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HEALTH ECONOMICS**
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EPIDURAL INJECTIONS FOR NEUROPATHIC PAIN

SUMMARY OF THE LITERATURE

**Canadian Pain Society Special Interest Group on
Neuropathic Pain**

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PREFACE

During 2005 and 2006, the Canadian Pain Society Special Interest Group on Neuropathic Pain (NeP SIG) produced a clinical practice guideline on the pharmacological management of neuropathic pain. In 2007 the NeP SIG began developing a guideline on the use of other interventions for neuropathic pain, such as spinal cord stimulation, deep brain stimulation, nerve blocks (sympathetic blocks; nerve and nerve root blocks; trigger point blocks, epidural blocks, and other spinal injections); psychological treatments such as cognitive behavioural therapy, relaxation, biofeedback, meditation, hypnosis; physical and occupational therapy modalities/interventions such as graded exposure to stimulation, mirror visual reprogramming, stretching, exercises, acupuncture, transcutaneous electrical nerve stimulation, transcranial magnetic stimulation, and multidisciplinary pain management programs. In 2007, a survey of NeP SIG members was undertaken to help prioritize this list of interventions. The results of the survey indicated that among the aggressive treatments used for neuropathic pain, the following four were considered high priority by the NeP SIG members.

- Epidural blocks
- Nerve blocks
- Intravenous infusions
- Spinal cord stimulation

In order to facilitate the development of the NeP SIG guideline on interventions for neuropathic pain, the Institute of Health Economics was recruited to assist in gathering and rating the quality of the available scientific literature on these four abovementioned interventions.

SCOPE OF THE PAPER

This report is the third of a set of four documents that provide a summary and critical appraisal of the available published evidence from the international medical literature regarding the use of epidural blocks, nerve blocks, intravenous infusions, and spinal cord stimulation for the treatment of neuropathic pain.

This literature summary was conducted according to a predefined methodology that was formulated in consultation with NeP SIG representatives. It does not represent a systematic review of the literature on epidural blocks for the treatment of neuropathic pain; thus, no firm conclusions are offered on the safety or effectiveness of this intervention. In addition, the evidence was only summarized and no attempt was made to assess the veracity of the information contained within the included studies.

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METHODS

Inclusion criteria

Types of studies

Systematic reviews (SRs), randomized controlled trials (RCTs), and clinical practice guidelines (CPGs) were included.

Systematic reviews

An article was deemed to be a SR if it met all of the following criteria as defined by Cook et al.¹

- 1) Focused clinical question.
- 2) Explicit search strategy.
- 3) Use of explicit, reproducible, and uniformly applied criteria for article selection.
- 4) Critical appraisal of the included studies.
- 5) Qualitative or quantitative data synthesis.

Randomized and quasi-randomized controlled trials

RCTs were included. Trials using a quasi-random method of treatment allocation (quasi-randomized controlled trials), such as date of birth, day of the week, or medical record number, were also included.

Clinical practice guidelines

CPGs are most commonly defined as “systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances”.² For a CPG to be valid, the evidence supporting its recommendations must be cited.^{2,3} Therefore, an article was deemed to be a CPG if it met all of the following criteria.

- 1) It contained the word ‘guideline’ or ‘recommendation’ in its title or introduction, or contained recommendations on managing patients with neuropathic pain in the form of advice or instructions.⁴
- 2) It was developed by at least two authors.
- 3) It was evidence-based.

CPGs that were not evidence-based, such as consensus statements that contained recommendations based only on expert opinion, were excluded.

Only CPGs formulated in countries with developed market economies were included since the health status, cultural norms, access to health care, and disease burden of individuals from countries with transitional or developing economies were likely to be too different from those of Canada to be clinically relevant. Countries deemed to have developed economies, as defined by the United Nations, were as follows: Australia, Canada, Japan, New Zealand, the United States of America, and Europe (except for

Albania, Bulgaria, Czech Republic, Hungary, Poland, Romania, Slovakia, Bosnia and Herzegovina, Croatia, Slovenia, the former Yugoslav Republic of Macedonia, Yugoslavia, Estonia, Latvia, Lithuania, Belarus, the Republic of Moldova, the Russian Federation, and Ukraine).⁵

Participants

Data were collected on adult patients (18 years of age or older) with a peripheral or central neuropathic pain condition of any duration. Studies that referred to ‘patients’ or ‘adult patients’ without providing a specific age range were also included. However, any study that clearly included patients under the age of 18 years was excluded.

Patients with cancer pain were excluded unless they had a defined post-surgical pain syndrome with neuropathic contribution, such as post-mastectomy pain. Patients with visceral pain, migraine, headache, fibromyalgia, or ischemic pain were excluded. Studies that included data for patients with neuropathic pain and those with non-neuropathic pain conditions were excluded unless the data subset for the patients with neuropathic pain could be separated from the aggregate data.

Index Intervention

Epidural injection of any drug via a caudal, interlaminar, or transforaminal approach for treating neuropathic pain. Diagnostic epidural injections were not included. Given the overlap between diagnostic and non-diagnostic epidural injections, a specific definition for diagnostic epidural injections was not used. Epidural injections were considered diagnostic if they were examined using a diagnostic study design, or if the study specifically stated that the epidural injection was used for diagnostic purposes. All reports of epidural injections that used an interventional study design were included, regardless of the length of follow up or number of injections administered.

Comparative intervention

Any medical, mechanical, or surgical intervention designed to treat patients with neuropathic pain. Placebo and no treatment comparisons were also included. Studies that compared technical aspects of epidural injections were excluded.

Literature search strategy

The medical literature was searched to identify relevant, publicly available SRs, RCTs, and CPGs published in English from January 1997 to May 2008 (see Appendix A for the search terms and databases used). Although the bibliographies of articles retrieved in hard copy form were not systematically searched for relevant references that may have been missed in the database searches (pearling), any additional relevant references accidentally uncovered during the examination of these full-text articles were retrieved.

Literature selection process

Study selection was conducted by one reviewer. Articles were excluded that, on the basis of their abstract, clearly did not meet the inclusion criteria. Copies of the full text of potentially eligible studies were retrieved. In some cases, when the full text of the article was retrieved, closer examination revealed that it did not meet the inclusion criteria. Consequently, these papers were excluded (Appendix B).

Systematic reviews

In cases where multiple SRs on a single topic were identified that were of the same quality and had identical comparators and patient populations, only the most recently published SR was included. In cases where a SR described a particular subgroup of neuropathic pain patients (e.g. postherpetic neuropathy, radiculopathy) or used different or additional comparators to those of the most recent SR, both SRs were included.

Randomized and quasi-randomized controlled trials

RCTs or quasi-RCTs that covered the same interventions and patient groups detailed in the included SRs and were published after the end date of the search strategy of the included SRs were also included. Thus, the intent was only to update the included SRs. RCTs on conditions or interventions that were not within the scope of the included SRs were excluded. When overlapping patient groups were reported in RCTs, only the paper quoting the most complete data set was used.

Clinical practice guidelines

In cases where multiple CPGs on a single topic were identified that were of the same quality and had identical comparators and patient populations, only the most recently published CPG was included. In cases where a CPG described a particular subgroup of neuropathic pain patients (e.g. postherpetic neuropathy, radiculopathy) or used different or additional comparators to those of the most recent CPG, both CPGs were included.

In cases where multiple CPGs on a single topic were identified that had identical comparators but were of differing quality, only the highest quality CPG was included if it was also the most recent. If the highest quality CPG was not the most recent, then both the highest quality CPG and the most current CPG, regardless of its quality, were included.

