EXHIBIT M-1

Format: Abstract

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Muscle strain injury: diagnosis and treatment.

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Author information

Abstract

Muscle strain is a very common injury. Muscles that are frequently involved cross two joints, act mainly in an eccentric fashion, and contain a high percentage of fast-twitch fibers. Muscle strain usually causes acute pain and occurs during strenuous activity. In most cases, the diagnosis can be made on the basis of the history and physical examination. Magnetic resonance imaging is recommended only when radiologic evaluation is necessary for diagnosis. Initial treatment consists of rest, ice, compression, and nonsteroidal anti-inflammatory drug therapy. As pain and swelling subside, physical therapy should be initiated to restore flexibility and strength. Avoiding excessive fatigue and performing adequate warm-up before intense exercise may help to prevent muscle strain injury. The long-term outcome after muscle strain injury is usually excellent, and complications are few.

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LinkOut - more resources

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Wolters Kluwer
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Treatment of Skeletal Muscle Injury: A Review

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Abstract

Skeletal muscle injuries are the most common sports-related injuries and present a challenge in primary care and sports medicine. Most types of muscle injuries would follow three stages: the acute inflammatory and degenerative phase, the repair phase and the remodeling phase. Present conservative treatment includes RICE (rest, ice, compression, elevation), nonsteroidal anti-inflammatory drugs (NSAIDs) and physical therapy. However, if use improper, NSAIDs may suppress an essential inflammatory phase in the healing of injured skeletal muscle. Furthermore, it remains controversial whether or not they have adverse effects on the healing process or on the tensile strength. However, several growth factors might promote the regeneration of injured skeletal muscle, many novel treatments have involved on enhancing complete functional recovery. Exogenous growth factors have been shown to regulate satellite cell proliferation, differentiation and fusion in myotubes in vivo and in vitro, TGF-β1 antagonists behave as inhibitors of TGF-β1. They prevent collagen deposition and block formation of muscle fibrosis, so that a complete functional recovery can be achieved.

1. Introduction

Skeletal muscle injuries are the most common sports-related injuries and present a challenge in primary care and sports medicine. Athletes sustain muscle injuries through a variety of mechanisms, including direct trauma (e.g., lacerations, strains, and contusions) and indirect injuries (related to ischemia and neurological dysfunctions).

A regeneration process that is similar in most types of muscle injuries, has been observed. However, complete recovery from the injury is compromised due to the development of fibrosis in the second week after the injury. The formed scar tissue always is mechanically inferior and therefore much less able to perform the functions of a normal muscle fiber. It is also more susceptible to reinjury [1, 2]. To minimize the disability and enhance full functional recovery after skeletal muscle injuries, the current conservative treatment includes limiting the bleeding with compression, elevation, and local cooling, nonsteroidal anti-inflammatory drugs (NSAIDs), and physical therapy [3].

Recently, it has been suggested that growth factors might promote the regeneration of injured skeletal muscle, and many novel treatments have been developed.

This review paper focuses on therapeutic approaches including new knowledge of routine NSAIDs, novel biological repair, and physical therapy. A search of the literature on the treatment of skeletal muscle injuries was conducted using PubMed and Medscape.

2. The Pathological Process Following Muscle Injury

The general injury and repair mechanism is similar in most types of muscle injuries. Three stages are distinguished: the destruction and inflammatory phase (1 to 3 days), the repair phase (3 to 4 weeks), and the remodeling phase (3 to 6 months) [4, 5]. The last two phases tend to overlap.

When a muscle is injured, the myofibers rupture and necrotize. A haematoma is formed. At the same time during this first phase, the inflammatory cells can freely invade the injury site because the blood vessels are torn. The most abundant inflammatory cells are the polymorphonuclear leukocytes. These are replaced by monocytes, a few hours after the injury. These cells eventually transform into macrophages. Macrophages have 2 functions. Firstly, they remove the necrotic myofibers by phagocytosis. Secondly, they produce, together with fibroblasts, chemotactic signals such as growth factors, cytokines, and chemokines. The extracellular matrix (ECM) also contains growth factors that become active when tissue is damaged. Some of these growth factors, such as FGF (fibroblast growth factor), IGF-1 (insulin-like growth factor-1), IGF-2 (insulin-like growth factor-2), TGF-β (transforming growth factor-β), HGF (hepatocyte growth factor), TNF-α (tumor necrosis factor-α), and IL-6 (interleukin-6) can activate myogenic precursors, called the satellite cell [3, 6, 7].

The next phase, the repair phase, consists of 2 concomitant processes. The first is the regeneration of the disrupted myofibers. Regeneration can occur because there still is a pool of undifferentiated reserve cells, also called myogenic precursors or satellite cells under the basal lamina of the myofiber. The satellite cells will proliferate and eventually differentiate into myoblasts. Because these new myoblasts fuse with the injured myofibers, the gap formed between the two ends of the injured myofiber is refilled. The second process of the repair phase is the formation of a connective tissue scar by fibrin and fibronectin, derived from blood of the haematoma that was formed immediately after the injury. The scar tissue gives the muscle strength to withstand contractions, and it gives the fibroblasts an anchoring site to invade the granulation tissue. However, in case of excessive proliferation of these fibroblasts, dense scar tissue is formed within the injured muscle. This not only interferes with the repair process but also interrupts the muscle regenerative process and contributes to incomplete functional recovery of the injured muscle during the third phase, the remodeling phase. In this last phase, the newly formed myofibers mature. At the same time, the scar tissue is reorganized and it contracts [3, 6, 7].

Due to an injury, the intramuscular nerve branches can be damaged. Hence, the muscle fibers may be denervated, which might affect the healing process negatively [8].

The whole process is coordinated through different mechanisms like cell-cell and cell-matrix interactions as well as extracellular secreted factors. HGF, IL-1, and IL-6 are secreted factors that can stimulate the activity of satellite cells. FGF and IGF can also activate satellite cells, but in contrast to IGF, FGF can also inhibit their differentiation, while IGF stimulates the differentiation. TGF-β1 stimulates collagen deposition, leading to the formation of fibrotic scar tissue [9–13].

3. Therapeutic Strategies

A variety of conservative treatment strategies exist for acute and chronic skeletal muscle injuries [14, 15]. The primary treatment goals are to minimize further damage, relieve pain and spasm, reduce haemorrhage and edema, and promote healing. Furthermore, the recurrent nature of muscle injuries often requires a functional approach from the acute phase to the final goal of return to sports.

4. RICE

The best known treatment immediately after a muscle injury is the "RICE approach". This acronym stands for rest, ice, compression and elevation. The aim is to minimize the haematoma of the injured muscle and, subsequently, the size of the connective tissue scar. However, the effectiveness of this approach has not been proven in any randomized clinical trial [3]. Ice should be applied intermittently for 15 to 20 minutes with an interval of 30 to 60 minutes. Longer periods of cold application lead to increased circulation and increased bleeding [8].

5. Physiotherapy

Early mobilization accelerates capillary ingrowth and promotes the regeneration of muscle fibers. The healed muscle also more rapidly regains its preinjury level of strength. However, early mobilization also has disadvantages. The scar that is formed will be larger, and reruptures will be more common. Therefore, rest is advised during the first 3 to 7 days to allow the scar tissue to gain strength. Subsequently, mobilization within the painfree limits is initiated. Continued inactivity can lead to atrophy of the healthy muscles, excessive deposition of connective tissue within the muscles and a substantially retarded recovery of the strength of the injured skeletal muscle. Exercises should be started gradually. Isometric training should be followed by isotonic training and isotonic training by isokinetic training once the respective exercises can be performed without pain [3].

6. NSAIDs

NSAIDs are primarily used for their analgesic, anti-inflammatory, and antipyretic properties [16]. Inflammatory cells play an important role in the healing process of an injured muscle. Therefore, the use of drugs that inhibit these cells, such as NSAIDs, is questioned nowadays. Experimental studies in which NSAIDs were given immediately after the injury, have shown conflicting results. NSAIDs would not have a greater effect on the pain of a muscle injury than paracetamol, but they have more side effects including asthma exacerbations, gastrointestinal and renal side effects, hypertension, and other. However, NSAIDs also have beneficial effects. The inflammatory process can be excessive and cause edema, resulting in anoxia and further cell death. This can be prevented by the administration of low-dose NSAIDs [17].

Rahusen et al. reviewed earlier reports on the use of NSAIDs to clarify recommendations for their use [18]. Basically, NSAIDs should be given no sooner than 48 hours following exercise-induced muscle injuries to provide analgesia and to reduce the early inflammatory response. Earlier use can interfere with the cell chemotaxis that is necessary for the repair and remodeling of regenerating muscle. In the 2 days after the injury, paracetamol can be used for analgesia. Prolonged use of NSAIDs (over 7 days) is not recommended as it would delay muscle regeneration by inactivating the proliferation and differentiation of satellite cells and inhibiting the production of growth factors [18, 19].

It would also reduce the biomechanical strength of the injured muscle and delay elimination of the haematoma and the necrotic tissue [20]. In contrast with the findings of these authors, Engelberg et al. and Almekinders [21] showed no significant effect on tensile strength recovery following NSAID treatment for muscle strain injury. Engelberg et al. further demonstrated that muscle strength also remained unaltered [22].

7. Biological Repair

Recently, several studies have led to the identification of growth factors that have the potential to influence the regeneration of injured muscles. Since then, multiple research groups have been trying to find drugs that work on this natural basis and can help an injured muscle to recover better and/or faster [12, 23, 24] (Figure 1). To achieve this goal, the researchers investigated several biological growth factors, such as exogenous growth factors which would promote healing of injured muscle fibers, and TGF-β1, the inhibition of which would block the muscle fibrosis (Table 1).

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Figure 1

Autologous platelet tissue graft: mechanism of action.

Table 1

Effect of growth factors in musculoskeletal tissues.

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$^{+}$Positive effect; $^{-}$no or negative effect; blank: not tested; IGF-1: insulin-like growth factor-1; bFGF: basic fibroblast growth factor; NGF: nerve growth factor; PDGF: platelet-derived growth factor; EGF: epidermal growth factor; TGF: transforming growth factor; BMP-2: bone morphogenetic protein-2.

Several growth factors are capable of promoting muscle regeneration [13, 25]. These include basic fibroblast growth factor (bFGF), insulin growth factor (IGF), nerve growth factor (NGF), TGF-β1, and platelet-derived growth factor (PDGF). Mitchell et al. reported that the short biologic half-life of

administered bFGF may limit its stimulatory effect on satellite cells [26]. They coinjected bFGF with heparin and used sustained release polymers without success. Conversely, Armand et al. found that the direct delivery of recombinant bFGF-6 into the site of injury can accelerate the regeneration of the soleus muscle in adult mice by stimulating the differentiation process of the myotubes [27].

Takahashi et al. observed that gene delivery of IGF-1 via electroporation resulted in an increased number of regenerating myofibers by 2 weeks after injury and in an increased regenerating myofiber size by 4 weeks after injury [28]. Huard et al. injected IGF in healthy old men, thus preventing the loss of muscle mass that is typical of aging. However, IGF-injection has side effects in that it promotes the development of fibrosis by stimulating the production of matrix components such as collagen and decreasing the expression of matrix-degrading enzymes such as collagenase [29]. In a mice model of muscle strain, Kasemkijwattana et al. evaluated the ability of bFGF, NGF and IGF-1 to promote muscle regeneration in vivo by three repeated injections of 100 ng into the injury site 1, 3, and 5 days after the injury [30]. In this study, physiologic strength testing was correlated with histologic analysis of the treated and nontreated muscles; the number and diameter of regenerating myofibers were monitored as an index of muscle regeneration. Their data indicated that bFGF and IGF-1, properly applied, can improve muscle performance after a strain injury. Throughout this study, growth factors had been injected on only 1 to 3 and 5 days after injury, resulting in an improvement of the tetanic and fast-twitch strength of the treated muscle, when compared with sham-injected strain-injured muscle. In addition, NGF was found capable of enhancing fast-twitch strength, but the titanic strength was not significantly different between the treated and nontreated muscle [30].

Miller et al. postulated that local delivery of HGF would augment satellite cell activation in regenerating muscle, and that this increased number of myogenic precursor cells would lead to an enhancement of muscle repair. Their study showed that, when HGF was injected in injured muscles, the number of myoblasts increased, but this increase did not lead to a better regeneration of the injected muscle. Instead, when HGF was injected the first 4 days after injury, muscle regeneration was inhibited. When it was administered later, the injection had no effect. Miller et al. also found that HGF had a dose-dependent effect on the number of myoblasts in regenerating muscles [31]. Two different doses of HGF, 6.25 and 50 ng, were used in this study. Treatment with 6.25 ng HGF did not significantly increase the number of myoblasts compared with control at any time tested. In contrast, muscles treated with 50 ng HGF on the day of injury and analyzed 1 day later yielded about threefold more MyoD-positive cells than did control muscles. In muscles further treated with HGF on subsequent days and analyzed either 2 or 3 days after injury, no significantly increased number of myoblasts was observed. This study demonstrated the effects of exogenous HGF administration on satellite cell activation and differentiation in regenerating mouse muscles after trauma. It showed the dual role HGF plays in regulating satellite cell activation and differentiation [31].

Kasemkijwattana and Menetrey et al. observed that b-FGF, IGF-1, and NGF are potent stimulators of the proliferation and fusion of myoblasts in vivo [1, 30, 32]. These growth factors were injected into mice with lacerations of the gastrocnemius muscle. Muscle regeneration was evaluated at 1 week by histological staining and quantitative histology. Muscle healing was assessed histologically and the contractile properties were measured 1 month after injury. In the treated group, the number of regenerating myofibers was increased 3.5 times for bGF and IGF-1 and 1.5 times for NGF. Those data suggested that specific growth factors were able to improve regeneration of injured muscle by stimulating myogenic proliferation and differentiation.

As discussed above, regeneration of an injured muscle consists of 2 elements. First, there needs to be proliferation and differentiation of myoblasts. This is promoted by growth factors (Table 1). Secondly, scar tissue has to be minimal. Many studies indicate that the overproduction of TGF-β1 is responsible for the tissue fibrosis both in animals and humans [33]. Therefore, researchers have also tried to develop drugs that inhibit TGF-β1. Chan et al. used the TFG-β1 antagonist suramin in their study. Suramin is an antiparasitic and antitumor drug that competitively binds to the TGF-β1 receptor. When suramin was injected immediately or 7 days after the injury, it had only a minor effect on muscle fibrosis. However, when a high dose of suramin was injected 14 days after injury, it prevented fibrosis more effectively than did a lower concentration or no suramin. There were more regenerating myofibers in all the suramin-treated groups than in the control groups. Just as the prevention of fibrosis, the number of regenerating myofibers was dose dependent. Side effects of suramin are adrenocortical insufficiency, malaise, neuropathy, and corneal deposits. Occasionally, neutropenia, thrombocytopenia, and renal failure may occur. However, the toxicity of suramin delivered via intramuscular injection has not yet been determined. In the study, no side effects were encountered [33]. These results are consistent with those of Nozaki et al. who injected 2.5 mg of suramin 2 weeks after contusion. They also found less fibrosis and better healing of the muscle. Once healed, the injected muscle was also stronger than the control muscles. A dose-response effect was not observed [34].

Decorin also inactivates the effect of TGF-β1. Fukushima et al. found that the injection of decorin at 10 and 15 days after injury significantly decreased the amount of fibrosis. Decorin had the additional advantage of enhancing the regeneration of the injured muscle. There seemed to be a dose-response effect. No side effects were observed [6].

8. Operative Treatment

Menetrey et al. used a muscle laceration model developed in mice to investigate whether surgery is a better technique to accelerate recovery of a muscle injury than immobilization. At 2 days after the laceration, the mice that had surgery only had a superficially located minor haematoma, while the immobilized mice had a larger and deeper haematoma. At the end, the immobilized mice had more and deeper scar tissue than the sutured mice. The functional results of surgery were also superior to those of immobilization [35].

Surgery can only be implemented in specific conditions. These include a large intramuscular haematoma, a complete strain or tear of a muscle with few or no agonist muscles or a partial strain if more than half of the muscle belly is torn and if the patient complains of persistent (>4–6 months) extension pain. After surgery, the operated limb should be placed in a cast and immobilized in a neutral position with an orthosis.

9. Discussion

When a skeletal muscle is injured, satellite cells are activated by a variety of growth factors within 18 hours of injury, as a result of a response to a chemical stimulus [5, 36, 37]. At the same time, inflammatory cells migrate to the injury site from healthy areas of the muscle. Regeneration of single muscle fibers or entire muscles can only occur when satellite cells are activated. The optimal treatment for these muscle injuries remains obscure in routine clinical practice.

The RICE approach is generally used in the acute stage. The value of this treatment is not fully known, but most authors consider it as not harmful and maybe helpful to limit the bleeding in the muscles. It consists of rest, ice, compression, and elevation [3]. During the first 7 days after a muscle injury, rest should be taken, so that the scar tissue can gain strength. Afterwards, physiotherapy can be started [3].

Whether or not NSAIDs should be used in the treatment of muscle injuries is still controversial. They have long been the first choice to relieve pain after a skeletal muscle injury. NSAIDs may suppress the inflammatory response and thus reduce the pain and swelling. However, this response is an essential phase in the healing of injured skeletal muscle. Attempts to inhibit this phase will lead to an incomplete functional recovery. NSAIDs could interfere with macrophage action, limit phagocytic function, and impede production of growth-promoting factors that are responsible for regeneration after muscle injury. Experimental investigations showed that NSAIDs might also decrease the tensile strength of the injured muscle. Delayed muscle regeneration has been observed in treated animals [38]. Other studies did not come to this conclusion. Therefore, the exact role of NSAIDs should be established in animal models and in controlled clinical studies of skeletal muscle injuries. Until then, most authors advise that NSAIDs should not be given the first 48 hours after the injury. If the patient is in pain, paracetamol can be administered for analgesia.

A better understanding of the biological and pathological processes of muscle repair following skeletal muscle injury has led to the use of growth factors.

Growth factors have been shown to regulate satellite cell proliferation, differentiation, and fusion in myotubes in vivo and in vitro. Recently, growth factors have been found to promote the differentiation of myogenic cells in vivo and in vitro and eventually enhance complete functional recovery after muscle injury. Among these growth factors, NGF was the first to be identified and used to promote repair in peripheral and central nervous system injuries [39]. NGF may also be useful in muscle regeneration, especially during the reinnervation phase [40]. Injection of IGF increases the number and the size of regenerating myofibers after muscle injury [41]. Injection of b-FGF showed that this growth factor is a potent stimulator of the proliferation and fusion of myoblasts in vivo and in vitro [42].

TGF-β1 is a key factor, responsible for the formation of muscle fibrosis during the repair process by stimulating a variety of cells to increase the synthesis of numerous matrix proteins [43]. In response to muscle injury, TGF-β1 provides an upregulated immune mechanism which leads to an increased cellular adhesion to the ECM and ultimately enhances myofibroblast survival by inhibiting apoptosis. TGF-β1 is expressed at high levels and is associated with massive muscle fibrosis observed in patients with Duchenne muscular dystrophy. Based on this biological rationale of the role of TGF-β1, several novel researches have focused on the inhibition of TGF-β1 in muscle healing.

TGF-β1 antagonists behave as inhibitors of TGF-β1 by binding to its receptor and blocking its actions, in order to prevent collagen deposition and to block formation of muscle fibrosis. Among these antifibrotic agents, decorin and suramin have been demonstrated to block fibrosis and promote functional recovery of injured skeletal muscle. Decorin binds to TGF-β1 in order to counteract its action and suramin competitively binds to the TGF-β1 receptor that inhibits TGF-β expression [44]. However, the side effects of growth hormone factors must be taken into account, edema, and arthralgia or myalgia being most common in adults [45].

Surgery should be preserved for special cases as mentioned before. If symptoms fail to improve, the possibility of intramuscular haematoma and tissue damage should be reconsidered. Measurement of intramuscular pressure, soft-tissue X-rays, or ultrasound examination may be required [8].

Authors' Recommendations

After a muscle injury, the RICE principle should be implemented immediately. Seven days of rest are advised, after which physiotherapy should be started. NSAIDs can be used after 48 hours. The rationale for using NSAIDs in these conditions is based on their anti-inflammatory properties. Inflammation is an essential component of the healing process. Therefore, the appropriate timing of NSAID administration may play a key role in the therapeutic approach to skeletal muscle injuries [46]. In the future, the routine use of NSAIDs in muscle injuries should be further critically evaluated and compared with other treatment strategies in prospective randomized controlled trials.

The use of growth factors, particularly bFGF, NGF, and IGF-1, is a novel therapeutic approach to promote full functional recovery after muscle injuries. Autologous growth factors might induce myogenic proliferation, stimulate differentiation, and as such accelerate the healing of inflamed and injured muscle. Inhibition of TGF-β1 expression contributes to the blocking of muscle fibrosis in order to minimize the formation of fibrous scar tissue and to promote the restoration of functional muscle fibers within the injured site.

A treatment that enhances the repair of injured muscle could have significant clinical applications [47]. Therefore, further studies must be conducted to evaluate the safety of using growth factors and antifibrotic agents. Future research should focus on the use of growth factors that facilitate muscle regeneration in vivo. The balance between growth and differentiation must be maintained in order to restore functional muscle structure and to identify the different roles of the various growth factors.

Their clinical application in skeletal muscle injuries should be optimized and even combined with new techniques such as gene therapy and tissue engineering, not merely based on experimental studies or empirical evidence.

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EXHIBIT M-3

ACP

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Noninvasive Treatments for Acute, Subacute, and Chronic Low Back Pain: A Clinical Practice Guideline From the American College of Physicians FREE

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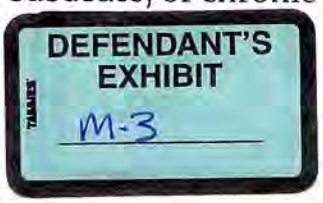
Abstract

Description: The American College of Physicians (ACP) developed this guideline to present the evidence and provide clinical recommendations on noninvasive treatment of low back pain.

Methods: Using the ACP grading system, the committee based these recommendations on a systematic review of randomized, controlled trials and systematic reviews published through April 2015 on noninvasive pharmacologic and nonpharmacologic treatments for low back pain. Updated searches were performed through November 2016. Clinical outcomes evaluated included reduction or elimination of low back pain, improvement in back-specific and overall function, improvement in health-related quality of life, reduction in work disability and return to work, global improvement, number of back pain episodes or time between episodes, patient satisfaction, and adverse effects.

Target Audience and Patient Population: The target audience for this guideline includes all clinicians, and the target patient population includes adults with acute, subacute, or chronic low back pain.



Recommendation 1: *Given that most patients with acute or subacute low back pain improve over time regardless of treatment, clinicians and patients should select nonpharmacologic treatment with superficial heat (moderate-quality evidence), massage, acupuncture, or spinal manipulation (low-quality evidence). If pharmacologic treatment is desired, clinicians and patients should select nonsteroidal anti-inflammatory drugs or skeletal muscle relaxants (moderate-quality evidence). (Grade: strong recommendation)*

Recommendation 2: *For patients with chronic low back pain, clinicians and patients should initially select nonpharmacologic treatment with exercise, multidisciplinary rehabilitation, acupuncture, mindfulness-based stress reduction (moderate-quality evidence), tai chi, yoga, motor control exercise, progressive relaxation, electromyography biofeedback, low-level laser therapy, operant therapy, cognitive behavioral therapy, or spinal manipulation (low-quality evidence). (Grade: strong recommendation)*

Recommendation 3: *In patients with chronic low back pain who have had an inadequate response to nonpharmacologic therapy, clinicians and patients should consider pharmacologic treatment with nonsteroidal anti-inflammatory drugs as first-line therapy, or tramadol or duloxetine as second-line therapy. Clinicians should only consider opioids as an option in patients who have failed the aforementioned treatments and only if the potential benefits outweigh the risks for individual patients and after a discussion of known risks and realistic benefits with patients. (Grade: weak recommendation, moderate-quality evidence)*

Low back pain is one of the most common reasons for physician visits in the United States. Most Americans have experienced low back pain, and approximately one quarter of U.S. adults reported having low back pain lasting at least 1 day in the past 3 months (1). Low back pain is associated with high costs, including those related to health care and indirect costs from missed work or reduced productivity (2). The total costs attributable to low back pain in the United States were estimated at $100 billion in 2006, two thirds of which were indirect costs of lost wages and productivity (3).

Low back pain is frequently classified and treated on the basis of symptom duration,

potential cause, presence or absence of radicular symptoms, and corresponding anatomical or radiographic abnormalities. Acute back pain is defined as lasting less than 4 weeks, subacute back pain lasts 4 to 12 weeks, and chronic back pain lasts more than 12 weeks. Radicular low back pain results in lower extremity pain, paresthesia, and/or weakness and is a result of nerve root impingement. Most patients with acute back pain have self-limited episodes that resolve on their own; many do not seek medical care (4). For patients who do seek medical care, pain, disability, and return to work typically improve rapidly in the first month (5). However, up to one third of patients report persistent back pain of at least moderate intensity 1 year after an acute episode, and 1 in 5 report substantial limitations in activity (6). Many noninvasive treatment options are available for radicular and nonradicular low back pain, including pharmacologic and nonpharmacologic interventions.

Guideline Focus and Target Population

The purpose of this American College of Physicians (ACP) guideline is to provide treatment guidance based on the efficacy, comparative effectiveness, and safety of noninvasive pharmacologic and nonpharmacologic treatments for acute (<4 weeks), subacute (4 to 12 weeks), and chronic (>12 weeks) low back pain in primary care. This guideline does not address topical pharmacologic therapies or epidural injection therapies. It serves as a partial update of the 2007 ACP guideline (it excludes evidence on diagnosis). These recommendations are based on 2 background evidence reviews (7, 8) and a systematic review sponsored by the Agency for Healthcare Research and Quality (AHRQ) (9). The target audience for this guideline includes all clinicians, and the target patient population includes adults with acute, subacute, or chronic low back pain.

