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Evidence-based approaches for the management of fibromyalgia syndrome: a scoping review

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ABSTRACT

Background: Fibromyalgia syndrome (FMS) is a chronic widespread pain syndrome characterized primarily by widespread pain, fatigue, sleep dysfunction and low exercise tolerance. The pathophysiology is complex and its understanding evolving, and clinical management is difficult, with heterogeneous interventions employed.

Objectives: This scoping review provides an overview of fibromyalgia syndrome, and the evidence for the principal rehabilitation approaches. CINAHL, Cochrane, Medline and PubMed databases were searched from 1996 to 2021. Rehabilitation approaches included exercise, psychologically-based approaches, multicomponent approaches, and complementary and alternative therapies.

Major findings: Due to factors such as methodological shortcomings of existing studies, and the lack of evidence on individual modalities, it is difficult to draw definitive conclusions as to which is the most appropriate rehabilitation approach in FMS. However, there is evidence from meta-analyses and several international guidelines for the use of approaches incorporating exercise. There is also some evidence for the use of psychologically-informed interventions such as cognitive-behavioural therapy (CBT) approaches. Evidence for other interventions is more equivocal.

Conclusions: It appears that a combination of interventions (e.g. exercises combined with education and psychological approaches), is the most promising means of managing patients with FMS. Issues such as high numbers of drop-outs from exercise programmes, lack of long-term follow-up in many studies, and patients' preferences warrant further investigation. An individualized approach based upon extent of psychological involvement, severity of symptoms and level of disability is also recommended.

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Introduction

Chronic widespread musculoskeletal pain conditions (CWP), such as fibromyalgia syndrome (FMS), have a prevalence of approximately 2% in the general population with a higher proportion of women affected [1,2], though issues such as variable diagnosis and gender bias have been reported in several studies [2,3]. FMS is associated with high disease-related costs and places a significant burden upon medical systems, with a high unemployment rate, large number of claims for incapacity benefit and high levels of absenteeism [4]. Although controversial, FMS is a well-recognised, multifactorial syndrome, for which there are broadly accepted diagnostic criteria. The syndrome is characterised by widespread pain and muscle tenderness, accompanied by debilitating fatigue and other comorbid symptoms, including

psychological factors [5,6]. FMS has no specific diagnostic test with diagnosis based upon symptoms, as there is no 'cure' *per se*, management options therefore tend to be symptom-led.

Although fibromyalgia's existence as a distinct clinical entity is debated, it is accepted that the syndrome causes great suffering and distress for those affected. Affected individuals experience poor physical and social functioning and considerable distress compounded by a feeling of living with a condition sufferers find to be extremely limiting, whilst at the same time is 'invisible' to other individuals [7–9], with social and financial impacts on families and carers and reported feelings of isolation from healthcare professionals [10].

The pathophysiology of FMS is complex and its understanding evolving. Multiple systems are reported to be involved in the pathology of FMS,

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encompassing diverse physical and psychological issues such as disturbed patterns of sleep, altered cognitive impairment processing, decreased conditioned pain modulation at the spinal level, and increased connectivity between various pain-processing areas of the brain. Depression, anxiety and the role of emotional processing and psychological distress are also implicated in the pain experience in FMS [6,11,12]. It is also frequently co-morbid with other conditions.

Clinical management is often difficult, with heterogeneous interventions being employed [13–15], which can have variable outcomes. Patients with FMS have reported considerable dissatisfaction with existing services, which are often patchy and unavailable [16–18]. Patients' reports indicate frustration with the lack of success of conventional treatments and often resort to complementary or alternative medicine (CAM) [19,20]. Surveys have suggested that 66–98% of people with FMS had used some form of CAM [21,22].

FMS, therefore, represents a major social and economic burden for sufferers, families, and society, with important physical and psychological concerns for individuals. Reduced health-related quality of life (HRQoL) has been demonstrated in a number of cross-sectional studies using the Short-Form Health Survey (SF-36) [23,24], negatively impacting on activities of daily living, mental health, work and social role functioning, personal relationships and relationships with health professionals.

The main objective of this review is to present a comprehensive update on current research on the management of FMS. This review will improve understanding and treatment of FMS and support clinicians to provide evidence-based, patient-centred care for those with this complex condition.

Concept

The key concept of this scoping review is to present the current evidence for the management of FMS. Fibromyalgia has long been a contested condition where the diagnosis itself has been the subject of heated debate [25,26], and management, for the most part, yields limited success. Physical activity is often recommended in FMS, and is a central component of many clinical guidelines, though small sample size, heterogeneity of interventions and lack of long-term follow-up are limitations of current evidence [27,28]. Attrition tends to be high with a lack of reporting of adverse events [27], with qualitative studies reporting many patients expressing dissatisfaction with care [16], including struggling with exercise due to fatigue and pain [9,15]. Given the number of evidence-based guidelines that have examined the, often conflicting,

data regarding management options and, persistent misconceptions about FMS with no consensus on best management, it is perhaps inevitable that those managing people with FMS may struggle [29].

Participants

Intervention studies that included participants with FMS using any of the recognised diagnostic criteria were considered. Studies that include children (younger than 18 years) were excluded.

Context

This scoping review aims to present current evidence-based management of FMS, studies were included in any setting or geographical region.

Types of studies

This scoping review examined all quantitative or mixed methods studies that reported interventions for the management of FMS. Studies were limited to those published in English.

