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Management of Pain in the Fibromyalgia Syndrome

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Abstract

The objective of this manuscript is to summarize some of what is known about managing the pain of fibromyalgia syndrome [FMS]. Brief introductory discussions of six related topics: 1. categories of pain; 2. pharmacological versus complementary interventions; 3. efficacy versus safety; 4. confidence in data; 5. evidence-based medicine; and 6. outcome-based compensation; will be provided. Patients with FMS typically exhibit several key clinical manifestations [also called comorbidities or domains]. Pain is one of them, but treatment focused on the pain alone will likely fail. Meta analyses based on controlled clinical trials provide near-truths about the effectiveness of a given intervention. It is currently believed that optimal treatment of FMS will involve a combination of a one or more pharmacologic and aone or more complementary interventions. The pharmaceutical industry has extensively studied several medications which offer benefits of relatively small effect sizes. Studies of complementary therapies have disclosed larger effect sizes, generally but based upon with lower quality data. Unfortunately, almost novery little systematic research has been devoted to the study of combinations of promising pharmacologic and complementary therapies. In the future, progress will likely come from research focused on the disordered biology of FMS and from meta-analyses of controlled clinical trials involving combinations of promising pharmacologic and complementary therapies.

Keywords: Fibromyalgia syndrome; Neurotherapy

Introduction

Understanding the fibromyalgia syndrome [FMS] and how to manage the pain experienced by FMS patients depends upon a working knowledge of several historical and contemporary concepts which will be addressed in the following paragraphs:

Categories of pain

Acute and chronic pain is clinically and physiologically different even though they can coexist in the same patient, and both can lead to a substantial compromise in a patient's quality of life [1]. Acute pain typically has an acute onset, directly resulting from an event, such as ischemia, trauma, or surgery, and resolves with healing of the injured tissues. On the other hand, chronic pain develops insidiously, sometimes as sequelae of an acute pain problem, but often no apparent antecedent injury can be identified [2-4]. Chronic pain is defined as an unpleasant sensory and emotional experience persisting longer [by definition, more than three months] than expected from the normal process of healing [1]. Compared with acute pain, chronic pain is less likely to involve a specific organ, or to exhibit an anatomic dermatomal pattern, and is more likely to exhibit comorbid psychological pathology [4,5]. Seldom is it clear that the psychological process is etiologic to the pain process, but the reverse certainly may occur. Only rarely does the chronic pain respond to otherwise successful psychological therapy. Acute pain can develop in FMS patients in association with an acute event. When that occurs, healing of the injured tissues in the FMS patients, and resolution of the acute pain problem, tends to follow a normal pattern and rate.

It has been estimated that about one fifth of the world's population suffers from chronic pain [6]. That may be why there is so much excitement regarding the discovery of pattern recognition receptors [PRRs] in the central nervous system that alert the individual to body injury [7]. The problem is that this warning system can malfunction and can inappropriately-warn constantly [and chronically] via pain messaging, even in the absence of injury. The good news is that awareness of such a system provides a unique biological target for new kinds of therapeutic interventions.

The pain of FMS meets the definition of chronic widespread pain but the potential role of PRRs in FMS is yet to be explored. Perhaps, a young reader of this manuscript will become a pain researcher and will follow that lead to a marvelous discovery. However, a "divide and conquer" issue may prove to be counterproductive toward progress with FMS. Many international clinicians have expressed their preference for a condition name called "chronic widespread pain" [CWP] which may represent a larger, but less well defined chronic pain population than FMS. Butler and colleagues [8] have called for a better case definition for CWP. Similarly, Kosek and colleagues [9] have suggested that a new mechanistic category of pain should be created to help distinguish these disorders.

Another pain/tenderness duo distinction which has become useful in the study of FMS is that of "allodynia versus hyperalgesia". In the early days of the study of pain, anesthesiologist, J. J. Bonica was the leader and teacher. He recruited a few colleagues to write chapters for a two-volume textbook about pain (see John J. Bonica, Wikipedia). That book, which they called "The Management of Pain", was intended to guide the concurrent and future efforts of clinicians and researchers who would study and treat painful conditions. Bonica reserved the chapter on definitions of terminologies for himself, because, as he told this author, that he had "a burden to get it right" (1989, Bonica,

personal communication). The resultant chapter in volume one of the second edition was called Definitions and Taxonomy of Pain [1]. In that chapter, Bonica defined two forms of induced pain [tenderness]: allodynia was perceived pain caused by a stimulus [such as pressure or heat] that would not cause pain in a normal individual. He defined hyperalgesia as tenderness an overly aggressive withdrawal response to cause by a stimulus that would be expected to be painful even for a normal individual. Allodynia applies uniquely to FMS in humans, it seems, because humans can verbally report feeling pain before the threshold for hyperalgesia [evidenced by withdrawal] is achieved. Hyperalgesia is typically used as an outcome in the study of stimulus-induced pain among experimental animal models, and typically because it depends on a withdrawal response which is readily observable by the investigator. Hyperalgesia also occurs in many FMS patients, but allodynia is a more sensitive measure of their human pain experience. As a noxous stimulus is gradually introduced to a FMS patient at one of the anatomically-defined tender points, the experience of allodynia is reached achieved before the experience of hyperalgesia is observed.

Categories of interventions

Pharmacologic therapy refers to the use of one or more medications to manage a medical problem. The term "complementary" or "alternative" therapy refers to the use of one or more non-pharmaceutical interventions [10]. Examples of complementary interventions that have been studied in FMS include: education, peer group support, aerobic exercises, hydrotherapy, electrical stimulation, and cognitive behavioral therapy. It should be recognized that intentionally-prescribed therapy of any kind is probably not pure in the "real world". Prescribed complementary therapy may be accompanied by over-the-counter medications taken by the patient without the knowledge of the clinician. Similarly, patients taking a prescribed pharmacotherapy may be simultaneously trying a variety of complementary interventions on the advice of family, acquaintances, media advertisements, or internet sources. A frank and completely open relationship between the patient and the clinician may help to ensure that therapies actually being used by the patient are accurately documented in the medical record, so they can have been professionally interrogated to ensure safety and efficacy, while the assumed goal is efficacy.

