

# 2012 Canadian Guidelines for the diagnosis and management of fibromyalgia syndrome

**Mary-Ann Fitzcharles<sup>1,2</sup>, Peter A. Ste-Marie<sup>2,3</sup>, Don L. Goldenberg<sup>4</sup>, John X. Pereira<sup>5</sup>, Susan Abbey<sup>6</sup>, Manon Choinière<sup>7</sup>, Gordon Ko<sup>8</sup>, Dwight Moulin<sup>9</sup>, Pantelis Panopalis<sup>1</sup>, Johanne Proulx<sup>10</sup>, Yoram Shir<sup>2</sup>**

<sup>1</sup> Division of Rheumatology, McGill University, Montreal, Quebec, Canada

<sup>2</sup> Alan Edwards Pain Management Unit, McGill University Health Center, Montreal, Quebec, Canada

<sup>3</sup> Faculty of Law, Université de Montréal, Montreal, Quebec, Canada

<sup>4</sup> Division of Rheumatology, Tufts University School of Medicine, Boston, Massachusetts, USA

<sup>5</sup> Faculty of Medicine, University of Calgary, Alberta, Canada

<sup>6</sup> Department of Psychiatry, Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada

<sup>7</sup> Centre de la recherche du Centre hospitalier de l'Université de Montréal; Department of Anesthesiology, Faculty of Medicine, Université de Montréal, Montreal, Quebec, Canada

<sup>8</sup> Division of Physiatry, University of Toronto, Toronto, Ontario, Canada

<sup>9</sup> Departments of Clinical Neurological Sciences and Oncology, University of Western Ontario, London, Ontario, Canada

<sup>10</sup> Patient representative

Address corresponding author: Mary-Ann Fitzcharles, Montreal General Hospital, McGill University Health Centre, 1650 Cedar ave, Montreal, Quebec, H3G 1A4

Tel no: (514)-934-1934#44176

Fax no: (514)-934-8239

E-mail: [mary-ann.fitzcharles@muhc.mcgill.ca](mailto:mary-ann.fitzcharles@muhc.mcgill.ca)

## Canadian Fibromyalgia Guidelines Committee (CFGFC)

Mary-Ann Fitzcharles (rheumatologist/pain physician)

Peter Ste-Marie (research assistant/coordinator)

Don Goldenberg (rheumatologist and external advisor)

John Pereira (family physician)

Susan Abbey (psychiatrist)

Manon Choinière (psychologist)

Gordon Ko (physiatrist)

Dwight Moulin (neurologist)

Pantelis Panopalis (rheumatologist/epidemiologist)

Johanne Proulx (patient representative)

Yoram Shir (pain physician)

**This document and its recommendations have been endorsed by the Canadian Pain Society (CPS) and the Canadian Rheumatology Association (CRA).**

### Conflicts of interest

Mary-Ann Fitzcharles has received consulting fees, speaking fees and/or honoraria from Biovale, Janssen, Lilly, Pfizer, Purdue, and Valeant (less than \$10,000).

Peter Ste-Marie is supported by a grant from the Louise and Alan Edwards Foundation.

Don Goldenberg has received consulting fees, speaking fees and/or honoraria from Forest, Lilly and Pfizer (less than 10 000\$). He has also received grant support from Pfizer.

John Pereira has received independently-awarded research support from Pfizer Canada (greater than \$10,000).

Susan Abbey has received consulting fees, speaking fees and/or honoraria from Lilly, Lundbeck and Pfizer (less than \$10,000).

Manon Choinière has received unrestricted research support from Pfizer Canada and AstraZeneca. Consulting fees and honoraria were also given from Pfizer (less than \$5,000).

Gordon Ko has received consulting fees, speaking fees and/or honoraria from Allergan, Mayer, Boehringer-Ingelheim, Genzyme, Janssen, Lilly, Merck, Pfizer, Purdue, Shire and Valeant.

Dwight Moulin has received consulting, speaking fees and/or honoraria from Janssen, Lilly, Paladin, Pfizer and Valeant. He has also received independently-awarded research funding from Pfizer Canada (greater than 10 000\$).

Pantelis Panopalis has received consulting fees and/or honoraria from Abbott, Bristol-Myers Squibb and Pfizer (less than \$10,000).

Joanne Proulx has no conflicts of interest.

Yoram Shir has received consulting, speaking fees and/or honoraria from AstraZeneca, Janssen, Paladin, Pfizer and Purdue.

The needs assessment was funded by Valeant.

### National Fibromyalgia Guideline Advisory Panel (NFGAP)

Dr. Pierre Arsenault, Dr. Arsenio Avila, Dr. André Bélanger, Judy Boyd, Dr. Monique Camerlain, Dr. Doreen Campbell, Dr. Ken Chisholm, Dr. Manon Côté, Betty Downey, Dr. Ruth Dubin, Dr. Alan Faiers, Dr. Lena Galimova, Dr. Bruce Garfield, Dr. Rodney Glynn-Morris, Dr. Allan Gordon, DC François Hains, Dr. Richard Henry, Dr. David Hunt, Suzie Joseph, Dr. Roman Jovey, Dr. Alan Kaplan, Dr. André Lalonde, Louise Lamb, Dr. Howard Margolese, Dr. May Ong, Dr. Saul Pilar, Anna Serapins, Dr. Ian Shiozaki, Dr. David Shulman, Dr. Pamela Squire, Dr. Allen Steverman, Dr. Ellen Thompson, Dr. Cory Toth, Dr. Jean-Luc Tremblay, Dr. Paula Williams

Disclaimer: This document, including all annexes and particularly the recommendation statements, was created to provide guidance for healthcare professionals. Therefore, the document has no legal value.

## **ABSTRACT**

**Background/Purpose:** The healthcare community remains challenged regarding the care of fibromyalgia (FM) patients. Previous guidelines have mostly addressed treatment options rather than provide an overall approach to FM care. With new evidence concerning pathogenesis and more diverse treatment strategies, updated direction for global care in FM is needed. These evidence-based guidelines for the diagnosis, management, and patient trajectory of persons with FM were developed taking into account these new advances and new American College of Rheumatology 2010 diagnostic criteria.

**Methods:** A needs assessment by structured consultation with 139 healthcare professionals from relevant disciplines across Canada generated 18 key questions. Questions drove a literature search to identify evidence, which was graded according to the classification system of the Oxford Centre for Evidence Based Medicine, and supporting recommendations were drafted. Recommendations were edited and appraised by an advisory panel to reflect meaningful clinical practice. The whole document was reviewed by an international expert.

**Results:** Forty six recommendations pertaining to the identification, evaluation, and management of persons with FM, incorporating new clinical concepts are presented. The essence of the recommendations is as follows: FM represents a composite of symptoms, with body pain present as the pivotal symptom. There is a spectrum of severity which associates with functional outcome, with fluctuating symptoms over time. The diagnosis of FM is clinical, not one of exclusion, not needing specialist confirmation, and requires only limited laboratory testing. A physical examination is required to exclude other conditions presenting with body pain, but tender point examination is not required to confirm the diagnosis. There is no confirmatory laboratory test and excessive testing is strongly discouraged. Ideal care for most patients is in the primary care setting. Treatments should be multimodal, incorporating non-pharmacologic and pharmacologic strategies, with focus towards reduction of symptoms and improvement of function. Patients must be active participants in their healthcare and non-pharmacologic strategies are imperative. Patient-tailored management that is symptom-based is recommended. In the absence of an ideal pharmacologic treatment, an agent impacting multiple symptoms is desirable. Doses of medications lower than those used in clinical trials and combination of medications may facilitate adherence. Emphasis on healthy lifestyle practices, maintenance of function including retention in the workforce, periodic assessment for the need for continued medication, and evaluation of efficacy/side effects of ongoing treatments is recommended. New symptoms should be evaluated according to good clinical practice to exclude another illness without summarily attributing symptoms to FM.

**Conclusion:** These new Canadian guidelines for the care of patients with FM should provide the health community with confidence in the global care of these patients and thereby improve patient outcome.

Fibromyalgia (FM) was recognized as a true syndrome with the publication of the American College of Rheumatology (ACR) classification criteria in 1990, which were updated in 2010 [1, 2]. Taking into account neurophysiologic evidence of pain dysregulation as well as newer treatment options, these guidelines provide direction for optimal patient care and align with best clinical practice. Clinical challenge persists as symptoms are subjective, assessment is dependent entirely on patient report, no objective or laboratory test exists to confirm the diagnosis, and there is an absence of a gold standard of treatment.

With the pivot symptom of pain, the syndrome of FM includes fatigue, nonrestorative sleep, cognitive dysfunction, mood disorder, as well as variable somatic symptoms [3]. Canadian prevalence rates are in the order of 2% - 3%, with females affected between 6 to 9 times more commonly than males [4]. Although seen most commonly in middle-aged women, FM can also affect children, teenagers, and the elderly.

Patients with FM commonly experience symptoms for a number of years prior to diagnosis. Repeated investigations, referral to various specialists, and frequent healthcare visits all contribute to considerable cost associated with this condition. Direct healthcare costs attributed to patient care are over \$4000 Canadian per year, an amount 30% higher than non-FM patients in a Quebec healthcare database [5]. Although a reduction in healthcare utilization occurred immediately following a diagnosis of FM, this was not sustained in subsequent years [6].

While there is currently no cure for FM, ideal management will address pain as well as the composite of symptoms that comprise this syndrome. Treatment must incorporate non-pharmacologic strategies and may also include drug therapy, in a patient-tailored approach. Healthcare professionals must understand the interplay of neurophysiologic and psychological mechanisms operative in FM and appreciate that a spectrum of symptoms exists.

These guidelines are presented as recommendations pertinent to patient care in Canada, graded according to the level of supporting evidence, and accompanied by a brief explanation to clarify their context and facilitate clinical care. They should be viewed as an aid in the care of patients with FM, taking into account the unique needs of an individual patient, and should not be interpreted as the rule by which each patient should be managed.

### **Need for a Guideline**

As previous guidelines for the management of FM were based on literature searches up to December 2006, updating is required [7-9]. There is a need for guidance which goes beyond management, and also incorporates diagnosis and the patient trajectory. We have set out to consolidate information published mostly in the last two decades to develop evidence based recommendations which will have good clinical utility in the day to day management of FM patients.

### **Leadership**

The Canadian Fibromyalgia Guidelines Committee (CFGC) is a multidisciplinary team representing healthcare professionals from relevant fields managing FM patients, a

patient representative, an external international expert, and a research coordinator. All CFGC members are listed as authors, had access to all data, participated in the data compilation, analysis, and writing of this report.

### **Objectives**

To develop evidence-based guidelines for the evaluation, diagnosis and management of persons with FM in Canada taking into account new advances in the understanding of the pathogenesis of FM and new diagnostic criteria, and to identify and assess the evidence supporting these recommendations. Application of these guidelines should facilitate patient care with the goal to reduce symptoms and maintain function.

### **Target Audience**

The target of this guideline is all Canadian healthcare professionals including primary care providers, medical specialists, and members of multidisciplinary teams who treat patients with FM. To a lesser degree, it is also relevant to patients with FM, who will also benefit from an understanding of this condition.

### **The Area the Guideline Does Not Cover**

This guideline is limited to the adult population who suffer from FM. It does not address other conditions associated with a chronic pain syndrome such as peripheral neuropathy, regional pain syndrome, complex regional pain syndrome, etc.

### **Limitations**

It is recognized that each patient is unique and treatments should be individualized, with recommendations serving as a starting template. There is currently a paucity of evidence to support many aspects of these guidelines, with reliance therefore placed on clinical experience and consensus in some areas. As access to care is not equal across all geographic regions of Canada, differences in care will be evident. Although no cost analysis of the implementation of these guidelines has been made, development of simple clinically useful tools will be required. The full document is extensive and lengthy and should therefore serve as a reference frame, rather than as a tool for day to day clinical practice.

### **Involvement and Affiliations of Other People or Organizations Including User-representative Organizations and Pharmaceutical Companies in the Development of the Guideline**

All members of the CFGC are listed as authors. A patient representative made a significant contribution to these guidelines. No representatives of pharmaceutical companies were involved in the guideline development. These guidelines have been formally endorsed by the Canadian Rheumatology Association (CRA) and have been submitted to the executive committee of the Canadian Pain Society (CPS) with comments contributing to the final version.

## ***Development***

### **Needs assessment**

A needs assessment developed a series of questions following input from 139 Canadian healthcare professionals. Participants included family physicians, anaesthesiologists, neurologists, psychiatrists, psychologists, physiatrists, rheumatologists, nurses, chiropractors, physiotherapists, and a single naturopathic doctor. Input was sought regarding current knowledge, knowledge gaps, uncertainties, and challenges in the clinical care of patients with FM.

### **Scope of literature search, strategy employed, and document revision**

A comprehensive literature search, directed by each question, was conducted at the McGill University Health Sciences library. Databases searched were EMBASE, MEDLINE, PSYCHINFO, PUBMED, and Cochrane Library within a 20 year timeframe from 1990 to July 2010. The details of individual search strategies were recorded (Appendix A). A manual search from the references cited by original studies, reviews, and evidence-based guidelines was also used. Two authors (MAF & PSM) extracted data independently onto a specially designed pro forma and cross checked the data. Evidence was graded according to the strength of literature to support each statement according to the classification system of the Oxford Centre for Evidence Based Medicine (Appendix B) and the document was prepared in accordance with the principles outlined [10].

Sixty recommendations were initially drafted, assigned a level of evidence, and graded by the CFGC. Recommendations were then submitted via Internet to the 35 members who form the National Fibromyalgia Guidelines Advisory Panel (NFGAP). Recommendations were accepted if they obtained 80% approval after a first pass. Eleven recommendations that did not obtain approval at the initial vote were modified according to suggestions, submitted to a second vote, and achieved approval at the second vote. The entire document was reviewed by Dr. Don Goldenberg, our external expert and first author of the American Pain Society fibromyalgia guidelines, who was then asked to become a member of the CFGC after his formal review of the manuscript. Further external review was conducted by the executive committee of the CPS using the AGREE II Score Sheet guideline appraisal tool, with resulting shortening of the guideline document and combination but not elimination of recommendations to reduce the number from 60 to 46 (Appendix C).

### **Updating**

These guidelines will be in the governance of both endorsing bodies, CRA and CPS, who will oversee the updating process in 2015.

### **Implementation**

All members of the CFGC will participate in the dissemination process in order to have maximum visibility across all relevant disciplines throughout Canada. These guidelines have been presented at the 2012 annual meetings of the CRA and CPS, and updates will be presented by members of the CFGC at various regional meetings. Clinical review papers will be submitted by members of the CFGC to various peer-reviewed journals addressing some of the strategies outlined in these guidelines. Cards and pamphlets that are easily applicable and provide advice for certain areas of FM management will be

produced and disseminated to healthcare professionals who have contact with FM patients.

**Funding and conflict of interest**

These guidelines were developed at the request of the CPS. The needs assessment was supported by an unrestricted educational grant from Valeant. The process of guideline development was facilitated by funding from the Louise and Alan Edwards Foundation. None of the funding sources had a role in the collection, analysis or interpretation of the data or in the decision to publish this report. Conflicts of interest for all members of the steering committee have been declared.

## **SECTION 1 : The diagnosis**

### **1.1 How is fibromyalgia diagnosed?**

FM is a syndrome of diffuse body pain with associations of fatigue, sleep disturbance, cognitive changes, mood disturbance, and other variable somatic symptoms [3]. A diagnosis of FM is made following a clinical evaluation which includes a history of current complaints, attention to past health status and a physical examination, without any confirmatory diagnostic test. Although criteria for the diagnosis of FM were developed for research purposes, they may be used to validate a clinical diagnosis.

#### ***1.1.1 The clinical presentation of fibromyalgia***

FM may affect persons of all ages and of both genders, but is most prevalent in female patients in the third to fifth decade. There are no studies examining diagnostic criteria in the clinical setting and there is no confirmatory laboratory test for FM [11]. Symptoms wax and wane over time, but seldom disappear [12, 13].

#### ***1.1.2 The symptom complex in persons with fibromyalgia***

##### **a) Pain**

Pain is the primary complaint in persons with FM and should have been present for at least 3 months. Pain onset is usually insidious, sometimes beginning in a localized area, may initially be intermittent, and then progressively becomes more persistent. Although pain is felt in muscle or joint areas, there is no physical abnormality of these tissues. A neuropathic mechanism to the pain may be suggested by report of a burning quality to the pain [14, 15]. Pain may vary in location and intensity from day to day, and can be modulated by factors such as weather or stress [16]. Cold and humid weather tends to be associated with increased symptoms [16, 17]. Although the most frequently reported sensory symptom in FM is pressure induced pain, this was only reported to be severe in 58% of FM patients [14].

##### **b) Other associated symptoms present in FM**

Symptoms other than pain are common in FM and can contribute to one third of the global suffering [2, 3, 18].

#### ***b.I Fatigue***

Fatigue, reported to be present in over 90% of FM patients, is the most common associated complaint [3]. Fatigue may even be more disabling than pain for some, and contributes to subjective report of functional impairment. Fatigue is challenging to measure, with reliance on subjective patient report to gauge severity. Overlap with chronic fatigue syndrome has been described, although pain is more prominent in patients with FM [19].

#### ***b.II Nonrestorative sleep***

Nonrestorative sleep is associated with FM [20]. Abnormal components of sleep that have been measured include sleep latency, sleep disturbance, and fragmented sleep leading to impaired daytime function [21, 22]. Poor sleep negatively impacts fatigue, affect, and pain, with improvement in these parameters when sleep specifically is addressed [23-26]. Other sleep disorders such as restless leg syndrome or sleep apnoea may also occur in patients with FM.

### ***b.III Cognitive dysfunction***

Cognitive dysfunction which includes poor working memory, spatial memory alterations, free recall, and verbal fluency associates with pain in FM as well as other pain patients and is different from healthy controls [27-30].

