Dextrose Prolotherapy for Musculoskeletal Pain

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PREFACE

The VA Evidence Synthesis Program (ESP) was established in 2007 to conduct timely, rigorous, and independent systematic reviews to support VA clinicians, program leadership, and policymakers improve the health of Veterans. ESP reviews have been used to develop evidence-informed clinical policies, practice guidelines, and performance measures; to guide implementation of programs and services that improve Veterans' health and wellbeing; and to set the direction of research to close important evidence gaps. Four ESP Centers are located across the US. Centers are led by recognized experts in evidence synthesis, often with roles as practicing VA clinicians. The Coordinating Center, located in Portland, Oregon, manages program operations, ensures methodological consistency and quality of products, engages with stakeholders, and addresses urgent evidence synthesis needs.

Nominations of review topics are solicited several times each year and submitted via the ESP website. Topics are selected based on the availability of relevant evidence and the likelihood that a review on the topic would be feasible and have broad utility across the VA system. If selected, topics are refined with input from Operational Partners (below), ESP staff, and additional subject matter experts. Draft ESP reviews undergo external peer review to ensure they are methodologically sound, unbiased, and include all important evidence on the topic. Peer reviewers must disclose any relevant financial or non-financial conflicts of interest. In seeking broad expertise and perspectives during review development, conflicting viewpoints are common and often result in productive scientific discourse that improves the relevance and rigor of the review. The ESP works to balance divergent views and to manage or mitigate potential conflicts of interest.

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Operational Partners

Operational partners are system-level stakeholders who help ensure relevance of the review topic to the VA, contribute to the development of and approve final project scope and timeframe for completion, provide feedback on the draft report, and provide consultation on strategies for dissemination of the report to the field and relevant groups.

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Technical Expert Panel

To ensure robust, scientifically relevant work, the technical expert panel (TEP) guides topic refinement; provides input on key questions and eligibility criteria, advising on substantive issues or possibly overlooked areas of research; assures VA relevance; and provides feedback on work in progress. TEP members included:

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Disclosures

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The findings and conclusions in this document are those of the author(s) who are responsible for its contents and do not necessarily represent the views of the Department of Veterans Affairs or the United States government. Therefore, no statement in this article should be construed as an official position of the Department of Veterans Affairs. The final research questions, methodology, and/or conclusions may not necessarily represent the views of contributing operational and content experts. No investigators have affiliations or financial involvement (*eg*, employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties) that conflict with material presented in the report.

Executive Summary

KEY FINDINGS

- Among 90 eligible studies on dextrose prolotherapy, most had fewer than 100 participants and nearly half were rated as high risk of bias. Studies varied greatly in dextrose concentrations employed, injection technique, cointerventions, and comparators.
- Evidence on adverse effects of dextrose prolotherapy was very uncertain for all included musculoskeletal pain conditions and comparators (very low certainty of evidence [COE]).
- For **knee osteoarthritis**, intra-articular dextrose prolotherapy probably has little to no benefit for pain-related functioning, physical performance, and health-related quality of life, compared with normal saline injection (moderate and high COE). It may also have little to no benefit for pain-related functioning, compared with ozone injection (low COE). Evidence was very uncertain on benefits versus platelet-rich plasma (very low COE).
- For **knee osteoarthritis**, the evidence was very uncertain on the effects of combined intra-articular and extra-articular dextrose prolotherapy on pain-related functioning at short and medium-term follow-up (very low COE) but it may improve long-term outcomes (low COE), compared with either normal saline injection or physical therapy (PT) and home exercise programs.
- For **plantar fasciitis**, dextrose prolotherapy may improve pain-related functioning, compared with normal saline injection (low COE), but may have little to no benefit compared with extracorporeal shockwave therapy (ESWT; low COE). The evidence was very uncertain on benefits for pain-related functioning (very low COE), and it may have little to no benefit for health-related quality of life versus corticosteroid injection (low COE).
- For **shoulder pain** (due to mixed bursitis and rotator cuff pathology), the evidence was very uncertain on the benefit for pain-related functioning (very low COE), and dextrose prolotherapy may have little to no benefit for physical performance (low COE), compared with normal saline injection. The evidence was also very uncertain on the benefit for pain-related functioning (very low COE), and it probably resulted in worse physical performance (moderate COE), compared with corticosteroid injection.
- For **lateral elbow tendinopathy**, dextrose prolotherapy may improve pain-related functioning (low COE), but the evidence was very uncertain or suggested little to no benefit for physical performance over different timeframes (very low or low COE), compared with normal saline injection. The evidence was also very uncertain or suggested little to no benefit for pain-related functioning (very low or low COE), compared with corticosteroid injection.
- For **chronic low back pain**, the evidence was very uncertain on the benefits of dextrose prolotherapy for pain-related functioning, compared with normal saline or corticosteroid injection (very low COE).
- For **temporomandibular joint (TMJ) disorders**, the evidence was very uncertain on the benefits of dextrose prolotherapy compared with normal saline or autologous blood injection (very low COE).

