Beyond pain in fibromyalgia: insights into the symptom of fatigue

Ann Vincent1,2*, Roberto P Benzo3, Mary O Whipple3, Samantha J McAllister2, Patricia J Erwin4 and Leorey N Saligan5

Abstract

Fatigue is a disabling, multifaceted symptom that is highly prevalent and stubbornly persistent. Although fatigue is a frequent complaint among patients with fibromyalgia, it has not received the same attention as pain. Reasons for this include lack of standardized nomenclature to communicate about fatigue, lack of evidence-based guidelines for fatigue assessment, and a deficiency in effective treatment strategies. Fatigue does not occur in isolation; rather, it is present concurrently in varying severity with other fibromyalgia symptoms such as chronic widespread pain, unrefreshing sleep, anxiety, depression, cognitive difficulties, and so on. Survey-based and preliminary mechanistic studies indicate that multiple symptoms feed into fatigue and it may be associated with a variety of physiological mechanisms. Therefore, fatigue assessment in clinical and research settings must consider this multi-dimensionality. While no clinical trial to date has specifically targeted fatigue, randomized controlled trials, systematic reviews, and meta-analyses indicate that treatment modalities studied in the context of other fibromyalgia symptoms could also improve fatigue. The Outcome Measures in Rheumatology (OMERACT) Fibromyalgia Working Group and the Patient Reported Outcomes Measurement Information System (PROMIS) have been instrumental in propelling the study of fatigue in fibromyalgia to the forefront. The ongoing efforts by PROMIS to develop a brief fibromyalgia-specific fatigue measure for use in clinical and research settings will help define fatigue, allow for better assessment, and advance our understanding of fatigue.

Fatigue in fibromyalgia: common problem, multiple causes

Fibromyalgia is a chronic, multi-symptom complex with no effective treatment. It affects 2% of the United States population and significantly impacts both healthcare costs and utilization of healthcare resources [1,2]. In addition to unrefreshing sleep, cognitive difficulties and affective symptoms, chronic widespread pain and fatigue are its cardinal symptoms [3,4]. For patients with fibromyalgia and their treating clinicians, fatigue is a complicated, multifactorial, and vexing symptom that is highly prevalent (76%) and stubbornly persistent, as evidenced by longitudinal studies over 5 years [5-7].

Despite its disabling effects, fatigue has not received the same research attention in fibromyalgia as has pain, for a variety of reasons. First, there is no established nomenclature with which to describe the multiple types and manifestations of fatigue. Patients with fibromyalgia may experience fatigue physically (lack of energy, physical exhaustion), emotionally (lack of motivation), cognitively (inability to think or concentrate), or via the symptom’s impact on virtually any aspect of living, such as the ability to work, meet family needs, or engage in social activities [8]. Patients may experience these different types of fatigue simultaneously, but clinicians rarely sort this through during the typical office visit, and the complaint is often chronicled simply as ‘fatigue’. Second, clinical experience indicates that patients usually do not feel comfortable making an appointment for ‘just’ fatigue. They need a medical condition or an acceptable symptom (as institutionally and culturally dictated), such as pain, despite the fact that fatigue is reported as a bothersome symptom in up to 80% of patients with chronic conditions and is a common complaint in both primary and specialty clinics [9-11]. Third, the lack of
understanding of the mechanisms of fatigue contributes to poor assessment and treatment strategies, and may make providers wary of broaching the topic in a clinical encounter.

Fortunately, two recent initiatives, the Outcome Measures in Rheumatology (OMERACT) [12-15] and the Patient Reported Outcomes Measurement Information System (PROMIS) [16], are helping to move the study of fatigue in fibromyalgia forward. OMERACT organized focus groups and Delphi studies of both patients with fibromyalgia and physician experts that have resulted in important recommendations for assessment and treatment of fatigue. First among these was the ranking of fatigue, pain, sleep, quality of life, mood, and cognition as the most relevant symptoms in fibromyalgia, and second, the recommendation that fatigue be assessed in all clinical trials of fibromyalgia. PROMIS, an initiative of the National Institutes of Health, developed item response theory-based banks to assess symptoms such as fatigue, pain, and sleep, as well as quality of life measures. The goal of this initiative was to 1) create measures that are valid, reliable, and generalizable for clinical outcomes that are important to patients, 2) reliably assess patient response to interventions, and 3) inform treatment modifications. The PROMIS Fatigue Item Bank (PROMIS-FIB) contains 95 items that evaluate the spectrum of fatigue from mild subjective feelings of tiredness to an overwhelming, debilitating, and sustained sense of exhaustion that interferes with activities of daily living, family, and social roles [17]. The assessment categories are divided into the experience (frequency, duration, and intensity) and impact of fatigue on physical, mental, and social activities. Work is currently underway to assess the psychometric properties of the PROMIS-FIB and develop a brief fibromyalgia-specific measure for clinical and research purposes.

The objectives of this narrative review are to 1) provide a general overview of the current knowledge of fatigue in the context of fibromyalgia, 2) suggest a rationale for assessment of fatigue, and 3) describe non-pharmacological and pharmacological management modalities studied in the context of fibromyalgia that also improve fatigue. While this is not a systematic review, this critical narrative review may guide clinical decisions when faced with a fatigued patient with fibromyalgia.

**Search strategy**

The search was performed using Ovid MEDLINE, Ovid EMBASE, and EBSCO CINAHL (Cumulative Index of Nursing and Allied Health Literature), covering 2000 through May 2013. The search strategy used controlled vocabulary (subject headings) and text words in the title.
and/or abstract - fibromyalgia, fatigue and synonyms related to fatigue (for example, weakness, tiredness, exhaustion, stiffness, depression). The results were limited to English, publication format (review, meeting abstract) and study designs (trials, cohort studies, systematic reviews), yielding a total of 644 unique publications.

**Fatigue characteristics: qualitative research**
Results of qualitative studies provide insights into the encumbrance that fatigue inflicts on patients with fibromyalgia and the concomitant problem of articulating to their doctors what is wrong. Patients with fibromyalgia describe fatigue as ‘an inescapable or overwhelming feeling of profound physical tiredness,’ ‘weakness in the muscles,’ ‘an uncontrollable, unpredictable constant state of never being rested,’ ‘a ghastly sensation of being totally drained of every fiber of energy,’ ‘not proportional to effort exerted,’ ‘not relieved by rest,’ ‘having to do things more slowly,’ and ‘an invisible foe that creeps upon them unannounced and without warning’ [8,18,19]. Patients also report that fatigue is interwoven, influenced, and intensified by pain, and is sometimes more severe than pain [18]. Although fatigue is reported by both men and women with fibromyalgia, one study demonstrated that men had less fatigue compared to women and a second study reported that men tend to focus more on pain and women on fatigue [8,20].