Assessment methods

Study methodology appraisal

The included studies were assessed with respect to various aspects of methodology and reporting using checklists specific for each particular study type (Appendices C, D, and E). The quality assessments were undertaken independently by two reviewers. The checklists were operationalized by constructing dictionaries that explained each criterion. The two reviewers discussed the dictionaries with respect to the interpretation of questions prior to assessing the studies. Critical appraisal results for all included studies are tabulated in Appendices C, D, and E.

Systematic reviews

The included SRs were assessed using a checklist developed in-house that was adapted from a number of sources (Appendix C).⁶⁻⁹ This tool was chosen because it is more detailed and less subjective than other commonly used tools, such as the AMSTAR¹⁰ and Oxman and Guyatt¹¹ checklists, and the reviewers were very experienced in its use. Any disagreements in scoring between the two reviewers that could not be resolved by discussion were referred to a third reviewer for mediation until consensus was reached.

The quality of SRs was assessed according to how well their methods excluded bias and confounding by examining: the search strategy used; how the data extraction, quality assessment of the included studies, and data analysis/synthesis were conducted; and whether the conclusions of the review match the results. Thus, the quality of the SR was rated numerically with respect to six quality subsections (grey boxes in checklist) as follows:

Good – six criteria met (✓✓✓✓✓✓), or five criteria met and one criterion ‘unclear’ (✓✓✓✓✓?).

Average – one criterion not met (✓✓✓✓✓×), or one criterion not met and one criterion ‘unclear’ (✓✓✓✓×?), or two criteria ‘unclear’ (✓✓✓✓??).

Poor – at least two criteria not met (✓✓✓✓××).

Randomized controlled trials

The included RCTs were assessed using the criteria list recommended in the method guidelines of the Cochrane Back Review Group for SRs¹² (Appendix D). This list has been used in a number of SRs¹³⁻¹⁵ in the field of chronic pain and includes all the criteria from the lists generated by Jadad et al.¹⁶ and Verhagen et al.¹⁷. It consists of internal and external validity criteria, as well as statistical criteria. The list was modified by removing items E (Was the care provider blinded?) and G (Was compliance acceptable?), since blinding of the care provider is not always possible for some of the neuropathic pain treatments being considered and compliance is not a relevant issue when epidural injection is the sole treatment. In addition, some instructions were reworded or supplemented with more detailed criteria descriptions from Downs and Black¹⁸. A simple nominal rating scale was used such that the studies were scored as positive (yes), negative (no), or unclear (don’t know) for each quality criterion. Any disagreements in scoring between the two reviewers that could not be resolved by discussion were referred to a third reviewer for mediation until consensus was reached.

For descriptive purposes, the included RCTs were referred to as being good, moderate, or poor quality with respect to internal and external validity according to the total number of criteria met as follows:

- Internal validity (total number of criteria = 9) – good (≥ 7 criteria met), moderate (between 4 and 6 criteria met), poor (< 4 criteria met);
- External validity (total number of criteria = 6) – good (≥ 5 criteria met), moderate (3 or 4 criteria met), poor (< 3 criteria met).

Clinical practice guidelines

The included CPGs were assessed using the Appraisal of Guidelines for Research and Evaluation (AGREE) instrument¹⁹ (Appendix E). The AGREE instrument is an internationally developed, generic tool that is validated, transparent, and widely accepted, with satisfactory reliability for most domains. The instrument has 23 key items organized into six domains: scope and purpose (items 1-3); stakeholder involvement (items 4-7); rigor of development (items 8-14); clarity of presentation (items 15-18); applicability (items 19-21); and editorial independence (items 22-23).

The tool is accompanied by a detailed User Guide that explains how to score the 23 items. Each guideline is assessed using a 4-point scale (ranging from 4 = “strongly agree” to 1 = “strongly disagree”) to rate each of the 23 items. These scores are then combined for each of the six domains and converted into standardized domain scores according to the following formula:

$$\text{Standardized domain score (\%)} = \frac{\text{obtained score} - \text{minimum possible score}}{\text{maximum possible score} - \text{minimum possible score}} \times 100$$

The six domain scores are independent and cannot be combined into a single score. Instead, appraisers can provide an overall assessment of the guideline according to the following categories:

- Strongly recommended;
- Recommended (with provisos or alterations);
- Would not be recommended;
- Unsure.

Two modifications were made to the AGREE tool to reduce the ambiguity and subjectivity associated with item scoring, and to enable the differentiation of good from poor quality guidelines.

- 1) A detailed set of instructions, or dictionary, based on the AGREE guidance was constructed using logical operators (AND, OR, NOT) to quantify what constitutes a score of 4, 3, 2, or 1 for each of the 23 items.
- 2) Seven “essential” criteria were identified for categorizing guidelines as good, moderate, or poor quality.²⁰
 - Item 8: Systematic search conducted
 - Item 10: Methods used to formulate recommendations described
 - Item 12: Link between recommendations and evidence
 - Item 13: External review by experts
 - Item 15: Specific, unambiguous recommendations
 - Item 22: Editorially independent from funder
 - Item 23: Conflicts of interest reported

The scores from the two reviewers were combined into an average quality score (maximum possible of 28 [7x4]), which was then rated as follows:

Good –score of 22 to 28;

Average –score of 15 to 21;

Poor –score 0 to 14.

Outcome measures and data extraction

Study profile information, as well as relevant safety and efficacy data, was extracted by one reviewer using standardized data extraction forms developed *a priori*.

SUMMARY OF THE LITERATURE

Fifty-eight studies were identified that potentially met the inclusion criteria. On closer examination of the full text article, 46 of these studies were excluded and the reasons documented (Appendix B). Three SRs and four CPGs were included (Table 1). Five RCTs that were published after the end date of the search strategy of the included SR, covered the same interventions and patient groups detailed in the included SRs, and met the inclusion criteria were also included. When overlapping patient groups were reported in the RCTs, only the paper quoting the most complete data set was used.

Details of one potentially relevant RCT that could not be retrieved in hard copy form before the report deadline (March 31, 2009) are listed in Appendix B, Table B.2.

Study profiles of the included studies are summarized in Tables 2 to 4. The relevant safety and efficacy data extracted from each of the included studies are tabulated in Tables 5 to 7.

Table 1: Summary of included studies

Study	Year	Quality Rating	Pain Condition/Treatment Comparisons
Systematic Reviews			
Abdi et al. ²¹	2007	Average (4/6)	Chronic spinal pain of at least 3 months' duration
Forouzanfar et al. ²²	2002	Average (4/6)	Complex regional pain syndrome type I or reflex sympathetic dystrophy
Kumar et al. ²³	2004	Poor (3/6)	Postherpetic neuralgia
Randomized Controlled Trials			
Ackerman and Ahmad ²⁴	2007	<i>Internal validity</i> Good (8/9) <i>External validity</i> Good (5/6)	Lumbar radicular pain Caudal epidural (n=30) vs interlaminar epidural (n=30) vs transforaminal epidural (n=30)
Dincer et al. ²⁵	2007	<i>Internal validity</i> Good (7/9) <i>External validity</i> Moderate (4/6)	Subacute/chronic low back pain with radicular pain Caudal epidural plus therapeutic exercise (n=34) vs NSAIDs plus exercise (n=30)
Owlia et al. ²⁶	2007	<i>Internal validity</i> Moderate (6/9) <i>External validity</i> Good (5/6)	Lumbar radicular pain >2 weeks' duration Epidural injection 80 mg (n=43) vs 40 mg (n=41) methylprednisolone
Pasqualucci et al. ²⁷	2007	<i>Internal validity</i> Poor (3/9) <i>External validity</i> Good (5/6)	Acute or chronic unilateral cervicobrachial pain Single epidural injection (n=80) vs continuous epidural infusion (n=80)

