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Evaluation of Treatments for Myofascial Pain Syndrome and Fibromyalgia

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Myofascial pain syndrome (MPS) and fibromyalgia (FM) are complex conditions and pose significant challenges to clinicians and patients. This chapter explores available treatments for MPS and FM in the context of pathophysiology, clinical evidence, and experimental support. This information may prove to be helpful in designing individualized treatment for patients with these complex syndromes. New treatments should be critically and carefully evaluated as they appear.

Introduction

Myofascial pain syndrome (MPS) and fibromyalgia (FM) are musculoskeletal pain ailments commonly encountered in clinical practice. FM may be present in up to 2% of the general population [1] and MPS may be the primary cause of pain in 30% [2] to 85% [3] of patients with a primary complaint of musculoskeletal pain. Despite their high prevalence, the pathophysiology of these syndromes remains incompletely understood. There is an ongoing debate regarding whether MPS and FM are even valid as disease entities [4–6], although both syndromes are widely accepted as useful clinical constructs.

For the clinician faced with a patient suffering from MPS or FM, choosing the appropriate therapy poses a significant challenge. Health care providers, Internet web sites, the popular press, and a seemingly endless array of commercial firms tout a remarkable variety of treatments for MPS and FM. Although some therapies appear to be medically sound and are experimentally supported, others only have anecdotal proof of efficacy and some actually may be harmful.

This article is intended to help the clinician make some sense of the available treatment options. The epidemiology, diagnostic criteria, and pathophysiology of MPS and FM are discussed briefly. Each treatment then is evaluated in the context of its scientific rationale and its support in the medical literature. The practitioner is encouraged to apply this approach to newer treatments for MPS and FM as they emerge, keeping the following considerations firmly in mind when choosing and monitoring each treatment: Does it relieve pain? Does it improve function? Do the benefits outweigh the risks?

Myofascial Pain Syndrome

Epidemiology and diagnosis

Myofascial pain syndrome is extremely common. In patients whose primary complaint is musculoskeletal pain, MPS is found in 30% [2] to 85% [3] of patients. MPS was found in 37% of new patients evaluated at a tertiary pain treatment center (Rudin, unpublished observations). Despite its high prevalence, MPS often remains unrecognized and untreated.

Myofascial pain syndrome is characterized by the presence of myofascial trigger points (TrPs), which are tender, hypersensitive points in skeletal muscles contained within palpable taut bands. The presence of a palpable tender spot within a tender taut band is the minimum criterion for the diagnosis. Pressure on a TrP produces local pain at the TrP site and often produces distant referred pain, which follows predictable patterns. Other findings may include weakness, decreased sensation, lacrimation, or increased sweating [7••]. Transverse "snapping" of a finger across a taut band may produce a palpable or visible muscle twitch known as the local twitch response (LTR) [8]. The LTR has an electromyographic correlate detectable when an electromyography (EMG) needle penetrates the TrP [9].

Pathophysiology

Three major constructs have emerged as explanations for the pathophysiology of MPS. The first theory assumes that TrPs are the primary generators of myofascial pain and are caused by repetitive muscle overload (microtrauma) or direct muscle injury (macrotrauma). Tissue injury is followed by the release of kinins and inflammatory mediators, with consequent sensitization of peripheral nociceptors decreasing their response threshold and increasing their firing frequency [10–12]. According to this theory, local hypersensitivity and pain (primary hyperalgesia) at the injury site leads to painful local muscle contraction and development of TrPs. The main problem with this concept is a lack of convincing histopathologic support for inflammatory changes, receptor upregulation or sensitization, or tissue trauma at TrP sites.

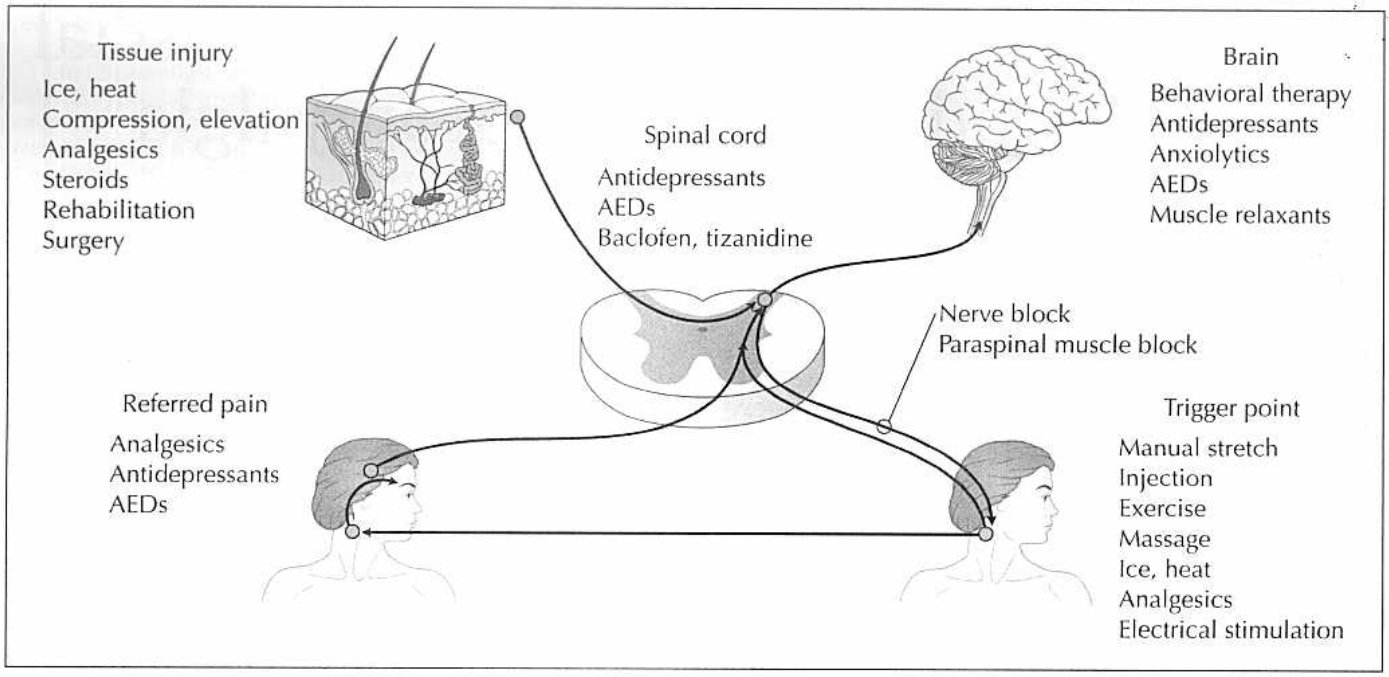

Figure 1. Current pathophysiologic theory of myofascial pain syndrome, including purported action sites of various treatments. Tissue injury leads to central sensitization and generation of trigger points. AEDs—antiepileptic drugs.

The second construct suggests that TrPs originate from dysfunction at the muscles themselves. It has been proposed that TrP sites correspond to the location of muscle spindles, suggesting that local spindle dysfunction produces the TrP [9]. This theory remains unproven. Another theory posits excessive activity of acetylcholine (ACh) at the motor endplate, with resultant increased muscle firing causing cellular overload; this concept has been explored using a rat model [13], but whether it can be proven in human MPS remains unknown.

