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Part I: Incorporating
Complementary/Alternative
Modalities

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Prolotherapy in Primary Care Practice

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Prolotherapy is an injection-based complementary and alternative medical (CAM) therapy for chronic musculoskeletal pain. It has been used for approximately 100 years; however, its modern applications can be traced to the 1950s when the prolotherapy injection protocols were formalized by George Hackett,[1] a general surgeon in the United States, based on his clinical experience of more than 30 years. Prolotherapy techniques and injected solutions vary by condition, clinical severity, and practitioner preferences; a core principle is that a fairly small volume of an irritant or sclerosing solution is injected at sites on painful ligament and tendon insertions and in adjacent joint space over several treatment sessions.[1,2] Interest in prolotherapy among physicians and patients is high. It is becoming increasingly popular in the United States and internationally and is actively used in clinical practice.[3,4] A 1993 survey sent to osteopathic physicians estimated that 95 practitioners in the United States were estimated to have performed prolotherapy on approximately 450,000 patients. However, only 27% of surveys were returned; consequently, the true number of practitioners was probably dramatically underestimated.[5] No formal survey has been done since 1993. The current number of practitioners actively practicing prolotherapy is unknown but is probably several thousand in the United States based on attendance at continuing medical education (CME) conferences and physician listings on relevant Web sites. Prolotherapy has been assessed as a treatment for a wide variety of painful chronic musculoskeletal conditions that are refractory to "standard-of care" therapies. Although anecdotal clinical success guides the use of prolotherapy for many conditions, clinical trial literature supporting evidence-based

decision-making for the use of prolotherapy exists for low back pain (LBP), several tendinopathies, and osteoarthritis (OA).

The name of prolotherapy has changed over time. Consistent with existing hypotheses and understanding of possible mechanisms of action, the name of this therapy has evolved. Nomenclature has reflected practitioners' perceptions of prolotherapy's therapeutic effects on tissue. Historically, this injection therapy was called sclerotherapy because early solutions were thought to be scar-forming. Prolotherapy is currently the most commonly used name and is based on the presumed "proliferative" effects on chronically injured tissue. It has also been called regenerative injection therapy (RIT),[2,6] and some contemporary authors name the therapy according to the injected solution.[7] The precise mechanism of action is not known.

The National Institute of Health identifies prolotherapy as a CAM therapy and has funded 2 ongoing clinical prolotherapy trials. The Centers for Medicare and Medicaid Services and Veteran's Administration have reviewed the prolotherapy literature for LBP and all musculoskeletal indications and determined existing evidence to be inconclusive. Neither recommends third-party compensation for prolotherapy. However, their review did not include the most recent clinically positive studies or reviews.[7–9] Private insurers are beginning to cover prolotherapy for selected indications and clinical circumstances; however, most patients pay "out-of-pocket."

PROLOTHERAPY TECHNIQUE

Although no formal practice guidelines have been published, prolotherapy treatment commonly consists of several injection sessions delivered every 2 to 6 weeks over several months. During an individual prolotherapy session, therapeutic solutions are injected at sites of painful and tender ligament and tendon insertions and in adjacent joint spaces. Injected solutions ("proliferants") have historically been hypothesized to cause local irritation, with subsequent inflammation and tissue healing, resulting in enlargement and strengthening of damaged ligamentous, tendon, and intra-articular structures.[10,11] These processes were thought to improve joint stability, biomechanics, and function, and ultimately, to decrease pain.[1,2]

MECHANISM OF ACTION

The mechanism of action for prolotherapy has not been clearly established and, until recently, received little attention. Supported by pilot-level evidence, the 3 most commonly used prolotherapy solutions have been hypothesized to act via different pathways: hypertonic dextrose by osmotic rupture of local cells, phenol-glycerine-glucose (P2G) by local cellular irritation, and morrhuate sodium by chemotactic attraction of inflammatory mediators[12] and sclerosing of pathologic neovascularity associated with tendinopathy.[13,14] The potential of prolotherapy to stimulate release of growth factors favoring soft tissue healing has also been suggested as a possible mechanism.[15,16]

