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Mark S. Wallace *Editors*

Fibromyalgia

Clinical Guidelines and Treatments

Springer

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Preface

Fibromyalgia is a prevalent disease state, necessitating priority in both primary care and pain management practices. Since Fibromyalgia can be associated with rheumatological disease, patients have historically been referred to rheumatologists. In addition, the American College of Rheumatology were the first to publish diagnostic criteria and recently published extensively revised criteria. However, the vast majority of fibromyalgia patients have no underlying rheumatological disease; therefore, fewer are being referred to rheumatologists and more are being diagnosed by their primary care physicians. The current and future leaders in the management of fibromyalgia are primary care and pain medicine physicians/providers. In this text, we created a unique collaborative effort by pain medicine fellows who were mentored by prominent pain medicine faculty at separate institutions to provide the following chapters. The authors have researched the complexity of this disease and have provided evidence-based guidelines and treatments for patients with fibromyalgia. Here you will find the most up-to-date review of the literature on the etiology, diagnosis, and treatment for fibromyalgia. This includes recent research showing possible genetic components, acupuncture as an adjuvant therapy, which lifestyle modifications help the most, and what to avoid, such as benzodiazepines.

For centuries, this disease state has been described with minimal treatment modalities. Only in recent decades has extensive research been performed to validate and treat this disease. There are now three FDA-approved drugs to treat fibromyalgia (surpassed only by postherpetic neuralgia which has four). We now have the tools to provide patients with fibromyalgia a better quality of life and a better prognosis. This text is unique as it focuses on the current literature and evidence-based data to guide practitioners in the management of fibromyalgia. We also discuss emerging developments and research to come. We hope you find this text useful in the management of fibromyalgia, as a patient and/or a healthcare provider.

We would like to thank all the authors who contributed to this text. This text would not be possible without their thorough approach and thoughtful perspective.

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Chapter 1
The Epidemiology and Prevalence of Fibromyalgia (FMS)

Jeffrey L. Chen and Anne Marie McKenzie-Brown

Key Points

- Fibromyalgia is a chronic disorder characterized by widespread musculoskeletal pain often accompanied by fatigue, headaches, sleep disturbance, and mood problems.
- Understanding the epidemiology of this chronic pain disorder is important in treating this patient population as it will help us understand how the disease is distributed in a population and the risk for the disease.
- Epidemiology is important as it shapes our practice of medicine, as the processes of diagnosis, prognostication, and the selection of appropriate therapies are population and evidence based.
- The overall prevalence of fibromyalgia in the general population is about 2–4 %, and affects about five million Americans.
- Fibromyalgia is more common in females, with a female-to-male ratio of about 7–9:1.
- Most patients are diagnosed sometime around the middle of life.
- The newer 2010 clinical case definition of fibromyalgia, classifies patients fairly consistently compared to the older 1990 American College of Rheumatology (ACR) criteria, without physical or tender point examination.
- This new diagnostic criteria is thought to be especially useful in the longitudinal evaluation of patients with marked symptom variability, and may help our epidemiological understanding [1].
- The prevalence of fibromyalgia is greater among first-degree relatives, suggesting a genetic predisposition to the disease.

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- The prevalence of fibromyalgia seen in specialty clinics is similar to that seen in the general population.
- Global prevalence of fibromyalgia is about 2.7%, more common in women, patients over age 50, low socioeconomic status, and those living in rural areas.
- There are limited data on incidence rates, with age-adjusted incidence rates estimated to be around seven cases per 1000 person-years for males and over 11 cases per 1000 person-years for females [2].
- Limited data suggest that the prevalence of fibromyalgia syndrome in children and adolescents is between 1 and 6%.
- In children with fibromyalgia, anxiety is common.
- Mortality among adults with fibromyalgia is similar to the general population, although death rates from suicide and accidental injuries are higher among fibromyalgia patients.
- Fibromyalgia patients averaged almost ten outpatient medical visits per year and are considered heavy users of physician services, with an estimated 5.5 million ambulatory care visits for patients with fibromyalgia on average per year.
- Estimates of average yearly direct medical costs per fibromyalgia patient are about US$ 6000–7000 per person.
- From a workplace perspective, fibromyalgia places a significant cost, absence, and productivity burden on employers.

Introduction

Fibromyalgia (FMS) is a chronic disorder characterized by widespread musculoskeletal pain often accompanied by fatigue, headaches, sleep disturbance, and mood problems. Understanding the epidemiology of this chronic pain disorder is important in treating this patient population as it will help us understand how the disease is distributed in a population and the risk for the disease. Epidemiology is important as it shapes our practice of medicine, as the processes of diagnosis, prognostication, and the selection of appropriate therapies are population and evidence based. Additionally, we will understand better the extent or burden of the disease in the community, the natural history of the disease, how to evaluate measures of healthcare delivery, and how to provide the foundation for developing public policy and making regulatory decisions regarding FMS.

FMS, initially termed “muscular rheumatism,” and then “tender points,” was described in Europe in the mid-nineteenth century [3] and then coined “fibrositis” by the neurologist Sir William Gowers in a British Medical Journal article in 1904. He chose the term “fibrositis” in finding a definition for inflammation of fibrous tissue [4]. By the end of the twentieth century, many rheumatologists recognized FMS as more of a discrete syndrome with diagnostic classification criteria proposed, evaluated, and validated.

The most popular and frequently followed diagnostic criteria for FMS is the American College of Rheumatology (ACR) criteria proposed in 1990, based on a sample of 293 patients with mean age 44.7 years. The diagnosis using these

guidelines requires widespread pain for at least 3 months, and at least 11 of 18 tender points at 18 potential predetermined body sites on examination, using less than 4 lb/in^2 of pressure [5]. Using such criteria, FMS is estimated to affect 2–4% of the population [6], with a much higher female-to-male ratio of 9:1 [7] with most patients diagnosed sometime around the middle of life. Overall, about five million Americans aged 18 and older are affected by FMS [8].

Recently in 2010, there have been more revolutionary changes in the diagnosis classification criteria and guidelines by the American College of Rheumatology (ACR). The governing body felt that the original diagnostic criteria from the 20 years prior was not utilized by many primary care physicians, and would therefore limit the diagnoses. Further, several key comorbid conditions were not included such as fatigue, cognitive and somatic symptoms; and patients that improved could then not satisfy the 1990 criteria for their condition. The proposed 2010 criteria are covered in detail in another chapter of this book. A patient satisfies diagnostic criteria for FMS if using the 2010 criteria the following three conditions are met: (1) Widespread pain index (WPI) 7 and symptom severity (SS) scale score 5 or WPI 3–6 and SS scale score 9. (2) Symptoms have to be present at a similar level for at least 3 months. (3) The patient does not have a disorder that would otherwise explain the pain. The ACR panel found that the 2010 clinical case definition of FMS correctly classified 88.1% of cases classified by the ACR classification criteria, without physical or tender point examination. The symptoms severity scale enables assessment of FMS SS in persons with current or previous FMS. Now, we have an easier methodology to diagnose these patients, and an alternative method for capturing these epidemiological data. This new diagnostic criterion is thought to be especially useful in the longitudinal evaluation of patients with marked symptom variability [1].

Search Strategy

The search for the majority of publications that were reviewed for this chapter utilized the PubMed Advanced Search Builder. PubMed is from the US National Library of Medicine National Institutes of Health and comprises more than 23 million citations for biomedical literature from MEDLINE, life science journals, and online books. Medical Subject Headings (MeSH) is the NLM-controlled vocabulary thesaurus used for indexing articles for PubMed. To start, the search term "fibromyalgia" was performed yielding 6514 items. This was then placed into the MeSH search, yielding 5884 entries. The search was then expanded in two directions and then unified. The first area of interest was looking at the MeSH subsets of "fibromyalgia" including "epidemiology," "ethnology," "mortality," or "statistics and numerical data" tags, yielding 736 items. The other search arm used the MeSH subsets of "fibromyalgia" looking at "cohort studies" or "vital statistics" yielding 855 articles. After putting the two searches together and removing duplicates, the number of items for review was 1223. Non-English articles were removed, leaving 1100 articles. The bulk of the concentration was then placed on other full-text

journal options and highly referenced journal articles. Weekly automated searches were then reviewed for the same search criteria through the National Center for Biotechnology Information (NCBI) at the US National Library of Medicine (NLM) up until the chapter was submitted for publication.

Definitions: Epidemiology, Incidence, Prevalence

Epidemiology is defined as the study of how a disease is distributed in a population. Epidemiology is important as the processes of diagnosis, prognostication, and the selection of appropriate therapies are population based. Population studies and estimates are only as good as the information that can be captured.

The major goal is to identify subgroups in the population who are at high risk for the disease. Understanding the epidemiology of FMS is important to understand our patient's risk for the disease, the extent or burden of the disease in the community, to understand the natural history of the disease, to evaluate measures of health-care delivery, and to provide the foundation for developing public policy and making regulatory decisions.

Prevalence and incidence are often confused, so it is helpful to understand their relationship. In a steady-state circumstance, prevalence is equal to the incidence multiplied by the duration of disease. Incidence conveys information about the risk of contracting the disease, whereas prevalence indicates how widespread the disease is in a population. Prevalence can be thought of as a measure of the burden of the disease on society with no regard to time at risk or exposure. Because incidence is related to the risk, it can be more helpful in understanding the etiology of the disease [9].

Prevalence

Prevalence of a disease is defined as the number of cases of a disease present in the population at a specific time divided by the number of persons in the population.

Prevalence per 1000 = (Number of cases of a disease present in the population at a specified time)/(Number of persons in the population at that specified time) × 1000.

The prevalence of FMS in the general population is thought to be around 2% and affect about five million people in the USA. Wolfe and colleagues conducted a landmark study of the prevalence of primary FMS in the USA in 1993 in Kansas. The authors chose a random sample from 3006 adults, over 18 years old, and found 193 individuals with chronic widespread pain, and after physical examination diagnosed 36 cases of 1990 ACR-defined FMS cases. From this, the authors determined that the overall prevalence among adults was about 2% (95% CI 1.4–2.7); prevalence was higher among women than among men about 7:1 (3.4% vs. 0.5%). Furthermore, the prevalence of FMS in women rose sharply in middle age, to a maximum of 7.4% in the 70–79–year-old age group before dropping off. The

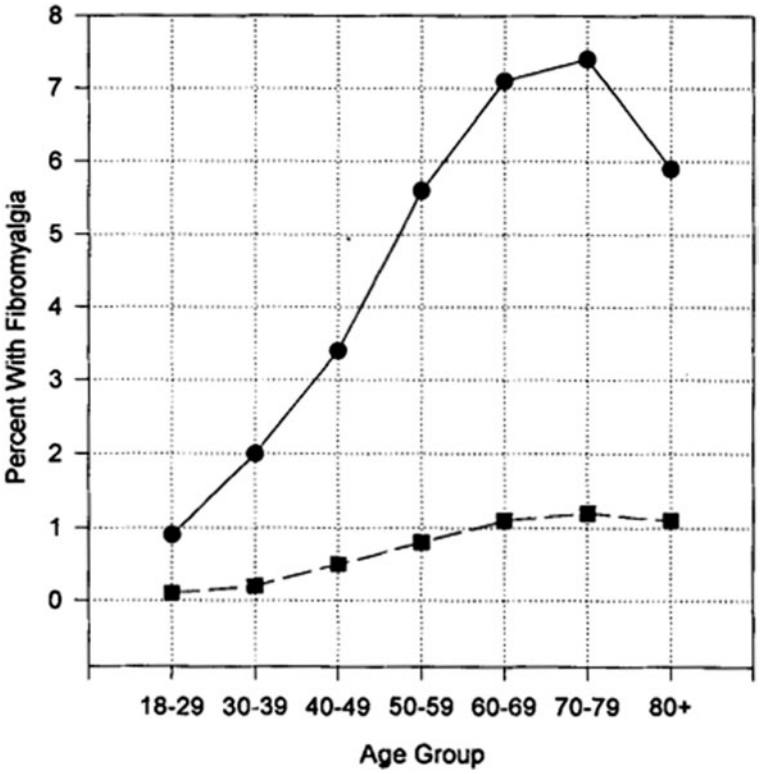

Fig. 1.1 From Wolfe's Wichita, KS study, prevalence is strikingly different between sex and age, and is most common in women over age 50, while peaking in the 70–79 age group. (Reproduced with permission from Wiley [10])

prevalence of FMS in men similarly peaked in the 70–79-year-old age group, but was only slightly more than 1% among men in this age group. See Fig. 1.1 [10]. Extrapolating from the Wolfe study, Lawrence et al. (2008), and using 2005 population estimates from the United States Census Bureau, they estimated that a 2% prevalence was equivalent to five million adults aged 18 years and older that have primary FMS [8]. The authors denote that the generalizability of these estimates to the US population is uncertain as the demographic from the Wolfe study may not have matched the overall demographics of the USA at that time. However, this is still considered the best estimated and the current number utilized by the Centers for Disease Control and Prevention (CDC) today.

The prevalence of FMS is greater among first-degree relatives of individuals than in the general population, suggesting a genetic predisposition to the disease. Buskila et al. (1997) studied patients with FMS and a random sample of their close relatives (parents, brothers, sisters, children, husbands) who were assessed and diagnosed using the 1990 ACR criteria. The authors found that the prevalence among blood relatives was 26%, and among their husbands 19%. Prevalence in female relatives was 41% and in male relatives was 14%. They concluded that relatives of

patients with FMS have a higher prevalence of FMS and can be attributed to genetic and environmental factors [11].

Weir et al. in 2006 conducted a retrospective cohort study of 2595 incident cases of adult and juvenile FMS using ICD-9 diagnoses from a large, stable health insurance claims database of 62,000 enrollees per year, between the years of 1997 and 2002. In this study, the authors found that females were 1.64 times (95 % confidence interval = 1.59–1.69) more likely than males to have FMS. Patients with FMS were 2.14–7.05 times more likely to have one or more of the following comorbid conditions: depression, anxiety, headache, irritable bowel syndrome, chronic fatigue syndrome, systemic lupus erythematosus, and rheumatoid arthritis. The diagnostic criterion for FMS was not evaluated by the authors specifically in these cases [2].

The prevalence of FMS seen in specialty clinics is similar to that seen in the general population. FMS is about six times more common in females than in males in reports from specialty clinics, which is a little less than what is seen in the general population [12].

More than 40 % of patients referred to a tertiary pain clinic meet the diagnostic criteria for FMS. Brill et al. (2012) assessed the prevalence of FMS in patients referred to a tertiary pain clinic. In their study, 85 consecutive patients (38 males, 47 females) attending a pain clinic were assessed for FMS using the 1990 ACR criteria. The authors found that 41.2 % of patients fulfilled the criteria [13].

Prevalence of FMS in the USA using the newer 2010 ACR criteria is relatively unknown. Speculation is that the prevalence would increase given the method of survey. The only published study at this time is from Vincent et al. (2013) in which the authors estimate and compare the prevalence of FMS by two different methods in Olmsted County, Minnesota. First, they conducted a retrospective review of 3410 medical records between 2005 and 2009 to estimate the prevalence of FMS in clinical practice; after age and sex adjustment, the prevalence was found to be 1.1 %. In the second method, they did a random survey of 2994 adults in Olmsted County using the FMS research survey criteria to estimate the percentage of responders who met the FMS research survey criteria. A total of 5.3 % met the FMS research survey criteria, with calculated age- and sex-adjusted prevalence of FMS in the general population of Olmsted County at 6.4 % [14]. This study shows the potential of the newer 2010 ACR survey criteria, and alludes to the possibility that the prevalence of FMS in the general US population may possibly be higher than previously thought.

McBeth et al. published a review in 2012 discussing the newer ACR 2010 criteria and assessing the probable impact of the ACR 2010 criteria on future research efforts, particularly in regard to the etiology and study design. The authors felt that the new criterion gives researchers the ability to assess the large numbers of people necessary to identify sufficient numbers of incident cases of FMS. They argue that the new criteria increase heterogeneous phenotyping of FMS, which will decrease the correlation of etiology, given pain is already heterogeneous. Overall, they note that the 2010 ACR criteria correctly classifies about 80 % of subjects who would have been classified with FMS using the 1990 criteria. Overall, in clinical populations, estimates of the proportion of patients reporting symptoms that satisfy criteria for FMS range from 2 to 22 %. The end range is higher than that seen in the general population, as would be expected in specialty clinics (Table 1.1) [15].

Table 1.1 Reported prevalence of fibromyalgia, by study. (Reprinted by permission from Macmillan Publishers Ltd: Nature Reviews Rheumatology: 8, 108–116. Copyright (2012))

Study	Study characteristics and findings					
	Classification criteria used	Study population	Cohort size	Study type	Type of prevalence estimate	Reported prevalence (%)
Clinical studies						
Yunus et al. (1981)[8]	≥4 tender points, diffuse musculoskeletal aching	Rheumatology clinic	100	Cross sectional	Point	20.0
Wolfe and Cathey (1983)[10]	≥7 tender points, diffuse musculoskeletal aching	Rheumatology clinic	1473	Cross sectional	Period	1°=3.7 2°=10.9 Σ=14.6
Campbell et al. (1983) [111]	Questionnaire and physical exam	General medical clinic	596	Cross sectional	Period	5.7
Wolfe et al. (1984) [113]	Multiple tender points, diffuse musculoskeletal aching, and skin fold tenderness	Rheumatology clinic	280	Prospective	Period	13.6
Hartz et al. (1987) [114]	Yunus et al. (1981) [8]	Family practice clinic	692	Cross sectional	Point	2.1
Muller (1987) [115]	Spontaneous pain, multiple tender points, psychological changes	Hospital	11,500	Cross sectional	Period	7.5
Greenfield et al. (1992) [116]	≥7 tender points, diffuse musculoskeletal aching	Rheumatology clinic	2781	Cross sectional	Period	4.6
Middleton et al. (1994) [117]	ACR 1990 criteria	SLE clinic	102	Cross sectional	Period	22.0
Borenstein (1995) [118]	Scoring ≥6 on 10 point pain scale and 11 of 18 tender points	Spine clinic	125	Prospective	Period	1°=4.8 2°=7.2 Σ=12.0
Pamuk et al. (2008) [119]	ACR 1990 criteria	Outpatients with iron-deficiency anemia or minor thalassemia, and healthy controls	205, 40, and 100, respectively	Cross sectional	Point	17.6, 20, and 6, respectively

Table 1.1 (continued)

Study	Study characteristics and findings					
	Classification criteria used	Study population	Cohort size	Study type	Type of prevalence estimate	Reported prevalence (%)
Tietjen et al. (2009) [120]	Physician diagnosis	Migraine clinics	1413	Cross sectional	Point	9.8
Bannwarth et al. (2009) [121]	ACR 1990 criteria	Rheumatology clinic	178	Cross sectional	Point	10.6
Almodovar et al. (2010) [122]	ACR 1990 criteria	Rheumatology clinic	462	Cross sectional	Point	4.1
Branco et al. (2010) [24]24	ACR 1990 criteria	Rheumatology clinic	1125	Cross sectional	Point	14
Population-based studies						
Jacobsen et al. (1989) [123]	Yunus et al. (1981) [8]	Malmo health survey, 1984	876	Cross sectional	Point	1.0
Makela and Heliovaara (1991) [21]	Yunus et al. (1981) [8]	Mini-Finland health survey	7217	Cross sectional	Point	0.75
Forseth and Gran (1992) [124]	ACR 1990 criteria	General population	2038	Cross sectional	Point	10.5
Lydell (1992) [125]	ACR 1990 criteria	General population	1102	Cross sectional	Point	3.2
Raspe et al. (1993) [126]	CWP in the presence of ≥17 tender points and ≤2 control tender points	General population	541	Cross sectional	Point	3.0
Prescott et al. (1993) [127]	ACR 1990 criteria	General population	1219	Cross sectional	Period	0.66
Buskila et al. (1993) [128]	ACR 1990 criteria	School children (11–15 years)	338	Cross sectional	Point	6.2
Wolfe et al. (1995) [15]	ACR 1990 criteria	General population	3006	Cross sectional	Point	2.0
Clark et al. (1998) [129]	ACR 1990 criteria	General population	548	Cross sectional	Point	1.2
White et al. (1999) [130]	LFESSQ and ACR 1990 criteria	General population	3395	Cross sectional	Point	3.3

Table 1.1 (continued)

Study	Study characteristics and findings					
	Classification criteria used	Study population	Cohort size	Study type	Type of prevalence estimate	Reported prevalence (%)
Haq et al. (2005) [131]	COPCORD [132] and physical examination	General population	2635	Cross sectional	Point	4.4
Wenzel et al. (2009) [133]	Self-report of physician diagnosis	General population	55,046	Cross sectional	Point	2.0
Davatchi et al. (2009) [134]	COPCORD and physical examination	General population	1192	Cross sectional	Point	0.06
Bannwarth et al. (2009) [121]	LFESSQ (by telephone)	General population	1014	Cross sectional	Point	2.2
Santos et al. (2010) [135]	ACR 1990 criteria	General population	361	Cross sectional	Point	5.5
Branco et al. (2010)[136]	LFESSQ	General population	4517	Cross sectional	Point	4.7

1° primary, 2° secondary, Σ overall, *ACR* American College of Rheumatology, *COPCORD* community orientated program for control of rheumatic disorders, *CWP* chronic widespread pain, *LFESSQ* London fibromyalgia epidemiology study screening questionnaire, *SLE* systemic lupus erythematosus

Global Prevalence

Macfarlane et al. (2009) performed a study to evaluate the international differences in prevalence of chronic widespread pain (CWP) in middle-aged men. This information may be extrapolated to FMS, as it is the cardinal symptom of FMS [16].The European Male Ageing Study (EMAS) sampled from population registers in eight European countries, each with an age-stratified sample of men aged 40–79 years. Information on pain was collected by questionnaire and subjects were classified according to whether they satisfied the ACR definition of CWP. There were significant differences in prevalence with 5–7 % in Italy, England, Belgium, and Sweden; 9–15 % in Spain, Poland, and Hungary and 15 % in Estonia [12]. The prevalence of CWP is much higher than the prevalence of FMS.

Although the prevalence of chronic widespread pain internationally gives one an idea of FMS, it is much higher than the latter. One must look to several other studies more specific to FMS.

While the prevalence of FMS in the general population in the USA is about 2 %, the prevalence in European countries ranged from 1 % in Finland, Denmark, and Sweden to 1.6–2 % in Spain and France, to 3 % in Canada showed a prevalence of 3.3 %, to 2–4 % in Germany.

In Finland, Makela (1999) performed a cross-sectional study of 8000 patients in Finland aged 30 years and older in a mobile clinic for musculoskeletal disorders. They found

the prevalence of FMS to be as low as 0.75% or 54 cases, with the peak prevalence in the 55–64 age range, and twice as prevalent in women. FMS did not predict mortality [17].

In Denmark, Prescott et al. (1993) performed a study using the Danish national health interview survey carried out by the Danish Institute for Clinical Epidemiology in 1990 on 6000 randomly selected Danish citizens about widespread muscle pain. Of those that fulfilled the screening criteria, clinical examination could be performed on 53% of the subjects. From this study, the prevalence of FMS in the Danish population between 18 and 79 years of age was found to be a minimum estimate of 0.66% (95% confidence limits 0.28–1.29%) [18]. FMS, like most non-inflammatory musculoskeletal diseases are more common in women than in men. In this case, the prevalence in females to males is about 9:1 in a Danish study [7].

In Sweden, Lindell et al. (2000) explored the prevalence of FMS using a structured interview and clinical examination in 1995 on 2425 subjects, ages 20–74. They found 303 individuals with suspected chronic widespread pain. From these subjects, they estimated the prevalence in Sweden to be 1.3% [19].

In Spain, Carmona et al. (2001) looked at FMS in the adult Spanish population to assess the impact on function and quality of life, and use of health and social resources. This study looked at 2998 subjects with structured visits with rheumatologists. They found the estimated prevalence of FMS to be 2.4% (1.5–3.2) [20].

In France, the prevalence is about 1.6–2.2%. Looking at the prevalence of FMS in France, Bannwarth et al. (2009) distributed a validated French version of the London Fibromyalgia Epidemiology Study Screening Questionnaire (LFESSQ) administered via telephone to a representative community sample of 1014 subjects. Based on positive screens for LFESSQ-4, the prevalence of FM was estimated at 2.2% (95% CI 1.3–3.1) in the French general population, which was also estimated to be approximately 680,000 patients [21]. Perrot et al. (2011), also performed an epidemiological study aimed to assess FMS prevalence in the French metropolitan population, based on a multistep sampling analysis, combining national screening and clinical confirmation by trained specialists looking at 3081 patients. The final estimated FM prevalence was 1.6% [22].

In Canada, White et al. (1999) evaluated 3395 adults in Canada, and found a prevalence of 3.3%, with a female-to-male ratio of roughly 3 to 1. In addition, this study determined that middle age, less education, lower socioeconomic status, being divorced, and being disabled are associated with increased odds of having FM [23].

In Germany, Hauser et al. (2009) surveyed 4064 persons in Germany and found an overall prevalence of 3.8% [24]. Using the 2010 ACR criteria, Wolfe et al. (2013) studied 2445 subjects randomly selected from the German general population in 2012 and found a prevalence of 2.1% with prevalence rising with age [25].

Branco et al. (2010) did a survey of five European countries (France, Germany, Italy, Portugal, and Spain) and estimated the prevalence of FMS in the general population using the LFESSQ4 and LFESSQ6. This study estimated the overall prevalence of FMS of 4.7% using the LFESSQ4, and 2.9% using the LFESSQ6 [26].

Queiroz et al. (2013) from Brazil published a review article of prevalence and incidence studies worldwide. From the 26 studies that they evaluated, the authors determined that the global prevalence of FMS is about 2.7%, more common in women, patients over age 50, low socioeconomic status, and living in rural areas (Table 1.2) [27].

Table 1.2 Prevalence of fibromyalgia in the general population. ([27], with kind permission from Springer Science and Business Media)

Country	Author	Case definition	*N*	Age range (year)	Prevalence (%) Overall	female	male
Africa							
Tunisia	Guermazi [9]	LFESSQ	1000	≥15	9.3	–	–
Americas							
Brazil	Senna [10]	COPCORD	3038	≥16	2.5	3.9	0.1
Canada	White [11]	1990 ACR	3395	≥18	3.3	4.9	1.6
Canada	McNally [12]	Self-reported	131,535	≥12	1.1	1.8	0.3
USA	Wolfe [13]	1990 ACR	3006	≥18	2.2	3.4	0.5
USA	Vincent [14●]	2010 ACR	3410	≥21	6.4	7.7	4.9
Asia							
Bangladesh	Haq [15]	COPCORD	5211	≥15	3.6	6.2	0.9
China	Scudds [16]	1990 ACR	1467	–	0.8	–	–
Israel	Ablin [3]	LFESSQ + 1990 ACR	1019	≥18	2.0	2.8	1.1
Malaysia	Veerapen [17]	COPCORD	2594	≥15	0.9	1.5	0.2
Pakistan	Farooqi [18]	COPCORD	1997	≥15	2.1	–	–
Thailand	Prateepavanich [19]	2010 ACR	1000	–	0.6	–	–
Europe							
Denmark	Prescott [20]	1990 ACR	1219	18–79	0.7	–	–
France	Bannwarth [21]	LFESSQ + 1990 ACR	1014	≥15	1.4	2.0	0.7
France	Perrot [22●]	LFESSQ + 1990 ACR	3081	≥18	1.6	–	–
Finland	Mäkelä [23]	Yunus criteria	7217	≥30	0.75	1.0	0.5
Germany	Branco [24●]	LFESSQ + 1990 ACR	1002	≥15	3.2	3.9	2.5
Germany	Wolfe [25●]	2010 ACR	2445	≥14	2.1	2.4	1.8
Greece	Andrianakos [26]	1990 ACR	8740	≥19	0.4	–	–
Italy	Salafti [27]	1990 ACR	2155	≥18	2.2	–	–
Italy	Branco [24●]	LFESSQ + 1990 ACR	1000	≥15	3.7	5.5	1.6
Portugal	Branco [24●]	LFESSQ + 1990 ACR	500	≥15	3.6	5.2	1.8
Spain	Branco [24●]	LFESSQ + 1990 ACR	1001	≥15	2.3	3.3	1.3
Spain	Mas [28]	1990 ACR	2192	≥20	2.4	4.2	0.2
Sweden	Lindell [29]	1990 ACR	2425	20–74	1.3	2.4	0.0

Table 1.2 (continued)

Country	Author	Case definition	*N*	Age range (year)	Prevalence (%) Overall	female	male
Turkey	Turhanoglu [30]	1990 ACR	600	–	8.8	12.5	5.1
Mean					2.7	4.1	1.4

● Of importance
LFESSQ London Fibromyalgia Epidemiology Study Screening Questionnaire, *COPCORD* Community Oriented Program for the Control of Rheumatic Diseases, *ACR* American College of Rheumatology

Incidence of a disease is a measure of risk, and is defined as the number of new cases of a disease occurring in a population during a specified period of time in a population at risk for developing the disease. Because incidence is related to the risk, it can be more helpful in understanding the etiology of the disease.

Incidence rate per 1000 = (Number of new cases of a disease occurring in a population during a specified time period)/(Number of persons who are at risk of developing the disease during that time period) × 1000.

The incidence of FMS is an area without a significant amount of reliable research.

Weir et al. in 2006 conducted a retrospective cohort study of 2595 incident cases of adult and juvenile FMS using ICD-9 diagnoses from a large, stable health insurance claims database of 62,000 enrollees per year, between the years of 1997 and 2002. Age-adjusted incidence rates were 6.88 cases per 1000 person-years for males and 11.28 cases per 1000 person-years for females [2].

Foresth et al. (1997) conducted a population survey to assess the incidence of FMS among females in Norway. They used a screening questionnaire on 2498 females aged 20–49. Subsets of the subjects and controls underwent further structural interviews and examination for tender points, and categorized as positive or negative responders. These subjects were then followed to see if they remained in the same category or converted to the other. The calculated annual incidence of FMS in females was 583/100,000 or 5.83 cases per 1000 females [28].

Choi et al. (2010) investigated the association between incident self-reported FMS and prior somatic diseases, lifestyle factors, and health behaviors in a cohort of 3136 women in a 25-year follow-up of the Adventist Health Study. A total of 136 women reported a diagnosis of FMS, giving a period incidence of 43/1000 or 1.72/1000 per year. The authors also found high odds ratios for smoking, prevalent allergies, and a history of hyperemesis gravidarum concluding that these risks may help predict the development of FMS in these women, and may be considered for effective prevention strategies [29].

Lee et al. (2013) studied the incidence of secondary FMS in relation to inflammatory arthritis. They prospectively followed 1487 patients in an early inflammatory arthritis cohort in Canada, and assessed the association between pain, inflammation, psychosocial variables, and the clinical diagnosis of FMS. The authors found the incidence of FMS to be from 3.58 to 6.77 cases per 100 person-years; it was highest during the first 12 months after diagnosis of inflammatory arthritis. Although in-

flammation was not associated with the clinical diagnosis of FM, pain severity and poor mental health were associated with the clinical diagnosis of FM [30].

Wolfe et al. (2011) looked at the relationship of FMS to rheumatoid arthritis (RA) by studying FMS development in 9739 rheumatoid arthritis patients with initial limited FMS symptoms during 42,591 patient-years of follow-up using a modification of the ACR 2010 FMS criteria. The authors found that 7.4% of patients satisfied their diagnostic criteria, although 19.8% satisfied criteria at some point during follow-up, an incidence rate of 5.3 (95% CI 5.1, 5.6) per 100 patients years, and at rates that were similar in men (7.0%) and women (8.1%). Clinically important conclusions were that social disadvantage, psychological distress, comorbidity (composite of 11 conditions: pulmonary disorders, myocardial infarction, other cardiovascular disorders, stroke, hypertension, diabetes, spine/hip/leg fracture, depression, GI ulcer, other GI disorders, and cancer) rheumatoid arthritis severity, and FMS variables predict future development of FMS [31].

Juvenile Fibromyalgia

There is a lot less published work concerning juvenile FMS compared to that of adults. Though FMS is most commonly seen during the middle of life, it can be seen at any age, even in childhood. Limited data suggest that the prevalence of FMS in children and adolescents is between 1 and 6%.

Buskila, et al. (1993) assessed 338 healthy Israeli schoolchildren, 179 boys and 159 girls, between the ages of 9 and 15, for tenderness threshold and prevalence of FMS using the 18 tender points using the 1990 ACR criteria. Twenty-one children or 6.2% had FMS based on this criterion, with the authors finding it to be relatively common in the pediatric age group. This study also concluded that boys have lower tenderness thresholds than girls, and children with FMS have lower thresholds for tenderness compared to those without it [32].

Clark et al. in 1998 did a clinical study of 548 Mexican children, 264 boys and 284 girls, ages 9–17. With a two-stage classification using 1990 ACR criteria, they administered a pain questionnaire and then had two rheumatologists examine the children for tender points in both the study and control groups. In this study, seven girls and no boys fulfilled the ACR diagnostic criteria for FMS, with a prevalence of 1.2%. Once again, pain thresholds were lower in children with FMS than the control group [33].The authors of this study felt that the variation could be possible secondary to racial and sociocultural differences as well as the methodological approach with tenderness thresholds. This was thought to be a favorable outcome in children with FMS. In a study by Buskila et al. 11 of 15 children, or 73%, initially diagnosed with FMS no longer fulfilled the criteria 30 months later [32, 34].

Mikkelsson et al. performed a study using a pain questionnaire with 1-year follow-up data to assess the prevalence and persistence of musculoskeletal pain in 1756 Finnish third and fifth grade children. Widespread pain, determined as in the criteria for FMS per the authors, was found in 132 children (7.5%) and persisted in 35 children (29.7%, 95% CI 21.9–38.4) at follow-up [35]. Mikkelsson then

reported further data 2 years later that 22 children with FMS from this 1756 Finnish preadolescents were prospectively and blindly followed for 1 year to determine persistence. The ACR 1990 criteria for FM were used. The authors found that the prevalence of FM was 1.3% (95% CI 0.8–1.9) at baseline. At the 1-year follow-up, 16 of 22 (73%) children were available for evaluation, and 4 (25%) had persistent FM demonstrating that FM in children has a good outcome [36].

Weir et al. in 2006 conducted a retrospective cohort study of 2595 incident cases of adult and juvenile FMS using ICD-9 diagnoses from a large, stable health insurance claims database of 62,000 enrollees per year, between the years of 1997 and 2002. The estimated prevalence of FMS per age group was 0.5 and 1% for 0–4–year-olds; 1 and 1.4% for 5–9-year-olds; 2 and 2.6% for 10–14-year-olds; and 3.5 and 6.2% for 15–19-year-olds, respectively. The diagnostic criteria for FMS for these cases were not evaluated by the authors [2].

Siegel et al. in 1998 performed a retrospective medical record review from 1989 to 1995 of a pediatric rheumatology clinic in a university medical center setting, to identify cases of FMS, and then perform a structured telephone interview served to determine current status and response to treatment. A total of 45 subjects were identified of which 41 were female, 42 were white, with a mean age of 13.3 years. Patients with FMS account for about 7% of all cases referred to tertiary pediatric rheumatology centers, with a strong female predominance in the pediatric population, similar to that seen in adults. Furthermore, the authors reported that over 90% of the patients with FMS experience diffuse pain and sleep disturbance. The authors also conclude that in terms of tender points, the majority of patients improved over 2–3 years of follow-up [37].

Lommel et al. in 2009 looked at 62 adolescent females, ages 12–18 years old, who were admitted to an inpatient psychiatric unit who met their criteria for juvenile primary fibromyalgia syndrome (JPFS). The participants completed questionnaires and were examined for 21 (18 bilateral and 3 control) tender points. The authors found that 32 girls, or 52% of this population met criteria for JPFS and concluded that FMS is highly prevalent in an adolescent inpatient psychiatric unit [38].

Kashikar-Zuck et al. looked at children at four different pediatric rheumatology clinics to assess the prevalence of mood, anxiety, and behavioral disorders in a clinical sample of children and adolescents with JPFS and assess the relationship between psychiatric disorders and JPFS. They evaluated 76 children with JPFS, ages 11–18 years old. In this sample, 67.1% of patients had at least one current and 71.5% had at least one lifetime DSM-IV (Diagnostic and Statistical Manual of Mental Disorders-fourth edition) psychiatric diagnosis with the most frequent psychiatric diagnosis being anxiety disorder for 57.5% of JPFS patients, demonstrating a high prevalence [39].

Gedalia et al. in 2000 reported their experience of FMS in a pediatric rheumatology clinic setting by reviewing clinic and laboratory data in all their patients with FMS seen over 4 years period. All the patients fulfilled the ACR criteria for the diagnosis of primary FMS. The authors reported 59 children, 47 female and 12 males, diagnosed with primary FMS with a mean duration of follow-up of 18.3 months. The mean age at onset for this cohort was 13.7 years, and the mean age at diagnosis

was 15.5 years. Diffuse aching was reported in 57 patients (97%), headaches in 45 (76%), and sleep disturbances in 41 (69%). Fifty patients available for follow-up, and of these children 30 (60%) had improved, while 18 (36%) remained unchanged, and 2 (4%) became worse when compared with initial presentation. The authors concluded that the clinical spectrum of FMS in children is similar to that of adults but with better outcomes and that active exercise programs seem to correlate with better outcomes [40]. This is supported by the prior findings of Buskila et al. in 1995, in which the authors performed a 30-month follow-up study of children with FMS. In their original study, they enrolled 21 children with FMS using 1990 ACR criteria, and an additional seven children fulfilling the tender point count criterion only (11 of 18). Of these children, 15 of the 21 with FMS and seven with tender points were recruited for the follow-up study. The authors found that after 30 months, 11 of the 15 children with FM (73%) no longer had FMS and that none of the seven children fulfilling the tender point count criterion had developed FM [34].

In summary, FMS can be seen in children of all ages, more often in girls than in boys. The prevalence is around 1–6% of the population. In one study, the mean age of onset was 13.7 years, and the mean age at diagnosis was 15.5 years. Diffuse pain, headaches, sleep disturbances, and anxiety are common. In juvenile patients with psychiatric disorders and diffuse pain, the diagnosis of fibromyalgia should be considered. Furthermore, children with fibromyalgia have lower thresholds for tenderness compared to those without it. Finally, there is generally a better outcome in children with fibromyalgia than adults.

Miscellaneous Topics

Mortality

Mortality is of strong epidemiological interest. When one studies disease occurrence, expressing mortality in quantitative term can help differentiate the risk of dying from a disease, serve as a measure of disease severity, and help us determine the treatment and efficacy. In some cases, such as when a disease is severe and fatal, mortality can be used to study risk. However, given the chronicity in fibromyalgia, mortality would not be a good index of risk or incidence, but still serves as a measure of disease severity [9]**.**

Using the International Classification of Diseases, 9th Revision, Clinical Modification FM diagnostic code (ICD-9 729.1) “Myalgia and myositis, unspecified” for FMS, the CDC reports about 23 deaths per year from 1979 to 1998, with eight deaths reported in 1979, with a high of 45 deaths reported in 1997. In 1998, code 729.1 accounted for only 42 deaths out of 9367 deaths, or 0.45%, attributed to arthritis and other rheumatic conditions [41].

In 2011, Wolfe et al., performed a study to determine if mortality increased among patients diagnosed as having FMS as compared to the general population. The au-

thors studied 8186 FMS patients seen between 1974 and 2009 and measured death rates. They reported a hazard ratio for FMS compared with osteoarthritis at 1.05 (95% CI 0.94–1.17). The standardized mortality odds ratio (OR) compared with the US general population was increased for suicide (OR 3.31, 95% CI 2.15–5.11) and for accidental deaths (OR 1.45, 95% CI 1.02–2.06), but not for malignancy. The authors concluded that mortality among adults with FMS is similar to the general population, although death rates from suicide and accidental injuries are higher among FMS patients [42].