Search

The following search terms and their combinations were used to search the CINAHL, COCHRANE, MEDLINE and PUBMED databases from January 1996 to October 2021: 'fibromyalgia', 'pathophysiology', 'experiences', 'physical function', 'psychological variables', 'anxiety', 'depression', 'quality of life', 'coping', 'social support', 'musculoskeletal disorders', 'patient education', 'pain management', 'cognitive behaviour therapy', 'acceptance an commitment therapy,' 'mindfulness,' 'non-pharmacological interventions', 'aerobic exercise', 'strengthening exercise', 'aquatic therapy', 'randomized controlled trial', and 'review article'. Grey literature was also searched to include key government reports on the subject. The reference lists in key studies provided a further source of literature. NA screened all papers, SA screened all papers related to diagnosis and the other authors verified the selected papers.

Results

In order to meet the aims of this review it was important to set the management of FMS in context, therefore, the clinical presentation, diagnosis, aetiology and pathophysiology, including the psychological and emotional factors associated with FMS, are presented. A total of 155 papers were included in the review, of which 23 were systematic reviews. A comprehensive overview of the evidence on the management of FMS is outlined including

pharmacological and non-pharmacological interventions. The mainstay of FMS intervention is non-pharmacological interventions, consequently this review presents current evidence on: patient education; psychologically-informed interventions; physical activity or exercise-based rehabilitation; complementary and alternative medicine approaches and finally multidisciplinary treatment interventions for those with FMS.

Fibromyalgia symptoms

The characteristic symptoms of widespread pain and debilitating fatigue tend to be combined with a range of associated symptoms (Table 1), such as irritable bowel syndrome, cognitive dysfunction, cold sensitivity, and depression, which can impact the lives of patients to varying degrees [2,22,30]. FMS does not uniquely fit it into one illness classification. It is frequently co-morbid with other conditions, and is often associated with abnormal stress reactivity and other psychological factors, with patients reporting that their symptoms worsened after physiological or mental stress and anxiety due to distressing occasions [12,31], thus compounding the condition.

Diagnosis of FMS

There are no direct diagnostic tests for FMS; it can be confused with other conditions and is frequently co-morbid with chronic inflammatory diseases [32]. Once other conditions that mimic FMS have been eliminated, diagnosis is made according to the American College of Rheumatology (ACR), criteria which were first developed in 1990, and started a period of increasing acknowledgment of this syndrome [33]. The 1990 ACR criteria for FMS diagnosis specified that the pain must be chronic and widespread, defined as axial pain, affecting both sides of the body, above and beneath the waist. Furthermore, the criteria also specified that the patient must have pain in at least 11 out of 18 anatomic sites, known as ‘tender points’, on digital palpitation using a force of about 4 kilograms

(kg), and that symptoms must last for no less than three months. In 2010 and again in 2016, the 1990 diagnosis criteria were updated to provide an alternative technique of analysis, where the diagnosis of FMS is no longer based on counting the number of tender points [5,34]

While tender points seemed to be stable in the short-term [35] they were excluded from the diagnosis as it became apparent that tender point counts were rarely correctly performed in primary care. As such, in the updated diagnostic criteria of 2010 and 2016, all other characteristic features of FMS, such as symptoms of fatigue, sleep disturbance, and cognition problems were taken into consideration, and the tender points were replaced with the Widespread Pain Index (WPI) and the Symptom Severity (SS) Scales [5,34]. The WPI comprises a total of 19 predefined body areas, and the score represents the number of painful areas in which the patient has experienced pain in the previous 14 days (scoring 0–19). In the SS test (scoring 0–12), the severity level over the 14 days period is noted for the following three features: fatigue, waking unrefreshed and cognitive symptoms, as shown in Table 2. The severity level is rated from 0 to 3, where 0 represents no problem, and 3 represents a severe problem. The extent of somatic symptoms in general is also noted in the SS scale, and is scored from 0 to 3, where 0 means no symptoms, and 3 indicates a great number of symptoms [5,34]. Given the scores from the WPI and SS tests, the criteria for FMS diagnosis were developed as follows:

- WPI score of at least 7 and SS score of at least 5, or WPI 3–6 and SS \geq 9.
- Symptoms have been present at a similar level for at least three months.
- No other diagnosable disorder otherwise explains the pain.

There has been much debate regarding the diagnostic labelling of FMS, with some authors considering that the diagnostic label of FMS medicalizes

Table 1. Main and associated symptoms of FMS [30].

Main symptoms of FMS	Associated symptoms of FMS	Conditions that can mimic FMS symptoms
Widespread muscular pain	Irritable bowel syndrome	Sero-negative rheumatoid arthritis
Generalised stiffness	Cognitive dysfunction	Ankylosing spondylitis
Persistent fatigue	Exercise intolerance	Lyme disease
Non-refreshing sleep	Anxiety and reactive depression	Polymyalgia rheumatica
	Numbness and tingling	Lupus
	Cold sensitivity	Hypothyroidism
	Headaches	Anaemia
	Temporomandibular joint (TMJ) dysfunction	Scleroderma
	Myofascial pain syndrome	Multiple sclerosis
	Raynaud's phenomenon	Small fiber polyneuropathy
	Irritable bladder	Cancer
	Dysmenorrhoea	
	Skin disorders	
	Multiple sensitivities	
	Autonomic dysfunction	

Table 2. Symptom severity (SS) scale [5,34].

Fatigue	Waking unrefreshed	Cognitive symptoms
0 = No problem	0 = No problem	0 = No problem
1 = Slight or mild problems; Generally mild or intermittent	1 = Slight or mild problems; Generally mild or intermittent	1 = Slight or mild problems; Generally mild or intermittent
2 = Moderate; considerable problems; often present and/or at a moderate level	2 = Moderate; considerable problems; often present and/or at a moderate level	2 = Moderate; considerable problems; often present and/or at a moderate level
3 = Severe: pervasive, continuous, life disturbing	3 = Severe: pervasive; continuous, life-disturbing	3 = Severe: pervasive, continuous, life disturbing

symptoms, therefore promoting an increase in symptoms, as well as excessive somatic concern [36,37]. A qualitative meta-ethnographic study [8], found that whilst patients welcomed a diagnosis as legitimatisation of their condition, disappointment often ensued, as obtaining the diagnosis often did not lead to clinical management that abated their condition.