The third and most promising construct is grounded in theories of pain neurophysiology. This theory suggests that the TrP may not be a primary muscle lesion, but a referred-pain phenomenon (Fig. 1). After tissue injury, prolonged nociceptive input produces neuronal sensitization in the spinal dorsal horn, leading to widening of the neuron's receptive field to produce a spatially enlarged, hypersensitive area (secondary hyperalgesia). This referred pain may be contiguous with or distant from the injured area. The spinal cord and peripheral nerves may play an important role in MPS. The LTR appears to be a spinal reflex; it is abolished by blockade or transection of the nerve innervating the TrP region [14]. Spinal facet joint injection, traction, postural exercises, and nerve root block can abolish TrPs within the affected myotomes, presumably by reducing nociception at its primary source of origin. Injection of local anesthetics into proximal muscles sharing a myotome with TrPs can abolish or attenuate the TrPs [15]. Peripheral nerve trunk injury can cause a deep, spreading, aching muscular pain with referral patterns similar to those documented for MPS and abolished by neural blockade [16•]. If TrPs represent secondary hyperalgesia, effective therapy may require identification and treatment of their primary nociceptive source.

Treatments

Muscle stretch

Stretching is perhaps the most common method used for the treatment of MPS. A sustained stretch is applied to muscles containing TrPs. The goal is to restore the muscle to its full length, eliminating focal contracture at the TrP site, thus inactivating the TrP. To reduce pain and facilitate relaxation, vapocoolant spray often is applied to the skin before and during the stretch (stretch-and-spray technique) [17]. The spray is an effective temporary local anesthetic [18]; the main benefit of this technique is achieved by stretching. Once TrPs are inactivated, the patient is taught a home self-stretch program to use regularly for prevention and treatment [7••].

Stretch-and-spray produces an immediate increase in pain threshold [19] accompanied by improved range of motion [20]. The long-term effects are less well defined and have not been studied using controlled trials. The Lewit technique in which stretch is followed by sequential isometric contraction and relaxation was effective in an uncontrolled trial [21]. Stretch-and-spray should be followed by a regimen of repeated stretch plus strengthening and postural retraining when needed.

Exercise

No single exercise program for MPS has been proven to be superior in clinical trials. Clinicians generally agree that graded stretching and strengthening should be included in any program [22,23], although experimental support is scant.

Active range-of-motion exercise produced immediate pain reduction in cervical MPS [20]. In patients with painful temporomandibular joint disorders, postural training and active and passive jaw-motion exercises combined with relaxation training were helpful for pain reduction [24,25].

Trigger point injection

Trigger point injection is used as a method of directly inactivating TrPs, particularly those refractory to stretch therapy [7••]. The TrP is penetrated with a fine needle, eliciting an LTR. The TrP region then is repeatedly and systematically probed with the needle until the LTR becomes quiescent and the taut band relaxes, eliminating the TrP as a painful focus. Post-injection soreness is brief and easily managed with ice and mild analgesics. Although trigger point injection appears to be a helpful technique, there is no evidence that it is more effective than placebo [26••,27].

It is not necessary to inject drugs during trigger point injection. Direct needling of TrPs using a small-diameter, solid (dry) needle is effective for the treatment of MPS [26••,28]. Gunn [29] posits that solid needles may be less likely to cause tissue damage than wider hollow needles. Dry needling during an EMG inhibits spontaneous electrical activity in rabbit TrPs [30], supporting the concept that needle stimulation of the TrP, not the use of a medication, leads to local relaxation at the tender site.

Different drugs may be injected during trigger point injection in attempts to reduce the pain of injection or prolong the efficacy of needle therapy. However, a systematic review of the literature suggests that all of the TrP needling therapies have equal efficacy. The choice of drug does not appear to make much of a difference, except perhaps in short-term comfort for the patient. However, whether or not drugs are used, the clinician must elicit an LTR and repeatedly probe the TrP to achieve the desired effect [7••].

Simons [17] advocates the injection of 0.5% procaine during a trigger point injection specifically to reduce pain during the procedure; there is no expectation that the drug will increase the magnitude or duration of relief. Procaine is the least myotoxic of the commonly used local anesthetics and has a very short duration of action. Lidocaine is an acceptable alternative, although standard 1% lidocaine may be less painful and better tolerated if diluted to 0.25% concentration [31]. The longer-acting agent bupivacaine is not recommended because it can be quite myotoxic [32] and is more painful than lidocaine [33].

Corticosteroids are used widely in trigger point injections, but there is no scientific rationale for this practice because there is no evidence of local inflammation in TrPs. A controlled trial found methylprednisolone to be no better than isotonic saline in trigger point injections [34]. The use of steroids in trigger point injections is not recommended.

Botulinum toxin is increasingly used for trigger point injection, but its efficacy is not well supported in the literature despite a number of small studies over the past several years [35,36]. Botulinum toxin may be superior to steroids in the treatment of MPS [37]. Small controlled trials of botulinum toxin for tension-type headache produced conflicting results [38,39]. Further investigation is needed to define whether botulinum toxin has a place in the management of MPS.

Sarapin (High Chemical Co., Levittown, PA), a distillate of the pitcher plant, has been used as an anesthetic in humans and horses and is touted as a useful agent in trigger point injections. However, there is no scientific support for its use. There are no published randomized, controlled trials (RCTs) of the drug in human MPS and a veterinary study found no significant anesthetic efficacy in horses [40].

Special techniques

Certain techniques address the theory that TrPs represent referred pain from dysfunction at the spinal nerve. Fischer's [15] "paraspinal block" technique involves injection of local anesthetic into the paraspinal muscles corresponding to the myotome containing the TrP. The technique reportedly attenuates or abolishes more distal TrPs innervated by that myotome. All of the data reported thus far are anecdotal. Gunn [29] employs solid needles to accomplish a similar goal using "intramuscular stimulation," in which multiple TrPs along a myotome are needled using features of trigger point injections and acupuncture.

Massage

Massage techniques often are employed to promote relaxation and elongation of painful muscles. Myofascial release techniques, which include passive soft-tissue stretches, are used frequently [41] and may be helpful [42]. The effects of massage treatment on MPS remain poorly studied [43]. The relief afforded by massage often is temporary, although it may last longer when combined with an effective exercise program.

Simons *et al.* [7••] suggest direct (ischemic) compression over the TrP as a means of inactivation. Numerous devices are available to facilitate this practice and patients report that they provide temporary relief (Rudin, unpublished observations). Focal TrP compression, when followed by a sustained stretch, proved to be superior to simple range-of-motion exercises in an RCT [44].

Drugs

Although many different medications are used to treat MPS, few have been studied in detail, perhaps because most MPS therapy is focused on direct TrP inactivation. Nonsteroidal anti-inflammatory drugs (NSAIDs) and opioid analgesics are used frequently in clinical practice, but are virtually unexamined in the MPS literature. Theories of TrP pathogenesis suggest that neuromodulating agents, such as antidepressants and antiepileptic drugs (AEDs), may help relieve MPS by attenuating referred pain; however, the AEDs have not been studied in MPS. The tricyclic antidepressant (TCA) amitriptyline has been shown to reduce tenderness in

myofascial/tension-type headache when compared with citalopram and placebo [45]. Few additional data are available on the effects of antidepressants in MPS.

Clonazepam was shown to reduce MPS pain in an open clinical trial [46] and in a double-blinded pilot study [47]. However, the risks of sedation, hepatotoxicity, and addiction limit its use in clinical practice. The topical analgesic capsaicin reduced chronic neck pain in an uncontrolled open-label trial [48]; however, the condition being treated was not clearly MPS and more specific studies are needed. The muscle relaxant carisoprodol was ineffective for facial MPS in a double-blind, placebo-controlled trial [49]. None of the other muscle relaxants have been formally studied in MPS.

