Fontys Paramedic University of Applied Sciences

Department of Physiotherapy
Bachelor Thesis

The most effective multidisciplinary treatment approach for patients with fibromyalgia based on the outcomes pain and fatigue: a systematic literature review

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Preface

Writing my bachelor thesis have been one of the most challenging tasks I have come across during my time as a student at Fontys University of Applied Sciences. After redoing the first year of physiotherapy, I felt that I had to prove to my friends, family and outmost myself that I was eligible enough to become a physiotherapist. I became stricter, took charge and pushed myself to get to the point where I am now. The last step. Starting up with the bachelor thesis project turned out to be nothing like I thought it would be. I dared myself to be structured, time-efficient and independent of others. Spending twelve hours a day in front of my computer reading and researching about fibromyalgia syndrome became my lifestyle. Strangely enough, I enjoyed it. To me, fibromyalgia syndrome was all but boring. I daydreamed about being able to organize research myself to test out different hypothesis. Even though I don't have that much clinical experience yet, I am under the impression that fibromyalgia syndrome is very relevant for the time we are in, and therefore the motivation regarding the importance of this research became even stronger.

I would like to thank my supervisors Tim van der Stam, and Mitchel van Eeden, for good constructive feedback and for keeping me confident during this project. I would also like to thank Nicholas Quinn and Einar Egenberg for their willingness to provide feedback, and for genuinely being interested in the progress of this bachelor thesis project.

Without further ado I hereby present you my work,

Sara Sindre
7th of June 2016

Abstract

Introduction: 2-5% of the worlds' population are diagnosed with fibromyalgia syndrome, and suffer from various symptoms. Pain and fatigue have been established at the two worst experienced symptoms, and is therefore the main focus regarding treatment. A multidisciplinary treatment approach has been recommended for the management of fibromyalgia syndrome, however the ideal treatment regime remains yet to be established. This systematic literature review aims to investigate what the most effective multidisciplinary treatment approach for patient with fibromyalgia syndrome is, based on the outcomes pain and fatigue.

Methods: A search for the relevant literature was conducted between the 15th of February and 1st of May 2016 through the PubMed, Cochrane Library, MEDLINE, ScienceDirect and Springer Link databases. All articles that met the inclusion and exclusion criteria were retrieved for methodological quality appraisal using the PEDro scale. The best evidence synthesis was performed using a classification developed by Van Tulder.

Results: 481 articles were obtained and lastly four met the inclusion and exclusion criteria. All of the studies were RCTs that used a multidisciplinary intervention to assess the outcomes of pain and/or fatigue. Statistical significant results were obtained from two of the studies, demonstrating the multidisciplinary treatment approach for pain outcomes. No significant results were attained from either of the studies showing the effectiveness of a multidisciplinary treatment approach for fatigue.

Conclusion: Based on findings in research, there are not enough evidence to suggest the most effective multidisciplinary treatment approach for patients with fibromyalgia syndrome, based on the outcomes pain and fatigue. Recommendations for further research involve dividing patient groups based on baseline characteristics, physical level and motivation to improve own health. Multidisciplinary approaches should at least include physiotherapy, cognitive behavioural therapy, exercise therapy and pharmacological therapy.

Key words: Fibromyalgia syndrome, multidisciplinary approach, pain, fatigue

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1. Introduction

Fibromyalgia, also known as fibromyalgia syndrome (FMS), is a common form of incurable, nonarticular rheumatism, that affects approximately 2-5% of the worlds' population(1-14). It predominantly occurs in women between 40-60 years of age. However, FMS can occur in both genders at any age(2, 5, 15). The cause of FMS is unknown, but individuals can be at higher risk if they have had previous episodes of depression, easily feel stressed, or are inclined to feel increased sensitivity to pain stimuli or experienced trauma such as abuse or sexual assault in early life(16).

The classification of FMS is highly debated amongst researchers(17-19), however FMS is generally characterized as chronic widespread musculoskeletal pain and fatigue(2). Accompanied by other symptoms such as general stiffness, sleep disturbance, irritable bowel syndrome, psychological stress, depression, anxiety, headaches and cognitive dysfunction(1, 2, 4, 5, 7, 10, 12, 16, 17, 19-24), FMS should therefore be seen as a complex syndrome.

The effect FMS has on society and patients' ability to work has shown to be extensive(25). A study from 2008(25) reported that 20-50% of all individuals diagnosed with FMS were unable work most days, and 36% were missing work two or more times per month. In 2005, Dutch patients diagnosed with FMS had a mean of 34 sick-leave days per working year(26). Boonen et al.(26) presented in 2005 that the annual direct medical cost per patient was 1311€, exposing the social burden to be substantial for diagnosed FMS patients.

FMS is acknowledged as a biological-psychological-sociological disorder(5). The pathophysiologic definition of FMS is suggested to be "central nervous system hypersensitivity"(5), and research recognizes it as dysfunction of pain processing within the central nervous system via the mechanism of central sensitization(16, 27). In February 1990, 'The American College of Rheumatology (ACR) 1990 criteria' was developed for the classification of fibromyalgia(3, 21, 28). The ACR criteria were updated for the first time in 2010(5), and again in 2011(5, 19) (see appendix I). There have been discussions between researchers questioning the reliability of the ACR criteria and if it should be used as a diagnostic tool(18, 19, 29), though some literature states that the ACR criteria are accepted by investigators and a commonly utilized tool by investigators(3). On a morphological basis, there have been abnormalities found in the neuroendocrine system, the autonomic nervous system, the neurotransmitter system and the central nervous system(5), however to this date, there are no 'gold-standard' tests that can be performed to verify the diagnosis of FMS.

Despite the difficulties in diagnosing FMS, once the diagnosis has been made, patients are usually started on a pharmacological treatment(2)(see appendix II). Those diagnosed with FMS report pain and fatigue (or lack of energy) as being the two most debilitating symptoms(5, 10) Therefore it is not unexpected that pain is the priority focus regarding treatment for general practitioners (GP)(1, 5). The

main goal for treatment of FMS is generally to improve quality of life by decreasing pain and increasing physical function(3, 5). The determination of sub-goals are also important for the individual patient. These may include improving sleep, manage depression, anxiety, headaches, fatigue and abdominal discomfort(3, 5, 16, 20, 30). The effort to achieve this is done through either pharmacological and/or non-pharmacological treatments, though literature recommends treatments to be part of a multidisciplinary approach (MDA)(3, 5, 21, 30). Medicine alone has not proven to eliminate symptoms(5). The non-pharmacological therapies with the most evidence support are patient education, cognitive behavioral therapy (CBT), exercise therapy(2, 16, 27, 31). Patient education concerning the body's pain response is important, in combination with CBT to address the matter of central sensitization, and reduce the patient's attention of pain(2, 16). Exercise has a central role in balancing modulation and perception of pain, and physically active FMS patients have shown to control pain better than those who are less active(16, 32). However, no monotherapy involving neither drug nor non-pharmacological treatment has proven to be very effective(5). General consensus advice the multidisciplinary approach to combine exercise such as aerobic exercise(3), psychological therapy, such as; cognitive behavioral therapy (CBT), physiotherapy(5, 13, 21), and hydrotherapy(31).

Physiotherapists (PT) play a role in the multidisciplinary and non-pharmacological treatments of FMS(5, 6, 33, 34). The most common physiotherapeutic techniques are hands on treatments such as massage, stretching, mobilization, modalities (ultrasound, heat and electrical stimulation) and exercising(5). There is various evidence to support the use of aerobic exercise(5, 16, 35). Strength training has also shown to have a positive effect on FMS patients, and has proven to be even better in combination with aerobic therapy(16, 35, 36). Other treatment options such as mind-and-body therapies(37), acupuncture(5), relaxation therapy(5) or Whole-Body Vibration Therapies(38) have presented some positive effect on FMS symptoms.

Considering a MDA is the most recommended treatment approach(3, 5, 21, 30), there is a variety of therapies that can be included in the management of FMS. Practitioners have a lot of alternatives regarding what interventions they desire to be part of their chosen treatment regime. It is clear what therapies are effective and ought to be included in a MDA(3, 5, 13, 21, 31). However, it is not clear the greatest combination if interventions are, in terms of an optimal MDA with regards to reducing key symptoms. This is fundamental knowledge for practitioners to be able to offer their patients the most efficient, evidence-based multidisciplinary treatment, which is essential and for the sake of reducing key symptoms, hours of sick-leave from work and lowering the overall individual social burden of FMS. The research question for this systematic literature review is: what is the most effective multidisciplinary treatment approach for patients with fibromyalgia syndrome, based on the outcomes pain and fatigue?

2. Methods

The search for the relevant literature for this systematic literature review, was conducted using the following databases: PubMed, Cochrane Library, MEDLINE, ScienceDirect and Springer Link. The search was performed in the time period of 15th February 2016 to 1st of May 2016, at Fontys University of Applied Sciences' TF building in Eindhoven, The Netherlands.

2.1 Electronic Search

The entire search was conducted in the English language. Three keywords and their synonym were combined into one large search string, visible below (Figure 1). Keywords are coded for the convenience of the reader as follows: 'fibromyalgia' (keyword A), 'multidisciplinary approach' (keyword B) and 'outcome' (keyword C). Whenever search filters were presented the key words were used to emphasize inclusion and exclusion criteria. Builders such as: 'Title', 'Abstract', 'MeSh' were applied if available, and when these builders gave less than 10 findings, 'All Fields' were added.