In vitro and animal model data have not fully corroborated these hypotheses. An inflammatory response in a rat knee ligament model has been reported for each solution, although it was not significantly different from that caused by needle stick alone or saline injections.[17] However, animal model data suggest a significant biologic effect of morrhuate sodium and dextrose solutions compared with controls. Rabbit medial collateral ligaments injected with morrhuate sodium were significantly stronger (31%), larger (47%), and thicker (28%), and had a larger collagen fiber diameter (56%) than saline-injected controls[10]; increase in cell number, water content, ground substance amount, and various inflammatory cell types were hypothesized

to account for these changes.[11] Rat patellar tendons injected with morrhuate sodium were able to withstand a mean maximal load of 136% ($\pm$28%)—significantly more than the uninjected control tendon.[18] In the same study, tendons injected with saline control solution were significantly weaker than uninjected controls.[18] Dextrose has been minimally assessed in animal models. Recent studies showed that injured medial collateral rat ligaments injected with 15% dextrose had a significantly larger cross-sectional area compared with injured and noninjured saline-injected controls.[19] P2G solution has received the least research attention; although it is in active clinical use, no animal or in vitro study has assessed P2G effect using an injury model. Most clinicians report using these solutions as single agents, although concentration varies. In clinical practice, physicians sometimes mix prolotherapy solutions or use solutions serially in a single injection session depending on experience and local practice patterns. Neither effect of varied concentration nor mixtures have been assessed in basic science or clinical studies and no clinical trial has compared different solutions against one another.

CLINICAL EVIDENCE
Early Research

Since its inception, prolotherapy has been primarily used outside of academic centers. This has led to a pragmatic orientation of existing prolotherapy studies and a relative paucity of major rigorous clinical trials despite significant clinical activity. Although the first randomized controlled trial (RCT) did not appear until 1987, clinicians have enthusiastically reported the results of more modest, pilot-level clinical trials.

A 2005 systematic review of prolotherapy for all indications found 42 published reports of clinical prolotherapy trials since 1937.[20] Thirty-six of the studies were case reports and case series that included 3928 patients aged from 12 to 88 years. These uncontrolled studies provide the earliest and most clinically-oriented evidence for prolotherapy. Each study reported positive findings for patients with chronic, painful, refractory conditions. Report quality of the included studies varied widely; their internal methodological strength was generally consistent with publication date. The older case studies documented injectants and methods that are no longer in use. Contemporary solutions were noted to start with P2G in the 1960s, dextrose in the 1980s, and morrhuate sodium in the early 1990s. The case reports and case series highlighted that, over time, prolotherapy has been used and studied for a growing set of clinical indications. These case studies have also been used as pilot studies to develop new assessment techniques that could help elucidate the pathophysiology of a given condition[7] and test methodology for future, more robust randomized trials.[21] In general, although lacking control groups and randomization, these pragmatic studies[22] had the advantage of assessing effectiveness of prolotherapy in "real life settings" that patients encounter, including the prolotherapist's ability to select the patient and to individually tailor the injection protocol. Most subjects (72%, 2691 of 3741) assessed in the early literature were treated for LBP. However, other indications assessed by these early studies included knee OA, shoulder dislocation, neck strain, costochondritis, lateral epicondylosis (LE), and fibromyalgia.

Contemporary Research

Since the mid 1980s, research on prolotherapy effects has accelerated, with a dramatic increase in number and improvement in methodological quality of studies assessing prolotherapy (Fig. 1).
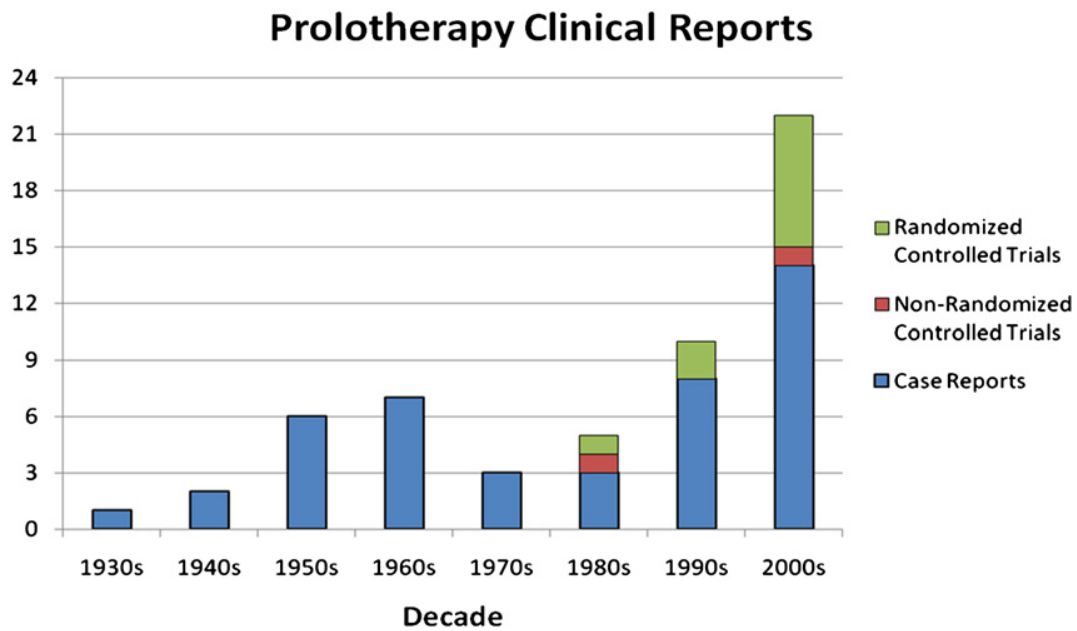
Prolotherapy Clinical Reports