The antispasticity agents baclofen and tizanidine act centrally to decrease spasticity and also may have some use in treating musculoskeletal pain. Neither drug has been formally studied as a treatment for MPS and RCTs are indicated.

Physiotherapeutic modalities

Heat and cold treatments often are used to treat MPS. However, experimental support for their use is scant. When combined with other treatment modalities such as range-of-motion exercise, hot packs, which improve local circulation to the warmed area [50], were associated with reduced pain and increased range of motion in upper trapezius MPS. Unfortunately, the effect of hot packs alone was not examined [20]. Ultrasound, a deep-heating modality commonly used in rehabilitation [50], was found to be effective for facial MPS in an uncontrolled case series [51]; however, a controlled trial on neck and shoulder MPS showed no difference between ultrasound and placebo [52]. Cold therapy, which retards local blood flow and can induce brief local analgesia [50], often is used on TrPs, using ice packs or vapocoolant. However, there are no studies examining its clinical effectiveness in MPS as a single modality.

Transcutaneous electrical nerve stimulation (TENS) delivers a low-level electrical current to attenuate pain, apparently by producing sensations that interfere with pain perception [53]. TENS studies are difficult to compare and interpret because of problems with placebo control and variations in stimulation type. Effect magnitude and duration remain poorly defined for TENS. TENS for low back pain appeared to reduce pain intensity when compared with placebo, but treatment and placebo groups reported similar reductions in pain unpleasantness [54]. The addition of TENS to conservative therapy (splinting, exercise, and NSAIDs) did not improve treatment outcome in facial MPS [55]. Other electrical stimulation techniques have been employed in MPS, but remain largely unstudied.

Psychologic therapies

Psychologic techniques are employed frequently to treat MPS. The goal is to teach patients to recognize situations contributing to excessive muscle tension and postural dysfunction while providing techniques to help avoid those situations or reduce the tension. Coexisting psychologic disorders also are addressed. EMG biofeedback often is used to teach patients to self-monitor and reduce muscle activity.

The effectiveness of psychologic techniques in MPS has not been well studied. When cognitive-behavioral therapy (CBT) and EMG biofeedback were compared with conservative medical treatment for musculoskeletal pain, all of the treatments produced improvement; the EMG biofeedback group had the best short-term and long-term results. However, this study did not specifically target patients with MPS [56]. A hypnotic relaxation technique was associated with reduced pain in facial MPS [57]. Most other examinations of psychologic treatment in MPS have occurred in the context of multidisciplinary treatment programs.

Multidisciplinary pain treatment

Bonica [58] championed the concept of multidisciplinary pain rehabilitation in which a team of specialists with varying backgrounds works to reduce pain, improve function, and augment coping in patients with persistent pain. Because considerable suffering, functional limitation, and changes in life roles may accompany persistent MPS, the disorder is a natural target for multidisciplinary treatment, which incorporates medication, psychologic therapies, and exercise-based therapies [59].

Although a number of studies have explored the efficacy of multidisciplinary treatment, few focus specifically on MPS and none of these are RCTs. Multidisciplinary treatment reduced pain and pain-associated dizziness in patients with cervical MPS [60]. Coping resources and socioeconomic variables may be predictors of success in the multidisciplinary treatment of neck and back MPS [61]. A case series of 62 patients with facial MPS showed approximately 70% pain reduction after multidisciplinary treatment [62]. Whether multidisciplinary treatment is superior to single treatments remains unexamined.

Acupuncture

The similarities between the locations, pain referral patterns, and treatments of acupuncture points and TrPs [63] have prompted explorations of acupuncture's efficacy in MPS. Studies have demonstrated some short-term efficacy for acupuncture in lumbar [64] and shoulder [65] MPS. Placebo control for acupuncture is difficult in MPS; because sham acupuncture involves penetration of the skin, it may be a therapeutic injection technique rather than a placebo. Japanese acupuncture produced superior pain relief to control (no acupuncture) and irrelevant (acupuncture not directed at neck pain) interventions in cervical MPS [66].

These studies are difficult to interpret because of differences in acupuncture techniques and research quality. A review focusing specifically on acupuncture for facial MPS reached similar conclusions [67]. Acupuncture may be a useful modality for the treatment of MPS [68], but needs further study.

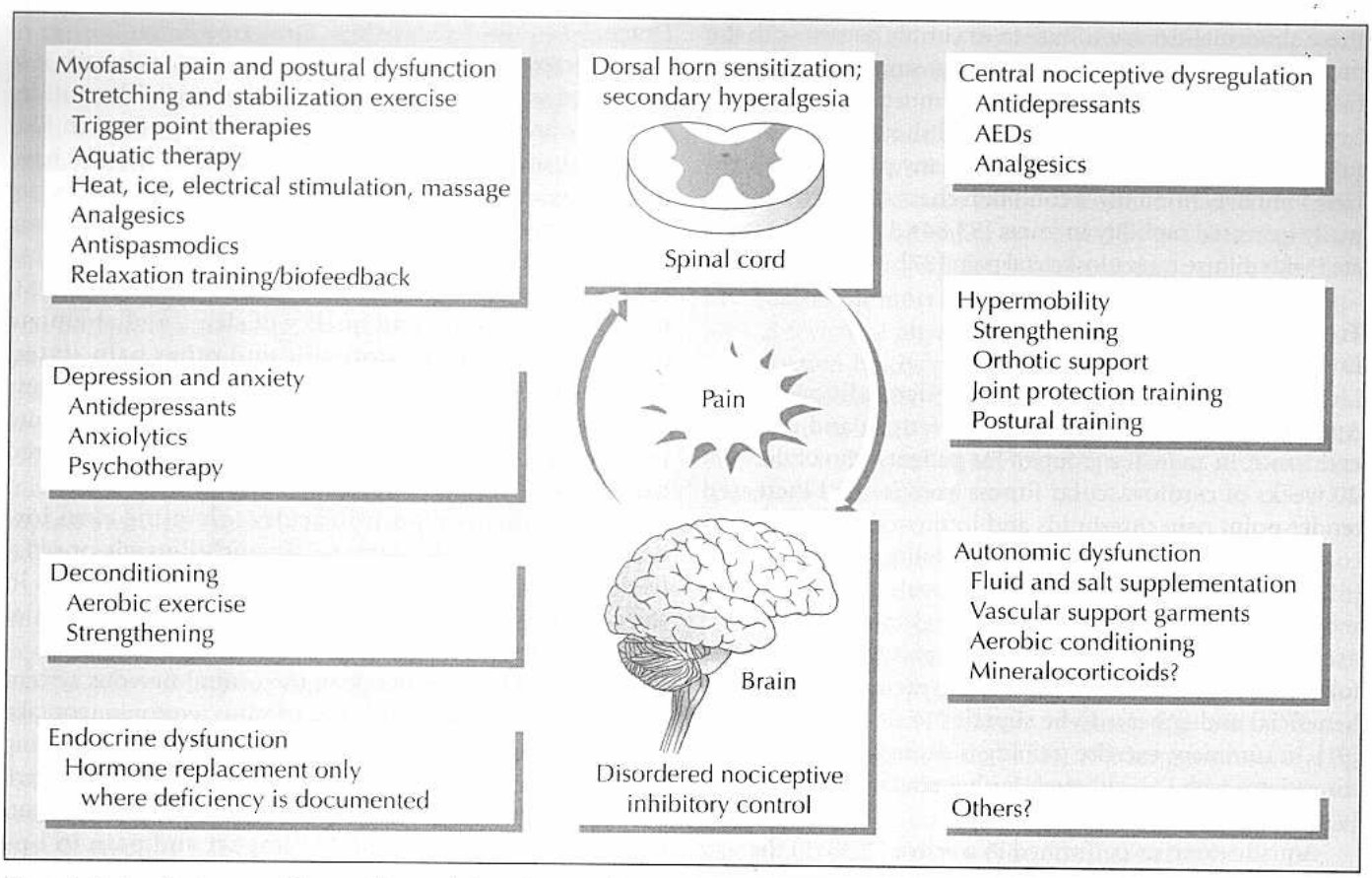

Figure 2. Factors that may contribute to fibromyalgia syndrome and purported action sites of various treatments. AEDs—antiepileptic drugs.