Figure 1 *Keywords & synonyms that were used in the search for literature*

2.2 Inclusion and Exclusion Criteria

Studies that didn't meet the following requirements were not included for further quality appraisal, data extraction or the resulting best evidence synthesis.

2.2.1 Literature Requirements

Only articles from 1st of January 2005 and onwards were included. The reason being because the first FMS guideline was provided in 2005 by American Pain Society (APS)(13). Only articles in English were chosen, with the full text available online. Randomized controlled trials (RCTs) and controlled clinical trials (CCTs) were included as attempt to draw conclusions from reliable study designs.

Articles with ‘interdisciplinary’ treatment approaches were excluded unless they in fact were using a ‘multidisciplinary’ approach (see 2.2.3 Intervention Requirements). However interdisciplinary intervention was not a part of the keyword search term.

2.2.2 Participant Requirements

Only adult (over 18 years old) participants were included, with no exception, even if there was a juvenile or combination of adolescents and adult participants in the patient group. Participants all had to be diagnosed with fibromyalgia syndrome by meeting the American College of Rheumatology 1990/2010/2011 criteria(5). No gender requirements for participation was applied for this review.

2.2.3 Intervention Requirements

The intervention for this systematic literature review was a multidisciplinary approach(MDA). A MDA is different from an interdisciplinary approach (IDA). “Multidisciplinary draws on knowledge from different disciplines but stays within the boundaries of those fields, whereas interdisciplinary analyzes, synthesizes and harmonizes links between disciplines into a coordinated and coherent whole”(39). These two definitions were used to assess whether the interventions applied in the article were part of a multidisciplinary approach or not. If an IDA was listed in an RCT or CCT found during the Electronic Search, and it was clear that a MDA had been used, the article would be included. If the article stated using an IDA and had in fact used that intervention, the article was excluded.

2.2.4 Outcome Requirements

The outcomes for this systematic literature review were based on the results which came from the MDA found in the articles meeting the inclusion criteria. The observed outcomes were ‘pain’ and/or ‘fatigue’ and had to be stated in those words, or one of their synonyms listed in Electronic Search, Keyword C. The outcomes had to be presented with their respective outcome measurement(s) visibly recorded throughout the study. The outcomes were analyzed regardless of what outcome measurement used (subjective or objective) to explain the results.

2.3 Selection of The Relevant Literature

Selection of the relevant literature was done using the inclusion and exclusion criteria in the title, abstract and full text. After entering the search string in the different databases, resulting titles and abstracts were scanned by researcher for relevance regarding this literature review. Following, the abstract was read to investigate whether the article met the requirements or not. The full text was obtained if available online, and duplicates were excluded. If the article met the inclusion criteria, or if there were any uncertainties in the abstract that could lead to either inclusion or exclusion, the full article was obtained nonetheless and investigated for further analysis.

2.4 Methodological Quality Appraisal

The quality assessment of the selected literature was performed using the PEDro assessment scale (see Appendix III), and then put together in a modified PEDro scale to demonstrate what articles fulfill what criteria by listing the PEDro scale items and answering them with YES/NO. The PEDro scale has proven to be a reliable tool for assessing RCTs and CCTs(40, 41). It is an 11-point checklist developed for the assessment of the methodological quality of an RCTs, that consist of the following: eligibility criteria; random allocation; concealed allocation; baseline similarity; blinding of subjects, therapists and assessors; measures of key outcomes from more than 85% of subjects; intention to treat analysis; between-group statistical comparisons, and at last; point measures and measures of variability(41). However, the first item (eligibility criteria) was not taken into account as it is referring to external validity of the article(41), and was therefore not included as a part of the total PEDro score. For this reason, the maximum achievable score was 10, and minimum 0. The methodological quality levels were set as either 'high' or 'low' quality The levels of methodological quality are presented in table 1.

Table 1 *Levels of methodological quality based on PEDro score(42)*

PEDro Score	Classification
4-10 points	High
0-3 points	Low

2.5 Data Extraction

For each study the following data was extracted: author(s) and name of the study, year of publication, relevant anthropological details such as age, sex, number of subject involved and the amount of dropouts was collected. Furthermore, study design, type of interventions used by authors, frequency, duration, practitioners involved, outcome measures, time of measurements, follow ups, and outcomes of pain and fatigue was collected. Between-group significant difference was collected together with the outcomes, and wherever additionally; within-group difference.

2.6 Best Evidence Synthesis

A best evidence synthesis (BES) was executed on based on Van Tulder(42-44), taking the methodological quality of studies into account(44). The BES was performed to achieve an overall finding of the level of evidence. Results were divided into following sections: Strong evidence, Moderate Evidence, Limited Evidence, Indicative Findings, No/Insufficient evidence (See appendix IV)

3. Results

3.1 Identification of The Relevant Literature

A total of 481 articles were identified and retrieved for further analysis (see Figure 2) in the time period of March and April 2016 by a single researcher. The search was performed according to the criteria set in the method.

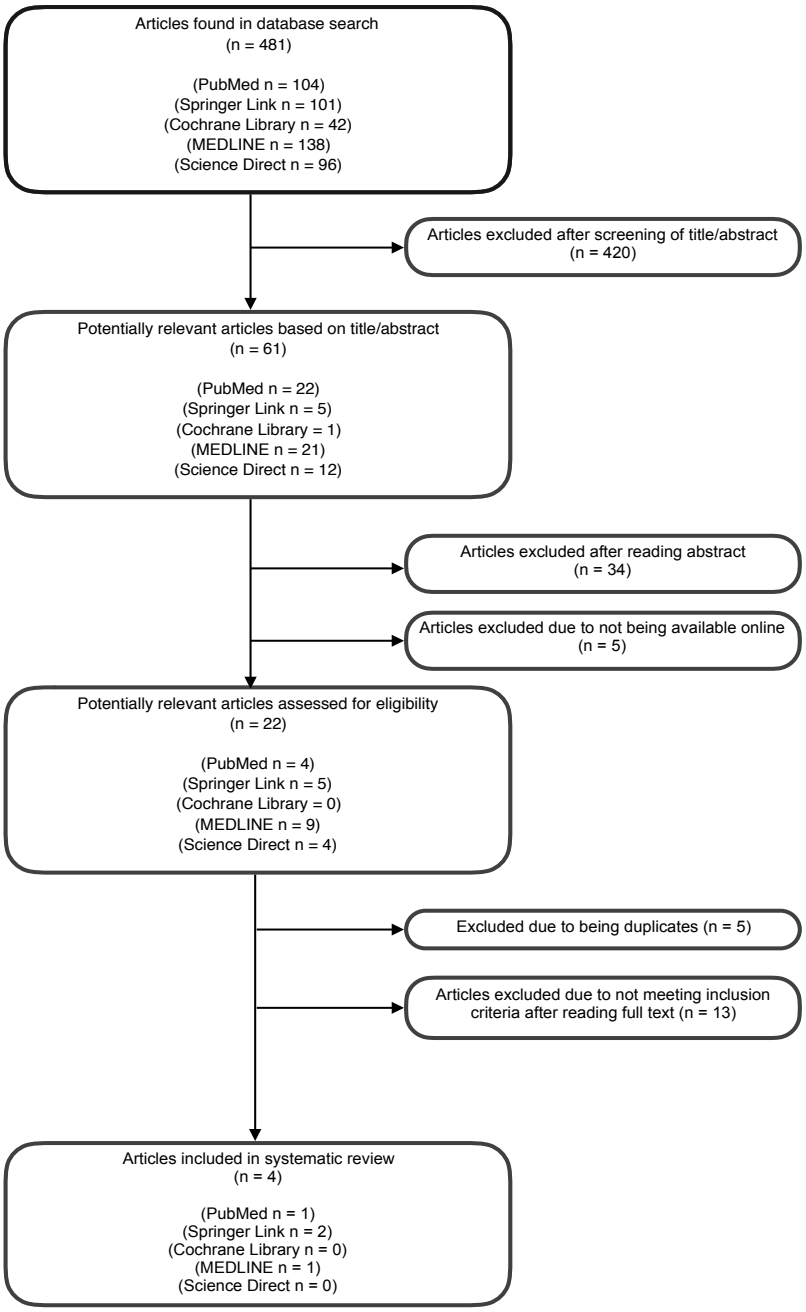

Figure 2 *Flowchart of the included and excluded literature*

Firstly, all articles were screened on title/abstract, and 420 articles did not meet the inclusion criteria. The main reason for exclusion based on screening the title/abstract was that the articles found were not relevant for the purpose of this research. Secondly, 61 articles were investigated based on their abstract, where 39 did not meet the inclusion criteria. The main causes for exclusion was that studies compared only one intervention to another, or did not measure pain or fatigue outcomes explicitly. Five articles were not available online. Thirdly, 22 articles were assessed for eligibility, where five were excluded due to being duplicates. 17 articles were read carefully, and 13 did not meet the inclusion criteria based on the following: four articles did not list pain or fatigue, two articles had no control group, five articles were not using a MDA because they only compared one intervention against another, and two articles used an IDA. Remaining was four articles that were considered suitable based on all meeting the inclusion and exclusion criteria.

3.2 Quality Appraisal

The selected four articles were all RCTs and evaluated based on the PEDro assessment scale (see appendix XIII).