Hospitalizations

Hospital data is an important source of epidemiological data. However, it also has limitations. For example, hospital admissions are selective in relation to the patient's personal characteristics, disease severity, comorbid conditions and the hospital and physicians' admissions policies and character. Furthermore, hospital records are not designed for research and may be variable to diagnostic quality, incomplete, illegible, or even missing. Certainly, with the current use of electronic medical records, some of these issues will improve. However, the population at risk may not be defined well and the principal diagnosis may not be properly recorded [9].

Lethbridge-Cejku et al. (2003) set out to describe the impact of arthritis and other rheumatic conditions on hospitals by describing the magnitude and characteristics of these hospitalizations. They reviewed data from the 1997 National Hospital Discharge Survey. The authors found that in 1997, there were an estimated 744,000 hospitalizations with a principal arthritis diagnosis or 3% of hospitalizations, which was composed of ten mutually exclusive subgroups of arthritis, including FMS, listed with ICD-9 729.1, "Myositis and Myalgia, unspecified" as the principal diagnosis. Overall, these hospital patients with primary diagnosis of arthritis were found to be healthier and have fewer comorbidities, had shorter hospital stays, and were less likely to undergo a procedure than their nonarthritis counterparts. In contrary, 9% or 2.5 million hospitalizations with a primary medical diagnosis and "any-listed arthritis diagnosis," demonstrated an older demographic with more comorbidities, longer hospital stays, and a sicker profile [43].

In a prospective survey study of 538 patients with FMS in 1997, Wolfe et al. concluded that patients with FMS were hospitalized approximately once every 3 years, and required about 5.4 FMS-related drugs per year. They also reported that almost 50% of hospitalizations occurring during the study were related to FMS-associated symptoms [44].

Haviland et al. (2011) reviewed hospital discharge data from the Nationwide Inpatient Sample (NIS) for records between 1999 and 2007 that contained ICD-9 code 729.1 "Myositis and Myalgia, unspecified." The authors reported 1,727,765 discharges with a 729.1 diagnostic code during this 9 years span with a composition of 213,034 men (12.3%) and 1,513,995 women (87.6%) with hospital discharges coded for FMS increasing steadily each year. Women have higher hospitalization

rates than men at all ages. The most common comorbidities with FMS as the primary diagnosis were nonspecific chest pain, mood disorders, and spondylosis/intervertebral disc disorders/other back problems. Persons hospitalized with primary cardiovascular conditions had a high prevalence of reporting FMS as a secondary condition [45].

Ambulatory Care Setting

In a prospective survey study of 538 patients with FMS in 1997, Wolfe et al. concluded that FMS patients averaged almost ten outpatient medical visits per year, and when nontraditional treatments were considered, this number increased to approximately one visit per month [44].

Using data from the 2001–2005 National Ambulatory Medical Care Survey and 2001–2005 National Hospital Ambulatory Medical Care Survey, Sacks et al. (2010), estimated annual ambulatory health-care visits for ICD-9 arthritis and other rheumatic conditions. The authors estimate that overall prevalence of adults with medically treated arthritis and other rheumatic conditions was 29,150,000 adults (95% confidence interval [95% CI] 26,473,000–31,826,000) and accounted for 77,887,300 ambulatory care visits (95% CI 71,266,000–84,508,000). Of these, there were an estimated 5.5 million ambulatory care visits for patient with FMS on average per year [46].

It is reported that patients with FMS are heavy users of physician services. Medical and psychiatric comorbidities are stronger determinants of high health-care utilization than functional comorbidity among patients with FMS. FMS represents a major burden on limited health-care resources. Some advocate that physicians should focus clinical efforts at efficiently addressing treatable medical and psychiatric comorbidities that contribute to poor health, thus reducing health service use in these patients [47].

Costs of Fibromyalgia

Cost is important to understand the burden on society and the effectiveness of treatment of a disease. Estimates of average yearly direct medical costs per FMS patient are about US$ 6000–7000 per person.

To study costs in FMS, Sanchez et al. (2011), evaluated health-care resource utilization and costs 1 year before and 3 years after a FMS diagnosis using retrospective cohort analysis claims of 2613 patients from Humana between 2003 and 2005. The authors found that a FMS diagnosis was associated with increased utilization and pain-related medication cost up to the first 6 months post-diagnosis followed by stabilization over 3 years post-diagnosis. They reported that the mean per patient was US$ 3481 for the 6-month post-diagnosis, and US$ 3588 for the final 6 months,

or over US$ 7000 per year. The largest components of direct medical costs among patient with FMS were for office and emergency room visits, procedures and tests, and hospitalizations [48].

In another study by Knight et al. (2013), adjusted prescription medication costs were nearly 11 times higher in the US (US$ 3419) than in France (US$ 312), and nearly six times higher than in Germany (US$ 606). Adjusted direct costs due to physician office visits were five times higher in the US (US$ 1528) than in France (US$ 297), and nearly three times higher than in Germany (US$ 564). The authors felt that the cost differential between countries is driven by differences in utilization as well as differences in the cost of physician visits between countries [49].

The cost of FMS care has been increasing over time. The average yearly cost for service utilization among FMS patients was reported at US$ 2274 per year in 1996, and even at that time FMS patients were thought to have a high lifetime and current rate of utilization of all types of medical services. The total annual cost of FMS in 1996, including direct and indirect costs, was US$ 5945 per patient [44].

Another recent study on hospitalization costs of FMS was by Haviland et al. (2012) looking at patients in the USA from 1999 to 2007, using data from the Nationwide Inpatient Sample. Over the study period, an estimated 63,772 patients—two thirds women, one third men—had been hospitalized for FMS. Survey-adjusted total Consumer Price Index adjusted charges over the study period were estimated to be approximately US$ 1.0 billion. The majority of procedures for FMS patients were related to musculoskeletal, gastrointestinal, or cardiovascular systems [50].

Fibromyalgia in the Workplace

FMS has been associated with lower levels of health-related quality-of-life and more work productively loss. One study by McDonald et al. (2011) looked at data from the 2008 US National Health and Wellness Survey to investigate the impact of musculoskeletal pain on health-related quality of life and work productivity losses among US workers. The demographics were aged 20–64 years (N=30,868), workers with arthritis (n=2670), back pain (n=4920), and FMS (n=439) pain were compared with workers without those respective musculoskeletal pain conditions. The authors found that arthritis, back, and FMS pain were all associated with significantly lower levels of health-related quality of life, and higher levels of work productivity loss [51].

In a study by Kleinman et al. (2009), working adults with FMS averaged almost 16.8 days of missed work per year compared to 6.4 days for persons without FMS. They also reported that total health benefit costs for FMS were US$ 8452 versus US$ 4013 without FMS. The authors concluded that FMS places a significant cost, absence, and productivity burden on employers [52].

Working age women with FMS hospitalized for occupational musculoskeletal disorders were almost ten times less likely to return to work and more than four times less likely to retain work at 1 year post hospitalization per Howard et al. (2010). Howard et al. also report that patients with FMS were found to show greater

psychosocial distress in addition to significantly poorer rates of work return and after treatment [53].

Conclusion

There is still a lot to study and learn about FMS. Epidemiological studies will continue to help us understand the risk and distribution of this disease. The prevalence of FMS is 2–4 % of the general population, seen across the lifespan affecting females over males. FMS is costly, both with direct medical costs, and indirectly with decreased productivity in the workforce. We hope that further understanding of the epidemiology of this disease will in turn help shape our practice of medicine and the use of appropriate, economical, and evidence-based therapies for this patient population.

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Chapter 2
Fibromyalgia Diagnosis

Omar H. Henriquez and Devin Peck

Key Points

- Fibromyalgia (FM) is associated with fatigue, insomnia, stiffness, irritable bowel, cognitive dysfunction, and insomnia.
- The prevalence has been reported to be 2–4 % of the general population.
- The pathogenesis involves central sensitization with attenuation of the descending inhibitory pathway.
- The diagnosis is based on the new definition for FM designated by the American College of Rheumatology (ACR) in 2010.
- Two key measures for the diagnosis of FM include the widespread pain index (WPI) and severity scale (SS).
- Patients with chronic pain conditions other than FM may subsequently develop secondary FM.

Introduction

Fibromyalgia (FM) is a condition found in many patients complaining of chronic widespread pain. Pain is mostly within the soft tissue and musculoskeletal structures. Symptoms are chronic and persistent leading to increased cost of care by way of recurrent medical visits. Increasing amounts of research and publications have been produced since the release of the American College of Rheumatology (ACR) 1990 criteria for the classification of FM, which provided universal diagnostic

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criteria for FM. Since this publication, multiple other literature reviews and research publications have reflected an evolving understanding of FM, and provided more tools for its diagnosis. Characteristics associated with FM include fatigue, insomnia, stiffness, irritable bowel syndrome (IBS), and symptoms of anxiety and depression. A family history of depression or a past history of depression has also been associated with FM [1].

Treatment of FM has a substantial impact on the health-care economy. Wolf et al. performed a study examining service utilization and the cost of care in FM patients. The authors estimated that for each individual FM patient, the service utilization cost was approximately US$ 2274 annually [2].

Epidemiology and Prevalence

In 1990, the ACR released a set of criteria for diagnosing FM. These ACR criteria had been widely accepted by the medical community. Unfortunately, these criteria led to some confusion in diagnosing FM, leading in turn to inaccurate reports of prevalence [3]. This prevalence has been reported to range from 2 to 4% in the general population. It has been found in all ethnic groups that have been studied up until now. The incidence of FM is higher among females than males (3.4 vs. 0.5%) and it increases with age. Wolfe et al. found that FM peaks in middle age with highest peak among women 70–79 years of age (7.4%) compared to age-matched males (1%) [1].

In a study examining the prevalence of FM within the Canadian population, 100 out of 3395 randomly selected adults were diagnosed with FM (3.3% incidence). It was more commonly seen in females than in males with an approximately 3:1 female to male ratio. In this study performed by White et al., the authors found that FM was seen in 4.9% of adult females and 1.9% of adult males. They also found that the prevalence of FM increased with age, peaking in females between 55 and 64 years of age (7.9%) and peaking in males between 45 and 52 years of age (2.5%) [4].

There was a discrepancy between subspecialty clinics diagnosing this condition. Within most rheumatology clinics, approximately 15% of patients were classified as having FM. In other subspecialty clinics, the prevalence rate of FM was only 6%. However, the greatest number of FM diagnosis comes from the primary care clinics [1].

Pathogenesis

FM is one cause for chronic widespread pain, which traditionally has been thought to be due to muscle pathology. However, several trials have refuted this idea. In addition, most researchers now believe that any muscle pathology that is related to FM is secondary to pain and inactivity, rather than a primary process [5]. Today,

central sensitization is the most established pathophysiological mechanism of FM. It is associated with hyperalgesia and allodynia, which are commonly experienced in patients with FM. In fact, patients with FM seem to be more sensitive to multiple different stimuli, including heat, cold, and electrical stimulation [6]. Interestingly, these patients have also been noted to have hypersensitivity to auditory and visual stimuli, which suggests that FM patients experience a global altered sensory processing that is not specific to painful stimuli alone [7]. In a study comparing brain magnetic resonance imaging (MRI) scans of FM patients and controls, those with FM showed an increase in activation of neurons with low-intensity painful stimulation when compared to the control group [8]. In addition, studies have shown that FM patients have structural deformities of forebrain areas involved in pain processing which include the thalamus, striatum, insular cortex, and cingulate cortex [9].

FM patients have also been noted to have a deficiency in the descending inhibitory pathway within the central nervous system (CNS). In healthy patients, pain is transmitted from the periphery to the CNS and the cerebral cortex by way of thalamocortical tract. There are descending inhibitory neurons that release neurotransmitters at the spinal level in order to prevent windup phenomena from occurring. In studies measuring the cerebrospinal fluid of FM patients, there was an increased amount of neurotransmitters associated with nociception such as substance P, excitatory amino acids (e.g., glutamine, glycine, arginine, glutamic acid), and nerve growth factor (NGF). In addition, there was a decreased amount of antinociceptive neurotransmitters such as the biogenic amines (e.g., serotonin, norepinephrine, dopamine). This may explain the attenuation of the descending antinociceptive pain pathways and the increased activation of the ascending pain pathways in patients with FM [10, 11].

One factor associated with the predisposition to FM is a polymorphism in the catechol-*O*-methyltransferase (COMT) enzyme, which breaks down catecholamines such as dopamine and norepinephrine as well as the endorphins. This genetic defect has been linked to depression and chronic pain, and now it is being linked to FM [12]. Interestingly, it has been shown that endogenous opioid levels in FM patients are increased as compared to healthy patients. By looking at mu-opioid receptor (MOR) positron emission tomography (PET), the occupancy of the MOR was compared between 17 FM patients and 17 control patients of same age and sex. Investigators found that the MOR binding potential was reduced in FM patients. This is one possible explanation for the lack of response to opioid medication in the FM patient population [13].

Diagnostic Criteria

Prior to the 1990 ACR publication, FM was known as a chronic manifestation of symptoms including pain, fatigue, stiffness, and insomnia as mentioned by Smythe and Modofsky [14]. Later, Yunus et al. reinforced this view. They also reported that many of these patients were being seen multiple times by different physicians,

Table 2.1 The American College of Rheumatology 1990 criteria for the classification of fibromyalgia[a]. From [16]. With permission from John Wiley and Sons

1. History of widespread pain
Definition. Pain is considered widespread when all of the following are present: pain in the left side of the body, pain in the right side of the body, pain above the waist, and pain below the waist. In addition, axial skeletal pain (cervical spine or anterior chest or thoracic spine or low back) must be present. In this definition, shoulder and buttock pain is considered as pain for each involved side. "Low back" pain is considered lower segment pain
2. Pain in 11 of 18 tender point sites on digital palpation
Definition. Pain, on digital palpation, must be present in at least 11 of the following 18 tender point sites:
Occiput: bilateral, at the suboccipital muscle insertions
Low cervical: bilateral, at the anterior aspects of the intertransverse spaces at C5–C7
Trapezius: bilateral, at the midpoint of the upper border
Supraspinatus: bilateral, at origins, above the scapula spine near the medial border
Second rib: bilateral, at the second costochondral junctions, just lateral to the junctions on upper surfaces
Lateral epicondyle: bilateral, 2 cm distal to the epicondyles
Gluteal: bilateral, in upper outer quadrants of buttocks in anterior fold of muscle
Greater trochanter: bilateral, posterior to the trochanteric prominence
Knee: bilateral, at the medial fat pad, proximal to the joint line
Digital palpation should be performed with an approximate force of 4 kg
For a tender point to be considered "positive," the subject must state that the palpation was painful. "Tender" is not to be considered "painful"

[a]For classification purposes, patients will be said to have fibromyalgia if both criteria are satisfied. Widespread pain must have been present for at least 3 months. The presence of a second clinical disorder does not exclude the diagnosis of fibromyalgia

leading to an increased number of unnecessary diagnostic tests [15]. Subsequently, in 1990, the ACR developed diagnostic criteria in the hopes of providing guidance to physicians in diagnosing FM. A multicenter study was performed, including a total of 558 subjects.— Of these subjects, 293 had FM and 265 were either pain-free or had other painful conditions. The authors concluded that there were two requirements for diagnosis: widespread pain (defined as axial pain with upper and lower segment pain) for at least 3 months and 11 or more of 18 specified tender points on palpation (Table 2.1). The combination of both of these factors resulted in a sensitivity of 88.4 % and a specificity of 81.1 % for diagnosing FM [16].

These criteria were widely accepted within the medical community. However, many primary care physicians (who diagnose the majority of FM cases) were either not performing tender point examinations at all or performing them inaccurately. Those that were not performing the tender point examinations were basing their diagnosis on somatic and cognitive symptoms, as well as symptoms of fatigue [17, 18]. In addition, a problem arose when trying to diagnose FM patients who had improved and were no longer tender at 11 out of 18 tender points since they did not meet the ACR criteria classification [19].

Not present within the ACR criteria was the mention of symptoms most commonly associated with FM. Examples of some of these symptoms include headache, fatigue, IBS, mood disorders, and cognitive dysfunction. These associated symptoms suggest that FM is actually a more complex and multidimensional syndrome that requires a more comprehensive definition than that included within the original ACR criteria [20].

In an attempt to improve some of the problems presented against the ACR criteria, Wolfe and colleagues performed a multicenter study that would lead to the development of a new definition for FM. This study reflected the severity spectrum of patients with FM without the need to implement a tender point examination. The study included 829 total patients and compared those with FM to those with no pain or other pain syndromes. They were each examined and interviewed. The interview included a measurement of the widespread pain index (WPI), which designates the number of painful body regions. Categorical scales were formulated which could be used to evaluate patients' cognitive symptoms, fatigue, somatic symptoms, and sleep. In addition, the authors used these scales to formulate a severity scale (SS). By combining both the WPI and SS, they were able to generate new criteria for FM (Table 2.1). Based on this new definition, 88.1 % of FM cases classified by the original ACR criteria were also included within the new definition. Furthermore, the SS allows for a description of symptom severity, which is extremely helpful in following FM patients with highly variable temporal symptomology [21].

Through this investigation, the ACR identified an alternative method of diagnosis of FM to the classic tender-point criteria, specifically integrating SS-based symptoms [21]. These new alternative diagnostic criteria published in 2010 rely on the WPI and SS as follows: (WPI ≥ 7 and SS ≥ 5) or (WPI 3–6 and SS ≥ 9). The WPI is scored 0–9 based on areas of pain present (Table 2.2). SS is the sum of the severity of three symptoms (fatigue, waking unrefreshed, cognitive symptoms) and the extent of somatic symptoms. The three major symptoms of fatigue, waking unrefreshed, and cognitive symptoms are graded 0 = no problem through 3 = severe: pervasive, continuous, and life-disturbing problems. The severity of somatic symptoms is graded 0 = no symptoms through 3 = a great deal of symptoms. The ACR includes a list of suggested somatic symptoms to consider for this portion of the evaluation [21] (Table 2.2). While this new alternative method to diagnosis is perhaps more lengthy than the previous method, it does not include a physical or tender point examination. In effect, these diagnostic criteria can be used to reliably identify patients with FM by health-care providers who do not plan and perform the tender point examination or who perform the tender point examination incorrectly.

Evaluation

As mentioned earlier, the common manifestations of FM include clusters of symptoms that may be confused with other disease processes. Evaluation for FM includes pain assessment by way of a proper history and physical examination, laboratory evaluation to rule out other causes of pain if indicated, and any other evaluations

Table 2.2 American College of Rheumatology fibromyalgia diagnostic criteria (2010 Alternate). From [21]. Table 4 Fibromyalgia diagnostic criteria. With permission from John Wiley and Sons

Criteria
A patient satisfies diagnostic criteria for fibromyalgia if the following three conditions are met:
1. Widespread pain index (WPI) > 7 and severity scale (SS) score > 5 or WPI 3–6 and SS scale score > 9
2. Symptoms have been present at a similar level for at least 3 months
3. The patient does not have a disorder that would otherwise explain the pain
Ascertainment
1. WPI: note the number areas in which the patient has had pain over the last week. In how many areas has the patient had pain? Score will be between 0 and 19
Shoulder girdle, left hip (buttock, trochanter), left jaw, left upper back
Shoulder girdle, right Hip (buttock, trochanter), right jaw, right lower back
Upper arm, left upper leg, left chest neck
Upper arm, right upper leg, right abdomen
Lower arm, left lower leg, left
Lower arm, right lower leg, right
2. SS scale score:
Fatigue
Waking unrefreshed
Cognitive symptoms
For each of the three symptoms above, indicate the level of severity over the past week using the following scale:
0 = no symptoms
1 = few symptoms
2 = a moderate number of symptoms
3 = a great deal of symptoms
The SS scale score is the sum of the severity of the three symptoms (fatigue, waking unrefreshed, cognitive symptoms) plus the extent (severity) of somatic symptoms in general. The final score is between 0 and 12.
Somatic symptoms that might be considered: muscle pain, irritable bowel syndrome, fatigue/tiredness, thinking of remembering problem, muscle weakness, headache, pain/cramps in the abdomen, numbness/tingling, dizziness, insomnia, depression, constipation, pain in the upper abdomen, nausea, nervousness, chest pain, blurred vision, fever, diarrhea, dry mouth, itching, wheezing, Raynaud's phenomenon, hives/welts, ringing in ears, vomiting, heartburn, oral ulcers, loss of/change in taste, seizures, dry eyes, shortness of breath, loss of appetite, rash, sun sensitivity, hearing difficulties, easy bruising, hair loss, frequent urination, painful urination, and bladder spasms

as needed, such as mood, sleep, or neurological evaluations. In order to facilitate diagnosis, and to reduce the time and cost involved in workup, certain common symptoms and findings can be sought. Common patient complaints that may indicate FM include "I feel as if I hurt all over" and "I feel as if I always have the flu" [22]. Other common symptoms and findings can include:

1. Chronic widespread pain for greater than or equal to 3 months
2. Excess tenderness in soft tissues

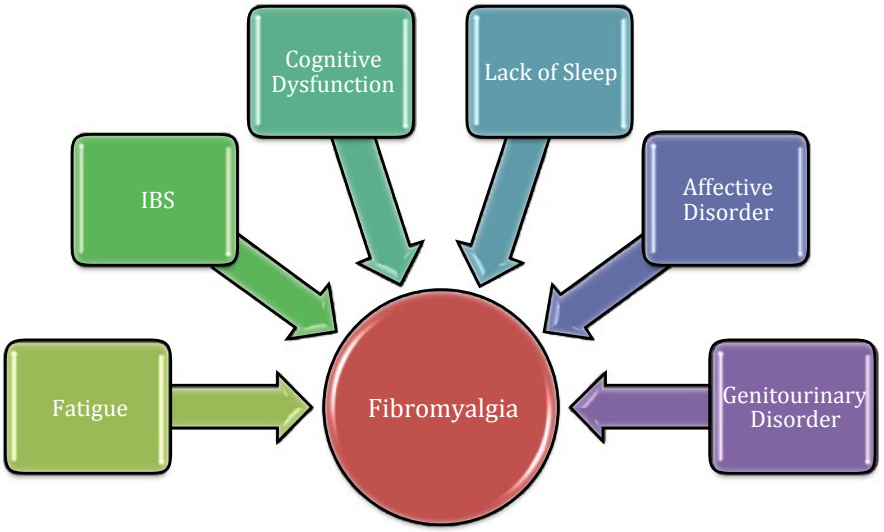

Fig. 2.1 Clinical features associated with fibromyalgia

3. Absence of other conditions that may explain the pain patient is experiencing
4. Other clinical features (Fig. 2.1) such as fatigue, insomnia, emotional distress, stiffness, cognitive dysfunction, IBS, interstitial cystitis, and ureteral syndrome [23].

Fatigue

One of the most common associated symptoms of FM is fatigue. Approximately 80% of patients with FM also fall under the criteria for chronic fatigue syndrome, which include: fatigue for greater or equal to 6 months, sore throat, joint pain, muscle pain, and unrefreshing sleep [24]. The fatigue is commonly worse upon waking, slowly improves over the morning, and becomes worse again in the afternoon. Patients complain of difficulty with sleep and frequent waking in the middle of the night. The fatigue experienced by patients is described as exhausting, both mentally and physically [25]. It may be difficult to identify FM as the cause for fatigue as many other causes may be present in these patients, including sleep disorders and medications such as tricyclic antidepressants and opioids.

Lack of Sleep

Most patients with FM complain of nonrestorative sleep (NRS). NRS leads to impairment in daytime functioning [26]. In these patients, it is harder to take small naps during the day than it is to fall asleep at night. Nonetheless, most of these

patients are energy-deprived and fatigued most of the day. Most patients wake up in the morning with increased fatigue and stiffness, feeling mentally drained and sleep deprived. It is very important to rule out a primary sleep disorder in these patients, such as restless leg syndrome [27] or obstructive sleep apnea.

Affective Disorder

Chronic pain may lead to an increased incidence of affective distress. FM is most commonly associated with anxiety and depression. Approximately 13–71 % of FM patients have associated anxiety. Depression may be seen in 20–80 % of FM patients [28–30]. These associated affective issues may contribute to increased severity of physical symptoms due to enhanced pain perception, decreased activity level, and impaired coping skills.

Patients with chronic pain syndromes are frequently assumed to be the victims of childhood trauma or sexual abuse. There are conflicting studies that both support and refute this idea. A prospective study performed by Raphael KG and colleagues disputed this theory by performing a prospective cohort study which examined patients that had been part of childhood abuse or neglect. Subjects were followed into their adulthood. No association was found between childhood abuse and chronic pain problems during adulthood [31]. However, a prospective observation study performed by Hart-Johnson and colleagues supported the fact that mental and physical abuse is strongly correlated with chronic pain related outcomes in males and females [32].

Stiffness

Patients diagnosed with FM often complain of morning stiffness. This can be very debilitating and may last from 45 min to 4 h. In 2005, a survey questionnaire consisting of 121 items was developed by the National Fibromyalgia Association (NFA) and was administered to 2569 FM patients. Morning stiffness was rated as the most troublesome symptom experienced, followed by fatigue and nonrestorative sleep [33].

Muscle elasticity is decreased with age. A study from McHugh and colleagues found that muscle stiffness may worsen muscle damage incurred during strenuous exercise [34]. It is generally well accepted that concentric muscle contraction and passive stretch can improve stiffness. Thus, increasing activity with limitation of strenuous exercises may improve stiffness in some patients.

Cognitive Dysfunction

Most patients with FM complain of short-term memory loss, difficulty with multitasking, and poor concentration. When compared to patients without FM of the

same age group, FM patients showed decreased working memory, free recall, and verbal fluency but they had the same processing speed for information. When compared to an older population without FM, the FM group had similar performance for working memory and free recall, poorer vocabulary, and faster processing speed. The cognitive delay seen in FM patients seems to be correlated with pain and not with the presence or degree of affective disorder [35].

Irritable Bowel Syndrome

About 30–50 % of patients with FM also have associated IBS. IBS is characterized by increased bowel movements and its severity may be correlated with patients' self-perception of their disease process. IBS in FM patients may be related to widespread central sensitization [36].

Genitourinary Disorders

Approximately 12 % of patients with FM meet the criteria for the diagnosis of female urethral syndrome. Female urethral syndrome is characterized by urinary frequency, urethral pain, suprapubic discomfort, and dysuria. In addition, 60 % of patients with FM complain of urinary urgency [37]. FM also appears to have significant clinical overlap with interstitial cystitis [38].

Related Syndromes

Patients with chronic pain conditions other than FM may eventually develop FM with time. These patients are said to have secondary FM. Primary and secondary FM may not be clinically distinguishable from one another [16]. Common rheumatologic and systemic diseases that present concomitantly with FM include Sjogren's syndrome (50 % of FM patients also present with SS), rheumatoid arthritis (30 % of patients with FM present with RA), and systemic lupus erythematosus (40 % of FM patients present with SLE) [39].

Fortunately, through diligent physical examination and laboratory workup, it is easy to distinguish secondary FM from these co-occurring diseases. For example, RA can present with small joint swelling in the distal upper and lower extremities, which is not present with FM. SLE can present with skin rash and other systemic symptoms that are not present in FM patients. Both of these conditions will also result in elevated erythrocyte sedimentation rate (ESR), which is usually normal in FM [40].

In addition to inflammatory conditions, some environmental factors have been shown to play a role in triggering FM. These factors may include trauma, catastrophic events, emotional incapacitation, and infections [41]. Some infections that have

been noted to trigger FM have been hepatitis C, HIV, Lyme disease, coxsackie B, and parvovirus [42]. It has been noted that in patients with comorbid FM and Lyme disease, symptoms of FM occurred after Lyme disease was contracted, and FM symptoms persisted after resolution of Lyme disease from an antibiotic therapy [43].

Laboratory Evaluation

Laboratory workup is useful when trying to rule out certain conditions that may be part of the differential diagnosis of FM. No specific laboratory finding is correlated with FM. The differential diagnosis includes but is not limited to systemic and inflammatory illnesses (RA, SS, SLE, ankylosing spondylitis, polymyalgia rheumatica, inflammatory myositis), infections (hepatitis C, HIV, Lyme disease, coxsackie B, and parvovirus), endocrine disorders (hypothyroidism, hyperparathyroidism, Cushing's syndrome), peripheral neuropathy, and myofascial pain syndrome associated with trigger points.

Due to the long list of possible diseases that may mimic FM, it is very easy to fall into the trap of ordering laboratory values carelessly. Initial laboratory evaluation should consist of a complete blood count (CBC) with an ESR. One may order a C-reactive protein (CRP) instead of an ESR depending on the disease process being investigated. Recall that FM is not an inflammatory disease and would not result in an elevated ESR and CRP. Furthermore, if an endocrine disorder is suspected, it is reasonable to order laboratory values related to the suspected disorder, such as thyroid function test for suspected hypothyroidism. Other laboratory tests such as antinuclear antibody and rheumatoid factor should be ordered on a case-by-case basis when there is high clinical suspicion for an inflammatory rheumatic disease. These tests have a high rate of being falsely positive in healthy individuals and have poor predictive value when clinical suspicion is low [40].

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Chapter 3
Etiology

Omar I. Halawa and David A. Edwards

Key Points

1. Central sensitization is the leading explanation for generalized pain in fibromyalgia syndrome (FMS).
2. Monoamine (serotonin and norepinephrine) neurotransmission is disrupted in FMS patients, which may explain the increased sensitivity to pain, the association with mood disorders, and the benefit seen by treating patients with tricyclic antidepressants (TCA), selective serotonin reuptake inhibitor (SSRI), and serotonin-norepinephrine reuptake inhibitors (SNRI) medications.
3. FMS is found in higher frequency among relatives with FMS, and genetic biomarkers involved in monoamine modulation cluster among the related individuals.
4. Chronic oxidative stress may be a risk factor for neural damage leading to FMS.
5. Physical trauma can be an instigating factor that sensitizes the central nervous system (CNS) and leads to chronic pain syndromes like FMS.
6. FMS is more frequent among individuals who suffer from depression, anxiety, or have experienced emotional trauma; each of these may be a causative factor, an antecedent factor that defines at-risk individuals, or a factor that contributes to the severity of FMS symptoms.

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Introduction

Fibromyalgia syndrome (FMS) is a multifactorial disease initially defined by the American College of Rheumatology (ACR) as a chronic disorder characterized by the presence of widespread pain and accompanied by tenderness upon palpation of at least 11 out of 18 predefined tender points throughout the musculoskeletal system [1]. A modern and more inclusive preliminary diagnostic model classifies patients with FMS as those with widespread pain and severe symptoms for at least 3 months in the absence of another disorder that would otherwise explain the pain [2]. Progression of the diagnostic criteria over the past few years has coincided with our understanding of the etiology of FMS as well as inclusion of commonly associated symptoms such as fatigue, sleep disturbance, and cognitive dysfunction.

Patients diagnosed with FMS universally have widespread pain but otherwise may express a heterogeneous complex of symptoms and comorbid conditions. There may be subgroups of differing tenderness, psychological involvement, and genetic propensity [3]. A significant number of patients with FMS also have functional somatic syndromes such as chronic fatigue syndrome [4]. A leading hypothesis to explain the diversity of symptoms and sensitivity is the concept of central sensitivity, whereby the CNS maintains a lower threshold for pain [5]. Not all patients with FMS have all of these symptoms or comorbidities; however, a significant proportion share enough that a more clear etiology is beginning to emerge.

In overview, there are several possible etiologies of FMS under investigation. Quantitative tests of pain hypersensitivity suggest that FMS may be a disease of altered neuronal signaling. The search for biomarkers of FMS has focused on levels of neurotransmitters that mediate pain signaling. Sleep and mood disturbances may be causative factors of FMS, rather than the result of it. The incidence of FMS in different populations and between men and women differs, raising the possibility of genetic or environmental susceptibility. Finally, we will review the finding that FMS is more common in individuals who have experienced certain types of psychological or physical trauma.

Pathophysiology

Background

Fibromyalgia is, by derivation of the word, a pain syndrome of muscle and its connective tissues. Yet, there is no evidence of decreased mechanical strength or physiological function of the muscle per se [6, 7]. It has been suggested that the pain is not derived from the muscle itself, but rather that there is a lasting change in the gain of sensory pathways from muscle. This is the rationale behind the original diagnostic criteria for FMS, specifically that there are several regions of the body where tender points can be found. However, tenderness by itself is not specific enough to

exclude the many acute pain scenarios and inflammatory states. What makes FMS different is that it is a *chronic* pain state, which means that it is pathological, or maladaptive. In the history of the FMS patient, there may have been an inciting event such as a traumatic accident or an environmental trigger that, for as yet unclear reasons, set in motion changes that outlived the normal period of recovery. There may be many susceptibility factors that determine why one person develops a chronic pain syndrome like FMS and others do not.

Mechanisms of Pain Sensation

Pain can be divided into multiple categories: acute or chronic, central or peripheral, adaptive or maladaptive [1]. Acute pain is adaptive, or in other words, the sensation of pain serves as a protective signal to the individual to prevent further injury while the healing process occurs. The normal process of nociception begins when noxious stimuli (mechanical, thermal, chemical) are detected peripherally by the terminals of first-order neurons that have their cell bodies within the dorsal root ganglia [8]. These neurons are medium-sized A-δ fibers, which are myelinated and transmit fast and well-localized pain, and small unmyelinated C-fibers transmit delayed and poorly localized pain. Peripheral nociceptive signals are converted into electrical signals and then conducted along the neuronal axon by sodium-channel-mediated action potentials to the CNS in the dorsal horn of the spinal cord. Both A-δ and C-fibers terminate in laminae I–II of the dorsal horn [9]. With arrival of the signal at the central synapse of the dorsal horn, nerve terminals are depolarized and neurotransmitters are released. C-fibers release substance P, calcitonin gene-related peptide (CGRP), neuropeptide Y, and glutamate. With prolonged and repetitive nociception, *N*-methyl-D-aspartate (NMDA) channels are activated and an influx of sodium and calcium into the nerve terminal signals downstream cascades that result in modification of the synapse.

The nociceptive signal is transmitted through the spinal cord by second-order neurons from laminae I and V, along the anterolateral tract and the spinobulbar tracts, to the periaqueductal gray and the parabrachial region of the pons. Third-order neurons carry discriminatory pain sense from the thalamus to the somatosensory cortex and affective sense to the limbic and frontal brain. Aversive response to pain is mediated by projections from the parabrachial pons to the amygdala.

The higher brain centers can modulate nociception by way of descending pathways. C-fiber signals can be inhibited in lamina I and V of the dorsal horn in the spinal cord, through descending pathways from the cortex, hypothalamus, and amygdala. Descending inhibition is mediated by the neurotransmitters serotonin and norepinephrine, and also by the endogenous opioids enkephalin, dynorphin, and endorphin [10, 11].

Chronic Pain and Central Sensitization

Chronic pain is the persistence of pain beyond the normal healing process, and so it is no longer adaptive, it no longer serves a protective purpose. Chronic pain is a pathological sensation of pain, meaning that pain may be perceived in the higher centers of the CNS in the absence of peripheral nociceptive input, or that the threshold for transduction, conduction, and transmission of pain has been lowered chronically so that light touch is painful (allodynia) and lesser pain becomes more severe (hyperalgesia). The process of plastic change in the CNS that establishes a perpetual pain hypersensitivity state is called *central sensitization* [12].

The process that results in central sensitization begins in the periphery. When pain persists or tissue damage occurs, proalgesic and proinflammatory mediators are released from the destroyed tissue. Basal cells, mast cells, and macrophages also release an *inflammatory soup* of cytokines, chemokines, neurotrophins, peptides (substance P, CGRP), and eicosanoids. The inflammatory soup enhances synaptic signaling and lowers the threshold for painful stimuli [12]. This state is called primary hyperalgesia.

In secondary hyperalgesia, pain spreads beyond the initial site of injury or inflammation. The only way pain can spread from one site to a distant site is by way of common pathways in the CNS. The synaptic changes that underlie secondary hyperalgesia and central sensitization are mediated by ion channel phosphorylation and changes in transcription and translation within A-fibers and C-fibers [5]. Constant and prolonged activation results in degeneration of C-fiber terminals in lamina II [13]. A-β fibers, which normally sense touch and position, grow into lamina II. Now touch and position sense activate the same second-order neurons that lead to areas of the brain that perceive pain [14] (Fig. 3.1).

Fibromyalgia is a maladaptive chronic pain process that may have many similarities to other central sensitivity syndromes like chronic fatigue syndrome, posttraumatic stress disorder (PTSD), and irritable bowel syndrome. Similar to other chronic pain states, FMS cannot be explained by active, ongoing, peripheral injury or inflammation, although it may have started that way. As with central sensitization due to injury or chronic inflammation, nociception is enhanced in FMS due to facilitated neuronal signaling. Quantitative neurophysiological tests show FMS patients to be hyperalgesic to electrical stimulation, and their receptive fields for pain sensation are enlarged [15]. Whiplash and fibromyalgia patients show facilitated withdrawal to nociception, a measure of spinal cord hypersensitivity [16]. In functional magnetic resonance imaging (MRI) studies of regional blood flow in response to nail bed-induced pain, FMS patients showed 13 regions of greater activation compared to matched controls, supporting facilitated pain processing in FMS patients [17]. In another test of central sensitivity, temporal summation, or windup, is exaggerated in FMS [18–21].

The underlying changes in the chemical milieu that sustain central sensitization can be found in FMS patients as well. The most consistently affected in FMS are levels of serotonin (5-HT) and substance P [22] (Table 3.1). Serotonin has a role in

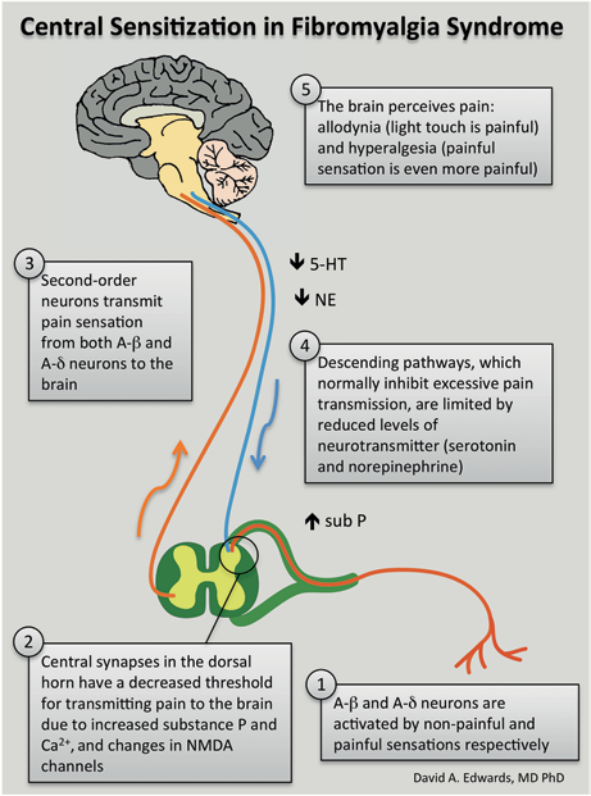

Fig. 3.1 Altered neural transmission of pain sensation in fibromyalgia

Table 3.1 Gene polymorphisms associated with fibromyalgia [77]

Gene	Gene name	Function
5-HTTPLR	Serotonin transporter promoter	Codes for a monoamine transporter protein that clears 5-HT from the synaptic cleft into the synaptic bouton where it can be recycled. The target of SSRI's and SNRI's
5-HT2A	Serotonin 2A receptor	Codes for an excitatory receptor protein activated by serotonin that modulates mood and sleep
COMT	Catechol-O-methyltransferase	Codes for an enzyme that metabolizes catecholamine neurotransmitters (dopamine, epinephrine, and norepinephrine)

COMT catechol-O-methyltransferase, *SSRI* selective serotonin reuptake inhibitor, *5-HTTPLR* serotonin-transporter-linked polymorphic region, *SNRI* serotonin and norepinephrine reuptake inhibitors

modulation of pain signals via descending pathways to the spinal cord, regulation in sleep–wake cycles [23], and regulation of the hypothalamic–pituitary–adrenal (HPA) axis that contributes to fatigue [24]. Levels of 5-HT metabolites (5-HIAA) and norepinephrine metabolites (3-methoxy-4-hydroxyphenethylene) are decreased in the cerebral spinal fluid of FMS patients [25]. Several studies have shown that the phenomenon of diffuse noxious inhibitory control (DNIC), where brief intense pain results in short-lasting whole-body analgesia, is attenuated in FMS and other chronic pain conditions such as irritable bowel syndrome [26, 27]. In FMS, particularly, DNIC is attenuated by modification of the descending monoamine (noradrenergic and serotonergic) pathways.

