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The Pharmacologic Treatment of Muscle Pain

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MYOFASCIAL pain is a significant source of discomfort in individuals with regional pain symptomatology. The prevalence of myofascial pain ranges from around 20% in patients with chronic low back pain (LBP)[1] to 30% in patients with regional pain complaints seen in primary care clinics[2] to upward of 85% in patients presenting to specialized pain management centers.[3]

To understand the origin of myofascial pain, it is first necessary to possess a fundamental understanding of two related concepts, muscle tension and trigger points (TPs). Muscle tension is the product of two distinct factors: viscoelastic tone and contractile activity.[4] Viscoelastic tone can be classified into two parts, elastic stiffness and viscoelastic stiffness. Both of these can be quantified only in the absence of electromyographic activity. Elastic stiffness is a function of distance moved, whereas viscoelastic stiffness considers the effect of velocity.

Contractile activity is composed of three different subunits: contracture (no electromyographic activity), electrogenic spasm (pathologic), and electrogenic stiffness (normal). Contractures originate endogenously within muscle fibers independent of electromyographic activity. *Electrogenic spasm* refers to involuntary, pathologic contractions arising from the electrical activity occurring in alpha motor neurons and motor endplates. *Electrogenic stiffness* refers to muscle tension that derives from electrogenic muscle contraction in individuals who are not relaxed. The latter two terms are associated with measurable electromyographic activity.

Trigger points are defined as taut bands of muscle that produce pain in characteristic reference zones. These taut bands of contracted muscle can be classified into two main types, active TPs and latent TPs, the latter of which is more common. Depending on the pain condition, and even within certain subgroups of soft tissue disorders, muscle pain may be associated with TPs, increased muscle tension, or various combinations of these pathologic processes. Common clinical conditions in which muscle pain is caused primarily by spasm include torticollis, trismus, and nocturnal leg cramps. A painful condition that is defined by the presence of active TPs is myofascial pain syndrome (MPS). Tension headache and temporomandibular disorder (TMD) are conditions that may be associated with both increased muscle tone and TPs.

Other mechanisms and physiologic processes can contribute to muscle pain in addition to tone and TPs. These include but are not limited to increased metabolism or diminished perfusion leading to local ischemia, peripheral and central sensitization, and autonomic hyperactivity.[5,6] Not infrequently, psychogenic factors are found to play a role in soft tissue disorders.[7,8]

Although local anesthetic TP injections have been advocated in the treatment of a wide variety of myofascial pain disorders including tension headache, MPS, TMD, and LBP,[9] these injections are beyond the scope of this review article. Fibromyalgia, which shares some characteristics with myofascial pain but which the authors consider a disorder of sensory processing,[10] will also not be considered. MPS is considered to be a distinct disorder with major and minor diagnostic criteria, and the authors will limit the use of this term to the syndrome outlined by Simons.[11] The term *myofascial pain* is used more broadly and refers to soft tissue pain of unclear etiology.

Study Populations, Limitations, and Search Methods

There are several inherent limitations in a review of the pharmacologic management of muscle pain. First, myofascial pain represents a heterogeneous group of disorders, each characterized by its own unique pathophysiology. There are considerable differences in the mechanisms underlying acute muscle injury such as occurs with muscle tears and succinylcholine-induced myalgia and those responsible for chronic conditions in

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which muscles play a role, such as MPS and TMD. Second, different mechanisms of nociception may exist even within a particular subgroup. For example, in TMD, the primary source of pain is myogenous in some patients and arthrogenous in others. Many clinical investigators have not or perhaps could not distinguish between different pain generators. Other examples of disorders for which this problem exists include LBP and tension-type/muscle contraction headaches. Third, because the category of *muscle pain* itself so broad, so too are the drugs used to treat it. For some agents, such as topical nonsteroidal antiinflammatory drugs (NSAIDs) and quinine, the indications for use are relatively narrow, but for drug classes that act on a broad range of systems, such as antidepressants, their antinociceptive effects are not limited to myofascial pain. Unfortunately, most clinical studies are not capable of distinguishing between pain relief that results from central analgesic effects and those that are due to peripheral mechanisms.

The evidence for involvement (or lack thereof in the case of fibromyalgia) of muscle pain in the most common medical conditions mentioned in this article is reviewed in the appendix. These include fibromyalgia, tension-type headache, MPS, TMD, LBP, and muscle cramps. The studies evaluated were obtained *via* a MEDLINE search from 1966 through March 2004 using the limit *clinical trial* and a bibliographic review of these articles. Only human studies in which muscle seemed to play a significant role in the pathogenesis of pain were considered. Heterogeneous and variable, the study populations for each cited article are outlined in the accompanying tables. For drugs in which there was a lack of controlled trials for muscle pain, uncontrolled studies were considered. This review is neither quantitative (statistical pooling) nor qualitative (best evidence synthesis). Evidence for the efficacy of each drug class in muscle pain was classified as strong, moderate, limited, conflicting, or no evidence. Finally, it must be remembered that pharmacologic treatment is best considered as an adjuvant to a multimodal therapeutic approach when treating muscle pain. The multidisciplinary treatment of myofascial pain should also consider noninvasive treatments such as biofeedback and relaxation training, lifestyle alteration, psychological counseling, alternative treatments such as acupuncture, invasive procedures such as TP injections, and for some conditions, even surgical intervention. Considering these limitations, the purpose of this article is to review the wide range of pharmacologic treatment options available for acute and chronic painful conditions in humans in which muscle pathology is believed to play a significant role.

Mechanisms of Muscle Pain

Unlike cutaneous pain for which there exists a plethora of experimental research and animal models, there is a relative lack of basic science and clinical data available for deep tissue pain, which is more clinically relevant. Muscle pain is generally described as a deep, achy, cramping-like sensation in contrast to the sharp, localized characteristics of cutaneous pain. This pain is often poorly localized by patients. Convergent afferent input from skin, joints, and viscera to the spinothalamic tract and other ascending pain pathways may cause misinterpretation of information arising from Aδ- and C-fiber polymodal muscle nociceptors, as is the case with other types of referred pain.

Pain in response to muscle injury is transmitted by the same basic pathways as those involved for other somatic structures. After a noxious stimulus, an inflammatory response occurs, which results in the accumulation of neuropeptides and inflammatory cells *via* chemotaxis. Release of these peptides results in altered excitability of sensory and sympathetic nerve fibers and the release of chemical mediators. These substances act to sensitize high-threshold nociceptors, a phenomenon known as *peripheral sensitization*. This manifests as spontaneous pain and tenderness after acute muscle injury.

Just as prolonged stimulation of nociceptors can lead to altered pain states (peripheral sensitization), so too can repetitive stimulation of second- and higher-order neurons (central sensitization). In a study by Wright *et al.*[12] assessing the temporal summation of painful stimuli in skin, joint, and muscle, summation was most pronounced in muscle tissue, illustrating the underappreciated role deep tissues play in the development and maintenance of central sensitization. Hyperalgesia may be more likely to occur in small rather than large muscles, which may explain why TMD is so common.[13] Central sensitization may also be responsible for referred pain. Hoheisel *et al.*[14] found that the injection of bradykinin into one muscle in rats unmasked receptive fields in other muscles. These findings may partially explain the phenomenon of referred pain after muscle injury. Peripheral mechanisms are primarily responsible for the pain experienced after acute muscle injury, but central mechanisms are believed to predominate in chronic muscle pain disorders, such as chronic tension-type headache and TMD.

Tricyclic Antidepressants

In the 1960s, clinical studies began to show that tricyclic antidepressants (TCAs) contain analgesic properties independent of their antidepressant effects.[15,16] The effects of TCAs on central and peripheral pathways modulating pain are widespread and profound, extending beyond the modulation of neural transmission by norepinephrine and serotonin reuptake inhibition. For a review of these properties, readers are referred to the work of Eschalier *et al.*[17,18] and Cohen and Abdi.[19]

The pain-relieving properties of TCAs have been extensively studied in a wide array of clinical contexts,

including several disorders involving a myofascial component. In a double-blind, randomized, controlled trial conducted to assess the tertiary amine TCA dothiepin, a sulfur-containing analog of amitriptyline, in 93 patients with chronic atypical facial pain and arthromyalgia, 71% of patients in the treatment group became pain-free after 9 weeks *versus* 47% in the placebo group.[20] At their 1-yr follow-up, 68 (81%) of the 84 patients who elected to continue treatment with the drug were pain free. In a similar study by Sharav *et al.*[21] in 28 patients with chronic facial pain, most of whom had evidence of musculoskeletal dysfunction, the administration of both low-dose ($\leq$ 30 mg) and high-dose ($\leq$ 150 mg) amitriptyline was found to reduce pain intensity significantly compared with placebo. No dose–response relation for analgesia was noted. In an uncontrolled study evaluating the effect of low-dose amitriptyline (10–30 mg) in patients with TMD, subjects in both the myofascial and mixed (both myofascial and joint problems) groups had improved visual analog scale (VAS) pain scores 6 weeks after treatment.[22] At their 1-yr follow-up, pain relief in both groups had significantly declined, with the myofascial patients faring worse than the mixed group. In this study and the study of Sharav *et al.*,[21] scores on the Beck and Hamilton Depression Inventories were reduced in depressed patients but not in nondepressed people during TCA treatment.

Previous studies have shown TCAs to be effective tools in the management of tension headaches.[15,23] In a double-blind, placebo-controlled, three-way crossover study by Bendtsen and Jensen,[24] intermediate doses of amitriptyline (75 mg/day) significantly reduced myofascial scalp tenderness and headache intensity compared with the serotonin-specific reuptake inhibitor citalopram and placebo. Interestingly, amitriptyline had no effect on either pressure or electrical pain thresholds. In summary, there is strong evidence for the use of TCAs in tension-type headaches and facial pain/TMD, which is likely because of the central and peripheral analgesic effects of these drugs. There is no evidence for their use in other myofascial pain conditions (table 1).

Anticonvulsants

Anticonvulsants relieve pain by suppressing abnormal neuronal discharges and increasing the threshold for nerve activation. Different anticonvulsants are effective in different pain contexts, but as a general rule, antiseizure medications are more effective in neuropathic pain states than in acute and chronic nociceptive pain.[25] These neurogenic conditions tend to be characterized by sharp, lancinating pain and electrical-like sensations rather than the dull, aching discomfort typically seen with soft tissue pain.

Chronic daily headache is a clinical condition in which the patient experiences daily or near daily headaches, lasting 4 or more hours, for at least 15 days each month.[26] Studies have shown that a majority of patients with chronic daily headache have at least a component of tension-type headache,[27] a condition many believe involves muscle pathology. In an open-label study evaluating low-dose gabapentin in 21 patients with chronic daily headache, 19% of patients rated the treatment as excellent, 48% rated it as good, and one third rated it as either fair or poor.[28] The outcome measure in this small, uncontrolled, prospective study was "patient impression of change." In a similar, open-label study assessing the use of sodium valproate in 30 patients with persistent chronic daily headaches unresponsive to other interventions, two thirds of patients improved significantly.[29] Commonly experienced adverse effects included weight gain, tremor, hair loss, and nausea.

The effects of gabapentin in chronic pain states were studied by Rosenberg *et al.*[30] in 97 patients with neuropathic pain, 16 patients with chronic LBP, and 9 patients with myofascial pain by means of a retrospective chart review. A significant decrease in VAS pain scores was found in the neuropathic pain group (7.3 to 5.4; $P < 0.0001$) and the myofascial group (7.2 to 6.4; $P = 0.04$) but not the LBP group. Serrao *et al.*[31] evaluated the use of moderate doses (mean peak dose, 892 $\pm$ 180 mg) of gabapentin in an open-label study involving 30 patients with a variety of different diseases who had muscle cramps. Gabapentin was found to have significantly reduced muscle cramps at the first 2-week follow-up visit; by 3 months, cramps had resolved in 100% of patients, an effect that lasted throughout the 6-month treatment period. In the 10 patients who were followed up during the 3-month washout period, the mean number of muscle cramps remained significantly lower than the number of cramps recorded during the qualification phase. In an interesting prospective, randomized trial designed to assess the ability of phenytoin to reduce succinylcholine-induced myalgia, both phenytoin and tubocurarine pretreatment decreased fasciculations, but only phenytoin reduced postoperative myalgia.[32] The evidence for the use of anticonvulsants in muscle pain is extremely limited based on existing studies. The results of mostly uncontrolled studies indicate further research is necessary before any conclusions can be made (table 2).

Skeletal Muscle Relaxants

The mechanism of analgesia for skeletal muscle relaxants is not fully known. Animal studies have shown that skeletal muscle relaxants do not act at the neuromuscular junction, nor do they have any direct effect on skeletal muscle fibers. These drugs are believed to exert their effects primarily within the brain, although some also act at spinal motor neurons. Clinically, skeletal muscle relaxants relieve muscle spasm of local origin without interfering with muscle function.

