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Trajectories of change in symptom severity in patients with fibromyalgia: exploratory analyses of a randomised controlled trial

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Abstract

The clinical picture of fibromyalgia (FM) symptoms fluctuates, and the symptom severity varies within and between patients. The current study aimed to identify groups of PDS trajectories and to explore differences in baseline characteristics between the potential groups of trajectories. We included patients from a completed randomised controlled trial, in total 170 patients diagnosed with FM according to the ACR 2010 criteria. The mean age was 40 years, and 94% were women. Symptom severity was assessed by the Polysymptomatic distress scale (PDS) [range 0 (no symptoms) to 31] at four timepoints over 13–18 months. Latent class growth analysis was used to identify patient trajectories based on their response pattern on the PDS. Potential differences in baseline characteristics between the trajectories were compared using appropriate statistical tests. Two distinct PDS trajectories were identified with 110 patients (65%) classified as the "no improvement" group and 60 (35%) as the "some improvement" group. Mean PDS scores at pre-baseline were ≥ 20 in both groups. At 12 months, the groups diverged, mean (SD) PDS score was 14 (3.82) in the "some improvement" group and 21 (4.12) in the "no improvement" group. There were no significant differences in baseline characteristics between the groups of PDS trajectories. We identified one group of FM patients that improved slightly during the study period and one group that not improved. There were no differences in baseline characteristics between the two groups.

Keywords Fibromyalgia · Polysymptomatic distress scale · Latent class growth analysis · Trajectory

Introduction

Fibromyalgia (FM) patients have been shown to suffer from heavy symptom burden over time [1]. The underlying mechanisms of FM are not fully understood, and to date, there is no curative treatment [2].

The first American College of Rheumatology (ACR) classification criteria for FM were based on the doctor's examination of bilateral pain in the axial skeleton in upper and lower parts of the body; at least 11 of 18 tender points were needed to be diagnosed with FM [3]. In 2010, new diagnostic FM criteria were developed [4]. These criteria recognized that FM patients in addition to pain could have co-occurring symptoms, such as fatigue, non-restorative sleep, mood disturbances, and cognitive impairment that fluctuate and vary in terms of expression and intensity within and between patients, at different times and intervals [5, 6]. The criteria were based on the assessment of two scales, the Widespread pain index (WPI) and the Symptom severity scale (SSS), that were summed up in

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the Polysymptomatic distress scale (PDS) and measures the magnitude and severity of FM symptoms [4, 7]. It was suggested that patients' FM-associated symptoms might be graded on a continuum as "fibromyalgianess", rather than a discrete diagnosis [7, 8]. The PDS scores can also be categorised into none, mild, moderate, severe, and very severe to better assess and interpret the severity of symptoms [7]. In 2011, the ACR 2010 criteria were modified to allow for self-report of FM severity in clinical research [9]. The PDS has been translated and validated in several languages, including Norwegian [10].

We have conducted a randomised controlled trial (RCT) to evaluate the effects of a mindfulness- and acceptance-based group-intervention, the Vitality Training Programme (VTP), followed by supervised physical exercise, compared to treatment as usual, for patients with recently diagnosed FM [11]. The VTP comprised 10 four-hour sessions once a week and aimed to enhance patients' health-promoting resources [12, 13]. All eligible participants received a three-hour patient education programme to provide a basic understanding of FM, pain mechanisms, psychological factors, physical activity, and coping strategies before inclusion and randomisation. Control group participants did not receive any organised intervention other than diagnostic clarification and the patient education programme, but they were free to attend any treatment and activity of their own choice. The outcomes in the RCT were self-perceived change in health status, pain, fatigue, sleep quality and psychological distress. Outcomes were assessed at baseline, three and 12-month follow-up. We found no statistically significant differences between the groups in any outcomes during follow-up. The PDS was assessed at all time-points, but was not included as an outcome measure in the RCT.

The mean symptom burden in the RCT was high in both groups at baseline and did not improve throughout the study period. Based on these results, the aim of the present study was to explore if we could identify groups of PDS trajectories during the study period. Furthermore, we aimed to explore if there were any differences in baseline characteristics between the groups of PDS trajectories.