Methods

Systematic Review of the Evidence

The evidence review was conducted by the AHRQ's Pacific Northwest Evidence-based Practice Center. Additional methodological details can be found in the Appendix as well as in

the accompanying articles (7, 8) and full report (9). Reviewers searched several databases for studies published in English from January 2008 through April 2015 and updated the search through November 2016. Studies published before 2007 were identified using the 2007 ACP/American Pain Society (APS) systematic reviews (10, 11). Reviewers combined data when possible using meta-analysis and assessed risk of bias and study quality according to established methods. The study population included adults (aged ≥18 years) with acute, subacute, or chronic nonradicular low back pain, radicular low back pain, or symptomatic spinal stenosis.

The review evaluated pharmacologic (acetaminophen, nonsteroidal anti-inflammatory drugs [NSAIDs], opioids, skeletal muscle relaxants [SMRs], benzodiazepines, antidepressants, antiseizure medications, and systemic corticosteroids) and nonpharmacologic (psychological therapies, multidisciplinary rehabilitation, spinal manipulation, acupuncture, massage, exercise and related therapies, and various physical modalities) treatments for low back pain. Evaluated outcomes included reduction or elimination of low back pain, improvement in back-specific and overall function, improvement in health-related quality of life, reduction in work disability, return to work, global improvement, number of back pain episodes or time between episodes, patient satisfaction, and adverse effects.

The magnitude of effect (small, moderate, or large) was determined as previously described (10, 11). A small effect on pain was defined as a mean between-group difference after treatment of 5 to 10 points on a visual analogue scale of 0 to 100 or equivalent, a mean between-group difference of 0.5 to 1.0 point on a numerical rating scale of 0 to 10, or a standardized mean difference of 0.2 to 0.5. A moderate effect was defined as a mean between-group difference of greater than 10 to no more than 20 points on a visual analogue scale of 0 to 100 or equivalent, a mean between-group difference of greater than 1.0 to no more than 2.0 points on a numerical rating scale of 0 to 10 or equivalent, or a standardized mean difference greater than 0.5 but no more than 0.8. For function, a small effect was defined as a mean between-group difference of 5 to 10 points on the Oswestry Disability Index (ODI), a mean between-group difference of 1 to 2 points on the Roland Morris Disability Questionnaire (RDQ), or a standardized mean difference of 0.2 to 0.5. A moderate

effect on function was defined as a mean between-group difference of greater than 10 to no more than 20 points on the ODI, a mean between-group difference of greater than 2 to no more than 5 points on the RDQ, or a standardized mean difference greater than 0.5 but no more than 0.8. No large effects were found with any intervention.

Grading the Evidence and Developing Recommendations

This guideline was developed by ACP's Clinical Guidelines Committee (CGC) according to ACP's guideline development process, details of which can be found in the methods paper (12). The CGC used the evidence tables in the accompanying evidence reviews (7, 8) and full report (9) when reporting the evidence and graded the recommendations using the ACP's guideline grading system (Table).

Table. The American College of Physicians Guideline Grading System*

Table. The American College of Physicians Guideline Grading System*

Quality of Evidence	Strength of Recommendation	
	Benefits Clearly Outweigh Risks and Burden or Risks and Burden Clearly Outweigh Benefits	Benefits Finely Balanced With Risks and Burden
High	Strong	Weak
Moderate	Strong	Weak
Low	Strong	Weak
Insufficient evidence to determine net benefits or risks		

* Adopted from the classification developed by the GRADE (Grading of Recommendations Assessment, Development and Evaluation) workgroup.

Peer Review

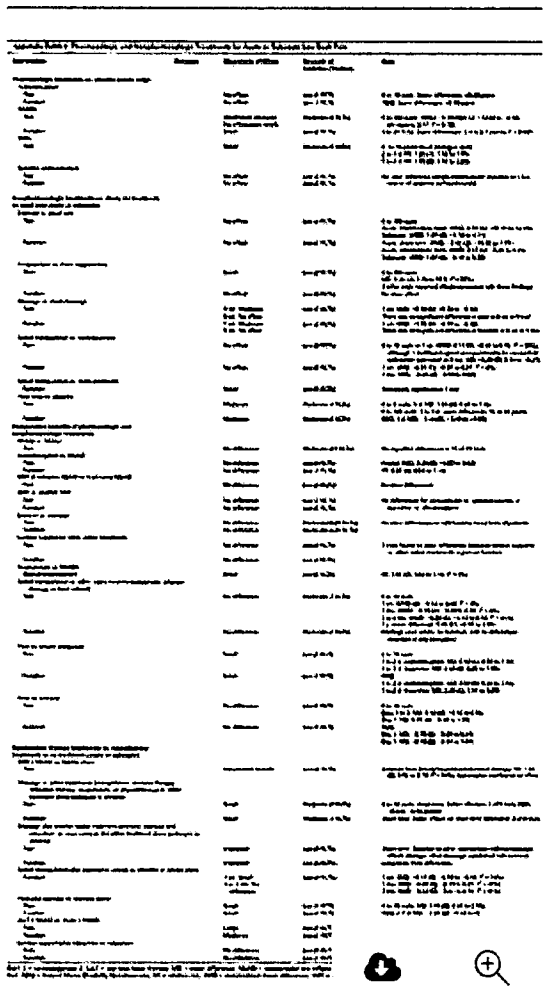
The AHRQ systematic review was sent to invited peer reviewers and posted on the AHRQ Web site for public comments. The accompanying evidence reviews (7, 8) also underwent a peer review process through the journal. The guideline underwent a peer review process through the journal and was posted online for comments from ACP Regents and ACP Governors, who represent ACP members at the regional level.

Benefits and Comparative Benefits of Pharmacologic Therapies

Acute or Subacute Low Back Pain

Appendix Table 1 summarizes the findings for all therapies for acute or subacute low back pain.

Appendix Table 1. Pharmacologic and Nonpharmacologic Treatments for Acute or Subacute Low Back Pain



Acetaminophen

Low-quality evidence showed no difference between acetaminophen and placebo for pain intensity or function through 4 weeks or between acetaminophen and NSAIDs for pain intensity or likelihood of experiencing global improvement at 3 weeks or earlier (13, 14).

NSAIDs

Moderate-quality evidence showed that NSAIDs were associated with a small improvement in pain intensity compared with placebo (14, 15), although several randomized, controlled trials (RCTs) showed no difference in likelihood of achieving pain relief with NSAIDs compared with placebo (16–18). Low-quality evidence showed a small increase in function with NSAIDs compared with placebo (19). Moderate-quality evidence showed that most head-to-head trials of one NSAID versus another showed no differences in pain relief in patients with acute low back pain (14). Low-quality evidence showed no differences in pain

between cyclooxygenase (COX)-2–selective NSAIDs versus traditional NSAIDs (14).

SMRs

Moderate-quality evidence showed that SMRs improved short-term pain relief compared with placebo after 2 to 4 and 5 to 7 days (20, 21). Low-quality evidence showed no differences between different SMRs for any outcomes in patients with acute pain (20). Low-quality evidence showed inconsistent findings for the effect on pain intensity with a combination of SMRs plus NSAIDs compared with NSAIDs alone (20, 22, 23).

Systemic Corticosteroids

Low-quality evidence showed no difference in pain or function between a single intramuscular injection of methylprednisolone or a 5-day course of prednisolone compared with placebo in patients with acute low back pain (24, 25).

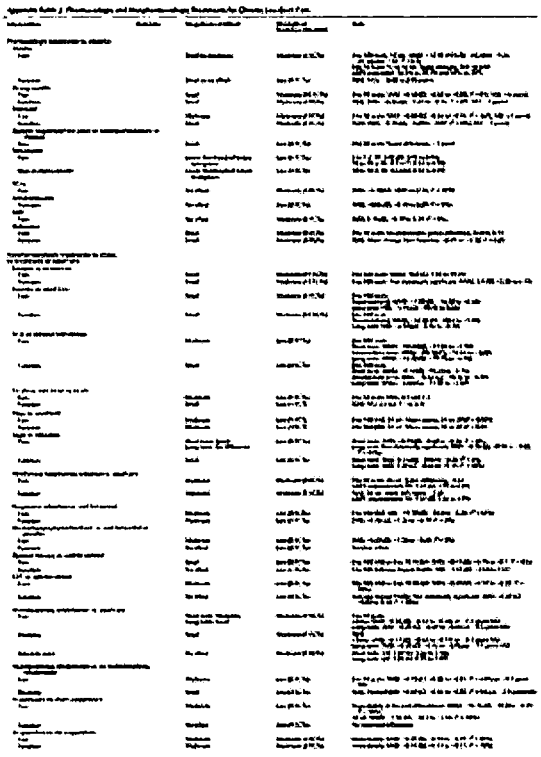
Other Therapies

Evidence was insufficient to determine effectiveness of antidepressants, benzodiazepines (26, 27), antiseizure medications, or opioids versus placebo in patients with acute or subacute low back pain.

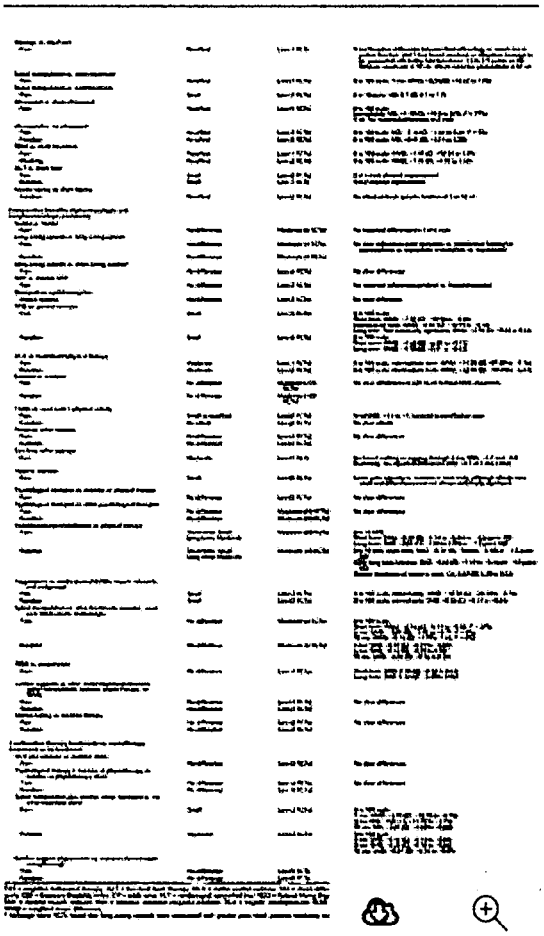
Chronic Low Back Pain

Appendix Table 2 summarizes the findings for all therapies for chronic low back pain.

Appendix Table 2. Pharmacologic and Nonpharmacologic Treatments for Chronic Low Back Pain



Appendix Table 2. Continued



NSAIDs

Moderate-quality evidence showed that NSAIDs were associated with small to moderate pain improvement compared with placebo (14, 28, 29). Low-quality evidence showed that NSAIDs

were associated with no to small improvement in function (28–31). Moderate-quality evidence showed that most head-to-head trials of one NSAID versus another showed no differences in pain relief in patients with chronic low back pain (14). There were no data on COX-2–selective NSAIDs.

Opioids

Moderate-quality evidence showed that strong opioids (tapentadol, morphine, hydromorphone, and oxymorphone) were associated with a small short-term improvement in pain scores (about 1 point on a pain scale of 0 to 10) and function compared with placebo (32–36). Low-quality evidence showed that buprenorphine patches improved short-term pain more than placebo in patients with chronic low back pain; however, the improvement corresponded to less than 1 point on a pain scale of 0 to 10 (37–40). Moderate-quality evidence showed no differences among different long-acting opioids for pain or function (33, 41–44), and low-quality evidence showed no clear differences in pain relief between long- and short-acting opioids (45–50). Moderate-quality evidence showed that tramadol achieved moderate short-term pain relief and a small improvement in function compared with placebo (32, 51, 52).

SMRs

Evidence comparing SMRs versus placebo was insufficient (53–55). Low-quality evidence showed no differences in any outcome between different SMRs for treatment of chronic low back pain (20).

Benzodiazepines

Low-quality evidence showed that tetrazepam improved pain relief at 5 to 7 days and resulted in overall improvement at 10 to 14 days compared with placebo (20).

Antidepressants

Moderate-quality evidence showed no difference in pain between tricyclic antidepressants (TCAs) or selective serotonin reuptake inhibitors (SSRIs) versus placebo, and low-quality evidence showed no differences in function for antidepressants (56). Moderate-quality evidence showed that duloxetine was associated with a small improvement in pain intensity and function compared with placebo (57–59).

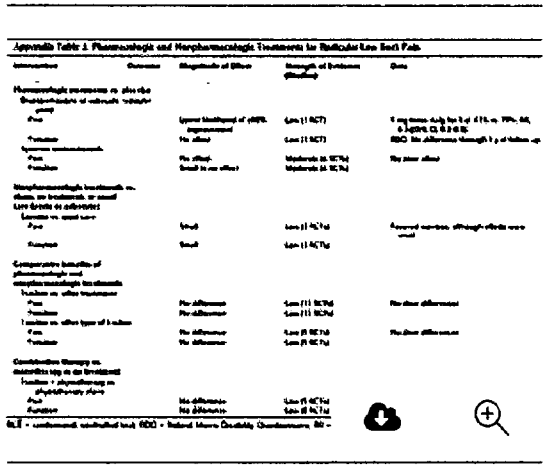
Other Therapies

Evidence was insufficient to determine the effect of acetaminophen, systemic corticosteroids, or antiseizure medications on chronic low back pain.

Radicular Low Back Pain

Appendix Table 3 summarizes the findings for all treatments for radicular low back pain.

Appendix Table 3. Pharmacologic and Nonpharmacologic Treatments for Radicular Low Back Pain



Benzodiazepines

Low-quality evidence showed no difference between diazepam and placebo for function at 1 week through 1 year and analgesic use, return to work, or likelihood of surgery through 1 year of follow-up in patients with acute or subacute radicular pain (60). Diazepam resulted in a lower likelihood of pain improvement at 1 week compared with placebo.

Systemic Corticosteroids

Moderate-quality evidence showed no differences in pain between systemic corticosteroids and placebo and no to small effect on function in patients with radicular low back pain (61–66).

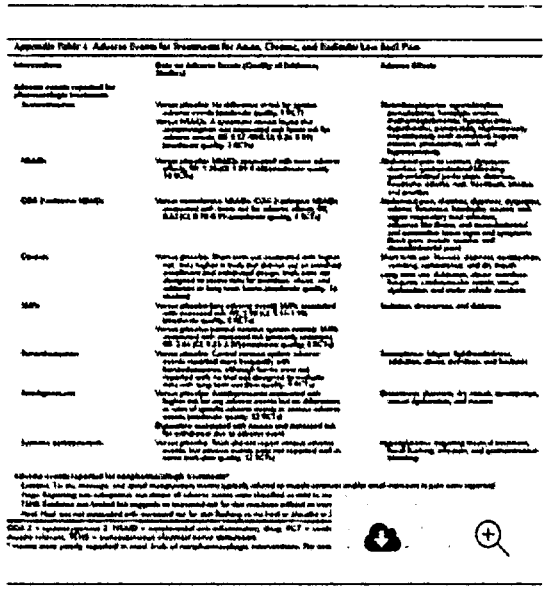
Other Therapies

No RCTs evaluated acetaminophen, SMRs, antidepressants, or opioids for radicular low back pain. Results for NSAIDs were inconsistent for pain, and evidence was therefore insufficient (22). There was insufficient evidence to determine the effect of antiseizure medications on radicular low back pain (67–71).

Harms of Pharmacologic Therapies

Harms were derived from the identified systematic reviews. Adverse effects generally associated with the drugs can be found in Appendix Table 4.

Appendix Table 4. Adverse Events for Treatments for Acute, Chronic, and Radicular Low Back Pain



Moderate-quality evidence showed no difference among scheduled acetaminophen, acetaminophen taken as needed, or placebo for serious adverse events (13). Moderate-quality evidence showed that more adverse effects occurred with NSAIDs than placebo, COX-2–selective NSAIDs were associated with a decreased risk for adverse effects compared with traditional NSAIDs, and acetaminophen was associated with a lower risk for adverse effects than NSAIDs (14). Moderate-quality evidence showed that short-term use of opioids increased nausea, dizziness, constipation, vomiting, somnolence, and dry mouth compared with placebo, and SMRs increased risk for any adverse event and central nervous system adverse events (mostly sedation) compared with placebo (20). Moderate-quality evidence showed that antidepressants increased risk for any adverse event compared with placebo, although rates of specific adverse events did not differ (72). The risk for serious adverse events did not differ between duloxetine and placebo, although duloxetine was associated with increased risk for withdrawal due to adverse events (57–59). Low-quality evidence showed no clear differences in adverse effects for gabapentin versus placebo (67, 68). Low-quality evidence showed that benzodiazepines caused more frequent somnolence, fatigue, and lightheadedness than placebo (20). Harms were not well-reported, and no RCTs assessed long-term use of benzodiazepines or risks for addiction, abuse, or overdose. Adverse events

for systemic corticosteroids were not well-reported in RCTs, but the largest trial found that oral prednisone was associated with increased risk for any adverse event, insomnia, nervousness, and increased appetite (66). However, low-quality evidence showed no cases of hyperglycemia that required medical attention (24, 61, 64).

Comparative Benefits of Nonpharmacologic Therapies

Acute or Subacute Low Back Pain

Exercise

Low-quality evidence showed no difference between exercise therapy and usual care for pain or function in patients with acute or subacute pain (11); additional trials reported inconsistent results (73–75). Moderate-quality evidence showed no clear differences between different exercise regimens in more than 20 head-to-head RCTs in patients with acute low back pain.

Acupuncture

Low-quality evidence showed that acupuncture resulted in a small decrease in pain intensity compared with sham acupuncture with nonpenetrating needles, but there were no clear effects on function (76–78). Low-quality evidence showed that acupuncture slightly increased the likelihood of overall improvement compared with NSAIDs (76, 79–83).

Massage

Low-quality evidence showed that massage moderately improved short-term (1 week) pain and function compared with sham therapy for subacute low back pain (84), although 1 trial (85) showed no difference in pain or function at 5 weeks. Moderate-quality evidence showed that massage improved short-term pain relief and function compared with other interventions (manipulation, exercise therapy, relaxation therapy, acupuncture, or physiotherapy) for patients with subacute to chronic low back pain, but effects were small (84, 86). Low-quality evidence showed that a combination of massage plus another intervention (exercise, exercise and education, or usual care) was superior to the other intervention alone for short-term pain in patients with subacute to chronic low back pain

(84).

Spinal Manipulation

Low-quality evidence showed that spinal manipulation was associated with a small effect on function compared with sham manipulation; evidence was insufficient to determine the effect on pain (87, 88). Low-quality evidence showed no difference in pain relief at 1 week between spinal manipulation and inert treatment (educational booklet, detuned ultrasound, detuned or actual short-wave diathermy, antiedema gel, or bed rest), although 1 trial showed better longer-term pain relief (3 months) with spinal manipulation (89). Function did not differ between spinal manipulation and inert treatment at 1 week or 3 months (89). Moderate-quality evidence showed no difference between spinal manipulation and other active interventions for pain relief at 1 week through 1 year or function (analyses included exercise, physical therapy, or back school as the comparator) (89, 90). Low-quality evidence showed that a combination of spinal manipulation plus exercise or advice slightly improved function at 1 week compared with exercise or advice alone, but these differences were not present at 1 or 3 months (89).

Superficial Heat

Moderate-quality evidence showed that a heat wrap moderately improved pain relief (at 5 days) and disability (at 4 days) compared with placebo (91). Low-quality evidence showed that a combination of heat plus exercise provided greater pain relief and improved RDQ scores at 7 days compared with exercise alone in patients with acute pain (92). Low-quality evidence showed that a heat wrap provided more effective pain relief and improved RDQ scores compared with acetaminophen or ibuprofen after 1 to 2 days (93). Low-quality evidence showed no clear differences between a heat wrap and exercise in pain relief or function (92).

Low-Level Laser Therapy

Low-quality evidence showed that a combination of low-level laser therapy (LLLT) and NSAIDs largely decreased pain intensity and resulted in a moderate improvement in function (as measured by the ODI) compared with sham laser therapy plus NSAIDs in patients with acute or subacute pain (94).

Lumbar Supports

Low-quality evidence showed no difference in pain or function between lumbar supports added to an educational program compared with an educational program alone or other active interventions in patients with acute or subacute low back pain (95).

Other Therapies

Evidence was insufficient to determine the effectiveness of transcutaneous electrical nerve stimulation (TENS), electrical muscle stimulation, inferential therapy, short-wave diathermy, traction, superficial cold, motor control exercise (MCE), Pilates, tai chi, yoga, psychological therapies, multidisciplinary rehabilitation, ultrasound, and taping.

Chronic Low Back Pain

Exercise

Moderate-quality evidence showed that exercise resulted in a small improvement in pain relief and function compared with no exercise (11, 96). Moderate-quality evidence showed that compared with usual care, exercise resulted in small improvements in pain intensity and function at the end of treatment, although effects were smaller at long-term follow-up (96). Moderate-quality evidence showed no clear differences between different exercise regimens in more than 20 head-to-head RCTs in patients with chronic low back pain.

MCE

Motor control exercise focuses on restoring coordination, control, and strength of the muscles that control and support the spine. Low-quality evidence showed that MCE moderately decreased pain scores and slightly improved function in short- to long-term follow-up compared with a minimal intervention (97). Low-quality evidence showed that MCE resulted in small improvements in pain intensity at short-term (≥6 weeks to <4 months) and intermediate-term (≥4 to <8 months) follow-up compared with general exercise, although improvements were small and no longer significant at long-term follow-up (97). Motor control exercise also resulted in small improvements in function in the short and long term (97). Low-quality evidence showed that MCE resulted in a moderate improvement in pain intensity and function compared with multimodal physical therapy at intermediate follow-up (97). Low-quality evidence showed no clear differences in pain with

a combination of MCE plus exercise versus exercise alone (98, 99).

Pilates

Low-quality evidence showed that Pilates resulted in small or no clear effects on pain and no clear effects on function compared with usual care plus physical activity (100–107). Low-quality evidence showed no clear differences between Pilates and other types of exercise for pain or function (108–110).

Tai Chi

Low-quality evidence showed that tai chi resulted in moderate pain improvement compared with wait-list controls or no tai chi (111, 112), and 1 study showed a small increase in function (111). Moderate-quality evidence showed that tai chi moderately decreased pain intensity at 3 and 6 months compared with backward walking or jogging but not versus swimming (112).

Yoga

Low-quality evidence showed that Iyengar yoga resulted in moderately lower pain scores and improved function compared with usual care at 24 weeks (113). Low-quality evidence showed that yoga resulted in a small decrease in pain intensity compared with exercise (114–118). Low-quality evidence showed that, compared with education, yoga resulted in a small decrease in short-term (≤12 weeks) but not long-term (about 1 year) pain intensity and a small increase in short- and long-term function (119).

Psychological Therapies

Low-quality evidence showed that progressive relaxation therapy moderately improved pain intensity and functional status compared with wait-list controls (120). Low-quality evidence showed that electromyography biofeedback training moderately decreased pain intensity (reduction of 5 to 13 points on a 100-point pain scale) compared with wait-list controls, but there was no effect on function (120). Low-quality evidence showed that operant therapy (behavioral therapy involving reinforcement) slightly improved pain intensity compared with wait-list control, although there was no difference for function (120). Low-quality evidence showed that cognitive behavioral therapy (CBT) and other combined psychological therapies (involving education, problem-solving training, coping techniques, imagery, relaxation, goal setting, cognitive pain control, and exercises) were associated with

moderately improved pain intensity compared with wait-list controls, but there was no difference in function (120). Moderate-quality evidence showed that mindfulness-based stress reduction is an effective treatment for chronic low back pain. One study showed a small improvement in pain at 26 and 52 weeks and in function at 26 weeks compared with usual care (121). The same study showed no difference between mindfulness-based stress reduction and CBT for improvements in pain or function. Two other studies showed improvement in pain and function compared with education (122, 123). Low-quality evidence showed no difference between psychological therapies and exercise or physical therapy for pain intensity (120). Low-quality evidence showed no differences in pain or function between a combination of psychological therapy plus exercise or physiotherapy compared with exercise or physiotherapy alone (120). Moderate-quality evidence showed no differences between different psychological therapies for pain or function outcomes (120).

Multidisciplinary Rehabilitation

Moderate-quality evidence showed that multidisciplinary rehabilitation moderately reduced short-term (<3 months) and slightly reduced long-term pain intensity and disability compared with usual care, although there was no difference in return to work (124). Low-quality evidence showed that multidisciplinary rehabilitation was associated with moderately lower short-term pain intensity and slightly lower disability than no rehabilitation (124). Moderate-quality evidence showed that multidisciplinary rehabilitation was associated with slightly lower short-term pain intensity and disability, moderately lower long-term pain intensity, and improved function compared with physical therapy and a greater likelihood of returning to work compared with nonmultidisciplinary rehabilitation (124).

Acupuncture

Low-quality evidence showed that acupuncture was associated with moderate improvement in pain relief immediately after treatment and up to 12 weeks later compared with sham acupuncture, but there was no improvement in function (125–130). Moderate-quality evidence showed that acupuncture was associated with moderately lower pain intensity and improved function compared with no acupuncture at the end of treatment (125). Low-quality evidence showed a small improvement in pain relief and function compared with

medications (NSAIDs, muscle relaxants, or analgesics) (125).

Massage

Low-quality evidence showed no difference in pain between foot reflexology and usual care for patients with chronic low back pain (131–133). Moderate-quality evidence showed that massage improved short-term pain relief and function compared with other interventions (manipulation, exercise therapy, relaxation therapy, acupuncture, physiotherapy, or TENS) for patients with subacute to chronic low back pain, although effects were small (84, 86). Low-quality evidence showed that a combination of massage plus another intervention (exercise, exercise and education, or usual care) was superior to the other intervention alone for short-term pain in patients with subacute to chronic low back pain (84).