**Fatigue correlates: insights into etiology**
The key symptoms of fibromyalgia - pain, fatigue, unrefreshing sleep, dyscognition, and depressed mood - do not occur in isolation. Rather, they often present concurrently, in varying severity, and are intertwined with and influence each other (Figure 1). Indeed, studies demonstrate that chronic persistent pain (both from abnormal central sensitization and maintenance of nociceptive pain from peripheral pain generators), poor sleep quality (subjective report and objective measures), depressed mood, anxiety, or combinations of these are associated with fatigue [21-23] (Table 1). In addition to common fibromyalgia symptoms, clinical characteristics (for example, body mass index), health behaviors (for example, physical activity levels), and psychological variables (for example, negative affect, catastrophizing, affect regulation),

| Correlate                  | Design and sample                                | Direction                                      |
|----------------------------|--------------------------------------------------|-----------------------------------------------|
| Pain                       | 4 cross-sectional [5,31-33]                       | Positive                                      |
|                            | 6 longitudinal (5 months, 30 days, 10 days, 6 days) [21,22,28,29,34-36] | Negative                                      |
| Sleep duration             | 1 longitudinal (30 days) [34]                    | Negative                                      |
| Sleep quality              | 2 longitudinal (6 days, 3 days) [21,37]          | Negative                                      |
| Sleep disturbance          | 1 cross-sectional [5]                            | Positive                                      |
|                            | 1 longitudinal (30 days) [29,35]                 | Positive                                      |
| Anxiety and depression     | 5 cross-sectional [5,31,38-40]                    | Positive                                      |
|                            | 4 longitudinal (5 months, 30 days, 6 days) [21,22,29,34,35] | Positive                                      |
| Tenderness                 | 2 cross-sectional [5,38]                         | Positive                                      |
| Stiffness                  | 1 cross-sectional [33]                           | Positive                                      |
|                            | 1 longitudinal (10 days) [28]                    | Positive                                      |
| Disability                 | 2 cross-sectional [5,33]                         | Positive                                      |
| Cognitive complaints       | 1 cross-sectional [41]                           | Positive                                      |
| Gastrointestinal distress  | 1 cross-sectional [5]                            | Positive                                      |
| Negative events            | 1 longitudinal (30 days) [35]                    | Positive                                      |
| Positive events            | 1 longitudinal (30 days) [35]                    | Negative same day, positive following day     |
| Positive affect            | 1 cross-sectional [42]                           | Negative                                      |
|                            | 1 longitudinal (30 days) [29]                    | Negative                                      |
| Negative affect            | 1 longitudinal (30 days) [29]                    | Positive                                      |
| Internal locus of control  | 1 cross-sectional [43]                           | Negative                                      |
| External locus of control  | 1 cross-sectional [43]                           | Negative                                      |
| Emotional distress         | 1 longitudinal (30 days) [36]                    | Positive                                      |
| Fibromyalgia severity      | 2 cross-sectional [5,44]                         | Positive                                      |
also demonstrate strong associations with fatigue [22-27] (Table 1). In addition to cross-sectional associations, diurnal rhythmicity and lag relationships have also been demonstrated between fatigue and other fibromyalgia symptoms (particularly pain, stiffness, and affect), suggesting that one variable can influence or predict the others [28,29]. Appreciating these associations is important in fatigue assessment because daily assessment of fatigue may uncover lag relationships with other symptoms, providing avenues for intervention. Collectively, these studies indicate that many symptoms feed into fatigue and the implication of this finding, for both clinical practice and research, is that fatigue assessment must consider this multi-dimensionality. This is not unlike pain in fibromyalgia, which is increasingly demonstrated to be multidimensional, with contributions from central pain, peripheral musculoskeletal pain generators, and neuropathic pain, among other pathways [30].

The association of objective tests assessing the hypothalamic-pituitary-adrenal axis, hypothalamic-pituitary-gonadal axis, and corticotropin releasing factor in the cerebrospinal fluid with fatigue have been negative or inconclusive [38,45,46]. However, preliminary studies indicate that histological characteristics of skeletal muscle, such as muscle fiber distribution and capillary density, may be correlated with post-exertional malaise [47]. More recently, genomic studies have sought to identify possible physiologic pathways to explain the symptoms experienced by patients with fibromyalgia. Gene expression studies suggest the significant role of the catechol-O-methyltransferase, cytokine, adrenergic, dopamine, glucocorticoid and mineralocorticoid receptors, iron channel receptors and serotonin transporter in developing and maintaining the symptom complex [48,49]. However, most of the early studies were conducted using pre-selected gene single nucleotide polymorphisms, which may introduce selection bias in assuming the disease etiology of fibromyalgia. One recent study investigating whole genome expression in patients with fibromyalgia with fatigue found an upregulation of centromere protein K (CENPK) and heat shock protein 90 kDa alpha (cytosolic, class A member 1 (HSP90AA1)) genes in fibromyalgia subjects when compared with age-, gender-, and race-matched healthy controls [50]. These genes are associated with glucocorticoid receptor signaling and the protein ubiquitination pathway (GIN1, GRAMD1C, ZNF880, NFYB, CENPK, CA1, and TNS1) [51]. Impairment of the ubiquitination pathways has been demonstrated to be associated with neurodegenerative

![Figure 2](image_url)
diseases (for example, Alzheimer’s and Parkinson’s disease) and depression [52]. Additionally, interferon signaling and interferon regulatory pathways (associated with spinal nociception) distinguished between the pain groups, and dendritic cell maturation (associated with mood) delineated between the catastrophizing groups [50]. Collectively, these studies suggest that multiple physiological mechanisms may be associated with the symptom of fatigue.

**Fatigue assessment**

In the absence of objective biomarkers, assessment of fatigue is guided solely by patient-reported symptoms. Presently, there are no algorithms with which to systematically assess and treat fatigue. As noted, assessment must consider fatigue’s multidimensional manifestations. In clinical practice, therefore, evaluation of fatigue must account for both the experience of fatigue, as well as its functional impact, and place these in the context of other symptoms and co-morbidities specific to the particular patient.

The assessment begins with a thorough history and physical examination (to identify reversible causes of fatigue), and a systematic symptom-centered assessment pertaining not only to fatigue but also to pain, sleep, autonomic symptoms, causes of unrefreshing sleep (for example, obstructive sleep apnea, restless leg syndrome), psychiatric disorders, such as depression and anxiety, and inquiry into health behaviors, daily practices, such as physical activity, and dietary habits (Figure 2). Table 2 illustrates common fibromyalgia symptoms, sample assessment tools, conditions to consider and suggestions for objective tests to evaluate abnormal symptoms.