Not surprisingly, there have been a substantial number of clinical studies evaluating skeletal muscle relaxants in

Table 1. Randomized, Controlled Trials Evaluating Antidepressants in Myofascial Pain Conditions

Study (Year)	Pain Condition	No. of Patients Completing Study	Drugs	Dose, mg/d	Outcome
Lance and Curran[15] (1964) (crossover study for amitriptyline; randomized for multiple other meds)	Tension headache	280 (27 for amitriptyline crossover study)	Amitriptyline Imipramine Multiple other drugs	30–75 30–75	Amitriptyline and imipramine > chlordiazepoxide > placebo. Other drugs including orphenadrine, diazepam, methysergide, and barbiturates were no greater than placebo. 12-mo follow-up period.
Feinmann *et al.*[20] (1984)	Facial arthromyalgia and atypical facial pain	93 with 2 dropouts	Dothiepin	130 (mean)	> Placebo after 9-wk treatment period, after which placebo failure switched to dothiepin
Sharav *et al.*[21] (1987) (crossover study)	Facial pain with myofascial component	28 with 4 dropouts	Amitriptyline	129 (mean)	> Placebo after 4 wk of treatment
Diamond and Baltes[23] (1971)	Tension headache	58 with 27 dropouts	Amitriptyline	10–25	10 mg amitriptyline > 25 mg amitriptyline > placebo after 4-wk treatment period
Bendtsen and Jensen[24] (2000) (crossover study)	Chronic tension-type headache	33 with 7 dropouts	Amitriptyline Citalopram Placebo	75 20	Amitriptyline > citalopram = placebo over 8-wk treatment period
Fogelholm and Murros[231] (1985) (crossover study)	Tension headache	34 with 4 dropouts	Maprotiline	25–75	> Placebo after 3-wk treatment period
Indaco and Carrieri[232] (1988)	Tension headache	31 patients with Parkinson disease, with 5 dropouts	Amitriptyline	25	> Placebo after 12-wk treatment period
Langemark *et al.*[233] (1990)	Tension-type headache	82 with 32 dropouts	Clomipramine Mianserin	75–150 30–60	> Both treatments slightly > placebo during 6-wk treatment period
Sjaastad[234] (1983) (crossover study)	Tension headache	16	Femoxetine	400	> Placebo after 4-wk treatment period
Saper and Silberstein[235] (1994)	Tension-type headache	64	Fluoxetine	40	> Placebo after 16 wk (4 wk without drug + 12-wk treatment period)
Manna *et al.*[236] (1994)	Tension-type headache	40	Mianserin Fluvoxamine	30–60 50–100	> Placebo > placebo after 8-wk treatment period. Fluvoxamine > mianserin in nondepressed patients.
Gobel *et al.*[237] (1994)	Tension-type headache	53 with 25 dropouts	Amitriptyline	75	> Placebo after 6-wk treatment period
Singh and Misra[238] (2002)	Tension-type headache	50 with 10 dropouts	Sertraline	100	No difference in headache index* or frequency during 4-wk treatment phase or 6-wk posttreatment follow-up. Significant reduction in analgesic intake during study.
Pfaffenrath *et al.*[239] (1994)	Tension-type headache	149 with 48 dropouts	Amitriptylineoxide Amitriptyline	60–90 50–75	> Placebo. No difference after 16-wk treatment phase.
Langemark and Olesen[240] (1994) (response-conditional, crossover study)	Tension headache	48 with 2 dropouts	Paroxetine Sulpiride	20–30 200–400	Sulpiride > paroxetine > baseline during 8-wk treatment phase with each medication
Lascelles[241] (1966) (crossover study)	Atypical facial pain	40	Phenelzine	45	> Placebo after 4-wk treatment period
Rizzatti-Barbosa *et al.*[242] (2003)	TMD	12 female patients with 8 dropouts	Amitriptyline	25	> Placebo during 2-wk treatment period and 1-wk follow-up visit

*Headache index is calculated as the product of headache frequency/week × severity of pain × duration of pain.[243]

Headaches classified as *tension type* are based on the definition of the Headache Classification Committee of the International Headache Society.[41]

Placebo-controlled trials are parallel-group studies unless otherwise specified.

TMD = temporomandibular disorder.

Table 2. Clinical Studies Evaluating Anticonvulsants in the Treatment of Myofascial Pain Conditions

Study (Year)	Pain Condition	No. of Patients Completing Study	Drug	Dose, mg/d	Study Design	Outcome
Fragoso and Carrazana[28] (2000)	Chronic daily headache (most with transformed migraine)	21	Gabapentin	1,200	Open label	Improvement (67% good or excellent relief); follow-up ranged from 2 wk to 3 mo
Mathew and Ali[29] (1991)	Chronic daily headache	30	Sodium valproate	1,000–2,000	Open label	Improvement in two thirds of patients during 12-wk treatment period
Rosenberg *et al.*[30] (1997)	Neuropathic, low back, and myofascial pain	97 (19 with myofascial pain)	Gabapentin	600–1,800 in myofascial pain group	Retrospective chart review	Improvement in neuropathic ($P < 0.0001$) and myofascial ($P < 0.05$) pain groups but not LBP
Serrao *et al.*[31] (2000)	Muscle cramps associated with medical illness (50% with neuropathy)	28 plus 2 dropouts	Gabapentin	Mean dose 892 ± 180	Open label	Significant relief noted after 2 wk; by 3 mo, cramps had resolved in 100% of patients
Hatta *et al.*[32] (1992)	Suxamethonium-induced myalgia	60 ASA I patients for minor surgery	Phenytoin	5 mg/kg	Prospective, randomized	Phenytoin pretreatment reduced myalgia compared with control group ($P < 0.05$) up to 72 h after extubation

ASA = American Society of Anesthesiologists (physical status); LBP = low back pain.

myofascial pain conditions. In an often cited study by Brown and Womble[33] comparing cyclobenzaprine to diazepam and placebo in patients with chronic neck and LBP aggravated by muscle spasm, both treatment arms experienced greater pain relief than the placebo group. There were more adverse effects in the cyclobenzaprine group, with the three most common being dry mouth, drowsiness, and dizziness. In two other randomized, placebo-controlled trials assessing the effectiveness of cyclobenzaprine for muscle spasm and pain in the lumbar and cervical spine regions, Bercel[34] and Basmajian[35] both found significant clinical improvement in patients taking the muscle relaxant. Both of these studies used patient self-report and muscle spasm algometry as outcome measures. The magnitude of improvement in the cyclobenzaprine group was found to be greater than with diazepam in the Basmajian study. Follow-up time in both studies was less than 1 month.

Schwartz *et al.*[36] performed a double-blind, placebo-controlled study on the effects of carisoprodol in TMD in one of the oldest studies evaluating muscle relaxants in myofascial pain. Carisoprodol, a precursor of the sedative-hypnotic meprobamate, is purported to produce muscle relaxation by blocking interneuronal activity in the descending reticular formation and spinal cord. In this study, with a follow-up period of 1 week, no difference was found between treatment and control groups. In a double-blind, placebo-controlled trial completed in the early 1970s comparing the sedative/muscle relaxant meprobamate in myofascial pain-dysfunction syndrome (*i.e.*, TMD), Greene and Laskin[37] reported a significant improvement in subjective complaints in patients given meprobamate. In a more recent double-blind, placebo-controlled trial evaluating the effectiveness of adding a nighttime dose of either cyclobenzaprine or clonazepam to a patient education and self-care program in patients with TMD and MPS, cyclobenzaprine was found to be superior to both placebo and clonazepam in the primary outcome measure of jaw pain on awakening.[38] No difference was found in the quality of sleep between groups, and the benzodiazepine clonazepam was no more effective than placebo. In fact, all three groups showed a statistically significant decrease in jaw pain between their pretreatment and posttreatment VAS pain scores, which is consistent with the widely held belief that psychological factors play a role in this disorder. The latter finding is in conflict with other research showing that benzodiazepines are effective for chronic orofacial pain of myogenic origin.[39]

In a meta-analysis reviewing 14 studies on the use of cyclobenzaprine for back pain, Browning *et al.*[40] found the muscle relaxant to be more effective than placebo, especially in the first 4 days of treatment. All 14 studies focused on LBP with muscle spasm, with 5 also includ-

ing data on neck pain. Eleven of the studies considered only patients with acute back pain; 3 studied patients with reports of chronic pain.

There have been numerous clinical studies demonstrating the effectiveness of the muscle relaxant tizanidine in patients with cervical and lumbar pain. In a randomized, double-blind study comparing tizanidine with diazepam in patients with acute paravertebral muscle spasm, tizanidine was found to provide relief comparable with that of diazepam, while being better tolerated.[41] Similar positive results were obtained by Lepisto,[42] who compared tizanidine to placebo in patients with painful muscle spasm after lumbar disk surgery. Results have been mixed for tension-type headaches. A double-blind, placebo-controlled study and an open-label trial both found tizanidine to be an effective treatment for tension-type headaches,[43,44] but another study found no difference between sustained-release tizanidine and placebo.[45]

Spasticity that results from lesions in the central nervous system is a frequent cause of muscle pain. In a Cochrane review of pharmacologic interventions for patients with spinal cord injury–related spasticity,[46] the authors concluded that only intrathecal baclofen, which showed a positive effect in both of two studies analyzed,[47,48] was effective in reducing spasticity. In the largest and only placebo-controlled trial on tizanidine,[49] Ashworth scores measuring spasticity were found to be significantly lower in patients taking the muscle relaxant. A significant reduction was noted only in the early treatment phase for muscle spasm.

In a similar Cochrane review of patients with multiple sclerosis,[50] the authors concluded that no definitive recommendations could be made because of the negative outcomes and poor methodology of the studies analyzed. However, in one of the randomized trials comparing oral baclofen with placebo, a significant reduction in painful muscle spasm and improved range of motion were noted in the baclofen group.[51] No significant reductions in muscle spasm were noted in the two placebo-controlled trials assessing tizanidine.[52,53]

Dantrolene sodium is a muscle relaxant best known for its efficacy in treating malignant hyperthermia, but it has also been shown to be an effective treatment for myalgia. In a double-blind study comparing dantrolene sodium with placebo in 30 athletes with painful muscle contractures, 71% of patients in the treatment group *versus* 21% taking placebo reported decreased muscle pain at rest.[54] These percentages were 79% and 36%, respectively, for movement pain. Similar beneficial effects have been reported in a patient who developed severe muscle spasm after teeth extraction,[55] in patients with muscular dystrophy,[56] and in a randomized, controlled trial evaluating the preoperative use of dantrolene in succinylcholine-induced myalgia.[57] Overall, there is strong evidence for the efficacy of muscle relaxants in muscle spasm involving the cervical and lower lumbar region and in TMD. The evidence is either conflicting (tension headache) or limited (muscle cramps) for other conditions containing a myofascial component (table 3).

5-Hydroxytryptamine Agonists

The analgesic efficacy of drugs that increase serum serotonin concentrations by inhibiting neurotransmitter reuptake has been well documented in a wide variety of pain conditions (see Antidepressants). The analgesic properties of 5-hydroxytryptamine (5-HT) agonists such as sumatriptan, a mainstay of treatment for migraines, have been less studied. Sumatriptan has been shown in clinical studies not only to abort migraines, but also to relieve tension-type headaches.[58,59] The precise mechanisms for this effect are unclear, but it may be due to overlapping etiologies between different types of headaches. That is, although nociception in tension headaches is primarily myofascial, vascular input and even supraspinal facilitation may play a role.[60] In a study by Bono *et al.*[61] evaluating the 5-HT precursor L-hydroxytryptophan in patients with headache, the authors observed a similar therapeutic effect for migraine and tension headaches.

Some researchers have attempted to treat facial pain with sumatriptan because of its modulating effect on nociceptive input in the central nervous system and trigeminal nuclei. In a small (n = 7), randomized, double-blind, placebo-controlled crossover study evaluating oral sumatriptan in myofascial pain of the temporal muscles, both sumatriptan and placebo reduced pain intensity, with no significant differences occurring between groups.[62] Six of the seven patients reported no interest in retaking the medication. In a similarly designed study involving 19 patients with atypical facial pain given 6 mg subcutaneous sumatriptan, Harrison *et al.*[63] found that patients taking sumatriptan showed a small, temporary reduction in sensory pain 120 min after treatment and in the affective manifestations of pain 60 and 120 min after treatment. Eighty-three percent of patients had reactions they considered to be moderate to severe. The high incidence of adverse effects and the small, transient improvement of pain led the authors to conclude that sumatriptan is not an appropriate treatment for atypical facial pain. Interestingly, in a double-blind study comparing the 5-HT_2 antagonist ritanserin to amitriptyline in patients with depression and chronic tension-type headaches, Nappi *et al.*[64] found the two treatments to be comparable. In summary, there is no evidence to support the clinical use of 5-HT agonists in myofascial pain conditions. Even in patients with tension-type headaches, the high incidence of adverse effects, including medication-overuse headaches, precludes its use on a regular basis (table 4).

