

# Prolotherapy injections for chronic low-back pain (Review)

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[Intervention Review]

# Prolotherapy injections for chronic low-back pain

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## ABSTRACT

### Background

Prolotherapy involves repeated injections of irritant solutions to strengthen lumbosacral ligaments and reduce some types of chronic low-back pain; spinal manipulation and exercises are often used to enhance its effectiveness.

### Objectives

To determine the efficacy of prolotherapy in adults with chronic low-back pain.

### Search strategy

We searched CENTRAL 2006, Issue 3 and MEDLINE, EMBASE, CINAHL, and AMED from their respective beginnings to October 2006, with no restrictions on language, and consulted content experts.

### Selection criteria

We included randomised (RCT) and quasi-randomised controlled trials (QRCT) that compared prolotherapy injections to control injections, alone or in combination with other treatments, which measured pain or disability before and after the intervention.

### Data collection and analysis

Two review authors independently selected the trials and assessed methodological quality. Intervention protocols varied from study to study, making meta-analysis impossible.

### Main results

We identified five high quality studies with a total of 366 participants. All measured pain or disability levels at six months, and four measured the proportion of participants reporting a greater than 50% reduction in pain or disability scores.

Three randomised controlled trials (206 participants) found that prolotherapy injections alone are no more effective than control injection for chronic low-back pain and disability. At six months, there was no difference between groups in mean pain or disability scores (2 RCTs; 184 participants) and no difference in proportions who reported over 50% improvement in pain or disability (3 RCTs; 206 participants). These trials could not be pooled due to clinical heterogeneity.

Two RCTs (160 participants) found that prolotherapy injections, given with spinal manipulation, exercise, and other therapies, are more effective than control injections for chronic low-back pain and disability. At six months, one study reported a significant difference

between groups in mean pain and disability scores, whereas the other study did not. Both studies reported a significant difference in the proportion of individuals who reported over 50% reduction in disability or pain. Co-interventions confounded interpretation of results and clinical heterogeneity in the trials prevented pooling.

### Authors' conclusions

There is conflicting evidence regarding the efficacy of prolotherapy injections for patients with chronic low-back pain. When used alone, prolotherapy is not an effective treatment for chronic low-back pain. When combined with spinal manipulation, exercise, and other co-interventions, prolotherapy may improve chronic low-back pain and disability. Conclusions are confounded by clinical heterogeneity amongst studies and by the presence of co-interventions.

## PLAIN LANGUAGE SUMMARY

### Prolotherapy injections for chronic low-back pain

Chronic low-back pain is a very common problem for which there is currently no universally effective treatment. Patients with chronic low-back pain have many treatment options and it is important for them to understand the evidence behind each treatment option they may be considering. Prolotherapy injections have been used to treat chronic low-back pain for over 50 years but their use remains controversial. They involve repeatedly injecting ligaments with compounds such as dextrose (sugar) and lidocaine (anaesthetic) to help restart the body's natural healing process by causing controlled acute inflammation (swelling) in the areas injected. Proponents believe this leads to stronger ligaments that can better support the low-back. Prolotherapy injections are often combined with other treatments such as spinal manipulation, exercises, and corticosteroid injections into tender muscles to maximize its effect.

This review included five studies that examined the effects of prolotherapy injections on 366 patients with low-back pain that had lasted for longer than three months. Because these studies used different types of prolotherapy injections and different treatment protocols, their results could not be combined. The five studies we examined were therefore divided according to whether they used prolotherapy injections alone or combined prolotherapy injections with spinal manipulation, exercise, and other treatments. Of the five studies we reviewed, three found that prolotherapy injections alone were not an effective treatment for chronic low-back pain and two found that a combination of prolotherapy injections, spinal manipulation, exercises, and other treatments can help chronic low-back pain and disability. Minor side effects such as increased back pain and stiffness were common but short-lived. Based on these five studies, the role of prolotherapy injections for chronic low-back pain is still not clear.

## BACKGROUND

Chronic low-back pain places an enormous burden on society, in terms of both patient suffering and cost (Deyo 2006). This makes the search for more effective treatments a priority in research. Prolotherapy (also called ligament sclerotherapy) is an injection-based treatment for chronic musculoskeletal pain. Its proposed mode of action is the reduction of joint instability through the strengthening of stretched or torn ligaments (Klein 1997). Its most common application in the back is chronic non-specific low-back pain that has not responded to other therapies. Protocols for prolotherapy for back pain in scientific studies to date vary, but all include the injection of an irritant (proliferant) solution into ligaments and tendinous attachments at weekly or fortnightly intervals for three to eight treatments.

Proponents of prolotherapy believe that ligament injections trigger an influx of granulocytes, macrophages and fibroblasts, the release of growth factors and ultimately, collagen deposition. They

hypothesise that this leads to strengthening of ligaments and a reduction in pain and disability. There are three major classes of proliferants commonly used in prolotherapy -- the irritants, the chemotactics and the osmotics (Banks 1991). There is some overlap in their purported actions. Irritants act by either damaging cells directly or by rendering the cells antigenic through alteration of surface proteins. Irritants include phenol, guaiacol and tannic acid. There is another category of irritants called particulates, exemplified by pumice flour. These act by triggering cellular trauma following injection into target tissues, and by directly attracting macrophages, which ingest them and secrete polypeptide growth factors. Chemotactics also act by attracting inflammatory cells. The only agent in this class is sodium morrhuate. The osmotic class of proliferants includes concentrated solutions of glucose, glycerin and zinc sulphate. They act by causing an osmotic shock to cells leading to the release of pro-inflammatory substances. Local anaesthetic (commonly lignocaine) is often added to proliferant

solutions to reduce the pain of the irritant injections. An increase in mass and thickness in animal and human ligaments has been demonstrated in response to repeated injections of a commonly used solution containing glucose (dextrose), glycerine, phenol and lignocaine (lidocaine) (Klein 1989).

Prolotherapy injections are often supplemented by co-interventions to enhance its effectiveness (Dhillon 1997; Klein 1993; Ongley 1987; Yelland 2004A). Prior to commencing prolotherapy injections, these may include, alone or in any combination, triamcinolone injections into hypersensitive tender points, infiltration of lumbosacral ligaments with lignocaine, or spinal manipulation with or without intravenous sedation and analgesia. During and after the course of prolotherapy injections, co-interventions may include, alone or in any combination, lumbar flexion and extension exercises to induce optimal strengthening of the treated ligaments, regular walking, encouragement to recommence previously painful activities, paracetamol, corsets, instructions on back care, and use of oral vitamin C, zinc and manganese supplements, ostensibly to facilitate collagen growth. Use of oral anti-inflammatory medications is discouraged during the treatment period as this may, in theory, suppress the inflammation triggered by the prolotherapy injections and reduce its long-term effects.