In the research setting, in the absence of an objective measure, fatigue in fibromyalgia can only be assessed with validated, self-report questionnaires. Although the OMERACT Fibromyalgia Working Group recommends the assessment of fatigue in all clinical trials of

| Table 2 Symptom assessment in the clinical setting |
|-----------------------------------------------|
| **Symptom** | **Sample assessment tools** | **Conditions to consider** | **Objective tests** |
| Activity intolerance | BPI pain interference [53] | Deconditioning | 6 minute walk test |
| | MFI reduced activity [54] | Obesity | Cardiopulmonary exercise test |
| | SF-36 role emotional, role physical [55,56] | Neuromuscular disorder | 30-second chair-stand test |
| Affective | GAD-7 [57] | Anxiety disorder | Body mass index |
| | PHQ-9 [58] | Generalized anxiety disorder | |
| | HADS [59] | Depression | |
| | CES-D [60] | Dysthymia | |
| | | Somatoform disorder | |
| Autonomic | ASP-31 [61] | Orthostatic intolerance | Thermoregulatory sweat test |
| | | Autonomic neuropathies | Autonomic reflex screen |
| | | Postural orthostatic tachycardia syndrome | |
| Pain | BPI [53] | Regional pain syndromes | Imaging |
| | Pain VAS | Neuropathy | Electromyography |
| | | Inflammatory arthritis | Laboratory testing for inflammation |
| | | Degenerative arthritis | Muscle biopsy |
| | | Headaches | Quantitative sensory testing |
| | | Myopathy | |
| Unrefreshing sleep | MOS-Sleep [62] | Insomnia | Overnight oximetry |
| | Berlin Sleep Questionnaire | Obstructive sleep apnea | Polysomnography |
| | Restless legs screen | Restless legs syndrome | Actigraphy |
| | | Periodic limb movement disorder | |
| | | Narcolepsy | |
| | | Sleep phase disorder | |

ASP-31, Autonomic Symptom Profile-31; BPI, Brief Pain Inventory; CES-D, Center for Epidemiologic Studies Depression Scale; GAD-7, Generalized Anxiety Disorder questionnaire; HADS, Hospital Anxiety and Depression Scale; MFI, Multidimensional Fatigue Inventory; MOS-Sleep, Medical Outcomes Study Sleep Scale; PHQ-9, Patient Health Questionnaire; SF-36, Medical Outcomes Study Short Form-36; VAS, Visual Analogue Scale.
Fatigue assessment in clinical trials has utilized single item measures (visual analog scale - fatigue), multidimensional fatigue measures (for example, Multidimensional Fatigue Inventory and Multidimensional Assessment of Fatigue), or single items from composite measures, such as the Fibromyalgia Impact Questionnaire - Revised and the Medical Outcomes Study Short Form-36 [54,55,63-66] (Table 3).

Table 3 Sample list of questionnaires that have been used in the assessment of fatigue in clinical trials

| Measure                                      | Dimensions of fatigue                                      | Scaling and number of items | Features                                                                 |
|----------------------------------------------|------------------------------------------------------------|-----------------------------|-------------------------------------------------------------------------|
| Chalder Fatigue Questionnaire [67,68]         | Physical and mental                                        | 11 items                    | 2-3 minute administration time                                         |
|                                              |                                                             | 4-point Likert scale        | Higher = worse                                                          |
|                                              |                                                             |                             | Recall period for the past month                                       |
| Checklist Individual Strength (CIS) [69]       | Subjective experience, concentration, motivation, and physical activity | 20 items                    | 4-5 minute administration time                                         |
|                                              |                                                             | 7-point Likert scale        | Higher = worse                                                          |
|                                              |                                                             |                             | Designed for chronic fatigue syndrome, but also used with fibromyalgia and healthy populations |
|                                              |                                                             |                             | Recall period for past 2 weeks                                          |
| Fatigue Severity Scale (FSS) [70]              | Physical, social, and cognitive                            | 9 items                     | 2-3 minute administration time                                         |
|                                              |                                                             | 7-point Likert scale        | Higher = worse                                                          |
|                                              |                                                             |                             | Recall period for the past week                                         |
| Medical Outcome Study Short Form-36 (SF-36) Vitality Subscale [55,56] | Energy and vitality                                      | 4 items                     | 1-2 minute administration time                                         |
|                                              |                                                             | 6-point (version 1) or 5-point (version 2) Likert scale | Higher scores = better                                                  |
|                                              |                                                             |                             | Recall period for the past 4 weeks                                      |
| Multidimensional Assessment of Fatigue (MAF) [64] | Severity, stress, degree of interference with activities of daily living, timing, and global | 16 items                    | 5-8 minute administration time                                         |
|                                              |                                                             | 10-point rating scales for 1–14, 15 and 16 have 4 ordinal responses | Higher scores = worse                                                  |
|                                              |                                                             |                             | Designed for rheumatoid arthritis, but also used in fibromyalgia       |
|                                              |                                                             |                             | Recall period for the past week                                         |
| Multidimensional Fatigue Inventory (MFI) [54]  | Global experience and somatic, cognitive, affective, and behavioral symptoms | 20 items                    | 4-5 minute administration time                                         |
|                                              |                                                             | 5-point Likert scale        | Higher scores = worse                                                  |
|                                              |                                                             |                             | Recall period is stated as ‘lately’                                     |
| Visual Analogue Scale (VAS)                   | Any dimension required, typically severity or intensity     | 1 item                      | <1 minute administration time                                          |
|                                              |                                                             | 100 mm horizontal line anchored by two statements           | Recall period typically 1 week, varies                                 |

Debate also remains concerning the aspects of fatigue that must be assessed and whether measurement of fatigue requires subsets of questions targeting its separate manifestations (for example, global, somatic, affective, cognitive, and behavioral). Ongoing work from PROMIS and other groups will bring clarity to these issues. Until then, when selecting a fatigue questionnaire, researchers must consider its purpose. If the questionnaire is to be used as a screening tool, a shorter, single-item measure may be appropriate, or if the need is to evaluate an intervention, a multidimensional scale may be more appropriate.

