Prolotherapy

Clinical Policy ID: CCP.1217

Recent review date: 2/2026

Next review date: 6/2027

Policy contains: Musculoskeletal pain; prolotherapy; regenerative injection therapy.

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Coverage policy

Prolotherapy for musculoskeletal conditions is investigational/not clinically proven, and therefore, not medically necessary.

Limitations

No limitations were identified during the writing of this policy.

Alternative covered services

Surgical treatment.

Non-surgical approaches, including anti-inflammatory medications; physical or occupational therapy; immobilization; thermotherapy; reducing workload and increasing rest, relaxation, and biofeedback techniques; strengthening and conditioning exercises; stretching exercises; and therapeutic massage.

Background

Musculoskeletal conditions are among the most disabling and costly conditions suffered by Americans of all

ages. Causes of musculoskeletal pain include the wear and tear of daily activities or trauma to an area, postural strain, repetitive movements, overuse, and prolonged immobilization. Changes in posture or poor body mechanics may bring about spinal alignment problems and muscle shortening, causing other muscles to be misused and become painful. Trauma, back pain, and arthritis are the most common musculoskeletal conditions in the United States (Orthopaedic Research Society, 2022).

Musculoskeletal pain is best treated by addressing its cause. Non-surgical approaches include anti-inflammatory medications; physical or occupational therapy; immobilization; using heat or cold; reducing workload and increasing rest, relaxation, and biofeedback techniques; strengthening and conditioning exercises; stretching exercises; and therapeutic massage. Integrative therapies such as chiropractic care, acupuncture, or acupressure may be used (National Academies of Sciences, Engineering, and Medicine, 2020).

When conservative treatments fail to alleviate the pain, injection therapies in or around the painful sites may be used. Prolotherapy, also known as regenerative injection therapy, involves injecting an irritant into an injured joint, ligament, or tendon to relieve pain (American Osteopathic Association of Prolotherapy Regenerative Medicine, 2020). Used since the 1930s, prolotherapy (termed from proliferant therapy) has emerged as a treatment option for chronic musculoskeletal injuries. Its mechanism of action has not been clearly established but is hypothesized to stimulate growth factors in the inflammatory healing cascade and promote growth of new ligament or tendon fibers by producing new collagen tissue.

Injection agents may include ingredients such as dextrose, morrhuate sodium, saline, sarapin, procaine, or lidocaine. In recent years, platelet-rich plasma and autologous adult stem cell sources typically taken from bone marrow or adipose (fat) tissue have emerged. Prolotherapy techniques and injected solutions vary by condition, clinical severity, and practitioner preferences and commonly consist of several injection sessions delivered every three to six weeks over several months (American Osteopathic Association of Prolotherapy Regenerative Medicine, 2020).

The U.S. Food and Drug Administration has approved the most commonly used agents, such as dextrose and lidocaine, for injection, but these substances are not specifically approved for prolotherapy for joint and ligamentous injections, making such use off-label. Morrhuate sodium is not currently listed as an approved sclerosing agent (U.S. Food and Drug Administration, 2026).

Findings

Guidelines

Few professional guidelines address prolotherapy. A guideline on low back pain from the Institute for Health Economics determined that prolotherapy was not recommended as a sole treatment, and there was insufficient evidence from systematic reviews to recommend for or against prolotherapy as an adjunctive therapy (Institute of Health Economics, 2022).

For sacroiliac joint complex pain, an international consensus panel agreed that dextrose-based prolotherapy may be effective six months post-procedure. The statement was based on weak Grade C evidence supporting a small net benefit of dextrose-based prolotherapy to provide at least three months of pain relief, but the available was considered insufficient to assess effects on treatment or other outcomes of interest, resulting in a low level of certainty in the findings (McCormick, 2025).

The American College of Rheumatology/Arthritis Foundation issued a conditional recommendation against using prolotherapy in patients with knee or hip osteoarthritis, but issued no recommendation for or against in patients with hand osteoarthritis (Kolasinski, 2020).

The American Association of Oral and Maxillofacial Surgeons (2024) does not mention intra-articular injections

as conservative treatment options for temporomandibular joint disorders.

The American Academy of Orthopaedic Surgeons (undated) does not mention prolotherapy as a treatment option for lateral epicondylosis (tennis elbow).

Evidence review

The best available evidence consists of systematic reviews and meta-analyses of randomized controlled trials. The most commonly studied indications for prolotherapy were knee osteoarthritis and tendinopathies such as lateral epicondylitis, rotator cuff tendinopathies, plantar fasciitis, Osgood-Schlatter disease, and Achilles tendinosis. Hypertonic dextrose solution was the most commonly applied proliferant.

