1. The use of therapeutic medications for soft-tissue injuries in sports medicine

Justin A Paoloni and John W Orchard

The widespread use of non-steroidal anti-inflammatory drugs and corticosteroid injections for treating soft tissue injuries is not always appropriate

ABSTRACT

- The use of non-steroidal anti-inflammatory drugs (NSAIDs) to treat most muscle, ligament and tendon injuries should be reassessed. They have, at best, a mild effect on relieving symptoms and are potentially deleterious to tissue healing.
- Soft-tissue injury associated with definite inflammatory conditions such as bursitis or synovitis or involving nerve impingement does warrant short-term treatment with NSAIDs.
- Paracetamol has similar efficacy to NSAIDs in soft-tissue injury, is cheaper, and has a lower side-effect profile. It is the analgesic of choice for most soft-tissue injury.
- Cyclo-oxygenase-2 (COX-2) inhibitors should not be used to treat soft-tissue injuries unless impingement is a major feature and non-selective NSAIDs are contraindicated (eg, coexisting gastric disorder), and the patient is not at cardiovascular risk.
- Corticosteroid injections for tendon injuries may achieve a mild to moderate reduction in pain for up to 6 weeks. However, they do not promote tendon healing, so should generally be used only when healing is not a critical goal.
- Promising new therapeutic treatments for soft-tissue injuries include topical glyceryl trinitrate, aprotinin injections, and prolotherapy.

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Soft-tissue injuries are injuries to skin, fascia, ligament, muscle, and tendon. Currently, many therapeutic medications are commonly used in the management of soft-tissue injuries, including: analgesics, non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, prolotherapy sclerosant agents, aprotinin, glyceryl trinitrate, botulinum toxin, and glucosamine. Despite their regular use for soft-tissue injury, few medications have strong evidence of a consistent therapeutic effect. In this article, we review the proposed mechanisms of action, side effects, and the evidence base (based on National Health and Medical Research Council levels of evidence[1]) for common soft-tissue injury treatments. We also suggest appropriate circumstances for using therapeutic medications, with emphasis on the Hippocratic principle of *primum non nocere* (first do no harm).

Non-steroidal anti-inflammatory drugs for ligament and muscle injury

NSAIDs are among the most widely used medications for common soft-tissue injuries such as muscle contusions, muscle tears, and ligament tears. The mechanism of action of NSAIDs is through non-specific cyclo-oxygenase inhibition, thereby blocking the production of prostaglandins from arachidonic acid. Prostaglandin inhibition by NSAIDs decreases the inflammatory response, which can have both positive and negative effects. For example, the arachidonic acid "overflow" pathway may lead to increased leukotriene production and potential tissue damage. Other known negative NSAID class side effects include hypertension, altered renal function, gastrointestinal disturbance (including peptic ulceration), and the recently discovered increased rates of myocardial infarction with non-selective NSAIDs, such as diclofenac and ibuprofen (evidence level III-2 [$E3_2$]).[2] Potentially desirable class effects of NSAIDs include reduced risk of bowel cancer and increased blood clotting times. Side effects, whether positive or negative, are generally far more relevant for long-term use (such as in patients with rheumatoid arthritis) than with short-term use for sports injury. Many NSAIDs are available as topical preparations. Although the results of tissue penetration studies are variable, for injured body structures which are close to the surface (eg, limbs), topical NSAIDs may offer the advantages of higher local tissue concentrations with reduced risk of systemic side effects.

The balance of evidence suggests that NSAID use is associated with a short-term mild to moderate decrease in pain in "minor sports injury" (E2),[3] ankle sprains and knee pain (E2),[4] and shoulder pain (E1).[5] The number needed to treat (NNT) for a positive effect greater than placebo for most conditions is 3–4 patients. There is no evidence that NSAIDs improve muscle function after injury.

