Chapter 2

Predictors of multidisciplinary treatment outcome in fibromyalgia: a systematic review

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Abstract

Purpose: To identify outcome predictors for multidisciplinary treatment in patients with chronic widespread pain (CWP) or fibromyalgia (FM).

Methods: A systematic literature search in PubMed, PsycINFO, CINAHL, Cochrane Library, EMBASE and Pedro. Selection criteria included: age over 18; diagnosis CWP or FM; multidisciplinary treatment; longitudinal study design; original research report. Outcome domains: pain, physical functioning, emotional functioning, global treatment effect and 'others'. Methodological quality of the selected articles was assessed and a qualitative data synthesis was performed to identify the level of evidence.

*Result*s: Fourteen studies (all with FM patients) fulfilled the selection criteria. Six were of high quality. Poorer outcome (pain, moderate evidence; physical functioning and quality of life, weak evidence) was predicted by depression. Similarly, poorer outcome was predicted by the disturbance and pain profile of the Minnesota Multiphasic Personality Inventory (MMPI), strong beliefs in fate and high disability (weak evidence). A better outcome was predicted by a worse baseline status, the dysfunctional and the adaptive copers profile of the Multidimensional Pain Inventory (MPI), and high levels of pain (weak evidence). Some predictors were related to specific multidisciplinary treatment (weak evidence). Inconclusive evidence was found for other demographic and clinical factors, cognitive and emotional factors, symptoms and physical functioning as predictors of outcome.

Discussion: It was found that a higher level of depression was a predictor of poor outcome in FM (moderate evidence). In addition, it was found that the baseline status, specific patient profiles, belief in fate, disability, and pain were predictors of the outcome of multidisciplinary treatment. Our results highlight the lack of high quality studies for evaluating predictors of the outcome of multidisciplinary treatment in FM. Further research on predictors of multidisciplinary treatment outcome is needed.

Implications for rehabilitation

- Predictors can be used either to adjust treatment to the needs of specific patients, or to allocate patients to suitable programs.
- Depression seems to predict poor multidisciplinary treatment outcome in FM.
- More well designed studies are needed to investigate predictors of treatment outcome.

Introduction

The prevalence of chronic widespread pain (CWP) and fibromyalgia (FM) in Western populations is estimated at 11%[1] and 5.8%[2], respectively. Patients with FM and CWP typically present complex symptoms resulting in a reduced quality of life and disability, and is associated with a negative long-term outcome[3].

A variety of treatment strategies are available for patients with CWP and FM, ranging from monotherapy (e.g. pharmacological interventions) to multidisciplinary treatment. Multidisciplinary treatment programs are recommended in patients with FM and CWP and the associated problems[4,5]. The term multidisciplinary team is defined as referring to activities that involve the efforts of individuals from a number of disciplines. These efforts are disciplinary-orientated and, although they may impinge upon clients or activities dealt with by other disciplines, they approach them primarily through each discipline relating to its own activity[6]. It is often not realistic for one caregiver alone to manage the complex problems of these patients. Assistance of multidisciplinary teams are often required[4,5,7]. Multidisciplinary treatment programs typically approach pain and disability as an interaction of physiologic, psychological and social factors and not as a solely biomedical or one sided problem[4,5]. The multidisciplinary team works synergistically and produces more than each member individually and separately could accomplish[6].

Beneficial effects for multidisciplinary treatment are found for these patients compared to mono disciplinary treatment programs[8]. Multidisciplinary treatments are effective[8-11], however on average the effects are limited. FM appears to affect a heterogeneous group of patients who can differ with regard to the symptoms and also in their physical and psychological characteristics[12,13]. It is likely that the effect of multidisciplinary treatment depends on these characteristics. It is still not known whether the heterogeneous group of FM patients would profit all from multidisciplinary treatment. It is desirable to differentiate between patients who are likely to benefit from multidisciplinary treatment and those who are not. As Scascighini et al.[8] concluded in their review "further studies are needed to establish determinants or prognostic indicators of success for a successful rehabilitation".

Although empirical studies are available, no systematic review has been done which summarizes the research evidence for prognostic factors of the outcome of multidisciplinary treatment in patients with FM and CWP. Therefore the aim of the present study was to systematically review predictors of the outcome of multidisciplinary treatment in patients with FM and CWP.

Materials and methods

Literature search. A protocol for conducting this review was developed with reference to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[14]. A systematic, computerized literature search was made in PubMed, PsycINFO, CINAHL, Cochrane library and EMBASE for the period from 1966 to September 2010. A manual search was made in the Pedro database up until September 2010. The search terms were specifically chosen to identify studies focussing on the multidisciplinary treatment of chronic pain syndromes (for further details,

see appendix A). Furthermore, references of the included studies were checked for additional articles.

Articles were included if: (1) the study population involved (a subgroup of) patients over 18 years of age (2) the study population consisted of (a subgroup of) patients diagnosed with CWP or FM; (3) the intervention consisted of multidisciplinary rehabilitation treatment, defined as treatment including minimal two components of treatment (i.e. exercising, relaxation techniques, education, cognitive behavioural therapy, operant behaviour therapy, acquisition of pain management skills or pharmacological treatment, and involving at least two disciplines (i.e. occupational therapist, physical therapist, psychologist, social worker, or physician); (4) the study had a longitudinal design, with at least one follow-up measurement; (5) the article was an original research report; (6) the article was written in the English, Dutch or German language. The selection of potentially relevant articles was made by two independent reviewers (AdR, MS) based on title and abstract according to the inclusion criteria. The final assessment of the articles was based on the full text of the articles by two independent reviewers (AdR, LR). Disagreements between the two reviewers were discussed with a third reviewer (MS) until consensus was achieved.

Assessment of methodological quality. The methodological quality was assessed to determine whether the study designs, the analyses, and the interpretation of the results reduced the risk of bias. The methodological quality of the selected articles was independently assessed by two reviewers (AdR, LR) based on a minor adaptation of the standardized Hayden criteria (available from the first author). This quality assessment is appropriate to assess the methodological quality of studies on prognosis and prognostic factors[15]. The Hayden criteria pertain to six areas of potential bias: bias related to: (1) participation, (2) study attrition, (3) measurement of prognostic factors, (4) outcome measurement, (5) confounding, and (6) analysis. The risk of bias for all six areas was rated as low, moderate or high. As recommended by Hayden et al.[15], the studies were classified as being of high quality if in all six areas the rating was a low or moderate risk of bias. Studies with a high risk for at least one area of bias were defined as low-quality studies. Any differences between the two reviewers were discussed with a third reviewer (MS) until consensus was reached.