### ***b.IV Mood disorder***

Mood disorder, including depression and/or anxiety, is present in up to three quarters of persons with FM, but mood disorders and FM are likely distinct [31]. Anxiety commonly coexists with depression, but is also independently increased in FM patients [32, 33]. Depression is influenced by low family cohesion, high pain and helplessness, and passive coping skills [34]. First-degree relatives of individuals with either FM or major depressive disorder (MDD) demonstrated similar rates of MDD suggesting that these two conditions share similar risk factors which may be genetically driven [35].

### ***b.V Pain-related somatic symptoms***

Somatic symptoms, including irritable bowel syndrome, migraine headaches, severe menstrual pain, lower urinary tract symptoms, myofascial facial pain, and temporomandibular pain have all been associated with FM [36-39].

### ***b.VI Non-pain related symptoms***

Sexual dysfunction has recently been reported to occur in 97% of FM patients [40]. FM patients may be more vulnerable to posttraumatic stress disorder (PTSD), with depressed FM patients having a three-fold increase in PTSD compared to those with chronic fatigue only [41]. Breast implants, at one time implicated in FM, are not associated with FM [42, 43]. Similarly, cigarette smoking has been associated with more severe FM symptoms, rather than FM per se, and should be discouraged for global health reasons [44].

## **Recommendations:**

- 1. Fibromyalgia, a condition that can wax and wane over time, should be diagnosed in an individual with diffuse body pain that has been present for at least 3 months, and who may also have symptoms of fatigue, sleep disturbance, cognitive changes, mood disorder, and other somatic symptoms to variable degree, and when symptoms cannot be explained by some other illness [Level 5 [2, 12, 45, 46], Grade D].**

## **1.2 What physical abnormalities may be present in fibromyalgia?**

The physical examination, specifically musculoskeletal and neurological, is usually within normal limits except for tenderness of soft tissues. Soft tissue tenderness can include pain report on examination of the tender points, however, as described in the 2010 ACR diagnostic criteria, specific tender point count is no longer required for a diagnosis of FM [2].

Sensitivity to light touch, interpreted as dysaesthesia or touch allodynia (unpleasant sensation or pain after a non-painful stimulus), may occur, but without other objective neurological findings. Expression of pain or pain behaviours may be present but should not imply faking of symptoms [47].

### ***1.2.1 The tender point examination***

The tender point examination has been widely disputed as an objective test in FM [48-56]. Embedded in the diagnostic criteria established for research purposes and not applicable to an individual patient in clinical practice, the 1990 ACR criteria for a diagnosis of FM required 11/18 tender points to be present in designated areas [1]. These points, located at soft tissue sites, reflect a reduction in pain threshold without underlying tissue pathology and show variable reliability [57, 58]. Reduced pain threshold has also been documented by application of a pneumatic tourniquet cuff [59]. The weight attributed to the tender point examination has detracted from the global concept of FM and was thus revisited in the new 2010 ACR criteria [60].

The correct examination method for tender points, which can be performed by digital palpation, myalgic scoring or dolorimetry has also been debated, with digital examination most commonly used [61]. The presence of tender points may even associate more with distress rather than as an indicator of pain [62]. Examination of even a few selected points may be sufficient to identify FM [63]. Tender points may even be faked, but truly bear no consequence to the composite of suffering of FM [64].

The new criteria for a diagnosis of FM, with the elimination of the tender point examination, perform well in identifying patients with a previous diagnosis of FM [2]. A recent German working group has concluded that FM can be diagnosed for clinical purposes on the basis of symptoms without a tender point examination [65].

#### **Recommendations:**

- 2. All patients with a symptom complaint suggesting a diagnosis of fibromyalgia should undergo a physical examination which should be within normal limits except for tenderness on pressure of soft tissues (ie. hyperalgesia which is increased pain following a painful stimulus) [Level 4 [2, 3, 66], Grade D].**
- 3. Examination of soft tissues for generalized tenderness should be done by manual palpation with the understanding that the specific tender point examination according to the 1990 ACR diagnostic criteria is not required to confirm a clinical diagnosis of fibromyalgia [Level 5 [1, 2], Grade D].**

### **1.3 What investigations should be done in a patient presenting with widespread pain?**

No laboratory investigation confirms a clinical diagnosis of FM and unnecessary investigations which may be detrimental to patient well-being should be avoided. FM is not a diagnosis of exclusion [67]. Simple laboratory testing should be limited to a complete blood count (CBC), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), thyroid stimulating hormone (TSH), and creatine kinase to rule out conditions that can present similarly to FM. These may include endocrine disease (hypothyroidism), rheumatic conditions (early inflammatory arthritis or polymyalgia rheumatica) or neurological disease (myopathy, or multiple sclerosis), depending upon the clinical

evaluation. Appropriate additional testing, which might include referral for sleep evaluation, or formal psychological evaluation may be required in selected patients.

Reduced levels of vitamin D or vitamin D supplementation have no effect on pain in FM [68-70]. A positive antinuclear antibody (ANA) in low titre, present in 8-11% of FM patients, similar to healthy controls, does not predict future connective tissue disease [71-73]. As no consistent abnormality has been identified in immune function, any screening should only be driven by clinical findings [74-76].

#### **Recommendations:**

- 4. Fibromyalgia should be diagnosed as a clinical construct, without any confirmatory laboratory test, and with testing limited to simple blood testing including a full blood count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), creatine kinase, and thyroid stimulating hormone (TSH). Any additional laboratory or radiographic testing should depend on the clinical evaluation in an individual patient that may suggest some other medical condition [Level 5 [75, 76], Grade D].**

#### **1.4 How should the diagnosis of fibromyalgia be confirmed?**

The responsibility for the diagnosis and management of FM should be shifted away from the specialist and concentrated in the primary care setting. Specialist confirmation or fulfilling diagnostic criteria is not required [1, 77-79]. Most physicians rely on a combination of symptoms and normal blood testing to diagnose FM with less than 10% using criteria [80]. Questionnaires used in the research setting are also not clinically useful in daily practice [81].

Early diagnosis will avoid lengthy, costly and unnecessary investigations, a cause for patient uncertainty that will prolong healthcare behaviours and foster medicalization [6, 82, 83]. An early diagnosis will allow attention to be focused towards symptom management, attainment of optimal health and maintenance or improvement of function.

New symptoms should be evaluated on merit. Seldom does FM herald some other disease with only 2 of 91 patients developing some other condition over a 4 year period [84].

#### **Recommendations:**

- 5. The primary care physician should establish a diagnosis of fibromyalgia as early as possible, without need for confirmation by a specialist, and communicate this diagnosis to the patient. Repeated investigations after diagnosis should be avoided unless driven by the onset of new symptoms, or signs on physical examination [Level 5[6, 77, 82, 83], Grade D].**

#### **1.5 Is there a role for application of diagnostic criteria for an individual patient?**

The concept of FM was initially crystallized by the American College of Rheumatology (ACR) in 1990, and was further revised in 2010, taking into account symptoms other than pain, as well as the questionable value of the tender point examination [1, 2]. FM represents a spectrum of symptoms which fluctuate in intensity, although the underlying

condition persists [58, 66, 85]. These criteria were developed to identify patients for research study and not for application to an individual patient in the clinical setting. A modification of the original 2010 ACR criteria requires that the questionnaire be entirely completed by the patient, without need for additional physician questioning, simplifying the tool (Appendix D).

**Recommendation:**

- 6. The ACR 2010 diagnostic criteria for fibromyalgia can be used at initial assessment to validate a clinical diagnosis of fibromyalgia with the understanding that symptoms vary over time [Level 3 [1, 2, 58], Grade B].**

**1.6 What conditions can present similarly to FM?**

A number of conditions may present similarly to FM, and may be identified by a thorough clinical evaluation. Diagnoses that can be confused with FM may be grouped into the following categories: musculoskeletal, neurological, psychiatric/psychological and drug related [76].

Although patients with an early stage of an inflammatory rheumatic condition such as rheumatoid arthritis, inflammatory spondyloarthritis, systemic lupus erythematosus, polymyalgia rheumatica or myositis may have generalized body pain, identifiable physical or laboratory abnormalities will develop over time [86, 87]. The presence of a single abnormal laboratory test such as a positive rheumatoid factor, positive ANA, or raised ESR is not evidence alone for the presence of a connective tissue disease [71, 72]. Myofascial pain syndromes tend to present with more localized pain and are associated with “trigger points” [88].

Neurological conditions with body pain include multiple sclerosis, neuropathies, with pain more specifically localized, and myopathies [87]. Hypothyroidism should also be remembered as a condition that may present with ill-defined pain and fatigue. Depression can present with pain, although local tenderness is more common in FM patients compared to those with depression [89].

FM may develop after an infectious illness, most commonly viral, but a search for an infectious aetiology is not routinely required. Infectious diseases such as Lyme disease, hepatitis C infection, and human immunodeficiency disease may have symptoms mimicking FM, but any testing in this regard should be dependent upon a clinical suspicion of these infections [90, 91]. Medications such as lipid lowering agents in the category of statins, aromatase inhibitors used to treat breast cancer and bisphosphonates for the treatment of osteoporosis and bone metastases may cause body pain [92-94].

FM may occur concomitantly with other medical, neurological or rheumatologic illnesses [76]. Recognition of the co association of FM may influence treatments. For example, a patient with rheumatoid arthritis, in the absence of inflammatory activity, may experience pain due to FM.

## **Recommendations:**

- 7. Healthcare professionals should be aware that some medical or psychological conditions may present with body pain similar to fibromyalgia, and patients with other medical illnesses may have an associated fibromyalgia [Level 5 [76, 86, 87, 90, 91], Grade D].**

### **1.7 What is the recommended patient trajectory?**

Delay in diagnosis of FM may be attributed to poor recognition of FM by patients and healthcare professionals, with adverse effect on health and considerable healthcare and personal costs [5, 6, 95]. Patients with FM will first present to a primary care physician and ideal care should remain in the primary care setting without any clear advantage for care by a specialist [77, 78, 96, 97]. Whether a diagnosis of FM is advantageous from the pharmacoeconomic perspective remains debatable with reports of both increased as well as reduced healthcare utilization and costs [6, 98]. Education and improved knowledge translation will reassure healthcare professionals to diagnose and manage persons with FM more effectively.

Specialist consultation should be reserved for patients with atypical symptoms which might suggest an alternate diagnosis and is not required to confirm a diagnosis of FM [97, 99]. In selected cases referral for sleep evaluation or psychological consultation may be indicated. No advantage was observed when patients were followed in a specialist setting compared to primary care [97].

Although care in a multidisciplinary setting may be desirable, this is not realistic for most patients [100]. Multidisciplinary teams may include nurses, physiotherapists, kinesiologists, social workers and psychologists amongst others. Nursing support for FM patients has been underutilized, can provide a valuable contribution to patient care and can reduce waiting time to consultation and increase patient satisfaction [101]. Nursing care can help the patient identify realistic outcome goals and focus towards attaining optimal health [102]. Public education will also facilitate an earlier diagnosis and promote the belief that FM patients are best managed in the primary care setting.

## **Recommendations:**

- 8. Management of persons with fibromyalgia should be centered in the primary care setting with knowledgeable healthcare professionals, and ideally, where possible, this care may be augmented by access to a multidisciplinary team [Level 1 [96, 97], Grade A] or team member to provide support and reassurance [Level 3 [101, 102], Grade C].**
- 9. Specialist consultation, including referral to a sleep specialist or psychologist may be required for selected subjects, but continued care by a specialist is not recommended and should be reserved for those patients who have failed management in primary care or have more complex co morbidities [Level 5 [77], Grade D].**

### **1.8 How can prejudice and scepticism regarding the validity of fibromyalgia be countered?**

Knowledge that FM is grounded in neurophysiological mechanisms will reduce scepticism regarding a syndrome of subjective complaints. Physician comfort with a biomedical paradigm which prioritizes diagnostics adds to the insecurity in management of these patients, with some authors contending that the label of FM promotes poor health [103-105]. Patient preoccupation with physical symptoms rather than developing control over illness invokes frustration for the healthcare professional and erodes a good therapeutic relationship [106]. The construct of somatization has however never been validated in situations involving pain, and particularly in FM. In contrast, patients with FM report frustration with healthcare professionals, dissatisfaction with the clinic visit and seek a concrete somatic diagnosis [107, 108]. Although discordance between patient and physician assessment of health perceptions has been reported, physicians have expressed the desire to comply with patients' wishes and avoid frustration [103, 108]. When physicians prejudge FM patients in moralising terms and believe them to be illness-focused, demanding and medicalized, the patient doctor alliance will be eroded with adverse effect on patient outcome [109]. Both the individual patient's concept of illness as well as perceived attitudes of the healthcare team impacts on global well-being. Shared decision-making between patient and physician can improve the quality of interaction [110]. An early diagnosis may have pharmacoeconomic implications with reduced healthcare costs as measured by fewer investigations, less referral to specialists and reduced healthcare visits [6, 83].

#### **Recommendation:**

- 10. In caring for persons with fibromyalgia, healthcare professionals should be educated regarding the pathogenesis of fibromyalgia [Level 5, Consensus], empathetic, open, honest, should not demonstrate negative attitudes, and should practice shared decision-making [Level 3 [106, 107, 110], Grade D].**

### **1.9 What causes fibromyalgia and how is this condition explained in physiological terms?**

Although the cause of FM is unknown, understanding that neurophysiological changes present in FM will reassure healthcare professionals that this condition is valid. An elementary appreciation but not in-depth knowledge of neurophysiological mechanisms will also help towards treatment choices. Neurophysiologic testing remains in the research domain and is not currently available for routine patient care, nor should be required to confirm a diagnosis of FM.

Abnormalities in pain processing have been identified at various levels in the peripheral, central, and sympathetic nervous systems, as well as the hypothalamo-pituitary-adrenal (HPA) axis stress-response system. Documented abnormalities include evidence of peripheral sensitization and wind-up phenomenon, central sensitization with changes in functional MRI and SPECT scans of the brain, increased levels of substance P in the cerebrospinal fluid, and impairment of descending noxious inhibitory control (DNIC) [111-118].

Familial studies point to some genetic predisposition with up to 26% of relatives of patients with FM reporting chronic widespread pain (CWP), and FM diagnosed in 28% of offspring of FM women [119, 120]. Genetic factors may predispose some individuals to a dysfunctional stress response via the HPA axis [121]. While no individual gene has been associated with FM, there is increasing evidence of a polygenic effect, with polymorphism of genes affecting serotonergic, catecholaminergic and dopaminergic systems playing a role [122, 123].

Psychosocial distress has been shown to predict onset of chronic widespread pain in population studies conducted in England [124, 125]. Early life adversity is linked to chronic widespread pain in adult life [126]. Abuse, which may have been sexual, physical or psychological, particularly in childhood has been reported with greater frequency in FM patients than controls [127-129]. These numerous interacting factors may be the setting in which a stressful event, which could be physical such as a viral illness, traumatic, or psychological, can lead to a vulnerable health status and may be a trigger for FM as reported for nearly a quarter to a third of persons with FM [130].

**Recommendations:**

- 11. Healthcare professionals should be knowledgeable that objective neurophysiologic abnormalities have been identified in patients with fibromyalgia in the research setting, but are not available in clinical practice for either the diagnosis or care of persons with fibromyalgia [Level 5 [111, 117], Grade D].**
- 12. Patients and healthcare professionals should acknowledge that genetic factors as well as previous adverse events may have contributed to the development of fibromyalgia, but focusing excessively on a triggering event could compromise patient care and should therefore be discouraged [Level 5 [123, 126, 130], Grade D].**

## **SECTION 2 : Management**

### **2.1 What are the treatment strategies for fibromyalgia?**

There is currently no cure for FM and treatment recommendations should be directed to reduction of symptoms and maintenance of optimal function, with patient outcome goals clearly defined at outset. Symptom based management, taking into account the heterogeneous nature of this condition, can help direct a patient tailored approach [131]. Ideal management includes both non-pharmacologic and pharmacologic treatments in a multimodal approach, with active patient participation fostered by a strong patient-centered locus of control [132]. The essence of the evidence is that there is no “gold standard” of treatment; with responses mostly modest at best. Self-efficacy and adherence to treatment recommendations will favourably influence outcome [133]. Although attempts have been made to subgroup FM patients in order to direct treatments, these remain preliminary [32, 134-136].

#### **Recommendations:**

- 13. A treatment strategy for patients with fibromyalgia should incorporate principles of self-management using a multimodal approach [*Level 1 [131, 132], Grade A*]. It is recommended that attention should be paid to individual symptoms in a patient tailored approach, with close monitoring and regular follow-up, particularly in the early stages of management [*Level 5 [131] Grade D*].**
- 14. Patients should be encouraged to identify specific goals regarding health status and quality of life at the initiation of treatment, with re-evaluation of goals during the follow-up [*Level 5 [102], Grade D*].**

### **2.2 Non-pharmacologic treatment**

Non-pharmacologic treatments have a positive effect with improvements in self-reported outcome measures including physical status, FM symptoms, psychological status and daily functioning, but unfortunately many studies have been poorly executed [132]. In this meta-analysis of 49 outcome studies published 10 years ago, non-pharmacologic treatments appeared more effective than pharmacological interventions. Although no single strategy outperforms others, education, exercise activity, cognitive behavioural therapy (CBT), and multidisciplinary therapy, incorporating at least 1 educational/psychological therapy with 1 exercise therapy, will offer an advantage [137, 138].

#### ***2.2.1 Self-management strategies***

Education and active participation with reassurance regarding “no harm” caused by physical activity should be the focal point of treatment, especially if a patient is passive regarding health and lifestyle practices [139]. Education can improve attitudes, coping skills, and help shift the locus of control towards a patient orientated approach. A positive attitude and patient-centered internal locus of control with positive expectations strongly determines response to treatment [140]. Self-efficacy and good social support promoted healthy lifestyle practices in 198 women with FM [141]. Self-efficacy enhancement

programs may be a valuable inclusion in the treatment of FM patients [142]. Pacing of daily activities can improve day to day function [143].

