30

Local Therapy for Fibromyalgia and Nonneuropathic Pain

Lan Chen, Jodi Goldman-Knaub, and Sally Pullman-Mooar

Local therapy for fibromyalgia (FM) and other painful conditions can be an alternative for both patients and their healthcare providers. Local measures can be perceived as going directly to the source of pain, although this is not always the case, but they do generally carry less risk compared to systemic delivery. The "hands on" approach of some these local therapies is also often an important part of a therapeutic relationship. Despite their obvious potential advantages, many patients do not receive local measures. This chapter will review the following local therapy modalities, which can help providers judge for themselves how to use topical drugs, local injections, and various physical measures:

Topical Remedies

- Topical nonsteroidal anti-inflammatory drugs
- Capsaicin
- Local anesthetics
- Topical antidepressant
- Topical gabapentin (neurontin)
- Topical traditional Chinese medicine

Tender Point Injections

- Botox
- Steroid
- Xylocaine
- Dry needling

Physical Measures and Other Devices

- Massage
- Balneotherapy
- Heat therapy
- Ultrasound
- Phonophoresis
- Transcutaneous electrical nerve stimulation (TENS)

TOPICAL REMEDIES

An alternative and attractive approach to pain control is to apply drugs locally to the peripheral site of origin of the pain. Topical applications include cream, lotion, gel, oil, aerosol, or patch to somatic sites. These topical remedies allow for a high local concentration of the drug at the site of the pain and lower or negligible systemic drug levels, producing fewer or no adverse drug effects. Other advantages of topical application are the lack of drug interactions and the ease of use.

The general pharmacokinetic principles governing drugs applied to the skin are the same as those involved in other routes of drug administration (1). Major variables that determine pharmacologic response to drugs applied to the skin include the following:

1. Regional variation in the drug penetration. For example, the face, axilla, scrotum, and scalp are far more permeable than the forearm and may require fewer doses for an equivalent.
2. Concentration gradient. Increasing the concentration gradient increases the mass of drug transferred per unit of time.
3. Dosing schedule. Because of the skin's physical properties, the skin acts as a reservoir. For drugs with a short systemic half-life, topical application may be long enough to permit "once-a-day" application.
4. Vehicles and occlusion. An appropriate vehicle maximizes the drug's ability to penetrate the skin's outer layers. Occlusion (application of a plastic wrap to hold the drug and its vehicle in close contact with the skin) is extremely effective in maximizing efficacy.

Topical applications differ from transdermal delivery systems, which are not discussed in detail here. In transdermal delivery systems, the skin is used as an alternative systemic delivery system. For topical application, the target site is immediately adjacent to the site of the delivery, with very limited systemic affects. The actions of topical drugs may decrease production of local inflammatory mediators, block the action of inflammatory mediators or altered impulse generation through actions on up-regulated sodium channels, or attenuate action of the sensory neurons through actions at specific receptors. In chronic-pain states, the effectiveness of a topical approach may depend on the degree of inflammation, the degree of alteration in peripheral sensory processing, and the degree of central sensitization involved. In most chronic-pain conditions, both peripheral and central elements are present. The topical approaches are more likely to be effective where there is a prominent peripheral component (2).

Bioavailability and plasma concentration following topical application are 5% to 15% of those achieved by systemic delivery (3). Adverse effects with topical remedies can be classified as cutaneous and systemic reactions; the local reaction is more commonly compared to systemic reaction. Skin rash and itch at the site of application are accounted for most local reactions (3,4). Systemic adverse effects do occur but much less often compared to systemic delivery (5).

TOPICAL NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

Traditional nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most commonly prescribed drugs worldwide and are responsible for approximately one-fourth of all adverse drug reaction reports. NSAIDs are widely prescribed for patients with rheumatic disease. Topical application of NSAIDs offers the advantage of local, concentrated drug delivery to affected tissues with a reduced incidence of systemic adverse effects, such as peptic ulcer disease and gastrointestinal (GI) hemorrhage.

Steen et al. (6) tested topically applied acetylsalicylic acid (ASA), salicylic acid (SA), and indomethacin in an experimental pain model in humans. In 30 volunteers, sustained burning pain was produced in the palmar forearm through a continuous intradermal pressure infusion of a phosphate-buffered isotonic solution (pH 5.2). In five different, double-blind, randomized crossover studies with six volunteers each, the flow rate of the syringe pump was individually adjusted to result in constant pain ratings of around 20% (50% in study 4) on a visual analog scale (VAS). The painful skin area was then covered with either placebo or the drugs, which had been dissolved in diethylether. In the first study of six volunteers, ASA (60 mg per mL) or lactose (placebo) in diethylether (10 mL) was applied, using both arms at 3-day intervals. Both treatments resulted in sudden and profound pain relief due to the cooling effect of the evaporating ether. With lactose, however, the mean pain rating was restored close to the baseline within 6 to 8 minutes, while with ASA it remained significantly depressed for the rest of the observation period (another 20 minutes). A loss of tactile sensation did not accompany this deep analgesia. The further studies served to show that indomethacin (4.5 mg per mL) and SA (60 mg per mL) were equally as effective as ASA. These antinociceptive effects were felt to be due to local but not systemic actions, since ASA and SA did not reach measurable plasma levels up to 3 hours after topical applications.

Topical application leads to relatively high NSAID concentrations in the dermis. Concentrations achieved in the muscle tissue below the site of application are variable, but they are at least equivalent to that obtained with oral administration (3). NSAIDs applied topically over joints do reach the synovial fluid, but the extent and mechanism (topical penetration vs. distribution via the systemic circulation) remain to be determined. In addition, marked interindividual variability has been noted in all studies; individual skin properties may strongly influence percutaneous absorption. In general, interpretation of clinical studies measuring efficacy of topical NSAIDs in rheumatic disease states is difficult because of a remarkably high placebo response rate, the use of rescue paracetamol (acetaminophen), and a significant variability in percutaneous absorption and response rates between patients. Overall efficacy rates attributable to topical NSAIDs in patients with rheumatic disorders ranged from 18% to 92% of treated patients.

In a clinical context, there have been sufficient studies of soft tissue conditions to demonstrate the superiority of topical NSAIDs over placebo and to suggest equivalent efficacy in comparison to some oral NSAIDs. The effectiveness and tolerability of tolmetin as Tolectin Gel 5% was evaluated in an open, multicentric study (7). Two hundred and five patients suffering from osteoarthritis (OA), spondylarthrosis, soft tissue rheumatism, and posttraumatic pain were treated under conditions similar to practice. The topical preparation was administrated alone or when needed, associated with tolmetin 400 mg capsules. Evaluation of symptoms and signs revealed no statistical difference of effectiveness between the two dosage groups. The opinions of the doctors and patients about the clinical course supported this positive result. Dose reduction of oral or other parenteral preparations is often possible by means of concomitant topical treatment. In some types of soft tissue and joint pain, chiefly in mild cases, the local application alone can be sufficient.

Bruhlmann and Michel assessed the efficacy and safety of a diclofenac hydroxyethylpyrrolidine (DHEP) patch in the treatment of symptomatic OA of the knee joint. A double-blind, randomized, placebo-controlled trial was carried out on 103 outpatients for 2 weeks. The main efficacy parameters were spontaneous pain and the Lequesne Index. Secondary endpoints were walking time over a standard distance, global assessment of efficacy and tolerability, and paracetamol consumption. The active treatment group showed a significant improvement in pain, Lequesne Index, and the physician's and patient's global assessment of efficacy. For these parameters the difference between groups was statistically significant in favor of the DHEP patch (8).

NSAIDs administered topically penetrate slowly and in small quantities into the systemic circulation; bioavailability and maximal plasma NSAID concentrations after topical application are generally <5% and 15%, respectively, compared to equivalent oral administration. The adverse event profile of topical agents is reasonable: Minor cutaneous effects occur in up to 2% of patients but tend to be self-limiting (3). GI events appear from the existing literature to be infrequent and minor, although long-term studies are required. Bronchospasm and renal impairment have been reported and may be more frequent in patients who have experienced these effects with oral agents (4), so great caution should be exercised in such patients.

CAPSAICIN

Capsaicin is a natural constituent in pungent red chili peppers. It can selectively activate, desensitize, or exert a neurotoxic effect on sensory neurons, depending on the concentration and the delivery mode (9,10).

Activation of sensory neurons occurs because of interaction with a ligand-gated nonselective cation channel, and receptor occupancy triggers Na^+ and Ca^{2+} ion influx and action potential firing as the burning sensation occurs with spicy food or capsaicin-induced pain (11). Desensitization occurs with repeated administration of capsaicin and is a receptor-mediated process. This process involves Ca^{2+} and calmodulin-dependent phosphorylation of the cation channel. As a consequence of desensitization, secretion of substance P (SP) from both peripheral and central terminals of sensory neurons is inhibited (9). Neurotoxicity is partially osmotic and partially due to Ca^{2+} entry with activation of Ca^{2+}-sensitive protease (10). Repeated application to the skin produces desensitization to this response and thus forms the basis of the therapeutic use of topical capsaicin in chronic-pain conditions (12).

Topical capsaicin preparations of 0.025% and 0.075% are available for human use. It is interesting to know that extracts from red chili peppers have long been used in traditional topical Chinese medication mixes for joint pain. McCarthy and McCarty evaluated topical capsaicin 0.075% for the treatment of the painful joints of rheumatoid arthritis (RA) and OA patients in a 4-week double-blind, placebo-controlled, randomized trial. Twenty-one patients were selected, all of whom had either RA ($n = 7$) or OA ($n = 14$) with painful involvement of the hands. Assessments of pain (VAS), functional capacity, morning stiffness, grip strength, joint swelling, and tenderness (dolorimeter) were performed before randomization. Treatment was applied to each painful hand joint four times daily with reassessment at 1, 2, and 4 weeks after entry. One subject did not complete the study. Capsaicin reduced the tenderness ($p < 0.02$) and pain ($p < 0.02$) associated with OA but not RA as compared to placebo. A local burning sensation was the only adverse effect noted. These findings suggest that topical capsaicin is a safe and potentially useful drug for the treatment of painful OA of the hands (13).

FM patients commonly have pain in the head and neck. Epstein and Marcoe reviewed an open series of 24 consecutive cases of head and neck pain treated with topical capsaicin. Complete remission of pain was seen in 31.6% of patients; partial remission was achieved in 31.6% of patients. Trigeminal neuralgia with an intraoral trigger was less responsive to topical therapy than neuropathic pain. Further study is needed to clarify the efficacy of topical capsaicin in neuropathic and nonneuropathic pain and the effect of differing dosages and frequency of application (14).

