# What kind of exercise is best in fibromyalgia therapeutic programmes? A practical review

M. Cazzola<sup>1</sup>, F. Atzeni<sup>2</sup>, F. Salaffi<sup>3</sup>, S. Stisi<sup>4</sup>, G. Cassisi<sup>5</sup>, P. Sarzi-Puttini<sup>2</sup>

<sup>1</sup>Unit of Rehabilitation Medicine, "Ospedale di Circolo" Busto Arsizio, Presidio di Saronno, Italy; <sup>2</sup>Rheumatology Unit, Luigi Sacco University Hospital, Milan, Italy; <sup>3</sup>Department of Rheumatology, Polytechnic University of the Marche Region, Ancona, Italy; <sup>4</sup>Department of Rheumatology, Azienda Ospedaliera "G. Rummo", Benevento, Italy; <sup>5</sup>Rheumatology Branch, Specialist Outpatients Department, hBelluno, Italy.

Marco Cazzola, MD Fabiola Atzeni, MD, PhD Fausto Salaffi, MD, PhD Stefano Stisi, MD Gianniantonio Cassisi, MD Piercarlo Sarzi-Puttini, MD

Please address correspondence and reprint requests to: Marco Cazzola, MD, Responsabile Degenza Riabilitativa Ortopedica, Azienda Ospedaliera "Ospedale di Circolo" di Busto Arsizio – Presidio di Saronno (VA), Italy. E-mail: mcazzola@aobusto.it

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## ABSTRACT

All of the specialists who deal in some way with fibromyalgia (FM) broadly agree that physical reconditioning programmes are useful, but it is not yet clear what type of physical activity is the most appropriate for different subsets of patients.

The aim of this review was to examine the randomised controlled trials (RCTs) published between 1985 and August 2010 whose outcome measures indicate the effectiveness of different types of physical exercise (PE) on the main health domains affected by FM: pain, and physical and mental function. Studies that simultaneously used different types of PE or multimodal treatment strategies were excluded from the analysis, as were those in which the primary and secondary endpoints prevented any assessment of treatment efficacy in all three health domains.

Twenty-seven studies were selected: 15 considered land-based physical aerobic exercise (PAE); seven exercises in water; and five muscle strengthening exercise (MSE). There was substantial uniformity in assessing the effectiveness of land- or water-based PAE and MSE in improving aerobic physical fitness (PF) and functional state. Waterbased PAE offers some advantages over similarly intense land-based PAE in reducing spontaneous pain and improving depressive symptoms, but the data are insufficient to establish its overall superiority. Regardless of method, the latest findings concerning the neurophysiology of nociception indicate the fundamental importance of assigning workloads that do not exacerbate postexercise pain.

## Introduction

Fibromyalgia (FM) is the prototypical form of a central sensitisation syndrome

(1). In addition to its core symptom of widespread chronic musculoskeletal pain, patients also complain of various other more or less severe symptoms that worsen their quality of life (2, 3). Many studies have found that patients with FM are less physically fit than control groups of the same age, gender and occupations (4, 5). The causes of the functional limitations reported by patients include reduced exercise tolerance, fatigue, and the exacerbation of pain caused by the activities of daily living (ADL) (6), and so non-pharmacological therapeutic strategies aimed at improving aerobic fitness, muscular strength and endurance may be important options for reducing their diseaserelated disabilities (7, 8).

It has been shown that physical aerobic activity (PAA) and physical exercise (PE, defined as a sub-category of PAA that is planned, structured and repetitive, and leads to the improvement or maintenance of one or more physical aspects) are effective in improving psychological function, muscle reconditioning and asthenia, and reduce psychological stress (9-11). According to some authors, it is also more effective than the pharmacological approach when used as a single therapeutic strategy (12), and all of the recently published guidelines of various scientific societies recommend including a personalised physical reconditioning programme as part of the treatment of FM (13-15). However, it is not clear what is meant by customising reconditioning programmes as many studies have failed to consider the patients' baseline level of fitness and training, and used the same method for all participants. As a result, the lack of adherence to non-pharmacological treatments based on PE, and the large number of dropouts in the treated group, are probably

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at least partially due to excessive workloads.