**Recommendation:**

- 15. Non pharmacologic strategies with active patient participation should be an integral component of the therapeutic plan for the management of fibromyalgia [Level 1 [132, 137], Grade A]. Encouraging self-efficacy and social support will facilitate the practice of health promoting lifestyles [Level 3 [141, 142], Grade D].**
- 16. Persons with fibromyalgia should be encouraged to pursue as normal a life pattern as possible, using pacing and/or graded incremental activity to maintain or improve function [Level 4 [143, 144], Grade D].**

### ***2.2.2 Multicomponent therapy***

Multicomponent therapy is currently recognized to comprise at least one educational or other psychological therapy and at least one exercise therapy, although there is no accepted formal definition. Ideal care will therefore be given by a team of individuals, rather than reliance on contact with a single healthcare professional. A recent meta-analysis has shown that multicomponent treatment is effective in the short term for improving key symptoms of FM including pain, fatigue, depression and quality of life, but disappointingly without evidence for continued effect other than maintenance of physical fitness [137].

There is currently limited information on effectiveness of combination psychological and pharmacologic treatments, strategies that can be applied in clinical practice and may yield positive results. Catastrophizing, defined as viewing situations or symptoms as being much worse than they truly are, is recognized to have negative effects on outcome in chronic pain patients, and strategies aimed at reduction are desirable. The results of an ongoing combined pharmacologic and psychological intervention study aimed at reducing catastrophizing in FM patients will be of interest [145]. Other resources such as self-help groups, patient forums and information sessions, when information is reliable, can improve patient knowledge and can enhance locus of control.

**Recommendation:**

- 17. The attainment of effective coping skills and promotion of self-management can be facilitated by multicomponent therapy [Level 5 [137], Grade D].**

### ***2.2.3 Psychological interventions***

Untreated psychological distress, depression in particular, is a barrier to optimal health status. As psychological status affects quality of life, attention to previous or current comorbid psychological complaints is required [146-148]. Medical and psychiatric comorbidity was a strong determinant of the number of physician visits for 180 FM women, which could be interpreted as a surrogate for patient distress and poor psychological status [146]. In turn, improved psychological status and physical activity associate with reduced pain intensity in FM [149].

Even in the absence of overt psychopathology, psychological interventions such as traditional CBT, group therapy sessions or motivational interviewing may be helpful. CBT helps patients to cope better with pain by improving pain-related behaviour, self-efficacy, and overall physical functioning, but without evidence for long-term effect when applied alone [150, 151]. Overall improvement in depression and less use of analgesic medication was reported in a controlled study of CBT in 60 patients [152]. When CBT was combined with an aerobic exercise program over a three week period, there was sustained improvement in multiple outcomes up to one year, suggesting that the CBT facilitated adherence to a physical exercise regimen [153]. As CBT is more costly than an education program alone, and may not be easily accessible for many, limited programs via the internet, telephone interview or an attenuated program may be useful [154, 155].

Other modalities to address attitudes and psychological status include motivational interviewing or group sessions. Motivational interviewing, by means of six telephone calls over a ten week period improved adherence to an exercise program [156]. Group sessions that incorporate education, a psychological intervention, as well as an exercise component have some benefit in the short-term, up to six months [157, 158]. Other psychological interventions reporting some benefit include written emotional expression, psychomotor therapy, meditation-based stress reduction program and EMG-biofeedback therapy [159-162]. Even a brief interdisciplinary program lasting one and a half days has shown positive effect in patients with FM [163]. Chronic pain self-management programs are increasingly available to address this need.

Distraction, by means of pleasant imagery, had better effect on pain reduction in FM patients, than focused attention imagery towards active control of pain mechanisms [164]. Hypnosis with analgesia suggestion showed a positive effect on pain compared to hypnosis with relaxation suggestion or relaxation alone in a study of 45 patients [165]. Guided imagery by means of audiotaped scripts improved functional status as well as self-efficacy for managing pain in a randomised controlled trial (RCT) of 48 patients [166]. However the authors of a recent systematic review and meta-analysis of hypnosis/guided imagery call for improved methodology before conclusions regarding the key domains of FM can be drawn [167]. Mind-body therapies can improve self-efficacy, although alone have not been shown to affect specific symptoms of FM [168]. In a systematic review of thirteen trials, mind-body therapies combined with an exercise program were more effective than waiting list or “treatment as usual” [168].

Transcranial magnetic stimulation (TMS), a treatment modality used to manage psychological/psychiatric illness, reduced pain and depressive symptoms in FM patients in one study, with no effect in a second study [169, 170]. Transcranial direct current stimulation to the primary motor cortex, but not the dorsolateral prefrontal cortex, was associated with improved sleep efficiency, reduced arousals and improvement in FM symptoms [171].

As fear of pain and activity is reported by almost 40% of FM patients and is associated with greater disability, depressed mood and pain severity, fear avoidance should be addressed to maintain adherence to exercise recommendations [172]. Patients with FM

identified more problems than those with ankylosing spondylitis and perceived themselves to be more negatively affected by their condition [173]. Attention to pain has been associated with increased pain related fear and pain severity.

#### **Recommendations:**

- 18. Interventions that improve self-efficacy should be encouraged to help patients cope with symptoms of fibromyalgia [Level 1 [168], Grade A].**
- 19. Psychological evaluation and/or counselling may be helpful for persons with fibromyalgia in view of the associated psychological distress [Level 5, Consensus], and patients should be encouraged to acknowledge this distress when present and be informed about the negative impact this may have on wellbeing [Level 3 [149], Grade D].**
- 20. CBT even for a short time is useful and can help reduce fear of pain and fear of activity [Level 1 [150, 151], Grade A].**

#### **2.2.4 Exercise**

Exercise has overall benefit on global well-being, physical function and pain and is currently recommended as the first step of a multimodal treatment strategy [174-178]. Exercise may take a number of forms such as aerobic, strengthening, water, home based or group programs. In a Cochrane review of 16 trials, 7 of which were high quality, supervised aerobic exercise improved physical capacity and FM symptoms [176]. The evidence for effect of strengthening exercises is less clear as studies are rated as low quality [174, 175]. In a meta-analysis of 45 studies, ten of which were eligible for inclusion, exercise, which included aerobic, strength training, pool and multi-component exercise, successfully improved pain in the short-term; but with a call for long-term studies [179]. Water exercise, or combined with education, is associated with improvements in both physical and emotional aspects of FM, but with a question as to whether the benefit is derived from the aerobic exercise component that almost always accompanies water exercise [180-185].

A Pilates exercise program over a 12 week period improved pain compared to a relaxation program, but this effect was not sustained due to poor adherence to treatment [186]. Tai Chi is an exercise activity that combines both a physical and mental component and is ideally suited to persons with FM, with report of improved function and quality of life [187-189]. When traditional yoga was compared to yoga combined with a yoga touch technique “Tui Na”, improvement was more sustained in the yoga group only [190].

Although FM patients often report poor exercise capacity, reduced cardiorespiratory fitness was similar to controls, suggesting that FM patients overscore their perception of exertion [191]. A report of subjective muscle pain may be a barrier to optimal exercise activity [192]. In the absence of a single exercise program outperforming others, patients should be encouraged to choose an activity either land based or water, that is enjoyable, easy to follow, convenient and within budget in order to improve adherence.

**Recommendation:**

- 21. Persons with fibromyalgia should participate in a graduated exercise program of their choosing to obtain global health benefits and probable effects on fibromyalgia symptoms [Level 1 [174-178, 184, 185], Grade A].**

**2.2.5 Complementary and alternative medicines (CAMs)**

CAMs are commonly used by FM patients with studies reporting over 90% use [193]. CAMs may be divided into four broad categories, namely products ingested, practitioner administered treatments, dietary interventions and treatments in the spiritual domain. There is little or poor evidence for efficacy of any intervention, with many studies having suboptimal design and reporting effects in small cohorts of patients. In a systematic review that also included the Chinese literature, Cao et al reported that there were some positive effects of Chinese herbal medicine on pain reduction in FM, compared with conventional medications [194]. However, the systematic review by De Silva et al, reported that there was insufficient evidence for the use of ingested or topically applied complementary agents for the management of FM symptoms [195]. Similarly, studies of homeopathy treatment, often of poor quality, indicate that this treatment cannot be recommended [196].

Acupuncture has been evaluated by at least two meta-analyses and three systematic reviews without showing evidence for prolonged effect on symptoms of FM, other than immediate pain reduction following treatment [194, 197-200]. However, when combined with other treatments including exercise and tricyclic antidepressants (TCAs), there was improvement in all measures of pain [201]. Similar to Tai Chi, Qigong with origins in Eastern medicine, but with differences in breathing patterns and meditation, has been shown to have some effect for up to four months when studied in 57 FM patients [202]. Chiropractic treatment, specifically manipulation, has also not been shown to have any appreciable effect on symptoms of FM, but may be useful for patients presenting with associated mechanical low-back pain [203, 204]. Hydrotherapy, which includes spa-, balneo-, and thalassotherapy has been evaluated in at least one meta-analysis and three systematic reviews and has shown short term benefits for pain and health related quality of life (HRQOL), although studies are mostly of low quality [180, 183-185]. Interestingly, most hydrotherapy programs also include an exercise component which may have important positive effects [184].

**Recommendations:**

- 22. Patients should be informed that there is currently insufficient evidence to support the recommendation of complementary and alternative medicine (CAM) treatments for the management of fibromyalgia symptoms, as they have mostly not been adequately evaluated regarding benefit [Level 1 [194, 195, 200], Grade A].**
- 23. Patients should be encouraged to disclose use of CAMs to the healthcare professional who should be understanding and tolerant of this disclosure and should provide information on current evidence-based understanding of efficacy and risks where available [Level 5, Consensus].**

### 2.3 Pharmacologic treatments

Symptom-based treatment represents a rational approach to pharmacologic choices, with drugs impacting more than one symptom adding advantage [111, 131]. There is a notion that the ideal treatment for FM is likely a combination of treatments, often in lower doses than reported in the study setting, with possible benefits of adherence. The traditional pharmacologic treatment paradigm begins with the use of simple analgesics and TCA's. Other pharmacologic treatments including other antidepressants, gabapentinoids, dopaminergic agents and sleep modifiers are now more commonly used. Any treatment recommended requires repeated re-evaluation, with vigilance regarding continued benefit or side effects especially in the setting of polypharmacy. Pharmacologic adverse effects are seldom serious or life threatening but can be insidious and mistaken for FM symptoms, especially for opioid use [205]. Fatigue may be aggravated by gabapentinoids, antidepressants or analgesics; depression may be exacerbated by opioids; gastro-intestinal symptoms may be affected by non-steroidal anti-inflammatory agents (NSAIDs), opioids and antidepressants; sleep disturbance may be aggravated by opioids and antidepressants. Careful scrutiny of pharmacotherapy with reduction of excessive medication use resulted in an improved outcome for FM patients in a multidisciplinary setting [206].

#### Recommendations:

- 24. Physicians should identify the most bothersome symptom(s) in order to help direct pharmacologic treatments according to a symptom-based approach. An ideal pharmacologic choice may address multiple symptoms simultaneously and may require a combination of medications, in which case attention must be paid to drug interactions [Level 5 [111, 131], Grade D].**
- 25. Pharmacologic treatments should be initiated in low doses with gradual and cautious upward titration to reduce medication intolerance [Level 5 [131], Grade D] with regular evaluation regarding continued efficacy and side effect profile, with the knowledge that drug side-effects may appear similar to symptoms of fibromyalgia [Level 5, Consensus].**
- 26. Physicians prescribing medications for fibromyalgia should be open-minded and aware of the broader spectrum of agents available to treat symptoms, and should not confine treatments to a single category of medications [Level 5, Consensus].**

#### ***2.3.1 Analgesic treatments (Acetaminophen and Nonsteroidal anti-inflammatory drugs [NSAIDs])***

Although traditionally recommended as a step one agent in the analgesic ladder by the World Health Organization (WHO), acetaminophen has never been formally examined in FM other than when compounded with tramadol [207, 208]. It is generally a safe drug, but with caution regarding hepatotoxicity when doses above 2 grams a day are used continuously. When compounded with another analgesic prescription, supplementing with over-the-counter acetaminophen preparations may be dangerous [209, 210]. Acetaminophen modulates COX-1, COX-2 or COX-3 enzymes in the brain, impacts on neurogenic inflammation or serotonergic mechanisms, and can boost the endocannabinoid system [211-214]. Notwithstanding lack of evidence, patients preferred NSAID's to acetaminophen, which were amongst the medications most commonly used

[215-217]. As NSAID's act mostly in the periphery, there is little rationale for their use, except perhaps for treatment of an associated condition such as osteoarthritis, but with attention to toxicity [218]. In order to limit side effects that can occur in the gastrointestinal, renal, and cardiovascular systems, NSAIDs should be used at the lowest dose and for the shortest periods of time [219-223].

**Recommendation:**

- 27. In line with the World Health Organisation step-up analgesic ladder, acetaminophen may be useful in some patients, but with attention to safe dosing [Level 5, Consensus].**
- 28. In the event that NSAID's are prescribed, particularly for associated conditions such as osteoarthritis, they should be used in the lowest dose and for the shortest period of time in view of possible serious adverse events [Level 5 [218, 219], Grade D].**

**2.3.2 Opioid treatments**

Tramadol, an opioid with more than one analgesic mechanism, is the only opioid that has been studied in FM, with positive effect on pain and improved quality of life [208, 224]. Treatment trials in patients with non- cancer pain, including some with FM, report that opioids offer good short-term analgesia, although treatments are often discontinued [225]. Due to lack of evidence opioid use is not recommended by any previous FM guidelines [7, 9, 226].

Opioids are used by up to 30% of FM patients and are perceived to provide best symptom relief when surveyed by internet [205, 216]. Opioids are associated with negative psychosocial effects including unstable psychiatric disorder, history of substance abuse, unemployment and disability payments [205]. The role of the endogenous opioid system in pain expression in FM is open to debate, with reports of down as well as upregulation of opioid receptors, elevated levels of cerebrospinal fluid enkephalin and variable response to naltrexone, an opioid antagonist [112, 227]. Naltrexone had no important effect on pain sensitivity or mood when studied in 20 women with FM, and was also not associated with self-reported opioid withdrawal symptoms, suggesting a limited role of the endogenous opioid system [227].

In clinical practice opioids may be useful in selected patients, but with caution. Treatments should be initiated with weaker opioid agonists such as codeine or tramadol, before moving to the stronger opioids, but without any convincing evidence. The analgesic properties of codeine are dependent upon conversion to morphine via the cytochrome P450 isoenzyme 2D6, an enzyme absent in up to 10% of individuals, or by ultra-metabolism with resulting toxic effects [228].

Currently, tramadol, tapentadol and methadone are analgesic agents with multiple effects. The parent compound tramadol has added serotonin and norepinephrine effects, whereas tapentadol has effects on noradrenergic receptors. Tramadol is predominantly metabolized via the cytochrome-P450 (CYP) isoenzyme 2D6, whereas tapentadol is metabolized to a non-active component via hepatic glucuronidation resulting in less drug-

drug interactions. These agents could be used for pain relief as a step up from acetaminophen and prior to the use of more potent opioid analgesics.

The progressive increase in opioid prescription has seen a parallel increase in their use as drugs of abuse, with reports of increased deaths associated with overdosing especially when combined alcohol or benzodiazepines [229-232]. Guidelines for safe and effective use of opioids for chronic pain have been published by the APS and also in Canada, with notes of caution [233, 234]. Physicians should practice responsible prescribing behaviours, pay attention to physical and psychosocial aspects, and constantly re-evaluate the risk benefit ratio. Long term effects of chronic opioid use are not yet fully clarified, but effects on mood, cognitive function, hormonal effects and increased pain due to hyperalgesia, need to be constantly re-evaluated [234]. Although extended-release formulations are touted as advantageous, evidence is lacking.

**Recommendations:**

- 29. A trial of opioids, beginning with a weak opioid such as tramadol, should be reserved for treatment of patients with moderate to severe pain that is unresponsive to other treatment modalities [Level 2 [208, 224], Grade D].**
- 30. Strong opioid use is discouraged, and patients who continue to use opioids should show improved pain and function. Healthcare professionals must monitor for continued efficacy, side effects or evidence of aberrant drug behaviours [Level 5 [233], Grade D].**

**2.3.3 Cannabinoid treatments**

Clinical cannabinoid use for pain relief remains controversial [235, 236]. The endocannabinoid system influences both inflammatory and pain pathways with two cannabinoid receptors distributed throughout the body [237]. Prescription cannabinoids are available in Canada as an oromucosal extract of cannabis based medicine, or the oral agents, dronabinol and nabilone. Herbal cannabis, whether smoked or ingested, is illegal without Health Canada exemption.

In a small trial of 40 patients over a 4 week period, nabilone was associated with improved pain, functional status, and anxiety compared to the placebo group, but with more side effects in the nabilone group [238]. In a comparator study of nabilone and amitriptyline addressing sleep disturbance, both agents performed equivalently for sleep, but without effect on pain or quality of life and with more adverse effects in the cannabinoid treatment group [239]. In a recent systematic review of 18 randomized controlled trials in chronic non cancer pain, 2 of which were for FM, cannabinoids were superior to placebo for analgesic effect, with some also showing improvement in sleep [236]. Long term effects of therapeutic cannabinoid treatment in FM are not known.

**Recommendation:**

- 31. A trial of a prescribed pharmacologic cannabinoid may be considered in a patient with fibromyalgia, particularly in the setting of important sleep disturbance [Level 3 [236, 238, 239], Grade C].**

#### ***2.3.4 Antidepressants with pain modulating effects***

Antidepressant medications have an effect on pain in treatment of FM independent of the effect on mood, by influencing diffuse noxious inhibitory control (DNIC) via augmentation of serotonin and norepinephrine [111]. Beginning with the tricyclic antidepressants (TCA's) and the selective serotonin reuptake inhibitors (SSRI's), recent study has focussed on the serotonin norepinephrine reuptake inhibitors (SNRI's) [240-248]. Two early meta-analyses reported a favourable effect on pain, sleep disturbance, fatigue and overall well-being in FM patients [240, 242]. As the term antidepressant may induce bias and stigma, the term pain modulator has been proposed [249].