Fig. 1. Number of published clinical studies on prolotherapy since 1937.

To date, prolotherapy has been best assessed as a treatment for LBP, OA, and tendinopathy, each of which is a significant cause of pain and disability and is often refractory to best standard-of-care therapies. The severity and prevalence of each condition is age-related. Because the US population is aging, finding new effective therapies for these conditions can have an impact on individual patient care and overall public health. Prolotherapy has also been assessed as a treatment for nonspecific, nonsurgical LBP, OA of the knee and hand, and for several tendinopathies, including LE and Achilles, adductor, and plantar fasciitis. The following sections give a brief description of studies assessing prolotherapy for these clinical indications and level of evidence associated with each condition; this information is additionally summarized in **Table 1**.

LBP

LBP is among the most common reason patients see a primary care provider. Approximately 80% of Americans experience LBP during their lifetime. An estimated 15% to 20% of patients develop protracted pain, and approximately 2% to 8% experience chronic pain. LBP is second only to the common cold as a cause of lost work time. Productivity losses from chronic LBP approach $28 billion annually in the United States.[31]

Nonspecific LBP

Four RCTs evaluated prolotherapy for musculoskeletal LBP; 3 used P2G as the injectant[23,24,32] and the fourth used dextrose.[25] Each study used a protocol involving injections to the ligamentous insertions of the L4-S1 spinous processes, sacrum, and ilium. Although outcome measures varied, a common measure was the percentage of participants reporting more than 50% improvement in pain/disability scores at 6 months.

Two of these 4 RCTs reported positive findings compared with control injections. Ongley and colleagues[32] and Klein and colleagues[23] compared the treatment effects of prolotherapy combined with an adjunctive treatment with injected steroids, spinal manipulation, and exercise. In the Ongley study,[32] the intervention and control groups differed markedly on the makeup of initial injections and type of spinal manipulation

Table 1 Strength of evidence for prolotherapy as a treatment for chronic musculoskeletal conditions		
Key Clinical Recommendation on Prolotherapy	**Evidence Rating**	**References**
Nonspecific LBP: may be effective; conflicting results in several RCTs	B	[23–26]
Sacroiliac joint dysfunction: may be effective in patients with documented failure of load transfer (disability) at the sacroiliac joint	B	[27]
Coccygodynia: may be effective based on prospective case series	B	[28]
LE: probably effective based on strong positive data in these small RCTs	A	[6,7]
Achilles tendinopathy: may be effective based on high quality prospective case series	B	[9]
Plantar fasciitis: may be effective, based on high-quality prospective case series	B	[29]
OA: may be effective for knee and finger OA, based on RCTs of moderately strong methodological quality	B	[17,30]

associated with the injections. Significantly more subjects in the prolotherapy (88%) group reported at least 50% reduction in pain severity compared with controls (39%). Also, prolotherapy subjects reported significantly decreased pain and disability levels compared with controls.[32] Klein and colleagues[23] used more similar treatment protocols in the 2 assessed groups, with subjects in both groups receiving steroid injections and spinal manipulation before prolotherapy. Again, significantly more prolotherapy subjects improved by 50% or more on pain or disability scores (77%) than controls (53%). Pain grid scores were also significantly lower in the prolotherapy group, with individual pain ($P = .06$) and disability ($P = .07$) scores trending toward significance compared with the control group.