Aetiology and pathophysiology of FMS

The aetiology and pathophysiology of the condition involves a number of factors, such as abnormalities in the neuroendocrine and autonomic nervous systems, genetic factors, environmental stressors, and psychosocial variables [38–42], though the precise mechanisms have not been fully elucidated.

Central nervous system (CNS) sensitization in FMS

Central sensitization refers to hypersensitivity and enhancement of pain sensations in the central nervous system [43]. Central pathophysiological models in the mechanism of FMS can be described in terms of an enhanced response to stimulation mediated *via* CNS signalling with an abnormality of nociception and impairments in pain inhibitory mechanisms. This is supported by the existence of hyperalgesia and allodynia, low thresholds and tolerance to pain, development of pain sensitization in the dorsal horn of the spinal cord in response to repeated pain and greater brain responses to evoked pain observed in areas of the pain neuromatrix [44]. Objectively, the 25-item Central Sensitization Inventory (CSI), was designed to evaluate symptoms related to central sensitization (CS) and central sensitivity syndromes (CSS) [45] with a validated cut-off score of 40/100 [46], indicating presence and severity level of CS [47]. A recent multi-national large scale study developed a Calculator to provide an efficient way of classifying subjects into cluster groups of low, medium and high [48], with subsequent implications for identifying more tailored approaches for specific subgroups.

Nociceptor systems in the skin and muscles appear to undergo changes in FMS patients. This phenomenon, termed ‘wind-up’, appears as one main

mechanism that reflects the increased excitability of spinal cord neurons after a painful stimulus, where subsequent stimuli of the same intensity are perceived as stronger [49], indicating both an increased and a prolonged decay of nociceptive contribution in FMS patients. A neurological origin of FMS has been proposed, based on the discovery of small fibre and large fibre neuropathy in affected patients [50]. Recently, the involvement of idiopathic cerebrospinal pressure in FMS pathology is also suggested [51].

The neuroendocrine system, autonomic nervous system and FMS

Stress-related conditions may increase the risk of developing FMS, depending on different susceptibility factors, such as genetic and environmental factors and gender [52]. However, it is still uncertain which physiological developments mediate the relationship between stress and the development of FMS. Dysregulation of stress response mechanisms including abnormal functioning in the hypothalamic-pituitary-adrenocortical axis (HPA), are often considered to be such mediators [38,53]. Patients show blunted HPA reactivity which leads to an inappropriate cortisol response to stress or daily activities. Whether this plays a role in the progress of stress-related conditions, or happens through the natural history of FMS disorder has yet to be elucidated.

Levels of clinical pain have been related to the concentrations of corticotropin-releasing hormone (CRH) in the cerebrospinal fluid (CSF), and the salivary cortisol level [54], with exaggerated corticotrophin (ACTH) response to the exogenous CRH neurons demonstrated [55], as a result of the upregulation of pituitary CRH receptors in FMS. Hepatic clearance of cortisol has been reported to be lower in those with FMS than in matched controls [42]. Whilst there appears to be some evidence relating to HPA dysregulation, there is considerable heterogeneity among patients with regard to this disturbance.

Aberrant autonomic regulation is also often demonstrated in FMS patients with lowered activity of both the sympathetic and parasympathetic branches of the autonomic nervous system (ANS), with reduced reactivity to physical and psychosocial stressors [41], subsequently impacting upon ability to deal with daily demands.

Sleep disturbance in FMS

FMS is often considered to be related to sleep disturbance, characterized by the experience of non-restorative sleep, and linked to the fatigue experienced by patients [39]. In polysomnographic studies, alpha-delta sleep patterns, correlated to interrupted and non-restorative sleep, have been studied in FMS patients, with findings of disturbances in cycling alternating pattern with abnormalities seen in the continuity and architecture of sleep, characterized by the diminished efficiency of sleep, with increased numbers of awakenings [41,56].

Genetic and environmental factors in FMS

Based on incidences of FMS in families, several investigations have found that genetic factors can be associated with a predisposition to FMS, in combination with environmental triggers, such as infections, physical and/or psychosocial trauma [41,57], including work involving repetitive motions and maintaining certain positions for extended periods of time [58]. Some studies have shown a role for gene polymorphisms in the serotonergic, dopaminergic and catecholaminergic systems in the pathogenesis of FMS [58]. Polymorphisms in the serotonin 5-HT_{2A} receptor (T/T phenotype), serotonin transporter, and in the dopamine 4 receptor have hence been identified at the highest incidences in FMS patients [59].

Psychological and emotional factors in FMS

Lower cognitive performance has been found in FMS patients compared to healthy controls with patients reporting cognitive impairments, especially problems in planning, attention and memory, executive functions and processing speed [60,61]. Findings concord with self-reported cognitive deficits such as concentration difficulties and forgetfulness. Higher levels of fatigue have also been found during cognitive tasks in FMS patients compared with healthy controls [31]. The main mediating factor of these cognitive deficits is the severity of clinical pain. Secondary explanatory factors are emotional-affective factors (anxiety, depression and negative emotional states), fatigue and insomnia, which may also explain heterogeneity across studies [60].