Musculoskeletal disease is the most common reason for chronic pain among adults in the United States (US). Globally, osteoarthritis is the most common musculoskeletal disease, impacting approximately 595 million individuals (7.6% of the worldwide population). Osteoarthritis is a degenerative condition that generally affects older adults and is a leading cause of pain and disability in this population. The knee is the most commonly afflicted joint and an estimated 14 million US adults have symptomatic knee osteoarthritis. Other joint and peri-articular conditions are also common and have substantial associated morbidity. For example, shoulder pain due to various etiologies accounts for 16% of musculoskeletal complaints in US primary care patients, and heel pain from plantar fasciitis has a lifetime incidence of 10% among US adults.

Musculoskeletal pain conditions are often challenging for patients and clinicians, driving demand and health care utilization. The breadth of treatments includes non-pharmacological interventions (*eg,* physical therapy [PT]), topical and systemic pharmacologic therapies, localized injection therapies, and surgical procedures. Most of these treatments address symptoms such as pain and joint instability, without changing disease progression. Additionally, disease severity based on imaging findings often does not correlate with pain and functioning reported by patients (*eg*, for knee osteoarthritis). Because some patients have insufficient improvement in their symptoms from non-pharmacologic and topical/systemic pharmacologic treatments, targeted injection therapies are often offered before more invasive surgical procedures. Surgery is also not the best option for certain patients due to a variety of factors, including patient preferences and individualized expectations for benefits versus risks.

Hypertonic dextrose prolotherapy has been used to treat a variety of musculoskeletal pain conditions, including osteoarthritis and different tendinopathies. Prolotherapy involves injecting an irritant solution into or around an affected structure to improve musculoskeletal pain and function. The true physiologic effects are not well understood but the putative mechanism involves eliciting a low-grade inflammatory response that stimulates natural healing processes in connective tissues and potentially alters pain perception pathways. Hypertonic dextrose is the most commonly utilized prolotherapy solution, but there is variation in dextrose concentration and inclusion of additional chemicals.

In fiscal year 2023, a total of 1,454 dextrose prolotherapy injection procedures were administered in VA health care facilities, and there were 59 VA Care in the Community claims (totaling $20,839). Dextrose prolotherapy is also commonly used in practice outside of VA care, but the total costs and utilization in non-VA settings are difficult to ascertain as these procedures are not covered by major health insurers and there is no corresponding Current Procedural Terminology (CPT) code for it.

CURRENT REVIEW

VA Pain Management, Opioid Safety and Prescription Drug Monitoring Program, and VA Physical Medicine and Rehabilitation are coleading an Integrated Project Team (IPT) to develop VA practice recommendations on injection therapies for musculoskeletal pain conditions. To support these efforts, they requested this evidence report on the effects of dextrose prolotherapy. Evaluation of the current evidence for dextrose prolotherapy is also needed to guide future research in this area.

In this systematic review, we synthesize evidence on the benefits and harms of dextrose prolotherapy for a range of musculoskeletal pain conditions, including knee osteoarthritis, plantar fasciitis, shoulder pain, lateral elbow tendinopathy, chronic low back pain, and pain due to temporomandibular joint (TMJ) dysfunction. Findings within each pain condition are provided separately for different comparators (*eg*, normal saline or corticosteroid injections).

