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ORIGINAL ARTICLE

Tailored Cognitive–Behavioral Therapy and Exercise Training for High-Risk Patients With Fibromyalgia

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Objective. **The treatment of patients with fibromyalgia (FM), a high-prevalence chronic pain condition with a high impact on both patients and society, poses a great challenge to clinicians due to a lack of effective treatments. In view of the large individual variability in outcome, selecting patients at risk of long-term dysfunction and offering tailored treatment may be promising for beneficial treatment effects.**

Methods. **High-risk patients were selected and classified into 2 groups (pain-persistence and pain-avoidance groups) and subsequently randomized in groups to either a treatment condition (TC) or a waiting list control condition (WLC). Treatment consisted of 16 sessions of cognitive–behavioral therapy (CBT) and exercise training in groups, tailored to the patient's specific cognitive–behavioral pattern, delivered within 10 weeks. Physical and psychological functioning and impact of FM were assessed at baseline, posttreatment, and 6-month followup. Treatment effects were evaluated using a linear mixed model.**

Results. **The treatment effects were significant for all primary outcomes, showing significant differences in physical (pain, fatigue, and functional disability) and psychological (negative mood and anxiety) functioning, and impact of FM for the TC in comparison with the WLC. Effect sizes in the TC were overall large, and reliable change indices indicated a clinically relevant improvement among the TC.**

Conclusion. **The presented results demonstrate for the first time that tailored CBT and exercise training for high-risk patients with FM is effective in improving short- and long-term physical and psychological functioning, indicating that tailoring treatment is likely to promote beneficial outcomes in FM and reduce the burden for patients and society.**

INTRODUCTION

Fibromyalgia (FM) is a high-prevalence chronic pain condition without clear pathophysiologic mechanisms and is estimated to have the highest impact and highest financial burden of all rheumatic and chronic pain conditions (1). In addition to chronic, widespread pain, patients report high levels of accompanying symptoms such as fatigue, functional disability, and psychological distress. Due to the lack of effective treatment options, treating patients with FM poses a great challenge to clinicians (2). To date, combinations of cognitive–behavioral therapy (CBT) and physical exercise training have yielded the most promising results, but overall, effects were modest and showed large individual variability (3–5). In line with findings in various other conditions associated with chronic physical symptoms, recent developments in FM research suggest that the effectiveness of interventions may be improved by taking the heterogeneity of the patient group into consid-

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eration, with tailored approaches yielding promising outcomes (6–9).

Tailoring approaches may involve the selection of specific patient groups as well as customizing the type, content, and timing of the intervention. Patients with FM with high levels of dysfunction reporting relatively high levels of psychological distress have been shown to be more likely to benefit from treatment (10–12). Furthermore, subgroups can be identified within this distressed group that present with specific cognitive–behavioral patterns that are responsible for the maintenance of their pain and disability. Fear-avoidance models postulate that mechanisms such as pain-avoidance behavior, fear of pain, catastrophizing, and hypervigilance account for the continuation and exacerbation of the symptoms (13,14). However, there is growing attention for mechanisms underlying pain that are not captured by the fear-avoidance model. Preliminary evidence suggests a distinctive pattern in patients who tend to persist in their activities in spite of the pain, which can lead to overuse and more symptoms in the long run (15–17). Several studies have demonstrated the prognostic value of both pain-avoidance and pain-persistence factors for the development and maintenance of physical and psychological impairments in various chronic pain disorders, including FM (6,18–21). There is further evidence that tailoring treatment to these specific cognitive–behavioral patterns could improve treatment outcomes. Thieme and colleagues (22), for example, found that the FM responders to a pain-avoidance treatment aimed at increasing daily activities and diminishing fear of pain reported higher levels of pain behavior, social reinforcement, and catastrophizing at baseline than the nonresponders, while responders to a pain-persistence treatment aimed at pacing activities and changing high self-demands reported less pain behavior and social reinforcement than the nonresponders. However, more direct evidence underscoring the efficacy of treatment approaches that are tailored to these specific cognitive–behavioral patterns in improving physical and psychological functioning in FM is needed. Also, with regard to the timing of the treatment, the significance of treatment in an early stage is increasingly recognized as being able to help prevent a worsening of the symptoms and long-term dysfunction. In addition, several studies have shown that patients with chronic pain with a shorter duration of symptoms benefit most from CBT (23,24).