Publications (45-48) which were assessed using PEDro scale all scored points for allocating subjects in a random matter (criterion 2), sections of similarity on the baseline (criterion 4), measures of at at least one key outcome from more than 85% of subjects initially recruited (criterion 8), and between-group statistical comparison (criterion 10). Allocation concealment (criterion 3) was reported in Van Eijk-Hustings et al.(46), Hamnes et al.(47) and Castel et al.(48), but not in Casanueva-Fernández et al.(45). However Casanueva-Fernández et al.(45) was the only one to blind all subjects (criterion 5), Van Eijk-Hustings et al(46), Hamnes et al.(47) and Castel et al.(48) did not. None of the authors (45-48) blinded the therapists who administered the therapy (criterion 6). Casanueva-Fernández et al.(45) and Castel et al.(48) blinded the assessors who measured at least one key outcome (criterion 7) whilst Van Eijk-Hustings et al.(46) and Hamnes et al.(47) did not. Only Van Eijk-Hustings et al.(46) and Castel et al.(48) fulfilled criteria 9 and 11 by reporting received outcome measures for treatment or control group, and when this was not the case, data for at least one key outcome was analyzed by “intention to treat” (criterion 9) and providing both point measures and measures of variability for at least one key outcome (criterion 11), whereas Casanueva-Fernández et al.(45) and Hamnes et al.(47) did not.

Castel et al.(48) achieved a total score of 8/10, Van Eijk-Hustings et al.(46) a total score of 7/10, Casanueva-Fernández et al.(45) a total score of 6/10, and Hamnes et al.(47) 5/10. Overall all articles(45-48) assessed by PEDro represent ‘high’ methodological quality.

3.3 Data Extraction

3.3.1 Study design

Four randomized controlled trials(45-48) were included in this systematic literature review, with publication dates ranging between 2011-2013.

3.3.2 Participants

All of the included articles had subjects diagnosed with FMS in both control and intervention groups, diagnosed based on the American College of Rheumatology Criteria(28), and was published between 2011-2013(45-48).

Van Eijk-Hustings et al.(46) was the only study that had two experimental groups, and presented the largest number of participants in total (n=203). This study(46) also had the greatest amount of dropouts (n=69), remarkably all from the intervention groups. Furthermore, Van Eijk-Hustings et al.(46) also presented the largest difference between numbers of subjects in control group and intervention groups respectively (see table 2). Casanueva-Fernández et al.(45) had the smallest population group (n=34) and additionally the least dropouts (n=6). Overall, the majority of subjects in the studies(45-48) were female, however Castel et al.(48) presented the only study which did not have a single male participant included. Hamnes et al.(47) had the largest amount of male participants in the intervention group. Castel et al.(48) was the only author to have a specific study population ('women with low educational levels').

All participants were over 18 years old, and the mean age varied between the studies(45-48) from 41,6 – 52,18 years old.

Table 2 *Baseline Characteristics of Participants*

Author, year	Number (CG/IG(s)	Gender CG / IG(s)	CG Mean Age ± SD (range)	IG(s) Mean Age ± SD (range)	Dropouts CG/IG(s)
Casanueva-Fernández et al. (45), 2011	n = 34 (17/17)	17F / 16F, 1M	52,18 ± N/A (37-68)	47,46 ± N/A (30-58)	5/1 6 dropouts
Van Eijk-Hustings et al. (46), 2012	n = 203 (48/108(47)	47F, 1M / 101F, 7M(47F)	42,9 ± 11.0 (N/A)	41,6 ± 8.8 (N/A) (43,9 ± 7.6 (N/A))	0/41(28) 69 dropouts
Hamnes et al. (47), 2012	n =147 (72/75)	F72 / F69, M6	49,7 ± 4.0 (N/A)	45,4 ± 9.4 (N/A)	12/17 29 dropouts
Castel et al. (48), 2013	n =155 (74/81)	74F / 81F	48,9 ± 7.2 (26-60)	49,0 ± 6.8 (26-60)	39/28 67 dropouts

Number (CG/IG(s) = Number (Control Group/Intervention Group(s)) CG = control group; IG = intervention group(s), F = female, M = male, ± SD = standard deviation (applied when available), N/A = not available

3.3.3 Interventions

Casanueva-Fernández et al.(45), Van Eijk-Hustings et al.(46) and Castel et al.(48) all had a treatment intervention for the control group, except for Hamnes et al.(47) where the control group were put on a waiting list. See table 3.

Casanueva-Fernández et al.(45) presented a multidisciplinary intervention for the experimental (MD) versus a control group (CG) that continued their current medical treatment. The CG received four 1-hour educational sessions concerning relaxation techniques, CBT, diet, benefits of exercising and medical treatment. The multidisciplinary intervention group received the same initial treatment as the CG, but additionally also weekly 1-hour treatments including massage therapy; ischemic pressure; aerobic exercise; and thermal therapy. The program lasted for 8 weeks, and follow up measurements were taken one month after the end of the treatment(45). Casanueva-Fernández et al.(45) was the only study to have massage therapy and ischemic pressure as a part of the intervention, and it was not stated which practitioners were involved in the experiment(45). (Appendix V)

Van Eijk-Hustings et al.(46) was the only study that had two experimental groups, and the only one with an aftercare program included. The control group (UC) received 'care as usual', containing patient education, lifestyle advice, and could also include a diversity of other treatments such as physiotherapy and social support. The experimental group 'multidisciplinary intervention' (MD) received sociotherapy, physiotherapy, psychotherapy and creative arts therapy. Sociotherapy included patient education, and aimed to increase social behavior strategies and social support. Physiotherapy focused on graded activity and improving physical fitness, functioning and lastly enjoying exercise. It involved aerobic exercise, strength training of arms and legs, different form of relaxation techniques and alternating movement patterns. Both sociotherapy and physiotherapy was given twice a week. Psychotherapy and creative arts therapy was given once a week, and consisted of general information about FMS, pain mechanisms and expressing feelings by visual arts, respectively. MD was the only experimental group that were a part of the 'aftercare program'. The additional experimental group (AE) 'aerobic exercise' received a specific exercise program twice a week. The total duration for both MD and AE was 12 weeks. The aftercare program consisted of five meetings spreading over nine months, aiming to repeat the key messages about coping in order to preserve the behavioral changes achieved in the first phase. Including the follow up measurements (12-24 months) the total study duration was 1 year. A rheumatology nurse (UC) and physiotherapist (AE) were involved in the experiment, however it is not stated what practitioners were involved in the MD group(46). Van Eijk-Hustings et al.(46) was the only study that implemented psychotherapy (appendix VII).

Hamnes et al.(47) presented a one week self-management program. The control group were put on a waiting list, and did not receive any intervention throughout the study. The self-management program consisted of several parts: physiotherapy including exercising and relaxing, exercising in a swimming pool (hydrotherapy), a medical consultation, creative arts therapy, Nordic walking, and patient education regarding diet, stress management, disease and treatment, awareness of own health and everyday life advice. The self-management program was a one-week program, and had follow up measurements taken 3 weeks after post treatment. Total duration time was therefore 4 weeks. A nurse, physiotherapist, rheumatologist, assistant doctor, representatives from patient organizations, occupational therapist, assisting occupational therapist, social worker and dietician were involved in

the program(47). Hamnes et al.(47) was the only study that did not have aerobic exercise explicitly as a part of the treatment program (appendix IX).

Castel et al.(48) presented a conventional pharmacological treatment (CG) versus multidisciplinary treatment (MD). Both the CG and MD received a conventional pharmacological treatment, however this was the only intervention for the CG. The MD additionally received CBT and physiotherapy. CBT included patient education, theory of pain perception, goal setting, management of primary insomnia, assertiveness training, activity pacing, cognitive restructuring skills training, pleasant activity scheduling training and relapse prevention. Home tasks were also given and revised every session. Physiotherapy treatment emphasized aerobic capacity combined with diaphragmatic breathing, muscular strengthening, flexibility, hydrokinesiotherapy, and kinesiotherapy. Both cognitive behavioral therapy and physiotherapy treatment lasted for 1 hour each and was given two days per week, for 12 weeks, resulting in 24 sessions. Home tasks were planned and revised every treatment. Measurements and follow ups were taken until 12-months post treatment, meaning the total duration of the study was 1 year and 2,5 months. Castel et al.(48) was the only author to execute five measurements of outcomes. A psychologist and physiotherapist were involved in the treatment program(48) (appendix XI).

3.4 Outcome Measures and Reported Results

Hamnes et al.(47) and Castel et al.(48) were the only two articles that did not measure fatigue, but only pain. Casanueva-Fernández et al(45). and Van Eijk-Hustings et al.(46) had both pain and fatigue as a part of their outcome measures. All listed P-values are presented as they were in the articles.

Casanueva-Fernández et al.(45) measured both pain and fatigue throughout the study. McGill pain questionnaire (MPQ), Visual Analogue Scale (VAS and The Medical Outcomes Survey Short Form-36 (SF-36) were used to measure pain outcomes. MPQ revealed a between-group significant comparison during follow up measurement at 8^{th} week of treatment ($P<0.0002$) and 1-month post treatment ($P<0.001$). SF-36 showed no between-group significant difference, however the experimental group showed improvement in the 8^{th} week of treatment and 1-month post treatment with 12,53% and 13,57% respectively. VAS was used to obtain information about both pain and fatigue. Neither pain nor fatigue results showed any between-group significant difference, though the experimental group revealed pain improvement at 8^{th} week of treatment with 2,18%, and 1-month post treatment with 15,82%. VAS fatigue showed improved scores at 8^{th} week of treatment with 19,07%, and 1-month post treatment with 15,92%. Notably, 25% of the participants met the requirement (threshold for clinical efficacy set at improvement of 30% or above) listed by Casanueva-Fernández et al.(45) for improvement VAS fatigue. The second fatigue measurement tool was Fatigue Severity Scale (FSS). FSS revealed no between-group significant difference during any times of measurements, however the experimental group had an overall improvement of scores. 8^{th} week of treatment FFS scores were improved with 5,71%, and 1-month post treatment; 13,47%(45).. The improved scores of the

experimental group were all higher than those available from the control group. Casanueva-Fernández et al.(45) concluded that patients with severe FMS refractory to conventional treatments could obtain beneficial results from the multidisciplinary treatment program applied (appendix VI).