Spinal Manipulation

Low-quality evidence showed no difference in pain with spinal manipulation versus sham manipulation at 1 month (134, 135). Low-quality evidence showed that spinal manipulation slightly improved pain compared with an inert treatment (136–142). Moderate-quality evidence showed no clear differences in pain or function compared with another active intervention. Low-quality evidence showed that a combination of spinal manipulation with another active treatment resulted in greater pain relief and improved function at 1, 3, and 12 months compared with the other treatment alone (134, 143–147).

Ultrasound

Low-quality evidence showed no difference between ultrasound and sham ultrasound for pain at the end of treatment or 4 weeks after treatment (148–150). Low-quality evidence showed no difference between ultrasound and no ultrasound for pain or function (151, 152).

TENS

Low-quality evidence showed no difference between TENS and sham TENS for pain intensity or function at short-term follow-up (153). Low-quality evidence showed no difference between TENS and acupuncture in short- or long-term pain (154).

LLLT

Low-quality evidence showed that LLLT slightly improved pain compared with sham laser

(155–157), and 1 RCT (155) showed that LLLT slightly improved function compared with sham laser.

Lumbar Support

Evidence was insufficient to compare lumbar support versus no lumbar support. Low-quality evidence showed no difference between a lumbar support plus exercise (muscle strengthening) versus exercise alone for pain or function at 8 weeks or 6 months (158). Low-quality evidence showed no clear differences between lumbar supports and other active treatments (traction, spinal manipulation, exercise, physiotherapy, or TENS) for pain or function (159–161).

Taping

Low-quality evidence showed no differences between Kinesio taping and sham taping for back-specific function after 5 or 12 weeks, although effects on pain were inconsistent between the 2 trials (162, 163). Low-quality evidence showed no differences between Kinesio taping and exercise for pain or function (164, 165).

Other Therapies

Evidence was insufficient to determine the effectiveness of electrical muscle stimulation, interferential therapy, short-wave diathermy, traction, or superficial heat or cold.

Radicular Low Back Pain

Exercise

Low-quality evidence showed that exercise resulted in small improvements in pain and function compared with usual care or no exercise (166–168).

Traction

Low-quality evidence showed no clear differences between traction and other active treatments, between traction plus physiotherapy versus physiotherapy alone, or between different types of traction in patients with low back pain with or without radiculopathy (169).

Other Therapies

Evidence was insufficient for ultrasound, MCE, Pilates, tai chi, yoga, psychological therapies, multidisciplinary rehabilitation, acupuncture, massage, spinal manipulation, LLLT, electrical muscle stimulation, short-wave diathermy, TENS, interferential therapy, superficial heat or cold, lumbar support, and taping.

Harms of Nonpharmacologic Therapies

Evidence on adverse events from the included RCTs and systematic reviews was limited, and the quality of evidence for all available harms data is low. Harms were poorly reported (if they were reported at all) for most of the interventions.

Low-quality evidence showed no reported harms or serious adverse events associated with tai chi, psychological interventions, multidisciplinary rehabilitation, ultrasound, acupuncture, lumbar support, or traction (9, 95, 150, 170–174). Low-quality evidence showed that when harms were reported for exercise, they were often related to muscle soreness and increased pain, and no serious harms were reported. All reported harms associated with yoga were mild to moderate (119). Low-quality evidence showed that none of the RCTs reported any serious adverse events with massage, although 2 RCTs reported soreness during or after massage therapy (175, 176). Adverse events associated with spinal manipulation included muscle soreness or transient increases in pain (134). There were few adverse events reported and no clear differences between MCE and controls. Transcutaneous electrical nerve stimulation was associated with an increased risk for skin site reaction but not serious adverse events (177). Two RCTs (178, 179) showed an increased risk for skin flushing with heat compared with no heat or placebo, and no serious adverse events were reported. There were no data on cold therapy. Evidence was insufficient to determine harms of electrical muscle stimulation, LLLT, percutaneous electrical nerve stimulation, interferential therapy, short-wave diathermy, and taping.

Comparison of Conclusions With Those of the 2007 Guideline

Some evidence has changed since the 2007 ACP guideline and supporting evidence review.

The 2007 review concluded that acetaminophen was effective for acute low back pain, based on indirect evidence from trials of acetaminophen for other conditions and trials of acetaminophen versus other analgesics. However, this update included a placebo-controlled RCT in patients with low back pain that showed no difference in effectiveness between acetaminophen and placebo (low-quality evidence). In addition, contrary to the 2007 review, current moderate-quality evidence showed that TCAs were not effective for chronic low back pain compared with placebo. Additional pharmacologic treatments addressed in the current review included duloxetine and the antiseizure medication pregabalin. Many conclusions about nonpharmacologic interventions are similar between the 2007 review and the update. Additional modalities assessed (with at least low-quality evidence) include mindfulness-based stress reduction, MCE, taping, and tai chi. Additional evidence or changes from the updated review include that superficial heat was found to be more effective for acute or subacute low back pain (moderate-quality evidence) and neither ultrasound nor TENS was shown to be effective compared with controls (low-quality evidence).

The Figure summarizes the recommendations and clinical considerations. Additional details on the evidence are available in Appendix Tables 1, 2, 3 and 4 and the accompanying evidence reviews (7, 8).

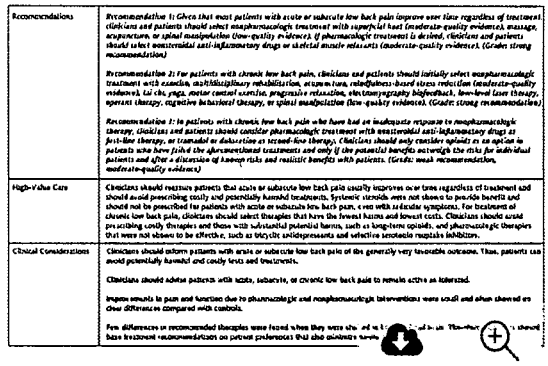
FIGURE.

Summary of the American College of Physicians guideline on noninvasive treatments for acute, subacute, or chronic low back pain.

COX-2 = cyclooxygenase-2; LLLT = low-level laser therapy; NSAID = nonsteroidal anti-inflammatory drug; SMR = skeletal muscle relaxant.

FIGURE.

Continued



Recommendations	*Recommendation 1: Given that most patients with acute or subacute low back pain improve over time regardless of treatment, clinicians and patients should select nonpharmacologic treatment with superficial heat (moderate-quality evidence), massage, acupuncture, or spinal manipulation (low-quality evidence). If pharmacologic treatment is desired, clinicians and patients should select nonsteroidal anti-inflammatory drugs or skeletal muscle relaxants (moderate-quality evidence). (Grade: strong recommendation)* *Recommendation 2: For patients with chronic low back pain, clinicians and patients should initially select nonpharmacologic treatment with exercise, multidisciplinary rehabilitation, acupuncture, mindfulness-based stress reduction (moderate-quality evidence), tai chi, yoga, motor control exercise, progressive relaxation, electromyography biofeedback, low-level laser therapy, operant therapy, cognitive behavioral therapy, or spinal manipulation (low-quality evidence). (Grade: strong recommendation)* *Recommendation 3: In patients with chronic low back pain who have had an inadequate response to nonpharmacologic therapy, clinicians and patients should consider pharmacologic treatment with nonsteroidal anti-inflammatory drugs as first-line therapy, or tramadol or duloxetine as second-line therapy. Clinicians should only consider opioids as an option in patients who have failed the aforementioned treatments and only if the potential benefits outweigh the risks for individual patients and after a discussion of known risks and realistic benefits with patients. (Grade: weak recommendation, moderate-quality evidence)*
High-Value Care	Clinicians should reassure patients that acute or subacute low back pain usually improves over time regardless of treatment and should avoid prescribing costly and potentially harmful treatments. Systemic steroids were not shown to provide benefit and should not be prescribed for patients with acute or subacute low back pain, even with sciatic symptoms. For treatment of chronic low back pain, clinicians should select therapies that have the fewest harms and lowest costs. Clinicians should avoid prescribing costly therapies and those with substantial potential harms, such as long-term opioids, and pharmacologic therapies that were not shown to be effective, such as tricyclic antidepressants and selective serotonin reuptake inhibitors.
Clinical Considerations	Clinicians should inform patients with acute or subacute low back pain of the generally very favorable outcome. Thus, patients can avoid potentially harmful and costly tests and treatments. Clinicians should advise patients with acute, subacute, or chronic low back pain to remain active as tolerated. Improvements in pain and function due to pharmacologic and nonpharmacologic interventions were small and often showed no clear differences compared with controls. Few differences in recommended therapies were found when they were stratified by [illegible] should base treatment recommendations on patient preferences that also minimize harms.

Recommendations

Recommendation 1: Given that most patients with acute or subacute low back pain improve over time regardless of treatment, clinicians and patients should select nonpharmacologic treatment with superficial heat (moderate-quality evidence), massage, acupuncture, or spinal manipulation (low-quality evidence). If pharmacologic treatment is desired, clinicians and patients should select nonsteroidal anti-inflammatory drugs or skeletal muscle relaxants (moderate-quality evidence). (Grade: strong recommendation)

Clinicians should inform all patients of the generally favorable prognosis of acute low back pain with or without sciatica, including a high likelihood for substantial improvement in the first month (5, 180). Clinicians should also provide patients with evidence-based information with regard to their expected course, advise them to remain active as tolerated, and provide information about effective self-care options. Clinicians and patients should use a shared decision-making approach to select the most appropriate treatment based on patient preferences, availability, harms, and costs of the interventions. Nonpharmacologic interventions shown to be effective for improving pain and function in patients with acute or subacute low back pain include superficial heat (moderate-quality evidence and moderate improvement in pain and function) and massage (low-quality evidence and small to moderate improvement in pain and function). Low-quality evidence showed that acupuncture had a small effect on improving pain and spinal manipulation had a small effect on improving function compared with sham manipulation but not inert treatment. Harms of nonpharmacologic interventions were sparsely reported, and no serious adverse events were

reported. Superficial heat was associated with increased risk for skin flushing, and massage and spinal manipulation were associated with muscle soreness.

We recommend that the choice between NSAIDs and SMRs be individualized on the basis of patient preferences and likely individual medication risk profile. Treatment with NSAIDs resulted in a small improvement in both pain intensity (moderate-quality evidence) and function (low-quality evidence), and treatment with SMRs resulted in a small improvement in pain relief (moderate-quality evidence). There was no evidence for the effect of SMRs on function. Nonsteroidal anti-inflammatory drugs are associated with gastrointestinal and renal risks. Clinicians should therefore assess renovascular and gastrointestinal risk factors before prescribing NSAIDs and recommend the lowest effective doses for the shortest periods necessary. Although they are associated with lower risk for adverse effects than nonselective NSAIDs, COX-2–selective NSAIDs were not assessed for improvement in pain or function. Skeletal muscle relaxants are associated with central nervous system adverse effects, especially sedation.

The updated evidence showed that acetaminophen was not effective at improving pain outcomes versus placebo. However, this study assessed pain at 3 weeks after the intervention, and evidence from head-to-head trials showed no difference between acetaminophen and NSAIDs. Low-quality evidence showed that systemic steroids were not effective in treating acute or subacute low back pain, and we recommend against these drugs for treatment of acute low back pain.

Recommendation 2: For patients with chronic low back pain, clinicians and patients should initially select nonpharmacologic treatment with exercise, multidisciplinary rehabilitation, acupuncture, mindfulness-based stress reduction (moderate-quality evidence), tai chi, yoga, motor control exercise, progressive relaxation, electromyography biofeedback, low-level laser therapy, operant therapy, cognitive behavioral therapy, or spinal manipulation (low-quality evidence). (Grade: strong recommendation)

Nonpharmacologic interventions are considered as first-line options in patients with chronic low back pain because fewer harms are associated with these types of therapies than with

pharmacologic options. It is important that physical therapies be administered by providers with appropriate training. Moderate-quality evidence showed that exercise therapy resulted in small improvements in pain and function. Specific components associated with greater effects on pain included individually designed programs, supervised home exercise, and group exercise; regimens that included stretching and strength training were most effective. Moderate-quality evidence showed that, compared with usual care, multidisciplinary rehabilitation resulted in moderate pain improvement in the short term (<3 months), small pain improvement in the long term, and small improvement in function in both the short and long term. Low-quality evidence showed that multidisciplinary rehabilitation resulted in a moderate improvement in pain and a small improvement in function compared with no multidisciplinary rehabilitation. Acupuncture had a moderate effect on pain and function compared with no acupuncture (moderate-quality evidence) and a moderate effect on pain with no clear effect on function compared with sham acupuncture (low-quality evidence). Moderate-quality evidence showed that mindfulness-based stress reduction resulted in small improvements in pain and function (small effect), and 1 study showed that it was equivalent to CBT for improving back pain and function.

Low-quality evidence showed that tai chi had a moderate effect on pain and a small effect on function. Tai chi sessions in included studies lasted 40 to 45 minutes and were done 2 to 5 times per week for 10 to 24 weeks. Low-quality evidence showed that yoga improved pain and function by a moderate amount compared with usual care and by a small amount compared with education. Low-quality evidence showed that MCE had a moderate effect on pain and a small effect on function. Motor control exercise, tai chi, and yoga were favored over general exercise (low-quality evidence).

Low-quality evidence showed that progressive relaxation had a moderate effect on pain and function, electromyography biofeedback and CBT each had a moderate effect on pain and no effect on function, and operant therapy had a small effect on pain and no effect on function. Low-quality evidence showed that LLLT had a small effect on pain and function. Low-quality evidence showed that spinal manipulation had a small effect on pain compared with inert treatment but no effect compared with sham manipulation. There were no clear differences between spinal manipulation and other active interventions (moderate-quality evidence).

Harms were poorly reported for nonpharmacologic therapies, although no serious harms were reported for any of the recommended interventions. Muscle soreness was reported for exercise, massage, and spinal manipulation.

Ultrasound, TENS, and Kinesio taping had no effect on pain or function compared with control treatments (low-quality evidence).

Recommendation 3: In patients with chronic low back pain who have had an inadequate response to nonpharmacologic therapy, clinicians and patients should consider pharmacologic treatment with nonsteroidal anti-inflammatory drugs as first-line therapy, or tramadol or duloxetine as second-line therapy. Clinicians should only consider opioids as an option in patients who have failed the aforementioned treatments and only if the potential benefits outweigh the risks for individual patients and after a discussion of known risks and realistic benefits with patients. (Grade: weak recommendation, moderate-quality evidence)

Pharmacologic therapy should be considered for patients with chronic low back pain who do not improve with nonpharmacologic interventions. Nonsteroidal anti-inflammatory drugs had a small to moderate effect on pain (moderate-quality evidence) and no to small effect on function (low-quality evidence) and should be the first option considered. Moderate-quality evidence showed no difference in pain improvement when different NSAIDs were compared with one another. Nonsteroidal anti-inflammatory drugs are associated with gastrointestinal and renal risks. Clinicians should therefore assess renovascular and gastrointestinal risk factors before prescribing NSAIDs and should recommend the lowest effective doses for the shortest periods necessary. COX-2–selective NSAIDs were not assessed for improvement in pain or function, although they are associated with lower risk for adverse effects than nonselective NSAIDs.

For second-line therapies, moderate-quality evidence showed that tramadol had a moderate effect on pain and a small effect on function in the short term. Of note, tramadol is a narcotic and, like other opioids, is associated with the risk for abuse (181). Moderate-quality evidence showed that duloxetine had a small effect on pain and function.

Moderate-quality evidence showed that opioids (morphine, oxymorphone, hydromorphone, and tapentadol) had a small effect on short-term pain and function. Low-quality evidence showed that buprenorphine (patch or sublingual) resulted in a small improvement in pain. Opioids should be the last treatment option considered and should be considered only in patients for whom other therapies have failed because they are associated with substantial harms. Moderate-quality evidence showed no difference in pain or function when different long-acting opioids were compared with one another. Harms of short-term use of opioids include increased nausea, dizziness, constipation, vomiting, somnolence, and dry mouth compared with placebo. Studies assessing opioids for the treatment of chronic low back pain did not address the risk for addiction, abuse, or overdose, although observational studies have shown a dose-dependent relationship between opioid use for chronic pain and serious harms (182).

Moderate-quality evidence showed that TCAs did not effectively improve pain or function (low-quality evidence) in patients with chronic low back pain, which is contrary to the 2007 guideline. In addition, moderate-quality evidence showed that SSRIs did not improve pain.

Areas of Inconclusive Evidence

Evidence is insufficient or lacking to determine treatments for radicular low back pain. Most RCTs enrolled a mixture of patients with acute, subacute, and chronic low back pain, so it is difficult to extrapolate the benefits of treatment compared with its duration. Use of opioids for chronic pain is an important area that requires further research to compare benefits and harms of therapy. The evidence is also insufficient for most physical modalities. Evidence is insufficient on which patients are likely to benefit from which specific therapy. Evidence on patient-important outcomes, such as disability or return to work, was largely unavailable, and available evidence showed no clear connection with improvements in pain.

High-Value Care

Clinicians should reassure patients that acute or subacute low back pain usually improves

over time, regardless of treatment. Thus, clinicians should avoid prescribing costly and potentially harmful treatments for these patients, especially narcotics. In addition, systemic steroids were not shown to provide benefit and should not be prescribed for patients with acute or subacute low back pain, even with radicular symptoms. For treatment of chronic low back pain, clinicians should select therapies that have the fewest harms and lowest costs because there were no clear comparative advantages for most treatments compared with one another. Clinicians should avoid prescribing costly therapies; those with substantial potential harms, such as long-term opioids (which can be associated with addiction and accidental overdose); and pharmacologic therapies that were not shown to be effective, such as TCAs and SSRIs.

Appendix: Detailed Methods

The evidence review was conducted by the AHRQ's Pacific Northwest Evidence-based Practice Center. Details of the ACP guideline development process can be found in ACP's methods paper (12). Disclosures of interests and management of any conflicts can be found at www.acponline.org/clinical_information/guidelines/guidelines/conflicts_cgc.htm.

Key Questions Addressed

1. What are the comparative benefits and harms of different pharmacologic therapies for acute or chronic nonradicular low back pain, radicular low back pain, or spinal stenosis, including NSAIDs, acetaminophen, opioids, muscle relaxants, antiseizure medications, antidepressants, corticosteroids, and topical or patch-delivered medications?

2. What are the comparative benefits and harms of different nonpharmacologic, noninvasive therapies for acute or chronic nonradicular low back pain, radicular low back pain, or spinal stenosis, including but not limited to interdisciplinary rehabilitation, exercise (various types), physical modalities (ultrasound, TENS, electrical muscle stimulation, interferential therapy, heat [various forms], and ice), traction tables/devices, back supports/bracing, spinal manipulation, various psychological therapies, acupuncture, massage therapy (various types), yoga, magnets, and low-level lasers?

Search Strategy

Reviewers searched MEDLINE, the Cochrane Central Register of Controlled Trials, and the Cochrane Database of Systematic Reviews for trials published from January 2008 through April 2015. Searches were updated through November 2016. Studies published before 2008 were identified using the 2007 ACP/APS systematic reviews (10, 11).

Quality Assessment

Randomized trials were evaluated using methods developed by the Cochrane Back Review Group and the AHRQ (183), and systematic reviews were assessed using AMSTAR (A Measurement Tool to Assess Systematic Reviews) (184).

Population Studied

Adults with acute, subacute, or chronic nonradicular low back pain, radicular low back pain, or symptomatic spinal stenosis.

Interventions Evaluated

Oral or topical pharmacologic therapies included NSAIDs, acetaminophen, opioids, tramadol and tapentadol, antidepressants, SMRs, benzodiazepines, corticosteroids, antiepileptic medications, capsaicin, and lidocaine.

Noninvasive, nonpharmacologic therapies included interdisciplinary or multicomponent rehabilitation (physical therapy plus psychological therapy with some coordination), psychological therapies, exercise and related interventions (such as yoga or tai chi), complementary and alternative medicine therapies (spinal manipulation, acupuncture, and massage), passive physical modalities (such as heat, cold, ultrasound, TENS, electrical muscle stimulation, interferential therapy, short-wave diathermy, traction, LLLT, and lumbar supports/braces), and taping.

Comparators

Interventions were compared with each other or with placebo (drug trials), sham (functionally inert) treatments, or no treatment.

Outcomes

Outcomes included reduction or elimination of low back pain (including related leg

symptoms), improvement in back-specific and overall function, improvement in health-related quality of life, reduction in work disability and return to work, global improvement, number of back pain episodes or time between episodes, patient satisfaction, and adverse effects of interventions.

Timing

Timing of outcomes was stratified as long-term (≥1 year) and short-term (≤6 months).

Setting

Settings included inpatient and outpatient.

Target Audience

The target audience includes all clinicians.

Target Patient Population

The target patient population includes adults with acute (<4 weeks), subacute (4 to 12 weeks), or chronic (>12 weeks) nonradicular low back pain, radicular low back pain, or symptomatic spinal stenosis. Children or adolescents with low back pain; pregnant women; and patients with low back pain from sources outside the back (nonspinal low back pain), fibromyalgia or other myofascial pain syndromes, and thoracic or cervical back pain are not included.

Peer Review

The AHRQ systematic review was sent to invited peer reviewers and posted on the AHRQ Web site for public comments. The accompanying evidence reviews (7, 8) also underwent a peer review process through the journal. The guideline underwent a peer review process through the journal and was posted online for comments from ACP Regents and ACP Governors, who represent ACP members at the regional level.

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EXHIBIT M-4

Wolters Kluwer

Subacute and chronic low back pain: Nonpharmacologic and pharmacologic treatment

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INTRODUCTION

Up to 84 percent of adults have low back pain at some time in their lives [1,2]. The long-term outcome of low back pain is generally favorable. In one prospective study, 90 percent of patients with low back pain seen initially in primary care did not seek care after three months [3]. However, symptoms may not completely resolve even among persons who no longer seek care. Given how common low back pain is, persistent symptoms affect millions of individuals. Subacute low back pain is commonly defined as back pain lasting between 4 and 12 weeks and chronic low back pain as pain that persists for 12 or more weeks.

The initial evaluation of patients with low back pain, regardless of its duration, includes history taking and a targeted physical examination focusing on neurologic screening to exclude serious underlying pathology (eg, malignancy, infection, or cauda equina syndrome). On the basis of this evaluation, patients are triaged into broad diagnostic categories that include nonspecific low back pain, radiculopathy, or other specific pathology (eg, spinal stenosis, ankylosing spondylitis, and vertebral compression fracture) [4-6]. (See "Evaluation of low back pain in adults".)

Most patients (>85 percent) who are seen in primary care have "nonspecific low back pain," which

is low back pain that cannot reliably be attributed to a specific disease or spinal pathology [7]. Rapid improvement in pain and disability and return to work are the norm in the first month [8]. Patients who do not improve within four weeks of the onset of low back symptoms should be reevaluated and may require further diagnostic testing to identify a specific cause for their symptoms. (See "Evaluation of low back pain in adults", section on 'Risk assessment subacute back pain' and "Evaluation of low back pain in adults", section on 'Risk assessment chronic back pain'.)

Despite persistent pain, patients with subacute symptoms still have a favorable prognosis. For patients whose symptoms persist beyond three months, however, the goal of treatment moves from "cure" to controlling pain, maintaining function, and preventing disability. Factors associated with development of chronic disability include preexisting psychologic conditions, other types of chronic pain, job dissatisfaction or stress, and dispute over compensation issues [9]. Effective methods for reducing the risk of progression to chronic pain have not been definitively identified [10,11].

It is likely that many patients with chronic low back pain are not receiving evidence-based care. One survey of households in North Carolina, for example, identified 732 adults with chronic low back pain [12]. Responses indicated overutilization of unproven interventions (traction, corsets), high use of second-line medications (opioids and muscle relaxants), and underutilization of exercise therapy and, for patients with depression, antidepressants.

A glossary of terms used in the discussion of low back pain is presented in the table (table 1). Criteria used in this review to classify magnitude of benefits for the most commonly reported outcomes (pain relief or improvement in function) are presented in the table (table 2).

Relatively few randomized trials have evaluated patients specifically with subacute low back pain [13], sciatica, or spinal stenosis [14,15]. Results from trials evaluating mixed populations (subacute with either acute or chronic patients) are commonly applied to both groups. This topic presents recommendations for initial management of patients with subacute and chronic low back pain. Interventional and surgical therapies for subacute and chronic low back pain and treatment recommendations for acute low back pain are discussed separately. (See "Subacute and chronic low back pain: Nonsurgical interventional treatment" and "Subacute and chronic low back pain: Surgical treatment" and "Treatment of acute low back pain".)

A summary of the multiple interventions for subacute and chronic low back pain discussed in these topics is presented in the tables (table 3 and table 4 and table 5 and table 6).

GENERAL APPROACH TO CARE

Overview — All patients with subacute and chronic low back pain should receive advice on self-care and instruction on the importance of maintaining activity as tolerated (see 'Self-care advice' below). We generally advise nonpharmacologic therapy initially and favor "active" interventions that are movement-based and/or address psychosocial contributors to pain. These include exercise, cognitive behavioral therapy (CBT), tai chi, yoga, other relaxation techniques (mindfulness-based stress reduction [MBSR], biofeedback, and progressive relaxation), and multidisciplinary rehabilitation. An emphasis on active therapies is consistent with a biopsychosocial approach to pain, engages patients in their care, and more directly aims to improve function, not just reduce pain. More "passive" interventions, such as acupuncture or spinal manipulation, can be used as adjunctive treatments during symptom flares.

For patients with subacute low back pain who have a high likelihood of spontaneous remission, self-care interventions and patient education may be sufficient. In persons with more severe symptoms who have risk factors for chronicity or who are not improving with self-care and education, short-term interventions such as superficial heat, massage, exercise therapy, spinal manipulation, or acupuncture may be considered. The choice among these interventions also depends on patient preference and their cost and accessibility; there are no data demonstrating superiority of one over another [6]. The STarT Back randomized trial showed that a risk-stratified approach in which patients with risk factors for chronicity received more intensive CBT-based exercise therapy was more effective than usual care [16]. (See 'Activity and physical treatments' below and 'Psychologic interventions' below and 'Physical modalities' below.)