NSAIDs (and corticosteroids) are catabolic in nature, particularly having their effect on tissues such as the soft-tissue structures of muscles, ligaments, tendon, and fascia, with very little effect on neural tissue. Therefore, in conditions where the pathological disorder is entrapment or impingement of nerves because of soft-tissue proliferation, such as carpal tunnel syndrome, Morton's neuroma, thoracic outlet syndrome, and intervertebral disc prolapse, there is a strong theoretical basis to support the use of anti-inflammatory medications like NSAIDs (and corticosteroids). There is level II evidence of efficacy of NSAIDs on the inflammatory components of disorders such as bursitis in rotator cuff

SERIES EDITORS: JOHN ORCHARD AND PETER BRUKNER

University of New South Wales, Sydney, NSW.
Justin A Paoloni, PhD, MSpMed, FACSP, Sports Physician, and Conjoint Senior Lecturer, Orthopaedic Research Institute, St George Hospital Campus; John W Orchard, MB BS, PhD, FACSP, Sports Physician, and Conjoint Senior Lecturer, NSW Injury Risk Management Research Centre (IRMRC).
Reprints will not be available from the authors. Correspondence: Dr Justin A Paoloni, Premier Orthopaedics, 55 Montgomery Street, Kogarah, NSW 2217. pao_26@hotmail.com

Case study — a torn tendon and bursitis in the shoulder

A 46-year-old left-handed woman with a 6-month history of left shoulder pain initially injured the shoulder while playing tennis. She felt a dull ache in the lateral arm immediately after the game, and now has night pain, and pain with activities of daily living.

Examination showed restricted range of shoulder motion, muscle weakness, and positive impingement signs.

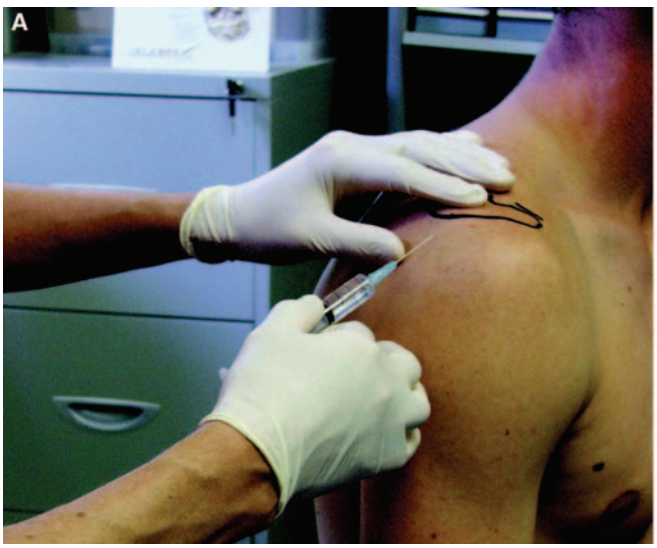
Her x-rays were unremarkable. Ultrasound showed a supraspinatus tendon tear with bursal thickening, and supraspinatus tendon tear with supraspinatus bursitis was diagnosed.

Therapy is dictated by the patient's activity level. If she requires strong overhead function then the goal of treatment should be healing of the tendon tear. However, if she generally only requires use of the arm for activities below shoulder height, then relief of impingement is the primary goal of treatment.

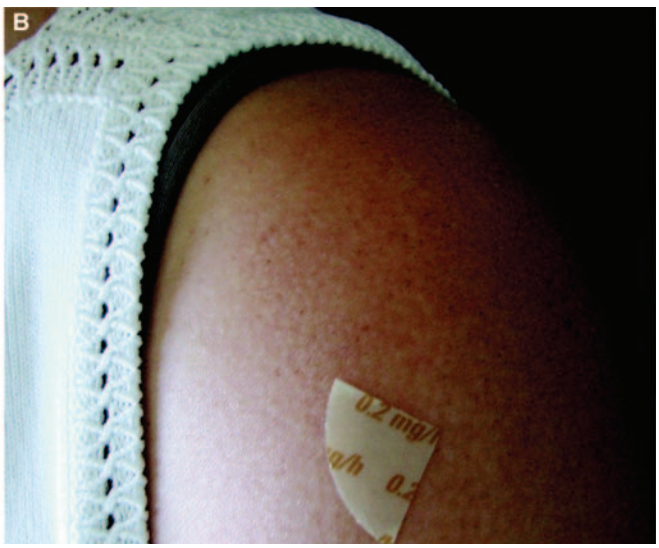
Anti-inflammatory treatment for 6 weeks and/or subacromial corticosteroid and local anaesthetic injections (Figure A) are among the best therapeutic options for giving pain relief. These will generally provide analgesia, but may have potentially deleterious effects on tendon healing. Regular use of ice and paracetamol may be used for analgesia as alternatives if healing is considered important.Topical glyceryl trinitrate patches (1.25 mg/24 h) are an appropriate option to help relieve symptoms and increase function with chronic injury (Figure B).

