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ORIGINAL REPORT

PREDICTORS OF IMPROVEMENT IN OBSERVED FUNCTIONAL ABILITY IN PATIENTS WITH FIBROMYALGIA AS AN OUTCOME OF REHABILITATION

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Objective: **To investigate predictors of improvement in observed ability to manage activities of daily living as an outcome of rehabilitation in fibromyalgia.**

Methods: **Exploratory analyses used data from the Interdisciplinary Rehabilitation and Evaluation Programme for Patients with Chronic Widespread Pain (the IMPROvE study); a randomized controlled trial including 191 females with fibromyalgia randomized (1:1) to rehabilitation or a waiting list. The primary outcome was observed activities of daily living ability evaluated with the Assessment of Motor and Process Skills (AMPS) 6 months post-intervention.**

Results: **Overall, 38.7% of subjects were AMPS responders, i.e. having a clinically meaningful improvement in AMPS activities of daily living ability measures at 6 months post-intervention. In the exploratory analysis, only 4 baseline variables out of the 52 analysed showed a statistically significant interaction with treatment allocation (at the 0.05 level) indicating possible predictive value. Statistical analyses that used continuous variables dichotomized at the median suggested a predictive value of a low intake of weak and strong analgesics, and a high score of current pain and total score on the Pain Detect Questionnaire.**

Conclusion: **The results of this exploratory study suggest that several subgroups of patients, specifically those with a low baseline intake of weak and strong analgesics, and more pronounced clinical signs of central sensitization, may gain most clinical benefit from specialized rehabilitation when the outcome of interest is improvement in observed activity of daily living ability.**

Key words: chronic widespread pain; fibromyalgia; rehabilitation; multi-component therapy; outcome; functional ability; Assessment of Motor and Process Skills; predictor.

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INTRODUCTION

Clinical guidelines for the management of fibromyalgia recommend a symptom-based approach targeted at symptom reduction and maintenance of the best possible functioning (1, 2). Multi-component therapy is recommended for patients with a high disease burden who do not respond to mono-component pharmacological or non-pharmacological treatment (1, 2). However, fibromyalgia is not a homogenous entity. Several interacting factors, including neurobiological, psychosocial, cognitive and environmental factors, may add to this variability (3–6), and influence the outcome of standardized intervention programmes, including functional outcomes (7, 8). Outcome studies evaluating multi-component therapy for fibromyalgia show that, on average, the effects are limited, and a substantial proportion of patients do not demonstrate sustainable, clinically meaningful benefits (9, 10). The identification of predictors of differential treatment effect could therefore assist in tailoring the therapeutic decision for specific patients, and create a better match between patients' characteristics and the programme content, compared with offering generic intervention programmes based only on a diagnosis of fibromyalgia. A next step would be to determine whether such treatment matching enhances the therapeutic gains of rehabilitative interventions for fibromyalgia.

Although functioning is considered a core outcome domain in fibromyalgia (11), few studies have explored predictors of functioning as an outcome of multi-component therapy in this patient population. In a recent review, Rooij et al. (12) included 14 studies evaluating predictors of the outcome of multi-component therapy in fibromyalgia, but only 5 studies addressed predictors of functioning as an outcome of the intervention. In these studies the outcome assessment was based solely on self-report of functioning (13–17) and only one study used a randomized trial design (16). The review reported weak evidence for poorer outcomes for functioning being associated with higher baseline levels of depression, and for better outcomes for functioning being associated with worse baseline status and high pain intensity (12).

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This report presents an exploratory analysis of the data from the Interdisciplinary Rehabilitation and Evaluation Programme for Patients with Chronic Widespread Pain (the IMPROvE study); a randomized controlled trial evaluating the functional and psychological outcomes of a rehabilitation programme at the 6-month follow-up (18). The results of that study supported an overall beneficial outcome of the intervention on observed ability to manage activities of daily living (ADL), as measured with the Assessment of Motor and Process Skills (AMPS). It is important to note that the responder analyses for that study demonstrated large inter-individual patient variability and that only 74 (38.7%) were AMPS responders, i.e. achieved a clinically meaningful improvement in AMPS ADL ability measures (18).

Therefore, the goal of the present study was to explore whether any of the baseline variables predicted differential treatment effects when the outcome of interest was defined as a clinically meaningful improvement in AMPS ADL ability measures at the 6-month follow-up.