Table 1: Summary of included studies (cont'd)

Study	Year	Quality Rating	Pain Condition/Treatment Comparisons
Randomized Controlled Trials (cont'd)			
Zambello et al. ²⁸	2006	<i>Internal validity</i> Moderate (6/9) <i>External validity</i> Moderate (3/6)	Lumbar radicular pain Epidural steroid injection (n=171) versus paravertebral O ₂ O ₃ injection (n=180)
Clinical Practice Guidelines			
Boswell et al. ²⁹	2007	Average (20.5/28)	Chronic spinal pain
Dubinsky et al. ³⁰	2004	Average (17/28)	Postherpetic neuralgia of at least 8 weeks' duration
Hunter Integrated Pain Service ³¹	2009	Poor (10/28)	Neuropathic pain, spinal and radicular pain, tissue ischemia pain, cancer pain
North American Spine Society ³²	2007	Good (23.5/28)	Degenerative lumbar spinal stenosis

NSAIDs - non-steroidal anti-inflammatory drugs

STUDY PROFILES – SYSTEMATIC REVIEWS

Table 2: Study profiles for *systematic reviews* on epidural injections for neuropathic pain

Systematic Review	Population	Selection Criteria/Outcomes	Methods
<p>Abdi et al. (2007)²¹</p> <p>Objective: To evaluate the effect of various types of epidural steroid injections in managing various types of chronic spinal pain in the neck and low back regions.</p> <p>Financial support: None.</p> <p>Conflict of interest: None.</p>	<p>Total number: <i>Interlaminar epidural:</i> Cervical - 2 randomized controlled trials (RCTs); Lumbar – 11 RCTs <i>Transforaminal epidural:</i> Cervical – 1 RCT, 2 prospective observational studies, 1 retrospective observational study; Lumbar – 6 RCTs, 6 prospective observational studies, 6 retrospective observational studies <i>Caudal epidural:</i> 8 RCTs, 5 prospective observational studies.</p> <p>Age: Not stated.</p> <p>Included conditions: Chronic spinal pain of at least 3 months' duration.</p> <p>Excluded conditions: None stated.</p>	<p>Intended comparators: Placebo, any active treatment.</p> <p>Study inclusion criteria: Randomized and non-randomized studies and reports of complications. Included studies must meet an algorithmic criterion and should answer positive questions (at least partially) in all three categories.³³ If there were at least 10 RCTs for a particular injection type, no observational studies were included.</p> <p>Study exclusion criteria: Outcome evaluations of <3 months.</p> <p>Outcomes measured: <i>Primary:</i> pain relief <i>Secondary:</i> functional or psychological improvement, return to work, complications.</p>	<p>Literature search: <u>Time period:</u> From January 1966 to October 2006. <u>Limits:</u> English language publications only. <u>Databases:</u> PubMed, EMBASE, Web of Science. <u>Other sources:</u> Additional reports were identified from reference lists of known primary and review articles, as well as abstracts from scientific meetings within the last two years.</p> <p>Data extraction: A standardized list was used to guide data extraction. Further details not reported.</p> <p>Appraisal of study quality: The quality of individual studies was assessed using criteria from the Agency for Healthcare Research and Quality³⁴ and the Cochrane Musculoskeletal Group¹².</p> <p>Data analysis: Qualitative.</p> <p>Conclusions supported by results: Yes.</p>

Table 2: Study profiles for systematic reviews on epidural injections for neuropathic pain (cont'd)

Systematic Review	Population	Selection Criteria/Outcomes	Methods
<p>Forouzanfar et al. (2002)²²</p> <p>Objective: To ascertain appropriate therapies for complex regional pain syndrome type I based on a systematic review of the literature.</p> <p>Financial support: Not reported.</p> <p>Conflict of interest: Not reported.</p>	<p>Total number: Epidural clonidine: n = 26 (one randomized controlled trial (RCT))</p> <p>Age: Not stated.</p> <p>Included conditions: Complex regional pain syndrome type I or reflex sympathetic dystrophy.</p> <p>Excluded conditions: None stated.</p>	<p>Intended comparators: Placebo, any active treatment.</p> <p>Study inclusion criteria: Double-blinded or single-blinded RCTs using pain intensity as the main outcome measure.</p> <p>Study exclusion criteria: Non-randomized studies, case reports, and clinical observations.</p> <p>Outcomes measured: Pain intensity.</p>	<p>Literature search: <u>Time period:</u> From January 1966 to June 2000. <u>Limits:</u> Dutch, German, and English language publications only. <u>Databases:</u> PubMed, MEDLINE, EMBASE, <i>The Cochrane Library</i>. <u>Other sources:</u> Additional reports were identified from reference lists of retrieved studies and review articles.</p> <p>Data extraction: Method not reported.</p> <p>Appraisal of study quality: RCTs assessed independently by two reviewers with De Vet et al. (1997)³⁵ scale. Disagreements were resolved by consensus. Unresolved disagreements were referred to a third reviewer.</p> <p>Data analysis: Qualitative.</p> <p>Conclusions supported by results: Yes.</p>
<p>Kumar et al. (2004)²³</p> <p>Objective: To evaluate and synthesize existing evidence for using nerve blocks with various injectants in treating pain of <i>Herpes zoster</i> and postherpetic neuralgia.</p> <p>Financial support: Supported in part by the University of Cincinnati, Cincinnati, Ohio, USA.</p> <p>Conflict of interest: Not reported.</p>	<p>Total number: Epidural local anaesthetic plus steroid: n = 91 (two case series studies)</p> <p>Age: Not stated.</p> <p>Included conditions: <i>Herpes zoster</i> and postherpetic neuralgia.</p> <p>Excluded conditions: None stated.</p>	<p>Intended comparators: Placebo, any active treatment.</p> <p>Study inclusion criteria: RCTs, cohort studies, case-control studies, case series studies.</p> <p>Study exclusion criteria: Review articles, expert opinion, case reports; studies looking exclusively at other peripheral nerve blocks and local infiltrations.</p> <p>Outcomes measured: Pain relief.</p>	<p>Literature search: <u>Time period:</u> From 1966 to 2001. <u>Limits:</u> English language publications only. <u>Databases:</u> MEDLINE, EMBASE, Cochrane Clinical Trials databases. <u>Other sources:</u> Manual search of journal articles.</p> <p>Data extraction: Method not reported.</p> <p>Appraisal of study quality: The quality of individual studies was assessed using Methodologic Quality Score criteria.³⁶ Grades of recommendation were then made in accordance with the Oxford Centre for Evidence-Based Medicine.³⁷</p> <p>Data analysis: Semi-quantitative.</p> <p>Conclusions supported by results: Yes.</p>

STUDY PROFILES – RANDOMIZED CONTROLLED TRIALS

Table 3: Study profiles for *randomized controlled trials* on epidural injections for neuropathic pain