Table 3. Randomized, Controlled Trials Evaluating Skeletal Muscle Relaxants in Myofascial Pain Conditions (Excluding Spasticity)

Study (Year)	Pain Condition	No. of Patients Completing Study	Drugs	Dose, mg/d	Outcome
Brown and Womble[33] (1978)	Cervical and lumbar spinal pain with superimposed muscle spasm	49	Cyclobenzaprine Diazepam Placebo	30 15	Cyclobenzaprine > diazepam > placebo at 2-wk follow-up
Bercel[34] (1977)	Skeletal muscle spasm of cervical and lumbar spine secondary to osteoarthritis	54	Cyclobenzaprine	30	> Placebo after 2 weeks of treatment for pain, spasm and tenderness. Posttreatment (end of third week), > placebo for spasm but not pain or tenderness.
Basmajian[35] (1978) (two studies)	Skeletal muscle spasm of cervical and lumbar spine	105 with 15 dropouts	Cyclobenzaprine Diazepam Placebo	30–60 15	For clinical efficacy, no difference between groups at 2-week follow-up; for electromyographic measurements: cyclobenzaprine > diazepam or placebo
Schwartz *et al.*[36] (1960)	TMD	34	Carisoprodol	1,400	No difference compared with placebo after 1 wk
Greene and Laskin[37] (1971)	TMD with myofascial pain	90	Meprobamate	400	> Placebo at 5-d follow-up
Herman *et al.*[38] (2002)	TMD with myofascial pain	41	Cyclobenzaprine Clonazepam	10 0.5	Cyclobenzaprine > clonazepam and placebo at 3-wk follow-up
Fryda-Kaurimsky and Muller-Fassbender[41] (1981)	Acute cervical and lumbar paravertebral muscle spasm	20	Tizanidine Diazepam	4–8 5–10	No difference between groups for 14 of 16 variables after 7-day treatment period (tizanidine > diazepam for lateral lumbar flexion)
Lepisto[42] (1981)	Postsurgical paravertebral muscle spasm	50	Tizanidine	12	> Placebo for subjective, not objective, measures during 10-d study
Fogelholm and Murros[43] (1992) (crossover study)	Tension-type headache	37 women with 8 dropouts	Tizanidine	6–18	> Placebo after 6-wk treatment period
Murros *et al.*[45] (2000)	Tension-type headache	160 with 25 dropouts	Tizanidine slow release	6 or 12	No difference in headache reduction between either dose of tizanidine and placebo at 6-wk follow-up
Flacco *et al.*[54] (1989)	Traumatic muscle contractures from sports injuries	28 athletes, 2 dropouts	Dantrolene	50	> Placebo after 4 d of treatment
Hennies[89] (1981)	Cervical and lumbar paravertebral muscle spasm	29 with 1 dropout	Tizanidine Diazepam	12 15	No difference between groups for muscle pain or tension after 7 d; tizanidine > diazepam for tests of lumbar mobility
Franks[244] (1965)	TMD of predominantly myogenous origin	112 with 18 dropouts	Orphenadrine	200	> Placebo after 5 d of treatment
Basmajian[245] (1989)	Posttraumatic paravertebral muscle spasm	175	Cyclobenzaprine Diflunisal Placebo	10 1,000	Combined therapy > cyclobenzaprine, diflunisal, and placebo only on day 4. No difference on day 2 or days 7–10.

(*Table continues*)

Table 3. *Continued*

Study (Year)	Pain Condition	No. of Patients Completing Study	Drugs	Dose, mg/d	Outcome
Larsson *et al.*[246] (1990) (crossover study)	Tension-type headache	48 adolescents with 5 dropouts	Chlormezanone Self-help relaxation	400	Addition of chlormezanone did not help nonresponders in relaxation training during 5-wk treatment period
Borenstein *et al.*[247] (1990) (open label)	Acute (1–10 d) LBP with muscle spasm	40	Naproxen Naproxen and cyclobenzaprine	1,000 1,000 and 30	Combination therapy > naproxen alone after 14 d
Valtonen[248] (1975)	Painful muscle spasms in neck and low back	400	Orphenadrine–paracetamol Orphenadrine Chlormezanone Placebo	105/1,300 200 600	Orphenadrine–paracetamol ≥ orphenadrine > chlormezanone at 1-wk follow-up. No difference between chlormezanone and placebo (53% improved on placebo).
Miller[249] (1976)	Painful muscle conditions in neck and trunk	50	Parafon forte (250 mg chlorzoxazone + 300 mg acetaminophen; McNeil Laboratories, Fort Washington, PA) Soma (carisoprodol + phenacetin; Wallace Laboratories, Cranbury, NJ)	8 tablets/d 8 tablets/d	Parafon forte > Soma on day 2 of therapy, or up to 2 wk in nonresponsive patients
Vernon[250] (1972)	Back pain, mostly "acute lumbosacral muscle strain"—three separate studies	53	Study 1: Parafon forte (250 mg chlorzoxazone + 300 mg acetaminophen) Chlorzoxazone Placebo Each group also received PT	8 tablets/d 2,000	Parafon forte ≥ chlorzoxazone or placebo by day 10
		59 with 1 dropout	Study 2: Chlorzoxazone Placebo No patient received PT	3,000	Chlorzoxazone > placebo during 10-d trial
		66	Study 3: Parafon forte Chlorzoxazone Acetaminophen No group received PT	8 tablets/d 3,000 2,400	Parafon forte > chlorzoxazone or placebo during 7-d observation period
Scheiner[251] (1972)	LBP associated with muscle spasm	189 with 3 dropouts	Parafon forte Chlorzoxazone Acetaminophen Placebo	4 tablets/d 1,500–3,000 1,200	Parafon forte > chlorzoxazone > acetaminophen, mean duration of treatment 6½ d. No difference between acetaminophen and placebo.
Atkinson[252] (1979)	Tension headache	88	Solpadeine (500 mg paracetamol + 8 mg codeine + 30 mg caffeine; Winthrop Laboratories, New York, NY) + placebo Solpadeine + chlormezanone	2 tablets 2 tablets 200 mg	Solpadeine + chlormezanone slightly better than Solpadeine + placebo ($P > 0.05$) at 4-h follow-up
Diamond[253] (1966)	Muscle spasm	100	Metaxalone	3,200	> Placebo after 10-d treatment period
Perchuk *et al.*[254] (1961) (partial crossover study)	Nocturnal leg cramps	27	Methocarbamol	Variable	> Placebo during 18-mo follow-up

(*Table continues*)

Calcium Channel Blockers

Calcium channels of the N, P, and Q types have all been implicated in pain perception. Of these, the best studied is the N-type calcium channel, localized to terminals on sensory nerve fibers. In clinical studies, both N- and L-type calcium channel blockers have been

Table 3. *Continued*

Study (Year)	Pain Condition	No. of Patients Completing Study	Drugs	Dose, mg/d	Outcome
Turturro *et al.*[255] (2003)	Acute myofascial strain	77 with 25 dropouts	800 mg ibuprofen + 10 mg cyclobenzaprine 800 mg ibuprofen	1–3 tablets of each 1–3 tablets	No difference between treatment groups for pain over 48-h observation period, but combination group experienced more side effects
Borenstein and Korn[256] (2003) (two studies)	Acute skeletal muscle spasm	1,389 with 133 dropouts	Cyclobenzaprine Placebo	7.5, 15, or 30	30 mg cyclobenzaprine = 15 > 7.5 cyclobenzaprine or placebo over 7-d study period
Tuzun *et al.*[257] (2003)	Acute LBP with muscle spasm	137 with 12 dropouts	Thiocolchicoside Placebo	8 mg intramuscular	> Placebo for pain relief and muscle tenderness over 5-d treatment period. For range of motion, thiocolchicoside ≥ placebo.

LBP = low back pain; PT = physical therapy; TMD = temporomandibular disorder.

shown to produce analgesia when injected neuraxially.[65–67]

There have been few clinical studies assessing calcium channel blockers in myofascial pain. In two open-label trials, the calcium antagonist flunarizine was shown to be an effective treatment over a 6-month period in patients with migraine interval headache (*i.e.*, transformed migraine), a headache that frequently contains a significant myofascial component.[68,69] However, in a double-blind crossover study evaluating the effect of the calcium channel blocker nifedipine in the prophylaxis of migraine and tension headaches, whereas 71.4% of the migraineurs obtained a satisfactory response, only 28.6% of the patients with tension headaches experienced significant relief of symptoms (P = NS).[70]

Muscle cramps can be a considerable source of discomfort, especially in patients undergoing hemodialysis. In a randomized, controlled, double-blind trial evaluating nifedipine in 19 hemodialysis patients with muscle cramps, Peer *et al.*[71] found that patients in the nifedipine group obtained significant pain relief. In an open-label trial evaluating verapamil in elderly patients with nocturnal leg cramps unresponsive to quinine sulfate, Baltodano *et al.*[72] reported relief in seven of eight patients. In short, there is no evidence for the use of calcium channel blockers in the treatment of soft tissue disorders other than muscle cramps, for which the evidence is limited (table 4).

α-Adrenergic Antagonists

In healthy subjects, muscle blood flow increases in response to stressful events,[73] a phenomenon that can be further enhanced by the administration of an α-blocking agent.[74] To determine whether muscle perfusion similarly increases in patients with myofascial pain, Acero *et al.*[75] compared the intramuscular hemodynamic changes in response to a cold pressor stimulus between patients with chronic trapezius muscle pain and control subjects. The authors found a significant decrease in muscle perfusion in the patients with muscle pain when compared with control subjects, a finding supported by other investigators.[76] This may indicate an impaired ability to vasodilate intramuscular vasculature in these patients.

The analgesic effects of drugs affecting the sympathetic nervous system have not been extensively studied in humans. Denaro *et al.*[77] conducted a double-blind, placebo-controlled study comparing the efficacy of the α_2 agonist clonidine with the tetracyclic antidepressant mianserin, a drug possessing significant α-adrenergic blocking activity, in patients with tension and migraine headaches. The investigators found that whereas mianserin decreased headache frequency and intensity in both groups at 90 days (in the migraine group, headache frequency was increased during the first 30 days), clonidine decreased headache intensity only in migraine patients.

Following up on a previous study indicating that head-up tilt in hemodialysis patients with frequent muscle cramps results in greater increases in plasma norepinephrine concentrations than in patients with infrequent cramps,[78] Sidhom *et al.*[79] evaluated the effect of administering low-dose prazosin at the start of hemodialysis in a double-blind, placebo-controlled crossover trial. The authors demonstrated that patients experienced a 58% reduction in muscle cramping when pretreated with prazosin (P = 0.03). Not surprisingly, intradialytic hypotension was noted to occur more frequently after administration of prazosin. In summary, there is no clinical evidence supporting the use of sympathetic blocking agents in myofascial pain (table 4).

Table 4. Randomized, Controlled Studies Evaluating Calcium Channel Blockers, 5-Hydroxytryptamine Agonists, and Sympatholytics in Myofascial Pain Conditions

Study (Year)	Pain Condition	No. of Patients Completing Study	Drugs	Dose, mg/d	Outcome
Brennum *et al.*[58] (1992) (crossover study)	Tension-type headache	36 with 6 dropouts	Sumatriptan	2 and 4 mg subcutaneous injection	> Placebo for both 2- and 4-mg groups after 2 h. No difference between treatment groups.
Dao *et al.*[62] (1995) (crossover study)	Myofascial pain of temporalis muscles	7 women	Sumatriptan	100–200	No significant difference between sumatriptan group and placebo for 4 h after treatment. Six of 7 patients said they would not take medication again.
Harrison *et al.*[63] (1997) (crossover study)	Atypical facial pain without sensory deficit	17 with 2 dropouts	Sumatriptan	6 mg subcutaneous injection	Small temporary decrease in pain in treatment group at 2 h after treatment. Most patients in both groups considered the treatment ineffective.
Micieli *et al.*[69] (1985) (two studies: flunarizine open-label study and indoprofen double-blind, crossover study)	Migraine interval headache and chronic tension headache	40 in flunarizine study with 2 dropouts; 26 in indoprofen study with 4 dropouts	1. Flunarizine 2. Indoprofen Placebo	10 600	1. Flunarizine effective in 65% of patients over 6 mo 2. Indoprofen > placebo for migraine interval headache but not chronic tension over 30-d treatment phase
Shukla *et al.*[70] (1995) (crossover study)	Migraine and tension-type headache	28 patients each with tension and migraine headache (4 dropouts in tension headache and 8 in migraine group)	Nifedipine	15	No difference between nifedipine group and placebo for tension headaches after 4 wk of treatment; for migraine headaches, nifedipine > placebo
Peer *et al.*[71] (1983) (crossover study)	Hemodialysis-induced muscle cramps	19	Nifedipine	10–20	Nifedipine > placebo during dialysis
Denaro *et al.*[77] (1985)	Histamine-induced migraine and tension headache	20 patients each with migraine and tension headache	Clonidine Mianserin	0.15 30	Mianserin but not clonidine decreased headache frequency and intensity in tension headache patients at 90-d follow-up
Sidhom *et al.*[79] (1994) (crossover study)	Hemodialysis-induced muscle cramps	5	Prazosin	0.25–1.0	Prazosin > placebo during dialysis sessions for 16-wk trial; treatment group also had higher incidence of hypotension
Lipton *et al.*[258] (2000) (crossover study)	Headache	215 migraineurs with a variety of headaches, with 34 dropouts	Sumatriptan	50	> Placebo for all headache types including tension 4 h after treatment