PATIENTS AND METHODS

Study design and participants

The design and primary results of the IMPROvE study have been published previously (18). In brief, the study was designed as a randomized, controlled, single-centre trial, evaluating the functional and psychological outcomes of a 2-week, group-based multi-component rehabilitation programme tailored to patients with chronic widespread pain (CWP) (Clinical-Trials.gov identifier: NCT01352052). The IMPROvE study was approved by the local ethics committee of The Capital Region of Denmark (H-2-2010-139). The intention to treat (ITT) population included 191 patients randomized (1:1), stratified by baseline AMPS measures, to either rehabilitation therapy or a waiting list control group. Co-primary outcomes were the AMPS and the SF-36 Mental Composite Score (MCS) evaluated at 6-month follow-up. This paper only investigates the AMPS as an outcome, as no improvement was observed in the SF-36 MCS at 6 months post-intervention. Participants included in the study were female patients fulfilling the American College of Rheumatology (ACR) 1990 criteria for fibromyalgia (19), consecutively recruited from a tertiary care setting and enrolled in the IMPROvE study. Eligible patients were 18 years old or older, without concurrent psychiatric disorders or uncontrolled rheumatic or medical disease capable of causing CWP (18). The participants enrolled in the IMPROvE study averaged over 100 months of pain duration, demonstrated extensive limitations in ADL task performance, and a potential need for support for community living, and only approximately 21% were employed at the time of referral.

Baseline assessment

All patients enrolled in the IMPROvE study underwent a comprehensive baseline assessment, which included several self-report instruments and observation-based assessments. Patients completed the Fibromyalgia Impact Questionnaire (FIQ), SF-36, Major Depression Inventory (MDI), General Anxiety Disorder inventory (GAD-10), Coping Strategy Questionnaire (CSQ), Pain Detect Questionnaire (PDQ) and the Pain Self-Efficacy Questionnaire (PSEQ). In addition to the AMPS, observation-based assessments included a manual tender point examination, measurements of maximal isokinetic knee muscle strength, maximal grip strength, a 6-min walk test, and measurement of pressure pain thresholds using cuff pressure algometry (CPA). A detailed description of the self-report instruments and observation-based assessments used for this study is included in a supplementary Annex[1]

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Assessment of Motor and Process Skills (AMPS). The AMPS, described in detail elsewhere (18, 20–22), is an individualized, observation-based evaluation of functional ability, developed to measure the extent of an individual's ability to perform and complete familiar and relevant ADL. When the AMPS is administered, the person chooses and performs 2 relevant and familiar ADL tasks with an appropriate level of challenge to his or her level of ability. During the performance of each ADL task, a trained occupational therapist, who is calibrated as a rater, observes 36 ADL skills and rates the person's performance of each skill on a 4-point ordinal scale. The ordinal ADL scores are then converted into 2 overall linear ADL ability measures; 1 for ADL motor ability (self-moving and moving objects) and 1 for ADL process ability (organizing and adapting actions), by a Rasch-based computer-scoring software. These ADL ability measures are expressed in transformed probability units (i.e. logits) (21). The AMPS has demonstrated stability over repeated measurements, as well as sensitivity to change in ADL task performance in women with CWP (22).

Intervention

The 2-week, non-residential, group-based, multi-component rehabilitation programme evaluated in the IMPROvE study is described in detail in a previous article (18). In summary, the rehabilitation programme was conducted by an interdisciplinary team, comprising a rheumatologist, a psychologist, a nurse, and occupational and physical therapists. The participants had a daily time schedule of between 3 and 5 h for a total of 35 h. The intervention programme was based on an interactive, participatory approach, and comprised a combination of presentations and group discussions, as well as instructions during physical exercise and performance of ADL tasks. The overall focus was on increasing participants' ADL ability and pain coping through patient education and adjustment in everyday life.

Outcomes

The 2 domains of the AMPS, the ADL motor ability measure and the ADL process ability measure were considered co-primary outcomes in the initial study (19). In the current study we chose not to look at the 2 domains of the AMPS separately, but to define AMPS responders as those patients who achieved an improvement of at least 0.3 logits on the AMPS ADL motor and/or ADL process scale, which is considered to represent a clinically meaningful change (23).

Statistical methods

Personalized medicine seeks to identify those who will have the most clinical benefit from a specific treatment (24). Prognostic factor research forms a cornerstone of personalized medicine with regard to the identification of factors that predict differential treatment response (25). In this study, the potential predictor factors were all the demographic and clinical characteristics assessed at baseline. In preliminary analyses, we used Wald tests from logistic regression models to evaluate the bivariate associations of the demographic and clinical characteristics assessed at baseline with the outcome of interest (AMPS responder yes/no). The variables identified in these bivariate analyses as being associated with the outcome at a significance level of 0.05, together with the randomization stratification variable, were included as covariates in all subsequent logistic regression models.