Authors/Study Details	Intervention/Outcome Measures	Study Design/Execution
<p>Ackerman and Ahmad (2007)²⁴ United States <u>Study design:</u> Prospective randomized, concurrently controlled trial. <u>Follow-up:</u> 2, 12, and 24 weeks after final injection. <u>Study period:</u> Not stated. <u>Setting:</u> Not stated. <u>Financial support:</u> Not stated.</p>	<p>Caudal epidural; n=30 Interlaminar epidural; n=30 Transforaminal epidural; n=30</p> <p>Caudal epidural <u>Procedure:</u> With the patient in a prone position, the L5-S1 interspace was identified by fluoroscopy. A 22 gauge Tuohy needle (bevel in cranial direction) was directed into the epidural space with fluoroscopic guidance. Epidurography was used to confirm dispersion of injectant. <u>Injectant:</u> 3 mL of isohexol 300 followed by 4 mg (1 mL) of preservative-free saline with 40 mg of triamincinolone.</p> <p>Interlaminar epidural <u>Procedure:</u> With the patient in a prone position, a 22 gauge Tuohy needle was guided 1.5 cm into the epidural space from the sacrococcygeal membrane. Epidurography was used to confirm dispersion of injectant. <u>Injectant:</u> 3 mL of isohexol 300 injected into the epidural space. After proper needle position was confirmed, 19 mL of preservative-free saline with 40 mg (1 mL) triamincinolone.</p> <p>Transforaminal epidural <u>Procedure:</u> With the patient in a prone position, the L5 transverse process on the side of the radicular pain was identified with fluoroscopy. A 22 gauge Tuohy needle was guided to the transverse process of the 5th lumbar vertebra with fluoroscopic guidance. The needle was withdrawn slightly and advanced medially into the posterior aspect of the L5-S1 foramina. Epidurography was used to confirm dispersion of injectant. <u>Injectant:</u> 3 mL of isohexol 300 was injected. After proper needle position was confirmed, 4 mL of preservative-free saline with 40 mg (1 mL) triamincinolone. Patients were excluded if contrast material spread through the foramina at the level of the disc herniation because these patients would experience postganglion nerve root injection rather than transforaminal epidural injection.</p> <p>Caudal, interlaminar & transforaminal groups <u>Adjunct medications:</u> Intravenous midazolam 2 mg and 50 µmol of fentanyl were used during each procedure. Each patient was prescribed tizanidine (6 mg to 12 mg/24 hours) as needed for muscle spasms, celecoxib as needed for pain, and amitriptyline. <u>Subsequent treatments:</u> If a patient had complete or no pain relief, no further injection therapy was done. Otherwise, a repeat epidural injection was performed. <u>Outcome measures:</u> Contrast dispersion patterns; pain intensity (visual analog scale); pain relief; Oswestry Low Back Pain Scale; Beck depression score.</p> <p>There was no statistically significant difference between the groups with respect to age, sex distribution, body surface area, or duration of symptoms (P>0.05).</p>	<p><u>Method of randomization:</u> Computer-generated randomization sequence. <u>Time of randomization:</u> Not reported. <u>Method of allocation concealment:</u> Not reported. <u>Details of blinding:</u> Outcome assessors blinded to the type of injection the patients received. Patients unlikely to know what treatment they received. <u>Participation rate:</u> 70.9% (202/285). <u>Eligibility rate for study:</u> 58.5% (285/487). <u>Intention-to-treat analysis:</u> By default as there were no dropouts or withdrawals. <u>Crossovers:</u> None occurred. <u>Provider:</u> Not reported. <u>Assessor details:</u> A physician trained in epidurogram interpretation evaluated each patient's postprocedure epidurogram. Details about other outcome assessors were not reported. <u>Inclusion criteria:</u> Radicular pain consistent with the S1 dermatomal distribution and a diagnosis of L5-S1 disc herniation documented by magnetic resonance imaging and electromyographic evidence of S1 nerve root involvement; pain intensity score >7 on a visual analog scale (range 0 to 10). <u>Exclusion criteria:</u> Pregnancy, allergies to steroids, steroid use within 3 weeks to participating in the study, history of bleeding, infection, use of anticoagulants, allergies to the adjunct medications used in the study. <u>Conclusions supported by results:</u> Yes.</p>

Table 3: Study profiles for randomized controlled trials on epidural injections for neuropathic pain (cont'd)

Authors/Study Details	Intervention/Outcome Measures	Study Design/Execution
<p>Dincer et al. (2007)²⁵ Turkey <u>Study design:</u> Prospective randomized, concurrently controlled trial. <u>Follow-up:</u> 15 days, 1 month, and 3 months after injection. <u>Study period:</u> Not stated. <u>Setting:</u> Not stated. <u>Financial support:</u> Not stated.</p>	<p>Caudal epidural plus therapeutic exercise; n=34 Non-steroidal anti-inflammatory drugs (NSAIDs) plus therapeutic exercise; n=30 Caudal epidural <u>Procedure:</u> With the patient in a prone position, a 20 gauge needle was introduced through the sacral hiatus to the epidural space. Correct needle position was determined by asking patients for tingling or numbness of their lower extremities after approximately 5 mL to 6 mL of injectant was administered. When the needle was correctly placed, aspiration was performed to exclude venous or dural puncture. <u>Injectant:</u> 20 mL solution containing 40 mg (1 mL) of methylprednisolone acetate, 8 mg (2 mL) of dexamethasone phosphate, 7 mL of 2% prilocaine, and 10 mL of 0.9% NaCl. NSAIDs Diclophenac sodium 75 mg sustained release pills twice daily with 12 hour intervals were prescribed. Patients were recommended to take the pills continuously for 14 days. Caudal epidural & NSAID groups <u>Therapeutic exercise:</u> Patients were instructed to perform lumbopelvic mobilization and lumbar stabilization exercises daily. <u>Adjunct medications:</u> After day 15, patients were permitted to use paracetamol. No other treatments were authorized. <u>Subsequent treatments:</u> None. <u>Outcome measures:</u> Pain intensity (visual analog scale); straight leg raise test result; Oswestry Low Back Pain disability questionnaire. There was no statistically significant difference between the groups with respect to age, straight leg raise test result, pain intensity, or Oswestry score (P>0.05).</p>	<p><u>Method of randomization:</u> Not reported. <u>Time of randomization:</u> Not reported. <u>Method of allocation concealment:</u> Not reported. <u>Details of blinding:</u> Outcome assessors were blinded to the type of treatment the patients received. It was not possible to blind patients to treatment allocation. <u>Participation rate:</u> Not reported. <u>Eligibility rate for study:</u> Not reported. <u>Intention-to-treat analysis:</u> By default as there were no dropouts or withdrawals. <u>Crossovers:</u> None occurred. <u>Provider:</u> The same physiatrist performed all injections. <u>Assessor details:</u> An independent physiatrist unaware of treatment allocation conducted the clinical measurements and evaluations. <u>Inclusion criteria:</u> Subacute or chronic low back pain with radicular pain lasting from 30 days to 12 months; pain intensity score >4 on a visual analog scale (range 0 to 10). <u>Exclusion criteria:</u> Patients with spondyloarthropathies, spondylolisthesis, congenital lumbar vertebral anomalies, lumbar spinal stenosis, systemic infectious disease, local skin infection, vertebral operation history, cardiopulmonary disease, any chronic disease, extruded or sequestered disc herniation. <u>Conclusions supported by results:</u> Yes.</p>

Table 3: Study profiles for randomized controlled trials on epidural injections for neuropathic pain (cont'd)

