7 months from the planned 1.5 years. After the extended recruitment period of 7 months, the study had to be terminated due to financial/logistic reasons although the intended number of participants was still not reached.

Table 2. Characteristics of study participants at baseline ($n = 53$, $n = 7$ missing)

	Exposure program ($n = 25^{**}$)	Care as Usual ($n = 28^{**}$)	Total ($n = 53$)
Age (years) – mean (<i>SD</i>)	15.9 (1.99)	16.2 (1.79)	16.0 (1.87)
Sex (female) – n (%)	24 (96%)	25 (89%)	49 (92%)
Relative with pain complaints – n (%*)	13 (62%) (4 missing)	15 (60%) (3 missing)	28 (61%)
Other health issues – n (%*)	8 (38%) (4 missing)	11 (44%) (3 missing)	19 (41%)
Onset of current pain complaints – n (%*)	(4 missing)	(4 missing)	(8 missing)
<1 year	5 (24%)	12 (50%)	17(38%)
1-5 years ago	14 (67%)	11 (46%)	25(56%)
>5 years ago	2 (10%)	1 (4%)	3(7%)
Problems with sleep – n (%)	14 (67%) (4 missing)	17 (68%) (3 missing)	31(67%) (7 missing)
Education - n (%*)	(3 missing)	(3 missing)	(6 missing)
Low	11 (55%)	16 (64%)	27 (58%)
Middle	5 (23%)	6 (24%)	11 (23%)
High	6 (27%)	3 (12%)	9 (19%)
Absence at school in the past year - n (%*)	(3 missing)	(3 missing)	(6 missing)
0-14 days	14 (64%)	15 (60%)	29(62%)
15-30 days	3 (14%)	1 (4%)	4(9%)
1-3 months	2 (9%)	6 (24%)	8(17%)
4-6 months	2 (9%)	1 (4%)	3(6%)
7-12 months	1 (4%)	2 (8%)	3 (6%)
FDI, scored 0-60) – mean (<i>SD</i>)	24.7 (10.3)	23.1 (8.1)	23.8(9.1)
QLA CP, scored 0-3) – mean (<i>SD</i>)			
Domain Psychological Functioning	1.57 (0.47)	1.67 (0.51)	1.62(0.49)
Domain Functional Status	1.74 (0.53)	1.86 (0.44)	1.80 (0.48)
Domain Physical Status	1.81 (0.63)	1.76 (0.64)	1.78 (0.63)
Domain Social Functioning	1.72 (0.60)	1.81 (0.59)	1.77(0.59)
FOPQ, scored 0-96) – mean (<i>SD</i>)	40.1 (16.7)	38.7 (13.7)	39.3(15.0)
PCS, scored 0-52) – mean (<i>SD</i>)	22.1 (11.0)	20.3 (9.5)	21.1 (10.2)
CDI, scored 0-54) – mean (<i>SD</i>)	26.1 (2.55)	25.7 (2.53)	25.9(2.51)
VAS 0-100) – mean (<i>SD</i>)	53 (14)	55 (22)	54 (18)
PHODA-Youth, scored 0-510) – mean (<i>SD</i>)	191 (121)	180 (119)	185 (119)
Credibility (CEQ, scored 3-27) – mean (<i>SD</i>)	17.7 (5.1)	18.3 (5.2)	18.0 (5.0)
Expectancy (CEQ, scored 2-18) – mean (<i>SD</i>)	13.2 (2.6)	12.5 (3.5)	12.8 (3.1)

Note. *Valid percent

FDI (Functional disability index) = functional disability, QLA-CP (Quality of Life in Adolescent with Chronic pain, FOPQ (Fear of Pain Questionnaire) = pain related fear,

PCS-C (Pain Catastrophizing Scale-Child version)= pain catastrophizing, CDI (child Depression Inventory)= depressive symptoms, PHODA-Youth (Photograph Series of Daily Activities-Youth)= perceived harmfulness.

3.2 Effects of the multimodal rehabilitation program

Table 3 shows treatment effects of EP compared with CAU. No variables were significantly related to missing values in the outcome measures at any time point. For all dependent variables, a random intercept model was the best fitting model.