FMS is linked to greater negative affect which involves a general state of distress composed of aversive emotions, such as sadness, fear, anger and guilt [6], which is enhanced and maintained by catastrophizing, avoidance or inhibition of emotion [62,63]. FMS patients tend to experience high levels of stress, anger, rumination and pain catastrophizing (conceptualized as an exaggerated negative orientation to pain, which provokes fear and discomfort with increased pain perception). Activity avoidance is associated with poor

physical and psychological functioning and higher pain related interference in daily activities [64,65]. Pain related self-efficacy (beliefs about the ability to perform activities despite pain), has also been found to be low in FMS patients [66]. These factors are frequently associated with a worsening of symptoms, including cognitive symptoms and compounded by the sequelae of physical inactivity on physical and psychosocial functioning. Self-efficacy has been demonstrated to be an important determinant of outcome for patients with FMS [67,68] and promoting self-efficacy is recommended as an important component of exercise prescription for individuals with FMS [69].

FMS patients often display a high rate of anxiety and depressive disorders. A higher prevalence is also observed for generalised anxiety disorder (GAD), panic attacks, obsessive-compulsive disorder (OCD) and post-traumatic stress disorder (PTSD) [11,70].

The intensity of negative affect states is positively associated with increased pain intensity, irritability, stress, functional limitations, non-restorative sleep, cognitive deficits and impact of illness on quality of life. Feelings of isolation are common which may contribute to depression. There is also evidence of high levels of anxiety related to heightened perception of pain and somatosensory amplification [6] with an inability to differentiate emotions from somatic sensations reflecting a deficiency in the cognitive development and control of emotion. It is suggested that emotional aspects may be linked to different extents of awareness that demonstrate the psychological and theoretical perspectives of people's attitudes, including: listening, understanding, acceptance, tolerance, confirmation and satisfaction. Pain and reduced functional ability increases depression and anxiety, exacerbating primary symptoms of FMS, and further increasing the negative influence upon all dimensions of HRQoL [71].

Some authors have stated that emotional features associated with FMS reflect the appearance of alexithymia [72]. The term alexithymia is derived from the Greek words 'a' (lack), 'lexis' (word), and 'tymos' (emotion) and means difficulty in classifying and describing feelings. Alexithymia is a multifaceted identity characterised by inability to control external feelings. A high prevalence of alexithymia-related behaviours in fibromyalgia sufferers has been found [73], with a strong link between alexithymia and depressive symptoms, using the Hospital Anxiety and Depression Scale (HADS), and Toronto Alexithymia Scale (TAS) [74]. Given the involvement of cognitive and emotional factors in FMS, psychologically-informed interventions are often included as a management approach and will be reviewed in this paper.

It can be seen that there are a variety of issues involving a range of pathophysiological mechanisms, with concomitant and consequent sequelae that may impact upon the physical and emotional experience of this condition. In addition, controversies and discrepant diagnoses by health professionals also affect the subsequent management and experience of health care, and health care seeking by patients [8]. The following section discusses current management approaches to the condition.

Management and treatment approaches to FMS

Because of its unidentified aetiology and vague pathogenesis, there is as yet no standard treatment that can 'cure' FMS. The treatment of FMS is mainly focused on the management of the disease to reduce the severity of symptoms. In recent years, a number of recommendations have been published by several organizations, including the European League Against Rheumatism (EULAR) [21,75], the Association of the Scientific Medical Societies in Germany (AWMF) [76], the Canadian Pain Society (CPS) [77], and the American Pain Society (APS) [78]. Israeli guidelines have also been published in an effort to standardize the treatment of FMS [79]. These organizations have provided evidence-based recommendations related to the evaluation and diagnosis of FMS, and the non-pharmacological and pharmacological therapies that can be used in its management, and there is agreement on the principles of approach to management and the need for tailored therapy to the individual. All recommend the first line approach to be non-pharmacological with recommendations for patient education, aerobic exercise, CBT and multicomponent treatment. There are some differences in strength of recommendation relating to pharmacological therapies and some non pharmacological approaches which may be more specific to particular countries (e.g. spa therapy or meditative movement).

Surveys of therapeutic management report that the main aim of therapy is to improve patients' daily function and provide education, together with pain reduction and fatigue management [13,14]. Commonly used interventions were exercise programmes, hydrotherapy and multidisciplinary pain management programmes.

Pharmacological approaches to FMS

Pharmacological approaches are used to control symptoms, aiding patients to cope better with their condition. Analysis of the results of pharmacological management of FMS have shown equivocal findings,

with some medications appearing to provide relief of some symptoms for some patients, but not for numerous others. Pharmacological agents influencing the central nervous system are considered the most effective.

Around 20 to 40% of patients with FMS experience depression. The regular comorbidity of FMS with depression supports the utilization of antidepressant drugs for FMS [80–82], to treat mood, sleep and pain symptoms. Such drugs include amitriptyline as well as the selective serotonin reuptake inhibitors (SSRIs), duloxetine and milnacipran [83]. Some benefits have been reported with the use of duloxetine, milnacipran and amitriptyline; however, numerous individuals encounter more unfavourable impacts than benefits [82]. A systematic review and meta-analysis of 37 RCTs of antidepressants in FMS patients with pharmacological placebo concluded that physicians and patients should be realistic about the potential benefits of using antidepressants in treating FMS symptoms [84]. The EULAR revised guidelines recommend a low dose of 25 mg per day for 6–8 weeks could achieve 30% pain reduction and small effects on sleep and fatigue. Anticonvulsant drugs such as pregabalin and neurontin are also used for FMS treatment, with some evidence of up to 30% pain reduction and small effects on fatigue and sleep [21].

From these international guidelines, it is apparent that pharmacological therapy can play a role in the management of symptoms, however, many of the side-effects are not tolerated well by patients.