Methods

Study overview

This study was an exploratory analysis of data from a completed RCT in patients with FM that was conducted from 2016 to 2019. Study details are described elsewhere (ISRCTN 96836577) [11]. The study was approved by the Regional Committee for Medical and Health Research Ethics (2015/2447/REK sør-øst A).

Participants and procedures

All randomised patients in the RCT were included in the present study ($n = 170$). The patients were recruited from rural and urban areas in the South-Eastern part of Norway. General practitioners (GPs) referred patients with widespread pain lasting for more than 3 months to specialist health care rheumatologists for diagnostic clarification and assessment of study eligibility. Eligibility criteria were patients aged 20–50 who were engaged in work or studies at present or during the past 2 years and diagnosed with FM according to the ACR 2010 criteria.

Outcome

The outcome in the present study was the PDS comprising two subscales, the WPI and the SSS. The WPI score is a 0–19 (worst) summary count of 19 painful regions from the self-reported Regional Pain Scale. The SSS is a 0–12 (worst) measure of symptom severity that includes fatigue, sleep, and cognitive problems (range 0–9) and the sum (range 0–3) of symptoms from headaches (range 0–1), pain or cramp in lower abdomen (range 0–1) and depression (range 0–1) that patients have been bothered with during the previous 6 months [7, 14]. The PDS is the sum score of the SSS and WPI, making the maximum score of PDS 31. Higher scores represent higher severity and more extensive symptoms. The cut-off for FM-diagnosis is PDS score ≥ 12 [4]. Furthermore, the symptom severity may be categorised according to the PDS score from none (0–3), mild (4–7), moderate (8–11), severe (12–19), to very severe (20–31) [7, 10].

Baseline characteristics

Baseline characteristics included age, gender, disease duration, number of comorbidities, education, and marital status.

Data collection

The PDS was self-reported at referral to specialist health care (pre-baseline) and collected electronically at inclusion in the study (baseline), after the VTP (3 months), and at 12-month follow-up. The time from pre-baseline to baseline differed in individual patients; thus, the total follow-up time spanned from 13 and 18 months.

Statistical analysis

Latent class growth analysis (LCGA) was used to identify groups of patients with similar symptom severity trajectories based on patients' responses on the PDS at four time-points.

The number of trajectory groups was determined by first estimating a sequence of models, each with a different number of groups, and then selecting the one with the best-fit. The model sequence started with a single group, and the group number was successively increased, and the model re-estimated. The Bayesian Information Criterion (BIC) was used to identify the best-fitted model and a corresponding number of trajectory groups [15]. The mean response within each group was estimated by treating time as a categorical variable, while the group-specific error covariance matrix was estimated in three different ways, treating it as diagonal, exchangeable, and unstructured. The selected error covariance matrix was also based on the BIC [16]. The LCGA was carried out using the function gsem in Stata v16 [17]. Each patient was assigned to their most likely trajectory class to identify differences in baseline characteristics between the groups of PDS trajectories. This was determined by the posterior class probability estimate based on the four time-points. Baseline characteristics were then compared using two-sample t-tests and Chi-square tests as appropriate.

Results

A total of 170 patients were included in the present analyses. The mean (SD) age was 40 (7.1) years, 94% were women, the mean (SD) symptom duration was 10 (7.7) years, and the median number of comorbidities was 2 (range 1–6). The mean (SD) PDS score was high throughout the study period (pre-baseline: 21 (4.2), baseline: 21 (4.5), 3 months: 19 (5.4), 12 months: 18 (5.3). However, there were individual variations in the PDS trajectories across time-points for all included patients.

Trajectories of change

Two distinct groups of PDS trajectories were identified with 65% of the patients classified into the first group denoted "no improvement" and 35% into the second group denoted "some improvement" (Fig. 1).

At pre-baseline, the mean scores in both trajectory groups fell within the PDS category "very severe". The scores diverged between the groups at all time-points from baseline, and the estimated trajectories displayed significant differences in PDS scores (Table 1). In the "some improvement" group, 15 patients reported PDS score < 12 at 12-month follow-up.