These logistic regression models, 1 for each potential predictor, included the covariates, main effects (treatment group and the potential predictor) and their interaction. According to our Statistical Analysis Plan, we looked for evidence of a difference in treatment effect by performing Wald tests for interaction between treatment group and patient characteristic (i.e. Group × Characteristic) at a significance level of 0.05. For the variables that satisfied this criterion, to describe the nature of the interaction, we presented adjusted odds ratios (ORs) with corresponding 95% confidence intervals (95% CIs) for the associations between treatment group and the outcome, separately for each "subgroup" corresponding to the binary predictor variables or obtained by dichotomizing the continuous predictor variables at the

median. Statistical analyses were performed using SAS v. 9.3 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Baseline characteristics

Baseline characteristics for the study participants ($n = 191$), who were randomly assigned to either the intervention group ($n = 96$) or the waiting list control group ($n = 95$) in the original study, are presented in Table I. As a consequence of randomization, no differences between groups were observed with respect to any of the baseline variables. Seventy-four (38.7%) of the 191 participants included in the overall ITT-population could be classified as AMPS responders, i.e. obtained an improvement of > 0.3 logits in the AMPS ADL motor ability measure and/or ADL process ability measure during the study period (i.e. the number of responders were 43 and 31, respectively, according to the original group). For both groups combined (intervention and waiting list control group), being an AMPS responder was associated with a lower reported intake of weak analgesics ($p = 0.019$), better social functioning ($p = 0.032$) and

Table I. *Baseline characteristics of study participants (*n = *191)*

	Rehabilitation group ($n = 96$)		Control group ($n = 95$)	
Variable	Median (IQR)	*n*	Median (IQR)	*n*
Age, years	44.9 (37.7–52.2)	96	44.0 (36.0–50.3)	95
Tender points	18 (18–18)	95	18 (18–18)	94
Weight, kg	70 (61–80)	94	74 (65–84)	91
Height, cm	167 (161–171)	94	167 (162–170)	91
BMI, kg/m^2	25.4 (22.1–29.7)	94	26.4 (23.4–30.5)	91
Pain duration, years	11 (5–18)	94	10 (5–15)	91
Years since diagnosis	1 (1–3)	81	1 (1–2)	78
	n (%)	*n*	*n* (%)	*n*
Weak analgesics	81 (86)	94	77 (85)	91
Non-steriod anti-inflammatory drugs	56 (60)	94	57 (63)	91
Strong analgesics	45 (48)	94	49 (54)	91
Antidepressants	29 (31)	94	26 (29)	91
Anticonvulsants	9 (10)	94	10 (11)	91
Pending social application	50 (52)	96	39 (41)	95
Change in work status	67 (71)	94	69 (76)	91
	Median (IQR)	*n*	Median (IQR)	*n*
AMPS ADL motor (logits)	1.18 (0.92–1.48)	96	1.16 (0.95–1.39)	95
AMPS ADL process (logits)	1.01 (0.87–1.28)	96	1.03 (0.86–1.29)	95
Grip strength (Nm)	200 (124–248)	93	180 (124–236)	95
Muscle strength UE (PTQ extension)	70.9 (46.7–92.1)	87	65.4 (41.8–102.5)	87
Muscle strength UE (PTQ flexion)	36.9 (26.8–49.4)	87	34.2 (25.5–49.3)	87
6-minute walk (m)	451 (365–506)	93	439 (371–504)	93
Pain detection threshold (kPa)	11.67 (9.9–16.1)	95	11.62 (9.18–14.6)	95
Pain tolerance threshold (kPa)	28.75 (22.5–38.0)	95	29.05 (23.9–36.8)	95
SF-36 MCS	39.0 (30.4–48.7)	95	36.3 (31.6–45.7)	95
SF-36 PCS	27.0 (23.2–30.6)	95	26.2 (22.2–31.9)	95
SF-36 vitality	20 (10–30)	95	15 (10–25)	95
SF-36 role emotional	33 (0–100)	95	33 (0–67)	95
SF-36 social functioning	50 (25–63)	95	38 (25–63)	95
SF-36 mental health	56 (40–72)	95	56 (40–68)	95
SF-36 bodily pain	22 (10–31)	95	22 (12–31)	95
SF-36 physical functioning	40 (25–55)	95	40 (25–50)	95
SF-36 role physical	0 (0–25)	95	0 (0–0)	95
SF-36 general health	30 (20–45)	95	30 (20–40)	95
FIQ total	64.6 (55.1–72.1)	94	65.1 (56.6–72.9)	92
FIQ function	6.0 (4.1–7.0)	94	6.0 (4.0–7.1)	92
FIQ wellbeing	7.1 (5.7–8.6)	94	7.1 (5.7–10)	92
FIQ work interference	7.1 (5.0–8.7)	27	7.8 (7.0–8.6)	20
FIQ days missed at work	0 (0–2.9)	27	0 (0–1.4)	20
FIQ pain	7.3 (6.1–8.5)	94	7.7 (6.5–8.8)	92
FIQ fatigue	8.7 (7.8–9.6)	94	9.1 (8.0–9.9)	92
FIQ restedness	8.9 (7.4–9.8)	94	8.6 (7.1–9.8)	92
FIQ stiffness	7.7 (5.2–8.9)	94	7.8 (6.2–9.3)	91
FIQ anxiety	5.4 (1.8–7.6)	94	5.0 (1.8–7.9)	91
FIQ depression	3.7 (0.4–6.9)	93	3.5 (0.5–6.3)	90