Exercise rehabilitation is the cornerstone of managing tendinopathies to regain function — in this situation, concentrating on scapula stabilisation and rotator cuff strengthening. This may be managed by the general practitioner confident in exercise prescription for this shoulder injury, or with the assistance of a sports physician or physiotherapist with experience in rehabilitating such injuries.

Surgery may have a role if other treatments are not successful. If the patient requires high levels of shoulder function, direct repair of a tendon tear has a good rate of success, but requires prolonged rehabilitation. Arthroscopic acromioplasty is a procedure with quicker recovery which, like anti-inflammatory agents, is directed at providing pain relief rather than maximising shoulder function.



***A:** Corticosteroid injections for tendon injuries, such as this subacromial injection, provide a short term reduction in pain of 6–8 weeks duration in most soft-tissue conditions.*



***B:** Quartered 5 mg/24 h glyceryl trinitrate patch, used for treatment of shoulder tendinopathy.* ◆

disease or iliotibial band friction syndrome,[6] and synovitis in Morton's neuroma[7] or carpal tunnel syndrome.[8]

Thus, current evidence does not support NSAID use as solo therapy or long-term therapy for soft-tissue injury, except when the primary disorder is soft-tissue impingement, or predominantly inflammatory (such as bursitis or synovitis). NSAIDs should not be used routinely in soft-tissue injury, as they are, at best, an adjunct to treatment through symptom relief, most notably analgesia (see Case study), and these benefits must be weighed against the risks of gastrointestinal side effects, especially with prolonged use.

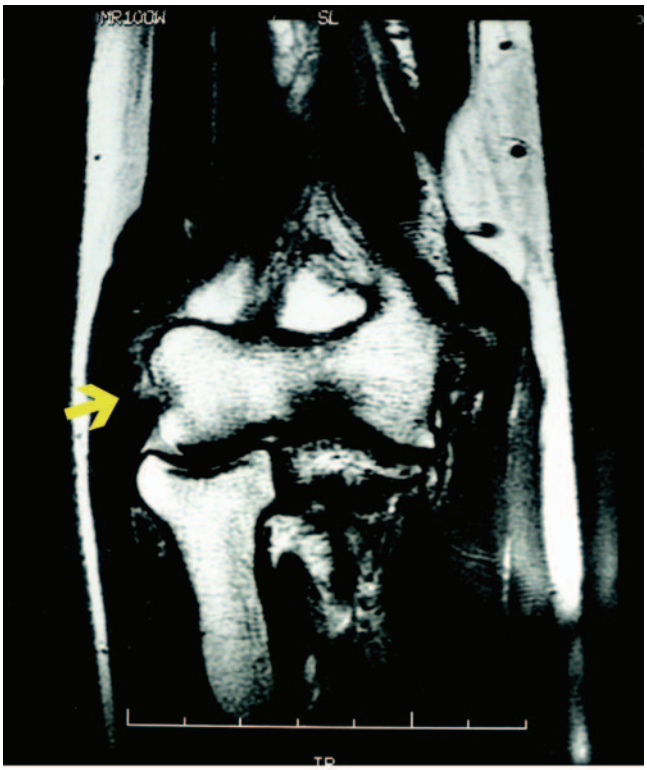
Non-steroidal anti-inflammatory drugs for tendinopathy

