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Effects of a mindfulness- and acceptance-based group-programme followed by physical activity for patients with fibromyalgia: a randomised controlled trial

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Abstract

Introduction: Non-pharmacological approaches are recommended as first-line treatment for patients with fibromyalgia. This randomised controlled trial investigated the effects of a multicomponent rehabilitation programme for patients with recently diagnosed fibromyalgia in primary and secondary health care.

Methods: Patients with widespread pain ≥3 months were referred to rheumatologists for diagnostic clarification and assessment of study eligibility. Inclusion criteria were age 20 to 50, engaged in work or studies at present or during the past two years, and fibromyalgia diagnosed according to ACR 2010 criteria. All eligible patients participated in a short patient education programme before inclusion and randomisation. The multicomponent programme, a 10-session mindfulness- and acceptance-based group programme followed by 12 weeks supervised physical exercise was evaluated in comparison to treatment as usual. The primary outcome was the Patient Global Impression of Change (PGIC). Secondary outcomes were self-reported pain, fatigue, sleep quality, psychological distress, physical activity, health related quality of life and work ability at 12-month follow-up.

Results: In total, 170 patients were randomised, 1:1, intervention:control. Overall, the multicomponent rehabilitation programme was not more effective than treatment as usual; 13% in the intervention group and 8% in the control group reported clinically relevant improvement in PGIC (p=0.28). No statistically significant between-group differences were found in any disease-related secondary outcomes. There were significant between-group differences in patient's tendency to be mindful (p=0.016) and perceived benefits of exercise (p=0.033) in favour of the intervention group.

Conclusions: A multicomponent rehabilitation programme combining patient education with a mindfulness- and acceptance-based group-programme followed by supervised physical

activity was not more effective than patient education and treatment as usual for patients with recently diagnosed fibromyalgia at 12-month follow-up.

Trial registration: The trial is registered at BMC ISRCTN96836577.

Article Summary

Strengths and limitations of this study

- This pragmatic randomised controlled trial was conducted according to a predefined published protocol.
- The main treatment effects were analysed on an intention-to-treat basis at 12 months follow-up, with all randomised patients retaining their original allocated groups.
- Although we intended to capture patients with FM at an early stage of their disease, the included patients reported median symptoms duration of eight years.
- There was a high drop-out rate from the physical activity intervention.
- We did not monitor the content of 'treatment as usual' in the control group other than physical activity.

Protocol

A published protocol article can be found at https://bmjopen.bmj.com/content/8/6/e021004

Introduction

Fibromyalgia (FM) is characterised by widespread pain and symptoms such as fatigue, unrefreshed sleep, mood disturbances and cognitive impairment that have persisted more than three months without any alternative explanation (1). Patients report unpredictable symptoms that vary in terms of expression and intensity, and reduced quality of life (2-5). The estimated prevalence of FM in the general population worldwide is between 2% and 7%, with women being predominantly affected (6). Many patients experience lack of understanding from their primary care physicians, insufficient health care, and deficient treatment (7, 8).

For optimal management of FM, the European League Against Rheumatism (EULAR) recommends prompt diagnosis and patient education as first-line treatment. The effects of pharmacological treatments are inadequate (4). The management should aim at improving patients' health-related quality of life and initially focus on non-pharmacological modalities (4, 9). Individualised physical exercise is recommended for all patients with FM. Cognitive behavioural therapy, mindfulness-based stress reduction, meditative movement (i.e. qigong, yoga, tai chi), and hydrotherapy have shown promising effects for some patients, although the evidence is still insufficient (4). Further, multicomponent programmes combining physical exercise with either of these modalities have shown beneficial synergetic effects on FM symptoms in terms of reduced pain and FM impact, and increased physical fitness at the end of treatment (4, 10).

Three recent systematic reviews and meta-analyses have shown that mindfulness- and acceptance-based interventions had short-term small to moderate effects on pain, depression, anxiety, sleep quality and health-related quality of life in patients with FM (11-13). Systematic reviews and meta-analyses on physical exercise in patients with FM have shown beneficial effects on symptoms, such as pain, sleep, and physical function (14-18).

A Norwegian mindfulness- and acceptance-based intervention, the Vitality Training Programme (VTP), aimed at strengthening participants health-promoting resources and ability to make choices in accordance with own values, has been evaluated in two randomised controlled trials in persons with chronic musculoskeletal pain and inflammatory arthritis (IA). The VTP improved pain, fatigue, psychological distress, pain coping, and self-efficacy for pain and other symptoms (19, 20). The effects persisted at 12-month follow-up in both studies. However, a preceding longitudinal pre-post-test study on the VTP in patients with IA and FM showed substantial improvements in patients with IA, but no changes in patients with FM (21). In a nested qualitative study, the FM patients described how they had struggled for years to be believed and taken seriously (22). The authors suggested that the lack of effects in patients with FM might have been related to long symptoms duration without recognition and treatment, which may have led to the development of maladaptive patterns of coping strategies that are difficult to change. They proposed that future studies should investigate the effects of the VTP in FM patients at an early stage of their disease.

The aim of the present randomised controlled trial was to study the effects of a community-based multicomponent rehabilitation programme comprising the VTP followed by 12 weeks of physical activity counselling in patients with recently diagnosed FM. More specifically, we examined whether the multicomponent rehabilitation programme improved patients' self-perceived health, pain, fatigue, sleep quality, psychological distress, physical activity and work ability, compared to treatment as usual.

Methods

Study design

We conducted a two-armed parallel randomised controlled trial in rural and urban communities in the South-Eastern part of Norway. Patients were allocated to the VTP and physical activity (intervention group) or treatment as usual (control group). More details can be found in the published protocol (ISRCTN 96836577) (23). We followed the Consolidated Standards of Reporting Trials (CONSORT) in this report (24, 25).

Participants

General practitioners and physiotherapists referred patients who had widespread pain that had lasted for at least three months to rheumatologists in specialist health care for diagnostic clarification and assessment of study eligibility. Inclusion criteria were age 20 to 50 and FM diagnosed according to the American College of Rheumatology (ACR) 2010 criteria (1, 26). Patients were excluded if they had an inflammatory rheumatic disease, had a severe psychiatric disorder, another disease that did not allow physical activity, or if they were unable to understand or write Norwegian. We also excluded patients who had been out of work for more than two years.

Procedure and interventions

All eligible patients received a three-hour patient education programme and oral information about the study. Patients who agreed to participate completed written informed consent before inclusion. The VTP was organised in the local communities with seven to 12 patients in each group. It comprised ten weekly four-hour sessions plus a booster session after approximately six months. Every session addressed a specific topic: If my body could talk/ Who am I?/ My resources and potentials/ Values—what is important to me?/ What do I need?/ Strengths and limitations/ Bad conscience/ Anger/ Joy/ Resources, potentials and choices/ Closure and the way ahead. These were explored by various creative methods, such as guided imagery,

music, drawing, poetry, metaphors and reflections. The patients wrote logs after all exercises and shared their experiences with other group participants.

Moreover, patients were invited to attend mindfulness meditation, i.e. body scan, sitting and walking meditation, and gentle yoga exercises (27). They were encouraged to listen to guided mindfulness meditation audio files and practice awareness in their daily activities between sessions (28). The group facilitators were experienced nurses and physiotherapists, who were certified by a one-year post-graduate training programme (30 credits). The facilitators followed a standardised manual with a thorough programme description and monitored the attendance throughout the programme. Based on previous studies, the patients needed to attend at least five sessions to expect effect (20, 23). Supplementary file 1 describes an example of the structure and content of one of the sessions.

The supervised physical exercise was conducted at a Healthy Life Centre (HLC), which is a low threshold health care service provided in Norwegian communities designed as easily accessible generic services aimed at lifestyle changes. HLCs typically offer a 12-week programme during daytime, comprising individual counselling based on Motivational Interviewing (MI), individual and group physical activities (29). A physiotherapist provided the individual physical activity counselling. This intervention aimed at helping patients to set tailored goals, identifying and overcoming barriers to physical activity, and guiding them into exercises that they could continue after the 12-week period to increase the level of physical activity gradually.

Control group patients did not receive any organised intervention other than diagnostic clarification and the patient education session but were free to attend any treatment and activity at their own initiative. The control group was offered the VTP and the HLC intervention after completion of the data collection at 12-month follow-up.

Outcomes

The outcome measures were selected according to a core set of domains for FM defined by the Outcome Measures in Rheumatology Clinical Trials (OMERACT) (30, 31). Self-reported questionnaires comprising baseline demographics and all outcome measures were collected electronically before randomisation (baseline), after the VTP (three months) and at 12 months from baseline.

Primary outcome: Patient Global Impression of Change (PGIC)

PGIC is a validated ordinal seven-point self-reported scale that measures how patients feel that their health has changed from they entered the trial to post-intervention data collections. The scale ranges from 1 (I feel very much worse) through 4 (no change) to 7 (I feel very much better) (32). Scores 6 and 7 are considered a clinically relevant improvement. Patient Global Impression of Change (PGIC) has previously been used in FM trials and is recommended as a core measure to improve the applicability of information from clinical trials to clinical practice (33-35). Higher scores in PGIC has been associated with more significant improvements in key FM symptoms and correlates well with FM outcomes (33). The scores can be dichotomised into 'Less than much better' (scores 1 to 5) and 'Much better' (scores 6 and 7) (34).