Authors/Study Details	Intervention/Outcome Measures	Study Design/Execution
<p>Owlia et al. (2007)²⁶ Iran <u>Study design:</u> Prospective randomized, concurrently controlled trial. <u>Follow-up:</u> 2 weeks, 1 month, and 3 months after injection. <u>Study period:</u> April 2003 to March 2005. <u>Setting:</u> Rheumatology clinics. <u>Financial support:</u> Not stated.</p>	<p>Epidural injection (80 mg methylprednisolone); n=43 Epidural injection (40 mg methylprednisolone); n=41 Epidural injection (80 mg) <u>Injectant:</u> 80 mg of methylprednisolone diluted in 8 mL to 10 mL of normal saline. Epidural injection (40 mg) <u>Injectant:</u> 40 mg of methylprednisolone diluted in 8 mL to 10 mL of normal saline. Epidural 80 mg & 40 mg groups <u>Procedure:</u> With the patient in a lateral recumbent position, an 18 gauge Tuohy needle was inserted into the epidural space at the L4-L5 level. Needle position was confirmed after sensory or even motor evidence of the proper injection site was achieved following injection of 2 mL to 4 mL of 2% lidocaine. Epidurography was used to confirm access of the injectant to the lumbar epidural space. <u>Adjunct medications:</u> Patients were allowed to have acetaminophen 500 mg as rescue medication as needed. <u>Subsequent treatments:</u> All patients had rehabilitative management for at least 2 weeks after injection. <u>Outcome measures:</u> Pain intensity (visual analog scale); adverse effects. There was no statistically significant difference between the groups with respect to age, sex distribution, body mass index, duration of symptoms, limitation in daily activity, straight leg raise test result, pain radiation, claudication, Achilles tendon reflex, muscle force, or sensory deficit (P>0.05).</p>	<p><u>Method of randomization:</u> Not reported. <u>Time of randomization:</u> Not reported. <u>Method of allocation concealment:</u> Not reported. <u>Details of blinding:</u> Not reported. Patients were unlikely to know what treatment they received. <u>Participation rate:</u> Not reported. <u>Eligibility rate for study:</u> Not reported. <u>Intention-to-treat analysis:</u> By default as there were no dropouts or withdrawals. <u>Crossovers:</u> None occurred. <u>Provider:</u> The same operator performed all injections. <u>Assessor details:</u> Not reported. <u>Inclusion criteria:</u> Patients with lumbar radicular pain for more than 2 weeks after ruling out infectious or neoplastic causes, and who had magnetic resonance imaging of proven intervertebral disc herniation and refractory pain even after a full dose of NSAIDs, opioids, and physical therapies for more than 2 weeks. <u>Exclusion criteria:</u> Patients who were reluctant or non-compliant; signs or symptoms denoting an underlying infection, bleeding tendency, or malignancy; previous back surgery and radiologically proven facet syndrome. <u>Conclusions supported by results:</u> Yes.</p>

Table 3: Study profiles for randomized controlled trials on epidural injections for neuropathic pain (cont'd)

Authors/Study Details	Intervention/Outcome Measures	Study Design/Execution
<p>Pasqualucci et al. (2007)²⁷ Italy</p> <p><u>Study design:</u> Prospective randomized, concurrently controlled trial.</p> <p><u>Follow-up:</u> 24 to 36 hours after each treatment cycle; 1 week, 1 month, and 6 months after the end of treatment.</p> <p><u>Study period:</u> Not stated.</p> <p><u>Setting:</u> University medical centres.</p> <p><u>Financial support:</u> Department of Anesthesiology and Intensive Care, University of Pavia, Italy.</p>	<p>Group A (pain onset 15 to 30 days); n=40</p> <p>Group B (pain onset 31 to 60 days); n=40</p> <p>Group C (pain onset 61 to 180 days); n=40</p> <p>Group D (pain onset >180 days); n=40</p> <p>Patients in each of the four groups were randomly allocated to single epidural injection (n=20) or continuous epidural infusion (n=20)</p> <p>Single epidural injection <u>Procedure:</u> Epidural injections administered every 4 to 5 days using the hanging drop technique via a 16 to 18 gauge Tuohy needle introduced at the level of the C6-C7, C7-T1, or T1-T2 intervertebral space. <u>Injectant:</u> The first block consisted of 6 mL of 0.25% bupivacaine with epinephrine (1:200,000) and 80 mg of methylprednisolone acetate. The second block, after 4 to 5 days, consisted of 6 mL of 0.25% bupivacaine with epinephrine (1:200,000) and 40 mg of methylprednisolone acetate. The third block, after another 4 to 5 days, used the same drugs as the second block. <u>Subsequent treatments:</u> None of the patients had surgical interventions during the follow-up period. Treatment was suspended upon reaching pain control $\geq 80\%$ for more than 24 to 36 hours. If this was not reached, the treatment was continued up to a total of 9 blocks.</p> <p>Continuous epidural <u>Procedure:</u> Placement of an epidural catheter using the hanging drop technique via a 16 to 18 gauge Tuohy needle introduced at the level of the C6-C7, C7-T1, or T1-T2 intervertebral space and inserted upwards for approximately 3 to 5 cm. Positioning was verified by direct fluoroscopy and with a lidocaine test. <u>Injectant:</u> 6 mL of 0.25% bupivacaine with epinephrine (1:200,000) and 80 mg of methylprednisolone acetate was administered. After 12 to 24 hours, 6 mL of 0.25% bupivacaine was administered every 6, 12, or 24 hours with the timing dependent on ensuring pain-free periods of 24 hours. Methylprednisolone acetate (40 mg) was administered every 4 to 5 days via the catheter. <u>Subsequent treatments:</u> None of the patients had surgical interventions during the follow-up period. Treatment was suspended upon reaching pain control $\geq 80\%$ for more than 24 to 36 hours after the first 10 days of administration. If this was not reached, the cycle of treatment was repeated up to a total treatment period of 30 days.</p>	<p><u>Method of randomization:</u> Not reported.</p> <p><u>Time of randomization:</u> Not reported.</p> <p><u>Method of allocation concealment:</u> Not reported.</p> <p><u>Details of blinding:</u> Not reported. Patients were unlikely to know what treatment they received.</p> <p><u>Participation rate:</u> Not reported.</p> <p><u>Eligibility rate for study:</u> Not reported.</p> <p><u>Intention-to-treat analysis:</u> Per protocol analysis as 19 patients withdrew, dropped out, or were excluded.</p> <p><u>Crossovers:</u> None occurred.</p> <p><u>Provider:</u> In each of the four university medical centres, one operator administered the blocks, placed the catheter, and arranged the drugs.</p> <p><u>Assessor details:</u> In each of the four university medical centres, a second operator evaluated the patients, but it was unclear if the second operator was blinded to treatment allocation.</p> <p><u>Inclusion criteria:</u> Unilateral cervicobrachial pain (acute or chronic in the area of the last four cervical nerves and the first thoracic nerve) with or without sensory and motor symptoms in the same distribution of pain with a clinical and historical evaluation; VAS score ≥ 6 (range 0 to 10) for at least 15 days and resistant to conventional pharmacologic and physical approaches; computed tomography or magnetic resonance imaging with evidence of herniation of the nucleus pulposus or cervical spondylosis compatible with the pain.</p> <p>(cont'd next page)</p>

Table 3: Study profiles for *randomized controlled trials* on epidural injections for neuropathic pain (cont'd)

Authors/Study Details	Intervention/Outcome Measures	Study Design/Execution
<p>Pasqualucci et al. (2007)²⁷ (<i>cont'd</i>)</p>	<p>Single and continuous epidural injection groups <u>Adjunct medications:</u> Not stated. <u>Outcome measures:</u> Visual analog scale (VAS) pain score; index of pain control (%) = 100 x ((initial VAS - final VAS)/initial VAS); hours of pain-free sleep. There was no statistically significant difference between the groups with respect to age, sex distribution, VAS score, or hours of pain-free sleep (P-value not stated).</p>	<p><u>Exclusion criteria:</u> History of peptic ulcers, diabetes, serious and diffuse osteoporosis, alterations in blood clotting tests, cervical spine surgery, neoplastic pathology, trauma in the last 15 days; allergy to local anaesthetics or corticosteroids; computed tomography or magnetic resonance imaging evidence of myelopathy, neoplastic pathology, infection, anatomic alterations of the cervical or thoracic spine; cervical-root compression in presence of functional motor deficit. <u>Conclusions supported by results:</u> Yes.</p>