Fibromyalgia Syndrome

Epidemiology and diagnosis

Fibromyalgia is a syndrome characterized by widespread musculoskeletal pain and tenderness. The disorder is diagnosed by identifying tenderness in 11 of 18 standardized body locations on application of ≤ 4 kg of pressure. Tenderness must involve at least three body quadrants and be present for at least 3 months [69••]. Tenderness can be assessed using a calibrated pressure meter (dolorimeter) or a standardized manual palpation technique [70•]. Other than tenderness, there usually is a relative paucity of findings on physical examination. Common comorbidities include fatigue, depression, anxiety, disturbed sleep, and MPS. Although most patients continue to have symptoms over time [71], many studies report gradual improvements in pain and fatigue over years in the community and in specialty pain centers.

Fibromyalgia is remarkably common; the estimated prevalence is 3.4% in adult women and 0.5% in adult men, for a total population incidence of approximately 2% [1]. FM accounted for 21% of new patients referred to a single provider's tertiary pain practice over 18 months (Rudin, unpublished observations). Public awareness of the disorder and public expense have grown considerably; increasing numbers of FM sufferers are filing disability claims [72]. Scientific interest in FM also has increased and, in recent years, FM has been subjected to considerable study.

Pathophysiology

Many factors may contribute to the development of FM, but all of them appear to converge in a final common pathway mediating the experience of widespread pain. There is increasing evidence that the pain of FM is a manifestation of altered pain processing in the central nervous system. Psychophysical studies demonstrate heightened pain perception in patients with FM [73•,74]. Levels of substance P in the cerebrospinal fluid are elevated in patients with FM compared with control subjects [75]. Functional brain imaging studies of FM patients show reduced caudate and thalamic blood flow [76•]. These and numerous other studies support the conclusion that pain perception is amplified in patients with FM (Fig. 2).

Current research suggests that neuroendocrine dysfunction is involved in FM [77••,78]. This may partially explain the overlap of FM symptoms with those of other conditions. Hormone deficiencies, especially those of thyroid and growth hormones (GH), can mimic FM. Patients with FM have high rates of orthostatic hypotension and vasovagal syncope during autonomic tilt-table testing [79,80] and increased heart rate variability [81]. Sleep is disordered in many patients with FM [82] and re-establishment of restorative sleep is a treatment priority. Although depression and anxiety are frequently found in patients with FM, evidence suggests that affective disorders are not the cause of FM.

Careful examination of patients with FM may reveal other musculoskeletal problems amenable to treatment. Whether

these abnormalities contribute to or simply coexist with the pain of FM remains unclear. Common postural abnormalities include weak abdominal and gluteal musculature, lumbar hyperlordosis, and protracted head and shoulders with painful TrPs present in various muscles. Many patients with FM have joint hypermobility, a condition characterized by abnormally increased mobility in joints [83,84•,85,86] and associated with diffuse musculoskeletal pain [87].

Treatments

Exercise

Most patients with FM are physically deconditioned [88]. Appropriate exercise should reduce fatigue and improve endurance. In an RCT, a group of FM patients who underwent 20 weeks of cardiovascular fitness exercise had increased tender-point pain thresholds and improved aerobic fitness compared with a group receiving flexibility exercise training [89]. Another RCT showed improved health self-ratings and increased tender-point thresholds after 3 months of aerobic exercise; these improvements were maintained at 1-year follow-up [90]. Muscle strengthening exercise also may be beneficial and appears to be superior to flexibility training [91]. In summary, exercise training is strongly recommended for patients with FM, although further research still is needed [92,93,94••].

Aquatic exercise, performed in a warm (≥ 88°F) therapy pool, is widely prescribed for FM patients, but has not been studied thoroughly. In an RCT with 58 subjects, a 6-month program of aquatics and education was associated with reduced pain, improved physical function, and reduced affective distress [95]; pain reduction, fatigue reduction, and improved social function were still reported 2 years after the conclusion of the program [96].

Exercise can be quite painful for patients with FM, which tends to limit adherence. Careful individualization of the exercise prescription, including a slow-graded titration of activity level, may be essential for establishing adherence [97]. Not all patients will benefit from the same exercise program; for example, a hypermobile patient is unlikely to benefit from a regimen of flexibility training, but may gain significant benefit from a strengthening program designed to stabilize painful, lax joints [87].

Injection

Myofascial TrPs often occur in patients with FM. Inactivating TrPs may reduce pain and facilitate the ability to participate in other treatment. Trigger point injection may be beneficial in patients with coexisting MPS and FM [27], although patients without FM had better results from trigger point injection in one blinded study [98]. The benefit of injection therapy is less clear for FM patients without MPS. One uncontrolled study reported weeks of improvement after tender point injections of lidocaine and triamcinolone [99]. However, injecting tender points is not standard practice.

Drugs

Drug therapy is a mainstay of FM treatment, although it is combined with nonpharmacologic therapies. The antidepressants are the best-studied class of drugs used in FM. TCAs are used commonly in the treatment of FM and have the strongest experimental support for their use. They act by increasing the synaptic availability of various biogenic amines, most notably serotonin and norepinephrine. TCAs reduce the depression commonly seen in patients with FM, improve the amount and quality of sleep, and attenuate pain perception in neuropathic and other pain states. Numerous controlled trials in FM have shown effectiveness of TCAs when compared with placebo [100–102]. TCAs are recommended for FM therapy and should be considered early in the course of treatment.

Many patients report difficulty tolerating even low doses of TCAs, usually because of anticholinergic or sedative side effects. Selection of less anticholinergic drugs in the class and slow titration upward from very low initial doses can improve tolerability.

Serotonin is an analgesic in the central nervous system and it was widely hoped that the selective serotonin reuptake inhibitors (SSRIs) would prove to be effective for reducing pain. However, the results of clinical trials have been mixed. Fluoxetine was associated with improvement in multiple outcome measures, including FM impact and pain in one blinded trial [103], but was no better than placebo in another [104]. Citalopram and sertraline have been studied, also with conflicting results. SSRIs do not appear to be as analgesic as TCAs. However, most studies agree that SSRIs reduce the depression and anxiety commonly seen in patients with FM, making them valuable adjuncts to therapy.

Several newer agents, including venlafaxine, mirtazapine, and bupropion, have become clinically available for the treatment of depression. Only venlafaxine has been studied in FM, with no efficacy found in one RCT [105].

The NSAIDs were heavily used in FM treatment for a number of years. Placebo-controlled trials produced no convincing evidence of efficacy in FM [100]. FM is no longer thought to be an inflammatory condition and NSAIDs are no longer recommended as monotherapy, although they may be useful adjunctive analgesics.