Pharmacologic therapy is reasonable for those who have inadequate symptom control with nonpharmacologic measures. For patients with subacute low back pain who warrant pharmacologic therapy, a nonsteroidal antiinflammatory drug (NSAID) with or without a nonbenzodiazepine skeletal muscle relaxant is preferred over acetaminophen. For patients with chronic low back pain who have had an inadequate response to nonpharmacologic therapy, we suggest an NSAID as initial therapy and tramadol or duloxetine as second-line therapy. (See

'Pharmacologic therapies' below.)

Given the limited benefits and serious harms associated with opioids, clinicians should consider opioids as an option only in patients who have not responded to these management approaches and if the potential benefits outweigh the risks. (See 'Use of opioids' below.)

This approach is consistent with the 2017 updated guideline from the American College of Physicians for the management of acute, subacute, and chronic low back pain [17].

Self-care advice — All patients with low back pain, regardless of duration or severity, should be instructed in self-care techniques. Initial advice should stress the importance of maintaining activity as tolerated [6]. Patients who require a period of bedrest to relieve severe symptoms should be encouraged to return to normal activities as soon as possible.

A systematic review of randomized trials found that bedrest did not improve either function or pain, compared with usual activity, for patients with sciatica [18]. Advice to remain active was as effective as "standard" physical therapy (any combination of exercises, mobilization and/or manipulation, superficial heat or cold, and advice) for improvement in function in a randomized trial [19]. However, patients randomly assigned to physical therapy were more likely to report a perceived benefit than those receiving activity advice.

Self-care education books based on evidence-based guidelines (such as The Back Book [20]) are an inexpensive method for supplementing clinician-provided back information and advice [21]. Several randomized trials have shown self-care education books to be similar in effectiveness, or only slightly inferior, to interventions with higher direct costs, such as supervised exercise, massage, acupuncture, and spinal manipulation [18,22-24].

Bed mattress choice — Evidence regarding how bed mattress choice impacts back pain is limited. A medium-firm mattress may be the preferred mattress choice for patients with chronic back pain, based on findings from a European randomized trial (n = 313) in which patients randomly assigned to a firm mattress, compared with a medium-firm mattress, were less likely to experience improvement in pain-related disability at 90 days (68 versus 82 percent) [25]. The medium-firm mattress was superior to a firm mattress for improvement of pain while lying in bed (odds ratio [OR] 2.36, 95% CI 1.13-4.93) and pain-related disability (OR 2.10, 95% CI 1.24-3.56).

Although these results suggest providers should not recommend a firm mattress for chronic low back pain, the firmness rating scale was a European standard, and the term "medium-firm" may mean different things to different manufacturers in different countries.

Another randomized study comparing back conforming mattresses (waterbed and foam) with a firm mattress suggested less pain and improved sleep for the conforming mattresses, with higher dropout rates for patients assigned to the firm mattress [26].

Lumbar supports — There is no compelling evidence that lumbar supports are effective in patients with chronic low back pain. A systematic review of eight trials for the use of lumbar supports in the treatment of low back pain found overall poor study quality, inadequate randomization, and generally low compliance with the intervention [27]. The conclusion was that there was conflicting evidence whether lumbar supports used as supplements to other treatments were effective in the treatment of low back pain. A French multicenter open-label randomized trial published subsequent to the systematic review found that use of an elastic belt in patients with subacute low back pain modestly reduced the need for pain medication and improved functional status at 30 and 90 days [28]. However, longer-term outcomes are unknown, and if use of a belt leads to avoidance behaviors by reinforcing awareness of a "back problem" and activity restriction, it may discourage exercise participation. Thus, while lumbar supports are not routinely recommended, they may provide some benefit for patients with subacute low back pain who are actively engaged in recommended therapies, such as exercise, and who will remain active.

ACTIVITY AND PHYSICAL TREATMENTS

In addition to self-care instruction, all patients with subacute and chronic low back pain should be advised to remain as active as possible and to incorporate physical therapies into their treatment plan.

Exercise therapy — A number of different types of exercise are commonly used in patients with subacute or chronic low back pain. Exercise programs include motor control exercise (also known as specific stabilization exercise), core strengthening (eg, abdominal and trunk extensor), flexion/extension movements, directional preference, general physical fitness, aerobic exercise, mind-body exercises (eg, yoga and Pilates), and functional restoration programs. Most exercise

programs appear to be similarly effective, though a systematic review found that motor control exercise was associated with slightly less pain intensity and better function than general exercise [29]. Exercise therapy is safe, readily available, helps alleviate pain symptoms, and improves functionality. (See "Exercise-based therapy for low back pain".)

Spinal manipulation — Spinal manipulation is a form of manual therapy that involves the movement of a joint beyond its usual end range of motion, but not past its anatomic range of motion (termed the "paraphysiologic zone"). Loads are applied to the spine using short- or long-lever methods. Short-lever high-velocity movement of the joint is frequently accompanied by an audible cracking or popping sound. Spinal manipulation is most commonly associated with chiropractic providers, but is also performed by other providers, including osteopathic clinicians and physical therapists. (See "Spinal manipulation in the treatment of musculoskeletal pain", section on 'Types of manipulation'.)

A 2011 meta-analysis including 26 randomized trials in patients with chronic low back pain compared spinal manipulation with multiple treatments (general practitioner care, analgesics, physical therapy, exercises, or back school, massage, ultrasound, transcutaneous muscle stimulation, and attending a pain clinic) [30]. Spinal manipulation had small short-term effects on reducing pain and improving functional status compared with other interventions. Subsequent randomized trials support the finding of short-term benefits of spinal manipulation in patients with subacute and chronic low back pain [31,32]. A randomized trial of 192 patients with subacute and chronic back-related leg pain evaluated home exercise and advice with or without spinal manipulative therapy [32]. Spinal manipulation modestly improved leg pain at 12 weeks but not at 52 weeks. Another randomized trial in 107 adults with acute and subacute low back pain found that compared with usual care, manual spinal manipulation improved self-reported short-term disability and pain scores [33].

Serious adverse events following lumbar spinal manipulation (such as worsening lumbar disc herniation or cauda equina syndrome) are rare. (See "Spinal manipulation in the treatment of musculoskeletal pain", section on 'Risks of spinal manipulation'.)

Acupuncture — Acupuncture is an intervention consisting of the insertion of needles at specific predetermined acupuncture points. Evidence on the efficacy of acupuncture versus sham acupuncture is inconsistent. Systematic reviews found acupuncture moderately more effective than

no treatment for short-term (<3 months) pain relief and improvement in function, and more effective than sham acupuncture for pain relief, but not for improvement in function [34,35]. However, two well-blinded trials not included in the systematic reviews found no difference between acupuncture and sham acupuncture for either pain or function [36,37], although a subsequent meta-analysis including these studies still found that acupuncture reduced pain compared with sham and improved function compared with no intervention [38]. It is unclear if the effectiveness of sham acupuncture derives from some attribute of superficial needling or is solely a placebo effect. Acupuncture is likely to be most beneficial in patients who have high expectations of benefit [39]. (See "Acupuncture", section on 'Low back pain'.)

Massage — Interpretation of studies to evaluate the effectiveness of massage therapy in chronic low back pain is hampered by differences in the comparator interventions, types of massage, and duration and frequency of massage sessions. A systematic review including 25 trials found limited evidence for short-term benefits of massage. When compared with inactive controls, there was evidence of short-term improvement in symptoms for subacute and chronic low back pain, but no long-term benefits [40].

For example, one large randomized trial in 579 patients with chronic or recurrent low back pain found that six sessions of massage therapy, with or without a minimal exercise intervention, reduced disability and pain at three months compared with usual care, but benefits were not sustained at 12 months [41]. Another trial in 401 patients with chronic, nonspecific low back pain found that 10 sessions of massage therapy reduced disability and pain at 10 weeks compared with usual care [42]. The benefits waned over time with no clinically meaningful difference at 12 months' follow-up.

PSYCHOLOGIC INTERVENTIONS

These interventions are designed to address the negative psychologic impact of persistent pain, although yoga also involves movement that can directly affect pain and function.

Cognitive behavioral therapy — A variety of psychologic approaches to patients with chronic low back pain have been evaluated. A systematic review found cognitive behavioral therapy (CBT) superior to waitlist control for short-term pain relief, although there were no differences in function

[43]. Results were less conclusive for other types of psychologic intervention [44]. In a subsequent, 12-month randomized trial in patients with subacute or chronic low back pain, those randomly assigned to group CBT reported less pain and disability compared with no further treatment [45].

Mind-body interventions — Mind-body interventions, such as meditation and mindfulness techniques, have been evaluated for the treatment of chronic low back pain. Such interventions often incorporate cognitive behavioral principles and may include a movement component (eg, tai chi, yoga). There is some evidence that these interventions may be effective, but more research is needed to define optimal approaches.

Mindfulness-based stress reduction is a mind-body intervention that can be administered in group settings by laypersons. In a meta-analysis of seven randomized controlled trials involving 864 patients with low back pain, mindfulness-based stress reduction (MBSR) was associated with modest short-term improvements in pain intensity (mean difference [MD] -0.96 point on an 11-point numerical rating scale; 95% CI, -1.64 to -0.34) and physical functioning (MD 2.50 on SF-36 physical functioning subscale; 95% CI, 0.90 to 4.10) compared with usual care [46]. There were no serious adverse events reported.

As an example, in one of the trials included in the meta-analysis, among 342 adults with chronic low back pain, MBSR or CBT (training to change pain-related thoughts and behaviors) were more likely to have clinically meaningful improvement in self-reported function (MBSR, 60.5 percent; CBT, 57.7 percent; usual care, 44.1 percent) and pain bothersomeness (MBSR, 43.6 percent; CBT, 44.9 percent; usual care, 26.6 percent) [47]. There were no differences between the MBSR and CBT groups.

Yoga for low back pain is discussed elsewhere. (See "Exercise-based therapy for low back pain", section on 'Yoga'.)

EDUCATIONAL AND COMBINED INTERVENTIONS

Education — A number of educational interventions have been evaluated for chronic low back, including self-care advice and written booklets (see 'Self-care advice' above). Evidence on the effectiveness of more intensive, individualized educational interventions is limited. A systematic review identified no trials of individual education versus no education, although it included three

trials that found no differences between individual education and non-educational interventions (exercise therapy, yoga, or back school) in pain or function [48]. Data on the comparative effectiveness of different educational approaches or content are also limited. A 2011 systematic review and meta-analysis of pain neurophysiology education, also known as pain neuroscience education (ie, education that focuses on the neurophysiology of pain, including psychosocial contributors) identified two randomized controlled trials (n = 122) that met inclusion criteria [49]. The meta-analysis found that pain neurophysiology education was slightly more effective at improving short-term pain (difference of about 5 points on a 0 to 100 point pain scale) than education that focused on biomechanical aspects of pain. Education was provided by trained physical therapists. Independent validation of these results is needed, as both small trials in the meta-analysis were conducted by the same group that published the pain neurophysiology education manual. A subsequent small trial also found that pain neurophysiology education combined with exercise therapy was beneficial for reducing pain intensity and improving function compared with exercise therapy alone [50], but more rigorous trials are need to confirm the efficacy of this intervention.

Back school — Back school is an intervention originally developed in Sweden consisting of education and a skill program including exercise therapy. Generally, lessons are provided to groups of patients and supervised by a physical therapist or other therapist trained in back rehabilitation, although the content of back school interventions vary and back school based on the traditional Swedish approach is not widely available in the United States. Back school may be a reasonable therapeutic option in patients with subacute or chronic low back pain who are interested in it, but there is limited evidence supporting its effectiveness. There is overlap between back school and group exercise, educational interventions, and multidisciplinary rehabilitation.

A 2017 meta-analysis found very low-quality evidence that back school was modestly more effective than no treatment for short-term pain control (six trials; mean difference [MD] -6.10 on 0-100 point scales, 95% CI -10.18 to -2.01) and reducing short-term disability (three trials; MD -3.38 on 0-100 scales, 95% CI -6.70 to -0.05), but these effects were not seen in intermediate- or long-term follow-up [51]. In addition, back school was no more effective for pain control than medical care, passive physiotherapy, or exercise in intermediate- or long-term follow-up.

Multidisciplinary (interdisciplinary) rehabilitation — Multidisciplinary, or interdisciplinary, rehabilitation combines physical, vocational, educational, and/or behavioral components provided

by multiple health care professionals. Intensity and content of interdisciplinary therapy vary widely. These programs combine graded exercise therapy with a psychosocial approach, generally involving a psychologist. Multidisciplinary therapy can be similar to functional restoration programs which often focus on occupational aspects of rehabilitation; both approaches emphasize functional improvement and typically utilize a multidisciplinary approach with a strong psychological component.

A systematic review of 41 trials found multidisciplinary rehabilitation that included a physical component with a psychological component and/or a social/work-targeted component delivered by clinicians with different professional backgrounds was associated with larger improvements in pain and function than usual care or non-multidisciplinary physical treatments (eg, exercise therapy, physical modalities, manual therapy, education) [52]. Differences were about 0.5 points on a 0 to 10 point pain scale and 1.5 points on the Roland Morris functional scale. Multidisciplinary treatment also increased the likelihood of return to work compared with non-multidisciplinary physical treatments (odds ratio [OR] 1.87, 95% CI 0.73 to 1.47). There was no clear effect of intervention intensity on effectiveness of multidisciplinary rehabilitation.

Patients are more likely to benefit from multidisciplinary rehabilitation and functional restoration if they are highly motivated, as the regimens can be intensive (eg, >20 hours per week). The high cost of the more intensive programs limit their applicability; they may be most appropriate for patients who do not respond to single interventions or as an alternative to surgery. We advise referring clinicians be familiar with outcomes for specific programs, given the cost and heterogeneity of quality among programs [53].

Multidisciplinary programs may not be available in many communities. They are usually practiced in pain clinics or rehabilitation centers. It is uncertain whether providing the components of multidisciplinary rehabilitation outside of a formal program is as effective as a coordinated program. If not available, the primary care clinician may be left the task of coordinating a collaborative arrangement between the various specialists, for which the logistics are burdensome. Primary care clinicians may need to develop and coordinate an individualized care program, involving a physical or occupational therapist, a behavioral psychologist experienced in patients with musculoskeletal symptoms, and a rehabilitation or occupational clinician.

Functional restoration — Functional restoration, also known as work hardening, work

conditioning, or physical conditioning involves simulated or actual work tests in a supervised environment to improve strength, endurance, flexibility, and fitness [54]. This can be used for patients with subacute and chronic low back pain and for injured workers. (See "Exercise-based therapy for low back pain", section on 'Graded activities exercise/back boot camp/functional restoration'.)

PHYSICAL MODALITIES

A large number of physical modalities, in addition to the physical treatments already discussed, have been used in patients with chronic low back pain. For most of these modalities, there is little evidence of benefit from randomized, controlled studies [55], although patient expectations of benefit and placebo effects may play a role in their therapeutic value [39]. (See 'Activity and physical treatments' above.)

- **Interferential therapy** – Interferential therapy is the superficial application of a medium-frequency alternating current, modulated to produce low frequencies up to 150 Hz. There is no convincing evidence from three trials that interferential therapy is effective for chronic low back pain [56-58].

- **Low-level laser therapy** – Low-level laser therapy, used by some physical therapists, is provided as a single wavelength of light, between 632 and 904 nm, directed at the area of discomfort. For chronic low back pain or back pain of unspecified duration, four trials found laser therapy superior to sham therapy for pain relief and improvement in function up to one year following treatment [59-62]. However, another trial found no difference between laser and sham in patients also receiving exercise [63]. Another trial found no differences between laser, exercise, and the combination of laser plus exercise [64].

  A systematic review found some evidence of short-term benefit in relief of low back pain, compared with sham therapy, but protocols for treatment dose, duration, and wavelength were inconsistent [65]. The review concluded that data were insufficient to draw conclusions regarding effectiveness.

- **Ultrasound** – Despite being widely used for the treatment of many musculoskeletal pain syndromes, few studies have evaluated ultrasound. It is usually performed in combination with

other physical therapy modalities, and its beneficial effect is thought to be due to heating of deep tissues. For chronic low back pain, two small (n = 10 and n = 36) trials reported inconsistent results for ultrasound versus sham ultrasound, with the larger trial reporting no differences [66,67]. A systematic review concluded that ultrasound is ineffective in the treatment of chronic low back pain [68].

- **Shortwave diathermy** – Shortwave diathermy is the elevation of the temperature of deep tissues by application of shortwave electromagnetic radiation with a frequency range from 10 to 100 MHz. Two trials found no differences between shortwave diathermy and sham diathermy manipulation for chronic low back pain [69,70].

- **Traction** – Traction involves drawing or pulling in order to stretch the lumbar spine. A variety of methods are used and typically involve a harness around the lower rib cage and around the iliac crest, the pulling action performed via free weights and a pulley, motorized equipment, inversion techniques, or an overhead harness.

  For mixed-duration low back pain with or without sciatica, a systematic review found no convincing evidence from nine trials that continuous or intermittent traction is more effective than placebo, sham, or no treatment [71]. Although autotraction was more effective than placebo, sham, or no treatment in patients with sciatica, it was only evaluated in two trials with methodologic shortcomings.

- **Transcutaneous electrical nerve stimulation** – Transcutaneous electrical nerve stimulation (TENS) refers to the use of a small battery-operated device to provide continuous electrical impulses via surface electrodes, with the goal of providing symptomatic relief by modifying pain perception. A meta-analysis of nine trials comparing TENS with sham, placebo, or pharmacologic therapy found no improvement in lower back pain scores [72].

- **Percutaneous electrical nerve stimulation** – Percutaneous electrical nerve stimulation (PENS) involves insertion of acupuncture-like needles and applying low-level electrical stimulation. The insertion points target dermatomal levels for local pathology, rather than acupuncture points.

  Although several trials found PENS moderately to substantially superior to sham PENS for pain relief, effects on function were inconsistent, all trials had methodologic shortcomings, and

some trials only measured outcomes at the end of a two-week course of treatment [73-76]. PENS is not widely available in the United States.

PHARMACOLOGIC THERAPIES

Medications are commonly used for patients with low back pain. Most evidence of efficacy comes from short-term trials, so the relative benefits and safety of use for prolonged periods in patients with subacute and chronic pain is uncertain. Thus, limiting the duration of use for most medications is reasonable.

We recommend a nonsteroidal antiinflammatory drug (NSAID) for most patients with subacute or chronic back pain in whom medication is indicated. Representative data from two national databases in the United States, in which data from nearly 24,000 visits for spine disorders were analyzed (representative of approximately 440 million visits), found that use of NSAIDs and acetaminophen decreased between 2000 and 2010 (from 37 to 29 percent), while use of opioids increased (from 19 to 29 percent) [77].

Initial therapy — We suggest a short course of NSAIDs for an acute exacerbation of subacute or chronic low back pain. Acetaminophen may be a reasonable alternative in patients with a contraindication to NSAIDs, although evidence of its efficacy is limited.

A systematic review of randomized trials found that, compared with placebo, nonsteroidal medications are slightly more effective for pain relief and function in patients with chronic low back pain [78]. Systematic reviews of patients with osteoarthritis (not limited to the back) consistently found acetaminophen slightly inferior to NSAIDs for pain relief [79-82]. A 2016 Cochrane review concluded that there was high-quality evidence that acetaminophen showed no benefit compared with placebo in acute low back pain; there were no trials evaluating the effectiveness of oral acetaminophen versus placebo for subacute or chronic low back pain [83].

NSAIDs are associated with well-known gastrointestinal and renal side effects. Additionally, exposure to cyclooxygenase (COX)-2 selective inhibitors is associated with an increased risk of myocardial infarction [84]. Cardiovascular and gastrointestinal risk factors should be assessed before prescribing NSAIDs, and the lowest effective dose should be prescribed for the shortest period necessary. (See "Nonselective NSAIDs: Overview of adverse effects".)

Acetaminophen overdose can lead to severe hepatotoxicity and is the most common cause of acute liver failure in the United States [85]. Other possible adverse effects that have been associated with acetaminophen include chronic kidney disease, hypertension, and peptic ulcer disease. (See "Acetaminophen (paracetamol) poisoning in adults: Pathophysiology, presentation, and diagnosis" and "Epidemiology and pathogenesis of analgesic-related chronic kidney disease", section on 'Acetaminophen' and "Unusual causes of peptic ulcer disease", section on 'Acetaminophen' and "NSAIDs and acetaminophen: Effects on blood pressure and hypertension", section on 'Effects of acetaminophen on blood pressure'.)

Second-line therapy

Subacute low back pain — For patients who have subacute low back pain that does not respond to initial pharmacotherapy, we suggest the addition of a short course of nonbenzodiazepine muscle relaxant. In patients who cannot tolerate or have contraindications to muscle relaxants, combining NSAIDs and acetaminophen is an option, although there are few data to support the use of this combination.

A systematic review found insufficient evidence to determine whether skeletal muscle relaxants are effective for subacute or chronic low back pain [86]. In the only trial evaluating efficacy of a skeletal muscle relaxant available in the United States, there was no difference in short-term reduction of muscle spasm between cyclobenzaprine and placebo [87]. Pain relief and improvement in function were not reported in this trial. Two other trials evaluated flupirtine and tolperisone, which are not available in the United States. Both medications were more effective than placebo. The systematic review also found skeletal muscle relaxants associated with more central nervous system adverse events (primarily sedation) than placebo (relative risk [RR] 2.04, 95% CI 1.23-3.37) [86]. The skeletal muscle relaxant carisoprodol is classified as a controlled substance by the US Drug Enforcement Agency (DEA) because it is metabolized to meprobamate, a substance with abuse and addiction potential.

Chronic low back pain — We suggest tramadol or duloxetine as second-line therapy for patients with chronic low back pain that does not respond to NSAID therapy [17].

Tramadol is a dual mechanism drug that has weak affinity for the opioid receptor and is also a norepinephrine reuptake inhibitor. Tramadol may have a lower risk of constipation and dependence

than conventional opioids but carries a risk of serotonin syndrome, especially when combined with other serotonergic agents [88,89].

Three randomized trials found duloxetine more effective than placebo for low back pain [90-92]. However, all trials were sponsored by the drug manufacturer, differences were small (<1 point on 0 to 10 pain or function scales), and patients were more likely to discontinue duloxetine compared with placebo due to adverse effects. Duloxetine was approved by the US Food and Drug Administration (FDA) in 2012 for treatment of low back pain.

Short-term use of skeletal muscle relaxants may be considered as adjunctive therapy in patients with acute exacerbations of chronic low back pain [86], but there are insufficient data to recommend their use for chronic stable low back pain. The lack of clear benefit, the well-known side effects affecting the central nervous system, and the potential for dependence with some skeletal muscle relaxants suggest that this class of medication should not be recommended for prolonged use.

Use of opioids — Opioids may be appropriate for short-term use in selected patients with severe acute exacerbations of low back pain but should not be used routinely and should be used with caution for long-term treatment of patients with chronic back pain [93]. Opioid use should be monitored closely and restricted to patients not highly vulnerable to drug dependence, abuse, or addiction. (See "Overview of the treatment of chronic non-cancer pain".)

Systematic reviews and meta-analyses of opioid use specifically for chronic back pain identified few high-quality or long-term trials [94-96]. Compared with placebo, opioids had short-term efficacy for the relief of pain and improvement of function, but the degree of improvement in pain and function was modest and of questionable clinical significance. Very few trials compared opioids with NSAIDs or antidepressants; in those trials, no difference was seen in pain or function.

The first long-term (one year) randomized trial of an opioid versus nonopioid medication strategy for chronic low back pain and osteoarthritis included 240 patients from Veterans Affairs primary care clinics with moderate to severe chronic back pain or hip or knee osteoarthritis [97]. Improvement in pain-related function was no different in opioid-treated patients compared with nonopioid-treated patients, while pain intensity was slightly better in nonopioid-treated patients. Patients treated with opioids experienced more side effects.

Studies of the use of opioids for chronic and subacute low back pain rarely quantify the risk of important adverse events, such as abuse or addiction, and typically excluded patients at higher risk for these types of adverse events. One systematic review found aberrant drug-taking behaviors in up to 24 percent of patients receiving opioids for low back pain, but most studies had important methodologic shortcomings, including poorly described or validated methods for identifying aberrant drug-related behaviors [94]. The use of opioids for patients with low back symptoms increased in the United States between 2000 and 2010 [77].

Other drugs

Antidepressants — Duloxetine, a serotonin-norepinephrine reuptake inhibitor, is a reasonable adjunctive option for patients with chronic back pain who do not respond to initial pharmacotherapeutic interventions (see 'Chronic low back pain' above). Otherwise, the role of antidepressants for the treatment of back pain is limited. Although tricyclic antidepressants have been used to treat various other chronic pain syndromes (see "Overview of the treatment of chronic non-cancer pain"), their small and inconsistent benefits in studies of back pain do not outweigh their known side effects (most commonly drowsiness, dry mouth, and dizziness).

Meta-analyses evaluating the effect of antidepressant therapy versus placebo for short-term therapy (eight weeks or less) in patients with nonspecific back pain have led to conflicting results [98-100]. Longer-term trials of antidepressants for chronic low back pain are not available. Use of antidepressants was slightly more effective than placebo for low back pain in two meta-analyses [98,99], with an estimated standard mean difference [MD] of 0.41 (95% CI 0.22-0.61) for pain relief but no difference for activities of daily living [98]. Use of tricyclic antidepressants, but not selective serotonin reuptake inhibitors (SSRIs) or trazodone, was associated with improvement. Another meta-analysis (which differed from the earlier studies in the selection criteria used, trials included, and methods for analyzing results) found no difference between antidepressant (primarily tricyclic antidepressants) and placebo treatment for relief of pain or depression and no difference between types of antidepressants [100].

It is important to be aware that depression is common in patients with chronic low back pain, and clinicians should assess for and treat depression appropriately [101]. (See "Evaluation of chronic pain in adults", section on 'Psychiatric comorbidity' and "Unipolar major depression in adults: Choosing initial treatment".)