Summary

FMS has many pathophysiological features consistent with chronic pain conditions. Treatment strategies that target etiological features of neuropathic pain have also been shown to be effective in treating FMS and the central sensitization syndromes. Medications that increase serotonin and norepinephrine levels, including the tricyclic antidepressants (amitriptyline and nortriptyline), the serotonin-norepinephrine reuptake inhibitors (duloxetine, milnacipran and tramadol), are the primary pharmacological tools used for treatment of FMS.

Genetic Susceptibility

Background

When studying FMS on a population scale, a familial association is evident and is supportive of the existence of fibromyalgia as disease. The increased likelihood among related persons could be due to inherited genetic factors, or similar psychosocial environments, or both. In early studies, FMS was found to be more prevalent among offspring of mothers with FMS compared to control families [28]. Sixteen offspring out of 58 (35 males and 23 females) were found to have FMS with a male-to-female ratio of 0.8 among affected individuals. Among the offspring, there was no difference in anxiety, depression, well being, quality of life, and physical function between those with or without FMS. Several follow-up studies have substantiated this familial component [3]. Furthermore, FMS co-aggregates with pain sensitivity [29] and co-aggregates with major mood disorders [30], both of which strongly aggregate in families.

The strong evidence of familial aggregation of FMS individuals has prompted a search for underlying genetic loci. At this time, there is no single gene found in all FMS patients, and no monogenetic inheritance pattern. FMS is likely a polygenetic disorder with a multifactorial mode of transmission.

Specific Genes

The most common genetic polymorphisms found in FMS patients are involved in monoamine (serotonergic, dopaminergic, and noradrenergic) neurotransmission (Table 3.1). This is consistent with the pathophysiological mechanisms associated with the development of central sensitization and also with the co-aggregation of FMS and major mood disorders, both of which involve dysregulation of these neurotransmitters [31].

Besides its role in modulation of pain, serotonin is integral to the regulation of sleep, mood, appetite, hormone secretion, and sexual behavior and is implicated in many mood and behavioral disorders including depression, anxiety, and autism [32]. Two major polymorphisms occur in the promoter region of the serotonin transporter gene (5-HTTLPR), yielding a short (S) and long (L) transcript. The S allele is more prevalent in the FMS population, and many FMS patients have lower levels of serotonin in both serum and the CNS and higher mean levels of depression and psychological distress [33−35]. Two common polymorphisms (T102C) exist for the serotonin 5-HT2A receptor gene. In FMS patients, T/C and C/C receptor genotypes are increased and T/T receptor genotypes are decreased compared to the control population [36].

The primary enzyme involved in metabolism of catecholamines such as dopamine and norepinephrine is catechol-O-methyltransferase (COMT). There are three polymorphisms of the *COMT* gene: LL, LH, and HH types. The combination of LH and LL genotypes were more prevalent in FMS patients and the HH genotype was less prevalent [37]. Some FMS patients have lower levels of norepinephrine metabolite in their CSF compared with normal controls [38]. It is assumed from this that FMS patients have weaker descending pain inhibitory systems (that require norepinephrine) resulting in unchecked ascending pain signals.

Haplotype analysis of *COMT* gene polymorphisms has been used to identify three subsets of patients with variations in pain sensitivity. These have been designated low pain sensitivity (LPS), average pain sensitivity (APS), and high pain sensitivity (HPS). Among FMS patients, those with HPS and APS haplotypes show higher sensitivity to thermal and pressure pain tests [39]. Moreover, higher genetic variability in the *COMT* gene is associated with low COMT enzyme activity and this condition is found more frequently in FMS patients [39].

Dopamine is another neurotransmitter involved in the CNS and its role in psychiatric disease is established. In FMS, dopamine's role is unclear. There may be an increased sensitivity or density of D2 dopamine receptors in FMS patients [40]. There is a decreased frequency of the dopamine D4 gene in FMS patients [41].

Summary

Polymorphisms in serotonergic, dopaminergic, and noradrenergic-associated genetic loci are found in increased frequency among FMS patients especially in patients

with concurrent psychiatric comorbidities. What role they may play in patients with FMS who are free of mood disorders has yet to be shown.

Environmental Risks Factors

Background

The familial inheritance patterns and genetic associations with FMS have been used to cluster subsets of patients, but not every patient with FMS can be categorized by this method alone. Given the strong association that FMS has with mood disorders, it is clear that a patient's life experiences are important in determining their risk. Physical experience and exposures may also contribute and either increase or decrease the risk of FMS, just as the risk of chronic pain depends upon some nongenetic factors like physical disease, inflammation, and tissue damage.

Free Radicals

Local tissue hypoxia may be a contributing factor to the development of FMS [42, 43]. Free radicals in the body are produced through redox reactions; they exist as reactive oxygen species (ROS) or reactive nitrogen species (RNS) with unpaired electrons making them highly reactive molecules in the body. Antioxidant systems exist in the body to remove ROS and reduce cellular and tissue damage caused by free radicals. Enzymatic antioxidants include superoxide dismutase, glutathione peroxidase, and catalase. The nonenzymatic antioxidants include ascorbic acid (vitamin C), nitrite, and alpha tocopherol (vitamin E). The human body maintains a balanced ratio of ROS to antioxidants within cells [44]. When this ratio tilts towards free radicals, this causes protein damage, lipid peroxidation, and DNA damage [43, 44].

The role of free radicals in FMS remains controversial. It is postulated that tissue damage by ROS can lead to the development of various neurobiological disorders including rheumatoid arthritis, ankylosing spondylitis, Alzheimer's, depression, chronic fatigue syndrome, and FMS [45−48]. Malondialdehyde (MDA) is the product of lipid peroxidation and is used as a marker of free radical damage and neurodegenerative disease. Levels of MDA in FMS patients have been reported to be elevated [44, 49] or unchanged [43]. Bagis et al. compared females with FMS to controls and found a higher ratio of oxidants to antioxidants, higher MDA levels, and lower superoxide dismutase [43]. The protective enzymatic antioxidants, catalase and glutathione peroxidase, are lower in FMS pateints [50]. There seems to be an overall decreased antioxidant capacity in FMS patients [51] and significant overlap with chronic fatigue syndrome in this respect [4, 52].

Summary

Evidence for treatment of fibromyalgia using antioxidants is preliminary. Increasing antioxidants by eating fresh fruit and vegetables or ingesting supplements could be part of the therapy for FMS or used as a preventative measure. However, supporting outcome studies for antioxidant treatment in FMS do not exist [53].

Physical Trauma As an Inciting Event

Background

Physical insults have been reported in the literature as inciting events for many rheumatologic and musculoskeletal conditions, including osteoarthritis [54]. Between 25 and 50% of FMS patients report a triggering event (mostly physical) immediately prior to the onset of their symptoms [55, 56]. Determining the causal relationship between physical trauma and FMS is complicated but makes sense in light of recent understanding of the development of neuropathic pain and central sensitivity following tissue injury as summarized above.

Whiplash

Perhaps the most common example of physical trauma studied in relation to FMS is whiplash. The biomechanical disruption of the cervical spine has been studied extensively in trauma. One group showed that 2 years after cervical trauma resulting in whiplash, 18% of patients developed persistent fatigue, headaches, anxiety, and light and noise sensitivity [57]. The similar symptom pattern found in FMS led Buskila et al. to study the incidence of FMS after neck injury and compare them to control patients who had experienced lower extremity trauma. Their study showed that FMS was 13 times more likely in adults with traumatic neck injury compared to control patients [58]. The authors hypothesized that traumatic neck injury may cause a localized regional pain syndrome that then develops into a widespread pain syndrome like FMS. Tishler et al. were unable to repeat this finding. They compared 153 patients presenting to the emergency room with whiplash injury to 53 control patients with fractures of the limbs, spine, or ribs. Patients were followed prospectively and only one patient in the study group and no patients in the control group developed FMS as defined by the older criteria of tender point counts [59].

Summary

Whiplash as a representative example of traumatic etiology of FMS is a mixed bag. The literature is inconsistent, partially due to the change in diagnostic criteria for FMS. In addition, a patient's recall and the frequency of litigation in this population, bias retrospective observation, and making a causal connection difficult.

Although it is unclear why some individuals suffering physical trauma develop conditions like FMS, determining the contributing factors would be important for targeted therapy in at-risk individuals. For example, windup in the CNS and the development of chronic pain following tissue injury could also lead to generalized sensitivity. In genetically predisposed individuals that have suffered trauma, early pharmacologic intervention that prevents the progression of acute pain to chronic pain syndromes may be beneficial [21].

Sleep and Mood Disorders As Causative Factors

Background

The strongest associations with FMS are the presence of headache, chronic fatigue, nonrestorative sleep, and mood disorders with the main feature being chronic pain. When patients present, they often have a complex of these comorbidities and, as a result, it can be difficult to tell which is antecedent and which is a consequence. Pain can certainly wake a patient and chronically disrupt the homeostatic and restorative properties of sleep, and sleep impairment lowers the threshold for pain [23, 60]. Rates of depressive symptoms are higher in patients as a consequence of chronic pain, but also a predisposition to depression may impact the development of FMS [61]. Moreover, there is a complex interaction between sleep characteristics in FMS patients and the impact of pain on comorbid anxiety and depression [62, 63].

Sleep Disorders

Sleep may be impaired in up to 75% of patients with FMS [63]. When sleep is chronically disturbed, individuals develop muscle pain [23]. Non-restorative sleep is one of the strongest predictors of new-onset widespread pain in older adults [64]. In FMS patients, the disruption of deep sleep (stage 4 non-REM) results in pain and fatigue symptoms [65], is associated with an increased number of tender points and musculoskeletal symptoms [62], and magnifies pain-related outcomes such as anxiety and depression [66]. The inhibitory modulation of pain signaling is impaired in sleep-disturbed FMS patients [60]. In addition, sleep disturbances in FMS diminish the ability of patients to recover from the psychosocial stressors as a result of pain

[66]. In summary, poor sleep is not only the result of chronic pain in FMS but also a causative and exacerbating factor. Treatment strategies should include methods to improve the quality of sleep in FMS patients.

Mood Disorders

There is a strong statistical association of depression and chronic pain [61]. The longer a patient experiences pain, the more likely they are to also be depressed [67, 68]. There is also a strong relationship between the severity of perceived pain and the degree of depression; [61] the more severely depressed a patient is, the greater they rate their pain. The number of pains a patient complains of and the frequency of pain are also associated with the severity of depression [61]. In all of these scenarios, pain is the antecedent event that leads to depressed mood. On the other hand, there is some evidence that when depression is the antecedent dysfunction, it can be the causative factor in the development of pain, but studies supporting this hypothesis are outnumbered by those that do not [61].

Fishbain et al. reviewed several studies that investigated the antecedent role of depression in respect to the onset of chronic pain [61]. In the cognitive mediation hypothesis, a patient's psychological perceptions such as life interference and decreased self-control may mediate the development of depression and pain. The mediators could occur before the onset of pain, and similar psychogenetic pathways put a patient at risk of developing both depression and pain [69]. In the scar hypothesis, episodes of depression before the onset of pain predispose a patient to depression with the onset of pain. These hypotheses are consistent with a genetic predisposition to depression and FMS. Still, the data are not there to support a *causative* role of mood disorders in the development of pain syndromes despite the fact that pain is definitely perceived to be higher when coincident with a mood disorder. Even less is known about antecedent mood disorders as causative factors in FMS.

Patients with FMS have higher current (36–48 %) and lifetime (75–88 %) prevalence of psychological comorbidities [70] and familial studies show FMS aggregates in families with anxiety and mood disorders [30]. Psychiatric disorders heighten the impact of psychological distress and worsen functional outcomes in FMS patients [70]. Many studies have shown that in FMS patients, tender point counts and pain thresholds are influenced by anxiety, depression, and self-reported pain [60, 71]. There is obviously a complex interplay between mood disorders and FMS, as there is with pain generally. There are some early studies of childhood emotional experiences and mood disorders that may put them at risk for FMS later in life [72].

Psychological Trauma

After psychological trauma, many patients develop symptoms similar to those seen in major depressive disorder, chronic fatigue syndrome, irritable bowel syndrome,

and FMS [73]. There is considerable overlap with the symptomatology of PTSD as well. How people respond to psychological stress (the peritraumatic cognitive response) can determine the risk of PTSD and the development of FMS-like symptoms [74, 75]. When comparing patients with FMS to those without, more report a history of psychological stress consistent with the diagnosis of PTSD [76]. Early life adversity and emotional trauma are risk factors for the development of chronic pain and FMS later in life [72]. Here, it is postulated that early adversity alters neuroendocrine function and leads to impaired adult pain processing.

Summary

FMS is defined by the major symptoms of diffuse chronic pain, poor sleep, and high coincidence with mood disorders. Disturbance of monoamine neurotransmission may be the common underlying physiological mechanism. Disruption of this neurotransmitter system could lead to concurrent development of mood disorders and pain, and so it may be impossible to show that one is causative of the other. What we do know now is that FMS, mood disorders, and poor sleep occur frequently together and that a successful treatment strategy will probably include therapy for each of these.

Conclusions

It is more common now to diagnose someone with FMS as a result of broader diagnostic criteria and recognition of the symptoms that are associated with it. Among the large population now diagnosed with FMS, several associations have been found in the search for causative factors. FMS is clearly familial and there are many genetic polymorphisms that are more common in this group. The monoamines, serotonin, and norepinephrine, are decreased in the cerebral spinal fluid of FMS patients, so not surprisingly, the polymorphisms are genes involved in monoamine neurotransmitter mobilization and metabolism. Monoamine neurotransmission mediates descending inhibitory control of ascending pain signals so dysfunction results in a lower threshold for pain, a feature of the central sensitivity syndromes, and a feature seen in FMS patients as well. Dysfunction of monoamine neurotransmission also leads to mood disorders including depression and anxiety that are common in FMS patients. The best medical treatments at this time are the SNRI or TCA class of antidepressants that increase the level of serotonin and norepinephrine and thereby elevate mood, but also decrease pain.

Not all FMS patients present with all the common features of depression, anxiety, and poor sleep along with the presence of multiple tender points. There is no laboratory or genetic test, and no quantitative sensory exam that can definitively include or exclude a patient with FMS. However, given what we know so far, it may

Table 3.2 Points to consider when taking a history of a patient with possible FMS, based upon current possible etiological factors

Pain
The duration of chronic pain with details about its onset (gradual, sudden, traumatic)
History of prolonged low-grade or high-grade pain episodes that may contribute to a central sensitivity syndrome (i.e., prolonged painful menses in teenagers, chronic headaches, irritable bowel, prior surgery)
Mood
History of a mood disorder (depression, anxiety, childhood or adult emotional trauma)
Sleep
History of chronic fatigue and/or poor sleep
Family history
Family history of FMS, chronic pain, and/or mood disorders
Environmental exposures
Diet (intake of foods high in antioxidants)

FMS Fibromyalgia syndrome

be helpful in forming a more complete and patient-focused diagnosis of FMS by including in the patient's history details about possible etiological factors (Table 3.2). Alleviation and recovery from FMS is more effective when considering and treating associated symptoms as well. As a patient with FMS learns about their disease, they can more effectively take the needed steps to improve their function. Likewise, the scientific field is beginning to understand the complex interplay of susceptibility and triggering factors that cause fibromyalgia which will further define the diagnosis and, no doubt, lead to better treatment.

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Chapter 4
Prognosis

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Key Points

- Fibromyalgia (FMS) is idiopathic, but the array of disease features is suggestive of a polygenic origin. This is further supported by the improved outcomes in patients treated with multimodal therapies. Efficacies of centrally acting medications suggest that the neurological dysfunction is central rather than peripheral.
- It is nonfatal and non-deforming. The prognosis reflects overall disease burden.
- Classification of patients based on symptom severity can more accurately predict prognosis and optimize therapeutic strategy.
- Multimodal therapeutic strategies incorporating a combination of medication, physical therapies, and cognitive-behavioral therapies are most effective at improving symptoms and maintaining a durable response.
- Prognostic factors include age of onset, symptom severity, degree of interpersonal distress, overall functional capacity, form of coping mechanisms, comorbid psychiatric disorders, and comorbid substance abuse/dependence.
- Current Food and Drug Administration (FDA)-approved medications include duloxetine, milnacipran, and pregabalin. Gabapentinoids in particular demonstrate a durable improvement in symptoms, with pregabalin being superior to gabapentin. These agents are selected based on the clinical presentation by considering a patient's predominating symptoms, comorbidities, and medication tolerance.

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- In particular, nonsteroidal anti-inflammatory drugs (NSAID's), corticosteroids, and opioids have no role in the treatment of FMS. In fact, the hypothesized centrally mediated pain may be exacerbated by mechanisms such as opioid-induced hyperalgesia.
- Investigation of the efficacy of other medications is ongoing. Certain medications show promise, but to date no changes have been made to the list of FDA-approved medications used to treat FMS.
- No particular physical therapy is advantageous over another. However, exercise should be aerobic, low impact, and regular. Group therapy is beneficial in some patients.
- Cognitive-behavioral therapy (CBT) should focus on identifying life stressors, developing adaptive coping mechanisms, and reassurance that the disease is not known to be progressive, deforming, or fatal.
- Complementary and alternative medicine approaches may be beneficial to some patients who seek them, and are unlikely to have any negative impact. Currently, no strong supportive evidence of their efficacy as individual therapies exists.
- Symptoms are largely qualitative. Attempts to quantify symptoms using various scales and indices are subject to variability. This inherent truth complicates the interpretation of data regarding prognosis, as it may not only vary between patients but also between clinicians, specialists, and health-care settings.

Overview

Fibromyalgia (FMS) is a noninflammatory chronic pain syndrome that burdens a significant portion of the population. It is, in some cases, disabling [1]. The largely subjective symptoms in FMS have been historically difficult to quantify, limiting the understanding of pathogenesis, evaluation of treatment efficacy, and overall prognosis. The symptoms of FMS are dominated by widespread pain and tenderness as well as fatigue, cognitive impairment, disrupted sleep, reduced physical activity, and disability. New understanding of chronic pain states and central nervous system (CNS) plasticity support the theory of neuropathic pain as etiopathogensis for FMS. Also evolving are objective evaluations and new potential therapeutic targets with potential for patients suffering from FMS. However, FMS is a polygenic disorder often presenting with comorbid psychiatric, neurologic, and rheumatologic conditions making treatment challenging. Improved patient outcomes are associated with a multidisciplinary approach that combines both pharmacologic and non-pharmacologic therapies (physical therapy, behavioral therapy, lifestyle modifications).

The symptoms of FMS may self perpetuate one another with no particular causal order. Patients often present with significant distressing symptoms such as depression and anxiety, non-restorative sleep, fatigue, stiffness, and deconditioning pain. Diagnosis and evaluation of FMS relies on careful history taking and thorough exclusion of other possibilities. Many of the subjective complaints gathered on history taking from FMS patients have been compiled into questionnaires and

grading scales that quantify disease burden and increase the sensitivity of physician diagnostic skills. These quantified analyses have been used to assess response to therapy during follow up, and potentially provide insight to a patient's prognosis. Stratification of patients based on disease severity may be predictive of their prognosis [2, 3]. The efficacies of existing therapies have been evaluated over different periods of time, both individually and combined. Recent evidence has not revealed a change in the traditionally poor prognosis overall; however, newer objectified evaluations and targeted therapies in combination may offer both a more durable beneficial response for patients and more precise clinical assessment tools for clinicians on initial and follow-up visits. Prognosis is variable in these patients ranging from complete remission to persistent widespread pain refractory to intervention.

It has long been debated whether FMS is a peripheral pathology resulting from either soft tissue inflammation or neuropathic pain signaling in peripheral nerves, or if the symptoms are due to CNS dysregulation. Studies evaluating the efficacy of different medications to treat FMS, acting both centrally and peripherally, support both possibilities.

Epidemiology

FMS is more prevalent in females than in males, though an increased incidence in males has been reported using newer modified diagnostic criteria [4]. FMS has been documented in most ethnic groups and countries across all climates, with no evidence to support greater incidence in industrialized nations [5]. FMS is as prevalent as 2–8 % in the population [6], with an estimated five million cases among adults in the USA [7].

FMS can affect all age groups, though it more commonly presents in adults. Of the patients, 10–30 % with rheumatic diseases associated with chronic pain (i.e., rheumatoid arthritis—RA, osteoarthritis—OA, systemic lupus erythematosus—SLE) also meet diagnostic criteria for FMS [8]. Up to 25 % of patients that carry a diagnosis of FMS are completely disabled. Albeit uncommonly, FMS has been documented in children in a disorder termed juvenile-onset fibromyalgia (JFM) associated with a poor prognosis. Genetic predisposition may explain the increased incidence in first-degree relatives of affected persons with FMS [9], with potential abnormalities in genes affecting the neurotransmission involved in the development of pain sensitization and inflammation. It is known that FMS symptoms are potentially triggered or exacerbated by physical or psychological stresses.

Pathophysiology

The pathogenesis of FMS has been debated historically, with toggling theories supporting both central and peripheral origins. It was postulated that the multiple widespread tender points throughout the body in FMS resulted from peripheral soft

tissue pathology, in a disorder originally termed "fibrositis" [10]. In the absence of pathological tissue samples, proposed underlying psychiatric causes such as hysteria, conversion, or malingering were further invalidated in 1975 when the electroencephalogram challenged this idea of "psychogenic rheumatism." Non-rapid eye movement (NREM) 4 and 3 intrusions by alpha rhythms may explain the non-restorative sleep patterns and fatigue reported by patients [11]. Today, FMS is understood to be a centralized pain state characterized by a broader range of symptoms in addition to widespread pain. The theory of central sensitization to noxious stimuli has gained support in recent years and is likely to underlie the development of pain in patients with FMS [12, 13]. Contrary to the previous notion of peripherally generated pain in FMS [14], anti-inflammatory medications have demonstrated less efficacy compared to centrally acting medications in this patient population. As occurs in many types of neuropathic pain, central sensitization is likely a phenomenon that occurs as a function of *long-term potentiation*. Advancing knowledge of the underlying cellular signaling cascades renders specific molecular targets for pharmaceutical therapy. Endogenous ligand binding to *N*-Methyl-D-aspartic acid (NMDA) and adjacent α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors is thought to upregulate their concentration on postsynaptic nociceptive neurons of the dorsal horn. This neuronal plasticity may, in turn, disrupt descending inhibitory pain pathways resulting in stimulus amplification.

The increased concentration of both AMPA and NMDA receptors effectively reduces the amount of stimulus required to depolarize the nociceptive neuron in a feed-forward mechanism, with repetitive stimuli fueling this pathway resulting in heightened nociception following a smaller stimulus. Hyperalgesia may result from an increase in the duration of the native response to a stimulus, while further progression to allodynia may occur with the CNS neuron sensitization, manifesting as pain to a nonpainful stimulus [15]. Furthermore, the patient's subjective perception of nociception may be augmented by dysregulation of neurotransmitters such as substance P, resulting in the discernment of pain as widespread.

The theory of central dysregulation in FMS does not altogether preclude the presence of peripheral tissue damage. Although nonspecific, tissue deconditioning is certainly present in FMS patients, and is potentially the result of previously unidentified peripheral tissue pathology, limited physical activity, or neurotransmitter and hormonal imbalance. Reduced levels of somatomedin C in FMS patients reduce the anabolic effects of growth hormone on tissues and may prolong soreness and recovery after physical exertion. Lower levels of somatomedin C and growth hormone may also result from reduced NREM 4 and lack of exercise, creating a progressive cycle of tissue deconditioning and potentiation of FMS symptoms. Support for peripheral generators underlying FMS had reemerged in recent studies reporting objective evidence of small-fiber pathology and small-fiber polyneuropathy in some patients with FMS, but the implication of this phenomenon on prognosis remains unclear and has not resulted in dramatic changes in management [16].

Prognostic Factors

The prognosis of FMS varies and may correlate with certain behaviors and psychological features of patients. FMS is a chronic condition with relapsing symptoms often punctuated by periods of remission. "Catastrophizing" correlates to a heightened sense of awareness of pain and worsening of symptoms, with functional magnetic resonance imaging (fMRI) evidence of increased brain activity in response to painful stimuli [17]. In general, better prognostic signs in patients are increased sense of control over pain, belief that one is not disabled, and belief that pain is not a sign of damage. Behaviors including seeking help from others, decreased guarding during examination, more exercise, and pacing activities are associated with better outcomes. It is known that patients treated by primary care physicians in the community setting have better outcomes long term than patients who receive their care in tertiary centers. Academic medical centers have reported an average of 10 outpatient visits annually and an average of one hospitalization every 3 years. Many patients suffer from persistent symptoms despite various interventions. However, less than half of those diagnosed with FMS are disabled from working.

The negative impact of FMS symptoms on quality of life can promote the development of other syndromes that impact patient's overall prognosis. Chronic pain and dysregulated restorative sleep can result in fatigue, which may contribute to reduced physical activity, increasing the risk of developing metabolic syndrome, weight gain, and osteoarthritis. Symptoms can often be controlled or even improved, but complete remission may not necessarily be achieved in all patients. One group of 1555 patients with FMS followed for 11 years had generally persistent high levels of symptoms and distress with only 25% of patients reporting even moderate improvement in pain over time [18]. Efficacy of treatment is limited without reduction of ongoing life stressors, both physical and psychological. Commonly, FMS patients believe that stopping work will improve their symptoms. Contrary to their belief, going on disability is associated with a worse prognosis [2, 3] and leads to further reduction in physical activity. The incidence of disability is higher in patients with FMS than other subsets of chronic pain patients, with approximately 10–30% of patients reporting work disability (up to three times greater than disability rates among patients with other widespread musculoskeletal pain that does not meet full American College of Rheumatology (ACR) criteria for FMS) [19]. Despite being educated that FMS is not a progressive or deforming disease and does not pose a threat to life, patients struggle to maintain or improve their work or career lives. They often modify their work to maintain employment by reducing their hours or changing jobs to reduce mental and physical strain. Some patients ultimately lose their careers, suffer increased financial hardship and mental stress, and further exacerbate their symptoms of FMS.

FMS patients have been subcategorized by Turk et al. based on psychosocial and behavioral characteristics based on disease severity [2]. Three subgroups are described along a spectrum of symptom severity, and studies have shown variable prognoses directly related to disease burden [3]. Categorization of patients as either

Table 4.1 Supportive evidence of poor prognostic factors in patients with fibromyalgia syndrome, independent of treatments and interventions

Prognostic factors	Manifestation	Authors	Year	Ref.
Juvenile onset	Generally worse disease burden with poorer prognosis	Kashikar-Zuck et al.	2014	[21]
Catastrophizing	Preoccupied with their condition to the point of worsening their overall prognosis	Gracely et al.	2004	[17]
Employment disability	Associated with worse prognosis than those who remain employed	Turk et al.	1996, 1998	[2, 3]
		White et al.	1999	[19]
Interpersonally distressed	Require the addition of counseling to resolve life stressors	Turk et al.	1996, 1998	[2, 3]
Dysfunctional	High levels of anxiety, pain, impaired daily functioning, often opioid dependence	Turk et al.	1996, 1998	[2, 3]
Major psychiatric disease	Severe depression and anxiety, high levels of distress, embedded pattern of work or physical activity avoidance, long-standing FMS, coexistent alcohol dependence, persistence of functional impairment despite tailored comprehensive treatment	Fitzcharles et al.	2003	[20]
		Claw	2014	[6]

FMS Fibromyalgia syndrome

adaptive copers, interpersonally distressed, or *dysfunctional* may be prognostic and help to tailor a personalized treatment plan of maximal efficacy. These substantial differences in clinical presentation are suggestive of heterogeneity in FMS (see Tables 4.1 and 4.2).

This spectrum of disease severity may help to explain the variable prognoses. *Adaptive copers* often do not seek treatment and have relatively less pain, sleep disturbance, and fatigue than patients categorized to the other subgroups. *Interpersonally distressed* patients exist in the middle of the spectrum of disease severity and often improve with interdisciplinary therapeutic approaches including counseling and resolution of life stressors. The poorest prognosis is associated with the higher disease burden seen in *dysfunctional* patients, who exhibit high levels of

Table 4.2 Supportive evidence of positive prognostic factors in patients with fibromyalgia syndrome, independent of treatments and interventions

Prognostic factors	Manifestation	Authors	Year	Ref.
Adaptive coping	Less pain, sleep disturbance, and fatigue	Turk et al.	1996, 1998	[2, 3]
Community-based treatment setting	Majority of treatment by primary care physician in community setting, with tertiary level care only utilized for either initial diagnostics or treatment recommendations	Fitzcharles et al.	2003	[20]
		Clauw	2014	[6]

anxiety and pain, as well as severely impaired daily functioning, often accompanied by opioid dependence. Inappropriate narcotic use and opioid dependence can result from ineffective treatment plans for widespread hyperalgesia in patients with FMS. Iatrogenic or not, opiate dependence negatively impacts prognosis in FMS.

Other poor prognostic factors include the presence of major psychiatric diseases including severe depression and anxiety, high levels of distress, an embedded pattern of work or physical activity avoidance, long-standing FMS, coexistent alcohol dependence, and persistent marked functional impairment despite tailored comprehensive treatment modalities. It is known that prognosis is better overall for community-based patients [20], which may reflect an increased functional capacity in this group. With appropriate treatment, 24% of community patients with FMS may achieve complete remission by 2 years; while up to 47% of patients may fall short of criteria for FMS at 2-year follow-up [20]. Nonetheless, even with appropriate treatment, approximately 35% of patients will not benefit and continue to have widespread pain at 2 years.

JFM is associated with a particularly poor prognosis. At 6 years of treatment, more than half of patients meet ACR criteria with only a reported 15% having remission of pain (average age 21 years). Up to 80% of cases have persistent symptoms into adulthood with more pain, anxiety, depression, medical visits, and worse physical function than unaffected persons of the same age group [21]. Paradoxically, providing a diagnosis to juvenile patients with FMS may actually worsen their prognosis, inciting physical activity avoidance at a young age [6].

Overall mortality rate is not directly increased in FMS, but suicide risk may be elevated in specific populations, with up to a tenfold increased frequency of suicide as observed in some populations [22]. This was seen in cohort of Danish patients with FMS followed for 16 years [22] who were also noted to have increases in liver cirrhosis and biliary disease (sixfold), as well as cerebrovascular disease (threefold). Patients should be screened specifically for suicidality in addition to other symptoms of major depression on initial and subsequent clinic visits. Further studies are needed to evaluate other populations for mortality associations.

Follow-up

Follow-up of patients being treated for FMS is guided by assessment of symptoms and interval change in response to therapy. Combinations of subjective and objective parameters are used to evaluate a patient's response to therapy. Widespread pain and tender points found in association with other symptoms including neuropsychiatric disturbances (impaired memory, depression), symptoms of irritable bowel syndrome (IBS), non-restorative sleep, fatigue, morning stiffness, and paresthesias account for many nonspecific complaints reported by patients. Other complaints include aching, stiffness, weakness, radicular low-back pain, joint pain, pain worse in the morning that improves throughout the day, poor sleep, morning fatigue, feeling cold, Raynaud's-like symptoms, hyperalgesia, and allodynia. El-

derly and/or anxious patients may attribute the persistence of widespread pain to underlying tissue damage, disease progression, or life-threatening illness.

Variability in prognosis is likely multifactorial and may be reduced with appropriate interval history taking and physical examination at follow-up. Regular screening for anxiety and depression on initial and follow-up visits is essential in order to optimize treatment efficacy and adherence. Physical examination in these patients is also nonspecific, but useful in assessment of interval improvement or decompensation. The presence of diffuse tender points' assessment should prompt a pain threshold assessment. Patients have reported disproportionate discomfort with inflation of a blood pressure cuff [23]. Firm palpation of interphalangeal joints and forearm muscles can help differentiate lower central pain threshold from other inflammatory rheumatic diseases predominantly affecting the interphalangeal joints. However, the medial malleolus, medial one third of the clavicle, and forehead can serve as control points. and tenderness to palpation in these regions should prompt investigation of an alternative or additional explanation for pain, including psychiatric diagnoses.

Patient disease courses do vary, and commonly symptoms remit and relapse despite therapy. Durability of therapeutic response can be evaluated on subsequent visits using a number of parameters that collectively quantify many subjective aspects reported by patients with FMS. Some parameters include:

SF-36 36-item short-form health survey, physical component, mental component
PGIS Pittsburg sleep quality index
VAS Visual-analogue scale, global assessment by patient and physician
CES-D score Center for Epidemiologic Studies Depression index
CPSS Chronic Pain Self Efficacy Scale
PSQI score
Beck Depression Questionnaire
6-min walk test
Self-report forms for assessment of pain, fatigue, and overall status

Psychometric testing

Minnesota—Multiphasic Personality Inventory
Social Support Questionnaire
Sickness Impact Profile
Multidimensional Pain Inventory

- Modified Health Assessment Questionnaire
- FIQ
- Checklist for current symptoms
- Scales for helplessness and cognitive performance
- The Physician Health Questionnaire (nine for depression?)
- The Generalized Anxiety Disorder (seven questionnaire for anxiety)
- The Mood Disorder Questionnaire (screen for bipolar disease)

Therapeutic Response

The presence of widespread hyperalgesia and allodynia may never be completely reversed, but symptoms may improve or fluctuate in severity over time. FMS is most responsive to an approach that combines both pharmacologic and non-pharmacologic interventions along with patient education, reassuring, and participation in their own wellness. Evidence supports better outcomes under the care of primary care doctors in the community setting; however, specialists may aid in confirming an uncertain diagnosis, handling significant psychiatric comorbidities, or by treatment of patients with persistent pain refractory to therapy [6]. Physical and occupational therapists improve body kinetics and exercise, while psychologists and psychiatrists provide counseling and cognitive-behavioral therapy to help patients cope with their illness, actively participate in its improvement, and address comorbid psychological issues often present in this population. Educating patients engages them in their own comprehensive treatment plan and improves compliance and outcome. Reassuring patients that their illness is not progressive or deforming reduces their stress, which is a known trigger for FMS symptom flare-ups. The goal of therapy includes both pain reduction and improving functional status, and thus reinforcing regular exercise and adequate sleep hygiene is beneficial. Pharmacologic therapy in the absence of appropriate education and counseling belittles patient participation and can reduce the potential for improvement of symptoms. Multimodal treatment approaches to patients with FMS result in the greatest reduction in symptomatology. Patients with FMS achieve maximum benefit with a combination of a gabapentinoid and serotonin–norepinephrine reuptake inhibitors (SNRI; namely, pregabalin and either duloxetine or milnacipran) used in combination with regular aerobic exercise and cognitive-behavioral therapy [24].

Non-pharmacologic Therapies

Combining exercise, cognitive-behavioral therapy, and patient education is associated with the greatest improvement in patients with FMS 6. Overall function is the most responsive parameter to treatment and sustained improvements lasting greater than 1 year have been noted [25, 26]. Pain is commonly reduced with increased physical activity, and the magnitude of response may be compounded by improved mood and cognition following increased social interaction [27]. Practical limitations do exist in many community-based clinical settings and may include limited patient access to physical and psychological therapists, as well as reduced monitoring of patient compliance with treatments.

Educated patients receiving habitual reassurance prior to receiving other treatment reduces anxiety that facilitates compliance with therapy. Compliance then improves efficacy with all therapies thereafter. Early identification of life stressors can help patients develop coping mechanisms to minimize their disease burden. Patient-centered

multidisciplinary approaches may include different aspects of treatment by multiple specialists including pain management, physical medicine and rehabilitation, physical therapy, psychiatry, and group therapy.

Many alternative therapies may prove useful on a personal basis for patients with FMS, but strong supporting evidence is limited. Complementary and alternative exercise for FMS patients might give them a greater sense of control over their illness, as long as they do not cause harm [28]. Among these complementary interventions are chiropractic manipulation, trigger-point injections, acupuncture, yoga, tai chi, and myofascial release therapy. Some smaller individual studies have evaluated the efficacy of individual exercises and body kinetics in treating FMS pain. Belly dance improved FIQ scores and lowered mental and emotional activity scores quantified using the SF-36 questionnaire [29]. Patients have reported improvement in quality of life with performing belly dance, which may result from an improved self-image. Qigong—an ancient oriental method of respiratory and mental training—has been used to treat FMS patients, as has the Resseguier method of mind–body therapy aimed to increase control of body perception. Improvement in pain, disability, and quality of life has been reported with both qigong and the Resseguier method [30]. Interestingly, yoga may only play a weak role in management of FMS symptoms [31]. Limited evidence supports treatment of FMS with both myofascial release therapy and Swedish massage [28, 32]. In addition, a combination of somatic and abdominal acupuncture has reduced pain in FMS patients [33].

Nerve stimulation has been used to treat musculoskeletal pain in the past. Particularly with musculoskeletal pain of peripheral origin, transcutaneous nerve stimulation has some benefit in some patients. Short-term improvements in quality of life, reduced anxiety, and increased tender point pain threshold occur in some patients with FMS using transcutaneous electrical nerve stimulation (TENS) [34]. Central stimulation of pain processing structures appears to have some potential at treating FMS symptoms along with other centrally mediated pain syndromes [35, 36]. Transcranial direct current stimulation (tDCS) induces changes in neuronal activity traceable on fMRI that may impact cognition and analgesia [37, 38]. Patients with FMS may benefit from repetitive tDCS treatments, with reduced Beck Depression Questionnaire scores and FIQ scores [39] in addition to improved cognition [40], with fewer adverse affects than FDA-approved pharmacologic therapy [41].

Nutritional modification and supplementation, as well as other unique approaches provide adjuvant relief in FMS. Magnesium citrate supplementation has been used with positive effect in combination with amitriptyline [42]. FMS patients with comorbid IBS especially may benefit from an MSG-free diet [43]. The addition of ozone therapy per rectal insufflation to an existing treatment regimen improved FMS patient scores in FIQ, depression, and the physical summary score of the SF-12 in a pilot study [44]. Coenzyme Q10 supplementation has been suggested to be associated with improved pain, fatigue, morning tiredness, and FIQ scores [45].

Despite the majority of support for FMS pain as being centrally mediated, there is still some evidence supporting the treatment of peripheral pain generators. This is based on the notion that the development of central sensitization results, in part, from repetitive peripheral nociceptive input [39, 46]. Local therapies to pain

regions are most efficacious when patients have coexistent myofascial pain and osteoarthritis [47]. There is evidence of small-fiber neuropathy on some muscle biopsies of patients with FMS [48]; however, this does not render alternative pharmaceuticals effective when tailoring a treatment plan for a patient. Furthermore, biopsy currently plays no role in the diagnosis or severity ranking of FMS.

Pharmacologic Therapies

Varying degrees of evidence exist to support the use of different classes of pharmaceuticals as adjuvant therapies in treating FMS pain [49]. The best prognosis is associated with the use of a combination of either individual medications or medication combinations accompanied by non-pharmacological therapies. As in other polygenic pain syndromes, patients with FMS make greater improvements with combination pharmaceutical therapy. The additive effects allow patients to benefit from different mechanisms of action, while smaller individual doses minimize the side effects of individual agents. Pharmacotherapy for FMS effectively aims to antagonize the effects of excitatory neurotransmitters such as glutamate (Gabapentinoids) [50, 51], or to agonize the native effects of inhibitory neurotransmission often mediated by 5-HT, NE, and gamma-aminobutyric acid (GABA). Antidepressant therapy improves outcomes in patients with comorbid anxiety and depression, and strong evidence continues to support the use of tricyclic compounds as the mainstay of pharmacotherapy for FMS [52, 53]. Tricyclic antidepressants (TCAs) such as nortriptyline or desipramine improve pain, fatigue, and quality of sleep at low doses [54]; however, the side-effect profile of these TCAs can limit the potential for symptom control with dose escalation, particularly in the older patient population. Older patients who do not tolerate the anticholinergic burden of tricyclic therapy have greater benefit with an SNRI such as duloxetine or milnacipran. Durable responses with twice-daily dosing of duloxetine as well as milnacipran have been shown at 3 months reflected by improvement on FIQ in addition to reported improvement in pain and mood [55, 56].