The very different symptoms that FM patients have in addition to the skeletal muscle pain characterising the disease has led some authors to suggest that their drug treatments should be adjusted on the basis of their needs and prominent symptoms (16, 17), and we believe that this principle should also be adopted when choosing nonpharmacological therapies. However, it is not clear what type of PE may be more effective in improving a particular health domain that may be the most impaired in a particular patient: in other words, it is difficult to say what works in which patients.

The aim of this review is to try to define the effects of different forms of PAA and PE on the different health domains that may affect different patient subsets.

## Methods

We searched the Medline, EMBASE, the Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews for papers published in English between January 1985 and August 2010, using the keywords "fibromyalgia" and "exercise" with the limits "guideline" (MeSH) or "review"(publication type) or "literature review (MeSH) or "randomised controlled trial" (MeSH). The search identified 437 publications: 150 reviews, 95 clinical trials, 74 randomised controlled trials (RCTs), six meta-analyses and four guidelines; a further 108 were case reports and abstracts.

Of the 74 RCTs, we considered those in which the groups were prescribed only one type of exercise and the outcome measures allowed us to assess the effectiveness of the treatment in improving mental function (anxiety, depression, psychological well-being), physical function (such as aerobic fitness or muscular strength), and pain (a visual analogue scale [VAS] and/or the number of tender points [TPs]). Flexibility exercises (stretching) carried out during the warm-up or cooling-down

Table I. Land-based aerobic exercise vs. controls (no exercise).	

Author (year) [reference	] Treatment (methods)	Controls	Experimental design (no. of patients)	Drop-outs (treated/controls)	Improvement areas (statistically significant differences between aerobic exercise <i>vs</i> . controls)
Mengshoel (1992) [20]	Aerobic dance twice a week for 20 weeks	No treatment	RCT (35)	7/3	Muscular resistance in upper limbs
Wigers (1996) [21]	Aerobic exercise 3 sessions/ week for 14 weeks	Stress management No treatment	RCT (60)	1/1/1	Cardiopulmonary function, pain, TP score
Verstappen (1997) [28]	Running/jogging, bicycling, swimming: 2 sessions/week for 24 weeks	No treatment	RCT (72)	10/2	No between-group difference
Gowans (2001) [19]	Floor and water aerobic exercise 3 sessions/week for 23 weeks	No treatment	RCT (50)	12/16	Anxiety, auto-efficiency, psychological well-being, depression, resistance (6 min walk test)
Etnier (2009) [47]	Physical aerobic activity for 18 weeks	No treatment	RCT (16)	0/0	Depression, cognitive disturbance
Van Santen (2002) [29]	Aerobic exercise 2 sessions/ week for 24 weeks	Biofeedback between usual treatment	RCT (143)	8/6	Modest improvement in all evaluated parameters with no between-group difference
Van Santen (2002) [48]	Group 1: 3 sessions of 60 min/week for 20 weeks	Group 2: 2 sessions di 60 min/week per 20 week	RCT (37)	1/2	QOL, physical fitness and psychological well-being with no between-group difference
King (2002) [23]	Aerobic exercise for 12 weeks	Exercise + Education Education No treatment	RCT 152	57	Resistance (6 min walk test) Auto-efficiency between groups 1 and 2 In comparison with no treatment
Schachter (2003) [49]	Group 1: 1 daily session for 16 weeks Group 2: 2 daily sessions for 16 weeks	No treatment	RCT (107)	7/21/10	Physician/patient judgement; pain in groups 1 and 2 in comparison with no treatment
Da Costa 2005 [22]	Aerobic exercise at home for 12 weeks	Usual care	RCT (79)	6/5	FIQ total score, pain, functional capacity
Fontaine (2010) [24]	Physical aerobic activity in more than one session for a total of 30 min./day for 7 days/week	Education	RCT (84)	6/5	Pain, functional capacity (FIQ, total number of steps/day)

phases of the PAA were not considered as mixed interventions, and were included in the study.