The use of opioid analgesics in FM remains controversial. Opioids have been used widely to treat FM in clinical practice, but there is virtually no experimental evidence proving that these drugs are effective in FM. Research in this area is sorely needed. One blinded, placebo-controlled study of intravenous morphine showed no effect on FM pain [106]. In general, opioids should be reserved for FM cases in which all other treatments have failed and then only with careful consideration of each individual case. Long-term opioid treatment may be justified only if associated with noticeable improvements in pain and physical function.

Antiepileptic drugs are effective in the treatment of neuropathic pain. As FM is thought to result from a defect

in central pain processing, AEDs have been proposed as potential therapeutic agents. Gabapentin, a well-tolerated agent used to treat neuropathic pain conditions [107], has been frequently employed in FM, but no RCTs assessing its efficacy have been published. A newer agent, pregabalin, is now in clinical trials and shows promise as an FM treatment. A host of new AEDs are now on the market and their efficacy in FM should be investigated.

Tramadol is a weak opioid that also inhibits serotonin and norepinephrine reuptake. Tramadol appears to be well tolerated and effective for reducing pain in FM [108,109], although long-term treatment has not been studied. Disadvantages include frequent dosing, seizures with high doses [110], physical dependence and withdrawal [111], and interactions with other serotonergic agents (*eg*, SSRIs and triptan migraine drugs) [112]. When carefully used, tramadol can be a useful component of FM therapy.

The antispasticity agents baclofen and tizanidine have analgesic properties and sedative side effects. They have been used clinically in FM to promote sleep and reduce pain. Neither drug has been experimentally studied in FM. Routine use is not recommended.

Studies of the hypothalamic-pituitary-adrenal axis in FM reveal altered responsiveness to stress and hormonal stimulation [77••], but not adrenal insufficiency. Corticosteroid therapy has shown no benefit for FM in blinded trials [113]. Steroids should be used for FM patients only when treating documented coexisting inflammatory disease or adrenal insufficiency.

Growth hormone deficiency has been postulated as a cause of FM. Low levels of GH and a related hormone, insulin-like growth factor-1 (IGF-1), have been documented in approximately 30% of patients [114]. GH supplementation was clinically helpful for patients with FM who had low IGF-1 levels [115]. However, the expense of GH makes routine use impractical. Patients with FM who are undergoing a strength program showed acute increases of GH during exercise that became longer-lasting by the end of the 21-week training program [116], making a further case for exercise as a mainstay of FM therapy.

Hypothyroidism occurs in some FM patients, but the prevalence is no higher than that in the general population. Thyroid hormone deficiency should be treated when diagnosed and occasionally FM symptoms will improve with treatment. However, there are no data to support the routine use of thyroid hormone supplementation in FM.

Many other drugs, some available as supplements in health food stores, have been employed to treat FM. Agents such as 5-hydroxytryptophan, S-adenosylmethionine, and methylsulfonylmethane have been used despite little or no experimental support and, in some cases, significant potential toxicity. Guaifenesin, an agent widely used as a mucolytic, has been proposed as a therapy for FM; its chief proponent reports significant efficacy [117], but a controlled trial following his protocol showed no benefit over placebo [118]. The use of guaifenesin in FM is not recommended. Various special diets have been proposed, none with clear effectiveness.

Physiotherapeutic modalities

Exercise, along with individualized treatment addressing the patient's particular biomechanical and postural deficits, is the main modality employed by physical therapists treating FM. Numerous other therapeutic methods have been used, but most have limited or no experimental support. A review of physical therapy for FM [119] summarizes the situation nicely; physical therapy appears to reduce FM pain and disability, but there is no clearly superior single treatment modality. TENS, massage, acupuncture, heat, and cold treatments have been employed with modest short-term success.

Psychologic and multidisciplinary treatments

The use of CBT in FM is associated with improvements in pain, function, and physical status [120]. Outcomes improve when CBT is combined with exercise and education as part of a multidisciplinary program [94••,121]. Multidisciplinary treatment for FM is effective immediately after treatment and at the 6-month follow-up [122,123]; long-term follow-up studies are needed. When available, a multidisciplinary program combining exercise, CBT, education, and appropriate medication may be the preferred treatment for FM.

Conclusions

Many treatment options are available for MPS and FM. Although a considerable variety of treatments exists for MPS, few are well studied or supported in the medical literature. Trigger point injections appear to be effective for at least short-term pain relief and dry needling is as effective as injection with drugs; of the available drugs, only local anesthetics are recommended and their effect is solely to reduce pain during the actual injection. Stretch, exercise, and physiotherapeutic modalities may be helpful; considerable further study of their effects is warranted. No medication has been clearly proven effective for the treatment of MPS.

Fibromyalgia has been considerably better studied than MPS throughout the past decade; consequently, there is stronger experimental support for FM treatment, although further research is needed. Exercise and TCAs are the best-supported single treatment measures. CBT also can produce significant benefit and multidisciplinary treatment combining these approaches may have the best overall efficacy.

This chapter summarizes and evaluates the multifaceted array of treatments available for MPS and FM. No single treatment regimen will work for every patient; each patient has a particular constellation of problems and needs and the sensitive clinician will tailor therapy to the patient after careful evaluation. It is hoped that this summary will help caregivers make educated and effective decisions regarding the treatment of these challenging disorders.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Wolfe F, Ross J, Anderson J, *et al.*: **The prevalence and characteristics of fibromyalgia in the general population.** *Arthritis Rheum* 1995, **38**:19–28.
2. Skootsky SA, Jeager B, Oye RK: **Prevalence of myofascial pain in general internal medicine practice.** *West J Med* 1989, **151**:157–160.
3. Fishbain DA, Goldberg M, Meagher BR, *et al.*: **Male and female chronic pain patients categorized by DSM-III psychiatric diagnostic criteria.** *Pain* 1986, **26**:181–197.
4. Quintner JL, Cohen ML: **Fibromyalgia falls foul of a fallacy.** *Lancet* 1999, **353**:1092–1094.
5. Cohen M, Quintner L: **Fibromyalgia syndrome, a problem of tautology.** *Lancet* 1993, **342**:906–909.
6. Bohr TW: **Fibromyalgia syndrome and myofascial pain syndrome: Do they exist?** *Neurol Clin* 1995, **13**:365–384.
7. •• Simons DG, Travell JG, Simons PT: *Travell and Simons' Myofascial Pain and Dysfunction: The Trigger Point Manual, vol 1: Upper Half of Body.* Baltimore: Williams and Wilkins; 1999.

The definitive reference on myofascial pain and TrPs. Worth reading for anyone interested in MPS.

8. Gerwin R, Shannon S, Hong CZ, *et al.*: **Interrater reliability in myofascial trigger point examination.** *Pain* 1997, 69:65–73.
9. Hubbard DR, Berkoff GM: **Myofascial trigger points show spontaneous needle EMG activity.** *Spine* 1993, **18**:1803–1807.
10. Sato J, Perl ER: **Adrenergic excitation of cutaneous pain receptors induced by peripheral nerve injury.** *Science* 1991, **251**:1608–1610.
11. Janig W: **The sympathetic nervous system in pain: physiology and pathophysiology.** In *Pain and the Sympathetic Nervous System.* Edited by Stanton-Hicks M. Boston, London: Kluwer Academic Publishers; 1990:17–89.
12. Birklein F, Schmelz M, Schifter S, *et al.*: **The important role of neuropeptides in complex regional pain syndrome.** *Neurology* 2001, **57**:2179–2184.
13. Mense S, Simons DG, Hoheisel U, *et al.*: **Lesions of rat skeletal muscle after local block of acetylcholinesterase and neuromuscular stimulation.** *J Appl Physiol* 2003, 94:2494–2501.
14. Rivner MH: **The neurophysiology of myofascial pain syndrome.** *Curr Pain Headache Rep* 2001, **5**:432–440.
15. Fischer AA: **Treatment of myofascial pain.** *J Musculoskel Pain* 1999, **7**:131–142.
16. • Quintner JL, Cohen M: **Referred pain of peripheral nerve origin: an alternative to the "myofascial pain" construct.** *Clin J Pain* 1994, **10**:243–251.