Dual reuptake inhibiting antidepressants such as duloxetine [57] and milnacipran [58] have been shown strongly efficacious for pain reduction for patients with FMS [59, 60]. Duloxetine and milnacipran are two of three pharmaceuticals currently FDA approved (in addition to pregabalin) to treat FMS. They are superior with regard to efficacy and side-effect profile in comparison to older serotonin-specific reuptake inhibitor's (SSRI) with norepinephrine reuptake inhibitor (NRI) activity at higher doses (such as fluoxetine), which were previously used in combination with amitriptyline [61, 62]. Indeed, both milnacipran and duloxetine are of limited value in patients with end-stage renal disease (ESRD) without dose reduction, which may limit their efficacy and long-term practicality. Milnacipran may have only a modest effect as monotherapy; however, it is effective in treating patients who respond poorly to duloxetine [63] with reported improvement of some associated symptoms of FMS such as fatigue and cognitive impairment [64]. As with any pharmaceutical,

Table 4.3 Supportive evidence of favorable responses to pharmacological and multimodal therapies in patients with fibromyalgia syndrome

Pharmacologic class	Specific agents	Manifestations	Authors	Year	Ref.
Gabapentinoid + SNRI combined with aerobic exercise and CBT	Pregabalin + duloxetine or milnacipran	*Benefits* Pain reduction Control of neuropsychiatric symptoms Improved functional status Stress reduction Greatest likelihood of a durable response	Nüesch	2013	[24, 6]
TCA	Desipramine, nortriptyline	*Benefits* Low doses shown to improve pain, fatigue, and sleep quality *Drawbacks* Anticholinergic burden poorly tolerated in elderly, who respond more favorably to SNRI	Goldenberg et al. Gendreau et al. Arnold et al.	2004 2003 2004	[54] [55] [56]
Dual reuptake inhibitors	Duloxetine, milnacipran	*Benefits* Strongly efficacious at pain reduction Better side effect (SE) profile than older SNRI and NRIs	Arnold et al. Geisser et al. Häuser et al. Fishbain	2009 2011 2012 2000	[57] [58] [59] [60]
	Milnacipran monotherapy	Improves fatigue and cognitive impairment in patients who have responded poorly to duloxetine Physical function improvement if combined with CBT	Bernstein et al. Ang et al. Häuser et al.	2013 2013 2010	[64] [65] [49]
Gabapentinoids	Pregabalin >> gabapentin	Prolonged duration of therapeutic response Reduced occurrence of relapse Particularly useful with prominent anxiety in absence of depression	Tzellos et al. Crofford et al. Arnold et al. Häuser et al.	2010 2008 2007 2010	[66] [67] [68] [49]

SNRI serotonin–norepinephrine reuptake inhibitor, *NRI* norepinephrine reuptake inhibitor, *TCA* tricyclic antidepressant, *CBT* cognitive-behavioral therapy

milnacipran is more efficacious in FMS patients when combined with other therapeutic modalities (see Table 4.3). Despite only a small reduction in pain, milnacipran combined with cognitive behavioral therapy (CBT) does moderately improve physical function [65].

Gabapentinoids such as pregabalin and gabapentin also have strong evidence supporting their use to treat FMS pain [66]. Pregabalin may improve prognosis in patients who tolerate it and has provided patients with durable relief of symptoms

over time and reduced the occurrence of relapse [67]. α-2-delta ligands such as pregabalin are particularly useful in patients with prominent anxiety in the absence of depression. As the molecular precursor of pregabalin, gabapentin has also provided symptomatic relief to middle-aged adults with FMS [68]. Comparison of the risks and benefits using duloxetine, milnacipran, and pregabalin in FMS has strongly supported improvement with all three agents [49].

More recently, the use of various intravenous infusions has shown promise in treating generalized chronic pain and central pain states, including FMS. Ketamine infusions have shown benefit in patients with FMS, as with other chronic pain states such as central and peripheral neuropathic pain, complex regional pain syndrome (CRPS), and post-herpetic neuralgia. Ketamine 0.3 mg/kg infused over either 10 or 30 min, has been shown to reduce muscular hyperalgesia and muscle pain at rest [69]. Sorensen et al. showed reduced VAS scores at 20–80 min following 10-min ketamine infusion at 0.3 mg/kg, in addition to improvement in pain tolerance at pressure points [69]. Lidocaine infusions also have potential to improve pain score in chronic painful conditions, but further studies are needed to demonstrate if lidocaine infusions can benefit patients with FMS. Currently, little evidence exists to support improvement over the long term in cohorts receiving serial analgesic infusions.

Less supportive evidence exists for the use of other pharmaceutical agents including the older SSRIs (paroxetine, sertraline, and fluoxetine) [62], low-dose naltrexone [70, 71], and cannabinoids [72]. Citalopram is ineffective in controlling symptoms in FMS [73], in contrast to paroxetine, sertraline, and fluoxetine. Novel approaches using 5-HT(2 °C) agonists, lorcaserin, vabicaserin, and YM348, on animal models have shown promise for treating FMS as they have for the treatment of other CNS disease including schizophrenia and obesity [74]. Currently, these results serve to support the role of serotonin in muscular hyperalgesia, which is prominent in FMS. Future studies evaluating the efficacy of these agents in humans are needed. Cyclobenzaprine certainly reduces pain in FMS [54]; however, its use in this population is limited by its potential anticholinergic burden [75] (see Table 4.4).

Less commonly, treatment with gamma-hydroxyglutamate to potentiate gamma-hydroxybutyric acid in FMS patients has been a suggested therapeutic strategy; however, it is not currently FDA approved [76, 77]. Tramadol improves pain and physical function, but it is unclear whether this relief is a function of treating pain of coexistent osteoarthritis in these patients [78, 79].

Several classes of medications used to treat other types of pain have been shown ineffective in treating FMS pain. NSAID's, corticosteroids, and opioids have no role in treating FMS. There exists evidence that treatment with opiates could worsen FMS pain via opioid-induced hyperalgesia [80]. In fact, patients with FMS may be rendered refractory to opioid therapy [79, 81] due to hyperactivity of their endogenous opioid system [82]. This is further supported by newer, seemingly paradoxical evidence of pain reduction in FMS with opioid receptor antagonism using low-dose naltrexone [71].

Over time, positive outcomes are described in terms of improvement in quality of life, physical function, and pain scores. A multidisciplinary program inclusive of psychological, medical, educational, and physiotherapeutic regimens as opposed

Table 4.4 Pharmacological therapies lacking sufficient evidence for use, or associated with an unfavorable response in patients with fibromyalgia syndrome

Rx Treatment class	Individual agents	Manifestations	Authors	Year	Ref.
Older SSRI	Paroxetine, sertraline, fluoxetine	Dose required for therapeutic effect limited by side-effect profile	Arnold et al.	2002	[62]
Opioid antagonism	Low-dose naltrexone	n.a.	Younger et al.	2013, 2009	[70, 71]
Cannabinoids		n.a.	Skrabek et al.	2008	[72]
Serotonin receptor subtype agonists	5-HT (2 °C) agonists: lorcaserin, vabicaserin, YM348	Experimental models only	Ogino et al.	2013	[74]
Skeletal muscle relaxants	Cyclobenzaprine	Reduces pain but more studies are needed	Goldenberg et al.	2004	[54]
GHB	GHB	Not currently FDA approved	Foerster et al. Russell et al.	2012 2011	[76] [77]
Dual-reuptake inhibitor combined with opioid receptor agonist	Tramadol	Unclear if the demonstrated pain reduction is a function of treatment of coexistent OA in studied patients	Bennett et al. Katz	2003 1996	[78] [79]
NSAIDs, corticosteroids, opioids		No role in the treatment of FMS. Potential to worsen pain sx via hyperalgesia			
NMDA receptor antagonists	Ketamine IV infusion 0.3 mg/kg for 10–30 min	*Benefit* Short-term reduced muscular hyperalgesia and muscle pain at rest Increased threshold to pressure pain and pain at tender points, increased muscle endurance *Drawback* Only short term efficacy demonstrated Further studies needed to assess long-term efficacy in pain reduction in conjunction with functional capacity	Boleslay et al.	2013	[69]

SSRI serotonin-specific reuptake inhibitor, *5-HT* 5-hydroxytryptamine, NSAIDs nonsteroidal anti-inflammatory drugs, FDA Food and Drug Administration, *NMDA N*-Methyl-D-aspartic acid, *FMS* fibromyalgia syndrome, *GHB* gamma-hydroxybutyrate, *OA* osteoarthritis

to an isolated pharmaceutical treatment offers the greatest chance for improvement or remission. Patient-centered programs increase compliance and adherence to therapy, improving the likelihood of a durable therapeutic response. A personally tailored plan engages patients in the treatment process and is reassuring to patients that their clinician is invested in their wellness. Regular reassurance that FMS is not deforming or progressive and that treatment exists reduces anxiety. Abating the psychological stress associated with chronic pain ultimately increases the possibility of pain reduction or even remission. The majority of evidence currently available supports the use of complementary and alternative medicine modalities in the treatment of FMS. However, the studies frequently lack appropriate design having deficiencies in sample size and control groups [83]. Despite the consistency across multiple recent studies supporting improvement in FMS patients treated with a multidisciplinary approach, further studies are still needed to improve the accuracy of follow-up reports of improved pain, mood, and disability. The prognosis in a particular patient depends on a variety of biopsychosocial factors, in addition to their management approach.

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Chapter 5
Lifestyle Modification and Fibromyalgia

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Key Points

- Fibromyalgia patients have a tendency to adopt sedentary behaviors that reinforce preexisting physical disabilities and ultimately lead to increased disease burden.
- A multidisciplinary team approach should be used to treat patients involving cognitive, behavioral, and physical therapeutic strategies in addition to the judicious use of medications.
- Lifestyle-oriented interventions with proven efficacy include weight management, smoking cessation, promotion of restorative sleep, and patient education strategies.

Introduction

Fibromyalgia can be a disabling condition associated with chronic widespread musculoskeletal pain and reduced pain thresholds [1, 2]. In a population study of ten chronic diseases, fibromyalgia was highest ranked in long-term disability, pain, and poor self-rated health by survey participants [3]. Fibromyalgia has been ranked as one of the most expensive chronic diseases in terms of health-care utilization costs,

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in part due to the severity of the functional limitations experienced by some fibromyalgia patients.

The clinical symptoms of fibromyalgia are complex and include sleep disturbances, mood disorders, chronic fatigue, reduced exercise tolerance, and pain exacerbations which may severely limit a patient's activities of daily living [4]. As a result, fibromyalgia patients have a tendency to adopt sedentary behaviors that reinforce preexisting physical disabilities and ultimately lead to increased disease burden. A recent study has reported that the average 40-year-old fibromyalgia patient can become so debilitated that they have the physical fitness level expected of a 70–80-year-old [5].

Fibromyalgia symptoms may affect a patient's ability to work, their interpersonal relationships, and overall mental health. Due to the complex presentation of symptoms and physical and psychological comorbidities of many fibromyalgia patients, it is recommended to involve a multidisciplinary team approach to treating patients. A comprehensive management plan may involve using cognitive, behavioral, and physical therapeutic strategies in addition to the judicious use of medications [4].

Only about 40% of fibromyalgia patients derive benefit from the use of US Food and Drug Administration (FDA)-approved medications such as duloxetine, milnacipran, and pregabalin [6, 7]. Non-pharmacologic treatments such as exercise and cognitive-behavioral therapy generate improvements in outcome and cost–benefit ratios comparable to medication management [8]. Other lifestyle-oriented interventions with proven efficacy include weight management, smoking cessation, promotion of restorative sleep, and patient education strategies [9].

Physical Exercise

Based on the published research, exercise should be strongly recommended as an important therapy for fibromyalgia. Over 70 types of exercise interventions in fibromyalgia have been described, many of which have been evaluated in randomized controlled trials [10, 11–15]. Effective exercise-based modalities include land- or water-based aerobics, strength training, flexibility training, and movement therapies such as tai chi, qigong, and yoga. In randomized controlled trials, fibromyalgia patients who engaged in regular physical aerobic exercise reported decreased pain intensity compared to controls [12]. Other non-pharmacologic interventions such as massage therapy and nutritional approaches have been shown to benefit fibromyalgia patients in some studies, yet do not have as great an efficacy as exercise [16].

Aerobic exercise is a simple, cost-effective, and commonly recommended non-pharmacologic strategy in the management of fibromyalgia. However, as many as 83% of fibromyalgia patients do not engage in aerobic exercise [17]. In a systematic review of fibromyalgia treatments, aerobic and mixed exercise were found to consistently improve physical function and depression in fibromyalgia patients [15]. Low-intensity, low-impact aerobic exercise programs with the ability to tailor the exercise prescription to the needs of the individual show the strongest evidence for

clinical improvement in symptoms. Water-based exercise may offer some advantage over land-based exercise in reducing depressive symptoms and spontaneous pain, yet the availability of aquatic sports facilities may limit access. Overall, the effectiveness of land- and water-based physical exercise in improving functional state and aerobic physical conditioning are similar. Evidence for the beneficial effects of strength training is emerging quickly, while stretching modalities and movement therapies like tai chi have less of an evidence base [13, 18].

Despite the strong research evidence that supports the benefits of exercise, many fibromyalgia patients struggle with compliance. Commonly, fibromyalgia patients complain they feel more tired and state that they feel more pain after physical exertion. High-dropout rates are evident in many studies [19]. Attrition rates in randomized controlled trials of aerobic exercise ranged between 27 and 90 % [10]. Attrition rates are greater in exercise protocols with higher-impact activities such as aerobics as well as in activities that resulted in greater post-exercise pain.

Experts recommend that exercise should be integrated into the patient's existing lifestyle to increase the likelihood of continued patient compliance and tailored to the patient's existing fitness level and symptom severity to minimize discouragement [4]. A study by Hauser et al. reported that aerobic exercise of slight-to-moderate intensity two to three times a week was more effective than regimens of other intensity or frequency [20]. With this type of modest approach to exercise, improvements in mood, quality of life, and physical fitness were maintained in patients at follow-up intervals between 3 and 17 months.

It has been demonstrated that exercise adherence often declines after the supervised phase of an exercise program [20]. Supervised group activities may be preferable to home-based, solitary activities since participation in a group setting offers a social support mechanism and provides encouragement for patients to continue with an exercise regimen [21]. Fibromyalgia patients who have good baseline functioning may be able to participate in group exercise programs offered to healthy individuals. Patients with lower baseline function, such as those who consider themselves disabled and who are largely homebound, may benefit more from a program of gradual incremental increases in walking and stretching over several weeks [4]. Graded activity in low-functioning patients may begin with daily 1–10-min walks and increased in 1–5-min intervals over several weeks until total walking time improves to 10–30 min, 5–7 days a week. Such small, gradual increases in exercise are unlikely to exacerbate baseline symptoms [4].

Fibromyalgia patients often explore complementary and alternative exercise therapies such as tai chi, qigong, yoga, Pilates, and other movement therapies. Yet, few studies have compared the efficacy of complementary and alternative exercise regimens to traditional aerobic exercise regimens. A recent meta-analysis by Mist et al. of 832 fibromyalgia patients in 16 randomized controlled trials showed that alternative exercises are safe and effective at reducing pain with a relatively low-dropout rate of 19 %. However, the quality of evidence of these studies is subject to several limitations such that these reports were deemed to have lower methodological quality [22].

Table 5.1 Exercise promotion strategies in fibromyalgia patients

1. Provide education about exercise techniques through books and web resources. Many exercise programs specifically designed for fibromyalgia patients are commercially available (for example: www.myalgia.com/exercise)
2. Treat peripheral pain generators, such as bursitis, tendonitis, plantar fasciitis, and myofascial trigger points, to increase the likelihood of exercise success. Modify exercises to minimize aggravation of these pain generators
3. Increase exercise intensity in a stepwise progression. Begin with breath, posture, and relaxation training. Then, move patients on to flexibility training. Next, improve strength and balance before finally progressing to aerobics
4. Begin exercise slowly. Too little exercise will be inadequate to obtain results, while too much too quickly may exacerbate symptoms. Patients should increase exercise intensity by approximately 10% only after they feel comfortable at a given level for 2 or more weeks
5. Posture and body alignment work may alleviate pain-perpetuating postures (i.e., head forward, shoulders raised, back-rounded posture)
6. Avoid exercise programs that require complex dance routines that may be difficult for those with significant cognitive deficits.
7. Plan exercise during a patient's optimum hours of functioning (often between 10:00 a.m. and 3:00 p.m.) rather than at the end of the day when patients are most tired
8. Screen for autonomic dysfunction such as near-syncopal episodes, orthostatic hypotension, or chronic low blood pressure, especially in patients taking tricyclic antidepressants, trazodone, dopamine antagonists, or antihypertensives. Those with autonomic dysfunction may benefit from chair exercises and slow transitions from lying to standing
9. Modify exercise for other common comorbidities, such as irritable bowel syndrome, overactive bladder, and pelvic pain syndromes, by avoiding jarring exercises and exercising near a restroom
10. Design an exercise program that is realistic to encourage patients to celebrate their successes
11. Encourage supervised group exercise which has a better adherence rate than home-based programs
12. Invite patients to watch exercise classes even if they have no intention of participating. After weeks of seeing others be successful, they may be more willing to it themselves
13. Tell patients that you are confident they will be successful in their attempts to exercise. Verbally persuade them to continue

Massage therapy has also been investigated as a means of alleviating symptoms in fibromyalgia patients. A meta-analysis by Li and colleagues of nine randomized controlled trials involving 404 patients found that massage therapy of greater than 5 weeks' duration statistically improved pain, anxiety, and depression in fibromyalgia patients but surprisingly did not improve sleep disturbances [23].

Considering that regular exercise eludes at least 70% of Americans, it is not surprising that patients with fibromyalgia find regular exercise a challenge [24]. Given the high-attrition rates of patients with fibromyalgia in exercise programs, successfully prescribing an exercise regimen requires a certain amount of finesse on the part of clinicians. Jones and Lipton provide many useful guidelines for promoting exercise in fibromyalgia patients listed in Table 5.1 [25].

Diet

Definitive data linking fibromyalgia symptoms to dietary changes are lacking, yet many fibromyalgia patients believe their symptoms are affected by what they eat [26]. In an Internet survey of 2596 fibromyalgia patients, 40 % believed their pain, stiffness, and fatigue were exacerbated after exposure to certain foods and 68 % used nutritional supplements in an attempt to control their symptoms [27]. Similarly, Haugen and colleagues found that 42 % of 65 patients with fibromyalgia believed their symptoms were worsened after eating certain foods [28].

Nine trials of dietary intervention in fibromyalgia patients have been conducted to date that enrolled patients according to the American College of Rheumatology definition of fibromyalgia. Many of these trials showed a modest improvement in somatic symptoms on restrictive diets, yet it is unclear if these improvements were due primarily to weight loss or to the types of food used in the diet itself. One randomized controlled crossover trial compared the effects of a vegetarian diet to those of using amitriptyline in 78 patients [29]. The patients who were prescribed amitriptyline achieved statistically significant relief of fatigue, insomnia, non-restorative sleep, and tender point count, while the patients on the vegetarian diet had only a mild decrease in pain. All patients in the vegetarian group chose to discontinue the diet after 6 weeks and crossed over to the amitriptyline group due to the inefficacy in reducing symptoms and the monotony of the vegetarian diet prescribed in the study.

Raw vegetarian or vegan diets free of alcohol, caffeine, meat, and dairy have been investigated in at least three studies. One study of 33 fibromyalgia patients showed a decrease in pain and morning stiffness after 3 months of a restrictive vegan diet [30]. Another study of 18 self-selected patients found that patients on a vegan-diet protocol experienced improved pain, stiffness, and better sleep compared to controls [31]. An observational study of 18 participants who consumed a raw vegetarian diet found that patients had an improved score on the Fibromyalgia Impact Questionnaire (FIQ), improved flexibility, and an improvement in 6-min-walk test after 7 months. Conclusions from this study were limited by the lack of a control group and the study's small sample size [32].

Some researchers believe the dietary intake of neurotransmitter amino acids such as aspartate, glutamate, aspartame, and monosodium glutamate (MSG) that are found in meat and food additives may act as excitatory neurotransmitters and could promote central sensitization and pain windup in fibromyalgia patients [26, 33]. A case series of four patients with fibromyalgia has reported complete or near-complete resolution of symptoms with the elimination of MSG and aspartame from the diet of these patients and the recurrence of symptoms when these substances were reintroduced [34]. Additionally, two studies have shown a correlation between glutamate levels in the cerebrospinal fluid and pain levels in fibromyalgia [35, 36]. Other foods or food additives that have been suggested as possible fibromyalgia triggers include cow's milk, shellfish, chocolate, food coloring, and caffeine. However, further research is needed to clarify the exact role of food additives and diet in fibromyalgia.

Proponents of dietary modification in fibromyalgia point out that this type of management is relatively safe, inexpensive, and provides patients with a sense of control. Unfortunately, no dietary studies to date have definitively identified specific foods or additives that exacerbate fibromyalgia [26]. Also, many patients find restrictive diets unfeasible in the long term, especially in the face of only modest benefits. Since many patients with fibromyalgia experience chronic ongoing symptoms, it is generally advised to encourage patients to focus on making healthy lifestyle changes rather than adhering to a severely restrictive diet that may not be ultimately sustainable [33].

Weight Reduction

Several nonrandomized, uncontrolled studies evaluating musculoskeletal symptoms in patients who have lost weight through diet, exercise, and as a result of gastric bypass surgery have shown improvement in fibromyalgia symptoms and quality of life following weight reduction. However, it is unclear whether these improvements can be attributed to the weight loss itself, to the counseling and support provided, or to the increased level of physical activity in these patients [26, 37, 38]. In a survey of 211 fibromyalgia patients, Yunus and colleagues identified a correlation between increased body mass index (BMI), number of tender points, and lower score on the Health Assessment Questionnaire that measures activities of daily living. Unfortunately, it could not be determined by the survey if increases in BMI preceded or were a contributing factor to the onset of fibromyalgia symptoms [39].

Shapiro and colleagues investigated the effects of weight loss in fibromyalgia patients during a 20-week study of 31 patients with a BMI greater than or equal to 25 kg/m^2. In this study, patients' caloric intake was limited to 1200–1500 calories per day, and they were encouraged to engage in at least 30 min of physical activity per day. Participants were able to significantly reduce their BMI from baseline, had improved pain, improved scores on the Beck Depression Inventory, and improved quality of life. The authors found that the percentage of weight loss predicted improvements in the FIQ score and the Beck Depression Inventory [38]. It is unclear from this study whether symptom improvement was due to the weight loss itself, increased exercise, dietary changes, or the effects of participating in a support group. The study was furthermore limited by a high-participant dropout rate (26%), nonrandomized design, lack of a control group, and failure to adjust for the effects of medication use [33].

Quality of Sleep

Fibromyalgia patients consistently rank disturbed sleep as a highly disruptive symptom. In a recent survey, over 74% of fibromyalgia patients complained of nonrestorative sleep and poor sleep quality [40]. Patients also report difficulty falling

asleep, an increased number of nighttime awakenings, and awakening feeling tired [40, 41]. Despite receiving between 6 and 8 h of sleep, fibromyalgia patients complain that they wake up stiff, fatigued, and in pain. This suggests that a focus for fibromyalgia patients should be to improve sleep quality rather than to consider only sleep quantity. Evidence has shown that although 44 % of fibromyalgia patients rate their sleep as bad or fairly bad, only 22 % have objective sleep deficits [42].

Disturbed sleep itself may be a predictor or risk factor for the development of chronic pain. In a population survey of over 4000 healthy adults in the UK, non-restorative sleep was the strongest independent predictor of new-onset widespread pain [43]. Interestingly, over 25 years ago, Moldofsky and colleagues showed that the selective disruption of stage 3 slow-wave sleep in healthy volunteers resulted in increased widespread musculoskeletal pain symptoms similar to fibromyalgia [44]. In subsequent polysomnographic studies over the decades, fibromyalgia patients have been found to demonstrate abnormal sleep architecture including increased sleep-onset latency [45], increased number of nighttime arousals [46], reduced restorative stage 3 and stage 4 sleep, and greater alpha-wave intrusion [44]. Additionally, several studies have suggested a high prevalence of restless leg syndrome in fibromyalgia patients [47].

The "cognitive activation theory" of stress suggests that there is a relationship between stress, sleep, and pain. Lack of restorative sleep is thought to lead to changes in the functioning of the hypothalamic–pituitary–adrenal axis and central nervous system that cause an increased sensitivity to pain [57]. Poor sleep has been shown to be both a consequence of pain [48] and a maintenance mechanism for chronic pain [49, 50]. Furthermore, sleep disruption is predictive of increased next-day clinical pain in fibromyalgia patients [49, 51] and in other individuals with chronic pain such as burn patients [52]. In healthy adults, additional studies have shown that sleep deprivation results in decreased pain thresholds the following day and increased areas of muscle tenderness similar to the pain experienced by patients with fibromyalgia [53, 54]. Furthermore, Ablinshowed that in healthy volunteers, restricting sleep to 6 h a night and the cessation of physical exercise for 10 days resulted in increased symptoms of pain, fatigue, cognitive dysfunction, and negative mood compared to controls [55]. Even one night of total sleep deprivation has been associated with a state of generalized hyperalgesia and increased anxiety [56].

Behavioral therapies aimed at improving sleep hygiene have been found to be effective in improving pain, fatigue, and sleep quality in fibromyalgia patients [58]. Treatment of non-restorative sleep in fibromyalgia patients should begin by obtaining a thorough sleep history and encouraging patients to maintain a sleep diary [59]. A sleep history should include symptoms of daytime fatigue, sleep hygiene, sleeping patterns, caffeine intake, activity before sleep, physical exercise patterns, and medication dosage and timing [59]. Patients should be evaluated for other organic sleep disorders such as obstructive sleep apnea or restless leg syndrome. Sleep hygiene recommendations typically include such simple yet effective interventions as establishing a bedtime routine, optimizing conditions to encourage sleep in the bedroom, and avoiding caffeine and stimulants after 5 p.m. Additionally, physical exercise has been shown to improve sleep quality in fibromyalgia patients [60], whereas obesity is associated with a poorer quality of sleep [61].

Pharmacologic methods to improve sleep have limited efficacy compared to cognitive-behavioral therapy and efforts to improve sleep hygiene in fibromyalgia patients. Traditional sedative-hypnotic sleep aids such as benzodiazepines, zolpidem, and Zopiclone (which is sold in the USA as its stereoisomer, eszopiclone) may result in improved daytime sleepiness but have not been shown to improve pain symptoms in fibromyalgia patients [59]. Over-the-counter herbal therapies such as melatonin have met with mixed results. Care should be exercised if recommending over-the-counter herbal therapies to promote sleep since they may interact with prescription medications and have associated side effects [59, 62, 63].

The FDA-approved medications for fibromyalgia such as duloxetine, pregabalin, and milnacipran all improve sleep. Duloxetine and milnacipran have been found to reduce the duration of rapid eye movement (REM) sleep and improve sleep quality. Duloxetine also increases stage 3 slow-wave sleep, whereas milnacipran facilitates stage 2 non-REM sleep in depressed patients [64–66]. Pregabalin has also been shown to improve pain, fatigue, and the quality of sleep in fibromyalgia patients and enhances slow-wave sleep in healthy volunteers [67–69]. Other medications which are not FDA approved are frequently used to treat fibromyalgia and include tricyclic antidepressants, muscle relaxants, anticonvulsants, and antidepressants, although they have little effect on sleep architecture [70–72].

Alcohol Use

Studies have shown that modest alcohol intake may be associated with a lower risk of cardiovascular disease and ischemic stroke, even though long-term, large quantity alcohol use has many negative health consequences. Regular low-to-moderate alcohol intake has also been associated with improved quality of life, mood, and subjective improvement in health in adults [73]. In patients with fibromyalgia, a recent cross-sectional study demonstrated that low-to-moderate alcohol consumption is similarly associated with less severe symptoms and a better quality of life [74].

Researchers have proposed several theories to explain this finding. Alcohol may increase the threshold for pain in fibromyalgia and provide a short-term analgesic benefit [75]. Alternatively, alcohol may reduce certain inflammatory mediators thought to be important in fibromyalgia. For example, alcohol has been found to suppress the synthesis of proinflammatory cytokines such as tumor necrosis factor and interleukin-6 [76], yet the association of cytokines with fibromyalgia is controversial [77]. Additionally, lower levels of the inhibitory central nervous system neurotransmitter γ-aminobutyric acid (GABA) have been noted in the central nervous system of fibromyalgia patients [78]. Kim and colleaguespostulated that alcohol attenuates the pain of fibromyalgia by increasing the release of GABA [74]. Sodium oxybate and its sodium salt, γ-hydroxybutyrate(GHB), commonly known as the "date-rape" drug, are also effective at improving sleep and reducing fibromyalgia symptoms; however, these drugs have not received FDA approval due to concerns for abuse [79–81]. In summary, caution is needed with regard to alcohol use in

fibromyalgia. It is not recommend that patients with fibromyalgia start or increase alcohol use to treat their symptoms [74].

Tobacco Use

Smoking status is a documented risk factor for disease activity in autoimmune disorders such as rheumatoid arthritis, systemic lupus erythematosus, and ankylosing spondylitis [82]. Smoking behavior also exacerbates many chronic pain conditions. A prospective study showed an association between smoking and weekly headache intensity [83]. Similarly, smokers enrolled in the National Spine Network database had more severe back pain than nonsmokers. A large systematic review of 38 studies by Goldberg et al. concluded that smoking is also associated with an increased incidence of nonspecific low back pain [84].

With regard to musculoskeletal pain, epidemiologic data from the Norwegian Health Survey in 1985 first showed an association between smoking and increased pain [85, 86]. Subsequent population studies in Norway and Germany showed similar results [87]. Even a history of former tobacco use was identified as a major risk factor for developing musculoskeletal pain in a population study of 21,000 adults in Great Britain [88]. More recently, a survey in 2011 found that daily smokers were twice as likely as nonsmokers to report chronic musculoskeletal pain and those who smoke more than one pack per day were the most likely to report a high burden of chronic pain [89]. Daily smoking was associated more strongly with chronic pain than older age, obesity, and lower education level.

Controversy exists among researchers regarding the impact of smoking on the clinical features of fibromyalgia [90–92]. A majority of the research suggests that smoking increases the severity of symptoms. For example, Yunus et al. reported that of 223 patients evaluated at a fibromyalgia clinic, smokers had greater pain intensity and functional disability than nonsmokers and that these parameters showed a dose–response effect with the number of packs smoked per day [92]. Other studies suggest that smoking could be an environmental trigger that leads to aggravation of clinical features of fibromyalgia [93].

The redundancy of these findings suggest that tobacco use is associated with more severe impairment in patients with fibromyalgia; however, the mechanism by which tobacco use results in increased pain complaints has not yet been clearly elucidated. Smoking is associated with multiple socioeconomic variables such as lower education level, higher rates of divorce, and increased unemployment which also correlate with more severe manifestations of fibromyalgia symptoms. Psychiatric disorders like major depression are also associated with tobacco use, and symptoms of depression have been associated with more severe fibromyalgia symptoms [94].

Tobacco and nicotine may affect pain perception through a variety of mechanisms related to the neurobiology of chronic pain. Nicotine may decrease pain thresholds by sensitizing pain receptors. However, tobacco has been found to have antinociceptive properties in experimental pain models using electrical, cold,

thermal, and ischemic pain stimuli [92]. Meanwhile, smoking has been associated with higher levels of substance P in the cerebrospinal fluid (CSF) of patients with fibromyalgia [92]. Functional neuroimaging studies have shown that both smoking and fibromyalgia are associated with similar alterations of endogenous opioid activity in pain-modulating regions of the brain including the nucleus accumbens, amygdala, and dorsal cingulate [89]. In general, the majority of studies suggest that tobacco use is adversely related to chronic pain complaints, and that smoking cessation should be recommended.

Conclusion

Lifestyle modification strategies for patients with fibromyalgia may include recommendations for increasing physical activity, dietary changes, weight reduction, improving the quality of sleep, and eliminating cigarette smoking. Due to the complex interplay between physical, social, and psychological factors, the pain from fibromyalgia is extremely difficult to predict, prevent, or manage. Despite their efficacy, a number of challenges prevent the broader adoption of lifestyle interventions to treat fibromyalgia. Unfortunately, few fibromyalgia patients achieve pain-free status solely through pharmacologic management, so lifestyle changes should not be ignored.

For fibromyalgia patients who achieve substantial reduction in pain symptoms through lifestyle modification, long-term maintenance of such improvement depends on carefully managing lifestyle to avoid or reduce triggers that could cause a recurrence of pain. Despite a lack of prospective studies demonstrating a clear cause–effect relationship, fibromyalgia patients who smoke should clearly be encouraged to quit. Avoiding excess alcohol consumption and promoting restorative sleep are also paramount to a sustainable recovery from symptoms. Recommending an active exercise regimen in fibromyalgia patients with severe functional limitations is challenging because many patients associate negative emotions with the idea of exercise. However, an extensive body of literature proves that engaging in regular physical activity will likely provide the biggest benefit in the treatment of and recovery from fibromyalgia symptoms. Exercise should be a mainstay of therapy for all fibromyalgia patients.

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Chapter 6
Psychological Treatment for Fibromyalgia

Jeffrey T. Hopcian and David R. Lindsay

Key Points

- Fibromyalgia syndrome (FMS) is associated with physical, psychological, and social symptoms as characterized by the biopsychosocial model of illness.
- Cognitive behavioral therapy (CBT) is a mainstay of psychological treatment for fibromyalgia. CBT attempts to provide patients with insight into their disease process, specific skill sets for the management of symptoms, and a structured program through which these skills are applied to real-life situations.
- Skills for managing fibromyalgia symptoms include graded activity exposure, pacing, relaxation techniques, sleep hygiene, exercise, and biofeedback.

Introduction

Theories of Chronic Pain

Like many chronic pain syndromes, fibromyalgia syndrome (FMS) is a severely debilitating condition with complications extending far beyond the physical stress of pain. Medical sociology has long described the pervasive suffering associated with chronic pain syndromes, including demoralization, affective disorders, mood disorders, increased consumption of medications and health care services as well as a far-reaching impact on personal, social, and work activities [1]. In populations suffering from fibromyalgia, several studies have shown high levels of emotional stress and increased prevalence of psychological and psychiatric disorders [2–4].

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In the late 1970s, Engel developed the *biopsychosocial* model of illness, challenging traditional reductionist models of medicine and positing every disease can be explained by deviation from normal function as related to some injury, pathogen, or abnormality in genetics and/or development [5]. The biopsychosocial model explains illness in the context of biological, psychological, and social factors. Each of these dimensions affects the development, perpetuation, and alleviation of disease. This recognition has been a call to caregivers to adopt a comprehensive view of human functioning and illness [6]. When Melzack developed the *neuromatrix theory of pain* (Fig. 6.1), this theory was applied to fibromyalgia and other chronic pain syndromes. This model is an extension of the *gate control* theory of pain famously developed by Melzack and Wall in the 1960s [7]. It integrates psychological and physiological models of disease and describes complex peripheral and central factors that interact to produce the high pain levels and sensitivity characteristic of fibromyalgia [8]. This theory has added credence to the notion that biological, psychological, and social factors all play a role in the experience of pain and, by extension, treatments addressing these dimensions may aid in modulating pain.

As our understanding of FMS grows, it is not surprising that treatments focused solely on pain symptoms yield only modest outcomes in overall health status. In a recent review, Williams noted that pharmacologic treatments improved functional status for just over 10% of patients [9]. Ongoing improvements in the availability and efficacy of pharmacologic therapies notwithstanding, it is widely recognized that a more multidimensional approach should be adopted. In this chapter, we will

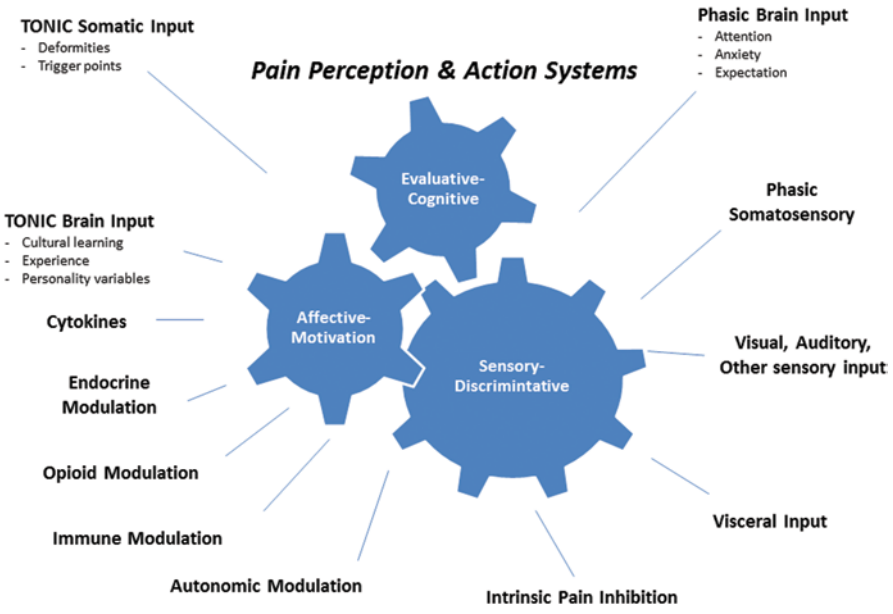

Fig. 6.1 The neuromatrix. (Adopted from [8])

discuss the psychological approaches to treating patients suffering from FMS to explore the ways in which these treatments augment other therapies and impact overall outcomes.

The Biopsychosocial Model Applied to Fibromyalgia

Biological

The role of biology in the etiopathogenesis of FMS remains unclear. Familial aggregation has been demonstrated in FMS [10, 11]. Several animal and human studies have suggested that responsiveness to pain stimuli is a function of genotype. Investigators also studied possible associations between polymorphisms in serotonergic and adrenergic systems and abnormal pain processing in FMS [12–17].

In FMS as in many chronic pain syndromes, the lines of between psychology and physiology become blurred. Although many symptoms cannot be conclusively attributed to abnormal physiology (e.g., tinnitus, paresthesia, sicca, dizziness), limited diagnostic technology may be responsible rather than the absence of physiological causation. For some symptoms of FMS, physiological abnormalities have been demonstrated. A surrogate measure using quantitative sensory testing has demonstrated the evidence for central sensitization in an FMS population [18]. *Central sensitization* describes the phenomena of hyperalgesia, allodynia, spread of symptoms, and chronicity associated with alterations in sensory processing and modulation (i.e., changes in the ascending and descending pain modulating pathways) in the central nervous system [19, 20]. Discussed later in this chapter is the notion that variances in psychological health impact pain symptoms at the central level as modeled by the neuromatrix and gate theories, therein providing part of the basis by which psychological treatments may impact overall outcome.

Psychological

The psychological dimension of FMS has been a focus of patients, caregivers, and researchers for years. In 2010, the *American College of Rheumatology* updated the diagnostic criteria for FMS. In addition to the widespread pain index (WPI) as a measure of the diffuse musculoskeletal aches and tender points characteristic of the disease, the criteria also include a measure of symptom severity for fatigue, non-restorative sleep, and cognitive symptoms [21]. Cognitive dysfunction has been demonstrated in fibromyalgia patients in multiple controlled studies and validated with neuropsychological testing [22–26]. Impaired memory, attention, language fluency, and cognitive processing have been demonstrated in over 60% of FMS patients [22]. Though not part of the diagnostic criteria, additional psychological symptoms are very common in FMS: As many as 60% of patients experience anxiety, stress, and/or depression [21, 27].