The original Cochrane review on this topic (Yelland 2004B) was conducted to focus solely on prolotherapy injections, following an earlier Cochrane review of all injection therapies for low-back pain (Nelemans 2003) in which the only treatment that showed significant, sustained reductions in pain and disability at six months involved prolotherapy injections (Ongley 1987). Following the publication of the original review, it was brought to our attention that a potentially relevant study had been overlooked. Since two years had passed since its publication, this review was updated to search for additional studies, as recommended by the Cochrane author guidelines.

## OBJECTIVES

The objective of this updated review is to determine the efficacy of prolotherapy injections in reducing pain and disability in chronic low-back pain in adults, aged 18 and older.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

We included all randomised controlled trials (RCT) and quasi-randomised controlled trials (QRCT; using, for example, birth

date to assign participants to groups) that compared prolotherapy injections to control injections or other therapies. We included trials with co-interventions. Trials had to include measures of pain or disability before and after the intervention.

We excluded non-randomised controlled studies and non-controlled experimental studies such as case series. There were no limits on publication dates of trials or language of publication.

#### Types of participants

We selected studies that included participants aged 18 years and over, with a history of non-specific low-back pain longer than three months duration. Low-back pain was defined as pain in the lumbar region, with or without pain in the sacral region, gluteal regions and radiation to the lower extremities. Exclusion criteria in studies were lumbar/sacral radiculopathies and pathological causes of back pain, such as infection, neoplasm, metastasis, osteoporosis, rheumatoid arthritis, or fractures. The presence of participants with unresolved litigation or compensation claims was not a reason for exclusion.

#### Types of interventions

For inclusion, prolotherapy injections had to be administered to at least one group within the trial. Comparison groups could include injections with a control solution or a different therapy not involving injections. For chronic non-specific low-back pain, the prolotherapy solutions are injected into the ligaments and tendons regarded as the sources of the pain. The choice of injection sites is determined either by a standard list of points (Ongley 1987) or by the patterns of pain and tenderness (Dhillon 1997). The skin through which injections are given at each treatment visit is anaesthetised with wheals of local anaesthetic. The number of injection treatments ranges from three to eight and the interval between treatments commonly ranges from one to two weeks (Dechow 1999; Dhillon 1997; Ongley 1987). Co-interventions used with prolotherapy injections vary with different protocols and are described in the background section above and the table of *Characteristics of Included Studies*.

#### Types of outcome measures

The choice of outcomes for inclusion in this systematic review was based on those recommended by the Cochrane Back Review group (Deyo 1998):

- low-back pain: Measures included visual analogue scale (Huskisson 1974), McGill Pain Questionnaire (Melzack 1987) or other validated quantitative measures. The mean (standard deviation (SD)) pain scores and the proportion achieving more than 50% reduction in pain scores (if reported) were used.
- low-back-related disability: Measures included the Oswestry disability questionnaire (Fairbank 1980),

Roland-Morris disability scale (Roland 1983) (or its adaptations (Patrick 1995)) or other validated measures of disability. Both the mean (SD) disability and the proportion achieving more than 50% reduction in disability (if reported) were used.

- overall improvement or satisfaction with treatment.
- well-being: measured by SF-12 (Ware 1996), SF-36 (Ware 1992), or EuroQoL (EuroQoL 1990).
- return-to-work, days of absenteeism, or days of reduced activities (Deyo 1998).
- physical examination: measuring range of motion, spinal flexibility, or muscle strength.
- side effects, medication use and health care use.

The primary outcomes of interest to this review were pain and disability related to the low-back.

## Search methods for identification of studies

### Data sources

The following electronic databases were searched using the strategy outlined in Table 1:

- Cochrane Central Register of Controlled Trials (The Cochrane Library 2006, issue 3)
- MEDLINE (January 1966 to October 2006)
- EMBASE (January 1992 to October 2006)

- CINAHL (January 1982 to October 2006)
- AMED (January 1985 to October 2006)

We sent content experts the list of studies identified from these databases to check it for completeness and to inform us of any missing studies or unpublished studies.

## Data collection and analysis

### Selection of studies for inclusion

Two authors independently applied the inclusion criteria to the titles and abstracts of studies identified through aforementioned search strategies, to select studies for inclusion. There were no disagreements about the eligibility of studies for inclusion.

### Assessment of methodological quality

The full text of all studies meeting inclusion criteria was obtained. The methodological quality of these studies was assessed independently by two authors, neither of whom were co-authors of those studies. They rated each study according to the criteria for methodological assessment and their methods of operationalization recommended by the Cochrane Back Review group (van Tulder 2003) and outlined in Table 1. Criteria were scored as “Yes”, “No” or “Don’t know”, depending on how successfully they were met. Studies meeting six or more of the 11 criteria were considered to be of high quality.

**Table 1. Criteria for methodological quality assessment and their operationalisation**

Was the method of randomisation adequate? A random (unpredictable) assignment sequence. Examples of adequate methods are computer-generated random numbers table and use of sealed opaque envelopes. Methods of allocation using date of birth, date of admission, hospital numbers, or alternation should not be regarded as appropriate.
Was the treatment allocation concealed? Assignment generated by an independent person not responsible for determining the eligibility of the patients. This person has no information about the persons included in the trial and has no influence on the assignment sequence or on the decision about eligibility of the patient.
Was the patient blinded to the intervention? The review author determines if enough information about the blinding is given in order to score a “yes.”
Was the care provider blinded to the intervention? The review author determines if enough information about the blinding is given in order to score a “yes.”
Was the outcome assessor blinded to the intervention? The review author determines if enough information about the blinding is given in order to score a “yes.”

**Table 1. Criteria for methodological quality assessment and their operationalisation** (Continued)

Was the drop-out rate described and acceptable? The number of participants who were included in the study but did not complete the observation period or were not included in the analysis must be described and reasons given. If the percentage of withdrawals and drop-outs does not exceed 20% for immediate and short-term follow-ups, 30% for intermediate and long-term follow-ups and does not lead to substantial bias a “yes” is scored.

Did the analysis include an intention-to-treat analysis? All randomized patients are reported/analyzed in the group to which they were allocated by randomization for the most important moments of effect measurement (minus missing values), irrespective of noncompliance and co-interventions.

Were the groups similar at baseline regarding the most important prognostic indicators? In order to receive a “yes,” groups have to be similar at baseline regarding demographic factors, duration and severity of complaints, percentage of patients with neurological symptoms, and value of main outcome measure(s).