Van Eijk-Hustings et al.(46) used only one measurement tool to assess the outcomes of the interventions. Fibromyalgia Impact Questionnaire (FIQ) was applied to detect the impact on FMS on daily functioning for both pain and fatigue. No between-group significant difference was found between neither of the two intervention groups (MD and AE) versus the control group (UC) for pain nor fatigue. However, Van Eijk-Hustings et al.(46) found in the MD group for both pain and fatigue a within-group significant difference during 'endpoint' measurement for the 'intention to treat' and 'per protocol' groups. The AE intervention group improved their scores for both pain and fatigue throughout the study, and so did the MD group, except for between 'after 12-week program' and 'endpoint' where the result remained the same. The UC control group did not improve their scores in pain from 'inflow' to '12-week after program' but at 'endpoint' the score was lower than initially measured at 'inflow'. Regarding fatigue outcomes for UC, there was improvement in results from first two measurements, but results in the final 'endpoint', revealed a result that was higher than initially measured at 'inflow'. Van Eijk Hustings et al.(46) concluded that for patients recently diagnosed with FMS, which comprised of several outcomes of societal relevance, it was not possible to demonstrate significant between-group differences at end of study. Methodological limitations of the study prevented to draw firm conclusion about the effects attributable to the multidisciplinary intervention(46).

Table 3 *Interventions and revealed significant outcomes and improvements*

Author	N	Interventions	TLOS	Outcome effect	Overall Improvement
Casanueva-Fernández et al.(45)	CG (n=17)	Medical treatment and patient education	12.3 weeks	P: NSF F: NSF	P: Yes F: Yes
	MT (n=17)	Medical treatment, patient education, massage therapy, ischemic pressure, aerobic exercise and thermal therapy.	12.3 weeks	P: **SF** F: NSF	P: Yes F: Yes
Van Eijk-Hustings(46)	UC (n=48)	Patient education, lifestyle advice, occasionally also physiotherapy and social support.	52 weeks	P: NSF F: NSF	P: Yes F: Yes
	MD (n=108)	Sociotherapy, physiotherapy, psychotherapy and creative arts therapy.	52 weeks	P: NSF F: NSF	P: Yes F: Yes
	AE (n=47)	Aerobic exercise, home exercises.	52 weeks	P: NSF F: NSF	P: Yes F: Yes
Hamnes et al.(47)	CG (n=72)	Waiting list	4 weeks	P: NSF F: N/A	P: Yes F: N/A
	SMP (n=75)	Self-management program; patient education, physiotherapy, pharmacological therapy, creative arts therapy	4 weeks	P: NSF F: N/A	P: Yes F: N/A
Castel et al.(48)	CG (n=74)	Conventional pharmacological treatment.	64 weeks	P: NSF F: N/A	P: No F: N/A
	MD (n=81)	Conventional pharmacological treatment, CBT, and physical therapy	64 weeks	P: **SF** F: N/A	P: Yes F: N/A

N = number of subjects in control group and intervention groups, TLOS = length of study in weeks, Outcome effect = if a P-value was present, Overall Improvement = If outcome scores were improved or maintained at any point nondependent of a between-group significant difference, CG = control group, MT = multidisciplinary treatment, UC = usual care, MD = multidisciplinary intervention, AE =

aerobic exercise, SMP = self-management program, CBT = cognitive behavioral therapy, NSF = no significant finding, SF = significant finding, N/A = not available.

Hamnes et al.(47) only measured pain and not fatigue throughout the study. The Arthritis Self-Efficacy Scale (ASES) was used as a measurement tool and aimed to detect levels of self-efficacy in relation to pain. No between-group significant difference was found after the one-week intervention was finished or during the follow up measurements, however improvements in scores were detected. SMP's baseline measurements were 50,6 and at post-treatment; 54,8. CG improved the scores as well from baseline measurement to post-treatment, but not as much as SMP (appendix X). Hamnes et al.(47) concluded that for patients with FMS the self-management program had no effect on self-efficacy(47).

Castel et al.(48) used the Numeric Rating Scale (NRS) as a measurement tool, however only pain intensity was assessed during the study, and not fatigue. A between-group significant difference ($P<0.01$) was found between CG and MD at post-treatment measures. No between-group significant difference was found between CG and MD at either baseline, 3-month follow up, 6-month follow up or 12-month follow up. MD group improved their outcome results until the 6-month follow up, and presented a higher result for the 12-month follow up which was almost as high as the initial baseline outcome. The CG improved their score until the 3-month follow up, and presented worsened outcome results till the 12-month follow up (appendix XII). Castel et al.(48) concluded that a multidisciplinary treatment program for FMS that combined the the applied interventions, demonstrated efficacy in the treatment of the key symptoms of FMS and the long-term maintenance of these improvements(48).

3.5 Best Evidence Synthesis

A best evidence synthesis (BES) was performed based on pain and fatigue outcomes using Van Tulder(42). The BES was applied for pain and fatigue separately and was based the levels of evidence presented in appendix IV. The included studies are presented in table 4.

3.5.1 Effectiveness of a multidisciplinary approach on pain outcomes

All the four studies(48-51) included pain levels as part of their outcome measurements. Both Casanueva-Fernández et al.(45) and Castel et al.(48) discovered a between-group significant difference between the control group and intervention group, (respectively $P<0.0002$, $P<0.001$ and $P<0.0$). Hamnes at al.(47) found a within-group difference of $P<0.387$ which was not significant, and Van Eijk-Hustings et al.(46) presented no P-value. All studies(45-48) above were of 'high quality' based on the methodological quality assessment applied via PEDro scale(41). Provided by statistically significant findings in outcome measures in at least two high-quality RCTs (that were not less than 50% of the included studies) with PEDro scores of at least four points, there is 'strong evidence' that a multidisciplinary approach has a positive effect on pain outcomes.

Table 4 *Best Evidence Synthesis on pain and fatigue*

Author	Methodological Quality	Pain outcome	Fatigue Outcome
Casanueva-Fernández et al.(45)	"High quality"	MPQ **P<0.0002** & **P<0.001**	No P-value reported
Van Eijk-Hustings et al.(46)	"High quality"	No P-value reported	No P-value reported
Hamnes et al.(47)	"High quality"	ASES P<0.387 (no statistically significant)	-
Castel et al.(48)	"High quality"	NRS **P<0.01**	-

MPQ = McGill pain questionnaire, ASES = arthritis self-efficacy scale, NRS = numeric rating scale. (P-value is listed as from authors)

3.5.2 Effectiveness of a multidisciplinary approach on fatigue outcomes

Two(45, 46) of the four included studies had fatigue as a part of their outcome measurement, whilst Hamnes et al.(47) and Castel et al.(48) did not. Neither Casanueva-Fernández et al.(45) or Van Eijk-Hustings et al.(46) found a between-group significant difference for fatigue outcomes. Both Casanueva-Fernández et al.(45) and Van Eijk-Hustings et al.(46) were of 'high quality' based on the methodological quality assessment applied via PEDro scale(41). Provided that none of the results of the two evaluated studies(45, 46) met the criteria for either of the levels of evidence, there is 'no, or insufficient evidence' that a multidisciplinary approach has an effect on fatigue outcomes.

The conclusion drawn from BES and the methodological quality of the individual studies(45-48) showed that there is no evidence that a MDA had an effect on patients fatigue outcomes, but that there is strong evidence that a MDA had an effect on pain outcomes for patients with FMS. Considering the small number of articles included in the BES, the effectiveness of pain improvement should be interpreted with caution.

4. Discussion

This aim of this study was to investigate what multidisciplinary approach (MDA) would lead to the best results in regards to pain and fatigue for patients with fibromyalgia syndrome. After a systematic search, four articles(45-48) met the inclusion and exclusion criteria and were further analyzed in a organized manner. All the four articles(45-48) evaluated whether the applied multidisciplinary intervention had an effect on the outcomes of patients diagnosed with FMS. Pain was measured in all four studies(45-48), whereas fatigue was measured in two(45, 46). All studies(45-48) were of high methodological quality according to PEDro scale(41) and in this study were therefore treated equally in the best evidence synthesis (BES)(42). The similarities of the two studies(45, 48) that presented a between-group significant difference in regards to pain outcomes, were that they both included pharmacological treatment, a form of patient education and aerobic exercise. What the four studies(45-48) had in common in terms of applied interventions were patient education, and physiotherapy treatment.