The a priori protocol for this review was registered on the PROSPERO international prospective register of systematic reviews (CRD42024531179). We searched MEDLINE, Embase, and Scopus databases from inception to February 2024, using key words and subject headings for dextrose prolotherapy and musculoskeletal pain conditions (*eg*, prolotherapy, regenerative injection, dextrose or glucose injection for joint or back conditions). Additional citations were identified from consultation with content experts. We also searched clinicaltrials.gov for recently completed and ongoing trials.

Eligible studies evaluated hypertonic dextrose prolotherapy injections for treatment of acute or chronic musculoskeletal pain in outpatient settings. Eligible outcomes of interest were pain-related functioning or interference, physical performance (*eg*, gait speed, strength, range of motion), pain intensity or severity, general health-related quality of life, adverse events, costs, and treatment burden. Studies were required to be randomized controlled trials (RCTs); observational cohorts with ≥ 1 concurrent comparator group; or a single-arm observational cohort (only if including ≥ 100 participants and reporting results on adverse events).

Abstracted data included participant characteristics and eligibility criteria, intervention characteristics (*eg*, content and location of injections, content of exercise programs, frequency, duration), study design and settings, and findings for outcomes of interest, as noted above. For synthesis of findings, we first grouped studies by pain condition (*eg*, knee osteoarthritis, shoulder pain, plantar fasciitis) and then by intervention and comparator characteristics. We conducted meta-analyses when there were ≥3 studies for a given pain condition that evaluated sufficiently similar interventions and comparators, and reported the same outcome (*eg*, comparable measures of pain-related functioning or interference). Otherwise, we provided narrative syntheses of study characteristics and findings. For efficacy outcomes, we focused on between-group comparisons of the mean scores at follow-up time points. When summarizing whether individual studies reported meaningful differences between groups, we compared the study findings against the minimal clinically important difference (MCID), whenever we were able to locate a suitable published reference for MCID. For effect measures without published MCID references, we used statistical significance as reported by the included studies to determine if there were any between-group differences.

With input from IPT members, we prioritized 4 outcomes for certainty of evidence (COE) assessments. The top 3 prioritized efficacy outcomes were pain-related functioning or interference, physical performance, and quality of life. As evidence on adverse events is crucial for weighing the balance of risks and benefits, we also rated COE for adverse events. We assessed COE separately for dextrose prolotherapy compared with different treatments (*eg*, corticosteroid injections or exercise) when there were at least 2 studies evaluating the same comparison. We also separately assessed COE for outcomes at short-term (3-6 weeks), medium-term (3-4 months), and long-term (≥ 6 months) follow-up.

We used the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) methodology to rate overall COE as high, moderate, low, or very low. We systematically evaluated 5 domains: study limitations (risk of bias [RoB]), imprecision (limitations in precision of effect estimates), inconsistency (in direction and magnitude of effects across studies), indirectness (applicability of the results), and other considerations (including publication bias). For imprecision, we also considered the optimal information size (OIS) for efficacy outcomes and adverse events.

ES Table. GRADE Certainty of Evidence Ratings: Definitions and Recommended Statements

Certainty of Evidence	Rating Definition	Recommended Statements ("What Happens")
High	We are very confident that the true effect lies close to that of the estimate of the effect.	*Intervention reduces/increases/improves outcome.* *Intervention results in little to no difference in outcome.*
Moderate	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.	*Intervention probably reduces/increases/improves outcome.* *Intervention probably results in little to no difference in outcome.*
Low	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.	*Intervention may reduce/increase/improve outcome.* *Intervention may result in little to no difference in outcome.*
Very Low	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.	*The evidence is very uncertain about the effect of intervention on outcome.*

From 4,742 unique citations, we identified 91 eligible articles reporting 90 unique primary studies (80 RCTs, 10 observational studies). Eligible studies addressed a variety of musculoskeletal pain conditions, with a quarter focused on knee pain from osteoarthritis ($k = 22$). Nearly a fifth of studies evaluated dextrose prolotherapy for TMJ dysfunction ($k = 16$), while remaining studies addressed shoulder pain ($k = 12$), lateral elbow tendinopathy ($k = 11$), low back pain ($k = 9$), plantar fasciitis ($k = 8$), and a variety of other conditions ($k = 12$ single studies of different conditions such as fibromyalgia or patellar tendinopathy). We also found 49 underway or completed studies without publications.