Table 1 PDS scores across time-points in the two groups

Characteristic	No improvement, $n=110$	Some improvement, $n=60$	P value*
Pre-baseline PDS	20.95 (4.46)	20.05 (3.72)	0.18
Baseline PDS	21.9 (4.31)	18.02 (3.74)	< 0.001
3-month PDS	22.17 (4.04)	14.53 (3.68)	< 0.001
12-month PDS	20.96 (4.12)	13.66 (3.82)	< 0.001

Data are mean (SD)

*Differences between groups assessed by t tests

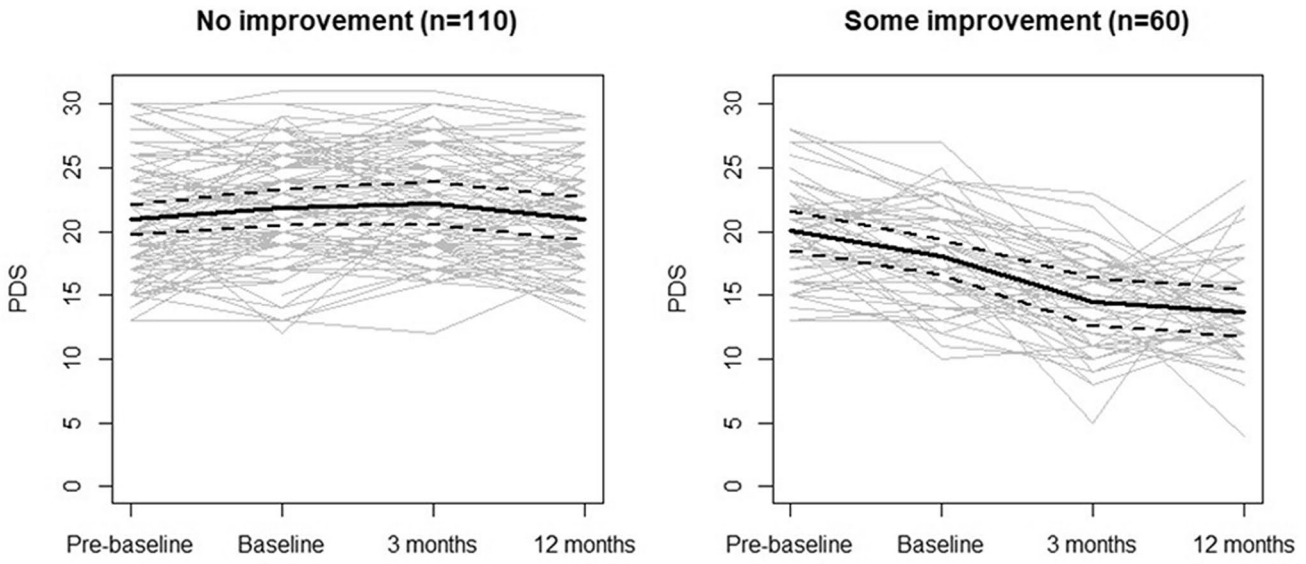

Fig. 1 Trajectories of the PDS measured at four time-points. The solid lines show the mean and the dotted lines show the 95% CI

Changes of PDS categories across time-points

In the "some improvement" trajectory, the number of patients in the category "very severe" decreased, whereas the proportion of patients in the "severe" and "moderate" categories increased stepwise across the time-points. In the group of "no improvement", the numbers were stable across all time-points (Fig. 2).

Differences in baseline characteristics between groups of PDS trajectories

There were no statistically significant differences in baseline characteristics between the two groups of PDS trajectories (Table 2). However, 57% in the "some improvement" group had been randomised to the intervention group compared to 46% in the "no improvement" group ($p = 0.26$).