Table 3 Results of Linear Mixed Model analyses for all outcome measures (*n* = 53 at baseline)

	Estimated mean difference* (95% CI); <i>p</i> -value							
	At 2 months (N=43)		At 4 months (N=37)		At 10 months (N=22)		At 12 months (N=22)	
FDI	-9.96 (-15.39 to -4.53);	.000	-9.16 (-14.79 to -3.52);	.002	-10.09 (-17.17 to -3.01);	.006	-8.81 (-15.59 to -2.044);	.011
FOPQ	-3.61 (-12.60 to 5.37);	.427	-8.00 (-17.26 to 1.26);	.090	-6.43 (-18.16 to 5.31);	.280	-8.08 (-19.21 to 3.044);	.153
PHODA-Youth	-82.19 (-131.06 to -33.32);	.001	-108.62 (-159.21 to -58.03);	.000	-134.32 (-203.17 to -65.46);	.000	-96.12 (-157.63 to -34.61);	.002
PCS	-5.86 (-11.42 to -0.30);	.039	-4.96 (-10.75 to 0.83);	.092	-4.89 (-12.15 to 2.37);	.185	-5.58 (-12.46 to 1.31);	.112
CDI	-1.57 (-5.04 to 1.90);	.371	-1.14 (-4.72 to 2.44);	.530	-6.16 (-10.70 to -1.62);	.008	-3.27 (-7.57 to 1.03);	.135
Pain intensity	-11.80 (-24.70 to 1.10);	.073	-14.88 (-28.08 to -1.67);	.028	-21.94 (-39.76 to -4.13);	.016	-10.74 (-26.79 to 5.30);	.187
QLA – Psychological Functioning	5.55 (0.15 to 10.95);	.044	3.90 (-1.71 to 9.51);	.171	7.58 (0.49 to 14.66);	.036	4.94 (-1.79 to 11.68);	.149
QLA – Functional Status	3.96 (1.12 to 6.80);	.007	3.63 (0.68 to 6.58);	.016	3.71 (-0.01 to 7.43);	.051	3.52 (-0.01 to 7.06);	.051
QLA – Physical Status	0.62 (-1.51 to 2.75);	.567	0.66 (-1.56 to 2.87);	.559	0.77 (-2.01 to 3.55);	.585	1.02 (-1.64 to 3.68);	.448
QLA – Social Functioning	-0.25 (-4.55 to 4.05);	.909	2.88 (-1.30 to 7.07);	.176	2.74 (-2.85 to 8.33);	.334	1.97 (-3.37 to 7.31);	.467

Note. * corrected for baseline, center, age and sex (Random Intercept model)

FDI (Functional disability index) = functional disability, FOPQ (Fear of Pain Questionnaire) = pain related fear, PHODA-Youth (Photograph Series of Daily Activities-Youth)= perceived harmfulness, PCS-C (Pain Catastrophizing Scale-Child version)= pain catastrophizing, CDI (child Depression Inventory)= depressive symptoms, QLA (Quality of Life in Adolescent with Chronic Pain).

For the primary outcome FDI, estimated mean differences of at least 8.8 points (p -values ≤ 0.011) between EP and CAU, in favor of EP, were observed for all time points, corrected for baseline (Table 3, Figure 2).