There was wide variation in the dextrose concentration used, as well as the number of injection treatment sessions (range = 1-6) and the overall duration of treatment (up to 5 months). Most studies did not use imaging guidance ($k = 57$), while a third used ultrasound guidance ($k = 30$). There were also a wide variety of comparators examined, with the most common being normal saline or water ($k = 25$) and corticosteroid injection ($k = 14$).

Most studies assessed pain-related functioning or interference ($k = 62$) and pain intensity or severity ($k = 70$); fewer evaluated adverse events ($k = 54$) or physical performance ($k = 42$). Half of all studies were very small ($k = 41$ with total $N \leq 50$), and only 17 studies had total $N > 100$. Nearly all studies were conducted outside of the US ($k = 83$). Most studies included middle-aged adults ($k = 71$) and half were majority women ($k = 45$). Nearly half of studies were rated high RoB ($k = 36$ RCTs) or serious/critical ($k = 7$ observational studies). Only 10 studies were assessed as low RoB, and the remaining studies were rated either some concerns or moderate RoB ($k = 37$).

Key Question (KQ) 1: What Are the Benefits and Harms of Dextrose Prolotherapy for Acute and Chronic Musculoskeletal Pain?

For knee osteoarthritis, we identified 13 RCTs that evaluated intra- or extra-articular dextrose prolotherapy interventions (range = 10-25% dextrose), and 9 studies ($k = 8$ RCTs, $k = 1$ observational

study) that employed combined intra- and extra-articular dextrose injections (range 5-25% dextrose). A third of studies used imaging guidance. Three RCTs compared intra-articular dextrose prolotherapy with normal saline or water injections, and overall, dextrose prolotherapy probably has little to no benefit for pain-related functioning or physical performance at short, medium, and long-term follow-up. Dextrose prolotherapy also had little to no effect on health-related quality of life at long-term follow-up, compared with normal saline injection. Three RCTs evaluated dextrose prolotherapy against platelet-rich plasma (PRP), and the evidence is very uncertain at short and long-term follow-up for pain-related functioning. Dextrose prolotherapy may result in little to no difference in pain-related functioning at medium-term follow-up, compared with PRP. Two RCTs compared dextrose with ozone injection, and overall, dextrose prolotherapy may have little to no benefit for pain-related functioning. The evidence is very uncertain on adverse effects of intra-articular dextrose prolotherapy, compared with other treatments. Two RCTs compared intra- versus extra-articular dextrose prolotherapy, and there is probably little to no difference in pain-related functioning between these injection locations. The remaining RCTs used a variety of other comparators, including hyaluronic acid (HA), PT, autologous conditioned serum, erythropoietin, and pulsed radiofrequency waves.

Among the 9 studies that evaluated combined intra- and extra-articular dextrose injections for knee osteoarthritis, 7 used PT and/or home exercise programs as at least 1 of the comparators. The evidence is very uncertain for the effects of dextrose prolotherapy on pain-related functioning and physical performance at short and medium term, compared with PT/home exercise program, but it may improve these outcomes in the long term. Two of these studies also included normal saline injection as a comparator, and similarly, the evidence is very uncertain for effects on pain-related functioning in the short and medium term, but dextrose prolotherapy may have benefits in the long term. The evidence is very uncertain on adverse effects of combined intra and extra-articular dextrose prolotherapy, compared with either PT/home exercise, or normal saline injection. Remaining comparators examined included HA, corticosteroid, and ozone injections.

For plantar fasciitis, 8 eligible RCTs compared dextrose prolotherapy (range = 3.5-27% dextrose) with normal saline injection ($k = 2$), corticosteroid injection ($k = 2$), extracorporeal shock wave therapy (ESWT, $k = 2$), and a variety of other treatments. Most studies employed imaging guidance for dextrose injections. Dextrose prolotherapy may improve pain-related functioning at short- and medium-term follow-up, compared with normal saline injection, but compared with corticosteroid injection, the evidence is very uncertain for pain-related functioning, and there may be little to no difference in health-related quality of life. The evidence is also very uncertain on benefits of dextrose prolotherapy compared with ESWT. The evidence is very uncertain on adverse effects of dextrose prolotherapy, compared with any of these treatments.