Goals of therapeutic research

Clinical research pertaining to any therapeutic intervention must determine whether the intervention is safe for use by humans with FMS [safety], and whether the intervention is capable of reducing the severity of the target symptom[s] [efficacy]. In the case of some interventions, these two kinds of outcomes are unrelated to each other, while unfortunately, in other cases, they are known to be inversely-related. Often, it is observed that increasing the dosage of a medication results in greater efficacy, but. I it can also lead to increasing risk of injury [decreased safety]. The clinician must inform the patient of this relationship and the patient's preference should guide the therapeutic plan. The plan should be based on what the well-informed and compliant patient considers to be an acceptable balance between efficacy and safety. When the emergence of risk[s] associated with a given therapy is[are] known to be idiosyncratic, the patient must be informed regarding that known potential for unpredictable therapy-related injury and must be made aware of the fact that the seriousness onset of the worrisome side effect[s] cannot be accurately predicted in advance, or even at onset. If the patient still elects to take the therapy, the clinician must then be ever-watchful for the typical manifestations of iatrogenic injury.

Unfortunately, many clinicians have carried throughout their careers an inappropriate bias against FMS as a medical condition and against FMS patients, because they complain of symptoms that the clinician is unsure how to manage. That bias has, at times expressed itself as anger and verbal abuse directed at the patient. In 2006, the following phrase was coined to illustrate that situation: "Fibromyalgia syndrome patients who fail to respond to a clinician's misguided and futile attempts at therapy are at risk of meeting primitive human behavior disguised as treatment" [11].

Confidence in research data

It is widely acknowledged that the internet is not a consistently reliable source of medical information. There is little doubt, however, that there is information on some web sites which is well sourced and accurate. The implication is that medical information on the internet can be expected to range from accurate/useful, through inaccurate/useless, to self-serving/fraudulent. What is needed is a way to classify medical information on the basis of its level of accuracy. The same applies to all of the data that is referred to as medical information.

The quality of medical information data can be considered to be multi-tiered [ranging from "high", to "moderate", to "low", to "very low"]; see the presentation of data quality grading provided on the following website: https://cebgrade.mcmaster.ca/Intro/index.html].

In general, there is a consensus that the most reliable research-derived information is meta-analyses data, obtained by analyzing the combined data from many randomized, controlled clinical trials, selected for further study according to prospectively designed rules. Meta-analysis data is more likely to represent a universe of high quality studies and less likely to misrepresent the truth [12]. Even with meta-analysis of controlled clinical trials, however, the accuracy of the final data is dependent on the numbers of subjects in each included clinical trial and upon the quality of the outcome assessments used [13]. According to the four-tiered hierarchy described above, a step down in data quality from the meta-analysis would be data derived from a single, large, randomized, controlled, clinical trial. Ranking down further, would be data from a variety of clinical study designs, including most kinds of observational protocols, and finally, near the bottom of the accuracy scale, would be a single case report.

Despite the perceived value of this hierarchy, there are situations in which meta-analysis data is not available to guide an important medical decision. The clinician who is caring for a patient with a rare disease, not yet extensively studied, or a patient who has developed a unusual complication from an indicated therapy, may have to base a clinical decision on what is known from a single case report, or from a small series of case reports, because they provide the only data currently available [14].

There have been many [N=28] meta-analysis-type studies and systematic reviews examining the management of FMS (Table 3), so there is no reason to argue that insufficient research regarding FMS care has prevented that condition from being approached therapeutically, with a relatively high level of medical sophistication. If there remains a deficiency, it is due to a paucity of controlled clinical trials examining various combinations of pharmacotherapies co-administered and co-assessed with a variety of beneficial complementary interventions. As a result, a clinician may not currently

know which intervention from the list of studied complementary interventions will best match the clinician's choice of a pharmacotherapy intervention.

Evidence-based medicine [EMB]

The concept of evidence-based medicine [EBM] is not new, having been proposed and practiced in Paris as early as the mid-19th century [12]. Sackett and colleagues [12] have defined EMB as "the conscientious, explicit, and judicious use of current best evidence in making medical decisions about the care of individual patients." The same authors indicated that "the practice of EBM means integrating the care giver's clinical expertise with the best available external clinical evidence from systematic research" [12]. It is clear, however, that the definition and practice of EBM is ever evolving and grows increasingly more demanding upon the clinician's expertise.

Critical to the ultimate definition of EBM are the factors which must be resourced in the process of applying its methods. For example, EBM has traditionally been modeled as utilizing the best balance of information from three sources [clinical expertise, research evidence, and patient preferences] but Haynes et al., [15], have proposed an updated model based on information from the original three sources plus one additional source [the patient's clinical state and circumstance]. Consider an acute event, such as a penetrating head injury, in a primitive location, far away from any modern medical resource. That patient's circumstance may exclude many potentially useful interventional choices, which would be available if the circumstances were more favorable. There have been concerns that EBM might lead to a constrained form of cookbook medicine, which third party payers would require clinicians to follow in hopes of reducing the costs of care. These concerns have been specifically addressed by Sackett and colleagues [12]. Indeed they have stated that, contrary to the expectations of many, EBM "may [actually] raise, rather than lower, the cost of ...care." [12].

Most of the arguments against application of EBM in the care of FMS patients are not valid. FMS is not new, not rare, and not unstudied. Not new, since it was initially named "fibrositis" in 1904 [16]. Not rare, since it affects about 2% of the general population in the United States, which makes FMS about twice as common as rheumatoid arthritis [17,18]. Not rare since it is projected that there are about five million people with FMS in the United States [19], nearly one million in Mexico [20-22], and about fourteen million in China [23]. Not unstudied, since the Cochran index lists 28 systematic reviews pertaining to different aspects of the management of FMS.