Secondary outcomes

Pain, fatigue, and sleep quality were assessed by Numerical Rating Scales (NRS) scored from 0 to 10 (10 is intolerable pain/ fatigue/ very bad sleep) (31). Psychological distress was assessed by the General Health Questionnaire-12 (GHQ-12) that comprises six positively phrased items indicating psychological health and six negatively phrased items indicating psychological distress (36). The respondents scored their condition during the last two weeks compared to what they perceived as their 'normal' condition on a four-point Likert scale, reported from 0 (less than usual) to 3 (much more than usual). The scale was reversed for

negatively phrased items. Data were analysed and reported as mean sum score; higher scores represented higher psychological distress (37, 38). A general tendency to be mindful in daily life situations was assessed by the Five Facet Mindfulness Questionnaire (FFMQ) that comprises 39 items rated on a five-point Likert scale from 1 (never true) to 5 (always true) (39). Higher scores reflected higher levels of mindfulness. The scale was reversed for negatively phrased items. Data were analysed and reported as a mean sum score, comprising all five facets. Physical activity (PA) was assessed by three questions from the Nord-Trøndelag Health Study (HUNT1) (40). The questions measure frequency, intensity and duration of leisure-time physical exercises such as walking, skiing, swimming or other training/-sport activities that improve physical fitness. A summary index of weekly PA was calculated from the frequency, intensity and duration scales with scores from 0 to 15. Higher scores indicate increased PA. Motivation and barriers for physical activity were assessed by the Exercise Beliefs and Exercise Habits questionnaire comprising 20 items scored on a five-point Likert scale ranging from 'strongly agree' to 'strongly disagree' (41). The items were divided into four sub-scales calculated and reported separately as beliefs about one's ability to exercise, barriers to exercise, benefits of exercise, and impact of exercise on muscular pain. Work ability was assessed by the Work Productivity and Activity Impairment General Health V2.1 (WPAI:GH) comprising six questions to determine employment status; hours missed from work because of health problems or other reasons, and hours worked (42). Higher scores indicate more significant impairment and less productivity. For this study, we calculated the outcomes 'overall work impairment' and 'daily activity impairment'. Health-related quality of life was assessed with EuroQol (EQ-5D-5L) comprising five dimensions; mobility, self-care, usual activities, pain/discomfort and anxiety/depression scored on five levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The EQ-5D-5L scores range between 0–1, 0 indicates death, and 1 indicates perfect health (43). Secondly,

the participants rate their overall health on a 0 - 100 hash-marked, vertical visual analogue scale (EQ-VAS), 0 is as bad as it could be, and 100 as good as it could be (44).

Harms

Patients were asked to report adverse events at 12 months and major symptoms that were associated with these events.

Randomisation and blinding

A statistician generated an electronic randomisation list for each geographical area to ensure approximately equal sample sizes. A research assistant not involved in the study generated the allocation sequence and assigned patients to study groups. Further, the facilitators of the VTP groups organised and administered the enrolment. Due to the nature of the intervention, it was not possible to blind the patients and the VTP facilitators to group allocation. The project leader and the research coordinator who were responsible for the data collection and data analysis were blinded to the allocation.

Sample size

Sample size calculation was based on the primary outcome assuming that 10% in the control group would report clinically relevant improvement at 12 months follow-up, and that at least 20% absolute difference in improvement rate between the groups would be considered a minimum clinically relevant difference. With allowance for 10% losses to follow-up, 70 patients in each group were needed to have at least 80% power of detecting differences with 5% alpha level.

Statistical analyses

Mean values and standard deviation (SD) were calculated for continuous variables or as median with minimum and maximum values if skewed. Frequency numbers and percentages were calculated for categorical variables. Baseline differences in patients' characteristics

between intervention and control group were assessed by independent group t-test or Mann Whitney U test for continuous variables. For categorical variables, we used Pearson's Chi-square test or Fisher's exact test when the expected cell count fell below five. The treatment effects were analysed on an intention-to-treat basis with all randomised patients retaining their original allocated groups at 12 months. The distribution of the primary outcome (PGIC) was analysed as an ordinal variable by Mann Whitney U test. When dichotomised, the difference between groups was tested with Chi-square statistics and Fisher's exact tests. Treatment effects in secondary outcomes were estimated by Analysis of Covariance (ANCOVA) at three and 12-month follow-up adjusted for the baseline values. The level of statistical significance was set to ≤0.05. We used STATA V.14.0 (45) to analyse the data. Missing values in single items of FFMQ and GHQ-12 were imputed by calculating the mean value of the registered values multiplied with the number of questions.

Patient and public involvement

Representatives from the Patient Advisory Board at the Diakonhjemmet Hospital were involved in the development of the study, such as study design, research questions and recruitment of patients. The electronic questionnaires were tested and amended by user representatives. More information is described elsewhere (23).

Results

Of the 289 patients who were referred to the rheumatologists, 208 (72%) were eligible for inclusion. A total of 170 consented to participate and were randomised; 85 to the intervention group and 85 to the control group. Figure 1 illustrates the flow of patients through the study.

Figure 1. Flow chart of patients

The intervention group had a slightly higher median age and symptoms duration in years compared to the control group. All other baseline characteristics were equally distributed between the groups (Table 1).

Table 1. Patients' characteristics at baseline

Of the 75 patients who attended the VTP, 67 (89%) completed five sessions or more; 21 (31%) of these patients completed all ten sessions, 20 (30%) completed nine, and nine (13%) completed eight sessions. The average attendance rate was 7.5 sessions. Thirty-two patients (43%) attended the physical activity intervention after the VTP, but only a few completed the 12-week programme. The data collection was completed by 160 (94%) at three months and 153 (90%), and 12 months. Recruitment of patients started in September 2016 and ended in August 2018. Electronic data collection started in February 2017 and ended in September 2019 when the complete 12-month follow-up data were attained.

Patient Global Impression of Change

We found statistically significant differences between groups in distribution of the PGIC-scores at three-month follow up (p=0.01), but not at 12-month follow up (p=0.06). The distribution across all response categories is shown in Figure 2.

Figure 2. The distribution of PGIC scores

There were no statistically significant differences between the intervention group and the control group at three- and 12-month follow-ups when the PGIC was dichotomised into 'Less than much better' and 'Much better'. At 12-month follow-up, 13 per cent in the intervention group reported 'Much better' compared to eight per cent in the control group (Table 2).

Table 2. Effect of intervention, primary outcome: Patient Global Impression of Change

Secondary outcomes

There were no statistically significant differences between the groups at 12-month follow-up in any disease-related outcomes (Table 3). However, there was a statistically significant improvement in favour of the intervention group in 'general tendency to be mindful'. Moreover, there was a statistically significant difference between groups in 'perceived benefits of exercise' due to a small deterioration in the control group (Table 3). The numbers of people working, assessed by the WPAI:GH, was 56 (67%) at baseline and 48 (64%) at 12-month follow-up in the intervention group, compared to 52 (61%) at baseline and 50 (64%) at 12-month in the control group.

Table 3. Effects of intervention, secondary outcomes estimated by ANCOVA adjusted for baseline scores

Harms

A total of 34 patients reported adverse events, 21 (28 %) in the intervention group, and 13 (17 %) in the control group. Increased pain and fatigue were the most frequent adverse events. Thirteen (nine in the intervention group and four in the control group) related the events to medication; 21 (12 in intervention and nine in control) to physical activity; four in the intervention group related the events to the VTP; two (one in intervention and one in control) related the events to alternative treatment.

Discussion

In this pragmatic randomised controlled trial, we examined the effects of a multicomponent rehabilitation programme for patients with FM. The study demonstrated that a mindfulness- and acceptance-based intervention, the VTP, followed by supervised physical activity in patients with recently diagnosed FM was not more effective than treatment as usual. Only 13 per cent in the intervention group reported clinically relevant improvement in self-perceived health status at 12-month follow-up compared to eight per cent in the control group. We did not observe differences between the groups in any disease-related secondary outcomes. However, there were statistically significant differences between groups in tendency to be mindful and perceived benefits of exercise in favour of the intervention group. The latter was due to a slight deterioration in the control group.

The results of this trial both negate and support earlier studies on the VTP for patients with FM. One randomised controlled trial in patients with musculoskeletal pain conditions, including FM, demonstrated substantial health improvements (19). In contrast, a longitudinal study in patients with IA and FM showed improvements in the IA group, but not in the FM group (21). Based on the latter study, it was hypothesised that the lack of effects in patients with FM might have been related to living with distressing symptoms over a long time without receiving any diagnosis. The present study aimed to improve the management of FM by following the EULAR recommendations for management of FM in a Norwegian context. We assumed that offering patients who had been recently diagnosed with FM a mindfulness- and acceptance-based intervention might help them overcome some of their internal barriers to physical activity before they attended a physical activity intervention. However, we found no support for this assumption.

There were statistically significant differences between the groups in distribution of the PGIC-scores at three-month follow-up, but not at 12months. This corresponds to other studies on mindfulness- and acceptance-based interventions that have shown beneficial short-term effects, but no evidence for long-term effects (10, 11). Our primary outcome, the PGIC scale, was dichotomised to distinguish between those who reported clinically relevant improvement in self-perceived health and those who did not. This has also been performed in previous studies, in which clinically relevant improvements have been shown (33, 34). However, we did not find any clinically relevant differences between the groups in our study. Previous systematic reviews and meta-analyses on mindfulness- and acceptance-based interventions have shown small to moderate beneficial effects on pain, sleep quality and health-related quality of life for patients with FM (10-13). In the present study, we did not see any of these effects. However, we found a statistically significant effect in tendency to be mindful. Improvement in mindfulness may be associated with enhanced mental health outcomes (46, 47). Longer follow-up may be needed to see if this improvement will result in effects in other outcomes, such as perceived health status and physical activity.

As many as 57 per cent of the patients never attended the HLC intervention, and they did not report any increase in physical activity at 12-month follow-up. Twelve of the 32 patients who took part in the HLC intervention reported adverse events, such as increased pain and fatigue, which may have been one reason for quitting the training. This corresponds to other studies, which have shown that many patients report physical activity to be challenging, and that adherence to exercise interventions is poor (18, 48-50). Further studies are needed to explore ways to improve adherence to physical activity.

Because we wanted to investigate if it was possible to prevent work loss and improve work participation, we excluded patients that had been out of work for more than two years. Long-term absence from work due to illness has been identified as a risk factor for transition

into disability pension (51, 52). Seventy-one per cent of the patients in our study had paid work. Previous studies have shown that nonworking FM patients have more severe symptoms than working patients (53, 54). Despite the high number of workers in our study, the patients reported high symptoms burden, in terms of pain, fatigue and psychological distress.

Because we assumed that higher age might be associated with more comorbid conditions, we defined 50 years as the upper age limit for inclusion. Nevertheless, the median number of comorbidities in the included patients was two.

Although we intended to capture patients with FM at an early stage of their disease, the included patients reported median symptoms duration of eight years. These findings, although contrary to our expectations, corresponds to other studies, which have shown that patients wait a significant time before presenting symptoms to a physician (55). Further, there may be a delay in diagnosis in primary health care due to an overlap of symptoms with other conditions and patients may have difficulties in communicating their symptoms (56). Other reasons for the delay in diagnosis and treatment may be lack of knowledge and understanding of FM from primary care physicians (57).