Benzodiazepines — Benzodiazepines are often used as skeletal muscle relaxants, although not approved by the FDA for this indication. Data on effectiveness of benzodiazepines for subacute or chronic low back pain are limited. A systematic review identified three trials of benzodiazepines, but two evaluated a benzodiazepine not available in the United States (tetrazepam) [86]. Both trials found tetrazepam more effective than placebo for short-term pain intensity (pooled RR 0.82, 95% CI 0.72-0.94 after five to seven days and RR 0.71, 0.54-0.93) and overall improvement (pooled RR 0.63, 0.42-0.97). The only trial evaluating a benzodiazepine available in the United States found no difference between diazepam and placebo for muscle spasm [87]. Because of limited evidence on efficacy and potential for addiction and abuse, benzodiazepines should not be used for long-term treatment of chronic low back pain, although a short course may be indicated for acute exacerbations of chronic low back pain in patients less vulnerable to abuse and addiction. The combination of benzodiazepines and opioids should be avoided whenever possible, as this combination is associated with a marked increase in risk of overdose compared with an opioid alone [102,103].

Antiepileptic medications — Despite the common use of antiepileptic medications for symptomatic treatment of patients with subacute or chronic low back pain, evidence supporting their use is limited.

Agents that have been investigated include gabapentinoids and topiramate:

- Gabapentinoids – In a 2017 meta-analysis of eight randomized control trials evaluating gabapentinoids (gabapentin or pregabalin) for the treatment of chronic low back pain, gabapentin showed nonsignificant minimal improvement of pain compared with placebo (three studies; n = 185; MD -0.22 on a 0 to 10 scale, 95% CI -0.07 to 0.5; very low-quality evidence) [104]. Pregabalin was slightly less effective than other analgesics (amitriptyline, celecoxib, or tramadol/acetaminophen) (three studies; n = 332; MD 0.42 on a 0 to 10 scale, 95% CI 0.20 to 0.64; very low-quality evidence), and its use as adjuvant therapy (added to other medications) in other studies did not show benefit. Gabapentin was associated with an increased risk of side effects, including dizziness, fatigue, difficulties with mentation, and visual disturbances, compared with placebo.

  For chronic radiculopathy, two trials of gabapentin [105,106] and one trial of pregabalin [107] showed only small or unclear effects on pain, which may be offset by their side effects. For

spinal stenosis, one small (n = 55) randomized trial added gabapentin, titrated to 2400 mg/day, to a regimen of supervised exercise therapy, lumbar supports, and NSAIDs in patients with pseudoclaudication and spinal stenosis on computed tomography (CT) or magnetic resonance imaging (MRI) [108]. Patients who took gabapentin had moderately improved mean pain scores at four months (2.9 versus 4.7 on a 0 to 10 scale). Another small (n = 26) randomized trial of patients with neurogenic claudication compared pregabalin titrated to 150 mg twice daily with an active placebo (diphenhydramine). There were no differences in function, pain with ambulation, walking distance, or the Swiss Spinal Stenosis Questionnaire after 10 days [109].

- Topiramate – One trial found topiramate moderately superior to placebo for pain relief and slightly superior for functional improvement in patients with nonradicular chronic low back pain [110]. In another trial, topiramate modestly improved pain in patients with chronic radiculopathy; however, it caused frequent side effects, and many patients dropped out of the trial [111].

Glucosamine — Glucosamine has been extensively studied and is widely used to treat osteoarthritis, particularly of the knee and hip. However, there are little data to support its use for low back pain. In a six-month randomized trial of 250 patients with chronic low back pain and degenerative lumbar osteoarthritis, there were no differences in pain or quality-of-life scores between the glucosamine sulfate (1500 mg daily) and placebo arms [112]. The use of glucosamine for the treatment of knee osteoarthritis is discussed elsewhere. (See "Management of knee osteoarthritis", section on 'Glucosamine and chondroitin'.)

Herbal therapies — The role of herbal medications in the management of low back pain is uncertain. A 2014 systematic review evaluated randomized trials of herbal therapies in patients with acute, subacute, and chronic low back pain. The review found that compared with placebo, the evidence for effectiveness was the best for topical *Capsicum frutescens* (cayenne), with some evidence for oral *Harpagophytum procumbens* (Devil's claw), oral *Salix alba* (white willow bark), topical *Symphytum officinale* (comfrey root extract), and topical lavender essential oil [113]. However, there were methodologic limitations to the trials, outcomes assessed were short-term, and it is not clear how these treatments compare with over-the-counter medications such as NSAIDs or acetaminophen. Additionally, herbal medications may interact with other medications and may contain impurities, and some have significant adverse effects. Patients should be asked

about what nonprescription and herbal medications they are taking for their pain, and this information should be recorded in the medical record. Use and effects of herbal medicines are discussed in more detail separately. (See "Overview of herbal medicine and dietary supplements".)

Anti-TNF-alpha therapy — Systemic anti-tumor necrosis factor (TNF)-alpha therapy, which is primarily used in the treatment of inflammatory rheumatologic and bowel disease, does not appear to have a role for patients with chronic low back pain. This was suggested in the FIRST II trial (n = 40), which found no differences in pain or functional outcomes between a single intravenous infusion of infliximab or saline infusion at three-month and one-year follow-up [114,115]. Epidural and intradiscal injections of anti-TNF-alpha therapy have also been evaluated. (See "Subacute and chronic low back pain: Nonsurgical interventional treatment", section on 'Intradiscal injection'.)

OPTIMIZING THERAPY

There are no trials evaluating optimal sequencing of therapies, and there is no evidence that care directed by one spine provider specialty is superior to other specialties or primary care providers. Decision tools and other methods for individualizing therapy are in early stages of development and may not be practical for use in primary care settings [116].

Patient expectations of benefit from a treatment should be taken into consideration when choosing interventions, as they appear to influence outcomes. Other factors to consider when choosing among therapies include cost, convenience, and availability of skilled providers for specific therapies. Clinicians should avoid interventions not proven effective, as a number of nonpharmacologic therapies are supported by at least fair evidence of moderate benefits.

PREVENTION

There are insufficient data to recommend the use of specific interventions for primary prevention of low back pain [117]. Primary prevention is a challenge due to the limited inability to predict a person's likelihood of developing low back pain. However, exercise therapy may have a role in secondary prevention, particularly for those predisposed to having recurrent low back pain. (See "Exercise-based therapy for low back pain", section on 'Exercise for prevention of low back pain'.)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Lower spine disorders".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topic (see "Patient education: Low back pain in adults (The Basics)")
- Beyond the Basics topic (see "Patient education: Low back pain in adults (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- Most patients who are seen in primary care have "nonspecific low back pain." Rapid improvement in pain and disability and return to work are the norm in the first month. Subacute low back pain is commonly defined as back pain lasting between 4 and 12 weeks and chronic low back pain as pain that persists for 12 or more weeks. (See 'Introduction' above.)
- We advise all patients on self-care and ideally provide evidence-based information to

supplement verbal advice. We suggest that patients remain active and limit bedrest (**Grade 2B**). We suggest not advising patients to switch to a very firm mattress or other surface (**Grade 2B**), and we suggest not advising routine use of lumbar supports (**Grade 2C**). (See 'Self-care advice' above and 'Bed mattress choice' above and 'Lumbar supports' above.)

- We generally emphasize nonpharmacologic therapy (see 'Overview' above):
  - For patients with chronic low back pain, we suggest "active" interventions that are movement-based and/or address psychosocial contributors to pain rather than passive interventions (**Grade 2C**). We suggest home or supervised exercise therapy (including an individualized regimen for motivated patients) (**Grade 2B**). A trial of cognitive behavioral therapy, mind-body interventions, and relaxation techniques can be used in addition to or as equally effective alternatives to exercise therapy. For patients who do not respond to such active interventions, we suggest a trial of spinal manipulation or acupuncture (**Grade 2B**). The choice among these interventions also depends upon patient preference and their cost and accessibility; there are no data demonstrating superiority of one over another. (See 'Activity and physical treatments' above and 'Psychologic interventions' above and 'Physical modalities' above.)
  - For patients who are more severely impaired by their back pain, we suggest functional restoration or multidisciplinary rehabilitation (**Grade 2B**). (See 'Multidisciplinary (interdisciplinary) rehabilitation' above and 'Functional restoration' above.)
  - For patients with subacute low back pain, short-term interventions such as superficial heat, massage, exercise therapy, spinal manipulation, or acupuncture may be adequate because of the high likelihood of spontaneous remission (see "Treatment of acute low back pain", section on 'Nonpharmacologic therapies'). Should their pain persist beyond 12 weeks, we manage them as patients with chronic low back pain.
- We suggest **not** using the following modalities for low back pain: interferential therapy, low-level laser therapy, shortwave diathermy, traction, transcutaneous electrical nerve stimulation (TENS), ultrasound, or percutaneous electrical nerve stimulation (PENS) (**Grade 2B**). (See 'Physical modalities' above.)
- For patients with subacute or chronic low back pain in whom nonpharmacologic approaches

are insufficient to control pain, we suggest a nonsteroidal antiinflammatory drug (NSAID) rather than acetaminophen (**Grade 2B**). For patients with subacute low back pain who have had an inadequate response to NSAIDs, we suggest the addition of a nonbenzodiazepine skeletal muscle relaxant (**Grade 2C**). For patients with chronic low back pain who have had an inadequate response to NSAIDs, we suggest tramadol or duloxetine as an alternative treatment (**Grade 2B**). (See 'Pharmacologic therapies' above.)

- We suggest prescribing opioids for chronic low back pain only for short-term use in patients with low risk for drug abuse who are experiencing severe acute exacerbations of back pain (**Grade 2C**). Rarely, opioids may also be appropriate for severely disabled patients with chronic low back pain who do not respond to other measures and who are assessed to have a low risk for drug abuse. (See 'Use of opioids' above.)

- We suggest **not** using benzodiazepines or other skeletal muscle relaxants for chronic low back pain (**Grade 2C**). We suggest **not** treating patients for chronic low back pain with antiepileptic medications (**Grade 2C**). (See 'Other drugs' above.)

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Topic 7770 Version 57.0

GRAPHICS

Glossary of low back pain terms

Acupuncture	An intervention consisting of the insertion of needles at specific acupuncture points.
Artificial disc replacement	Replacement of a degenerated vertebral disc with an artificial (prosthetic) disc.
Back school	An intervention consisting of an education and a skills program, including exercise therapy, in which all lessons are given to groups of patients and supervised by a paramedical therapist or medical specialist.
Biofeedback	The use of auditory and visual signals reflecting muscle tension or activity in order to inhibit or reduce the muscle activity.
Brief educational interventions	Individualized assessment and education about low back pain problems without supervised exercise therapy or other specific interventions.
Chemonucleolysis	Treatment of herniated discs with intradiscal injections of an enzyme extracted from papaya (chymopapain). Chymopapain acts by digesting the jelly-like inner portion of the disc known as the nucleus pulposus, while at the same time, leaving the outer portion, the annulus fibrosis, essentially intact. Collagenase (which may be less likely to induce an allergic reaction) has also been used.
Cognitive behavioral therapy	An intervention that involves working with cognitions to change emotions, thoughts, and behaviors.
Discectomy	Removal of all or parts of an intervertebral disc in order to relieve pressure on adjacent nerve roots.
Epidural steroid injection	An intervention that involves the administration of steroids in the space between the dura and the spine via a catheter. Epidural injections can be performed by the translaminar approach (via the interlaminar space in the spine), the transforaminal approach (through the neuroforamen ventral to the nerve root), or the caudal approach (through the sacral hiatus at the sacral canal).
Exercise therapy	A supervised exercise program or formal home exercise regimen, ranging from programs aimed at general physical fitness or aerobic exercise to programs aimed at muscle strengthening, flexibility, stretching, or different combinations of these elements.
Facet joint injection	Injection of a glucocorticoid into the facet joints in order to reduce inflammation and/or swelling.
Functional restoration (also referred to as work hardening or work conditioning)	An intervention that involves simulated or actual work tests in a supervised environment in order to enhance job performance skills and improve strength, endurance, flexibility, and cardiovascular fitness in injured workers.
Fusion surgery	A surgical procedure that unites (fuses) two or more vertebra together. The goal behind fusion surgery is to restrict spinal motion in order to relieve symptoms. A variety of spinal fusion techniques are practiced. All involve the placement of a bone graft between the vertebrae. In addition, fusion can be performed with or without the use of supplemental hardware (instrumentation), such as plates, screws, or cages that serve as an internal splint while the bone graft heals.
Interdisciplinary	An intervention that combines and coordinates physical, vocational, and behavioral

therapy (also referred to as multidisciplinary therapy)	components and is provided by multiple healthcare professionals with different clinical backgrounds. The intensity and content of interdisciplinary therapy varies widely.
Interferential therapy	The superficial application of a medium frequency alternating current modulated to produce low frequencies up to 150 Hz.
Intradiscal glucocorticoid injection	Injection of a glucocorticoid directly into a lumbar disc in order to reduce swelling and inflammation.
Intradiscal electrothermal therapy (IDET)	An intervention involving the placement of an electrode into the intervertebral disc in patients with presumed discogenic back pain. The catheter is slowly heated and kept at a predetermined temperature for a predetermined time in order to coagulate and shrink adjacent tissues.
Laminectomy	Removal of the vertebral lamina in order to relieve pressure on the spinal cord or nerve roots.
Local injections	Injections into the soft tissues surrounding the back with a local anesthetic, sometimes with a glucocorticoid. A variety of target sites have been proposed, including tender points and various anatomic sites.
Low-level laser therapy (LLLT)	The superficial application of lasers at wavelengths between 632 and 904 nm. Optimal treatment parameters (wavelength, dose, dose-intensity) are uncertain.
Massage	Soft tissue manipulation using the hands or a mechanical device through a variety of specific methods.
Medial branch block	Injection of a local anesthetic (with or without a glucocorticoid) into the area of the nerve innervating the facet joint. Medial branch blocks may be used diagnostically (to determine whether the facet joint is the source of back pain) or therapeutically.
Percutaneous electrical nerve stimulation (PENS)	An intervention involving the insertion of acupuncture-like needles and applying low-level electrical stimulation. It differs from electroacupuncture in that the insertion points target dermatomal levels for local pathology, rather than acupuncture points.
Percutaneous intradiscal radiofrequency thermocoagulation (PIRFT)	An intervention similar to IDET, this intervention involves insertion of an electrode or catheter into the intervertebral disc. Unlike IDET, the electrode or catheter itself does not become hot. Instead, heat is generated in surrounding tissues by an alternating radiofrequency current.
Progressive relaxation	A technique that involves the deliberate tensing and relaxation of muscles, in order to facilitate the recognition and release of muscle tension.
Provocative discography	A procedure involving injection of radiographic contrast material into the nucleus of an intervertebral disc, which may elicit pain. It is most commonly performed in patients with chronic low back pain in order to help identify those who are more likely to benefit from interventional procedures intended to treat "discogenic" back pain.
Radiofrequency denervation	Destruction of nerves using heat generated by a radiofrequency current. It involves the placement of a catheter or electrode near or in the target nerve. Once the position of the catheter is confirmed by fluoroscopy, a radiofrequency current is applied in order to heat and coagulate adjacent tissues, including the target nerve.
Sacroiliac joint injection	Injection of glucocorticoid into the area near the sacroiliac joint, in order to reduce inflammation and/or swelling.

Shortwave diathermy	Therapeutic elevation of the temperature of deep tissues by application of shortwave electromagnetic radiation with a frequency range from 10 to 100 MHz.
Spinal manipulation	Manual therapy in which loads are applied to the spine using short- or long-lever methods. High velocity thrusts are applied to a spinal joint beyond its restricted range of movement. Spinal mobilization, or low velocity, passive movements within or at the limit of joint range, is often used in conjunction with spinal manipulation.
Transcutaneous electrical nerve stimulation (TENS)	Use of a small battery-operated device to provide continuous electrical impulses via surface electrodes, with the goal of providing symptomatic relief by modifying pain perception.
Yoga	An intervention distinguished from traditional exercise therapy by the utilization of specific body positions, breathing techniques, and emphasis on mental focus. Many styles of yoga are practiced, each emphasizing different postures and techniques.

Graphic 79662 Version 2.0

Definitions for estimating magnitude of effects

Size of effect	Definition
Small/slight	**Pain scales:** Mean 5 to 10 mm improvement on a 100 mm visual analogue scale (VAS), or equivalent
	Back-specific functional status: Mean 5 to 10 mm improvement on the Oswestry Disability Index (ODI), 1 to 2 points on the Roland-Morris Disability Questionnaire (RDQ), or equivalent
	All outcomes: Standardized mean difference (SMD) 0.2 to 0.5
Moderate	**Pain scales:** Mean 10 to 20 mm improvement on a 100 mm VAS, or equivalent
	Back-specific functional status: Mean 10 to 20 mm improvement on the ODI, 2 to 5 points on the RDQ, or equivalent
	All outcomes: SMD 0.5 to 0.8
Large/substantial	**Pain scales:** Mean >20 mm improvement on a 100 mm VAS, or equivalent
	Back-specific functional status: Mean >20 mm improvement on the ODI, >5 points on the RDQ, or equivalent
	All outcomes: SMD >0.8

Graphic 58592 Version 2.0

Medications for subacute or chronic low back pain

Drug	Net benefit*	Graded recommendation¶	Comments
Acetaminophen	Small to none	Suggested as alternative therapy in patients who cannot tolerate NSAIDs, although evidence of efficacy is lacking **(2C)**	Asymptomatic increased liver function tests at therapeutic doses
Antiepileptic drugs	Unable to estimate	Suggest not using **(2C)**	Gabapentin, pregabalin, and topiramate evaluated in short-term trials, primarily in patients with radiculopathy
Benzodiazepines	Unable to estimate	Suggest not using **(2C)**	
Duloxetine	Small	Suggested as alternative regimen for patients with chronic low back pain who do not respond to NSAIDs **(2B)**	
Nonbenzodiazepine skeletal muscle relaxants	Unable to estimate	Suggested as adjunctive therapy for patients with subacute low back pain who to not respond to NSAIDs **(2C)**	Cyclobenzaprine is most the commonly prescribed drug
NSAIDs	Moderate	Suggested as first-line therapy **(2B)**	May cause serious gastrointestinal and cardiovascular adverse events Insufficient evidence to judge benefits and harms of aspirin or celecoxib for low back pain
Opioids	Unable to estimate	Suggest not using as first-line therapy **(2C)**	No reliable data on risks of abuse or addiction
Tramadol	Small to moderate	Suggested as alternative therapy for patients with chronic low back pain who do not respond to NSAIDs **(2B)**	
Tricyclic antidepressants	Unable to estimate	Suggest not using **(2C)**	

NSAIDs: nonsteroidal antiinflammatory drugs.

* Based on evidence showing medication is more effective than placebo, and/or evidence showing medication is at least as effective as other medications or interventions thought to be effective, for one or more of the following outcomes: pain, functional status, or work status. Versus placebo, small benefit defined as 5 to 10 points on a 100-point Visual Analogue Scale (VAS) for pain (or equivalent), 1 to 2 points on the Roland Morris Disability Questionnaire (RDQ), 10 to 20 points on the Oswestry Disability Index (ODI), or a standardized mean difference (SMD) of 0.2 to 0.5. Moderate benefit defined as 10 to 20 points on a VAS for pain, 2 to 5 points on the RDQ, 10 to 20 points on the ODI, or a SMD of 0.5 to 0.8. Large benefit defined as >20 points on a 100-point VAS for pain; >5 points on the RDQ, >20 points on the

ODI, or a SMD of >0.8.

¶ Grading:

1A - Strong recommendation. High-quality evidence. Strong recommendation, can apply to most patients in most circumstances without reservation.

1B - Strong recommendation. Moderate-quality evidence. Strong recommendation, likely to apply to most patients.

1C - Strong recommendation. Low-quality evidence. Relatively strong recommendation; might change when higher quality evidence becomes available.

2A - Weak recommendation. High-quality evidence. Weak recommendation, best action may differ depending on circumstances or patients or societal values.

2B - Weak recommendation. Moderate-quality evidence. Weak recommendation, alternative approaches likely to be better for some patients under some circumstances.

2C - Weak recommendation. Low-quality evidence. Very weak recommendation; other alternatives may be equally reasonable.

§ Due to safety profile.

Graphic 72902 Version 7.0

Nonpharmacologic therapies for subacute or chronic low back pain

Intervention	Net benefit*	Graded recommendation ¶	Comments
Acupuncture	Moderate	Suggested **(2B)**	Efficacy of acupuncture versus sham acupuncture inconsistent
Cognitive behavioral therapy	Moderate	Suggested **(2B)**	
Exercise therapy	Moderate	Suggested **(2B)**	
Functional restoration	Moderate	Suggested **(2B)**	
Interdisciplinary rehabilitation	Moderate	Suggested **(2B)**	More intense interdisciplinary rehabilitation more effective than less intense interdisciplinary rehabilitation
Interferential therapy	Unable to estimate	Suggest not using **(2B)**	
Low-level laser therapy	Unable to estimate	Suggest not using **(2B)**	Trials evaluated different types and intensity of laser, with inconsistent findings
Lumbar supports	Unable to estimate	Suggest not using **(2C)**	
Massage therapy	Unable to estimate	Suggested not using **(2B)**	Some trials evaluated minimal or light massage techniques
Mindfulness-based stress reduction	Moderate	Suggested **(2B)**	
Percutaneous electrical nerve stimulation	Unable to estimate	Suggest not using **(2B)**	
Shortwave diathermy	Not effective	Suggest not using **(2B)**	
Spinal manipulation	Moderate	Suggested **(2B)**	
Traction	Not effective (for continuous traction)	Suggest not using **(2B)**	
Transcutaneous electrical nerve stimulation	Unable to estimate	Suggest not using **(2B)**	
Ultrasound	Unable to estimate	Suggest not using **(2B)**	
Yoga	Moderate (for Viniyoga)	Suggested **(2B)**	Insufficient evidence to judge non-Viniyoga techniques

* Based on evidence showing medication is more effective than placebo, and/or evidence showing medication is at least as effective as other medications or interventions thought to be effective, for one or more of the following outcomes: pain, functional status, or work status. Versus placebo, small benefit defined as 5 to 10 points on a 100-point Visual

Analogue Scale (VAS) for pain (or equivalent), 1 to 2 points on the Roland Morris Disability Questionnaire (RDQ), 10 to 20 points on the Oswestry Disability Index (ODI), or a standardized mean difference (SMD) of 0.2 to 0.5. Moderate benefit defined as 10 to 20 points on a VAS for pain, 2 to 5 points on the RDQ, 10 to 20 points on the ODI, or a SMD of 0.5 to 0.8. Large benefit defined as >20 points on a 100-point VAS for pain; >5 points on the RDQ, >20 points on the ODI, or a SMD of >0.8.

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Graphic 61982 Version 3.0

Interventional therapies for low back pain

Intervention	Population	Net benefit*	Graded recommendation ¶	Comments
Epidural steroid injection	Sciatica or prolapsed lumbar disc with radiculopathy	Moderate (short-term only)	Suggested **(2B)**	Some higher-quality trials found no benefits.
Intradiscal corticosteroid injection	Sciatica or prolapsed lumbar disc with radiculopathy	No effect (versus chemonucleolysis)	Suggest not using **(2C)**	
Local injections	Sciatica or prolapsed lumbar disc with radiculopathy	Unable to determine	Suggest not using **(2C)**	
Radiofrequency denervation	Sciatica or prolapsed lumbar disc with radiculopathy	Unable to determine	Suggest not using **(2C)**	
Facet joint (intraarticular) injection	Presumed facet joint pain	No effect	Suggest not using **(2C)**	
Medial branch block (therapeutic)	Presumed facet joint pain	Unable to determine	Suggest not using **(2C)**	
Radiofrequency denervation	Presumed facet joint pain	Unable to determine	Suggest not using **(2C)**	
Intradiscal corticosteroid injection	Presumed discogenic low back pain	No effect	Suggest not using **(2C)**	
Intradiscal electrothermal therapy	Presumed discogenic low back pain	Unable to determine	Suggest not using **(2B)**	
Intradiscal anti-TNF injections	Presumed discogenic low back pain	No effect	Suggest not using **(2C)**	
Intradiscal methylene blue injection	Presumed discogenic low back pain	Unable to determine	Suggest not using **(2C)**	
Percutaneous intradiscal radiofrequency thermocoagulation	Presumed discogenic low back pain	No effect	Suggest not using **(2B)**	
Radiofrequency denervation	Presumed discogenic low back	Unable to determine	Suggest not using **(2C)**	

	pain			
Epidural steroid injection	Spinal stenosis	No effect	Suggest not using **(2C)**	
Epidural steroid injection	Nonspecific low back pain	Unable to determine	Suggest not using **(2C)**	
Botulinum toxin injection	Nonspecific low back pain	Moderate (short-term only)	Suggest not using **(2C)**	
Local injections	Nonspecific low back pain	Unable to determine	Suggest not using **(2C)**	Interventions varied substantially between trials. No higher-quality trials, all trials had small sample sizes.
Prolotherapy	Nonspecific low back pain	No effect	Suggest not using **(2B)**	

TNF: tumor necrosis factor.

* Based on evidence showing medication is more effective than placebo, and/or evidence showing medication is at least as effective as other medications or interventions thought to be effective, for one or more of the following outcomes: pain, functional status, or work status. Versus placebo, small benefit defined as 5 to 10 points on a 100-point Visual Analogue Scale (VAS) for pain (or equivalent), 1 to 2 points on the Roland Morris Disability Questionnaire (RDQ), 10 to 20 points on the Oswestry Disability Index (ODI), or a standardized mean difference (SMD) of 0.2 to 0.5. Moderate benefit defined as 10 to 20 points on a VAS for pain, 2 to 5 points on the RDQ, 10 to 20 points on the ODI, or a SMD of 0.5 to 0.8. Large benefit defined as >20 points on a 100-point VAS for pain; >5 points on the RDQ, >20 points on the ODI, or a SMD of >0.8.

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2C - Weak recommendation. Low quality evidence. Very weak recommendation; other alternatives may be equally reasonable.