Were co-interventions avoided or similar? Co-interventions should either be avoided in the trial design or be similar between the index and control groups.

Was the compliance acceptable in all groups? The review author determines if the compliance to the interventions is acceptable, based on the reported intensity, duration, number and frequency of sessions for both the index intervention and control intervention(s).

Was the timing of the outcome assessment in all groups similar? Timing of outcome assessment should be identical for all intervention groups and for all important outcome assessments.

### Data extraction

Data were extracted independently by the two authors using a common data extraction form. Data were extracted on study design and setting, participant characteristics, interventions, outcomes, timing of outcomes and duration of effects, main results, withdrawals, adverse effects and conclusions.

### Data analysis

For dichotomous outcome measures, the differences between groups in each study were expressed as the relative risk (RR) and risk difference (RD) with their respective 95% confidence intervals (95% CI). For between-group comparisons of continuous measures, the effect size was estimated as weighted mean differences (WMD) or standardised mean differences (SMD) with 95% CI to accommodate the different scales used in each study. An effect size between 0.2 and 0.5 was considered a small effect size, between 0.5 and 0.8 a medium effect size, and of 0.8 or more a large effect size (Cohen 1988).

We evaluated clinical homogeneity by exploring the differences between the RCTs with regard to study population, types of interventions in treatment and control groups and the types of comparisons and outcomes. We decided against pooling of the study results because of the clinical heterogeneity amongst intervention groups and amongst control groups. No two studies tested the same component(s) of treatment or had the same number of injection treatments.

## RESULTS

### Description of studies

See: [Characteristics of included studies](#); [Characteristics of excluded studies](#).

See table of *Characteristics of Included Studies* (Dechow 1999; Klein 1993; Mathews 1987; Ongley 1987; Yelland 2004A).

### Risk of bias in included studies

All of the studies were of high quality, and four of the studies met at least nine of the 11 internal validity criteria set by the Cochrane Back Review Group (van Tulder 2003). Ongley 1987 fulfilled all but one of the criteria regarding comparable co-interventions. This study was designed to concurrently compare four interventions (including prolotherapy injections) with four control interventions. Three of these co-interventions, the initial lignocaine injections into ligaments, the manipulation following these injections, and the injection of muscle tender points with triamcinolone/lignocaine, were not blinded to the treating doctor, but the prolotherapy injections given by a different doctor were double-blinded. Klein 1993 fulfilled all 11 criteria. Dechow 1999 fulfilled nine of the criteria as it was unclear if treatment allocation was concealed and whether the care provider was blinded to the type of injections given. Yelland 2004A had a factorial design to test the efficacy of prolotherapy injections and exercises in the same study. It fulfilled all 11 criteria for the injections factor and nine of the

criteria for the exercises factor, as the care provider was not blinded to the exercise status of participants. [Mathews 1987](#) fulfilled six of the criteria as interventions were not blinded to the treating doctor, it was unclear if treatment allocation was concealed, if compliance was acceptable in all groups, if the outcome measure (i.e. six-point visual analogue scale used to create three categories of improvement) was relevant, and if intention-to-treat analysis was used. See [Figure 1](#).



Figure 1. Summary of risks of bias

	Adequate sequence generation?	Allocation concealment?	Blinding? (All outcomes - patients?)	Blinding? (All outcomes - providers?)	Blinding? (All outcomes - outcome assessors?)	Incomplete outcome data addressed? (All outcomes - drop-outs?)	Incomplete outcome data addressed? (All outcomes - ITT analysis?)	Similarity of baseline characteristics?	Co-interventions avoided or similar?	Compliance acceptable?	Timing outcome assessments similar?
Dechow 1999	+	?	+	?	+	+	+	+	+	+	+
Klein 1993	+	+	+	+	+	+	+	+	+	+	+
Mathews 1987	+	?	+	-	+	+	?	+	+	?	?
Ongley 1987	+	+	+	+	+	+	+	+	-	+	+
Yelland 2004A	+	+	+	+	+	+	+	+	+	+	+

## Effects of interventions

The search strategy identified seven studies, five of which were eligible for inclusion in the review (Dechow 1999; Klein 1993; Mathews 1987; Ongley 1987; Yelland 2004A). One study was excluded as a pilot comparative study with concurrent controls since randomisation was not used (Yelland 2000). The second excluded study was unpublished at the time of our initial review and discovered by contacting content experts (Wilkinson 2003), but subsequently published (Wilkinson 2005). It was excluded because 20% of its participants had thoracic or cervical spinal pain and the study design involved crossover between experimental and control injections on the second treatment, making long term results uninterpretable.

### Study population

Four of the studies included adult patients whose pain had been present for over six months and had failed prior treatments (Dechow 1999; Klein 1993; Ongley 1987; Yelland 2004A), while one study included adult patients whose pain had been present for over three months (Mathews 1987). They all excluded patients with possible pathological causes of back pain, such as cancer, spondylolisthesis and radiculopathy. Four studies also excluded patients whose pain was the subject of unresolved workers' compensation or legal action (Dechow 1999; Klein 1993; Ongley 1987; Yelland 2004A). Three of the studies required patients to have attempted other forms of conservative care prior to enrolling in their trial (Klein 1993; Ongley 1987; Yelland 2004A).

### Study design and interventions

The protocols for experimental and control groups were complex and varied, making inter-trial comparisons difficult. They are outlined in the table of *Characteristics of Included Studies*. No study had a control group that did not receive injections. Within each study, the experimental and control groups received similar protocols of ligament injections, but with different solutions. Ongley 1987 compared glucose/glycerine/phenol/lignocaine solution with a normal saline control solution, while Klein 1993 and Dechow 1999 compared glucose/glycerine/phenol/lignocaine solution with a lignocaine control solution, Yelland 2004A compared a glucose/lignocaine solution with a saline solution, and Mathews 1987 compared phenol/dextrose/glycerine/procaine solution with a procaine control solution.

Both Mathews 1987 and Dechow 1999 differed markedly from the other three studies by administering only three injection treatments (compared with at least six in the other studies) and injecting only 10 ml of solution during each treatment (compared with at least 20 ml in the other studies). Yelland 2004A also tested the effect of the exercise co-intervention using a factorial design, with independent random allocation of participants to either exercises or normal activity. This design allowed separate analysis of the attributable effects of the injections and the exercises. In contrast, Ongley 1987 tested several co-interventions with allocation tied to the injection group. The day before commencing the course

of prolotherapy injections, the experimental group received initial triamcinolone/lignocaine injections into muscle tender points and high dose lignocaine injections into ligaments followed by manipulation, whereas the control group had lignocaine-only injections into muscle tender points and then low dose lignocaine injections into ligaments followed by a sham manipulation. This design made it impossible to attribute any effect to a single component of the treatment protocol. Mathews 1987 gave injections into lumbosacral ligaments for the experimental group while the control group received injections in an unspecified tender spot, confounding results by varying both the solution injected and the location of injections.