This study was conducted according to a predefined published protocol (23). It was well-powered, and all included patients were allocated to the groups to which they were randomised, ensuring valid treatment comparisons and assessment of treatment effects (58). The losses to follow-up were within our assumption of 10 %. We had predefined that patients needed to attend at least 50 per cent of the sessions to expect effects of the VTP intervention, and nearly 90 per cent attended more than half of the VTP sessions (23). This attendance rate is comparable to other studies on mindfulness- and acceptance-based interventions (13). The percentage of patients with complete follow-up data was high. The VTP facilitators were certified and followed a manualised programme, which improves transparency and replication

(59). Moreover, the 12 months follow-up time was relatively long, and in line with what has been asked for in previous research (13).

Several limitations need to be mentioned. Firstly, before randomisation, all study participants received a short patient education session, which is recommended as a first-line intervention by the EULAR recommendations. This might have served as a validation of the FM diagnosis and may have provided the patients with knowledge and information about possible coping strategies. The control group could include strategies and activities at their own initiative. We did not monitor the content of 'treatment as usual' in the control group other than physical activity. Thus, we do not know if the patients had initiated beneficial self-management strategies during the control period.

Secondly, our study was a pragmatic randomised controlled trial, which makes it difficult to differentiate between the effects of the various interventions and to interpret the lack of effects. Moreover, we did not monitor the adherence to the homework between the VTP sessions. Consequently, we do not know to what extent the patients practised mindfulness training and integrated the training in their daily life. A recent review on mindfulness- and acceptance-based interventions showed a small but significant association between the extent of formal practice and positive intervention outcomes (60). It is recommended that future research should adopt a standardised approach for monitoring home-practice across mindfulness- and acceptance-based interventions (61). Further, we included already existing HLCs in the communities. The activities offered vary between centres, and consequently, it was not possible to standardise the frequency, intensity, duration, progression or type of exercise. Moreover, the HLCs offer physical exercise counselling at daytime only, making the intervention challenging to combine with a daytime job. Subsequently, a physical activity intervention with more flexible access might have increased the patient participation.

Thirdly, we did not include any coping measures, such as self-efficacy, to assess the coping with their symptoms. We used the GHQ-12 to assess mental health status because this was found to be sensitive to change in previous studies on the VTP. The GHQ-12 does not capture more severe symptoms of depression and anxiety but is a widely used instrument to assess psychological distress.

Finally, we could have applied other statistical analyses, such as Linear Mixed Models rather than ANCOVA, to estimate effects. However, ANCOVA was chosen because it has shown great power and low variability when compared to other traditional analyses approaches, and it is regarded as a preferred analysis when post-treatment assessments adjusted for the pre-treatment assessments are measured (62, 63).

This study has demonstrated that a multicomponent rehabilitation programme combining recent diagnosis and patient education with a mindfulness- and acceptance-based intervention followed by supervised physical exercise was not more effective than recent diagnosis, patient education and treatment as usual for patients with FM.

There was a high drop-out rate from the physical activity intervention. Further, studies on how to adapt and tailor physical activity interventions to patients with FM are needed.

Our intention to include patients at an early stage of the disease was not fulfilled. The patients reported high symptoms burden and had a median symptoms duration of eight year. Thus, future research should aim at including patients with more recent disease onset and explore the effects of prompt diagnosis and patient education.

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Ethical approval: This study was performed in line with the principals of the Declaration of Helsinki. Study design, information strategy, written consent formula and data security are approved by the Regional Committee for Medical and Health Research Ethics (2015/2447/REK sør-øst A).

Consent to participate: Informed consent was obtained from all individual patients included in the study.

Author contributions: Kåre Birger Hagen and Heidi A. Zangi contributed to the initial design of the project, and all authors contributed to the conception of the study. Material preparation, data collection and analysis were performed by Trond Haugmark, Sella A. Provan and Geir Smedslund. All authors contributed to the interpretation of the data. The first draft of the manuscript was written by Trond Haugmark and all authors commented and revised previous versions of the manuscript. All authors read and approved the final manuscript.

Conflicts of interest: The authors declare that they have no conflict of interest.

Variables	All Patients (n=170)	Intervention Group (n=85)	Control Group (n=85)	P-value
Age, years, median (min, max)	42 (24, 52)	44 (26, 52)	41 (24, 51)	0.02[1]
Gender, women	159 (94%)	78 (92%)	81 (95%)	0.54[3]
Education:				0.60[2]
Primary/ middle school (1-10 years)	20 (12%)	8 (9%)	12 (14%)	
Upper secondary school/ Vocational 10-12 years	68 (40%)	36 (42%)	32 (38%)	
Bachelor/ University>12 years	81 (48%)	40 (47%)	41 (48%)	
Work status:				
Currently in paid work	119 (70%)	59 (69%)	60 (71%)	0.94[2]
Not in paid work	48 (28%)	24 (28%)	24 (28%)	0.94[2]
In paid work but on sick leave (100%)	8 (17%)	3 (13%)	5 (21%)	
Work assessment allowance	35 (73%)	20 (83%)	15 (62%)	
Unemployed	4 (8%)	1 (4%)	3 (13%)	
Student	1 (2%)		1 (4%)	
Married/ living with partner	120 (71%)	54 (64%)	66 (78%)	0.06[2]
Symptoms duration, years, median, (min, max)	8 (1, 32)	10 (1, 32)	7 (1, 30)	0.05[1]
Comorbidities, median (min, max)	2 (1, 6)	2 (1, 6)	2 (1, 6)	0.24[1]
Smokers	23 (14%)	14 (17%)	9 (11%)	0.25[2]
FM in family	57 (34%)	27 (32%)	30 (35%)	0.55[2]
Use of medication in the last three months				
Pain medications:	149 (88%)	73 (86%)	76 (89%)	0.64[2]
Hypnotics:	51 (30%)	27 (32%)	24 (28%)	0.63[2]
Antidepressants:	20 (12%)	8 (9%)	12 (14%)	0.48[2]
Anxiolytics:	8 (5%)	2 (2%)	6 (7%)	0.28[3]

Values are means (SD) or numbers (%). FM: fibromyalgia, [1]Mann Whitney U test, [2]Pearson's Chi-Square test, [3]Fisher's exact test.

PGIC	3 months			12 months		
	Intervention (n=76)	Control (n=84)	P-value	Intervention (n=76)	Control (n=77)	P-value
Much better (scores 6 and 7), n (%)	6 (7.9)	4 (4.8)	0.52[1]	10 (13.2)	6 (7.8)	0.28[2]

[1]Fisher's exact, [2]Pearson's Chi-Square test

	Intervention (n=76) Mean (SD)	Control (n=77) Mean (SD)	Baseline adjusted mean difference (95% CI)	P-value
Pain (NRS 0-10, 0 = no pain)				
Baseline	6.7 (1.6)	6.8 (1.9)	-	-
3 months	6.4 (1.7)	6.6 (1.8)	0.30 (-0.15 to 0.75)	0.19
12 months	5.8 (2.1)	6.4 (1.8)	0.55 (-0.00 to 1.11)	0.05
Fatigue (NRS 0-10, 0 = no fatigue)				
Baseline	7.5 (2.0)	7.4 (2.0)	-	-
3 months	7.2 (1.9)	7.1 (2.2)	-0.03 (-0.60 to 0.54)	0.92
12 months	6.8 (2.3)	6.8 (2.3)	0.12 (-0.56 to 0.80)	0.72
Sleep (NRS 0-10, 0 = no sleep)				
Baseline	6.8 (2.3)	7.1 (2.5)	-	-
3 months	6.6 (2.5)	6.9 (2.5)	0.27 (-0.42 to 0.97)	0.44
12 months	6.5 (2.5)	6.3 (2.5)	-0.24 (-0.99 to 0.50)	0.52
Psychological distress (GHQ-12, mean sum score, 0-36, 0 = no distress)				
Baseline	16.5 (6.6)	19.2 (6.8)	-	-
3 months	13.4 (6.5)	16.5 (7.0)	1.57 (-0.37 to 3.50)	0.11
12 months	14.8 (6.8)	16.6 (6.9)	1.03 (-1.08 to 3.14)	0.34
Five Facet Mindfulness Questionnaire (Mean sum score, 39-195, low to high)				
Baseline	119 (17.2)	113 (16.9)	-	-
3 months	124 (19.1)	118 (16.3)	-1.07 (-4.73 to 2.58)	0.56
12 months	126 (17.6)	118 (16.3)	-4.72 (-8.57 to -0.9)	0.02
Physical activity (0-15, 0 = inactive)				
Baseline	3.0 (2.4)	2.8 (1.8)	-	-
3 months	2.3 (1.6)	2.7 (1.9)	0.53 (-0.04 to 1.10)	0.07
12 months	2.9 (2.3)	2.8 (1.8)	0.10 (-0.60 to 0.79)	0.78
Motivation and barriers for Physical Activity				
Self-Efficacy (4-20, low to high)				
Baseline	12.0 (2.9)	12.0 (3.2)	-	-
3 months	12.5 (3.1)	12.6 (3.1)	0.08 (-0.70 to 0.86)	0.84
12 months	13.1 (3.5)	12.8 (3.1)	-0.33 (-1.27 to 0.62)	0.50
Barriers (3-15, low to high)				
Baseline	12.1 (2.4)	12.1 (2.0)	-	-
3 months	11.8 (2.3)	11.8 (1.9)	-0.00 (-0.48 to 0.47)	0.99
12 months	12.2 (2.4)	12.2 (1.7)	-0.07 (-0.61 to 0.46)	0.79
Benefits (5-25, low to high)				
Baseline	20.4 (3.2)	21.1 (2.7)	-	-
3 months	20.3 (3.0)	20.4 (2.7)	-0.19 (-0.89 to 0.50)	0.59
12 months	20.7 (3.0)	20.1 (2.9)	-0.90 (-1.73 to -0.07)	0.03
Impact (8-40, low to high)				
Baseline	28.8 (4.6)	29.0 (4.8)	-	-
3 months	28.4 (4.8)	28.5 (4.3)	0.08 (-0.90 to 1.06)	0.87
12 months	28.9 (5.4)	28.3 (4.6)	-0.49 (-1.63 to 0.65)	0.40
Work Productivity and Activity Impairment General Health				
Work impairment (0-10, 10 = completely impaired)				
Baseline	5.2 (2.5)	6.2 (2.2)	-	-
3 months	5.1 (2.4)	5.4 (2.5)	-0.15 (-1.05 to 0.76)	0.75
12 months	4.9 (3.2)	5.3 (2.9)	0.73 (-0.58 to 2.03)	0.27
Daily activity impairment (0-10, 10 = completely impaired)				
Baseline	7.0 (2.0)	7.1 (1.9)	-	-
3 months	6.9 (1.7)	6.7 (2.3)	-0.25 (-0.83 to 0.34)	0.41
12 months	6.3 (2.5)	6.5 (2.2)	0.07 (-0.65 to 0.79)	0.84
EQ-5D-5L				
Index (0–1, 1 = perfect health)				
Baseline	0.51 (0.2)	0.47 (0.2)	-	-
3 months	0.55 (0.2)	0.53 (0.2)	0.02 (-0.05 to 0.09)	0.86
12 months	0.54 (0.2)	0.50 (0.2)	0.04 (-0.03 to 0.11)	0.48
VAS (0-100, 100 = as good as it could be)				
Baseline	44.6 (16.5)	41.61 (17.0)	-	-