Compensation for care

The provision of medical care must be sufficiently well compensated in order to attract some of the world's best young minds into the medical profession. If this ploy is not successful, those promising young people will be attracted away to other challenging careers. No one really argues against that concept, but the debate has, for years, been about how the level of that compensation should be determined. The highly-refined model currently used in Western medicine is "activity-based funding" while the proposed "pay-for-performance" model still awaits its opportunity to be adequately tested [24,25]. One potentially-promising form of the pay-for-performance model is "outcome-based compensation [OBC]." The OBC model depends on the extent of the patient's response to treatment, so documentation of outcome is another necessary task that would will likely be required of the clinician.

Fortunately for clinicians who care for FMS patients, extensive research and experience has provided a simple, but validated self-report outcome measure that can be used as a component of the medical record. At each clinical visit, after the diagnosis of FMS has been made, the clinician's staff can provide a simple two-page questionnaire, called the "Revised form of the Fibromyalgia Impact Questionnaire [FIQR]", to the patient for completion, and the staff can easily score it, to achieve a single outcome number [26]. That number quite accurately represents the FMS patient's "current clinical status", which can be graphed on the "Y" axis against "time" on the "X" axis. Over the course of the patient's care for their FMS, that graph will indicate the change in severity with time to represent the patient's "outcome" [presumably hopefully, progressive improvement] for use as a basis for compensating the care provider.

In many countries, it has become nearly universal that the medical record is generated at the site of care and stored electronically as an "electronic medical record [EMR]" [27-29]. Essentially all of the EMR programs in wide-spread use provide special locations in the program for entry of the vital signs, measured at each clinical visit, and a built-in software routine to graph those variables with time. In essentially all of such EMR programs, there is space for additional "vital sign-like" data to be defined, entered, and processed graphically. The serial FIQR score could be defined as one such serially-derived vital sign-like variable, and can be similarly graphed at intervals to document an outcome worthy of compensation for skilled care.

Clinical Information

History and epidemiology

The early history of FMS was elegantly reviewed in 2004 [30]. To briefly summarize a few key historical points regarding nomenclature, it should be noted that descriptions of this condition date back to 1592 when it was referred to as muscular rheumatism [31]. The term fibrositis was introduced by Gowers in 1904 [32] and the current term fibromyalgia was coined by P.K. Hench in 1976 [33] because the "-itis" suffix on the term "fibrositis" improperly implied that the condition was an inflammatory disorder. We now know that low grade inflammation is an objective laboratory aspect of FMS, but the physician group most interested in censuring fibrositis at the time were mainly rheumatologists and it is truewho judged that fibrositis was not very inflammatory, when compared with other diseases presenting in the rheumatology clinic, such as rheumatoid arthritis, systemic lupus, scleroderma, vasculitis and polymyalgia rheumatica.

This author prefers to use the two-word term "fibromyalgia syndrome" [FMS] because FMS does not meet this author's favored criteria for a "disease". There are so many definitions of a "disease" that use of the term clearly requires stepping out on a slippery slope [34]. Favored by this author is the definition for a disease which requires a specific constellation of symptoms [OK true for FMS] caused by an established pathogenesis [not yet known for FMS] and a treatment that specifically addresses one or more aspect[s] of the pathogenesis to successfully improve the symptoms [not yet a reality for FMS]. One must then ask: which of the many clinical manifestations of FMS are physiologically-related to an established pathogenesis of FMS? And, what successful treatment for FMS is specifically directed at some specific aspect[s] of the underlying pathogenesis?

The role of P.K. Hench was interesting, because his father, P.S. Hench, was a Nobel Laureate, given that award for his discovery of the glucocorticoid-induced temporary ameliorating effects of glucocorticoids on the ravages of rheumatoid arthritis. Working at the Mayo Clinic as a clinician and researcher, P.S. Hench was similarly fascinated with FMS as early as 1938 [35] [when it was still called fibrositis] and struggled with characterization of individual cases, as being either primary or secondary fibrositis. His son, P.K. Hench later expanded on this quandary [36]. The contemporary view was that fibrositis/FMS should be considered primary when there was no relevant underlying disorder and secondary when it occurred in patients with an underlying rheumatic disease or other organic disease. As fibrositis became better defined, the list of underlying disorders grew, so the characterization of fibrositis/FMS required increasingly careful diagnostic study. The differentiation of primary and secondary fibrositis/FMS was also [and still is] believed to bear therapeutic implications. One of those implications was that secondary fibrositis/FMS might be expected to respond to treatment of the underlying disorder, whereas primary fibrositis/FMS requires management directed at the FMS symptoms, such as the musculoskeletal pain, the insomnia, and the emotional disturbances that can be comorbid with the body pain. To complete the official acknowledgments of FMS, the American Medical Association recognized it as a distinct disease back in 1987, and the World Health Organization recognized FMS as a real illness in 1991, and accepting the American College of Rheumatology's criteria for that diagnosis.

Fibromyalgia syndrome is "a relatively common chronic pain disorder," according to Marco Loggia at Harvard University. Loggia added that "it can be extremely debilitating." Loggia is associate director of the Center for Integrative Pain Neuroimaging at Massachusetts General Hospital in Charlestown, Mass. "Most of the patients we encounter in our research studies are significantly impacted by this disorder," Loggia noted, "which sometimes prevents them from having normal work and social lives".

Perhaps the first study to examine the prevalence of FMS was conducted in the area of Wichita, Kansas, USA [37] where it was discovered: that FMS affected about 2% of the general population, ; that FMS was more common in adult females than adult males; and that the prevalence of FMS increased with the age of the general population. In that study, adult females aged 50-60 years of age, exhibited a prevalence of about 8% [37]. Similar studies have been conducted in many other countries with similar findings. By contrast, a study conducted in southern Norway [38] found a prevalence of 10% among women ages 20-49 years. That apparently higher prevalence was not due to an unusual level of FMS saavy on the part of area physicians, but rather, probably related to the appeal of that region to Norwegian retirees. A full prevalence study of FMS in China is in the planning stages, but preliminary data from a Hong Kong study [23] showed a 1% prevalence of FMS among Chinese people in that city. When that prevalence is projected to the current population of mainland China, it would predict that there are about fourteen million people with FMS in China.