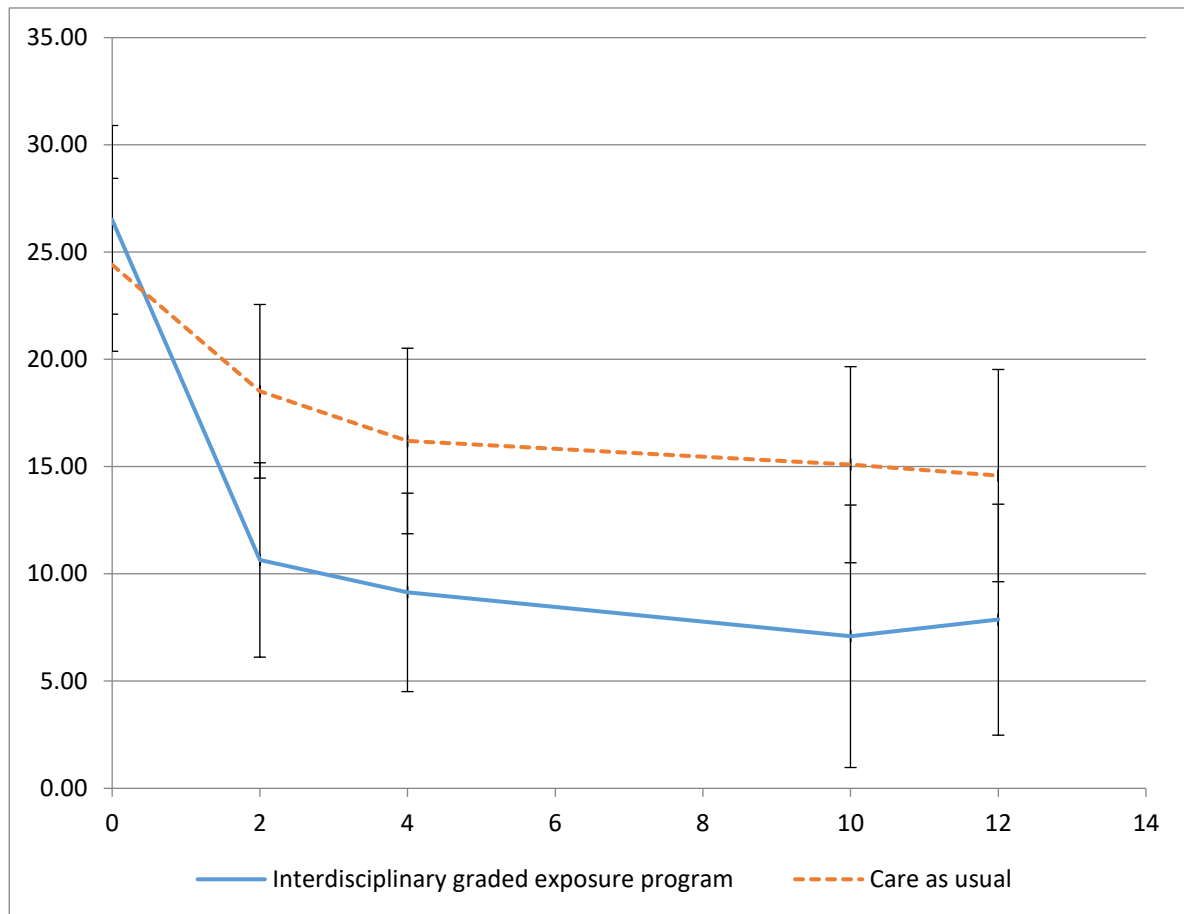


Figure 2. Estimated mean group scores on the FDI at baseline and after 2, 4, 10 and 12 months with a 95% confidence interval.

On the secondary outcomes, significant differences in favor of EP were found for perceived harmfulness at all time points (p -values ≤ 0.002), for pain catastrophizing (PCS) at 2 months follow-up (p -value=0.039), for depressive symptoms at 10 months follow-up (p -value=0.008), for pain intensity at 4 and 10 months follow-up (p -values ≤ 0.028), for quality of life for the domain Psychological Functioning at 2 and 10 months follow-up (p -value ≤ 0.044), and for the domain Functional Status at 2 and 4 months follow-up (p -values ≤ 0.016).

An additional analysis was performed excluding adolescents with hypermobility syndrome from both EP (6) and CAU (4). Identical results were found in this analysis.

3.3 Health care utilization and school support and absenteeism

Monthly cost diaries were filled by 22 adolescents (13 EP and 9 CAU). During 12 months after treatment, adolescents in EP had less hours of contacts with general practitioner (EP: $M=8.0$; $SD=1.77$ / CAU: $M=6.58$; $SD=9.47$), other health care providers (EP: $M=4.28$; $SD=7.34$ / CAU: $M=7.12$; $SD=14.72$), alternative health care (EP: $M=3.8$; $SD=9.6$ / CAU: $M=1.12$, $SD=3.35$) and less hours of

school support (EP: $M=2.03$; $SD=.55$ / CAU 2.83 , $SD=4.07$) compared to adolescents in CAU. Adolescents in CAU visited the medical specialist less often (EP: $M=2.28$, $SD=5.06$ / CAU: $M=1.66$, $SD=2.74$). Furthermore, adolescents who received EP were more absent from school ($M=45.85$, $SD=93.10$) compared to those who received CAU ($M=19.31$, $SD=39.57$). On the other hand, adolescents in CAU missed more hours of self-study and home work ($M=30.25$, $SD=60.30$) compared to adolescents who followed the EP program ($M=1.74$, $SD=6.28$).