	3 months	46.4 (16.1)	51.5 (21.7)	-5.1 (-12.10 to 1.90)	0.03
	12 months	49.0 (20.6)	46.8 (18.5)	2.19 (-4.67 to 9.05)	0.77

NRS=Numeric Rating Scale, GHQ-12=General Health Questionnaire, EQ-5D-5L=Health-related quality of life

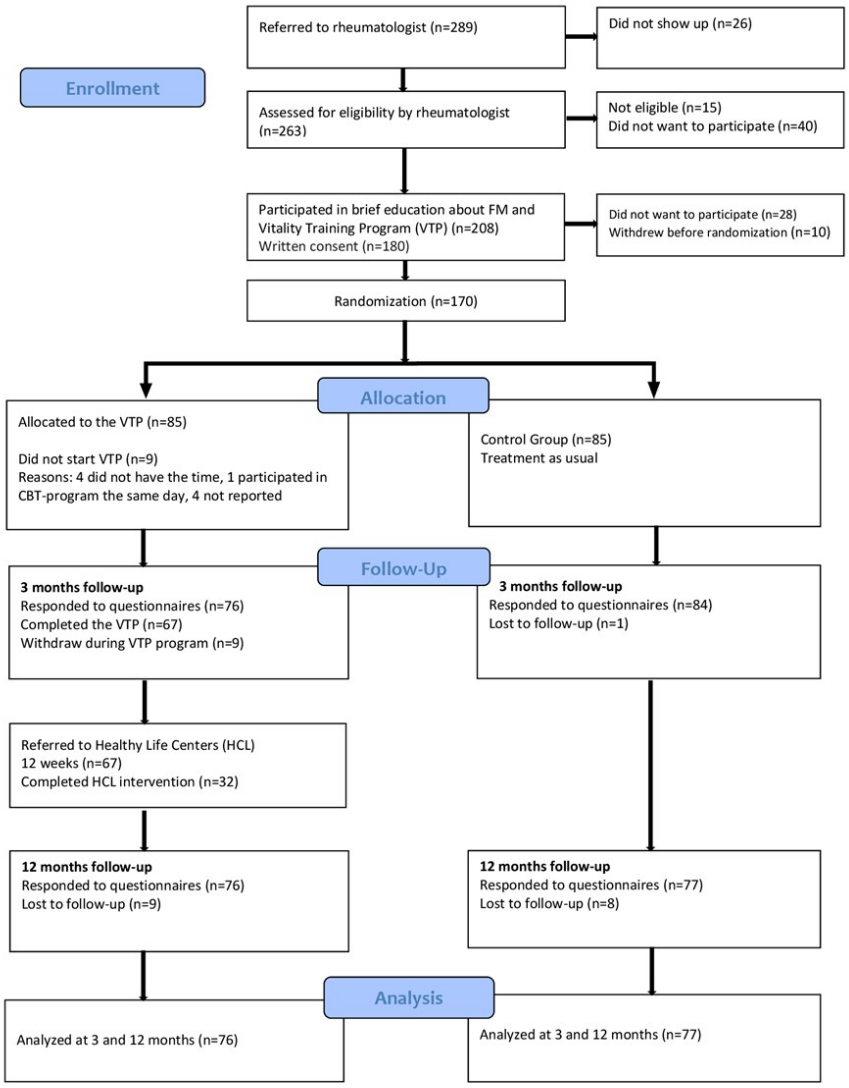

Figure 1. Flow chart of patients

160x207mm (150 x 150 DPI)

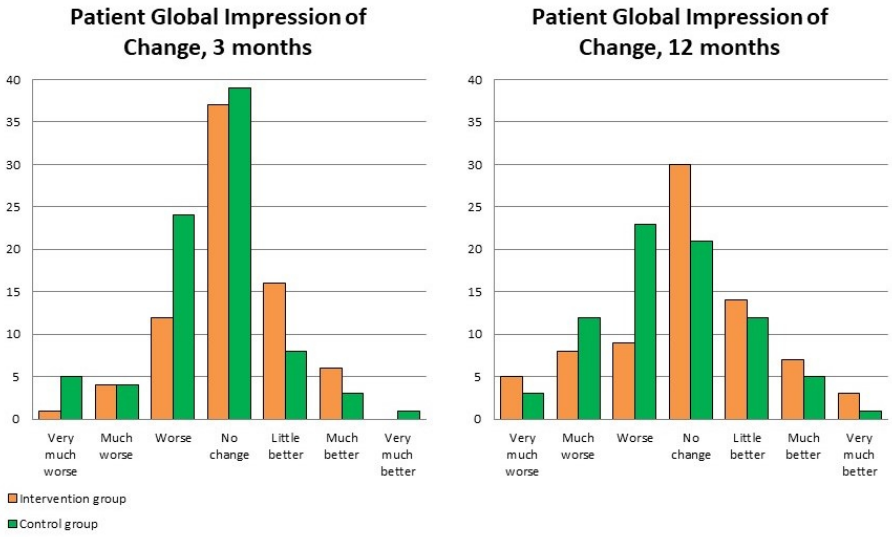

Figure 2. The distribution of PGIC scores

252x150mm (96 x 96 DPI)

Supplementary file

Online Supplementary file 1

Example from group session 6 in the Vitality Training Programme: Anger

The first part of the program is standard in all sessions: Participants are invited to share their reflection on experiences from home exercises after the previous session in groups of three to four persons. They are encouraged to read their reflective diaries for each other and to share and listen with an open, non-judgmental attitude without discussing or giving advice. Next, participants are invited to take part in an awareness exercise instructed by one of the group facilitators. They are guided to attend to their thoughts, feelings and bodily senses in the present moment with openness, acceptance and curiosity. After the exercise, they are invited to share their experiences with one other person in the group. In the next part of the session, the group facilitators introduce the topic "anger" by giving a short introduction about relationship between chronic illness and emotions and the purpose of addressing emotions. The participants are then invited to take part in an exercise with awareness of anger, introduced by one of the facilitators: "Think of the word anger… or to be angry. Notice what you become aware of… thoughts, maybe concrete situations, perhaps memories from the past… Are the situations that you become aware of new or old? Maybe both?... What do you experience in your body right now when you think of anger or being angry?... Also note whether the word anger or being angry evokes any other feelings…" Awareness of anger is continued in movement to music. The music allows participants to express anger with their body, and they are invited to let their bodies do what they want to do while listening to the music. Then, written hypothetical sentences are used to enhance discovery to tacit knowledge, for example: "If there are any other emotions related to my feeling of anger, it must be…" Participants are further invited to share and reflect upon experiences and discoveries from the exercise in small groups and in a plenary session. The next exercise is a guided imagery intending to help individuals connect to their experiences of anger in the present moment, and to explore its meaning. Further, crayons and white paper are used to draw an image of anger as experienced here and now. Again, participants are invited to share and reflect in small groups and in plenary, with focus on new discoveries and the consequences of these discoveries from the participants' daily life. Finally, they write a diary about their experiences from the whole session. Before closing the session, participants are asked to be aware of how they relate both to their own anger and anger from others in their daily lives. They are provided with guided mindfulness audio files and are encouraged to practice these exercises in everyday life and to train awareness in daily activities. They are asked to write reflective diaries about their thoughts, emotions and bodily senses.

Each session follows the same structure with exercise adapted to the particular topic. The group facilitators are health professionals, such as nurses and physiotherapists, and certified through a one-year university training programme (30 credits) at VID Specialized University in Oslo.

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2,3
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	4,5
	2b	Specific objectives or hypotheses	5
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	6
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	NA
Participants	4a	Eligibility criteria for participants	6
	4b	Settings and locations where the data were collected	6,7
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	6,7
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	8,9,10
	6b	Any changes to trial outcomes after the trial commenced, with reasons	NA
Sample size	7a	How sample size was determined	10
	7b	When applicable, explanation of any interim analyses and stopping guidelines	NA
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	10
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	10
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	10
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	10
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	10

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	NA
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	10,11
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	NA
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	12
	13b	For each group, losses and exclusions after randomisation, together with reasons	12
Recruitment	14a	Dates defining the periods of recruitment and follow-up	12
	14b	Why the trial ended or was stopped	12
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	12
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	12
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	13
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	NA
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	NA
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	14
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	18
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	15-17
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	15-19
Other information			
Registration	23	Registration number and name of trial registry	3
Protocol	24	Where the full trial protocol can be accessed, if available	3
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	24

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

BMJ Open

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Effects of a mindfulness- and acceptance-based group-programme followed by physical activity for patients with fibromyalgia: a randomised controlled trial

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Abstract

Introduction: Non-pharmacological approaches are recommended as first-line treatment for patients with fibromyalgia. This randomised controlled trial investigated the effects of a multicomponent rehabilitation programme for patients with recently diagnosed fibromyalgia in primary and secondary health care.