We also identified 12 RCTs that evaluated dextrose prolotherapy (range = 13.5-25% dextrose) for shoulder pain due to either mixed rotator cuff pathology and/or subacromial bursitis ($k = 8$) or specifically supraspinatus tendinopathy ($k = 4$). Each study in the latter group used a different comparator (PRP, corticosteroid, PT, or normal saline injection). Most studies used imaging guidance for dextrose injections. In studies addressing shoulder pain due to mixed pathology, comparators were normal saline ($k = 4$), corticosteroid injection ($k = 3$), or PT/exercise programs ($k = 2$). Compared with normal saline injection, the evidence is very uncertain for pain-related functioning, and dextrose prolotherapy may have little to no benefit for physical performance. The evidence is also very uncertain on the benefits for pain-related functioning, compared with corticosteroid injection or PT/home exercise. For physical performance, dextrose prolotherapy probably results in less improvement in range of motion (*eg*, forward flexion, abduction) compared with corticosteroid

injection. Compared with PT/home exercise, the evidence varied across different timeframes: dextrose prolotherapy may have little to no benefit at short-term follow-up, but it may improve outcomes in the long term. The evidence is very uncertain for physical performance at medium-term follow-up, compared with PT/home exercise. The evidence is also very uncertain on adverse effects of dextrose prolotherapy compared with any of these treatments.

For pain due to lateral elbow tendinopathy, there were 11 RCTs that compared dextrose prolotherapy (range = 5-25% dextrose) to normal saline injection (k = 3), corticosteroid injection (k = 3), ESWT (k = 2), and a variety of other treatments (*e*g, HA and PT). Only a few studies used imaging guidance for dextrose injections. Compared with normal saline, dextrose prolotherapy may improve pain-related functioning at short- and medium-term follow-up, but it may have little to no benefit, or the evidence is very uncertain, for physical performance. Dextrose prolotherapy may also have little to no benefit for physical performance, compared with corticosteroid; the evidence is very uncertain for pain-related functioning for this comparator. The evidence is also very uncertain for pain-related functioning and physical performance, compared with ESWT. The evidence is very uncertain on adverse effects of dextrose prolotherapy, compared with any of these treatments.

For chronic low back pain, 7 studies (k = 4 RCTs, k = 3 observational studies) addressed non-specific low back pain, and 2 RCTs focused on pain due to sacroiliac joint dysfunction. Range of dextrose used was 12.5-25% and a third of studies employed imaging guidance for injections. Of studies examining non-specific low back pain, 5 administered multiple dextrose injections distributed over L4/S1 and sacroiliac areas, and 4 of these used normal saline as the comparator. Two studies on non-specific low back pain administered focal injections (either intradiscal or single-level facet capsule), compared with either corticosteroid or intradiscal electrothermal treatment. Both studies focusing on sacroiliac joint dysfunction used corticosteroid injections as the comparator. The evidence is very uncertain for pain-related functioning, compared with either normal saline or corticosteroid injections. The evidence is also very uncertain for adverse events.

Finally, 16 studies (14 RCTs, 2 observational studies) evaluated dextrose prolotherapy (range = 6.7-50% dextrose) for treatment of symptomatic TMJ dysfunction. No study used imaging guidance for dextrose injections. Half of these studies enrolled participants with normal or reduced TMJ mobility, while the other half included participants with TMJ hypermobility at baseline. For TMJ with normal or reduced mobility, 3 studies used normal saline or water as the comparator, and the remaining studies all employed different comparators (arthrocentesis and lavage, laser, arthrocentesis and HA or PRP, or occlusal splints). Studies addressing TMJ with hypermobility compared dextrose with normal saline injection (k = 3), or autologous blood injection (ABI, k = 4). One of these studies compared dextrose injections at different locations. For TMJ dysfunction with normal/reduced mobility or hypermobility, the evidence is very uncertain for pain-related functioning and physical performance, compared with normal saline or water injection. For TMJ with hypermobility, the evidence is also very uncertain for physical performance, compared with ABI. The evidence is very uncertain on adverse effects of dextrose prolotherapy, compared with any treatment.