TCA's in doses lower than used to treat depression have been the cornerstone drug treatment for FM. When 21 trials were meta-analysed, 16 with TCAs, these latter when compared to placebo showed a larger effect size for improved sleep, but with modest effect on other symptoms [240]. In a recent systematic review of 10 TCA trials, short term efficacy up to 8 weeks for lower doses but not higher doses was noted for pain, sleep, fatigue and global patient and physician impression [245]. Amitriptyline, with low cost and on provincial formularies, remains a reasonable choice, but limited by anticholinergic and antihistaminic side effects (eg, mouth dryness, weight gain, and drowsiness) and questions regarding long-term sustained efficacy [245]. Nortriptyline is less effective than amitriptyline [250]. Cost due to healthcare resource use/costs was less for those prescribed TCA's compared to pregabalin [25].

Cyclobenzaprine, technically a muscle relaxant, structurally similar to the TCAs, has shown moderate benefit for global improvement with an odds ratio (OR) of 3.0 (95% CI 1.6-5.6) [251]. When used in doses of 1-4 mg at night, there was improvement in sleep physiology, fatigue and depression [24].

Due to the side effects of TCAs, evaluation of other antidepressants was prompted. When 26 studies evaluated antidepressants in FM by meta-analysis, 13 for amitriptyline, 12 for SSRIs (5 paroxetine, 4 fluoxetine, 2 citalopram, 1 sertraline), and 3 for SNRIs (2 duloxetine, 1 milnacipran), all agents with the exception of citalopram, showed a positive effect on pain, fatigue, depression, sleep and quality of life [248]. In a subsequent meta-analysis by the same group examining 18 RCTs with a median duration of 8 weeks (range 4-28), the effect size for pain reduction was most evident for TCAs, with SSRIs and SNRIs showing a smaller effect [243]. There have been no high quality RCTs examining venlafaxine in FM, an agent with predominant effect on serotonin at low dose and norepinephrine at higher dose, but with possible benefit [138].

Duloxetine, the only antidepressant approved by Health Canada for the treatment of FM, and milnacipran, currently not available in Canada, are SNRI's with effect on pain and functioning in FM patients. For duloxetine, pain effect is independent of effect on mood, and some response is seen within 8 weeks [252, 253]. In a Cochrane systematic review of 3 studies, duloxetine in a dose of 60mg or 120mg daily was effective for pain relief over 12 and 28 weeks [244]. When duloxetine was studied up to one year, significant adverse events were few, but 29% of patients experienced troublesome side-effects including nausea, headache, dry-mouth and insomnia, with discontinuation of treatment in 16-20% of patients [244, 254]. The risk of suicide in patients of all age groups treated with any antidepressant should be appreciated. These agents have potential for interactions with

other serotonin-elevating agents such as tramadol however serotonin syndrome is rare, but appropriate monitoring is required.

In the setting of overall equivalency of effect on symptoms, side effect profile and cost considerations should be taken into account. When factors influencing initiation of drugs were examined in a database of almost 120,000 FM patients, TCA's, SSRI's, duloxetine, tramadol and gabapentin were initiated almost equally in about 5% of individuals, with 9% initiating pregabalin, and 60% initiating non tramadol opioids. [255]. Prior treatment with pregabalin was associated with initiation of duloxetine [255].

### **Recommendations:**

- 32. The pain-modulating effects of antidepressant medications should be explained to patients with fibromyalgia in order to dispel the concept of a primarily psychological complaint [Level 5 [249], Grade D].**
- 33. All categories of antidepressant medications including TCAs, SSRIs and SNRIs may be used for treatment of pain and other symptoms in patients with fibromyalgia [Level 1 [243, 248], Grade A], with choice driven by available evidence for efficacy, physician knowledge, patient characteristics, and attention to side effect profile [Level 5, Consensus].**

#### ***2.3.5 Anticonvulsants with pain modulating effects ( $\alpha$ 2- $\delta$ ligand drugs)***

Analgesic effects of anticonvulsants have been recognized since the 1970's with initial reports of carbamazepine for treatment of facial pain [256]. Subsequent effects on neuropathic pain prompted study in FM. These drugs act as neuromodulators to dampen neuronal excitability, although the precise mechanism of action is unclear [257]. They act at a number of sites, including voltage-gated ion channels, ligand-gated ion channels, receptors of glutamate and N-methyl-D-aspartate (NMDA), and receptors for  $\gamma$ -aminobutyric acid (GABA) and glycine [258]. The inhibitory neurotransmitter GABA served as a structural template for development of the gabapentinoids ( $\alpha$ 2- $\delta$  ligand drugs), including gabapentin and pregabalin, although neither binds appreciably to GABA receptors.

Gabapentinoids, classified as second-generation anticonvulsants, have shown clinical efficacy in the treatment of FM, although the clinical meaningful effect may be small [259-261]. Moore reports that only a minority of patients will have substantial benefit, with more having moderate benefit [262]. In an analysis of 127 RCT's, with five studies included for meta-analysis, there was strong evidence for reduced pain, improved sleep and quality of life for gabapentin and pregabalin, independent of anxiolytic effects [259]. Effect on fatigue and anxiety were less substantial.

Both gabapentin and pregabalin are well absorbed after oral administration, have good bioavailability, and are excreted unchanged by the kidneys, requiring dosage adjustment in the presence of renal impairment [263]. There are few serious side effects or drug interactions, but adverse side effects including cognitive changes, weight gain and oedema lead to discontinuation or failure to achieve optimal doses. High doses of pregabalin used in trials and recommended by formularies (300, 450, 600 mg/day) are seldom used in clinical practice. When used as monotherapy, pregabalin improved pain,

global assessment and function, and sleep at doses of 450mg/day, but not 300 or 600mg/day [26]. Average daily dosing of pregabalin was noted to increase from about 150mg/day at initiation of treatment to about 300mg/day over 12-months in a US administrative claims database [264]. A new prescription for pregabalin was associated with reduced use of NSAIDs, anticonvulsants and other combination therapies, whereas gabapentin was associated with increased prescriptions for opioids, SNRIs, anticonvulsants, benzodiazepines and topical agents [265].

**Recommendation:**

**34. Anticonvulsant medication use should be explained as having pain-modulating properties and treatment should begin with the lowest possible dose followed by up titration, with attention to adverse events [Level 1 [259, 261, 262], Grade A].**

**2.3.6 Other pharmacologic agents**

Novel pharmacologic agents, each with unique mechanisms of action, may eventually be useful for FM pain management, although evidence is preliminary. The categories of drugs include dopaminergic agents, sodium oxybate, 5-hydroxytryptamine 3 receptor antagonists, and *N*-methyl D-aspartate (NMDA) receptor antagonists.

Anti-parkinsonian drugs that augment dopamine are an effective treatment for restless legs, a frequent association with FM. Pramipexole was studied in 60 FM patients at a dose of 4.5mg per day, and reduced pain by one third, although use is tempered by gastrointestinal side effects [266]. In contrast, terguride, a partial dopamine agonist, showed no advantage over placebo in a study of 99 patients [267]. There have been reports of impulse control disorders associated with these agents [268].

Gamma-hydroxybutyric acid (GHB), a naturally occurring substance, likely synthesized from GABA in neurones, has an agonist action at two receptor sites [269]. Binding to the GHB receptor is excitatory, whereas binding to the GABA<sub>B</sub> receptor is inhibitory. GHB has a biphasic effect on dopamine release, with high concentration inhibiting release from the GABA<sub>B</sub> receptor and low concentrations stimulating dopamine release from the GHB receptor, accounting for the dual sedative and subsequent activating effects, as well as addictive properties. In a study of 188 FM patients treated with sodium oxybate, benefit was observed for both pain and subjective sleep quality, with good tolerability apart from nausea and dizziness reported by one third of patients, but concerns regarding long term use and potential for addiction remain [270]. The improvement in sleep seen with sodium oxybate may be due to reduction of alpha intrusion and increase in slow-wave sleep, as well as boosting of growth hormone levels [271]. FDA approval for treatment of FM was denied due to concerns of abuse [272].

The 5-hydroxytryptamine-3 (5-HT<sub>3</sub>) receptor antagonist dolasetron, infused monthly over a period of 3 months, reduced pain intensity [273]. When evaluated in two studies, tropisetron, a selective, oral competitive 5-HT<sub>3</sub>-receptor antagonist, improved pain in the short term [274, 275]. In contrast, the 5-HT-2 receptor blocker ritanserin showed no effect on the key symptoms of FM over 16 weeks [276].

There are no studies in FM of NMDA receptor antagonists including ketamine, dextromethorphan, amantadine, memantine, and methadone, agents moderating chronic pain. When pain mechanisms were examined in FM using ketamine, some patients demonstrated reduced local and referred pain areas, supporting the concept of central hypersensitization [277]. Cognitive and psychological side effects of ketamine preclude current use for FM.

Peripheral pain generators may augment sensitization in FM. Lidocaine, the local anesthetic agent active on sodium channels, was tested by local injection and intravenously. Local injection into the trapezius region reduced local pain threshold at the injection site, whereas intravenous lidocaine showed a modest effect on pain in 75 patients followed for four weeks [278, 279]. When trigger point injections, joint injections or myofascial release techniques were tested, reduced pain persisted for three weeks [280, 281]. Therefore, attention to local factors may have some place in the treatment of FM. Botulinum toxin-A injections have been studied in small uncontrolled pilot studies with conflicting report of efficacy [282, 283].

Agents without effect in FM include dehydroepiandrosterone in postmenopausal women, human interferon-alpha, and the antiviral agent valacyclovir [284-286]. Growth hormone injections, evaluated in two studies, improved overall symptoms but safety concerns and cost issues preclude recommendation [287, 288].

Subjective sleep improved with zopiclone in two studies of 41 and 33 patients, but without change in polysomnography [289, 290]. Very low doses of cyclobenzaprine increased restorative sleep, with improvement in fatigue and pain [24]. A combination treatment with tenoxicam and bromazepan may have some effect in FM, although a study of 164 patients over 8 weeks showed no significant difference compared to placebo [291]. Quetiapine, an atypical second generation antipsychotic agent, commonly used off-label for sleep, reduced FIQ stiffness and fatigue, but not FIQ pain [292]. Melatonin, with potential to improve sleep was tested in a pilot study of 21 patients over 4 weeks with some suggestion of improvement [293].

A common trend for all of the aforementioned agents is lack of concrete evidence, either for or against use in FM. Larger well-designed RCTs are required to provide evidence for use.

**Recommendation:**

**35. Physicians should be aware that only pregabalin and duloxetine have Health Canada approval for management of fibromyalgia symptoms and all other pharmacologic treatments constitute “off label use” [Level 5, Consensus].**

## **SECTION 3 : The outcome**

### **3.1 How should patients with FM be followed?**

The optimal clinical follow up for FM patients will depend on good clinical judgement. Healthcare visits will occur more frequently at treatment initiation, and then be less frequent when the treatment strategy has been stabilized. The ideal outcome measurement for use in clinical practice is also unknown. Although improvement in pain is paramount, change in other symptoms may hold equal importance and should be addressed. A recently proposed severity index for FM symptoms requires testing in clinical practice to determine sensitivity to change [294].

As treatment objective should be reduction of symptoms and improved function, symptom improvement alone requires reassessment of treatments, with side effects possibly contributing to poor function, or other factors such as poor patient motivation. Realistic outcome goals should be emphasized.

New symptoms should be clinically evaluated with appropriate testing where required and healthcare professionals should be cautious about attributing any new symptom to FM. Alternately, prudence should be exercised regarding additional investigations, which should be driven by sound clinical principals. As FM patients generally undergo more tests and are more costly to the healthcare system than the average population, excessive testing should be avoided [5, 6, 295].

#### **Recommendations:**

- 36. Clinical follow up should be dependent on the judgement of the physician or healthcare team with likely more frequent visits during the initial phase of management or until symptoms are stabilized [Level 5, Consensus].**
- 37. In the continued care of a patient with fibromyalgia, the development of a new symptom requires clinical evaluation to ensure that symptoms are not due to some other medical illness [Level 5, Consensus].**

### **3.2 What factors may help predict outcome in FM?**

There are currently no reliable predictors of outcome or response to treatment for patients with FM. In a single study a response to treatment with duloxetine within the first 1-2 weeks predicted continued response at 3 months, suggesting that early treatment response to this specific medication could be a treatment effect indicator [296]. Contrary to popular belief, outcome is not universally poor in the majority of patients, although symptoms do persist and fluctuate over time, with record of persistence up to seven years [12, 13].

A favourable outcome has been reported when patients were followed in community studies, with some even reporting resolution of symptoms, especially for those with recent onset [12, 297-299]. Improved outcome is further supported by the findings that 65% of subjects improved over a 2-year period in a community based study in England [300]. Although early life adverse events are associated with FM, they did not predict response to treatment in a single trial [127]. Some authors have reported a poorer

outcome in patients who developed FM following a traumatic event [130, 301]. FM affects health-related quality of life from multiple perspective including physical functioning, emotional and psychological health [302]. Factors that may affect outcome include personality traits such as neuroticism and catastrophizing, poor internal locus of control, uncontrolled depression, and extreme obesity [303, 304].

Confirmation of a diagnosis of FM has a positive effect on overall healthcare costs in studies conducted in Europe [6]. Additionally, a definitive diagnosis does not adversely affect outcome from the patient perspective, is likely reassuring and facilitates engaging in optimal healthcare management [95]. Reduction in excessive use of pharmacotherapy improved outcome in a single study [206].

### **Recommendations:**

- 38. Patients should be informed that the outcome in many individuals is favourable even if symptoms of fibromyalgia tend to wax and wane over time [Level 3 [297-299], Grade B].**
- 39. Patients who have experienced previous adverse lifetime events that have impacted on psychological wellbeing and have not been effectively addressed should be offered appropriate support to facilitate attaining health-related outcome goals [Level 5, Consensus].**
- 40. Physicians should be alert that factors such as passivity, poor internal locus of control and prominent mood disorder may have a negative influence on outcome [Level 5, Consensus].**

### **3.3 What measures of outcome may be used to follow patients with FM?**

Any measurement tool for outcome must be reliable and valid, simple to use and reflect change over time. Physicians generally remain reticent regarding the usefulness of questionnaires to follow patients in clinical practice.

Patient narrative report of symptoms or a report of global impression of change (PGIC), measured as a 7-point Likert scale, ranging from 1=much worse, to 7=much better, are simple and practical assessments for clinical practice [305, 306]. Documenting patient goals and their levels of achievement is a strategy that has concrete meaning for a patient [109]. Questionnaires that have been used include measures of function such as the Fibromyalgia Impact Questionnaire (FIQ), Revised FIQ (FIQR), Health Assessment Questionnaire (HAQ), as well as others measuring pain, sleep, fatigue and depression [307-310]. Measurement of tender points or pain intensity of tender points is not a clinically relevant or reliable outcome measurement [58].

#### **3.3.1 Examples of tools to assess function, global status and quality of life**

Various questionnaires specific to FM have been used mostly in the research setting, but are less applicable to routine patient care.

1. The Fibromyalgia Impact Questionnaire (FIQ) is a disease-specific composite instrument that measures quality of life in patients with FM [308]. A change of 14% on the FIQ indicates a clinically meaningful difference in health status [311]. It is complex

to score, has questions that may not be currently applicable today and does not address cognition.

2. A modification of the FIQ, termed the revised FIQ (FIQR) can be completed in two minutes, is simpler to score than the FIQ and includes questions regarding cognition, environmental sensitivity, balance and tenderness [307]. It has shown good reliability and equivalency with the original FIQ as well as the generic functional questionnaire, the SF36.

3. The FM Severity Scale, a measurement tool component of the revised diagnostic criteria, has not yet been tested in the trial or clinical setting. This simple tick sheet questionnaire is scored out of 31, with a value of 13 or more used to identify patients with FM [294].

4. Quality of life measures in FM patients, such as SF36, consistently show important effects, but are not practical for use in routine clinical care [312].

### **3.3.2 Examples of tools to assess pain**

Numerous measures can be used to assess pain in FM, with recognition that pain is a single component of this condition, and therefore should not be assessed in isolation.

1. The numerical pain intensity scale (0=no pain, 10= worst possible pain) and the pain visual analogue scale (VAS) are validated and simple measurements. These measures do not address other aspects of pain such as the quality, interference of daily function or timing of pain [313, 314]. A change in pain score of 30 % reflects a clinically meaningful change [315].

2. Body pain diagrams may identify the distribution of pain, although the pain of FM is fluid and moves location in time frames from hours to days to weeks. Pain diagrams give a pictorial image of the location of pain, but do not address intensity, quality or variation over time [316].

3. Tender point count: although previously used as an outcome measure, the tender point count correlates poorly with global patient status and should not be used. When objective dolorimetry was applied in a random way, the correlation with subjective report was more consistent [317].

#### **Recommendations:**

- 41. Outcome can be measured by narrative report of symptom status or patient global impression of change (PGIC), without need for more complex questionnaires [Level 3 [305, 306], Grade C].**
- 42. Patient goals and their levels of achievement should be recorded as a useful strategy to follow outcome [Level 5, Consensus].**
- 43. Tender point examination should not be used as an outcome measure [Level 3 [58], Grade C].**

### **3.4 What recommendations can be given regarding work?**

The work ability of persons with FM is often contentious, with subjective report of functional impairment difficult to reconcile with a mostly healthy looking person. In the United States up to 35% of patients with FM are receiving work disability benefits [318].

FM patients in the workforce have generally less severe symptoms and better quality of life than those unemployed, but without evidence that remaining in the workforce positively affects health status [319, 320]. This finding holds true when patients were followed longitudinally over a five year period [321]. Therefore, it might be surmised that symptom severity is a determining factor in ability to work, missed workdays and loss of productivity, indicating a substantial burden of illness [322]. Compared to persons with RA, those with FM reported more short-term disability days, but overall mean costs for absence from work were similar for the two conditions [323].