Methods: Patients with widespread pain ≥3 months were referred to rheumatologists for diagnostic clarification and assessment of study eligibility. Inclusion criteria were age 20 to 50, engaged in work or studies at present or during the past two years, and fibromyalgia diagnosed according to ACR 2010 criteria. All eligible patients participated in a short patient education programme before inclusion and randomisation. The multicomponent programme, a 10-session mindfulness- and acceptance-based group programme followed by 12 weeks physical activity counselling was evaluated in comparison to treatment as usual, i.e. no treatment or any other treatment of their choice. The primary outcome was the Patient Global Impression of Change (PGIC). Secondary outcomes were self-reported pain, fatigue, sleep quality, psychological distress, physical activity, health related quality of life and work ability at 12-month follow-up.

Results: In total, 170 patients were randomised, 1:1, intervention:control. Overall, the multicomponent rehabilitation programme was not more effective than treatment as usual; 13% in the intervention group and 8% in the control group reported clinically relevant improvement in PGIC (p=0.28). No statistically significant between-group differences were found in any disease-related secondary outcomes. There were significant between-group differences in patient's tendency to be mindful (p=0.016) and perceived benefits of exercise (p=0.033) in favour of the intervention group.

Conclusions: A multicomponent rehabilitation programme combining patient education with a mindfulness- and acceptance-based group-programme followed by physical activity counselling was not more effective than patient education treatment as usual for patients with recently diagnosed fibromyalgia at 12-month follow-up.

Trial registration: The trial is registered at BMC ISRCTN96836577.

Strengths and limitations of this study

- This pragmatic randomised controlled trial was conducted according to a predefined published protocol.
- The main treatment effects were analysed on an intention-to-treat basis at 12 months follow up, with all randomised patients retaining their original allocated groups.
- Although we intended to capture patients with FM at an early stage of their disease, the included patients reported median symptoms duration of eight years.
- There was a high drop-out rate from the physical activity intervention.
- We did not monitor the content of 'treatment as usual' in the control group other than physical activity.

Protocol

A published protocol article can be found at https://bmjopen.bmj.com/content/8/6/e021004

Introduction

Fibromyalgia (FM) is characterised by widespread pain and symptoms such as fatigue, unrefreshed sleep, mood disturbances and cognitive impairment that have persisted more than three months without any alternative explanation (1). Patients report unpredictable symptoms that vary in terms of expression and intensity, and reduced quality of life (2-5). The estimated prevalence of FM in the general population worldwide is between 2% and 7%, with women being predominantly affected (6). Many patients experience lack of understanding from their primary care physicians, insufficient health care, and deficient treatment (7, 8).

For optimal management of FM, the European League Against Rheumatism (EULAR) recommends prompt diagnosis and patient education as first-line treatment. The effects of pharmacological treatments are inadequate (4). The management should aim at improving patients' health-related quality of life and initially focus on non-pharmacological modalities (4, 9). Individualised physical exercise is recommended for all patients with FM. Cognitive behavioural therapy, mindfulness-based stress reduction, meditative movement (i.e. qigong, yoga, tai chi), and hydrotherapy have shown promising effects for some patients, although the evidence is still insufficient (4). Further, multicomponent programmes combining physical exercise with either of these modalities have shown beneficial synergetic effects on FM symptoms in terms of reduced pain and FM impact, and increased physical fitness at the end of treatment (4, 10).

Three recent systematic reviews and meta-analyses have shown that mindfulness- and acceptance-based interventions had short-term small to moderate effects on pain, depression, anxiety, sleep quality and health-related quality of life in patients with FM (11-13). Systematic reviews and meta-analyses on physical exercise in patients with FM have shown beneficial effects on symptoms, such as pain, sleep, and physical function (14-18).

A Norwegian mindfulness- and acceptance-based intervention, the Vitality Training Programme (VTP), aimed at strengthening participants health-promoting resources and ability to make choices in accordance with own values, has been evaluated in two randomised controlled trials in persons with chronic musculoskeletal pain and inflammatory arthritis (IA). The VTP improved pain, fatigue, psychological distress, pain coping, and self-efficacy for pain and other symptoms (19, 20). The effects persisted at 12-month follow-up in both studies. However, a preceding longitudinal pre-post-test study on the VTP in patients with IA and FM showed substantial improvements in patients with IA, but no changes in patients with FM (21). In a nested qualitative study, the FM patients described how they had struggled for years to be believed and taken seriously (22). The authors suggested that the lack of effects in patients with FM might have been related to long symptoms duration without recognition and treatment, which may have led to the development of maladaptive patterns of coping strategies that are difficult to change. They proposed that future studies should investigate the effects of the VTP in FM patients at an early stage of their disease.

The aim of the present randomised controlled trial was to study the effects of a community-based multicomponent rehabilitation programme comprising the VTP followed by 12 weeks of physical activity counselling in patients with recently diagnosed FM. More specifically, we examined whether the multicomponent rehabilitation programme improved patients' self-perceived health, pain, fatigue, sleep quality, psychological distress, physical activity and work ability, compared to treatment as usual, i.e. no treatment or any other treatment of their choice.

Methods

Study design

We conducted a two-armed parallel randomised controlled trial in rural and urban communities in the South-Eastern part of Norway. Patients were allocated to the VTP and physical activity (intervention group) or treatment as usual (control group). More details can be found in the published protocol (ISRCTN 96836577) (23). We followed the Consolidated Standards of Reporting Trials (CONSORT) in this report (24, 25).

Participants

General practitioners and physiotherapists referred patients who had widespread pain that had lasted for at least three months to rheumatologists in specialist health care for diagnostic clarification and assessment of study eligibility. Inclusion criteria were age 20 to 50 and FM diagnosed according to the American College of Rheumatology (ACR) 2010 criteria (1, 26). Patients were excluded if they had an inflammatory rheumatic disease, had a severe psychiatric disorder, another disease that did not allow physical activity, or if they were unable to understand or write Norwegian. We also excluded patients who had been out of work for more than two years.

Procedure and interventions

All eligible patients received a three-hour patient education programme and oral information about the study. Patients who agreed to participate completed written informed consent before inclusion. The VTP was organised in the local communities with seven to 12 patients in each group. It comprised ten weekly four-hour sessions plus a booster session after approximately six months. Every session addressed a specific topic: If my body could talk/ Who am I?/ My resources and potentials/ Values—what is important to me?/ What do I need?/ Strengths and limitations/ Bad conscience/ Anger/ Joy/ Resources, potentials and choices/ Closure and the way ahead. These were explored by various creative methods, such as guided imagery,

music, drawing, poetry, metaphors and reflections. The patients wrote logs after all exercises and shared their experiences with other group participants.

Moreover, patients were invited to attend mindfulness meditation, i.e. body scan, sitting and walking meditation, and gentle yoga exercises (27). They were encouraged to listen to guided mindfulness meditation audio files and practice awareness in their daily activities between sessions (28). The group facilitators were experienced nurses and physiotherapists, who were certified by a one-year post-graduate training programme (30 credits). The facilitators followed a standardised manual with a thorough programme description and monitored the attendance throughout the programme. Based on previous studies, the patients needed to attend at least five sessions to expect effect (20, 23). Supplementary file 1 describes an example of the structure and content of one of the sessions.

The physical activity counselling was conducted at a Healthy Life Centre (HLC), which is a low threshold health care service provided in Norwegian communities designed as easily accessible generic services aimed at lifestyle changes. HLCs typically offer a 12-week programme during daytime, comprising individual counselling based on Motivational Interviewing (MI), individual and group physical activities (29). A physiotherapist provided the individual physical activity counselling. This intervention aimed at helping patients to set tailored goals, identifying and overcoming barriers to physical activity, and guiding them into exercises that they could continue after the 12-week period to increase the level of physical activity gradually.

Control group patients did not receive any organised intervention other than diagnostic clarification and the patient education session but were free to attend any treatment and activity at their own initiative. The control group was offered the VTP and the HLC intervention after completion of the data collection at 12-month follow-up.

Outcomes

The outcome measures were selected according to a core set of domains for FM defined by the Outcome Measures in Rheumatology Clinical Trials (OMERACT) (30, 31). Self-reported questionnaires comprising baseline demographics and all outcome measures were collected electronically before randomisation (baseline), after the VTP (three months) and at 12 months from baseline.

Primary outcome: Patient Global Impression of Change (PGIC)

PGIC is a validated ordinal seven-point self-reported scale that measures how patients feel that their health has changed from they entered the trial to post-intervention data collections. The scale ranges from 1 (I feel very much worse) through 4 (no change) to 7 (I feel very much better) (32). Scores 6 and 7 are considered a clinically relevant improvement. Patient Global Impression of Change (PGIC) has previously been used in FM trials and is recommended as a core measure to improve the applicability of information from clinical trials to clinical practice (33-35). Higher scores in PGIC has been associated with more significant improvements in key FM symptoms and correlates well with FM outcomes (33). The scores can be dichotomised into 'Less than much better' (scores 1 to 5) and 'Much better' (scores 6 and 7) (34).