**Fatigue management**

Our current understanding of the pathophysiology of fatigue suggests that its management in patients with fibromyalgia is most successful if developed by a multi-disciplinary team with the patient as an equal participant. The treatment program should be individualized, and likely will incorporate combinations of behavioral, pharmacological, and rehabilitative interventions. Management is not aimed at the etiology of fatigue; rather, the focus is on symptoms, contributing factors, and treatment of comorbidities. Clinical experience suggests that a step-wise approach integrating different modalities with periodic assessment is ideal. This approach should be continued until clinically meaningful symptom improvement is achieved.
Care should always begin with patient education on the nature of fatigue and fibromyalgia, setting pragmatic goals for symptom reduction, and improvement of function. Patient education can include strategies such as pacing, energy conservation, increasing lifestyle physical activity, getting regular exercise, rest-activity balance, balanced diet, lifestyle moderation, stress management, and sleep hygiene. As previously mentioned, daily symptom logs can help identify activities that exacerbate fatigue and other fibromyalgia symptoms. They can also guide individualization of non-pharmacological modalities. A selected listing of pharmacological and non-pharmacological clinical trials conducted in fibromyalgia where fatigue was also assessed is given in Tables 4, 5 and 6.

### Table 4 Non-pharmacological strategies

| Intervention | Design and sample | Scales used | Effect on fatigue |
|--------------|-------------------|-------------|------------------|
| **Conventional therapies** | | | |
| Cognitive behavioral therapy | One RCT comparing multidisciplinary treatment to treatment augmented with CBT (n = 83) of women with FM [71] | FIQ | Cannot draw conclusion |
| Exercise - aerobic exercise | 1 single-arm study of women with FM, CFS, and CFIDS (n = 7) [72] | VAS fatigue | Cannot draw conclusion in single arm study, 2 meta-analyses found improvement, MCID cannot be determined |
| | 2 meta-analyses of 28 RCTs (n = 2,494) [73] and 34 RCTs (n = 2,276) [74] | | |
| Exercise - strength training | 1 RCT (n = 26) of postmenopausal women with FM [75] | VAS fatigue | Clinically meaningful improvement in 2 RCTs, cannot draw conclusion in 1 RCT |
| Multicomponent/ multidisciplinary treatment | 1 double-arm study of aerobic versus strength training (n = 30) of women with FM [76] | | |
| | 1 RCT (n = 21) of premenopausal women with FM [77] | | |
| | 2 single-arm studies (n = 305) of patients with FM [78,79], 4 RCTs (n = 513) of patients with FM [80-83], 1 RCT (n = 855) in patients with FM, OA, and RA [84] | FIQ fatigue | Clinically meaningful improvement in 4 RCTs, no clinically meaningful improvement in 3 RCTs |
| | 1 meta-analysis of 9 RCTs (n = 1119) [85] | VAS fatigue | Meta-analysis found no evidence for efficacy in long-term follow-up |
| **Complementary and alternative medicine** | | | |
| Acupuncture | 1 meta-analysis of 7 RCTs (median treatment time 9 sessions, n = 385) [86] | | No improvement |
| Meditative movement therapies | 1 meta-analysis of 7 RCTs (n = 362) [87] | | Improvement overall, in subgroup analysis, only yoga improved fatigue |

*aMultidisciplinary treatments varied between studies but typically included education, exercise, psychotherapy (that is, cognitive behavioral therapy (CBT), dialectical behavior therapy (DBT), and so on), and occupational and physical therapies. CF, chronic fatigue; CFIDS, chronic fatigue and immune dysfunction syndrome; FIQ, Fibromyalgia Impact Questionnaire; FM, fibromyalgia; MCID, minimal clinically important difference; OA, osteoarthritis; RA, rheumatoid arthritis; RCT, randomized controlled trial; VAS, Visual Analogue Scale.

### Table 5 Food and Drug Administration-approved pharmacological strategies

| Intervention | Design and sample | Scales used | Mechanism of action | Effect on fatigue |
|--------------|-------------------|-------------|---------------------|------------------|
| Duloxetine | 3 double-blind, placebo-controlled RCTs of patients with FM (n = 899) [88-90] | MFI | Blocks reuptake of serotonin and norepinephrine within the central nervous system | Clinically meaningful improvement in 2 of the RCTs, no clinically meaningful improvement in the other |
| | | FIQ fatigue | | |
| Milnacipran | 6 double-blind, placebo-controlled RCTs of patients with FM (n = 4,243) [91-96] | MFI | Blocks reuptake of serotonin and norepinephrine within the central nervous system | No clinically meaningful improvement in 4 RCTs using MFI, cannot draw conclusion in 2 RCTs, and clinically meaningful improvement in 1 RCT (VAS fatigue) |
| | 1 double-blind, dose finding trial (n = 466) [97] | VAS fatigue | | |
| Pregabalin | 3 double-blind, placebo-controlled RCTs of patients with FM (n = 2,328) [98-100] | MAF | Interacts with the alpha-2-delta subunit of voltage-regulated calcium channels | No clinically meaningful improvement in 2 RCTs, cannot draw conclusion in 1 RCT |