In sum, selecting high-risk patients and offering them a treatment consisting of CBT and exercise training tailored to their pain-avoidance or pain-persistence patterns at a relatively early stage after diagnosis is likely to promote beneficial treatment outcomes in FM. In the present study we evaluated the effects of such an approach in a randomized controlled trial. We hypothesized that, in comparison with a waiting list control condition (WLC), patients in the treatment condition (TC) would demonstrate statistically and clinically significant improvements in the primary outcome measures of physical functioning (pain, fatigue, and functional disability) and psychological functioning (anxiety and negative mood) and in the overall impact of FM, with at least medium to large effects posttreatment and at 6-month followup.

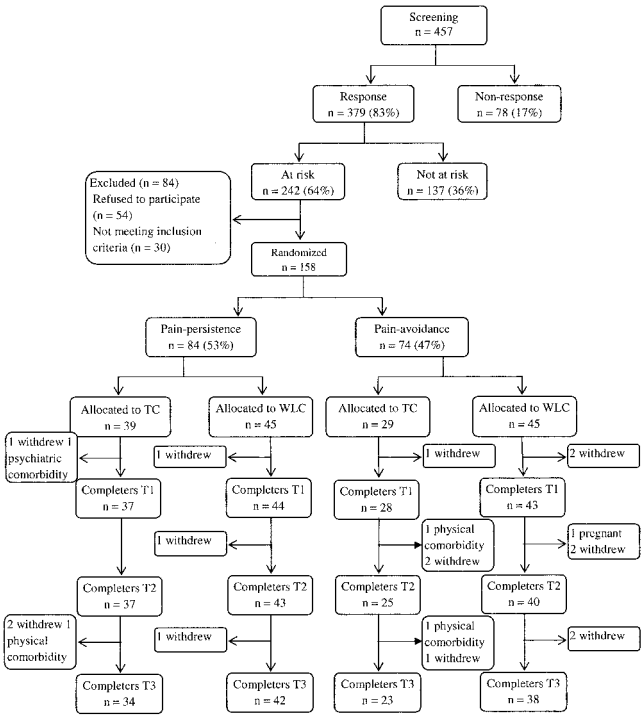

Figure 1. Flow chart showing participant selection and loss to posttest (T2) and followup (T3) for the 2 study conditions. TC = treatment condition; WLC = waiting list control condition; T1 = pretreatment.

PATIENTS AND METHODS

Participants and procedure. Patients with FM were referred by their rheumatologists from 6 regional hospitals in the area of Nijmegen, The Netherlands. To ensure a relatively early intervention (6,25,26), the inclusion criterion was a relatively recent diagnosis of FM (diagnosis <5 years previously by the American College of Rheumatology criteria [1]). Exclusion criteria were age <18 years, severe physical and psychological comorbidity that might interfere with the study protocol, FM secondary to another rheumatic condition, pregnancy, illiteracy and difficulty/inability to communicate in Dutch, participation in other clinical trials, and current psychological treatments. The study was approved by the medical ethics committee of the Radboud University Nijmegen Medical Centre and the trial was registered in a clinical trial registration.

A total of 457 eligible patients were sent a screening questionnaire assessing sociodemographic variables (sex, age, marital status, and educational level), physical and psychological functioning, and the screening instrument of pain-avoidance behavior. The questionnaire was returned by 379 patients (83%) (Figure 1), of whom the greater majority were women (95%) and were married or cohabiting (89%). Their mean ± SD age was 41.7 ± 10.9 years and 4% had a primary, 82% a secondary, and 14% a tertiary educational level, representing an average of 7, 12, and 17 years of formal education, respectively. Of this sample, 242 patients (64%) had a risk profile of heightened psychological distress based on cutoff scores for negative mood and/or anxiety of norm groups with risk scores of

distress previously validated in FM (15,26–28). In addition, these high-risk patients had, in comparison with patients not at risk, significantly higher levels of pain, fatigue, functional disability, and impact of FM on daily life (all $P < 0.001$). These high-risk patients were sent a written invitation within 4 weeks to take part in a randomized controlled trial. Of these patients, 54 declined to participate, most because of lack of interest or practical concerns such as traveling distance and scheduling difficulties (inability to combine the intervention with work and other daily activities). During the intake procedure by the therapists who checked the inclusion and exclusion criteria, 30 patients failed to meet the inclusion criteria, due to severe physical and psychiatric comorbidity (n = 27), pregnancy (n = 1), and insufficient motivation (n = 2) (Figure 1). No significant differences were found between the excluded 84 patients and the included patients (n = 158) with regard to sociodemographic variables or physical and psychological functioning.