An important paper linking MPS to advances in pain neurophysiology.

17. Simons DG: **Myofascial pain syndrome due to trigger points.** In *Rehabilitation Medicine.* Edited by Goodgold J. St. Louis: C.V. Mosby; 1988:686–723.
18. Cohen Reis E, Holubkov R: **Vapocoolant spray is equally effective as EMLA cream in reducing immunization pain in school-aged children.** *Pediatrics* 1997, **100**:E5.
19. Jaeger B, Reeves JL: **Quantification of changes in myofascial trigger point sensitivity with the pressure algometer following passive stretch.** *Pain* 1986, **27**:203–210.
20. Hou CR, Tsai LC, Cheng KF, *et al.*: **Immediate effects of various physical therapeutic modalities on cervical myofascial pain and trigger-point sensitivity.** *Arch Phys Med Rehabil* 2002, **83**:1406–1414.
21. Lewit K, Simons DG: **Myofascial pain: relief by post-isometric relaxation.** *Arch Phys Med Rehabil* 1984, **65**:452–456.
22. Rosen NB: **Physical medicine and rehabilitation approaches to the management of myofascial pain and fibromyalgia syndromes.** *Baillieres Clin Rheum* 1994, **8**:881–916.
23. McClaflin RR: **Myofascial pain syndrome: primary care strategies for early intervention.** *Postgrad Med* 1994, 96:56–59, 63–56, 69–70.
24. Wright EF, Domenech MA, Fischer JR: **Usefulness of posture training for patients with temporomandibular disorders.** *J Am Dent Assoc* 2000, **131**:202–210.
25. Nicolakis P, Erdogmus B, Kopf A, *et al.*: **Effectiveness of exercise therapy in patients with myofascial pain dysfunction syndrome.** *J Oral Rehab* 2002, **29**:362–368.
26. •• Cummings TM, White AR: **Needling therapies in the management of myofascial trigger point pain: a systematic review.** *Arch Phys Med Rehabil* 2001, **82**:986–992.

Excellent review of trigger point injection.

27. Borg-Stein J, Stein J: **Trigger points and tender points: one and the same? Does injection treatment help?** *Rheum Dis Clin North Am* 1996, **22**:305–322.
28. Lewit K: **The needle effect in the relief of myofascial pain.** *Pain* 1979, 6:83–90.
29. Gunn CC: **Intramuscular stimulation (IMS): the technique.** http://www.istop.org/html/ims.htm. Accessed July 2003.
30. Chen JT, Chung KC, Hou CR, *et al.*: **Inhibitory effect of dry needling on the spontaneous electrical activity recorded from myofascial trigger spots on rabbit skeletal muscle.** *Am J Phys Med Rehabil* 2001, **80**:729–735.
31. Iwama H, Akama Y: **The superiority of water-diluted 0.25% to neat 1% lidocaine for trigger-point injections in myofascial pain syndrome: a prospective, randomized, double-blinded trial.** *Anesth Analg* 2000, **91**:408–409.
32. Pere P, Watanabe H, Pitkanen M, *et al.*: **Local myotoxicity of bupivacaine in rabbits after continuous supraclavicular brachial plexus block.** *Reg Anesth* 1993, **18**:304–307.
33. Iwama H, Ohmori S, Kaneko T, *et al.*: **Water-diluted local anesthetic for trigger-point injection in chronic myofascial pain syndrome: evaluation of types of local anesthetic and concentrations in water.** *Reg Anesth Pain Med* 2001, **26**:333–336.
34. Frost FA, Toft B, Aaboe T: **[Isotonic saline and methylprednisolone acetate in blockade treatment of myofascial pain: a clinical controlled study].** *Ugeskr Laeger* 1984, 146:652–654.
35. Sheean G: **Botulinum toxin for the treatment of musculoskeletal pain and spasm.** *Curr Pain Headache Rep* 2002, **6**:460–469.
36. Nixdorf DR, Heo G, Major PW: **Randomized controlled trial of botulinum toxin A for chronic myogenous orofacial pain.** *Pain* 2002, 99:465–473.
37. Porta M: **A comparative trial of botulinum toxin type A and methylprednisolone for the treatment of myofascial pain syndrome and pain from chronic muscle spasm.** *Pain* 2000, **85**:101–105.
38. Freund BJ, Schwartz M: **Treatment of chronic cervical-associated headache with botulinum toxin A: a pilot study.** *Headache* 2000, **40**:231–236.
39. Rollnik JD, Tanneberger O, Schubert M, *et al.*: **Treatment of tension-type headache with botulinum toxin type A: a double-blind, placebo-controlled study.** *Headache* 2000, **40**:300–305.
40. Harkins JD, Mundy GD, Stanley SD, *et al.*: **Lack of local anesthetic efficacy of Sarapin in the abaxial sesamoid block model.** *J Vet Pharmacol Ther* 1997, **20**:229–232.
41. Gerwin RD, Dommerholt J: **Treatment of myofascial pain syndromes.** In *Pain Management: A Practical Guide for Clinicians.* Edited by Weiner RS. Boca Raton, FL: CRC Press; 1998:217–229.
42. Chaitow L: **Positional release techniques in the treatment of muscle and joint dysfunction.** *Clinical Bulletin of Myofascial Therapy* 1998, **3**:25–35.
43. Harris RE, Clauw DJ: **The use of complementary medical therapies in the management of myofascial pain disorders.** *Curr Pain Headache Rep* 2002, **6**:370–374.
44. Hanten WP, Olson SL, Butts NL, *et al.*: **Effectiveness of a home program of ischemic pressure followed by sustained stretch for treatment of myofascial trigger points.** *Phys Ther* 2000, **80**:997–1003.