The 27 RCTs that met these characteristics were selected for analysis: 15 considered aerobic exercise on land, seven aerobic exercise in water, and five muscle strengthening exercise programmes.

## Effects of exercise on physical function Physical function (PF) is frequently

used as an outcome measure in studies evaluating the effectiveness of exercise programmes in the treatment of FM, and is quantified various ways ranging from simple self-report scales or performance evaluations (the walking test, the sit and reach test, etc...) to more complex methods such as maximal volume oxygen consumption (VO2 max) determinations or dynanometric quantifications of strength and muscular endurance.

In the late 1980s, McCain et al. (18) conducted the first study of the effectiveness of PAA as a non-drug treatment for FM. The treated group carried out a PAA (defined by the authors as moderately intense) three times a week for 20 weeks and showed an improvement in aerobic capacity and general well-being in comparison with control subjects who did flexibility exercises. Eight other studies have found that land-based aerobic exercise programmes significantly improved PF in comparison with control groups, of which four were untreated (19-22), two underwent an educational programme (23, 24), and two flexibility and stretching exercises (25, 26) (Tables I and II).

Bircan et al. (27) evaluated the effectiveness of two different treatment programmes (PAA and strength-training exercises [STE]) in 30 FM patients. The PAA consisted of three weekly sessions involving five minutes of stretching followed by 20-30 minutes of walking with progressive intensity up to 60-70% of the maximum expected heart rate (MEHR), and five minutes of cooling down and stretching; the STE consisted of five minutes of warm-up and stretching, 30 minutes of general strengthening exercises (from 4-5 repetitions per muscle group up to a maximum of 12 repetitions in each session), and five minutes of cooling down and stretching. At the end of the 8-week treatment period (a total of 24 sessions), PF had improved in both groups with no statistically significant between-group difference.

Only two authors have found no significant difference in PF at the end of a treatment programme: Verstappen (28) who used untreated controls, and Van Santen (29) who used controls undergoing biofeedback treatment. There is therefore a good correlation among the published studies concerning the possibility of improving the PF of FM patients by means of land-based aerobic exercises (Table III).

Four studies of water-based PAA alone have recorded an improvement in PF: two used untreated controls (30, 31), one a control group of patients who carried out recreational physical activities other than swimming (32), and one a control group of patients practising land-based PAA (33).

The five studies of STE (other than the above-mentioned study by Bircan) (27) all found a significant improvement in PF in comparison with untreated controls (34-37) or controls doing flexibility exercises (38) (Table IV).

## Effects of exercise on pain

Pain is the cardinal symptom of FM, and therefore often the primary endpoint of clinical trials involving FM patients, although its intensity has been measured in many different ways, including myalgic scores, the number of TPs, diagrams, VAS, and self-administered questionnaires.

Albeit with a few exceptions (38), none of the considered forms of exercise reduced the number of TPs, whereas some studies have reported a reduction in myalgic scores (21, 25, 27), which supports the hypothesis that PE increases the nociceptive threshold, at least in the short term. However, the effectiveness of PAA in reducing patient-assessed subjective pain is more controversial.

A land-based PAA programme led to a statistically significant reduction in spontaneous pain in about half of the published RCTs, four (18, 19, 23, 28) found no significant improvement, and Van Santen (29) reported a slight reduction in pain that was not significantly different from that experienced by the control group treated with biofeedback (Tables I and II).

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Table II. I	Land-Dased	aerobic	exercise	vs. other	exercise	programmes.