Subsequently, these 158 patients were assigned to a pain-avoidance or a pain-persistence group based on a previously validated procedure consisting of the judgment of a trained therapist based on a semistructured interview and a screening instrument of pain-avoidance behavior (2,15). The therapist's judgment and the screening instrument were concordant with regard to the classification in pain-avoidance and pain-persistence patterns for the majority of patients, except for 17 patients (11%) who were assigned according to the judgment of the therapist (15,29). The cutoff score of the screening instrument was based on the previously assessed mean of pain-avoidance behavior in several populations with chronic pain to distinguish between pain-persistence and pain-avoidance patterns, reflecting a level of pain-avoidance behavior below and above the cutoff, respectively (2,15). According to this procedure, 84 patients (53%) were assigned to the pain-avoidance group and 74 patients (47%) to the pain-persistence group. Written informed consent was obtained from all participants.

Subsequently, these 158 patients included in the trial were randomized in clusters to the TC or the WLC separately for the pain-avoidance and pain-persistence groups. These randomization clusters consisted of 8 patients because of the group size for the treatment, but the size of the clusters varied from 1 to 9 due to reasons such as the inclusion of WLC patients who were offered treatment at the end of their followup according to protocol and treatment that was scheduled on fixed months. For example, when 3 patients from the WLC were included in the next treatment group, the randomization clusters consisted of 5 patients due to the maximum group size of 8 patients for every treatment group. As a result of randomization, 39 patients (5 clusters) were allocated to pain-persistence TC, 45 patients (6 clusters) to the pain-persistence WLC, 29 patients (6 clusters) to pain-avoidance TC, and 45 patients (6 clusters) to pain-avoidance WLC. The primary outcome measures were assessed pretreatment (T1), posttreatment (T2), and at a 6-month followup (T3) in the TC group and at corresponding intervals in the WLC group using validated self-report questionnaires.

Pain-avoidance treatment	**Pain-persistence treatment**
Changing pain-avoidance mechanisms:	Changing pain-persistence mechanisms:
➢ Increasing daily activities	➢ Regulating and increasing daily activities
➢ Reduction of pain-avoidance behaviors, pain-behavior, and fear of pain	➢ Increasing activity pacing and changing pain-persistence cognitions
➢ Increasing the physical condition	➢ Increasing the physical condition

Figure 2. Overview of the treatment aims and targets of the pain-avoidance and pain-persistence treatments.

Tailored treatment. The patients assigned to the TC received a highly structured outpatient treatment program in a group setting of 8 participants. Patients received a pain-avoidance or a pain-persistence treatment, depending on their specific pain-avoidance or pain-persistence cognitive–behavioral pattern (Figure 2). Both the pain-avoidance and the pain-persistence treatments consisted of 16 twice weekly sessions and 1 booster session 3 months after treatment completion, with every regular session starting with 2 hours of CBT followed by 2 hours of exercise training. The patient's partner (or another significant relation) attended the third, ninth, and fifteenth sessions. The treatment protocols for the pain-avoidance and pain-persistence interventions were developed mainly based on techniques from standardized treatment protocols for FM and also on treatment protocols for other chronic physical conditions (6,8–10). For both treatments, CBT was aimed at diminishing the daily perceived cognitive, behavioral, emotional, and social consequences of pain and accompanying symptoms. Every CBT session started with the discussion of the homework, then the specific topic of the session was introduced and practiced with the other participants, and finally the homework for the next session was explained. Exercise training was aimed at increasing the level of physical fitness and flexibility. Each exercise session consisted of relaxation training, aerobic exercises (e.g., cycling, gymnastic exercises), and hydrotherapy or anaerobic exercises (e.g., strength and flexibility exercises, functional walking training).

The pain-avoidance treatment was specifically aimed at increasing the patient's level of daily activities and diminishing their pain-avoidance behaviors by stimulating them to gradually and systematically increase their daily activities with individual goals and exposure to fear-related situations as the guiding principle. During the CBT, patients learned to set goals with regard to specific daily life domains and increase their daily activities regardless of the symptoms. In the sessions during which the patient's partner was present, the importance of reinforcing healthy behaviors and ignoring possible pain behaviors was discussed and practiced. During the exercise training, patients also learned to gradually and systematically increase their daily exercises.