Topical capsaicin is attractive because it is a simple, safe treatment and has been studied in a variety of conditions in uncontrolled and a few controlled trials. However, even though these studies suggest an analgesic effect, it has been impossible to blind even for placebo-controlled trials, due to the burning sensation induced by the capsaicin. A high placebo response rate in the controlled trials is an interesting observation in these studies and may account for the apparent salutary effect reported in the studies lacking a control. A careful scrutiny of the current results of these trials, as well as clinical experience, indicate there is a modest effect with the currently available preparations, although many patients failed to find relief or found the relief insufficient or were unable to tolerate the burning sensation. Occasional patients appear to have very good pain relief, and clinical trials may not reflect these unusual cases. Topical capsaicin is generally not satisfactory as a sole therapy for chronic-painful conditions, although it may serve as an adjuvant to other approaches (15). Topical capsaicin is not associated with any severe systemic adverse effects. However, many patients report stinging and burning, particularly during the first week of therapy (16). Caution must be exercised to avoid touching the eyes. Topical capsaicin merits consideration as a part of multidisciplinary therapy in conditions where the pain can be chronic and difficult to treat.

LOCAL ANESTHETICS (LIDOCAINE PATCHES AND GELS)

Local anesthetics have long been used to abolish pain temporarily by blocking nerve conduction, but local anesthetics, such as lidocaine patch or gel, are now used as an effective treatment for many chronic-pain conditions (17). Local anesthetics block voltage-gated sodium channels (VGSCs), which play a fundamental role in the control of neuronal excitability (2). Alteration in the expression, distribution, and function of VGSCs occurs following chronic inflammation, nerve injury, and other chronic-pain conditions (18).

Systemically administered local anesthetics such as IV lidocaine, oral mexilitine, and oral tocainamide are effective in a number of chronic-pain conditions (17). However, despite this efficacy in different clinical pain conditions, systemic anesthetics are limited by their adverse central nervous system (dizziness, lightheadedness, and somnolence) and cardiac effects. Clinical attention has recently been focused on topical formulations of lidocaine. Topical lidocaine as a 5% gel or patch provides pain relief in several chronic-pain conditions. Galer et al. compared the efficacy of topical lidocaine patches to vehicle (placebo) patches applied directly to the painful skin of subjects with postherpetic neuralgia (PHN) using an "enriched enrollment" study design. All subjects had been successfully treated with topical lidocaine patches on a regular basis for at least 1 month prior to study enrollment. Subjects were enrolled in a randomized, two-treatment period, vehicle-controlled, crossover study. The primary efficacy variable was "time to exit"; subjects were allowed to exit either treatment period if their pain relief score decreased by two or more categories on a six-item pain relief scale for any 2 consecutive days. The median time to exit with the lidocaine patch phase was >14 days, whereas the vehicle patch exit time was 3.8 days ($p < 0.001$). At study completion, 25 of 32 (78.1%) subjects preferred the lidocaine patch treatment phase as compared to 3 of 32 (9.4%) who preferred the placebo patch phase ($p < 0.001$). No statistical difference was noted between the active and placebo treatments with regard to side effects. Thus, topical lidocaine patches provide significantly more pain relief for PHN than vehicle patches with limited side effects (19).

Topical local anesthetics have shown promise in both uncontrolled and controlled studies. Thirty-five subjects with established PHN affecting the torso or extremities completed a four-session, random order, double-blind, vehicle-controlled study of the analgesic effects of topically applied 5% lidocaine in the form of a nonwoven polyethylene adhesive patch (20). All subjects had allodynia on examination. Lidocaine-containing patches were applied in two of the four 12-hour sessions. In one session vehicle patches were applied, and one session was a no-treatment observation session. Lidocaine-containing patches significantly reduced pain intensity at all time points from 30 minutes to 12 hours compared to no-treatment observation and at all time points from 4 to 12 hours compared to vehicle patches. Lidocaine patches were superior to both no-treatment observation and vehicle patches in averaged category pain relief scores. The highest blood lidocaine level measured was 0.1 micrograms/mL, indicating minimal systemic absorption of lidocaine. Patch application was without systemic side effects and was well-tolerated when applied on allodynic skin for 12 hours. This study demonstrates that topical 5% lidocaine in patch form is easy to use and relieves postherpetic neuralgia.

Most published studies of lidocaine gel or patch have focused on PHN. The patch itself provided some pain relief, likely due to the protection afforded to allodynic skin (20).

The question is whether these local anesthetics may also provide pain relief in FM or other nonneuropathic pain conditions. A randomized controlled trial was carried out on patients with chronic muscle pain syndromes. Sixty-one patients (42 with FM and 19 with myofascial pain syndrome [MPS]) completed the trial. Outcome measures included pain intensity, a daily pain diary, headache frequency, sensitivity to pressure using a dolorimeter, anxiety, depression, and sleep quality. Patients were randomized to receive either 4% lidocaine applied over tender points (TePs) or sterile water (placebo) six times over a 3-week period. Both subjects and investigators were blind to treatment allocation. The results showed that 4% lidocaine had no superiority over placebo in any of the outcome measures. Twenty-one subjects (35%) showed a decrease in pain that was $>$30% of their baseline value. Of these 21 subjects, 10 received lidocaine and 11 received placebo. These data suggest that, in this population, 4% lidocaine is no better than placebo in the treatment of chronic muscle pain (21). This study was done with 4% lidocaine gel rather than the 5% gel or patch used in PHN studies. Further studies are needed to document any efficacy of the lidocaine patch or a higher concentration of lidocaine gel for FM or other more localized nonneuropathic pain conditions.

ANTIDEPRESSANTS

Antidepressants given orally have been used to treat chronic pain for 40 years (22). Tricyclic compounds given systemically have been the most often used agents for treatment of FM (23). Initially, the efficacy of antidepressants was attributed to central action in the spinal cord and at supraspinal levels (24). Recently, peripheral activity also was noted in a visceral pain model (25), a formalin model of tonic pain (26), and a model of neuropathic pain (27). Amitriptyline, a tricyclic antidepressant, can increase local release of adenosine and activation of adenosine A1 receptor (27). These peripheral actions raise the possibility that topical formulations of antidepressants may be a useful alternative drug delivery system for analgesia. Antidepressants exhibit a number of pharmacologic actions: They block reuptake of noradrenaline and 5-hydroxytryptamine; have direct and indirect actions on opioid receptors; inhibit histamine, cholinergic, 5-hydroxytryptamine, and *N*-methyl-D-aspartate receptors; inhibit ion channel activity; and block adenosine uptake. But the contribution of these actions to analgesia by antidepressants, locally or systemically, remains to be determined.

Topical doxepin cream has been reported to produce analgesia in one randomized double-blind placebo-controlled study (28). The analgesic efficacy of topical administration of 3.3% doxepin hydrochloride, 0.025% capsaicin, and a combination of 3.3% doxepin and 0.025% capsaicin were assessed in human chronic neuropathic pain. A total of 200 patients were enrolled in this randomized, double-blind, placebo-controlled study. Patients applied placebo, doxepin, capsaicin, or doxepin/capsaicin cream daily for 4 weeks. Patients recorded on a daily basis overall pain, shooting, burning, paraesthesia, and numbness using a 0 to 10 VAS during the week prior to cream application (baseline levels) and for the 4-week study period. Side effects and the desire to continue treatment were also recorded. Overall pain was significantly reduced by all three groups—doxepin, capsaicin, and doxepin/capsaicin—to a similar degree. The analgesia with doxepin/capsaicin was of more rapid onset. Side effects were minor. It was concluded that topical application of 3.3% doxepin, or 0.025% capsaicin, or 3.3% doxepin/0.025% capsaicin produces analgesia of similar magnitude. However, the combination produces more rapid analgesia.

Antidepressants show promise as a useful class of agents to be used as analgesics in chronic-pain conditions. They provide options to both topical applications and systemic delivery.

GABAPENTIN

Gabapentin (GP) is an amino acid that has a mechanism that differs from other anticonvulsant drugs such as phenytoin, carbamazepine, or valproate. Several hypotheses of cellular mechanisms have been proposed to explain the pharmacology of GP:

1. GP crosses several membrane barriers in the body via a specific amino acid transporter (system L) and competes with leucine, isoleucine, valine, and phenylalanine for transport.
2. GP increases the concentration and probably the rate of synthesis of γ-amino-butyric acid (GABA) in the brain, which may enhance nonvesicular GABA release during seizures.
3. GP binds with high affinity to a novel binding site in brain tissues that is associated with an auxiliary subunit of voltage-sensitive Ca^{2+} channels. Recent electrophysiology results suggest that GP may modulate certain types of Ca^{2+} current.
4. GP reduces the release of several monoamine neurotransmitters.
5. Electrophysiology suggests that GP inhibits voltage-activated Na^{+} channels, but other results contradict these findings.

6. GP increases serotonin concentrations in human whole blood, which may be relevant to neurobehavioral actions.
7. GP prevents neuronal death in several models, including those designed to mimic amyotrophic lateral sclerosis (ALS). This may occur by the inhibition of glutamate synthesis by branched-chain amino acid aminotransferase (BCAA-t) (29).

Carlton and Zhou (30) reported that local GP has been shown to have antihyperalgesic properties at the site of drug application. Rats received different doses of local GP (intraplantar 20-microl injections of 6, 60, or 600 microg GP). High-dose GP (600 microg) significantly reduced these nociceptive behaviors. The antihyperalgesic effect of GP was not due to a systemic effect, since animals injected with 600 microg GP in one hindpaw and 2% formalin into the contralateral hindpaw developed nociceptive behaviors that were no different from those seen in animals injected with formalin alone. Although the mechanism of action of GP has yet to be elucidated, the results indicated that GP has a peripheral site of action and thus may offer a novel therapeutic agent for topical or local treatment of pain of peripheral origin.

There has been one clinical trial using oral pregabalin in treating FM (31). These preclinical and clinical data support the potential for development of topical formulations of GP.

TOPICAL TRADITIONAL CHINESE MEDICINE

Topical traditional Chinese medicine and other alternative remedies are still widely used, especially in Chinese and other ethnic communities. When all the "modern" preparations have been exhausted, our patients have tried falling back on some "old remedies." Litt (32) has offered a list of 73 alternative topical measures that are often beneficial, mostly for dermatologic disorders. Topical traditional Chinese medicines (TTCMs) have many varieties. A common misconception is that TTCM is a complicated, exotic art. Difficulties in understanding these measures arise because formulations have more than one ingredient, myriad preparations are available, and labels can be confusing, with brands like Tiger Balm, 3-Snake Oil, and Dragon Balm. First and foremost, it must be understood that brand names are just brand names. The names are symbolic. Tiger Balm and 3-Snake Oil do not contain any material from these animals. Indeed, TTCMs are mixtures containing many herbs, ranging from 3 to 20 different types (33). Mixtures are based on the concepts of traditional Chinese medicine. The formulations use different ingredients to balance the body and to balance the opposite properties of different herbs. However, all these many preparations can be grouped into three classes, according to usage. In each class the ingredients revolve around a common theme, with only minor differences. The three classes are: (1) oils, ointments, and pastes for aches and pains; (2) oils, ointments, and pastes for orthopedic injuries; and (3) lotions and ointments for skin diseases. Here, only the first class will be briefly summarized.