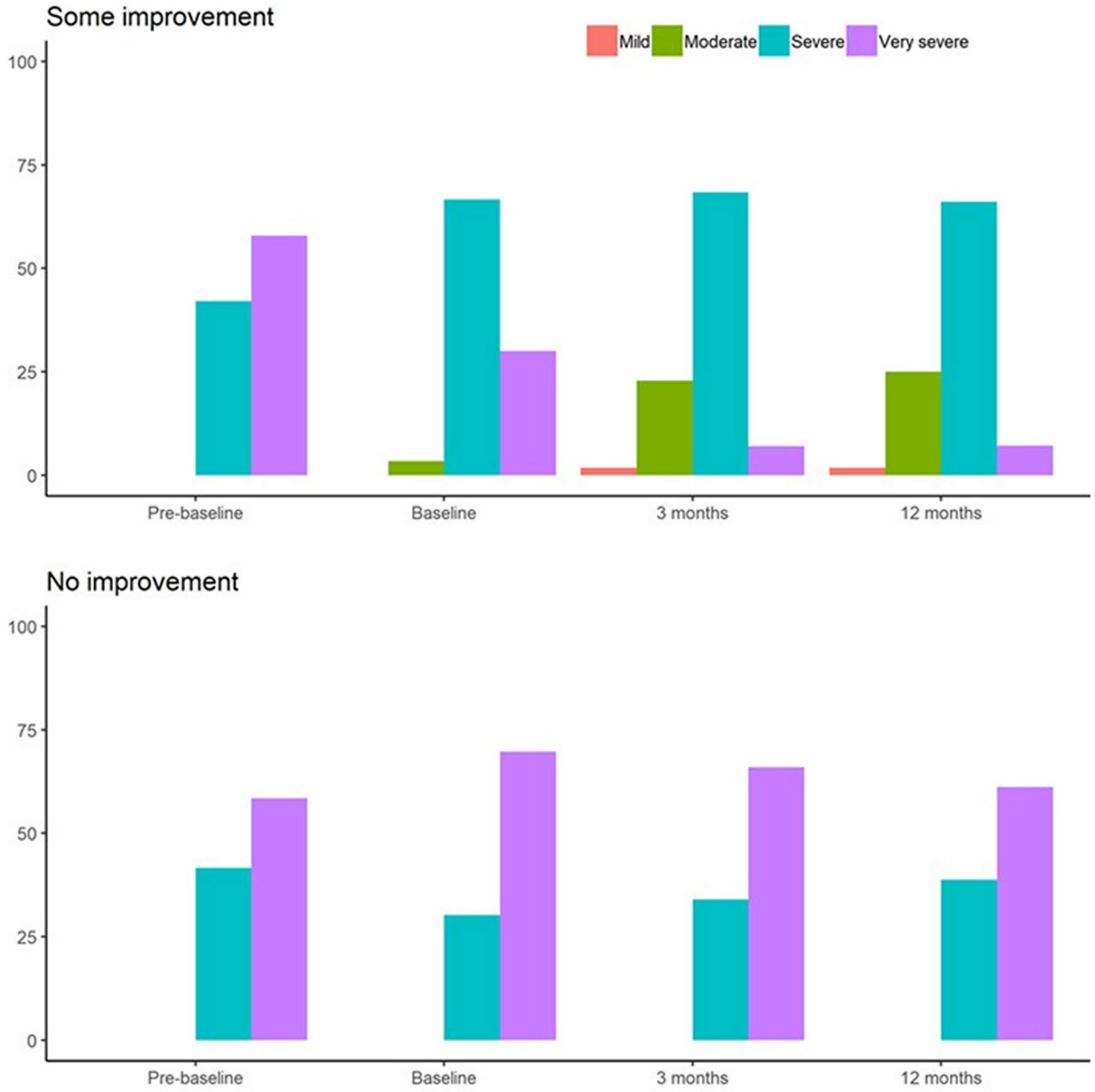

Fig. 2 Changes of PDS categories across time-points

Table 2 Differences in baseline characteristics between groups of PDS trajectories

Characteristic	No improvement ($n=110$)	Some improvement ($n=60$)	*P* value
Age (mean) (years)	40.38 (7.32)	41.25 (6.94)	0.45
Female *n* (%)	104 (95%)	55 (92%)	0.69
Intervention group *n* (%)	51 (46%)	34 (57%)	0.26
Living with partner (%)	73 (66%)	47 (78%)	0.10
Symptoms duration (mean) (years)	10.17 (7.09)	10.88 (8.82)	0.60
Number of comorbidities (mean)	1.99 (1.05)	2.08 (1.38)	0.72
Education *n* (%)			0.45
Primary/ lower secondary school (1–10 years)	14 (13%)	6 (10%)	
Vocational school (10–12 years)	26 (24%)	21 (35%)	
Upper secondary school (10–12 years)	16 (15%)	5 (8%)	
Bachelor/ University < 4 years	30 (28%)	18 (30%)	
Bachelor/ University > 4 years	23 (21%)	10 (17%)	