Data-extraction analysis. The data for each study were extracted by two reviewers (AdR, LR), and included year of publication, study design, number of patients, treatment, timing of outcome assessment, predictors (univariate and multivariate associations with outcome) and outcome, recorded on a standardized scoring sheet. Reporting a significant association of baseline characteristics with treatment outcome, without mentioning the size of the estimate, was considered as a relevant finding in this review, if the direction of the association with the outcome was described. A non-significant association between a baseline characteristic and the outcome was merely an indication that this characteristic did not predict the outcome of the treatment, if the size of the study sample was large enough ($N \geq 100$ [16]).

Analyses. Outcome measures were categorized into five outcome domains: (1) pain, (2) physical functioning, (3) emotional functioning, (4) global treatment effect, and (5) “other”. Because the studies included in this review were heterogeneous with respect to study design, predictors, treatment, and outcome measures, pooling of data for meta-analysis was not possible. Therefore, a qualitative data-synthesis was performed[17-19]. Five levels of evidence (strong, moderate, weak,

inconclusive and inconsistent) were defined to summarize the available evidence for the predictive value of the predictors[20], based on Ariens et al.[21] and Sackett et al.[22] (Table I). In order to establish the level of evidence, the number of studies evaluating a predictor associated with outcome, the methodological quality of the studies, and the consistency of a predictor for outcome were taken into account. Findings were deemed to be consistent if in >75% of the studies reporting on a predictor the direction of the association was the same[20].

Table 1. Level of evidence for predictors of the treatment outcome in FM

	Level of evidence
Statistically significant associations	
Strong	Consistent significant associations found in at least two high-quality studies
Moderate	Consistent significant associations found in one high-quality study and at least one low-quality study
Weak	Significant association found in one high-quality study or consistent significant associations found in at least three low-quality studies
Inconclusive	Significant association found in less than three low-quality studies
Inconsistent	Inconsistent significant findings irrespective of study quality
Statistically non-significant associations (sample size ≥ 100 persons)	
Strong	Consistent non-significant associations found in at least two high-quality studies
Moderate	Consistent non-significant associations found in one high-quality study and at least in one low-quality study
Weak	Non-significant association found in one high-quality study or consistent non-significant associations found in at least three low-quality studies
Inconclusive	Non significant associations found in less than three low-quality studies
Inconsistent	Inconsistent non-significant findings irrespective of study quality

Results

Description of the included studies. The literature search identified, 10.703 articles. After screening for title and abstracts, 322 publications were considered for inclusion, but after full-text assessment, only 14 articles were included (see Figure 1). All the included studies focussed on FM patients. The two Turk studies[23,24] used data derived from the same cohort, but reported on different predictors, so both studies were included in the review.

Outcome assessment. *Pain* was assessed with the Fibromyalgia Impact Questionnaire (FIQ), sub-scale pain and number of tender points, the Multidimensional Pain Inventory (MPI), subscale pain severity, and the Short Form 36 (SF-36), sub-scale bodily pain.

Physical functioning was measured with the FIQ sub-scale physical functioning, the MPI subscale interference, and the SF-36 physical and role physical subscales.

Emotional functioning was assessed with the Center for Epidemiological Studies Depression Scale (CES-D), the Beck Depression Index (BDI), the Beck Anxiety Inventory (BAI), and the SF-36 subscales of mental health and role emotional.

Global treatment effect comprised aggregated treatment effectiveness indicators: 'responders vs nonresponders' (i.e. 50% reduction in the scores for MPI pain and FIQ-physical impairment), or

successful vs. unsuccessful (i.e. patient rating of overall improvement). Overall scores for the Oswestry Disability Scale (ODI) and the Pain Disability Index (PDI), and the total FIQ score were also used as indicators of global treatment effect. These were combined scores for different domains of general functioning, (e.g. physical functioning, work, sleep and self-care).

'Other' referred to measures of various outcome domains: the Quality of Life Scale (QOLS), return to work, and the SF-36 subscales of general health, vitality and social functioning.

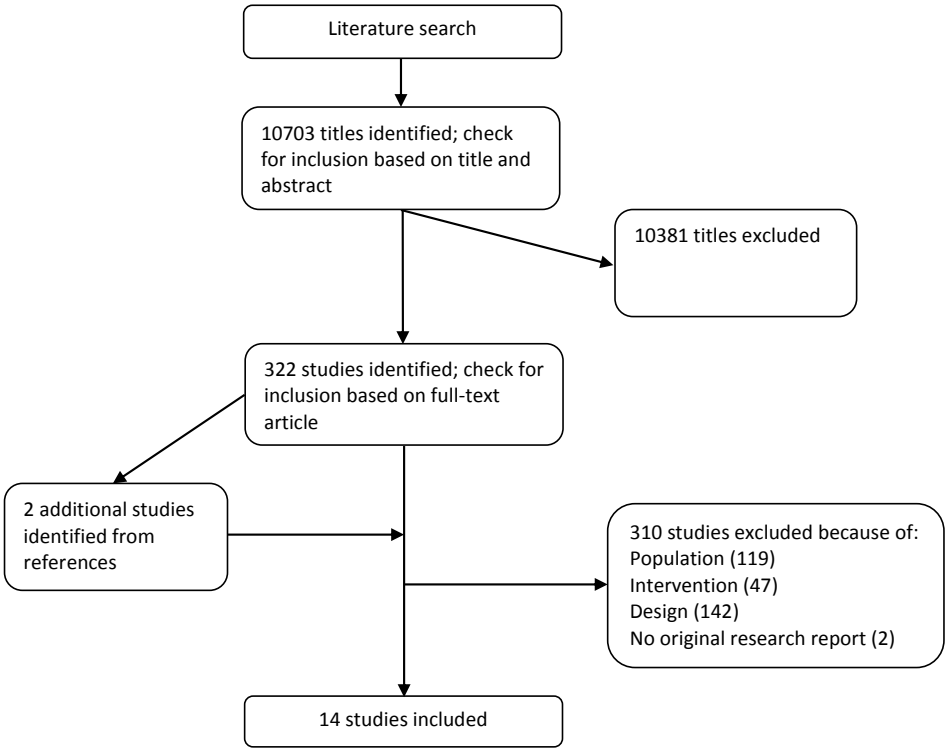

Figure 1: Flow chart of study selection

Table 2 provides an overview of the studies included in this review, which only focussed on patients with FM. The number of patients varied from 32 to 332, and the period follow-up measurements ranged from post-treatment to a 15-month follow-up period after the termination of treatment. At least ten studies concerned outpatient programs. All programs were conducted by two or more disciplines, were multimodal and were mainly provided in group format. The intensity of the treatment programs ranged from 12 h to 120 h. Of the six RCTs included in this review, only predictors for the outcome of the multidisciplinary treatment were included. In general, the strength of the association between predictor and outcome (regression coefficients or odds ratios) was not well presented in the original papers, i.e. only a *p*-value or some other indicator of significance was presented.