Social

Exposure to environmental stressors may play a role in the development and severity of FMS and other chronic pain syndromes. Among patients with FMS, those who report histories of abuse (physical, emotional, or sexual) experience higher levels of pain, fatigue, and functional disability than their counterparts do [28, 29]. Although some data show that stressful life events may trigger FMS symptoms, there are few controlled studies to support conclusions about the genesis of FMS [30].

Patient perceptions of the quality of social support systems seem to play an important role in affecting disease course. Pain and functional outcomes for FMS patients have been shown to be higher for those with healthy support systems [31]. Indeed, pain severity to controlled stimuli was reduced in the presence of significant others [32].

The notion of *locus of control* was developed by Rotter in the 1950s. It has been applied to medicine to characterize the degree to which individuals believe in their ability to impact a disease process. Patients with an external locus of control believe that outcomes are mainly controlled by some "powerful other." In an internal locus of control, the patient believes he/she affects outcomes [33]. FMS patients tend to adopt external loci of control to a greater degree than counterparts suffering from rheumatoid arthritis, and those with external loci of control report higher levels of pain and greater symptom severity than counterparts with internal loci of control [34, 35]. One's locus of control has been shown to be plastic and, as we discuss later in this chapter, is one focus of psychological treatments for FMS.

Cognitive Behavioral Therapy

Cognitive behavioral therapy (CBT) is a psychotherapy technique that integrates behavior therapy (i.e., behavior modification techniques) with cognitive psychology. Under the purview of CBT, there is great variation in form, technique, and practice. However, common features (in accord with the biopsychosocial model of illness) are intended to modify the dynamic connection between individuals, their social milieu, and their illnesses [36]. The common focus of CBT therapies is a challenge to maladaptive beliefs (i.e., expectations of failure) and a movement to develop goals for adaptive behaviors (e.g., sleep hygiene). Historically, CBT for chronic pain is aimed at improvements in mood, functional status, and behaviors. Three phases in application of CBT to chronic pain have been described [36]:

1. Education: The basics of CBT and how it may be helpful in chronic pain
2. Skills training: Learning techniques to manage symptoms and problems
3. Application phase: Gradual and systematic trials in real-life situations

CBT is a broad term. CBT may incorporate a number of different techniques to treat pain and may dovetail with other approaches to the psychological management of pain. Some of these techniques exist both in and out of a CBT context. For example, we discuss *operant conditioning* theories and techniques in treating FMS below. This technique has infinite applications outside of pain treatment. Additionally, it

incorporates certain techniques (e.g., graded exposure) which some may use in the treatment of FMS outside of an *operant conditioning* perspective. Like much of medicine, the application of CBT to fibromyalgia is both a science and an art. In its practical execution, CBT may incorporate different techniques for different patients. Each technique is, naturally, applied to an individual's own life and circumstances. The result is that there is no uniform protocol for CBT. Rather, clinicians adhere to the principles described above and draw upon a collective pool of data and experience to develop a program that best suits the patient.

Goals for Psychological Treatment

Although there exists a significant heterogeneity among patients and, consequently, among individualized treatment plans, the general goals of treatment may be applied across most populations of FMS patients. Additionally, just as single-agent pharmacotherapy is generally less effective than a multimodal approach; a comprehensive psychological treatment plan may include a number of different techniques. General goals for psychological treatment for FMS appear in Table 6.1. Many of these goals may be encapsulated by a single technique (e.g., CBT). Other techniques have a very specific focus (e.g., relaxation techniques).

Patient Assessment

Any treatment program begins with a thorough assessment of a patient's disease process and symptoms across the biopsychosocial model. Psychological treatments for fibromyalgia aim to address an individual's particular needs. While patients

Table 6.1 Common goals for psychological treatment of fibromyalgia syndrome [36–37]

Education	Reduction of fear and anxiety
	Laying groundwork for realistic expectations
Acceptance	Acknowledgment of chronicity
	Accept that pain is central and not associated with peripheral tissue damage
	Necessary step before behavior changes can begin
Focus	Changing attention to potential gains from therapy
	Distracting focus from disease and related losses
Pacing	"Unlearning" associations between activity and pain by gradual, controlled activity
Sleep	Sleep disturbances are common in FMS and negatively affect symptoms; improving sleep quality with behavior changes (i.e., hygiene)
Cognition	Addressing deficits in attention, memory, and focus associated with FMS
Relapse skills	Relaxation, imagery/attention diversion

Table 6.2 Patient profiles from the Multidimensional Pain Index (MPI) [39]

	Increased	Decreased
Dysfunctional	Pain severity	Perceived control
	Symptoms interference with life	Activity levels
	Psychological distress	
Interpersonally distressed	Perception of "punishment" from others	Perception of support from significant others
Minimizer/adaptive coper	Daily activity	Pain severity
	Perceived control	Symptom interference with life
	Minimizing behavior	Affective distress

must be treated as individuals, they can generally be differentiated into subgroups based on their individual responses to pain symptoms. One method is to use the West Haven-Yale Multidimensional Pain Inventory (MPI) [38] to assign patients to one of three subgroups: dysfunctional, interpersonally distressed, and adaptive copers [39]. Investigators have shown that more than 85 % of FMS patients can be placed into one of these categories [40, 41]. The characteristics of these subgroups are shown in Table 6.2. Several studies have shown the value of basing treatment on the three profiles described [42–45].

A comprehensive intake assessment at the beginning of any psychological treatment for FMS includes screening for concomitant psychological illness, particularly depression, as well as perceived disability. A variety of techniques and tools are available to aid in this process, including the Oswestry Disability Index [46], the Functional Status Questionnaire (FSQ) [47], the Global Assessment of Functioning (GAF) scale [48], and most recently, the World Health Organization Disability Assessment Schedule (WHODAS) 2.0, which will replace the GAF in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) [49].

Cognitive–Behavioral Skills

Self-Monitoring

There is a distinct difference between *beliefs* and *knowledge*. Beliefs are often emotionally based and are not necessarily aligned with the factual sphere of knowledge. In an effort to align beliefs and knowledge, CBT aims to make patients objective observers of their symptoms, the interventions applied and, in turn, associated responses. This process of *cognitive restructuring* is an important first step in CBT.

Patients are charged with replacing maladaptive behavior and thoughts ("I will never get better") with *mindfulness* in speech, thoughts and actions ("It may take time and, although I may not feel perfect, I can feel better than I do today"). Practical techniques may involve keeping a journal to systematically record activity and

possibly success on various symptom dimensions: energy, stress, fatigue, or pain. The practice of monitoring one's actual activity level and symptom severity in real time helps promote belief systems less rooted in emotionality and more rooted in facts.

Goal Setting

The purpose of goal setting is, in part, to add structure and direction to CBT. Progress and efficacy are assessed both during CBT and at its conclusion. Goal setting is typically a collaborative agreement between the clinician and patient on treatment outcomes. These outcomes associate cognitive–behavioral patterns with a patient's pain and any associated social dysfunction, functional impairment, or emotional duress. Goals should be observable, realistic, and measureable [50].

Broad goals are typically identified and then prioritized. A process of operationalization may then occur wherein the clinician and patient work together to list all the steps necessary to make achieving a goal possible.

Operant Conditioning

Initially described by Jerzy Knorski and later popularized by B. F. Skinner, operant conditioning concerns learned behaviors that may be modified by antecedents and consequences. Operant conditioning differs from classical conditioning in that there is some active participation on the part of the learner by way of incentives and positive reinforcement. In the 1960s, Fordyce's *operant model of chronic pain* suggested that the development of chronic pain syndromes is affected by positive or negative reinforcement of pain behaviors (e.g., inactivity, medication intake, moaning). In other words, the positive consequences of a patient's pain-related behavior may encourage future pain-related behavior and may even be responsible for the experience of pain itself [51]. Three decades later, studies from Flor et al. suggest that patients with chronic pain may be more susceptible to operant conditioning than matched counterparts [52].

The *operant model of chronic pain* is a subject of ongoing debate. It is, however, relevant to clinical treatment of chronic pain and FMS. If chronic pain syndromes involve some degree of learned behavior via an incentive and reward-based conditioning process, a similar conditioning process may be utilized in *un*learning said behaviors. In 1973, Fordyce et al. published a study on operant conditioning in chronic pain patients that demonstrated effective decreases in medication intake and increases in functional level [53]. These have become the goals in ongoing applications of operant conditioning to a variety of chronic pain conditions, including fibromyalgia.

Although it is not used as a sole treatment for FMS, operant conditioning may be useful as part of a multidisciplinary program. The purpose is to decrease the presence of unhealthy "pain behaviors" (e.g., avoiding activities, seeking attention or validation from others, taking medications that do not reduce pain or increase func-

tionality) and/or to increase the presence of healthy behaviors that promote mental and physical wellness and maintain functionality. Incentives are shifted away from pain behaviors to healthy behaviors. Common techniques include *graded activity exposure*, *activity pacing*, and *time-contingent medication management* [54].

Graded Activity Exposure

The association between physical activity and exacerbation of chronic pain symptoms in FMS is extremely common. Fear of pain and subsequent avoidance of certain activities known to exacerbate pain is also extremely common. In some, a cognitive error phenomena known as *catastrophizing* may occur wherein patients develop disproportionate, debilitating thoughts or images of a negative outcome, or misinterpret the outcome of an event as extremely negative [55]. These patients may benefit from graded exposure therapy.

The first step is to identify patients suffering from significant fear-based avoidance of activity as well as those activities that invoke the most pronounced catastrophizing thoughts and behaviors. Though it may seem a simple question, many patients may be unaware of fear-based thoughts and behaviors. For this reason, many practitioners find usefulness in questionnaires that help identify pain-based avoidance. Examples of these tools include: the Pain Anxiety Symptoms Scale (PASS), Fear-Avoidance Beliefs Questionnaire (FABQ), Tampa Scale for Kinesophobia (TSK), and Survey of Pain Attitudes (SOPA) [56].

In graded exposure, the clinician and patient work together to identify certain exercises or activities associated with the patient's pain symptoms. An assessment phase typically measures a patient's capacity to perform an exercise until fatigue or exacerbation of pain symptoms prompts him to stop. For some, anxiety and fear of pain may be severe enough to warrant limiting this first step to observation of a given task and working through relaxation techniques before attempting physical participation. A treatment phase typically begins by issuing a baseline "quota" (for example, an average of the distance walked during the assessment phase, often reduced slightly to avoid cause excess duress). The patient is then asked to meet this quota over some period of time, always receiving some incentive and reinforcement for doing so. This quota is then slowly increased over time to promote improved functionality.

Pacing

Pacing is distinguished from *graded activity exposure* by a shift in focus from fear of activity to increasing physical ability. Physical overexertion and subsequent exacerbation of pain is a common feature of FMS. Time-based graded increases in activity (i.e., pacing) is a useful technique both in treating pain symptoms and minimizing future flare-ups, likely accomplished by treated chronic deconditioning associated with inactivity [57].

A baseline functional ability is assessed and activity is introduced in a controlled, systematic manner. Caution is taken to keep activity levels below anticipated thresholds to avoid injury or exacerbation of pain symptoms.

Relaxation Techniques

An important focus of CBT is learning to actively manage stress and anxiety. There is a clear connection between anxiety and physical tension and therefore anxiety becomes all the more provocative to the myofascial-type pain associated with fibromyalgia [50].

Relaxation therapies in CBT vary in focus and perspective but are unified in their aim to reduce anxiety, stress, and tension. Examples of common relaxation techniques are outlined in Table 6.3.

Sleep Hygiene

Sleep is an essential physiologic function and is associated with physical repair of stressed or injured tissues as well as psychological repair (layering memories, recovery from stress). In healthy populations, disruption of sleep patterns is associ-

Table 6.3 Relaxation techniques in cognitive behavioral therapy

Progressive muscle relaxation	Deep breathing technique	Guided visual imagery
Muscle groups sequentially tensed and relaxed	Aims to reduce rapid–shallow breathing and associated hyperventilation, dizziness, and difficulty concentrating	Cognitive relaxation technique, as opposed to physiologic techniques like muscle relaxation and deep breathing. Aims to distract and refocus attention away from symptoms
Attention to sensations at each group	Patient practices assessing his own breathing	Guided visualization of pleasant memories, places, and activities. Clinician encourages fidelity by helping explore the five senses during imagery
Patient learns to pinpoint areas of tension	Deeper breaths encouraged by slowing rate (counting breaths) and increasing depth (placing hand over diaphragm, assessing movement)	Clinician-guided assessment of responses
Patient gains control over muscle tension	Patient assesses emotional and physical states at the beginning and end of breathing exercises	
Ongoing practice is essential; may eventually be *applied ad hoc* to pain exacerbations		

ated with increased pain, fatigue, and difficulty with memory, and cognition. Interestingly, experimental studies by Moldofsky et al. showed that symptoms of sleep disruption closely mimic those of fibromyalgia [58, 59]. Fibromyalgia, however, is not a consequence of a primary sleep disturbance. Rather, the relationship between sleep and chronic pain symptoms is reciprocal, and improving sleep quality is an essential step in symptom management of fibromyalgia [60].

Pharmacological treatments for pain are common. Their adverse effects and the absence of demonstrable long-term benefits to sleep quality are obvious drawbacks. Behavioral modification, on the contrary, has been demonstrated in multiple studies to be an effective treatment option for insomnia, and these techniques have been successfully applied to a fibromyalgia population [61, 62]. Behavioral modifications aimed at improving sleep quality (often referred to as *sleep hygiene*) include removing those behaviors and environmental stimuli associated with delaying, disrupting, or decreasing sleep and introducing behaviors and environments that promote a routine, scheduled pattern of restful sleep. Common strategies for improving sleep hygiene are described in Table 6.4.

Exercise

In a randomized controlled trial, Wigers et al. demonstrated the positive benefits of aerobic exercise for fibromyalgia symptoms in the short- and intermediate-term [64]. Small data sets suggest adherence to sustained aerobic exercise programs continues these benefits in the long term [64, 65]. Exercise has an analgesic effect,

Table 6.4 Sleep hygiene strategies [37, 62]

Timing	Aim to establish a regular, schedule sleep pattern. Attempt sleep at the same time every night. Rise at the same time every day regardless of sleep quantity/quality. Avoid naps during the day. Do not sleep more than prescribed amount (7–8 h) even if fatigued
Behavior	Aim to associate the bed only with sleep. Do not lie in bed except for scheduled sleep. Avoid reading, eating, watching TV in bed (or bedroom if possible). If unable to sleep after 15 min, get up and engage in a quiet activity elsewhere (avoid watching TV). Return to bed when sleepy
Temperature	Sleeping is associated with a decrease in core temperature following a state of peak core temperatures (typically in the evening for persons with normal sleep cycles). Attempt to raise the body temperature 3–4° before bed with warm bath or warm blanket
Environment	Keep the room dark (switch off TV and illuminated displays including clocks associated with waking). Maintain a steady temperature.
Diet	Avoid stimulants (e.g., caffeine, nicotine) at least 4–6 h before sleep. Alcohol may initially promote sleep but often disrupts later sleep cycles. Avoid heavy meals immediately before sleep
Mind	Anxiety and stress surrounding sleeplessness are counterproductive. Avoid "willing" oneself to sleep. Utilize relaxation techniques
Tracking	Keep a log of sleep and sleep hygiene techniques to track successes or failures

possibly via activation of endogenous opioid and cannabinoid receptor systems [66–68]. There is strong evidence that regular aerobic exercise has a significant anxiolytic and antidepressant effect [68–70].

In general, the introduction of aerobic exercise to fibromyalgia patients should adhere to the same principles set out for CBT. Education and assessment are key initial steps. Clear and realistic goals should be set. Activity is introduced at levels high enough to exert an analgesic and anxiolytic effect but low enough to avoid exacerbation of pain symptoms. Supervision by a physical therapist or personal trainer may avoid inducing musculoskeletal injuries during certain activities such as weight training, cycling, or running. Whatever the modality, gradual progression, regular practice, and lifelong adherence are necessary to achieve maximum benefit.

Biofeedback

In 2007, the Association for Applied Psychophysiology and Biofeedback (AAPB), International Society for Neurofeedback and Research (ISNR), and the Biofeedback Certification International Alliance (BCIA) published a consensus statement that defines *biofeedback*: "A process that enables an individual to learn how to change physiological activity for the purposes of improving health and performance." Precise instruments measure physiological activity such as brainwaves, heart function, breathing, muscle activity, and skin temperature. These instruments rapidly and accurately *feeds back* information to the user. The presentation of this information—often in conjunction with changes in thinking, emotions, and behavior—supports desired physiological changes. Over time, these changes can endure without continued use of an instrument [71, 72].

By far the most common incarnation of biofeedback in fibromyalgia is *electromyography* (EMG). EMG measures impulses generated over muscle groups as an indicator of muscle use and tone. In FMS, leads are placed over tender points and observing empiric measurements of muscle activity helps patients gain some control over muscle tension and relaxation [73]. Patients are given information about muscle activation, tension, and relaxation in real time throughout their daily activities. This process is a powerful tool in improving the fidelity of relaxation techniques (i.e., progressive muscle relaxation) as well as cultivating activity schedules that promote well-being. Additional modalities include heart-rate variability and temperature monitoring.

Among the benefits of biofeedback in fibromyalgia, are noted improvements in functional status and reduction in the number of tender points and in pain severity. This modality is exceptional among the treatment techniques for fibromyalgia for its reduction in pain severity, which has been re-demonstrated in a number of studies [74–76]. The detectable benefits of other psychological treatments for fibromyalgia have historically been limited to improvements in functionality, reductions in pain flare-ups, and reduction in psychological duress rather than reduction in pain severity itself.

Conclusions

At present, little is known about the etiopathogenesis of fibromyalgia. We continue to grow in our understanding of its impact on emotional, social, psychological, and physiological dimensions of an individual. Through understanding, we have become better equipped to offer patients effective coping and symptom-management strategies.

Preliminary data suggest that patients receive benefit from CBT and other psychological treatment strategies. The variety of psychological treatments for FMS and a virtually infinite variability in patient needs and responsiveness present important opportunities for future research. Indeed, one hopes for a future in which clinicians use evidence-based approaches to stratify patients totherapy based on predicted responsiveness.

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Chapter 7
Medications

A. Morgan Kelly and Kimberly Mauer

Key Points

1. Medications are an important component of a multimodal approach to treatment of fibromyalgia.
2. The FDA-approved medications for fibromyalgia include pregabalin, duloxetine, and milnacipran.
3. Opioids in general should be avoided in fibromyalgia.

Major Classes of Medication for Treatment of Fibromyalgia

Tricyclic Antidepressants

Historically, tricyclic antidepressant medications are some of the longest used medications to inhibit the reuptake of 5-hydroxytryptamine (5-HT) serotonin and norepinephrine. These drugs act on the transporters of the presynaptic terminal of neurons [3]. Amitriptyline is by far the most studied in this class. It is more selective to block the reuptake of serotonin than norepinephrine while nortriptyline, a

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metabolite of amitriptyline, has slightly more selective effect on the norepinephrine reuptake. Nortriptyline also has an improved side-effect profile with less anticholinergic side effects.

In general, this class of medications is often poorly tolerated causing drowsiness, anticholinergic effects, arrhythmias, and can be contraindicated in some patients with multiple medical comorbidities. This is due to its cholinergic, histaminergic, and adrenergic receptor cross-reactivity [4]. It is hepatically metabolized, and should be used with caution in the elderly and in patients taking other serotonergic medications. Tricyclic antidepressants (TCA) should also be carefully titrated in patients with liver dysfunction, cardiac disease, or those taking other hepatically metabolized medications. They are contraindicated with concurrent use of monoamine oxidase inhibitors as the combination could cause overload of serotonin, potentially leading to serotonin syndrome. Dosing for this class of medication is displayed in Table 7.1.

Serotonin Norepinephrine Reuptake Inhibitors

There has been a recent resurgence of interest in serotonin and norepinephrine reuptake inhibitors (SNRI) and their use in fibromyalgia. These medications increase the concentration of serotonin and norepinephrine in an attempt to reestablish balance to the descending inhibitory pain pathways. Milnacipran is the newest SNRI that has obtained FDA approval for treatment of fibromyalgia in 2009. SNRIs have far fewer and milder side effects than TCAs, while acting on the same pain modulation pathways. Prior to the development of milnacipran, duloxetine and pregabalin were the only FDA-approved medications for fibromyalgia.

Duloxetine is another SNRI with benefit in fibromyalgia. Duloxetine-treated patients with fibromyalgia showed improvements as compared to placebo in two randomized control trials (RCT) by Arnold et al. A total of 54% of the treatment group experienced a 30% pain reduction compared to 33% of those in placebo group [5]. Further data from this study also demonstrated improvement of symptoms associated with fibromyalgia independent of mood. The standard dose that was shown to have most clinical efficacy was 60 mg, dosed twice daily. Most side effects are minimal and dose dependent. The most common side effects include nausea (29.3%), headache (20%), dry mouth (18.2%), insomnia (14.5%), fatigue (13.5%), constipation (14.5%), diarrhea (11.6%), and dizziness (11.0%) [6].

Milnacipran has similar side effects to duloxetine but is usually well tolerated. It is unique in that its preference for reuptake inhibition is 3:1 norepinephrine to serotonin ratio [4]. In an RCT, looking at 100 mg/day dose of milnacipran versus placebo, results demonstrated improvement of multiple variables over the placebo group [7]. Milnacipran was found only to be more effective than duloxetine in measures of fatigue. Both milnacipran and duloxetine were found to be inferior to amitriptyline in treatment of fibromyalgia-associated pain based on a recent meta-analysis by Hauser [8].

Selective Serotonin Reuptake Inhibitor

A selective serotonin reuptake inhibitor (SSRI) is an alternative class of antidepressants. These medications are much better tolerated and have been effective for

Table 7.1 Medications for treatment of fibromyalgia

Medication	Brand name	Dose	Side effects	Comments
TCA				
Amitriptyline	Elavil	10–50 mg/day	Cardiovascular, heart block, anticholinergic	Baseline EKG; caution serotonin syndrome; use with caution in hepatic dysfunction
Nortriptyline	Pamelor	75–150 mg/day	Less anticholinergic side effects	–
SNRI				
Duloxetine	Cymbalta	20–120 mg/day	Nausea, dizziness, dry mouth, tachycardia	Caution serotonin syndrome; reduced dose in renal failure
Venlafaxine	Effexor	75–150 mg/day		–
Milnacipran	Savella	100–200 mg/day		–
SSRI				
Buproprion	Wellbutrin	150–300 mg/day	Nausea, dizziness, sexual side effects, diarrhea	Caution serotonin syndrome
Fluoxetine	Prozac	10–80 mg/day		–
Sertraline	Zoloft	50–200 mg/day		–
Muscle relaxants				
Tizanidine	Zanaflex	4–8 mg TID-QID	Drowsiness, dizziness	–
Cyclobenzaprine	Flexeril	5–10 mg TID		–
Opioid				
Tramadol	Ultram	50–100 mg QID	Dizziness, nausea/vomiting, sedation	–
Tapentadol	Nucynta	50–100 mg QID		–
Antiepileptic				
Pregabalin	Lyrica	50–100 mg TID	Dizziness, blurry vision	Decrease dose in renal dysfunction
Gabapentin	Neurontin	300–900 mg TID		–

EKG electrocardiogram, *TCA* tricyclic antidepressants, *SNRI* serotonin–norepinephrine reuptake inhibitor, *SSRI* selective serotonin reuptake inhibitor

treatment of major depression and anxiety. The data are equivocal to support the use of this medication for pain in fibromyalgia [9]. However, many patients with fibromyalgia have concomitant depression or anxiety that may respond better to an SSRI than an antidepressant of another class. SSRI side effects include, weight gain, insomnia, and sexual side effects. There are no SSRIs with FDA approval for treatment of fibromyalgia.

Serotonin Syndrome
This is a serious and life-threatening drug reaction or interaction of multiple medications that causes an overdose of serotonin. The syndrome results in a spectrum of effects on central (CNS), autonomic, and somatic nervous systems. Less severe cases present as increased heart rate, sweating, dilated pupils, hyperactive bowels, agitation, and elevated temperature. Symptoms can be as severe as seizures, rhabdomyolysis, and renal failure. Treatment for serotonin syndrome is to stop using the offending agents and supportive care. If there is a case of overdose, activated charcoal can be given within an hour of ingestion to lessen absorption of the agent. To avoid serotonin syndrome, multiple serotonergic drugs should be used in lower doses and with great caution, medication should be initiated with slow titration, and use of serotonin agents concurrently with monoamine oxidase inhibitors should be avoided.

Antiepileptic/Antineuropathic Medications
Gabapentin and pregabalin are two medications that were originally designed as gamma-aminobutyric acid (gaba) analogs for neuronal membrane stabilization in seizure disorders. Both are also used for the treatment of chronic pain and fibromyalgia. Both of these molecules bind to the alpha-2-delta subunit of calcium channels to inhibit the release of inflammatory mediators and neurotransmitters. Pregabalin was FDA approved for treatment of fibromyalgia in 2009. The Fibromyalgia relapse evaluation and efficacy for durability of meaningful relief (FREEDOM) study showed lasting therapeutic response in the pregabalin group as compared with controls [10]. Gabapentin use in fibromyalgia is off label, though these drugs act similarly with major differences being easier absorption of pregabalin as it does not rely on transporter molecules for gastrointestinal (GI) absorption. Study by Arnold et al. suggests that 1200–2400 mg/day gabapentin dosing is the ideal profile of safety with efficacy in fibromyalgia [5].

Others

Muscle Relaxants
Drugs like cyclobenzaprine and tizanidine used for the treatment of muscle spasm are commonly used in musculoskeletal injury. Muscle relaxants are slightly different in their structure and function but act at the level of the brainstem or higher, often also causing sedation. Cyclobenzaprine is similar in structure to amitriptyline

so often has some anticholinergic side effects as well. In most painful conditions, muscle relaxants demonstrate benefit for the first couple of weeks with waning long-term benefits, thus they are generally not a recommended long-term treatment. Muscle spasm is not a classic finding in fibromyalgia syndrome; however, these medications are used commonly for muscle relaxation and also for their sedative effect at night.

Numerous studies have shown benefits of low-dose and high-dose muscle relaxants used for fibromyalgia. Moldofsky studied the use of low-dose nighttime administration of cyclobenzaprine to combat poor sleep and sympathetic arousal while optimizing side-effect profile. The main side effect of this medication is sedation, and if given at night, may limit the adverse effect of increasing daytime sleepiness. This blinded and randomized placebo-controlled study used 1 mg dose of cyclobenzaprine at night and showed improvement over placebo for "pain, tenderness, fatigue, mood, and sleep quality" [11]. Cyclobenzaprine is contraindicated when used with monoamine oxidase inhibitors (MAOI) and may cause development of serotonin syndrome when used with other serotonergic agents. Other muscle relaxants must be used with caution in the elderly and when in combination with other sedating medications.

Dopamine Agonists

Even less understood remains the role of dopamine receptor agonists in the treatment of fibromyalgia pain. Dopamine has a major role in autonomic regulation, sleep, and behavior. These medications bind to postsynaptic dopamine D2 and D3 receptors, which decrease the turnover and increase the release of dopamine. Examples of medications in this class include ropinirole, pramipexole, and rotigotine. An RCT of pramipexole in fibromyalgia did have promising results with efficacy greater in the treatment group than placebo when looking at multiple measures [12]. However, this is only one of the two studies examining dopamine agonists in this patient population, and more data are needed before making generalized recommendations for treatment with this class of medication.

NMDA Agonists

Fibromyalgia syndrome presents itself as a disease that demonstrates musculoskeletal hyperalgesia with decreased pain threshold. *N*-methyl-D-aspartate (NMDA) receptor activation and potentiation is an important process in the development of central sensitization that causes hyperalgesia. The NMDA receptors thus seem to be a likely target for treatment aimed at reversing or preventing these neural changes. NMDA antagonists, such as ketamine, have been shown to reduce pain in patients with fibromyalgia [13]. Dextromethorphan is another NMDA receptor antagonist that is commonly used. It has been studied for use in the management of opioid-induced hyperalgesia as it also influences pain transmission by interacting with the NMDA receptors. Studies looking at the effect of dextromethorphan on surgical pain were inconclusive and it has not been studied in the fibromyalgia population [14]. However, newer data may question the effect of ketamine on the NMDA receptor. Research by Wood suggests that it is ketamine's activity at the dopamine receptor, in conjunction with the dopamine-depleted state of fibromyalgia that is the

underlying mechanism of action. This is an area of research that also needs further study [15].

Stimulants

In addition to pain, fatigue is one of the most debilitating symptoms of fibromyalgia. Fatigue associated with other chronic illnesses such as multiple sclerosis or daytime sleepiness secondary to sleep apnea may be treated with stimulants such as modafinil and armodafinil. Both of these medications are stimulants approved for treatment of narcolepsy, shift work sleep disorder and fatigue associated with chronic illness. Common side effects of this medication include nausea, tachycardia, and headache. Modafinil showed promise in one study where a third of the patients with fibromyalgia taking 200–400 mg/day showed 50% reduction in fatigue [16]. Later, Shwartz et al. studied armodafinil also in this population who produced disappointing results. There was significant placebo effect and no lasting effect on reduction of fatigue [17]. While stimulants are sometimes used in this patient population, at present there is no convincing evidence that this is an effective class of medications in this patient population.

Sodium oxybate is a medication commonly used for treatment of cataplexy and narcolepsy. It is a metabolite of gamma-aminobutyric acid and has recently been studied for use in fibromyalgia to treat the underlying disordered sleep patterns in this syndrome. Russell et al. conducted an 8-week randomized, placebo-controlled trial of this medication in patients with fibromyalgia and found that the medication was well tolerated and had positive effects in reducing pain, insomnia, and fatigue [18]. Though the FDA has been pushed to approve this medication, it was not FDA approved for use in treatment of fibromyalgia. This medication has had much scrutiny for any type of therapeutic use as it is considered a drug of great potential for misuse and abuse. It continues to be highly regulated and monitored as dispensed for therapeutic use but may be used off label in treatment for fibromyalgia.

Nonsteroidal Anti-inflammatory Drugs

There are limited studies on acetaminophen or other nonsteroidal anti-inflammatory drugs (NSAIDS) used for fibromyalgia. A very early study by Goldenberg compares naproxen use to amitriptyline and showed no efficacy of the NSAID medication group compared to placebo group [19]. NSAIDS may have some value and synergy when used as adjuvants but do not have a primary role in treatment of this syndrome. Furthermore, NSAIDS with prolonged use can also have serious side effects such as ulcers, gastrointestinal bleeding, and renal injury. In addition, NSAIDS can predispose to cardiac events by causing an imbalance of prostaglandins leading to thrombosis and acute coronary syndrome.

Naltrexone

The opioid antagonist, naltrexone, has also been studied in fibromyalgia. This medication has been studied only in very low doses. The mechanism of action of

naltrexone is thought to be the reduction of inflammatory mediators and potentially act on microglia to prevent central inflammation changes [20]. This pilot study did have promising outcomes with 30% reduction in symptoms in the treatment group over placebo.

Opioid Use in Fibromyalgia

As described previously, patients with fibromyalgia have decreased pain threshold as a result of sensitization of neural pathways. A defining feature of fibromyalgia is to have increased sensitivity and pain with mechanical palpation of at least 11 out of 18 selected tender points [21]. Gibson et al. also showed that patients with fibromyalgia had decreased pain thresholds on the dorsum of their hands as compared to matched controls [22]. Whether this is a result of central or peripheral neuronal sensitization has not been fully elucidated.

The debate is ongoing for use of opioids for any chronic nonmalignant pain. Though many patients with fibromyalgia are treated with short- and long-acting opioids, there are data suggesting that patients with fibromyalgia are especially poor responders to this type of treatment. Sorensen et al. demonstrated in a small placebo-controlled study that there was no significant response to point tenderness in patients with fibromyalgia after a dose of 10 mg of IV morphine [23].

Opioids act on central and peripheral mu, kappa, and delta opioid receptors to inhibit the release of neurotransmitters such as acetylcholine, glutamate, and substance P. Baraniuk et al. have also shown that patients with fibromyalgia have high levels of endogenous enkephalins. This may support why patients with fibromyalgia have a profoundly blunted response to opioids, as their opioid receptors are already saturated with enkephalins. Alternatively, this may also result in downregulation of receptors [24]. This is further demonstrated by Harris et al. by measuring reduced mu-opioid receptor binding potential in key areas of the CNS involved with pain modulation and nociceptive processing [25].

Opioids further add morbidity to patients with fibromyalgia as they may increase fatigue, worsen sleep patterns, cause cognitive dysfunction, and constipation symptoms that exacerbate concomitant irritable bowel syndrome (IBS). Over time, opioids have adverse effects such as hormone imbalance. Patients with fibromyalgia may also have comorbid anxiety or depression of which opioids may provide a dissociative or euphoric state causing rapid psychological dependence and potential for abuse. This is why opioids are not included in any of the algorithms or treatment recommendations for fibromyalgia [26].

As described previously, patients with fibromyalgia have a decreased pain threshold as a result of sensitization of neural pathways. A defining feature of fibromyalgia is to have increased sensitivity and pain with mechanical palpation of selected tender points. Gibson et al. also showed that patients with fibromyalgia had decreased pain thresholds on the dorsum of their hands as compared to matched controls [22]. Whether this is a result of central or peripheral neuronal sensitization

has not been fully elucidated. Given that they already have this increased sensitivity, they may be even more vulnerable to the effects of opioid-induced hyperalgesia (OIH).

OIH is another disadvantage of the use of opioids. This phenomenon takes place when escalated doses of opioids result in a paradoxical increase in pain, a result of neuroplastic changes in the central and peripheral nervous system. OIH is poorly understood and there are limited data regarding this phenomenon in patients with fibromyalgia though it is a theoretical concern.

Buprenorphine, a partial mu agonist, is the only opioid shown to have some antihyperalgesic effects secondary to its kappa and delta antagonism [27]. Therefore, opioid partial agonists may be an opioid of choice if this class of medication must be used. The only other opioids that have demonstrated any efficacy for fibromyalgia is tramadol and tapentadol. In addition to acting on the mu-opioid receptor, tramadol also causes inhibition of the reuptake of serotonin. Similarly, tapentadol also acts as an alpha agonist and inhibits reuptake of norepinephrine.

Conclusion

While medical management with pharmaceuticals is only one aspect of treatment for patients with fibromyalgia, it is definitely an important component of comprehensive therapy. As described previously, there are few medications specifically indicated for fibromyalgia that have been shown to be efficacious and these should be carefully considered and titrated based on a particular patient's comorbidities and other medications. Other medication options have less data though may still be effective and can be considered for patients in whom there is little risk of side effects.

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Chapter 8
Adjuvant Treatments for Fibromyalgia

Anna Woodbury and Albert Leung

Key Points

- Fibromyalgia patients often seek complementary and alternative treatment modalities as adjuncts for conventional therapy to improve their pain and function.
- Acupuncture, repetitive transcranial magnetic stimulation (rTMS), biofeedback, and alternative exercise modalities such as yoga and tai qi have been studied in fibromyalgia patients, with promising results.
- If acupuncture is used, electroacupuncture is the preferred modality based on current evidence.
- If biofeedback is used, electromyogram (EMG) biofeedback has been shown to be more effective than electroencephalogram (EEG) biofeedback.
- Herbs, massage, balneotherapy (spa therapy), hypnotherapy, and music therapy may be useful for fibromyalgia patients as well, but the current level of evidence for these modalities is insufficient to conclude whether or not these treatments would provide sustained benefit.

Introduction

Fibromyalgia involves diffusely increased central sensory input that is clinically diagnosed by the presence of multiple tender points and several associated autonomic symptoms. These tender points are not trigger points, and are functionally different

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as there are usually no muscle bands or knots at the tender areas. Conventional medical therapy with pharmaceuticals, physical therapy, aerobic exercise, and psychotherapy is often insufficient to manage the pain, fatigue, and mood disorders these patients experience. Therefore, many patients have turned to alternative treatments. Reviews of literature have shown that while strong evidence exists for aerobic exercise and cognitive behavioral therapy (CBT) in fibromyalgia, there is also moderate evidence in support of acupuncture, massage, spa therapy, and muscle training, but limited evidence in support of spinal/chiropractic manipulation, vitamins, herbs, and dietary modification [1, 2]. Given that sufficient evidence of benefit for fibromyalgia patients has been established for several adjuvant modalities including acupuncture, repetitive transcranial magnetic stimulation (rTMS), transcutaneous electrical nerve stimulation (TENS), biofeedback, and massage therapy with minimal risk and reasonably low financial cost, it would be prudent to try some of these interventions as adjuncts to conventional fibromyalgia therapy on an individual, patient-specific basis.

Acupuncture

Acupuncture has become a popular adjunct for fibromyalgia treatment, as one in five fibromyalgia patients use acupuncture within 2 years of diagnosis [3]. Acupuncture involves the insertion of needles at specific points to treat pain with a goal of restoring the body's homeostasis. In fibromyalgia, needles can be inserted both at tender points and at specific pre-mapped acupuncture points to improve pain, sleep, physical function, stiffness, fatigue, and sense of well-being [3–5]. Acupuncture modalities include manual acupuncture (MA), where needles are inserted and twirled or stimulated by hand, or electroacupuncture (EA), where needles are connected to an electrical stimulator and the frequency of stimulation is adjusted to provide appropriate levels of electrical input to the needles. Other modalities include acupressure, auricular acupuncture, scalp acupuncture, and hand acupuncture, but these have not been well studied in the treatment of fibromyalgia, though they may still be of some benefit.

There appears to be a correlation between the location of hypersensitive tender points in fibromyalgia and hypersensitive acupuncture points. Both are rich in C-fibers and transient receptor potential vanilloid type 1 (TRPV1, heat pain) receptors. Therefore, it is not a large logical leap to assume that acupuncture may have some benefit for these patients. The insertion of needles at acupuncture points to provide analgesia works through a variety of mechanisms including: reducing inflammation and decreasing tumor necrosis factor alpha (TNF-α), chemokines, and interleukins; releasing endogenous endorphins, serotonin, and other neurohormones that are involved in pain inhibition; and acting at a variety of receptors including the TRPV1 and N-methyl-D-aspartate (NMDA)/α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)/kainite receptors [6]. With repeated treatments, acupuncture can lead to neuroplasticity and long-term depression of pain pathways

in experimentally-induced pain, although this has not been clinically validated in patients with chronic pain syndromes [7, 8]. This acupuncture-induced neuroplasticity and modulation of the brain's resting state connectivity has been studied using functional magnetic resonance imaging (fMRI) in healthy patients receiving acupuncture as well as those who experience pain [4, 5].

A 2013 Cochrane database systematic review evaluated acupuncture for fibromyalgia with respect to pain, function, fatigue, sleep, stiffness, and sense of well-being [3]. Nine randomized control trials with a total of 395 patients were analyzed. Three studies involved EA, and the remainder used only MA. In one study, EA reduced pain by 22 %, on average. A sense of physical well-being and decrease in stiffness was also improved when EA was employed in several trials [3, 9–11] although only modest if any benefit for sleep was noted. The authors concluded that acupuncture improves pain and stiffness in fibromyalgia patients in comparison to no treatment or standard therapy. In general, the effect lasted up to 1 month, but disappeared at 6 months after the final treatment. However, some trials have shown improvements up to 1 year after treatment. Treatment protocols varied, but generally involved between six and ten treatments over 3–5 weeks. In one study showing benefit with six treatments over 3 weeks, 4–10 stainless steel needles were inserted in each trial patient to a depth of 10–25 mm (insertion depth was dependent on "needling sensation," also known as "de qi") and electric current < 10 mA was applied [9]. Controls received similar numbers of needles 20 mm away from the points used in trial subjects. These studies also suggest that EA was better than MA or sham, and that acupuncture generally appears safe and offers a reasonable alternative, alone, or as an adjunct to exercise and medication. The overall level of evidence was weakened due to small sample sizes of 50 patients or less, a scarcity of studies for comparison, and a lack of an ideal sham affected by the inability to blind patients to the "de qi" sensation, which some argue is necessary for effective acupuncture [3, 12–16].