Discussion

In this exploratory study, we have examined repeated self-reported PDS scores in patients with FM to identify potential PDS trajectories in FM patients. The mean PDS score was high throughout the study period for all patients, though there were individual variations throughout the study period. We identified two distinct groups of trajectories, labelled as "no improvement" and "some improvement". The mean PDS scores in the two groups displayed significant and increasingly diverging differences from the time they were seen by a rheumatologist (pre-baseline) to baseline, and from baseline to 12 months. In the group "some improvement" there was a stepwise decreasing proportion of patients in the category "very severe" and a corresponding increase in the categories "severe" and "moderate" showing a continuously improvement across the time-points. By the end of the study, 15 patients no longer fulfilled the criteria for FM-diagnosis (PDS ≥ 12). The patients in the group "no improvement" reported no mean changes in severity across the four time-points. We found no differences in baseline characteristics between the two PDS trajectories. Although not statistically significant, a higher proportion of the patients in the group "some improvement" had been randomised to the intervention group in the RCT compared to the patients in the "no improvement" group.

These results are similar to those of an observational study that tracked 1555 patients with FM with semi-annual questionnaires for up to 11 years [18]. The majority of the included patients reported high levels of symptoms and no change in overall symptom severity over time, only 25% of the patients reported a slight trend toward improvement. Another longitudinal study observed patients with FM at two time-points over 2 years and reported high levels of disease burden at both time-points [1]. Furthermore, the patients included in our study reported fluctuating FM symptoms and transition between categories of symptoms severity over time, which has also been found in other longitudinal studies [19, 20].

Because the patients in our study had participated in an RCT in which both groups had received an intervention (patient education ± VTP and exercise) and attention, we would have expected improvement over time. The lack of time-effect was, therefore, somewhat surprising. It might be that the patients need longer time to integrate new strategies to manage stress into their daily lives.

A longitudinal study that followed 166 women with FM and chronic widespread pain (CWP) for 10–12 years after an RCT found that a majority of the included women showed improvement of pain over time [21]. Moreover, the study showed that reduced stress levels contributed to improvement over time. We, therefore, consider it a limitation of the RCT that the follow-up time was only 12 months.

A limitation of this study was that we did not include disease-related symptom variables as potential predictors. A systematic review that aimed to identify predictors of outcomes from multidisciplinary treatment in patients with FM showed that a higher level of depression predicted poorer outcomes [22]. Other predictors were baseline status, specific patient profiles, belief in fate, disability, and pain. Another study examined patients with FM after completion of a multidisciplinary group programme and found that the improvers reported lower baseline anxiety, depression and less fear of pain due to movement than the non-improvers [23].

Strength of the present study was that all patients at the point of inclusion fulfilled the ACR 2010 diagnostic criteria for FM [24]. Recruitment from both rural and urban areas ensured a heterogeneous sample. Moreover, the time-points for data collection were distributed over more than a year, reducing the potential bias of seasonal FM symptoms variations. The LCGA is a statistical model that estimates the

number of trajectories present based on BIC. The LCGA allowed us to examine trajectories of PDS over the study period and to our knowledge few studies have used this method in studies in patients with FM [16]. A limitation of the model is that the trajectories may not be clinically relevant, in that the improvements are mean differences and not individual movements across disease states. Although four time-points is sufficient for LCGA, the inclusion of more time-points would have provided a more detailed picture of groups of PDS trajectories [25]. Finally, we consider it a strength that we could repeatedly monitor PDS changes over a relatively long period in a sample of FM patients with high symptoms burden.

Previously, it has been proposed that in clinical settings, the use of the PDS provides a method to quantify severity and may be a way to overcome the difficulties and uncertainty of binary diagnosis in research settings [26]. Furthermore, knowledge of longitudinal patient movements across the PDS categories might be comprehensible in communication with patients about management strategies.

Conclusion

In this exploratory study we found individual variations in symptom severity among patients with FM who had been included in an RCT. We identified two groups of FM trajectories, one group that improved slightly during the study period and one group with no improvements. We found no differences in baseline characteristics between the two groups.

Author contributions KBH and HAZ contributed to the initial design of the project. All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by TH, JS and SAP. All authors contributed to the interpretation of the data. The first draft of the manuscript was written by TH, and all authors commented and revised previous versions of the manuscript. All authors read and approved the final manuscript.

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Compliance with ethical standards

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

Ethics 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).

Informed consent Informed consent was obtained from all individuals patients included in the study.

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