Table 2. Description of studies

Author, Year	Study design Number of patients	Treatment	Timing of outcome assessment	Outcome and (non-) predictors
Bailey A. et al. 1999 [28]	Prospective cohort Referred: 227 Selected: 154 Participated: 149 Completed: 106	Setting: unclear Content: interdisciplinary education and exercise Form: outpatient, group therapy, extra individual therapy possible Involved disciplines: D, K, OT, P, PT, SW Intensity: ? hrs, 12 wks, 36 sessions	Post-treatment	**Pain** (unclear) - Pain was predicted by smoking (*P* not presented) - Pain was not predicted by taking pain or antidepressant medications (*P* not presented)
Bennet R.M. et al. 1996 [25]	Prospective cohort Referred: 170 Selected: 170 Participated: 117 Completed: 104	Setting: university health sciences Content: behaviour modification, counselling, education, exercise, medication management, muscle awareness, myofascial injections, teaching spouses, treatment of sleep disturbance Form: outpatient, group therapy, individual therapy Involved disciplines: EP, N-co-ordinator, Ps, Rh Intensity: 44 hrs, 6 months, 26 sessions	Post- treatment	**Pain** (no. of tender points) - Pain was predicted by the (MMPI) psychological disturbance profile ($P < 0.01$) and major depression (BDI) (*P* not presented) - Pain was not predicted by the (MMPI) pain profile (ns) and physical fitness (VO2max, maximum workload, respiratory quotient) (*P* not presented) **Physical functioning** (FIQ-physical functioning) - Physical functioning was predicted by the (MMPI) pain profile *(P* < 0.01), the (MMPI) psychological disturbance profile ($P < 0.01$) and depression (*P* not presented) - Physical functioning was not predicted by physical fitness (*P* not presented) **Emotional functioning** (BDI, BAI) - Emotional functioning was not predicted by physical fitness (*P* not presented) **Global treatment effect** (FIQ total) - Global treatment effect was predicted by the (MMPI) psychological disturbance profile ($P < 0.01$) and depression (*P* not presented) - Global treatment effect was not predicted by the (MMPI) pain profile (ns) and physical fitness (*P* not presented) **'Other'** quality of life (QOLS) - Quality of life was predicted by the (MMPI) psychological disturbance profile ($P < 0.01$) and depression (BDI) (*P* not presented)

Table 2. Description of studies *(continued)*

Author, Year	Study design Number of patients	Treatment	Timing of outcome assessment	Outcome and (non-) predictors
Glattacker M. et al. 2010 [29]	Prospective cohort Referred: 412 Selected: 332 Participated 332 Completed: 245	Setting: rehabilitation centre for rheumatic diseases Content: education, physical therapy, psychology (autogenic training, coping, muscle relaxation,) Form: inpatients, group therapy or individual therapy Involved disciplines: Ps, PT, other ? Intensity: ? hrs, 3 wks, sessions ?	4 weeks and 6 months after treatment	**Pain** (SF-36 bodily pain) - Pain, at 4 wks after treatment was predicted by duration of the illness (1-2 year) ($P < 0.05$) - Pain was not predicted by demographic factors (age, higher level of education, employed, partnership), general self-efficacy and illness perceptions (identity, timeline, consequences, personal control, treatment control, coherence and emotional representations) (ns) **Physical functioning** (SF-36 physical functioning, role physical) - Role physical at 4 wks after treatment was predicted by beliefs in consequences (IPQ) ($P < 0.01$) - Role physical at 6 months after treatment was predicted by beliefs in timeline ($P < 0.05$) - Physical functioning was not predicted by demographic factors, general self-efficacy and other illness perceptions (ns) **Emotional functioning** (SF-36 mental health, role emotional) - Mental health, at 4 wks after treatment was predicted by partnership ($P < 0.05$), duration of the illness of < 1 year ($P < 0.01$) and 1-2 years ($P < 0.05$), general self-efficacy (GSS) ($P < 0.01$) and beliefs in identity (IPQ) ($P < 0.01$) - Role emotional, at 4 wks after treatment was predicted by age, beliefs in consequences (IPQ) ($P < 0.05$) and beliefs in timeline (IPQ) ($P < 0.05$) - Role emotional, at 6 months after treatment was predicted by age ($P < 0.05$) - Emotional functioning was not predicted by other demographic factors and illness perceptions (ns) **Global treatment effect** (FIQ total) - Global treatment effect, at 4 wks after treatment was predicted by beliefs in consequences (IPQ) ($P < 0.01$) - Global treatment effect, at 6 months after treatment was predicted by beliefs in timeline (IPQ) ($P < 0.05$) - Global treatment effect was not predicted by demographic factors, general self-efficacy and other illness perceptions (ns) **'Other'** (SF-36 general health, vitality, social functioning) - General health, at 4 wks after treatment was predicted by emotional representations (IPQ) ($P < 0.05$) - General health was not predicted by demographic variables, general self-efficacy and other illness perceptions (ns) - Vitality, at 4 wks after treatment was predicted by, general self-efficacy ($P < 0.01$), beliefs in consequences (IPQ) ($P < 0.01$) and beliefs in timeline (IPQ) ($P < 0.05$) - Vitality, at 6 months after treatment was predicted by beliefs in timeline (IPQ) ($P < 0.05$) - Vitality was not predicted by demographic variables and other illness perceptions (ns)