Two of the 4 RCTs reported negative outcomes compared with control injections.[24,25] Dechow and colleagues[24] implemented a refined study protocol; subjects in both groups underwent 3 injection therapy sessions without adjacent spinal manipulation or physical therapy. Although both groups showed a trend toward improved severity scores on pain questionnaire, pain grid, and somatic perception measures, these changes did not reach statistical significance over time within or between groups. At 6 months, improvements in both groups were smaller than those of the other RCTs. Yelland and colleagues[25] have conducted the largest and most methodologically rigorous prolotherapy study published to date. Study subjects (N = 110), with an average of 14 years of LBP, were randomized to one of 4 intervention groups: dextrose and physical therapy, dextrose and "normal activity," saline injections ("control" injection) and physical therapy, or saline injections and normal activity. By 12 months, subjects in all groups reported improved pain (26%–44%) and disability (30%–44%) scores, without significant differences between groups. Most subjects (55%) stated that their improvement in pain and disability had been worth the effort of undergoing the intervention. The percentage of subjects who reached at least 50% pain reduction varied between 36% and 46% though these differences were not statistically significant.

Overall, interpretation of findings from these 4 RCTs is challenging. Both experimental and control groups received different treatment protocols, and none of the

trials was designed to elicit a possible mechanism of prolotherapy action. Therefore, it is impossible to attribute effects to prolotherapy or any other specific intervention. A recent Cochrane Collaboration systematic review[26] did not find sufficient evidence to recommend prolotherapy for nonspecific LBP. However, these 4 RCTs present promising results overall, calling for well-designed, sufficiently powered research. All RCTs report improvements for pain and disability in all treatment groups consisting of subjects with chronic, moderate-to-severe LBP. In particular, Yelland and colleagues[25] reported clinical improvement in excess of minimal clinically important difference[33–35] and in excess of subjects' own perception of the minimum improvement necessary for prolotherapy to be worthwhile (25% for pain and 35% for disability).[21,25]

LBP due to specific causes

Prolotherapy research methods for LBP have been evolving amid much debate surrounding effectiveness, indications, treatment protocols, and solution types.[36,37] Given the promising aspects of the RCTs discussed earlier for nonspecific LBP combined with anecdotal clinical success, later clinical research has begun to assess prolotherapy in patients with more specific forms of LBP and loss of function in an effort to determine specific causes of LBP for which prolotherapy may be most effective.

Cusi and colleagues[27] assessed 25 subjects with sacroiliac joint dysfunction and pain refractory to 6 months or more of physical therapy and with documented failure of load transfer (disability) at the sacroiliac joint. They used a strong prolotherapy solution of 18% dextrose, delivered in 3 sets of injections over 12 weeks. Compared with baseline, pain and disability scores on 3 multidimensional outcome measures significantly improved at 26-month follow-up in excess of minimal clinically important difference.

Khan and colleagues[28] assessed 37 subjects with refractory coccygodynia. Using 25% dextrose in up to 3 prolotherapy injection sessions over 2 months, average pain scores, evaluated using a 0 to 10 visual analog scale (VAS), significantly decreased from a baseline score of 8.5 to 2.5 points at 2 months, far in excess of reported minimal clinically important difference for chronic pain.[38] The authors reported "good" pain relief for 30 of 37 subjects, and no improvement for the remaining 7.

In an especially novel study, Miller and colleagues[39] assessed prolotherapy for leg pain due to moderate-to-severe degenerative disc disease as determined by computed tomographic discography. Subjects (N = 76) who failed physical therapy and had substantial but temporary pain relief with 2 fluoroscopically guided epidural steroid injections were included. After an average of 3.5 sessions of biweekly, fluoroscopically-guided injections to the relevant disc space with 25% dextrose with bupivacaine, 43% of responders showed a significant, sustained treatment response of 71% improvement in pain score, with VAS score for responders at 8.9 ($\pm$1.4), 2.5 ($\pm$2.0), and 2.6 ($\pm$2.2) at baseline, 2, and 18 months, respectively. Although these 3 recent studies of prolotherapy for "specific" LBP were uncontrolled, they suggest the need for future RCTs with more focused clinical indications of axial pain and disability.