One well-designed trial regarding acupuncture for the treatment of fibromyalgia showed a significant positive benefit in physical well-being as well as reducing fatigue, anxiety, and pain, although the sample size was small with only 50 patients [10]. This study was particularly instrumental in demonstrating that adequate blinding and nonpenetrating sham controls were possible, with patients unable to differentiate whether they had received real or sham acupuncture. Furthermore, the difference between real and sham acupuncture was significant for multiple outcomes. Patients in the acupuncture group received a total of six treatments over the course of 3 weeks, and showed improvement at 1 and 7 months follow-up after treatment. In addition, instead of individualizing treatments for each patient as in clinical practice, a standardized acupuncture protocol was used to minimize confounding factors in the study. However, whether individualized or standardized treatment protocols would be better for fibromyalgia patients are still unclear at this time.

Comparing acupuncture to fluoxetine control, another study found a significant improvement in fatigue and anxiety in acupuncture patients relative to control. This benefit was present at 1-year follow-up, and the treatment was well-tolerated with minimal side effects [17].

Acupuncture is not without risks. These risks are primarily associated with the skill of the practitioner and needle placement. These include bleeding, infection, nerve injury, pneumothorax (with needles incorrectly placed in the chest area), and vertebral artery dissection (with needles incorrectly placed in the cervical spine area). Relative contraindications include pregnancy due to induction of preterm labor through oxytocin release, and bleeding diathesis/anticoagulation due to the risk of hematoma and excessive bleeding. However, the incidence of serious adverse events is extremely small (estimated to occur in 0.0005% of total treatments and 0.0055% of individuals treated), and lower than the incidence of serious adverse events with most other minimally invasive procedures used to manage chronic pain [18]. Although acupuncture was found to be relatively safe, informed consent with a discussion of all the potential risks, benefits, and alternatives should be conducted prior to the treatment [19, 20].

Transcranial Magnetic Stimulation

Transcranial magnetic stimulation (TMS) and its variant, repetitive transcranial magnetic stimulation (rTMS), use a rapidly changing magnetic field to induce electrical currents that can be applied, noninvasively, to stimulate regions of the brain that may have pain relief or mood-enhancing benefits. rTMS has been well studied for psychiatric disorders and was approved by the Food and Drug Administration (FDA) in 2008 for the treatment of depression in the USA. Given the correlation between fibromyalgia and depressive symptoms, it was thought that rTMS may have some beneficial effects in fibromyalgia patients as well. According to a recent meta-analysis, rTMS has been shown to be effective in the treatment of neuropathic pain, particularly with multiple sessions and treatment frequency range between 1 and 10 Hz [21]. Additionally, the analgesia appears to be more effective for centrally-mediated rather than peripherally-mediated pain.

Central mechanisms of muscle fatigue experienced by fibromyalgia patients have been associated with decreased intracortical inhibition (ICI) at the motor cortex. ICI is thought to be related to gamma-aminobutyric acid (GABA) inhibitory and NMDA excitatory mechanisms. With physiological fatigue, ICI, as measured by TMS, is reduced in healthy subjects after they begin a fatiguing exercise. However, with fibromyalgia patients and those with muscular dystrophy, ICI is reduced at baseline (pre-exercise), possibly contributing to generalized feelings of ongoing fatigue related to a reduction in GABA activity, an increase in glutamate activity, and/or an increase in NMDA receptor activation [22]. Another study involving TMS of the motor cortex provided further evidence for this centrally-mediated mechanism for fibromyalgia, showing lower intracortical facilitation and short intracortical inhibition (SICI), correlated to increased fatigue, catastrophizing, and depression [23]. Therefore, the analgesic effects found with rTMS at the motor cortex may be related to the restoration of SICI [24].

Brain stimulation sites for rTMS have included either the motor cortex or the dorsolateral prefrontal cortex, using either high-frequency or low-frequency stimulation at each site. In general, patients experience analgesic and antidepressant benefits and fewer side effects using rTMS than with conventional FDA-approved pharmaceuticals for fibromyalgia, with the main side effects being transient headaches or scalp discomfort at the stimulation site [25, 26]. The pain-modulating effects of rTMS have been found to be longer lasting for affective rather than sensory pain [27].

In fibromyalgia patients, long-term analgesia with rTMS was observed up to 1 month after a 14-session series (an induction phase of five daily sessions followed by a maintenance phase of three sessions a week apart, then three sessions a fortnight apart, then three sessions 1 month apart), where each session consisted of 1500 pulses at 10 Hz [28]. This analgesic effect was present at day 5 through week 25, which was 1 month after the final treatment, and correlated with long-term improvement in fatigue, activity, and sleep in these patients that likewise lasted through week 25. In another smaller study, ten sessions of rTMS were used comparing low-frequency stimulation (1 Hz) to the right dorsolateral prefrontal cortex and high-frequency stimulation (10 Hz) to the left motor cortex, with longer-term antidepressant and analgesic effects found with low-frequency stimulation as opposed to high-frequency stimulation, where the effects were immediate but not maintained at 1-month follow-up [29]. Aside from the stimulation parameters, the configuration of the magnetic coils may produce differential results for pain. For example, 10 Hz stimulation was associated with better results than 1 Hz stimulation when a specific configuration was used in one study [30]. With the use of brain-magnetic resonance imaging (MRI)-based stereotaxic neuronavigation guidance, TMS can now be consistently applied to the same cortical location with each treatment (Fig. 8.1).

Transcranial direct current stimulation and electroconvulsive therapy are other modalities that have been investigated for fibromyalgia and involve noninvasive brain stimulation to correct altered central pain processing [31]. Based on the analysis by Short et al., early studies are promising, particularly given the neuroendocrine abnormalities present in fibromyalgia, but further studies need to be performed.

Risks associated with rTMS or transcranial direct current stimulation (tDCS) are minimal. A potential side effect of rTMS is a mild headache, resulting from muscle stimulation on the scalp. Typically, the headache will resolve spontaneously a few hours after the treatment or with a dose of acetaminophen. Occasionally, skin irritation can occur. This occurrence may be managed conservatively. Noise during treatment may also be a concern. Subjects can wear earplugs during the treatment session to minimize noise-related discomfort. Some patients may experience sleep disturbance during the course of rTMS or a feeling of increase/decrease of energy level. Although seizure occurrence was reported in the past, to the best knowledge of the authors, no seizure occurrence has been reported since the introduction of standard treatment guidelines in 1998 [32]. Patients with a history of seizure, prior intracranial metallic implant or acute intracranial injury should be excluded from these treatment options.

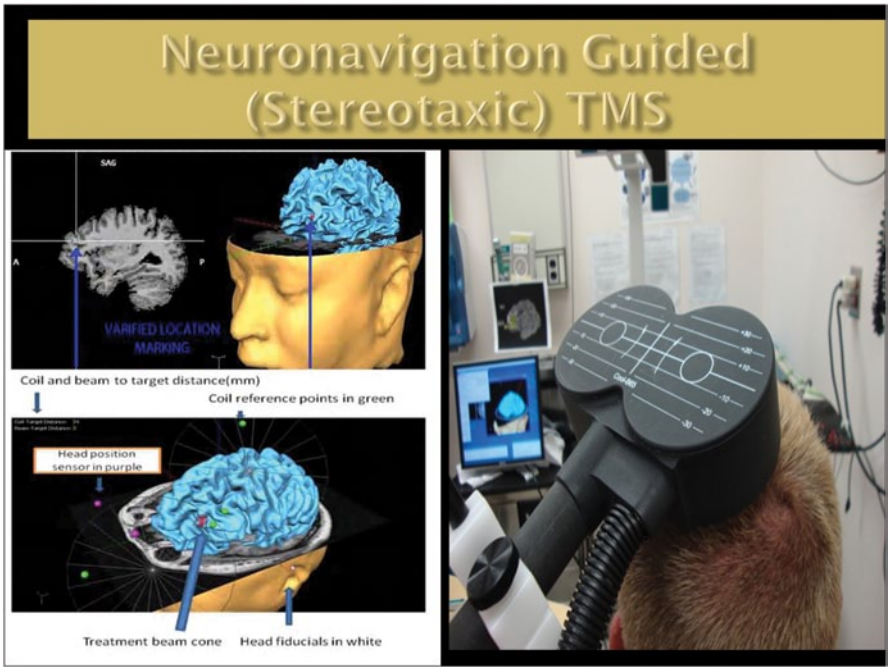

Fig. 8.1 Brain-MRI-based stereotaxic neuronavigation-guided TMS. The established treatment site is marked on the surface of the cortex so that each treatment is provided at the same location. TMS transcranial magnetic stimulation

Transcutaneous Electrical Nerve Stimulation (TENS)

Another form of noninvasive electrical stimulation known as TENS involves the application of electrodes to the skin overlying muscles or peripheral nerves. TENS works through activation of central inhibitory pathways and diminution of central hyperexcitability states, such as those present in fibromyalgia. It can be used either alone or in combination with other therapies to decrease pain and fatigue. In fibromyalgia, TENS applied at either the cervicothoracic junction or the lumbosacral junction has been shown to provide at least a short-term relief with significantly decreased pain sensitivity at tender points (both close to and distal from the TENS application sites), decreased fatigue with activity, and improved range of motion compared to placebo and no TENS [33]. When combined with a supervised exercise program, TENS seems particularly useful for decreasing the myalgic pain score (MPS), which is measured by the degree of tenderness at tender points [34].

The analgesic mechanisms of TENS appear to be frequency-dependent. High-frequency (150 Hz) TENS, which is typically used for acute pain, has also been shown in fibromyalgia to reduce anxiety and improve patients' capacity to work when applied to tender points [35]. High-frequency (>50 Hz), low-intensity TENS differs from low-frequency (<10 Hz), high-intensity TENS in that the former

activates *delta* rather than *mu* opioid receptors [36, 37]. In one study, both TENS at 80 Hz and superficial warmth provided comparable analgesic benefit [38].

One of the downsides of TENS is that daily, repetitive use may worsen pain by increasing opioid tolerance. In rats, once daily repeated administration of either low- or high-frequency TENS for 20 min over 6 days led to decreased responsiveness to TENS, increased hypersensitivity to pain, and decreased effectiveness of morphine [39]. It can therefore be inferred that long-term use of TENS may thereby decrease the effectiveness of other treatments, especially in patients using opioid therapy. However, this has not been validated in human studies. In fact, one study that involved simultaneous application of two TENS devices (at L5 and at C7-T1) for 20 min every 12 h consecutively over 7 days showed a significant reduction in pain and fatigue for single active TENS relative to placebo, and an even greater reduction in pain and fatigue with dual active TENS [40]. It might be most prudent to approach the use of TENS in two ways: (1) allow the patient to use TENS (whether one or two) at 20 min intervals as frequently as needed until it no longer works, in which case tolerance to the device can be assumed, and a rest period should be obtained before restarting or (2) use TENS only 1–2 times per day, for up to 7 consecutive days, only when absolutely needed to avoid the potential development of tolerance. The choice may need to be individualized based on the severity of the patient's symptoms, the use of other adjunctive medications, and the effectiveness of TENS for that particular patient.

Biofeedback

Biofeedback is another electrotherapeutic modality used in physical therapy in an attempt to improve relaxation and reduce pain. It involves skin electrodes on the patient that connect to a computer system, which provides visual and auditory feedback to the patient so that they can learn to control their involuntary physiologic responses such as muscle tone, heart rate, brainwaves, and pain perception. These responses are measured with physiologic monitors such as electromyogram (EMG), electrocardiogram (EKG), electroencephalogram (EEG), skin thermometers, photoplethysmographs, and capnography. Several randomized control trials of biofeedback for fibromyalgia have been performed. However, the validity of these studies has been limited by small sample sizes.

In a randomized control trial of 30 fibromyalgia patients with no comorbid, psychiatric, or cardiac conditions, true EMG biofeedback was evaluated against sham biofeedback in a 6-day treatment schedule of 45 min sessions per day. EMG biofeedback focuses on the patient's ability to control muscle relaxation. Both sham and true biofeedback groups experienced improvements in psychological and physical function based on fibromyalgia impact questionnaire (FIQ), 6-min walk test (SMWT), and visual analog scale (VAS) scores. The true biofeedback group experienced a greater, statistically significant decrease in pain and number of tender points than the control group [41].

Neurofeedback (NFB), or EEG biofeedback, has also been tested in a randomized controlled trial for fibromyalgia in 36 patients. Eighteen patients received 20 sessions of NFB over 4 weeks and were compared to 18 control patients who received 10 mg escitalopram per day over 8 weeks. Both groups showed significant improvements in anxiety, depression, pain, and FIQ scores. However, the NFB group obtained statistically significant greater improvements in all parameters than the control group [42].

A 2013 meta-analysis of EMG- and EEG-biofeedback for fibromyalgia that included seven studies showed EMG-biofeedback, but not EEG-biofeedback reduced pain intensity relative to control. For other factors such as sleep, depression, and fatigue, there was no significant difference between biofeedback and control groups [43]. Although there is no significant difference relative to control, given that both control (sham biofeedback) and treatment (true biofeedback) tend to decrease FIQ scores, it is possible that the psychological effect of even an attempt to control physiological responses could have a beneficial impact on quality of life for fibromyalgia patients in general. In light of these findings, it may be advisable for fibromyalgia patients to try EMG-based biofeedback first before other biofeedback methods.

Massage

Given the widespread myalgia present in the disease pathology, focusing on muscle stretch, whether active or passive, may be of benefit in fibromyalgia patients. Massage therapy allows for passive, mechanical manipulation of the body with the purpose of relieving pain and improving relaxation.

In one randomized controlled trial, massage therapy was compared to relaxation therapy in 24 patients with fibromyalgia. Massage was administered for 30 min twice weekly for 5 weeks using moderate pressure and including massage of tender points. The relaxation group was taught how to progressively relax their muscles while lying on a massage table. Both groups showed improvements, but the massage group experienced improved sleep and decreased depression, pain, fatigue, stiffness, and number of tender points. Additionally, the massage therapy group exhibited a decrease in substance P levels between the first and the last day of massage, whereas the relaxation group had increased substance P levels [44].

Another study compared massage–myofascial release therapy to placebo over the course of 20 weeks. The study was completed with 30 patients in the experimental group and 29 patients in the placebo group. Treatment resulted in an immediate decrease in anxiety and pain, with improvements in quality of sleep and quality of life that were still present at 1 month after the completion of massage therapy. Quality of sleep was still significantly improved even at 6 months after the last treatment session [45]. Therefore, although some of the benefits of massage may be long lasting, fibromyalgia patients would receive greater benefit from massage therapy at intervals of less than 6 months.

Yoga and Tai Qi (Tai Chi)

In addition to the passive stretching that occurs with massage and with some dry needling/acupressure maneuvers, active stretching with exercises such as yoga and tai qi have also been found to be of benefit in fibromyalgia patients. “Tai qi” and “tai chi” can be used interchangeably for the purposes of the studies discussed; the different spellings exist due to the Romanization of the mandarin dialect, and both spellings can be found in the medical literature. Tai chi and yoga are particularly well suited to the treatment of fibromyalgia because of their mind–body orientation, thereby treating the psychological and emotional as well as physical components present in fibromyalgia. Both involve the cultivation of slow, controlled movements combined with breathing exercises (Fig. 8.2).

A pilot study of yoga for the treatment of fibromyalgia showed significant improvements in pain scores, pain catastrophizing, pain acceptance, and mindfulness. Interestingly, salivary cortisols were higher in patients following the completion of their 8 weeks, biweekly yoga program [46]. Also, a small study showed that while the addition of acupressure (tui na) to yoga may improve symptoms over the course of therapy, only fibromyalgia patients who did yoga alone had long-term improvement in their pain and function (4–6 weeks after the last session). The authors suggest that the addition of passive therapy may decrease patients’ self-efficacy for pain control [47] .

Fig. 8.2 Yoga practice in natarajasana pose. Yoga embodies a meditative philosophy of tolerance, patience, stillness, and acceptance in conjunction with physical postures designed to induce muscle stretch. The combination is used to alleviate health problems, strengthen the spine and surrounding ligaments, and reduce stress, by enhancing the practitioner’s ability to find quietude and stillness while moving through the asanas (body positions). In this figure, Dr. Annie Morrison is performing the “king dancer pose” (natarasajana), which is designed to stretch the shoulders, chest, thighs, groin, abdomen, strengthen legs and ankles, and improve balance. There are more than 100 yoga asanas designed to strengthen, stretch, and provide pain relief to various body parts

Several randomized control trials have been performed regarding the effectiveness of tai chi for symptomatic relief of fibromyalgia. Different forms of tai chi involve different movements and postures. Yang style is one of the most popular styles. In a study of Yang style tai chi (33 patients) compared to regular stretching exercises (33 patients) for 60-min periods twice weekly over 12 weeks, patients who participated in tai chi had statistically significant improved scores in FIQ and SF-36 relative to control patients. These improvements were sustained at 6 months after the intervention, showing long-term benefit with these specialized exercises [48]. In a subsequent study of 101 patients using Yang style tai chi training (90-min sessions twice weekly over 12 weeks) compared to education alone, tai chi significantly improved FIQ scores, pain severity, quality of sleep, self-efficacy for pain control, functional mobility, and balance. There were no adverse events, and patients remained on their fibromyalgia medications—typically an antidepressant and an analgesic [49]. It seems that pain reduction may accrue over time with an extended treatment period. For example, a study of fibromyalgia pain reduction in 27 women showed immediate pain reduction as measured by VAS scores following each Yang style tai chi session. At 12 weeks of tai chi practice, pre-session scores before each session did not vary greatly. However, after 12 weeks of tai chi practice, pre-session VAS scores also began to diminish, suggesting a cumulative impact of tai chi so that by the 24th week, pre-session VAS scores had significantly decreased as well. This suggests that a longer course of regular tai chi practice can have a greater impact on baseline pain and functioning in fibromyalgia patients [50, 51].

Other mind–body stretching exercises such as qigong and pilates have also been studied for fibromyalgia. A meta-analyses of complementary exercises for the treatment of fibromyalgia validated the safety of these alternative exercise regimens in deconditioned fibromyalgia patients. The analysis also suggests that no one exercise form is consistently better than the others, although the strongest evidence exists for qigong and tai chi [52].

Thus, mind–body exercises such as tai chi and yoga provide a safe and effective way to improve pain and functioning in fibromyalgia patients, both short- and long term. The mechanisms of action involve both psychological as well as physical components. Long-term improvements in pain are easier to sustain with longer treatment periods, suggesting that lifestyle changes related to regular practice may be involved. Additionally, the addition of passive therapies seems to decrease the effectiveness of the exercises, suggesting that the greatest improvements may come from an increased sense of self-efficacy and personal pain control, possibly related to the meditative training some receive in other modalities such as CBT.

Balneotherapy (Spa Therapy)

Balneotherapy involves hydrotherapy using hot or cold water baths, with or without minerals, to decrease pain and improve relaxation. It has been found to be beneficial for fibromyalgia patients. In one randomized control trial, balneotherapy in

addition to pharmacological treatment was found to be superior to pharmacological treatment alone in terms of significantly improving FIQ scores, Beck Depression Inventory scores, and SF-36 scores [53]. These findings have been confirmed in several other randomized controlled trials of balneotherapy for fibromyalgia, and a review of the literature suggests that an increase in endorphin and cortisol levels with a decrease in inflammatory mediators interleukin-1 (IL-1), IL-6, prostaglandin E2 (PGE2), leukotriene B4 (LTB4), TNF-α occurs with balneotherapy and may contribute to its effectiveness for fibromyalgia [54]. A meta-analysis of randomized control trials for balneotherapy in fibromyalgia including 13 trials and 446 subjects has also shown moderate evidence for pain reduction and improved health-related quality of life at the end of therapy as well as at a median follow-up duration at 14 weeks [55]. There is some evidence that, while balneotherapy gives temporary relief, mud-baths may provide relief greater than 3 months following treatment [56]. Given the low risk and potential benefit associated with this treatment modality, balneotherapy can be considered as adjuvant therapy for fibromyalgia patients at their own discretion.

Other Complementary Therapies

A variety of complementary therapies for fibromyalgia have been studied. In addition to the most commonly studied modalities presented above, other modalities with less supportive evidence include hypnotherapy, music therapy, and the addition of vitamins and herbs [57]. Hypnotherapy has been shown to enhance the improvements obtained with CBT when compared to CBT alone [58]. However, a systematic review and meta-analysis of controlled trials regarding hypnosis for fibromyalgia concluded that health-related quality of life in hypnotized patients was not improved relative to controls, and that significant reductions in pain were questionable due to low methodological quality in the trials analyzed [59]. And, while there have been no randomized control trials to date studying the effects of music in fibromyalgia, other studies have shown that music has analgesic effects at least in the acute pain setting [60]. Some herbal formulations may be of benefit. For example, oral anthocyanidins (found in Acai and other purple and blue fruits) and topical capsaicin improve sleep and tenderness, but not overall pain [61]. Some herbal remedies have similar mechanisms of action to conventional therapies. Kava kava acts on the GABA receptor. St. John's Wort shares similar mechanisms with some antidepressants, and herbs such as Devil's Claw, which contain salicylate, may have anti-inflammatory actions. Despite these potential mood enhancing and analgesic benefits, it may not be safe to recommend these medications because of the lack of FDA control and standardization in dosing. However, it is important for pain physicians to recognize the prevalence in the usage of these herbal remedies, to document their use, and to be cognizant of interactions with conventional pharmacologic therapies.

Table 8.1. Level of evidence for fibromyalgia

Treatment modality	Supporting evidence	Level of recommendation
Acupuncture	Cochrane database systematic review [3]	High (EA preferred)
Repetitive transcranial magnetic stimulation (rTMS)	Systematic review [25]	High
Transcutaneous electrical nerve stimulation (TENS)	>3 RCT's supporting use	Low-moderate
Biofeedback	Systematic review and meta-analysis [43]	Moderate (EMG preferred)
Massage	> 3 RCT's supporting use	Low–moderate
Yoga	Meta-analysis [52]	Low–moderate
Tai Qi (Tai Chi; Qigong)	Meta-analysis [52]	Moderate
Balneotherapy	Meta-analysis [55]	Moderate
Hypnotherapy	Systematic review and meta-analysis [59]	Low

EA electroacupuncture, *EMG* electromyogram, *RCT* randomized controlled trial

Conclusions

Many alternative therapies have evidence of benefit in fibromyalgia patients (Table 8.1). Expectation management is important. Acupuncture treatments biweekly for 3–5 weeks have shown to be beneficial for global well-being and a decrease in pain and stiffness. Evidence of benefit with repeated rTMS treatments has also been demonstrated. EMG-biofeedback and massage may also be beneficial for symptom management. For home maintenance therapy, TENS, massage, balneotherapy, and tai qi/yoga can be used to help the patient manage their pain when they are unable to make multiple visits to a physician or other medical expert. Many of these treatments may be costly, but it is reasonable to attempt treatment with these therapies as long as both the physician and patient participate in informed consent, with a detailed discussion of costs as well as risks, benefits, and alternatives.

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Chapter 9
Utilizing Clinical Treatments with a Limited Evidence Base

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Key Points

- Management of patients with fibromyalgia (FM) is confounded by factors including: diversity of presenting symptoms, multiple functional domain dysfunction (sleep, mood, etc.), lack of consensus on its pathophysiology, controversy about its clinical definition.
- Wide variation in practice exists, including utilizing treatments with limited evidence basis in the literature
- Multimodality therapy is associated with better treatment outcomes over single component therapy as part of an individualized treatment plan for patients with FM.
- Compared to muscle strengthening and aerobic exercises, flexibility-only and single modality movement exercises have limited evidence for efficacy in pain reduction for patients with FM.
- Most studies of chiropractic and massage therapy for FM have a very small sample size and have not demonstrated improved outcomes in the treatment of FM.
- Small sample studies of electrotherapy have not demonstrated improved outcomes in the treatment of FM.
- Despite the lack of evidence of efficacy in FM and the risk of adverse effects, benzodiazepine, opioid, muscle relaxant, and nonsteroidal medications are prescribed to patients with FM at a high frequency.
- Interventional therapies such as trigger point injections when used as a single modality have not been shown to improve outcomes in patients with FM.

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Introduction

There are limited systematic studies on treatment options for fibromyalgia (FM), and an even greater paucity of high-quality-blinded randomized controlled clinical trials. Among the reasons for lack of well-conducted clinical trials is the diversity of symptoms associated with this condition and the lack of consensus on defining the pathophysiology of the disease. Patients may complain of a host of complex and often debilitating symptoms including chronic multifocal pain, fatigue, insomnia, cognitive dysfunction, psychologic distress, along with physical impairment. Each of these symptoms may be treated separately and respond to therapy individually, making it difficult to assess which treatment is associated with which outcome.

Further complicating the definition of this disorder is the high frequency of co-existing syndromes with overlapping signs and symptoms such as headaches, musculoskeletal pain syndromes, chronic fatigue syndrome, irritable bowel syndrome, interstitial cystitis and pelvic pain. Lack of evidence basis in treatment can be attributed to the breadth and variable nature of this disease, along with the lack of consensus about the definition of the disease, which outcomes to evaluate, and the lack of knowledge of underlying pathophysiologic mechanisms. As such, a wide variation in practice exists in the medical community caring for patients with FM and many treatments exist that do not yet enjoy support by randomized controlled trials (RCT) but that are considered clinically relevant and appropriate in managing these patients. The purpose of this chapter is to identify and discuss some of these common treatments for FM and the current state of the literature in evaluating their effectiveness.

Challenges in the Study of FM

FM is a medical condition thought to be characterized by disordered afferent neural processing. However, there are several practical as well as theoretical challenges to the study of FM. While experimental pain testing has demonstrated that FM is associated with augmented pain sensitivity and disordered sensory processing, neither the precise underlying mechanisms nor the etiologic factors associated with the development of symptoms are yet understood [1–5]. This complicates the diagnosis, classification, management, and prognosis of FM. There is no biopsy, laboratory study, or radiographic imaging that is pathognomonic for FM. It remains a diagnosis based on patient symptoms and complaints.

Further complicating this gap in pathophysiologic understanding are recent changes that have been made to diagnostic criteria and assessment of severity in various outcome domains. The American College of Rheumatology (ACR) classification criteria for FM originally published in 1990 required that patients have 11 of 18 tender points present on examination as well as widespread pain defined as axial, left- and right-sided pain, and upper and lower segment pain [6]. Over time, it

became apparent that specifically accounting for the defined tender points was rarely performed in the primary care setting and when performed, the examination was often done so incorrectly [7, 8]. In 2010, the ACR Multicenter Criteria Committee conducted an analysis to validate an alternative diagnostic method that did not rely on tender point examination and developed a symptom severity scale to measure complaints often associated with FM, including fatigue, waking unrefreshed, cognitive symptoms, headaches, pain or cramps in lower abdomen, and depression [9, 10]. Despite modifications to the definition of what constitutes a clinical diagnosis of FM, consistent application of diagnostic criteria still relies on the interpretation and personal judgment of the diagnosing physician.

Other problems with arriving to a consensus on the definition of FM include the overlap between FM and other central pain syndromes, the subjective nature of patients' presenting symptoms, and the lack of an objective "gold standard" test for FM [11, 12]. While the recent modifications to the ACR criteria have enabled severity assessment in several outcome domains such as sleep or mood, criticism has been directed at the introduction of phenotypic heterogeneity to an already heterogeneous disease entity which could decrease the likelihood of identifying etiologic disease pathways [12]. Indeed, the lack of uniformity in choosing outcome domains to study has made FM particularly difficult to study. One review of 24 clinical trials of FM found that no two trials used same outcome measures and that as many as nine different instruments were used for a single outcome measure [13].

Review of Select Common Treatment Modalities for FM: Multimodal Versus Single-Modality Treatment in FM

As FM is a disease that presents with multiple symptoms and has an effect on multiple functional domains, there is rarely a singular effective treatment. Therefore, clinicians have touted a logical and practical approach using a multidisciplinary treatment plan that is tailored to the needs of the individual. The prevailing expert opinion in the field is that single modalities of treatment may not be sufficient to treat chronic pain from FM and that analgesic therapy which addresses only one component of the pain experience is destined to fail [14, 15]. This view is also reflected in the most recent German (2012), Canadian (2012), and European League Against Rheumatism (EULAR) guidelines (2007) [16–18]. However, research in support of this treatment recommendation is limited to small-scale trials [19, 20] which did not prove the efficacy of multicomponent therapy on FM in the long run.

In 2009, Hauser et al. performed a meta-analysis of nine RCTs with a total of 1119 subjects and found that although there was strong evidence that multicomponent treatment resulted in a short-term effectiveness in FM, evidence for long-term efficacy was lacking [21]. The investigators chose to define "multicomponent" treatment to consist of at least two nonpharmacologic therapies (at least one educational or other psychological therapy, and at least one exercise therapy) and the range of follow-up of subjects was between 3 and 15 months.

There is a discrepancy between the strength of recommendations found in national and international guidelines (multimodal therapy is strongly recommended by both Canadian and German guidelines) and the actual quality of the underlying evidence, which is sparse apart from the meta-analysis by Hauser. This can be partially explained by the nature of treating a complex, multidimensional disease such as FM and the challenge of defining individual patient characteristics and subgroups that will respond best to a specific therapy. Future trial design may benefit from techniques such as performing randomized trials of treatment in individual patients rather than multi-patient RCTs [22]. In the meantime, the heterogeneity of disease symptoms in FM and the complexity of evaluating outcomes lend themselves well to multimodal therapy. Multimodal therapy remains part of a rational, individualized treatment plan and there are consensus-based guidelines that state it should be offered to FM patients who have relevant limitations in daily functioning and who do not respond to pharmacologic or nonpharmacologic monotherapy.

Physical Modalities Used to Treat FM

Physical modalities used to treat FM include a spectrum of treatment types, and there can be multiple definitions of what actually constitutes a treatment. A Cochrane review of exercise for treatment of FM in 2002 and updated in 2008 defined "exercise" to include aerobics, such as stepping and walking, and strengthening exercises such as resistance training and weightlifting and stretching for flexibility [23]. The authors pointed to the lack of high-quality clinical trials for stretching and flexibility exercises which were defined as "controlled static stretching in which a subject assumes a position and holds it for a given duration." The review identified 3 studies out of a total 34 exercise studies which examined flexibility-only or stretching-only exercises. Of these, one study in FM patients reported that flexibility-only exercise compared to strength exercise had a large positive effect on flexibility but no effect on tender points or depression. In that study, a small number of participants had an increase in pain levels related to exercise [24].

More recent systematic reviews of exercise treatment studies for FM done by Jones et al. and the Ottawa Panel evidence-based guidelines committee found that the evidence for flexibility training is lacking, Only 3 trials were found evaluating flexibility training out of 46 exercise trials reviewed from 1988 to 2005 [25–27]). The same reviews found that "movement" therapies such as Tai Chi, Yoga, Qi Gong also had positive evidence in small case series but that there was a lack of good quality trials [25]. Despite the lack of evidence for these physical modalities as a monotherapy, any one physical activity still constitutes an important part of multimodal therapy which together with other treatments can be effective for treating FM [28].

Complementary and Alternative Medicine

Many common complementary and alternative medicine (CAM) techniques are characterized by significant variations in practice and have not been subjected to high-quality clinical trials of their efficacy. Manipulative and massage therapies are done for patients with FM, but there is limited evidence base in the literature. A systematic review by Terhorst et al. in 2011 found 18 high-quality studies out of 60 RCTs comparing pain treatment of FM patients with a CAM therapy versus a control group [29]. The CAM categories utilized for treatment included balneotherapy, massage, manipulative (including chiropractic), vibration, magnetic, homeopathic/nutritional supplements, mind–body movement therapies, energy medicine, acupuncture, and miscellaneous.

The authors found that there were two and five low-moderate quality studies, respectively, that evaluated FM patients treated with chiropractic and massage techniques. In four of the five studies in the massage group, there was no treatment benefit for FM patients. While both the chiropractic studies were included in the systematic review, combined they did not show an overall treatment effect due to their very small sample sizes [29]. However, in a small uncontrolled trial, when chiropractic spinal manipulation and soft tissue massage were combined, they decreased tenderness in patients with FM [30]. Connective tissue manipulation and massage have been found to produce positive results by reducing depression, pain intensity, and amount of analgesics used [31, 32]. In general, most CAM studies evaluating effectiveness of treatment in FM have small sample sizes and larger trials are needed.

Electrotherapy

A feature common in patients who suffer from both FM and depression is altered. Since electrotherapy directed at modulating brain sensory processing has been used successfully in reducing depression, several types of electrotherapy of the brain have been tried in pain syndromes including FM [33]. Electrical stimulation procedures such as electroconvulsive therapy (ECT) or repetitive transcranial electromagnetic stimulation (TES) have been attempted in FM. However, the evidence for ECT has been limited to small, uncontrolled, or poorly controlled trials [34].

Thus far, preliminary data from several small randomized controlled pilot studies of other electrotherapy modalities like transcranial direct current stimulation, transcranial magnetic stimulation, and cranial electrical stimulation are unconvincing with small effect sizes and lacking long-term follow-up [35–37].

To date there is only one trial by Almeida and colleagues involving combined ultrasound and inferential current electrotherapy. While the trial did show improved pain levels and sleep in FM patients compared with sham treatment demonstrated by objective and subjective measures, the study was limited by an extremely small sample size [17] and an unblinded study design [38].

Pharmacotherapy

While its pathophysiology is not well understood, FM has both clinical and biologic features in common with other types of neuropathic pain. For example, patients with FM and neuropathic pain both experience similar clinical phenotypes as demonstrated by standardized subjective symptoms, comorbidities, and sensory profiles [39]. Oaklander and colleagues recently demonstrated similarities between the skin biopsies of patients with FM and those with small fiber neuropathy [40]. Thus, the current pharmacologic treatment paradigm for FM consists primarily of analgesics typically used to treat neuropathic pain. Currently, there are three US Food and Drug Administration (FDA)-approved pharmacologic agents for FM: pregabalin, duloxetine, and milnacipran. Prior to FDA approval of the initial agent, pregabalin, in 2007, all pharmacologic therapy for FM was considered an "off-label" use.

Some other categories of pharmacologic agents have not been validated in clinical studies to have efficacy in treating FM. Opioid medications are often considered for patients with chronic, severe pain, but there are currently no RCTs studying the treatment efficacy of pure mu-opioid agonists in FM [41]. If opioids are given at high doses to patients who have a poor treatment response, these patients may be at a higher risk of developing opioid-induced hyperalgesia. A recent Cochrane review examining the effect of oxycodone on neuropathic pain and FM found that the risk of adverse events favored oxycodone over placebo with a number needed to harm of 4.3 [42]. Adverse events from the use of pure mu-opioid agonists in FM can include sedation, respiratory depression, constipation, nausea, opioid induced hyperalgesia, physical dependence, addiction, and tolerance. In evaluating other clinical conditions with neuropathic pain features, three RCTs of patients with diabetic peripheral neuropathy or post herpetic neuralgia failed to show good or moderate quality evidence for improved pain efficacy with the use of opioids [42]. Therefore, opioid use has been discouraged as a treatment for FM pain in recent national and international guidelines [16–18].

Benzodiazepines are another category of drugs with poor treatment efficacy for FM patients. Furthermore, the use of benzodiazepines may be associated with similar side effect profile including promoting respiratory depression, physical dependence, addiction, and tolerance. Muscle relaxants such as cyclobenzaprine have been commonly prescribed to FM patients but have poor quality evidence for efficacy. A review of four placebo controlled trials of cyclobenzaprine over 4–12 weeks found only two trials demonstrating efficacy in patients with FM [43–47].

Nonsteroidal anti-inflammatory drugs (NSAIDs) are another category of drugs with no evidence of clinical effectiveness when used alone in FM, although they may be useful adjuncts for analgesia when combined with tricyclic medications [48]. In a controlled study of corticosteroids in patients with FM, it was reported that 10 mg of prednisone daily was not an effective treatment [49].

Despite the lack of evidence of efficacy of any of these classes of drugs and the risk of potential medication-induced side effects, the prevalence of patients diagnosed with FM receiving benzodiazepine, opioid, muscle relaxant, and nonsteroidal medications remains high [50]. These are not only commonly prescribed for

FM patients as part of an overall treatment plan but also sometimes represent the single type of treatment given to patients to manage their FM symptoms. Despite the lack of demonstrated efficacy, surveys of patients have found that FM patients may actually perceive these classes of medications to be most effective [50]. However, Hooten and colleagues have demonstrated that patients with FM who were enrolled in an intensive outpatient rehabilitation program, in which their opioid, benzodiazepine, muscle relaxant, and nonsteroidal medications were withdrawn, improved in several pain outcome domains including overall pain, physical and emotional functioning after treatment [51]. Thus, future public health efforts should be directed toward not only providing evidence-based treatments to patients with FM but also preventing treatments that have been shown to lead to worse outcomes. In some cases, it is important to wean and rehabilitate patients chronically treated with medications that are not appropriate for FM.

Interventional Therapy in FM

While trigger point injections (TPIs) are commonly used in the treatment of FM, the literature evidence for this practice is sorely lacking. The recommendations to perform TPIs to treat FM pain is limited to uncontrolled studies as there are currently no RCTs of single modality treatment with TPI for FM. In addition, there is some evidence that TPI may have a greater side effect profile in FM. One small study by Hong et al. found that in patients with combined myofascial pain syndrome (MPS) and FM, postinjection soreness was more severe, developed sooner and lasted longer in this group than in patients with MPS alone [52]. Furthermore, a widely referenced systematic review of TPI therapy in MPS conducted by Cummings and White did not find any trials of sufficient quality to test the efficacy of any needling technique beyond placebo in the treatment of myofascial pain [53]. However, Affaitati and colleagues conducted a small RCT in 2011 which found that in FM patients with comorbid myofascial trigger points identified by strict application of Simons' criteria, the patients improved not only in terms of myofascial pain but also FM symptoms in the short term [54, 55]. While encouraging, future large-scale studies are needed to further substantiate these findings. Whereas there may be individual patients who benefit from TPI for well-circumscribed trigger points in the setting of FM, the ongoing treatment of general FM symptoms with TPIs is not currently recommended.

Conclusion

There continues to be a lack of general consensus in the overall treatment plan for many patients with FM. Commonly held beliefs in the effectiveness of treatments such as multimodal therapy, the use of massage and chiropractic modalities will require further validation with well-conducted clinical trials. Furthermore, the use

of several categories of analgesic and anxiolytic medications (opioids, benzodiazepines, muscle relaxants, NSAIDs) seems to carry more risk than benefit for many patients. And the widespread use of TPIs for patients with diffuse FM symptoms cannot be recommended based on the current level of literature that exists.

With a better understanding of the pathophysiology and etiology of the disease, it is hoped that more directed treatments become available that treat FM as a single entity rather than a collection of symptoms. More consensus is needed on a widely accepted definition of the syndrome. In light of all of these considerations, it is important to recognize that the current state of the medical literature and lack of evidence for certain treatments do not invalidate the possibility that any of these treatments may be singularly effective for subgroups or individual patients. Patients should not be denied treatments based on group outcomes when individual outcomes may vary substantially.

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Chapter 10
Treatment of Special Groups: Children, Pregnant, Elderly, and Mentally Disabled

Sunjay Nath Mathur and Dominika Lipowska James

Key Points

- Some patients, especially pregnant women, children, and the elderly, should refrain from medication management due to safety concerns. Non-pharmacologic treatments become essential to reduce symptoms and improve function.
- Children and the elderly may be misdiagnosed with other medical conditions, especially rheumatologic disorders, early in their clinical course.
- Clinicians must weigh the risks and benefits of treatment options with pregnant patients to help balance the needs of the mother and the fetus. The needs of the mother and fetus are not always at odds, even with pharmacologic treatment.