Secondary outcomes

Pain, fatigue, and sleep quality were assessed by Numerical Rating Scales (NRS) scored from 0 to 10 (10 is intolerable pain/ fatigue/ very bad sleep) (31). Psychological distress was assessed by the General Health Questionnaire-12 (GHQ-12) that comprises six positively phrased items indicating psychological health and six negatively phrased items indicating psychological distress (36). The respondents scored their condition during the last two weeks compared to what they perceived as their 'normal' condition on a four-point Likert scale, reported from 0 (less than usual) to 3 (much more than usual). The scale was reversed for

negatively phrased items. Data were analysed and reported as mean sum score; higher scores represented higher psychological distress (37, 38). A general tendency to be mindful in daily life situations was assessed by the Five Facet Mindfulness Questionnaire (FFMQ) that comprises 39 items rated on a five-point Likert scale from 1 (never true) to 5 (always true) (39). Higher scores reflected higher levels of mindfulness. The scale was reversed for negatively phrased items. Data were analysed and reported as a mean sum score, comprising all five facets. Physical activity (PA) was assessed by three questions from the Nord-Trøndelag Health Study (HUNT1) (40). The questions measure frequency, intensity and duration of leisure-time physical exercises such as walking, skiing, swimming or other training/-sport activities that improve physical fitness. A summary index of weekly PA was calculated from the frequency, intensity and duration scales with scores from 0 to 15. Higher scores indicate increased PA. Motivation and barriers for physical activity were assessed by the Exercise Beliefs and Exercise Habits questionnaire comprising 20 items scored on a five-point Likert scale ranging from 'strongly agree' to 'strongly disagree' (41). The items were divided into four sub-scales calculated and reported separately as beliefs about one's ability to exercise, barriers to exercise, benefits of exercise, and impact of exercise on muscular pain. Work ability was assessed by the Work Productivity and Activity Impairment General Health V2.1 (WPAI:GH) comprising six questions to determine employment status; hours missed from work because of health problems or other reasons, and hours worked (42). Higher scores indicate more significant impairment and less productivity. For this study, we calculated the outcomes 'overall work impairment' and 'daily activity impairment'. Health-related quality of life was assessed with EuroQol (EQ-5D-5L) comprising five dimensions; mobility, self-care, usual activities, pain/discomfort and anxiety/depression scored on five levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The EQ-5D-5L scores range between 0–1, 0 indicates death, and 1 indicates perfect health (43). Secondly,

the participants rate their overall health on a 0 - 100 hash-marked, vertical visual analogue scale (EQ-VAS), 0 is as bad as it could be, and 100 as good as it could be (44).

Harms

Patients were asked to report adverse events at 12 months and major symptoms that were associated with these events.

Randomisation and blinding

A statistician generated an electronic randomisation list for each geographical area to ensure approximately equal sample sizes. A research assistant not involved in the study generated the allocation sequence and assigned patients to study groups. Further, the facilitators of the VTP groups organised and administered the enrolment. Due to the nature of the intervention, it was not possible to blind the patients and the VTP facilitators to group allocation. The project leader and the research coordinator who were responsible for the data collection and data analysis were blinded to the allocation.

Sample size

Sample size calculation was based on the primary outcome assuming that 10% in the control group would report clinically relevant improvement at 12 months follow-up, and that at least 20% absolute difference in improvement rate between the groups would be considered a minimum clinically relevant difference. With allowance for 10% losses to follow-up, 70 patients in each group were needed to have at least 80% power of detecting differences with 5% alpha level.

Statistical analyses

Mean values and standard deviation (SD) were calculated for continuous variables or as median with minimum and maximum values if skewed. Frequency numbers and percentages were calculated for categorical variables. Baseline differences in patients' characteristics

between intervention and control group were assessed by independent group t-test or Mann Whitney U test for continuous variables. For categorical variables, we used Pearson's Chi-square test or Fisher's exact test when the expected cell count fell below five. The treatment effects were analysed on an intention-to-treat basis with all randomised patients retaining their original allocated groups at 12 months. The distribution of the primary outcome (PGIC) was analysed as an ordinal variable by Mann Whitney U test. When dichotomised, the difference between groups was tested with Chi-square statistics and Fisher's exact tests. Treatment effects in secondary outcomes were estimated by Analysis of Covariance (ANCOVA) at three and 12-month follow-up adjusted for the baseline values. The level of statistical significance was set to ≤0.05. We used STATA V.14.0 (45) to analyse the data. Missing values in single items of FFMQ and GHQ-12 were imputed by calculating the mean value of the registered values multiplied with the number of questions.

Patient and public involvement

Representatives from the Patient Advisory Board at the Diakonhjemmet Hospital were involved in the development of the study, such as study design, research questions and recruitment of patients. The electronic questionnaires were tested and amended by user representatives. More information is described elsewhere (23).

Results

Of the 289 patients who were referred to the rheumatologists, 208 (72%) were eligible for inclusion. A total of 170 consented to participate and were randomised; 85 to the intervention group and 85 to the control group. Figure 1 illustrates the flow of patients through the study.

Figure 1. Flow chart of patients

The intervention group had a significant higher median age (p=0.02) and symptoms duration in years (p=0.05) compared to the control group. All other baseline characteristics were equally distributed between the groups (Table 1).

Table 1. Patients' characteristics at baseline

Variables	All Patients (n=170)	Intervention Group (n=85)	Control Group (n=85)	P-value
Age, years, median (min, max)	42 (24, 52)	44 (26, 52)	41 (24, 51)	0.02[1]
Gender, women	159 (94%)	78 (92%)	81 (95%)	0.54[3]
Education:				0.60[2]
Primary/ middle school (1-10 years)	20 (12%)	8 (9%)	12 (14%)	
Upper secondary school/ Vocational 10-12 years	68 (40%)	36 (42%)	32 (38%)	
Bachelor/ University>12 years	81 (48%)	40 (47%)	41 (48%)	
Work status:				
Currently in paid work	119 (70%)	59 (69%)	60 (71%)	0.94[2]
Not in paid work	48 (28%)	24 (28%)	24 (28%)	0.94[2]
In paid work but on sick leave (100%)	8 (17%)	3 (13%)	5 (21%)	
Work assessment allowance	35 (73%)	20 (83%)	15 (62%)	
Unemployed	4 (8%)	1 (4%)	3 (13%)	
Student	1 (2%)		1 (4%)	
Married/ living with partner	120 (71%)	54 (64%)	66 (78%)	0.06[2]
Symptoms duration, years, median, (min, max)	8 (1, 32)	10 (1, 32)	7 (1, 30)	0.05[1]
Comorbidities, median (min, max)	2 (1, 6)	2 (1, 6)	2 (1, 6)	0.24[1]

Smokers	23 (14%)	14 (17%)	9 (11%)	0.25[2]
FM in family	57 (34%)	27 (32%)	30 (35%)	0.55[2]
Use of medication in the last three months				
Pain medications:	149 (88%)	73 (86%)	76 (89%)	0.64[2]
Hypnotics:	51 (30%)	27 (32%)	24 (28%)	0.63[2]
Antidepressants:	20 (12%)	8 (9%)	12 (14%)	0.48[2]
Anxiolytics:	8 (5%)	2 (2%)	6 (7%)	0.28[3]

Values are means (SD) or numbers (%). FM: fibromyalgia, [1]Mann Whitney U test, [2]Pearson's Chi-Square test, [3]Fisher's exact test.

Of the 75 patients who attended the VTP, 67 (89%) completed five sessions or more; 21 (31%) of these patients completed all ten sessions, 20 (30%) completed nine, and nine (13%) completed eight sessions. The average attendance rate was 7.5 sessions. Thirty-two patients (43%) attended the physical activity intervention after the VTP, but only 14 patients participated more than 12 times during the 12-week programme. The data collection was completed by 160 (94%) at three months and 153 (90%), and 12 months. Recruitment of patients started in September 2016 and ended in August 2018. Electronic data collection started in February 2017 and ended in September 2019 when the complete 12-month follow-up data were attained.

Patient Global Impression of Change

The median PGIC score was 4 (range 1 to 7) in both groups at three and 12-month follow-up. However, we found statistically significant differences between the groups in distribution of the PGIC-scores at three-month follow up (p=0.01), but not at 12-month follow up (p=0.06). The distribution across all response categories is shown in Figure 2.

Figure 2. The distribution of PGIC scores

There were no statistically significant differences between the intervention group and the control group at three- and 12-month follow-ups when the PGIC was dichotomised into 'Less than much better' and 'Much better'. At 12-month follow-up, 13 per cent in the intervention group reported 'Much better' compared to eight per cent in the control group (Table 2).

Table 2. Effect of intervention, primary outcome: Patient Global Impression of Change

PGIC	**3 months**			**12 months**		
	Intervention (n=76)	Control (n=84)	P-value	Intervention (n=76)	Control (n=77)	P-value
Much better (scores 6 and 7), n (%)	6 (7.9)	4 (4.8)	0.52[1]	10 (13.2)	6 (7.8)	0.28[2]

[1]Fisher's exact, [2]Pearson's Chi-Square test

Secondary outcomes

There were no statistically significant differences between the groups at 12-month follow-up in any disease-related outcomes (Table 3). However, there was a statistically significant improvement in favour of the intervention group in 'general tendency to be mindful'. Moreover, there was a statistically significant difference between groups in 'perceived benefits of exercise' due to a small deterioration in the control group (Table 3). The numbers of people working, assessed by the WPAI:GH, was 56 (67%) at baseline and 48 (64%) at 12-

month follow-up in the intervention group, compared to 52 (61%) at baseline and 50 (64%) at 12-month in the control group.

Table 3. Effects of intervention, secondary outcomes estimated by ANCOVA adjusted for baseline scores