Tendinopathies

The strongest data supporting the efficacy of prolotherapy for any musculoskeletal condition compared with control injections are for chronic, painful tendon-overuse conditions that were formerly called tendonitis and are now more correctly termed tendinosis or tendinopathy to reflect existing, underlying pathophysiology.[40] Patients

with tendinopathies commonly present to primary care providers and various medical specialists.[41,42] Tendinopathies are sometimes discussed as a group because the current understanding of overuse tendinopathies identifies them as sharing underlying noninflammatory pathology resulting from a repetitive motion or overuse injury and associated with painful degenerative tissue. Histopathology of tendon biopsies in patients undergoing surgery for painful tendinopathy reveals collagen separation[43]—thin, frayed, and fragile tendon fibrils, separated from each other lengthwise and disrupted in cross section and increase in tenocytes with myofibroblastic differentiation (tendon repair cells)—proteoglycan ground substance, and neovascularization. Classic inflammatory cells are usually absent.[43] Although this aspect of tendinosis was first described 25 years ago[44] and content experts have advocated a change in nomenclature (from tendonitis to tendinosis),[40] the use of the misnomer, tendonitis, continues.[45] Prolotherapy has been assessed as a treatment for 4 tendon disorders: LE, hip adductor, Achilles tendinopathy, and plantar fasciitis.

LE (tennis elbow) is an important common condition of the upper extremity with an incidence of 4 to 7per 1000 patients per year in primary care settings.[46–48] Its greatest impact is on workers with repetitive and high-load upper extremity tasks and on athletes. Its most common cause may be low-load, high-repetition activities, such as keyboarding, though formal data are lacking.[49] Cost and time away from job or activity are significant.[50,51] Although many nonsurgical therapies have been tested for LE refractory to conservative measures, none have demonstrated uniform effectiveness in the long term.[52–54] Scarpone and colleagues[8] conducted an RCT to determine whether prolotherapy improves self-reported elbow pain, and objectively measured grip strength and extension strength in patients with chronic LE. Twenty adults with at least 6 months of moderately-to-severely painful LE refractory to rest, nonsteroidal anti-inflammatory medications (NSAIDs), and corticosteroid injections, were randomized to prolotherapy with dextrose and morrhuate sodium (1 part 5% sodium morrhuate, 1.5 parts 50% dextrose, 0.5 parts 4% lidocaine, 0.5 parts 0.5% bupivacaine hydrochloride (Sensorcaine), and 3.5 parts normal saline) or control injections with normal saline. Three prolotherapy sessions were administered, with injection at the supracondylar ridge, lateral epicondyle, and annular ligament. Compared with controls, prolotherapy subjects reported significantly decreased pain scores at 8 and 16 weeks. These pain score differences between the groups were associated with a significant improvement in prolotherapy subjects (from 5.1 ± 0.8 at baseline, down to 0.5 ± 0.4 at 16 weeks), whereas the controls did not report significant change (4.5 ± 1.7 to 3.5 ± 1.5). In addition to pain reduction, prolotherapy subjects also showed significantly improved isometric strength compared with controls and grip strength compared with baseline. These clinical improvements seen in prolotherapy subjects were maintained at 52 weeks.

Achilles tendinopathy is a common overuse injury seen in athletes and in the general population. This painful condition is a cause of considerable distress and disability.[55] Maxwell and colleagues[7] conducted a well-designed case series to assess whether prolotherapy, administered during a mean of 4 injection sessions, at 6-week intervals, would decrease pain in 36 adults with painful Achilles tendinopathy. In this study, 25% dextrose solution was injected into hypoechoic regions of the Achilles tendon under ultrasonographic guidance. In addition to self-reported measures, the investigators also assessed ultrasonography-based tendon thickness and the degree of hypoechogenicity and neovascularity—ultrasonographic findings recently reported to correlate to tendinopathy severity.[56,57] At 52 weeks, prolotherapy-treated subjects reported decrease in VAS-assessed pain severity by 88%, 84%, and 78% during rest, "usual activity", and sport, respectively. In addition, tendon thickness decreased

significantly. The overall grade of tendon pathology, hypoechoic and anechoic tendon regions, and neovascularity were all improved in some, but not all, subjects who reported clinical improvement. Therefore, the relationship between ultrasonographically assessed characteristics and the degree of clinical improvement remains unclear.