Clinical presentation and diagnosis of FMS

On the occasion of their initial presentation, new patients with FMS typically have complained of persistent, widespread pain, saying "I hurt all over". In addition, they have exhibited dramatic tenderness to palpation at anatomically-defined tender points [TePs] located in soft tissue musculoskeletal structures [39]. As more was learned about the initial presentation of FMS, it has become clear that pain and tenderness are not sufficient as diagnostic criteria, because FMS is actually composed of several other clinically-related symptoms. Associated symptoms usually, but variably-included insomnia, cognitive dysfunction, depression, anxiety, recurrent headaches, dizziness, fatigue, morning stiffness, extremity dysesthesia, irritable bowel syndrome, and irritable bladder syndrome. Table 1 illustrates this phenomenon with documentation of the relative frequency of each of these comorbid manifestations [40].

The 1990 American College of Rheumatology Research Classification Criteria [1990 ACR RCC] were published [41]. Those criteria required the presence of widespread pain for a period of 3 months, and the finding of painful tenderness at 11 or more of 18 anatomically-defined tender points This set of criteria, validated for use in research were proved to be very useful, because for the first time in history, it was possible for research groups, working in different physical locations around the world, to identify comparable patient populations for entry into research study protocols. They greatly facilitated research on FMS but they were never validated for use in community clinical care. In addition, there was concern that this approach to diagnosis addressed only the pain/tenderness domain of FMS, leaving the other apparently-important clinical domains undervalued.

In an attempt to correct that deficiency, a new set of criteria was developed in 2010, and was were validated for use in community clinical care [42]. The new criteria addressed the historical chronic widespread pain issue with what was called the Widespread Pain Index [WPI, range 0-19] and some of the other FMS domains with what was called the Somatic Severity Scale [SSS, range 0-12]. As these criteria were reported in 2010, the format required the physician to personally collect all of the relevant information by interview with the patient.

In 2011, an important revision of the 2010 protocol allowed the same data to be collected via a self-report questionnaire which was to be completed by the patient, and reviewed by the clinician. While the distinction may seem to be a bit semantic, the authors of the new criteria emphasized that the objectives were to facilitate epidemiological research and to remove some of the interview burden on the physician. The fact that the questionnaire was self-report was not intended to imply that the patient could self-diagnosis diagnose.

The same scoring requirements used in 2010 applied in 2011, so when the sum of the WPI and the SSS equaled or exceeded 13, the physician was supported in making the diagnosis of FMS [43]. Despite the development of the 2011 ACR Fibromyalgia Diagnostic Criteria [2011 ACR FDC], and its value in epidemiology studies, the 1990 ACR RCC remained the conceptual gold standard for the research diagnosis of FMS. Approximately five years after publication of the 2011 ACR FDC, the same consensus group of authors revisited the use of the 2011 ACR FDC and responded to concerns [44].

Comorbid manifestations [domains]

The FMS has been physiologically-defined as" the human model of chronic widespread allodynia" [45]. While management of the chronic FMS pain is the focus of this treatise, it should be clear, from the list of symptoms on Table 1, that the syndrome is much more complicated than its pain component alone. The presence of several other apparently-interrelated comorbidities, prompted a research clinical assessment expert panel [called "Objective Measures in Rheumatic Diseases", OMERACT] to designate that six of the most characteristic

["the core"] domains should be evaluated in all future research studies [46]. That list of six core domains included: pain, tenderness, sleep disturbance, fatigue, patient global impression of severity, and impairment of multidimensional function. In addition, it was judged that dyscognition and depression should be measured in some, but nor all, trials, while stiffness, anxiety, functional imaging, and cerebrospinal fluid biomarkers should be viewed as domains of research interest, to document in selected studies [46].

Clinical feature	Prevalence
Widespread pain	100%
Peripheral pain generators like active trigger points	70%
Sleep disorder	90%
Fatigue	80%
Depression: current prevalence	20–40%
Depression: lifetime prevalence	58–71%
Irritable bowel syndrome	30–50%
Irritable bladder syndrome	12%
Urinary urgency	60%
Headache: severe muscle contraction type	Often
Cold intolerance	Often
Cognitive deficits	Often
Palpitations, chest wall pain mimicking angina	Often
Morning stiffness	Often
Dizziness and lightheadedness	Occasional

Table 1: Frequency of manifestations in fibromyalgia syndrome (65).

Pathogenesis of FMS

Some readers will be surprised to learn that there is much to know within the topic of "FMS pathogenesis" but all of that information is beyond the scope of this presentation. Readers interested in that topic are referred to the Library of Congress PubMed, Scholar Google, Science Citation Index, or other referencing services for what will prove to be extensive bibliographies on that topic.

Management of FMS

An earlier attempt to organize the management of FMS for easy clinician memory resulted in the development of a six-step approach, symbolized by the acronym “ADEPT Living” [11]. That approach has been slightly modified in its "Treatments" section so it will better match progress in the field (Table 2). Notice the first letter of each underlined subheading below:

Attitude	Patient/HCP/Family/Others
Diagnosis	Diagnosis/Differential Diagnosis
Education	Psychosocial/Biomedical/CBT
Physical	Home [pace, exercise, heat]/PT
Treatments	Pharmaceutical/Complementary
Living	Follow-up Assessment and Support
Abbreviations: HCP=Health Care Professional; PT=Physical Therapy; CBT=Cognitive Behavioral Therapy.	

Table 2: Six Steps to ADEPT LIVING for Fibromyalgia syndrome therapy.

Attitude: Attitude in Table 2 refers to the frame of mind that each participant brings to the therapeutic interaction. Clinicians must be prepared to accept FMS as a real syndrome, which exerts a tremendous impact on the patient’s life. One can expect that eEmpathy will prove to be should be more therapeutic than baseless recriminations for having an unpopular medical problem. From the patient’s perspective, it will be important to understand: 1. that FMS is just one of thousands of medical conditions of concern to the health care provider; 2. that the presenting symptoms for different medical conditions can be very similar; 3. that therapy for FMS is still experimental; and 4. that the physician’s time with each patient is necessarily limited. The attitudes of family members, employers, policy makers, and politicians, all in their own way, impact importantly on the patient’s care and outcome.