Pacing, especially when applied to the workforce, may improve retention in employment [143]. Specific reasonable adjustments in the working environment may be helpful [144]. Although the physical and psychological demands of a job influence employment and eventual return to work, the life situation, attitude of the patient and ability to influence work parameters are additional contributing factors [324]. Combined exercise and cognitive strategies improved return to work in one study, and physical fitness in another [325, 326]. Regularity in scheduling will encourage a steady routine and regular sleep pattern. In an internet survey, FM patients reported higher physical function to be associated with younger age, higher education, less fatigue, less medication use and more exercise activity [327]. Pain locus of control with positive expectations was a good predictor of return to work in a Spanish multidisciplinary treatment program [140]. Patients' perceived physical limitation better predicted employment status than affective symptoms or pain [328]. Although return to work is perceived as an ideal health economic outcome, this may not be applicable for many women with FM who may be homemakers [326].

#### **Recommendations:**

- 44. Physicians should encourage patients to remain in the workforce, and if necessary may provide recommendations that could help maintain optimal productivity, as outcome is generally more favourable for those who are employed [Level 3 [321], Grade C].**
- 45. Patients with fibromyalgia on a prolonged sick leave should be encouraged to participate in an appropriate rehabilitation program with focus on improving function, including return to work if possible [Level 5 [326], Grade D].**

### **3.5 How can healthcare costs be contained when treating patients with FM?**

FM is a condition associated with considerable direct and indirect healthcare costs. Costs are reported to be equal to persons with low back pain and rheumatoid arthritis and greater than persons with ankylosing spondylitis [323, 329]. In the US, the cost for service utilization in an individual FM patient was over \$2000 in 1997, with reports in the order of \$4000 per year per patient for Canada and Europe [5, 295, 330, 331]. Healthcare

costs were three times higher for FM patients compared to other randomly selected patients over a 12 month period [332].

Treatment strategies to reduce healthcare costs have seldom been examined. Social support or social support and education did not reduce costs when compared to a control group over a one year period [333]. Healthcare costs for FM are greatest for non-drug therapies, with a threefold increase over drug therapy [330]. Even in the primary care setting, FM patients incurred higher annual costs compared to a reference population of non-FM patients [334] This is particularly true for FM patients with other comorbidities [335]. Concomitant depression and FM resulted in greater healthcare use, with mean incremental employer payments over 9000\$, an amount greater than for FM or depression alone [336].

Using prediction of cost analysis over four years in the United Kingdom, a diagnosis of FM reduced healthcare costs and resource utilization driven by less tests, imaging, medication use, specialist referrals and primary care visits [82].

**Recommendation:**

**46. In persons with fibromyalgia, other co morbid conditions including depression should be recognized and addressed in order to reduce healthcare costs [Level 3 [335, 336], Grade C].**

**Conclusion**

FM is a valid syndrome affecting approximately one million Canadians. In the absence of any confirmatory test, the diagnosis is based clinically on the chief complaint of pain and associated symptoms of fatigue, sleep disturbance, cognitive changes, mood disorder and other somatic symptoms. A physical examination is within normal limits apart from tenderness of soft tissues, but without the requirement of examination of tender points to confirm a diagnosis. Investigations should be limited to simple laboratory testing, unless the clinical picture suggests some other diagnosis.

Primary care physicians are encouraged to establish a diagnosis of FM as early as possible without need for specialist confirmation. Symptoms of FM persist over time without any current treatment option offering a cure and with ideal care centered in primary care, incorporating a multimodal approach. Treatment plans should incorporate self-management techniques, goal setting and healthy lifestyles, with acknowledgement of psychological distress when present. Pharmacologic treatments should be initiated in low doses with gradual and cautious upward titration to minimize side effects. Continued medication use requires diligent evaluation with attention to need for continued use and emergence of adverse effects. Clinical outcome can be measured by a simple narrative report of symptom status without need for use of specific questionnaires. Any new symptom requires appropriate clinical evaluation and should not immediately be attributed to FM. Although there is currently no cure for FM, many patients achieve moderate symptom control and are able to lead active and fulfilling lives.

## References

1. Wolfe, F., et al., *The American College of Rheumatology 1990. Criteria for the classification of fibromyalgia. Report of the Multicenter Criteria Committee.* Arthritis and Rheumatism, 1990. **33**(2): p. 160-172.
2. Wolfe, F., et al., *The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity.* Arthritis care & research, 2010. **62**(5): p. 600-10.
3. Mease, P., et al., *Fibromyalgia syndrome module at OMERACT 9: domain construct.* Journal of Rheumatology, 2009. **36**(10): p. 2318-29.
4. McNally, J.D., D.A. Matheson, and V.S. Bakowsky, *The epidemiology of self-reported fibromyalgia in Canada.* Chronic Dis Can, 2006. **27**(1): p. 9-16.
5. Lachaine, J., C. Beauchemin, and P.-A. Landry, *Clinical and economic characteristics of patients with fibromyalgia syndrome.* Clinical Journal of Pain, 2010. **26**(4): p. 284-90.
6. Hughes, G., et al., *The impact of a diagnosis of fibromyalgia on health care resource use by primary care patients in the UK: an observational study based on clinical practice.* Arthritis & Rheumatism, 2006. **54**(1): p. 177-83.
7. Carville, S.F., et al., *EULAR evidence-based recommendations for the management of fibromyalgia syndrome.* Annals of the Rheumatic Diseases, 2008. **67**(4): p. 536-41.
8. Hauser, W., et al., *Fibromyalgia syndrome: classification, diagnosis, and treatment.* Deutsches Arzteblatt International, 2009. **106**(23): p. 383-91.
9. Burckhardt, C., Goldenberg, D., Crofford, L., Gerwin, R., Gowans, S., Kackson, et al., *Guideline for the management of fibromyalgia syndrome. Pain in adults and children. APS Clinical practice guideline Series No. 4 Glenview, IL: American Pain Society; 2005.*
10. Howick, J., Chalmers, I., Glasziou, P., Greenhalgh, T., Heneghan, C., Liberati, A., Moschetti, I., Phillips, B., Thornton, H., Goddard, O., Hodgkinson, M., *The Oxford 2011 Table of Evidence. Oxford Centre for Evidence-Based Medicine.* <http://www.cebm.net/index.aspx?o=5653>
11. Yunus, M.B., *A comprehensive medical evaluation of patients with fibromyalgia syndrome.* Rheumatic Diseases Clinics of North America, 2002. **28**(2): p. 201-17.
12. Wolfe, F., et al., *Health status and disease severity in fibromyalgia: results of a six-center longitudinal study.* Arthritis & Rheumatism, 1997. **40**(9): p. 1571-9.
13. Walitt, B., et al., *The longitudinal outcome of fibromyalgia: a study of 1555 patients.* Journal of Rheumatology, 2011. **38**(10): p. 2238-46.
14. Rehm, S.E., et al., *A cross-sectional survey of 3035 patients with fibromyalgia: subgroups of patients with typical comorbidities and sensory symptom profiles.* Rheumatology, 2010. **49**(6): p. 1146-52.
15. Simms, R.W. and D.L. Goldenberg, *Symptoms mimicking neurologic disorders in fibromyalgia syndrome.* Journal of Rheumatology, 1988. **15**(8): p. 1271-3.
16. Hagglund, K.J., et al., *Weather, beliefs about weather, and disease severity among patients with fibromyalgia.* Arthritis Care and Research, 1994. **7** (3): p. 130-135.
17. Macfarlane, T.V., et al., *Whether the weather influences pain? Results from the EpiFunD study in North West England.* Rheumatology, 2010. **49**(8): p. 1513-20.
18. Mease, P., et al., *Fibromyalgia syndrome.* Journal of Rheumatology, 2007. **34**(6): p. 1415-25.
19. Yunus, M.B., *Fibromyalgia and overlapping disorders: the unifying concept of central sensitivity syndromes.* Seminars in Arthritis & Rheumatism, 2007. **36**(6): p. 339-56.
20. Chiu, Y.H., et al., *Poor sleep and depression are independently associated with a reduced pain threshold. Results of a population based study.* Pain, 2005. **115**(3): p. 316-21.
21. Osorio, C.D., et al., *Sleep quality in patients with fibromyalgia using the Pittsburgh Sleep Quality Index.* Journal of Rheumatology, 2006. **33**(9): p. 1863-5.
22. Moldofsky, H., *The significance of the sleeping-waking brain for the understanding of widespread musculoskeletal pain and fatigue in fibromyalgia syndrome and allied syndromes.* Joint Bone Spine, 2008. **75**(4): p. 397-402.
23. Hamilton, N.A., et al., *Fibromyalgia: the role of sleep in affect and in negative event reactivity and recovery.* Health Psychol, 2008. **27**(4): p. 490-7.
24. Moldofsky, H., et al., *Effects of Bedtime Very Low Dose Cyclobenzaprine on Symptoms and Sleep Physiology in Patients with Fibromyalgia Syndrome: A Double-blind Randomized Placebo-controlled Study.* Journal of Rheumatology, 2011. **38**(12): p. 2653-63.
25. Gore, M., et al., *Clinical characteristics, pharmacotherapy, and healthcare resource use among patients with fibromyalgia newly prescribed pregabalin or tricyclic antidepressants.* J Med Econ, 2012. **15**(1): p. 32-44.

26. Pauer, L., et al., *An International, Randomized, Double-blind, Placebo-controlled, Phase III Trial of Pregabalin Monotherapy in Treatment of Patients with Fibromyalgia*. Journal of Rheumatology, 2011. **38**(12): p. 2643-2652.
27. Canovas, R., et al., *Virtual reality tasks disclose spatial memory alterations in fibromyalgia*. Rheumatology, 2009. **48**(10): p. 1273-8.
28. Park, D.C., et al., *Cognitive function in fibromyalgia patients*. Arthritis & Rheumatism, 2001. **44**(9): p. 2125-33.
29. Rodriguez-Andreu, J., et al., *Cognitive impairment in patients with fibromyalgia syndrome as assessed by the mini-mental state examination*. BMC Musculoskeletal Disorders, 2009. **10**: p. 162.
30. Walitt, B., et al., *Automated neuropsychiatric measurements of information processing in fibromyalgia*. Rheumatology International, 2008. **28**(6): p. 561-6.
31. Epstein, S.A., et al., *Psychiatric disorders in patients with fibromyalgia. A multicenter investigation*. Psychosomatics, 1999. **40**(1): p. 57-63.
32. de Souza, J.B., et al., *Fibromyalgia subgroups: profiling distinct subgroups using the Fibromyalgia Impact Questionnaire. A preliminary study*. Rheumatology International, 2009. **29**(5): p. 509-15.
33. Thieme, K., D.C. Turk, and H. Flor, *Comorbid depression and anxiety in fibromyalgia syndrome: relationship to somatic and psychosocial variables*. Psychosom Med, 2004. **66**(6): p. 837-44.
34. Nicassio, P.M., et al., *The contribution of family cohesion and the pain-coping process to depressive symptoms in fibromyalgia*. Annals of Behavioral Medicine, 1995. **17**(4): p. 349-356.
35. Raphael, K.G., et al., *Familial aggregation of depression in fibromyalgia: a community-based test of alternate hypotheses*. Pain, 2004. **110**(1-2): p. 449-60.
36. de Araujo, M.P., et al., *Urodynamic study and quality of life in patients with fibromyalgia and lower urinary tract symptoms*. Int Urogynecol J Pelvic Floor Dysfunct, 2008. **19**(8): p. 1103-7.
37. Dao, T.T., W.J. Reynolds, and H.C. Tenenbaum, *Comorbidity between myofascial pain of the masticatory muscles and fibromyalgia*. J Orofac Pain, 1997. **11**(3): p. 232-41.
38. Plesh, O., F. Wolfe, and N. Lane, *The relationship between fibromyalgia and temporomandibular disorders: Prevalence and symptom severity*. Journal of Rheumatology, 1996. **23**(11): p. 1948-1952.
39. Poyhia, R., D. Da Costa, and M.A. Fitzcharles, *Previous pain experience in women with fibromyalgia and inflammatory arthritis and nonpainful controls*. Journal of Rheumatology, 2001. **28**(8): p. 1888-91.
40. Orellana, C., et al., *Sexual dysfunction in fibromyalgia patients*. Clinical & Experimental Rheumatology, 2008. **26**(4): p. 663-6.
41. Roy-Byrne, P., et al., *Post-traumatic stress disorder among patients with chronic pain and chronic fatigue*. Psychological Medicine, 2004. **34**(2): p. 363-368.
42. Lipworth, L., R.E. Tarone, and J.K. McLaughlin, *Breast implants and fibromyalgia: a review of the epidemiologic evidence*. Annals of Plastic Surgery, 2004. **52**(3): p. 284-7.
43. Wolfe, F., *"Silicone related symptoms" are common in patients with fibromyalgia: No evidence for a new disease*. Journal of Rheumatology, 1999. **26**(5): p. 1172-1175.
44. Weingarten, T.N., et al., *Impact of tobacco use in patients presenting to a multidisciplinary outpatient treatment program for fibromyalgia*. Clinical Journal of Pain, 2009. **25**(1): p. 39-43.
45. Walitt, B., et al., *The Longitudinal Outcome of Fibromyalgia: A Study of 1555 Patients*. J Rheumatol, 2011.
46. Mease, P., et al., *Fibromyalgia syndrome module at OMERACT 9: Domain construct*. J Rheumatol, 2009. **36**(10): p. 2318-2329.
47. Gervais, R.O., et al., *Effort testing in patients with fibromyalgia and disability incentives*. J Rheumatol, 2001. **28**(8): p. 1892-9.
48. Croft, P., *Testing for tenderness: what's the point?* Journal of Rheumatology, 2000. **27**(11): p. 2531-3.
49. Tunks, E., et al., *The reliability of examination for tenderness in patients with myofascial pain, chronic fibromyalgia and controls*. Journal of Rheumatology, 1995. **22**(5): p. 944-52.
50. Cott, A., et al., *Interrater reliability of the tender point criterion for fibromyalgia*. Journal of Rheumatology, 1992. **19**(12): p. 1955-9.
51. Jacobs, J.W., et al., *Lack of correlation between the mean tender point score and self-reported pain in fibromyalgia*. Arthritis Care & Research, 1996. **9**(2): p. 105-11.
52. Lundberg, G. and B. Gerdle, *Tender point scores and their relations to signs of mobility, symptoms, and disability in female home care personnel and the prevalence of fibromyalgia syndrome*. Journal of Rheumatology, 2002. **29**(3): p. 603-13.
53. McCarberg, B., et al., *Tender points as predictors of distress and the pharmacologic management of fibromyalgia syndrome*. American Journal of Therapeutics, 2003. **10**(3): p. 176-92.
54. McIntosh, M.J., et al., *Protocol for verifying expertise in locating fibromyalgia tender points*. Arthritis Care & Research, 1998. **11**(3): p. 210-6.
55. McVeigh, J.G., et al., *Tender point count and total myalgic score in fibromyalgia: changes over a 28-day period*. Rheumatology International, 2007. **27**(11): p. 1011-8.

56. Harth, M. and W.R. Nielson, *The fibromyalgia tender points: use them or lose them? A brief review of the controversy.* Journal of Rheumatology, 2007. **34**(5): p. 914-22.
57. Okifuji, A., et al., *A standardized manual tender point survey. I. Development and determination of a threshold point for the identification of positive tender points in fibromyalgia syndrome.* Journal of Rheumatology, 1997. **24**(2): p. 377-83.
58. Bidari, A., B. Ghavidel-Parsa, and B. Ghalehbaghi, *Reliability of ACR criteria over time to differentiate classic fibromyalgia from nonspecific widespread pain syndrome: a 6-month prospective cohort study.* Mod Rheumatol, 2009. **19**(6): p. 663-9.
59. Jespersen, A., et al., *Computerized cuff pressure algometry: A new method to assess deep-tissue hypersensitivity in fibromyalgia.* Pain, 2007. **131**(1-2): p. 57-62.
60. Wolfe, F. and W. Hauser, *Fibromyalgia diagnosis and diagnostic criteria.* Annals of Medicine, 2011. **43**(7): p. 495-502.
61. Tastekin, N., M. Birtane, and K. Uzunca, *Which of the three different tender points assessment methods is more useful for predicting the severity of fibromyalgia syndrome?* Rheumatology International, 2007. **27**(5): p. 447-51.
62. Petzke, F., et al., *What do tender points measure? Influence of distress on 4 measures of tenderness.* Journal of Rheumatology, 2003. **30**(3): p. 567-74.
63. Tastekin, N., et al., *Discriminative value of tender points in fibromyalgia syndrome.* Pain Medicine, 2010. **11**(3): p. 466-71.
64. Khostanteen, I., et al., *Fibromyalgia: Can one distinguish it from simulation? An observer-blind controlled study.* Journal of Rheumatology, 2000. **27**(11): p. 2671-2676.
65. Eich, W., et al., *[Definition, classification and diagnosis of fibromyalgia syndrome].* Schmerz, 2008. **22**(3): p. 255-66.
66. Katz, R.S., F. Wolfe, and K. Michaud, *Fibromyalgia diagnosis: a comparison of clinical, survey, and American College of Rheumatology criteria.* Arthritis Rheum, 2006. **54**(1): p. 169-76.
67. Russell, I.J., *Fibromyalgia syndrome: Presentation, diagnosis, and differential diagnosis.* Primary Psychiatry, 2006. **13**(9): p. 40-45.
68. Daniel, D. and M.V. Pirota, *Fibromyalgia--should we be testing and treating for vitamin D deficiency?* Australian family physician, 2011. **40**(9): p. 712-6.
69. Tandeter, H., et al., *Serum 25-OH vitamin D levels in patients with fibromyalgia.* Isr Med Assoc J, 2009. **11**(6): p. 339-42.
70. Warner, A.E. and S.A. Arnsperger, *Diffuse musculoskeletal pain is not associated with low vitamin D levels or improved by treatment with vitamin D.* J Clin Rheumatol, 2008. **14**(1): p. 12-6.
71. Al-Allaf, A.W., L. Ottewell, and T. Pullar, *The prevalence and significance of positive antinuclear antibodies in patients with fibromyalgia syndrome: 2-4 years' follow-up.* Clinical Rheumatology, 2002. **21**(6): p. 472-7.
72. Kotter, I., et al., *Is there a predisposition for the development of autoimmune diseases in patients with fibromyalgia? Retrospective analysis with long term follow-up.* Rheumatology International, 2007. **27**(11): p. 1031-9.
73. Yunus, M.B., F.X. Hussey, and J.C. Aldag, *Antinuclear antibodies and connective tissue disease features in fibromyalgia syndrome: a controlled study.* Journal of Rheumatology, 1993. **20**(9): p. 1557-60.
74. Landis, C.A., et al., *Pain, psychological variables, sleep quality, and natural killer cell activity in midlife women with and without fibromyalgia.* Brain, Behavior, & Immunity, 2004. **18**(4): p. 304-13.
75. Yunus, M.B., et al., *Fibromyalgia syndrome: Clinical features and spectrum.* Journal of Musculoskeletal Pain, 1994. **2**(3): p. 5-21.
76. Goldenberg, D.L., *Diagnosis and differential diagnosis of fibromyalgia.* Am J Med, 2009. **122**(12 Suppl): p. S14-21.
77. Shir, Y. and M.-A. Fitzcharles, *Should rheumatologists retain ownership of fibromyalgia?* Journal of Rheumatology, 2009. **36**(4): p. 667-70.
78. Buskila, D., et al., *Awareness of diagnostic and clinical features of fibromyalgia among family physicians.* Family Practice, 1997. **14**(3): p. 238-41.
79. Wolfe, F., *Stop using the American College of Rheumatology criteria in the clinic.* Journal of Rheumatology, 2003. **30**(8): p. 1671-2.
80. Katz, J.D., et al., *Gender bias in diagnosing fibromyalgia.* Gend Med, 2010. **7**(1): p. 19-27.
81. Coster, L., et al., *Chronic widespread musculoskeletal pain - a comparison of those who meet criteria for fibromyalgia and those who do not.* European Journal of Pain: Ejp, 2008. **12**(5): p. 600-10.
82. Annemans, L., et al., *Health economic consequences related to the diagnosis of fibromyalgia syndrome.* Arthritis & Rheumatism, 2008. **58**(3): p. 895-902.
83. Annemans, L., K. Le Lay, and C. Taieb, *Societal and patient burden of fibromyalgia syndrome.* Pharmacoeconomics, 2009. **27**(7): p. 547-59.
84. Norregaard, J., et al., *A four-year follow-up study in fibromyalgia. Relationship to chronic fatigue syndrome.* Scandinavian Journal of Rheumatology, 1993. **22**(1): p. 35-8.
85. Wolfe, F., *Fibromyalgia: On diagnosis and certainty.* Journal of Musculoskeletal Pain, 1993. **1**(3-4): p. 17-35.
86. Fitzcharles, M.A. and J.M. Esdaile, *The overdiagnosis of fibromyalgia syndrome.* American Journal of Medicine, 1997. **103**(1): p. 44-50.