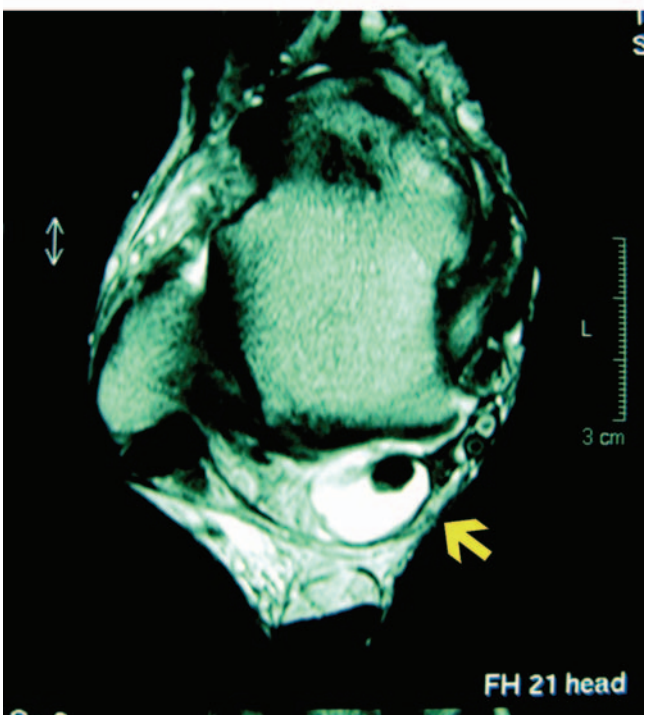
The abnormality in chronic tendinopathy in most cases is degeneration, with no evidence of inflammation (Box 1). Despite this, there is level II evidence that NSAIDs provide short-term mild to moderate decreases in pain in lateral epicondylosis,[9] increased abduction in rotator cuff disease,[10] but have no efficacy in treating Achilles tendinopathy.[11] The mechanism of action of NSAIDs in tendinopathy is unclear.

NSAID use decreases fibroblast proliferation and increases "overflow" leukotriene production in tendon both at rest and during exercise, which is additive to the normal effect of increased leukotriene production with cyclic tendon loading. So, there is potential for NSAIDs to cause tendon damage through increased leukotriene formation. Further, as tendinopathies have a tendency to chronicity, the side effects of NSAIDs with prolonged use are an even greater limitation than with other soft-tissue injuries.

Thus, the evidence does not support the use of NSAIDs in pure tendinopathy, given their small effect on relieving symptoms and potential adverse effects. Short-term use of ice and paracetamol should provide an equivalent analgesic effect without serious side effects.

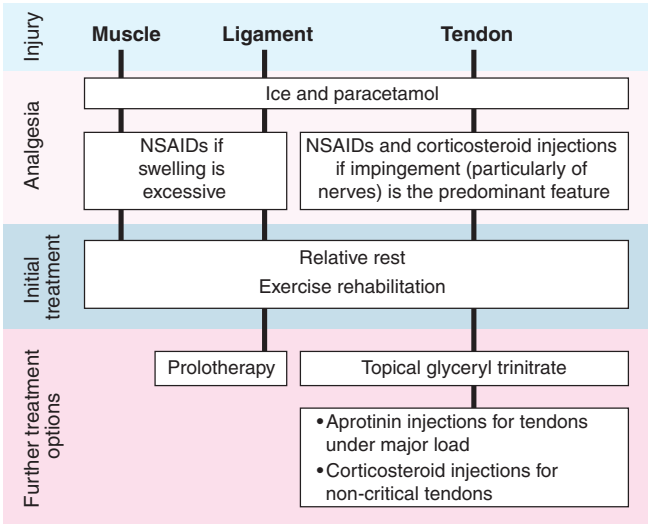
1 Tendinopathies





Tendon injuries, such as in lateral epicondylosis (tennis elbow, top) and tibialis posterior tenosynovitis (bottom), can be recalcitrant to treatment; conventional treatments such as non-steroidal anti-inflammatory drugs and corticosteroid injections may have a short term analgesic effect, while there is some evidence of efficacy with newer treatments such as topical glyceryl trinitrate therapy. ◆

2 Evidence-based medical management of soft–tissue injuries



NSAIDs = non-steroidal anti-inflammatory drugs. ◆

Non-steroidal anti-inflammatory drugs compared with paracetamol for soft-tissue injury

Paracetamol is an analgesic with a centrally mediated mechanism of action.With comparable efficacy to NSAIDs for pain in soft-tissue injury (E2),[12] and being both opioid-sparing and NSAID-sparing, it can be used in combination analgesia. It also has a low cost, low side-effect profile, and no risk of local soft-tissue injury. It is often the analgesic of choice for soft-tissue injury.