Hip adductor tendinopathy associated with groin pain is a common problem among those who engage in kicking sports.[58] Topol and colleagues[59] conducted a case series assessing prolotherapy for chronic groin pain, a condition involving pain and tenderness at tendon and ligament insertions in the groin area. Male athletes (N = 24), with an average duration of 15.5 months of groin pain despite standard therapy were injected with 12.5% dextrose at the thigh and suprapubic abdominal insertions of the adductor tendon and at the symphysis pubis at 4-week intervals until pain resolved or subjects had no improvement for 2 consecutive sessions. On average, subjects received 3 prolotherapy sessions. At a mean of 17 months, subjects reported dramatic significant improvements on 2 pain scales (VAS and the Nirschl pain phase scale). Of 24 subjects, 20 had no pain and 22 returned to sports without restrictions after therapy.

Plantar fasciitis is a common injury among athletes engaged in sports requiring running and among general primary-care patients. It is reported to account for 15% of all adult foot complaints requiring professional consultation, and in a 2002 survey of running-related injuries, plantar fasciitis was the third most prevalent injury.[60,61] Among standard-of-care approaches, there is limited evidence for the effectiveness of any one treatment for plantar fasciitis, including steroid injections.[29] Ryan and colleagues[30] assessed prolotherapy for chronic plantar fasciitis refractory to conservative care. Twenty adults with an average of 21 months of heal pain underwent ultrasound-guided 25% dextrose injections for an average of 3 treatment sessions delivered at 6-week intervals. Pain scores were assessed using a 100-point VAS at baseline and at 11.8 months. Pain severity significantly improved at rest, during activities of daily living, and during sporting activities by 26.5, 49.7, and 56.5 points, respectively compared with baseline, and 16 of 20 subjects reported good or excellent treatment effects.

OA

Prolotherapy has been assessed as a treatment for knee and finger OA[16,62] and is the subject of ongoing studies.[63] Arthritis is a leading cause of disability in the world and in the United States where it affects 43 million persons.[64–66] OA is the most common form of arthritis and the most common joint disorder.[67] In the United States, symptomatic knee OA is present in up to 6% of the population older than 30 years,[67] and it has an overall incidence of 360,000 cases per year.[68] Incidence increases up to 10-fold from ages 30 to 65 years and more thereafter.[69] OA results in a high burden of disease and substantial economic impact through its high prevalence, time lost off work, and frequent use of health care resources.[64,70]

Allopathic and CAM treatment recommendations for OA have been published, aimed at modifiable risk factor correction, symptom control, and disease modification.[71,72] Although these modalities may help some patients, none has been proven to provide definitive pain control or disease modification for patients with knee OA. The Agency for Research Health and Quality has recently evaluated the most common standard treatment options, including glucosamine, chondroitin, viscosupplementation, and arthroscopic debridement.[73] These have not demonstrated effectiveness compared with placebo. The high burden of knee OA and the absence of a cure

continue to stimulate intense search for new agents to modify disease and control symptoms.

Reeves and colleagues[16,62] assessed prolotherapy as a treatment for knee and finger OA. Subjects with finger or knee pain and radiological evidence of OA were randomly assigned to receive 3 injection sessions of prolotherapy with 10% dextrose and lidocaine or lidocaine and bacteriostatic water (control group). In the finger OA trial, intervention subjects significantly improved in "pain-with-movement" and "flexion-range" scores compared with controls; pain scores at rest and with grip showed a tendency to improvement, without reaching statistical significance. In the knee OA trial, subjects in both groups reported significant improvements in pain and swelling scores, number of buckling episodes, and flexion range of motion compared with baseline, but without statistically significant differences between the groups. Twelve-month follow-up in both studies included improved radiological features of OA on plain radiographic films: investigators reported decreased joint space narrowing and osteophytic grade in the finger study and increased patellofemoral cartilage thickness in the knee study. These radiological findings may suggest disease modification properties of prolotherapy. Whether or not subjects in the knee study had a baseline concomitant meniscal pathology was not reported or included in entry criteria. Furthermore, the ability of plain radiograph to quantify patellofemoral cartilage thickness is questionable, limiting impact of these findings.

CONTRAINDICATIONS, SIDE EFFECTS AND ADVERSE EVENTS
Contraindications

Absolute contraindications to prolotherapy are few and include acute infections such as cellulitis, local abscess, or septic arthritis. Relative contraindications include acute gouty arthritis and acute fracture.