87. Fitzcharles, M.A. and P. Boulos, *Inaccuracy in the diagnosis of fibromyalgia syndrome: analysis of referrals*. Rheumatology (Oxford), 2003. **42**(2): p. 263-7.
88. Schneider, M.J., *Tender points/fibromyalgia vs. trigger points/myofascial pain syndrome: a need for clarity in terminology and differential diagnosis*. Journal of Manipulative & Physiological Therapeutics, 1995. **18**(6): p. 398-406.
89. Fassbender, K., et al., *Tender points, depressive and functional symptoms: comparison between fibromyalgia and major depression*. Clinical Rheumatology, 1997. **16**(1): p. 76-9.
90. Hsu, V.M., S.J. Patella, and L.H. Sigal, "*Chronic Lyme disease*" as the incorrect diagnosis in patients with fibromyalgia. Arthritis & Rheumatism, 1993. **36**(11): p. 1493-500.
91. Kozanoglu, E., et al., *Fibromyalgia syndrome in patients with hepatitis C infection*. Rheumatology International, 2003. **23**(5): p. 248-251.
92. Abd, T.T. and T.A. Jacobson, *Statin-induced myopathy: a review and update*. Expert Opin Drug Saf, 2011. **10**(3): p. 373-87.
93. Henry, N.L., et al., *A prospective study of aromatase inhibitor-associated musculoskeletal symptoms and abnormalities on serial high-resolution wrist ultrasonography*. Cancer, 2010. **116**(18): p. 4360-7.
94. Papapetrou, P.D., *Bisphosphonate-associated adverse events*. Hormones (Athens), 2009. **8**(2): p. 96-110.
95. White, K.P., et al., *Does the label "fibromyalgia" alter health status, function, and health service utilization? A prospective, within-group comparison in a community cohort of adults with chronic widespread pain*. Arthritis & Rheumatism, 2002. **47**(3): p. 260-5.
96. Shleyfer, E., et al., *Accuracy of the diagnosis of fibromyalgia by family physicians: is the pendulum shifting?* Journal of Rheumatology, 2009. **36**(1): p. 170-3.
97. Garcia-Campayo, J., et al., *A meta-analysis of the efficacy of fibromyalgia treatment according to level of care*. Arthritis Res Ther, 2008. **10**(4): p. R81.
98. White, L.A., et al., *Comparison of health care use and costs in newly diagnosed and established patients with fibromyalgia*. Journal of Pain, 2009. **10**(9): p. 976-83.
99. Zih, F.S.W., D. Da Costa, and M.-A. Fitzcharles, *Is there benefit in referring patients with fibromyalgia to a specialist clinic?* Journal of Rheumatology, 2004. **31**(12): p. 2468-71.
100. Kroese, M.E.A.L., et al., *Therapeutic approaches to fibromyalgia in the Netherlands: a comparison between 1998 and 2005*. Journal of Evaluation in Clinical Practice, 2008. **14**(2): p. 321-5.
101. Kroese, M.E., et al., *Substitution of specialized rheumatology nurses for rheumatologists in the diagnostic process of fibromyalgia: a randomized controlled trial*. Arthritis Rheum, 2008. **59**(9): p. 1299-305.
102. Becker, H., et al., *The use of goal attainment scaling to facilitate and assess individualized change in a wellness intervention for women with fibromyalgia syndrome*. Journal of Holistic Nursing, 2009. **27**(4): p. 232-40.
103. Hellstrom, O., et al., *Doctors' attitudes to fibromyalgia: a phenomenological study*. Scandinavian Journal of Social Medicine, 1998. **26**(3): p. 232-7.
104. Ehrlich, G.E., *Fibromyalgia, a virtual disease*. Clinical Rheumatology, 2003. **22**(1): p. 8-11.
105. Hazemeijer, I. and J.J. Rasker, *Fibromyalgia and the therapeutic domain. A philosophical study on the origins of fibromyalgia in a specific social setting*. Rheumatology, 2003. **42**(4): p. 507-15.
106. Walker, E.A., et al., *Predictors of physician frustration in the care of patients with rheumatological complaints*. General Hospital Psychiatry, 1997. **19**(5): p. 315-23.
107. Haugli, L., E. Strand, and A. Finset, *How do patients with rheumatic disease experience their relationship with their doctors? A qualitative study of experiences of stress and support in the doctor-patient relationship*. Patient Education & Counseling, 2004. **52**(2): p. 169-74.
108. Dobkin, P.L., et al., *Patient-physician discordance in fibromyalgia*. Journal of Rheumatology, 2003. **30**(6): p. 1326-34.
109. Asbring, P. and A.-L. Narvanen, *Ideal versus reality: physicians perspectives on patients with chronic fatigue syndrome (CFS) and fibromyalgia*. Social Science & Medicine, 2003. **57**(4): p. 711-20.
110. Bieber, C., et al., *A shared decision-making communication training program for physicians treating fibromyalgia patients: effects of a randomized controlled trial*. Journal of Psychosomatic Research, 2008. **64**(1): p. 13-20.
111. Perrot, S., A.H. Dickenson, and R.M. Bennett, *Fibromyalgia: harmonizing science with clinical practice considerations*. Pain Practice, 2008. **8**(3): p. 177-89.
112. Abeles, A.M., et al., *Narrative review: the pathophysiology of fibromyalgia*. Ann Intern Med, 2007. **146**(10): p. 726-34.
113. Gracely, R.H., M.A.B. Grant, and T. Giesecke, *Evoked pain measures in fibromyalgia*. Best Practice & Research in Clinical Rheumatology, 2003. **17**(4): p. 593-609.
114. Staud, R., *Biology and therapy of fibromyalgia: pain in fibromyalgia syndrome*. Arthritis Res Ther, 2006. **8**(3): p. 208.
115. Gracely, R.H., et al., *Functional magnetic resonance imaging evidence of augmented pain processing in fibromyalgia*. Arthritis Rheum, 2002. **46**(5): p. 1333-43.
116. Petzke, F. and D.J. Clauw, *Sympathetic nervous system function in fibromyalgia*. Curr Rheumatol Rep, 2000. **2**(2): p. 116-23.

117. Price, D.D. and R. Staud, *Neurobiology of fibromyalgia syndrome*. Journal of Rheumatology - Supplement, 2005. **75**: p. 22-8.
118. Julien, N., et al., *Widespread pain in fibromyalgia is related to a deficit of endogenous pain inhibition*. Pain, 2005. **114**(1-2): p. 295-302.
119. Buskila, D. and L. Neumann, *Fibromyalgia syndrome (FM) and nonarticular tenderness in relatives of patients with FM*. Journal of Rheumatology, 1997. **24**(5): p. 941-4.
120. Buskila, D., et al., *Familial aggregation in the fibromyalgia syndrome*. Seminars in Arthritis & Rheumatism, 1996. **26**(3): p. 605-11.
121. McBeth, J., et al., *Moderation of psychosocial risk factors through dysfunction of the hypothalamic-pituitary-adrenal stress axis in the onset of chronic widespread musculoskeletal pain - Findings of a population-based prospective cohort study*. Arthritis and Rheumatism, 2007. **56**(1): p. 360-371.
122. Smith, S.B., et al., *Large candidate gene association study reveals genetic risk factors and therapeutic targets for fibromyalgia*. Arthritis Rheum, 2011.
123. Buskila, D. and P. Sarzi-Puttini, *Biology and therapy of fibromyalgia. Genetic aspects of fibromyalgia syndrome*. Arthritis Res Ther, 2006. **8**(5): p. 218.
124. Gupta, A., et al., *The role of psychosocial factors in predicting the onset of chronic widespread pain: results from a prospective population-based study*. Rheumatology (Oxford), 2007. **46**(4): p. 666-71.
125. Gormsen, L., et al., *Depression, anxiety, health-related quality of life and pain in patients with chronic fibromyalgia and neuropathic pain*. European Journal of Pain: Ejp, 2010. **14**(2): p. 127 e1-8.
126. Jones, G.T., C. Power, and G.J. Macfarlane, *Adverse events in childhood and chronic widespread pain in adult life: Results from the 1958 British Birth Cohort Study*. Pain, 2009. **143**(1-2): p. 92-6.
127. Pae, C.U., et al., *History of early abuse as a predictor of treatment response in patients with fibromyalgia: a post-hoc analysis of a 12-week, randomized, double-blind, placebo-controlled trial of paroxetine controlled release*. World J Biol Psychiatry, 2009. **10**(4 Pt 2): p. 435-41.
128. Ruiz-Perez, I., et al., *Risk factors for fibromyalgia: the role of violence against women*. Clin Rheumatol, 2009. **28**(7): p. 777-86.
129. Boisset-Piuro, M.H., J.M. Esdaile, and M.A. Fitzcharles, *Sexual and physical abuse in women with fibromyalgia syndrome*. Arthritis & Rheumatism, 1995. **38**(2): p. 235-41.
130. Greenfield, S., M.A. Fitzcharles, and J.M. Esdaile, *Reactive fibromyalgia syndrome*. Arthritis & Rheumatism, 1992. **35**(6): p. 678-81.
131. Boomershine, C.S. and L.J. Crofford, *A symptom-based approach to pharmacologic management of fibromyalgia*. Nature Reviews Rheumatology, 2009. **5**(4): p. 191-9.
132. Rossy, L.A., et al., *A meta-analysis of fibromyalgia treatment interventions*. Annals of Behavioral Medicine, 1999. **21**(2): p. 180-91.
133. Dobkin, P.L., et al., *Predictors of disability and pain six months after the end of treatment for fibromyalgia*. Clinical Journal of Pain, 2010. **26**(1): p. 23-9.
134. Giesecke, T., et al., *Subgrouping of fibromyalgia patients on the basis of pressure-pain thresholds and psychological factors*. Arthritis & Rheumatism, 2003. **48**(10): p. 2916-22.
135. Turk, D.C., et al., *Pain, disability, and physical functioning in subgroups of patients with fibromyalgia*. Journal of Rheumatology, 1996. **23**(7): p. 1255-62.
136. Rutledge, D.N., M. Mouttapa, and P.B. Wood, *Symptom clusters in fibromyalgia: potential utility in patient assessment and treatment evaluation*. Nursing Research, 2009. **58**(5): p. 359-67.
137. Hauser, W., et al., *Efficacy of multicomponent treatment in fibromyalgia syndrome: a meta-analysis of randomized controlled clinical trials*. Arthritis & Rheumatism, 2009. **61**(2): p. 216-24.
138. Goldenberg, D.L., C. Burckhardt, and L. Crofford, *Management of fibromyalgia syndrome*. JAMA, 2004. **292**(19): p. 2388-95.
139. Karsdorp, P.A. and J.W. Vlaeyen, *Active avoidance but not activity pacing is associated with disability in fibromyalgia*. Pain, 2009. **147**(1-3): p. 29-35.
140. Torres, X., et al., *Pain locus of control predicts return to work among Spanish fibromyalgia patients after completion of a multidisciplinary pain program*. General Hospital Psychiatry, 2009. **31**(2): p. 137-45.
141. Beal, C.C., A.K. Stuijbergen, and A. Brown, *Predictors of a health promoting lifestyle in women with fibromyalgia syndrome*. Psychology Health & Medicine, 2009. **14**(3): p. 343-53.
142. Du Plessis, M., H.R. Steel, and A.T. Moller, *The relationship between psychosocial variables and measures of health status in fibromyalgia*. South African Family Practice, 2009. **51**(1): p. 42-45.
143. Henriksson, C. and C. Burckhardt, *Impact of fibromyalgia on everyday life: a study of women in the USA and Sweden*. Disability & Rehabilitation, 1996. **18**(5): p. 241-8.
144. Henriksson, C. and G. Liedberg, *Factors of importance for work disability in women with fibromyalgia*. Journal of Rheumatology, 2000. **27**(5): p. 1271-6.

145. Garcia-Campayo, J., et al., *Effectiveness of the psychological and pharmacological treatment of catastrophization in patients with fibromyalgia: a randomized controlled trial*. *Trials* [Electronic Resource], 2009. **10**: p. 24.
146. Bernatsky, S., et al., *Co-morbidity and physician use in fibromyalgia*. *Swiss Medical Weekly*, 2005. **135**(5-6): p. 76-81.
147. Ciapparelli, A., et al., *The impact of psychiatric comorbidity on health-related quality of life in women with fibromyalgia*. *Clinical Neuropsychiatry*, 2008. **5**(5): p. 217-224.
148. Dobkin, P.L., et al., *Predictors of health status in women with fibromyalgia: a prospective study*. *Int J Behav Med*, 2006. **13**(2): p. 101-8.
149. Hughes, L., *Physical and psychological variables that influence pain in patients with fibromyalgia*. *Orthopaedic Nursing*, 2006. **25**(2): p. 112-9.
150. Bennett, R. and D. Nelson, *Cognitive behavioral therapy for fibromyalgia*. *Nat Clin Pract Rheumatol*, 2006. **2**(8): p. 416-24.
151. Bernardy, K., et al., *Efficacy of cognitive-behavioral therapies in fibromyalgia syndrome - a systematic review and metaanalysis of randomized controlled trials*. *Journal of Rheumatology*, 2010. **37**(10): p. 1991-2005.
152. Falcao, D.M., et al., *Cognitive behavioral therapy for the treatment of fibromyalgia syndrome: A randomized controlled trial*. *Journal of Musculoskeletal Pain*, 2008. **16**(3): p. 133-140.
153. Suman, A.L., et al., *One-year efficacy of a 3-week intensive multidisciplinary non-pharmacological treatment program for fibromyalgia patients*. *Clinical & Experimental Rheumatology*, 2009. **27**(1): p. 7-14.
154. Goossens, M.E., et al., *Cognitive-educational treatment of fibromyalgia: a randomized clinical trial. II. Economic evaluation*. *Journal of Rheumatology*, 1996. **23**(7): p. 1246-54.
155. Ang, D.C., et al., *Cognitive-behavioral therapy attenuates nociceptive responding in patients with fibromyalgia: a pilot study*. *Arthritis Care & Research*, 2010. **62**(5): p. 618-23.
156. Ang, D., et al., *Exercise-based motivational interviewing for female patients with fibromyalgia: a case series*. *Clinical Rheumatology*, 2007. **26**(11): p. 1843-9.
157. Bennett, R.M., et al., *Group treatment of fibromyalgia: a 6 month outpatient program*. *Journal of Rheumatology*, 1996. **23**(3): p. 521-8.
158. Creamer, P., et al., *Sustained improvement produced by nonpharmacologic intervention in fibromyalgia: results of a pilot study*. *Arthritis Care & Research*, 2000. **13**(4): p. 198-204.
159. Broderick, J.E., D.U. Junghaenel, and J.E. Schwartz, *Written emotional expression produces health benefits in fibromyalgia patients*. *Psychosomatic Medicine*, 2005. **67**(2): p. 326-34.
160. De Voogd, J.N., et al., *Treatment of fibromyalgia syndrome with psychomotor therapy and marital counselling*. *Journal of Musculoskeletal Pain*, 1993. **1**(3-4): p. 273-281.
161. Drexler, A.R., E.J. Mur, and V.C. Gunther, *Efficacy of an EMG-biofeedback therapy in fibromyalgia patients. A comparative study of patients with and without abnormality in (MMPI) psychological scales*. *Clinical & Experimental Rheumatology*, 2002. **20**(5): p. 677-82.
162. Kaplan, K.H., D.L. Goldenberg, and M. Galvin-Nadeau, *The impact of a meditation-based stress reduction program on fibromyalgia*. *General Hospital Psychiatry*, 1993. **15**(5): p. 284-9.
163. Worrel, L.M., et al., *Treating fibromyalgia with a brief interdisciplinary program: initial outcomes and predictors of response*. *Mayo Clinic Proceedings*, 2001. **76**(4): p. 384-90.
164. Fors, E.A., H. Sexton, and K.G. Gotestam, *The effect of guided imagery and amitriptyline on daily fibromyalgia pain: a prospective, randomized, controlled trial*. *Journal of Psychiatric Research*, 2002. **36**(3): p. 179-87.
165. Castel, A., et al., *Effect of hypnotic suggestion on fibromyalgic pain: comparison between hypnosis and relaxation*. *European Journal of Pain: Ejp*, 2007. **11**(4): p. 463-8.
166. Menzies, V., A.G. Taylor, and C. Bourguignon, *Effects of guided imagery on outcomes of pain, functional status, and self-efficacy in persons diagnosed with fibromyalgia*. *Journal of Alternative & Complementary Medicine*, 2006. **12**(1): p. 23-30.
167. Bernardy, K., et al., *Efficacy of hypnosis/guided imagery in fibromyalgia syndrome--a systematic review and meta-analysis of controlled trials*. *BMC Musculoskeletal Disorders*, 2011. **12**: p. 133.
168. Hadhazy, V.A., et al., *Mind-body therapies for the treatment of fibromyalgia. A systematic review*. *Journal of Rheumatology*, 2000. **27**(12): p. 2911-8.
169. Carretero, B., et al., *Low-frequency transcranial magnetic stimulation in patients with fibromyalgia and major depression*. *Pain Medicine*, 2009. **10**(4): p. 748-53.
170. Short, E.B., et al., *Ten sessions of adjunctive left prefrontal rTMS significantly reduces fibromyalgia pain: A randomized, controlled pilot study*. *Pain*, 2011. **152**(11): p. 2477-84.
171. Roizenblatt, S., et al., *Site-specific effects of transcranial direct current stimulation on sleep and pain in fibromyalgia: a randomized, sham-controlled study*. *Pain Practice*, 2007. **7**(4): p. 297-306.
172. Turk, D.C., J.P. Robinson, and T. Burwinkle, *Prevalence of fear of pain and activity in patients with fibromyalgia syndrome*. *Journal of Pain*, 2004. **5**(9): p. 483-90.