Graphic 77165 Version 7.0

Surgery for chronic low back pain (excluding spinal stenosis)

Intervention	Population	Net benefit*	Graded recommendation ¶	Comments
Interbody fusion	Nonspecific low back pain or degenerative disc disease with presumed discogenic low back pain	Moderate versus standard physical therapy supplemented by other nonsurgical therapies, no benefit versus intensive rehabilitation	Suggested (for highly selected patient population) **(2B)**	Inconsistency between trials may be related to use of different comparator interventions.
Artificial disc replacement	Nonspecific low back pain or degenerative disc disease with presumed discogenic low back pain	No evidence	Suggest not performing **(2C)**	One trial found Charite artificial disc noninferior to fusion and one trial found Prodisc-L artificial disc superior to fusion.
Standard open discectomy or microdiscectomy	Lumbar disc prolapse with radiculopathy	Moderate	Suggested **(2B)**	In largest trial, 40 to 55% crossover in both arms; on-treatment analysis consistent with other trials. Benefits associated with surgery attenuated with longer-term follow-up.

* Based on evidence showing medication is more effective than placebo, and/or evidence showing medication is at least as effective as other medications or interventions thought to be effective, for one or more of the following outcomes: pain, functional status, or work status. Versus placebo, small benefit defined as 5 to 10 points on a 100-point Visual Analogue Scale (VAS) for pain (or equivalent), 1 to 2 points on the Roland Morris Disability Questionnaire (RDQ), 10 to 20 points on the Oswestry Disability Index (ODI), or a standardized mean difference (SMD) of 0.2 to 0.5. Moderate benefit defined as 10 to 20 points on a VAS for pain, 2 to 5 points on the RDQ, 10 to 20 points on the ODI, or a SMD of 0.5 to 0.8. Large benefit defined as >20 points on a 100-point VAS for pain; >5 points on the RDQ, >20 points on the ODI, or a SMD of >0.8.

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2B - Weak recommendation. Moderate quality evidence. Weak recommendation; alternative approaches likely to be better for some patients under some circumstances.
2C - Weak recommendation. Low quality evidence. Very weak recommendation; other alternatives may be equally reasonable.

Graphic 63348 Version 2.0

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A New Look at Trigger Point Injections

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Abstract

Trigger point injections are commonly practised pain interventional techniques. However, there is still lack of objective diagnostic criteria for trigger points. The mechanisms of action of trigger point injection remain obscure and its efficacy remains heterogeneous. The advent of ultrasound technology in the noninvasive real-time imaging of soft tissues sheds new light on visualization of trigger points, explaining the effect of trigger point injection by blockade of peripheral nerves, and minimizing the complications of blind injection.

1. Introduction

Myofascial pain syndrome is a common, painful musculoskeletal disorder characterized by the presence of trigger points. They have been implicated in patients with headache, neck pain, low back pain, and various other musculoskeletal and systemic disorders [1–4]. The prevalence of myofascial trigger points among patients complaining of pain anywhere in the body ranged from 30% to 93% [5]. Although the most important strategy in treatment of myofascial pain syndrome is to identify the etiological lesion that causes the activation of trigger points and to treat the underlying pathology [6], trigger point injections are still commonly practised pain interventional technique for symptomatic relief.

Despite the popularity of trigger point injections, the pathophysiology of myofascial trigger points remains unclear. Localization of a trigger point is often based on the physician's examination. However, such physical examination is often unreliable. Lack of objective clinical measurements has also been a barrier for critically evaluating the efficacy of the therapeutic methods.

Ultrasound is used extensively for noninvasive real-time imaging of soft tissues including muscle, nerve, tendon, fascia, and blood vessels. With the advent of portable ultrasound technology, ultrasound is now commonly employed in the field of regional analgesia. In this paper, we will look at the

potential application of ultrasound in trigger point injections.

2. Diagnosis of Trigger Points

Physician's sense of feel and patient expressions of pain upon palpation are the most commonly used method to localize a trigger point. The most common physical finding is palpation of a hypersensitive bundle or nodule of muscle fibre of harder than normal consistency. The palpation will elicit pain over the palpated muscle and/or cause radiation of pain towards the zone of reference in addition to a twitch response [7].

In myofascial pain syndrome, trigger points have been classified into active or latent. In an active trigger point, there is an area of tenderness at rest or on palpation, a taut band of muscle, a local twitch response, and referred pain elicited by firm compression similar to the patient's complaint. Latent trigger points are more commonly seen. They may display hypersensitivity and exhibit all the characteristics of an active trigger point except that it is not associated with spontaneous pain [7].

Trigger points have also been further classified into key or satellite. An active key trigger point in one muscle can induce an active satellite trigger point in another muscle. Inactivation of the key trigger point often also inactivates its satellite trigger point without treatment of the satellite trigger point itself [7].

The diagnosis of trigger points depends very much on the subjective experience of the physician. Pressure algometry has been used to quantify the sensitivity of trigger points. A hand-held pressure meter with a 1 cm^2 rubber disc attached to a force gauge calibrated up to 10 kg is applied over a trigger point to measure its pain threshold [8]. However, this method is not commonly employed clinically, and there have not been any imaging criteria for the diagnosis of trigger points.

3. Pathophysiology of Trigger Points

Trigger points are defined as palpable, tense bands of skeletal muscle fibres. They can produce both local and referred pain when compressed.

The local pain could be explained by the tissue ischemia resulting from prolonged muscle contraction with accumulation of acids and chemicals such as serotonin, histamine, kinins, and prostaglandins [9]. These changes are fed into a cycle of increasing motor or sympathetic activity and can lead to increased pain. A painful event can sustain itself once a cycle is established even after the initial stimulus has been removed [10].

The pathogenesis of trigger points is probably related to sensitized sensory nerve fibres (nociceptors) associated with dysfunctional endplates [11]. In fact, endplate noise was found to be significantly more prevalent in myofascial trigger points than in sites that were outside of a trigger point but still within the endplate zone [12].

Studies have found that development of trigger points is dependent on an integrative mechanism in the spinal cord. When the input from nociceptors in an original receptive field persists (pain from an active trigger point), central sensitization in the spinal cord may develop, and the receptive field corresponding to the original dorsal horn neuron may be expanded (referred pain). Through this mechanism, new "satellite trigger points" may develop in the referred zone of the original trigger point [11].

4. Mechanisms of Action of Trigger Point Injections

Noninvasive measures for treatment of trigger points include spray and stretch, transcutaneous electrical stimulation, physical therapy, and massage. Invasive treatments include injections with local anaesthetics, corticosteroids, or botulinum toxin, or dry needling [13–18].

Hong reported that with either lidocaine injection or dry needling of trigger points, the patients experienced almost complete relief of pain immediately after injection if local twitch responses were elicited. On the other hand, they experienced only minimal relief if no such response occurred during injection. Hong has suggested that nociceptors (free nerve endings) are encountered and blocked during trigger point injection if local twitch response can be elicited [19].

The mechanism of action of trigger point injections is thought to be disruption of the trigger points by the mechanical effect of the needle or the chemical effect of the agents injected, resulting in relaxation and lengthening of the muscle fibre. The effect of the injectate may include local vasodilation, dilution, and removal of the accumulated nociceptive substrates. Botulinum toxin A has been used to block acetylcholine release from the motor nerve ending and subsequently relieve the taut band [6].

While the relief of local pain could easily be explained by the relaxation of the muscle fibre, the relief of referred pain could not be explained without attributing it to a peripheral nerve blockade. However, little has been said in the literature regarding the mechanism of trigger point injection in this respect.

5. Could the Application of Ultrasound Solve the Mystery of Trigger Points?

5.1. Direct Visualization of Trigger Points

As mentioned above, the most common physical finding of a trigger point is palpation of a hypersensitive bundle or nodule of muscle fibre of harder than normal consistency. Attempts to confirm the presence of myofascial trigger points using imaging have been demonstrated by magnetic resonance elastography [20]. For ultrasound, earlier studies have failed to find any correlation between physical findings and diagnostic ultrasound [21]. This may be attributed to poorer quality of ultrasound imaging in earlier dates.

Recently, Sikdar et al. have tried to use ultrasound to visualize and characterize trigger points. They found that trigger points appeared as focal, hypoechoic regions of elliptical shape, with a size of 0.16 cm [22]. This is promising as ultrasound can provide a more objective diagnosis of trigger point. Even if visualization of individual trigger point is difficult due to the small size, some advocate the use of ultrasound to guide proper needle placement in muscle tissue and to avoid adipose or nonmusculature structures during trigger point injections [23].

5.2. Injection of Peripheral Nerves

Trigger point injections have been implicated in patients with headache, low back pain, and various other musculoskeletal and systemic disorders. Some of these injections may involve injectate deposition directly to the nerves supplying the region. Indeed, entrapment, compression, or irritation of the sensory nerves of local regions has been implicated in various conditions.

5.2.1. Greater Occipital Nerve Entrapment of the greater occipital nerve is often implicated as the cause of cervicogenic headache, and the characteristic occipital headache can be reproduced by finger pressure over the corresponding occipital nerve over the occipital ridge [3, 24–26]. This referral pattern

of pain coincides with that of the properties of a trigger point, and it could explain the mechanism of referred pain for trigger points.

Simons has considered that the effect of greater occipital nerve injection is due to the release of the entrapment by relaxation of semispinalis muscle [7]. However, injection of local anaesthetics with or without steroid over the occipital nerve has been found to result in alleviation of occipital headache [27]. In migraine headaches, local injection of local anaesthetics or botulinum toxin type A to the greater occipital nerve has been demonstrated to provide relief of the condition [24].

There are several techniques of ultrasound-guided blockade of greater occipital nerve. The classical distal block technique involves placing the transducer at the superior nuchal line, while for the new proximal approach, the transducer is placed at the level of C2, and the greater occipital nerve lies superficial to the obliquus capitis inferior muscle [28, 29].

5.2.2. Abdominal Cutaneous Nerve Kuan et al. showed that local injection of anaesthetics or steroid can treat some patients with lower abdominal pain presenting with trigger points in the abdomen, thus avoiding diagnostic laparoscopy and medications [30].

Trigger points over the abdominal wall may in fact be entrapped cutaneous nerves. Peripheral nerve entrapment (e.g., ilioinguinal-iliohypogastric nerves, thoracic lateral cutaneous nerve) has been suggested to cause lower abdominal pain [31, 32].

Ultrasound-guided blocks for ilioinguinal and iliohypogastric nerves have been practised widely in anaesthesia [33–35]. Recently, ultrasound-guided transversus abdominis plane (TAP) block is also commonly used to provide postoperative pain relief for patients undergoing laparotomy [35–38].

By placing the ultrasound probe about 5 cm cranial to the anterior superior iliac spine, the ilioinguinal and iliohypogastric nerves can be found between the transverse abdominal and the internal oblique muscle [39]. For TAP block, the transducer can be placed in a transverse plane between the iliac crest and the anterior axillary line. Local anaesthetics can be deposited between the transversus abdominis muscle and the internal oblique muscle [40].

5.2.3. Dorsal Ramus of Spinal Nerve Low back pain is a common chronic pain syndrome; however, in most cases, a specific diagnosis cannot be established. Trigger point injections have been found to relieve myofascial low back pains. However, there has been lack of evidence in the literature to support its efficacy. This could be attributed to the heterogeneity in the diagnosis and technique of localization of trigger points in low back pain. Most of the studies employed subjective localization of trigger points, and the techniques of localization and injection of trigger points were not well described.

Miyakoshi et al. demonstrated that CT-guided total dorsal ramus block was effective in the treatment of chronic low back pain in a group of patients with overlapping facet syndrome with myofascial syndrome with pain originating from myofascial structure, facet joint, or both [41]. They demonstrated that a single injection of a larger volume of local anaesthetics over the conventional target point for medial branch block, which was the junction of the L5 superior articular process and the transverse process, was effective to block the medial, intermediate, and lateral branches of the lumbar dorsal ramus, with significantly better pain reduction compared to conventional trigger point injection. The findings in this study shed light to the possibility of relief of myofascial pain syndrome by a single nerve injection. It may explain the poor results of pure intramuscular injections in controlled studies, in contrast to the better results with uncontrolled studies and case reports, in which some of the results may be attributable to accidental nerve injection using the conventional blind injection techniques.

For ultrasound-guided medial branch block, the transducer is first placed longitudinally to find the respective transverse process and localize the lumbar level. Then the transducer can be rotated into a transverse plane to delineate the transverse process and the superior articular process of the adjacent facet joint. The bottom of the groove between the lateral surface of the superior articular process and the cephalad margin of the respective transverse process was defined as the target site [42].

Ultrasound-guided technique may be adapted to perform injection of the lower back, targeting at the dorsal rami of the lumbar spinal nerves to increase the efficacy of injection.

5.2.4. Lumbar Plexus There have been case reports on the use of trigger point injection for treatment of pain that was remote from the site of trigger points. Interestingly, Iguchi et al. used trigger point injection for the amelioration of renal colic. In their paper, they described the injection technique as follows. Trigger points were located over the paraspinal region at around L3 level. A long needle (23-gauge 6 cm) was inserted deep into the trigger points, and 5–10 mL of 1% lignocaine was injected [43]. Such injection was in fact into the psoas muscle, and the effect could be attributed to a lumbar plexus block.

Lumbar plexus block with ultrasound guidance has been described. A curved transducer can be placed in the transverse plane at L2–L4 level for the lumbar plexus block. This transverse view should show the psoas muscle without the transverse process. The target of the needle tip is within the posterior 1/3 of the psoas muscle bulk [40].

5.2.5. Pudendal Nerve Langford et al. reported the effective use of levator ani trigger point injection in the treatment of chronic pelvic pain. Trigger points were identified by manual intravaginal palpation, and the trigger points were injected with a large volume (up to about 20 mL) of a mixture of local anesthetics and depot steroid. The effect of such injection might in fact be caused by the concomitant pudendal nerve block [44].

Pudendal nerve blockade with ultrasound guidance can be performed via the transgluteal approach. The probe is placed transverse to the posterior superior iliac spine and moved caudally until the piriformis muscle is seen. The probe is then moved further caudad to identify the ischial spine, in which the pudendal nerve will be seen lying medial to the pudendal artery [29].

6. Other Advantages of Ultrasound in Trigger Point Injections

Trigger point injections are commonly performed in clinics as an outpatient procedure. Serious complications, although of rare occurrence, have been reported (e.g., pneumothorax, haematoma, intravascular injection of local anaesthetics, and intrathecal injections) [45]. Direct visualization of surrounding soft tissues and important structures can reduce the risk of such complications. Moreover, ultrasound allows real-time imaging of the spread of the injectate around the relevant structures and increases the success rate of injection.

7. Future Directions

The nonspecific diagnosis and lack of objective clinical measurements for trigger points mean that the evidence for the effectiveness of trigger point injection remains heterogenous. There is so far no strong evidence for the effectiveness of trigger point injections, and many physicians consider trigger point injections a little more than, if not equivalent to, placebo effects.

With the advancement of ultrasound technology, the quality of scans for soft tissues and musculature has improved dramatically. Future studies may focus on more objective diagnostic criteria of trigger points using ultrasound imaging. For the technique of trigger point injections, real-time visualization of trigger points, relaxation of locally contracting muscles, and visualization of surrounding tissues or important structures may improve the outcome and minimize complications of such treatments.

Moreover, efficacy of some of the trigger point injections traditionally performed may be related to some kind of peripheral nerve blocks, the implication which is yet to be explored.

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EXHIBIT M-6

Medscape

Trigger Point Injection

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OVERVIEW

Background

Trigger point injections are an effective treatment modality for inactivating trigger points and providing prompt relief of symptoms from myofascial pain syndrome. [1] Myofascial pain syndrome is a common painful muscle disorder characterized by myofascial trigger points. This syndrome is distinct from fibromyalgia syndrome, which involves multiple tender points, though the two pain syndromes may be concurrent.

Myofascial trigger points are a major cause of pain and dysfunction. [1] They produce pain focally and in a referred pattern and often occur in conjunction with chronic musculoskeletal pain disorders. Various modalities for the treatment of trigger points include spray and stretch, ultrasound, manipulative therapy, and trigger point injections.

Not all trigger points require injection or needling. Many active trigger points will respond to physical therapy, especially in the early stages of trigger point formation. However, for chronic trigger points, trigger point injection and needling is an effective treatment. [2]

eMedicine

Indications

Trigger point injections are indicated for patients who have symptoms and examination findings consistent with active trigger points. Latent trigger points are clinically asymptomatic and do not require treatment. Trigger points should be limited in number and should be appropriate for injection.

Conditions involving widespread pain complaints, such as fibromyalgia or endocrine disorder, are not suitable for injections. Treatment is indicated for endocrine diagnoses or fibromyalgia before trigger point injections are considered. In addition, the finding of tenderness alone is not an indication for trigger point injection, because patients with fibromyalgia may also have myofascial pain trigger points.

When indications for injections are being considered, it is not always necessary to have the classical clinical examination findings of a taut band with local twitch response and referred pain

pattern. Within the total clinical context, the finding of tender points in typical trigger point locations that coincide with the patient's pain and a "jump sign" is sufficient to justify trigger point injections. [2]

Contraindications

Trigger points should not be injected in the presence of systemic or local infection. Injection of patients with bleeding disorders or patients on anticoagulation must be done with proper medical evaluation and control. Although bleeding may be increased in these patients, the risk of harmful bleeding remains very low.

Avoid injections in the pregnant patient or patients who feel or appear to be ill. Use precautions in patients who are at high risk for infection, including debilitated patients, patients with diabetes mellitus, or patients on steroids.

Technical Considerations

Pain from myofascial trigger points is often treated by needling, with or without injection, though the evidence is inconclusive on whether this is effective. A literature review examined seven studies that assessed the effects of dry needling. [3] One study concluded that direct dry needling was superior to no intervention; two studies comparing direct dry needling to needling elsewhere in the muscle produced contradictory results; and four studies used a placebo control and were included in a meta-analysis.

Upon analysis of these studies, needling was not found to be significantly superior to placebo; however, marked statistical heterogeneity was present. [3] Thus, this review found limited evidence deriving from only a single study that deep needling directly into myofascial trigger points has an overall treatment effect when compared with standardized care.

In a 2013 systematic review and meta-analysis of 12 randomized, controlled trials designed to assess the effectiveness of dry needling for upper-quarter myofascial pain (MPS), Kietrys et al reported the following findings [4] :

- Evidence from three studies of dry needling vs placebo suggested that dry needling could immediately decrease pain in patients with upper-quarter MPS; there was an overall effect in favor of dry needling
- Evidence from two studies of dry needling vs placebo suggested that dry needling could decrease pain after 4 weeks in patients with upper-quarter MPS; the impact of this decrease was limited by the wide confidence interval for the overall effect
- Studies of dry needling vs other treatments yielded highly heterogeneous results; evidence from two studies suggested that lidocaine injection may be more effective in reducing pain than dry needling at 4 weeks

On the basis of these findings, the authors of the meta-analysis recommended dry needling, as compared with sham or placebo, for decreasing pain immediately after treatment and at 4 weeks in patients with upper-quarter MPS. [4]

Several mechanisms have been suggested as possible explanations for the inactivation of trigger points by injection, including disruption of abnormal muscle fibers or nerve endings that make up the sensory and motor aspects of the feedback loop, which may be responsible for trigger point activity. Needling may cause a local release of intracellular potassium, which may depolarize and thus disrupt nerve conduction.

Injected fluid may dilute any nerve-sensitizing substances to reduce irritability and inactivate any neural feedback mechanisms. Procaine has a local vasodilatation effect that increases circulation at the trigger point, increasing the local removal of metabolites and increasing local energy supply. Further, a local anesthetic may interrupt feedback mechanisms between the trigger point and the central nervous system, limiting high frequency discharges transmitted by the nerve. Depending on the anesthetic, focal necrosis may destroy the trigger point. [5]

EXHIBIT M-7

Overview of soft tissue rheumatic disorders

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All topics are updated as new evidence becomes available and our peer review process is complete.

Literature review current through: Mar 2019. | **This topic last updated:** Jan 20, 2019.

INTRODUCTION

Soft tissue rheumatic disorders refer to nonsystemic, focal pathologic syndromes involving the periarticular tissues, including muscle, tendon, ligament, fascia, aponeurosis, retinaculum, bursa, and subcutaneous tissue. These disorders are extremely common. The archaic term "rheumatism" is sometimes used to refer to these manifestations.

Although soft tissue rheumatic disorders refer to nonarticular pain, patients often attribute their symptoms to nearby joints. Thus, when patients complain of hip pain, the cause is often not pain in the joint itself, but rather in the "hip region": the groin, buttock, upper lateral thigh, greater trochanteric area, and iliac crest. Similarly, complaints of elbow, wrist, knee, and shoulder pain frequently mean pain in the general region of those joints, and may reflect soft tissue conditions such as epicondylitis, tenosynovitis, and bursitis.

Soft tissue disorders may be divided into several broad categories and include:

- Tendinitis
- Enthesitis
- Fasciitis
- Bursitis

- Structural disorders
- Neurovascular entrapment disorders
- Complex regional pain syndromes (CRPS)
- Myofascial pain syndrome
- Generalized pain disorders

Many of these disorders occur in the absence of systemic disease, and some are a consequence of chronic repetitive low-grade trauma and overuse. Many are self-limiting and respond to conservative measures.

This topic will provide a brief overview of the soft tissue rheumatic disorders. A general discussion on the approach to the patient with these disorders is also included. More detailed discussions of these disorders are presented separately. (See appropriate topic reviews.)

SPECIFIC SYNDROMES

Tendinitis — Tendinitis (or tendonitis) is a clinical and pathologic disorder with common features of local pain and dysfunction, inflammation, and degeneration. Tendinitis often results from overuse or a sports injury but may also be due to inflammatory rheumatic diseases or metabolic disturbances such as calcium apatite deposition. Tendinitis and tendon rupture have also been associated with the use of fluoroquinolone antibiotics and statins [1-3].

Tendinitis, tendinosis, and tendinopathy are some of the terms used to characterize acute or chronic tendon pain. The term tendinitis can be confusing because inflammation is often not seen on histopathology, and the other terms may be more appropriate. For the purposes of this discussion, we will use the common term tendinitis. A more detailed discussion on terminology is included elsewhere. (See "Overview of overuse (persistent) tendinopathy", section on 'Pathology and terminology'.)

Common sites of tendinitis include supraspinatus tendinitis of the shoulder (rotator cuff tendinopathy), lateral and medial epicondylitis (tennis and golfer's elbow), bicipital tendinitis, Achilles tendinopathy, and flexor carpi radialis and flexor carpi ulnaris tendinitis. (See "Rotator cuff tendinopathy" and "Epicondylitis (tennis and golf elbow)" and "Biceps tendinopathy and tendon rupture" and "Achilles tendinopathy and tendon rupture".)

Enthesitis — The enthesis is the site of insertion of ligaments, tendons, joint capsules, and fascia to bone (figure 1). These areas are highly vascular and are susceptible to bacterial and antigen deposition [4]. Enthesitis is often seen in spondyloarthropathies; common sites are the insertion of the plantar fascia and the Achilles tendon region (see "Clinical manifestations and diagnosis of peripheral spondyloarthritis in adults", section on 'Musculoskeletal features'). Ultrasonography is helpful for delineation [5,6]. (See "Musculoskeletal ultrasonography: Clinical applications", section on 'Enthesitis'.)

Fasciitis — Fasciitis includes Dupuytren's palmar contracture, fascia lata fasciitis, and plantar fasciitis. They have discrete and disparate pathologies which include proliferation and degeneration of fascia. These disorders are discussed in more detail separately, as are other forms of fasciitis that have more systemic involvement, including necrotizing fasciitis and eosinophilic fasciitis (see "Dupuytren's contracture" and "Evaluation of the adult with hip pain" and "Plantar fasciitis" and "Necrotizing soft tissue infections" and "Eosinophilic fasciitis"). Magnetic resonance imaging (MRI) is often in useful in identifying these conditions.

Bursitis — Bursitis is inflammation of the small fluid-filled pads, called bursae, that act as cushions between the bones and adjacent tendons and muscles, protecting the soft tissues from underlying bony prominences. Bursitis may result from direct trauma, repetitive injury, or infection, or it may be a manifestation of a systemic disease such as rheumatoid arthritis or gout. A diagnosis of bursitis is based on the findings of exquisite local tenderness at bursal sites, pain on motion and at rest, and sometimes associated regional loss of active movement. Swelling may be evident when bursitis occurs close to the body surface (eg, bunion or prepatellar bursitis) [7]. (See "Bursitis: An overview of clinical manifestations, diagnosis, and management".)

Structural disorders — Musculoskeletal structural disorders are relatively common. In healthy young adults, for example, one study found that a total of 158 separate congenital, developmental, and acquired abnormalities were detected in 73 percent of 127 medical students [8]. Findings included decreased joint range of motion and articular laxity, as well as synovitis, tendinitis, and bursitis. Participants in contact sports had the highest prevalence. (See "Joint hypermobility syndrome", section on 'Epidemiology'.)

Subtle disorders often contribute significantly to pain syndromes in the lower extremity. "Miserable malalignment syndrome" is a term used to describe a combination of malalignments of the leg that

include excess femoral anteversion with internal rotation of the hip, genu valgus, squinting patellae, external tibial torsion, and flat feet. Affected individuals are predisposed to overuse injuries and are often advised to avoid sports such as long-distance running. Structural disorders frequently contribute to injury in sports participants. (See "Overview of running injuries of the lower extremity".)

Body asymmetry is a common cause of many regional pain disorders. When one side of the face is smaller, for example, temporomandibular joint dysfunction is more common (picture 1). The rest of the ipsilateral body may also be small in such patients, sometimes resulting in a scapulothoracic syndrome related to scoliosis or back pain in association with a short leg or an underdeveloped buttock.

Neurovascular entrapment — Neurovascular entrapment disorders may occur within the spinal canal (foraminal or central spinal stenosis) or nerve root, or along the course of a peripheral nerve. The peripheral sites most commonly affected are compression of the median nerve at the wrist (carpal tunnel syndrome), compression of the ulnar nerve at the cubital tunnel, and compression of the tibial nerve at the tarsal tunnel. Less commonly, the lateral femoral cutaneous nerve in entrapped under the inguinal ligament (meralgia paresthetica). (See "Overview of upper extremity peripheral nerve syndromes" and "Carpal tunnel syndrome: Clinical manifestations and diagnosis" and "Overview of lower extremity peripheral nerve syndromes" and "Meralgia paresthetica (lateral femoral cutaneous nerve entrapment)".)