Fibromyalgia and Children

Juvenile fibromyalgia syndrome (JFM) is a complex chronic pain condition that affects roughly 2–7% of school-age children [48, 160]. Fibromyalgia can be found at any age. Symptoms in children can include chronic and widespread musculoskeletal pain, fatigue, sleep, and mood disturbances [122, 280]. Somatic manifestations are also common and include headache, dysautonomia, subjective soft tissue swelling, and irritable bowel syndrome. These symptoms can interfere with physical, emotional, social, school, and home functioning. Stress, weather, and physical activities can influence symptom severity. While a diagnoses may be made by the

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1990 American College of Rheumatology (ACR) criteria, which was not validated in children, or the American Pain Society consensus statement of 2005 [11], many studies rely upon the criteria originally proposed by Yunus and Masi in 1985 [280].

A diagnosis of juvenile fibromyalgia according to Yunus and Masi requires generalized musculoskeletal aching at three or more sites for three or more months in the absence of an underlying condition (trauma, infection, rheumatic, endocrine, etc.). Tender points, particularly those around the medial knees, thoracic and lumbar paraspinals, and trapezius, are an important part of the diagnosis. At least five tender points should be identified. Additionally, three of the following ten features should be present: (1) chronic anxiety or tension, (2) fatigue, (3) poor sleep, (4) chronic headaches, (5) irritable bowel syndrome, (6) subjective soft tissue swelling, (7) numbness, (8) pain modulation by physical activities, (9) pain modulation by weather factors, and (10) pain modulation by anxiety/stress. Four tender points may suffice for a diagnosis if five of the above factors, rather than simply three, are also found.

Various intrinsic and extrinsic factors may predispose children to chronic pain states. Intrinsic factors that may predispose children to developing chronic pain include difficult temperament, maladaptive pain coping strategies, hypermobility, female gender, and low-pain thresholds [144]. External factors and triggers for pain are varied but can include weather, illness, mood, life stressors, and physical exertion [216].

The search for the cause of JFM has led investigators to look for associated characteristics. Studies have shown an association between sleep abnormalities and fibromyalgia [211], although direct causality is not clear [188]. Neuroendocrine dysregulation may play a role as well [273]. Joint hypermobility has also been found with higher frequencies among those with fibromyalgia [103, 113]. It has been postulated that the recurrent trauma from joint hypermobility causes persistent pain which may eventually lead to a centralized pain state. Premature birth may be associated with chronic widespread pain [140]. Children with growing pains have decreased pain thresholds [104], but fortunately the risk of developing fibromyalgia within 5 years is low [265]. When developing a differential diagnosis, growing pains are more common in pre-adolescents, occur mostly in the evening, and are limited; JFM usually develops in adolescents, affects daytime functioning as well as sleep, and is persistent.

There is conflicting evidence that childhood maltreatment may lead to the development of chronic pain syndromes or fibromyalgia. Repeated heel lances can lead to pain hypersensitivity and prolonged behavioral alterations in premature infants, suggesting that the mechanisms to develop chronic pain exist early in our development [88, 112]. Children with chronic musculoskeletal pain frequently describe a history of psychosocial stressors [134, 144, 232]. Sexual and physical maltreatment is associated with poor household experiences including distancing from parental emotional support, witnessing physical quarrels and addiction, and confronting separation and addiction [114]. Loss of parents in childhood can have significant consequences [116, 150, 151]. Researchers have found self-reported histories of childhood maltreatment as well as elevated scores for somatoform dissociation and depression in patients with fibromyalgia syndrome [33]. These studies suggest a link between childhood maltreatment and adult chronic pain syndromes.

Despite this evidence, many authors suggest that further scrutiny is required before drawing causality between childhood factors and the development of fibromyalgia. The magnitude of the relationship between childhood abuse and adult pain is not strong [207], and many adults who have witnessed such experiences do not develop fibromyalgia [60]. The retrospective self-reporting of abuse histories may methodologically limit conclusions that we can draw from the body of work previously done connecting childhood trauma and adult chronic pain syndromes [206]. A more cautious approach toward causality between childhood trauma and adult fibromyalgia appears warranted.

Genetics may play a role in determining those children who will develop JFM [44, 46, 47, 51, 53, 54]. Given that fewer men are diagnosed with fibromyalgia, it has been postulated that fibromyalgia is inherited in an autosomal dominant manner with variable expression based on gender. Fibromyalgia has been observed to run in families [14]. A genome-wide linkage scan in 203 affected sibling pairs found elevated sibling recurrence risk in families with one affected family member of 13.6, suggesting a strong genetic component to fibromyalgia [18]. One major locus that satisfies Lander and Kruglyak's criterion for linkage is mapped to the region that encodes a serotonin transporter gene and a transient receptor potential vanilloid 2 (TRPV2) gene, two potential candidate genes for fibromyalgia. These investigations lay the groundwork for further investigations into the connection between genotypes and phenotypes and may assist diagnostic accuracy. Further studies should investigate whether early genetic identification coupled with interventions can play a role in modulating disease onset or severity.

There are many approaches to the treatment of JFM. Non-pharmacologic treatment of JFM includes educating the patient and the parents about the condition. Involving parents in the treatment sessions can improve understanding throughout the family and improve cohesion in the treatment plan. Just as with adults with fibromyalgia, chronic aerobic activity can also benefit children with JFM. Authors have shown that performing a study on aerobic activity in children with fibromyalgia is feasible [249]. There is limited but growing evidence that alternative and complementary treatments are preferred by patients and may be helpful.

A well-studied non-pharmacologic intervention for juvenile fibromyalgia is cognitive behavioral therapy (CBT). Treatments for pediatric chronic pain have shown that CBT is helpful [194]. A study at four pediatric rheumatology centers found CBT superior to fibromyalgia education in reducing functional disability and symptoms of depression [122, 126]. CBT can teach self-management skills in 6–8 weekly sessions to help children reduce pain and disability through active and adaptive coping skills. Skill employed include relaxation-based treatments, distraction, activity pacing, enjoying regular pleasant activities, improved problem solving, and replacing catastrophic thoughts with more realistic appraisals. These skills are taught both to the patient, the child, and to the "coach," the parents. Those patients and families committed to this course of treatment will likely show improved participation and outcomes from this treatment [65]. A multidisciplinary approach has been found to be safe, not associated with adverse reactions, and well received with completion rates of 85 % [126].

Pharmacologic treatment has few randomized-controlled clinical trials focused on children and adolescents. There are no current evidence-based guidelines for the pharmacologic management and no current medications carry FDA-approved indications for JFM. There is growing attention paid to studying current compounds for efficacy in JFM.

Gabapentin, a compound frequently used for neuropathic pain conditions, has also been used off-label as a first-line agent in juveniles with some success [16]. Pregabalin, a gamma-aminobutyric acid analogue, has an FDA-approved indication for fibromyalgia, although studies of its efficacy in JFM are ongoing. Pfizer is currently sponsoring a study recruiting subjects between the ages of 12 and 17 looking to assess the effectiveness of pregabalin compared to placebo in treating adolescents with fibromyalgia (NCT01020474). Pregabalin has demonstrated efficacy in children with chemotherapy-induced neuropathic pain [269].

Selective serotonin reuptake inhibitors (SSRIs) are not commonly used for adults with fibromyalgia, but have shown some limited improvements in JFM with four subjects who completed 12 weeks of open-label treatment with fluoxetine [13, 146].

Although not studied in JFM, clinicians frequently utilize serotonin-norepinephrine reuptake inhibitors (SNRIs). These have demonstrated efficacy in treating adults with fibromyalgia [15, 17]. Case reports have shown the safety of duloxetine in children treated for depression [158]. Eli Lilly is also exploring the role of duloxetine in JFM (NCT01237587).

Tricyclic antidepressants (TCAs) are also employed to manage JFM. Although children may metabolize TCAs more quickly than adults, there remain 5–10% of children who are slow metabolizers, making careful titration important. Heightened concerns regarding TCA toxicity arose after the sudden death of four children with TCA treatment [32]. A review of the case reports did not find any effect of the common TCA used, desipramine, on the deaths of these children, suggesting that the occurrence of sudden death is either coincidental or idiosyncratic [69]. Clinical consensus continues to recommend routine electrocardiograms as well as serum TCA level monitoring, especially in patients with personal or family histories of premature cardiac disease, along with regular reevaluation for the appropriateness of TCA therapy. Educating parents about the lethal potential of TCAs, especially in the setting of accidental or purposeful overdose, can improve compliance and reduce the risk associated with these medications.

Opioid medications are used less frequently when treating fibromyalgia, and will likely continue to be used less for JFM. The benefit of these medications continues to be outweighed by the risks of dependency, sedation, and opioid-induced hyperalgesia [62] as well as potential for diversion and abuse, a particular concern in the adolescent population. A limited role for tramadol, a partial mu-opioid receptor agonist, may be reserved for those patients refractory to other treatments [27].

The prognosis for children with JFM is optimistic, with studies showing resolution of JFM symptoms in 50–70% of children after 2 years [50, 159]. Success rates in treating JFM will depend on early diagnosis and intervention, a multidisciplinary approach, and focus on functional outcomes.

Fibromyalgia and Pregnancy

Pregnancy induces widespread changes in the woman's body in order to accommodate the growing needs of the fetus. These changes require special attention for patients suffering from fibromyalgia.

There is a greater role for preconception counseling including interviewing health-care providers in preparation for their pregnancy and birth [167]. The labor process can also be less stressful through techniques such as imagining the birthing process, accommodating tender points during labor positioning, and performing relaxation techniques between contractions. Given that fibromyalgia and pregnancy share many symptoms, such as fatigue and muscle soreness, and that these symptoms may become worse as pregnancy progresses, it can be important to reframe a patient's increased pain as a time-limited exacerbation rather than a new baseline. Schaefer notes that identifying these symptoms as related to pregnancy can help with normalization, reframing, and acceptance [227].

Non-pharmacologic interventions for fibromyalgia in general are a cornerstone of effective treatment. Practitioners should emphasize the importance of techniques that are helpful for fibromyalgia in general and are not contraindicated during pregnancy.

Such techniques can include general recommendations for aerobic exercise to help reduce muscle soreness. Patients can walk regularly during their pregnancy and even during their labor period. Regular aerobic exercise is effective in the treatment of fibromyalgia in pregnant patients. Regular aerobic exercise is important for fibromyalgia in general and may benefit the mother's symptoms and fetal outcomes for pregnant patients. Official recommendations from the American College of Obstetricians and Gynecologists endorse moderate levels of activity for 30 min or more per day on most, if not all, days of the week [10]. Advice also includes pursuing low-impact exercises, as high-impact exercises may lead to injuries and trauma that can harm the mother and fetus. Women should avoid exercising in supine positions and use caution when exercising above 6,000 feet. Low-impact aerobic exercises can provide a convenient and healthy way to manage fibromyalgia symptoms as well as optimize obstetric outcomes.

Swimming can also be a viable low-impact aerobic activity with health benefits for both the mother and the fetus. Swimming can help those patients who have difficulty with weight-bearing exercises, and can be especially comfortable for gravid women with altered biomechanics. There has been concern that swimming can potentially increase patients' exposure to water-borne pathogens as well as expose the fetus to water disinfection chemicals and their by-products [35]. These risks have not been substantiated. Swimming has not been associated with adverse effects on fetal growth measures, birth weight, or congenital malformations [178]. A cohort study in Denmark found that swimming provided a slightly decreased risk of preterm birth and modestly decreased prevalence of congenital malformations compared to those who did not exercise [118]. The National Birth Defects Prevention

Study found no significant association between pool use and any birth defects, and also noted a significant negative association between frequent pool use and spina bifida [5]. Perrot et al. found that pool therapy improved more core symptoms of fibromyalgia than any other non-pharmacologic therapy in their review [197]. Scuba diving is an exception to recommending aquatic activities for health during pregnancy. Scuba diving should be avoided as the fetus is at greater risk of forming decompression bubbles that cannot be filtered in the fetal pulmonary circulation [56]. This particular risk is unique to scuba diving and is not a shared risk with shallow aquatic exercises. Clinicians may find swimming beneficial for both maternal and fetal health with a relatively low level of risk.

Fibromyalgia can make some pregnancy diagnoses more difficult. One area of caution in pregnant patients with fibromyalgia is the risk of undetected preterm labor. Many of the symptoms of preterm labor may go undetected due to their similarity to fibromyalgia pain. Although women with fibromyalgia do not have a higher risk of miscarriage [189], it is still important to be vigilant about these risks of preterm labor. Menstrual cramp symptoms are sometimes the only indication of preterm labor, and the prevalence of these symptoms is high in patients with fibromyalgia. Patients and their health-care teams need to work together and retain a high level of clinical suspicion for such symptoms to ensure the safety of the mother and fetus.

Massage and other relaxation therapies are other important non-pharmacologic treatment options for pregnant patients. Studies have shown support for treating fibromyalgia with massage [58, 119, 251, 254].Twice weekly massage may benefit the mother, the spouse, as well as the newborn, although these findings have not been replicated in the fibromyalgia population [86, 87]. Perrot et al. found that massage can improve some of the core symptoms of fibromyalgia [197]. Brattberg found that although the effects may be lost when treatment is discontinued, massage is an important and clinically significant treatment option [37]. Massage can be a useful non-pharmacologic treatment option for patients with fibromyalgia.

CBT and biofeedback can assist patients with managing their symptoms. Such treatments are effective for multiple somatic complaints and have durable benefit [231]. Patients with fibromyalgia benefit from procedural imagery; patients who are pregnant should use this technique to address the labor and delivery process [168]. The review by Perrot et al. also found CBT to benefit core fibromyalgia symptoms [197]. Other reviews have also demonstrated benefit in pain, mood, and reducing disability [30].

Improving quality of sleep can greatly improve fibromyalgia symptoms in pregnancy. Pregnancy imposes physical changes in patients' normal sleep positions, frequently fracturing the most restful part of the day. Patients with fibromyalgia often suffer from disordered sleep even prior to pregnancy. Basic tenets of sleep hygiene should be addressed in patients with poor sleep, including a regular rest schedule (sleeping early and rising early), avoidance of naps during the day, avoidance of excessive caffeine intake and appropriate timing of fluid consumption. In addition, patients with insomnia should focus on appropriate bedroom light and noise reduction strategies (dark drapes and curtains, avoidance of bedroom television, etc.).

Other treatments beyond discussing sleep hygiene may provide inroads to successfully improving sleep. CBT focused on improving sleep has demonstrated even greater efficacy than sleep hygiene alone in 64 women [148]. Other studies have found similar results [76]. Alternative therapies for sleep, such as delta-embedded music, may also offer promise [200]. These and other techniques may provide novel ways to improve sleep in pregnant patients with fibromyalgia.

Aspects of pregnancy and post-delivery care impose special challenges to patients with fibromyalgia. Breastfeeding was universally found to be frustrating in patients with fibromyalgia [228]. Insufficient milk supply is a frequent concern that leads women to question the adequacy of their attempts to provide for their newborns. Medications used to manage symptoms of fibromyalgia are frequently not recommended during breastfeeding. Patients who have been previously treated pharmacologically and must discontinue their medications experience both an exacerbation of symptoms by discontinuing their prescriptions as well as struggle with the unique physical challenges of breastfeeding. Breastfeeding itself requires prolonged postures that lead to pain, muscle stiffness, and fatigue in patients with fibromyalgia. It is no surprise that many patients with fibromyalgia find themselves required to abandon breastfeeding, further leading to a sense of failure as a parent with other psychological ramifications. One technique to help women with fibromyalgia address their breastfeeding concern is to create a breastfeeding plan early in the pregnancy. Patients should learn about the components of successful breastfeeding [228]. One should explore resources for at-home breastfeeding support after delivery. Placing referrals to lactation consultants, discussing pacing strategies for breastfeeding and rest periods, creating a quiet and supportive home atmosphere, and establishing contact with support groups can improve the odds of success. Discussing techniques on infant positioning and emphasizing the importance of position changes can reduce fatigue. Breastfeeding and other postpartum challenges can be individualized to patients with fibromyalgia to reduce frustration and improve the parental experience.

Medications are an important treatment option in patients with fibromyalgia. Medication use during pregnancy requires careful assessment of the risk to both the mother and the fetus. Around 10% of major congenital abnormalities are associated with drug exposure [42]. There are multiple systems in place to evaluate the safety of pharmaceuticals in pregnancy. The Advisory Committee on Prescription Medicines (ACPM) replaced the Australian Drug Evaluation Committee (ADEC) and provides recommendations to the Australian government regarding the inclusion and exclusion of drugs, including safety concerns. The Swedish Catalogue of Approved drugs (FASS) is another drug safety resource. The most commonly used resource in the USA is the US Food and Drug Administration's (FDA) safety rating system which was promulgated in 1979 [261]. Medications are rated in five categories based upon the amount of risk to the fetus. Category A and B medications are generally regarded as safe to take during pregnancy; less than 1% of all US medications are classified as Category A [42]. Most clinicians generally limit taking Category D or X medications during pregnancy, where there is positive evidence of human fetal risk alongside recognized circumstances of maternal benefit. The vast

majority of medications fall under Category C, where animal studies have shown an adverse effect on the fetus; there are no adequate studies in humans, and the benefit may outweigh the potential risks in pregnant women. Finally, there are medications for which no information is available.

Given the large number of medications that are grouped within each category of the FDA system, and the difficulty of the categories to accurately convey risk, a proposal to include a risk summary is currently under consideration [261, 264]. Descriptive passages detailing available data, whether from animal or human studies, would replace the current categories to give a better idea of the risks from drug exposure. As of January 25, 2014, a final action for the proposed rule was planned for May 2014 [235].

Clinicians should also avail themselves of emerging post-marketing surveillance data on the safety of medication use in pregnancy. REPROTEXT, REPROTOX, Shepard's Catalog of Teratogenic Agents, and Teratogen Information Systems (TERIS) are periodically updated scientific resources that delve in-depth into the literature regarding drug exposures in human and animal pregnancies. An online database to assist with assessments of risk during pregnancy, TERIS is composed of an expert advisory panel that evaluates medications' teratogenicity risk. Although TERIS provides a critical review of the literature, the quantity of human data is limited, resulting in indeterminate risk assessment for the majority of FDA-approved medications from 2000 to 2010 [3, 141].

Patients may also receive counseling from numerous organizations that may assist with safe medication use. The Organization of Teratology Information Specialists (OTIS) and the Hospital for Sick Children (MotherRisk) provide resources to clinicians and patients regarding the safe use of medications during pregnancy and breastfeeding.

Post-marketing surveillance data provides much of the information learned about the teratogenic effects of medications. Pregnancy exposure registries study post-approval exposure to medications during pregnancy and assess rates of adverse outcomes.

A careful analysis of risks and benefits must be undertaken whenever considering pharmacologic management of fibromyalgia during pregnancy. Past challenges faced while treating pregnant patients may provide helpful guidance. Treatment with antidepressants at one time was thought to be dangerous during pregnancy [55]. Paroxetine, a selective serotonin reuptake inhibitor (SSRI), highlights the saga that a drug may take from initial approval to heightened awareness of possible harm. Data from a large US insurance company UnitedHealthcare persuaded the US Food and Drug Administration to issue paroxetine a Category D status due to elevated risk of cardiovascular malformations, such as ventricular and atrial septal defects [64, 233]. Swedish researchers found that the use of paroxetine in early pregnancy had an odds ratio of 1.09 for cardiac malformations, although the 95% confidence interval ranged from 0.62 to 1.92 [120]. A population-based cohort study in the UK found paroxetine given during early pregnancy to show an increased adjusted odds ratio for congenital heart anomalies (aOR 1.78 with 95% confidence interval of 1.09–2.88, $P = 0.020$) [22]. In addition to cardiac malformations, paroxetine showed

an association with anencephaly, omphalocele, and gastroschisis. Fluoxetine has shown an association with craniosynostosis and sertraline with anencephaly [8]. Some reports show that sertraline does not represent an increased risk [172], while others show trends suggesting otherwise [22]. These reports cause many to be cautious about SSRI use during pregnancy. Looking at the aforementioned data, one could easily presume that this data could be extrapolated to other antidepressant medications used in fibromyalgia, such as SNRIs.

The evidence linking SSRI use with congenital malformations should be individualized, and the associations are far from certain. Many studies drawing such associations have been criticized for insufficient power, poor ascertainment of birth defects, and other methodological limitations [8]. Even those authors of studies finding statistically significant associations note the relatively low rate of malformation occurrence, large range of confidence intervals, and odds ratios that are at best modestly elevated from unity [233]. When drawing conclusions from future studies, looking at those studies with objective measurements, prospective sampling, and clinical significance will provide more robust clinical information [34]. One should interpret the increased risk of congenital malformations within the context of a baseline rate of malformations found in study controls.

Evidence that antidepressants do not represent clinically significant risk to pregnant and breastfeeding patients continues to build. A meta-analysis of prospective cohort studies compared outcomes from women exposed to antidepressants in their first trimester of pregnancy to those women who were not exposed. Only live birth malformation rates were measured, not incidence of abortion or neurobehavioral effects. Medications studied included fluoxetine, venlafaxine, nefazodone, and buproprion; outcomes were primarily physical birth defects rather than behavioral measures. With a sample size of 1774 women, the average rate of birth malformations was 2.0 % in both exposed and unexposed groups, which is within the baseline risk rate of 1–3 % for such defects [78]. Such studies suggest that malformation rates may not be significantly increased when treating pregnant patients with antidepressant medications.

The pharmacologic agents used to treat fibromyalgia continue to grow. Three medications are currently approved for treating fibromyalgia. Pregabalin was approved in June of 2007, duloxetine was approved in June of 2008, and milnacipran was approved in January of 2009 [263]. Pregnancy exposure registries exist for pregabalin and duloxetine [264]. Each of these agents has unique properties with different risks to the pregnant mother and fetus.

Pregabalin has undetermined magnitude of teratogenic risk with very limited data according to TERIS as of May 2011. Although maternal and neonatal toxicity were dose-dependent, Henck et al. found no association with major malformations in rat offspring [109]. Pregabalin appears in rat milk, although the consequences of this type of exposure are unclear. There is some concern that pregabalin concentrations in human milk are equal to concentrations in human serum [186]. Given the limited data, the risk of pregabalin to the fetus is unclear.

Duloxetine also has undetermined teratogenic risk with very limited data as of January 2011. Studies in female rats show that at supratherapeutic doses, duloxetine

may decrease fecundity, increase reactivity, and decrease habituation [41]. One infant of a mother treated with duloxetine throughout pregnancy developed transient neonatal respiratory distress, poor muscle tone, and seizures [84], while another infant whose mother was treated with duloxetine in the second half of pregnancy developed no such symptoms or other abnormalities [39]. An observational multicenter cohort study of 600 patients reported similar rates of major malformations when comparing patients who took duloxetine to those who did not [81]. Although the study is preliminary and supported by the manufacturer, these findings are critical to building evidence regarding the safety of this treatment option. The authors' discussion highlights the challenge that adequately powered studies would require over 2000 such patients to detect a twofold increase in major malformations.

TERIS reviewed Milnacipran in March 2011. At that time, milnacipran has an undetermined teratogenic risk with very limited data. Animal studies did not show any change in the frequency of malformations despite treatment up to 15 times the maximum human therapeutic dose [190]. At levels above 30 times human therapeutic dosages, animal studies showed decreased birth weight, delayed bone ossification, and maternal toxicity [223]. Similar to previously discussed agents, milnacipran's risk to the fetus is unclear.

Multiple other medications are sometimes employed to manage fibromyalgia. Venlafaxine has limited-to-fair data and demonstrates none-to-minimal risk to a child born after exposure during gestation as of the TERIS review in June 2013.The National Birth Defects Prevention study found an increased incidence of anencephaly, septal heart defects, omphalocele, cleft palate, and gastroschisis [201]. There are also reports of neonatal seizures after prenatal venlafaxine exposure [111, 193]. Prior to this, multiple studies have shown rates of adverse effects with venlafaxine that were less than baseline expected rates of malformations, suggesting low risk of use of this medication during pregnancy [79, 80, 137, 242]. Children born to mothers treated with venlafaxine did not show statistically significant intelligence quotient (IQ) differences when compared to mothers who were treated with SSRIs or mothers who were not treated for depression as measured by two time points up to 6 years after birth [182]. Rabbit studies have shown increased incidence of cardiac malformations at up to 18 times therapeutic dosages [243]. Venlafaxine has demonstrated clinical effectiveness in patients with fibromyalgia, especially those with comorbid psychiatric disorders [12, 72–74, 226]. Venlafaxine has a more robust literature base, suggesting minimal risk to the fetus.

Tricyclic antidepressants have been considered as one of the primary agents with which to treat fibromyalgia. Amitriptyline has been recognized for its effectiveness for pain, tender point sensitivity, sleep dysfunction, fatigue, morning stiffness, and well-being [57, 97, 234, 245]. Systemic reviews note the heterogeneity of studies with numerous biases limiting a definitive clinical recommendation; clinicians should be aware that a minority, not the majority, will benefit from treatment with amitriptyline [169, 179]. A TERIS review of Amitriptyline in June 2007 showed fair data and demonstrates none-to-minimal teratogenic risk to a child born after exposure during gestation. Animal studies have shown central nervous system and skeletal malformations in hamsters treated during pregnancy with amitriptyline in

doses up to 17 times human therapeutic doses [102]. There are reports of congenital anomalies of mothers taking amitriptyline, although the distribution of these anomalies did not seem unusual [213]. One case-control study found a statistically significant association between amitriptyline and congenital anomalies, but only three children in the exposed group were affected [36]. Infants of mothers who attempted suicide by taking an overdose of amitriptyline along with other drugs or alcohol in the second trimester of pregnancy have been born with Tetralogy of Fallot, cleft palate, mental retardation, and fetal alcohol syndrome [68]. The Collaborative Perinatal Project, however, did not show any congenital abnormalities in 21 infants exposed to amitriptyline [107]. Of 89 infants of mothers who took amitriptyline during pregnancy and referred prospectively to a teratogen information service, one had a major malformation at birth, one had neuromuscular retardation, one had hydrocephalus, one with pyloric stenosis, and one developed intracerebral hemorrhage and premature closure of the ductus arteriosus [153]. Other tricyclic antidepressants are also used to treat fibromyalgia. Nortriptyline and desipramine were found to have undetermined risk with very limited data with a TERIS reviews in February 2006 and September 2007, respectively. Imipramine was found to have an unlikely risk with limited-to-fair data while doxepin has undetermined risk with limited data according to TERIS from January 2007.

Gabapentin is also often employed in fibromyalgia management. Gabapentin has been shown to significantly improve pain severity, overall impact of fibromyalgia, global status, and sleep in 150 patients treated with gabapentin for a period of 12 weeks [16]. TERIS review showed undetermined risk with limited-to-fair data in June 2013. There are concerns of a higher rate of preterm birth and low birth weight for infants of women who were treated with gabapentin. A prospective comparative cohort study including 223 exposed and 223 unexposed pregnancies showed a higher rate of preterm birth and low birth weight in the gabapentin group without any evidence for major malformations [90]. With a fair amount of data, Gabapentin has evidence of unclear severity that may negatively influence fetal growth.

Non-steroidal anti-inflammatory drugs (NSAIDs) are frequently used to treat pain and may play a role for patients with fibromyalgia. Ibuprofen is an inhibitor of prostaglandin synthesis, and may lead to premature closure of the ductus arteriosus and lack of perfusion pressure in kidneys. TERIS review in September 2009 shows minimal risk based on maternal use of occasional low doses of ibuprofen with fair-to-good data. The Boston Collaborative Drug Surveillance Program showed the rate of congenital anomalies was no greater than expected with 51 infants [19]. The frequency of major malformations was not increased with ibuprofen and other NSAIDs early in pregnancy, but odds of cardiac defects were higher than expected [82]. There have been conflicting reports with certain malformations, with studies showing both association and lack of association with ibuprofen use [256, 274]. The risk of miscarriage was 40–80% higher among women who took NSAIDs early in pregnancy in three epidemiological studies [139, 176, 177]. Forty infants who were born with persistent pulmonary hypertension were found to have ibuprofen in the meconium [6]. Pregnancies where the mother is treated with NSAIDs such as ibuprofen and indomethacin to inhibit premature labor during second and third

trimesters have shown oligohydramnios and neonatal renal failure [110, 121, 275]. The risks of NSAIDs during pregnancy are well known, but these risks may not be as severe in terms of fetal malformations and need to be individualized to the pregnant fibromyalgia patient.

Fibromyalgia and the Elderly

The diagnosis of fibromyalgia in the elderly contains the basic aspects of the diagnosis in other patient populations. A high level of suspicion is required to diagnose fibromyalgia while carefully maintaining a differential of other possible painful comorbidities.

The elderly may include anyone who is 65 years of age and older. This segment of the population continues to grow. Clinicians must face the challenge of a growing number of people living with chronic medical conditions, of which fibromyalgia is one contributing illness. By some accounts, fibromyalgia prevalence peaks between the ages of 55–65 years [156]. The greater challenge is a timely and proper diagnosis, with patients being frequently identified with rheumatoid arthritis, osteoarthritis, and polymyalgia rheumatica [281].

Diagnosis of fibromyalgia is similar to that of younger patients, with the American College of Rheumatology modified 2010 criteria playing an important role. Widespread pain is a key finding per patient report and on physical examination. The severity of the pain may also be greater than one would expect for any rheumatologic disorder [277]. The evaluation for other painful conditions is important, and it is important not to discount or underestimate the role that pain and discomfort may play in limiting function.

Alternative pain evaluation tools may be employed to improve the reliability of pain assessments in the elderly. If necessary, the Faces Pain Scales or pain thermometer may be more helpful than the numeric rating scale or visual analogue pain scale. The Geriatric Pain Measure Questionnaire may also be useful. Additional information from family and caregivers can provide valuable information.

Treatment of fibromyalgia in the elderly should also begin with conservative and non-pharmacologic means. Physical function may be limited by other comorbidities. As much as they are able with their existing cardiopulmonary function, chronic aerobic exercise can alleviate their core fibromyalgia symptoms. The elderly should consider gradually amplified daily aerobic activity regimen especially if in the presence of concomitant preexisting cardiopulmonary conditions. CBT is an important component to help reduce catastrophizing, kinesiophobia, and pain severity. Complementary and alternative therapies, such as acupuncture and tai chi, present relatively low risk and may alleviate many of the fibromyalgia symptoms [247]. A long-term aerobic exercise program may be especially important for seniors, not just for their fibromyalgia symptoms, but also their overall medical health and maintenance of function. Limiting polypharmacy is an important consideration in the elderly, and non-pharmacologic means of treating fibromyalgia can assist in this effort.

Pharmacologic therapy should be employed if necessary in order to maintain function and preserve quality of life. Given their favorable side-effect profile, SNRIs may be used to manage fibromyalgia in the elderly. Milnacipran has been successfully used in a patient with Alzheimer's disease [164]. Although a first-line treatment in younger populations, TCAs are generally limited in the elderly given their anticholinergic side-effects and potential for worsening cognitive impairment, postural hypotension, and urinary retention issues. Gabapentin and pregabalin may also be used, although adjustment for impaired renal function should be made. There are case reports of heart failure exacerbations with pregabalin, so use of this medication in patients with preexisting heart failure history requires caution [171, 192]. NSAIDs are also frequently limited in seniors due to side effects and comorbidities, especially with risks of gastric ulcers, myocardial infarctions, and impaired renal perfusion. Opioids continue to have limited use, and care must be taken to avoid excessive sedation and constipation. A bowel regimen, including scheduled daily stool softener, should be initiated at the time of introduction to opioids.

Treating seniors with fibromyalgia emphasizes the importance of non-pharmacologic mean, as the adverse effects of pain medications may become more deleterious. Addressing the needs of this patient population will only become more important as their relative proportion in society grows.

Fibromyalgia in the Disabled and Cognitively Impaired

There is limited literature on the treatment of fibromyalgia in the mentally disabled and cognitively impaired. Some studies looking at mental disorders specifically exclude mental retardation and other cognitive impairment, limiting the evidence-based care for this population [91].

Challenges of treating the cognitively impaired begin with diagnosis. Earlier diagnosis of fibromyalgia based on a tender point examination as well as the current diagnosis based on patient's self-report may be limited if the reliability and consistency of reporting pain is not clear. There are no studies looking at the reliability of another person filling the widespread pain index and symptom severity score for a cognitively impaired patient, although it is reasonable that a family member or caregiver who has spent significant time with the patient may have a reasonable response to these questions. Care must be taken to evaluate for other conditions. Female carriers of the premutation in the fragile X mental retardation 1 (FMR1) gene frequently are diagnosed with central sensitivity syndromes such as fibromyalgia [136]. Physical examination may be limited, depending on the patient's willingness to be evaluated and consistency with exhibiting pain behaviors during parts of the examination. Depending on the severity of the cognitive impairment, the patient may or may not be able to use commonly used or available pain scales, such as the Faces Pain Scales or other pediatric pain measures.

Treatment may be employed if there is reasonable clinical suspicion of the diagnosis. Non-pharmacologic therapies remain a good starting place.

Cognitive-behavioral treatments may be limited if the level of the patient's insight is not amenable. Chronic aerobic exercise continues to be a relatively safe intervention, although the patient may require supervision to carry out this recommendation safely. There may be some benefit from complementary and alternative therapies, but results from such interventions may also be difficult to measure.

Pharmacotherapy may also be pursued in this population. Appropriate adjustments for comorbidities should be made. Care should be taken with NSAIDs. TCAs may be helpful if not contraindicated, and care must be taken to balance the risk of anticholinergic side effects on cognition with the potential for improving coexisting mood disorders if present. SNRIs, gabapentin, and pregabalin may also be used with careful monitoring for any adverse effects to see if these medications result in symptom improvement. As with all treatment decisions, a thorough discussion of risks and benefits should be made with the patient and the patient's authorized representative.

As of now, the confirmatory research data necessary to practice evidence-based medicine in treatment of mentally impaired patients suffering from fibromyalgia is limited to practically nonexistent. Studies which include these populations will help improve the evidence base upon which to base treatment decisions. Until that time, a careful clinical assessment with open discussion of risks followed by empiric treatment and frequent monitoring will be required to have improved outcomes and minimize the risk of harm.

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Chapter 11
Emerging Developments

Marni G. Hillinger and Ellen W. K. Rosenquist

Key Points

- There have been emerging developments in both pharmacologic and non-pharmacologic treatments for fibromyalgia in recent years.
- Pharmacologic advancements relate to the investigation of different neural receptors such as cannabinoid, opioid, *N*-methyl-D-aspartate (NMDA), and dopamine, in addition to various neurotransmitters such as gamma-aminobutyric acid (GABA), norepinephrine, and serotonin.
- Investigation into non-pharmacologic strategies has included exercise programs, acupuncture, cognitive behavioral therapy (CBT), motion-controlled video game systems, and transcutaneous magnetic stimulation.
- Fibromyalgia remains a difficult-to-treat disorder; however, recent research has led to an increased understanding of how various drug targets, existing agents, and non-pharmacologic strategies may help manage the symptoms of this disease.

Over the past decade, we have continued to gain further understanding of the pathophysiology of fibromyalgia. This has contributed to a growth in emerging treatments for this challenging and debilitating condition. Given the complex features of this disorder, many feel that a multimodal approach, which targets the numerous symptoms of this disease, will be most beneficial. This includes considering treatments that will help reduce both peripheral and deep tissue pain, modulate central sensitization, normalize sleep patterns, and adequately treat depression. This chapter reviews emerging developments in the treatment of fibromyalgia, which

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includes both pharmacologic and non-pharmacologic modalities. It is the hope that these emerging treatments, both pharmacologic and non-pharmacologic, will assist in the management of the symptoms associated with fibromyalgia and overall improve quality of life for these patients.

In terms of pharmacologic breakthroughs, there has been much interest in targeting different neural receptors such as cannabinoid, opioid, NMDA, and dopamine, in addition to modulating various neurotransmitters such as GABA, norepinephrine, and serotonin. There has been continued recent interest in investigating the role of endocannabinoid agents, which target the cannabinoid receptors, in the treatment of pain associated with fibromyalgia. Cannabinoid receptors are thought to be involved in many processes including pain modulation, appetite control, motor coordination, memory processing, and neuroprotection. Cannabinoid receptors are widely distributed throughout the central and peripheral nervous system. However, it is thought that the analgesic effect of this class of drugs is at the level of the peripheral nervous system [7]. A study performed by Agarwal and colleagues demonstrated that loss of peripheral cannabinoid receptors leads to a major reduction in analgesia produced by cannabinoids [2]. It is theorized that there is increased peripheral nociception in fibromyalgia patients and that the cannabinoid receptors may be a promising drug target. The studies, thus far, have varied in terms of their primary endpoints—some have investigated the use of these agents to treat fibromyalgia-related pain while others have focused on improvements in sleep and anxiety. Currently, there are two FDA-approved cannabinoids—nabilone which is a synthetic analogue of tetrahydrocannabinol (THC) and dranabinol which contains active THC. Most studies have examined the use of nabilone. Skrabek and colleagues in 2008 performed a randomized placebo-controlled trial of 40 patients which demonstrated improvements in analgesia utilizing the visual analogue scale, which was the primary endpoint, in addition to anxiety, when comparing nabilone versus placebo [44]. A later study demonstrated superiority of nabilone versus amitriptyline to improve sleep in fibromyalgia patients [48]. Thus far, there has been one published study investigating the efficacy of dronabinol in this patient population. A retrospective multicenter study of 124 patients given, on average, 7.5 mg of dronabinol daily demonstrated significant improvements in psychometric parameters and pain intensity, though there was a 25 % rate of mild adverse events [46].

There has also been interest in examining whether opioid receptor blockade and subsequent modulation of microglia could play a role in managing fibromyalgia symptoms. Mattioli demonstrated that naltrexone both antagonizes the opioid receptor and inhibits microglia activity [32]. It is thought that inhibiting microglia may decrease excitatory and neurotoxic agents, which may in turn modulate pain [26]. A single-blinded crossover study of 10 women demonstrated that low-dose naltrexone reduced fibromyalgia symptoms by > 30 % in comparison to placebo [50].

A few studies have investigated the GABA precursor, sodium oxybate. This medication is FDA approved as a treatment of cataplexy as it is thought to increase stage IV sleep. Abnormalities in stage IV sleep have been identified in fibromyalgia patients [34]. Spaeth et al. studied 573 fibromyalgia patients in a phase III double-blind randomized control trial and demonstrated significant improvements in pain,

sleep, and quality of life with sodium oxybate [46]. Prior studies also corroborated this evidence [34, 41]. The efficacy of this medication provides further support that sleep normalization is important in this patient population.

There has been some interest in investigating the role of NMDA receptor blockade in the fibromyalgia patient population; however, this body of research remains primarily at the bench science level. It is hypothesized that NMDA activation can lead to temporal summation and early central sensitization and that central sensitization plays a role in the pathophysiology of pain symptoms in fibromyalgia. NMDA receptors can be activated by excitatory amino acids, tachykinins, substance P, and neurokinin A [16]. There have been mixed results with the use of ketamine, an NMDA receptor antagonist, in this patient population. Early studies initially demonstrated promise. A study performed by Sorensen in 1995 demonstrated a significant reduction in pain in 11 fibromyalgia patients who received a single shot of ketamine [45]. A more recent study, however, failed to demonstrate a significant change in pain scores based on the visual analogue scale or fibromyalgia impact questionnaire (FIQ) at 8 weeks [36]. Further investigation into the potential long-term efficacy of ketamine is necessary; in addition, moderate adverse events may limit its use [36].

Dextromethorphan, another NMDA receptor antagonist, may hold some promise but also requires further investigation. Staud et al. performed a double-blind placebo-controlled crossover study of 20 normal controls and 24 fibromyalgia patients who were given a single oral dose of dextromethorphan to examine *windup* (WU) which is thought to be a form of nociception-dependent central sensitization [47]. He found that fibromyalgia patients required less stimulus intensity than controls to reach maximal WU but the reduction in central sensitization demonstrated in both normal controls and fibromyalgia patients after a single dose of dextromethorphan did not differ significantly between the two groups. Interestingly, an intravenous ketamine test may help to determine who may respond to dextromethorphan. Cohen and colleagues demonstrated a high degree of correlation between pain relief with low-dose intravenous ketamine and dextromethorphan [14].