173. Bakker, C., et al., *Problem elicitation to assess patient priorities in ankylosing spondylitis and fibromyalgia*. Journal of Rheumatology, 1995. **22**(7): p. 1304-10.
174. Brosseau, L., et al., *Ottawa Panel evidence-based clinical practice guidelines for strengthening exercises in the management of fibromyalgia: part 2*. Phys Ther, 2008. **88**(7): p. 873-86.
175. Brosseau, L., et al., *Ottawa Panel evidence-based clinical practice guidelines for aerobic fitness exercises in the management of fibromyalgia: part 1*. Phys Ther, 2008. **88**(7): p. 857-71.
176. Busch, A., et al., *Exercise for treating fibromyalgia syndrome*. Cochrane Database Syst Rev, 2002(3): p. CD003786.
177. Busch, A.J., et al., *Exercise for treating fibromyalgia syndrome*. Cochrane Database Syst Rev, 2007. **(4)**(4): p. CD003786.
178. Busch, A.J., et al., *Exercise for fibromyalgia: a systematic review*. Journal of Rheumatology, 2008. **35**(6): p. 1130-44.
179. Ramel, J., et al., *Exercise for Fibromyalgia Pain: A Meta-Analysis of Randomized Controlled Trials*. Current Rheumatology Reviews, 2009. **5**(4): p. 188-193.
180. Baranowsky, J., et al., *Qualitative systemic review of randomized controlled trials on complementary and alternative medicine treatments in fibromyalgia*. Rheumatology International, 2009. **30**(1): p. 1-21.
181. Mannerkorpi, K., et al., *Pool exercise for patients with fibromyalgia or chronic widespread pain: a randomized controlled trial and subgroup analyses*. Journal of Rehabilitation Medicine, 2009. **41**(9): p. 751-60.
182. Tomas-Carus, P., et al., *Aquatic training and detraining on fitness and quality of life in fibromyalgia*. Medicine & Science in Sports & Exercise, 2007. **39**(7): p. 1044-50.
183. McVeigh, J.G., et al., *The effectiveness of hydrotherapy in the management of fibromyalgia syndrome: a systematic review*. Rheumatology International, 2008. **29**(2): p. 119-30.
184. Perraton, L., Z. Machotka, and S. Kumar, *Components of effective randomized controlled trials of hydrotherapy programs for fibromyalgia syndrome: A systematic review*. Journal of Pain Research, 2009. **2**: p. 165-173.
185. Langhorst, J., et al., *Efficacy of hydrotherapy in fibromyalgia syndrome--a meta-analysis of randomized controlled clinical trials*. Rheumatology (Oxford), 2009. **48**(9): p. 1155-9.
186. Altan, L., et al., *Effect of pilates training on people with fibromyalgia syndrome: a pilot study*. Arch Phys Med Rehabil, 2009. **90**(12): p. 1983-8.
187. Taggart, H.M., et al., *Effects of T'ai Chi exercise on fibromyalgia symptoms and health-related quality of life*. Orthopaedic Nursing, 2003. **22**(5): p. 353-60.
188. Wang, C., *Tai chi and rheumatic diseases*. Rheumatic Diseases Clinics of North America, 2011. **37**(1): p. 19-32.
189. Wang, C., et al., *A randomized trial of tai chi for fibromyalgia*. New England Journal of Medicine, 2010. **363**(8): p. 743-54.
190. da Silva, G.D., G. Lorenzi-Filho, and L.V. Lage, *Effects of yoga and the addition of Tui Na in patients with fibromyalgia*. Journal of Alternative & Complementary Medicine, 2007. **13**(10): p. 1107-13.
191. Niелens, H., V. Boisset, and E. Masquelier, *Fitness and perceived exertion in patients with fibromyalgia syndrome*. Clinical Journal of Pain, 2000. **16**(3): p. 209-13.
192. Verstappen, F.T.J., et al., *Fitness characteristics of female patients with fibromyalgia*. Journal of Musculoskeletal Pain, 1995. **3**(3): p. 45-58.
193. Pioro-Boisset, M., J.M. Esdaile, and M.A. Fitzcharles, *Alternative medicine use in fibromyalgia syndrome*. Arthritis Care and Research, 1996. **9**(1): p. 13-17.
194. Cao, H., J. Liu, and G.T. Lewith, *Traditional Chinese Medicine for treatment of fibromyalgia: a systematic review of randomized controlled trials*. Journal of Alternative & Complementary Medicine, 2010. **16**(4): p. 397-409.
195. De Silva, V., et al., *Evidence for the efficacy of complementary and alternative medicines in the management of fibromyalgia: a systematic review*. Rheumatology (Oxford), 2010. **49**(6): p. 1063-8.
196. Perry, R., R. Terry, and E. Ernst, *A systematic review of homoeopathy for the treatment of fibromyalgia*. Clinical Rheumatology, 2010. **29**(5): p. 457-64.
197. Martin-Sanchez, E., et al., *Efficacy of acupuncture for the treatment of fibromyalgia: Systematic review and meta-analysis of randomized trials*. Open Rheumatology Journal, 2009. **3**: p. 25-29.
198. Mayhew, E. and E. Ernst, *Acupuncture for fibromyalgia--a systematic review of randomized clinical trials*. Rheumatology (Oxford), 2007. **46**(5): p. 801-4.
199. Berman, B.M., et al., *Is acupuncture effective in the treatment of fibromyalgia?* Journal of Family Practice, 1999. **48**(3): p. 213-8.
200. Langhorst, J., et al., *Efficacy of acupuncture in fibromyalgia syndrome--a systematic review with a meta-analysis of controlled clinical trials*. Rheumatology, 2010. **49**(4): p. 778-88.
201. Targino, R.A., et al., *A randomized controlled trial of acupuncture added to usual treatment for fibromyalgia*. Journal of Rehabilitation Medicine, 2008. **40**(7): p. 582-8.
202. Haak, T. and B. Scott, *The effect of Qigong on fibromyalgia (FMS): a controlled randomized study*. Disability & Rehabilitation, 2008. **30**(8): p. 625-33.
203. Ernst, E., *Chiropractic treatment for fibromyalgia: a systematic review*. Clinical Rheumatology, 2009. **28**(10): p. 1175-8.

204. Schneider, M., et al., *Chiropractic management of fibromyalgia syndrome: a systematic review of the literature*. Journal of Manipulative & Physiological Therapeutics, 2009. **32**(1): p. 25-40.
205. Fitzcharles, M.A., et al., *Opioid use, misuse, and abuse in patients labeled as fibromyalgia*. Am J Med, 2011. **124**(10): p. 955-60.
206. Hooten, W.M., et al., *Treatment outcomes after multidisciplinary pain rehabilitation with analgesic medication withdrawal for patients with fibromyalgia*. Pain Medicine, 2007. **8**(1): p. 8-16.
207. World Health Organization. *WHO Pain Ladder*. 1986 [cited 2011 22 November]; Available from: <http://www.who.int/cancer/palliative/painladder/en/>.
208. Bennett, R.M., et al., *Tramadol and acetaminophen combination tablets in the treatment of fibromyalgia pain: a double-blind, randomized, placebo-controlled study*. American Journal of Medicine, 2003. **114**(7): p. 537-45.
209. Guggenheimer, J. and P.A. Moore, *The therapeutic applications of and risks associated with acetaminophen use: a review and update*. Journal of the American Dental Association, 2011. **142**(1): p. 38-44.
210. Lynch, M.E. and C.P. Watson, *The pharmacotherapy of chronic pain: a review*. Pain Research & Management, 2006. **11**(1): p. 11-38.
211. Lynch, M.E., *The pharmacotherapy of chronic pain*. Rheumatic Diseases Clinics of North America, 2008. **34**(2): p. 369-85.
212. Chandrasekharan, N.V., et al., *COX-3, a cyclooxygenase-1 variant inhibited by acetaminophen and other analgesic/antipyretic drugs: cloning, structure, and expression*. Proc Natl Acad Sci U S A, 2002. **99**(21): p. 13926-31.
213. Hogestatt, E.D., et al., *Conversion of acetaminophen to the bioactive N-acylphenolamine AM404 via fatty acid amide hydrolase-dependent arachidonic acid conjugation in the nervous system*. J Biol Chem, 2005. **280**(36): p. 31405-12.
214. Bertolini, A., et al., *Paracetamol: new vistas of an old drug*. CNS Drug Rev, 2006. **12**(3-4): p. 250-75.
215. Wolfe, F., S. Zhao, and N. Lane, *Preference for nonsteroidal antiinflammatory drugs over acetaminophen by rheumatic disease patients: A survey of 1,799 patients with osteoarthritis, rheumatoid arthritis, and fibromyalgia*. Arthritis and Rheumatism, 2000. **43** (2): p. 378-385.
216. Bennett, R.M., et al., *An internet survey of 2,596 people with fibromyalgia*. BMC Musculoskeletal Disorders, 2007. **8**: p. 27.
217. Kroenke, K., E.E. Krebs, and M.J. Bair, *Pharmacotherapy of chronic pain: a synthesis of recommendations from systematic reviews*. General Hospital Psychiatry, 2009. **31**(3): p. 206-219.
218. Rao, S.G. and D.J. Clauw, *The management of fibromyalgia*. Drugs of Today, 2004. **40**(6): p. 539-54.
219. Tannenbaum, H., et al., *An evidence-based approach to prescribing nonsteroidal antiinflammatory drugs. Third Canadian Consensus Conference*. Journal of Rheumatology, 2006. **33**(1): p. 140-57.
220. Bjordal, J.M., et al., *Non-steroidal anti-inflammatory drugs, including cyclo-oxygenase-2 inhibitors, in osteoarthritic knee pain: meta-analysis of randomised placebo controlled trials*. BMJ, 2004. **329**(7478): p. 1317.
221. Trelle, S., et al., *Cardiovascular safety of non-steroidal anti-inflammatory drugs: network meta-analysis*. BMJ, 2011. **342**: p. c7086.
222. White, W.B., et al., *Risk of cardiovascular events in patients receiving celecoxib: a meta-analysis of randomized clinical trials*. Am J Cardiol, 2007. **99**(1): p. 91-8.
223. Soni, P., et al., *The hepatic safety and tolerability of the cyclooxygenase-2 selective NSAID celecoxib: pooled analysis of 41 randomized controlled trials*. Current Medical Research & Opinion, 2009. **25**(8): p. 1841-51.
224. Biasi, G., et al., *Tramadol in the fibromyalgia syndrome: a controlled clinical trial versus placebo*. International Journal of Clinical Pharmacology Research, 1998. **18**(1): p. 13-9.
225. Furlan, A.D., et al., *Opioids for chronic noncancer pain: a meta-analysis of effectiveness and side effects*. CMAJ Canadian Medical Association Journal, 2006. **174**(11): p. 1589-94.
226. Hauser, W., K. Thieme, and D.C. Turk, *Guidelines on the management of fibromyalgia syndrome - a systematic review*. European Journal of Pain: Ejp, 2010. **14**(1): p. 5-10.
227. Younger, J.W., A.J. Zautra, and E.T. Cummins, *Effects of naltrexone on pain sensitivity and mood in fibromyalgia: no evidence for endogenous opioid pathophysiology*. PLoS ONE [Electronic Resource], 2009. **4**(4): p. e5180.
228. Chen, Z.R., A.A. Somogyi, and F. Bochner, *Polymorphic O-demethylation of codeine*. Lancet, 1988. **2**(8616): p. 914-5.
229. Crofford, L.J., *Adverse effects of chronic opioid therapy for chronic musculoskeletal pain*. Nature Reviews Rheumatology, 2010. **6**(4): p. 191-7.
230. Hartung, D.M., et al., *Rates of adverse events of long-acting opioids in a state Medicaid program*. Ann Pharmacother, 2007. **41**(6): p. 921-8.
231. Manchikanti, L., et al., *Therapeutic use, abuse, and nonmedical use of opioids: a ten-year perspective*. Pain Physician, 2010. **13**(5): p. 401-35.
232. Okie, S., *A flood of opioids, a rising tide of deaths*. New England Journal of Medicine, 2010. **363**(21): p. 1981-5.
233. Furlan, A.D., R. Reardon, and C. Wepler, *Opioids for chronic noncancer pain: a new Canadian practice guideline*. CMAJ Canadian Medical Association Journal, 2010. **182**(9): p. 923-30.

234. Chou, R., et al., *Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain*. Journal of Pain, 2009. **10**(2): p. 113-30.
235. Campbell, F.A., et al., *Are cannabinoids an effective and safe treatment option in the management of pain? A qualitative systematic review*. BMJ, 2001. **323**(7303): p. 13-6.
236. Lynch, M.E. and F. Campbell, *Cannabinoids for treatment of chronic non-cancer pain; a systematic review of randomized trials*. Br J Clin Pharmacol, 2011. **72**(5): p. 735-44.
237. Pertwee, R.G., *Cannabinoid receptors and pain*. Prog Neurobiol, 2001. **63**(5): p. 569-611.
238. Skrabek, R.Q., et al., *Nabilone for the treatment of pain in fibromyalgia*. Journal of Pain, 2008. **9**(2): p. 164-73.
239. Ware, M.A., et al., *The effects of nabilone on sleep in fibromyalgia: results of a randomized controlled trial*. Anesth Analg, 2010. **110**(2): p. 604-10.
240. Arnold, L.M., P.E. Keck, Jr., and J.A. Welge, *Antidepressant treatment of fibromyalgia. A meta-analysis and review*. Psychosomatics, 2000. **41**(2): p. 104-13.
241. Crofford, L.J., *Meta-analysis of antidepressants in fibromyalgia*. Curr Rheumatol Rep, 2001. **3**(2): p. 115.
242. O'Malley, P.G., et al., *Treatment of fibromyalgia with antidepressants: a meta-analysis*. Journal of General Internal Medicine, 2000. **15**(9): p. 659-66.
243. Hauser, W., et al., *Treatment of fibromyalgia syndrome with antidepressants: a meta-analysis*. JAMA, 2009. **301**(2): p. 198-209.
244. Lunn, M.P., R.A. Hughes, and P.J. Wiffen, *Duloxetine for treating painful neuropathy or chronic pain*. Cochrane Database Syst Rev, 2009(4): p. CD007115.
245. Nishishinya, B., et al., *Amitriptyline in the treatment of fibromyalgia: a systematic review of its efficacy*. Rheumatology, 2008. **47**(12): p. 1741-6.
246. Perrot, S., et al., *Is there any evidence to support the use of anti-depressants in painful rheumatological conditions? Systematic review of pharmacological and clinical studies*. Rheumatology, 2008. **47**(8): p. 1117-23.
247. Sultan, A., et al., *Duloxetine for painful diabetic neuropathy and fibromyalgia pain: systematic review of randomised trials*. BMC Neurol, 2008. **8**(29): p. 29.
248. Uceyler, N., W. Hauser, and C. Sommer, *A systematic review on the effectiveness of treatment with antidepressants in fibromyalgia syndrome*. Arthritis Care and Research, 2008. **59** (9): p. 1279-1298.
249. Goldenberg, D.L., D.J. Clauw, and M.A. Fitzcharles, *New concepts in pain research and pain management of the rheumatic diseases*. Seminars in Arthritis & Rheumatism, 2011. **41**(3): p. 319-34.
250. Heymann, R.E., M. Helfenstein, and D. Feldman, *A double-blind, randomized, controlled study of amitriptyline, nortriptyline and placebo in patients with fibromyalgia. An analysis of outcome measures*. Clinical & Experimental Rheumatology, 2001. **19**(6): p. 697-702.
251. Tofferi, J.K., J.L. Jackson, and P.G. O'Malley, *Treatment of fibromyalgia with cyclobenzaprine: A meta-analysis*. Arthritis & Rheumatism, 2004. **51**(1): p. 9-13.
252. Arnold, L.M., et al., *Comparisons of the efficacy and safety of duloxetine for the treatment of fibromyalgia in patients with versus without major depressive disorder*. Clinical Journal of Pain, 2009. **25**(6): p. 461-8.
253. Chappell, A.S., et al., *A 1-year safety and efficacy study of duloxetine in patients with fibromyalgia*. Clinical Journal of Pain, 2009. **25**(5): p. 365-75.
254. Choy, E.H.S., et al., *Safety and tolerability of duloxetine in the treatment of patients with fibromyalgia: pooled analysis of data from five clinical trials*. Clinical Rheumatology, 2009. **28**(9): p. 1035-44.
255. Boulanger, L., et al., *Predictors of Pain Medication Selection Among Patients Diagnosed with Fibromyalgia*. Pain Pract, 2011.
256. Rasmussen, P. and J. Riishede, *Facial pain treated with carbamazepin (Tegretol)*. Acta Neurol Scand, 1970. **46**(4): p. 385-408.
257. Rogawski, M.A. and W. Loscher, *The neurobiology of antiepileptic drugs for the treatment of nonepileptic conditions*. Nat Med, 2004. **10**(7): p. 685-92.
258. Sills, G.J., *The mechanisms of action of gabapentin and pregabalin*. Curr Opin Pharmacol, 2006. **6**(1): p. 108-13.
259. Hauser, W., et al., *Treatment of fibromyalgia syndrome with gabapentin and pregabalin--a meta-analysis of randomized controlled trials*. Pain, 2009. **145**(1-2): p. 69-81.
260. Siler, A.C., et al., *Systematic review of the comparative effectiveness of antiepileptic drugs for fibromyalgia*. Journal of Pain, 2011. **12**(4): p. 407-15.
261. Holtedahl, R., *[Questionable documentation of the effect of pregabalin in fibromyalgia]*. Tidsskr Nor Laegeforen, 2010. **130**(10): p. 1032-6.
262. Moore, R.A., et al., *Pregabalin for acute and chronic pain in adults*. Cochrane Database Syst Rev, 2009(3): p. CD007076.
263. Randinitis, E.J., et al., *Pharmacokinetics of pregabalin in subjects with various degrees of renal function*. Journal of Clinical Pharmacology, 2003. **43**(3): p. 277-283.