Diagnosis: It is important that the correct diagnoses be made, not only to identify the FMS, but also to disclose any concomitant medical conditions. If the patient also has hypothyroidism, diabetes, mellitus, or renal insufficiency the approach to management of the FMS will need to accommodate those other conditions. For example, when rheumatoid arthritis and FMS are evident symptomatic in the same patient, treatment seems to be more successful when both conditions are treated separately.

Education: Education is important to the management of the FMS. Understanding is power for the patient when it comes to maintaining a proper attitude, adapting to limitations, and taking an active role in the therapeutic program. Several studies have examined the effects of cognitive-behavioral therapies on outcome in FMS patients and have demonstrated positive effects on pain scores, pain coping, pain behavior, depression, and physical functioning [47,48]. Such gains are often maintained for several months after completion of the therapy and periodic “booster sessions” may prolong the benefits. Support groups have been viewed negatively by some clinicians, as an environment for learning perpetual discontent. On the other hand, joining a resource-oriented support group can help FMS patients come to terms with a complicated set of symptoms and limitations.

Physical somatic approaches: A variety of physical modalities have been proposed as interventions for FMS. They can be logically segregated into two categories: those that the patients can accomplish by themselves and those that require active participation by a trained therapist. At home, the patient can pace activities by setting a clock to time necessary work activity and then balance the work times with an equal period of rest. Heat applied as simply as with a shower or bath, and Jacobsonian relaxation techniques can all be viewed as self-directed low cost therapies at minimal cost [47].

Aerobic exercise was among the first non-pharmacologic strategies advocated for FMS patients, with because there was convincing evidence for benefit [47,49]. Its goals were to maintain function for everyday activities and to prolong life through cardiovascular fitness. If carried out at low impact with an intensity sufficient to challenge aerobic capacity, exercise can also reduce pain, improve sleep, balance

mood, improve stamina, instill new perspectives, restore cognition, and facilitate a sense of wellbeing [50]. Patients who are able to exercise experience less negative impact of FMS in their lives.

On the other hand, it is perceived that imprudent levels of exertion, at least at first, may worsen the ambient pain for some patients. When the diagnosis of FMS is first made, the patient can be expected to be deconditioned and to have learned to fear that their pain will be exacerbated by exercise. Even an otherwise healthy, but deconditioned, person will experience transient muscle soreness after beginning an exercise program. When prescribing exercise for FMS patients, the clinician should begin with low intensity, low impact exercise, [such as walking in place on land or in a swimming pool] and should show advice the patient regarding how to avoid eccentric muscle contractions [50]. Initial compliance with a well-designed exercise program will usually be facilitated by a reduction of the FMS pain. For that reason, T there may be value in beginning an effective pharmacotherapy before initiating an exercise program. Compliance and continuation of a well-designed exercise program will usually be facilitated by a reduction of the FMS pain.

Most patients report benefit from heat in the form of a hot bath, hot-water bottles, electric heat pads, or sauna. Many find that a hot bath or shower can be more effective than an analgesic medication for headache, body pain, and stiffness. The application of heat can relax muscles, facilitate exercise, and produce a sense of well-being. Cold applications including brief exposures to frank subzero temperatures are preferred by some. Light massage that gradually progresses to deep sedative palpation of large body surfaces can reduce muscle tension, but its influence on FMS body pain usually is quite transient, lasting only a day or two.

Treatments: In the ADEPT acronym system, treatments refer to therapies prescribed by health care professionals. The characterization of the term "Pharmaceutical" is relatively clear but "Complementary" is more nebulous. A previous document introduced the concept of triangle-based strategic polypharmacy [51] as a way to optimize the use of medications in the management of more than one FMS clinical domain (Figure 1).

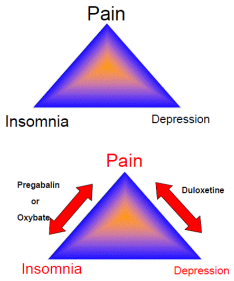

Figure 1: Illustration of the triangle method for conceiving strategic polypharmacy for the management of fibromyalgia syndrome [FMS]. UPPER: A triangle linking three important clinical domains in the treatment of the FMS. LOWER: A triangle showing use of low dosage pregabalin or sodium oxybate to treat both pain and sleep dysfunction, and concomitant use of duloxetine to treat concomitant pain and depression, when all three domains are prominent manifestations.

The term complementary therapies could properly have included the education and the physical somatic approaches discussed in separate ADEPT subsections above, but they were perceived as being so intuitively basic and necessary to any treatment program that they were given separate categories in the ADEPT classification. That may change with time. Relatively new to western medicine are complementary medical exercises rooted in Eastern Martial Arts, such as Qigong [pronounced "Chi-gong"] [52], Tai Chi [53], and Lu-Eight-Brocades [also known as "Ba Duan Jin"] [54]. These interventions can be specifically prescribed, can intrinsically encourage patient compliance, and can be therapeutically beneficial, so it appears that they belong in the category of complementary interventions category for FMS.

Living: The "Living" subcategory is important to the success of the Table 2 ADEPT LIVING management program because it involves documentation of outcomes with the FIQR, as described in subsection six of the Introduction, entitled "Compensation for care".

Systematic analyses

Table 3 shows a listing of studies pertaining to FMS included in the Cochrane Index of systematic analyses reported prior to the preparation of this manuscript. The Cochrane approach to the systematic review process is described on the Cochrane website [http://cochrane.org/]. Cochrane Reviews are systematic reviews of primary research in human health care and health policy, and Notably, they are internationally recognized as the highest standard in evidence-based health care resources. They utilize meta-analyses to investigate the effects of interventions for prevention, treatment, and rehabilitation. The reader should realize that Table 3 does not include all of the quality meta-analyses performed on the topic of managing FMS. Many authors have conducted such analyses without the involvement or assistance of the Cochrane organization, in which case, they would not be listed in Table 3.