Cyclo-oxygenase-2 (COX-2) inhibitors for soft-tissue injury

COX-2 inhibitors were developed to selectively block the COX-2 enzyme and the inflammatory process without inhibiting the effects of prostaglandins on gastroprotection or the effects of thromboxane on bleeding time and platelet aggregation.

The use of these agents is currently under review because of increased rates of myocardial infarction, with rofecoxib withdrawn from the market and celecoxib only recommended for use in rheumatoid arthritis and osteoarthritis at low dosages.

Given the lack of evidence of efficacy for these agents in soft-tissue injury, and significant cardiovascular safety concerns that are yet to be adequately researched, COX-2 inhibitors should generally not be used for treating soft-tissue injuries. They would only be recommended for patients in whom nerve or mechanical impingement is predominant, and non-specific NSAIDs are contraindicated because of a coexisting gastric disorder. They should not be used in patients at high risk of cardiovascular disease.

Corticosteroid injections for tendinopathy

Corticosteroids are injectable anti-inflammatory medications that inhibit the accumulation of neutrophils and the synthesis of inflammatory mediators, and prevent phagocytosis and lysosomal enzyme release. They have short-term efficacy in symptom relief for degenerative tendinopathies, bringing decreased pain in lateral epicondylosis (E1),[13] decreased pain and increased abduction in

rotator cuff tendinopathy (E1),[14] and decreased pain and increased function in trigger finger (E2).[15] However, there does not appear to be a positive effect of peritendinous injections in Achilles tendinopathy (E2).[16] Positive results noted in studies occur in, at most, 80% of patients, and are generally limited to 6–8 weeks after injection (Box 1). Longer-term studies (12 months' follow-up) of the effects of corticosteroid injections in lateral epicondylitis show inferior results to physiotherapy (E2).[17] Studies have not shown clinically significant improvements in function with corticosteroid injections (E1) or greater efficacy than NSAIDs for shoulder pain.

The demonstrated effect of corticosteroids in decreasing pain of tendinopathies may be the result of improvements in the inflammatory components of tendon injuries such as bursitis in shoulder tendinopathy, and tenosynovitis in trigger finger. The mechanism of any effect of corticosteroid injections in reducing symptoms in purely degenerative tendinopathies is unknown.

There is Level IV evidence of tendon rupture with both local corticosteroid injection and oral corticosteroid treatment. This risk may be overstated in view of the frequent use of corticosteroid injections, a lack of evidence of increased rates of tendon rupture with corticosteroid use, and the endstage tendon degeneration noted in tendon ruptures.[18] Animal studies indicate that corticosteroids weaken tendon whether injected into or proximal to the tendon, and it is possible that corticosteroid injections do lead to partial rupture of tendon substance. In non-weight-bearing tendons or patients who place little demand on the affected tendon through heavy loading at work or playing sport, this may lead to symptom abatement through a "medical tenotomy", with surprisingly little functional loss. Partial tendon rupture in weight-bearing tendons or patients who place higher demand on the tendon is much more significant, and frequently necessitates surgery.

Thus, the evidence suggests that a single corticosteroid injection for symptomatic tendon injuries may achieve a mild, short-term reduction in pain for up to 6 weeks, particularly for "non-critical" tendons where rupture may not be a deleterious outcome. This injection should be coupled with a tendon-specific rehabilitation program. Where actual tendon healing is critical to a good outcome, such as overuse injuries to major weight-bearing tendons like the Achilles, corticosteroid injections are probably contraindicated.