Author (year) [reference	] Treatment (methods)	Controls	Experimental design (t (no. of patients)	Drop-outs reated/controls)	Improvement areas (statistically significan differences between aerobic exercise vs. controls)
McCain (1988) [18]	Cycloergometry 3 sessions of 60 min/week for 20 weeks	Flexibility	RCT (42)	3/1	Cardiorespiratory function
Richards & Scott (2002) [25]	Aerobic exercise (bike or walking)	Relaxation Flexibility	RCT (136)	12/12	General state of health, TP score, FIQ total score
Valim (2003) [26]	Aerobic exercise 3 sessions/ week for 20 weeks	Stretching 3 sessions/week for 20 weeks	RCT (76)	=	Cardiorespiratory function (VO2 max), pain, depression
Bircan (2008) [27]	Aerobic exercise for 8 weeks	Strengthening exercise	RCT (30)	2/2	Pain, TP score, physical fitness, quality of sleep with no between-group difference

Author (year) [reference	Treatment (methods)	Controls (	1	Drop-outs ated/controls)	Improvement areas (statistically significant differences between aerobic exercise vs. controls)
Jentoft (2001) [39]	Aerobic pool-based exercise twice a week for 20 weeks	Land-based aerobic exercise for 20 weeks	RCT (34)	3/4	Pain, anxiety, depression
Altan (2004) [41]	Aerobic pool-based exercise for 35 min 3 times/week for 12 weeks	Balneotherapy without exercise	RCT (50)	1/3	Stiffness, depression, pain, asthenia (with no between-group difference)
Gusi (2006) [30]	Aerobic pool-based exercise 60 min, 3 times/week for 12 weeks	No treatment	RCT (34)	0/1	Pain, QoL, muscular health
Assis (2006) [33]	Aerobic pool-based exercise 3 sessions/week of 60 min each for 15 weeks	Floor aerobic exercise (walking/joggin for 15 weeks	RCT (60) g)	4/4	QOL pain, depression, cardiorespiratory function
Tomas-Carus (2007) [32]	Aerobic pool-based exercise 60 min each 3 times/week for 12 weeks	Games activities	RCT (34)	1/0	Pain, physical function, general and mental health, balance, scale
De Andrade SC (2008) [40]	Aerobic exercise in sea water for 12 weeks	Exercise in pool for 12 weeks	RCT (46)	4/4	Improvement in pain, total FIQ score, number of tender points, SF36 with no between-group difference. Talassotherapy > controls for BDI
Tomas-Carus (2008) [31]	Aerobic pool-based exercise for 8 months	No treatment	RCT (30)	0/0	Pain, physical and mental function, stiffness, anxiety, depression, scale, total FIQ score

QoL: quality of life; RCT: randomised and controlled trial; FIQ: Fibromyalgia Impact Questionnaire; BDI: Beck Depression Inventory.

### Table IV. Strengthening exercise.

Author (year) [reference]	Treatment (methods)	Controls	Experimental design (t (no. of patients)	Drop-outs treated/controls)	Improvement areas (statistically significant differences between aerobic exercise vs. controls)
Hakkinen (2001) [34]	Strengthening 2 sessions/ week per 21 weeks	No treatment Training in healthy subjects	RCT (33)	N/A	Pain Disability Depression Asthenia Muscular health
Hakkinen (2002) [35]	Strengthening 2 sessions/ week for 21 weeks	No treatment Training in healthy subjects	RCT (33)	N/A	Muscular health Knee extension Isometric strength
Jones (2002) [38]	Strengthening 60 min twice a week for 12 weeks	Flexibility exercises	RCT (68)	5/0	Pain, number of TPs muscular health
Valkeinen (2004) [36]	Strengthening 60-90 min twice a week for 21 weeks	No treatment	RCT (26)	1/0	Quadriceps strength, HAQ, walking speed, stairs
Kingsley (2005) [37]	Strengthening 2 sessions/ week for 12 weeks	No treatment	RCT (29)	7/2	Muscular strength Upper body function

Hakkinen *et al.* (34) used a twiceweekly strengthening programme for 21 weeks and obtained a reduction in spontaneous pain in comparison with untreated controls, but other STE studies (35-37) have observed a clinically and statistically less significant reduction. However, Jones *et al.* (38) found that spontaneous pain and the number of TPs were both significantly lower after STE treatment than in the control group that performed stretching exercises (Table III).