The results suggest hypertonic dextrose prolotherapy is safe with no serious adverse effects reported. It may be an efficacious alternative to other non-invasive treatments for the above indications, when the expected benefits in pain control or function have not been achieved by conservative care. It should not be used with other irritants, and it typically requires multiple injections and multi-session regimens to maximize its effectiveness. However, the quality of the evidence is low with moderate-to-high risk of bias, and evidence of comparative effectiveness to other non-invasive or injectable treatments is conflicting. All authors recommended studies of higher quality to confirm these findings and validate long-term efficacy.

Osteoarthritis

A systematic review of 14 randomized controlled trials (n = 936) examined the safety and effectiveness of hypertonic dextrose prolotherapy for treating osteoarthritis: 11 studies were of the knee, two of the hand, and one of the hip. Prolotherapy was compared to saline (five studies), exercise (three), intra-articular injections of hyaluronic acid (three), platelet-rich plasma (two), ozone prolotherapy (one), erythropoietin (one), pulsed radiofrequency (one), and local corticosteroid (one). All studies were classified as a high risk of bias due to insufficient blinding of participants and investigators and inadequate documentation of missing data and drop-outs (Waluyo, 2023).

For pain reduction, ten of 14 studies reported that prolotherapy was more effective than the other interventions. In 12 studies, prolotherapy was at least as effective in improving function outcomes as other interventions. In five studies, prolotherapy significantly improved pain intensity and function (Western and Ontario McMaster Osteoarthritis Index scores) compared with saline, but injections with a biological agent as the active substance were superior to prolotherapy. Although prolotherapy using hypertonic dextrose confers potential benefits for pain and functional outcome in osteoarthritis, its therapeutic benefit could not be quantified due to variation in study protocols and intervention choices and a high risk of bias across studies. Differences in the injection concentration, time intervals of injection, sites of injection, and type and severity of osteoarthritis are factors in achieving pain relief and functional recovery (Waluyo, 2023).

For patients with knee osteoarthritis who are unsuitable for surgery or have mild-to-moderate disease severity, non-surgical interventions are considered. A network meta-analysis of 71 studies (n = 5,414) demonstrated the superiority of exercise combined with pharmacological treatment over monotherapeutic approaches. Exercise therapy (primarily resistance training programs) combined with intraarticular injections of mesenchymal stem cells, dextrose, platelet rich plasma, platelet rich in growth factor, or botulinum toxin A were the most efficacious for pain reduction and physical function restoration with moderate-to-high certainty (Cheng, 2024).

Tendinopathies

As a treatment for sports-related tendinopathies, lateral epicondylitis, rotator cuff, and plantar fasciitis tendinopathies were the most studied conditions (17 studies), while Achilles tendinosis and Osgood-Schlatter disease were the least studied (three studies). Nineteen of 20 studies used dextrose solutions. In 85% of studies, prolotherapy was effective in treating tendinopathy. Prolotherapy was superior to control in all outcomes in 25%

of the studies, comparable or superior to control in specific outcomes (e.g., pain and function scores) in 60% of the studies, and inferior to control in 15% of the studies. While studies appear to be of higher quality, high heterogeneity between studies persists particularly with respect to dextrose solution, control groups (e.g., hyaluronic acid, steroids, or saline), and injection technique limit the certainty of the findings (Capotosto, 2024).

Wang's (2025) network analysis compared the efficacy of six injection therapies for plantar fasciitis from controlled studies. The interventions were placebo, corticosteroids, platelet-rich plasma, dextrose prolotherapy, botulinum toxin A, and autologous blood. The analysis included 59 trials (n = 3,833), of which five trials assessed dextrose prolotherapy. The visual analog scale and the American Orthopaedic Foot and Ankle Ankle-Hindfoot Score were used as measurement criteria for pain intensity and functional activity, respectively. Botulinum toxin A was the most effective treatment among injection therapies in terms of alleviating pain intensity and improving functional activity.

Similar conclusions were found in other secondary analyses. Goh (2021) analyzed the effectiveness of prolotherapy in 87 randomized controlled trials (n = 5,859) involving upper limb (74%), lower limb (23%), and truncal/hip (3%) chronic soft tissue injuries. Study quality was mixed, ranging from low to moderate. At all time points, prolotherapy had no statistically significant pain benefits over other therapies. Compared to placebo, the effect size for prolotherapy was marginally better for elbow injuries in the medium term (four to eight months) and for shoulder injuries in the short term (less than four months) and long term (more than eight months).