The pain-persistence treatment first focused on regulating and diminishing pain-persistence behaviors by teaching the participants to pace their activities and to alternate between activity and inactivity, followed by gradually increasing their daily activities. During the CBT, attention was paid to realistic goal setting, a balanced daily activity program, cognitive restructuring techniques, and assertive social skills. During the exercise training, patients learned to perform their exercises according to a systematic and gradual plan.

Table 1. Baseline sociodemographic characteristics of the participants for each of the study conditions*

	Pain persistence		Pain avoidance	
	TC (n = 39)	WLC (n = 45)	TC (n = 29)	WLC (n = 45)
Women	97	89	93	96
Married/cohabiting	82	77	72	76
Age, mean ± SD years	41.1 ± 9.4	40.9 ± 10.4	42.3 ± 12.4	39.4 ± 10.4
Educational level†				
Primary	9	5	4	2
Secondary	77	71	81	93
Tertiary	14	24	15	5

* Values are the percentage unless otherwise indicated. TC = treatment condition; WLC = waiting list control condition.
† Primary, secondary, and tertiary education represent an average of 7, 12, and 17 years of formal education, respectively.

In both the pain-avoidance and pain-persistence treatments, the patients received consolidating homework assignments (e.g., performing exercises at home, working on the individual goals, reading texts) supporting the CBT and exercise sessions, which took ~1.5 hours a day. The booster session focused on relapse prevention and a further improvement of the attained goals (for a more detailed treatment description, see the article by van Koulil et al [25]).

CBT was delivered by cognitive–behavioral therapists (a psychotherapist and a social worker) and the exercise training was led by physiotherapists (TvH, AV, HvH). All of the therapists were experienced in CBT for rheumatologic conditions, including FM, and were specifically trained in our tailored multidisciplinary treatment using an elaborated written manual (25) and regular supervision throughout the trial by senior cognitive–behavioral therapists. Additionally, an independent judge experienced with the treatment protocol performed an integrity check of a random sample of 5% of all audio-recorded CBT sessions. With regard to patient adherence in the TC, with 94% of the completers attending ≥14 treatment sessions and the remaining 6% attending ≥11 treatment sessions, attendance was high. In addition, the patients who withdrew before the start of the treatment attended evidently none of the treatment sessions, and the 3 patients who dropped out during treatment attended, on average, 3 treatment sessions. The judgment of the therapists about the level of the patients' adherence to the treatment protocol and homework assignments in a subgroup of patients (47%) also showed a relatively high to very high adherence for ≥80% of the treated patients.

Measures. *Sociodemographic variables.* Sociodemographic variables were assessed with a general checklist that inquired about the patient's sex, age, marital status, education, and medical history.

Physical functioning. Physical functioning was determined based on the outcomes of pain, fatigue, and functional disability. Pain was assessed using the 6-item pain scale (theoretical range 6–25, with higher scores indicating more pain) of the Impact of Rheumatic Diseases on General Health and Lifestyle (IRGL) instrument (27,28). The IRGL is derived from the Arthritis Impact Measurement Scales (30) and assesses physical, psychological, and social health in patients with rheumatic diseases, including patients with FM. Fatigue over the previous 2 weeks was measured with the 8-item fatigue scale (theoretical range 8–56, with higher scores indicating more fatigue) of the Checklist Individual Strength (31). Functional disability was assessed with the 7-item mobility scale (theoretical range 7–28) of the IRGL. A higher score on this latter scale indicates a lower level of functional disability.

Psychological functioning. Psychological functioning was determined based on the outcomes of negative mood and anxiety, assessed with the 6-item negative mood scale (theoretical range 0–24, with higher scores indicating a higher level of negative mood) and the 10-item anxiety scale (theoretical range 10–40, with higher scores indicating more anxiety) of the IRGL. Impact of FM on daily life was assessed with the 10-item Fibromyalgia Impact Questionnaire assessing physical impairment, pain, stiffness, fatigue, and anxiety and depressive symptoms (theoretical range 0–100, with higher scores indicating a greater impact of FM on daily functioning) (32,33).