Table 2. Description of studies *(continued)*

Author, Year	Study design Number of patients	Treatment	Timing of outcome assessment	Outcome and (non-) predictors
Glattacker M. et al. 2010 [29] *(continued)*				- Social functioning, at 4 wks after treatment was predicted by the duration of the illness (1-2 years) ($P < 0.05$), beliefs in identity (IPQ) ($P < 0.01$ and consequences (IPQ) ($P < 0.01$) - Social functioning, at 6 months after treatment was predicted by beliefs in consequences (IPQ) ($P < 0.01$) and timeline (IPQ) ($P < 0.01$) - Social functioning was not predicted by other demographic variables, self-efficacy and other illness perceptions (ns)
Hammond A. et al. 2006 [36]	RCT Referred:183 Selected: 183 Participated in the study 183 Participated in treatment arm: 97 Completed: 71	Setting: community leisure centres Content: education, exercise Form: outpatient, group therapy Involved disciplines: OT, PT Intensity: 20 hrs, 10 wks, 10 sessions	Unclear 4 or 8 months after baseline	**Global treatment effect** (treatment effectiveness) - Global treatment effect was predicted by self-efficacy for controlling pain (ASES) ($P < 0.01$), self-efficacy for other symptoms (ASES) ($P < 0.05$), levels of physical activity (self-reported level of physical activity) ($P < 0.05$) and use of cognitive symptom management methods (SPAQ) ($P < 0.01$)
Hooten WM. et al. 2007 [31]	Retrospective case-matched series Referred: ? Selected: 33 Participated: 33 men, 33 matched women Completed: 29	Setting: pain rehabilitation centre Content: biofeedback, CBT, education, physical reconditioning, relaxation Form: outpatient, group therapy Involved disciplines: PT, OT Intensity: 120 hrs, 3 wks, 15 sessions	Post-treatment	**Physical functioning** (SF-36 role physical, MPI-interference) - Role physical was predicted by gender ($P < 0.01$) - Interference was predicted by gender ($P < 0.01$) **'Other'** (SF36 general health, social functioning) - General health was predicted by gender ($P < 0.01$) - Social functioning was predicted by gender ($P < 0.01$)
Keel P. et al. 1998 [37]	RCT Referred: 55 Selected: 32 Participated: 32 Completed: 27	Setting: rheumatology clinic Content: treatment arm 1: gymnastics, information, instruction in self-control strategies, relaxation. treatment arm 2: discussion, relaxation.	4 months after baseline	**Global treatment effect** (combined score of overall improvement, pain, sleep disturbance, fatigue, medication) - Global treatment effect was predicted by disease duration (general symptom checklist) ($P < 0.01$), initiative for conflict resolution (RPFT) ($P < 0.01$) and levels of physical activity (pain diary) ($P < 0.05$)

Table 2. Description of studies *(continued)*

Author, Year	Study design Number of patients	Treatment	Timing of outcome assessment	Outcome and (non-) predictors
Keel P. et al. 1998 [37] *(continued)*		Form: outpatient, group therapy Involved disciplines: treatment arm 1: PT, Psy, Ps Treatment arm 2: PT, Psy Intensity: 30 hrs, 15 wks, 15 sessions		
Lemstra M. et al. 2005 [35]	RCT Referred: 82 Selected: 82 Participated in the study: 79 Participated in the treatment arm: 43 Completed: 35	Setting: non-clinical Content: Rh and PT intake, dietary, massage, pain/stress management, physical therapy, Rh and PT discharge Form: outpatient, group therapy Involved disciplines: ET, PT, Ps, Rh Intensity: 6 wks, 24 sessions, ? hrs	15 months after baseline	**Global treatment effect** (PDI) - Global treatment effect was predicted by income ($P < 0.05$)
Lera S. et al. 2009 [33]	RCT Referred: 171 Selected: 107 Participated: 83 Completed: 68	Setting: hospital fibromyalgia unit Content: treatment arm 1: multidisciplinary treatment: discussion, individual medical treatment, physical education, physical exercise, treatment arm 2: multidisciplinary treatment + CBT Form: outpatient, group therapy Involved disciplines: PT, Ps, Rh, RP Intensity: treatment arm 1: 14 hrs, treatment arm 2: 36.5 hrs, 4 months, 14 sessions	Post-treatment	**Global treatment effect** (FIQ) - Global treatment effect was predicted by the presence of fatigue ($P < 0.05$) and number of tender points ($P < 0.05$)

Table 2. Description of studies *(continued)*

Author, Year	Study design Number of patients	Treatment	Timing of outcome assessment	Outcome and (non-) predictors
Thieme K. et al. 2003 [30]	RCT Referred: ? Selected: 63 Participated in the study: 63 Participated in treatment the arm: 40 Completed: 38	Setting: hospital for rheumatic disorders Content: education, dealing with medical system, medication management, increase in activity, OPT, reduction of interference and pain behaviour, treatment in assertive pain incompatible behaviour. Form: inpatients, group therapy Involved disciplines: Ps, PT, N, Rh Intensity: 75 hrs, 5 wks, sessions?	15 months after baseline	**Physical functioning** (MPI-interference) - Physical functioning was predicted by interference of pain (MPI) ($P < 0.01$) and pain intensity (MPI) ($P < 0.05$)
Thieme K. et al. 2007 [34]	RCT Referred: ? Selected: 125 Participated in the study: 125 treatment arm OPT: 43, the treatment arm CBT: 42 Completed: OPT 40, CBT 40	Setting: rheumatology clinic Content: CBT or OPT and education Form: outpatient, group therapy Involved disciplines: Ps, Rh Intensity: 30 hrs, 15 wks, 15 sessions	12 months after baseline	**Global treatment effect (combined score reduction in pain (MPI) and physical impairment (FIQ))** **CBT:** - Global treatment effect was predicted by affective distress (MPI) ($P < 0.01$) solicitous spouse behaviour (MPI) ($P < 0.01$), use of adequate coping strategies (MPI) ($P < 0.01$) and pain behaviour (TBS) ($P < 0.01$) **OPT:** - Global treatment effect was predicted by physical impairment (FIQ) ($P < 0.01$), pain behaviour ($P < 0.01$), a history of frequent visits to physician ($P < 0.01$), solicitous spouse behaviour (TBS) ($P < 0.01$) and level of catastrophizing (PRSS) ($P < 0.01$)
Torres X. et al. 2009 [38]	Prospective cohort Referred: 176 Selected: 140 Participated: 98 Completed: 94	Setting: hospital fibromyalgia unit Content: CBT, education, individual pharmacological treatment, individual occupational therapy, physical therapy	Post-treatment 12 months after discharge	**'Other' (**return to work) - Return to work, on discharge was predicted by beliefs in fate (MHLC) ($P < 0.01$) and perceived disability (HAQ**)** ($P < 0.01$) - Return to work at 12 months was predicted by beliefs in fate (MHLC) ($P < 0.01$)