The diagnostic triad of peripheral neurovascular entrapment includes:

- A sensation of swelling and pain in the involved region
- Paresthesias distal to the site of entrapment
- Muscle weakness in advanced cases

Tapping over an involved peripheral nerve (eg, Tinel sign in carpal tunnel syndrome) or compression with an inflated blood pressure cuff proximal to the nerve may produce a sensation of electric shock and therefore aid in the diagnosis.

Complex regional pain syndromes — The complex regional pain syndrome (CRPS) may be related to nerve injury, other trauma, surgery, or a vascular event such as myocardial infarction or stroke, or there may be no obvious triggering event. Alternative names include reflex sympathetic

dystrophy (RSD), algodystrophy, causalgia, and shoulder-hand syndrome. It was renamed by a consensus development conference in 1995 as CRPS [9]. It is usually characterized clinically by exquisite burning pain, edema, allodynia, abnormal sudomotor activity, and hyperesthesia in the limb, which may feel cold or hot and may change color, and by local bone demineralization.

Two types of CRPS have been recognized:

- CRPS type I (formerly termed RSD) – Refers to patients without a definable nerve lesion
- CRPS type II (formerly termed causalgia) – Refers to patients with a definable nerve lesion

The causes, clinical features, diagnosis, prevention, and treatment of CRPS (RSD and causalgia) are presented separately. (See "Complex regional pain syndrome in adults: Pathogenesis, clinical manifestations, and diagnosis" and "Complex regional pain syndrome in adults: Prevention and management".)

Myofascial pain syndrome — Myofascial pain syndrome (MPS) is a regional pain disorder caused by the presence of trigger points within muscles or their fascia (figure 2) [10,11]. It has been described as "hyperirritable spots, usually within a taut band of skeletal muscle or in the muscle's fascia that is painful on compression and can give rise to characteristic referred pain, tenderness, and autonomic phenomena" [12]. MPS shares some similar features with fibromyalgia which are discussed separately (table 1). (See "Differential diagnosis of fibromyalgia", section on 'Myofascial pain syndromes'.)

MPS is a relatively common source of chronic pain in the general population. The lack of universally accepted diagnostic criteria has resulted in variable estimates from epidemiologic studies, and most of the available data pertain to musculoskeletal pain in general. One study that estimated the prevalence of myofascial pain in a general internal medicine practice found that the primary complaint of 30 percent of patients was due to myofascial pain [13].

The pain of MPS is of a deep aching quality, occasionally accompanied by a sensation of burning or stinging. The pain often occurs in just one anatomic region, and patients often complain of restricted active movement in that area.

Myofascial trigger points (MTP) are the characteristic findings on physical exam. One or more trigger (pain) points will be found if the examiner gains familiarity with the likely point locations for

each body region (figure 3A-B). Trigger points often feel indurated to palpation, and palpation reproduces the pain in the "target zone," often at some distance away. Trigger points may result from acute trauma, repeated minor microtrauma of daily living, or the chronic strain of sedentary work or living habits. Thus, evaluation of such patients with myofascial pain should include inquiry into activities and habits of movement. Patients with whiplash-associated myofascial pain have a higher prevalence of trigger points along the semispinalis capitis muscle than at other sites in the neck, jaw, and upper shoulder [14]. (See "Overview of joint protection".)

MPS may include other common regional pain disorders such as tension headaches, idiopathic low back and cervical strain disorders, repetitive strain syndromes, occupational overuse syndrome, cumulative trauma disorder, work-related musculoskeletal disorder, and temporomandibular joint (TMJ) syndrome [15-18]. In the head and neck, the pain may be associated with unexplained dizziness and with neurocognitive disturbances. The etiology of these complaints is not understood, although some neurovestibular abnormalities are often found in patients with TMJ and myofascial pain of the head. These poorly understood pain disorders are also associated with fatigue, sleep abnormalities, and mood disturbances, which may also be observed with fibromyalgia (see "Clinical manifestations and diagnosis of fibromyalgia in adults", section on 'Symptoms'). Chronic, unexplained pelvic and urethral pain, sometimes termed the female urethral syndrome, is often considered to be a variation of myofascial pain.

Many clinicians are skeptical about the existence of trigger points. Confusion also arises when differentiating trigger points from the tender points of fibromyalgia (figure 4). Fibromyalgia tender points are said to differ in that they typically are not indurated and occur in tissues other than muscle (table 1). However, some find little difference in the tender point and trigger point examination in patients with fibromyalgia and MPS. A number of reports have questioned the reliability of the tender point evaluation, and they have been eliminated from revised American College of Rheumatology (ACR) diagnostic criteria for fibromyalgia [19,20]. (See "Clinical manifestations and diagnosis of fibromyalgia in adults".)

Myofascial pain is generally treated similarly to fibromyalgia (see "Initial treatment of fibromyalgia in adults"). However, myofascial pain also responds well to local treatments such as application of a cold spray and passive stretch of the involved muscle. Trigger point injections, using dry needling, saline, or botulinum toxin, have been effective in clinical trials for the treatment of myofascial pain [16,17,21].

Generalized pain disorders — Generalized pain disorders include the hypermobility syndrome, fibromyalgia, and somatoform disorders. These disorders all may cause widespread pain and in some cases disability.

- The hypermobility syndrome results from loss of muscle tone in a person with joint laxity. Widespread arthralgias and a sensation of joint swelling (without objective physical signs of swelling) that lasts for hours rather than days are typical of this disorder. (See "Joint hypermobility syndrome".)

- Fibromyalgia is a clinical syndrome marked by widespread pain, fatigue, and is often associated with a variety of other symptoms. There is often overlap of fibromyalgia with chronic fatigue syndrome (CFS), also known as myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) (table 2). (See "Clinical manifestations and diagnosis of fibromyalgia in adults".)

GENERAL INITIAL APPROACH

Six points of management can often be initiated during the first visit in a patient with a suspected soft tissue rheumatic disorder, even before the results of appropriate laboratory or radiologic tests are available:

- Exclude systemic disease
- Eliminate aggravating factors
- Explain the illness
- Provide self-help strategies
- Provide pain relief
- Explain prognosis

Exclude systemic disease — Systemic rheumatic diseases such as rheumatoid arthritis and other disorders such as diabetes mellitus, thyroid dysfunction, occult neoplasm, and drug reactions should be considered and excluded, if possible, in patients presenting with a suspected soft tissue rheumatic disorder. Such concurrent disorders are common. In a classic study, nearly 300 patients with work-related carpal tunnel syndrome underwent a systematic search for concurrent medical diseases. One hundred and nine separate atraumatic illnesses (principally hypothyroidism,

diabetes mellitus, and various arthropathies) capable of causing arm pain or carpal tunnel syndrome were diagnosed. Nearly 70 percent of these conditions would have been missed if only record reviews and patient histories had been utilized [22].

The extent of the work-up is dependent upon the diagnosis. As an example, a patient with tendinitis or bursitis following a cumulative movement strain is not likely to benefit from radiologic or laboratory studies. By contrast, a patient presenting with enthesitis of the Achilles tendon and inflammatory back pain who is under the age of 40 may require additional studies to evaluate for ankylosing spondylitis. (See "Diagnosis and differential diagnosis of axial spondyloarthritis (ankylosing spondylitis and nonradiographic axial spondyloarthritis) in adults" and "Diagnosis and differential diagnosis of rheumatoid arthritis".)

Treatment can, in many cases, be initiated prior to receiving the test results. Furthermore, plain film radiographs or other imaging studies can often be deferred until a later visit if they are not likely to change initial management.

Eliminate aggravating factors — Events and activities preceding the pain state must be reviewed in order to recognize aggravating activities that can cause recurrences. (See "Overview of joint protection".)

- Improper resting, sitting, or working positions are common precipitating factors.
- Strain resulting from job performance, a new hobby, or repetitive tiring tasks should be recognized and modified.
- Strain resulting from structural disorders (eg, flat feet or heavy pendulous breasts) can also be altered with appropriate instructions.
- Psychosocial factors that might influence outcome including drug dependency, interpersonal relationships, and other stressors should be investigated.

Joint protection advice should be provided. (See appropriate topic reviews for the different joints.)

Explain the illness — Patients may be reassured when they are told that they have a soft tissue rheumatic disorder rather than more serious illnesses such as systemic lupus erythematosus or rheumatoid arthritis. In addition, validation that their problem is "real" (eg, in patients with

myofascial pain syndrome [MPS] or fibromyalgia) often relieves anxiety. (See "Initial treatment of fibromyalgia in adults".)

Explain self-help strategies — At-home physical therapy and exercises should be outlined on the first visit, if appropriate (see appropriate topic reviews for rehabilitation programs for the head and neck, upper limb, and lower limb). A good plan is to have the patient enroll in a program that combines an aerobic, strength training, and stretching program.

Pain relief — Pain may promote muscle spasm, leading to a vicious cycle of increased pain and spasm. In addition, the self-help therapy program is more effective and results are obtained more quickly when adequate pain relief is achieved.

Acute injuries should be treated with the RICE regimen:

- Rest
- Ice
- Compression of injured tissue
- Elevation

Despite the paucity of adequate controlled clinical studies, heat and cold modalities have been used for many years in the treatment of musculoskeletal disorders [23]. Heat can readily be applied by hot packs or hot water bottles and can increase the threshold for pain, produce analgesia by acting on free nerve endings, and decrease muscle spasm. A review of the effects of superficial heat on low back pain showed moderate evidence for heat therapy providing a small short-term reduction in pain and disability [24]. It is not at all clear that heat should be used to treat patients with inflammatory diseases. Heat is not indicated in acute arthritis, since it contributes to increased inflammation and pain, but may be helpful for some patients with moderate joint inflammation, where it may reduce pain and muscle spasm. Ice is sometimes useful to control pain and swelling because it induces vasoconstriction of superficial and intra-articular tissues, reduces local metabolism, and slows nerve conduction. It may be applied using cold packs, ice baths, and vapocoolant sprays [25].

In addition to the RICE regimen, other simple, frequently used measures include use of oral or topical nonsteroidal antiinflammatory drugs (NSAIDs), and other topical applications with agents such as lidocaine or capsaicin (table 3) [26,27].

If simple measures have not sufficed, injecting the affected area with a long-acting glucocorticoid-local anesthetic mixture can be effective in bursitis, tendinitis, carpal tunnel syndrome, or MPS. (See appropriate topic reviews for description of the injection technique in the different disorders.)

The use of diagnostic ultrasound promises to greatly improve our diagnostic accuracy and broaden our understanding of soft tissue rheumatic disorders [28]. Ultrasonography should also afford greater precision in defining sites to be injected with glucocorticoids [29,30].

Acupuncture is another method that is employed to relieve pain. Its clinical value varies and seems to be based on the condition being treated and the specific methodology employed. (See "Acupuncture".)

Since it is not at all clear that botulinum toxin injections are clearly superior to the injection of less costly agents, we do not recommend using botulinum toxin for tender or trigger point injections. Several studies suggest that botulinum toxin type A may provide pain relief in MPS [31-33], while others have found an analgesic effect similar to injection of glucocorticoids [33] or saline [34] and less than or similar to that of lidocaine [35,36]. (See "Overview of the treatment of chronic non-cancer pain".)

Explain prognosis — Most soft tissue rheumatic pain disorders are of short duration and the time until improvement becomes evident can be projected. Relief from carpal tunnel syndrome, bursitis, or tendinitis may require only a few days, while symptoms due to hypermobility syndrome or disorders of other structural deficits may require several months before moderate or great improvement is seen.

The expected clinical course should be explained to the patient at the initial visit if possible. Patients should also understand that this course is dependent upon the performance of the self-help program, and that their response to the program may impact the diagnosis.

SUMMARY AND RECOMMENDATIONS

- Soft tissue rheumatic disorders refer to nonsystemic, focal pathologic syndromes involving the periarticular tissues, including muscle, tendon, ligament, fascia, aponeurosis, retinaculum, bursa, and subcutaneous tissue. These disorders are extremely common. (See 'Introduction'

above.)

- Soft tissue disorders may be divided into several broad categories and include tendinitis, enthesitis, fasciitis, bursitis, structural disorders, neurovascular entrapment disorders, complex regional pain syndromes (CRPS), and myofascial pain syndrome (MPS). Many of these disorders occur in the absence of systemic disease, and some are a consequence of chronic repetitive low grade trauma and overuse. Many are self-limiting and respond to conservative measures. (See 'Specific syndromes' above.)

  - Tendinitis (or tendonitis), which often results from overuse, is a disorder with common features of local pain and dysfunction, inflammation, and degeneration.

  - Enthesitis, which is an inflammation of the site of the insertion of the tendon to the bone, is often seen in spondyloarthropathies. Common sites are the insertion of the plantar fascia and the Achilles tendon region. (See 'Enthesitis' above.)

  - Bursitis is inflammation of the small fluid-filled pads, called bursae, which provide a cushion between bones and tendons and/or muscles around a joint. Bursitis may result from direct trauma or repetitive injury, infection, or it may be a manifestation of a systemic disease such as rheumatoid arthritis or gout. (See 'Bursitis' above and "Bursitis: An overview of clinical manifestations, diagnosis, and management".)

  - Musculoskeletal structural disorders are relatively common, sometimes subtle, and often contribute to pain syndromes and to injury in sports participants. Body asymmetry is a common cause for many regional pain disorders. (See 'Structural disorders' above.)

  - Neurovascular entrapment disorders may occur within the spinal canal (foraminal or central spinal stenosis) or along the course of a peripheral nerve. The diagnostic triad of peripheral neurovascular entrapment includes a sensation of swelling and pain in the involved region, paresthesias distal to the site of entrapment, and weakness. (See 'Neurovascular entrapment' above.)

  - A diagnosis of CRPS requires the presence of regional pain and sensory changes usually following a noxious event, often far from the involved site. The pain is of a severity greater than that expected from the inciting injury and is associated with characteristic clinical

findings. (See 'Complex regional pain syndromes' above and "Complex regional pain syndrome in adults: Pathogenesis, clinical manifestations, and diagnosis" and "Complex regional pain syndrome in adults: Prevention and management".)

- In MPS, hyperirritable spots, often in just one body region, usually within a taut band of skeletal muscle or in the muscle's fascia, can give rise to characteristic referred pain. There are usually one or more trigger (pain) points; these are typically indurated and painful on compression. Myofascial trigger points may result from acute trauma, repeated minor microtrauma of daily living, or from a chronic strain of sedentary work or living habits. (See 'Myofascial pain syndrome' above and "Differential diagnosis of fibromyalgia", section on 'Myofascial pain syndromes'.)

- Six points of management can often be initiated during the first visit in a patient with a suspected soft tissue rheumatic disorder, even before the results of appropriate laboratory or radiologic tests are available. These are excluding systemic disease, eliminating aggravating factors, explaining the illness, explaining self-help strategies, providing pain relief, and explaining the prognosis. (See 'General initial approach' above.)

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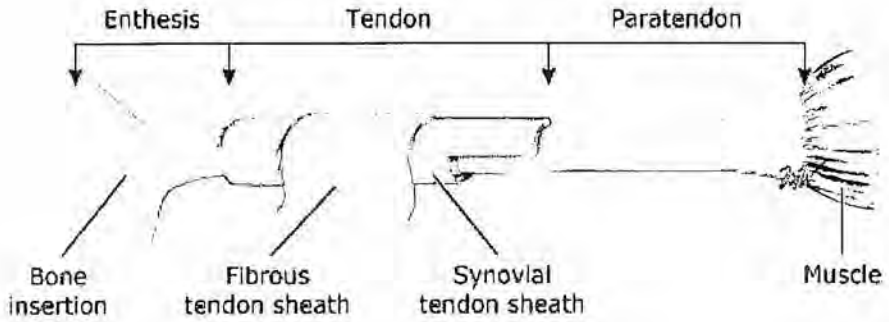
Topic 7757 Version 18.0

GRAPHICS

Tendon anatomy



Tendon sheaths, like bursae, develop in response to motion as tendons pull and transmit power. The visceral sheath has a flat synovial lining, and the parietal layer has vesicular and granular patches. There is no basement membrane, only a fatty or collagenous connective tissue. Tendon healing is facilitated by an intact tendon sheath. Snapping or triggering of joint movement can be due to nodular enlargement of the tendon, stenosis of the sheath, or both. Enthesitis involves the area of the tendon that inserts into bone, tendinitis typically involves the area of the tendon closer to the enthesis, peritendonitis involves the area that inserts into muscle, and tenosynovitis represents inflammation of the tendon and its enveloping sheath.

Modified with permission from: Sheon RP, Moskowitz RW, Goldberg VM. Soft Tissue Rheumatic Pain: Recognition, Management, Prevention, 3rd ed, Williams & Wilkins, Baltimore 1996.

Graphic 62565 Version 3.0

Facial asymmetry

The left side of this patient's face is smaller than the right. Temporomandibular joint dysfunction is more common in patients with facial asymmetry. Other associated features may include scoliosis and a short leg.

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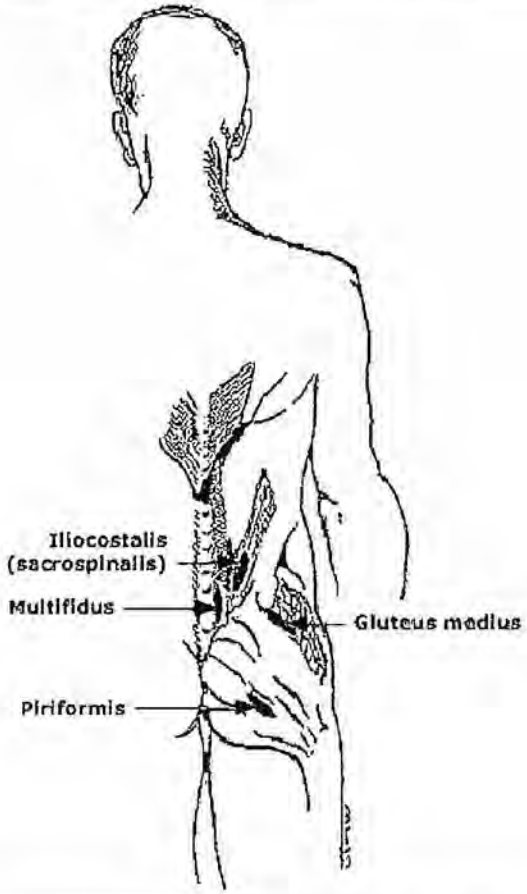
Graphic 64450 Version 3.0

Trigger points in myofascial pain syndrome



Patients with myofascial pain syndrome have tenderness within the affected muscle and soft tissue. Trigger points arising in the erector spinae muscles, the gluteal fascia, and the presacral fascia are common.

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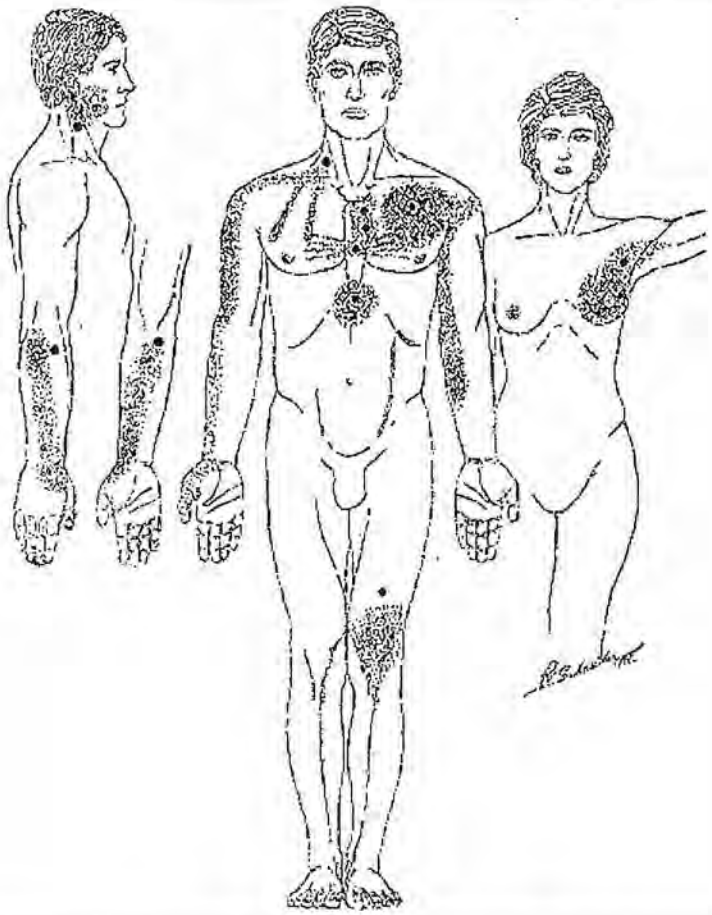
Graphic 81019 Version 2.0

Clinical features of fibromyalgia versus myofascial pain

Variable	Fibromyalgia	Myofascial pain
Pain	Generalized	Localized
Examination	Tender points	Trigger points
Fatigue	Prominent	Data unknown
Gender	90 percent female	Data unknown
Course	Chronic	May be self-limited

Graphic 81771 Version 4.0

Anterior trigger points associated with the myofascial pain syndrome



Palpation of a trigger point (black dots) in patients with the myofascial pain syndrome may cause pain at a distant point. This zone of reference (gray area) is usually quite characteristic for each trigger point.

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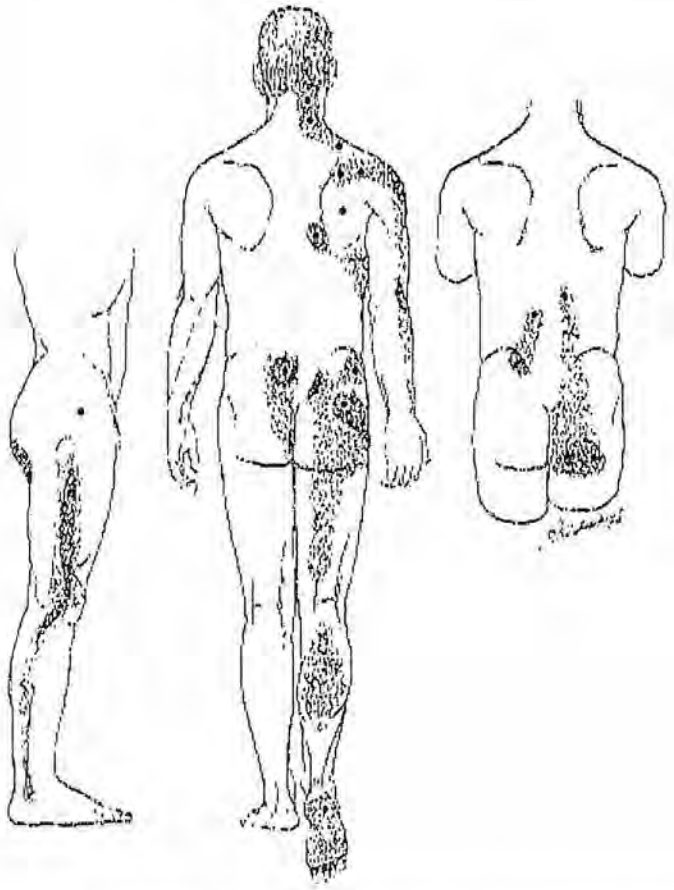
Graphic 66839 Version 1.0

Posterior trigger points associated with the myofascial pain syndrome



Trigger points and zones of reference are also present posteriorly in patients with the myofascial pain syndrome.

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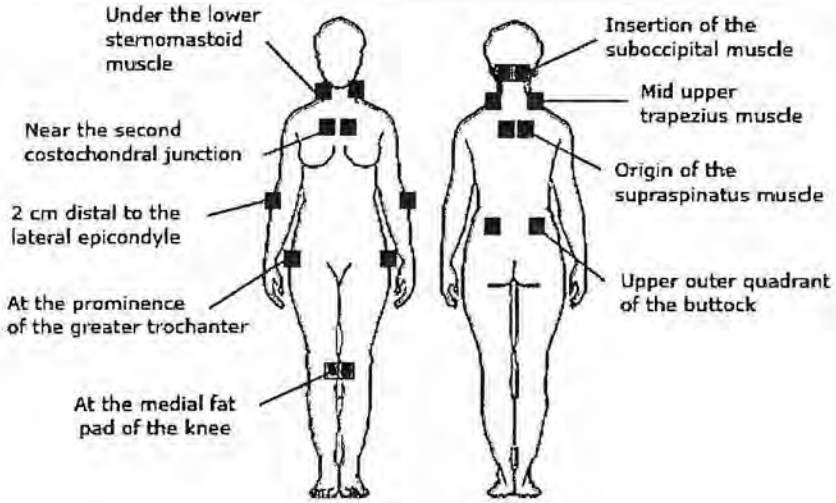
Graphic 79295 Version 1.0

Tender points in fibromyalgia



The 18 "tender points" important for the diagnosis of fibromyalgia. Note the bilateral symmetry of the labeled regions. Tenderness on palpation of at least 11 of these sites in a patient with at least a three-month history of diffuse musculoskeletal pain is recommended as a diagnostic standard for fibromyalgia.

Adapted from: Goldenberg DL. Diagnostic and therapeutic challenges of fibromyalgia. Hosp Pract (Off Ed) 1989; 24:39.