### Study funding

Ongley 1987 and Klein 1993 were funded by a combination of private research foundation grants and personal donations. Dechow 1999, Mathews 1987 and Yelland 2004A were funded by public research grants, and Yelland et al had additional funding from private research foundation grants. No conflicts of interest were declared in any study.

### Effect measurements

The primary outcomes in four studies were pain and disability (Dechow 1999; Klein 1993; Ongley 1987; Yelland 2004A), whereas one study reported only pain (Mathews 1987). Pain was measured on a visual analogue scale (VAS) in all studies, with the addition of a McGill Pain Questionnaire in one study (Dechow 1999), a six-point numerical rating scale in another study (Mathews 1987), and a pain drawing grid score in three studies (Klein 1993; Ongley 1987; Yelland 2004A). Disability was measured by a Roland-Morris disability questionnaire or a modification thereof in three studies (Klein 1993; Ongley 1987; Yelland 2004A) and by an Oswestry Disability Scale in one study (Dechow 1999). Four studies reported mean scores for these outcomes at zero and six months, whereas one study (Mathews 1987) used pain to classify participants in three pain categories (no further pain/occasional further pain/constant pain) without reporting mean scores. Three of the studies (Klein 1993; Ongley 1987; Yelland 2004A) also reported the proportion of participants who achieved at least 50% reduction in pain or disability scores, or both, at six months. For Mathews 1987, a dichotomous outcome was created by combining the first two pain categories (no further pain/occasional further pain), which was considered equivalent to the classification used in three other studies (i.e. more than 50% reduction in pain scores). Several secondary outcomes, including physical performance testing and medication usage were reported, but not consistently across studies. Follow-up periods were six months for three studies (Dechow 1999; Klein 1993; Ongley 1987), twelve months for one study (Mathews 1987), and twenty four months for one study (Yelland 2004A).

The key results are summarised in the table of *Characteristics of Included Studies*.

### Efficacy - Prolotherapy injections compared to

## control injections

### Pain - means

For between-group differences in mean VAS pain scores at six months, there were no significant differences reported. In [Dechow 1999](#), the SMD was 0.14 (95% CI: -0.32 to 0.59) and in [Yelland 2004A](#), the SMD was -0.10 (95% CI: -0.47 to 0.28) and there were no significant differences between groups in VAS pain at 12 and 24 months. See [Table 2](#). Mean pain scores were not reported in [Mathews 1987](#).

**Table 2. Prolotherapy vs control - Between group differences mean pain/disability**

Study	Time from baseline	Outcome variable	SMD (95% CI)
Yelland 2004	12 months	Pain	-0.13 (-0.51 to 0.25)
Yelland 2004	12 months	Disability	-0.28 (-0.67 to 0.10)
Yelland 2004	24 months	Pain	-0.17 (-0.59 to 0.25)
Yelland 2004	24 months	Disability	-0.13 (-0.55 to 0.29)

### Pain - proportions

For between-group differences in proportion of participants with more than 50% improvement in VAS pain from baseline, there were no significant differences reported. In [Yelland 2004A](#), proportions at six months were 50% (treatment) and 46% (control) with a RR of 1.10 (95%CI: 0.75 to 1.61). In [Mathews 1987](#), proportions at three months were 63% (treatment) and 33% (control) with a RR of 1.88 (95% CI: 0.57 to 6.19) and at 12 months were 63% (treatment) and 67% (control) with a RR of 0.94 (95% CI: 0.47 to 6.01); proportions at six months in this study were not specified but reported as not statistically significantly different. No such proportions were reported by [Dechow 1999](#).

### Disability - means

For between-group differences in mean disability scores at six months, there were no significant differences reported. In [Dechow 1999](#), the SMD was 0.03 (95% CI: -0.43 to 0.49) and in [Yelland 2004A](#), the SMD was -0.22 (95% CI: -0.59 to 0.16).

### Disability - proportions

For between-group differences in proportion of participants with more than 50% improvement in disability scores from baseline at six months, there were no significant differences reported. In [Yelland 2004A](#), proportions were 49% (treatment) and 32% (control) with a RR of 1.50 (95% CI: 0.94 to 2.40). Long term results showed a similar pattern. At 12 months, proportions were 42% (treatment) and 32% (control) with a RR of 1.31 (95% CI: 0.79 to 2.16) and at 24 months proportions were 48% (treatment) and 35% (control) with a RR of 1.37 (95% CI: 0.82 to 2.27). See [Table 3](#). No such proportions were reported by [Dechow 1999](#) or [Mathews 1987](#).

**Table 3. Prolotherapy vs control - Between group differences # patients >50% improvement**

Study	Time from baseline	Outcome variable	RR (95%CI)	RD (95% CI)	P-value
Yelland 2004	12 months	Pain	1.29 (0.81, 2.04)	0.10 (-0.08, 0.29)	0.32
Yelland 2004	12 months	Disability	1.31 (0.79, 2.16)	0.10 (-0.08, 0.28)	0.32
Yelland 2004	24 months	Pain	1.22 (0.75, 1.97)	0.08 (-0.12, 0.29)	0.39
Yelland 2004	24 months	Disability	1.37 (0.82, 2.27)	0.13 (-0.08, 0.33)	0.28

### interventions compared to control injections

A separate analysis of the exercise co-intervention in [Yelland 2004A](#) reported no differences in pain or disability results between exercise and normal activity groups at any point in the study.

### Efficacy - Prolotherapy injections combined with spinal manipulation, exercise, and other co-

### Pain - means

For between-group differences in mean VAS pain scores at six months, only one study reported statistically significantly greater

reductions favouring the treatment group. In [Ongley 1987](#), the SMD was -1.00 (95% CI: -1.46 to -0.53). In [Klein 1993](#), the SMD was -0.31 (95% CI: -0.76 to 0.13). A subgroup analysis excluding participants with hypersensitive gluteal tender points who were treated with triamcinolone injections on the first day of treatment achieved a statistically significant reduction favouring the treatment group ( $P = 0.03$ ) ([Klein 1993](#)). For between-group differences in mean pain grid scores at six months, only one study reported significantly greater reductions favouring the treatment group. In [Ongley 1987](#) the SMD was -5.15 (95% CI: -6.07 to -4.23), whereas in [Klein 1993](#), the SMD was 0.02 (95% CI: -0.42 to 0.46).