Pain-avoidance behavior. The screening instrument for pain-avoidance behavior consisted of the 5-item resting when in pain scale (theoretical range 0–4, with a higher score indication a higher level of pain-avoidance behavior) of the Pain Coping Inventory, which identifies cognitive and behavioral patterns that limit pain in daily life (28).

Statistical analyses. Differences between subgroups were tested with chi-square analyses for categorical data and with Student's *t*-test for continuous variables with a significance level of *P* values less than 0.05 (2-tailed). Treatment effects were evaluated using a linear mixed model, taking into account the specific design features of this trial. For each of the 6 primary outcomes, the posttreatment and followup measurements were used as dependent variables and treatment, baseline measurement, patient pattern (pain avoidance or pain persistence), and time were used as independent variables in the primary analyses. Random effects were added for randomization groups and an unstructured covariance matrix was used to model the dependence of the posttreatment and followup

Table 2. Mean ± SD scores, numbers of patients, and ES of primary outcome measures for the TC and the WLC at all 3 assessments*

	T1		T2		T3		ES	
	Mean ± SD	No. patients	Mean ± SD	No. patients	Mean ± SD	No. patients	T1–T2	T1–T3
Physical functioning								
Pain								
Pain avoidance								
TC	20.3 ± 2.4	28	16.0 ± 3.2	25	17.2 ± 3.3	21	1.56	1.13
WLC	19.8 ± 3.1	37	20.0 ± 4.3	39	20.4 ± 3.4	36	−0.07	−0.22
Pain persistence								
TC	19.1 ± 3.7	37	15.9 ± 3.8	36	16.4 ± 5.1	34	0.90	0.76
WLC	17.6 ± 3.4	43	17.4 ± 3.5	42	16.4 ± 3.6	42	0.06	0.34
Mean ES for TC							1.23	0.95
Mean ES for WLC							0.01	0.06
Fatigue								
Pain avoidance								
TC	50.5 ± 5.3	28	35.7 ± 9.9	25	39.4 ± 11.6	23	2.24	1.68
WLC	46.9 ± 7.9	39	47.0 ± 6.7	40	46.4 ± 6.5	37	0.02	0.08
Pain persistence								
TC	44.2 ± 9.1	37	34.4 ± 9.7	36	34.1 ± 12.6	33	1.14	1.17
WLC	44.7 ± 8.1	43	43.7 ± 8.2	42	42.6 ± 9.4	42	0.12	0.24
Mean ES for TC							1.69	1.43
Mean ES for WLC							0.07	0.16
Disability								
Pain avoidance								
TC	13.6 ± 3.0	28	18.4 ± 3.5	25	19.3 ± 3.8	22	1.60	1.90
WLC	13.6 ± 3.0	40	14.5 ± 4.3	39	14.5 ± 4.2	37	0.30	0.30
Pain persistence								
TC	18.6 ± 4.5	37	21.4 ± 4.0	36	22.2 ± 4.8	34	0.64	0.82
WLC	18.7 ± 4.3	43	19.4 ± 4.1	42	19.8 ± 4.4	42	0.16	0.25
Mean ES for TC							1.12	1.36
Mean ES for WLC							0.23	0.28
Total mean ES, physical functioning TC							1.35	1.25
Total mean ES, physical functioning WLC							0.10	0.17
Psychological functioning								
Negative mood								
Pain avoidance								
TC	8.9 ± 3.8	28	4.7 ± 3.7	25	5.0 ± 3.5	23	0.88	0.82
WLC	10.5 ± 5.7	40	8.8 ± 6.2	40	8.4 ± 5.2	36	0.36	0.44
Pain persistence								
TC	5.9 ± 3.3	37	4.0 ± 3.5	36	3.5 ± 2.6	34	0.54	0.69
WLC	5.6 ± 3.6	43	6.3 ± 3.7	42	6.1 ± 4.5	42	−0.20	−0.14
Mean ES for TC							0.71	0.78
Mean ES for WLC							0.08	0.15
Anxiety								
Pain avoidance								
TC	26.3 ± 5.9	28	21.6 ± 5.9	25	20.3 ± 5.6	23	0.76	0.98
WLC	27.0 ± 6.4	39	25.6 ± 6.7	40	26.0 ± 5.4	37	0.23	0.16
Pain persistence								
TC	23.2 ± 4.3	37	20.7 ± 4.3	35	19.0 ± 4.4	33	0.53	0.88
WLC	23.9 ± 5.1	43	23.6 ± 5.2	42	22.7 ± 5.4	41	0.06	0.26

(continued)

measurements. Secondary analyses contained pattern by treatment interactions (to test for a homogenous treatment effect in both patient patterns) or time by treatment interactions (to test for a stable treatment effect over the 2 posttreatment measurements). All analyses were performed using the intent-to-treat principle.