1	Afari (26)	Psychological trauma
2	Bidonde (27)	Aquatic exercise training
3	Busch (28)	Exercise therapy
4	Carville (13)	Discriminating power of outcome measures
5	Chan (29)	Qigong exercise treatment
6	Courtois (30)	Body awareness interventions
7	Ernst (31)	Chiropractic treatment
8	Garcia-Hermoso (32)	Effects of exercise on functional aerobic capacity
9	Giles (33)	Cognitive behavioral therapies
10	Hauser (34)	Antidepressant treatment
11	Hauser (35)	Serotonin and noradrenaline reuptake inhibitor treatment
12	Karjalainen (36)	Multidisciplinary rehabilitation
13	Kelley (37)	Effects of exercise on depression
14	Knijnik (38)	Repetitive Transcranial Magnetic Stimulation
15	Lami (39)	Psychological treatment

16	Lee (40)	Qigong exercise treatment
17	Lee (41)	Candidate gene studies
18	Li (42)	Massage therapy treatment
19	Lima (43)	Aquatic physical therapy treatment
20	Lynch (44)	Cannabinoids as treatment
21	Minelli (45)	Cognitive behavioral therapy
22	Moore (46)	Amitriptyline treatment
23	O'Connor (47)	Walking Exercise as treatment
24	Offenbacher (48)	Outcomes Classification - function and disability
25	Smith (49)	Mortality
26	Tang (50)	Nonpharmacological Treatments of Insomnia
27	Terry (51)	Complementary and alternative treatments
28	Wiffen (52)	Antiepileptic therapy

Table 3: Cochrane-Style Systematic Reviews Regarding Fibromyalgia Syndrome.

A metaanalysis of therapies directed at FMS core domains shortly after the official selection of six symptomatic domains to serve as the "FMS core" variables [See above Section "Clinical Information; subsection #4. Comorbid manifestations, domains"], a metaanalysis of FMS management studies assessing those outcomes was conceived [55]. The unique features of this metaanalysis were that it focused on the official FMS core domains as measured outcome variables, and that it evaluated pharmacotherapies and complementary therapies on the same "level playing field". The design of the study was to search the medical literature for randomized, placebo- or sham-controlled, clinical trials of FMS management by pharmacotherapy or complementary therapy interventions using FMS core outcome variables assessed for treatment effect size. PubMed, Embase, and the Cochrane Library were screened for candidate studies published between 1990 and September 2012. The FMS diagnostic criteria used as a requirement for inclusion in this study was the 1990 ACR RCC [see Clinical Information, subsection "2. Clinical presentation and diagnosis of FMS" above]. Excluded were studies in which some or all of the patients had concomitant inflammatory or psychiatric conditions. For this study, In addition, the FMS non-core "cognitive impairment" domain was substituted for the core domain "patient global impression of severity". Studies were included if they exhibited documentation of outcomes for at least two of the following FMS symptom domains: [pain, sleep disturbance, fatigue, affective symptoms, physical function deficit, and cognitive impairment]. The initial search yielded a total of 1516 published studies which were then critically interrogated against the entry criteria, leaving 25 eligible studies regarding pharmacotherapies and 67 reports regarding complementary intervention studies available for the planned meta-analysis. The pharmacotherapy studies exhibited high quality data [strong designs and large sample sizes], which often focused on the pain as one of two domains because the United States Food and Drug Administration [FDA] had previously defined reduction of FMS pain as the key to approval of a drug for treatment of FMS. By contrast, the complementary therapy studies offered generally lower quality data [weaker design features and smaller sample sizes]. However, the complementary intervention studies were more likely to have explored multiple relevant domains as outcomes. The FMS diagnostic criteria used as a requirement for inclusion in this study was the 1990 ACR RCC [see Clinical Information, subsection "2. Clinical presentation and diagnosis of FMS" above]. Excluded were studies in which some or all of the patients had concomitant inflammatory or psychiatric conditions. From the included pharmacotherapy studies, the effect size values for amitriptyline, citalopram, duloxetine, fluoxetine, growth hormone, milnacipran, pregabalin, and sodium oxybate were assessed. Of those, amitriptyline, duloxetine, fluoxetine, growth hormone, milnacipran, and oxybate all showed significant effect sizes on the pain variable. Surprisingly, the effect of pregabalin on the FMS pain domain was not significant but a metaanalysis of prior systematic reviews of pregabalin treatment of FMS indicated that there was significant efficacy in FMS with pregabalin and that the number needed to treat FMS with pregabalin ranged from 4 to 10 [56]. For the sleep dysfunction domain, amitriptyline, duloxetine, pregabalin, and sodium oxybate all met significance criteria but most of the effect sizes were small. For the fatigue domain, amitriptyline, duloxetine, milnacipran, and sodium oxybate met significance criteria. Affective domain measures responded significantly to duloxetine, fluoxetine, and milnacipran. The physical dysfunction domain variable responded significantly to duloxetine and milnacipran but the effect sizes were quite small. Translation of these meta-analysis findings into therapy recommendations is difficult because duloxetine would appear to be the winner of this analysis, but the effect sizes observed with that drug were generally quite small. Many of the studies of the candidate pharmacologic agents had not assessed some of the key FMS core, so much potentially helpful information was simply not available to analyze. Amitriptyline appeared strong for the three variables actually tested but a recent systematic review, which focused entirely on amitriptyline, failed to find much benefit when it was compared with the placebo effect [57]. In addition, the adverse effects profile of amitriptyline is of concern. In the United States, FMS is not an approved indication for amitriptyline, growth hormone, or sodium oxybate. Many of the FMS domains suffered from insufficient data. That was particularly true for the cognitive dysfunction variable.

Treatment	Pain	Sleep	Fatigue	Affect	Physical	Cognition
Amitriptyline	+	+	+	-	-	@
Citalopram	-	-	-	-	@	@
Duloxetine	+	+	+	+	+	+
Fluoxetine	+	-	-	+	-	@
Growth Hormone	+	@	@	@	-	@
Milnacipran	+	-	+	+	+	+
Pregabalin	-	+	@	@	-	@
Oxybate	+	+	+	@	@	@

Abbreviations: Sleep=Sleep Dysfunction; Affect=depression and/or anxiety; Physical=Physical Dysfunction; Cognition=cognitive dysfunction.
[+] available data met significance criteria;
[-] failure to meet significance criteria
[@] inadequate data for analysis.