On the basis of the literature, waterbased PAA seems to be the more effective in reducing subjective pain that similarly intense land-based PAA. Five studies have reported better results, two in comparison with untreated controls (30, 31) and three in comparison with land-based PAA (32, 33). De Andrade *et al.* (40) obtained a similar reduction in pain in two groups of patients who underwent a similar PAA programme in a pool or seawater, and Altan *et al.* (41) found that the reduction in pain in patients doing water-based PAA was

not significantly different from that observed in a control group of patients who underwent balneotherapy without exercise (Table IV).

## Effects of exercise on mental function The extra-skeletal symptoms of FM include psychological symptoms, of which anxiety and depression are among the most frequent (2), and it has also been found that a very high proportion of patients are affected by cognitive disorders such as a slowing down in more or less complex abstract thinking and short-term memory defects (42-44). It is known that exercise improves depression (45) and anxiety (46) in patients with psychiatric disorders, and land-based PAA has proved to be effective in reducing and improving the symptoms of anxiety and depression in patients with FM in comparison with untreated controls (19) and controls doing stretching exercises (26).

In a recent pilot study, Etnier *et al.* (47) explored the effect of PAA on both depression and the cognitive problems frequently experienced by FM patients. At the end of the 18-week PAA programme, there were statistically significant differences between the treated and control group in the scales assessing fatigue [effect size (ES)=1.86)], depression (ES=1.27) and patient-assessed cognitive symptoms (ES=1.19), as well as in seven objective measures of cognitive function (ES between 0.26 and 1.06) (Table I).

Five of the seven studies of water-based PAA found an improvement in mental function (31-33, 39, 40).

De Andrade et al. (40) obtained a greater improvement in the symptoms of depression assessed by means of Beck's Depression Inventory (BDI) in the patients who carried out their PAA programme in sea water (thalassotherapy) than in those who followed the same programme in a swimming pool, although the improvement in physical fitness and the reduction in pain were comparable in the two groups (Table III). It is likely that the marine environment rather than the particular characteristics of seawater was responsible for the improvements in emotional well-being.

Hakkinen *et al.* (34) and Jones *et al.* (38) have reported that STE has a positive effect on the symptoms of depression (Table IV).

## Exercise application methods

The main purpose of PAA is to improve aerobic capacity defined as VO2 max: the fitter a subject, the greater is his or her VO2 max, and therefore his or her ability to perform aerobic work.

We define PAA as any physical activity that makes muscles use oxygen, carbohydrates and fats to produce work (swimming, cycling, walking, lowimpact aerobic dance) with the aim of improving the physical fitness or health of patients by means of an appropriate training process. This process involves the repeated administration of a series of stimuli (individual workloads) that alter homeostasis by inducing acute and transient responses in multiple organ systems (cardiovascular, respiratory, neuromuscular). The repetition of these responses over time leads to the establishment of stable organo-functional (allostatic) modifications (adaptations), which form the physiological basis for improving a subject's physical abilities.

In most of the studies of land- and water-based PAA in FM patients, the exercises were done 2-3 times a week for 30-60 minutes for a total treatment period of between 12 and 32 weeks. The workloads were generally measured on the basis of the MEHR calculated using the formula [220 – chronological age (years)], and the aim was to reach at least 40% of the MEHR (range 40-80%). In most cases, exercise intensity was mild-moderate (50-80% of the MEHR).