Table I. *Contd.*

Variable	Rehabilitation group ($n=96$) Median (IQR)	*n*	Control group ($n=95$) Median (IQR)	*n*
GAD-10 anxiety	17.5 (13–26)	94	17 (13–23)	91
MDI depression	18 (13–27)	94	21 (15–27)	91
CSQ catastrophizing	14 (9–21)	94	17 (13–21)	93
PSQ pain self-efficacy	25 (16–33)	94	22 (17–30)	93
PDQ total score	21 (16–24)	94	20 (14–24)	93
PDQ NRS average pain	7 (6–8)	94	7 (6–8)	93
PDQ NRS worst pain	8 (8–10)	94	9 (8–9)	93
PDQ NRS current pain	6 (4–8)	94	7 (5–8)	93

BMI: body mass index; GAD-10: Generalized Anxiety Disorder inventory; AMPS: Assessment of Motor and Process Skills; MDI: Major Depression Inventory; MSC: mental composite score; CSQ: Coping Strategy Questionnaire; PMS: physical composite score; PSQ: Pain Self-efficacy Questionnaire; FIQ: Fibromyalgia Impact Questionnaire; PDQ: Pain Detect Questionnaire; NRS: numerical rating scale; SF-36: Short-Form 36; MCS: Mental Composite Score; UE: upper extremity; PTQ: peak torque; IQR: interquartile range; NSAIDS: non-steroidal anti-inflammatory drugs; ADL: activities of daily living.

less bodily pain ($p=0.010$) assessed with the SF-36, higher pressure pain threshold measured with cuff pressure algometry (CPA) ($p=0.042$), and a lower AMPS ADL motor ability measure ($p=0.004$) at baseline. These 5 variables together with the randomization stratification variable were used as covariates in the subsequent logistic regression models.

Baseline predictors of functional outcome

Out of the 52 baseline variables analysed, controlling for the 6 covariates, only 4 of them had potential predictive value as assessed by evaluating their interaction with group allocation (i.e. treatment group). These 4 baseline variables had the following *p*-values for their tests of interaction with treatment group: intake of weak analgesics ($p=0.013$), intake of strong analgesics ($p=0.017$), total score on the PDQ ($p=0.032$), and score of current pain on the PDQ ($p=0.036$). To describe the nature of the interactions, we dichotomized the 2 continuous variables (total score and score of current pain on the PDQ) at the median from the overall ITT population and presented results separately for each high/low subgroups. The medians used as cut-points for the definition of high/low predictor variable value at baseline were 20.0 for PDQ total score and 7.0 for PDQ current pain, respectively.

Table II. *Subgroup specific odds ratios for the association between treatment group and having clinically significant improvement in Assessment of Motor and Process Skills activities of daily living (AMPS ADL) ability measures at 6 months post-treatment*

Predictor variable	Predictor variable "low" at baseline OR (95% CI)	Predictor variable "high" at baseline OR (95% CI)
Intake of weak analgesics	25.55 (2.92–223.7)	1.45 (0.68–3.08)
Intake of strong analgesics	5.70 (1.85–17.54)	0.87 (0.32–2.35)
PDQ total score	1.28 (0.47–3.48)	3.41 (1.24–9.44)
PDQ current pain	1.30 (0.48–3.48)	4.08 (1.46–11.45)

*Values are the adjusted (for the covariates) odds ratios (OR) and corresponding 95% confidence intervals (CIs); for the last 2 predictors "low" corresponds to below the median and "high" to at or above the median.
PDQ: Pain Detect Questionnaire.