Table 4: Significant Effect Sizes from Meta-analysis on Core Domain Variables Resulting from Pharmacotherapy for Fibromyalgia Syndrome Patients.

Table 4 shows these findings in digital format, which brings out an observation that was not so readily apparent in the comparable table of the original manuscript. Duloxetine studies met significance criteria for all six of the studied symptom domains, while milnacipran failed to do so only because it did not meet significance with regard to the sleep dysfunction domain. From the included complementary studies, the effect size values for acupuncture, balneotherapy, cognitive behavioral therapy, exercise, education, exercise/education combined, homeopathy, magnetic cerebral stimulation, massage, neurotherapy, pool/water therapy, and UV/bright light were provided in the original manuscript. Pool/water, cognitive behavioral therapy, exercise and neurotherapy treatments had data to analyze across all FMS domains. Acupuncture, neurotherapy, and UV/bright light interventions were quite uniformly not beneficial and should no longer be prescribed for FMS therapy. Balneotherapy lacked data regarding three of the studied domains, but was significantly beneficial for each of the three domains that could bewere tested. Future studies of that modality should assess the missing outcome variables. Education alone failed to reach significance for sleep dysfunction and compromised physical function, but was significantly beneficial for pain, fatigue, and the affective symptoms domains.

Homeopathy was found beneficial for pain and compromised physical function but not for fatigue or affective symptoms. Magnetic cerebral stimulation was found significantly beneficial for pain, fatigue, and compromised physical function, but failed to help sleep dysfunction and affective symptoms. Massage was significantly beneficial only for the pain domain, but failed or lacked necessary data regarding all of the other domains. Since the apparent benefits from massage have been so transient, the cost of any further testing of that modality would probably be ill-spent. Neurotherapy was beneficial for pain but failed significance on all of the other domains, so its future for this indication is in serious doubt. It was hoped that UV/bright light would help with sleep dysfunction by resetting the biological clock, but it did not meet significance for sleep dysfunction, or any other FMS domain. No fFurther investment in that modality seems unwarranted. The three clear winners in this complementary therapy analyses were exercise, pool/water, and cognitive behavioral therapy. Exercise showed significant benefit on all six of the symptom domains tested, while pool/water lacked significance only on the dyscognition domain. Indeed the pool/water therapy studies usually involved a mild aerobic form of exercise. Finally, cognitive behavioral therapy led to significant benefit in all but the affective symptoms domain. Table 5 shows the significant findings in digital format, which highlights the consistent benefit of exercise and pool/water therapy and cognitive behavioral therapy across the analyzed domains.

Treatment	Pain	Sleep	Fatigue	Affect	Physical	Cognition
Acupuncture	-	-	-	@	-	@
Balneotherapy	+	@	@	+	+	@
Cognitive Behav. Ther	+	+	+	-	+	+
Exercise	+	+	+	+	+	+
Education	+	-	+	+	-	@
Exercise/Educat.	-	-	+	-	-	@
Homeopathy	+	@	-	-	+	@
Magnetic Cereb. Stim.	+	-	+	-	+	@
Massage	+	-	@	@	-	@
Neurotherapy	+	-	-	-	-	-
Pool/Water	+	+	+	+	+	-
UV/Bright Light	-	-	-	-	-	@

Abbreviations: Sleep=Sleep Dysfunction; Affect=depression and/or anxiety; Physical=Physical Dysfunction; Cognition=cognitive dysfunction; Behav.=Behavioral; Ther.=Therapy; Educat.=Education; Cereb.=Cerebral; Stim=Stimulation; UV=Ultra Violet.
[+] available data met significance criteria
[-] failure to meet significance criteria
[@] inadequate information for analysis

Table 5: Significant effect sizes from meta-analyses on core domain variables resulting from complementary therapy for fibromyalgia syndrome patients.

Attempts at interpretation of these complementary therapy meta-analysis findings suggest that the complementary intervention to prescribe for FMS patients would be a low impact form of exercise performed in a pool, if available. Not included in this study were the graceful forms of dance-like exercise, originally based on Eastern Martial Arts, but modified for the purpose of medical therapy, that are gradually becoming available to Western medicine [52-54]. Similarly, cognitive behavioral therapy could be expected to be beneficial if a therapist skilled with that modality for FMS is available. Williams and colleagues [48] have developed, and successfully field-tested, a web-based FMS therapy companion which includes elements of cognitive behavioral therapy. It That intervention is as close to every FMS patient as the world wide web and can be used free of charge [https://fibroguide.med.umich.edu].

Limitations

It is freely acknowledged that the FMS core domain metaanalysis described above did not include all of the medications, nor all of the complementary therapies that are in clinical use for the treatment of FMS. The authors were gratified that the available studies did provide a range of pharmacotherapies and complementary interventions to evaluate further.

It is now possible to select widely effective pharmacotherapies and complementary interventions to meet the needs of FMS patients but little is known about whether combining such therapies might provide subtractive, additive, or synergistic benefits. That remains a strategic area of need for further research.

Clearly, the most effective therapy for FMS will have its roots in a complete understanding of FMS pathogenesis. The pathogenesis of FMS is the topic of much ongoing research world-wide. That topic was not expanded upon in this document because of space limitations.

Treatment of a Hypothetical Case

How would the author treat a 35 year old female with a new diagnosis of primary FMS?

The author's answer is based on 35 years of basic clinical research and caring for FMS patients.

First, he would document the diagnosis of FMS in the medical record by both the 1990 ACR RCC and the 2011 ACR FDC. Besides added assurance that the diagnosis is correct, that extra effort helps to assure that legal challenge will be easily defended. He would conduct a careful medical history and examination to identify any other medical conditions that would require separate care. Laboratory studies would have included serum creatinine to be sure that renal function is adequate to consider pregabalin therapy. He would ask the patient to complete an FIQR questionnaire for the baseline record.