Prolotherapy and aprotinin injections

Prolotherapy generally refers to the injection of a sclerosant such as phenol, or hypertonic glucose. Theoretically, sclerosants may be useful for soft-tissue conditions, such as ligament injuries, in which joint laxity is an issue. There are no controlled studies examining prolotherapy as a treatment for soft-tissue injury, although there is some low-level evidence supporting prolotherapy for back pack pain and osteoarthritis.[19] Given the lack of evidence of efficacy, prolotherapy cannot yet be recommended for treating soft-tissue injury. Its major advantage is that side effects of treatment are likely to be minimal.

Aprotinin is a broad-spectrum metalloprotease (MMP) inhibitor used to treat many conditions, but particularly in preventing blood loss during cardiac surgery. Its use in chronic tendinopathy is attractive, as aprotinin may act as a collagenase inhibitor. Certain MMPs have been shown to be present in excessive proportions in patellar tendinopathy and rotator cuff tendinopathy, and aprotinin could potentially normalise the concentration of MMPs in chronic tendinopathy, which may help healing. In treatment for tendinopathy as a series of two to four injections into the peritendinous space, aprotinin provides superior analgesia when compared with corticosteroid injections and placebo in patella tendinopathy (E2),[20] and in Achilles tendinopathy (E3).[21]

Potential side effects include allergy and anaphylaxis, although death has only been reported when used intravenously for cardiac surgery; the "test dose" of 3–5 mL for major procedures is similar to the therapeutic dose for tendinopathy.[22] The use of aprotinin injections for tendon injuries is currently an "off-label" indication.

Evidence-based guidelines on newer therapies

- There is evidence for the efficacy of topical glyceryl trinitrate therapy in treating common chronic tendinopathies (Achilles tendinopathy, lateral epicondylosis, and supraspinatus tendinopathy) (E2),[27-29] and it can be used as an adjunct to tendon rehabilitation.
- Aprotinin provides superior analgesia compared with corticosteroid injections and placebo in patella tendinopathy (E2).[18] This therapy may be particularly useful for chronic tendinopathy of the major weightbearing tendons, where the use of cortisone is contraindicated.
- Given the lack of controlled efficacy studies, prolotherapy cannot yet be recommended for treating soft-tissue injuries.
- Current evidence does not support the use of botulinum toxin injections for tendon injuries.[23]
- There are no studies on the use of glucosamine in treating soft-tissue injuries. ◆

Botulinum toxin for tendinopathy

Botulinum toxin type A is a neurotoxin which inhibits the release of the neurotransmitter acetylcholine at the neuromuscular junction, and inhibits skeletal muscle contraction. It results in reduced muscular spasticity, reduces pain and increased function in "whiplash-associated disorder" (E2).[23] The use of multiple botulinum injections around the musculotendinous junction as a "last option" in the treatment of lateral epicondylosis has comparable results to extensor release surgery (E2);[24] however, placebo injections demonstrate equal efficacy.[25] These treatments may all induce local tissue healing responses. Side effects of botulinum injections include allergic reactions, and permanent muscle and tendon injury.

Current evidence does not support the use of botulinum toxin injections for tendon injuries. An exception may be in chronic recalcitrant cases of lateral epicondylosis where surgery is considered.

Glyceryl trinitrate treatment for tendinopathy

Glyceryl trinitrate is a donor of nitric oxide (the endothelium-derived relaxing factor), but the mechanism of action of topical glyceryl trinitrate therapy on tendon is unknown. Nitric oxide inhibition decreases collagen content and collagen synthesis by fibroblasts,[26] and nitric oxide donation may stimulate collagen synthesis by fibroblasts.