Although much effort was invested in obtaining all possible measurements (for example, in patients who developed comorbidity during the trial), some missing values did occur. In total, 2,546 observations (298 missing of a maximum of 2,844 observations) for the 6 primary outcome measures were evaluated in 158 participants, with complete data sets for 90% of all assessments at the 3 assessment points. For the 137 completers, data sets were

Table 2. *(Cont'd)*

	T1		T2		T3		ES	
	Mean ± SD	No. patients	Mean ± SD	No. patients	Mean ± SD	No. patients	T1–T2	T1–T3
Mean ES for TC							0.65	0.93
Mean ES for WLC							0.15	0.21
Total mean ES, psychological functioning TC							0.68	0.86
Total mean ES, psychological functioning WLC							0.12	0.18
Impact of FM on daily life								
Pain avoidance								
TC	66.3 ± 11.6	28	47.6 ± 14.7	25	50.0 ± 15.6	23	1.60	1.39
WLC	67.0 ± 11.8	40	63.6 ± 14.9	40	66.0 ± 13.9	37	0.29	0.09
Pain persistence								
TC	57.2 ± 11.0	37	46.8 ± 15.3	36	43.2 ± 18.5	34	0.81	1.09
WLC	54.1 ± 14.7	43	53.8 ± 12.8	42	50.8 ± 15.2	42	0.02	0.26
Mean ES for TC							1.21	1.24
Mean ES for WLC							0.16	0.18

* Negative ES indicate increases in symptoms and positive ES indicate decreases in symptoms. ES = effect size; TC = treatment condition; WLC = waiting list control condition; T1 = pretreatment; T2 = posttreatment; T3 = followup; FM = fibromyalgia.

complete for 98% of all assessments (55 missing of a maximum of 2,466 observations) at the 3 assessment points. Because we used a mixed model and missing data only occurred on the dependent variables, our present analyses can only be guaranteed to be valid when the missing values occurred as missing at random. We also performed an analysis using the last observation carried forward (LOCF) approach as a sensitivity analysis. To give an indication for the clinical relevance of the results, effect sizes were calculated for the pain-avoidance and the pain-persistence groups separately by computing the difference between the means of the assessment points divided by the pooled SD at baseline (34). Furthermore, the mean effect sizes for the outcomes of physical and psychological functioning were calculated for each of the groups. Additionally, we calculated a reliable change index for the pain-avoidance and the pain-persistence groups separately to determine the percentage of patients who showed a clinically relevant improvement (reliable change >1.64; $P < 0.05$), and also the mean percentage for physical and psychological functioning was calculated (8,35,36).

RESULTS

Baseline comparisons and dropouts. Baseline comparisons of the TC and the WLC revealed no significant differences with regard to their sociodemographic variables and primary outcomes. In addition, baseline comparisons of the pain-persistence TC with the pain-persistence WLC and the pain-avoidance TC with the pain-avoidance WLC also revealed no significant differences with regard to their sociodemographic variables and primary outcomes, with the exception of a slightly higher score on fatigue ($t = -0.25$, $P = 0.028$) for the pain-avoidance TC compared with the pain-avoidance WLC (Tables 1 and 2).

With regard to the dropouts, 5 patients withdrew shortly after the randomization due to treatment elsewhere (pain-avoidance WLC n = 2) or practical concerns (pain-persistence TC n = 1, pain-persistence WLC n = 1, and pain-avoidance TC n = 1). In addition, 1 patient (pain-persistence TC) was excluded due to psychiatric comorbidity that was discovered between the randomization and the first assessment. Between baseline (T1) and postassessment (T2), 7 patients dropped out. Reasons for dropping out were pregnancy (pain-avoidance WLC n = 1), newly acquired physical comorbidity (pain-avoidance TC n = 1), lack of sustained motivation to participate in the trial (pain-avoidance TC n = 2 and pain-avoidance WLC n = 2), and treatment elsewhere (pain-persistence WLC n = 1). Between postassessment (T2) and followup (T3), 8 patients dropped out. Reasons for dropping out during followup were lack of sustained motivation to participate in the trial (pain-persistence WLC n = 1, pain-persistence TC n = 2, pain-avoidance WLC n = 1, and pain-avoidance TC n = 1), treatment elsewhere (pain-avoidance WLC n = 1), and newly acquired physical comorbidity (pain-avoidance TC n = 1 and TC pain-persistence n = 1). No differences were found with regard to sociodemographic variables and the primary outcomes between the dropouts and the completers for the pain-avoidance and the pain-persistence groups, with the exception of higher scores on pain ($t = -2.84$, $P = 0.007$) and impact of FM ($t = -0.242$, $P = 0.018$) for the dropouts compared with the completers in the pain-avoidance group.