In terms of investigating the role of neurotransmitters in the modulation of fibromyalgia pain, the primary body of research surrounds serotonin–norepinephrine reuptake inhibitors (SNRIs). Both duloxetine and milnacipran are SNRIs, which are FDA approved to help manage the symptoms of fibromyalgia. This class of drugs favors reuptake inhibition of norepinephrine more so than serotonin and is widely used throughout Europe and Japan as antidepressants. The mechanism of pain reduction may be secondary to norepinephrine and serotonin signaling pathways via descending inhibitory pathways in the spinal cord [29]. Overall, this class of medication is thought to have fewer side effects in comparison to tricyclic antidepressants.

A recent Cochrane review investigated duloxetine for the treatment of fibromyalgia; six studies and 2249 patients were included in this analysis [27]. The authors concluded that duloxetine 60 mg daily was effective for treating fibromyalgia pain at both 12 and 28 weeks, in addition to treating painful physical symptoms of

depression. The evidence was of lower quality for fibromyalgia in comparison to the same doses of the medication for diabetic peripheral neuropathy [27].

Work by Clauw et al. demonstrated long-term pain relief at 3 years in 81% of fibromyalgia patients taking milnacipran [13]. Milnacipran has also recently been studied in those who have had incomplete pain relief with pregabalin; this randomized, multicenter open-label study of 184 patients demonstrated a significant improvement in Patient Global Impression of Change (PGIC) in patients taking both milnacipran and pregabalin in comparison to pregabalin alone [33]. In addition, the authors of a recent Cochrane review concluded that the SNRIs duloxetine and milnacipran provided a "small incremental benefit" in comparison to placebo in reducing pain associated with fibromyalgia. Based on these aforementioned studies, there appears to be continued promise in the use of SNRIs to treat pain in fibromyalgia patients.

Dopamine receptor agonists have also been studied in the treatment of pain from fibromyalgia—this class of medications includes ropinirole, pramipexole, and rotigotine. Ropinirole is currently FDA approved for both Parkinson's disease and restless leg syndrome; this medication has a high affinity for both the D2 and D3 dopamine receptors. Pramipexole has a similar mechanism of action as ropinirole; however, it has only a mild affinity to the D2 receptor sites. Rotigotine is also FDA approved for Parkinson's disease and drug delivery is achieved by a transdermal patch; this medication failed to demonstrate efficacy in fibromyalgia patients in a phase II randomized control trial [39]. Holman, in 2003, performed a preliminary investigation of the addition of ropinirole to the "best medical regimen" in 24 fibromyalgia patients [20]. Patients uptitrated the dose of the medication until their best perceived dose. He found that a calculated tenderness score (sum of 18 classic fibromyalgia tender points on a graded scale) was significantly decreased in all patients who completed the study. In 2005, Holman performed a double-blind, placebo-controlled trial of pramipexole in patients with fibromyalgia [21]. He found that at 14 weeks the visual analog scale (VAS) pain score, the primary endpoint, significantly decreased by about 36% in the pramipexole arm versus 9% in the placebo arm. Other secondary outcome measures trended toward favoring pramipexole over placebo, though they did not reach statistical significance. This class of medications holds promise in terms of its potential for pain relief; however, further research is necessary to more completely understand its utility in this patient population.

Another potential drug, which holds promise for the fibromyalgia population, is Tramadol. Tramadol is a unique medication as it is a relatively weak mu-opioid agonist plus a norepinephrine and serotonin reuptake inhibitor [40]. In 2003, Bennett and colleagues performed a multicenter, double-blind, placebo-controlled trial using a combination of acetaminophen and tramadol in comparison to placebo in 313 fibromyalgia patients [5]. The authors examined the rate of discontinuation in the treatment versus the placebo group and found a significantly lower rate of discontinuation of therapy for any reason in the tramadol/acetaminophen group in comparison to the placebo group. Secondary outcome measures such as pain score and pain relief score also demonstrated statistical significance. A recent study investigated the analgesic effect of tramadol in animal models of neuropathic and

fibromyalgia pain; this study demonstrated in both groups of animals that orally administered tramadol produced improvements in tactile allodynia which were dose dependent [23].

Of note, there has not been good evidence that pure opioid analgesic medications have been beneficial for this population [17]. It is hypothesized that fibromyalgia patients may have altered endogenous opioid analgesic activity and that opioid medications may therefore have reduced efficacy in this population [18]. Furthermore, there is some concern that since fibromyalgia is considered a pain amplification syndrome, these patients may be at further risk for developing opioid-induced hyperalgesia [38].

Topical agents are also possible options for the treatment of fibromyalgia related pain; however, there has been limited literature published in this patient population. At the time of this publication, there was only one recently published study of a topical therapy in fibromyalgia patients. Casanueva and colleagues performed a randomized control trial of topical capsaicin in 130 fibromyalgia patients. This study utilized a 0.075% capsaicin applied three times per day for a period of 6 weeks [9]. The study demonstrated significant improvements in the treatment group in both the myalgic score and global subjective improvements at the end of treatment. Significant treatment effect was also demonstrated when the experiment group was queried 6 weeks after completion of the trial [9].

As previously mentioned, fatigue can be a debilitating feature of fibromyalgia. Efforts to improve this symptom have led to the investigation of both modafinil and armodafinil to help improve fibromyalgia-related fatigue. In 2007, Schwartz and colleagues examined modafinil in a retrospective chart review [42]. Approximately two-thirds of patients experienced 50% or greater reduction in fatigue levels with this medication. A later study in 2010 examined armodafinil, which has a longer half-life than modafinil, failed to demonstrate efficacy for improvement of fatigue in this patient population [43].

In addition to pharmacologic strategies, there has been a significant body of literature published investigating non-pharmacologic approaches. Exercise has a very important role to play in the management of pain relief in this patient population. Further examination of specific exercise regimens, which may better target the needs of these patients, is underway. A qualitative study of group-based exercise programs in woman with fibromyalgia demonstrated improvements not only in fibromyalgia pain but the exercise programs helped counteract sensations of isolation, frustration, and depression [4]. Significant improvements in cardiovascular capacity, walking time, and daytime fatigue have been demonstrated in both pool- and land-based exercise regimens [22]. Lima and colleagues in 2013 reviewed 27 articles that examined the effectiveness of aquatherapy in fibromyalgia; they concluded that three of the meta-analyses demonstrated statistically significant improvements in the FIQ, 6-min walk test and stiffness [25]. The authors also comment, however, that many of the studies lacked rigor making it difficult to demonstrate statistically significant outcomes [25]. It has also been demonstrated that exercise can decrease inflammatory markers, such as interleukin-8, interleukin-6, and noradrenaline; this

suggests that part of the benefit of regular exercise in this patient population may be related to an anti-inflammatory effect [6, 37].

The use of technology in exercise programs, such as motion-controlled video game consoles, is also being employed. In 2013, Mortensen and colleagues examined the use of three different motion-controlled video game systems (MCVGs)—Nintendo Wii, PlayStation 3 Move, and Microsoft Xbox Kinect, to help improve pain relief during exercise in seven female fibromyalgia patients [35]. They conducted both pre- and post-intervention qualitative assessments and found that even though women did not report general improvement of symptoms or improvement in activities of daily living, they did feel MCVGs served as a distraction to the pain and provided a manageable form of exercise [35].

In addition to exercise strategies, acupuncture has long been a modality of investigation in fibromyalgia patients. A recent Cochrane review in May 2013 concluded that there was low to moderate evidence that compared with "standard" therapy or no treatment, acupuncture improves pain and/or stiffness in people with fibromyalgia. This study also concluded that electroacupuncture is "probably better" than manual acupuncture for pain and stiffness reduction and improvement of well-being [15]. Some recent small studies suggest that acupuncture and acupoint therapy may play a beneficial role in treating fibromyalgia patients [1, 8]. An additional study examined dry needling techniques as well—this randomized control study of 124 patients examined usual "medical treatment" in comparison to "medical treatment" plus 1 h per week of dry needling therapy to tender points. This study demonstrated significant short-term improvements in multiple measures of pain in the treatment versus control group at 6 weeks [10].

Sleep disturbances are a known and frequent feature of fibromyalgia. There has been increased interest in examining the effect of CBT to assist with sleep disturbances in fibromyalgia patients. A recent study of 64 women investigated cognitive behavioral therapies in comparison to sleep hygiene education in the treatment of sleep disturbances in fibromyalgia. The CBT group demonstrated significant improvement in several sleep variables, fatigue, daily functioning, pain, catastrophizing, anxiety, and depression in comparison to the sleep hygiene education group which only demonstrated improved sleep quality [31]. An additional study by Castel and colleagues in 2012 examined pharmacologic treatment versus CBT alone versus CBT plus hypnosis. The authors concluded that both the CBT group and the CBT group with hypnosis demonstrated significant improvements and the addition of hypnosis to CBT further enhanced the positive effects [11].

There has also been growing interest in repetitive transcranial magnetic stimulation (rTMS) in recent years. Most of this work has examined efficacy in the stroke and spinal cord population [28]. However, a few recent studies have investigated whether TMS may play a role in the treatment of fibromyalgia-type pain. Lee and colleagues performed a randomized controlled trial of low- or high-frequency rTMS in comparison to sham rTMS in 15 women with fibromyalgia [24]. The Barthel Disability Index was significantly decreased in both the low- and high-frequency TMS groups in comparison to placebo. Marlow and colleagues performed a systemic review investigating both rTMS and transcranial direct current stimulation (tDCS)

in fibromyalgia patients [30]. They included nine different studies and found that 80% of the rTMS studies demonstrated decreased measured pain while 100% of the tDCS studies had favorable effects on pain. The authors felt that both modalities demonstrated analogous reduction in pain with mild side effects. The authors felt that these modalities should be considered in the algorithm to treat fibromyalgia patients, especially in those with inadequate treatment with other types of therapies. Of note, there has been no recent new evidence on the efficacy of prolotherapy, massage, therapeutic ultrasound, or mineral baths in the treatment of fibromyalgia.

In summary, this chapter has served to outline emerging developments in both pharmacologic and non-pharmacologic therapies to treat fibromyalgia. Fibromyalgia remains a multifaceted and difficult-to-treat disorder; however, research over the past few years has led to increased understanding of how various drug targets and existing agents may help manage the symptoms of this disease. In particular, SNRI agents and dopamine receptor agonists appear to be particularly promising. In addition, we continue to gain an understanding of the importance of a multimodal and holistic approach to this patient population as more specific non-pharmacologic approaches are investigated. Improving upon our current exercise regimens for this patient population including incorporating novel approaches such as MCVGs as well as improved integration of CBT may be very beneficial. It is the hope that the coming years will provide even further insight into the most efficacious treatments for this patient population.

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Chapter 12
Nutrition

Donald Eli Lynch and Geeta Nagpal

Key Points

- Oxidative stress is a potential pathological mechanism responsible for symptoms frequently associated with fibromyalgia.
- It is common for patients with fibromyalgia to change their diet with the use of nutritional supplements or by eliminating the intake of specific food substances in an effort to reduce disease severity.
- There is insufficient evidence to support the use of any nutritional supplement for the treatment of fibromyalgia.
- When clinicians encounter fibromyalgia patients, especially those with increased body mass index (BMI), time should be invested to counsel and encourage increased activity and weight loss.
- Diet emphasizing vegetarian or plant-based options hold promise as a potential treatment option for fibromyalgia but more long-term studies are needed to help create specific guidelines.

Introduction

Fibromyalgia is a disorder characterized by diffuse musculoskeletal pain commonly accompanied by stiffness, headaches, irritable bowel syndrome, activity intolerance, and fatigue [1]. The cause of fibromyalgia is likely multifactorial in nature, but not completely understood [2]. Various interventions have been employed to

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treat fibromyalgia, including medications, exercise protocols, cognitive therapy as well as physical modalities [3–6]. However, these treatment interventions are not effective for all patients suffering from fibromyalgia [7]. Consequently, many patients with fibromyalgia will seek alternative treatment options, including the use of nutritional supplements and dietary restrictions [8, 9].

Evidence is now emerging that provides support for nutritional interventions in the treatment of fibromyalgia [10, 11]. A recent comprehensive review on fibromyalgia and nutrition concluded that it is necessary to give patients dietary advice to maintain optimal health [12]. Therefore, it is important that practitioners, caring for fibromyalgia patients, have a working knowledge of how nutrition is involved in the pathogenesis and treatment of this disease.

This chapter assists readers in the acquisition of relevant nutrition-based information by providing a review of studies outlining a link between metabolic dysfunction and symptoms common to fibromyalgia. Additionally, we examine the current evidence for antioxidant, vitamin, and mineral supplementation as well as specialized diets, including elimination, vegetarian, and vegan regimens.

Pathophysiology

Multiple factors have been cited as possible causes or contributors to symptoms commonly found in fibromyalgia. These include psychological stress, centrally mediated augmentation of pain and sensory mechanisms, genetic abnormalities, altered levels of central neurotransmitters, and noxious peripheral disturbances that perpetuate abnormal pain processing in the central nervous system [13]. In addition, impairments in oxidant and antioxidant pathways have been implicated as a probable cause or consequence of fibromyalgia [14–19].

Oxidant/Antioxidant Regulation and Impairments in Fibromyalgia

To better appreciate the potential for how nutritional interventions can serve fibromyalgia patients, an understanding of how oxidants are both generated and regulated in the body is necessary. Oxidants are agents capable of chemically combining molecules with oxygen. Atoms or molecules possessing a single unpaired electron are labeled as free radicals. Free radicals are the by-products of metabolic pathways in the cells and mitochondria utilizing oxygen. Common examples of free radicals include nitric oxide, superoxide, lipid peroxyl radical, and hydroxyl radical. Reactive oxygen and nitrogen species include both free radicals and non-radical but reactive molecules (e.g., hydrogen peroxide) [20].

Reactive oxygen and nitrogen species have both useful and detrimental effects in the body. Nitrous oxide is used to regulate blood pressure, and phagocytes produce

the superoxide radical to neutralize bacteria. Hydrogen peroxide assists in the enzyme production of thyroid hormones [21]. However, hydroxyl radical, produced through normal cellular metabolism, can cause damage to cell lipid membranes, a process known as lipid peroxidation [22].

Antioxidants are structures that neutralize reactive molecules and prevent the formation of oxidants. The human body processes an antioxidant arrangement made up of both enzymatic and nonenzymatic antioxidants. Antioxidant enzymes include superoxide dismutase, catalase, glutathione peroxidase, and glutathione reductase. Some examples of nonenzymatic antioxidants include reduced glutathione, vitamin C, vitamin E, ubiquinol, carotenoids, and flavonoids [23].

Studies have demonstrated lower levels of serum antioxidants in fibromyalgia patients, compared to healthy control subjects. Akkus and colleagues investigated the plasma levels of antioxidant vitamins, lipid peroxidation, and nitric oxide. Their study revealed fibromyalgia patients had significantly lower levels of vitamin A and E as well as significantly higher levels of lipid peroxidation in plasma compared to healthy controls. However, the study failed to find a significant difference in vitamin C, β-carotene, and nitric oxide levels [18]. A more recent study, by Sakarya et al., found no difference in the levels of vitamins A, C, and E between healthy controls and fibromyalgia patients [24]. In the Sakarya study, liquid chromatography was used to measure plasma vitamin levels, while Akkus used spectrophotometric analysis, which may have accounted for the significant difference in results between the two studies. It was concluded that more clinical trials were needed to explore this area. In a separate study, it was found that the serum antioxidants, glutathione, and catalase levels were significantly lower in fibromyalgia patients than controls. However, there was no significant difference in serum nitrous oxide levels between the two groups of healthy volunteers and fibromyalgia patients [25].

Oxidative stress is the metabolic phenomenon where oxidants overwhelm innate antioxidant systems in the body resulting in damaging alterations to cellular DNA, proteins, and lipids [26]. Oxidative stress can occur due to increased production of reactive species or diminished levels of antioxidants. Consequences of oxidative stress include cellular adaptation, tissue injury, and cell death [21]. The negative costs of oxidative stress have been linked to patients with fibromyalgia syndrome [27, 28]. La Rubia et al. found patients with fibromyalgia, compared to age-matched controls, had evidence of increased oxidative stress suggested by elevated levels of oxidative DNA damage and lower activity levels of the antioxidants superoxide dismutase and catalase [29].

Mitochondria are organelles found in eukaryotic cells that serve to balance oxidant/antioxidant regulation and manage oxidative stress. Mitochondria generate adenosine triphosphate (ATP), via an oxygen-dependent manner using pyruvate. The pyruvate substrate is processed through the citric acid cycle, also known as the Krebs cycle. The citric acid cycle goes on to produce reduced nicotinamide adenine dinucleotide (NADH) compounds, which are later oxidized within the mitochondrial intermembrane space by respiratory complexes and diffusible factors, including coenzyme Q10. Reactive oxygen species, generated in the process of ATP production, are neutralized by mitochondrial enzymes, including catalase and superoxide

dimutases [30]. Mitochondrial dysfunction is theorized to play a role in the pathogenesis of fibromyalgia [31]. A recent study found that blood mononuclear cells from fibromyalgia patients demonstrated a reduced concentration of coenzyme Q10 and mitochondrial DNA, while also revealing increased levels of inflammation by measurement of tumor necrosis factor (TNF)-α [17]. Sprott and coworkers found increased DNA fragmentation and changes in the number and size of mitochondria in symptomatic fibromyalgia patients [32].

Mineral deficiencies have also been associated with the pathogenesis of fibromyalgia [33]. Essential minerals assist in the regulation of oxidant formation. Copper is utilized by the antioxidant enzyme catalase, while selenium serves as a cofactor for the antioxidant enzyme glutathione. Zinc is a component of the antioxidant superoxide dismutase [34], and magnesium is needed for muscle metabolism and assists in ATP production [33]. Deficiencies in magnesium have been linked with muscle pain and tenderness [35], and may encourage the activation of *N*-Methyl-D-aspartate (NMDA) receptor leading to long-term sensitization of nociceptive pathways [36]. Multiple studies have found mineral levels to be significantly lower in patients with fibromyalgia when compared to normal healthy control subjects [29, 33, 35, 37], while a few have not [24, 38].

Vitamin D Deficiency in Fibromyalgia

Although controversial, there may be an association between fibromyalgia and vitamin D deficiency [39].The active form of vitamin D is able to produce a broad range of actions by activating receptor sites contained in different cell populations throughout the body. Once activated, the vitamin D receptor can express or suppress gene products unique to each individual cell type [40], such as calcium regulation, known to be associated with bone health [41]. Studies now support the existence of vitamin D receptors that are contained within muscle cells [42]. Animal studies have revealed that vitamin D deficiency results in altered muscle innervations and presumptive nociceptor axons, as well as, muscular hypersensitivity and pain [43]. Vitamin D is now also known to modulate the immune system, and minimize secretion of proinflammatory cytokines factors, such as interleukin (IL)-2, interferon-γ, and TNF-α [44]. Excessive cytokine production has been proposed as one of the possible contributing causes of fibromyalgia symptoms [19].

Despite mounting support for the role of vitamin D in muscle health and inflammatory regulation, its association with fibromyalgia remains controversial. Numerous studies examining the connection between vitamin D deficiency and fibromyalgia have not produced consistent results [45]. Earlier studies that found a positive correlation with vitamin D deficiency and fibromyalgia have been criticized for using poorly defined study cohorts and employing different measurement assay methods for quantifying serum vitamin D levels [46]. In a review of nine high-quality studies investigating the link between vitamin D and fibromyalgia, there were mixed results: Older studies suggested a positive relationship between

fibromyalgia and vitamin D deficiency, and more recent studies employing healthy control groups did not suggest a clear association. The authors concluded that there was not strong evidence available to support vitamin D deficiency contributing to fibromyalgia symptoms [47].

Link Between Fibromyalgia and Obesity

Obesity is a complex medical condition in which excess body fat has accumulated to the extent that it may lead to a negative effect on one's health. Obese individuals have more musculoskeletal pain and physical dysfunction than normal-weight individuals [48]. Obesity is commonly associated with fibromyalgia [49], with a prevalence of 47–73 % [50–52]. Furthermore, it has been found that overweight and obese fibromyalgia patients experience higher levels of pain compared to normal-weight subjects [53]. Obesity in fibromyalgia adversely affects pain sensitivity to pressure, both the quality and quantity of sleep, and physical strength and flexibility [51].

As one would expect, with a strong correlation of obesity and fibromyalgia, there is evidence to show that weight loss does affect the severity of fibromyalgia. In a retrospective chart review of patients with fibromyalgia who had undergone laparoscopic Roux-en-Y gastric bypass, there was a postoperative decrease in median body mass index (BMI) from 49.4 to 29.7 kg/m^2. This weight loss was associated with a statistically significant improvement in median pain scores (9/10–3/10) as well as median points of tenderness (14–3.5) [54]. In a longitudinal study involving gastric bypass patients, similar results were seen. Forty-eight subjects undergoing bariatric surgery had a 12 % prevalence of fibromyalgia preoperatively. After a mean BMI reduction from 51 to 36 kg/m^2, the prevalence of fibromyalgia fell to 1 % [55].

Stress, depression, anxiety, chronic sleep deprivation, and low physical activity have been linked to body weight in patients with fibromyalgia. And, obese women with fibromyalgia have significantly higher levels of these factors as compared with women with fibromyalgia who are not obese [53]. Vincent et al. recently evaluated the complex relationship between BMI, physical, and psychological factors in these patients. They found that depression and anxiety were not correlated with BMI and did not explain the relationship between BMI and fibromyalgia impact. However, physical factors such as pain with activity and being physically active did have a modest impact. They found that as BMI increased, it became more difficult for a patient to function and be active, leading to worsening of their fibromyalgia symptoms. Patients attempt to escape the pain by being less active, but based on their results, lower physical activity actually worsens the impact of the illness [56]. When clinicians encounter fibromyalgia patients, especially those with increased BMI, time should be invested to counsel and encourage increased activity and weight loss.

Fibromyalgia and Food Sensitivities

Gluten sensitivity has been associated with fibromyalgia symptoms [57]. Celiac disease is thought to be an autoimmune intolerance of gluten, a protein common to wheat products. Rodrigo et al. published a case series describing the clinical impact of a gluten-free diet in patients with fibromyalgia and celiac disease. In the study, 229 patients with a history of irritable bowel syndrome were screened for celiac disease. One hundred and four patients within this group had associated fibromyalgia syndrome. Screening tests included duodenal biopsy, short-form (SF)-metric testing, physical questionnaires, blood work, and genetic markers common for celiac disease. Once the screening was completed, a total of seven subjects, all from the fibromyalgia group, were diagnosed with celiac disease. Once diagnosed, the celiac patients started a gluten-free diet and were reassessed 1 year later. At the end of 1 year, results revealed a significant (greater than 50%) improvement in all outcome measures including complaints of pain, tiredness, and physical activity tolerance. The authors recommended that clinical practitioners should remain aware of the various symptoms associated with celiac disease and to consider serological testing when warranted. However, it was further recommended to obtain genetic testing markers and duodenal biopsy before recommending a gluten-free diet [58].

Tovoli et al. also studied the relationship between fibromyalgia and celiac disease. Internet sites and unofficial medical sources proclaiming a strong connection between gluten sensitivity and fibromyalgia influenced the study. Ninety patients populated from a rheumatology clinic, with confirmed fibromyalgia, were serologically screened for celiac disease. Additionally, a second group of patients with confirmed celiac disorder was assessed for symptoms common to fibromyalgia. The authors determined that the overall prevalence of celiac disease in fibromyalgia patients was the same as in the general population. The authors concluded that celiac screening is not recommended for fibromyalgia patients, and to avoid gluten-free diets in fibromyalgia patients in the absence of established celiac disease [59].

Excitotoxins

Some authors have suggested that fibromyalgia symptoms can result from ingestion of dietary excitotoxins [60]. Excitotoxins are described as neurotoxic substances that interact with excitatory amino receptor subtypes, such as glutamate and NMDA [60]. Many studies indicate that overactivation of excitatory glutamate/NMDA receptor serves a significant responsibility in activity-mediated central sensitization [36]. Two dietary sources of excitotoxins include monosodium glutamate (MSG), a flavor enhancer, and aspartame, an artificial food sweetener commonly used in carbonated beverages [61]. Ingestion of aspartame can lead to increased levels of aspartate, while MSG ingestion results in higher levels of glutamate [61, 62]. Excessive glutamate has been found to target mitochondria, resulting in increased reactive oxygen species and autophagy [63]. Animal studies found mice, fed moderate doses

of aspartame, suffered increased memory impairments and elevated oxidative stress levels [61].

Holton et al. examined the effects of MSG versus placebo on symptoms of fibromyalgia. All participants in the study were selected after experiencing greater than 30% remission of symptoms on an MSG- and aspartame-elimination diet. Patients were randomized to a 14-day double-blind placebo-controlled study, where they served MSG or placebo for 3 consecutive days each week. Patients, who consumed MSG, in comparison to placebo, experienced a statistically significant return of symptoms and a nonsignificant trend in worsening fibromyalgia pain [64]. However**,** it has also been proposed that dietary glutamate likely has little effect on pain modulation in fibromyalgia as chronic MSG has not been found to result in persistent elevation of fasting serum glutamate. Additionally**,** glutamate does not cross the blood–brain barrier and glutamate levels in the brain are regulated independent of fluctuation in serum glutamate concentration. Finally, widespread pain is not a symptom associated with MSG intolerance [65].

Treatment Section

Antioxidant Supplements

Antioxidant therapy has been investigated as a treatment pathway in fibromyalgia patients, with a heavy focus on the therapeutic effects of coenzyme Q10 (ubiquinone). Coenzyme Q10 functions as a crucial cofactor within the mitochondria. Inside the inner mitochondrial membrane, coenzyme Q10 is reduced to ubiquinol-10. Once converted to ubiquinol-10, this compound acts as a free radical scavenger independently or in conjunction with vitamin E [66]. In comparison to ubiquinone, oral supplementation with ubiquinol-10 has been found to result in significantly better bioavailability, leading to higher levels of plasma coenzyme Q10 [67].

A randomized, double-blind, placebo-controlled trial using coenzyme Q10 was performed to evaluate its effect on fibromyalgia symptoms and clinical gene expression. In this study, 20 women with fibromyalgia were randomized to either a treatment group or placebo group**.** The treatment group was given 300 mg of coenzyme Q10 per day for 40 days. At the follow-up evaluation, compared to the placebo group, the treatment group demonstrated significant clinical improvements in pain, fatigue, and morning tiredness according to pre- and post-fibromyalgia impact questionnaires. There was also significant reduction in the treatment group's visual analog pain scale as well as tender points. Gene expression in these same patients was analyzed by measuring the common inflammatory mediator genes (IL-6, IL-8, and TNF-α) and genes related to mitochondrial biogenesis (Peroxisome proliferator-activated receptor-gamma coactivator 1 alpha **PGC-1α**, transcription factor A, mitochondrial TFAM, Nuclear respiratory factor-1—NRF-1) from blood mononuclear cells. Samples from 20 healthy women were used to compare biochemical param-

eters. Pretreatment fibromyalgia groups demonstrated increased expression of inflammatory mediators and downregulated expression of antioxidant response genes and mitochondrial biosynthesis genes. However, the post-coenzyme Q10 treatment group demonstrated a reverse trend with decreased expression of inflammation genes, upregulation of mitochondrial biogenesis, and antioxidant formation [11]. In a similar study, Miyamae et al. evaluated the effects of ubiquinol-10 supplementation in juvenile subjects using a double-blind, placebo-controlled trial. The study consisted of three sequential double-blind phases, with phase 1 and 3 using 100 mg of oral ubiquinol-10 per day for 12 and 8 weeks, respectively. Phase 2 used placebo pills for 8 weeks. Serum plasma levels of ubiquinol as well as inflammatory markers were obtained at regular intervals throughout the study. In contrast to Cordero's study, supplementation of ubiqunol-10 did not have an effect on pain intensity. However, there was a significant improvement in fatigue. The authors speculated better relief might have been obtained with higher doses of ubiqunol-10 [66].

Synthetic vitamin C (ascorbic acid) and E (α-tocopheral) are popular over-the-counter antioxidant supplements that have been studied extensively for their therapeutic potential in various inflammatory-related conditions [68]. Vitamin E has reactive oxygen species-scavenging ability [69] and vitamin C works by reducing free radicals. It also converts vitamin E to its active form [18]. Despite little evidence supporting the role of vitamin C and E therapy in fibromyalgia, some resources have advocated its use as a treatment option [70] as synthetic vitamin C and E therapy have demonstrated benefits in select conditions [68]. However, other trials investigating moderate- to high-dose regimens have not only demonstrated a null benefit [71] but also harm [72], including diminished exercise-induced insulin sensitivity in healthy athletes [73]. Further, vitamin C and E therapy was associated with higher rates of cardiovascular disease as well as mortality from cancer recurrence [68, 74]. Paradoxically, diets rich in these vitamins have consistently shown beneficial results for other diseases including dementia and cardiovascular disease [68, 69]. The reasons for contradictory outcomes between vitamins obtained from food compared to intake of synthetic vitamins are not clear. One theory is that when antioxidants are consumed in excess they will actually encourage oxidant production [72]. Additionally, it is also known that vitamin E obtained from food exists in four different tocopheral forms (α-, β-, δ-, and γ-). It has been theorized that other forms of vitamin E tocopherals contribute important antioxidant functions in the body not supported by α-tocopheral alone. Another concern is that ingesting high doses of synthetic α-tocopheral vitamin E may diminish the serum levels of other vitamin E isoforms [69]. Vitamin C from food may be consumed in association with additional components (carotenoids and flavonoids) that may have beneficial effects in comparison to vitamin C supplements [74].

An extensive literature search produced only one study investigating the role of vitamin C and E in the treatment of fibromyalgia. This study examined the benefits of vitamin C and E supplementation combined with exercise in patients with fibromyalgia. Fibromyalgia patients were given oral supplements in the form of a 150 mg/day of vitamin E (α-tocopherol) and 500 mg/day of vitamin C (ascorbic acid) in combination for 12 weeks. The fibromyalgia patients were separated into

three groups, an exercise only group, vitamin supplementation group, and a combined exercise and vitamin supplementation group. Fasting blood levels of oxidative stress markers—vitamin A, E, and β-carotene—were obtained from control and fibromyalgia patients at baseline and then 12 weeks later. The study found higher levels of oxidative stress markers in fibromyalgia patients, compared to control subjects, and antioxidant enzymes and vitamin levels were diminished in fibromyalgia patients at baseline. Plasma levels of vitamins A and E and reduced glutathione were increased by vitamin therapy and exercise. Glutathione peroxidase activity increased with vitamin C and E intake, with or without exercise. Although plasma differences were observed with the treatment protocol, fibromyalgia symptoms did not improve with any of the treatments [75].

Vitamin D Supplements

Two separate studies have investigated the effects of vitamin D therapy on fibromyalgia symptom management. Each study produced a different conclusion. Warner and colleagues performed a double-blind randomized trial where fibromyalgia patients ($n=184$) were compared to patient controls with osteoarthritis ($n=104$). All patients in the study were assessed for vitamin D deficiency determined by 25-hydroxyvitamin D serum testing. Vitamin D deficiency was defined as ≤20 ng/ml. All fibromyalgia subjects ($n=50$) with vitamin D deficiency were then randomized in double-blind fashion to be given vitamin D2 (ergocalciferol) 50,000 IU orally every week or received placebo for 3 months. At the end of the study, serum 25-hydroxyvitamin D levels were reassessed. Mean vitamin D levels were significantly increased in the active treatment group. However, there was no significant difference in the active treatment group's functional pain scores and visual analog scale pain when compared to placebo. The study also failed to find a correlation between vitamin D level and pain on the visual analog scale [76].

In contrast, a more recent study by Wepner and coworkers demonstrated significant relief of pain with vitamin D supplementation. Thirty women with fibromyalgia and vitamin D deficiency (defined as ≤32 ng/ml) were randomized into two groups by double-blind fashion. The treatment group received 2400 IU of oral vitamin D3 (cholecalciferol) if their serum 25-hydroxyvitamin D level was ≤32 ng/ml or 1200 IU if the serum 25-hydroxyvitamin D level was between 32 and 48 ng/ml. The subjects continued therapy for 20 weeks. During the course of treatment, serum vitamin D levels were reassessed at 5 weeks and 13 weeks, to ensure serum vitamin D levels did not exceed 48 ng/ml. Results of the study demonstrated a significant, but low, decrease in visual analog scores for the treatment group. No significant differences were found in anxiety, depression, or somatization scores. Wepner speculated more robust results might have been achieved with longer treatment intervals, as well as a larger sample size [77].

Why these two trials reached different conclusions is not entirely clear. The Warner group did not monitor serum vitamin D levels or adjust dosage during the course

of their study. Additionally, this trial produced an average serum vitamin D level of 31.2 ng/ml at the end of 3 months of treatment. However, the Wepner study treatment group had an average serum value of 50 ng/ml after 3 months of treatment, and, it was at this time, they had the greatest reduction in pain and morning fatigue [76, 77].

Another difference between these two studies was the type of vitamin D supplement employed for treatment. Controversy exists as to which form of vitamin D is the most effective. Multiple studies have found vitamin D3 ingestion results in higher- and longer-lasting levels of 25-hydrovitamin D [78, 79]. Potential reasons for D3 being more potent include a stronger binding affinity for the vitamin protein-binding hormone, a higher affinity for the hepatic enzyme 25-hydroxylase, and poorer stability of synthetically produced vitamin D2 compared to D3 [78]. However, it has been found that ingestion of D2 at frequent and regular intervals is as effective as D3 in achieving increased blood levels of 25-hydrovitamin D and preventing bone pathology [80].

Diet Therapy

Elimination Diets

As outlined above, some authors have suggested that fibromyalgia symptoms can result from ingestion of dietary excitotoxins [81]. To this end, elimination diets have been proposed as a treatment option for fibromyalgia patients. Smith et al. published a case series of four women who experienced significant relief from all fibromyalgia-related symptoms after eliminating MSG from their diet [60]. Ciappuccini et al. documented a case series of two patients who achieved extensive pain relief by avoiding dietary intake of aspartame [81]. These case studies encouraged Vellisca et al. to further assess the effects of MSG- and aspartame-free diets. Seventy-two women with fibromyalgia were randomized into two groups of 36 members, an elimination (MSG- and aspartame-free diet) group versus a control group. Mean pain scores were measured at baseline and compared with mean pain scores after 3 months of dieting. At the completion of the study, the elimination diet group failed to demonstrate any significant improvements in pain over the control group [82].

Vegetarian Diets

Vegetarian diets have been implemented to ease symptoms related to fibromyalgia. The health benefits of vegetarian diets are numerous and well documented [83]. Studies have found that following a vegetarian diet is associated with reduced incidence of cardiovascular disease, lower blood pressure, and improved serum blood glucose in diabetics [84]. Health benefits associated with diets that emphasize vegetable and fruit foods are theorized to result from the high levels of antioxidant enzymes, lower levels of oxidized lipids, as well as high-fiber content promoting improved intestinal function [85].

Different types of vegetarian diets exist. Vegan diets comprise food consisting of fruit and vegetable products, while excluding any animal or animal-based products. Vegetarian diets that allow the consumption of eggs, milk, and milk products are called lacto–ovo vegetarian. Pesco-vegetarians consume fish in addition to eggs and milk products [86]. Plant-based diets include plant foods in whole form, emphasizing vegetables, fruits, seeds, nuts, and legumes. This type of diet limits animal product consumption [87].

Hostmark et al. appears to be the first group to publish results on the effects of a vegetarian diet in fibromyalgia patients. Ten patients with fibromyalgia were fed a vegetarian diet for 3 weeks. The diet resulted in decreased total cholesterol as well as a decrease in markers associated with heart disease, including plasma fibrinogen and serum peroxide. Patients also reported improvement in pain. However, the value of this study was limited by a lack of a control group. Further, patient's physical activity was not controlled during the course of treatment so it is difficult to determine what effect exercise had on the outcomes. Additionally, four of the ten patients fasted for 10 days, and the details were not provided as to what type of vegetarian diet was utilized for the study [88].

Following Hostmark's study, a group of researchers in Finland treated fibromyalgia patients utilizing a complex vegan diet known as a "living food diet." This type of diet consists of seeds, sprouts, vegetables, fruits, and nuts, while excluding tea, tobacco, alcohol, meat, fish, poultry, eggs, and dairy products [89]. Food items are not heated over 45°C to preserve natural food enzymes. This diet was used in an open nonrandomized controlled trial involving 18 fibromyalgia patients. The treatment group was fed the above diet for 3 months and compared to 15 fibromyalgia patients who continued their normal omnivorous diets. Compared to the control, the vegan-diet group experienced a significant reduction in pain and tender points, while also experiencing improvements in sleep and health assessment questionnaire scores. Dietary compliance, in the vegan group, was also supported by significant reductions in BMI and total serum cholesterol [90]. Patients noted that the positive results, from the living food diet, disappeared gradually after returning to an omnivorous diet.

Hanninen et al. published a report describing how the ingredients of "the living food" diet were likely to benefit fibromyalgia and rheumatoid arthritis patients. It was noted that diets rich in berries, fruits, vegetables, nuts, and germinated seeds provide a robust source of carotenoids, vitamin C, and E. The study found patients on the living food diet produced blood and urine analyses that demonstrated high antioxidant levels, including carotenoids, vitamin C, E, and polyphenolic compounds. It was theorized that these factors could reduce free radicals, therefore diminishing a potential inflammatory source contributing to symptoms common to rheumatic diseases. The study also revealed living food diet subjects had a significant change in intestinal microflora compared to omnivorous controls. Blood and urinary output demonstrated significantly lower levels of phenols, which are considered toxic. It was theorized that the high-fiber content of the diet resulted in increased gut mobility, thereby lessening the time for absorption of potentially harmful compounds from the intestines. Further, fecal samples revealed significantly diminished levels of urease activity. Urease is associated with toxic ammonia production [85].

Donaldson and coworkers also completed a vegetarian diet study on fibromyalgia patients. A total of 30 patients were enrolled and placed on a predominantly raw, vegetarian diet consisting of carrot juice, nuts, seeds, whole grains, fresh fruit, and leafy greens. Patients were told to exclude alcohol, caffeine, refined sugar, corn syrup, dairy, eggs, all meat, and hydrogenated oil. At the end of the study, 19 patients were considered responders to the diet. Responder patients reported a 46% improvement on their Fibromyalgia Impact Questionnaire, in addition to improvements in general health, vitality, social functioning, and mental health on SF-36 health survey. The study outlined its own limitations, including a failure for some participants to meet fibromyalgia diagnostic criteria [91]. The study was also limited by the lack of a control group.

No complications were noted in the above studies, but strict vegan or unbalanced vegetarian diets place users at risk for certain dietary deficiencies in B12, amino acids, iron, calcium, vitamin D, eicosapentaenoic (EPA) acid, and docsahexaenoic fatty acids [92]. However, balancing the right combination of plant-based foods, and incorporating B12 fortified foods, can allow for adequate quantities of these essential nutrients [87].

Conclusion and Recommendations

Studies examining the pathogenesis of fibromyalgia suggest dietary modifications may result in better symptom control and improved quality of life. However, conflicting results and methodological flaws continue to limit our understanding of nutrition and its relationship with fibromyalgia. There are no studies that provide enough high-quality evidence to support the long-term use of any particular diet or oral supplement. More studies are needed to help create specific nutritional guidelines. Currently, dietary advice should be limited to basic information outlining what is considered to be a balanced diet necessary to maintain a normal weight and adequate intake of essential nutrients. If a resource is needed, then patients may be referred to the US Department of Agriculture for access to websites resources, such as Dietary Guidelines for Americans or ChooseMyPlate.gov [87]. These websites provide national dietary recommendations for healthy eating as well as information about the nutritional composition of different food sources.

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