Common Side Effects

The main risk of prolotherapy is pain and mild bleeding caused by needle trauma. At the time of injections, patients frequently report pain, a sense of fullness, and occasional numbness at the injection site. These side effects are typically self-limited. A postinjection pain flare during the first 72 hours after the injections is common clinically, but its incidence has not been well documented. An ongoing study of prolotherapy for knee OA pain has noted that 10% to 20% of subjects experience such flares.[74] Pain flares are likewise typically self-limited, and usually respond well to acetaminophen (500–650 mg every 4 hours as needed). On rare occasions, the occurrence of strong, postinjection pain may require treatment with narcotic medication. NSAIDs are not routinely used after the procedure but may be indicated if the pain does not resolve with other measures. Most patients with pain flares experience diminution of pain in 5 to 7 days after injections; regular activities can be resumed at this time.

Adverse Events

Although prolotherapy performed by an experienced injector seems safe, the injection of ligaments, tendons, and joints with irritant solutions raises safety concerns. Theoretical risks of prolotherapy injections include lightheadedness, allergic reaction, and infection or neurologic (nerve) damage. Injections should be performed using universal precautions and the patient should be prone if possible. Dextrose is extremely safe; it is Food and Drug Administration (FDA)-approved for intravenous treatment of hypoglycemia and for caloric supplementation. Morrhuate sodium is

a vascular sclerosant used in gastrointestinal procedures and vein sclerosing. Allergic reactions to morrhuate sodium are rare. Although P2G is not FDA-approved for any indication, it has not been reported in clinical trials to cause significant side effects or adverse events.

Historically, a small number of significant, prolotherapy-related complications have been reported. They were associated with perispinal injections for back or neck pain using very concentrated solutions, and they included 5 cases of neurologic impairment from spinal cord irritation[75–77] and 1 death in 1959 following prolotherapy with zinc sulfate for LBP.[75] Neither zinc sulfate nor concentrated prolotherapy solutions are currently in general use. In a survey of 95 clinicians using prolotherapy, there were 29 reports of pneumothoraces after prolotherapy for back and neck pain, two of which required hospitalization for a chest tube, and 14 cases of allergic reactions, although none classified as serious.[5] A later survey of practicing prolotherapists yielded similar results for spinal prolotherapy: spinal headache, pneumothoraces, nerve damage, and nonsevere spinal cord insult and disc injury were reported.[78] The investigators concluded that these events were no more common in prolotherapy than for other spinal injection procedures. No serious side effects or adverse events were reported for prolotherapy when used for peripheral joint indications.

PRACTICAL PROLOTHERAPY
Incorporating Prolotherapy into Practice

Similar to corticosteroid injections, prolotherapy is an unregulated procedure without certification by any governing body. Formal training is not provided by most medical schools, residencies, and fellowships. However, to be performed appropriately and safely, prolotherapy requires specialized training. In the United States, it is taught to physicians and other health-care providers (authorized to deliver joint-type injections) in semiformal workshops and formal CME by several organizations, including university settings (**Table 2**).

Patients and physicians who desire consultation for prolotherapy may have difficulty finding an appropriate consulting prolotherapist. Online resources (see **Table 2**) are available that can help locate a prolotherapist, although information is limited by lack of a credentialing structure and governing body for prolotherapy.

Despite limited institutional support, interest in prolotherapy is increasing, and it is performed in increasing numbers, primarily in 2 settings. For several decades, prolotherapy has been mostly performed outside of mainstream medicine by independent physicians. Later, multispecialty groups that include family or sports medicine physicians, physiatrists, orthopedic surgeons, neurologists, or anesthesiologists have been incorporating prolotherapy because of positive clinical experience and research reports. Prolotherapy is one of several injection therapies that may promote healing of chronically injured soft tissue. Other therapies receiving active clinical and research attention for chronic musculoskeletal pain include whole blood, platelet rich plasma, and polidocanol injections.[9] In both settings, prolotherapy is viewed as a valued procedure, primarily reserved for patients who have failed other treatments or those who are not surgical candidates.