Table 3: Study profiles for randomized controlled trials on epidural injections for neuropathic pain (cont'd)

Authors/Study Details	Intervention/Outcome Measures	Study Design/Execution
<p>Zambello et al. (2006)²⁸ Italy <u>Study design:</u> Prospective randomized, concurrently controlled trial. <u>Follow-up:</u> 3 weeks and 6 months after treatment. <u>Study period:</u> January 2002 to January 2006. <u>Setting:</u> Not reported. <u>Financial support:</u> Not stated.</p>	<p>Epidural steroid injection; n=171 Paravertebral O₂O₃ injection; n=180 Epidural steroid injection <u>Procedure:</u> Epidural steroid injection into the intervertebral space of the herniated disc or into the space immediately above it. <u>Injectant:</u> Triamcinolone 80 mg diluted in 20 mL of saline. <u>Subsequent treatments:</u> A maximum of three injections were given at weekly intervals after no or only partial response to treatment. Paravertebral O₂O₃ injection <u>Procedure:</u> Mixture injected bilaterally into the paravertebral muscle 2 cm from the spinous apophysis of the herniated disc and into the space immediately above and below it. <u>Injectant:</u> 5 mL of O₂O₃ at a concentration of 10 to 20 µg/mL. <u>Subsequent treatments:</u> None stated. Epidural steroid and paravertebral O₂O₃ groups <u>Adjunct medications:</u> Not reported. <u>Outcome measures:</u> Control of pain. There was no statistically significant difference between the groups with respect to age, sex distribution, and response to conventional treatment (P>0.05).</p>	<p><u>Method of randomization:</u> Not reported. <u>Time of randomization:</u> Not reported. <u>Method of allocation concealment:</u> Not reported. <u>Details of blinding:</u> Not reported. Patients were unlikely to know what treatment they received. <u>Participation rate:</u> Not reported. <u>Eligibility rate for study:</u> Not reported. <u>Intention-to-treat analysis:</u> By default as there were no dropouts or withdrawals during the treatment period. <u>Crossovers:</u> Permitted if patients failed to respond to their allocated treatment after 4 weeks. <u>Provider:</u> Team of three anaesthetists <u>Assessor details:</u> Three doctors blinded to the type of treatment the patients received. <u>Inclusion criteria:</u> Patients with radiating low back pain over the sciatic nerve lasting less than 180 days and failure to respond to medical management with steroids, nonsteroidal anti-inflammatory drugs, tramadol, and muscle relaxants. <u>Exclusion criteria:</u> Patients with clinical or electromyographic features of neurogenic or denervating pain. <u>Conclusions supported by results:</u> Yes.</p>

STUDY PROFILES – CLINICAL PRACTICE GUIDELINES

Table 4: Study profiles for *clinical practice guidelines* on epidural injections for neuropathic pain

Guideline	Target Population	Selection Criteria/Outcomes	Methods
<p>Boswell et al. (2007)²⁹</p> <p>Objective: To develop evidence-based practice guidelines for interventional techniques in the diagnosis and treatment of chronic spinal pain.</p> <p>Target users: Interventional pain physicians and other physicians trained in interventional pain management.</p> <p>Financial support: Not stated.</p> <p>Conflict of interest: Not stated.</p>	<p>Age: Not stated.</p> <p>Included conditions: Chronic spinal pain.</p> <p>Excluded conditions: Not stated.</p>	<p>Interventions: Therapeutic interventional techniques including facet joint interventions, sacroiliac joint interventions, epidural injections, epidural adhesiolysis, intradiscal therapies, percutaneous discectomy and decompression techniques, vertebral augmentation techniques, and implantable therapies.</p> <p>Study inclusion criteria: Systematic reviews, randomized controlled trials, observational studies, and diagnostic accuracy studies. For a particular technique, if at least 10 randomized trials were not available, nonrandomized or observations studies were also included.</p> <p>Study exclusion criteria: Not stated.</p>	<p>Literature search: <u>Time Period:</u> Not stated. <u>Limits:</u> Not stated. <u>Databases:</u> Not stated. <u>Other sources:</u> Not stated.</p> <p>Appraisal of study quality: Included studies were evaluated utilizing the Agency for Healthcare Research and Quality³⁴, Quality Assessment of Diagnostic Accuracy Studies (QUADAS)³⁸, and Cochrane Collaboration Back Review Group¹² quality evaluation criteria.</p> <p>Formulation of recommendations: A policy committee consisting of academic and clinical practitioners recognized as experts in one or more of the interventional techniques of concern was convened to formalize the guidelines using consensus evaluation and open forum presentations. No further details provided.</p> <p>External review: Blinded peer review.</p> <p>Evidence linked to recommendations: Yes.</p>

Table 4: Study profiles for *clinical practice guidelines* on epidural injections for neuropathic pain (cont'd)

Guideline	Target Population	Selection Criteria/Outcomes	Methods
<p>Dubinsky et al. (2004)³⁰</p> <p>Objective: To determine which treatments provide benefit in terms of decreased pain and improved quality of life for patients with postherpetic neuralgia.</p> <p>Target users: Not stated.</p> <p>Financial support: Not stated.</p> <p>Conflict of interest: Not stated.</p>	<p>Age: Not stated.</p> <p>Included conditions: Postherpetic neuralgia of at least 8 weeks' duration.</p> <p>Excluded conditions: Not stated.</p>	<p>Interventions: Medical, interventional, and surgical treatment.</p> <p>Study inclusion/exclusion criteria: Articles that: addressed alleviation of pain in postherpetic neuralgia with a duration of at least 8 weeks after healing of the rash; were prospective, retrospective, or case series studies and provided clinical information on patients receiving treatment; provided detailed methodology and a clear outcome measure; had a primary purpose to demonstrate a decrease of pain related to postherpetic neuralgia; outlined treatment that was feasible in an outpatient setting.</p>	<p>Literature search: <u>Time period:</u> January 1960 to January 2004. <u>Limits:</u> Not stated. <u>Databases:</u> MEDLINE, the <i>Cochrane Database of Systematic Reviews</i>. <u>Other sources:</u> Additional reports were identified from reference lists of review articles and by searching MEDLINE using the names of authors who had published several articles on herpes zoster treatment.</p> <p>Appraisal of study quality: The evidence was graded. Disagreements among reviewers were resolved by consensus.</p> <p>Formulation of recommendations: Details not provided.</p> <p>External review: Peer review by the Quality Standards Subcommittee of the American Academy of Neurology, members of the American Academy of Neurology Member Review Network, and heads of sections of the American Academy of Neurology.</p> <p>Evidence linked to recommendations: Yes.</p>
<p>Hunter Integrated Pain Service (2009)³¹</p> <p>Objective: To assist health professionals to provide better pain management for their patients.</p> <p>Target users: Health professionals.</p> <p>Financial support: Not stated.</p> <p>Conflict of interest: Not stated.</p>	<p>Age: Not stated.</p> <p>Included conditions: Neuropathic pain, spinal and radicular pain, tissue ischemia pain, cancer pain.</p> <p>Excluded conditions: Not stated.</p>	<p>Interventions: Medical, interventional, and surgical treatment.</p> <p>Study inclusion/exclusion criteria: Not stated.</p>	<p>Literature search: <u>Time period:</u> Not stated. <u>Limits:</u> Not stated. <u>Databases:</u> Not stated. <u>Other sources:</u> Not stated.</p> <p>Appraisal of study quality: Details not provided.</p> <p>Formulation of recommendations: Details not provided.</p> <p>External review: Details not provided.</p> <p>Evidence linked to recommendations: Yes.</p>

Table 4: Study profiles for *clinical practice guidelines* on epidural injections for neuropathic pain (cont'd)