Primary analyses of outcome in physical and psychological functioning and impact of FM. With regard to physical functioning, a significant effect of condition was found for pain ($F[1,18.00] = 16.48$, $P < 0.001$); the TC showed a 2.30-point lower posttreatment and followup assessment score compared with the WLC. For fatigue ($F[1,134.95] = 55.85$, $P < 0.001$), the TC showed a 9.68-

point lower posttreatment score compared with the WLC. For functional disability ($F[1,16.28] = 48.96$, $P < 0.001$), the TC showed a 3.15-point higher posttreatment and followup assessment score compared with the WLC. With regard to psychological functioning, a significant effect of condition was found for negative mood ($F[1,15.87] = 19.92$, $P < 0.001$); the TC showed a 2.62-point lower posttreatment and followup assessment score compared with the WLC, and for anxiety ($F[1,14.33] = 18.76$, $P = 0.001$) the TC showed a 3.33-point lower posttreatment and followup assessment score compared with the WLC. Finally, a significant effect of condition was found for the impact of FM on daily life ($F[1,17.36] = 25.53$, $P < 0.001$); the TC showed a 11.07-point lower posttreatment and followup assessment score compared with the WLC. The mean scores of the TC and the WLC for the pain-avoidance and pain-persistence groups, separately, are shown in Table 2.

Secondary analyses of outcome in physical and psychological functioning and impact of FM. The pattern × condition interaction effects were not significant for the primary outcomes, with the exception of 1 significant pattern × condition interaction that was found for pain ($F[1,134.17] = 5.26$, $P < 0.05$). In the pain-persistence group the TC showed a 1.21-point lower posttreatment and followup assessment score compared with the WLC, and in the pain-avoidance group the TC showed a 3.72-point lower posttreatment and followup assessment score compared with the WLC. With regard to the time × treatment interaction effects, a significant effect was found for anxiety ($F[1,130.52] = 4.73$, $P < 0.05$). Directly following treatment, the TC score was 2.35 points lower compared with the WLC score, but at followup this difference was even larger: 3.96 points. The sensitivity analysis showed that the results of the analyses on the complete data set obtained after using the LOCF method were comparable with results presented above.

Clinical relevance. The effect sizes of all of the primary outcomes indicated overall relatively large posttreatment and followup effects (in most cases >0.70) for the TC and overall small effect sizes (in most cases <0.30) for the WLC for both the pain-avoidance and the pain-persistence groups (Table 2) (33). In addition, the reliable change index indicated a higher proportion of patients with clinically significant improvements on pain, fatigue, functional disability, anxiety, and negative mood scores in the TC relative to the WLC at posttreatment (Table 3) (8,35,36).

Table 3. Number of patients with clinically significant improvements in the TC and WLC at T3 for physical and psychological functioning and impact of FM on daily life*

	TC	WLC
Physical functioning		
Pain		
Pain avoidance	13/21 (62)	8/32 (25)
Pain persistence	19/34 (56)	23/41 (56)
Responders, %†	59	40.5
Fatigue		
Pain avoidance	16/23 (70)	6/34 (18)
Pain persistence	23/33 (70)	12/41 (29)
Responders, %†	70	23.5
Functional disability		
Pain avoidance	19/22 (86)	12/35 (34)
Pain persistence	20/34 (59)	15/41 (37)
Responders, %†	72.5	35.5
Responders physical functioning, %†	67.2	33.2
Psychological functioning		
Negative mood		
Pain avoidance	15/23 (65)	15/35 (43)
Pain persistence	15/34 (44)	9/41 (22)
Responders, %†	54.5	32.5
Anxiety		
Pain avoidance	17/23 (74)	9/34 (27)
Pain persistence	21/33 (64)	16/40 (40)
Responders, %†	69	33.5
Responders psychological functioning, %†	61.8	33
Impact of FM on daily life		
Pain avoidance	16/23 (70)	5/35 (14)
Pain persistence	17/34 (50)	14/41 (34)
Responders impact of FM, %†	60	24

* Values are the number of patients with improvement/total (percentage) unless otherwise indicated. See Table 2 for definitions.
† Mean percentage of patients with clinically significant improvement.