Non-pharmacological interventions

There is strong evidence for the use of non-pharmacological approaches in reducing symptoms, increasing functional activity and improving quality of life which is supported by several multidisciplinary international guidelines [75–79] and the American Psychological Association [85]. These include patient education, cognitive-behavioural and behavioural medicine therapies, exercise rehabilitation, massage therapy, complementary and alternative therapies, and multidisciplinary therapy.

Patient education

Education is widely used in the management of chronic musculoskeletal pain conditions, though often as part of a multidisciplinary management programme, where positive outcomes in terms of self-management and self-efficacy were demonstrated in a systematic review of 27 studies [86]. Self-management education interventions are complex behavioural interventions targeting patient education and behaviour modification in order to address symptoms, functional

activity and quality of life. A systematic review consisting of a meta-analysis of 9 randomized controlled trials (RCTs), of educational interventions for chronic pain [87], concluded that education alone is not effective in reducing pain intensity or the associated disability in chronic pain conditions. The authors noted heterogeneity of programmes, regarding content, delivery, duration of both the intervention and comparator groups and variable risk of bias in the studies reviewed. Pain Neurophysiology Education (PNE), has been used in studies with chronic musculoskeletal pain [88], though studies of FMS specifically tend to have focused on education about FMS and skills to manage the condition, as part of an interventional package or multidisciplinary management programme (reviewed in a later section). In a small scale uncontrolled study of seven women with FMS [89], attending a university-based group education programme three days per week, positive results in pain and fatigue were reported from participation in the programme. A combination approach of balneotherapy and patient education demonstrated short and long-term beneficial effects using the FIQ and BDI in randomised controlled trials when compared with education alone [90,91]. A self-management educational approach particularly as part of multidisciplinary management appears to improve the effectiveness treatment outcomes in chronic pain conditions, including FMS.

Psychologically-informed interventions: Cognitive-behaviour therapy (CBT) and behavioural medicine therapy (BMT)

CBT and other psychologically informed interventions been extensively studied as non-pharmacological interventions for FMS [92].

CBT is a composite of two methodologies; cognitive treatment, and behavioural treatment [93]. It is a form of psychotherapy that mainly focuses on the understanding of how the patients' thoughts and emotions may contribute to the dysfunctional negative thoughts and behaviours in chronic pain conditions and has been supported by systematic review and meta-analysis [94]. The fundamental aims of CBT are twofold: first, the recognition of, and change to, the dysfunctional thought patterns that are interfering with therapeutic progress; and secondly, the engagement of the individual in behavioural interventions aimed at improving physical activity, coping with pain, goal setting and pacing of activities, pain coping and reduction of catastrophizing. Coping strategies are a key element of any pain management programme and of CBT, and are designed to assist the patient to better manage their pain and other symptoms.

Behavioural interventions have shown some promise. Methodologically high-quality studies have concluded that physiotherapy with a behavioural medicine approach, including physical activity/exercise, was more effective in reducing disability than physical activity/exercise alone or in combination of physical activity, manipulation and passive modalities for chronic musculoskeletal pain, with effects maintained up to 2 to 5 years after the intervention [95,96]. A systematic review and meta-analysis of 23 trials found CBT therapies to be effective in reducing pain and disability in FMS, when compared with a variety of control groups. Importantly, results were maintained at follow-up [97,98] although there was wide heterogeneity of programmes and often low quality individual trials. The use of CBT within a multi-component approach has been found to yield the most benefits [99].

In an online application of CBT, a RCT of $n = 56$ subjects undertaking an internet-based CBT programme compared with standard care, using the Fibromyalgia Impact Questionnaire (FIQ), found no significant difference in the FIQ scores between groups [100]. Further, in a randomized study of $n = 58$ patients with FMS [101], combination CBT had a moderate effect on improving physical function and reducing pain compared to milnacipran alone.

In an economic evaluation alongside a 6 month RCT, CBT was found to be the most cost-effective treatment for adult FMS patients ($n = 168$), versus a combination of pregabalin and duloxetine and usual care [102].

In summary, interventions designed to improve cognitive and behavioural aspects of FMS have proved useful, with some evidence of clinical and cost effectiveness. However, these interventions are generally delivered as part of multimodal programmes that have combined CBT with physical exercise, rather than through CBT alone [21]. Different authors use differing classifications and techniques of CBT and BMT within their programmes, and thus comparison across cognate studies is often difficult. Therefore, it is difficult to determine whether the methods in themselves are effective and whether the effects differ between methods. Implementation in routine medical care would require policymakers to develop more widespread public access and develop training packages for therapists to deliver psychologically-based/informed therapies as part of their usual practice.

Acceptance and commitment therapy

There has been growing interest in the effectiveness of Acceptance and Commitment Therapy (ACT), and other third generation psychological therapies

for clinical improvement in patients with chronic pain with small but significant effects in pain intensity, depression, anxiety, physical well-being and quality of life [103,104]. According to ACT theory, and central to the concept is *psychological flexibility*. In the context of chronic pain, psychological flexibility means that painful sensation, feeling and thoughts are accepted, that attention is focused on the opportunities of the current situation rather than ruminating about the lost past or catastrophizing about the future, and that behaviour is focused on realising valued goals instead of pain control [105,106]. This is established through six main processes which are strengthened through ACT [107].