Guideline	Target Population	Selection Criteria/Outcomes	Methods
<p>North American Spine Society (2007)³²</p> <p>Objective: To provide a tool that assists practitioners in improving the quality and efficiency of care delivered to patients with degenerative lumbar spinal stenosis.</p> <p>Target users: Practitioners involved with patients who have degenerative lumbar spinal stenosis.</p> <p>Financial support: Not stated.</p> <p>Conflict of interest: Available on request.</p>	<p>Age: Adults (18 years or older).</p> <p>Included conditions: Neurogenic claudication without associated spondylolisthesis.</p> <p>Excluded conditions: Not stated.</p>	<p>Interventions: Medical, interventional, and surgical treatment.</p> <p>Study inclusion/exclusion criteria: All studies designs were included except for case reports and case studies.</p>	<p>Literature search: <u>Time period:</u> Not stated. <u>Limits:</u> Not stated. <u>Databases:</u> MEDLINE, EMBASE, the <i>Cochrane Database of Systematic Reviews</i>, the Cochrane Central Register of Controlled Trials, the Database of Abstracts of Reviews of Effectiveness (DARE), the ACP Journal Club.</p> <p>Appraisal of study quality: The evidence was graded.</p> <p>Formulation of recommendations: Multidisciplinary working groups assigned to specific clinical questions held face-to-face meetings to discuss the evidence-based answers to the clinical questions, the grades of recommendations, and the incorporation of expert consensus. Voting on guideline recommendations was conducted using a modified nominal group technique in which each working group member independently and anonymously ranked a recommendation on a scale ranging from 1 (“extremely inappropriate”) to 9 (“extremely appropriate”). Consensus was obtained when at least 80% of working group members ranked the recommendation as 7, 8, or 9. When the 80% threshold was not attained, up to three rounds of discussion and voting were held to resolve disagreements. If disagreements were not resolved after these rounds, no recommendation was adopted.</p> <p>External review: Peer review.</p> <p>Evidence linked to recommendations: Yes.</p>

SUMMARY OF RELEVANT DATA – SYSTEMATIC REVIEWS

Table 5: Summary of relevant data extracted from *systematic reviews* on epidural injections for neuropathic pain

Study/ Quality	Patients/ Pain Type	Comparators	Supporting Evidence*							Relevant Results/ Authors' Conclusions
			SR/MA	NR	RCT	NRCS	CS	G	Other	
Abdi et al. (2007) ²¹ Quality rating: Average (4/6)	Total number: <i>Interlaminar epidural:</i> Cervical - 2 RCTs; Lumbar – 11 RCTs <i>Transforaminal epidural:</i> Cervical – 1 RCT, 3 CS; Lumbar – 6 RCTs, 12 CS <i>Caudal epidural:</i> 8 RCTs, 5 CS. N.B. Some studies examined more than one type of epidural injection. Consequently, the number of studies listed here is greater than the number listed in the Supporting Evidence columns. Conditions reviewed: Chronic spinal pain of at least 3 months' duration.	Interlaminar epidural (placebo, active treatments): Interlaminar epidural, intramuscular injection, interspinous injection, caudal epidural, lumbar epidural, paravertebral local injection Transforaminal epidural (placebo, active treatments): Transforaminal epidural, trigger point injections, interspinous injection, intradiscal steroid injection, discectomy Caudal epidural (placebo, active treatments): Caudal epidural, epiduroscopy, lumbar epidural, tender spot injection, no treatment			27 39-67		13 68-80			Efficacy/effectiveness: <i>Interlaminar epidural injections:</i> <ul style="list-style-type: none"> For lumbar epidural steroid injections for lumbar radicular pain, the evidence is strong for short-term relief and limited for long-term relief. For cervical epidural steroid injections for cervical radiculopathy, the evidence was moderate for short-term and long-term improvement. The evidence is indeterminate for axial neck pain, axial low back pain, and lumbar stenosis. <i>Transforaminal epidural injections:</i> <ul style="list-style-type: none"> For lumbar epidural steroid injections for lumbar nerve root pain, the evidence is strong for short-term and moderate for long-term improvement. For cervical epidural steroid injections for cervical nerve root pain, the evidence is moderate for short-term and long-term improvement. The evidence is limited for epidural steroid injections for lumbar radicular pain in postlumbar laminectomy syndrome. The evidence is indeterminate for epidural steroid injections for axial low back pain, axial neck pain, and lumbar disc extrusions. <i>Caudal epidural injections:</i> <ul style="list-style-type: none"> For epidural steroid injections for chronic lumbar radicular pain and postlumbar laminectomy syndrome, the evidence is strong for short-term relief and moderate for long-term relief. For epidural steroid injections for chronic low back pain, the evidence is moderate for short-term and long-term improvement. (cont'd next page)

Table 5: Summary of relevant data extracted from *systematic reviews* on epidural injections for neuropathic pain (cont'd)

Study/ Quality	Patients/ Pain Type	Comparators	Supporting Evidence*							Relevant Results/ Authors' Conclusions
			SR/MA	NR	RCT	NRCS	CS	G	Other	
Abdi et al. (2007) ²¹ (cont'd)										<p>Safety: Complications of caudal, interlaminar, and transforaminal epidural injections include dural puncture, spinal cord trauma, infection, haematoma formation, abscess formation, subdural injection, intracranial air injection, epidural lipomatosis, pneumothorax, nerve damage, headache, death, brain damage, increased intracranial pressure, intravascular injection, vascular injury, cerebral vascular or pulmonary embolus, and the effects of steroids. Spinal cord trauma and spinal cord or epidural haematoma formation is rarely seen following interventional procedures in the cervical, thoracic, or upper lumbar spine. (Information based on 64 references cited in original publication. The references were not cited in this summary in the interests of brevity).</p> <hr style="border-top: 1px dashed black;"/> <p>Authors' conclusions: There is moderate evidence for the use of interlaminar epidurals in the cervical spine and limited evidence in the lumbar spine for long-term relief. The evidence for cervical and lumbar transforaminal epidural steroid injections is moderate for long-term improvement in managing nerve root pain. The evidence for caudal epidural steroid injections is moderate for long-term relief in managing nerve root pain and chronic low back pain.</p>

Table 5: Summary of relevant data extracted from *systematic reviews* on epidural injections for neuropathic pain (cont'd)

Study/ Quality	Patients/ Pain Type	Comparators	Supporting Evidence*							Relevant Results/ Authors' Conclusions
			SR/MA	NR	RCT	NRCS	CS	G	Other	
Forouzanfar et al. (2002) ²² Quality rating: Average (4/6)	Total number: n = 26 for epidural clonidine (1 RCT) Conditions reviewed: Complex regional pain syndrome type I or reflex sympathetic dystrophy	Placebo			1 ₈₁					<p>Efficacy/effectiveness: Epidural clonidine 700 µg and 300 µg both decreased pain significantly more than placebo.</p> <p>Safety: Not reported.</p> <hr/> <p>Authors' conclusions: There is limited evidence for the efficacy of epidural injection of clonidine for reflex sympathetic dystrophy.</p>
Kumar et al. (2004) ²³ Quality rating: Poor (3/6)	Total number: n = 91 for epidural local anaesthetic plus steroid Conditions reviewed: Postherpetic neuralgia	Not applicable					2 _{82,83}		<p>Efficacy/effectiveness: The two studies found that epidural local anaesthetic plus steroid significantly reduced the pain of postherpetic neuralgia.</p> <p>Safety: Not reported.</p> <hr/> <p>Authors' conclusions: Evidence for the use of epidural local anaesthetic plus steroid is supported by case series studies only. They may be considered useful, but lack good quality randomized controlled trials.</p>	

CS - case series study; G - guideline; NR – non-systematic/narrative review; NRCS – non-randomized comparative study; RCT – randomized controlled trial; SR/MA – systematic review/meta-analysis

*The integers listed in the Supporting Evidence columns represent the total number of discrete studies. Thus, when there are multiple publications for a single study, the integers are less than the number of references listed below them.