The Authors' Clinic

The authors practice in a community in which several primary care physicians and specialists perform prolotherapy; receptivity to prolotherapy in the authors' setting is growing. Some health insurance plans in the author's area cover prolotherapy for

Table 2
Educational and informational prolotherapy resources

Name/URL	Comments
The Anatomy, Diagnosis, and Treatment of Chronic Myofascial Pain with Prolotherapy http://www.ocpd.wisc.edu/Course_Catalog/	CME on the basics of prolotherapy. This 3.5 d conference is offered through the University of Wisconsin School of Medicine and Public Health. All aspects of clinical and research aspects of prolotherapy are covered.
Hackett-Hemwall Foundation list of prolotherapists http://www.hacketthemwall.org/HHF/List_of_Prolotherapists.html	The Hackett-Hemwall Foundation is a nonprofit medical foundation whose mission is to provide high-quality treatment of musculoskeletal problems to underserved people around the world. Physicians listed on the site have completed the foundation's high-volume CME experience in prolotherapy.
Commercial prolotherapy physician listing http://www.getprolo.com	This site lists physicians by state who perform prolotherapy. It includes contact information, a short biography, and prolotherapy credentials. Physicians pay to list themselves on this site.
AAOM http://www.aaomed.org	The AAOM is a nonprofit organization that provides information and educational programs on comprehensive nonsurgical musculoskeletal treatment, including prolotherapy. This searchable site lists AAOM members who perform prolotherapy.

Abbreviation: AAOM, American Association of Orthopaedic Medicine.

the indications discussed. Referrals can be made similar to those for more conventional procedures. An initial consultation, including a complete history and physical, is performed by the prolotherapist to determine if the patient is a candidate for prolotherapy. If so, side effects, adverse events, and expected course of injections are explained, and the patient is asked to sign a procedure consent form. Information is also provided to patients in written form. (**Table 3**) The patient is then scheduled for up to 3 outpatient prolotherapy sessions, typically 4 to 6 weeks apart. At each subsequent visit, an interval history is obtained and physical examination is performed. If the patient does not report improvement after 3 prolotherapy sessions, alternative interventions are pursued.

CLINICAL RECOMMENDATIONS

Present data suggest that prolotherapy is probably an effective therapy for painful overuse tendinopathy. Specifically, Scarpone and colleagues[8] provide level A evidence for prolotherapy as an effective therapy for LE. Subjects with refractory LE and treated with prolotherapy reported significant reduction in pain and improved isometric strength compared with those who received control injections. These findings are supported by the Maxwell,[7] Topol[59] and Ryan[30] studies that report strong case series results for Achilles, hip adductor, and plantar fasciitis, respectively and provide level B evidence for these conditions. Given that the underlying mechanism

Table 3
Prolotherapy at a glance

Definition of prolotherapy	Prolotherapy is an injection-based CAM therapy for chronic musculoskeletal pain. This treatment aims to stimulate a natural healing response at the site of painful soft tissue and joints.
What is involved	Prolotherapy treatment typically involves getting a series of 2–5 monthly injections of a topical anesthetic and a solution of other medicines directly on sore tendon or ligaments or into painful joints.
Conditions for which it is used and is it effective	Prolotherapy is generally used for musculoskeletal pain of more than 3 mo. Conditions that have responded well to prolotherapy in published studies include tennis elbow, Achilles tendinopathy, and other overuse injuries involving tendons. Prolotherapy is also probably effective for knee OA and LBP, although studies assessing these conditions are less conclusive.
Safety	Studies indicate that prolotherapy is safe when performed by an experienced practitioner. It does not seem to have a greater risk than other injection techniques, such as steroid injections.
Pain	No one loves getting a shot, although prolotherapy injections typically hurt less than most immunizations. Most patients tolerate prolotherapy injection-related pain well with only topical and conservative measures. Physicians can pretreat with a pain reliever if necessary.

of injury and pathophysiologic effects are similar for tendinopathies, prolotherapy is also a reasonable option for these conditions. Randomized controlled trials for all 3 and other tendinopathies are indicated.

Recommendations are more difficult to make for OA and LBP, both of which are associated with more complex anatomy and less clear pathophysiology than that seen in tendinopathies. Side effects and potential adverse events of prolotherapy are likely to be more serious when performed for spinal or intra-articular indications and must be weighed against the potential for improvement. Existing studies provide level B evidence that prolotherapy is effective for nonspecific LBP compared with a patient's baseline condition. Given that subjects with refractory, disabling LBP significantly improved compared with their own baseline status in the Yelland study,[25] patients may reasonably try prolotherapy when performed by an experienced injector. Future studies with more focused inclusion criteria may help determine which specific low back pathologies respond to prolotherapy. Existing studies provide level B evidence that prolotherapy is effective for knee and finger OA compared with control injections.[16,62] Prolotherapy by an experienced physician is a treatment modality worth considering by primary care physicians for these conditions, especially when they are refractory to more conventional therapy.

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