FIQ, Fibromyalgia Impact Questionnaire; FM, fibromyalgia; MAF, Multidimensional Assessment of Fatigue; MFI, Multidimensional Fatigue Inventory; RCT, randomized controlled trial; VAS, Visual Analogue Scale.
| Intervention                     | Design and sample                                      | Scales used                                      | Effect on fatigue                                                                 |
|---------------------------------|--------------------------------------------------------|--------------------------------------------------|-----------------------------------------------------------------------------------|
| Non-pharmacological             |                                                        |                                                  |                                                                                  |
| Balneotherapy                   | 3 RCTs (n = 128) of women with FM [101-103]            | VAS fatigue                                     | Clinically meaningful improvement                                                 |
| Cognitive behavioral therapy    | 1 RCT comparing multidisciplinary treatment to treatment augmented with CBT (n = 83) of women with FM [71] | FIQ fatigue                                     | Cannot draw conclusion                                                           |
| Electroconvulsive therapy       | 1 pilot study (n = 13) of patients with FM and concomitant depression [104] | FIQ fatigue                                     | Clinically meaningful improvement                                                 |
| Low-energy laser therapy        | 1 single-blind, placebo-controlled trial (n = 40) of women with FM [105] | Likert scale rating fatigue as mild, moderate, severe or extreme | Cannot draw conclusion in 1 RCT, clinically meaningful improvement in 1 RCT |
| Mindfulness                     | 1 open pilot study (n = 40) of women with FM [107]     | Not identified                                   | Cannot draw conclusion                                                           |
| Noninvasive cortical electrostimulation | 1 placebo-controlled RCT (n = 77) of patients with FM [108] | FIQ fatigue                                     | Clinically meaningful improvement                                                 |
| Pulsed ultrasound and interferential current | 1 double-blind, placebo-controlled RCT (n = 17) of patients with FM [109] | VAS fatigue                                     | Clinically meaningful improvement                                                 |
| Qigong                          | 1 single-arm pilot study (n = 10) in women with FM [110] | FIQ fatigue                                     | Cannot draw conclusion                                                           |
| Sensory motor rhythm treatment  | 1 RCT (n = 36) patients with FM [111]                  | VAS fatigue                                     | Clinically meaningful improvement                                                 |
| TENS                            | 1 RCT (n = 28) women with FM where TENS was used as an adjuvant to aerobic and stretching exercise [112] | FIQ fatigue                                     | Clinically meaningful improvement                                                 |
| Transcranial magnetic stimulation | 2 double-blind, placebo-controlled RCTs (n = 70) of patients with FM [113,114] | FIQ fatigue                                     | Clinically meaningful improvement                                                 |
| Vegetarian diet                 | 1 observational study (n = 30) of patients with FM [115] and 1 open RCT (n = 78) of patients with FM [116] | FIQ fatigue, VAS fatigue                       | Clinically meaningful improvement in 1 RCT, cannot draw conclusion in open RCT   |
| Whole-body vibration exercise   | 1 pilot study (n = 36) of women with FM [117]          | FIQ fatigue                                     | Clinically meaningful improvement                                                 |
| Written emotional expression    | 1 RCT (n = 92) of patients with FM [118]               | Vitality subscale of SF-36                      | Cannot draw conclusion                                                           |
| Yoga                            | 1 pilot RCT (n = 53) of women with FM [119]            | FIQ fatigue                                     | Clinically meaningful improvement                                                 |
| Pharmacological                 |                                                        |                                                  |                                                                                  |
| Amitriptyline                   | 2 placebo-controlled RCTs of patients with FM (n = 127) [106,120] | FIQ fatigue                                     | 1 RCT found clinically meaningful improvement, 1 RCT found no clinically meaningful improvement, cannot draw conclusion in 1 open-label RCT |
| Armodafinil                     | 1 open RCT (n = 78) of patients with FM [116]          | VAS fatigue                                     | 2 meta-analyses found improvement, but MCID cannot be determined                 |
| Brainwave suppression           | 2 meta-analyses of 10 RCTs (n = 615) [121] and 13 RCTs [122] in patients with FM |                                                  |                                                                                  |
| Cyclobenzaprine                 | 1 single-blind, placebo-controlled, RCT of patients with FM and fatigue (n = 60) [123] | BFI                                             | Cannot draw conclusion                                                           |
| Esreboxetine                    | 1 meta-analysis of 5 RCTs (n = 312) in patients with FM [124] | MAF                                             | No improvement                                                                  |
| Fluoxetine                      | 2 double-blind, placebo-controlled, multicenter RCTs (n = 1,389) [125,126] | MAF                                             | No clinically meaningful improvement                                               |
| Gamma-hydroxybutyrate/ sodium oxybate | 1 double-blind, placebo-controlled RCT of patients with FM (n = 60) [127] | FIQ fatigue                                     | Clinically meaningful improvement                                                 |
| Vegetarian diet                 | 1 open-label pilot study (n = 11) of patient with FM [128] | VAS, FIQ fatigue, Retrospective review           | Clinically meaningful improvement in 2 RCTs, cannot draw conclusion in 1 RCT and retrospective review |
studies, fatigue was only assessed as a secondary outcome (pain was primary). Even so, clinically meaningful changes in fatigue were demonstrated in some of these efficacy studies. This indicates that treatment modalities studied in the context of fibromyalgia could also be utilized to improve fatigue.

Non-pharmacological symptom management modalities, such as graded aerobic exercise, have demonstrated beneficial effects on physical capacity and fibromyalgia symptoms, including fatigue [73,74] (Table 4). Combining aerobic exercise with resistance and strength training may offer additional benefits [146,147]. Cognitive behavioral-based therapies (particularly for comorbid depression, anxiety, and pain), meditative movement therapies (for example, tai chi, yoga, qigong) and education sessions led by occupational therapists to enable patients to identify individual lifestyle factors that exacerbate fatigue and develop appropriate fatigue management and energy conservation techniques have good efficacy data [51,148-150]. As with medications that require an adequate dose and duration for clinical efficacy, non-pharmacological modalities will only be effective if they are adequately dosed over the period of time that is required for physical, cognitive, and psychological rehabilitation. In most cases this may require several months and a step-wise, graded approach. Patients should be educated upfront to optimize success and compliance with the management strategy. Complementary
and alternative therapies, such as acupuncture and homoeopathy, have not demonstrated benefit in clinical studies, although patients commonly utilize these modalities, citing clinical benefit [151]. Carefully designed future trials will shed light on their use.

Pharmacologic modalities
Tries of serotonin-norepinephrine reuptake inhibitors, selective serotonin reuptake inhibitors, tricyclics, and alpha-2 delta ligands that impact multiple fibromyalgia symptoms suggest that these medications could also improve the symptom of fatigue (Tables 5 and 6). The choice of medication depends on the patient’s comorbid symptoms and use of a single medication to address multiple symptoms may be beneficial to minimize side effects. For example, in a fatigued patient with fibromyalgia with comorbid depression, serotonin-norepinephrine reuptake inhibitors, selective serotonin reuptake inhibitors, or tricyclics that have a differential effect on mood may be the pharmacological agent of choice. On the other hand, an alpha-2-delta ligand or a tricyclic may be more appropriate for a patient with comorbid unrefreshing sleep. If insomnia and unrefreshing sleep are the most bothersome symptoms for the patient, then targeting this symptom domain alone may improve both sleep and fatigue. Central nervous system stimulants may be most appropriate for patients with fatigue and comorbid narcolepsy. Though this class of medications is widely adopted in clinical practices to help patients with function, there are not enough data to support this practice [52,123,152]. Despite the demonstrated efficacy of some of these pharmacological agents, the clinician should be mindful that not all patients with fibromyalgia can tolerate medications. Medication sensitivity and medication intolerance is a major patient concern. Judicious use of lower doses of medication with frequent assessment for efficacy and side effects may help some patients [153].

Botanicals and dietary supplements
Botanicals, such as ginseng, and dietary supplements, such as coenzyme Q10, s-adenosyl methionine and acetyl-l-carnitine, have been posited to relieve fatigue [120,140,144,145] (Table 6). Although these agents are largely devoid of the side effect profile of pharmacologic agents, only preliminary efficacy data are available.