Table 2. Description of studies *(continued)*

Author, Year	Study design Number of patients	Treatment	Timing of outcome assessment	Outcome and (non-) predictors
Torres X. et al. 2009 [38] *(continued)*		Form: in/out patients unclear, group therapy, individual therapy Involved disciplines: OT, PT, Rh Intensity: 60 hrs, 4 wks, 12 sessions		
Turk D.C. et al. 1998 [23]	Prospective cohort Referred: ? Selected: 76 Participated: 76 Completed: 70	Setting: university-based FM treatment programme Content: aerobics/ exercise, body mechanics, CBT, education, medical management, pacing, pain and stress management Form: outpatient, group therapy Involved disciplines: Ph, Ps, PT, OT Intensity: 25 hrs, 4 wks, 6 half day sessions	Post- treatment	**Pain** (MPI pain severity) - Pain was predicted by depression (CES-D), perceived disability (ODI), physical activity (MPI), perceived solicitous responses from others (MPI) and idiopathic onset of symptoms (P <0.05)
Turk D.C. et al. 1998 [24]	Prospective cohort Referred: ? Selected: 48 Participated: 48 Completed: 48	Setting: university-based FM clinic Content: aerobics/ exercise, body mechanics, CBT, education, medical sessions, medication management, pacing, pain and stress management Form: outpatient, group therapy Involved disciplines: Ph, PT, Ps, OT Intensity: 25 hrs, 4 wks, 6 half-day sessions	Post-treatment	**Pain** (MPI pain severity) - Pain was predicted by the dysfunctional profile (MPI) (P < 0.01) and the adaptive coper profile (MPI) (P < 0.05) **Physical functioning** (MPI interference) - Physical functioning was predicted by the dysfunctional profile (MPI) (P < 0.01) **Emotional functioning** (CES-D) - Emotional functioning was predicted by the dysfunctional profile (MPI) (P < 0.01) **Global treatment effect** (ODI)Global treatment effect was predicted by the dysfunctional profile (MPI) (P< 0.01)

Table 2. Description of studies *(continued)*

Author, Year	Study design Number of patients	Treatment	Timing of outcome assessment	Outcome and (non-) predictors
Worrel L.M. et al. 2001 [32]	Prospective cohort Referred: 180 Selected: 139 Participated: 100 Completed: 100	Setting: fibromyalgia clinic Content: education, energy conservation, exercise/ stretching, group discussion, proper body mechanics Form: in/outpatient unclear, group therapy Involved disciplines: N, PT, OT, Ph Intensity: hrs 12, 1,5 day, 3 half-day sessions	1 to 2 months after baseline	**Global treatment effect** (FIQ-total) Global treatment effect was predicted by the impact of FM (FIQ total) ($P < 0.01$)

Legend ASES: Arthritis Self-Efficacy Scale, BAI: Beck Anxiety Inventory, BDI: Beck Depression Index, CES-D: Epidemiological Studies Depression Scale, CBT: Cognitive Behavioural Therapy, D: dietician, EP: exercise physiologist, ET: exercise therapist, FIQ: Fibromyalgia Impact Questionnaire, GSS: General self-efficacy scale, HAQ: Health Assessment Questionnaire, hrs: hours, IPQ: Illness Perception Questionnaire, K: kinesiologist, med: medication, MHLC: Multidimensional Health Locus of Control-fate, MMPI: Minnesota Multiphasic Personality Inventory, MPI: Multidimensional Pain Inventory, N: nurse, ODI: Oswestry Disability Scale, OPT: Operant Pain Treatment, OT: occupational therapist, P: pharmacist, PDI: Pain Disability index, Ph: physician, PRSS: Patient Response Style Scale, Ps: psychologist, Psy: psychiatrist, PT: physiotherapist, QOLS: Quality Of Life Scale, RCT: randomized control trial, Rh: rheumatologist, RP: rehabilitation practitioner, RPFT: Rosenzweig Picture-Frustration Test, SF-36: Short-Form Health Survey, SPAQ: Scottish Physical Activity Questionnaire, SW: social worker, TBS: Tubingen Pain Behaviour Scale, wks: weeks.

Methodological quality. The overall agreement with regard to the methodological quality between reviewers was 77%. The disagreements, which mainly concerned the rating of participation and the attrition of patients, were resolved in a consensus meeting with the third reviewer. Six studies were considered to be of high quality, and eight studies were of low quality (Table 3). Table IV summarizes the direction and the level of evidence of the predictors of the five outcome domains. It should be noted that a number of trials were included in this review and the main goal of these trials was to evaluate the effectiveness of the treatment, and not the prognostic factors for outcome of the treatment. This may have resulted in a low quality score in this review, because these studies were evaluated for their prognostic qualities. Therefore, in such cases, a low score for quality does not necessarily mean that it was a poorly designed trial.

Table 3. Risk of bias and study quality

	Risk of Bias						Study Quality
Authors	**Partici-pation**	**Attrition**	**Prognostic factors**	**Outcome**	**Confoun -ding**	**Analysis**	**Total score**
Bailey et al. 2003 [28]	moderate	moderate	high	low	high	high	low
Bennet et al. 1996 [25]	moderate	low	low	low	moderate	low	high
Glattacker et al. 2010 [29]	low	moderate	low	low	high	high	low
Hammond et al. 2006 [36]	high	high	low	low	low	low	low
Hooten et al. 2007 [31]	moderate	high	low	low	low	high	low
Keel et al. 1998 [37]	moderate	high	high	high	high	low	low
Lemstra et al. 2005 [35]	low	high	high	low	low	low	low
Lera et al. 2009 [33]	low	low	moderate	low	high	high	low
Thieme et al. 2003 [30]	low	low	low	low	low	low	high
Thieme et al. 2007 [34]	low	low	low	low	low	low	high
Torres et al. 2009 [38]	low	low	moderate	low	low	low	high
Turk et al. 1998 [23]	low	low	low	low	low	high	low
Turk et al. 1998 [24]	low	low	low	low	low	low	high
Worrel et al. 2001 [32]	low	low	low	low	low	low	high