The classic example of class 1 TTCMs used for rheumatic pain is Tiger Balm (34). It is oil-based and contains camphor, menthol, and one or more essential oils, such as cinnamon oil, oil of clove, cassia oil, citronella oil, oil of lavender, and cajuput oil. These are mixed in a base oil or petrolatum. The formulation is meant to be soothing, and it is not usually irritating to the skin unless patients are allergic to these ingredients. Other paste preparations are mixtures of various herbs with a petrolatum base. Zingiber officinale rhizoma, polygonum multiflorum radix, peonia lactiflora radix, rhizoma et radix notopterygii, myrrha, and other herbs are commonly used for rheumatic pain, a bi syndrome in Traditional Chinese Medicine (TCM) (34). None of these have been assessed in controlled trials available in English.

TTCMs have been used to soothe pain and still retain some popularity in the modern age. More evidence-based medicine is needed to guide physicians and patients.

PHYSICAL MEASURES AND OTHER DEVICES

Numerous physical measures can be used in the treatment of pain in FM and other nonneuropathic syndromes. Many are drawn from theory, tradition, and belief. However, evidence-based medicine should support the choice of physical interventions in a treatment plan. The efficacy of many physical measures has not been fully established and the physiologic mechanisms for anecdotal improvement in pain, depression, and sleep are being investigated. It is important to realize that FM is a complicated musculoskeletal syndrome that presents with a wide variety of symptoms and considerable overlap with other conditions, such as myofasical pain syndrome and chronic fatigue syndrome. Thus, many different treatment interventions are used to reduce patient symptoms. The remainder of this chapter will discuss some of these interventions, including massage, biofeedback (BFB), heat therapy, balneotherapy, ultrasound, phonophoresis, and TENS.

MASSAGE THERAPY

In the early fifth century B.C., Hippocrates wrote, "The physician must be experienced in many things, but assuredly in rubbing…. For rubbing can bind a joint that is too loose, and loosen a joint that is too rigid." Massage is an ancient treatment for pain relief and is currently being used by 17% to 75% of FM patients (35). The variability in the use of this intervention may be attributed to many factors, including lack of awareness within the medical model, poor insurance reimbursement, and time constraints.

Massage may include both physiologic and psychological components (36). The possible physiologic benefits of massage include stimulation of nonnociceptive nerve endings, which contributes to the release of endorphins and increases serotonin levels (37). The reflex responses can also cause the reduction of blood pressure (38). Massage increases circulation and enhances venous return, which aids in the removal of metabolic waste products, helping to maintain healthy tissues (39). In the "gate theory," the notion is that the pressure receptors stimulated by massage are longer and more myelinated than pain receptors. When pain is experienced and the painful area is rubbed, the pressure message gets to the brain faster than the pain message and the gate is shut, thus blocking the entry of the pain message (40). The "language" of human touch may provide these patients with a feeling of relaxation, warmth, and renewed vitality, which can counteract the stresses and pressures one experiences in everyday life. Massage has been reported to increase mental clarity, reduce anxiety, increase general feelings of well-being, and release unexpressed emotions (39).

Danneskioid-Samsoe et al. (41) studied 26 patients with myofascial pain and found a significant increase in the plasma myoglobin concentration within 2 hours after the first massage. They found a positive correlation between the degree of muscle tension and pain and an increase in plasma myoglobin concentration. After the patients had repeated massage sessions, there was a gradual decline in the increase in plasma myoglobin concentration parallel to a reduction in the muscle tension and pain.

Patients with FM have a significantly elevated concentration of SP in the cerebrospinal fluid compared to normal controls (42,43). SP is a neuropeptide stored in the secretory granules of sensory nerves and released on axonal stimulation (44). The significance of SP continues to be investigated. It has been theorized that it is derived from overactive peripheral nociceptive fibers or from central neurons (44). Field et al. (45) found a significant decrease in SP with massage therapy performed for 30 minutes twice weekly for 5 weeks. This is a promising finding that will require further research.

Ironson et al. (37) demonstrated direct effects of massage on chronic disease outcomes in a group of human immunodeficiency virus (HIV) positive men compared to HIV positive controls. The men who received massage showed a significant increase in the number of natural killer cells, natural killer cytotoxity, soluble CD8, and cytotoxic subset of CD8 cells. Significant decreases in cortisol levels were observed before and after massage. Anxiety and relaxation significantly improved and were correlated with the increased number of natural killer cells (37).

There are many different forms of massage therapy, including classical, cross-fiber friction, connective tissue, myofascial release, soft tissue mobilization, Shiatsu, Swedish, and trigger point. The practitioner's sense of touch is fundamental to the massage technique, as the tactile sensation is the means of communication between the clinician and the patient. Most forms of massage can be used for patients with FM and other nonneuropathic pain syndromes. Pioro-Boisset's (35) interview-based study, however, supports less aggressive forms of massage, reporting greater satisfaction in FM patients when a "more toned down and less rigorous massage was used." This patient population tends to be more sensitive to pressure. Therefore clinicians need to consider patient positioning to promote comfort and to prevent further tension or stress. The therapist may consider beginning the massage in a distal or proximal area of the body to help the patient relax and then slowly work toward the problem areas (39).

Realistic individualized goals should be discussed and established with each patient at the initial evaluation. As treatment advances, the therapist should gradually incorporate active treatment, such as postural and therapeutic exercise. It is recommended that patients strive for independence with an exercise program and the ability to self-manage their symptoms. It is necessary to establish a network of support because chronic pain can be lifelong.

Numerous studies have suggested the effectiveness of massage in the reduction of pain, stiffness, fatigue, and sleeping difficulties in patients diagnosed with FM (35,45–48).

Brattberg (49) conducted a randomized, controlled trial investigating the effect of 15 sessions of connective tissue massage in a 10-week period in the treatment of 48 FM patients. The findings were positive in a self-reported reduction of pain in 85% of patients and a reduction in analgesic consumption in 30% of subjects. The massage group also showed a reduction in depression and a positive effect on quality of life. However, after a 6-month follow-up, 90% of the pain returned. This study's findings would suggest the need for maintenance massage therapy, as the results did not last long term.

Sunshine et al. (48) found favorable results in 30 FM patients randomly assigned to massage therapy (Swedish massage) or TENS or a no-current TENS group. Thirty treatment sessions were used twice weekly for 4 weeks. All three groups improved on the rheumatologists' assessment of the subject's clinical condition, which suggests that all these forms of tactile stimulation and attention are effective. However, only the massage therapy group improved on both the dolorimeter and the subjects' self reports of pain. The massage group had lower cortisol levels and reported significantly fewer symptoms at the end of the study, including less pain, stiffness, fatigue, and difficulty sleeping. Field et al. (45) supported these results in a similar study when comparing massage therapy to relaxation therapy in 24 FM patients. The authors found that both groups demonstrated a decrease in anxiety and depressed mood. Only the massage group reported an increase in the number of sleep hours and a decrease in their sleep movements, and the patients' physicians assigned lower disease and pain ratings and fewer TeP areas. Field (38) found similar results when investigating massage therapy against a sham TENS control group in patients diagnosed with chronic fatigue syndrome.

Contrary to these studies, Alnigenis et al. (50) completed a randomized, controlled study on the effect of Swedish massage in patients with FM and found no significant benefits in pain reduction, functional status, or psychological distress. High attrition and a small sample limit this study's findings.

Massage is a passive intervention in which the patient is dependent on the practitioner. New research by Field et al. (46) investigated Eutony, a combination treatment of massage and movement therapy. This includes self-administered massage using wooden dowels and tennis balls and stretching movements in lying, seated, and standing positions. Early findings were positive, showing this self-administered treatment effective in decreasing depression, anxiety, and pain. These findings are encouraging because they promote patient independence and may be a progression from passive massage to active therapeutic exercise.

In a recent review of randomized, controlled trials, Holdcraft et al. (51) concluded that there was "moderate" evidence to recommend massage therapy as a therapeutic modality to FM patients. The small sample sizes in most of the studies limit their statistical power and make it difficult to form conclusions on the effectiveness of the massage intervention.

Massage involves considerable one-on-one time, which is problematic in the current healthcare environment. Despite this, massage clearly has some benefit and may be shown to be a cost-effective tool in the treatment of FM and other chronic-pain syndromes.

ELECTROMYOGRAPHIC BIOFEEDBACK

Electromyographic (EMG) BFB is a treatment modality that consists of monitoring a physiologic system (muscle tension) of which the patient is not ordinarily aware, converting it electronically into signals (usually visual or auditory) of which the patient becomes aware and develops strategies for its modification (52). Molina et al. (53) indicated that EMG-BFB training reduced plasma adrenocorticotrophin hormone and β-endorphin levels during treatment of FM patients, signifying an opioid or neuroendocrine basis for some of the observed beneficial effects of EMG BFB.

Ferraccioli et al. (54) conducted an open study administering 20-minute EMG-BFB sessions to 15 FM patients twice weekly for 15 sessions. EMG BFB consisted of patients receiving auditory feedback of ongoing muscle tension in scalp muscles. Clinical improvement (TePs, pain intensity, and morning stiffness) was found in 56% of the subjects at 6 months. Ferraccioli et al. (54) supported these findings in a randomized, controlled study of 12 patients using EMG BFB or sham BFB. Improvement was found in all outcomes in the treatment group, whereas the control had improvement only in TeP count. The authors concluded that EMG BFB in FM appeared reproducible and had long-term effectiveness. Because a small sample size limited their results, further research is needed to confirm them.

Buckelew et al. (55) conducted a randomized, controlled study with 119 FM patients comparing (a) EMG BFB/relaxation, (b) exercise, (c) a combination of EMG BFB/relaxation/exercise, and (d) an educational/attention control program. Subjects received individual training sessions once weekly for 1.5 to 3 hours for 6 weeks. During the maintenance phase of 2 years, the subjects were treated in groups once a month for an hour. Buckelew et al. (55) concluded that all three interventions resulted in improved self-efficacy for physical function and that it was best maintained over a 2-year follow-up by the combination group. As a result, EMG BFB can be an integrated part of a treatment program for chronic-pain patients.

Santen et al. (56) reported contradictory results in a similar study design with a larger sample size. These authors randomized 143 FM patients into a fitness, BFB, or control group. Reliable outcome measures used included the VAS, dolorimetery, the Arthritis Impact Measurement Scales, and the Sickness Impact Profile. After the treatments, the patients did not improve in pain or in any other outcome measure compared to controls. The exercise group did, however, continue with a low impact fitness training at their own expense, which suggests an immeasurable benefit to the this treatment group. The inconsistent results compared to previous studies could be due to high dropout rates, a failure to measure the obvious positive effect of fitness training with fellow sufferers, and the subjectivity of the measurements used for evaluating change in FM (56). In addition, the control group was given treatment, if appropriate, with medication, physical therapy (PT) (excluding exercise or relaxation therapy), and medical counseling.