- Acceptance
- Cognitive Defusion
- Being present
- Self as context
- Values
- Committed Action

The latter connects life values, goals and actions. Acceptance is not an end in itself but is fostered as a method to increase value-based actions [103]. Increased acceptance of pain has been found to be associated with increased well-being and decreased pain severity, as well as improvements in work status [102,108]. Although patients' lives may not be entirely free of pain or fatigue, patients can learn to have more successes in life domains valuable to them. McCracken et al. [109] observed that higher pain acceptance among those with chronic pain was associated with fewer pain related health care visits and reduced prescribed analgesic medications. In an RCT of ACT versus a waiting list control for $n = 40$ women with fibromyalgia, significant differences were found for pain-related functioning, fibromyalgia impact and psychological variables [110]. A recent RCT randomized $n = 248$ patients to either physical therapy informed by ACT (PACT) versus usual care for chronic low back pain [111]. The PACT intervention consisted of a brief physical therapy intervention, guided by the principles of ACT to promote self-management. Improved functioning at 3 month follow-up was found, however this was not maintained at 12 months. A systematic review and meta-analyses of 9 clinical trials [112], found small to moderate effects in favour of mindfulness and acceptance-based interventions compared with controls in pain, depression, anxiety, sleep quality and HRQoL, though due to a number of study limitations, it was concluded that the results, whilst promising, are uncertain at present. There is scope to explore the utility of this approach for patients with fibromyalgia, and address

identified issues of adherence and fidelity in interventions.

Mindfulness based stress reduction (MBSR)

There are various theories which state that stress can play a critical role in triggering FMS symptoms, although whether this is aetiological or a result of the pain, fatigue and consequent reduced function, is unclear [113]. Psychological symptoms such as anxiety and depression are common in FMS [114]. Mindfulness-based interventions aim to develop non-judgmental awareness to noxious stimuli and improve coping mechanisms [115]. A systematic review and meta-analysis of six randomized controlled trials (RCTs) with a total of 674 FMS patients [116], used mindfulness-based stress reduction (MBSR) to treat fibromyalgia. Some improvements were found in pain, QoL, depression and anxiety post treatment when compared with active control interventions, though evidence was low-quality. Similar results have been reported by Cash et al. [117], in an 8-week programme incorporating weekly sessions and a self-management home programme that included breathing exercises, meditation and yoga. Further evidence of the effectiveness of psychological interventions is provided by an RCT comparing 8-weeks of meditation awareness with a CBT control. Improvements were reported for symptoms, (pain perception, psychological distress and sleep quality) and were maintained at 6-month follow-up [118]. Other recent studies have found greater sleep quality, pain interference and reduced anxiety and depression following a mindfulness intervention [119,120], with one study finding that MBSR combined with multicomponent treatment versus treatment as usual, significantly reduced indirect costs and primary health care services usage [121].

In a meta-analysis of 28 RCTs and 1285 patients with chronic pain (7 studies included patients with FMS), small effect sizes were found for acceptance and mindfulness-based interventions on all outcomes with moderate effects for anxiety and pain interference post-treatment, with higher effects on depression and anxiety than MBSR or MBCT (mindfulness-based cognitive therapy). [122]. The authors concluded that whilst acceptance and mindfulness based interventions have gained popularity, superior benefits have not been found compared with traditional CBT. Thus, mindfulness-based interventions may prove a suitable alternative for some patients, with further fully powered studies of patients with FMS required, in order for definitive conclusions to be drawn regarding effectiveness.

Exercise rehabilitation

There have been a number of reviews of exercise therapy for chronic pain and fibromyalgia including a Cochrane review of 47 different exercise interventions [27,28,123–126]. A systematic review and meta-analysis of 33 RCTs [28] concluded that aerobic and muscle strengthening exercises are the most effective ways of reducing pain and improving the general well-being in people with fibromyalgia. In addition, combined exercise produced the most beneficial effect on symptoms of depression. Most trials used the Fibromyalgia Impact Questionnaire (FIQ) as an outcome measure to assess pain, depression, physical and functional impact of fibromyalgia, and the general well-being (FIQ total score).

However, these reviews were not able to draw conclusions about type, dose and duration of exercise, as few studies included such details. While some studies have reported positive long-term outcomes with exercise interventions [127,128]. Adherence to exercise regimes is also an important issue that has been identified from reviews, and requires further investigation.

An assessor-blinded multi-centre randomized controlled trial of 130 women with FMS [129], concluded that resistance exercise was found to be a feasible mode of exercise for women with FMS compared with active exercise, improving muscle strength, health status, and current pain intensity. A sub-study of this trial [130], showed that person-centred progressive resistance exercise contributed to improvements in physical fatigue in these women with FMS. In addition, an RCT of eighty women with FMS, randomized to either strengthening or flexibility exercise groups, who completed the FIQ and a short-form health survey (SF-36), [131], concluded that strengthening exercises showed greater and more rapid improvements in pain and strength compared with flexibility exercises.

It has been demonstrated that low or moderate intensity exercises are more successful in reducing the symptoms of FMS [124]. The use of aerobic exercise received the strongest endorsement in the recently revised EULAR recommendations [21].

In view of the pain and fatigue that are characteristic of fibromyalgia syndrome, most patients are physically deconditioned. Water-based exercises are an appropriate starting point for patients who are very deconditioned, as an exercise programme which may progress in levels of intensity [132].

There have been some promising results from studies of hydrotherapy, however it should be noted that hydrotherapy refers not only to pool-based exercise but also to balneotherapy and spa therapy, which are popular in many European countries. A meta-analysis of $n = 10$ RCTs of hydrotherapy for

fibromyalgia [133] and systematic review [134], concluded that there was moderate evidence for reduction of pain and improved health-related quality of life (HRQoL) at the end of therapy. Both authors focused on thermal pool therapy, spa-, balneo- and thalassotherapy, hydrotherapy and compresses. Many of these therapies are considered as complementary and alternative therapies. Studies were heterogeneous and many were of low to moderate quality with small sample sizes. Studies with pool-based exercises are often included in exercise modalities interventions. Evidence from the above systematic reviews and meta-analysis suggests that therapeutic active aquatic exercise is beneficial to patients suffering from FMS, compared to control groups (inactive), or passive balneotherapy without exercise. A study of the effects of 20 weeks land-based and pool-based exercise interventions for 73 women with FMS concluded that pool-based programmes yielded greater reductions in the overall impact of FMS, in particular with respect to fatigue and depressive symptoms [135].