45. Bendtsen L, Jensen R: **Amitriptyline reduces myofascial tenderness in patients with chronic tension-type headache.** *Cephalalgia* 2000, **20**:603–610.
46. Fishbain DA, Cutler RB, Rosomoff HL, *et al.*: **Clonazepam open clinical treatment trial for myofascial syndrome associated chronic pain.** *Pain Med* 2000, **1**:332–339.
47. Harkins S, Linford J, Cohen J, *et al.*: **Administration of clonazepam in the treatment of TMD and associated myofascial pain: a double-blind pilot study.** *J Craniomandib Disord* 1991, **5**:179–186.
48. Mathias BJ, Dillingham TR, Zeigler DN, *et al.*: **Topical capsaicin for chronic neck pain: a pilot study.** *Am J Phys Med Rehabil* 1995, **74**:39–44.
49. Gallardo F, Molgo J, Miyazaki C, *et al.*: **Carisoprodol in the treatment of myofascial pain-dysfunction syndrome.** *J Oral Surg* 1975, **33**:655–658.
50. Lehmann JF, de Lateur BJ: **Diathermy and superficial heat, laser, and cold therapy.** In *Krusen's Handbook of Physical Medicine and Rehabilitation.* Edited by Kottke FJ, Lehmann JF. Philadelphia: W.B. Saunders; 1990:283–367.
51. Esposito CJ, Veal SJ, Farman AG: **Alleviation of myofascial pain with ultrasonic therapy.** *J Prosthet Dent* 1984, **51**:106–108.
52. Gam AN, Warming S, Larsen LH, *et al.*: **Treatment of myofascial trigger points with ultrasound combined with massage and exercise: a randomized controlled trial.** *Pain* 1998, **77**:73–79.
53. Basford JR: **Physical agents.** In *Rehabilitation Medicine: Principles and Practice.* Edited by DeLisa JA. Philadelphia: J.B. Lippincott; 1993:404–424.
54. Marchand S, Charest J, Li JX, *et al.*: **Is TENS purely a placebo effect: a controlled study on chronic low back pain.** *Pain* 1993, **54**:99–106.
55. Kruger LR, van der Linden WJ, Cleaton-Jones PE: **Transcutaneous electrical nerve stimulation in the treatment of myofascial pain dysfunction.** *S Afr J Surg* 1998, **36**:35–38.
56. Flor H, Birbaumer N: **Comparison of the efficacy of electromyographic biofeedback, cognitive-behavioral therapy, and conservative medical interventions in the treatment of chronic musculoskeletal pain.** *J Consult Clin Psychol* 1993, **61**:653–658.
57. Winocur E, Gavish A, Emodi-Perlman A, *et al.*: **Hypnorelaxation as treatment for myofascial pain disorder: a comparative study.** *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2002, **93**:429–434.
58. Loeser JD: **John J. Bonica 1917-1994. Emma B. Bonica 1915-1994.** *Pain* 1994, **59**:1–3.
59. Auleciems LM: **Myofascial pain syndrome: a multidisciplinary approach.** *Nurse Pract* 1995, **20**:18, 21–22, 24–28.
60. Krabak BJ, Borg-Stein J, Oas JA: **Chronic cervical myofascial pain syndrome: improvement in dizziness and pain with a multidisciplinary rehabilitation program: a pilot study.** *J Back Musculoskel Rehab* 2000, **15**:83–87.
61. Heikkila H, Heikkila E, Eisemann M: **Predictive factors for the outcome of a multidisciplinary pain rehabilitation program on sick-leave and life satisfaction in patients with whiplash trauma and other myofascial pain: a follow-up study.** *Clin Rehabil* 1998, **12**:487–496.
62. Gil IA, Barbosa CM, Pedro VM, *et al.*: **Multidisciplinary approach to chronic pain from myofascial pain dysfunction syndrome: a 4-year experience at a Brazilian center.** *Cranio* 1998, **16**:17–25.
63. Hong CZ: **Myofascial trigger points: pathophysiology and correlation with acupuncture points.** *Acupunct Med* 2000, **18**:41–47.
64. Ceccherelli F, Rigoni MT, Gagliardi G, *et al.*: **Comparison of superficial and deep acupuncture in the treatment of lumbar myofascial pain: a double-blind, randomized, controlled study.** *Clin J Pain* 2002, **18**:149–153.
65. Ceccherelli F, Bordin M, Gagliardi G, *et al.*: **Comparison between superficial and deep acupuncture in the treatment of the shoulder's myofascial pain: a randomized and controlled study.** *Acupunct Electrother Res* 2001, **26**:229–238.
66. Birch S, Jamison RN: **Controlled trial of Japanese acupuncture for chronic myofascial neck pain: assessment of specific and nonspecific effects of treatment.** *Clin J Pain* 1998, **14**:248–255.
67. Myers CD, White A, Heft MW: **A review of complementary and alternative medicine use for treating chronic facial pain.** *J Am Dent Assoc* 2002, **133**:1189–1196.
68. Anonymous: **NIH Consensus Conference: Acupuncture.** *JAMA* 1998, **280**:1518–1524.
69.•• Wolfe F, Smythe H, Yunus M, *et al.*: **The American College of Rheumatology 1990 criteria for the classification of fibromyalgia: report of the Multicenter Criteria Committee.** *Arthritis Rheum* 1990, **33**:160–172.

Paper defining the diagnostic criteria for FM.

70.• Starz TW, Sinclair JD, Turk DC: **Putting the finger on fibromyalgia: the manual tender point survey.** *J Musculoskel Pain* 1997, **14**:61–67.

Describes the standardized technique for tender point examination without special instrumentation.

71. Wolfe F, Anderson J, Harkness D, *et al.*: **Health status and disease severity in fibromyalgia: results of a six-center longitudinal study.** *Arthritis Rheum* 1997, **40**:1571–1579.
72. Wolfe F, Anderson J, Harkness D, *et al.*: **The work and disability status of persons with fibromyalgia [abstract].** *J Musculoskel Pain* 1995, **3**:155.
73.• Marchand S, Arsenault P: **Fibromyalgic pain: the possible role of a deficit of diffuse noxious inhibitory control (DNIC).** In *American Pain Society Annual Meeting 1999.* Fort Lauderdale, FL: American Pain Society; October, 1999.

First report of disordered descending pain modulation in FM.

74. Staud R, Robinson ME, Vierck CJ, Jr., *et al.*: **Diffuse noxious inhibitory controls (DNIC) attenuate temporal summation of second pain in normal males but not in normal females or fibromyalgia patients.** *Pain* 2003, **101**:167–174.
75. Russell I, Orr M, Littman B, *et al.*: **Elevated cerebrospinal fluid levels of substance P in patients with the fibromyalgia syndrome.** *Arthritis Rheum* 1994, **37**:1593–1601.
76.• Mountz J, Bradley L, Modell J, *et al.*: **Fibromyalgia in women: abnormalities of regional cerebral blood flow in the thalamus and caudate nucleus are associated with low pain threshold levels.** *Arthritis Rheum* 1995, **38**:926–938.

First report of abnormalities on functional brain imaging in FM.

77.•• Neeck G, Crofford LJ: **Neuroendocrine perturbations in fibromyalgia and chronic fatigue syndrome.** *Rheum Dis Clin North Am* 2000, **26**:989–1002.

Excellent summary of this important research topic.

78. Crofford LJ: **Neuroendocrine abnormalities in fibromyalgia and related disorders.** *Am J Med Sci* 1998, **315**:359–366.
79. Bou-Holaigah I, Calkins H, Flynn J, *et al.*: **Provocation of hypotension and pain during upright tilt table testing in adults with fibromyalgia.** *Clin Exp Rheum* 1997, **15**:239–246.
80. Visuri T, Lindholm H, Lindqvist A, *et al.*: **Cardiovascular functional disorder in primary fibromyalgia: a noninvasive study in 17 young men.** *Arthritis Care Res* 1992, **5**:210–215.
81. Martinez-Lavin M: **The autonomic nervous system and fibromyalgia.** *J Musculoskel Pain* 2002, **10**:221–228.
82. Moldofsky H, Scarisbrick P, England R, *et al.*: **Musculoskeletal symptoms and non-REM sleep disturbance in patients with "fibrositis syndrome" and healthy subjects.** *Psychosom Med* 1975, **37**:341–351.
83. Jessee E, Owen D Jr, Sagar K: **The benign hypermobile joint syndrome.** *Arthritis Rheum* 1980, **23**:1053–1056.
84.• Karaaslan Y, Haznedaroglu S, Ozturk M: **Joint hypermobility and primary fibromyalgia: a clinical enigma.** *J Rheumatol* 2000, **27**:1774–1776.

Discussion of the linkage between FM and hypermobility.