		Intervention (n=76) Mean (SD)	Control (n=77) Mean (SD)	Baseline adjusted mean difference (95% CI)	P-value
Pain (NRS 0-10, 0 = no pain)					
	Baseline	6.7 (1.6)	6.8 (1.9)	-	-
	3 months	6.4 (1.7)	6.6 (1.8)	0.30 (-0.15 to 0.75)	0.19
	12 months	5.8 (2.1)	6.4 (1.8)	0.55 (-0.00 to 1.11)	0.05
Fatigue (NRS 0-10, 0 = no fatigue)					
	Baseline	7.5 (2.0)	7.4 (2.0)	-	-
	3 months	7.2 (1.9)	7.1 (2.2)	-0.03 (-0.60 to 0.54)	0.92
	12 months	6.8 (2.3)	6.8 (2.3)	0.12 (-0.56 to 0.80)	0.72
Sleep (NRS 0-10, 0 = no sleep)					
	Baseline	6.8 (2.3)	7.1 (2.5)	-	-
	3 months	6.6 (2.5)	6.9 (2.5)	0.27 (-0.42 to 0.97)	0.44
	12 months	6.5 (2.5)	6.3 (2.5)	-0.24 (-0.99 to 0.50)	0.52
Psychological distress (GHQ-12, mean sum score, 0-36, 0 = no distress)					
	Baseline	16.5 (6.6)	19.2 (6.8)	-	-
	3 months	13.4 (6.5)	16.5 (7.0)	1.57 (-0.37 to 3.50)	0.11
	12 months	14.8 (6.8)	16.6 (6.9)	1.03 (-1.08 to 3.14)	0.34
Five Facet Mindfulness Questionnaire (Mean sum score, 39-195, low to high)					
	Baseline	119 (17.2)	113 (16.9)	-	-
	3 months	124 (19.1)	118 (16.3)	-1.07 (-4.73 to 2.58)	0.56
	12 months	126 (17.6)	118 (16.3)	-4.72 (-8.57 to -0.9)	0.02
Physical activity (0-15, 0 = inactive)					
	Baseline	3.0 (2.4)	2.8 (1.8)	-	-
	3 months	2.3 (1.6)	2.7 (1.9)	0.53 (-0.04 to 1.10)	0.07
	12 months	2.9 (2.3)	2.8 (1.8)	0.10 (-0.60 to 0.79)	0.78
Motivation and barriers for Physical Activity					
Self-Efficacy (4-20, low to high)					
	Baseline	12.0 (2.9)	12.0 (3.2)	-	-
	3 months	12.5 (3.1)	12.6 (3.1)	0.08 (-0.70 to 0.86)	0.84
	12 months	13.1 (3.5)	12.8 (3.1)	-0.33 (-1.27 to 0.62)	0.50
Barriers (3-15, low to high)					
	Baseline	12.1 (2.4)	12.1 (2.0)	-	-
	3 months	11.8 (2.3)	11.8 (1.9)	-0.00 (-0.48 to 0.47)	0.99
	12 months	12.2 (2.4)	12.2 (1.7)	-0.07 (-0.61 to 0.46)	0.79
Benefits (5-25, low to high)					
	Baseline	20.4 (3.2)	21.1 (2.7)	-	-
	3 months	20.3 (3.0)	20.4 (2.7)	-0.19 (-0.89 to 0.50)	0.59
	12 months	20.7 (3.0)	20.1 (2.9)	-0.90 (-1.73 to -0.07)	0.03
Impact (8-40, low to high)					
	Baseline	28.8 (4.6)	29.0 (4.8)	-	-
	3 months	28.4 (4.8)	28.5 (4.3)	0.08 (-0.90 to 1.06)	0.87
	12 months	28.9 (5.4)	28.3 (4.6)	-0.49 (-1.63 to 0.65)	0.40
Work Productivity and Activity Impairment General Health					
Work impairment (0-10, 10 = completely impaired)					
	Baseline	5.2 (2.5)	6.2 (2.2)	-	-
	3 months	5.1 (2.4)	5.4 (2.5)	-0.15 (-1.05 to 0.76)	0.75

	12 months	4.9 (3.2)	5.3 (2.9)	0.73 (-0.58 to 2.03)	0.27
Daily activity impairment (0-10, 10 = completely impaired)					
	Baseline	7.0 (2.0)	7.1 (1.9)	-	-
	3 months	6.9 (1.7)	6.7 (2.3)	-0.25 (-0.83 to 0.34)	0.41
	12 months	6.3 (2.5)	6.5 (2.2)	0.07 (-0.65 to 0.79)	0.84
EQ-5D-5L					
Index (0–1, 1 = perfect health)					
	Baseline	0.51 (0.2)	0.47 (0.2)	-	-
	3 months	0.55 (0.2)	0.53 (0.2)	0.02 (-0.05 to 0.09)	0.86
	12 months	0.54 (0.2)	0.50 (0.2)	0.04 (-0.03 to 0.11)	0.48
VAS (0-100, 100 = as good as it could be)					
	Baseline	44.6 (16.5)	41.61 (17.0)	-	-
	3 months	46.4 (16.1)	51.5 (21.7)	-5.1 (-12.10 to 1.90)	0.03
	12 months	49.0 (20.6)	46.8 (18.5)	2.19 (-4.67 to 9.05)	0.77

NRS=Numeric Rating Scale, GHQ-12=General Health Questionnaire, EQ-5D-5L=Health-related quality of life

Harms

A total of 34 patients reported adverse events, 21 (28 %) in the intervention group, and 13 (17 %) in the control group. Increased pain and fatigue were the most frequent adverse events. Thirteen (nine in the intervention group and four in the control group) related the events to medication; 21 (12 in intervention and nine in control) to physical activity; four in the intervention group related the events to the VTP; two (one in intervention and one in control) related the events to alternative treatment.

Discussion

In this pragmatic randomised controlled trial, we examined the effects of a multicomponent rehabilitation programme for patients with FM. The study demonstrated that a mindfulness- and acceptance-based intervention, the VTP, followed by physical activity counselling in patients with recently diagnosed FM was not more effective than treatment as usual. Only 13 per cent in the intervention group reported clinically relevant improvement in self-perceived health status at 12-month follow-up compared to eight per cent in the control group. We did not observe differences between the groups in any disease-related secondary outcomes. However, there were statistically significant differences between groups in 'tendency to be mindful' and 'perceived benefits of exercise' in favour of the intervention group. The latter was due to a slight deterioration in the control group.

The results of this trial both negate and support earlier studies on the VTP for patients with FM. One randomised controlled trial in patients with musculoskeletal pain conditions, including FM, demonstrated substantial health improvements (19). In contrast, a longitudinal study in patients with IA and FM showed improvements in the IA group, but not in the FM group (21). Based on the latter study, it was hypothesised that the lack of effects in patients with FM might have been related to living with distressing symptoms over a long time without receiving any diagnosis. The present study aimed to improve the management of FM by following the EULAR recommendations for management of FM in a Norwegian context. We assumed that offering patients who had been recently diagnosed with FM a mindfulness- and acceptance-based intervention might help them overcome some of their internal barriers to physical activity before they attended a physical activity intervention. However, we found no support for this assumption.

There were statistically significant differences between the groups in distribution of the PGIC-scores at three-month follow-up, but not at 12months. This corresponds to other studies on mindfulness- and acceptance-based interventions that have shown beneficial short-term effects, but no evidence for long-term effects (10, 11). Our primary outcome, the PGIC scale, was dichotomised to distinguish between those who reported clinically relevant improvement in self-perceived health and those who did not. This has also been performed in previous studies, in which clinically relevant improvements have been shown (33, 34). However, we did not find any clinically relevant differences between the groups in our study. Previous systematic reviews and meta-analyses on mindfulness- and acceptance-based interventions have shown small to moderate beneficial effects on pain, sleep quality and health-related quality of life for patients with FM (10-13). In the present study, we did not see any of these effects. However, we found a statistically significant effect in 'tendency to be mindful'. Improvement in mindfulness may be associated with enhanced mental health outcomes (46, 47). Longer follow-up may be needed to see if this improvement will result in effects in other outcomes, such as perceived health status and physical activity.

As many as 57 per cent of the patients never attended the HLC intervention, and they did not report any increase in physical activity at 12-month follow-up. Twelve of the 32 patients who took part in the HLC intervention reported adverse events, such as increased pain and fatigue, which may have been one reason for quitting the training. This corresponds to other studies, which have shown that many patients report physical activity to be challenging, and that adherence to exercise interventions is poor (18, 48-50). A recent systematic review showed that physical activity should be tailored to individual characteristics to be effective (51). Given the varied clinical picture associated with FM, the initial object of the HLC intervention was to adapt the physical activity to each patient's physical condition and individual preferences. The patients reported the type of physical activity they performed

in general terms, such as walking, strength training, cycling, spinning, etc. A limitation of our study is that we did not monitor to which degree the physiotherapists at the HLC adapted the physical activity to the individual patient's condition, nor did we monitor if the patients experienced that the physical activity was individually tailored. Further studies are needed to explore ways to improve adherence to physical activity.

Because we wanted to investigate if it was possible to prevent work loss and improve work participation, we excluded patients that had been out of work for more than two years. Long-term absence from work due to illness has been identified as a risk factor for transition into disability pension (52, 53). Seventy-one per cent of the patients in our study had paid work. Previous studies have shown that nonworking FM patients have more severe symptoms than working patients (54, 55). Despite the high number of workers in our study, the patients reported high symptoms burden, in terms of pain, fatigue and psychological distress.

Because we assumed that higher age might be associated with more comorbid conditions, we defined 50 years as the upper age limit for inclusion. Nevertheless, the median number of comorbidities in the included patients was two.

Although we intended to capture patients with FM at an early stage of their disease, the included patients reported median symptoms duration of eight years. These findings, although contrary to our expectations, corresponds to other studies, which have shown that patients wait a significant time before presenting symptoms to a physician (56). Further, there may be a delay in diagnosis in primary health care due to an overlap of symptoms with other conditions and patients may have difficulties in communicating their symptoms (57). Other reasons for the delay in diagnosis and treatment may be lack of knowledge and understanding of FM from primary care physicians (58).

This study was conducted according to a predefined published protocol (23). It was well-powered, and all included patients were allocated to the groups to which they were

randomised, ensuring valid treatment comparisons and assessment of treatment effects (59). The losses to follow-up were within our assumption of 10 %. We had predefined that patients needed to attend at least 50 per cent of the sessions to expect effects of the VTP intervention, and nearly 90 per cent attended more than half of the VTP sessions (23). This attendance rate is comparable to other studies on mindfulness- and acceptance-based interventions (13). The percentage of patients with complete follow-up data was high. The VTP facilitators were certified and followed a manualised programme, which improves transparency and replication (60). Moreover, the 12 months follow-up time was relatively long, and in line with what has been asked for in previous research (13).

Several limitations need to be mentioned. Firstly, before randomisation, all study participants received a short patient education session, which is recommended as a first-line intervention by the EULAR recommendations. This might have served as a validation of the FM diagnosis and may have provided the patients with knowledge and information about possible coping strategies. The control group could include strategies and activities at their own initiative. We did not monitor the content of 'treatment as usual' in the control group other than physical activity. Thus, we do not know if the patients had initiated beneficial self-management strategies during the control period.

Secondly, our study was a pragmatic randomised controlled trial, which makes it difficult to differentiate between the effects of the various interventions and to interpret the lack of effects. Moreover, we did not monitor the adherence to the homework between the VTP sessions. Consequently, we do not know to what extent the patients practised mindfulness training and integrated the training in their daily life. A recent review on mindfulness- and acceptance-based interventions showed a small but significant association between the extent of formal practice and positive intervention outcomes (61). It is recommended that future research should adopt a standardised approach for monitoring home-

practice across mindfulness- and acceptance-based interventions (62). Further, we included already existing HLCs in the communities. The activities offered vary between centres, and consequently, it was not possible to standardise the frequency, intensity, duration, progression or type of exercise. Moreover, the HLCs offer physical activity counselling at daytime only, making the intervention challenging to combine with a daytime job. Subsequently, a physical activity intervention with more flexible access might have increased the patient participation.