#### **Pain - proportions**

For between-group differences in proportion of participants with more than 50% improvement in pain or disability scores (separate results not reported for each outcome) from baseline to six months, [Klein 1993](#) reported statistically significantly different results favouring the treatment group: 77% (treatment) and 53% (control) with a RR of 1.47 (95% CI: 1.04 to 2.06). These proportions were not reported in [Ongley 1987](#).

#### **Disability - means**

For between-group differences in mean disability scores at six months, one study reported significantly greater reductions favouring the treatment group. In [Ongley 1987](#), the SMD was -0.81 (95% CI: -1.26 to -0.35). In [Klein 1993](#), the SMD was -0.09 (95% CI: -0.53 to 0.35). A subgroup analysis excluding participants with hypersensitive gluteal tender points who were treated with triamcinolone injections on the first day of treatment achieved a statistically significant reduction favouring the treatment group ( $P = 0.016$ ) ([Klein 1993](#)).

#### **Disability - proportions**

For between-group differences in proportion of participants with more than 50% improvement in disability scores from baseline to six months, one study reported statistically significantly different results favouring the treatment group. In [Ongley 1987](#), proportions were 88% (treatment) and 39% (control) with a RR of 2.24 (95% CI: 1.50 to 3.35). For between-group differences in proportion of participants with more than 50% improvement in pain or disability scores (separate results not reported for each outcome) from baseline to six months, one study reported statistically significantly different results favouring the treatment group. In [Klein 1993](#), proportions were 77% (treatment) and 53% (control) with a RR of 1.47 (95% CI: 1.04 to 2.06) ([Klein 1993](#)).

#### **Adverse events**

By far, the most commonly reported adverse events were temporary increases in back pain and stiffness following injections, reported by nearly all participants at some point in three studies (

[Klein 1993](#); [Ongley 1987](#); [Yelland 2004A](#)), with only a few reporting increased pain post-injection in [Dechow 1999](#). Post-injection headaches suggestive of lumbar puncture occurred in two per cent in [Klein 1993](#) and in four per cent in [Yelland 2004A](#). In [Ongley 1987](#), there was also a two per cent incidence of post-menopausal spotting, attributed to the initial triamcinolone injections. In [Yelland 2004A](#), four participants (4%) developed leg pain with neurological features, but CT or MRI scanning showed evidence of nerve root compression by herniated discs and/or osteophytes. Three of these resolved with symptomatic treatment and the fourth with a laminectomy. In [Yelland 2004A](#), there were also reports of nausea and diarrhoea in 42%, thoracic spinal pain in 10%, and other symptoms in 56%, but symptoms were generally transient. In [Mathews 1987](#), there were no reported adverse events. No study reported any significant differences in the incidence of adverse events between treatment and control groups.

## **DISCUSSION**

### **Study Selection**

Despite an extensive search, only five articles on prolotherapy injections for chronic low-back pain were identified for review. The treatment and control group protocols varied from study to study, making both meta-analysis and levels of evidence summaries impossible. Consequently, the conclusions of this review are based on the results of individual studies.

### **Methodological Quality**

The quality of studies was high, with four of five (80%) studies meeting nine or more of the 11 criteria used for the assessment of internal validity. [Ongley 1987](#); [Klein 1993](#); and [Yelland 2004A](#) all met the important criteria of allocation concealment and blinding of the treating doctor to the composition of the injection solution. It was unclear whether [Dechow 1999](#) or [Mathews 1987](#) met these criteria. Outcome assessment was blinded in all studies, but as the primary outcomes were self-assessed pain and disability, this criterion is less important than in studies where primary outcomes are measured objectively by an assessor.

### **Efficacy of Prolotherapy Injections**

It is challenging to interpret current evidence regarding the efficacy of prolotherapy injections for the treatment of chronic low-back pain since conclusions are confounded by clinical heterogeneity amongst studies and by the presence of co-interventions. Three studies that compared prolotherapy injections directly against control injections found no evidence that they are more effective (

Dechow 1999; Mathews 1987; Yelland 2004A), whereas two studies that compared prolotherapy injections and spinal manipulation, exercise, and other co-interventions against control injections with or without those co-interventions reported benefits (Klein 1993; Ongley 1987). One of these latter studies reported a greater proportion achieving more than 50% improvement in pain or disability (Klein 1993), but not for mean pain or disability scores. The study with the most positive results in this review - and in the previous Cochrane review on injection treatments for back pain (Nelemans 2003) - demonstrated that prolotherapy injections combined with spinal manipulation, exercise, and other co-interventions are more effective than control injections combined with control co-interventions (Ongley 1987). However, this study failed to define the contribution of the prolotherapy injections to the effectiveness of treatment, making it impossible to attribute improvements solely to prolotherapy injections. Further research will be necessary to reconcile these conflicting findings.

The confounding effect of co-interventions raises important questions about the active component(s) of treatment in prolotherapy protocols. Of note were the significant and sustained reductions in pain and disability in both the intervention and control groups of studies with six or more injection treatments with at least 20 ml of solution, in contrast with the lack of response in the study with three injection treatments with 10 ml of solution. This raises the question of a dose-response phenomenon with injections in the treatment of chronic low-back pain. However, in the absence of a study with randomisation to different doses of treatment, it would be improper to extrapolate a dose-response phenomenon for injections. An alternative explanation of this phenomenon is that a non-specific effect of increased contact with a confident and caring practitioner led to the improvement.

In all studies, part of the response, in both treatment and control groups, may be attributed to 'regression to the mean', the natural history of the back complaint, or both. The phenomenon of 'regression to the mean' results from an increased motivation by people to join trials when their problem is at its worst, making spontaneous improvement more likely. The natural history of low-back pain that is as long-standing as that described in the included studies is unclear, although evidence from a longitudinal study suggests that the longer the back pain is consistently reported, the more likely it is to persist (Smedley 1998).

The mean duration of pain in the three studies (Klein 1993; Ongley 1987; Yelland 2004A) showing sustained improvement in both treatment and control groups exceeded eight years, making it difficult to attribute much of the observed improvement to natural history. These three studies were also the studies with multiple co-interventions including an initial infiltration of ligaments with local anaesthetic followed by manipulation under sedation, superficial skin injections of local anaesthetic, the injection of gluteal tender points with triamcinolone/lignocaine, encouragement to perform previously painful activities (activation), vitamin and mineral supplements and flexion/extension exercises.