Opioids and Tramadol

The importance of peripherally located receptors in mediating analgesia by opioids is becoming better appreciated,[80] but the predominant pain-relieving effects of these drugs are still widely believed to reside in the central nervous system. Some opioids, such as methadone, which inhibits the reuptake of serotonin and norepinephrine and acts as an antagonist at *N*-methyl-D-aspartate (NMDA) receptors, exhibit additional analgesic properties not mediated through opioid receptors.[81]

Tramadol is an orally and parenterally active binary analgesic that possesses opioid and nonopioid mechanisms of action. Tramadol binds with modest activity to mu opioid receptors, with an affinity approximately 1/6,000 that of morphine. The drug has even weaker affinity for κ and σ receptors. In addition to its opioid properties, tramadol also weakly inhibits the reuptake of serotonin and norepinephrine. The opioid and nonopioid mechanisms of tramadol interact synergistically to relieve pain.[82]

There have been few studies assessing the efficacy of opioids in myofascial pain states and none involving tramadol. However, clinical studies support its efficacy in chronic LBP, a disorder that often contains a myofascial component, and fibromyalgia, a syndrome bearing clinical similarities to MPS.[83,84]

Table 5. Randomized, Controlled Trials Evaluating Opioids in Myofascial Pain Conditions

Study (Year)	Pain Condition	No. of Patients Completing Study	Drugs	Dose, mg/d	Outcome
Moulin *et al.*[85] (1996) (crossover study)	Regional pain of a myofascial, musculoskeletal, or rheumatic nature	46 with 15 dropouts	Morphine Benztropine	83.5 (mean) 1.7 (mean)	MSO_4 > benztropine for analgesia at end of 6-wk evaluation; no difference between treatments for functional improvement
List *et al.*[86] (2001)	Temporomandibular disorder	53	Morphine	1 or 0.1 intraarticular injection	0.1 mg MSO_4 injection > 1.0 mg MSO_4 or placebo at 5-d follow-up
Friedman[87] (1986)	Tension headache associated with muscle contraction in neck and shoulders	51 with 3 dropouts	Fiorinal (butalbital 50, caffeine 40, aspirin 200, phenacetin 130) + codeine (30 mg; Sandoz Pharmaceuticals, East Hanover, NJ) Fiorinal 30 mg codeine Placebo	4 tablets (2 tablets each for two headaches within 24 h)	Fiorinal + codeine > codeine ≥ Fiorinal > placebo over 4-h evaluation period
Harden *et al.*[88] (1998)	Tension-type headache	41	Intramuscular ketorolac Intramuscular meperidine + Intramuscular promethazine Placebo	60 50 + 25	Ketorolac > meperidine = placebo 2 h after treatment

In a randomized, double-blind crossover trial, Moulin *et al.*[85] examined the effect of sustained-release morphine *versus* an active placebo on pain and quality of life in 46 patients with chronic regional pain of soft tissue or musculoskeletal origin (excluding headache patients) who had not benefitted from previous trials with NSAIDs, TCAs, and codeine. The authors found that whereas morphine was more effective at relieving pain than benztropine, it did not yield any psychological or functional improvement. In this study, all patients were compliant with their medication regimens, and none exhibited drug-seeking behavior. List *et al.*[86] assessed the effect of 1.0- and 0.1-mg intraarticular morphine injections *versus* saline in a randomized, double-blind, placebo-controlled study involving 53 patients with temporomandibular joint (TMJ) arthralgias or arthritis. The authors found a significant decrease in VAS pain score at maximum mouth opening 5 days after the injection in the 0.1-mg group but not the 1.0-mg group. Although statistically significant, this diminution in pain score was not clinically relevant. In the immediate postinjection period, pain was reduced in all treatment groups, without a significant difference between them. In a randomized, double-blind, placebo-controlled, multicenter study involving 51 patients with chronic tension headache, Friedman[87] compared Fiorinal (Sandoz Pharmaceuticals, East Hanover, NJ) with codeine to each medicine individually and a placebo control group up to 4 h after ingestion. The combination medication was found to be better than each medication alone, which in turn were superior to placebo for both pain relief and the ability to perform activities of daily living. The authors did not statistically analyze the results for codeine *versus* Fiorinal, but the codeine group seemed to fare slightly better. This is in contrast to a randomized, double-blind trial by Harden *et al.*,[88] who found intramuscular ketorolac to be more effective in the treatment of tension headache than intramuscular meperidine and promethazine. Patients receiving the combination opioid–antihistamine treatment fared no better than those given placebo. When analyzing studies comparing drug combinations, caution must be used in extrapolating the results to conclusions about individual medications, given the drug interactions and other factors that are not controlled for. In summary, the evidence to support the use of tramadol or opioids in the treatment of any myofascial pain condition is extremely limited and conflicting (table 5).

Benzodiazepines

In the late 1970s and early 1980s, several studies were published comparing diazepam to the muscle relaxants cyclobenzaprine and tizanidine for cervical and lumbar paravertebral muscle spasm.[33,35,41,89] In the two studies comparing cyclobenzaprine to diazepam, one showed no clinical difference between the treatment groups,[35]

whereas the other found cyclobenzaprine to be superior to diazepam, which in turn was noted to be better than placebo.[33] The two studies that compared diazepam to tizanidine demonstrated no differences with regard to pain, activities of daily living, or patient self-assessment, but patients in the tizanidine groups had better range of motion in the lumbar spine.[41,89]

Animal and human studies have shown the short-acting benzodiazepine midazolam to possess antinociceptive properties in experiments involving induced facial pain.[90,91] In a randomized, double-blind study comparing diazepam, ibuprofen, the combination of the two agents, and placebo in 39 patients with chronic myofascial orofacial pain, statistical analysis revealed only diazepam to be an effective analgesic.[92] The efficacy of diazepam in the treatment of TMD has been demonstrated in other clinical trials as well.[93,94]

In a double-blind, placebo-controlled study undertaken in 20 patients with chronic TMD and myofascial pain unresponsive to conservative treatment, Harkins *et al.*[95] compared low doses of the long-acting benzodiazepine clonazepam with an inactive placebo. Five patients (50%) in the clonazepam group dropped out after 30 days because their symptoms had improved significantly and they did not want to continue on medications. In contrast, seven patients (70%) dropped out of the placebo group after 30 days because they experienced no improvement. The high percentage of dropouts in each group precluded a 60-day assessment, but the authors concluded that low-dose clonazepam may be effective in the relief of TMD and head/neck myalgia. In a randomized, double-blind, placebo-controlled crossover trial evaluating triazolam in patients with TMD, DeNucci *et al.*[96] demonstrated that although triazolam improved sleep, it did not reduce pain or nocturnal masticatory muscle activity compared with placebo.

There have been several studies assessing the effectiveness of benzodiazepines to prevent or reduce the incidence of succinylcholine-induced myalgia after general anesthesia. The results of these trials have been conflicting. Pretreatment with diazepam was shown to reduce the incidence of succinylcholine-induced muscle pain in four of these studies.[97–100] However, in several later randomized, controlled studies, pretreatment with neither midazolam nor diazepam was found to affect the incidence of fasciculations and postoperative muscle pain.[101–103]

Benzodiazepines have also been studied in the treatment of muscle contraction headache. A randomized, double-blind, placebo-controlled crossover study comparing alprazolam to placebo in 48 patients with chronic tension headache demonstrated that alprazolam reduced the intensity but not the frequency of headaches.[104] In contrast to other benzodiazepines, alprazolam possesses some antidepressant activity. In a single-blind crossover study, Weber[105] treated 19 patients with muscle contraction headache with 10–15 mg of either diazepam or placebo. Eighteen of the 19 patients reported no change with placebo. In the treatment limb, 12 of 19 reported "great" improvement, with another 4 reporting "mild" improvement in symptoms. Several months later, 13 of the 18 patients who continued to take diazepam reported persistent pain relief and anxiolysis. A double-blind, placebo-controlled study by Hackett *et al.*[106] assessing diazepam and flupentixol in 70 patients with muscle contraction headache found both treatments to be better than placebo. Lastly, Paiva *et al.*[107] compared electromyographic biofeedback with diazepam in 36 patients with chronic muscle tension headaches in a double-blind study using both placebo pills and sham electromyographic biofeedback. The authors concluded that both treatments were superior to placebo, although only in the diazepam group was the difference statistically significant ($P < 0.05$; diazepam > biofeedback ≥ placebo). However in the 4-week follow-up period, the biofeedback patients continued to experience a reduction in the frequency and intensity of headaches, whereas the decrease observed in the diazepam group disappeared. In summary, there is conflicting evidence to support the use of benzodiazepines in TMD and tension-type headaches. The evidence for their effectiveness in muscle spasm is moderate, but their adverse effect profile and clear-cut inferiority when compared to traditional muscle relaxants precludes their routine use to treat this condition (table 6).

N-*methyl-D-aspartate Antagonists*

N-methyl-D-aspartate receptor antagonists have been shown to possess analgesic properties in numerous studies involving both neuropathic and acute pain syndromes. There are several mechanisms by which NMDA glutamate antagonists are purported to exert their antinociceptive effects. These include the prevention and possibly even reversal of central sensitization and "windup," reducing tolerance to opioids, synergistic analgesic effects with opioids, and preemptive analgesia when administered in a timely fashion.[108–110] The excitatory neurotransmitter glutamate elicits spontaneous pain and a reduction in pressure-pain thresholds, consistent with allodynia, when injected into human masseter muscle.[111] This glutamate-evoked pain response was previously found to be greater in women than in men, which may explain the higher prevalence of some muscle pain conditions in female patients.[112] NMDA glutamate receptor antagonists available for clinical use in the United States include ketamine, dextromethorphan, methadone, d-propoxyphene, amantadine, and memantine. There are no clinical studies evaluating the effects of NMDA blockers in myofascial pain conditions.

Table 6. Randomized, Controlled Trials Evaluating Benzodiazepines in Myofascial Pain Conditions

Study (Year)	Pain Condition	No. of Patients Completing Study	Drugs	Dose, mg/d	Outcome
Herman *et al.*[38] (2002)	TMD	41	Cyclobenzaprine Clonazepam	10 0.5	Cyclobenzaprine > clonazepam and placebo at 3-wk follow-up
Singer and Dionne[92] (1997)	Chronic orofacial muscle pain	35 females, 4 men, with 10 dropouts	Diazepam Ibuprofen	20 2,400	Diazepam > ibuprofen or placebo after 4-wk treatment period
Jagger[93] (1973)	TMD	50 with 11 dropouts	Diazepam	15 mg, changed to 6 mg after first 10 patients	> Placebo at 1 wk follow-up in patients with "mechanical" TMD (rather than unknown etiology)
Harkins *et al.*[95] (1991)	TMD with disc dislocation and myofascial pain	7 with 13 dropouts	Clonazepam	Mean dose of 0.375 before bedtime, with 1 mg maximum	> Placebo after 30 d
DeNucci *et al.*[96] (1998) (crossover study)	TMD of musculoskeletal origin	20	Triazolam	0.5 before bedtime	No difference between triazolam and placebo for pain or nocturnal muscle activity after 4 nights of treatment
Shukla *et al.*[104] (1996) (crossover study)	Tension-type headache	62 with 14 dropouts	Alprazolam	0.75	> Placebo for headache index after 4-wk treatment period.* No difference between alprazolam and placebo for headache frequency.
Weber[105] (1973) (single-blind, crossover study)	Muscle contraction headache	19	Diazepam	10–15	> Placebo after 3-wk treatment period
Hackett *et al.*[106] (1987) (crossover study)	Tension headache	55 with 15 dropouts	Diazepam Flupenthixol	10 1	Flupenthixol ≥ diazepam > placebo after 12-wk treatment period
Paiva *et al.*[107] (1982)	Muscle tension headache	32 with 4 dropouts	Diazepam Electromyographic biofeedback False biofeedback Placebo	Not listed 4 weeks, 12 sessions	During 4-wk treatment period, diazepam > biofeedback > false biofeedback > placebo. During 4-wk follow-up, true biofeedback > false biofeedback > diazepam or placebo.
Roldan *et al.*[259] (1990)	TMD	41 with 19 dropouts	Diazepam Piroxicam	2 mg 20 mg	No difference between diazepam, piroxicam, or placebo after 15 treatment days

* Headache index is calculated as the product of headache frequency/week × severity of pain × duration of pain.

TMD = temporomandibular disorder.