DISCUSSION

Effects sizes were overall large at posttreatment and followup for the TC, and reliable change indices indicated that a significantly larger proportion of patients in the TC showed a clinically relevant change. The present results demonstrate that offering high-risk patients with FM a treatment tailored to their cognitive–behavioral patterns at a relatively early stage after the diagnosis is effective in improving both short- and long-term physical and psychological outcomes. Supporting evidence of the effectiveness of our tailored treatment was found with regard to the followup assessments and the low dropout rates. The effects were maintained at 6 months, suggesting that patients continued to benefit from the treatment. In contrast to previous studies, the dropout rate in our study was relatively low, indicating that our intervention was well accepted by the patients.

Although earlier studies have shown that multidisciplinary interventions combining CBT with exercise training improved functioning in patients with FM, the generally small to moderate effects and high dropout rates have proved a problem. Modest results were suggested to be due to the heterogeneity of the population (3,4,37). Several studies identified specific patient characteristics that predict treatment success. For example, it was shown that patients with FM reporting high levels of distress and a high impact of the condition benefit most from CBT (10,12). With regard to specific CBT interventions, a pain-avoidance treatment (exposure in vivo) aimed at improv-

ing performance by diminishing the fear of pain was found to be particularly effective in highly fearful patients with chronic low back pain (7). Furthermore, Thieme et al (22) recently reported that the responders to a pain-avoidance treatment for FM differed from the responders to a pain-persistence intervention. These findings offered promising possibilities for new treatments tailored to specific patient characteristics, which could enhance treatment outcomes. For example, Hasenbring and colleagues (38) investigated the effectiveness of CBT tailored to the pain-avoidance or pain-persistence patterns in patients with acute sciatic pain and reported beneficial results. Building on these findings, we can now report, for the first time to our knowledge, relatively large physical and psychological improvements in high-risk patients with FM following a treatment specifically addressing pain-avoidance and pain-persistence patterns.

Some limitations should be kept in mind when interpreting our results. We did not directly test the hypothesis that our tailored intervention is more effective than a standard, nontailored treatment. Future research should aim at demonstrating the possibly direct efficacy of the present tailored treatment approach by comparing the effects of tailored versus nontailored treatments. However, being that previous meta-analyses and recent studies of nontailored interventions in chronic physical conditions have overall shown not more than moderate effects (3,4,39), the results of the current study suggest that a tailored approach is promising for improving treatment effects. Furthermore, we found small improvements in our WLC, which consisted of high-risk patients with FM awaiting treatment. Because no change or a worsening of symptoms is usually observed in natural course studies in FM and waiting list conditions are well known to have possible beneficial effects (40,41), the small improvements might be due to the patient's expectation of treatment and the intake procedure in which patient education about the treatment was provided. In addition, the low attrition rate in the WLC might be due to the fact that these patients were awaiting a treatment that was not provided elsewhere, which might provide a strong motivation to remain in the trial. We also note that the allocation to the conditions and the execution of the measurements were not performed blinded. The risk of information bias, however, is limited because the investigator (SvK) had no influence on the decision to accept or reject participants, the participants were allocated in the order of their enrollment of the trial, and the TC and WLC received the same standardized assessments. Finally, future research should also establish the longer-term effects of the treatment approaches.

In conclusion and supporting our earlier prediction, the present study demonstrates for the first time that tailored CBT in combination with exercise training for high-risk patients with FM delivered at a relatively early stage after the diagnosis is effective in improving and maintaining both the patients' physical and psychological functioning.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Ms van Koulil had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Acquisition of data. Van Koulil, van Lankveld, Kraaimaat, van Helmond, Vedder, van Hoorn, de Jong, Haverman, Korff, van Riel, Cats, Evers.

Analysis and interpretation of data. Van Koulil, van Lankveld, Kraaimaat, Donders, van Riel, Evers.

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