A popular form of water-based exercise is deep water running (DWR). During DWR axial compression on the lumbar spine is minimized compared to exercising on a motor-driven treadmill or shallow water running. DWR guarantees predominantly aerobic exercise while at the same time positively affecting mobility, strength and muscular endurance, which are associated with reduced pain and physical disability [136–138]. DWR is a safe exercise that has been shown to reduce pain as effectively as land-based exercises in fibromyalgia [132,139]. Individual assessment of the aerobic threshold and patient's baseline function, symptom severity and tolerance of exercise-induced pain is recommended.

Exercise is therefore an important part of managing FMS, receiving the highest endorsement in international guidelines. The dose, duration and frequency of exercise required requires further investigation. In addition, many patients drop out of exercise programmes, reporting pain and fatigue as barriers to exercise [9,15], and therefore strategies to promote engagement and adherence require development.

Personalization and individualization of non-pharmacological approaches

Analyses within the subgroups in exercise interventions for FMS showed that patients with milder stress, pain or depression improved most with treatment as measured by the FIQ total (effect size > 0.50 , $p < 0.05$) compared with controls [139]. Furthermore, given the variability in patients' symptoms and functional limitations, it is suggested that exercise regimens should be also be individualized to the patient's baseline function, symptom severity and tolerance of

exercise-induced pain. However, variability in outcome efficacy has been reported in individualized approaches, with challenges in identifying which intervention is effective for specific types of patient.

In order to individualize non-pharmacological behavioural management approaches, Davydov et al. [140] proposed a ‘resource-matched’ hypothesis according to pain regulation mechanisms consistent with pain causality mechanisms such as depressive rumination, catastrophizing or pain hypervigilance. In a cross sectional study of $n=110$ FMS patients, the authors provided support for this hypothesis, using a battery of standardized psychological pain management instruments, identified specific types of pain causality mechanisms. The authors proposed that non-pharmacological approaches should be applied according to the mechanism of causality of the pain experience (the ‘resource’), and diverted to support another activity in order to reduce pain severity and the need for medications. Thus clinical and psychological assessment can identify patients who may respond optimally to specific interventions more ‘matched’ to their particular physiological and psychological sub-group, such as the use of physical activity if the psychological component is more associated with vagus (re)activity or coping and distraction strategies training if dominated by catastrophizing or depressive rumination. This promising avenue of research may allow individualization of different physiological and psychological strategies for pain management [140].

Massage therapy (MT)

MT has been broadly utilised by up to 70% of patients suffering from FMS and seeking symptom relief [141], and is often a popular choice with patients, despite limited evidence for its’ effectiveness [17,18].

It is claimed that massage can reduce pain and muscle tension, improve mood, and reduce sleep disturbance, *via* a complex interplay of both physical and psychological modes of action [142]. Single-arm studies have shown significant short-term benefits in improving restorative sleep, and reducing fatigue and stiffness in patients with FMS [143]. Another small-scale cohort study showed significant short-term improvements in pain intensity, and function, and a reduction in complaints of non-restorative sleep for 20 FMS patients receiving both massage and ultrasound [144]. Nevertheless, these outcomes must be treated with caution, as in studies that exclude a control group, placebo effects and spontaneous improvements in FMS symptoms cannot be eliminated.

A systematic review of nine randomized controlled trials involving 404 patients [145], reported benefits

in pain, anxiety and depression, but these were not associated with a statistically significant improvement in pain. There was a wide variability in duration of individual sessions and length of programme, type of massage employed. Comparator groups included a range of treatments. Methodological problems were noted in all studies. The authors concluded that massage was not associated with a significant improvement in pain, and that further larger-scale RCTs with long-term follow-up are warranted.

Complementary and alternative medicine approaches

Surveys have demonstrated that over 90% of patients with FMS use CAM to manage the symptoms of FMS, with 66% utilising more than one complementary treatment [13,14,20]. Such alternative therapies included holistic movement therapy, energy therapy, balneotherapy, and osteopathic and chiropractic manipulation. Treatment approaches are rarely standardised, and there is considerable heterogeneity of interventions. As such, evidence is weak, with a EULAR recommendation against chiropractic manipulation on safety grounds [21].

Meditative exercise therapies

The therapies classed as meditative movement approaches are yoga, qigong and Tai Chi or a combination. It is acknowledged that yoga is increasingly incorporated into exercise rehabilitation programmes in physical therapy. A recent systematic review and meta-analysis exploring the effect of exercise on fatigue and sleep quality in fibromyalgia (17 RCTs ($n=1003$ participants), were included for fatigue, and 12 RCTs ($n=731$), for sleep [146], found that in comparison to usual care, exercise had moderate effects on fatigue and a small effect on sleep quality; SMD (95% CIs -0.47 (-0.67 to -0.27 , $p<0.001$) and -0.17 (-0.32 to -0.01 , $p=0.04$). Importantly, meditative exercise programmes were the most effective for improving sleep quality, which concurs with an earlier systematic review [147], which similarly reported significant short-term effects for sleep disturbance, fatigue and depression, but not pain, compared with controls. The authors concluded that meditative exercise such as yoga had short-term beneficial effects.

Acupuncture

A small number of RCTs have been conducted relating to the effectiveness of acupuncture in FMS. A high quality systematic review included 9 trials of acupuncture and demonstrated that acupuncture, as

Table 3. Recommendations for practitioners.