Nonsteroidal Antiinflammatory Drugs

Nonsteroidal antiinflammatory drugs are the most commonly used medications in the treatment of myofascial pain. Their primary mechanism of action seems to be inhibition of the rate-limiting enzyme complex cyclooxygenase (COX), which in turn results in the reduced synthesis of prostaglandins in the periphery. Prostaglandins are substances involved in a wide range of physiologic activities, one of which is the sensitization of nociceptors. Evidence has accumulated showing that NSAIDs also act to inhibit prostaglandin production in the central nervous system, where they can modulate neurotransmitter release. In the late 1990s, several COX-2–specific inhibitors were introduced that only minimally interfere with the protective effects of prostaglandins on stomach mucosa and platelet function. These drugs have not been tested in disorders involving muscle pain. Recently, a COX-3 isoenzyme has been identified that is thought to be the target of antipyretic/analgesic drugs such as phenacetin and acetaminophen.[113–115]

Although NSAIDs are devoid of any direct effect on skeletal muscle contraction, they are frequently used as a first-line treatment for conditions involving muscle pain. Not all clinical research supports their efficacy in

these disorders. For exercise-induced muscle soreness, the efficacy of NSAIDs is supported by some studies[116] but refuted by others.[117,118]

Because the predominant site of action of NSAIDs lies in the periphery, it is no surprise that topical administration of this class of drugs has been shown in several randomized, double-blind studies to be an effective treatment for soft tissue injuries.[119–123] NSAIDs have also been shown to relieve muscle pain when delivered *via* phonophoresis[124] and, in one study, to be more effective than lidocaine when injected into TPs.[125] An interesting double-blind, placebo-controlled study comparing the effects of topical diclofenac with placebo on thigh soft tissue pain induced by electrical stimulation in male volunteers was conducted by Affaitati *et al.*[126] The results demonstrated that whereas no significant changes were noted in skin or subcutaneous thresholds in either group, muscle pain thresholds were significantly increased with diclofenac compared with placebo. This suggests that NSAIDs may have specific antinociceptive effects on algogenic conditions involving muscle.

For tension-type headaches, NSAIDs have become a consensus first-line treatment. In numerous randomized, controlled trials, this class of medications has been shown to reduce headache intensity[88,127,128] and even frequency when given in regular dosing schedules.[128] When taken in around-the-clock dosing schedules, rapid withdrawal of NSAIDs can lead to rebound headaches. NSAIDs with significant antiinflammatory effects have been shown to provide more effective pain relief than paraaminophenol analgesics largely devoid of these properties, such as acetaminophen or phenacetin.[129–132]

For TMD, NSAIDs have not been well demonstrated to be effective analgesics. In a double-blind, placebo-controlled study evaluating piroxicam in 26 patients with TMD, van den Berghe *et al.*[133] found no difference between the experimental and control groups on spontaneous pain, palpation-induced tenderness, joint noise, or range of motion. A similar negative outcome for ibuprofen was obtained in a placebo-controlled trial by Singer and Dionne.[92]

Ekberg[134] compared diclofenac to placebo in a series of studies conducted in patients with TMD. There was a trend toward greater improvement in the diclofenac group compared with placebo (50% *vs.* 32% of the 32 patients), but this effect did not reach statistical significance. Finally, in patients with TMJ osteoarthritis, Thie *et al.*[135] compared a midrange dose of ibuprofen (1,200 mg/day) with glucosamine sulfate (1,500 mg/day) for 90 days in a randomized, double-blind study. Within-group analysis revealed significant improvement from baseline in both treatments, with no significant differences between groups. However, from day 90 to day 120 (30 days after the cessation of treatment), between-group comparison revealed the patients in the glucosamine group to have significantly less TMJ pain than the patients who had taken ibuprofen. This result is not surprising, considering the contrasting effects the two treatments have on proteoglycan synthesis and the continued therapeutic benefit of glucosamine for weeks after discontinuation.[136–139] Previous reviews have also found little scientific support for the use of NSAIDs in patients with chronic temporomandibular pain.[140,141]

There are few studies assessing the effects of NSAIDs in the treatment of muscle spasm. In a single-blind crossover study comparing the muscle relaxant chlormezanone, chlormezanone plus aspirin, and placebo in patients with painful muscle spasm, the combination group was found to produce better relief than the group receiving chlormezanone alone, which in turn fared better than the placebo group.[142] There are several double-blind studies showing the efficacy of NSAIDs in acute LBP, including one demonstrating similar efficacy but fewer adverse effects than opioids and another involving a COX-2 selective inhibitor, but in none of these studies was the precise cause of pain noted.[143–145]

There have been several attempts to assess the ability of NSAIDs to prevent or reduce succinylcholine-induced myalgia. Naguib *et al.*[146] compared lysine acetyl salicylate to the muscle relaxant atracurium 3 min before paralysis. Both groups were found to have a lower incidence and intensity of postoperative myalgia than the control group, with no significant differences between treatment arms. In two follow-up studies, the effect of NSAIDs administered before the induction of anesthesia on the incidence of succinylcholine-induced myalgia were mixed.[147,148] Overall, there is strong evidence to support the use of NSAIDs in tension headache, with drugs containing antiinflammatory properties being more effective than acetaminophen. There is no evidence to support their use in TMD. The evidence supporting the use of NSAIDs for other myofascial pain conditions is limited (muscle spasm and succinylcholine-induced myalgia) to moderate (acute soft tissue injury) (table 7).

Botulinum Toxins

Clostridum botulinum is a gram-positive anaerobic bacteria that produces seven different toxins, of which serotype A (BTX-A) is best known. Botulinum toxins (BTXs) exert their toxic and therapeutic effects by binding to the presynaptic membrane of the motor end plate, thereby blocking the release of acetylcholine without affecting nerve conduction or the synthesis and storage of neurotransmitter. The first use of BTX-A was in the treatment of strabismus.[149] In the late 1980s, controlled trials began to appear showing that BTX-A was effective in reducing pain associated with conditions characterized by muscle hyperactivity, such as spasmodic torticollis.[150] Animal studies have recently suggested that BTXs may exert antinociceptive effects independent of its ef-

Table 7. Randomized, Controlled Trials Evaluating Nonsteroidal Antiinflammatory Drugs and Nonacidic Antipyretics in Myofascial Pain Conditions

Study (Year)	Pain Condition	No. of Patients Completing Study	Drugs	Dose, mg/d	Outcome
Baixauli *et al.*[119] (1990)	Acute soft tissue injury	30	Naprosyn gel Ketoprofen gel	10% twice daily 10% twice daily	Naprosyn gel = ketoprofen gel. By third day of 7-d treatment, naprosyn gel > ketoprofen gel for deep palpation pain.
Machen and Whitefield[120] (2002)	Acute soft tissue injury	84 with 4 dropouts	Ibuprofen gel Placebo gel	5%	Ibuprofen gel > placebo after 7-d treatment period
Shin and Choi[124] (1997)	TMD	20	Indomethacin phonophoresis	1% cream applied *via* ultrasound daily	Indomethacin phonophoresis > placebo after 2 d
Frost[125] (1986)	Localized myofascial pain	24	Diclofenac injection Lidocaine injection	50 mg (2 ml) 20 mg (2 ml of 1% solution)	Diclofenac > lidocaine during 5-h treatment period
Lange and Lentz[127] (1995)	Tension-type headache	345	Ketoprofen Ibuprofen Naprosyn	12.5 or 25 200 275	No differences between the four treatment groups during 4-h treatment period
Mongini *et al.*[128] (1993) (crossover study)	Headache and craniofacial pain	18 with 2 dropouts	Meclofenamate	200	Meclofenamate > placebo over 15-d treatment period
Steiner and Lange[129] (1998)	Episodic tension-type headache	300 with 48 dropouts	Ketoprofen Acetaminophen Placebo	25 1,000	Ketoprofen ≥ acetaminophen > placebo after 4 h
Packman *et al.*[130] (2000)	Episodic tension-type headache	154	Solubilized ibuprofen Acetaminophen Placebo	400 1,000	Solubilized ibuprofen provided faster and better pain relief than acetaminophen, which was superior to placebo (single-dose study)
Schachtel *et al.*[131] (1996)	Tension-type headache	151	Ibuprofen Acetaminophen Placebo	400 1,000	Ibuprofen > acetaminophen > placebo (single-dose study)
Mehlisch *et al.*[132] (1998)	Tension-type headache	631 with 72 dropouts	Ketoprofen Acetaminophen Placebo	12.5 or 25 1,000	Only 25 mg ketoprofen > placebo over 4-h observation period ($P < 0.05$). Ketoprofen 25 ≥ Ketoprofen 12.5 ≥ acetaminophen ≥ placebo (P = NS).

(*Table continues*)

fect on muscle, possibly by inhibiting inflammatory pain, blocking the release of glutamate, and reducing concentrations of substance P.[151–154] Evidence for the independent antinociceptive effects of BTX include the observation that injections often reduce pain before the decrease in muscle contraction and their beneficial effects in painful conditions not mediated through muscles.[154,155]

There are dozens of studies assessing BTX in muscle pain. Some of the earliest ones involved cervical dystonia, a disorder characterized by involuntary, patterned contractions of cervical or shoulder muscles or both,

Table 7. *Continued*

Study (Year)	Pain Condition	No. of Patients Completing Study	Drugs	Dose, mg/d	Outcome
van den Berghe *et al.*[133] (1986)	TMD	26 with 14 dropouts	Piroxicam + conventional treatment (occlusal adjustment, physiotherapy, bite plane, soft diet) Conventional treatment + placebo	20	No difference between groups for overall clinical subjective and dysfunction index (spontaneous pain, pain with function, muscle palpation pain, opening range, and joint noises). For subjective pain scores, piroxicam + conventional group > conventional group > conventional group + placebo. Treatment group received piroxicam for 8 wk and conservative treatment from weeks 10 to 18.
Ekberg[134] (1998)	TMD of predominantly arthrogenous origin	32	Diclofenac	150	No overall difference between diclofenac and placebo at 4-wk follow-up. Diclofenac > placebo for frequency of daily TMD pain and tenderness of masticatory muscles.
Thie *et al.*[135] (2001)	Temporomandibular joint osteoarthritis	39 with 6 dropouts	Ibuprofen Glucosamine	1,200 1,500	During the 90-day treatment period, there were no differences between glucosamine and ibuprofen. From day 90–day 120, glucosamine > ibuprofen (carryover effect).
Woolsey *et al.*[142] (1966) (single-blind, crossover study)	Pain associated with spasm of large muscle groups	22	Chlormezanone 100 mg tablets chlormezanone 100 mg + aspirin 300 mg combined tablets Placebo	4 tablets/day 4 tablets/day	Chlormezanone + aspirin > chlormezanone > placebo after 3 d of treatment
Martinez-Martin *et al.*[213] (2001)	Episodic tension-type headache	360 with 57 dropouts	Metamizol ASA Placebo	500 or 1,000 1,000	1 g metamizol = 0.5 g metamizol > ASA > placebo over 4-h study period

(*Table continues*)

Table 7. *Continued*

Study (Year)	Pain Condition	No. of Patients Completing Study	Drugs	Dose, mg/d	Outcome
Bouchier-Hayes *et al.*[260] (1990)	Acute soft tissue injury	384	Diclofenac gel Felbinac gel	4 g three times daily 4 g three times daily	Diclofenac gel > felbinac gel during 7-d treatment period
Birch and Jamison[261] (1998)	Chronic myofascial neck pain	36 with 10 dropouts	Japanese acupuncture Sham acupuncture Trilisate	NA	Real acupuncture > sham acupuncture > trilisate 3 mo after cessation of treatment
Prior *et al.*[262] (2003)	Tension-type headache	900 with 15 dropouts	Acetaminophen Naproxen Placebo	1,000 375	Acetaminophen and naproxen > placebo over 6-h study period. Acetaminophen > naproxen at 1 h.
Kubitzek *et al.*[263] (2003)	Episodic tension-type headache	620 with 64 dropouts	Diclofenac Ibuprofen Placebo	12.5 or 25 400	All three treatment groups > placebo over 6-h study period
Steiner *et al.*[264] (2003)	Tension-type headache	348 with 48 dropouts	500 or 1 g ASA 500 or 1 g paracetamol Placebo	1 dose	ASA ≥ 1 g paracetamol and 500 mg ASA > 500 mg paracetamol ≥ placebo at principal efficacy endpoint of 2 h

ASA = acetylsalicylic acid; GS = glucosamine sulfate; NA = not applicable; NS = not significant; TMD = temporomandibular disorder.

resulting in abnormal head postures sometimes associated with repetitive, rhythmic, jerky movements. Musculoskeletal pain frequently accompanies these irregular movements and postures. A double-blind study by Brans *et al.*[156] comparing BTX-A injections performed at 0 and 8 weeks and trihexyphenidyl in 66 patients with cervical dystonia demonstrated that the patients who received BTX reported significantly less disability and reduced impairment, as evaluated by the amplitude and duration of abnormal postures and movements, at their 12-week follow-up visits. However, the difference in pain scores between groups did not reach statistical significance. In this study, clinical measurements significantly correlated with electromyographic activity. In controlled studies assessing BTX-B, an alternative serotype used in BTX-A–resistant individuals, patients with cervical dystonia who received BTX injections reported significant improvements in severity, disability, and pain compared with placebo groups.[157,158] The duration of symptom relief with BTX is dose dependent.