EMG BFB is a cost-effective treatment modality because it educates patients to have control of their own bodies, whether it be movement control or autonomic, thus giving long-term benefits in both psychological and economic terms. In a recent survey of physical and occupational therapists in their therapeutic approaches to FM, Sim and Adams (57) found limited use of EMG BFB. The authors attribute this to inadequate training in this intervention. Further studies are need to better guide patients and health providers in the beneficial use of EMG BFB.

HEAT THERAPY

The benefits of using hot rocks and thermal baths to reduce joint stiffness and muscle spasm and to promote relaxation have been recognized ever since Hippocrates. The methods of applying heat have progressed since then, but many of the basic principles remain unchanged. Physical and occupational therapists use heating agents to provide pain relief and to prepare stiff joints and tight muscles for stretching and exercise. The physiologic effects of applying heat to the body include increasing blood flow, facilitating tissue healing, decreasing muscle tone, altering viscoelastic properties, altering nerve conduction velocity, and changing muscle spindle firing rates (58). Heating modalities are categorized by the mechanism of action (conduction, convention, and conversion) and the depth of penetration in elevating temperature in the tissues—superficial (1 cm) or deep (3 cm or more). Superficial modalities include hot packs, paraffin, fluidiotherapy, sauna, and hydrotherapy in different forms, such as hot baths, whirlpool, contrast baths, and balneotherapy. Deep heating includes shortwave diathermy and ultrasound.

The Philadelphia Panel (59), using evidence from randomized controlled trials and observational studies, determined that thermal modalities lacked evidence to include or exclude them as therapeutic interventions for chronic low back pain, neck pain, knee pain related to OA, or shoulder pain. Rakel and Barr (60) conducted a literature review and reported weak evidence that thermal modalities have a positive effect on chronic pain and that pain relief was mainly short term. Lin (61) demonstrated that cold packs have a more significant effect in comparison to heating pads in a randomized study comparing the two modalities in testing restriction of knee range of motion. Although cryotherapy is an additional modality used in PT, it is rarely used in FM patients due to their heightened sensitivity. Robinson et al. (62) performed a review of seven randomized, controlled trials on the effect of thermotherapy for treating RA. The authors found no significant effects of ice or heat packs and faradic baths on pain or medication intake; however, there were encouraging results with paraffin wax baths on pain, range of motion, and various functional measures after 4 weeks of treatment.

Superficial heat used in conjunction with an active exercise program may provide greater and longer lasting pain relief (63). The practical benefit of superficial heating is that it can be used at home, it is inexpensive, and there are very few contraindications. Contraindications include infections, acute inflammation, peripheral vascular disease, radiation therapy, malignancy, arterial insufficiency, and impaired circulation, sensation, and cognitive function (64). Treatment plans need to be individualized as FM patients have reported increased pain with heating agents (65). As always, treatment plans need to be individualized and based on goals mutually established by therapist and patient.

BALNEOTHERAPY

Balneotherapy is a treatment modality based on bathing in mineral-containing waters of hot springs or the use of mudpacks. The most popular area for this treatment is the Dead Sea region in Israel, which is the world's lowest and most saline lake (66). The unique climate it offers includes low humidity, high and stable temperatures, and high barometric pressures (the highest in the world) (67). Numerous controlled studies have shown that balneotherapy in this region is effective in the treatment of RA, psoriatic arthritis, and FM (66,68–73).

The mechanism by which these spa treatments work is not fully understood or supported in the literature. There has been no evidence of an actual influence on the disease process. Physiologic changes reported include significant diuresis and natriuresis, hemodilution, and increased cardiac output without significant change in blood pressure (66). The thermal stimuli may produce analgesia on nerve endings by increasing the pain threshold and decreasing muscle spasms (74). Tendon extensibility increases in joints and connective tissue. By causing peripheral vasodilatation, balneotherapy may help to wash out pain mediators (74). There are limited reports of the importance of the trace elements found in the mineral waters and whether they can be absorbed through the skin. This literature review found no adverse side effects of balneotherapy.

Buskila et al. (66) examined the effects of daily 20-minute sulfur baths with water from the Dead Sea in a randomized, controlled trial for 10 days with 48 FM patients. The control included a 10-day stay at the resort without treatment. Blinded assessments revealed that both groups improved on almost all areas measured (FM impact questionnaire, TeP count, tenderness threshold, visual analog scores, functional disability index, fatigue, stiffness, and anxiety). The improvements were significant in the treatment group and lasted for at least 3 months.

Evcik et al. (74) completed a randomized, controlled study with similar design at the natural springs of Afyon, Turkey. The authors compared the effect of balneotherapy in FM with treatments being received 20 minutes daily five times a week for 3 weeks to a control group receiving no treatment except instruction to continue with their daily activities. Their results were very promising for the treatment group, showing statistically significant differences in TePs, visual analog scores, Beck depression index, and FM impact questionnaire scores. After 6 months there was continued improvement in all areas except the depression scores.

Access to these areas of hot springs is limited due to location, expense, and dependability on a therapist. Further randomized controlled studies with longer follow-up periods are needed to strengthen these results.

Flusser et al. (75) performed a prospective, double-blinded, controlled study of 40 patients with knee OA that involved natural mineral-rich mud compresses versus mineral-depleted mud compresses being treated independently in the patient's home. These mud compresses were heated in a microwave or in a pot of hot water and then placed over the painful joints five times a week for 3 weeks. Outcome measures included the Lequesne Index of severity, self-assessments of pain score, and a VAS. Seventy-two percent of the patients in the treatment group had an improvement of more than 20% reduction in self-assessment of knee pain compared to 33% in the control group. Both groups showed significant improvement in pain severity, which was still observed at 3 months after completion of therapy. The authors concluded that efficacy for mud therapy was not clinically dramatic, but was statistically significant. The introduction of a placebo group would have improved the findings, as the local heat in both groups could have played a role in the improvement.

Balneotherapy could be a possible alternative treatment modality in FM and other nonneuropathic pain syndromes (66–74), but this will require continued investigation.

Although the specific mechanism of action of mud pack treatment, sulfur baths, mineral content, and trace elements remains unclear, evidence is mounting to support its use for the treatment of FM and certain chronic-pain syndromes. Balneotherapy may be a safe, practical, and effective physical agent that can be used in a patient's home.

ULTRASOUND

Ultrasound is a physical modality that has achieved recognition for over 40 years as an adjunct in the management of acute and chronic musculoskeletal disorders. It has been used in the treatment of various soft tissue dysfunctions, including scar tissue, tendonitis, bursitis, muscle spasms, joint contracture, OA, and pain. Ultrasound consists of inaudible acoustic waves delivered with a frequency range from 0.75 to 3 MHz and intensity between 0.5 and 3 w per cm^2. The absorption of ultrasound results in molecular oscillatory movements, and this energy transfer is converted into heat proportional to the intensity of the ultrasound (64).

The therapeutic effects include increasing soft tissue extensibility and increasing blood flow. Nonthermal changes occur by mechanical vibration and acoustic streaming, which is performed by using low intensities or a pulsed output of ultrasonic energy (76). The nonthermal properties of ultrasound are less well-defined, but may include altering cellular permeability and metabolism.

Because ultrasound can promote cell proliferation and activity, it is contraindicated over or close to sites of abnormal growth or rapid cell division such as cancer, tuberculosis, or a pregnant uterus. Diagnostic ultrasound, at 2.5 MHz, is used at a significantly lower dose than therapeutic ultrasound ($<0.1\%$ w per cm^2) (64). For similar reasons, it is contraindicated over epiphyseal plates in children, metal implants, cardiac pacemakers, or an area of a thrombus, due to the possibility of dislodgement (64).

Few studies were found on the use of ultrasound with FM or pain syndromes patients. The majority of randomized, controlled trials focused on specific musculoskeletal injuries such as epicondylitis, bursitis, shoulder pain, or tendonitis. Almeida (77) performed a study of 17 patients with FM, comparing the effect of combined therapy, including ultrasound and interferential current, against a sham procedure on pain and sleep. The treatment group underwent 12 sessions in 4 weeks of pulsed ultrasound and interferential current at different painful areas. The results were positive in demonstrating the combined treatment to be a therapeutic option in FM by improving pain manifestations (evaluated by a modified Wisconsin body map, VAS, TeP count, and tenderness threshold) and sleep pattern (assessed by the Brazilian inventory for sleep disorders and polysomnography). The small sample size limits these results.

Baker et al. (76) and Robertson and Baker (78) published reports reviewing randomized, controlled trials on both the biophysical effects and the therapeutic effectiveness of ultrasound. They concluded that there is an absence of evidence for a biologic rationale and provided little clinical evidence for the efficacy of therapeutic ultrasound. Although many clinicians regard ultrasound as a viable treatment, the majority of the literature supporting this application is empirical in nature and comes from studies lacking controls and proper designs (78).

Draper (79) critiqued Roberston and Baker's (76) literature review, pointing out that most of the studies reviewed did not use the generally recommended parameters for ultrasound. For example, the treatment area should be no more than twice the size of the effective radiating area of the crystal, and eight out of ten of the studies did not address this in their treatments. Treatment time was found to be inconsistent throughout the reviewed studies, with two studies with longer treatment times demonstrating ultrasound to be superior to placebo.

It seems that the "jury is still out" on the therapeutic effect of ultrasound (79). Although clinicians widely use ultrasound for localized pain, current reports are conflicting and studies are needed to clarify its efficacy. Ultrasound merits consideration as a treatment modality in conditions in which the pain is localized and difficult to treat.

PHONOPHORESIS

Phonophoresis is a physical modality that uses ultrasound to drive pharmacologic agents (such as hydrocortisone, dexamethasone, salicylates, and lidocaine) transdermally into subcutaneous tissues. Phonophoresis is indicated for musculoskeletal disorders with an inflammatory condition, such as bursitis, plantar fascitis, and epicondylitis. There are theoretical advantages of percutaneous administration of a drug, including: (1) suppression of first hepatic pass effect (2) stable plasma levels, and (3) absence of degradation by the digestive tract (80). The specific physiologic mechanism of phonophoresis remains unclear. Both the thermal and nonthermal properties of ultrasound have been cited as possible mechanisms for the penetration of the medications (81). The mechanisms responsible include increased skin permeability due to increased fluidity of intercellular lipids by heating or mechanical stress and /or by enlarging intercellular space, or by creating permanent or transient holes through corneocytes and keratinocytes as a consequence of cavitation, and/or by driving the drug and the vehicle through the permeabilized skin by convection (80).

The efficacy of phonophoresis has not been established. There have been conflicting results in human-controlled *in vivo* studies demonstrating an absence or mild effects of the technique and effect on skin permeability (80,82). Klaiman (81) discusses five studies that demonstrated drug penetration as deep as 10 cm, and Bare et al. (83) discussed four studies in addition to their own that failed to demonstrate any transdermal penetration *via* phonophoretic technique.