264. Sun, P., et al., *Medication dosing patterns associated with duloxetine and pregabalin among patients with fibromyalgia*. Current Medical Research & Opinion, 2011. **27**(9): p. 1793-801.
265. Gore, M., et al., *Clinical characteristics, pharmacotherapy and healthcare resource use among patients with fibromyalgia newly prescribed gabapentin or pregabalin*. Pain Practice, 2009. **9**(5): p. 363-74.
266. Holman, A.J. and R.R. Myers, *A randomized, double-blind, placebo-controlled trial of pramipexole, a dopamine agonist, in patients with fibromyalgia receiving concomitant medications*. Arthritis & Rheumatism, 2005. **52**(8): p. 2495-505.
267. Distler, O., et al., *Evaluation of the efficacy and safety of terguride in patients with fibromyalgia syndrome: results of a twelve-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study*. Arthritis & Rheumatism, 2010. **62**(1): p. 291-300.
268. Weintraub, D., et al., *Impulse control disorders in Parkinson disease: a cross-sectional study of 3090 patients*. Arch Neurol, 2010. **67**(5): p. 589-95.
269. Wu, Y., et al., *Gamma-hydroxybutyric acid (GHB) and gamma-aminobutyric acidB receptor (GABABR) binding sites are distinctive from one another: molecular evidence*. Neuropharmacology, 2004. **47**(8): p. 1146-56.
270. Russell, I.J., et al., *Sodium oxybate relieves pain and improves function in fibromyalgia syndrome: a randomized, double-blind, placebo-controlled, multicenter clinical trial*. Arthritis & Rheumatism, 2009. **60**(1): p. 299-309.
271. Scharf, M.B., M. Baumann, and D.V. Berkowitz, *The effects of sodium oxybate on clinical symptoms and sleep patterns in patients with fibromyalgia*. Journal of Rheumatology, 2003. **30**(5): p. 1070-4.
272. Staud, R., *Sodium oxybate for the treatment of fibromyalgia*. Expert Opinion on Pharmacotherapy, 2011. **12**(11): p. 1789-98.
273. Vergne-Salle, P., et al., *A randomised, double-blind, placebo-controlled trial of dolasetron, a 5-hydroxytryptamine 3 receptor antagonist, in patients with fibromyalgia*. European Journal of Pain: Ejp, 2011. **15**(5): p. 509-14.
274. Farber, L., et al., *Efficacy and tolerability of tropisetron in primary fibromyalgia--a highly selective and competitive 5-HT3 receptor antagonist*. German Fibromyalgia Study Group. Scandinavian Journal of Rheumatology - Supplement, 2000. **113**: p. 49-54.
275. Haus, U., et al., *Oral treatment of fibromyalgia with tropisetron given over 28 days: influence on functional and vegetative symptoms, psychometric parameters and pain*. Scandinavian Journal of Rheumatology - Supplement, 2000. **113**: p. 55-8.
276. Olin, R., R. Klein, and P.A. Berg, *A randomised double-blind 16-week study of ritanserin in fibromyalgia syndrome: clinical outcome and analysis of autoantibodies to serotonin, gangliosides and phospholipids*. Clinical Rheumatology, 1998. **17**(2): p. 89-94.
277. Graven-Nielsen, T., et al., *Ketamine reduces muscle pain, temporal summation, and referred pain in fibromyalgia patients*. Pain, 2000. **85**(3): p. 483-91.
278. McClean, G., *Does intravenous lidocaine reduce fibromyalgia pain?: A randomized, double-blind, placebo controlled cross-over study*. The Pain Clinic, 2000. **12**(3): p. 181-185.
279. Staud, R., et al., *Enhanced central pain processing of fibromyalgia patients is maintained by muscle afferent input: a randomized, double-blind, placebo-controlled study*. Pain, 2009. **145**(1-2): p. 96-104.
280. Affaitati, G., et al., *Effects of treatment of peripheral pain generators in fibromyalgia patients*. European Journal of Pain: Ejp, 2011. **15**(1): p. 61-9.
281. Castro-Sanchez, A.M., et al., *Effects of myofascial release techniques on pain, physical function, and postural stability in patients with fibromyalgia: a randomized controlled trial*. Clinical Rehabilitation, 2011. **25**(9): p. 800-13.
282. Ko, G.D., et al., *Effective Pain Palliation in Fibromyalgia Syndrome Patients with Botulinum Toxin Type-A: Case Series of 25*. Journal of Musculoskeletal Pain, 2007. **15**(4): p. 55-66.
283. Paulson, G.W. and W. Gill, *Botulinum toxin is unsatisfactory therapy for fibromyalgia*. Movement Disorders, 1996. **11**(4): p. 459.
284. Finckh, A., et al., *A randomized controlled trial of dehydroepiandrosterone in postmenopausal women with fibromyalgia*. Journal of Rheumatology, 2005. **32**(7): p. 1336-40.
285. Russell, I.J., et al., *Reduction of morning stiffness and improvement in physical function in fibromyalgia syndrome patients treated sublingually with low doses of human interferon-alpha*. Journal of Interferon & Cytokine Research, 1999. **19**(8): p. 961-8.
286. Kendall, S.A., et al., *No effect of antiviral (valacyclovir) treatment in fibromyalgia: a double blind, randomized study*. Journal of Rheumatology, 2004. **31**(4): p. 783-4.
287. Bennett, R.M., S.C. Clark, and J. Walczyk, *A randomized, double-blind, placebo-controlled study of growth hormone in the treatment of fibromyalgia*. American Journal of Medicine, 1998. **104**(3): p. 227-31.
288. Cuatrecasas, G., et al., *Growth hormone as concomitant treatment in severe fibromyalgia associated with low IGF-1 serum levels. A pilot study*. BMC Musculoskeletal Disorders, 2007. **8**: p. 119.
289. Drewes, A.M., et al., *Zopiclone in the treatment of sleep abnormalities in fibromyalgia*. Scandinavian Journal of Rheumatology, 1991. **20**(4): p. 288-93.

290. Gronblad, M., et al., *Effect of zopiclone on sleep quality, morning stiffness, widespread tenderness and pain and general discomfort in primary fibromyalgia patients. A double-blind randomized trial.* Clinical Rheumatology, 1993. **12**(2): p. 186-91.
291. Quijada-Carrera, J., et al., *Comparison of tenoxicam and bromazepan in the treatment of fibromyalgia: a randomized, double-blind, placebo-controlled trial.* Pain, 1996. **65**(2-3): p. 221-5.
292. Hidalgo, J., F. Rico-Villademoros, and E.P. Calandre, *An open-label study of quetiapine in the treatment of fibromyalgia.* Progress in Neuro-Psychopharmacology & Biological Psychiatry, 2007. **31**(1): p. 71-7.
293. Citera, G., et al., *The effect of melatonin in patients with fibromyalgia: a pilot study.* Clinical Rheumatology, 2000. **19**(1): p. 9-13.
294. Wolfe, F., et al., *Fibromyalgia criteria and severity scales for clinical and epidemiological studies: a modification of the ACR Preliminary Diagnostic Criteria for Fibromyalgia.* Journal of Rheumatology, 2011. **38**(6): p. 1113-22.
295. Penrod, J.R., et al., *Health services costs and their determinants in women with fibromyalgia.* Journal of Rheumatology, 2004. **31**(7): p. 1391-8.
296. Wang, F., et al., *Early improvement in pain predicts pain response at endpoint in patients with fibromyalgia.* Journal of Pain, 2011. **12**(10): p. 1088-94.
297. Fitzcharles, M.-A., D.D. Costa, and R. Poyhia, *A study of standard care in fibromyalgia syndrome: a favorable outcome.* Journal of Rheumatology, 2003. **30**(1): p. 154-9.
298. Granges, G., P. Zilko, and G.O. Littlejohn, *Fibromyalgia syndrome: assessment of the severity of the condition 2 years after diagnosis.* Journal of Rheumatology, 1994. **21**(3): p. 523-9.
299. Martinez, J.E., et al., *Fibromyalgia versus rheumatoid arthritis: a longitudinal comparison of the quality of life.* Journal of Rheumatology, 1995. **22**(2): p. 270-4.
300. MacFarlane, G.J., et al., *The natural history of chronic pain in the community: a better prognosis than in the clinic?* Journal of Rheumatology, 1996. **23**(9): p. 1617-20.
301. Turk, D.C., et al., *Effects of type of symptom onset on psychological distress and disability in fibromyalgia syndrome patients.* Pain, 1996. **68**(2-3): p. 423-30.
302. Campos, R.P. and M.I. Vazquez, *Health-related quality of life in women with fibromyalgia: clinical and psychological factors associated.* Clin Rheumatol, 2011.
303. Martinez, M.P., et al., *The relationship between the fear-avoidance model of pain and personality traits in fibromyalgia patients.* J Clin Psychol Med Settings, 2011. **18**(4): p. 380-91.
304. Kim, C.H., et al., *The association of body mass index with symptom severity and quality of life in patients with fibromyalgia.* Arthritis Care & Research, 2011.
305. Geisser, M.E., et al., *Contributions of change in clinical status parameters to Patient Global Impression of Change (PGIC) scores among persons with fibromyalgia treated with milnacipran.* Pain, 2010. **149**(2): p. 373-8.
306. Bakker, C., et al., *Patient utilities in fibromyalgia and the association with other outcome measures.* Journal of Rheumatology, 1995. **22**(8): p. 1536-43.
307. Bennett, R.M., et al., *The Revised Fibromyalgia Impact Questionnaire (FIQR): validation and psychometric properties.* Arthritis Res Ther, 2009. **11**(4): p. R120.
308. Burckhardt, C.S., S.R. Clark, and R.M. Bennett, *The fibromyalgia impact questionnaire: development and validation.* Journal of Rheumatology, 1991. **18**(5): p. 728-33.
309. Bennett, R., *The Fibromyalgia Impact Questionnaire (FIQ): a review of its development, current version, operating characteristics and uses.* Clinical & Experimental Rheumatology, 2005. **23**(5 Suppl 39): p. S154-62.
310. Bruce, B. and J.F. Fries, *The Stanford Health Assessment Questionnaire: dimensions and practical applications.* Health & Quality of Life Outcomes, 2003. **1**: p. 20.
311. Bennett, R.M., et al., *Minimal clinically important difference in the fibromyalgia impact questionnaire.* Journal of Rheumatology, 2009. **36**(6): p. 1304-11.
312. Martinez, J.E., et al., *Evaluation of the quality of life in Brazilian women with fibromyalgia, through the medical outcome survey 36 item short-form study.* Disability & Rehabilitation, 2001. **23**(2): p. 64-8.
313. Wewers, M.E. and N.K. Lowe, *A critical review of visual analogue scales in the measurement of clinical phenomena.* Research in Nursing & Health, 1990. **13**(4): p. 227-36.
314. Bigatti, S.M. and T.A. Cronan, *A comparison of pain measures used with patients with fibromyalgia.* Journal of Nursing Measurement, 2002. **10**(1): p. 5-14.
315. Farrar, J.T., et al., *The clinical importance of changes in the 0 to 10 numeric rating scale for worst, least, and average pain intensity: analyses of data from clinical trials of duloxetine in pain disorders.* Journal of Pain, 2010. **11**(2): p. 109-18.
316. Staud, R., et al., *Body pain area and pain-related negative affect predict clinical pain intensity in patients with fibromyalgia.* Journal of Pain, 2004. **5**(6): p. 338-43.
317. Harris, R.E., et al., *Comparison of clinical and evoked pain measures in fibromyalgia.* Journal of Pain, 2006. **7**(7): p. 521-7.

318. Wolfe, F., et al., *Work and disability status of persons with fibromyalgia*. Journal of Rheumatology, 1997. **24**(6): p. 1171-8.
319. White, D.H.N., K. Faull, and P.B.B. Jones, *An exploratory study of long-term health outcomes following an in-patient multidisciplinary program for people with fibromyalgia syndrome*. International Journal of Rheumatic Diseases, 2009. **12**(1): p. 52-6.
320. Reisine, S., et al., *Do employment and family work affect the health status of women with fibromyalgia?* Journal of Rheumatology, 2003. **30**(9): p. 2045-53.
321. Reisine, S., et al., *Employment and health status changes among women with fibromyalgia: A five-year study*. Arthritis Care and Research, 2008. **59** (12): p. 1735-1741.
322. Perrot, S., et al., *Characteristics of patients with fibromyalgia in France and Germany*. International Journal of Clinical Practice, 2010. **64** (8): p. 1100-1108.
323. Silverman, S., et al., *The economic burden of fibromyalgia: comparative analysis with rheumatoid arthritis*. Current Medical Research & Opinion, 2009. **25**(4): p. 829-40.
324. Henriksson, C.M., G.M. Liedberg, and B. Gerdle, *Women with fibromyalgia: work and rehabilitation*. Disability & Rehabilitation, 2005. **27**(12): p. 685-94.
325. van Koulil, S., et al., *Tailored cognitive-behavioural therapy and exercise training improves the physical fitness of patients with fibromyalgia*. Annals of the Rheumatic Diseases, 2011. **70**(12): p. 2131-3.
326. Skouen, J.S., A. Grasdal, and E.M.H. Haldorsen, *Return to work after comparing outpatient multidisciplinary treatment programs versus treatment in general practice for patients with chronic widespread pain*. European Journal of Pain: Ejp, 2006. **10**(2): p. 145-52.
327. Rutledge, D.N., K. Jones, and C.J. Jones, *Predicting high physical function in people with fibromyalgia*. Journal of Nursing Scholarship, 2007. **39**(4): p. 319-24.
328. Kurtze, N., K.T. Gundersen, and S. Svebak, *The impact of perceived physical dysfunction, health-related habits, and affective symptoms on employment status among fibromyalgia support group members*. Journal of Musculoskeletal Pain, 2001. **9** (2): p. 39-53.
329. Boonen, A., et al., *Large differences in cost of illness and wellbeing between patients with fibromyalgia, chronic low back pain, or ankylosing spondylitis*. Annals of the Rheumatic Diseases, 2005. **64**(3): p. 396-402.
330. Rivera, J., et al., *Resource utilisation and health care costs in patients diagnosed with fibromyalgia in Spain*. Clinical & Experimental Rheumatology, 2009. **27**(5 Suppl 56): p. S39-45.
331. Wolfe, F., et al., *A prospective, longitudinal, multicenter study of service utilization and costs in fibromyalgia*. Arthritis & Rheumatism, 1997. **40**(9): p. 1560-70.
332. Berger, A., et al., *Characteristics and healthcare costs of patients with fibromyalgia syndrome*. International Journal of Clinical Practice, 2007. **61**(9): p. 1498-508.
333. Oliver, K., et al., *Effects of social support and education on health care costs for patients with fibromyalgia*. Journal of Rheumatology, 2001. **28**(12): p. 2711-9.
334. Sicras-Mainar, A., et al., *Treating patients with fibromyalgia in primary care settings under routine medical practice: a claim database cost and burden of illness study*. Arthritis Res Ther, 2009. **11**(2): p. R54.
335. Walen, H.R., P.A. Cronan, and S.M. Bigatti, *Factors associated with healthcare costs in women with fibromyalgia*. American Journal of Managed Care, 2001. **7 Spec No**: p. SP39-47.
336. Robinson, R.L., et al., *Depression and fibromyalgia: treatment and cost when diagnosed separately or concurrently*. Journal of Rheumatology, 2004. **31**(8): p. 1621-9.