Table II presents the results for the associations between treatment group and having a clinically meaningful improvement in AMPS ADL ability measures at 6 months follow-up, separately for the high/low subgroups. The results of the exploratory analysis suggested that patients participating in the rehabilitation programme were significantly more likely to achieve a clinically meaningful improvement in observed functional ability (compared with those assigned to the waiting list) for specific subsets of patients, including those who had a low intake of weak and strong analgesics, a high total score on the PDQ, and also a high score of current pain on the PDQ. The strongest predictor of having a positive treatment outcome was found to be the baseline intake of weak analgesics. Among those with a low intake of weak analgesics at baseline the OR for the association of treatment with the outcome was 25.55 (95% CI 2.92–223.77) compared with an OR of 1.45 (95% CI 0.68–3.08) for those with a high intake of weak analgesics at baseline.

DISCUSSION

To our knowledge, this is the first study to explore predictors of improvement in observed ability to perform ADL as an outcome of rehabilitation in patients with fibromyalgia. Although exploratory, the study results suggest that several subgroups of patients, specifically those with a low baseline intake of weak and strong analgesics and more pronounced clinical signs of central sensitization, may benefit most from the specific rehabilitation programme, when the outcome of interest is defined as a clinically meaningful improvement in AMPS ADL ability measures 6 months post-intervention.

The analyses indicated that a low intake of weak analgesics, mainly acetaminophen, was the strongest predictor of a good outcome of intervention. Based on the general safety profile of acetaminophen, it seems unlikely that a high occurrence of drug-related side-effects may have impeded functional gains in the group of participants with a high intake of weak analgesics. However, cohort studies do support that opioid use in patients with fibromyalgia, including tramadol, is associated with negative health-related and functional outcomes (26). This

is in agreement with the findings in our study, where an initial low intake of strong analgesics (opioid medications including tramadol) seemed to predict a better functional outcome of intervention (OR = 5.70 for participants with a low intake vs OR = 0.87 for participants with a high intake at baseline). Baseline intake of non-steroidal anti-inflammatory drugs (NSAIDs) or other centrally acting drugs (antidepressants and anticonvulsants) showed no association with the functional outcome and no interaction with treatment allocation.

The relationship between pain and functional ability is likely to be complex. Functioning is increasingly recognized as a critical outcome in pharmacological pain trials and, in this context, improvements in the perceived level of disability are reported to occur in the subset of patients with fibromyalgia who obtain substantial pain relief (27). The main objective of pain rehabilitation programmes is not to cure pain, but to emphasize self-control and self-management of symptoms, which requires patients to make a number of lifestyle changes and to engage in active coping strategies. However, research suggests that people vary in their readiness to adopt a self-management approach to their pain as an alternative to traditional medical interventions, and that patients' own beliefs and expectations concerning how their pain should be managed may have an important influence on treatment outcomes (28–30). The current study did not include an assessment of patients' readiness to adopt a self-management approach to chronic pain, including patients' beliefs in medical cure for pain and the importance of medication as a treatment for pain. However, it may be speculated that patients with a low intake of analgesics are generally more inclined towards engagement in active pain-coping strategies, promoting more positive outcomes of rehabilitative interventions focusing on increased self-management, and improvement in functional ability through adjustment in everyday life. This hypothesis, however, needs to be tested and confirmed in future studies. Identification of patients' pre-treatment beliefs that may interfere with adherence to self-management and outcome of rehabilitation would permit targeting of patient education and structuring interventions to take advantage of important characteristics of patients that may enhance functional outcomes (31). Furthermore, the results of the study underline the need to control for medication in outcome studies focusing on non-pharmacological interventions.