Conclusion
Fatigue is a complex symptom that is differentially experienced by individual patients with fibromyalgia depending on their genetic, biological, and psychosocial makeup, self-efficacy and emotional regulatory capacity, and presence of comorbidities. The profile of fatigue in fibromyalgia is similar to that in many chronic conditions, although the presence of fibromyalgia with other rheumatological conditions seems to intensify fatigue [154,155]. A commonly observed theme in the literature is the co-occurrence of fatigue with other centrally mediated symptoms such as pain, unrefreshing sleep, affective symptoms, and the influence of psychosocial variables. This may imply that the same central mechanisms that drive pain, mood, and sleep also drive fatigue. Given that these symptoms (for example, pain, fatigue, sleep) occur concurrently, we tend to assume that they manifest at the same level. This may not be an accurate way to view fatigue. It may be that fatigue is a higher order construct, or meta-construct that is fed by other, more discrete symptoms. Only further inquiry will address these questions.

At the clinical level, given our current limitations, fatigue management is best facilitated by conducting a nuanced fatigue assessment in routine clinical encounters to include a thoughtful history and investigation for treatable causes of fatigue, and screening for fatigue and other common comorbid fibromyalgia symptoms such as pain, anxiety, depression, sleep, and stress. Fatigue assessment and management can also be enhanced by encouraging patients to keep symptom logs to gain insights into lag relationships among symptoms, educating patients about the nature of fatigue, and setting realistic goals for symptom management (that is, focus on decreasing the impact of symptoms and improve function rather than symptom alleviation alone).