Predictors of pain. Five studies assessed predictors of pain post-treatment (Tables II and IV). Poorer outcome for pain was predicted by higher levels of depression[23] and the presence of a major depression (according the DSM IIIR criteria) at baseline (moderate evidence), and by the psychological disturbance profile of the Minnesota Multiphasic Personality Inventory (MMPI[25]) (weak evidence). In contrast, better outcome for pain was predicted by two profiles of the MPI: the dysfunctional profile and the adaptive copers profile[24] (weak evidence). The MMPI[26] and MPI[27] profiles are described in Appendix B. Weak evidence suggesting that characteristics did not predict post-treatment pain was also found. Initial physical fitness (i.e. VO2 max, maximum workload, respiratory quotient) did not predict the outcome of pain[25]. The evidence for demographic factors (i.e. smoking[28]), social factors (i.e. solicitous response from others[23]), symptoms (i.e. duration of the illness 1–2 years[29]), onset of the pain[23]) and physical functioning (i.e. level of disability and activity[23]) as predictors for the outcome of pain was inconclusive. Finally, inconclusive evidence was found that other demographic and clinical factors (i.e. age, level of education, employment, partnership[29] and medication[28]), emotional and cognitive factors (i.e. general self-efficacy, illness perceptions; identity, timeline, consequences, personal control, treatment control, coherence and emotional representations[29]) did not predict the outcome of pain.

Predictors of physical functioning. Five studies assessed predictors related to post-treatment physical functioning (Tables II and IV). A poorer outcome for physical functioning was predicted by the presence of a major depression (according the DSM IIIR criteria), the MMPI psychological disturbance profile and the MMPI pain profile[25] (weak evidence). In contrast, a better outcome in physical functioning was predicted by the presence of the MPI dysfunctional profile[24]. Furthermore, a better outcome was predicted by worse baseline status and high pain intensity[30] (weak evidence). The evidence for demographic factors (i.e. gender[31]) emotional and cognitive factors (i.e. beliefs in consequences, and timeline[29]) as predictors for the outcome of physical functioning was inconclusive. Finally, inconclusive evidence was found that other demographic factors (i.e. age, level of education, employment and partnership[29]), cognitive and emotional factors (i.e. general self-efficacy, identity, personal control, treatment control, coherence and emotional representations[29]) and symptoms (i.e. duration of illness <1 years, 1–2 years, 3–5 years, 6–10 years[29]) did not predict the outcome of physical functioning.

Predictors of emotional functioning. Three studies evaluated predictors related to emotional functioning (Tables II and IV). A better outcome in emotional functioning was predicted by the MPI dysfunctional profile[24] (weak evidence). Furthermore, it was found that initial physical fitness (i.e. VO2 max, maximum workload and respiratory quotient) did not predict emotional functioning[25] (weak evidence). The evidence for demographic factors (i.e. partnership and age[29]), cognitive and emotional factors (i.e. beliefs in identity, consequences, timeline and general self-efficacy[29]) and symptoms (i.e. duration of the illness <1 years, 1–2 years, 3–5 years and 6–10 years[29]) as predictors for the outcome of emotional functioning was inconclusive. Finally, inconclusive evidence was found that other demographic factors (i.e. level of education and employment[29]) and cognitive and emotional factors (i.e. personal control, treatment control, coherence and emotional representations[29]) did not predict the outcome of emotional functioning.

Predictors of global treatment effect. Nine studies examined predictors related to global treatment effect (Tables II and IV). A poorer outcome in global treatment effect was predicted by the MMPI disturbance profile and the presence of a major depression (according the DSM IIIR criteria) at baseline[25] (weak evidence). In contrast, a better outcome in global treatment effect was predicted by worse baseline status[32], the MPI dysfunctional profile[24], less number of tender points, and fatigue[33] (weak evidence). Thieme et al.[34] provided evidence that characteristics such as higher levels of pain behaviour, catastrophizing, physical impairment, more solicitous spouse behaviour, and more visits to a physician predicted a better outcome when patients received OBT. Furthermore, they found that higher levels of affective distress, less solicitous spouse behaviour, lower coping strategies, and lower pain behaviour predicted a better treatment outcome when patients received CBT (weak evidence). Finally, initial physical fitness (i.e. VO2 max, maximum workload and respiratory quotient) did not predict global treatment effect[25] (weak evidence). There was inconclusive evidence that demographic factors (i.e. income status[35]), cognitive and emotional factors (i.e. beliefs in consequence and timeline[29], self-efficacy in controlling pain and symptoms, making use of cognitive symptom management[36], and initiative for conflict resolution[37]), symptoms (i.e. shorter disease duration[37], number of tender points and fatigue[33]) and physical function (i.e. level of activity[37]) were predictors of global treatment effect. Finally, there was inconclusive evidence that other demographic factors (i.e. age, level of diploma, employed and partnership[29]), symptoms (i.e. duration

of pain <1 year, 1–2 year, 3–5 year 6–10 years[29]), cognitive and emotional factors (i.e. general self-efficacy, identity, consequences, personal control, treatment control, coherence and emotional representations[29]) did not predict the outcome of global treatment effect.

Predictors of the outcome "other". Four studies examined predictors related to the residual category "other", which comprises measurements of quality of life, return to work, social functioning, vitality and general health (Tables II and IV). A poorer outcome in quality of life was predicted by the presence of a major depression (according the DSM IIIR criteria) and the MMPI psychological disturbance profile[25]. Furthermore, no return to work was predicted by strong beliefs in fate, both on discharge and at the 12-month follow-up, and by high perceived disability on discharge[38] (weak evidence). Furthermore, initial physical fitness (i.e. VO2 max, maximum workload, respiratory quotient) did not predict the outcome of quality of life[25] (weak evidence). Inconclusive evidence was also found for a number of (non-) predictors of treatment outcome. General health was predicted by gender[31] and emotional representations[29]. Furthermore, vitality was predicted by general self-efficacy, beliefs in consequences, and timeline[29]. Social functioning was also predicted by, gender[31], duration of the illness 1-2 years, beliefs in timeline and identity[29]. Other demographic factors, and emotional and cognitive factors did not predict the outcome of general health, vitality and social functioning[29].