Early noncontrolled clinical trials showed patients with inflammatory conditions treated with phonophoresis (using 10% hydrocortisone) with decreased pain and improved range of motion (84–86). More recent controlled trials on epicondylitis (hydrocortisone preparations of 1% and 10%) found no significant benefit when comparing phonophoresis to ultrasound alone (87,88).

Klaiman (81) found no significant difference in pain level or pressure tolerance when comparing phonophoresis to ultrasound in the treatment of musculoskeletal disorders. The groups received 8 minutes of continuous ultrasound at 1.5 W per cm^2, three times a week for 3 weeks; the phonophoresis group was treated with a gel containing 0.05% flucocinonide. The results found ultrasound to be effective in decreasing pain, with improved patient tolerance to algometer pressures after 3 weeks of treatment. There was no significant difference with the application of phonophoresis.

There is a paucity of evidence in clinical trials regarding the use of phonophoresis. Lack of standardization exists with preparation, concentration of active ingredients, dosage, treatment prescription, and parameters. Phonophoresis may be a safe alternative or adjuvant treatment to systemic medications. Although further study is recommended, clinicians continue to use this modality for localized musculoskeletal conditions.

TRANSCUTANEOUS ELECTRICAL NERVE STIMULATION

TENS is a noninvasive therapeutic modality widely used in clinical practice for pain relief by electrically stimulating peripheral nerves via skin surface electrodes. Most TENS devices today use an asymmetrical biphasic waveform, with frequency ranges from 1 to 150 Hz, pulse widths from 50 to 300 ms, and amplitudes through 75 mcmp (39). Melzack and Wall (40) attempted to explain the physiologic effect with the "gate theory," by which TENS stimulates the afferent nerve fibers that transmit or inhibit noxious input through the spinal cord to the brain. According to this theory, the analgesic effect is local, taking place in the dermatomes of the spinal segment recruited by the stimulation. The endorphin release phenomenon (89) is a theory in which TENS stimulates the sympathetic nervous system and brain stem nuclei to produce endorphins and possibly inhibit arthritis-related inflammation (63). The main indication for TENS is chronic pain—most commonly low back pain. Contraindications include demand type cardiac pacemaker, epilepsy, loss of sensation, and stimulation over carotid sinus or the eye (64). The major advantage of TENS is the applicability to a home program, which allows the patient to control the treatment independently. Adverse reactions are uncommon, but can include allergic dermatitis from the tape, gel, or electrodes, and, on rare occasions, transient increased pain.

Clinicians need to use the appropriate parameters and electrode placement in order to get the best possible outcome. Motor points, trigger points, and acupuncture points all represent electrically active and identifiable points that enhance the potential flow of current into the target tissue (64).

The bulk of research on TENS focuses on musculoskeletal pain, primarily back pain. FM patients present with multiple TeP areas, which mimic many musculoskeletal conditions. FM patients also typically present with diffuse musculoskeletal pain, while TENS is thought to be effective for localized pain only (65). TENS can be justified for site-specific pain commonly seen at the lateral epicondyle, low back, or upper trapezius area.

Clinical studies demonstrate a wide range of success rates with TENS, varying from 25% to 95% (65). The percentage of patients who benefit from short-term TENS has been reported to range from 50% to 80%, with good long-term benefit for between 6% to 44% (90). In a randomized survey (91) of 2003 chronic-pain patients using TENS for long-term (at least 6 months), the authors found that TENS was associated with a significant reduction in the utilization of pain medication and physical therapy and occupational therapy (PT/OT). Cost simulations of medication and PT/OT indicated that long-term TENS use was associated with a reduction of 55% for medications and up to 69% for PT/OT.

Systematic reviews of TENS in the treatment of chronic pain with placebo and control groups have reported inconclusive results (92–95). Sim and Adams (96) conducted a literature review of randomized controlled trials, finding limited studies showing successful use of TENS in the management of FM. Di Benedetto (97) compared S-adenosyl-L-methionine (SAMe, an antidepressant) to TENS and found that TENS was inferior to SAMe on 3 out of 13 outcomes measures and that there were no significant differences in respect to subjective pain, sleep, or fatigue. Brosseau et al. (98) concluded there was no evidence to support the use or nonuse of TENS in a meta-analysis of TENS in the treatment of low back pain. The Philadelphia Panel (59) evaluated evidence from randomized, controlled trials and observational studies in the use of TENS for chronic low back, knee, shoulder, and neck pain. The panel concluded that TENS was of clinically important benefit for knee OA but not for chronic neck pain. The panel (59) concluded that there was poor evidence to include or exclude TENS alone as an intervention for chronic low back pain.

In contrast, Rushton (99) completed a literature review and reported that TENS was remarkably safe and provided significant analgesia in about half of patients experiencing moderate predictable pain. The author found the implanted devices more effective than TENS used for chronic pain. A randomized survey (100) of 506 chronic-pain patients using TENS for pain management found that 74% were long-time users (more than 6 months) and there was statistically significant change or improvement that paralleled the introduction of TENS use with increased activity level and reduction in pain, drugs, and other therapies. It was suggested that good prognostic factors for the success of TENS in chronic pain include careful training in the use of the device and regular follow-up. Poor prognostic factors included significant depression and a progressive disease state (101).

Clinically, TENS remains a widely used and successful treatment option for some chronic-pain patients despite the conflicting literature. Some research indicated reduced therapy and medication use, increased activities, and improved treatment satisfaction, all contributing to restoring functional ability and an improved quality of life. These improvements, combined with the accompanying cost and complication considerations, are important points that clinicians must weigh when constructing a treatment plan for patients with chronic pain.

Other physical agents not included in this chapter, such as laser or cranial electrotherapy, may be additional tools in treatment of chronic pain.

TRIGGER POINT INJECTIONS

There are few studies that consider using trigger point injections for treating patients with fibromyalgia. Because large numbers of patients have coexisting myofascial pain syndromes and fibromyalgia, information about their use in myofascial pain may be useful.

Many clinicians have considered myofascial trigger points (102) to be the cause of soft tissue pain syndromes, particularly in the cervical–trapezius area and lower back. Travell and Simons (103) described these trigger points as an area of hyperirritability within a taut band of muscle. The trigger point can resemble a pea or a ropelike nodular band and can be associated with referred pain over reproducible and predictable myotomes with point pressure. Crepitation, grating, or a cracking sensation within a muscle may also be felt. A classic twitch response is described in which adequate pressure is applied in a perpendicular manner across the trigger point to elicit a spontaneous twitch. An alternative diagnostic method is one in which the patient verbalizes a painful response or withdraws upon palpation of a tender nodule or trigger point. A latent trigger point does not cause pain but may cause restricted range of motion and weakness in the muscle. Active trigger points cause pain at rest and with the use or contraction of the involved muscle, as well as limit the range of motion (104). With training, a fairly good localization of trigger points can be done clinically (105,106), but occasionally imaging techniques like magnetic resonance imaging (MRI) are necessary, particularly for deep structures in the lumbar area.

The pathogenesis or neurophysiology of trigger points is poorly understood. Overuse or trauma is a very common event preceding myofascial pain and is seen in cervical strain or “whiplash” injuries, but other events have been implicated as well. Usually, there is no systemic condition associated with myofascial pain other than the lack of a local twitch response with deep palpation, which also helps distinguish it from fibromyalgia. The incidence of myofascial pain in a pain clinic ranges from 30% to 85% and is more prevalent in women than in men (107). Ensenyal et al. (108) found that 89.3% of their patients with myofascial pain had high anxiety scores on the Taylor Manifest Anxiety Scale (TMAS). The American Pain Society performed surveys on more than 1,663 members, and these surveys indicated that myofascial pain syndrome (MPS) was a distinct clinical entity separate from fibromyalgia (109,110). There are many theories about the neurophysiology of MPS and myofascial trigger points (MTrPs) and about why these tender local nodules can have a decrease in pain with local irritation, either from wet or dry needling using various diluents. Some of these theories (103,108) include (a) mechanical disruption of the self-sustaining MTrP mechanism, (b) depolarization block of nerve fibers by released intracellular potassium, (c) washout of neurosensitizing substances by the injected fluid, (d) interruption of central feedback, (e) focal necrosis around the MTrP by the injection, such as a change in pH by using anesthetics.

DRY NEEDLING OR WET NEEDLING WITH XYLOCAINE OR STEROIDS

Many techniques and agents for MPS have been used with variable outcomes, and there is a dearth of large randomized controlled trials. Some of the treatments include "wet" needling, where various agents such as saline, sterile water, and long- and short-acting local anesthetics (111) are injected with and without steroids, and dry needlying of MTrP. A recent review (105) of 23 papers on using various needling techniques concluded that these studies were not well controlled, measured different outcomes, often did not have a placebo arm (usual care), and varied in follow-up from 10 minutes to 3 months after the procedure. Patient selection also was a problem, with patients with coexisting fibromyalgia having poorer outcomes, although many studies on MPS use the presence of fibromyalgia as a clinical exclusion for participation. The direction of the conclusions in this review seemed to be that MTrP injections appeared to be effective in decreasing pain, no matter what was injected, and that dry needling seemed to be comparable in efficacy. Many different combinations were used, including bupivacaine, mepivacaine, lidocaine versus lidocaine plus triamcinolone (1:1 with volume of 1.5 mL), 1 mL prednisolone with 1 mL 0.9% normal saline solution, and 2 mL diclofenac versus 2 mL 1% lidocaine. Volumes ranged from 0.5 mL to 2 mL of all diluents (112–114). Other reviews reported that needling interventions seem to provide benefit and that none of the interventions seems to be clearly better than the other (113).

Advocates of dry needling (115–117) using electromyogram (EMG) needles seem to believe strongly that this technique may be effective for pain relief, particularly when the pain is from a cervical radiculopathy. Different techniques are used, but a fine needle can be inserted from 0.3 mm up to 30 mm into an MTrP and be kept there for 30 seconds or until the referred, reproducible pain is gone. Deep needling, because it is very uncomfortable, was recommended for myofascial pain from radiculopathy. Critics of the studies note that in Chu's study only 48% of her patients responded to the follow-up questionnaire, and it was always hard to determine whether the daily exercises were also done. Follow-up for all studies of MPS should evaluate whether the original goal of an injection for decreasing local and referred pain will, at least temporarily, enable the patient to assume normal posture and stretching exercises in order to minimize long-term pain and dysfunction.

BOTULINUM TOXIN INJECTION

Ermangen identified botulinum toxin in 1897 as the culprit in an outbreak of food poisoning, and half a century later the physiology of the toxin was identified by blocking transmission at the neuromuscular junction. Starting in the late 1980s, botulinum toxin A (BT-A) had gained the approval of the U.S. Food and Drug Administration (FDA) for blepharospasm, strabismus, hemifacial spasm, and cervical dystonia. Both botulinum toxin and A and B are now being used for multiple "off label" uses and are being claimed as useful agents for refractory MPS (118).