Sarzi-Puttini et al.(2) conducted in 2011, that a multidisciplinary intervention should include pharmacological treatment, exercise, physical therapy and CBT. The utilization of these interventions as part of a multidisciplinary approach have support from other authors as well(3, 5, 13, 21). Castel et al.(48) had all of the recommended interventions included in the multidisciplinary intervention approach. Casanueva-Fernández et al.(45) had three of the listed interventions, but was missing CBT. Notably these two studies had the best outcome results in relation to pain improvement, and therefore it is suggestive that both Casanueva-Fernández et al.(45) and Castel et al.(48) were able to design the two most successful multidisciplinary approaches in comparison with the two other articles(46, 47). Strengths presented by Castel et al.(48) was firstly a larger sample group. Secondly, during CBT, subjects were divided into smaller groups and finally, the physical exercise levels were adapted to individuals during physical therapy sessions(48). Subjects completed a more extensive variety of treatments such as hydrokinesiotherapy, strength training and flexibility exercises. Nonetheless, Casanueva-Fernández et al.(45) was able to present a between-group significant difference at two measurement times throughout the study, whereas Castel et al.(48) presented one. It is however challenging to establish Casanueva-Fernández et al.(45) as the most successful multidisciplinary treatment approach based on significant findings alone. Firstly, because Casanueva-Fernández et al.(45) had the study with the lowest number of participants. Secondly, neither CBT, strength training nor hydrotherapy were included, which is seemingly odd considering recommendations for these interventions have existed since 2008. Thirdly, no between-group significant difference was established for fatigue(45). Both studies(45, 48) presented a somewhat short duration time, which could have an be the reason why they were not able to detect any changes in fatigue outcomes.

Compared with the interventions suggested by Sarzi-Puttini et al.(2), Van Eijk-Hustings et al.(46) did not include pharmacological treatment or CBT. Notably Sarzi-Puttini et al.(2) stated in the same article that: “psychological and physical therapy may sometimes be more effective than pharmacological treatment”, which is exactly what separates Van Eijk-Hustings et al.(46) from the other three(45, 47, 48) included articles, but unfortunately without statistical significant improvement for pain and fatigue outcomes. Castel et al.(48) and Van Eijk-Hustings et al.(46) were the only two studies to include strength training as an intervention. Vaughn et al.(16) concluded that there are possibly further additional advantages of including extremity strengthening exercises in a multidisciplinary treatment approach. Burwinkle et al.(49) described in 2005 that “FMS patients seem to avoid exercising because they fear pain following physical activities”. This could explain why Van Eijk-Hustings et al.(46) had 69 dropouts after subjects were informed about the intervention group they had been allocated to. Sarzi-Puttini et al.(2) suggested that moderate exercise could be more beneficial for deconditioned FMS patients. In other words there are suggestions that support the positive effects of strength training as a part of a multidisciplinary treatment approach, though perhaps not aimed at deconditioned FMS patients. The presented evidence seems to be conflicting and it appears that the treatment effect depends to a large extent on patients fear of movement, and the patients’ willingness to participate in developing their own physical health.

Hamnes et al.(47), similar to Casanueva-Fernández et al.(45) included three of the interventions recommended by Sarzi-Puttini et al.(2) except for CBT, although several other behavioral-management strategies were applied. In 2013, Vincent et al.(9) conducted a clinical feasibility assessment of a 1-week multimodal multidisciplinary fibromyalgia program based on self-management, CBT, active pacing and graded exercise activity. At the end of the program, Vincent et al.(9) discovered a statistical significance for fatigue improvement. It is not clear what is the cause of Hamnes et al.(47) not being able to significantly improve patients pain or fatigue levels, but it questions the importance of the role of CBT in the ideal MDA.

Improving patients' pain levels was somewhat accomplished throughout all the articles included(45-48) in this systematic literature review, however fatigue outcomes were raised to a significant level. Ericsson et al.(50) suggested in 2007 that fatigue should not be evaluated as a coherent whole, but split up into more specific parts such as 'general fatigue, 'physical fatigue' and 'mental fatigue'. This could make it possible for practitioners to evaluate what parts of fatigue were more inclined to improve as a results of the applied interventions. Researchers could structure their interventions in line with the different aspects of fatigue and aim to achieve superior results focused on one fatigue aspect at a time. Practitioners would have the ability to monitor fatigue at more detailed levels and apply for example: CBT to help with 'mental fatigue' instead of aerobic exercise. It is questionable whether the authors(45-48) of the studies have underestimated the complexity of fatigue for patients with FMS, considering it is one of the worst reported symptoms of FMS(10).

It is plausible that an attentive team of physiotherapists, psychologists, occupational therapists and general practitioner could apply a strategic plan to positively effect a fibromyalgia patient's understanding of pain, attitudes and motivation to affect own health. It is also arguable that group-training could help the results of these strategies. Studies with smaller population groups give patients the ability to get to know one-another better and the possibility of better cooperation and group-atmosphere, whereas larger sample groups might make this harder for patients whom are withdrawn or shy. Additionally, in a large sample group it could be harder for practitioners to pay enough attention to the subjects, give accurate feedback and correction. On the contrary, a larger sample group provides statistically stronger results. An additional factor that could impact the results is the patients' own health journal. Finding patients affected by FMS without other serious comorbidities could be challenging as fibromyalgia syndrome is often part of larger health picture containing several other diagnoses(51). Castel et al.(48) was in fact the only author in this systematic literature review to include serious comorbidities as part of the exclusion criteria. Giving treatment interventions to patients diagnosed with FMS whom also have other comorbidities is undeniably challenging because of the larger list of factors to be considered. This may affect the homogeneity of the sample being researched and therefore will affect the reliability and relevance of any resulting outcome.

Tailoring a treatment intervention that suits a larger sample group of patients diagnosed with FMS is not an easy process. Even though patients might be similar in regards to baseline characteristics, that

does not mean they present similar attitudes and motivation to participate towards the improvement of their own health status. For example, patients may come from different social backgrounds and experience dissimilar pain thresholds. These are only two of the many causes that could be of importance in regards to implementing a treatment regime. A multidisciplinary treatment program could benefit from dividing the subjects into smaller groups based on condition and motivation levels(52), which could make it easier to track what groups were able to improve their outcomes the most and what interventions work best for the different patient types. Between the multidisciplinary treatment approaches investigated(45-48) in this review, it becomes clear that certain interventions appear to be critical parts of successful multidisciplinary approaches. These include patient education, physical therapy, CBT and pharmacological interventions. However, enough strong evidence has not been established, and therefore it is not possible to determine the ideal approach to achieve optimal patient outcomes.

4.1 Strengths and Limitations

The strengths of this systematic literature review was that articles were extracted from a broad list of databases after conducting extensive research. The inclusion and exclusion criteria led to the relevant literature being located through a systematic search string. The strict criteria made it possible to investigate outcomes of the two most problematic symptoms of FMS, which is possibly the most serious and difficult symptoms to evaluate. The four included articles(45-48) presented high methodological quality, and obtained different variations of a multidisciplinary treatment approach which was an opportunity to explore the distinctive treatments applied. This study was able to provide an in-depth overview of the interventions utilized by the different authors, and what the outcomes these interventions yielded. On the contrary, the limitations of this systematic literature review were primarily the small amount of articles deemed to be eligible by the inclusion and exclusion criteria. Even though the methodological quality was established as ‘high’ in the included articles, the researcher was unexperienced using the PEDro scale and BES. The final PEDro scores could have been more reliable if non-involved parties had evaluated the articles separately and an average score was drawn from their results. Even though being a strength, only investigating the outcomes for pain and fatigue presents also a limitation. Positive outcomes from articles were overlooked due to not being relevant for this study, but does not necessarily indicate that the approach itself was not successful based on the overall treatment applied towards patients diagnosed with FMS.

4.2 Conclusion with Recommendations for Further Research

Preliminary findings suggest that patient education, cognitive behavioral therapy, aerobic exercise and physical therapy may be combined effectively with pharmacological interventions as part of a multidisciplinary approach to yield optimal patient outcomes in measurements of pain and possibly fatigue. Based on current research, it is not possible to determine what is the most effective multidisciplinary treatment approach for patients with fibromyalgia syndrome based on the outcomes

pain and fatigue. Therefore, more studies are recommended to investigate the most optimal approach to effect these outcomes.

A recommendation for further research is to include a large sample group of FMS patients, and firstly divide the subjects based on baseline characteristics, age, gender, physical level, comorbidities and possibly even include a questionnaire regarding motivation to record patients' willingness to partake in the treatment. This could give the researcher an opportunity to modify treatment of a patient group that is for example extremely pessimistic. Treatment duration is recommended to be minimum 12 weeks. Treatment approaches that should be included is pharmacological therapy, exercise (either aerobic and or strength training), physiotherapy and CBT. Considering the large amount interventions that have been investigated on FMS patients without a MDA, the researcher has a variety of options regarding what treatment interventions to include. It would be very interesting to see if FMS patients had greater benefit of a MDA that also contained rhythmic dancing or team-sports, however this has not yet been investigated. Additionally, it might be beneficial for further researchers to include an overview over the practitioners involved, so that it is clear for interested practitioners what role they should partake if wanting to base real treatment sessions on the explored research. Regarding fatigue, research could benefit from dividing the established three aspects. This could provide a larger interpretation of the changes that occur in fatigue for a FMS diagnosed patient. These are the recommendations that could lead to more developed multidisciplinary approach aiming to minimize key symptoms of FMS.