Table 4. Overview of predictors of treatment outcome

	Pain		Physical functioning		Emotional functioning		Global treatment effect		"Other"	
Demographics										
Younger age					+	i				
Female gender			+	i					+ [a, d]	i
Partnership					+	i				
Higher income status							+	i		
Smoking	-	i								
Cognitive and emotional and social factors										
Psychological disturbance profile (MMPI)	-	w	-	w			-	w	- [b]	w
Higher level of depression or major depression	-	m	-	w			-	w	- [b]	w
Pain profile (MMPI)			-	w						
Higher beliefs in identity					-	i			- [d]	i
Higher beliefs in consequence			-	i	-	i	-	i	- [d, e]	i
More illness representations									- [a]	i
High beliefs in fate									- [c]	w
Dysfunctional profile (MPI)	+	w	+	w	+	w	+	w		
Adaptive Copers profile (MPI)	+	w								
Higher levels of self-efficacy for controlling pain							+	i		
Higher levels of self-efficacy for other symptoms							+	i		
Higher general self-efficacy					+	i			+ [e]	i
More use of cognitive symptom management methods							+	i		
More initiative for conflict resolution							+	i		
More solicitous response from others	+	i								
More beliefs in a chronic timeline			+	i	+	i	+	i	+ [d, e]	i
Symptoms										
Higher levels of pain			+	w						
Higher impact of FM							+	w		
Less number of tender points							+	i		
Duration of illness 1-2 years	-	i			-	i			- [d]	i
Duration of illness <1 year					-	i				
Shorter disease duration							+	i		
Idiopathic onset of the pain	+	i								
Fatigue							+	i		
Physical function										
High perceived disability	-	i							- [c]	w
Higher levels of activity	+	i					+	i		
Higher interference of pain			+	w						
Responders to CBT had:										
- Higher levels of affective distress							+	w		
- Less solicitous spouse behaviour							+	w		
- Lower coping strategies							+	w		
- Lower pain behaviour							+	w		
Responders to OBT had:										
- Higher levels of pain behaviour							+	w		
- More solicitous spouse behaviour							+	w		
- Higher levels of catastrophizing							+	w		
- Higher level of physical impairment							+	w		
- More visits to physician							+	w		

+= associated with better treatment outcome, - = associated with poorer treatment outcome, m= moderate level of evidence, w= weak level of evidence, i= inconclusive level of evidence. Outcome domains "other": a general health, b quality of life, c return to work, d social functioning, e vitality. MMPI= Minnesota Multiphasic Personality Inventory, MPI= Multidimensional Pain Inventory, FM= fibromyalgia, CBT= cognitive behavioural therapy, OBT= operant behavioural therapy.

Discussion

The aim of the present study was to identify predictors for the outcome of multidisciplinary treatment in patients with CWP and FM through a systematic review of the literature. Fourteen studies on FM generated evidence for predictors of five outcome domains: pain, physical functioning, emotional functioning, global treatment effect, and a residual category "other". Although we found six studies that were of high methodological quality, no strong evidence was found for any predictor of treatment outcome, and the level of evidence was generally weak. This was mainly due to the fact that the predictors were only examined in one study. In addition, we found several predictors of inconclusive evidence.

In summarizing the measures of outcome, we defined three outcome domains in accordance with IMMPACT recommendations (i.e. pain, physical functioning and emotional functioning[39]). We defined two additional domains, i.e. global treatment effect and 'other'. The outcome for global treatment effect comprised aggregated measurements of treatment effects and the total scores of multidimensional measurements. The outcome domain "other" contained measures such as quality of life, return to work, social functioning, vitality, and general health.

Interestingly, the level of depression predicted a poorer outcome for pain[23,25] (moderate evidence), as well as physical functioning, global treatment effect and quality of life[25] (weak evidence). These results suggest that a subgroup of patients with pronounced emotional problems respond less well to multidisciplinary treatment. It is known that depression and chronic pain are associated[40-44], and that depression is common in patients with chronic pain[45]. Furthermore, co-morbid depression is associated with adverse psychosocial characteristics in patients with chronic pain[12,45,46]. These results indicate that depression and its associated problems are a barrier to effective multidisciplinary group treatment.

Weak evidence was found for seventeen predictors of the outcome of FM treatment. However, these predictors have so far only been investigated in one high quality study, so these results should be interpreted with care. It was found that a poorer outcome for pain, physical functioning and quality of life was predicted by the MMPI psychological disturbance profile[25]. Similarly, a poorer outcome for pain was predicted by the MMPI pain profile[25]. It was also found that no return to work was predicted by high disability and a strong belief in fate[38]. These results suggest that pronounced emotional and interpersonal problems are related to poorer treatment outcome.

In contrast, a better outcome was found for two specific patient profiles. It was found that a greater improvement in pain, physical, and emotional functioning and global treatment effect was predicted by the MPI dysfunctional profile[24]. This profile is characterized by high perceived pain, disability, and high solicitous responses from significant others. One might conclude that the characteristics of this profile match components of multidisciplinary treatment. Furthermore, a better outcome for pain was predicted by the MPI adapted coper profile[24]. More improvement in physical functioning was also predicted by a worse baseline in physical functioning status and higher levels of pain[30]. Furthermore, it was found that a worse baseline status for global treatment effect[32] was a predictor of more improvement in global treatment effect. As expected, higher baseline values for the outcome measures (indicating worse physical functioning and global treatment effect) are associated

with more change after treatment. This could be explained by a floor effect of the outcome measures which may have caused regression to the mean: patients with high baseline scores are able to improve more than patients who already have low baseline scores and therefore have less possibility to improve.

We found that some predictors were related to specific forms of multidisciplinary treatment. Patients with pronounced pain behaviour respond well to treatment when they receive specific OBT[34]. Pain is one of the key symptoms of FM, and OBT focuses specifically on the modification of pain behaviour: pain behaviour is not endorsed or rewarded. The present results suggest that patients with higher levels of pain respond well to the OBT approach. Furthermore, it was found that patients with more affective distress and less pronounced pain behaviour respond well to CBT[34] (weak evidence). This suggests that these patients benefit from restructuring maladaptive cognitions, whereas patients with pronounced pain behaviours need to reinstate healthy behaviour[34].