Graphic 77950 Version 3.0

Clinical similarities between fibromyalgia and chronic fatigue syndrome (CFS)

80 to 90% women, usual ages 20 to 55 years
Myalgias and fatigue in more than 90%
Associated common symptoms
Neurocognitive and mood disturbances
Headaches
Sleep disturbances
No identifiable cause
Testing is normal
Physical examination usually normal except for tender points which are required for diagnosis of fibromyalgia and present in most patients with chronic fatigue
Normal laboratory and radiologic tests
Chronic symptoms, no highly effective therapy

Graphic 56019 Version 6.0

Topical analgesics for treatment of superficial painful conditions

Topical analgesic	Usual dose (adult)	Characteristics
Topical nonsteroidal antiinflammatory drugs (NSAIDs)*		
Diclofenac topical gel (1%)	Knees: Rub in 4 g of gel to affected knee(s) three to four times daily. Hands: Rub in 2 g of gel to affected joint(s) three to four times daily. Maximum 16 g per joint per day; 32 g total per day.	Applies to all topically administered NSAIDs: ▪ Useful for treatment of musculoskeletal pain and osteoarthritis of superficial joints (eg, wrist, knee, hand) in combination with acetaminophen and/or tramadol, or as an alternative to systemic therapy ▪ Minimal systemic absorption ▪ Safety data are reassuring despite label warnings on United States products ▪ Local skin reactions include rash, itch, or burning (some products contain propylene glycol, a potential irritant and rarely an allergen) ▪ Refer to topic review on initial pharmacologic therapy of osteoarthritis
Diclofenac topical solution drops (1.5%)	Knees: Rub in 40 drops to affected knee(s) up to four times daily.	
Diclofenac topical solution pump (2%)	Knees: Rub in two pump actions to affected knee(s) up to two times daily.	
Ibuprofen topical gel (5, 10%); not available in United States	Knees or hands: Rub in dose (depends on joint size and location) up to four times daily; refer to product-specific information for detail.	
Ketoprofen topical gel (2.5%); not available in United States	Knees or hands: Rub in 2 to 4 g of gel two to four times daily (maximum 15 g of gel per day); refer to product-specific information for detail.	
Topical capsaicin¶		
Capsaicin creams, gels, liquids, or lotions (0.025 to 0.1%)	Rub in a small amount (pea sized) one to four times daily; the preparation most often studied in osteoarthritis was 0.025% cream.	▪ Useful for treatment of osteoarthritis pain and postherpetic neuralgia as an adjunct or alternative to systemic analgesics ▪ Local irritation may be intolerable ▪ Refer to topic review on initial pharmacologic therapy of osteoarthritis
Capsaicin topical patches (0.025 to 0.05%)	Apply one patch to affected area for up to eight hours (maximum four patches per day).	
Capsaicin topical patch (high concentration 8%)	Postherpetic neuralgia (single treatment): Apply up to four patches to the most painful area for 60 minutes. Treatment may be repeated after three months.	▪ Potential option for local pain relief in postherpetic neuralgia ▪ High-concentration patch must be administered by a health care professional and monitored for up to two hours after treatment ▪ Pretreatment with a local anesthetic (eg, lidocaine) is necessary ▪ After application, local cooling measures can decrease discomfort ▪ Local pain and irritation may be intolerable ▪ Refer to topic review on postherpetic

		neuralgia
Topical lidocaine		
Lidocaine topical patch (5%)	One to three patches applied for up to 12 hours in any 24-hour period.	▪ Low (3 to 5%) systemic absorption through intact skin ▪ Useful for local relief of pain (eg, due to postherpetic neuralgia) in limited areas of intact skin as an adjunct or alternative to systemic analgesics
Lidocaine topical creams, ointments, and gels (2 to 4%)	Apply a thin film two to four times daily (refer to product-specific instructions).	▪ Useful for local relief of minor superficial skin irritation and pain
Lidocaine topical cream (5%)	Apply a thin film three to four times daily (maximum six times daily).	▪ Useful for local relief of anorectal pain and itching

Topical analgesic therapies are moderately effective and useful in combination with systemic therapies for reducing medication load and side effects, and potentially, as monotherapy for adults with localized pain and contraindications to systemic therapies.

* For patients already on oral NSAIDs, topical therapies are generally not recommended because they are unlikely to provide additional pain relief. Gel measurements from tubes are approximate.
¶ Pain relief usually begins within the first week of treatment, and full effect is seen with regular application over approximately four weeks. Topical capsaicin should not come in contact with mucous membranes, abraded skin, eyes, or genital areas.

Graphic 93846 Version 6.0

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Conflict of interest policy

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Comparison of intravenous NSAIDs and trigger point injection for low back pain in ED: A prospective randomized study

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ABSTRACT

Introduction: Low back pain (LBP) is a common complaint originating from muscles
Myofascial pain syndrome (MPS) is mainly associated with trigger points (TrP) in the muscle tissue. We compared the intravenously administered non-steroidal anti-inflammatory drug (NSAID) and trigger point injection (TPI) in the treatment of LBP patients admitted to the emergency department due to pain caused by TrPs.
Material and method: After randomization, NSAID was administered intravenously in group 1 and TPIs were performed as specified by Travell and Simons in group 2. The TrPs were identified with the anamnesis and physical examination
Demographic characteristics and vital signs of the patients were recorded. Pain scores were measured with the Visual Analogue Scale (VAS) at admission; and in minutes 5, 10, 15, 30, and 60.
Results: There were 32 patients in group 1 and 22 patients in group 2. The demographics, vital signs, and pain scores at admission were not statistically significantly different between the groups. The pain scores decreased significantly in the TPI group. During the 60 min' follow-up period, the mean VAS pain score decreased by 0.41 $\pm$ 1.30 in the TPI group and by 2.59 $\pm$ 2.37 in the NSAID group ($p < 0.001$). Respond the treatment was significantly higher group TPI than Group NSAID (21/22 vs 20/32 respectively, $p = 0.008$).
Conclusion: In this small randomized study with several methodological limitations, TPI was superior to the intravenous NSAIDs in the treatment of acute LBP due to TrPs. TPI can be used in the emergency departments for the acute treatment of LBP in selected patients.

1. Introduction

Acute or chronic pain results in a remarkable burden for mankind from the clinical, economic, and social aspects. The most common cause of physician visits is the pain. Pain caused extra burden in the patients and their families; including opioid use and dependence, depression, poor social relationships and economic costs [1]. The feeling of pain is, in fact, one of the control mechanisms of the body. Pain transmits the information about the presence of injuries in the body tissues to the brain, allowing for awareness. This is a protective mechanism essentially [2].

Low back pain (LBP) is a common and expensive medical condition. LBP rarely refers to a serious disorder. The annual prevalence of low back pain in the US is estimated between 15% and 20% and its lifetime prevalence is over 60% [3]. LBP is one of the most common causes of admission to emergency departments (ED) [4,5]. LBP related accounts for approximately 2.5% of ED visits [6,7]. However the prevalence and analgesic management of LPB in the ED is still unclear [8].

Myofascial pain syndrome (MPS) is an uncommon cause of musculoskeletal pain. MPS is a neuromuscular disorder characterized by localized muscle tenderness and often manifests with pain in the back, shoulders, lower back; and tension-type headaches. The origin of the MPS is the presence of a hyperalgesic spot in the form of a painful band and it is called as a trigger point. A trigger point (TrP) is defined as a sensitivity felt at deeper levels in the musculoskeletal tissue, causing pain in the zone of reference, which is the region of pain associated with the TrP. The TrPs are localized only in the muscles and myofascial trigger points (MTrPs) are a common source of (regional) pain in patients presenting with musculoskeletal pain, with a lifetime prevalence of up to 85% in the general population [9]. The pain is usually localized in the TrP, and referred to the surroundings. The main objective in the treatment of MPS is to break the pain cycle by eliminating the trigger points. Currently, several therapies are available for treating myofascial trigger points; including massaging, stretching, dry needle injections, electrical stimulation, cold laser treatment, and ultrasound [10]. An insufficient treatment of pain will cause a significant socioeconomic

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burden, as well as, a reduction in the quality of lives of the affected individuals.

In our study, we aimed to compare the intravenously administered nonsteroidal anti-inflammatory drug (NSAID) treatment versus trigger point injection (TPI) in patients admitted to the emergency department due to pain caused by an LBP with TrPs.

2. Material and method

2.1. Study design and setting

All patients were informed about the study and its procedures, and informed consents on paper were collected from the agreeing volunteers before their inclusion in the study. The study was approved by the Ethics Committee at Ataturk University Faculty of Medicine. Our study was conducted in the emergency department at Ataturk University, Faculty of Medicine between 01.04.2018 and 30.10.2018. The patients presenting to the emergency department with the complaint of LBP, who had trigger points as the cause of pain, were included in the study and divided into two groups. A total of 80 patients were planned to be included in each group. The Patients were allocated to two groups; NSAID and TPIs groups.

2.2. Patients

The patients presenting to the ED with the complaint of LBP were considered eligible for the study. First, we investigated the presence of active TrPs in the previously identified muscles including the deep lumbar paraspinal muscles, the left and right quadratus lumborum muscles; and the left and right gluteus medius muscles. Delphi consensus criteria; consisting of a taut band, hypersensitive spot, and referred pain; were used for the active diagnosis of active TrPs [11]. According to these criteria, TrPs were identified based on the clinical findings and the characteristics of pain emerging upon exerting a pressure of 2 kg/cm^2 onto the suspected area and by comparing the elicited findings with the corresponding contralateral site. The pressure pain threshold of TrP was measured with a handheld mechanical pressure algometer. Palpating the active TrPs by exerting a constant pressure on them deeply by a fingertip, will cause a change in the characteristics of pain felt at the referred area (an increase or reduction in the intensity) and cause it to be referred further in the zone of reference. This phenomenon can be observed immediately or occur after a few seconds. In this way, the zone of reference is determined. The patient may sometimes react to the palpation. This is called as the "jump sign", which is manifested by several behavioral reactions including retraction of the head, grimace, wrinkling the forehead, or a verbal response. These findings help to identify the TrPs.

Inclusion Criteria

- Age > 18
- The patient should present to the emergency department with the complaint of LBP
- LBP should have a recent time of onset (duration of LBP should not be over 48 h)
- At least one TrP should be identified as the cause of the pain.

Exclusion Criteria

- LBP should not be associated with an organic cause
- Chronic illnesses including hypertension, diabetes mellitus, coronary artery disease, chronic pulmonary diseases, thyroid diseases, inflammatory rheumatic diseases, muscular diseases or lupus.
- Fibromyalgia
- Lumbar radiculopathies, lumbar disc herniations, degenerative joint diseases
- Individuals being allergic to local anesthetics or dexketoprofen
- The individuals to whom trigger point injections were applied
- Individuals with bleeding disorders
- Patients taking medications which increase the risk of bleeding
- A history of surgery on the neck or shoulders
- Pregnant patients
- Patients with cognitive impairments or psychiatric disorders
- Oral or topical use of NSAIDs
- A history of a gastrointestinal bleeding
- Patients with cancer
- Patients receiving physical therapy (in the last 6 months)

The patients were assigned to two groups randomly by means of the random allocation software (RAS). Gender was not taken into account during the randomization because it was not a factor that could affect patients' response to the treatment. The patients were planned to be allocated to two groups; NSAID and TPIs groups.

2.2.1. Injection procedure

TPIs were performed in compliance with the technique described by Travell ve Simons [12,13]. While the patient was lying in the prone position, TrPs were identified and the skin was cleaned with an appropriate antiseptic solution (Betadine). During the injections, 22 gauge 1.25-in. needles were used. The trigger point was stabilized between the thumb and forefinger. Then, the needle was inserted vertically into the skin and advanced until it reached the trigger point. After ensuring a negative aspiration, the local anesthetic (2% lidocaine, 2.5 cc from 100 mg-5 cc of ampoule with 2.5 cc saline mixture) was injected in small amounts to the identified point. Then the same point was needled several times. All injections were performed by the same physician. Trigger point injections were performed by experienced and trained professionals. Local twitch response was obtained for all patients in whom TPIs were performed. Local twitch response was defined "a transient contraction of a group of tense muscle (taut band) that traverses a trigger point. The contraction of the fibers is in the response to stimulation of the same trigger point or sometimes of a nearby trigger points. The injection site was then compressed for approximately 2 min to ensure hemostasis. Group 1 received 50 mg dexketoprofen in 100 cc isotonic solution over a period of 5 min.

2.3. Measurement

Age, sex, vital signs (blood pressure, pulse rate, respiratory rate, fever, and oxygen saturation) of the patients who agreed to participate in the study were recorded. The causes of LBP were categorized under three headings, which were sudden movement, lifting an object, and trauma. The means of arrival at the emergency department was categorized as either an ambulance or ambulatory transportation. The patients were asked to score the current intensity of the pain they experienced at several time points, which were the time of admission, minute 5, minute 10, minute 15, minute 30, and minute 60. Visual analog scale (VAS) was used for scoring. Marking of the pain scores on VAS was performed by the patients. A 10-cm Visual Analogue Scale (VAS) was used to score the pain, where 0 indicated the absence of pain and 10 indicated the highest intensity of pain felt ever. After procedure TPI or NSAID administration, VAS scores ≥4 is defined as unresponsive to treatment. Finally, occurrences of any side effects were questioned and the responses of the patients were recorded.

2.4. Statistical analysis

Statistical analyses were performed using SPSS 20 statistical analysis program (IBM). Data are presented as mean, standard deviation, and median; and with the minimum and maximum values, percentages,

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and numbers. Shapiro-Wilk and Kolmogorov – Smirnov tests were used to evaluate whether the data conformed to a normal distribution. Independent samples *t*-test was used for comparing normally distributed data between two independent groups, and the Mann–Whitney *U* test was used if the data were not normally distributed. Categorical variables were compared using Chi-square and Fisher's exact tests. A p value of <0.05 was considered to be statistically significant.

3. Results

Our study was conducted on patients who presented to the emergency department due to LBP associated with identified TrPs. The patients were allocated to two groups at the time of admission so that a total of 80 individuals would be included in the study with 40 patients in either group. As some patients did not agree to participate in the study or some met with at least one of the exclusion criteria, a total of 54 patients completed the study with 22 (40.7%) patients in the TPI group and 32 (59.3%) patients in the NSAID group. Eligible patients for this study were analysed for the primary outcomes and reshown in the CONSORT flow diagram (Fig. 1).

The examination of the causes associated with the presenting complaints of the study patients revealed that the most frequent cause of the emergency department visit was trauma (20 patients, 37%). The trauma resulting in LBP most commonly resulted either from an abrupt, shock-like movement in 17 (31.5%) patients or emerged after lifting a heavy object in 17 patients (31.5%). Five patients were transported to the emergency department with 112 emergency-call ambulances. All participating patients completed the study. No patients developed any side effects during the study.

The demographic data and the elapsed time since the onset of pain of the patients are summarized in Table 1. There were no significant changes between the groups.

The mean VAS mean scores of the groups at admission were 7.22 and 7.55, respectively; and there was not a significant association between the groups ($p > 0.05$). A significant difference between the study groups occurred after procedure starting from minute 5 ($p < 0.05$). The pain scores decreased significantly in the TPI group. The patients in the NSAI group also benefited from the treatment, but the trigger point injection group benefited more as observed in all time points of VAS scoring. During the 60 min' follow-up period, the mean VAS pain score decreased by 0.41 ± 1.30 in the TPI group and by 2.59 ± 2.37 in the NSAI group ($p < 0.001$). Respond the treatment was significantly higher group TPI than Group NSAID (21/22 vs 20/32 respectively, $p = 0.008$) The VAS scores and respond the treatment of the study groups are presented in Table 2 and Fig. 2.

4. Discussion

Our study was conducted on LBP patients who presented to the emergency department. Patients presenting to the emergency department due to LBP with TrPs; identified in the deep lumbar paraspinal muscles, right and left quadratus lumborum, and right and left gluteus medius muscles by means of the medical history and physical examination were included in the study. The aim of our study was to investigate the efficacy of trigger point injection in the emergency department. For this purpose, dexketoprofen was selected as the comparator treatment as it was used commonly in the emergency settings for the treatment of pain. The pain scores decreased in the patients staying in the TrP treatment after the first intervention. Our study is the first study in

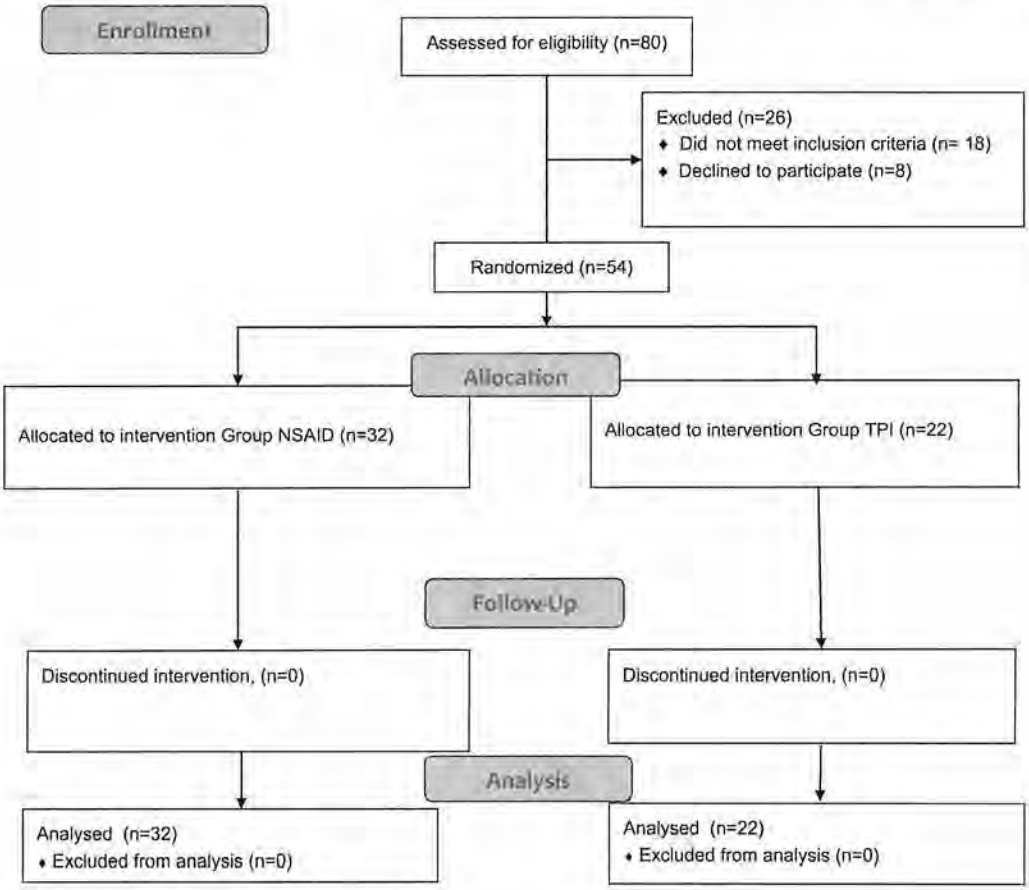

Fig. 1. CONSORT diagram.

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Table 1
Demographic details of patients.

	Group NSAID (n = 32)	Group TPI (n = 22)	p
Age	40.94 ± 13.18	45.14 ± 13.03	0.253*
Sex (M/F)	17/15	14/8	0.577†
Duration of back pain (hours)	9.03 ± 8.38	6.27 ± 6.16	0.296*

Values are presented as number or mean ± standard deviation. TPI: Trigger Point Injection, NSAID: nonsteroidal anti-inflammatory drug.
* p > 0.05 Independent sample *t*-test

the literature evaluating the efficacy of trigger point injections performed in the emergency department. Our study found that pain intensity decreased statistically significantly in the TPI group. Those reductions in the intensity of pain occurred starting from minute 5, suggesting evidence that TPI can be performed in the emergency departments.

LBP is accompanied with several diagnoses Most LBP is non-specific origin approximately 90%. Myofascial etiologies are uncommon cause of LBP [14]. However the prevalence of pain due to MPS is still unknown, 78% of these undiagnosed pain is referred to MPS [15]. MPS is associated with hypersensitive spots in a taut band in skeletal muscles [16]. These points are called trigger points [17,18]. Diagnosis and treatment of TrPs in emergency settings is important. The sooner they are diagnosed and treated, the lower number of TrPs will occur resulting in a musculoskeletal pain of lower intensity. Trigger points are actually very common, however, the information about them is limited in the literature. It might be because a diagnosis of a TrPs is usually missed, and the respective patients receive other treatments not allowing the prevention of TrPs from acquiring a chronic character. In daily clinical practice, MPS is often considered as myalgia. MPS patients receiving a misdiagnosis of myalgia often use NSAIDs, which is not a definite treatment. We would like to emphasize particularly this point in our study.

In literature review, TPI can be used in the treatment of renal colic pain and headache in emergency department [19,20]. The physicians working at emergency settings may identify TrPs by means of medical history and physical examination and treat them by applying TPI with proven efficacy to the patients with an emerging pain, which developed after trauma, lifting a heavy object, or following a sudden abrupt movement. Emergency physicians should exercise care for the recognition of this issue. In our study, the control group received an NSAID because TrP associated pain is commonly treated with this group of medications.

The pathophysiology underlying the emergence of TrPs and the development of the chronicity of the pain associated with the release of a number of mediators due to ischemia. [21-24]. Tissue injury releases the mast cells and leads to the stimulation of the nociceptors. The resulting pain is associated with histamine release leading to vasodilation and edema. The resulting increase in the metabolic rate causes lactic acid synthesis, stimulating the nociceptors [2].

Table 2
Pain scores and respond the treatment after procedure.

	Group NSAID (n = 32)	Group TPI (n = 22)	p
VAS 0.	7.22 ± 1.64	7.55 ± 1.68	0.339
VAS 5 min	6.22 ± 2.11	2.77 ± 2.81	<0.0001*
VAS 10 min	5.22 ± 2.41	1.45 ± 2.15	<0.0001*
VAS 15 min	4.25 ± 2.41	0.82 ± 1.71	<0.0001*
VAS 30 min	3.28 ± 2.44	0.55 ± 1.60	<0.0001*
VAS 60 min	2.59 ± 2.37	0.41 ± 1.30	<0.0001*
Respond to treatment (yes/no)	20/12	21/1	0.008†

Values are presented as number or mean ± standard deviation, TPI: Trigger Point Injection, NSAID: nonsteroidal anti-inflammatory drug, VAS: Visual Analogue Scale, min: minute, Respond to treatment: After procedure TPI or NSAID administration, VAS scores <4.
* p < 0.05 Independent sample *t*-test.
† Chi-square.

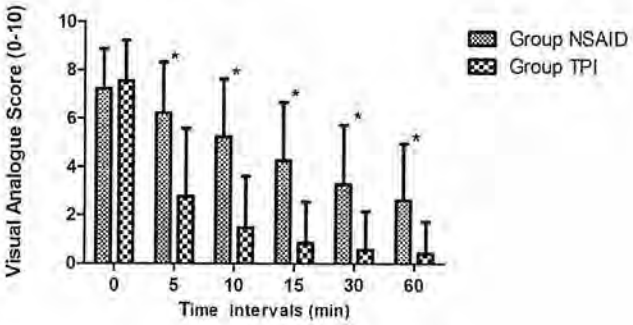

Fig. 2. Pain scores after procedure.

The aim of the treatment is, therefore, to break the "spasm-pain-spasm" cycle in the muscles associated with TrP induced pain, removing the TrPs. Several modalities are employed in the treatment of TrPs including patient education, NSAID medications, physiotherapy, spray and stretch technique, acupuncture, local injections, and workouts. TPI is one of the most effective methods in the treatment of MPS. Local anesthetic agents, saline, steroids, botulinum toxin, and dry needling are applied locally. Of them, the most common ones are the injection of local anesthetics and dry needling. Studies on these two latter modes of treatment report variable results [25]. In our study, local anesthetic agent injection method was used in TPIs as a lower intensity of pain [26,27], as well as the contribution of the local anesthetic effect, was reported after the injections with this method [21,28-31]. A study by Affaitati et al. [21] compared the efficacy of anesthetic agent injections, lidocaine patches, and placebo patches in MPS patients. It was found out that the treatments with lidocaine patches and bupivacaine injections were significantly more beneficial compared to placebo. The reported efficacy of lidocaine patches supports the use of a local anesthetic agent in the treatment in combination with dry needling.

The most common adverse effects of the regular TrP treatments were reported to be bruising, hemorrhage, and pain. As these adverse events were associated with a short-term duration without a need for further treatments, they were categorized as mild. The adverse effects of moderate and severe character (such as fainting, headache, and nausea) occurred at a rate of <0.04% [32]. And also in thoracic region pneumothorax was reported [33]. No adverse effects occurred in our study in none of the study patients. TPIs can be safely applied by the emergency department physicians owing to the remarkably lower frequency of the adverse effects.

The number of studies on the use of NSAIDs for the treatment of TrPs is limited. In our study, the NSAID group also benefited from the treatment. Our study is the first in the literature showing the efficacy of intravenously administered NSAIDs in the treatment of trigger point. It is well known that NSAIDs inhibit the activity of cyclooxygenase, suppressing prostaglandin synthesis from arachidonic acid. The efficacy of NSAIDs observed in our study can be explained by their ability to reduce local prostaglandin synthesis. As the pain is reduced as a result of NSAID use, patients begin to use their muscles more actively. This leads the corresponding muscles to reach the optimum length, and causes the taut bands caused by a reflex relaxation to be resolved; thereby disrupting the vicious contraction-ischemia-contraction cycle. The mechanism of an NSAID treatment for the trigger points can be explained this way.

In the literature various studies were reported for treatment of MPS involving low back pain [28]. This study supports our findings in the sense that TPI treatment is more beneficial.

The use of trigger point injections was reported for the treatment of chronic pain, however, our study evaluated the efficacy of TPI in acute LBP, highlighting its importance. Our study showed that, with the TPI treatment, the pain of the patients was controlled in a shorter period; patients could be discharged from the hospital earlier, return to their

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daily lives earlier, minimizing the loss of labor productivity and they benefited from a more comfortable mode of treatment.

The main limitation of this study was there was no attempt to determine the reliability/reproducibility of the identification of a trigger point. In study protocol we include only at least one TrP should be identified as the cause of the pain. In addition lumbar radiculopathies, lumbar disc herniations, degenerative joint diseases or chronic low back pains are excluded from study. Patients pain scores were follow-up only 60 min in ED. Long term results are not evaluated according to our study protocol. If long term results were evaluated different results could be obtained. One another limitation of the study is small sample size and selected patients groups (patients with TrP) are included the study. We focused on TrP related LBP so our results are cannot be generalized to all population.

5. Conclusion

In this small randomized study with several methodological limitations, TPI was superior to the intravenously administered NSAID in the acute treatment of LBP caused by trigger points. We believe that the trigger point injection should be a part of the acute treatment of LBP in the selected patient group.

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