3.4 Protocol adherence and contamination

Inter-rater reliability was Cohen's kappa =0.69 for the assessment of the treatment elements. Protocol adherence for EP was high since on average 80.8% ($SD=11.05$) of the essential treatment elements occurred [20]. Contamination was on average 4.9% ($SD=9.19$) in EP and 7.7% ($SD=10.30$) in CAU, below the threshold and therefore absent. Overall, 92% of the recordings were classified correctly as belonging to EP or CAU. One rater misclassified one CAU recording as EP; the other rater misclassified five CAU recordings as EP.

4. Discussion

This study demonstrated that in adolescents with CMP reporting pain-related fear, an interdisciplinary graded EP led to a significantly larger decrease in functional disability than usual care at all time points. The difference of at least 8.8 FDI points that was found between the groups is statistically significant and clinically relevant [33]. Additionally, the magnitude of this difference was almost twice that predicted during the design of this trial.

Considering the severity of functional disability, adolescents in EP on average improved from moderate to light/no disability. Adolescents in CAU remained, on average, in the moderately disabled category.[34]. Furthermore, EP was more effective in decreasing perceived harmfulness of feared and avoided activities at all time points. At some time points EP appeared more effective in reducing pain intensity, pain catastrophizing, depressive symptoms and in enhancing health-related quality of life. Furthermore adolescents in EP used slightly less health care and school support, were more absent from school, but less from self-study.

The results of this trial add to the evidence on interdisciplinary chronic pain treatment to improve functional ability (e.g. [35-41]), explicitly focusing on outpatient rehabilitation treatment for adolescents with CMP. To our knowledge, this is the first RCT investigating a graded EP targeting pain-related fear to improve functional ability, despite pain. By taking a 12-month follow-up period, the results provide insight into the treatment effects in the longer term. The results show that the magnitude of the estimated difference between 10 and 12 months decreased slightly. This decrease is difficult to interpret, since at those time points 22 adolescents still completed the questionnaires. Missing questionnaires at these time points could not be related to any measured variables, which makes selective drop out of the study unlikely. Moreover, the magnitude of the decrease still remains well within a clinically relevant change of eight FDI points [34]. Therefore, this decrease is not considered to be of significant importance. Furthermore, perceived harmfulness of previously avoided activities and social situations also decreased significantly more in the EP group compared to usual care, at all time points. For the remainder of the secondary outcome measures, results differed per time point. No significant differences were found for fear of pain at all time points. Pain catastrophizing differed only at 2 months after the start of the intervention. Depressive symptoms showed a difference at 10 months after the start of treatment, and pain intensity showed differences at 4 and 10 months after start of treatment. For health related quality of life, differences in improvement in favour of the EP was visible at 2 and 10 months for the domain of psychological functioning and at 2 and 4 months for the domain of functional status. No differences were visible for the domains of physical status and social functioning.

In EP, a subgroup of patients, those with hypermobility syndrome, received an additional physical training-program. Unfortunately, due to the lower number of participants as expected no subgroup-analysis could be performed to study, as intended, differences in effect size between those that were hypermobile and those who were not. An additional analysis in which hypermobile adolescents were excluded resulted however to comparable results, which emphasizes the effect of the exposure treatment alone in CMP.

With a pragmatic approach in this trial, results for the comparative effectiveness of EP and CAU are as close to routine practice as possible [42]. Furthermore, eligibility criteria for referral to outpatient chronic pain rehabilitation for the trial were the same as they were for rehabilitation care outside this study. This increases the external validity of this trial. Internal validity was guaranteed by encouraging treatment teams to adhere to the EP protocol, using randomization with concealed treatment allocation, and blinding of the data collection and analysis [42].