One study specifically examined the effect of the flexion/extension exercises (Yelland 2004A) and found they were no more effective than normal activity. Ongley 1987, the only one to show a clear difference between treatment and control groups in all relevant outcomes, has been construed in another review as evidence of the efficacy of manipulation (van Tulder 1997). However, it fails to support the efficacy of manipulation just as it fails to support the efficacy of prolotherapy injections, because the intervention group differed from the control group in four respects - the pre-manipulation injections, the manipulation, the muscle tender point injections and the prolotherapy injections.

In response to these criticisms, a subsequent study by the same group of investigators attempted to make the glucose/glycerine/phenol components of the proliferant solution the only variable between treatment and control groups (Klein 1993). In their study, which involved six injection treatments, the prolotherapy group had a statistically significant advantage over the control group in the proportion of participants showing more than 50% reduction in scores from baseline to six months. However, there were no statistically significant differences between the groups in mean pain and disability scores unless those with hyper-irritable gluteal tender points were excluded from the analysis. In their discussion, Klein et al considered a gradual denervating effect of the phenol component as a possible mechanism of pain relief. However, Dechow 1999, which used the same components of the injection solution (but with only three injection treatments of 10 ml compared with six injections of 20 to 30 ml), showed no such response and no significant differences between groups. Yelland 2004A evaluated the effects of glucose/lignocaine injections and found they resulted in no greater improvement than saline injections. However, both the prolotherapy and control groups in this study demonstrated significant and sustained reductions in pain and disability scores over a two-year period. Similarly, Mathews 1987 compared phenol/dextrose/glycerine/procaine solution injections to procaine injections and found no difference in pain improvement between groups at three, six, or 12 months.

Collectively, these findings leave many questions unanswered about the efficacy and mechanism of action of prolotherapy injections. Klein 1993 considered a gradual denervating effect of the phenol component as a possible mechanism of pain relief. Alternatively, the beneficial effect could be attributed to the needles rather than the specific injection solution, by a counter-irritation effect. This has been shown elsewhere to inhibit pain in humans (Reinert 2000). Finally, the original hypothesis that reductions in pain and disability stem from strengthening of ligaments by prolotherapy injections has been neither confirmed nor refuted by the evidence provided by the five studies.

Prolotherapy injections are not without adverse events, with the majority of participants experiencing a transient increase in pain and stiffness and a few per cent with severe headaches suggestive of lumbar puncture. However, no serious or permanent adverse events were reported. Patients considering prolotherapy should

balance the possibility of transient adverse events against the potential benefits of this therapy.

## AUTHORS' CONCLUSIONS

### Implications for practice

Given the present studies, prolotherapy injections alone do not have evidence of a role in the treatment of chronic low-back pain. However, repeated ligament injections, irrespective of the solution used, may give prolonged partial relief of pain and disability as part of a multimodal treatment programme when combined with spinal manipulation and exercise. Transient increases in pain and stiffness are likely with such treatment, but serious adverse events are unlikely.

### Implications for research

Further experimental and clinical studies are needed to elucidate the effects of prolotherapy injections. These studies should also investigate the specific effects of the most common co-interventions to prolotherapy injections, such as superficial and deep injections

of local anaesthetic, manipulation and vitamin/mineral supplements. Further research is needed into the predictors of treatment success, so that it can be better targeted to those who may benefit from it.

Apart from one non-randomised pilot study (Yelland 2000), no studies have compared prolotherapy with non-injection therapies. There is a need for RCTs in this area. There is also a need for RCTs on prolotherapy for discogenic back pain confirmed by discography, following promising results from a pilot study of this treatment (Klein 2003).

## ACKNOWLEDGEMENTS

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Patrick DL, Deyo RA, Atlas SJ, Singer DE, Chapin A, Keller RB. Assessing health-related quality-of-life in patients with sciatica. *Spine* 1995;**20**:1899–909.

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**Yelland 2004C**

Yelland MJ, Del Mar C, Pirozzo S, Schoene ML. Prolotherapy injections for chronic low back pain: a systematic review. *Spine* 2004;**29**(19):2126–33.

\* Indicates the major publication for the study



## CHARACTERISTICS OF STUDIES

### Characteristics of included studies [ordered by study ID]

#### Dechow 1999

Methods	Randomized allocation by random number list. Double blind (participants and observers).
Participants	Departments of Rheumatology and Orthopaedic Surgery, East Dorset. 74 participants with chronic non-specific back pain, duration over 6 months. Experimental: mean age (SD) 46 (11), 20 males, median duration of pain >10 years, past compensation 17%, past back surgery 11%. Control group: mean age (SD) 46 (11), 20 males, median duration of pain >10 years, past compensation 5%, past back surgery 11%
Interventions	Experimental group (E) (n = 36): Weekly injections of lumbopelvic ligaments with glucose (12.5%) glycerine (12.5%) phenol (1.2%) 0.25% lignocaine, 10 ml in total. 3 injection treatments. Control group (C) (n = 38): Weekly injections of lumbopelvic ligaments with 0.5% lignocaine, 10 ml in total. 3 injection treatments.
Outcomes	Mean (SD) of outcomes at baseline and at 1, 3 and 6 months after intervention: VAS pain - (E) 5.3 (5.4), 5.2 (4.8), 5.1 (4.8), 5.2 (5.4); (C) 5.3 (5.5), 4.8 (4.6), 5.3 (5.2), 4.4 (6.2). Oswestry disability scale - (E) 34 (36), 34 (36), 36 (36), 36 (30); (C) 33 (37), 33 (37), 34 (37), 35 (37).
Notes	Methodological quality score 9/11.

#### *Risk of bias*

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Randomized allocation by random number list.
Allocation concealment?	Unclear	B - Unclear
Blinding? All outcomes - patients?	Yes	
Blinding? All outcomes - providers?	Unclear	Unclear from text.