He would spend a few minutes telling teaching the patient about FMS, including what is known about its epidemiology. He would list , including the namesing of the core symptomatic domains, and would point out for the patient and sharing with the patient which of those domains she/he exhibits.; presenting briefly the epidemiology of FMS; and what He would discuss the potential benefits that would can be expected during from good compliance with a well-designed the course of therapy. He would also make it clear to the patient that her/his active involvement in the treatment program will be critical to its success.

He would consider pharmacotherapy by wondering if she is depressed, anxious or both. As a part of the initial medical history and examination, he would have asked a few direct questions whose answers will inform the savvy physician of hint at her/his affective status. The patient may deny feeling either affective symptom depressed or anxious, because she may fear that the clinician will not take her pain seriously if she is anxious or depressed. Realistically, only about 40% of FMS patients are depressed, so that symptom is relevant to less than half of the presenting patients [58]. Whether or not she is depressed, duloxetine therapy is indicated. In a research study, depressed FMS patients tended to experience more benefit from duloxetine therapy than did non-depressed FMS patients [59].

If the truth is: yes, she appears to be depressed, he might begin with duloxetine by giving a single sample capsule of 20 mg in the office before the patient leaves. The purpose of this approach is to identify that rare individual who will experience projectile vomiting with the initial dosage. The patient who does so adversely emit, is not likely to ever tolerate this drug, but might do well with milnacipran. If she does not experience emesis with that first dosage of duloxetine, he could prescribe 30 mg capsules to be taken one capsule daily with food at breakfast for one week and then could preprogram an increase in the dosage to 60 mg daily in the morning with food. For this purpose, a glass of milk probably would count as food but a cup of coffee or tea probably would not. Dosages larger than 60 mg have not been associated with any increase in benefit. The patient should return at week four for follow-up. A plan of close follow-up will increase the patient's confidence in access to the physician and in a good outcome.

If the patient was not depressed initially but did have trouble with sleep dysfunction, the physician might still have given duloxetine, and confirming normal renal clearance, could have begun off-label therapy with pregabalin 150 mg, one capsule at bedtime for two weeks and then two capsules of 150 mg [300 mg total] at bedtime.

If the initially depressed patient exhibited sleep dysfunction on duloxetine therapy, he might likely add pregabalin 150 mg, one capsule at bedtime to the 60 mg of duloxetine in the morning for two weeks, and then increase the pregabalin dosage to 150 mg, two capsules at bedtime. The main initial effect of the pregabalin will be night time sedation, just when sedation is desirable. Daytime sedation can be avoided in most patients by the evening administration of the drug. The patient will appreciate the ability to sleep with the initial dosage, but that effect will probably begin to wane after about two weeks. That night time sedation benefit is usually resumes newed with the increased dosage of 300 mg at bedtime. Occasionally, there may be transient dizziness with the increase in the pregabalin dosage but that effect is typically associated with the peak concentration of the drug which will typically occur while the patient is asleep. It will usually improve 2-3 hours after the dosage and quit happening within three to four weeks of continued therapy.

Only about 50-70% of patients will experience the anticipated benefit from these medications. Those patients, who do, are generally considering their status to be much improved. Clearly, it would be desirable to be able to predict in advance which patients will or will not benefit from one or the other of these medications. Unfortunately, it is not yet possible to predict such responses.

With some initial improvement of the symptoms, it will be time to initiate a complementary intervention. The author has long - favored pool-based mild, low impact aerobic exercise or land-based aerobic walking exercise if a pool resource is not available. This can be as simple as walk-in-place submerged to mid-chest in the pool for 20 minutes three times per week. After the first month of this kind of program, the patient will report feeling more energetic, less fatigue, and less pain. Often it helps to establish a buddy system for the exercise intervention, so the exercise is more enjoyable. Involving a relative or friend will likely help to maintain compliance by the peer group effect? The most reliable sign of therapeutic success is that the patient chooses to continue the therapy program.

The initial circumstances have great influence upon the success of this program. If the patient cannot afford the cost of the medications, free or low cost samples sometimes fill the gap. Often there is a social service program [including that of the manufacturer] to help defray some of the medication costs. If there is no local indoor pool, or its availability is seasonal, exercise therapy may have to be done in the home. If responsibilities for young children or work schedules conflict with pool times, there are usually solutions to be found. Failures of therapy for any reason will likely lead to gradual worsening of the symptoms over time. Watch for details regarding Ba Duan Jin therapy (Chiao, et al., 2018 unpublished), whose practice in the context of a Chinese research study has provided remarkable improvements for FMS patients.

Summary

The fibromyalgia syndrome [FMS] is a common painful disorder, the human model of chronic widespread allodynia. A number of clinically important comorbidities are integrally associated with the pain, so that treatment of the pain alone is usually not successful. Six of these comorbidities have been designated as core domains to be assessed in every FMS therapeutic research study. It is also expedient for the community clinician to be aware of their status. The diagnosis of FMS is easy to make and to document, given two related sets of validated diagnostic criteria. It is possible to effectively treat the FMS, and patients who are helped are very grateful, so it can be quite gratifying to care for FMS patients. The principals of evidence-based medicine apply to the care of FMS, as with any medical disorder, and serial outcome assessment using the FIQR can prepare the clinician for the age of outcome-based compensation. A metaanalysis has evaluated the effectiveness of pharmacotherapies and complementary interventions. In each category there were clear winners and losers.

With time, there will be new medications and new complementary interventions to evaluate but it is predicted that the next generation of researchers will find ways to study various combinations of pharmacotherapy and complementary interventions with a goal to achieve the best combined approach to the management of FMS and control its pain. Time will tell whether such combinations prove to be additive, synergistic, or subtractive, additive, or synergistic.

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Disclosures

Dr. Russell is a co-author on a research manuscript (in preparation) reporting the effects of pregabalin on substance P levels in FMS cerebrospinal fluid, and on a manuscript (submitted) reporting the clinical effects of Ba Duan Jin, a form of Qigong, on the management of FMS.

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