Patients' baseline level of pain and pain-related interference with functioning are reported to influence the outcome of multi-component therapy in patients with fibromyalgia (12). The results of the exploratory analysis from this study suggest that, not only the level of pain, but also patients' clinical pain phenotype, may influence the functional outcome of the intervention. The PDQ is a symptom-based assessment tool composed primarily of questions regarding the presence and severity of positive somatosensory signs that traditionally are ascribed to neuropathic pain (32). However, despite obvious differences, including the spatial distribution of pain, there are striking phenotypic similarities between neuropathic pain and pain in fibromyalgia, namely how patients express their abnormal sensory perceptions, and in particular the quality of their pain. When applied in fibromyalgia populations, the PDQ classifies this condition as non-nociceptive, i.e. having clinical features similar to those of established neuropathic pain (33–35). Studies support significant correlations between total score on the PDQ, VAS intensity values for pain, tender point count, and pressure pain thresholds measured with CPA in this patient population, and indicate that the presence of widespread pain hypersensitivity and other clinical manifestations of central sensitization are reflected in the PDQ score (33). The results indicated that among patients with a high score of current pain and total score on the PDQ, those treated were more likely to achieve a better functional treatment outcome than the controls. Thus, the results of the exploratory analysis suggested that patients with more pronounced clinical signs of central sensitization were more likely to benefit from the treatment by achieving a positive functional outcome of intervention. This finding was further supported by an observed borderline predictive value of the pressure pain threshold measured with CPA ($p = 0.058$), where an initial low pressure pain threshold seemed to correspond to a better functional outcome of intervention (OR = 3.50 (95% CI 1.17–10.47) for participants with a low pressure pain threshold vs. OR = 1.53 (0.60–3.89) for participants with a high pressure pain threshold at baseline).

Perceived muscle fatigue during exhaustive muscle contraction is prominent in fibromyalgia, and studies indicate that this may be of central, rather than peripheral, origin (36). Studies also provide evidence that the number of tender points in patients with fibromyalgia, which has been considered a primary clinical identifier of pain hypersensitivity, has a significant relationship with functional ability, as measured with the AMPS (37). The performance difficulties encountered by the women in the IMPROvE study were mostly related to ADL motor skill deficits, and it was within this domain that most patients achieved a clinically meaningful improvement, i.e. less observable effort and fatigability during ADL task performance (18). Exercise therapy, most often administered by physiotherapists, is recommended either alone or as an integrated part of multi-component therapy for patients with fibromyalgia (2, 38). Occupational therapy was a core modality in the current interdisciplinary rehabilitation programme, and was focused on adaptive and compensatory intervention strategies targeted at reducing the amount of effort and fatigue when performing daily life tasks. This could be argued to mainly affect ADL motor ability and, in particular, match the needs of patients with a more pronounced pain hypersensitivity and fatigability.

Although several psychosocial, cognitive, and behavioural factors have been reported to be predictive of functional outcomes for many pain syndromes, this exploratory study did not support a predictive value of study participants' baseline levels of self-reported or observed functional ability, psychological (depression, anxiety, mental wellbeing) or cognitive (catastrophizing, pain self-efficacy) factors, or overall symptom burden. In most studies of fibromyalgia, the outcome assessment has been based on self-report, including self-reporting of functional ability. Questionnaire-based, self-reporting of functional ability evaluates the amount of perceived difficulty, which may

be related to other factors associated with the pain problem, including patients' pain-related beliefs and ability to adjust to chronic pain. Studies of chronic pain populations, including fibromyalgia, have demonstrated poor correlation between self-report and observation-based assessment, and the influence of pain and psychosocial variables on self-reported functioning (39, 40). This may explain why our study, investigating predictors of observed ADL-ability as an outcome of rehabilitation, could not find evidence for such relationships.

The current study has several limitations. The study was conducted in a specialized tertiary care setting, thus included patients may not necessarily be representative of patients from the overall referral population. In addition, the study was limited by only including women. However, given the female predominance in fibromyalgia, the study results are relevant to the clinical practice. Furthermore, the analyses were exploratory, evaluating a relatively large number of baseline variables in the context of a randomized controlled trial designed to evaluate AMPS as the primary outcome, and not to identify predictors of differential treatment effect. Given that we have not adjusted for multiple testing, our results will need confirmation in future studies.

In conclusion, the results of this exploratory study suggest that several subgroups of patients, specifically those with a low baseline intake of weak and strong analgesics and more pronounced clinical signs of central sensitization, may have the most clinical benefit from rehabilitation when the outcome of interest is improvement in observed functional ability. This finding provides support for the advancement of a pain mechanism-oriented management of patients with fibromyalgia, rather than graded intervention models based on case severity defined by the level of overall symptom reporting. The results also suggest that patients' pre-treatment beliefs and readiness to engage in active pain-coping strategies may interfere with the functional outcomes of rehabilitation programmes focusing on adaptive and compensatory intervention strategies. Targeting of patient education and structuring interventions to meet these important characteristics may therefore increase adherence to self-management and promote more positive functional outcomes of such rehabilitative efforts.

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