McCain (18) used a training programme in which a high-intensity cycloergometer was used at a workload likely to induce a heart rate of 150 beats per minute, which was kept constant for 20-30 minutes. However, Van Santen *et al.* (48) did not observe any difference between the benefits of an intensive training programme of three sessions per week for 20 weeks and those of a low-intensity programme of two sessions per week. Administering workloads in one or two daily sessions does not seem to have any effect on the results (49).

Fontaine et al. (24) have recently shown that patients with FM who modified their lifestyle by following the 1996 US Surgeon General's physical activity recommendations for 12 weeks (50) achieved a greater reduction in subjective pain and a greater improvement in functional capacity than a control group of patients who followed an educational programme. The patients randomised to the exercise programme were instructed to accumulate at least 30 minutes of moderate exercise a day, broken down into a number of short periods of activity, such as climbing stairs or gradually increasing distances covered on foot. The workloads were empirically defined on the basis of the patients' feeling of fatigue: during the activity, they had to observe an increase in respiratory rate that did not impede conversation. The patients were first asked to increase their physical activity by 15 minutes daily for seven days a week, after which the activity was increased by five minutes per week until reaching 30 minutes per day, to be maintained up to the 12th week.

Stretching has been frequently used in the control groups used to make comparisons with the patients who followed the PAA or STE programmes. Jones et al. (38) found that stretching reduced overall Fibromyalgia Impact Questionnaire (FIQ) scores, VAS-assessed subjective pain and the number of TPs, and improved the quality of sleep; however, the degree of improvement in all of these parameters was significantly less than in the STE group. Similar results have been reported in studies comparing PAA with stretching programmes, with significantly greater improvements being observed in the PAA groups (18, 25, 26).

STE consists of performing isotonic contractions and/or isometric resistance using machines and/or weights; all of the major muscle groups of the upper limbs and lower torso should be involved. The protocols used for all of the studies require a workload that the patients could handle without too much difficulty, and eight consecutive repetitions of muscle movements in each area (which was gradually increased until they could do three sets of eight repetitions). When this goal was reached, the number of repetitions was progressively increased up to a maximum of 12 per area, and subsequently the resistance is increased. The frequency of each session was always twice a week and the duration of treatment between 12 and 21 weeks.

### Rehabilitation setting

In most of the published studies, the exercise treatments were administered in specialised rehabilitation centres, with the active intervention and/or supervision of a physiotherapist. However, there are some recent studies of the feasibility and effectiveness of PAA programmes done by patients at home after a demonstration session and/or with the aid of videotapes (22, 24, 49). These are particularly interesting because the majority of patients cannot attend daily clinical sessions to follow the programmes offered by specialised centres.

## Discussion

The overall figures in the literature support the efficacy of PAA and MSE in improving the symptoms characteristic of FM. The aim of this review was to identify the best method of treating a particular health domain in order to provide clinicians with practical guidance concerning the type of activity to recommend on the basis of their patients' individual problems. For this reason, all of the studies involving more than one method (such as exercise and education programmes) were excluded, as were those or in which different types of exercise were used at the same time.

The greatest agreement found between the various authors concerned the effectiveness of land-based PAA in improving physical function as assessed by a self-administered scale, the maximum VO2, or the observation of special activities (such as the walking test).

The most conflicting results concerned improvements in pain and the other extra-skeletal symptoms typical of the disease. Eight studies found a significant reduction in spontaneous pain (VAS) and/or the number of TPs and myalgic score, in comparison with both untreated controls and other types of exercise. However, it must be emphasised that seven studies found no significant differences. Redondo et al. (51) used a programme of water- and land-based aerobic exercise for a period of eight weeks and documented an up to one year improvement in the aerobic fitness of the subjects in the exercise group, in comparison with the control subjects who followed cognitive-behavioural therapy programme. However, as this was not associated with an improvement in the other clinical manifestations of FM, it is possible that it does not necessarily improve other key symptoms of the disease,

Flexibility exercises (stretching) improve pain and many of the accompanying symptoms of FM, but the results are almost always significantly worse than those obtained using MSE (38) or PAA (18, 25, 26). This is not surprising because stretching is invariably used during the warming up and cooling down phases that precede and conclude PAA and MSE programmes. Comparing these studies of different modes of operation, we can suggest that the observed differences between the groups were actually attributable to the additive effect of PAA or MSE.

such as pain and stiffness.