85. Goldman J: **Hypermobility and deconditioning: important links to fibromyalgia/fibrositis.** *South Med J* 1991, 84:1192–1196.
86. Fitzcharles MA: **Is hypermobility a factor in fibromyalgia?** *J Rheumatol* 2000, 27:1587–1589.
87. Russek LN: **Hypermobility syndrome.** *Phys Ther* 1999, 79:591–599.
88. Clark S, Burckhardt CS, Campbell S: **Fitness characteristics and perceived exertion in women with fibromyalgia.** *J Musculoskel Pain* 1993, 1:193–197.
89. McCain G, Bell D, Mai F, *et al.*: **A controlled study of a supervised cardiovascular fitness training program on the manifestations of primary fibromyalgia.** *Arthritis Rheum* 1988, 31:1135–1141.
90. Richards SC, Scott DL: **Prescribed exercise in people with fibromyalgia: parallel group randomised controlled trial.** *BMJ* 2002, 325:185.
91. Jones KD, Burckhardt CS, Clark SR, *et al.*: **A randomized controlled trial of muscle strengthening versus flexibility training in fibromyalgia.** *J Rheumatol* 2002, 29:1041–1048.
92. Forseth KO, Gran JT: **Management of fibromyalgia: What are the best treatment choices?** *Drugs* 2002, 62:577–592.
93. Busch A, Schachter CL, Peloso PM, *et al.*: **Exercise for treating fibromyalgia syndrome.** *Cochrane Database Syst Rev* 2002, 3:CD003786.
94.•• Sim J, Adams N: **Systematic review of randomized controlled trials of nonpharmacological interventions for fibromyalgia.** *Clin J Pain* 2002, 18:324–336.
Comprehensive review of this important treatment topic.
95. Mannerkorpi K, Nyberg B, Ahlmen M, *et al.*: **Pool exercise combined with an education program for patients with fibromyalgia syndrome: a prospective, randomized study.** *J Rheumatol* 2000, 27:2473–2481.
96. Mannerkorpi K, Ahlmen M, Ekdahl C: **Six- and 24-month follow-up of pool exercise therapy and education for patients with fibromyalgia.** *Scand J Rheumatol* 2002, 31:306–310.
97. Jones KD, Clark SR: **Individualizing the exercise prescription for persons with fibromyalgia.** *Rheum Dis Clin North Am* 2002, 28:419–436.
98. Hong CZ, Hsueh TC: **Difference in pain relief after trigger point injections in myofascial pain patients with and without fibromyalgia.** *Arch Phys Med Rehabil* 1996, 77:1161–1166.
99. Reddy SS, Yunus MB, Inanici F, *et al.*: **Tender point injections are beneficial in fibromyalgia syndrome: a descriptive, open study.** *J Musculoskel Pain* 2000, 8:7–18.
100. Goldenberg D, Felson D, Dinerman H: **A randomized controlled trial of amitriptyline and naproxen in the treatment of patients with fibromyalgia.** *Arthritis Rheum* 1986, 29:1371–1377.
101. Carette S, McCain GA, Bell DA, *et al.*: **Evaluation of amitriptyline in primary fibrositis: a double-blind, placebo-controlled study.** *Arthritis Rheum* 1986, 29:655–659.
102. Arnold LM, Keck PE Jr, Welge JA: **Antidepressant treatment of fibromyalgia: a meta-analysis and review.** *Psychosomatics* 2000, 41:104–113.
103. Arnold LM, Hess EV, Hudson JI, *et al.*: **A randomized, placebo-controlled, double-blind, flexible-dose study of fluoxetine in the treatment of women with fibromyalgia.** *Am J Med* 2002, 112:191–197.
104. Wolfe F, Cathey MA, Hawley DJ: **A double-blind placebo controlled trial of fluoxetine in fibromyalgia.** *Scand J Rheumatol* 1994, 23:255–259.
105. Zijlstra T, Barendregt P, VandeLaar M: **Venlafaxine in fibromyalgia: results of a randomized, placebo-controlled, double-blind trial.** *Arthritis Rheum* 2002, 46:S105.
106. Sorensen J, Bengtsson A, Ahlner J, *et al.*: **Fibromyalgia: Are there different mechanisms in the processing of pain? A double blind crossover comparison of analgesic drugs.** *J Rheumatol* 1997, 24:1615–1621.
107. Backonja M, Beydoun A, Edwards KR, *et al.*: **Gabapentin for the symptomatic treatment of painful neuropathy in patients with diabetes mellitus: a randomized controlled trial.** *JAMA* 1998, 280:1831–1836.
108. Russell IJ, Kamin M: **Efficacy of tramadol in treatment of pain in fibromyalgia.** *J Clin Rheumatol* 2000, 6:250–257.
109. Biasi G, *et al.*: **Tramadol in the fibromyalgia syndrome: a controlled clinical trial versus placebo.** *Int J Clin Pharmacol Res* 1998, 18:13–19.
110. Gardner JS, Blough D, Drinkard CR, *et al.*: **Tramadol and seizures: a surveillance study in a managed care population.** *Pharmacotherapy* 2000, 20:1423–1431.
111. Freye E, Levy J: **Acute abstinence syndrome following abrupt cessation of long-term use of tramadol (Ultram): a case study.** *Eur J Pain* 2000, 4:307–311.
112. Mason PJ, Morris VA, Balcezak TJ: **Serotonin syndrome: presentation of two cases and review of the literature.** *Medicine* 2000, 79:201–209.
113. McKenzie R, O'Fallon A, Dale J, *et al.*: **Low-dose hydrocortisone for treatment of chronic fatigue syndrome: a randomized, controlled trial.** *JAMA* 1998, 280:1061–1066.
114. Bennett RM: **Adult growth hormone deficiency in patients with fibromyalgia.** *Curr Rheumatol Reports* 2002, 4:306–312.
115. Bennett RM, Clark SC, Walczyk J: **A randomized, double-blind, placebo-controlled study of growth hormone in the treatment of fibromyalgia.** *Am J Med* 1998, 104:227–231.
116. Hakkinen K, Pakarinen A, Hannonen P, *et al.*: **Effects of strength training on muscle strength, cross-sectional area, maximal electromyographic activity, and serum hormones in premenopausal women with fibromyalgia.** *J Rheumatol* 2002, 29:1287–1295.
117. Amand RP: **The Use Of Uricosuric Agents in Fibromyalgia: Information For Physicians.** http://www.guaidoc.com/Research_Urico.htm. Accessed September 9, 2003.
118. Bennett RM, deGarmo P, Clark S: **A one-year double-blind, placebo-controlled study of guaifenesin in fibromyalgia.** *Presented at the American College of Rheumatology Annual Meeting:* Orlando; October 18–22,1996.
119. Offenbacher M, Stucki G: **Physical therapy in the treatment of fibromyalgia.** *Scand J Rheumatol* 2000, 113:78–85.
120. Rossy LA, Buckelew SP, Dorr N, *et al.*: **A meta-analysis of fibromyalgia treatment interventions.** *Ann Behav Med* 1999, 21:180–191.
121. Burckhardt CS: **Nonpharmacologic management strategies in fibromyalgia.** *Rheum Dis Clin North Am* 2002, 28:291–304.
122. Turk DC, Okifuji A, Sinclair JD, *et al.*: **Interdisciplinary treatment for fibromyalgia syndrome: clinical and statistical significance.** *Arthritis Care Res* 1998, 11:186–195.
123. Mason LW, Goolkasian P, McCain GA: **Evaluation of a multimodal treatment program for fibromyalgia.** *J Behav Med* 1998, 21:163–178.