The injection of BTX has been demonstrated to be an effective treatment for axial LBP in which muscle is purported to play a role. Foster *et al.*[159] injected either 40 units BTX-A or normal saline at five lumbar paravertebral levels on the side of maximum discomfort in a double-blind study involving 31 patients with chronic LBP of greater than 6 months' duration. At their 8-week follow-up visit, 73% of the patients who received BTX *versus* 12.5% of the placebo group reported pain relief of 50% or greater. BTX has also been shown in randomized, controlled trials to be a more effective treatment for piriformis syndrome than injections performed with placebo[160,161] and local anesthetic with steroid.[161]

The evidence for BTX use in regional pain syndromes is less clear-cut. In a placebo-controlled, double-blind crossover study comparing 50 units BTX-A, 100 units BTX-A, and normal saline in 33 patients with unilateral cervicothoracic paravertebral muscle pain, all groups showed clinical and algometric improvement at their follow-up visits (range, 1 week to 4 months), with no significant differences between groups.[162] A second injection of 100 units BTX was given in the same (n = 11) or a different (n = 2) site in 13 of these patients. In this subgroup, only 1 of the 4 patients who initially received a placebo injection showed clinical improvement, *versus* 7 of 9 patients who had received a BTX injection as their first treatment. In a randomized trial comparing BTX-A injections against methylprednisolone in 40 patients with chronic myofascial pain involving the iliopsoas, anterior scalene, or piriformis muscles, both groups demonstrated clinical improvement 30 days after injection.[163] The mean VAS score (0–10) decreased 3.9 points in the BTX group *versus* 3.5 in the steroid groups ($P = 0.06$). At 60 days after injection, the BTX group continued to show improvement (VAS score, −5.5), whereas the initial reduction in symptoms declined in the steroid group (−2.5).

Outcome trials for BTX injections in muscle contraction headaches have been mixed at best. Several controlled[164,165] and uncontrolled studies[166] have shown a beneficial effect for BTX-A treatment in tension headaches, but four placebo-controlled trials did not demon-

strate a positive outcome.[167–170] In two of these studies, the negative effect occurred despite electromyographic confirmation of diminished muscle tone.[168,169] These negative results support the hypothesis that central mechanisms play a key role in chronic tension-type headaches.

It is estimated that almost 90% of whiplash patients experience some degree of muscle spasm, a statistic supported by electromyography findings.[171,172] In two randomized, controlled trials evaluating BTX injections in patients with cervicogenic headaches and neck pain secondary to whiplash injury, the treatment groups fared better than the placebo groups at their latest follow-up 4 weeks after injection.[173,174] Beneficial effects were also observed in 75% (open-label, n = 44)[175] and 91% (placebo-controlled, n = 60)[176] of treatment patients in two studies conducted to assess the efficacy of BTX in chronic facial pain.

There is a paucity of information on BTX treatment for TMD. Bilateral injection of the masseter and temporalis muscles produced significant improvements in pain, function, mouth opening and tenderness at 8-week follow-up assessments in an open-label trial involving 46 patients.[177] In another uncontrolled trial, 80% of 41 TMD patients reported significant improvement in pain and function after BTX injections into the muscles of mastication (mean reduction in pain, 45%; average follow-up, 6.7 months).[178] Only 17% of patients in this study required a second injection for recurrent symptoms. In summary, there is strong evidence to support the use of BTX injections in painful conditions associated with spasticity. The evidence is mixed or limited for conditions associated with increased muscle activity, such as tension headaches and LBP (table 8). The conflicting data may reflect the heterogeneity of mechanisms for these conditions.

Miscellaneous Agents

Capsaicin. It is well established that repeated application of capsaicin cream depletes sensory C fibers of substance P, which is thought to be the principal transmitter of nociceptive impulses in type C sensory neurons. In an open-label, prospective pilot study performed in 23 patients with chronic, nonneurogenic neck pain, 48% of whom were diagnosed with myofascial pain, topically applied capsaicin cream was found to significantly reduce pain over the 5-week treatment period (mean reduction in VAS score, 23%).[179] The results of selected clinical trials evaluating miscellaneous analgesics in painful muscle conditions are summarized in table 9.

Quinine. Quinine sulfate has been prescribed for more than 60 yr in the treatment of nocturnal leg cramps[180,181] and until recently was the only drug shown to be effective for this problem.[182–187] The majority of studies show that quinine and its derivatives decrease the incidence, severity, and duration of night cramps, but not all report favorable results.[188–190] The effect of quinine is mediated by decreasing the excitability of the motor end plate to nerve stimulation and increasing the muscle refractory period.

Magnesium. Magnesium inhibits the release of acetylcholine from motor end plates and causes muscle relaxation in pharmacologic doses. Conversely, magnesium depletion facilitates neuromuscular excitability, producing tremor, cramps, and tetany. A randomized, double-blind, placebo-controlled trial demonstrated that oral magnesium significantly reduced leg cramps in pregnant women, without increasing serum concentrations.[191] These results are supported by Roffe *et al.*,[192] but in contrast, Frusso *et al.*[193] failed to find a difference between magnesium and placebo in a randomized, double-blind crossover study involving 45 subjects with nocturnal leg cramps. Regardless of the clinical evidence, magnesium salts are commonly used to relieve nocturnal leg pain in Europe and Latin America.

Naftidrofuryl. Although its mechanism of action is incompletely understood, naftidrofuryl is a 5-HT_2 serotonergic receptor antagonist that seems to act by improving cellular oxidative metabolism. This drug has traditionally been used to relieve pain associated with peripheral vascular disease. Various authors also have advocated its use in the treatment of nocturnal, lower extremity leg cramps.[194,195] In a double-blind, placebo-controlled study evaluating naftidrofuryl in 17 patients with rest cramp, Young and Connolly[196] found that administration of the drug significantly reduced the frequency of cramping and concluded that it was an effective alternative to quinine.

Vitamins. Medina Santillan *et al.*[197] performed a randomized, open-label comparative study examining the efficacy of dexamethasone alone *versus* dexamethasone plus vitamin B complex in 33 patients with acute LBP involving paravertebral muscle spasm. The investigators showed that adding B complex vitamins provided superior pain relief and greater improvement in muscle spasm than dexamethasone alone. Possible mechanisms for this effect involve synergy in the analgesic properties of the medications[198] and the modulating effect of vitamin B6 on steroid hormone-mediated gene expression.[199]

In two randomized, double-blind trials assessing the efficacy of vitamin E in hemodialysis muscle cramps, patients receiving the vitamin supplements reported significant reductions in the frequency and intensity of cramps.[200,201] In one study, the combination of vitamin C and E supplements produced a 97% decrease in muscle cramps.[201] Quinine sulfate but not vitamin E was found to be superior to placebo in a double-blind, placebo-controlled crossover trial comparing the two treatments in nocturnal leg cramps.[202]

Antihistamines. Histamine produces discomfort through stimulation of H_1 receptors on sensory nerve

Table 8. Randomized, Controlled Trials Evaluating Botulinum Toxins in the Treatment of Myofascial Pain Conditions Excluding Cervical Dystonia (Double Blind Unless Specified)

Study (Year)	Pain Condition	No. of Patients Completing Study	Drugs	Dose	Outcome
Foster *et al.*[159] (2001)	Chronic low back pain	28 with 3 dropouts	BTX-A	40 U/site injected at five lumbar paravertebral levels	> Placebo 8 wk after injections
Childers *et al.*[160] (2002) (crossover study)	Piriformis syndrome	9 women	BTX-A NS	100 U injected into piriformis muscle	> Placebo after 8 wk
Fishman *et al.*[161] (2002)	Piriformis syndrome	87 with 20 dropouts	BTX-A 2-ml solution of 2% lidocaine with triamcinolone NS	200 U 20 mg steroid 2 ml	BTX-A > steroid + lidocaine > NS during 12-wk follow-up
Wheeler *et al.*[162] (1998)	Unilateral, cervicothoracic, paraspinal myofascial pain	33	BTX-A NS	50 U or 100 U. 13 patients received repeat injections of 100 U.	All three groups showed significant improvement over the 4-mo follow-up period, with no significant differences between groups. In patients given two BTX injections, pain decreased significantly compared with those who received placebo followed by BTX.
Porta[163] (2000) (randomized comparative study)	Chronic muscle spasm in the neck, low back, or buttock	40 (3 patients had more than one injection)	BTX-A with 2 ml bupivacaine, 0.5% Methylprednisolone with 2–3 ml bupivacaine, 0.5%	80–150 U into a single muscle 80 mg injected into a single muscle	At 30 d, BTX-A ≥ steroid. At 60 d, BTX-A > steroid.
Smuts *et al.*[164] (1999)	Prophylactic treatment of chronic tension-type headache	37 with 4 dropouts	BTX-A NS	100 U divided by 12 injection sites	Treatment group reported decreased headache severity and increase in headache-free days over 4-mo treatment period
Porta[165] (2000) (randomized comparative study)	Chronic (n = 13) and episodic (n = 7) tension-type headache	20	BTX-A with lidocaine Methylprednisolone with lidocaine	Mean dose 9 U per site 40 mg Lidocaine dose and number of sites injected not specified	BTX-A > methylprednisolone 60 d after treatment. No differences at 30 d after treatment, although both treatments were effective. Differences between chronic and episodic tension headache groups not analyzed.
Schmitt *et al.*[167] (2001)	Tension-type headache	59 with 1 dropout	BTX-A NS	20 U/injection × four sites	No difference 8 wk after injection

(*Table continues*)

Table 8. *Continued*

Study (Year)	Pain Condition	No. of Patients Completing Study	Drugs	Dose	Outcome
Zwart *et al.*[168] (crossover study)	Tension-type headache with maximum pain in frontotemporal regions	6	BTX-A and NS	Unilateral NS injections followed by BTX injection 10 days later. Three patients underwent subsequent contralateral injections (total dose between 30 and 40 U).	No significant pain reduction despite electromyographic evidence of muscle paralysis for 5 wk after BTX injections
Rollnik *et al.*[169] (2001)	Tension-type headache	8	BTX-A NS	500 MU divided by 22 injection sites	No difference between groups 12 wk after injection despite decreased electromyographic recordings
Rollnik *et al.*[170] (2000)	Tension-type headache	21	BTX-A NS	20 U/injection × 10 injection sites	No difference between groups at 12 wk after injections
Freund and Schwartz[173] (2000)	Whiplash with neck pain of musculoskeletal origin	26 with 4 dropouts	BTX-A NS	100 U over 5 injection sites	> Placebo for pain and range of motion 4 wk after injections
Freund and Schwartz[174] (2000)	Whiplash with cervicogenic headache	26 with 4 dropouts	BTX-A NS	100 U over 5 injection sites	> Placebo for pain and range of motion 4 wk after injections
Von Lindern *et al.*[176] (2003) (single blinded)	Chronic facial pain with masticatory hyperactivity	90	BTX-A NS	Average dose of 35 MU injected on each side of muscle	> NS over 4 wk follow-up period
Cheshire *et al.*[265] (1994)	Myofascial pain syndrome involving cervical paraspinal and shoulder girdle muscles	6	BTX-A NS	50 MU	4 patients responded with > 30% pain relief 8 wk after BTX injections but not after NS
Keizer *et al.*[266] (2002)	Tennis elbow	37 with 3 dropouts	BTX-A Surgery	30–40 U once (n = 12) or twice (n = 8) Hohmann operation	75% in the BTX *vs.* 85% in the operative group had good to excellent results after 2 yr
Nixdorf *et al.*[267] (2002)	Myogenous orofacial pain	10 women with 5 dropouts	BTX-A NS	150 U divided over 12 injection sites in both masseter and temporalis muscles	No difference in pain or any other outcome measure except mouth opening 8 wk after injection

(*Table continues*)

terminals. Histamine also increases capillary permeability and dilates arterioles, with the latter effect produced by endothelial H_1 stimulation–induced release of nitric oxide, prostacyclin, or both. It is thought by some that these mechanisms contribute to pain and possibly stiffness in the fatigued muscles of patients with myofascial pain. In an attempt to clarify this issue, the activity of histidine decarboxylase, the enzyme that forms histamine, was examined in the masseter muscles of mice and was found to increase after electrical stimulation, peaking at 6–8 h after exercise.[203] In the second part of this study, the effect of an antihistamine (chlorphenylamine) was compared to an NSAID (flurbiprofen) for TMD in humans, which is known to produce myofascial pain involving facial, neck, and shoulders muscles. Chlorphenylamine was shown to reduce spontaneous pain and pain induced by chewing in 50% of subjects and to have a significantly greater effect than flurbipro-

Table 8. *Continued*

Study (Year)	Pain Condition	No. of Patients Completing Study	Drugs	Dose	Outcome
Jordan *et al.*[268] (2000) (retrospective crossover study)	Thoracic outlet syndrome	22 patients	BTX-A 2 ml of solution containing 2% lidocaine and betamethasone	12 U injected into the anterior and middle scalene muscle, 76 U into the trapezius muscle 1.5 mg steroid	14 of 22 patients had > 50% pain relief for at least a month after BTX (mean duration of improvement 88 days) *vs.* 4 of 22 patients after lidocaine and steroid
Ondo *et al.*[269] (2004)	Chronic daily headache	58 with 7 dropouts	BTX-A NS	200 U into various locations	> Placebo for 1° efficacy point of fewer headache days 8 wk after injections

BTX = botulinum toxin; MU = mouse units; NS = normal saline.

fen (50% *vs.* 13%) in relieving the associated symptoms of headache and shoulder stiffness.[203] In a double-blind, placebo-controlled crossover trial comparing the proprietary analgesic/antihistamine Mersyndol (Merrell Dow Pharmaceuticals, Slough, England) in patients with TMD, the drug was found to be markedly superior to placebo.[204] The relative contribution of the three active ingredients in Mersyndol, paracetamol, codeine, and doxylamine succinate, was not evaluated in this study.