5. Literature

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6. Appendix

I. American College of Rheumatology, FMS Criteria, 1990, 2010 and 2011

In February 1990, 'The American College of Rheumatology (ACR) 1990 criteria' was developed for the classification of fibromyalgia(3, 21, 28). The criteria were 1. Widespread pain *in combination with* 2. Tenderness at 11 or more of the specific 18 tender point sites. No exclusions were made with the presence of associated radiographic or laboratory abnormalities. Widespread pain (WSP) had to be felt for at least 3 consecutive months, and FMS was not to be excluded if in combination with other clinical disorders. Pain was considered widespread when felt at both sides of the body, as well as above and below the waist. In addition, axial skeletal pain (cervical spine, anterior chest, thoracic spine or low back) had to be present. The tender points had to be examined with approximately 4 kilograms of pressure(28)

Table 5 *American College of Rheumatology 1990, Tender Point Criteria (28)*

Anatomical Location	Details
Occiput	Bilateral, at sub-occipital muscle insertion
Low Cervical	Bilateral, at anterior aspects of intertransverse spaces at C5-C7
Trapezius	Bilateral, at the midpoint of the upper border
Supraspinatus	Bilateral, at origins, above the scapula spine near the medial border
Second Rib	Bilateral, at the second costochondral junctions, just lateral to the junctions on upper surfaces
Lateral Epicondyle	Bilateral, 2 cm distal to the epicondyle
Gluteal	Bilateral, upper outer quadrants of buttocks in anterior fold of muscle
Greater Trochanter	Bilateral, posterior to the trochanteric prominence
Knee	Bilateral, at the medial fat pad proximal to the joint line.

The ACR criteria was updated for the first time in 2010(5). The tender point count was eliminated, and a patient questionnaire with 2 scales, symptom severity score (SSS) and widespread pain index (WPI) was added. A numerical score was developed to determine the diagnosis of FMS(5). In 2011 the ACR criteria was updated again, and this time the WPI was expanded and the physician estimate of the somatic symptoms was eliminated. A new FMS symptom scale was developed and included 19 pain locations and 6 self-reported symptoms (including fatigue, headache, difficulty sleeping, headache, abdominal pain and depression)(5, 19)

II. FDA approved drugs for FMS treatment

Table 6 *Overview of Food and Drug Association approved drugs for FMS treatment (5)*

Drug	**Detail**	**Side Effect**
Pregabalin	Mechanism of action is that of a voltage-gated calcium channel blockade at the α2 delta submit modulation of nerve terminal calcium influx by inhibition of excitatory neurotransmitters.	Peripheral edema, ataxia, somnolence, dizziness, fatigue, cephalalgia, weight gain, xerostomia, visual blurriness, abnormal cognition, memory deficits, drunk feeling, constipation, euphoria, increased appetite, thrombocytopenia, asthenia, visual disturbance, and depression.
Duloxetine	Mechanism of action is attributed to monoamine reuptake inhibition of serotonin, norepinephrine and dopamine.	Headache, dose-related drowsiness, nausea and xerostomia, ataxia, diaphoresis, decreased appetite, emesis, platelet aggregation and hyponatremia.
Milnasipran	Mechanism of action are strong norepinephrine reuptake, and serotonin reuptake. May be beneficial in patients with asthenia and fatigue not responding to Duloxetine.	Insomnia, cephalalgia, hot flashes, nausea, constipation, increased heart rate, palpitations, dizziness, and emesis.

III. PEDro Scale Assessment.

Below is the downloaded version of PEDro score showing the different criteria(41).

PEDro scale

1.	eligibility criteria were specified	no ❑ yes ❑ where:
2.	subjects were randomly allocated to groups (in a crossover study, subjects were randomly allocated an order in which treatments were received)	no ❑ yes ❑ where:
3.	allocation was concealed	no ❑ yes ❑ where:
4.	the groups were similar at baseline regarding the most important prognostic indicators	no ❑ yes ❑ where:
5.	there was blinding of all subjects	no ❑ yes ❑ where:
6.	there was blinding of all therapists who administered the therapy	no ❑ yes ❑ where:
7.	there was blinding of all assessors who measured at least one key outcome	no ❑ yes ❑ where:
8.	measures of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups	no ❑ yes ❑ where:
9.	all subjects for whom outcome measures were available received the treatment or control condition as allocated or, where this was not the case, data for at least one key outcome was analysed by "intention to treat"	no ❑ yes ❑ where:
10.	the results of between-group statistical comparisons are reported for at least one key outcome	no ❑ yes ❑ where:
11.	the study provides both point measures and measures of variability for at least one key outcome	no ❑ yes ❑ where:

The PEDro scale is based on the Delphi list developed by Verhagen and colleagues at the Department of Epidemiology, University of Maastricht (*Verhagen AP et al (1998). The Delphi list: a criteria list for quality assessment of randomised clinical trials for conducting systematic reviews developed by Delphi consensus. Journal of Clinical Epidemiology, 51(12):1235-41*). The list is based on "expert consensus" not, for the most part, on empirical data. Two additional items not on the Delphi list (PEDro scale items 8 and 10) have been included in the PEDro scale. As more empirical data comes to hand it may become possible to "weight" scale items so that the PEDro score reflects the importance of individual scale items.

The purpose of the PEDro scale is to help the users of the PEDro database rapidly identify which of the known or suspected randomised clinical trials (ie RCTs or CCTs) archived on the PEDro database are likely to be internally valid (criteria 2-9), and could have sufficient statistical information to make their results interpretable (criteria 10-11). An additional criterion (criterion 1) that relates to the external validity (or "generalisability" or "applicability" of the trial) has been retained so that the Delphi list is complete, but this criterion will not be used to calculate the PEDro score reported on the PEDro web site.

The PEDro scale should not be used as a measure of the "validity" of a study's conclusions. In particular, we caution users of the PEDro scale that studies which show significant treatment effects and which score highly on the PEDro scale do not necessarily provide evidence that the treatment is clinically useful. Additional considerations include whether the treatment effect was big enough to be clinically worthwhile, whether the positive effects of the treatment outweigh its negative effects, and the cost-effectiveness of the treatment. The scale should not be used to compare the "quality" of trials performed in different areas of therapy, primarily because it is not possible to satisfy all scale items in some areas of physiotherapy practice.

Last amended June 21st, 1999

IV. Van Tulder, Best Evidence Synthesis

Table 7 *BES based on Van Tulder(42)*

Van Tulder		**Yes**	**No**
Strong Evidence	Provided by statistically significant findings in outcome measures in at least 2 high-quality randomized controlled trials (RCTs) with PEDro scores of at least 4 points*		
Moderate Evidence	Provided by statistically significant findings in outcome measures in at least 1 high-quality RCT and at least 1 low-quality RCT (< 3 points on PEDro) or high-quality CCT.		
Limited Evidence	Provided by statistically significant findings in outcome measures in at least 1 high-quality RCT or at least two high-quality CCTs (in the absence of high-quality RCTs)*		
Indicative Findings	Provided by statistically significant findings in outcome measures in at least 1 high-quality CCT or low-quality RCT (in the absence of high-quality RCTs), or two studies of a non-experimental nature with sufficient quality (in absence of RCTs and CCTs)*		
No/Insufficient Evidence	If the number of studies that have significant findings is <50% of the total number of studies found within the same category of methodological quality and study design.		
	OR In case the results of eligible studies do not meet the criteria for one of the above stated levels of evidence.		
	OR In case of conflicting (statistically significantly positive and statistically significantly negative) results between RCTs and CCT's.		
	OR In case of no eligible studies.		
	'*' if the number of studies that show evidence is < 50% of the total number of studies found within the same category of methodological quality and studying design (RCT, CCT or non-experimental studies), no evidence will be classified		

V. Casanueva-Fernández et al. study details

Table 8 *Study details by Casanueva-Fernández et al.(45)*

Author	Casanueva-Fernández et al.**(45)**
Year	2011
Name of study	*"Efficacy of a multidisciplinary treatment program in patients with severe fibromyalgia"*
Number of participants	34 (17 in control group, and 17 in intervention group, 6 dropouts)
Control Group Called C/E	Continued current medical treatment, (not modified during the study). Received patient education sessions concerning relaxation techniques, cognitive behavior therapy, diet and benefits from exercise in FM patients.
Intervention Group Called MT	Continued current medical treatment and had 4 educational sessions (same as control group) Additional weekly 1-h session for 8 weeks including: - Massage therapy: combination of superficial strokes, deep pressure and kneading upon the spinal column for 15 minutes. - Ischemic pressure: Direct and maintained pressure upon the 18 tender points for a maximum of 1 min per point, during a total time of about 25 minutes. - Aerobic exercise: using a stationary bicycle for 5 min and a treadmill for 5 min. - Thermal therapy using convective heat transfer with a 250-W infrared heat lamp for 10 min.
Frequency /duration	C/G: 4 1-hour patient education sessions. MT: 4 1-hour patient education session, plus weekly 1-hour intervention sessions for 8 weeks. All interventions make up 60 minutes. In total it took 12.3 weeks to finish the study. (8 weeks of treatment, + follow up 1 month (4.3 weeks) after treatment ended = 12.3)
Initial measurements & follow ups	1. Initial measurements done at beginning of study, 2. 8 weeks later (end of treatment) 3. 1 month later (1 month after end of treatment
Pain measurement details	1. VAS Pain. Visual Analogue Scale is a 100mm horizontal long line starting from 'no pain' to 'severe pain'. Patient draws a line at the spot he/she feels resembles the pain experienced. 2. Mc Gill pain questionnaire (MGP). A 66 descriptors about pain, that assesses both quality and intensity of subjective pain. 3. The Medical Outcomes Survey Short Form-36 (SF-36). SF-36 patient reported survey of 36 items used to assess patient health. F-36 is used to study medical outcomes. The range of scores for each dimension varies from 0-100. (100 equalizes no disability)
Fatigue measurement details	1. VAS Fatigue (Visual Analogue Scale) 2. Fatigue Severity Scale (FSS). FSS is a self-reported composed of 9 items with a 7-point response scale, where 1 = strongly disagree and 7 = strongly agree. Score can be calculated out as a mean where the minimum score is 1 and the maximum score is 7.
Result of study	1. VAS Pain: No significant findings. 2. MGP: No significant findings. 3. SF-36: No significant findings. 4. VAS fatigue: No significant findings for all phases. (However 25% of patients had more than 30% improvement in VAS Fatigue) 5. FSS: No significant findings for all phases.