In acute shoulder pain, there is evidence of an analgesic effect of 3 days duration (E2),[27] which is of lesser efficacy than corticosteroid injections (E2).[28] In chronic tendinopathies, topical glyceryl trinitrate therapy with 1.25 mg per 24 hours has level II clinical

evidence of decreased pain, increased tendon force, improved functional measures, and improved symptom resolution in Achilles tendinopathy,[29] lateral epicondylosis,[30] and supraspinatus tendinopathy.[31] Glyceryl trinitrate has a long history of therapeutic use in humans, and the common side effects of rash and headache are rapidly reversible on discontinuation of topical treatment. It should not be used concomitantly in patients taking phosphodiesterase inhibitors such as sildenafil (Viagra; Pfizer), as the additive effect may cause life-threatening hypotension. The use of topical glyceryl trinitrate for tendon injuries is currently an "off-label" indication, although medical practitioners may legally exercise discretion in prescribing this treatment for tendon conditions, provided likely effects, and side effects, such as rash and headache, are explained to the patient.

Topical glyceryl trinitrate therapy has robust evidence of efficacy in treating common chronic tendinopathies, the side-effect profile is known and reversible, and this therapy should be used as an adjunct to tendon rehabilitation in chronic tendinopathies (Box 1).

Glucosamine and soft-tissue injuries

Glucosamine has a significant analgesic effect in treating osteoarthritis, and it has been suggested that it may aid wound healing through enhanced fibroblastic production of hyaluronate (E5).[32] There are no studies on glucosamine in treating soft-tissue injury.

Conclusion

Box 2 provides a flowchart summarising the evidence-based options for medical treatment of soft-tissue injuries. The widespread use of NSAIDs and corticosteroid injections in the treatment of most soft-tissue injuries requires reassessment based on current evidence, while new drugs such as aprotinin and glyceryl trinitrate hold promise as effective adjunctive treatment for chronic tendinopathies.

Competing interests

None identified.