Botulinum toxin A is a 150-KDa protein made by *Clostridium botulinum*. The toxin is internalized into the presynaptic cholinergic nerve terminals, which in turn inhibit the release of the neurotransmitter acetylcholine, thereby inhibiting muscle contraction (119). Any pain-alleviating effect of BT-A and BT-B may not entirely be due to the neurophysiology of muscle relaxation, and the pain relief in treating cervical dystonia precedes any relief in spasm. Human studies and animal data supported a direct antinociceptive effect, with inhibition of release of substance P and acetylcholine but not norepinephrine (118,120). The toxin also seems to decrease the sympathetic transmission and perhaps reduces the dorsal root ganglion's hypersensitization in neuropathic pain. Botulinum toxin also probably blocks central glutamate release, which is important because glutamate and aspartate stimulate *N*-methyl-D-aspartate (NMDA). NMDA is important for neuroplasticity and central sensitization, which occurs in the dorsal root ganglion (118,121–125).

Besides modulation of the central pain pathways, the local installation of botulinum toxin into a trigger point in the involved muscle may enable decompression of the nerves entrapped by chronic muscle spasm and may also modify afferent muscle spindle discharges and facilitate physiotherapy by decreasing pain.

Botulinum toxin injections for MPS seem to now be used by some as adjunctive therapy for refractory MPS after failure with the traditional physical measures and trigger point injections.

As with many other studies of MPS, patients' selection criteria often lead to mixed or biased results, particularly when patients with fibromyalgia are included. Lalli et al. (126) studied 20 patients in a randomized controlled trial of BT-A compared to 1% lidocaine, and the BT-A group showed improved reduction in pain at 2 and 4 weeks. Porta (119) compared BT-A with methylprednisolone, both administered with 1% lidocaine, in the treatment of pain in the piriformis, scalenus, and iliopsoas muscles and found superior improvement in the BT-A group. He also noted that in the steroid group the effectiveness began to wane by 30 days and that by 60 days the BT-A group continued to have statistically significant improvement, with lower pain scores and better function. He emphasized the need for all patients to continue strict adherence to a physiotherapy program to maximize the benefits from the treatment.

Commercially available botulinum toxin preparations are available and can cost several hundred dollars per injection. In the United States, Botox (Allergan Inc.) and, internationally, Dysport (Ipsen Ltd., UK) and a Chinese product (Lanzhou Biological Products Institute, ROC) are available. BT-A has been more widely used and studied, but BT-B is also available (Elan Pharmaceuticals, Inc.) and may be a therapeutic alternative for patients who become refractory or hypersensitive to BT-A.

The clinical side effects of BT-A are mild and can include local anesthesia (usually lasting up to 72 hours), dry mouth, dysphagia (when used for cervical dystonia), transient weakness, and mild flulike illness (118,121).

A retrospective review of the literature by Smith et al. led to their conclusion that post-traumatic, particularly cervical-thoracic, MPS may respond better to botulinum injections than low back pain with MPS (121). Royal (118) found that low back MPS, when associated with a localized spasm and an asymmetric examination, predicted a better response and that careful selection is therefore important. Both Smith et al. and Royal note that higher doses of BT-A are needed for treating low back MPS (200 U for type A or 40 U per lumbar level on one side). This is compared to the 25 to 100 U that are required for treating pain in the trapezius or levator scapulae muscles.

Botulinum toxins A and B appeared to give a more sustained duration of action than other more standard and less expensive trigger point injections and can be used for myofascial and neuropathic pain syndromes. Their use is still only for patients with refractory MPS who have failed more conventional therapy. The appropriate dosages, the dosing interval, and the injection techniques, as well as patient selection, are reported to be crucial for good clinical outcomes (118,121).

Many of the studies on MPS have mixed the two groups, which makes interpreting the outcome, as well as overlapping the pain distribution, difficult, although the MPS is more localized, with fewer issues of somatization (127). One small study (128) separated patients with only MPS from patients with fibromyalgia and MPS and compared pain outcomes after trigger point injections with 0.5% lidocaine. The outcomes were measured in improved range of motion, pain intensity, and pain threshold. There was no significant difference in outcome at 2 weeks postinjection, although the FMS with MPS group had more postinjection soreness.

CONCLUSION

All pain, whether nociceptive, inflammatory, or neuropathic, depends to some degree on the peripheral activation of primary sensory afferent neurons. The localized peripheral administration of drugs, such as by topical application, can potentially optimize drug concentrations at the site of origin of the pain, while leading to lower systemic levels and fewer adverse systemic effects and drug interactions. At present, topical and other forms of peripheral administration of nonsteroidal anti-inflammatory drugs, opioids, capsaicin, and local anesthetics are being used in a variety of clinical states. There also are some preclinical and clinical data on the use of topical antidepressants and glutamate receptor antagonists. Given that activation of sensory neurons involves multiple mediators and pathways, combinations of agents targeting different mechanisms and delivery systems may be particularly useful. Topical analgesics represent a promising area for future drug development for fibromyalgia and chronic pain management.

Fibromyalgia and nonneuropathic pain syndromes are highly complex and present with a wide array of symptoms. An interdisciplinary approach needs to be considered with these patients in order to address them holistically. Physical agents are just one small part of this approach. Pain control is an essential component with these patients that is used to help them advance to higher levels of function and well-being as treatment progresses from more passive to more active interventions. As for physical measures and devices, successful management ultimately includes the patient's ability to self-manage symptoms and to maximize function and quality of life. Appropriate professional support and education for both the patient and the family are cornerstones of treatment. This chapter has reviewed the use of ultrasound, EMG-BFB, phonophoresis, TENS, balneotherapy, and heat therapy in patients with fibromyalgia and chronic pain. There is paucity of well-designed randomized controlled studies, which makes it difficult to draw any firm conclusions, although there is literature to "moderately" support some of these modalities as an adjuvant treatment in these difficult-to-treat populations.

Trigger point injection therapy for chronic severe myofascial pain still suffers from the cloud of a "hocus pocus" intervention, with variable results in multiple clinical trials and no clear scientific basis for many of the clinical findings or interventions. Conclusive evidence for one injection technique or injectable agent is lacking, but in multiple studies there might be some degree of benefit beyond placebo therapy. Dry needling may be slightly more effective for radicular pain associated with MPS; steroids mixed with local anesthetics have advocates for prolonging the effectiveness. Anesthesiologists are doing trials comparing different long-acting local anesthetics, with and without dilutions of steroids, to decide which may be the least painful locally and most effective in the long term (110). The new use of botulinum toxin injections, although extremely expensive, may be of valuable use to patients with severe disease and refractory myofascial pain.

SUMMARY POINTS

- Even "central" pain syndromes such as FM depend to some degree on the peripheral activation of primary sensory afferent neurons. Thus, the localized peripheral administration of drugs, such as by topical application, can potentially optimize drug concentrations at the site of origin of the pain while leading to lower systemic levels and fewer adverse systemic effects and fewer drug interactions.
- Primary sensory afferent neurons can be activated by a range of inflammatory mediators, such as prostanoids, bradykinin, adenosine triphosphate (ATP), histamine, and serotonin, and inhibiting their actions represents a strategy for the development of analgesics.
- Peripheral nerve endings also express a variety of inhibitory neuroreceptors, such as opioid, α-adrenergic, cholinergic, adenosine, and cannabinoid receptors, and agonists for these receptors also represent viable targets for drug development.
- At present, topical and other forms of peripheral administration of nonsteroidal anti-inflammatory drugs, opioids, capsaicin, local anesthetics, and alpha-adrenoceptor agonists are being used in a variety of clinical states.
- Given that activation of sensory neurons involves multiple mediators and pathways, combinations of agents targeting different mechanisms and delivery systems may be particularly useful.

Summary Table
Local Treatments for Fibromyalgia and Nonneuropathic Pain

TREATMENTS	DIRECTION OF EVIDENCE	COMMENTS
Topical NSAIDs	Tentatively positive	Few systemic side effects Easy to use May not be readily available at local pharmacy
Capsaicin	Tentatively positive	Readily available and easy to use Variable efficacy Eye or local skin irritation
Local anesthetics	Uncertain	Few systemic and local side effects Documented efficacy for neuropathic pain Unproven efficacy for fibromyalgia
Topical antidepressant	Unclear	Promising analgesic efficacy in neuropathic pain Few data for fibromyalgia or nonneuropathic pain
Topical gabapentin	Preclinical	Potential peripheral site of action Studied only in preclinical setting
Topical TCM (herbal)	Unclear	Little quality control Tradition- and experience-driven Not evidence-based
Massage	Highly positive	Time-consuming Short-term benefits Expensive
Electromyographic biofeedback (EMG-BFB)	Highly positive	Long-term benefits Limited use by PT/OTs
Superficial heat	Lack of evidence Possibly effective	Short-term benefit Used widely in conjunction with exercise
Balneotherapy	Highly positive	Limited access Expensive
Ultrasound	Unclear, conflicting evidence	Limited to localized area of pain, not for diffuse pain
Phonophoresis	Unclear, conflicting evidence	Limited to localized area of pain, not for diffuse pain Safe administration of medication (NSAIDs)
TENS	Unclear, conflicting evidence	Can be used at home Long-term benefits
Dry needling	Probably effective	Probably best for radicular pain Can be very uncomfortable No indication for primary FMS
Local injections (steroids, anesthetics)	Probably effective	All seemed to decrease pain over placebo Controversy about which is superior No indication for primary FMS
Botulinum toxin	Probably effective	Decreases pain for MPS and neuropathic pain syndromes Extremely expensive No indication for fibromyalgia

NSAIDs, nonsteroidal anti-inflammatory drugs; TCM, traditional Chinese medicine; TENS, transcutaneous electrical nerve stimulation; FMS, fibromyalgia syndrome; MPS, myofascial pain syndrome.

REFERENCES

1. Robertson DB, Maibach HI. Topical corticosteroids. *Int J Dermatol* 1982;21(2):59–67.
2. Sawynok J. Topical and peripherally acting analgesics. *Pharmacol Rev* 2003;55(1):1–20.
3. Heyneman CA, Lawless-Liday C, et al. Oral versus topical NSAIDs in rheumatic diseases: a comparison. *Drugs* 2000;60(3):555–574.
4. Tramer MR, Williams JE, et al. Comparing analgesic efficacy of non-steroidal anti-inflammatory drugs given by different routes in acute and chronic pain: a qualitative systematic review. *Acta Anaesthesiol Scand* 1998;42(1):71–79.
5. Vaile JH, Davis P. Topical NSAIDs for musculoskeletal conditions. A review of the literature. *Drugs* 1998;56(5):783–799.
6. Steen KH, Reeh PW, et al. Topical acetylsalicylic, salicylic acid, and indomethacin suppress pain from experimental tissue acidosis in human skin. *Pain* 1995;62(3):339–347.
7. Fellmann N. Clinical experiences with 5% Tolectin (tolmetin) gel in patients with degenerative joint and spine diseases and soft tissue rheumatism. *Z Rheumatol* 1983;42(5):280–284.
8. Bruhlmann P, Michel BA. Topical diclofenac patch in patients with knee osteoarthritis: a randomized, double-blind, controlled clinical trial. *Clin Exp Rheumatol* 2003;21(2):193–198.