KQ2: Do Benefits and Harms of Dextrose Prolotherapy Vary by Patient or Pain Condition Characteristics, Prior Treatment History, or Intervention Characteristics?

No study formally evaluated differences in outcomes by patient or pain condition characteristics, or prior treatment history. We did identify studies that compared different dextrose prolotherapy injection techniques or locations for knee osteoarthritis (k = 3), TMJ (k = 2), and for hip arthritis due to

developmental dysplasia ($k = 1$). There were also 4 studies that compared different dextrose concentrations for knee osteoarthritis ($k = 1$), lateral elbow tendinopathy ($k = 2$), and TMJ ($k = 1$). In general, variations in injection technique, location, or dextrose concentration had little to no impact on prioritized outcomes (pain-related functioning, physical performance, health-related quality of life, and adverse events), but there were some reported differences for reduction of pain severity.

KQ3: What Are the Costs of Dextrose Prolotherapy for Health Care Systems and Patients?

Only 2 studies addressed costs of dextrose prolotherapy treatment; both focused on health care system costs and did not address costs or treatment burden for patients or families. Neither study was conducted in the US. Yelland, 2021 reported a 3-arm RCT comparing dextrose prolotherapy versus supervised exercise program versus combination of both treatments for foot pain due to Achilles tendinosis, and found improvement in all groups in pain-related functioning over 1 year. This study was conducted in Australia and evaluated incremental cost-effectiveness ratio (ICER) in Australian dollars (A$) per additional responder. The ICER was A$1,716 per additional responder for dextrose prolotherapy, and A$1,539 per additional responder for combined dextrose and exercise. The other study examined treatment of osteochondral lesions of the talus and reported the direct cost per injection for the health care system, which was 30 Turkish lira for dextrose prolotherapy and 250 lira for PRP.

Evidence Gaps and Future Research

The evidence on efficacy and safety of dextrose prolotherapy for chronic musculoskeletal disorders is impeded by small sample sizes for most studies and a substantial number of methodological concerns (nearly half were rated high, serious, or critical RoB). There was considerable variation in intervention characteristics, cointerventions, study populations, and choice of outcome measures across studies. To provide clinically relevant interpretations, we assessed between-group differences using published MCID whenever available. The evidence suggests that efficacy of prolotherapy may be condition specific, since there was probably little to no benefit for knee osteoarthritis (for intra-articular injection compared with normal saline), but for conditions like lateral elbow tendinopathy and plantar fasciitis, there may be some benefit (also compared with normal saline). Whether specific populations and conditions benefit from dextrose prolotherapy (particularly compared with other non-surgical treatments) is an important area for future research as some patients do not have sufficient improvement with other treatments for musculoskeletal pain. There are also concerns with side effects of some recommended treatments when used chronically, and some patients may have contraindications to certain pharmacologic options.

Injection therapies for musculoskeletal pain conditions are known to have a large placebo effect that complicates their rigorous evaluation. The natural history of most of these conditions involves waxing and waning of symptoms, where patients seek medical attention during acute exacerbations of pain and pain-related disability, and then improve due to healing or homeostatic processes, lifestyle adjustments, and/or medical treatments. In a large, well-designed RCT, the rates and average timing of improvements are expected to be balanced between groups receiving interventions and comparators (including placebo when appropriate). However, small studies may not adequately achieve balance across arms on these non-intervention effects (and unmeasured confounding). Small trials are also more vulnerable to biases arising from attrition, particularly when the extent of attrition differs between groups. Furthermore, it may be challenging to maintain masking for injection interventions throughout a study, particularly when these involve multiple different injections in and around an

anatomic structure. These factors likely contributed to the low and very low COE for most findings in this report and could be addressed by larger trials with sufficient follow-up.