Water-based PAA seems to provide a better return in terms of pain and mental function, particularly depressive symptoms. STE is certainly the most appropriate method for increasing muscular strength and endurance, and it has been reported that it also has positive effects on symptoms such as pain and depression. However, the number of studies is limited and the primary goal of all of those included in the analysis was to improve muscular strength and endurance.

The differences between the various treatment strategies are not so clear as to allow any definite conclusions to be drawn concerning their application in clinical practice. Probably the best method is a programme in which various types of exercise are used in the same or different treatment sessions: for example, Cedraschi *et al.* (52) found that the combination of an educational

and water-based PAA programme not only improved the patients' QoL, FIQ score and psychological state, but also clearly improved treatment compliance (72.6%) in comparison with protocols based on a single method.

Mannerkorpi *et al.* (53) also obtained improvements in pain, and physical and mental function, using an educational programme and water-based PAA. Munguia-Izquierdo and Legaz-Arrese (54) treated 35 FM patients using different types of PE done in water (aerobic, stretching and strengthening) during the same thrice-weekly sessions for 16 weeks, and obtained similar results. Adherence to the proposed exercise programme was also particularly high, with 23 patients still exercising regularly after a follow-up of 12 months.

Altan et al. (55) recently used pilates exercises three times a week for 12 weeks in 25 FM patients, and achieved a significant reduction in pain and total FIQ scores, in comparison with the controls who did flexibility exercises at home. This is a particular form of exercise and can be described as being based on both Eastern philosophy (including yoga and dance) and Western philosophy based on PAA and MSE. It can therefore be considered a mixed exercise programme which, according to Altan, can be prescribed to FM patients because particularly focuses on isometric exercise and is less fatiguing than classical PAA and MSE. However, these findings do not fully agree with those recently reported by Nijs and Van Houdenhove (56), who recommend the use of mild-moderate exercise intensity with multiple recovery periods during training sessions in order to allow muscle reperfusion.

It is difficult to calculate workload in isometric PE, and this can lead to diminishing blood flow towards the working muscles both during and after exercising. As muscle nociceptors are sensitive to ischemia, this would lead to more nociceptive afferents that worsen the process of central neuronal sensitisation (57).

#### Conclusions

Most of the analysed studies support the effectiveness of PAA and PE in

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slightly to moderately improving the aerobic fitness, functional status and QoL in FM patients. There are no clear differences in effectiveness between the various types of PE (floor, water, aerobics and strengthening), different workloads (low-moderate intensity), or different rehabilitation settings (clinical environments, the home). Waterbased aerobic and strengthening PE seems to be slightly more effective in reducing spontaneous pain and depressive symptoms. However, in the absence of any clear evidence indicating the superiority of one method over the other, it seems reasonable to consider the availability of rehabilitation facilities and patient preference in everyday clinical practice.

In practical terms, regardless of the proposed method, it is vital to monitor post-exercise pain in order to assess whether the programme fits the requirements of actual and possible patient performance. Pain is exacerbated when the overall workload is too high or if the individual exercises are too vigorous and, in such cases, it is necessary to reduce the volume, intensity and frequency of work.

If it is not possible to plan a structured rehabilitation programme tailored to the patient's subjective or objective problems, it is important to remember that simply changing their physical activity habits is an effective means of reducing the impact of FM on their functional status and QoL. Future studies should consider the possible interactions between the different classes of drugs commonly used in managing FM and different types of PE in order to identify possible synergistic effects in different subsets of patients.

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