9. Holzer P. Capsaicin: cellular targets, mechanisms of action, and selectivity for thin sensory neurons. *Pharmacol Rev* 1991;43(2):143–201.
10. Winter J, Bevan S, et al. Capsaicin and pain mechanisms. *Br J Anaesth* 1995;75(2):157–168.
11. Caterina MJ, Schumacher MA, et al. The capsaicin receptor: a heat-activated ion channel in the pain pathway. *Nature* 1997;389(6653):816–824.
12. Nolano M, Simone DA, et al. Topical capsaicin in humans: parallel loss of epidermal nerve fibers and pain sensation. *Pain* 1999;81(1-2):135–145.
13. McCarthy GM, McCarty DJ. Effect of topical capsaicin in the therapy of painful osteoarthritis of the hands. *J Rheumatol* 1992;19(4):604–607.
14. Epstein JB, Marcoe JH. Topical application of capsaicin for treatment of oral neuropathic pain and trigeminal neuralgia. *Oral Surg Oral Med Oral Pathol* 1994;77(2):135–140.
15. Watson CP. Topical capsaicin as an adjuvant analgesic. *J Pain Symptom Manage* 1994;9(7):425–433.
16. Rains C, Bryson HM. Topical capsaicin: a review of its pharmacological properties and therapeutic potential in post-herpetic neuralgia, diabetic neuropathy and osteoarthritis. *Drugs Aging* 1995;7(4):317–328.
17. Fields HL. *Excitability blockers: anticonvulsants and low concentration local anesthetics in the treatment of chronic pain*. Berlin: Springer-Verlag, 1997.
18. McCleskey EW, Gold MS. Ion channels of nociception. *Annu Rev Physiol* 1999;61:835–856.
19. Galer BS, Rowbotham MC, et al. Topical lidocaine patch relieves postherpetic neuralgia more effectively than a vehicle topical patch: results of an enriched enrollment study. *Pain* 1999;80(3):533–538.
20. Rowbotham MC, Davies PS, et al. Lidocaine patch: double-blind controlled study of a new treatment method for post-herpetic neuralgia. *Pain* 1996;65(1):39–44.
21. Scudds RA, Janzen V, et al. The use of topical 4% lidocaine in spheno-palatine ganglion blocks for the treatment of chronic muscle pain syndromes: a randomized, controlled trial. *Pain* 1995;62(1):69–77.
22. Sindrup SH, Jensen TS. Efficacy of pharmacological treatments of neuropathic pain: an update and effect related to mechanism of drug action. *Pain* 1999;83(3):389–400.
23. Godfrey RG. A guide to the understanding and use of tricyclic antidepressants in the overall management of fibromyalgia and other chronic pain syndromes. *Arch Intern Med* 1996; 156(10):1047–1052.
24. Besson A, Privat AM, et al. Dopaminergic and opioidergic mediations of tricyclic antidepressants in the learned helplessness paradigm. *Pharmacol Biochem Behav* 1999;64(3): 541–548.
25. Su X, Gebhart GF. Effects of tricyclic antidepressants on mechanosensitive pelvic nerve afferent fibers innervating the rat colon. *Pain* 1998;76(1-2):105–114.
26. Sawynok J, Esser MJ, et al. Antidepressants as analgesics: an overview of central and peripheral mechanisms of action. *J Psychiatry Neurosci* 2001;26(1):21–29.
27. Esser MJ, Sawynok J. Caffeine blockade of the thermal antihyperalgesic effect of acute amitriptyline in a rat model of neuropathic pain. *Eur J Pharmacol* 2000;399(2-3): 131–139.
28. McCleane G. Topical application of doxepin hydrochloride, capsaicin, and a combination of both produces analgesia in chronic human neuropathic pain: a randomized, double-blind, placebo-controlled study. *Br J Clin Pharmacol* 2000;49(6): 574–579.
29. Taylor CP, Gee NS, et al. A summary of mechanistic hypotheses of gabapentin pharmacology. *Epilepsy Res* 1998; 29(3): 233–249.
30. Carlton SM, Zhou S. Attenuation of formalin-induced nociceptive behaviors following local peripheral injection of gabapentin. *Pain* 1998;76(1-2):201–207.
31. Crofford L, Russell IJ, Mease P, et al. Pregabalin improves pain associated with fibromyalgia syndrome in a multicenter randomized, placebo-controlled monotherapy trial. *Arthritis Rheum* 2002;46(9 Suppl):S613.
32. Litt JZ. Alternative topical therapy. *Dermatol Clin* 1989;7(1): 43–52.
33. Zizeng Lu, Shude Jiao. *Applied traditional Chinese medicine in rheumatisms*. Beijing: Peoples' Health, 1998.
34. Ng SK. Topical traditional Chinese medicine. A report from Singapore. *Arch Dermatol* 1998;134(11):1395–1396.
35. Pioro-Boisset M, Esdaile J, Fitzcharles M. Alternative medicine use in fibromyalgia syndrome. *Arthritis Care Res* 1996; 9(1):13–17.
36. Field T. Massage therapy effects in depression and somatic symptoms in chronic fatigue syndrome. *J Chronic Fatigue Syndr* 1997;3:43–51.
37. Ironson G, Field T, Scafidi F, et al. Massage therapy is associated with enhancement of the immune system's cytotoxic capacity. *Int J Neurosci* 1996;84:205–217.
38. Field T. Massage therapy effects. *Am Psychol* 1998;53(12): 1270–1281.
39. Rachlin E, Rachline I. *Myofascial pain and fibromyalgia trigger point management*, 2nd ed. Philadelphia, PA: Mosby, 2002.
40. Melzack R, Wall P. Pain mechanisms: a new theory. *Science* 1965;150:971–979.
41. Danneskiold-Samsoe B, Christiansen E, Anderson RB. Myofascial pain and the role of myoglobin. *Scand J Rheumatol* 1986;15:174–178.
42. Moldofsky H. A chronobiologic theory of fibromyalgia. *J Musculoskelet Pain* 1993;1:49–59.
43. Russell IJ, Orr MD, Littman B, et al. Elevated cerebrospinal fluid levels of substance P in patients with fibromyalgia syndrome. *Arthritis Rheumatol* 1994;37:1593–1601.
44. Clauw D. Fibromyalgia: more than just a musculoskeletal disease. *Disease* 1995;52(3):843–851.
45. Field T, Diego M, Cullen C, et al. Fibromyalgia pain and substance P decrease and sleep improves after massage therapy. *J Clin Rheumatol* 2002;8(2):72–76.
46. Field T, Delage J, Hernandez-Reif M. Movement and massage therapy reduce fibromyalgia pain. *J Bodywork Movement Ther* 2003;7(1):49–52.
47. Gam A, Warming S, Larsen L, et al. Treatment of myofascial trigger-points with ultrasound combined with massage and exercise—a randomised, controlled trial. *Pain* 1998;77:73–79.
48. Sunshine W, Field T, Olga Q, et al. Fibromyalgia benefits from massage therapy and transcutaneous electrical stimulation. *J Clin Rheum* 1996;2(1):18–22.
49. Brattberg G. Connective tissue massage in the treatment of fibromyalgia. *Eur J Pain* 1999;3(3):235–244.
50. Alnigenis MNY, Bradely JD, Wallick J, et al. Massage therapy in the management of fibromyalgia: a pilot study. *J Musculoskelet Pain* 2001;9(2):55–67.
51. Holdcraft LC, Assefi N, Buchwald D, et al. Complementary and alternative medicine in fibromyalgia and related syndromes. *Best Pract Res Clin Rheumatol* 2003;17(4):667–683.
52. Grzesiak R. Psychological considerations in myofascial pain, fibromyalgia, and related musculoskeletal pain. In: Rachlin ES, ed. *Myofascial pain and fibromyalgia trigger point management*, 2nd ed. Philadelphia, PA: Mosby, 2002.
53. Molina A, Cechettin M, Fontana S, et al. Failure of EMG biofeedback (EMG-BF) after sham BFB training in fibromyalgia. *Fed Proc* 1987;46:549.
54. Ferraccioli G, Ghirelli L, Scita F, et al. EMG – biofeedback training in fibromyalgia syndrome. *J Rheumatol* 1987;14:4.