Inconsistency in study findings was also likely due to the wide variation in dextrose concentrations, treatment duration and number of sessions, and other differences in injection technique, even for interventions addressing the same condition. Some of this variation may be clinically reasonable and expected due to differences in location of maximal pain for the affected joint or area, and factors like patient tolerance. In addition, and as customary in the overall treatment of musculoskeletal pain, there was no standardization of cointerventions or treatment algorithms that specified which options would be tried in sequence or concurrently. It is also possible that some cointerventions (*eg*, home exercise therapy) may be synergistic or antagonistic with the effects of the primary interventions being examined. All of these factors added to the challenges in interpretation of study findings and should be more systematically addressed in future studies.

Only 2 included studies reported on treatment costs for health care systems, and none evaluated cost and burden for patients. These are important considerations for both health care payors, facilities, and patients, particularly given the chronic nature of most musculoskeletal pain conditions. There are likely differences in costs and treatment burden between the wide variety of non-surgical treatment options and dextrose prolotherapy, which all involve somewhat different resource needs for health care facilities and clinician training, as well as demands on patient time and other potential access barriers. In terms of injection therapies, the number and frequency of treatment sessions, as well as any additional clinician education, would be important factors for health care facility resource needs. Future studies of dextrose prolotherapy for musculoskeletal pain conditions should include quantitative and qualitative assessments of the costs and treatment burden for health care systems and patients.

Included studies largely did not use clear and systematic methods to evaluate adverse events for dextrose prolotherapy and comparators. This is an essential gap for future research to address because this information will inform clinician decision-making, promote shared decision-making, and potentially impact prioritization of limited medical resources. Trials should assess adverse events for each treatment arm using open-ended questions and/or checklists administered to all participants on a regular basis. Additionally, studies should clearly define the severity of adverse events (*eg*, serious events can be defined as life threatening, requiring hospitalization, or resulting in persistent disability) and rates of events that led to discontinuation of the treatment. Evaluation of adverse events will also require larger studies for the different musculoskeletal pain conditions, since there is a strong possibility that some effects will be variable across conditions.

In summary, future studies of prolotherapy should be of sufficient size and methodological quality to systematically assess efficacy relative to currently recommended conservative treatments, as well as an appropriate placebo control given the strong placebo effect associated with injection therapies. More work is also needed to evaluate adverse events, cost, and treatment burden.

Implications for Policy and Practice

Regarding efficacy, dextrose prolotherapy appeared to have differential effects across different musculoskeletal pain conditions. Intra-articular dextrose prolotherapy probably had little to no benefit in pain-related functioning or physical performance for knee osteoarthritis, compared with normal saline injections. But evidence suggested benefits for plantar fasciitis and lateral elbow tendinopathy, compared with normal saline. In contrast, our findings indicated that for shoulder pain, dextrose prolotherapy probably led to worse physical performance outcomes, compared with corticosteroid

injections. Therefore, these observations should be explored more thoroughly in well designed and rigorous clinical trials that compare dextrose prolotherapy with other common conservative interventions for these pain conditions. The VA may be uniquely qualified and capable of undertaking these clinical investigations, as pharmaceutical companies are less likely to make the research investments needed to demonstrate the safety and efficacy of an inexpensive, non-proprietary, and easily accessible medication.

Generally, our findings indicate the evidence is very uncertain for adverse effects of dextrose prolotherapy, and more research is needed to establish the safety of these procedures. Most studies were small ($N < 100$) and thus of insufficient size to evaluate infrequent but potentially important adverse effects. Additionally, many did not systematically evaluate or report adverse events.

CONCLUSIONS

Intra-articular dextrose prolotherapy probably had little to no benefit for pain-related functioning or physical performance in knee osteoarthritis, compared with normal saline injections. For shoulder pain due to mixed bursitis and rotator cuff pathology, dextrose prolotherapy probably resulted in worse physical performance outcomes, compared with corticosteroid injections. However, dextrose prolotherapy may improve pain-related functioning for lateral elbow tendinopathy and plantar fasciitis, compared with normal saline injection. Evidence on adverse events was generally lacking and severely limited by methodological concerns. The evidence was also very uncertain on the benefits of prolotherapy compared with other treatments or for other pain conditions. Given the lack of efficacious therapies for musculoskeletal pain conditions, and interest in potential benefits of dextrose prolotherapy, future high-quality RCTs are needed to better understand the benefits and harms for this treatment.