References

1 National Health and Medical Research Council. A guide to the development, implementation and evaluation of clinical practice guidelines. Canberra: NHMRC, 1998.
2 Hippisley-Cox J, Coupland C. Risk of myocardial infarction in patients taking cyclo-oxygenase-2 inhibitors or conventional non-steroidal anti-inflammatory drugs: population based nested case-control analysis. *BMJ* 2005; 330: 1366.
3 Galer B, Rowbotham M, Perander J, et al. Topical diclofenac patch relieves minor sports injury pain: results of a multicenter controlled clinical trial. *J Pain Symptom Manage* 2000; 19: 287-294.
4 Vaile J, Davis P. Topical NSAIDs for musculoskeletal conditions: a review of the literature. *Drugs* 1998; 56: 783-799.
5 Van der Windt D, Van der Heijden GJ, Scholten RJ, et al. The efficacy of non-steroidal anti-inflammatory drugs (NSAIDs) for shoulder complaints: a systematic review. *J Clin Epidemiol* 1995; 48: 691-704.
6 Gunter P, Schwellnus MP. Local corticosteroid injection in iliotibial band friction syndrome in runners: a randomised controlled trial. *Br J Sports Med* 2004; 38: 269-272.
7 Thomson CE, Gibson JNA, Martin D. Interventions for the treatment of Morton's neuroma. Cochrane Database Syst Rev 2004; (3): CD003118.
8 Ly-Pen D, Andreu J-L, De Blas G, et al. Surgical decompression versus local steroid injection in carpal tunnel syndrome: a one-year, prospective, randomized, open, controlled clinical trial. *Arthritis Rheum* 2005; 52: 612-619.
9 Labelle H, Guibert R. Efficacy of diclofenac in lateral epicondylitis of the elbow also treated with immobilisation. *Arch Fam Med* 1997; 6: 257-262.
10 Green S, Buchbinder R, Glazier R, et al. Systematic review of randomised controlled trials of interventions for painful shoulder: selection criteria, outcome assessment, and efficacy. *BMJ* 1998; 316: 354-360.
11 McLauchlan G, Handoll HHG. Interventions for treating acute and chronic Achilles tendinitis. Cochrane Database Syst Rev 2001; (2): CD000232.
12 DeGara C, Taylor M, Hedges A. Assessment of analgesic drugs in soft tissue injuries presenting to an accident and emergency department: a comparison of antrafenine, paracetamol, and placebo. *Postgrad Med J* 1982; 58: 489-492.
13 Assendelft W, Hay EM, Adshead R, et al. Corticosteroid injections for lateral epicondylitis: a systematic review. *Br J General Practice* 1996; 46: 209-216.
14 Buchbinder R, Green S, Youd J. Corticosteroid injections for shoulder pain. Cochrane Database Syst Rev 2003; (1): CD004016.
15 Murphy D, Failla JM, Konuich MP. Steroid versus placebo injection for trigger finger. *J Hand Surg* 1995; 20A: 628-631.
16 DaCruz D, Geeson M, Allen MJ, et al. Achilles' paratendonitis: an evaluation of steroid injection. *Am J Sports Med* 1988; 22: 64-65.
17 Korthals-de Bos I, Smidt N, van Tulder M, et al. Cost effectiveness of interventions for lateral epicondylitis: results from a randomised controlled trial in primary care. *Pharmacoeconomics* 2004; 22: 185-95.
18 Tallon C, Maffulli N, Ewen SW. Ruptured Achilles tendons are significantly more degenerated than tendinopathic tendons. *Med Sci Sports Exerc* 2001; 33: 1983-1990.
19 Kim S, Stitik T, Foye P, et al. Critical review of prolotherapy for osteoarthritis, low back pain, and other musculoskeletal conditions: a physiatric perspective. *Am J Phys Med Rehabil* 2004; 83: 379-389.
20 Capasso G, Testa V, Maffulli N, et al. Aprotinin, corticosteroids and normosaline in the management of patellar tendinopathy in athletes: a prospective randomized study. *Sports Exerc Injury* 1997; 3: 111-115.
21 Capasso G, Maffulli N, Testa V, et al. Preliminary results with peritendinous protease inhibitor injections in the management of Achilles tendinitis. *J Sports Traumatol Rel Res* 1993; 15: 37-40.
22 Dietrich W, Spath P, Zuhlsdorf M, et al. Anaphylactic reactions to aprotinin reexposure in cardiac surgery. *Anesthesiology* 2001; 95: 64-71.
23 Freund B, Schwartz MB. Use of botulinum toxin in chronic whiplash associated disorder. *Clin J Pain* 2002; 18(6 Suppl): S163-S168.
24 Keizer S, Rutten HP, Pilot P, et al. Botulinum toxin injection versus surgical treatment for tennis elbow: a randomized pilot study. *Clin Orthop Rel Res* 2003; 401: 125-131.
25 Hayton M, Santini AJ, Hughes PJ, et al. Botulinum toxin injection in the treatment of tennis elbow. A double-blind, randomized, controlled, pilot study. *J Bone Joint Surg Am* 2005; 87-A: 503-507.
26 Schaffer M, Efron PA, Thornton K, Klingel SS. Nitric oxide, an autocrine regulator of wound fibroblast synthetic function. *J Immunol* 1997; 158: 2382-2389.
27 Barrazueta J, Losada A, Poveda J, et al. Successful treatment of shoulder pain syndrome due to supraspinatus tendinitis with transdermal nitroglycerin. A double blind study. *Pain* 1996; 66: 63-67.
28 Pons S, Gallardo C, Caballero J, et al. Topical nitroglycerin versus corticosteroid infiltration for rotator cuff tendinitis. *Atencion Primera* 2001; 28: 452-455.
29 Paoloni J, Appleyard RA, Nelson J, et al. Topical glyceryl trinitrate application in the treatment of noninsertional Achilles tendinopathy. A randomized, double-blind, placebo controlled trial. *J Bone Joint Surg Am* 2004; 86-A: 916-922.
30 Paoloni J, Appleyard RA, Nelson J, et al. A randomized, double-blind, placebo-controlled clinical trial investigating the use of topical nitric oxide application in the treatment of chronic extensor tendinosis at the elbow. *Am J Sports Med* 2003; 31: 915-920.
31 Paoloni J, Nelson J, Murrell GAC. Topical glyceryl trinitrate application in the treatment of chronic supraspinatus tendinopathy. A randomized, double-blind, placebo controlled clinical trial. *Am J Sports Med* 2005; 33: 8-16.
32 McCarty M Glucosamine for wound healing. *Med Hypotheses* 1996; 47: 273-275.

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