Phosphodiesterase Inhibitors/Caffeine. Caffeine possesses little or no analgesic activity when administered alone. Nevertheless, caffeine remains a widely used analgesic adjuvant in humans, having been shown to modestly, but significantly, potentiate the antinociceptive effects of a variety of different analgesic drug classes, including opiates and NSAIDs.[205] This capacity to facilitate analgesia may relate to the ability of methylxanthines to increase circulating catecholamines, augment the twitch response of muscles *via* the translocation of intracellular calcium, constrict cerebrovascular beds, and enhance mood. In six randomized, double-blind, two-period crossover studies of 2,811 subjects undergoing similar protocols, caffeine-containing nonopioid analgesics were found to be significantly superior to placebo and nonopioid analgesics devoid of caffeine (*i.e.*, acetaminophen) in the treatment of tension-type headache.[206] The ability of caffeine to potentiate nonopioid analgesics in tension headache have been demonstrated in other studies as well.[207–211] Gorlich *et al.*[212] found that theophylline markedly enhanced the effect of quinine sulfate in a multicenter, double-blind, placebo-controlled study comparing the combination of quinine and theophylline to quinine alone and placebo in 164 patients with nocturnal leg cramps.

Metamizol. Metamizol (dipyrone) is a nonopioid analgesic with antipyretic and spasmolytic properties. Recent evidence suggests metamizol may exert some of its antinociceptive effects *via* inhibition of COX-3.[113,115] A double-blind, placebo-controlled trial by Martinez-Martin *et al.*[213] comparing 0.5 and 1 g metamizol to 1 g acetylsalicylic acid in episodic tension-type headache demonstrated that both doses of metamizol were superior to acetylsalicylic acid. Whereas pain relief continued to improve for 4 h in all three treatment groups, the contrast between acetylsalicylic acid and metamizol gradually declined after 1 h. In a single-blind, placebo-controlled study assessing the efficacy of 1 g intravenous metamizol in patients with migraine and tension headaches, metamizol was shown to reduce pain intensity in both groups.[214] In a follow-up study by the same authors, Bigal *et al.*[215] compared 1 g intravenous metamizol with placebo in 60 patients with episodic tension-type headaches under double-blind conditions. A marked decrease in pain intensity was observed 30 min and 1 h after drug administration in the metamizol group. This decrease in pain persisted throughout the 24-h follow-up period, along with significant reductions in headache recurrence and the need for remedication. In an interesting study evaluating the prophylactic benefit of metamizol and naproxen plus paracetamol in experimental tension headache induced by intellectual challenge, Lujan *et al.*[216] found both treatment groups to be more effective than placebo, with the naproxen–paracetamol group reporting less pain than the metamizol group. These clinical trials demonstrate the beneficial effects of metamizol in tension headaches and encourage further studies assessing its efficacy in other soft tissue disorders.

L-Carnitine. There are conflicting reports as to whether carnitine deficiency occurs in dialysis patients and, if so, whether supplementation can improve cardiac function and intradialytic morbidity. Two randomized, double-blind, placebo-controlled studies have demonstrated that oral supplementation with carnitine can

Table 9. Select Trials Evaluating Miscellaneous Drugs and Mixed Analgesics in Myofascial Pain Conditions (Double Blind Unless Specified)

Study (Year)	Pain Condition	No. of Patients Completing Study	Drugs	Dose, mg/d	Outcome
Mathias *et al.*[179] (1995) (prospective, open label)	Chronic neck or shoulder girdle pain	23 with 2 dropouts	0.025% capsaicin cream	Applied four times daily	Improvement in pain scores over 5-wk study period
Jones and Castleden[182] (1983) (crossover study)	Muscle cramps	9	Quinine	300	> Placebo after 2 wk
Jansen *et al.*[183] (1997)	Muscle cramps	102 with 10 dropouts	Hydroquinine	300	> Placebo after 2-wk treatment period
Lee *et al.*[184] (1991)	Muscle cramps	31 patients with cirrhosis, with 12 dropouts	Quinidine	400	> Placebo after 4-wk treatment period
Fung and Holbrook[185] (1989)	Nocturnal leg cramps	8 elderly patients	Quinine	200	> Placebo after 4 wk
Diener *et al.*[186] (2002)	Muscle cramps	98	Quinine	400	> Placebo for frequency and intensity of pain over 2-wk treatment period
Kaji *et al.*[187] (1976)	Hemodialysis-induced muscle cramps	9	Quinine	320	> Placebo after 12-wk treatment period
Lim[188] (1986)	Nocturnal leg cramps	25	Quinine	300	No difference between quinine and placebo (variable treatment period)
Warburton *et al.*[189] (1987) (crossover study)	Leg cramps	22 elderly patients with 21 dropouts	Quinine	300	≥ Placebo ($P = 0.1$) over 3-wk treatment period. Correlation noted between serum quinine concentrations and cramp reduction.
Sidorov[190] (1993) (crossover study)	Leg cramps	16 with 7 dropouts	Quinine	200	No difference between quinine and placebo over 2-wk treatment periods
Dahle *et al.*[191] (1995)	Pregnancy-induced leg cramps	69 with 4 dropouts	Magnesium	15 mmol	> Placebo after 3-wk treatment period
Roffe *et al.*[192] (2002) (crossover study)	Muscle cramps	46 with 22 dropouts	Magnesium citrate	300	Mg^{++} ≥ placebo ($P = 0.07$) after 6-wk treatment period
Frusso *et al.*[193] (crossover study)	Nocturnal leg cramps	45	Magnesium	1,800	No difference between Mg^{++} and placebo over 4-wk treatment period
Young and Connolly[196] (1993) (crossover study)	Muscle cramps at rest	14	Naftidrofuryl	600	> Placebo after 4 wk
Medina Santillan *et al.*[197] (2000)	Acute low back pain with spasm	30 with 3 dropouts	Dexamethasone Dexamethasone + complex B vitamins	4 4 + thiamine (100), pyridoxine (100), and cyanocobalamin (1)	Dexamethasone + B vitamins > dexamethasone after 8 d
Roca *et al.*[200] (1992)	Hemodialysis-induced leg cramps	29 with 11 dropouts	Quinine Vitamin E Placebo	325 400 U	Quinine = vitamin E > placebo over 8-wk treatment period

(*Table continues*)

Table 9. *Continued*

Study (Year)	Pain Condition	No. of Patients Completing Study	Drugs	Dose, mg/d	Outcome
Khajehdehi *et al.*[201] (2001)	Hemodialysis-induced muscle cramps	60	Vitamin E Vitamin C Vitamins E and C Placebo	400 250 400/250	Vitamins E and C > vitamin E or C > placebo after 8-wk treatment period
Connolly *et al.*[202] (1992)	Nocturnal leg cramps	27 male veterans, 3 dropouts	Quinine Vitamin E Placebo	500 800 U	Quinine reduced frequency of cramps and sleep disturbance, but not average cramp severity at 4-wk follow-up. Vitamin E was no better than placebo.
Watanabe *et al.*[203] (1999) (single blind)	TMD	46	Chlorphenylamine Flurbiprofen	16 120	Chlorphenylamine ≥ flurbiprofen after 7 d of treatment with either drug
Gerschman *et al.*[204] (1984) (crossover study)	TMD	30 with 2 dropouts	Mersyndol (450 mg paracetamol, 9.75 mg codeine, 5 mg doxylamine succinate; Merrell Dow, Slough, England) Placebo	2 tablets every 4 h as needed	> Placebo after 1 wk of treatment
Migliardi *et al.*[206] (1994) (six crossover studies)	Muscle contraction headache	2,600 with 211 dropouts	Acetaminophen + aspirin + caffeine (four studies) Acetaminophen + caffeine (two studies) Acetaminophen Placebo	500 + 500 + 130 1,000 + 130 1,000	Acetaminophen + caffeine and acetaminophen + aspirin + caffeine > acetaminophen > placebo over 4 h
Ward *et al.*[207] (1991) (crossover study)	Non-migrainous headache	53 with 7 dropouts	Acetaminophen Caffeine Acetaminophen + caffeine Placebo	648 65 or 130 648 + 65 or 130	Acetaminophen + caffeine > caffeine or acetaminophen > placebo after 2 h. Dose response noted with caffeine (130 > 65).
Schactel *et al.*[208] (1991)	Muscle-contraction headache	302 with 25 dropouts	Aspirin + caffeine Acetaminophen Placebo	1,000 + 64 1,000	Aspirin + caffeine > acetaminophen > placebo after 4 h
Diamond *et al.*[209] (2000)	Tension-type headache	301 plus 74 dropouts	Ibuprofen Ibuprofen + caffeine Caffeine Placebo	400 400 + 200 200	Ibuprofen + caffeine > ibuprofen or caffeine ≥ placebo during 6-h study period
Borges and Zavaleta[210] (1976) (single blind)	Tension headache	40	5 mg hydroxyzine + 300 mg acetaminophen + 30 mg propoxyphene + 30 mg caffeine 500 mg acetaminophen	1–8 tablets	Combination drug > acetaminophen over 4-wk observation period
Wojcicki *et al.*[211] (1977) (crossover study)	Tension headache (and postoperative pain)	216 (144 patients with headache)	Paracetamol Aspirin Finimal (paracetamol + caffeine; Mepros, Bladel, The Netherlands)	500 500 Paracetamol 500 + caffeine 50	Finimal > paracetamol or aspirin > placebo for both groups (single-dose study)
Gorlich *et al.*[212] (1991)	Nocturnal leg cramps	126	Quinine Quinine + theophylline	520 520 + 390	Quinine + theophylline > quinine > placebo during 2 wk on treatment medication

(*Table continues*)

Table 9. *Continued*

Study (Year)	Pain Condition	No. of Patients Completing Study	Drugs	Dose, mg/d	Outcome
Bigal *et al.*[214] (2001) (single blind)	Episodic tension-type headache and acute migraine	269 (30 with tension headache)	Metamizol	1,000 mg intravenous	Metamizol > placebo for tension and migraine headache after 1 h
Bigal *et al.*[215] (2002)	Tension-type headache	60	Dipyryone Normal saline	1,000 mg intravenous	> Placebo over 60-min observation period and 24 h after injection
Lujan *et al.*[216] (1992)	Induced-tension headache in patients with chronic daily headaches	20	Naproxen + paracetamol Dipyrone Placebo No treatment	Naprosyn 275 + paracetamol 300 9,500	Naprosyn + paracetamol > dipyrone > placebo = no treatment during 2-h experiment
Bellinghieri *et al.*[217] (1983) (crossover study)	Hemodialysis-induced muscle cramps	13 with 1 dropout	L-carnitine	2,000	Oral L-carnitine reduced muscle cramps and asthenia over 8-wk treatment period
Ahmad *et al.*[218] (1990)	Hemodialysis-induced muscle cramps	82 with 15 dropouts	L-carnitine	20 mg/kg intravenous	> Placebo after 6 mo of treatment
Reid and Dionne[224] (1994)	TMD	56 with 3 dropouts	Dexamethasone Iontophoresis	Daily × 3 d	No difference between dexamethasone group and placebo over 18-d study period
Catto *et al.*[270] (1973) (crossover study)	Hemodialysis-induced muscle cramps	17 with 2 dropouts	Sodium chloride tablets	3.6 g given before, and 2.4 g given during and after dialysis	> Placebo during and for 2 h after dialysis
Jansen *et al.*[271] (1994)	Muscle cramps	19 with 1 dropout	Hydroquinine	300	> Placebo over 2-wk treatment period, which partially persisted during 2-wk posttreatment follow-up
Thorpe[272] (1970)	Tension headache	52	Fiorinal PA (200 mg aspirin, 130 mg phenacetin, 40 mg caffeine, 50 mg isobutylallybarbituric acid; Sandoz Pharmaceuticals, Vienna, Austria)	2–4 tablets	Fiorinal > placebo after 4 h
Kagan and Masheter[273] (1978)	Tension headache	12	Syndol (450 mg paracetamol, 30 mg caffeine, 10 mg codeine, 5 mg doxylamine succinate [antihistamine]; Richardson-Merrell Ltd., Slough, England)	2–6 tablets	> Placebo over 7-d evaluation period
Dao *et al.*[274] (1998) (open label)	Myofascial pain of masticatory muscles	11 females, 1 dropout	Oral contraceptives	Variable (normal prescribed regimen)	Oral contraceptive group reported less pain fluctuations than non-oral contraceptive group over duration of menstrual cycle
Lin *et al.*[275] (1994) (open label)	TMD	29 patients, 30 joints, 2 patients did not complete injection series	Superoxide dismutase	4 mg intraarticular injection every week × 4 wk	Injections effective in 83% of joints

(*Table continues*)