- Strategies to support self-management to promote behaviour change regarding exercise and physical activity are important components of any treatment programme.
- A person-centred care approach should be adopted incorporating individualized and tailored approaches to physical and psychological management.
- Patients' preferences regarding type of exercise or physical activity should be considered.
- Barriers to engaging in exercise or other movement activity should be identified and discussed with patients.
- Exercise and physical activity should start just below participants' capacity and increased gradually, until it is at the lower end of moderate intensity, with the same or lower levels of pain or fatigue.
- Education, support and strategies for fatigue management should be incorporated into the management approach.
- Training packages should be developed for therapists to develop psychologically-informed therapies as part of usual practice.

an adjunctive treatment to standard therapy, resulted in a 30% improvement in pain [148]. Electric acupuncture was also associated with improvements in pain and fatigue. Some adverse events were reported, but these were mild and transient. Equivocal results have been found regarding the use of real and sham acupuncture, indicating a potential placebo effect. EULAR recommendations [21], concluded that there was some evidence for the effectiveness of acupuncture

Spa therapy

A review conducted by Fioravanti et al. [149], on mechanisms of thermal water and the application of mud, concluded that such techniques alleviate suffering in rheumatic diseases. The study concluded that the beneficial effects of spa therapy in some rheumatic diseases include changes in the environment, pleasant surroundings, and the absence of work duties. Spa treatment is a popular treatment for FMS in numerous European nations and Japan. A narrative review [150] concluded that spa therapy can represent a useful adjunct to pharmacological treatment of FMS, or be a valid alternative for patients who do not tolerate pharmacological treatments. However, in spite of their long history, spa medications are still a subject of controversy, due to the lack of controlled trials and the heterogeneity of treatments.

Multidisciplinary therapy

A multidimensional approach to the management of FMS, to improve the physical and psychological health of the individual by improving functional capabilities, enhancing self-efficacy and inducing changes in behaviour, is supported by systematic review and meta-analysis and by international guidelines [21,77–79,151–153], concluding that there was strong evidence of beneficial short-term effects on key symptoms with a multicomponent, multidisciplinary approach. The components of treatment include a combination of some or all of the following:

- Patient education
- Pain relief (physical)
- Pain relief (medication)

- Stress management
- Aerobic exercise
- Sleep therapy
- Psychological intervention (e.g. coping skills, modifying pain beliefs, increasing self-efficacy).

However, the heterogeneity of multidisciplinary programmes is such that overall evaluation is difficult, mainly due to differences in patient characteristics, lack of standardization of programmes and assessment instruments used, in addition to methodological constraints. Further, due to limited follow-up in many of the studies, it is difficult to ascertain long-term benefits of such interventions.

A recent pragmatic study evaluated the long-term health related quality of life benefits (HRQoL), of a comprehensive 8-week group based multidisciplinary rehabilitation programme focusing on the coping ability and self-care of fibromyalgia patients [154]. It was found that the HRQoL improved in all domains following this programme and changes were maintained at long-term follow-up. Changes were more pronounced for younger patients and those with higher levels of depression prior to the intervention, which concurs with previous studies of predictors of multidisciplinary treatment outcomes for fibromyalgia [155].

Main points of the review

This review has comprehensively presented the current evidence on the management of FMS and made recommendations for practice. Fibromyalgia syndrome is a complex and debilitating condition; treatment interventions should be individualised to the patient taking into account patient preferences. Recommendations for practitioners derived from the review are shown in Table 3.

Strengths and limitations

The strength of this review is the wide-ranging and comprehensive evidence that has been included. Paradoxically the extensive nature of the review is also one of the limitations, the comprehensive nature of the review means that it is not focused on any narrow research question. A scoping review

does not answer questions of effectiveness *per se*, there has been no attempt to critically review the literature or identify risks of bias, this could be perceived as a limitation of the review, however this was not the aim of the review.

Conclusion

FMS is a complex syndrome that is often co-morbid with other conditions and differentially diagnosed. The evidence suggests that a multidisciplinary approach to treatment is optimal combining both pharmacological and non-pharmacological approaches which have been supported by systematic review and meta-analysis. Exercise receives the highest recommendation with psychologically-informed interventions such as CBT and newer mindfulness-based ACT interventions, the latter gaining popularity and showing promising results. Treatment approaches are rarely standardized, and there is great variability in management. Furthermore, patients' experiences of the condition need to be fully understood in order to manage the condition appropriately. Despite developments in research, FMS remains a challenging condition for many clinicians and patients, with many gaps in the existing literature.

Future interventional research should adopt a more systematic approach in order to draw conclusions about which treatment methods, for whom and in which context, are necessary and sufficient to provide long-term effects on sustained pain. Additionally, systematic replication of studies is needed, as this is lacking. Such studies would allow definitive conclusions on the generalizability of treatment effects for this heterogeneous group of patients. In addition, this could increase the opportunities to assess cost effectiveness of interventional packages.

Finally, identification of subsets of FMS patients may be an important factor in selecting an appropriate rehabilitation intervention. The subjective responses of patients to rehabilitation interventions, and the acceptability of these interventions in terms of their beliefs, lifestyles and preferences, have received valuable scrutiny but requires further investigation.

Gaps in literature and direction for future research have been identified as below:

- The types of exercise that are most effective and their dose, duration and intensity and how best to engage people with FMS is exercise and physical activity.
- Characteristics of patients with FMS that predict response to specific interventions.

- Identification of patients based upon the relative contributions of physical and psychosocial factors on severity of symptoms and levels of disability to determine which patients benefit most from rehabilitation programmes, and approaches adapted accordingly.

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