55. Bucklew SP, Conway R, Parker J, et al. Biofeedback/relaxation training and exercise interventions for fibromyalgia: a prospective trial. *Arthritis Care Res* 1998;11:196–209.
56. Van Santen M, Bolwijn P, Verstappen F, et al. Randomized clinical trial comparing fitness and biofeedback training versus basic treatment in patients with fibromyalgia. *J Rheumatol* 2002;29(3):575–581.
57. Sim J, Adams N. Therapeutic approaches to fibromyalgia syndrome in the United Kingdom: a survey of occupational therapists and physical therapists. *Eur J Pain* 2003;7(2):173–180.
58. Michlovitz S. *Thermal agents in rehabilitation*, 3rd ed. Philadelphia, PA: FA Davis Co, 1996.
59. Philadelphia Panel. Philadelphia panel evidence-based clinical practice guidelines on selected rehabilitation for knee pain. *Phys Ther* 2001;81:1675–1700.
60. Rakel B, Barr J. Physical modalities in chronic pain management. *Nurs Clin North Am* 2003;38:477–494.
61. Lin YH. Effects of thermal therapy in improving the passive range of knee motion: comparison of cold and superficial heat applications. *Clin Rehabil* 2003;17:618–623.
62. Robinson V, Brosseau L, Casimiro L, et al. Thermotherapy for treating rheumatoid arthritis (Cochrane Review). *The Cochrane Library*, Issue 4. Chichester, UK: John Wiley and Sons, 2002.
63. Minor MA, Sandord MK. The role of physical therapy and physical modalities in pain management. *Rheumatol Dis Clin North Am* 1999;25:233–248.
64. Behrens B, Michlovitz S. *Physical agents*. Philadelphia, PA: FA Davis Co, 1996.
65. Offenbacher M, Stucki G. Physical therapy in the treatment of fibromyalgia. *Scand J Rheumatol* 2000;29(Suppl. 113):78–85.
66. Buskila D, Mahmoud AS, Neumann L, et al. Balneotherapy for fibromyalgia at the Dead Sea. *Rheumatol Int* 2001;20:105–108.
67. Sukenik S, Baradin R, Codish S, et al. Balneotherapy at the Dead Sea area for patients with psoriatic arthritis and concomitant fibromyalgia. *Isr Med Assoc* 2001;3:147–150.
68. Sukenik S, Buskila D, Neumann L, et al. Sulphur bath and mud pack treatment for rheumatoid arthritis at the Dead Sea area. *Annu Rheumatol Dis* 1990;49:99–102.
69. Sukenik A, Buskila D, Neumann L, et al. Dead Sea bath salts for treatment of rheumatoid arthritis. *Clin Exp Rheumatol* 1990;8:353–357.
70. Sukenik S, Buskila D, Neumann L, et al. Mud pack therapy in rheumatoid arthritis. *Clin Rheumatol* 1992;11:243–247.
71. Sukenik S, Giryes H, Halvey S, et al. Treatment of psoriatic arthritis at the Dead Sea. *J Rheumatol* 1994;21: 1305–1309.
72. Sukenik S, Neumann L, Flusser D, et al. Balneotherapy for rheumatoid arthritis at the Dead Sea. *Isr J Med Sci* 1995;31:210–214.
73. Neumann L, Sukenik S, Bolotin A, et al. The effect of balneotherapy at the Dead Sea on the quality of life of patients with fibromyalgia syndrome *Clin Rheumatol* 2001;20:15–19.
74. Evcik D, Kizilay, B, Gokcen, E, The effects of balneotherapy on fibromyalgia patients. *Rheumatol Int* 2002;22:56–59.
75. Flusser D, Abu-Shakra M, Friger M, et al. Therapy with mud compresses for knee osteoarthritis. *J Clin Rheumatol* 2002; 8(4):197–203.
76. Baker K, Roberston V, Duck F. A review of therapeutic ultrasound: biophysical effects. *Phys Ther* 2001;81(7):1351–1358.
77. Almeida T, Roizenblatt S, Benedito-Silva AA, et al. The effect of combined therapy (ultrasound and interferential current) on pain and sleep in fibromyalgia. *Pain* 2003;104:665–672.
78. Robertson V, Baker K. 2001) A review of therapeutic ultrasound: effectiveness studies. *Phys Ther* 81(7):1339–1349.
79. Draper DO. Don't disregard ultrasound yet—the jury is still out. *Phys Ther* 2002;82(2):1909–1191.
80. Machet L, Boucaud A. Phonophoresis: efficiency, mechanism and skin tolerance. *Int J Pharm* 2002;242:1–15.
81. Klaiman M. Phonophoresis versus ultrasound in the treatment of common musculoskeletal conditions. *Med Sci Sports Exerc* 1998;30(9):1349–1355.
82. Cagnie B, Vinck E, Rimbaut S, et al. Phonophoresis versus topical application of ketoprofen: comparison between tissue and plasma levels. *Phys Ther* 2003;83(8):707–712.
83. Bare A, McAnaw M, Pritchard A, et al. Phonophoretic delivery of 10% hydrocortisone through the epidermis of humans as determined by serum cortisol concentrations. *Phys Ther* 1996;76(7):738–749.
84. Griffin JE, et al. Patients treated with ultrasonic driven hydrocortisone and with cortisol using phonophoresis. *Phys Ther* 1967;47:595.
85. Kleinkort JA, Wood F. Patients treated with ultrasonic driven hydrocortisone. *Phys Ther* 1975;55:1321.
86. Wing M. Phonophoresis with hydrocortisone in the treatment of temporomandibular joint dysfunction. *Phys Ther* 1982;62:33.
87. Holdsworth LK, Anderson DM. Effectiveness of ultrasound used with a hydrocortisone coupling medium or epicondylitis clasp to treat lateral epicondylitis: pilot study. *Physiotherapy* 1993;79:19.
88. Stratford P, et al. The evaluation of phonophoresis and friction massage as treatments for extensor carpi radialis tendonitis: a randomized, controlled trial. *Physiother Can* 1989;41:93.
89. Kumar VN, Redford JB. Transcutaneous nerve stimulation in rheumatoid arthritis. *Arch Phys Med Rehabil* 1982;63: 595–596.
90. Christian L, Kreczi T, Klingler D. Transcutaneous electrical nerve stimulation in the treatment of chronic pain: predictive factors and evaluation of the method. *Clin J Pain* 1998;14(2): 134–142.
91. Chabal C, Fishbain DA, Weaver M, et al. Long-term transcutaneous electrical nerve stimulation (TENS) use: impact on medication utilization and physical therapy costs. *Clin J Pain* 1998;14(1):66–73.
92. Carroll D, Moore R, McQuay H, et al. Transcutaneous electrical nerve stimulation (TENS) for chronic pain (Cochrane Review). *The Cochrane Library*, Issue 4. Oxford: Update Software, 2001.
93. Fargas-Babjak, A. Acupuncture, transcutaneous electrical nerve stimulation, and laser therapy in chronic pain. *Clin J Pain* 2001;17:S105–S113.
94. Reeve J, Menon D, Corabian P. Transcutaneous electrical nerve stimulation. *Int J Technol Assess Health Care* 1996; 12:299–324.
95. Robinson A. Transcutaneous electrical nerve stimulation for the control of pain in musculoskeletal disorders. *J Orthop Sports Phys Ther* 1996;24:208–226.
96. Sim J, Adams N. Physical and other non-pharmacological interventions for fibromyalgia. *Ballieres Clin Rheumatol* 1999;13(3):507–523.
97. Di Benedetto P, Iona LG, Zidarich V. Clinical evaluation of S-adenosyl-1-methionine versus transcutaneous electrical nerve stimulation in primary fibromyalgia. *Curr Ther Res* 1993; 53:222–229.
98. Brosseau L, Milne S, Robinson V, et al. Efficacy of the transcutaneous electrical nerve stimulation for the treatment of chronic low back pain. *Spine* 2002;27(6):596–603.
99. Rushton DN. Electrical stimulation in the treatment of pain. *Disabil Rehabil* 2002;24(8):407–415.
100. Fishbain DA, Chabal C, Abbott A, et al. Transcutaneous electrical nerve stimulation (TENS) treatment outcome in long-term users. *Clin J Pain* 1996;12:201–214.
101. Lampl C, Kreczi T, Klingler D. Transcutaneous electrical nerve stimulation in the treatment of chronic pain: predictive

factors and evaluation of the method. *Clin J Pain* 1998;14: 134–142.
102. Hanten WP. Effectiveness of a home program of ischemic pressure followed by sustained stretch for treatment of myofascial trigger points. *Phys Ther* 2000;80(10):997–1003.
103. Travell JG, Simons DG. Myofascial pain and dysfunction. *The trigger point manual*, Vol 1. Baltimore, MD: *Williams & Wilkins*, 1983.
104. Thompson JM. The diagnosis and treatment of muscle pain syndromes. In: Braddam R, ed. *Physical medicine and rehabilitation*, Chap. 43. Philadelphia: *WB Saunders*, 2002: 943–955.
105. Cummings TM, White AR. Needling therapies in the management of myofascial trigger point pain: a systematic review. *Arch Phys Med Rehabil* 2001;82(5):986–992.
106. Sciotti VM, Mittak VL, Dimarco L, et al. Clinical precision of myofascial trigger point location in the trapezius muscles. *Pain* 2001;93(3):259–266.
107. Han SC, Harrison P. Myofascial pain syndrome and trigger point management. *Reg Anesth* 1997;22(1):89–101.
108. Ensenyal M, Caglar N, Aldemir T. Treatment of myofascial pain. *Am J Phys Med Rehabil* 2000;79(1):48–52.
109. Buskila D. Fibromyalgia, chronic fatigue syndrome and myofascial pain syndrome. *Curr Opin Rheumatol* 2001; 13(2):117–127.
110. Iwama H, Akama Y. The superiority of water-diluted 0.25% to heat 1% Lidocaine for Trigger point injections in myofascial pain syndrome: a prospective, randomized, double blinded trial. *Anesth Analg* 2000;91(2):408–409.
111. Cohen JH, Gibbons RW. Raymond Nimmo and the evolution of trigger point therapy, 1929-1986. *J Manipulative Physiol Ther* 1998;21(3):167–172.
112. Krishman SK, Benzon HT, Siddigui T. Pain on intramuscular injection of bupivacaine, repivacaine with and without dexamethsone. *Reg Anesth Pain Med* 2000;25(6):615–619.
113. Cummings TM, White AR. Needling therapies in the management of trigger point pain: a systematic review. *Arch Phys Med Rehabil* 2001;82(7):986–982.
114. McMillan AS, Nolan A, Kelly PJ. The efficacy of dry needling and procaines in the treatment of myofascial pain in the jaw muscles. *J Orofac Pain* 1997;11(4):307–314.
115. Chu J. Does EMG (dry needling) reduce myofascial pain symptoms due to cervical nerve root irritation? *Electromyogr Clin Neurophysiol* 1997;37(5):259–272.
116. Baldry P. Superficial versus deep needling. *Acupuncture* 2002;20(2-3):78–81.
117. Baldry P. Management of myofascial trigger point pain. *Acupunct Med* 2002;20(1):2–10.
118. Royal M. Botulinum toxins in pain management. *Phys Med Rehabil Clin N Am* 2003;14:805–820.
119. Porta M. A comparative trail of botulinum toxin type A and methyl prednisolone for the treatment of myofascial pain syndrome and pain from chronic muscle spasm. *Pain* 2000; 85(1-2):101–105.
120. Hong C, Simons DG. Pathophysiologic and electrophysiologic mechanisms of myofascial pain. *Arch Phys Med Rehabil* 1998;79(7):863–872.
121. Smith HS, Audette J, Royal M. Botulinum toxin in pain management of soft tissue syndromes. *Clin J Pain* 2002; 18(Suppl. 6):S147–S154.
122. Childers MK. The importance of electromyographic guidance and electrical stimulation for injection of botulinum toxin. *Phys Med Rehabil Clin N Am* 2003;14:781–792.
123. DeAndres J, Cerda-Olmedo G, Valia JC, et al. Use of botulinum toxin in the treatment of chronic myofascial pain. *Clin J Pain* 2003;19(4):269–275.
124. Hong CZ, Simons DG. Pathophysiologic and electrophysiologic mechanisms of myofascial trigger points. *Arch Phys Med Rehabil* 1998;79(7):863–872.
125. Rivner MH. The neurophysiology of myofascial pain syndrome. *Curr Pain Headache Rep* 2001;5(5):432–440.
126. Lalli F, Gallai V, Tambasco N, et al. Botulinum A toxin versus lidocaine in the treatment of myofascial pain: a double-blind randomized control study. Presented at the International Conference 1999: Basic and Therapeutic Aspects of Botulinum and Tetanus Toxins, Orlando, FL, Nov. 16–18, 1999.
127. Aronoff GM. Myofascial pain and fibromyalgia: a critical assessment and alternate view. *Clin J Pain* 1998;14(1):74–78.
128. 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(11):1161–1166.