Thirdly, we did not include any coping measures, such as self-efficacy, to assess the coping with their symptoms. We used the GHQ-12 to assess mental health status because this was found to be sensitive to change in previous studies on the VTP. The GHQ-12 does not capture more severe symptoms of depression and anxiety but is a widely used instrument to assess psychological distress.

Finally, we could have applied other statistical analyses, such as Linear Mixed Models rather than ANCOVA, to estimate effects. However, ANCOVA was chosen because it has shown great power and low variability when compared to other traditional analyses approaches, and it is regarded as a preferred analysis when post-treatment assessments adjusted for the pre-treatment assessments are measured (63, 64). We did not adjust for multiple comparisons.

This study has demonstrated that a multicomponent rehabilitation programme combining recent diagnosis and patient education with a mindfulness- and acceptance-based intervention followed by physical activity counselling was not more effective than recent diagnosis, patient education and treatment as usual for patients with FM.

There was a high drop-out rate from the physical activity intervention. Further, studies on how to adapt and tailor physical activity interventions to patients with FM are needed.

Our intention to include patients at an early stage of the disease was not fulfilled. The patients reported high symptoms burden and had a median symptoms duration of eight year. Thus, future research should aim at including patients with more recent disease onset and explore the effects of prompt diagnosis and patient education.

Author contributions: Kåre Birger Hagen and Heidi A. Zangi contributed to the initial design of the project, and all authors contributed to the conception of the study. Material preparation, data collection and analysis were performed by Trond Haugmark, Sella A. Provan and Geir Smedslund. All authors contributed to the interpretation of the data. The first draft of the manuscript was written by Trond Haugmark and all authors commented and revised previous versions of the manuscript. All authors read and approved the final manuscript.

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Ethical approval: This study was performed in line with the principals of the Declaration of Helsinki. Study design, information strategy, written consent formula and data security are approved by the Regional Committee for Medical and Health Research Ethics (2015/2447/REK sør-øst A).

Consent to participate: Informed consent was obtained from all individual patients included in the study.

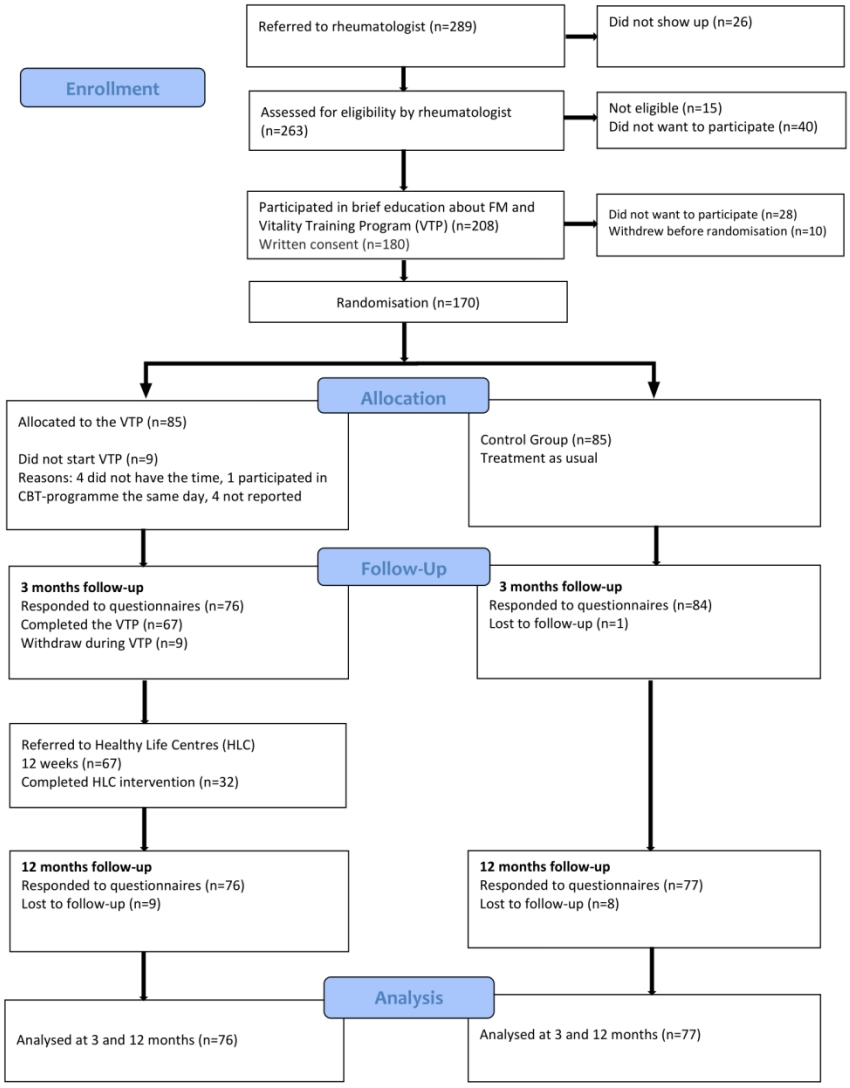

Figure 1. Flow chart of patients

599x776mm (72 x 72 DPI)

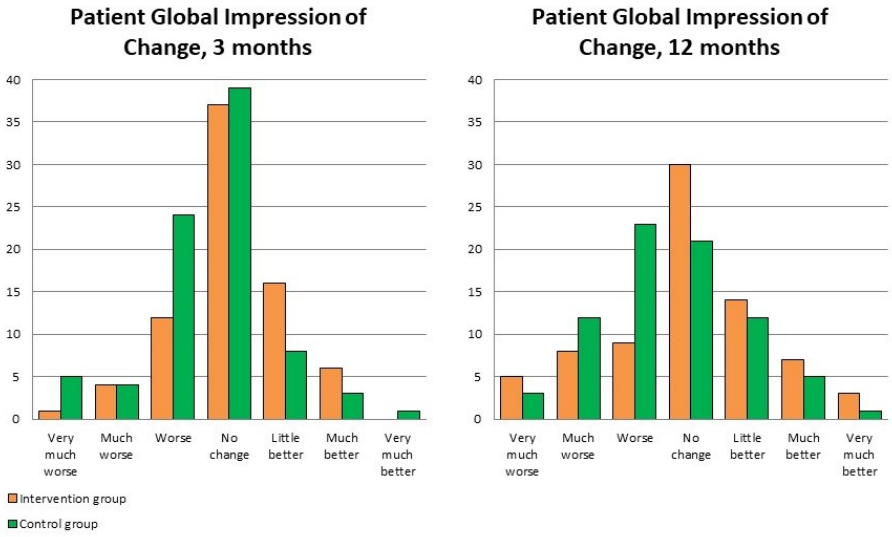

Figure 2. The distribution of PGIC scores

252x150mm (96 x 96 DPI)

Supplementary file

Online Supplementary file 1

Example from group session 6 in the Vitality Training Programme: Anger

The first part of the program is standard in all sessions: Participants are invited to share their reflection on experiences from home exercises after the previous session in groups of three to four persons. They are encouraged to read their reflective diaries for each other and to share and listen with an open, non-judgmental attitude without discussing or giving advice. Next, participants are invited to take part in an awareness exercise instructed by one of the group facilitators. They are guided to attend to their thoughts, feelings and bodily senses in the present moment with openness, acceptance and curiosity. After the exercise, they are invited to share their experiences with one other person in the group. In the next part of the session, the group facilitators introduce the topic "anger" by giving a short introduction about relationship between chronic illness and emotions and the purpose of addressing emotions. The participants are then invited to take part in an exercise with awareness of anger, introduced by one of the facilitators: "Think of the word anger… or to be angry. Notice what you become aware of… thoughts, maybe concrete situations, perhaps memories from the past… Are the situations that you become aware of new or old? Maybe both?... What do you experience in your body right now when you think of anger or being angry?... Also note whether the word anger or being angry evokes any other feelings…" Awareness of anger is continued in movement to music. The music allows participants to express anger with their body, and they are invited to let their bodies do what they want to do while listening to the music. Then, written hypothetical sentences are used to enhance discovery to tacit knowledge, for example: "If there are any other emotions related to my feeling of anger, it must be…" Participants are further invited to share and reflect upon experiences and discoveries from the exercise in small groups and in a plenary session. The next exercise is a guided imagery intending to help individuals connect to their experiences of anger in the present moment, and to explore its meaning. Further, crayons and white paper are used to draw an image of anger as experienced here and now. Again, participants are invited to share and reflect in small groups and in plenary, with focus on new discoveries and the consequences of these discoveries from the participants' daily life. Finally, they write a diary about their experiences from the whole session. Before closing the session, participants are asked to be aware of how they relate both to their own anger and anger from others in their daily lives. They are provided with guided mindfulness audio files and are encouraged to practice these exercises in everyday life and to train awareness in daily activities. They are asked to write reflective diaries about their thoughts, emotions and bodily senses.

Each session follows the same structure with exercise adapted to the particular topic. The group facilitators are health professionals, such as nurses and physiotherapists, and certified through a one-year university training programme (30 credits) at VID Specialized University in Oslo.

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2,3
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	4,5
	2b	Specific objectives or hypotheses	5
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	6
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	NA
Participants	4a	Eligibility criteria for participants	6
	4b	Settings and locations where the data were collected	6,7
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	6,7
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	8,9,10
	6b	Any changes to trial outcomes after the trial commenced, with reasons	NA
Sample size	7a	How sample size was determined	10
	7b	When applicable, explanation of any interim analyses and stopping guidelines	NA
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	10
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	10
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	10
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	10
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	10

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	NA
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	10,11
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	NA
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	12
	13b	For each group, losses and exclusions after randomisation, together with reasons	12
Recruitment	14a	Dates defining the periods of recruitment and follow-up	12
	14b	Why the trial ended or was stopped	12
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	12
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	12
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	13
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	NA
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	NA
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	14
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	18
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	15-17
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	15-19
Other information			
Registration	23	Registration number and name of trial registry	3
Protocol	24	Where the full trial protocol can be accessed, if available	3
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	24

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.