VI. Casanueva-Fernández et al. pain and fatigue outcomes in detail

Below are two illustrative tables demonstrating the different control and intervention groups with the number of participants involved from the study by Casanueva-Fernández et al.(45). Pain/Fatigue measurement tools are listed in code words, and more information about VAS (visual analogue scale), MGP (McGill Pain Questionnaire), SF-36 (Survey Short Form-36) and FFS (Fatigue Severity Scale) can be found in Appendix V study details. 'Mean of parameters at start', '% improvement after 8th week of treatment' and '% improvement at 1-month from treatment completion' are the times measurements were taken.

Pain outcomes:

Table 9 *Pain outcomes by Casanueva-Fernández et al.(45)*

Intervention Groups	Pain Outcomes	Mean of parameters at start	% improvement after 8th week of treatment	% Improvement at 1-month from treatment completion
CG (n = 12)	VAS	6,82	N/A	13,75
	MGP	37,15	N/A	N/A
	SF-36	36,91	N/A	12,97
MT (n = 16)	VAS	7,71	2,18	15,82
	MGP	40,5	**28,81***	**26,6***
	SF-36	36,33	12,53	13,57

Numbers marked in bold with a '*' indicate a P-value of P<0.0002, '**' indicate a P-value of P<0.001, MT = multidisciplinary treatment, CG = control group, VAS = visual analogue scale, MGP = McGill pain questionnaire, SF-36 = medical outcome survey short form-36, ± = standard deviation (applied when available), N/A = not available

Fatigue outcomes:

Table 10 *Fatigue outcomes by Casanueva-Fernández et al.(45)*

Intervention Groups	Fatigue Outcomes	Mean of parameters at start	% improvement after 8th week of treatment	% Improvement at 1 month from treatment completion
CG (n = 12)	VAS	7,19	N/A	7,59
	FSS	6,24	N/A	0,87
MT (n = 16)	VAS	8,31	19,07	15,92
	FSS	6,34	5,71	13,47

Numbers marked in bold with a '*' indicate a P-value of P<0.0002, '**' indicate a P-value of P<0.001. MT = multidisciplinary treatment, CG = control group, VAS = visual analogue scale, FSS = fibromyalgia severity scale, ± = standard deviation (applied when available), N/A = not available

VII. Van Eijk-Hustings et al. study details

Table 11 *Study details by Van Eijk-Hustings et al.(46)*

Author	Van Eijk-Hustings et al.**(46)**
Year	2012
Name of study	*"Challenges in demonstrating the effectiveness of multidisciplinary treatment on quality of life, participation, and health care utilization in patients with fibromyalgia: a randomized controlled trial."*
Number of participants	203 (UC n=48, MD=108, AE=47, 69 dropouts)
Control Group Called UC	Control Group: Usual Care (UC) Received care as usual that comprised at least individualized education about FMS and lifestyle advice by a rheumatologist or a specialized rheumatology nurse (RN) within one or two consultations, but could also include a diversity of other treatments such as physiotherapy or social support from the RN.
Intervention Group Called MD	Multidisciplinary Intervention (MD) was divided into 2 phases. MD Phase 1: 1. Sociotherapy: Given twice a week at the start and at the end of the week. Included education and connected the parts of the program. It was based on transactional analysis and aimed to increase social behavior strategies and social support. 2. Physiotherapy: Given twice a week. Focused on graded activity, based on time-contingent instead of pain-contingent training and aimed to improve physical fitness and functioning and at learning to enjoy exercise. Involving aerobic exercise, strength training of the arms and legs, different forms of relaxation and exercises focusing on alternative patterns of movement in order to improve awareness and reduce muscle tone during daylily activities. 3. Psychotherapy: Given once a week and consisted of general information about FM and pain mechanisms. Methods of core qualities, rational emotive therapy and transactional analysis were used in the sessions. 4. Creative Arts Therapy: Given once a week and focused on the opportunity to express feelings by visual arts instead of verbal expressions. MD Phase 2, Aftercare program: 1. The purpose of these meetings was to repeat the key messaged about coping in order to preserve the behavioral change achieved in Phase 1.
Intervention Group Called AE	Aerobic Exercise (AE) 1. Warm Up: 10 min, comprising AE and stretching, 2. Aerobic Part. 30 min, low intensity aimed to reach 55-64% of the predicted max HR. Patients monitored their own HR after the warm-up and after the aerobic part a few times during the course, and was asked to communicate to the trainer if the intensity was sufficient. 3. Resistance training was applied during 15 min to strengthen major muscle groups. The intensity of the resistance training increased in weights, frequency and tempo. 4. Cool Down: Every session was finished with a 5 min cool down. 5. Digital Video: Every patient was given a digital video disc presenting exercises to do at home, and were advised to do them once a week. The home exercises were not monitored.

Frequency /duration	MD: 12 week course /3,5 days per week + 5 aftercare meetings in 9 months. AE: Twice a week for 12 weeks. UC: Varied, but incorporated at least education and lifestyle advice. Total follow up duration of the study was 12-24 months. In total it took 1 year to complete the study.
Initial measurements & follow ups	1. Inflow 2. After the 12-week program 3. 18-months after end of program /endpoint
Pain measurement details	Fibromyalgia Impact Questionnaire (FIQ) was used. It is a 10-item multidimensional instrument on function in the past weeks. (0-10 score, total score 100) Pain is listed from 0-10 where lower is better
Fatigue measurement details	Fibromyalgia Impact Questionnaire (FIQ) was used. It is a 10-item multidimensional instrument on function in the past weeks. (0-10 score, total score 100) Fatigue is listed from 0-10 where lower is better
Result of study	FIQ: Both fatigue and pain outcomes demonstrated a statistical significant difference ($P<0.05$) at the Endpoint follow up. All other measurements showed NS.

N/S = no statistical significant finding

VIII. Van Eijk-Hustings et al. pain and fatigue outcomes in detail

Below are two illustrative tables demonstrating the different control and intervention groups with the number of participants involved(46). 'ITT' represents 'intention to treat' group, whereas 'PP' stands for 'per protocol'. Pain/Fatigue measurement tools are listed in code words, and more information about FIQ (fibromyalgia impact questionnaire) can be found in Appendix VII, Intervention Details. 'Inflow', 'after 12-week program' and 'endpoint' are the times measurements were taken.

Pain outcomes:

Table 12 *Pain outcomes by Van Eijk-Hustings et al.(46)*

Intervention Groups	Pain Outcomes	Inflow	After 12-week program	Endpoint
MD: PP (n = 67)	FIQ	6,3 ± 0,2	5,4 ± 0,2	5,4 ± 0,3^
MD: ITT (n = 108)	FIQ	6,3 ± 0,2	5,5 ± 0,2	5,4 ±0,3^^
AE: PP (n= 19)	FIQ	6,1 ± 0,3	5,3 ± 0,4	4,2 ± 0,5
AE: ITT (n = 47	FIQ	6,2 ± 0,26	5,3 ± 0,31	5,2 ± 0,37
UC (n = 48)	FIQ	5,5 ± 0,3	5,7 ± 0,3	5,3 ± 0,3

Numbers marked with a '^' indicate a within-group significant difference, Numbers marked with '^^' indicate a within-group significant P-value of P<0.001, MD = multidisciplinary intervention, AE = aerobic exercise, UC = usual care, ± = standard deviation (applied when available), FIQ = fibromyalgia impact questionnaire

Fatigue outcomes:

Table 13 *Fatigue outcomes by Van Eijk-Hustings et al.(46)*

Intervention Groups	Fatigue Outcomes	Inflow	After 12-week program	Endpoint
MD: PP (n = 67)	FIQ	8,3 ± 0,2	7,4 ± 0,3	7,2 ± 0,3^
MD: ITT (n = 108)	FIQ	8,3 ± 0,2	7,5 ± 0,2	7,0 ± 0,3^^
AE: PP (n= 19)	FIQ	7,7 ± 0,3	7,2 ± 0,5	6,0 ± 0,6
AE: ITT (47)	FIQ	8,0 ± 0,2	7,4 ± 0,23	7,0 ± 0,4
UC (n = 48)	FIQ	7,4 ± 0,3	7,2 ± 0,3	7,5 ± 0,4

Numbers marked with a '^' indicate a within-group significant difference, Numbers marked with '^^' indicate a within-group significant P-value of P<0.001, MD = multidisciplinary intervention, AE = aerobic exercise, UC = usual care, ± = standard deviation (applied when available), FIQ = fibromyalgia impact questionnaire