**Dechow 1999** (Continued)

Blinding? All outcomes - outcome assessors?	Yes	
Incomplete outcome data addressed? All outcomes - drop-outs?	Yes	
Incomplete outcome data addressed? All outcomes - ITT analysis?	Yes	
Similarity of baseline characteristics?	Yes	
Co-interventions avoided or similar?	Yes	
Compliance acceptable?	Yes	
Timing outcome assessments similar?	Yes	

**Klein 1993**

Methods	Randomized allocation by random numbers table. Double blind (participants and observers).
Participants	Sansum Medical Clinic, Santa Barbara, California 80 participants with chronic non-specific low back pain, duration over 6 months. Experimental: mean age (SD) 44.6 (8.6), 21 males, years of pain (SD) 11.2 (7.9). Control group: mean age (SD) 43.5 (9.2), 20 males, years of pain (SD) 11.8 (10.1).
Interventions	Experimental group (E) (n = 39, due to withdrawal of 1 participant due to development of acute radiculopathy following an athletic injury): Weekly injections of lumbopelvic ligaments with glucose (12.5%) glycerine (12.5%) phenol (1.25%) 0.25% lignocaine, up to 30 ml in total. 6 injection treatments. Control group (C) (n = 40): Weekly injections of lumbopelvic ligaments with 0.25% lignocaine, up to 30 ml in total. 6 injection treatments. Both groups: Initial injection of lumbopelvic ligaments with 0.5% lignocaine followed by forceful manipulation and injection of gluteal tender points (if present) with triamcinolone/lignocaine; 200 flexion/extension exercises daily and 1 mile walk 5 times per week
Outcomes	Mean (SD) of outcomes at baseline and at 6 months after intervention 1. VAS pain: (E) 4.88 (1.30), 2.29 (1.67); (C) 4.56 (1.12), 2.85 (1.88) 2. Roland disability questionnaire added with 9 questions from Waddell's chronic disability index: (E) 9.36 (3.56), 4.04 (3.71) (C) 8.25 (3.26), 4.38 (4.05).

**Klein 1993** (Continued)

Notes	Methodological quality score 11/11	
<b>Risk of bias</b>		
<b>Item</b>	<b>Authors' judgement</b>	<b>Description</b>
Adequate sequence generation?	Yes	Randomized allocation by random numbers table.
Allocation concealment?	Yes	A - Adequate
Blinding? All outcomes - patients?	Yes	
Blinding? All outcomes - providers?	Yes	
Blinding? All outcomes - outcome assessors?	Yes	
Incomplete outcome data addressed? All outcomes - drop-outs?	Yes	
Incomplete outcome data addressed? All outcomes - ITT analysis?	Yes	
Similarity of baseline characteristics?	Yes	
Co-interventions avoided or similar?	Yes	
Compliance acceptable?	Yes	
Timing outcome assessments similar?	Yes	

**Mathews 1987**

Methods	Randomized allocation by unspecified predetermined system.
Participants	St Thomas Hospital, London, UK 22 participants with low backache and local tenderness, duration over 3 months. Experimental: median age 36, 4 males, median duration of pain 6 months. Control group: median age 34, 1 male, median duration of pain 24 months.

**Mathews 1987** (Continued)

Interventions	<p>Experimental group (E) (n=16): fortnightly injections of lumpopelvic ligaments with phenol 1.0%, dextrose 10%, glycerin 12%, procaine 0.3%, 10 mL in total</p> <p>Control group (C) (n=6): fortnightly injections of lumpopelvic tender spot with procaine (0.5%), 10 mL in total. 3 injection treatments.</p> <p>Both groups: All patients were given tablets of 500 mg paracetamol, were offered a corset, and instructions on posture and back care.</p>
Outcomes	<p>Numerical pain rating scale.</p> <p>Horizontal 6-point visual analogue scale at 1, 3, 6, and 12 months. (mean values not reported)</p>
Notes	Methodological quality score 6/11

***Risk of bias***

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Randomized allocation by unspecified predetermined system.
Allocation concealment?	Unclear	B - Unclear
Blinding? All outcomes - patients?	Yes	
Blinding? All outcomes - providers?	No	
Blinding? All outcomes - outcome assessors?	Yes	
Incomplete outcome data addressed? All outcomes - drop-outs?	Yes	
Incomplete outcome data addressed? All outcomes - ITT analysis?	Unclear	Unclear from text.
Similarity of baseline characteristics?	Yes	
Co-interventions avoided or similar?	Yes	
Compliance acceptable?	Unclear	Unclear from text.
Timing outcome assessments similar?	Unclear	Unclear from text.

**Ongley 1987**

Methods	Randomized allocation by random numbers table. Double blind (participants and observers).
Participants	Sansum Medical Clinic, Santa Barbara, California 81 participants with chronic non-specific low back pain, duration over 1 year. Experimental: mean age (range) 45 (23-70), 18 males, years of pain (range) 8.98 (1-30), 12 with radiation of pain into legs. Control group: mean age (range) 43 (23-70), 20 males, years of pain (range) 10.72 (1-35), 12 with radiation of pain into legs.
Interventions	Experimental group (E) (n = 40): Injection of lumbopelvic ligaments with 60 ml of 0.5% lignocaine followed by forceful manipulation and injection of gluteal tender points with triamcinolone/lignocaine. Then weekly injections of lumbopelvic ligaments with glucose (12.5%) glycerine (12.5%) phenol (1.25%) 0.25% lignocaine, 20 ml in total. 6 injection treatments. Controls (C) (n = 41): Injection of lumbopelvic ligaments with 10 ml of 0.5% lignocaine followed by non-forceful manipulation and injection of gluteal tender points with lignocaine. Then weekly injections of lumbopelvic ligaments with 0.9% saline, 20 ml in total. 6 injection treatments. Both groups: Encouraged to do previously painful activities and 150 flexion exercises daily.
Outcomes	Mean (SD) of outcomes at baseline and at 1, 3 and 6 months after intervention 1. VAS pain: (E) 3.78 (1.20), 2.13 (1.39), 1.77 (1.39), 1.50 (1.34); (C) 3.99 (1.22), 3.06 (1.86), 2.93 (1.60), 3.08 (1.77). 2. Roland disability questionnaire added with 9 questions from Waddell's chronic disability index: (E) 11.45 (5.25, 4.00 (3.90), 4.70 (4.62), 3.43 (4.61); (C) 11.82 (5.31); 8.37 (6.66), 8.49 (6.66), 8.29 (7.04)
Notes	Methodological quality score 10/11.