From a research perspective, a disease-specific fatigue measure for fibromyalgia is needed to move the field forward. Additionally, studies to understand mechanisms (for example, biological, physiological, or psychological) and management of fatigue are also needed. As the study of fatigue in fibromyalgia advances, multidisciplinary collaborations that are patient-centered and facilitate patient engagement will guide treatment options to provide relief.
practice in rehabilitation medicine: a PROMIS fatigue item bank example. Arch Phys Med Rehabil 2011, 92:520–527.
18. Soderberg S, Lundman B, Norberg A: The meaning of fatigue and tiredness as narrated by women with fibromyalgia and healthy women. J Clin Nurs 2002, 11:247–255.
19. Sturge-Jacobs M: The experience of living with fibromyalgia: confronting an invisible disability. Res Theory Nurs Pract 2002, 16:19–31.
20. Yunus MB, Inanici F, Aldag JC, Mangold RF: Fibromyalgia in men: comparison of clinical features with women. J Rheumatol 2000, 27:485–490.
21. Nicasio PM, Moxham EG, Schuman CE, Gevirtz RN: The contribution of pain, reported sleep quality, and depressive symptoms to fatigue in fibromyalgia. Pain 2002, 100:271–279.
22. Nicasio PM, Schuman CC: The prediction of fatigue in fibromyalgia. J Musculoskelet Pain 2005, 13:15–25.
23. Finan PH, Zautra AJ: Fibromyalgia and fatigue: central processing, widespread dysfunction. PM R 2010, 2:431–437.
24. Arranz L, Canela MA, Rafesas M: Relationship between body mass index, fat mass and lean mass with SF-36 quality of life scores in a group of fibromyalgia patients. Rheumatol Int 2012, 32:3605–3611.
25. Guymier EK, Manoff P, Littlejohn GO: Clinical characteristics of 150 consecutive fibromyalgia patients attending an Australian public hospital clinic. Int J Rheum Dis 2012, 15:348–357.
26. Finan PH, Zautra AJ, Davis MC: Daily affect relations in fibromyalgia patients reveal positive affective disturbance. Psychosom Med 2009, 71:474–482.
27. Davis MC, Zautra AJ, Reich JW: Vulnerability to stress among women in chronic pain from fibromyalgia and osteoarthritis. Ann Behav Med 2001, 23:215–226.
28. Bellamy N, Sothern RB, Campbell J: Aspects of diurnal rhythmity in pain, stiffness, and fatigue in patients with fibromyalgia. J Rheumatol 2004, 31:379–389.
29. Zautra AJ, Fasman R, Parish BP, Davis MC: Daily fatigue in women with osteoarthritis, rheumatoid arthritis, and fibromyalgia. Pain 2007, 128:128–135.
30. Staud R: Peripheral pain mechanisms in chronic widespread pain. Best Pract Res Clin Rheumatol 2011, 25:155–164.
31. Kurtze N, Svebak S: Fatigue and patterns of pain in fibromyalgia: correlations with anxiety, depression and co-morbidity in a female county sample. Br J Med Psychol 2001, 74:523–537.
32. Hughes L: Physical and psychological variables that influence pain in patients with fibromyalgia. Orthop Nurs 2006, 25:112–119, quiz 120–111.
33. Wolfe F: Determinants of WOMAC function, pain and stiffness scores: evidence for the role of low back pain, symptom counts, fatigue and depression in osteoarthritis, rheumatoid arthritis and fibromyalgia. Rheumatology (Oxford) 1999, 38:355–361.
34. Hamilton NA, Affleck G, Tennen H, Karlson C, Luxton D, Preacher KJ, Tempnlin JL: Fibromyalgia: the role of sleep in affect and in negative event reactivity and recovery. Health Psychol 2008, 27:490–497.
35. Panish BP, Zautra AJ, Davis MC: The role of positive and negative interpersonal events on daily fatigue in women with fibromyalgia, rheumatoid arthritis, and osteoarthritis. Health Psychol 2008, 27:694–702.
36. Koblin R, Bradshaw DH, Donaldson GW, Turk DC: Sequential analyses of daily symptoms in women with fibromyalgia syndrome. J Pain 2011, 12:649–93.
37. Landis CA, Frey CA, Lentz MJ, Rothermel J, Buchwald D, Shaver JLF: Self-reported sleep quality and fatigue correlates with actigraphy in middle women with fibromyalgia. Nurs Res 2003, 52:140–147.
38. Gur A, Cevik R, Sarac AC, Colpan L, Em S: Hypothalamic-pituitary-gonadal axis and cortisol in young women with primary fibromyalgia: the role of potential roles, fatigue, and sleep disturbance in the occurrence of hypocrasitism. Ann Rheum Dis 2004, 63:1504–1506.
39. White KP, Nelson WR, Harth M, Ostbye T, Speechley M: Chronic widespread musculoskeletal pain with or without fibromyalgia: psychological distress in a representative community adult sample. J Rheumatol 2002, 29:588–594.
40. Nandku S, Gundersen KT, Svebak S: The role of anxiety and depression in fatigue and patterns of pain among subgroups of fibromyalgia patients. Br J Med Psychol 1998, 71:185–194.
41. Suh JH: Neuropsychological impairment in fibromyalgia: relation to depression, fatigue, and pain. J Psychosom Res 2003, 55:521–529.
84. Lorig KR, Ritter PL, Laurent DD, Plant K: The internet-based arthritis self-management program: a one-year randomized trial for patients with arthritis or fibromyalgia. Arthritis Rheum 2008, 59:1009–1017.
85. Hauser W, Bernardy K, Arnold B, Offenbacher M, Schiltenwolf M: Efficacy of multicomponent treatment in fibromyalgia syndrome: a meta-analysis of randomized controlled clinical trials. Arthritis Rheum 2009, 61:216–224.
86. Langhhorst J, Klose P, Musial F, Inich D, Hauser W: Efficacy of acupuncture in fibromyalgia syndrome - a systematic review with a meta-analysis of controlled clinical trials. Rheumatology (Oxford) 2010, 49:778–788.
87. Langhhorst J, Klose P, Dobos GJ, Bernardy K, Hauser W: Efficacy and safety of meditative movement therapies in fibromyalgia syndrome: a systematic review and meta-analysis of randomized controlled trials. Rheumatol Int 2013, 33:193–207.
88. Arnold LM, Wang F, Ahl J, Gaynor PJ, Wohleitner MM: Improvement in multiple dimensions of fatigue in patients with fibromyalgia treated with duloxetine: secondary analysis of a randomized, placebo-controlled trial. Arthritis Res Ther 2011, 13:806.
89. Chappell AS, Bradley LA, Wiltse C, Derke MJ, D’Souza DN, Saperth M: A six-month double-blind, placebo-controlled, randomized trial of duloxetine for the treatment of fibromyalgia. Int J Gen Med 2008, 1:91–102.
90. Arnold LM, Lu Y, Crofford LJ, Wohleitner M, Derke MJ, Iyengar S, Goldstein DJ: A double-blind, multicenter trial comparing duloxetine with placebo in the treatment of fibromyalgia patients with or without major depressive disorder. Arthritis Rheum 2004, 50:2974–2984.
91. Clauw DJ, Mease P, Palmer RH, Gendreau RM, Wang Y: Milnacipran for the treatment of fibromyalgia in adults: a 15-week, multicenter, randomized, double-blind, placebo-controlled, multiple-dose clinical trial. Clin Ther 2008, 30:1998–2004.
92. Clauw DJ, Zachrisson O, Perrot S, Mainou Y: A European multicenter randomized double-blind placebo-controlled monotherapy clinical trial of milnacipran in treatment of fibromyalgia. J Rheumatol 2010, 37:851–859.
93. Mease PJ, Clauw DJ, Gendreau RM, Rao SG, Kranzler J, Chen W, Palmer RH: The efficacy and safety of milnacipran for treatment of fibromyalgia. A randomized, double-blind, placebo-controlled trial. J Rheumatol 2009, 36:398–409. Published erratum appears in J Rheumatol 2009, 36:661.
94. Gendreau RM, Thom MD, Gendreau JF, Kranzler JD, Ribeiro S, Gracely RH, Williams DA, Mease PJ, McLean SA, Clauw DJ: Efficacy of milnacipran in patients with fibromyalgia. J Rheumatol 2005, 32:1975–1985.
95. Arnold LA, Gendreau RM, Palmer RH, Gendreau JF, Wang Y: Efficacy and safety of milnacipran 100 mg/day in patients with fibromyalgia: results of a randomized, double-blind, placebo-controlled trial. Arthritis Rheum 2010, 62:2745–2756.
96. Vitton O, Gendreau M, Gendreau J, Kranzler J, Rao SG: A double-blind placebo-controlled trial of milnacipran in the treatment of fibromyalgia. Hum Psychopharmacol 2004, 19:527–535.
97. Branco JC, Cherin P, Montagne A, Bourouibi A: Long-term therapeutic response to milnacipran treatment for fibromyalgia. A European 1-year extension study following a 3-month study. J Rheumatol 2011, 38:1403–1412.
98. Pauer L, Atkinson G, Murphy TK, Petersel D, Zehir B: Long-term maintenance of response across multiple fibromyalgia symptom domains in a randomized withdrawal study of pregabalin. Clin J Pain 2012, 28:609–614.
99. Mease PJ, Russell U, Arnold LM, Florian H, Young JP Jr, Martin SA, Sharma U: A randomized, double-blind, placebo-controlled, phase III trial of pregabalin in the treatment of patients with fibromyalgia. J Rheumatol 2008, 35:502–514.
100. Crofford LJ, Rowbotham MC, Mease PJ, Russell U, Dworkin RH, Corbin AE, Young JP Jr, LaMoreaux LK, Martin SA, Sharma U: Pregabalin 100–105: Study Group: Pregabalin for the treatment of fibromyalgia syndrome: results of a randomized, double-blind, placebo-controlled trial. Arthritis Rheum 2005, 52:1264–1273.
101. Domnez A, Karagulle MZ, Tercan N, Dinler M, Issever H, Karagulle M, Turan M: SPA therapy in fibromyalgia: a randomised controlled clinic study. Rheumatol Int 2005, 26:168–172.
102. Altan L, Bingol U, Aykac M, Koc Z, Yurtkuran M: Investigation of the effects of pool-based exercise on fibromyalgia syndrome. Rheumatol Int 2004, 24:272–277.
103. Sukola D, Abu-Shakra M, Neumann L, Odes L, Shneider E, Flusser D, Suenken S: Balneotherapy for fibromyalgia at the Dead Sea. Rheumatol Int 2001, 20:105–108.
104. Huusha MI, Haanpaa ML, Leinonen EN: Electroconvulsive therapy in patients with depression and fibromyalgia. Eur J Pain 2004, 8:371–376.
105. Gur A, Karakoc M, Nas K, Cevik R, Sarac J, Demir E: Efficacy of low power laser therapy in fibromyalgia: a single-blind, placebo-controlled trial. Lasers Med Sci 2002, 17:57–61.
106. Gur A, Karakoc M, Nas K, Cevik R, Sarac J, Ataoglu S: Efectos of low power laser and low dose amitriptyline therapy on clinical symptoms and quality of life in fibromyalgia: a single-blind, placebo-controlled trial. Rheumatol Int 2002, 22:188–193.
107. Maddali Bongi S, Di Felice C, Del Rosso A, Landi G, Maresca M, Giambalvo Dal Ben G, Matsuuci-Cennic M: Efficacy of the “body movement and perception” method in the treatment of fibromyalgia syndrome: an open pilot study. Clin Exp Rheumatol 2011, 29:323–329.
108. Hargrove JB, Bennett RM, Simons DG, Smith SJ, Nagool S, Deering DE: A randomized placebo-controlled study of noninvasive cortical electrostimulation in the treatment of fibromyalgia patients. Pain Med 2012, 13:115–124.
109. Almeida TF, Roizenblat S, Benedetto-Silva TA, Turf S: The effect of combined therapy (ultrasound and interferential current) on pain and sleep in fibromyalgia. Pain 2003, 104:655–672.
110. Chen KW, Hassett AL, Hou F, Staller J, Lichtbroch AS: A pilot study of external qigong therapy for patients with fibromyalgia. J Altern Complement Med 2006, 12:851–856.
111. Kayiran S, Dursun E, Dursun N, Ermutlu N, Karamursel S: Neurofeedback intervention in fibromyalgia syndrome; a randomized, controlled, rater blind clinical trial. Appi Psychophysiol Biofeedback 2010, 35:293–302.
112. Carbonato F, Matsutani LA, Yuan SI, Marques AP: Effectiveness of high-frequency transcutaneous electrical nerve stimulation at tender points as adjuvant therapy for patients with fibromyalgia. Eur J Phys Rehabil Med 2013, 49:197–204.
113. Mhalla A, Badic S, Ciampi di Andrade D, Gautron M, Perrot S, Teixeira MJ, Attal N, Bouhassira D: Long-term maintenance of the analgesic effects of transcranial magnetic stimulation in fibromyalgia. Pain 2011, 152:1478–1485.
114. Passard A, Attal N, Benadilha R, Braseur L, Saba G, Sichere P, Perrot S, Januel D, Bouhassira D: Effects of unilateral repetitive transcranial magnetic stimulation of the motor cortex on chronic widespread pain in fibromyalgia. Brain 2007, 130:2661–2670.
115. Donaldson NS, Speight N, Loomis S: Fibrinolysis in patients with depression and fibromyalgia. Eur J Neurol 2001, 8:47–53.
116. Azad KA, Alam MN, Haq SA, Nahar S, Chowdhury MA, Ali SM, Ullah AK: A pilot randomized, placebo-controlled trial of milnacipran in patients with fibromyalgia. J Altern Complement Med 2008, 14:197–201.
117. Carbonato F, Matsutani LA, Yuan SI, Marques AP: Effectiveness of high-frequency transcutaneous electrical nerve stimulation at tender points as adjuvant therapy for patients with fibromyalgia. Eur J Phys Rehabil Med 2013, 49:197–204.
118. Broderick JE, Junghaenel DU, Schwartz JE: Written emotional expression produces health benefits in fibromyalgia patients. Psychosom Med 2005, 67:326–334.
119. Carson WG, Carson KM, Jones KO, Bennett RM, Wright CL, Mist SD: A pilot randomized controlled trial of the Yoga of Awareness program in the management of fibromyalgia. Pain 2010, 151:530–539.
120. Bax AS, Morais LC, Paula AP, Diniz NF, Almeida RN: Effects of Panax ginseng extract in patients with fibromyalgia: a 12-week, randomized, double-blind, placebo-controlled trial. Rev Bras Fisioter 2013, 35:21–28.
121. Nishishinya B, Urruta G, Wallitt B, Rodriguez A, Bonfili A, Alegre C, Darko G: Amitriptyline in the treatment of fibromyalgia: a systematic review of its efficacy. Rheumatology (Oxford) 2008, 47:1741–1746.
122. Uceyler N, Hauser W, Sommer C: A systematic review on the effectiveness of treatment with antidepressants in fibromyalgia syndrome. Arthritis Rheum 2008, 59:1279–1298.
Reduction of fibromyalgia symptoms through intravenous S-adenosyl-L-methionine in patients with fibromyalgia. Scand J Rheumatol 1997, 26:206–211.