IX. Hamnes et al. study details

Table 14 *Study details by Hamnes et al.(47)*

Author	Hamnes et al.**(47)**
Year	2012
Name of study	*"Effects of a one week multidisciplinary inpatient self-management programme for patients with fibromyalgia: a randomised controlled trial"*
Number of participants	147 (CG = 72, SMP = 75, 29 dropouts)
Control Group Called CG	Control Group: Waiting list: no intervention was given.
Intervention Group Called SMP	A one-week self-management multidisciplinary intervention (self-management program: SMP) based on 6 interrelated concepts which are central in patient education; the participants learning abilities; pedagogical framework(s); teaching goals; contents; learning/teaching methods and evaluation. The week was set up as following: 1. Sunday evening: 1.1 Introduction by a nurse (N), welcoming and introducing, and preparing subject for following week. 2. Monday: 2.1 N discussing expectations, diagnosis, personal goals. 2.2 Exercises in a swimming pool with a physiotherapist (PT) 2.3 Medical consultation by a rheumatologist (RT) and an assistant doctor (AD). 3. Tuesday: 3.1 N teaching about stressors and awareness about triggers, also including individual exercises and group discussions. 3.2 Exercising and relaxing held by a PT. 3.3 A RT teaching and discussing about disease and treatment. 3.4 Representatives from patient organizations present themselves as an external resource. 4. Wednesday: 4.1 N holds self-management discussions and teachings. 4.2 Assisting occupational therapist (AOT) take group walking. 4.3 Occupational Therapist (OT) teach about own health and prioritization of energy and daily activities. 4.4 AOT takes group on a tour to museum or do a creative activity. 5. Thursday: 5.1 A social worker teaches and discusses health and social welfare. 5.2 AOT takes subjects Nordic walking in groups to try new activities. 5.3 OT demonstrates, teaches and discusses about ergonomics, aids and regulations of activity. 6. Friday: 6.1 Dietician talks about nutrition, digestion, nutritional supplements & intolerance. Promotes positive attitudes towards healthy eating. 6.2 N assesses the end of the program through an oral and written evaluation. Subjects discuss their experiences from SMP. 7. Monday, Tuesday, Thursday evening 7.1 Group sessions in smaller groups held by health- care professionals to articulate how it is to live with FMS and find new coping strategies.
Frequency /duration	Total of 1 week: 1. 1.1: 1 hour 2. 2.1: 2.5 hours. 2.2: 0.5 hours. 2.3: 0.5 hours. 3. 3.1: 1 hour. 3.2: 1 hour 3.3: 2 hours. 3.4: 1 hour

	4. 4.1: 2.5 hours. 4.2: 0.5 hours. 4.3: 1 hour. 4.4: 1.25 hour. 5. 5.1: 2.5 hours. 5.2: 0.5 hours. 5.3: 1.25 hours. 6. 6.1: 2 hours. 6.2: 0.5 hours. 7. 7.1: 1 hour. Total duration of the study was 4 weeks, (study: 1 week, 3 week follow up = 4 weeks).
Initial measurements & follow ups	1. Inclusion before randomization (baseline 1) 2. before the SMP (baseline 2) 3. 3 weeks after SMP
Pain measurement details	The Arthritis Self-Efficacy scale (ASES), has been developed to measure perceived self-efficacy in people with arthritis and captures how confident an individual feel in managing symptoms such as pain, functional limitations and emotional issues. It includes three subscales for pain, functioning and other symptoms. Each item is scored from 10 (very uncertain) to 100 (very certain).
Result of study	Pain measurement showed P value to be P<0.387 at end of SMP week.

CG = control group, IG = intervention group, F/D = frequency and duration, IM = initial measurements, PM = pain measurement, FM = fatigue measurement, NS = no significant difference

X. Hamnes et al. pain outcomes in detail

Below is one illustrative table demonstrating the control and intervention group, with their respective numbers of participants involved(47). Pain measurement used is listed as a code word (ASES) and can be read more about in the 'study details' section in Appendix IX. 'Baseline' and 'post treatment' follow up are the times measurements were taken.

Pain outcomes

Table 15 *Pain outcomes by Hamnes et al.*

Intervention Groups	Pain Outcomes	Baseline	Post treatment
SMP (n = 75)	ASES	50,6 (18.0-82.0)	54,8 (16.0-94.0)
CG (n= 72)	ASES	51,4 (10.0-98.0)	52,3 (10.0-82.0)

SMP = self-management program, CG = control group, ± = standard deviation (applied when available), ASEP = arthrities self-efficacy pain.

XI. Castel et al. study details

Table 16 *Study details by Castel et al.(48)*

Author	Castel et al.**(48)**
Year	2013
Name of study	*"Efficacy of a Multidisciplinary Fibromyalgia Treatment Adapted for Women With Low Educational Levels: A Randomized Controlled Trial"*
Number of participants	155 (CG n=74, MD n=81, 67 dropouts)
Control Group Called CG	Conventional Pharmacologic treatment (CPT) Essentially included analgesics, antidepressants (tricyclics, selective serotonin reuptake inhibitors, and dual reuptake inhibitors), benzodiazepine, and nonbenzodiazepine hypnotics. Pharmacological treatment started just after baseline measurements were taken, and re-assessed again after each follow up (3rd, 6th and 12th month post-treatment)
Intervention Group Called MD	Multidisciplinary treatment: (MDT) Received same conventional pharmacological therapy as control group, plus cognitive behavioral therapy (CBT) and physical therapy. The CBT program included information about FM, theory of pain perception, cognitive restructuring skills training, CBT for primary insomnia, assertiveness training, goal setting, activity pacing and pleasant activity scheduling training, life values and relapse prevention. Home tasks were planned and revised every session. The physical therapy (PT) treatment emphasized aerobic capacity, muscular strengthening, and flexibility and alternated with sessions of hydrokinesiotherapy and kinesiotherapy in a gymnasium. All of the sessions included overall aerobic work, coordination exercises and flexibility exercises. The difficulty of the exercises was individually tailored and progressively increased through the use of resistance media and a slow execution velocity. During the PT sessions, the participants practiced Schultz autogenic training. The sessions of hydrokinesiotherapy were conducted in a heated pool a 30°C. Each session started with global aerobic exercise combined with diaphragmatic breathing. Afterward, exercises to coordinate the upper and lower extremities followed. Finally, the session ended with relaxation exercises and gentle stretching of the thorax muscle groups and extremities. Each session of kinesiotherapy in a gymnasium started with a breath awareness of the work of pelvic floor muscles. Afterward, exercises that reinforce lumbar stabilization and lumbar-pelvic dissociation followed. Finally, each session ended with training of the deep cervical muscles. The intensity of each exercise was adapted to the patient because of the variability of physical conditions. PT was supplemented with an exercise routine between sessions and a scheduled daily march to facilitate the incorporation of the regular exercise into daily life.
Frequency /duration	MDT: 24 sessions, 2 days per week, = 12 weeks (2,7 months) Contained 1 hour of CBT and 1 hour of physical therapy per week. Treatment intervention lasted for 12 weeks, but including the follow ups, the total study duration was 1 year and 2,7 months.
Initial measurements & follow ups	1. Baseline 2. Posttreatment 3. 3-month follow up 4. 6-month follow up 5. 12-month follow up
Pain measurement details	NRS (numerical rating scale, 1-10) listing maximum, minimum and usual intensities of pain experienced in the last week. 1 is the lowest and 10 the highest imagining pain.
Fatigue measurement details	N/A
Result of study	Posttreatment follow up data showed significant statistical difference between MDT and CTP P<0.01

N/A = not available

XII. Castel et al. pain outcomes in detail

Below is one illustrative table demonstrating the control and intervention group, with their respective numbers of participants involved(48). Pain measurement used is listed as a code word (NRS) and can be read more about in the 'Intervention details' section in Appendix XI. 'Baseline', 'Posttreatment', '3-month follow up', '6-month follow up' and '12-month follow up' are the times measurements were taken.

Pain outcomes:

Table 17 *Pain outcomes by Castel et al(48)*

Intervention Groups	Pain Outcomes	Baseline	Post treatment	3-month follow up	6-month follow up	12-month follow up
CPT (n = 74)	NRS	7,1 ± 1,6	6,9 ± 1,8	6,8 ± 1,8	7,0 ± 1,9	7,1 ± 1,8
MDT (n = 81)	NRS	6,8 ± 1,4	**5,7 ± 1,9***	6,4 ± 1,9	6,4 ± 1,9	6,7 ± 1,6

Numbers marked in bold with a '*', indicate a P-value of P<0.01, CPT = Conventional pharmacological therapy, MDT = Multidisciplinary treatment, ± = standard deviation (applied when available), NRS = Numerical Rating Scale

XIII. Methodological quality assessment of the studies assessed by PEDro Scale

Below is a table demonstrating the scores the included articles received after being assessed by PEDro scale.

Table 18 *Methodological quality of the studies assessed by the PEDro Scale*

Author	1	2	3	4	5	6	7	8	9	10	11	TPS
Casanueva-Fernández et al.(2011) (45)	N	Y	N	Y	Y	N	Y	Y	N	Y	N	6/10
Van Eijk-Hustings et al. (2012) (46)	Y	Y	Y	Y	N	N	N	Y	Y	Y	Y	7/10
Hamnes et al. (2012) (47)	Y	Y	Y	Y	N	N	N	Y	N	Y	N	5/10
Castel et al (2013) (48)	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	8/10

Y = yes, N = No, 1st item '1' is not part of the total PEDro score, neither the letters underlined in the same section.