***Risk of bias***

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Randomized allocation by random numbers table.
Allocation concealment?	Yes	A - Adequate
Blinding? All outcomes - patients?	Yes	

**Ongley 1987** (Continued)

Blinding? All outcomes - providers?	Yes	
Blinding? All outcomes - outcome assessors?	Yes	
Incomplete outcome data addressed? All outcomes - drop-outs?	Yes	
Incomplete outcome data addressed? All outcomes - ITT analysis?	Yes	
Similarity of baseline characteristics?	Yes	
Co-interventions avoided or similar?	No	
Compliance acceptable?	Yes	
Timing outcome assessments similar?	Yes	

**Yelland 2004A**

Methods	Randomized allocation by random numbers table. Double blind (participants and observers).
Participants	Inala Health Centre General Practice, Brisbane, Australia 110 participants with chronic non-specific low back pain, duration over 6 months. Experimental: mean age (SD) 51.5 (10.6), 32 males, years of pain (SD) 14.8 (10.9), 24 with radiation of pain into legs. Control group: mean age (SD) 49.4 (10.4), 31 males, years of pain (SD) 13.8 (9.3), 23 with radiation of pain into legs.
Interventions	Experimental group (E) (n = 54): Fortnightly injections of lumbopelvic ligaments with glucose (20%) and lignocaine (0.2%), 10 to 30 ml, mean number of injection treatments 7 Control group (C) (n = 56): Fortnightly injections of lumbopelvic ligaments with saline (0.9%), 10 to 30 ml, mean number of injection treatments 7 Both groups: Superficial injections of lignocaine over deep injection points; oral vitamin C, zinc and manganese supplements daily. Randomly assigned to 40 flexion/extension exercises daily, experimental (n = 28), control (n = 27), or normal activity, experimental (n = 26), control (n = 29).

**Yelland 2004A** (Continued)

Outcomes	Mean (SD) of outcomes at baseline and 6, 12 and 24 months after commencing intervention. 1. VAS pain: (E) 51.9 (19.3), 31.4 (26.6), 33.1 (24.5), 32.8 (25.8); (C) 55.0 (20.7), 34.0 (27.5), 36.6 (27.9), 37.1 (24.6).	
Notes	Methodological quality score 11/11	
<b><i>Risk of bias</i></b>		
<b>Item</b>	<b>Authors' judgement</b>	<b>Description</b>
Adequate sequence generation?	Yes	
Allocation concealment?	Yes	A - Adequate
Blinding? All outcomes - patients?	Yes	Patients were blinded to the injection received but those randomly assigned to the daily exercise component could not be blinded to this activity. This does not seem to have affected the outcomes.
Blinding? All outcomes - providers?	Yes	The treating physician was blinded to the injection being given but was aware of the activity status of the patient (see p. 10). This does not seem to have affected the outcomes.
Blinding? All outcomes - outcome assessors?	Yes	Assessors were blinded to both injection and activity statuses.
Incomplete outcome data addressed? All outcomes - drop-outs?	Yes	
Incomplete outcome data addressed? All outcomes - ITT analysis?	Yes	
Similarity of baseline characteristics?	Yes	
Co-interventions avoided or similar?	Yes	
Compliance acceptable?	Yes	
Timing outcome assessments similar?	Yes	

### Characteristics of excluded studies *[ordered by study ID]*

Wilkinson 2003	20% of its participants had thoracic or cervical spinal pain and were not analysed separately. Study design involved crossover between experimental injections of bupivacaine/phenol/glycol and control injections of bupivacaine on the second treatment, making long term results uninterpretable.
Wilkinson 2005	Published report of previously unpublished Wilkinson 2003 study.
Yelland 2000	A multi-centre pilot study comparing the effectiveness of prolotherapy with a range of other conservative treatments for the treatment of chronic low back pain. Excluded as randomisation was not used.



## DATA AND ANALYSES

### Comparison 1. Prolotherapy vs control - Between group differences in proportions

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 >50% improvement from baseline	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 Pain at 3 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.2 Pain at 6 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.3 Pain at 12 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.4 Disability at 6 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

### Comparison 2. Prolotherapy vs control - Between group differences in means

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 pain or disability at 6 months	2		Std. Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.1 VAS pain at 6 months	2		Std. Mean Difference (IV, Fixed, 95% CI)	Not estimable
1.2 Disability at 6 months	2		Std. Mean Difference (IV, Fixed, 95% CI)	Not estimable

### Comparison 3. Prolotherapy+SMT+exercise+other vs control - Between group differences in proportions

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 >50% improvement from baseline	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 Pain or disability at 6 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.2 Disability at 6 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

#### Comparison 4. Prolotherapy+SMT+exercise+other vs control - Between group differences in means

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 pain or disability at 6 months	2		Std. Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.1 VAS pain at 6 months	2		Std. Mean Difference (IV, Fixed, 95% CI)	Not estimable
1.2 Pain grid at 6 months	2		Std. Mean Difference (IV, Fixed, 95% CI)	Not estimable
1.3 Disability at 6 months	2		Std. Mean Difference (IV, Fixed, 95% CI)	Not estimable

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## WHAT'S NEW

Last assessed as up-to-date: 23 October 2006.

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28 May 2008	Amended	Converted to new review format.
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## HISTORY

Protocol first published: Issue 1, 2003

Review first published: Issue 2, 2004

24 October 2006	New search has been performed	<p>Review updated Since it had been over 3 years since the original review was published, an update was performed.</p> <p>Authors The primary author for the update is Simon Dagenais from the Children's Hospital of Eastern Ontario Research Institute, the University of Ottawa, and CAM Research Institute. Simon is a scientist with research experience related to prolotherapy. The secondary author is Michael Yelland, the primary author on the original review.</p> <p>Search strategy The original search strategy was modified since it was brought to the author's attention that an additional randomized controlled trial related to prolotherapy for chronic low back pain had not been identified in the original review.</p>
24 October 2006	New citation required but conclusions have not changed	<p>The additional RCT was published by Mathews et al in 1987. No other trials were identified.</p> <p>The addition of this study did not substantially alter the review's main results or conclusions. However, results are now presented in two sections, one for the three studies that examined prolotherapy injections alone compared to control injections and one for the two studies that examined prolotherapy injections combined with spinal manipulation, exercise, and other co-interventions with control injections.</p>

## CONTRIBUTIONS OF AUTHORS

Simon Dagenais - lead author and content expert

Michael Yelland - co-author and content expert

Christopher Del Mar - co-author and non-content expert

Mark Schoene - consumer representative

## DECLARATIONS OF INTEREST

The lead author (SD) is a consultant to a nonprofit research organization involved in prolotherapy research. A co-author (MJY) was an author of one of the studies included in this review. He was not involved in the assessment of his trial for this review. Another author (MS) is a consumer representative for the Back Review Group.

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### External sources

- No sources of support supplied

## INDEX TERMS

### Medical Subject Headings (MeSH)

Chronic Disease; Combined Modality Therapy; Exercise Therapy; Glucose [administration & dosage]; Glycerol [administration & dosage]; Injections [adverse effects; \*methods]; Irritants [\*administration & dosage]; Lidocaine [administration & dosage]; Ligaments [\*drug effects]; Low Back Pain [\*drug therapy]; Phenol [administration & dosage]; Randomized Controlled Trials as Topic; Sclerotherapy [\*methods]; Therapeutics

### MeSH check words

Humans