A systematic review of ten studies (three randomized) of prolotherapy used in participants with chronic patellar tendinopathy showed a decrease in pain with no serious adverse events, leading authors to conclude that prolotherapy may be an effective treatment option to treat pain and improve function (Morath, 2020).

For treatment of temporomandibular disorders, a systematic review and meta-analysis identified six randomized controlled trials comparing the efficacy of prolotherapy to placebo and other active interventions, such as autologous blood products or botulinum toxin. The primary outcomes were maximal incisor opening, pain intensity using a visual analogue score for pain, and frequency of dislocations. Results were reported as mean difference with 95% confidence intervals. Compared to placebo, prolotherapy is more efficient in reducing pain intensity (1.20, 0.56 to 1.84, $P < .001$) and in improving perceived jaw mobility (0.47, 0.05 to 0.90, $P = .003$), but not in improving maximal incisor opening (0.84, -2.12 to 3.80, $P = .58$). Results of small single trials suggest prolotherapy may be more effective in improving outcomes than other modalities, but additional high-quality research is needed for confirmation (Saramantos, 2025).

For patients with Osgood-Schlatter disease unresponsive to conservative treatment, a secondary analysis of three small randomized controlled trials and one large case series found no improvement in patient-reported outcomes at three months, although hyperosmolar dextrose prolotherapy may safely facilitate a pain-free return to sports at three months and lead to patient-reported improvement at one year. The authors called for high-quality randomized controlled trials to corroborate these findings (Rhim, 2025).

For rotator cuff tendinopathy, two systematic reviews and meta-analyses assessed the comparative effectiveness of prolotherapy relative to placebo or other conservative treatments (Thamrongskulsiri, 2025; Wu, 2025). Thamrongskulsiri (2025) included eight comparative studies published in English. Compared to control treatments, prolotherapy was not superior in terms of patient-reported outcomes for pain and disability. Prolotherapy showed a small benefit in shoulder abduction (mean difference = 7.08 degrees, $P = .002$), but no significant differences in other range of motion parameters such as forward flexion, internal rotation, or external rotation.

Findings from a network meta-analysis of 29 randomized controlled trials (moderate-to-high heterogeneity, $I^2 \geq 50\%$), all conducted outside of the United States, suggest distinct temporal patterns in efficacy among various intra-articular injections for treatment of partial-thickness rotator cuff injuries. Prolotherapy and hyaluronic acid were optimal for early-stage pain control and functional recovery, while platelet-rich plasma provided superior

sustained long-term pain relief. Hyaluronic acid and prolotherapy showed advantages for long-term functional improvement. Corticosteroids were effective for short-term analgesia (Wu, 2025).

Other conditions

For chronic low back pain, Mociu (2025) included seven studies (n = 634 total participants) of mixed designs assessing the efficacy of prolotherapy. Dextrose prolotherapy may offer benefits in terms of pain improvement, but the evidence remains limited by small sample sizes, diverse etiologies of pain, lack of long-term follow-up, frequent use of subjective pain scales, and no consensus on optimal dosing, injection techniques, or anatomical targets. The authors recommend larger, high-quality randomized controlled trials and standardized protocols to better understand the efficacy and appropriate use of prolotherapy in this context.

In 2022, we updated the references and made no policy changes.

In 2023, we updated the references and made no policy changes.

In 2024, we updated the references and made no policy changes.

In 2025, we updated the references and deleted several older references, resulting in no policy changes.

In 2026, we updated the references with no policy changes warranted.

References

On January 7, 2026, we searched PubMed and the databases of the Cochrane Library, the U.K. National Health Services Centre for Reviews and Dissemination, the Agency for Healthcare Research and Quality, and the Centers for Medicare & Medicaid Services. Search terms were ("prolotherapy" (MeSH), "pain management" (MeSH), "musculoskeletal pain," "prolotherapy," and "regenerative injection therapy." We included the best available evidence according to established evidence hierarchies (typically systematic reviews, meta-analyses, and full economic analyses, where available) and professional guidelines based on such evidence and clinical expertise.

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Policy updates

1/2016: initial review date and clinical policy effective date: 4/2016

1/2017: Policy references updated.

1/2018: Policy references updated.

1/2019: Policy references updated. Policy ID changed to CCP.1217.

2/2020: Policy references updated.

2/2021: Policy references updated.

2/2022: Policy references updated.

2/2023: Policy references updated.

2/2024: Policy references updated.

2/2025: Policy references updated.

2/2026: Policy references updated.

Related Codes

Below are the most commonly submitted codes for the service(s)/item(s) subject to this policy CCP.1217. This is not an exhaustive list of codes. Providers are expected to consult the appropriate coding manuals and bill accordingly.

Code	Code Description
M0076	Prolotherapy