Finally, we found inconclusive evidence for several predictors related to one or more outcome domains. Inconclusive evidence means that the predictors were assessed in low-quality studies, and that more research is needed to support the evidence for these predictors. It was found that less improvement in treatment outcome was predicted by smoking[28], negative cognitions, and emotional characteristics (e.g. more pronounced illness representations and greater beliefs in the consequences of the illness[29]). In contrast, it was found that more improvement in the treatment outcome was predicted by demographic factors such as female gender[31], partnership[29], higher income[35], positive cognitions and emotional characteristics (e.g. higher self-efficacy[29,36]), less perceived symptoms (e.g. less tender points [33]) and, better physical functioning (e.g. higher levels of activity [37]).

There are some limitations in our study. First, we originally planned to include studies focussing on patients with CWP and FM. However, studies focusing on CWP patients could not be included because, in general, these studies include patients with CWP and patients with regional pain syndromes (e.g. low back pain), and therefore do not perform separate analyses of the CWP group. Secondly, we tried to summarize (non-) predictors for the outcome of treatment in FM patients. It is therefore possible that we did not provide a full overview of all predictors, because not all studies presented all univariate associations between the predictors and the outcome. Furthermore, it was difficult to evaluate the presence of non-predictors, because the studies had a small sample size or did not present the data in full. Thirdly, it was not possible to pool the data to quantify the strength of relationships between predictors and outcome, because of the heterogeneity of the study populations, the type and duration of the treatment, and predictor and outcome measurement. Like Hauser et al.[9], we were faced with the problem that there is no internationally accepted definition of multidisciplinary treatment, and no widely accepted standard for the minimum effective duration of multidisciplinary treatment. Multidisciplinary treatment programs generally include psychological, functional and physical components. Despite some important similarities in the studies included in this review (e.g. outpatient programs, integration of CBT or OBT with exercise therapy), there is heterogeneity in the treatment content, the duration, the intensity, and the follow-up. Our findings suggest that the benefits of treatment depend not only on patient characteristics, but also on the content of the treatment[34]. In further research on predictors for the outcome of multidisciplinary

treatment in patients with FM, more transparency in the content of the multidisciplinary treatment is desirable. It may be worthwhile to make a taxonomy for multidisciplinary treatment, as has been done by Abraham et al.[47] for behavioural change techniques. In addition, transparency about the duration and intensity of the multidisciplinary treatment is also needed, and to make the results of the research more comparable, future studies should aim at using uniform measurements, as recommended in the IMMPACT core set for chronic pain[39]. Further, we summarized the evidence of patient characteristics which predict the outcome of multidisciplinary treatment for chronic pain, based on the results of uncontrolled clinical trials. This provides practitioners and researchers with information about how to appreciate the role of individual differences in demographic factors, symptoms, physical functioning and psychological characteristics with regard to treatment outcome. However, identifying predictors of change in uncontrolled studies does not make it possible for practitioners and researchers to distinguish between predictors of the natural course of a disease and predictors of successful treatment. Finally, our review like other reviews is bound to publication bias and we cannot exclude that we may have missed some relevant studies, despite the fact that we used a sensitive search strategy, checked references of included studies, and consulted an experienced Medical Liberian. We are aware of the possibility of publication bias that could be introduced by restricting the inclusion criteria to three languages. However, by including three languages we think we cover a broad area of the literature.

The predictors identified in this review have several implications for the planning of treatment. Predictors can be used either to adjust treatment to the needs of specific patients, or to allocate patients to suitable programs. With regard to the first option, patients with emotional difficulties (i.e. depression) and interpersonal difficulties might benefit more from treatment components which specifically focus on depression, and interpersonal problem-solving techniques. For this group of patients it might be worthwhile to add these specific components to multidisciplinary group treatment. Another possibility is to offer these patients individual psychological treatment prior to the start of multidisciplinary group treatment. It was found that some predictors related to outcome depend on a specific form of multidisciplinary treatment. Patients characterized by high perceived levels of pain can be offered specific OBT because these patients seem to respond well to this kind of multidisciplinary treatment, whereas patients with affective distress and low pain behaviour seem to respond well to CBT. These predictors can therefore be used to allocate patients to suitable programs.

In conclusion, depression is a predictor of poor outcome in patients with FM, with moderate to weak evidence to support this claim. Weak evidence was found that baseline status, specific patient profiles, belief in fate, disability, and pain are predictors of treatment outcome. Furthermore, some other factors predict the outcome of specific forms of treatment.

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Appendix A

Pubmed search

Search ("Fibromyalgia"[Mesh]) OR (Fibromyalgi*[tiab] OR Fibromyositis[tiab] OR fibromyotic[tiab]) OR (("Chronic Disease"[Mesh] OR chronic[tiab]) AND ("pain"[MeSH Terms] OR "pain"[tiab]) AND ("wide spread"[tiab] OR widespread[tiab] OR aspecific[tiab] OR generalized[tiab] OR generalised[tiab] OR idiopathic[tiab] OR diffuse[tiab])) OR ("chronic pain"[tiab] OR "chronic wide spread pain"[tiab] OR "chronic widespread pain"[tiab] OR "chronic wide spread body pain"[tiab] OR "chronic widespread body pain" OR "chronic musculoskeletal pain"[tiab] OR "musculoskeletal pain syndrome"[tiab] OR "musculoskeletal pain syndromes"[tiab] OR "chronic pain syndrome"[tiab] OR "chronic pain syndromes"[tiab]) OR (fibrositis[tiab] OR fibrositides[tiab]) cohort studies[mesh] OR cohort[tiab] OR longitudinal[tiab] OR prospective[tiab] OR "follow up"[tiab] OR "follow-up"[tiab] OR followup[tiab] OR predict*[tiab] OR determinant*[tiab] OR fibromyalgia/therapy[mesh] AND ((Clinical Trial[ptyp] OR Meta-Analysis[ptyp] OR Randomized Controlled Trial[ptyp])) NOT ("drug therapy"[Subheading] NOT ("therapy"[Subheading:noexp] OR "diet therapy"[Subheading] OR "rehabilitation"[Subheading])) Limits: All Adult: 19+ years

Appendix B

Description of MMPI and MPI profiles

MMPI: Minnesota Multiphasic Personality Inventory[26]
Pain profile: Elevated scores T scores for hypochondriasis and hysteria, but not depression
Psychological disturbance profile: Elevated T scores for hypochondriasis, hysteria and depression

MPI: Multidimensional Pain Inventory[27]
Adaptive copers profile: patients characterized by low levels of disability and psychological distress and, a high level of perceived life-control
Dysfunctional profile: patients characterized by high levels of pain, disability, functional limitations, and psychological distress and low levels of activity and sense of control

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