145. Jacobsen S, Dansneskold-Samsoe B, Andersen RB: Oral S-adenosylmethionine in primary fibromyalgia. Double-blind clinical evaluation. Scand J Rheumatol 1991, 20:294–302.

146. Geel SE, Robergs RA: The effect of graded resistance exercise on fibromyalgia symptoms and muscle bioenergetics: a pilot study. Arthritis Rheum 2002, 47:82–86.

147. Sanudo B, Galliano D, Carasco L, Blajojevic M, de Hoyo M, Saxton J: Aerobic exercise versus combined exercise therapy in women with fibromyalgia syndrome: a randomized controlled trial. Arch Phys Med Rehabil 2010, 91:1838–1843.

148. Kollner V, Hauser W, Klimczyk K, Kuhn-Becker H, Settan M, Weigl M, Bernardy K: Psychotherapy for patients with fibromyalgia syndrome. Systematic review, meta-analysis and guideline. Schmerz 2012, 26:291–296.

149. Nuesch E, Hauser W, Bernardy K, Barth J, Juni P: Comparative efficacy of pharmacological and non-pharmacological interventions in fibromyalgia syndrome: network meta-analysis. Ann Rheum Dis 2013, 72:965–962.

150. Lami MJ, Martinez MP, Sanchez AI: Systematic review of psychological treatment in fibromyalgia. Curr Pain Headache Rep 2013, 17:345.

151. Langholtz J, Hauser W, Bernardy K, Lucius H, Settan M, Winkelmann A, Musial F: Complementary and alternative therapies for fibromyalgia syndrome. Systematic review, meta-analysis and guideline. Schmerz 2012, 26:311–317.

152. Frost J, Oikin S, Vaughan T, Heywood J, Wicks P: Patient-reported outcomes as a source of evidence in off-label prescribing: analysis of data from PatientsLikeMe. J Med Internet Res 2011, 13:e6.

153. Fitzcharles MA, Ste-Marie PA, Goldenberg DL, Pereira JX, Abbey S, Choinière M, Ko G, Moulin DE, Panopalis P, Proulx J, Shir Y, National Fibromyalgia Guideline Advisory Panel: Canadian Guidelines for the diagnosis and management of fibromyalgia syndrome: Executive summary. Pain Res Manag 2012, 17:119–126.

154. Priori R, Iannuccelli C, Alessandri C, Modesti M, Antonazzo B, Di Lollo AC, Valesini G, Di Franco M: Fatigue in Sjögren’s syndrome: relationship with fibromyalgia, clinical and biologic features. Clin Exp Rheumatol 2010, 28:582–586.

155. Iannuccelli C, Spinelli FR, Guzzo MP, Priori R, Conti F, Ceciarelli F, Pietropaolo M, Olivieri M, Minniti A, Alessandri C, Gattametata A, Valesini G, Di Franco M: Fatigue and widespread pain in systemic lupus erythematosus and Sjögren’s syndrome: symptoms of the inflammatory disease or associated fibromyalgia? Clin Exp Rheumatol 2012, 30:117–121.