Another strength of this trial was the evaluation of treatment delivery. Although in two of the four centers treatment teams offered either EP or CAU, in the other two centers each team offered both interventions, increasing the risk of contamination by the other intervention. Investigation showed that protocol adherence by the treatment teams in EP was high and contamination was absent, according to the pre-specified criteria. Inter-rater reliability for the rating of the treatment elements was substantial [32]. Protocol adherence was only evaluated for EP. Since CAU was not offered according to the same protocol in all centers, evaluation of protocol adherence was here considered inappropriate.

Some limitations need attention. The specified sample size was not attained. Since the difference between the treatment groups was almost twice as large as the minimum clinically relevant difference used in the sample size calculation, the smaller than desired sample size in this trial was less of an issue. Although this lower inclusion rate did not hinder evaluation of the primary research question, for the evaluation of the effect related to secondary outcome measures this might be a point needing attention. Even after a prolonged recruitment period of 25 months, in total only 60 adolescents were enrolled in the RCT. Increased efforts to enhance recruitment did not lead to the desired number of participants. These efforts consisted of activities such as prolonging the inclusion period, and increasing awareness of the treatment possibilities for adolescent CMP amongst referring physicians, increasing treatment capacity, raising awareness for treatment possibilities for adolescent chronic pain in the patient's association and publishing about the treatment possibilities in local (medical) monthly magazines. Factors that contributed to the lower recruitment are the fact that adolescents simply declined participation to a scientific study (almost 1/3 of the invited participants declined for various reasons) that involved some extra efforts as compared to normal treatment outside the RCT. Further, identification of pain-related fear was found to be challenging by the newly trained treatment teams. The most important criterion for offering EP is that pain-related fear is present in the patient [9]. This was not an explicit criterion in the eligibility criteria, but it was implicitly captured in the 'referral to outpatient rehabilitation'-criterion. It is, however, very important that pain-related fear is assessed during the screening. For treatment teams inexperienced in screening with a view to EP treatment, it can be a challenge to properly recognize the presence of pain-related fear. The use of the PHODA-Youth in this stage might offer a solution because this instrument was developed to identify those activities or situations perceived as harmful for the painful body part, and which are therefore feared [25]. Furthermore, if pain-related fear is not identified as a (major) problem during the screening it is less appropriate to start EP. Additionally, although clinical relevant change was investigated in a population of youth with fibromyalgia, this study provides the only reference point for interpreting treatment effects on the Functional Disability Inventory currently known. Last, clinical relevant change in the FDI was studied in youth with fibromyalgia [33]. To our knowledge, this is currently the only study reporting on clinical relevant change in the FDI.

Because of the pragmatic approach that was used in the RCT the results are highly applicable to rehabilitation care outside the study setting and therefore these findings are also relevant^[1] for other adolescents with CMP reporting pain-related fear. Due to the diversity in rehabilitation centers participating in the study, the study setting is a broad representation of the actual rehabilitation setting in the Netherlands. In the study, two pediatric rehabilitation centers, a rehabilitation department of a general hospital and a rehabilitation department of^[1] an academic hospital were represented.

As the consequences of the burden of chronic pain are not only felt by the adolescents themselves, but also by their families and by society as a whole, data of this study can be relevant to them as well. Parents and the family system are significantly influenced when they care for an adolescent with CMP. Amelioration of the adolescent's complaints benefits the parents and families as well. And as society bears the (large) financial consequences of increased health care utilization due to the pain complaints, there is a direct benefit if a treatment results in a reduction of these costs. The costs involved are however not only limited to direct and indirect medical costs, but also involve for example productivity losses of parents who care for their adolescent. These costs are of great importance to insurers, policy makers, and employers. Cost data were only explorative presented here, but should be assessed and evaluated in full in the future.

5. Conclusion

In adolescents with CMP, EP leads to a clinically relevant and significantly larger decrease in functional disability than does usual care. Furthermore, results on protocol adherence and contamination between interventions imply an honest comparison. Therefore, implementation of EP in rehabilitation care for adolescents with CMP and pain-related fear seems promising. However, further evaluation, such as a full cost-effectiveness of the new program, is first recommended.

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