Table 9. *Continued*

Study (Year)	Pain Condition	No. of Patients Completing Study	Drugs	Dose, mg/d	Outcome
Guidotti and Dilluvio[276] (1965)	Muscle spasm	50	Fluphenazine (0.5 mg) Fluphenazine (0.5 mg) + orphenadrine (100 mg)	1 tablet twice daily	Fluphenazine + orphenadrine > fluphenazine over 14-d study period
Ayres and Mihan[277] (1974) (open label)	Nocturnal leg cramps	125	Vitamin E (α-tocopherol)	Variable	Excellent relief in 103 patients, good or moderate relief in 20, variable follow-up
Saltman[278] (1973) (crossover study)	Tension headache	15 with 6 dropouts	Syndol (Richardson-Merrell Ltd.)	Variable	> Placebo over 7-d evaluation period
Scheepers[279] (1971)	Tension headache	30	Syndol (Richardson-Merrell Ltd.)	2–10 tablets	> Placebo, average duration of analgesia 2–6 h
Bigal *et al.*[280] (2002)	Tension-type headache	60	Chlorpromazine Normal saline	0.1 mg/kg intravenous	> Placebo throughout 60-min observation

TMD = temporomandibular disorder.

reduce muscle cramps and asthenia in hemodialysis patients.[217,218]

Corticosteroids. Corticosteroids exert their analgesic effects through inhibition of prostaglandin synthesis and suppression of ectopic discharges in injured nerves. They also possess potent antiinflammatory properties, mediated through their inhibition of prostaglandin production and proinflammatory cytokine and adhesion molecule expression.[219] Steroids have been shown to relieve pain in a wide array of disorders and are a mainstay of treatment for various forms of arthritis. Therefore, it seems logical that these drugs would be used in TMD. Interestingly, there are no published clinical trials assessing oral corticosteroids in this condition. However, several studies have reported that the intraarticular injection of steroids with and without local anesthetics[220–222] and steroids administered *via* iontophoresis[223] are beneficial. In contrast, Reid *et al.*[224] found that iontophoretically administered dexamethasone was no better than placebo in reducing pain or improving range of motion in patients with TMD. There was a trend toward improved pain relief with steroid in the subgroup of patients with TMJ osteoarthritis in this study. Some clinicians have reported adverse effects on the TMJ as a result of chronic corticosteroid use.[225,226]

In a cross-sectional analysis of 71 patients with systemic lupus erythematosus, 32% had frequent headaches, with the most common type being episodic tension headache.[227] Among these 23 patients, only 1 was noted to have a headache refractory to conventional analgesics that responded to an increase in corticosteroid dose. There are no other clinical trials evaluating steroids in tension-type headaches, despite the fact that NSAIDs are the most frequently used medications worldwide for this condition. In patients with inflammatory myopathies, the short-term use of corticosteroids is a first-line treatment,[228] but prolonged steroid use can also cause myopathy.[229,230]

Conclusion

Myofascial pain comprises a heterogeneous group of disorders. Therefore, it is not surprising to find conflicting outcomes as to the pharmacologic efficacy of different drugs. Even within a particular disorder such as tension headache or TMD, different drug mechanisms may play different roles in different patients. What is most surprising is how little basic science research has been completed to understand the mechanisms underlying soft tissue pathology. It is also striking that there is little evidence to support the use of many medications that are routinely prescribed for muscle pain. There are several different classes of medications that have been shown to be efficacious in the treatment of soft tissue pain, but no one class of drugs is beneficial across the entire spectrum of these conditions. It is imperative that further research be performed, both preclinically to help elucidate the mechanisms behind myofascial pain and clinically to justify specific treatments.[231–280]

Appendix: Evidence or Lack Thereof for Muscle Involvement in Painful Conditions

Fibromyalgia

Fibromyalgia syndrome is a constellation of symptoms characterized by widespread pain, fatigue, sleep abnormalities, and distress. The most widely used guidelines for making a diagnosis of fibromyalgia are those adopted in 1990 by the American College of Rheumatology. Their criteria consist of one historic feature and one physical finding. The historic element is pervasive, axial pain complaints on the left and right sides of the body above and below the waist, which persist for 3 months or longer. The physical finding requires the patient to experience pain in 11 of 18 designated tender point sites on digital palpation

with a force of 4 kg. Despite numerous studies that have attempted to identify a causative agent, none has yet to be identified (hence the term *syndrome* instead of *disease*). Some muscle biopsy studies have found patients with fibromyalgia symptoms to have reduced muscle fiber size, diminished capillary density, and decreased levels of high-energy phosphates,[281–283] but these findings have been inconsistent.[284] Recent investigations have therefore focused on central mechanisms of pain. In studies by Staud *et al.*,[285,286] the authors demonstrated exaggerated temporal summation of painful stimuli in fibromyalgia patients compared with control subjects, indicating central sensitization had occurred. Neuroendocrine and related abnormalities have also been found in fibromyalgia patients, including reduced serum concentrations of serotonin, increased cerebrospinal fluid concentrations of substance P, increased nitric oxide synthesis indicating NMDA receptor activation, alterations in autonomic nervous system function, increased concentrations of cytokines indicating possible neurogenic inflammation, mildly reduced baseline plasma concentrations of cortisol with a hyperreactive hypothalamic–pituitary–adrenal axis, growth hormone deficiency, low concentrations of oxytocin, increased cerebrospinal fluid concentrations of nerve growth factor, and stage IV sleep disturbances.[287–292] These findings have led researchers to conclude that fibromyalgia is predominantly a disorder of sensory processing rather than one caused by tissue abnormalities.[284] As such, the treatment of this disorder is beyond the scope of this review article.

Tension-type Headache

Recent studies have borne out the fact that there is a large degree of overlap among the various types of headache, particularly migraine and tension headaches.[293] This overlap includes both pathophysiology and clinical characteristics, which may explain the observation that drugs such as TCAs that are effective for one class of headache are often efficacious in other types. The mechanisms of head pain that may be shared to varying degrees between migraine and tension headaches include peripheral mechanisms, as manifested by myofascial tenderness and enhanced electromyographic and algometric pressure recordings, central sensitization secondary to enhanced nitric oxide production or NMDA receptor activation or both, and trigeminal vascular activation leading to neurogenic inflammation.[294–296] The first two factors are most important in the etiology of tension headaches, whereas the last two mechanisms predominate in migraines. Approximately 70% of patients with tension headache exhibit muscle tightness and tenderness, indicative of peripheral pain mechanisms, with the percentage being higher in individuals suffering episodic headaches.[297] The relative contribution of peripheral and central mechanisms to tension headache determines in part the responsiveness to various classes of analgesic medications. Stopping the evolution from primarily a peripheral to a central mechanism is of major importance in preventing episodic tension headaches from becoming chronic.

Low Back Pain

The demands on spinal structures are enormous. These functions include protecting the contents of the spinal canal, maintaining truncal stability, and providing a base for movements of the extremities. Bony structures and ligaments provide stability and protection, whereas muscles are the main component responsible for the coordination of spinal movement. In addition to providing a stable base, muscles must retain a certain amount of flexibility to permit movement in multiple planes. Back, abdominal, and other pelvic support muscles are constantly readjusting to maintain posture and redistribute loads to the lower extremities. These conflicting demands often result in stresses that lead to injury.[298]

It has long been known that LBP is associated with muscle pathology, particularly the postural muscles in the abdominal and paraspinous regions. This association has been confirmed by studies demonstrating increased paraspinal muscle activity in patients with chronic LBP compared with matched controls.[299] Not surprisingly, lumbar stabilization programs focusing on rehabilitation of the lumbar spine musculature have been shown to reduce pain and improve function.[300] Abnormalities in muscle that can cause or exacerbate preexisting LBP include increases in muscle tension, sprains, strains, tears, weakness, and spasm. These pathologic processes may be secondary to altered gait mechanics, impaired postural control, and diminished lumbar proprioception, often as a consequence of preexisting lumbosacral pathology.[301] The extent to which muscle pathology is the primary cause or merely an effect of LBP is unknown.

In a study by Long *et al.*[1] examining the causes of LBP in more than 2,000 patients, myofascial pain accounted for 20% of cases, making it the second most common cause, behind only herniated nucleus pulposus. The main problem with attributing muscle pathology as the primary cause of LBP is that in many instances, it is a diagnosis of exclusion. For this reason, unless myofascial pain was specifically designated as the primary cause of discomfort, LBP studies were not included in this review. Further evidence for the role muscles play in LBP can be seen by the beneficial effect treatments aimed at muscles such as muscle relaxants and BTX injections have in the condition.[40,298]

Temporomandibular Disorder

Temporomandibular disorder is a nonspecific term encompassing a wide range of pain and dysfunctional jaw conditions. These conditions include symptoms and pathology involving the muscles of mastication, the TMJ, the nervous system, and behavior. There is little consensus regarding the most favorable classification scheme for TMD. However, most recognize the need to classify TMD according to two distinct but interrelated components: (1) pathology originating in the TMJ or intracapsular region (arthrogenic) and (2) pathology originating in the masticatory musculature (myogenic). TMD affects patients across geographic, ethnic, and cultural boundaries. Arthrogenic TMD is more common in older patients, whereas the myogenic form is more prevalent in younger persons. Given the enhanced tactile sensibility of the oral cavity and the unremitting use of the TMJ, it is not surprising that TMD is such a common diagnosis. Across all age groups, women are affected more frequently than men.[302]

In epidemiologic studies involving both white and Asian patients, myogenic TMD has been found to be more common than the arthrogenic form.[303,304] List and Dworkin[303] found 76% of patients with TMD to have predominantly muscle pathology, which was far more common than their other two diagnostic classifications, disc displacement and arthralgia/arthritis/arthrosis. It is not surprising then that electromyographic studies have demonstrated increased tone in the masticatory muscles of patients with TMD[305] and that electromyographic biofeedback treatment has been shown to significantly reduce pain in the disorder.[306] Although poor oral habits and dysfunctional behaviors (bruxism, teeth clenching), malocclusion, previous surgical and orthodontic procedures, degenerative changes in the TMJ, inadequate coping skills, preexisting psychopathology, and the presence of associated pain disorders have all been reported to predispose patients to TMD, the risk factors for development of chronic TMD have not been definitively established.[307] There is some evidence that small muscles, such as those involved in mastication, may be more prone to hyperalgesia than larger muscles.[13]

Muscle Cramps

Muscle cramps occur when a muscle already in its most shortened natural position further contracts.[308] True cramps, which by definition occur in the absence of fluid or electrolyte imbalance, are more prevalent in patients with well-developed muscles, in the latter stages of pregnancy, and in patients with cirrhosis.[309] They are typically asymmetric, explosive in onset, and most frequently affect the gastrocnemius muscle and small muscles of the foot. The contraction, which is often visible, may leave soreness and swelling. The most common type of true muscle cramp occurs at rest, usually during the night.

Studies indicate that true muscle cramps tend to be of neuromuscular origin. They most frequently start in the intramuscular portion of motor nerve terminals and are characterized by motor unit action potentials.[310] When they commence, relief of common cramps can usually be effected by passively or actively stretching the cramped muscle. In addition to true muscle cramps, cramping is also seen in hyponatremia associated with salt depletion (*e.g.*, hemodialysis or heat cramps), neurologic disorders, hyperthyroidism, and certain medications.[309,311,312]

Myofascial Pain Syndrome

The MPSs are comprised of a large group of disorders whose hallmark is the presence of hypersensitive areas within muscles and/or the investing connective tissue, called *trigger points*, accompanied by pain, spasm, stiffness, tenderness, restricted range of motion, and weakness. The clinical features of MPS are best described by Simons *et al.*[313] in their classic work on TPs as consisting of (1) a palpable taut band of muscle, (2) localized tenderness within this taut band, (3) a characteristic pain referral pattern occurring when pressure is applied to this TP, and (4) a local twitch response to snapping palpation of the TP. Despite its acceptance, a major problem with this definition has been poor agreement between examiners in interrater reliability studies.[314,315]

Trigger points are usually subclassifed into two types, active and latent. Active TPs are associated with a specific pain that is reproduced when pressure is applied to the taut band of sensitive tissue. Latent TPs, the more common of the two, do not normally produce spontaneous pain, although they may be activated by weather changes, overuse of muscles, prolonged immobility, poor posture, and mechanical stressors. Not infrequently, myofascial pain is precipitated by a seemingly innocuous activity. Some studies suggest that latent TPs may be present in as many as half of asymptomatic young adults in the shoulder-girdle muscles and in 5–45% of lumbogluteal muscles.[316,317] In most instances, the only manifestations of latent TPs are decreased range of motion and easy fatigability.

The pathophysiology of TP formation is incompletely understood. Several studies have found electromyographic evidence of spike discharges and increased spontaneous activity in TP, although these findings have also been found in regions not causing symptoms.[318–322] Four main theories have been proposed to explain the formation of and findings seen in TP. These include muscle spindle hyperactivity, end plate hyperactivity, focal dystonia, and psychosomatic origin.[318,321,323,324] Each of these theories is supported by some studies but refuted by others.[323] It is plausible that several or even all of these hypotheses prevail in MPS.

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