SUMMARY OF RELEVANT DATA – RANDOMIZED CONTROLLED TRIALS

Table 6: Summary of relevant data extracted from *randomized controlled trials* on epidural injections for neuropathic pain

Study/Quality Rating	Interventions/Study Population	Relevant Results/Authors' Conclusions
<p>Ackerman and Ahmad (2007)²⁴ Prospective randomized, concurrently controlled trial Quality rating: <i>Internal validity</i> Good (8/9) <i>External validity</i> Good (5/6)</p>	<p>Caudal epidural; n=30 Interlaminar epidural; n=30 Transforaminal epidural; n=30 <u>Patient diagnosis:</u> L5-S1 disc herniations and radicular pain <u>Mean age:</u> Caudal: 36.4 years (standard deviation (SD) 4.0); Interlaminar: 39.2 years (SD 6.0); Transforaminal: 34 years (SD 5.0) <u>Sex distribution:</u> Caudal: M/F = 19 (63.3%)/11 (36.7%); Interlaminar: M/F = 21 (70.0%)/9 (30.0%); Transforaminal: M/F = 20 (66.7%)/10 (33.3%) <u>Pre-treatment mean visual analog scale pain score (scale 0 to 10):</u> Caudal: 8.9 (SD 0.7); Interlaminar: 8.8 (SD 0.8); Transforaminal: 8.6 (SD 0.9) <u>Mean duration of pain:</u> Caudal: 38 days (SD 4.0); Interlaminar: 33 days (SD 7.0); Transforaminal: 35 days (SD 5.0) <u>Disc pathology:</u> Combined patient groups - L5-S1 – 100% <u>Patient co-morbidities:</u> Not stated <u>Co-interventions:</u> Each patient was prescribed tizanidine (6 mg to 12 mg/24 hours) as needed for muscle spasms, celecoxib as needed for pain, and amitriptyline.</p>	<p>At 24 weeks' follow up: caudal (n=74), interlaminar (n=67); transforaminal (n=46) <u>Lost to follow-up:</u> 0% <u>Outcomes:</u> Pain scores improved within groups but were significantly lower after transforaminal epidurals. Disability, function, and depression scores were significantly improved within groups, but were not affected by injection technique. <i>Numeric pain intensity mean score (range 1 to 10) (SD):</i> Caudal, 6.1 (0.8); interlaminar, 5.7 (3.3); transforaminal, 2.4 (2.1) (P<0.01 for within group comparison to baseline; P<0.05 for transforaminal compared with other two techniques) <i>Oswestry Low Back Pain Scale mean score (SD):</i> Caudal, 14 (6); interlaminar, 13 (4); transforaminal, 14 (9) (P<0.01 for within group comparison to baseline) <i>Beck Depression Inventory mean score (SD):</i> Caudal, 13 (9); interlaminar, 11 (6); transforaminal, 12 (4) (P<0.01 for within group comparison to baseline) <u>Pain relief:</u> Caudal: complete, 3.3% (1/30); partial, 53.3% (16/30); none 43.3% (13/30); Interlaminar: complete, 10.0% (3/30); partial, 50.0% (15/30); none 40.0% (12/30); Transforaminal: complete, 30.0% (9/30); partial, 53.3% (16/30); none 16.7% (5/30) <u>Adverse events:</u> No patient experienced an infection, headache, intravascular or subarachnoid injection, or a reaction to the contrast material or steroid.</p> <hr/> <p>Authors' conclusions The transforaminal route of epidural steroid administration is more effective than the caudal or interlaminar routes in patients with lumbar disc herniations. This was attributed to a higher incidence of steroid placement in the ventral epidural space when the transforaminal method is used.</p>

Table 6: Summary of relevant data extracted from *randomized controlled trials* on epidural injections for neuropathic pain (cont'd)

Study/Quality Rating	Interventions/Study Population	Relevant Results/Authors' Conclusions
<p>Dincer et al. (2007)²⁵ Prospective randomized, concurrently controlled trial Quality rating: <i>Internal validity</i> Good (7/9) <i>External validity</i> Moderate (4/6)</p>	<p>Caudal epidural plus therapeutic exercise; n=34 Non-steroidal anti-inflammatory drugs (NSAIDs) plus therapeutic exercise; n=30</p> <p><u>Patient diagnosis:</u> Subacute or chronic low back pain with radicular pain</p> <p><u>Mean age:</u> Caudal: 28.2 years (standard deviation (SD) 5.5); NSAIDs: 28.7 years (SD 5.7)</p> <p><u>Sex distribution:</u> Caudal: M/F = 23 (67.6%)/11 (32.4%); NSAIDs: M/F = 23 (76.7%)/7 (23.3%)</p> <p><u>Pre-treatment mean visual analog scale pain score (scale 0 to 10):</u> Caudal: 6.9 (SD 1.0); NSAIDs: 6.8 (SD 1.0)</p> <p><u>Duration of pain:</u> Combined patient groups: range 30 days to 12 months</p> <p><u>Disc pathology:</u> Not reported.</p> <p><u>Patient co-morbidities:</u> Not stated.</p> <p><u>Co-interventions:</u> After day 15, patients in both groups were permitted to use paracetamol. No other treatments were authorized.</p>	<p>Caudal versus NSAIDs at 15 days' follow up: <u>Lost to follow-up:</u> 0%</p> <p><u>Outcomes:</u> <i>Mean straight leg raise (SLR):</i> Caudal, increased 67.6% (from 41.0 to 68.7 degrees); NSAID, increased 36.6% (from 36.3 to 49.7 degrees) (P=0.00 for between group comparison)</p> <p><i>Mean visual analog pain score (range 1 to 10):</i> Caudal, decreased 52.2% (from 6.9 to 3.3); NSAID, decreased 22.1% (from 6.8 to 5.3) (P=0.00 for between group comparison)</p> <p><i>Mean Oswestry Low Back Pain disability score:</i> Caudal, decreased 45.5% (from 35.8 to 19.5); NSAID, decreased 17.4% (from 34.4 to 28.4) (P=0.00 for between group comparison)</p> <p>The improvements of both groups in pain intensity, SLR, and Oswestry score were statistically significant compared to baseline (P<0.001).</p> <p>Caudal versus NSAIDs at 3 months' follow up: <u>Lost to follow-up:</u> 0%</p> <p><u>Outcomes:</u> <i>Mean SLR:</i> Caudal, increased 70% (from 41.0 to 69.7 degrees); NSAID, increased 71.6% (from 36.3 to 62.3 degrees) (P=0.03 for between group comparison)</p> <p><i>Mean visual analog pain score (range 1 to 10):</i> Caudal, decreased 52.2% (from 6.9 to 3.3); NSAID, decreased 39.7% (from 6.8 to 4.1) (P=0.05 for between group comparison)</p> <p><i>Mean Oswestry Low Back Pain disability score:</i> Caudal, decreased 54.8% (from 35.8 to 16.2); NSAID, decreased 41.0% (from 34.4 to 20.3) (P=0.10 for between group comparison)</p> <p>The improvements of both groups in pain intensity, SLR, and Oswestry score at 15 days, 1 month, and 3 months were statistically significant compared to baseline (P<0.001).</p> <p>Use of paracetamol: Caudal, 14.7% (5/34); NSAID, 26.7% (8/30)</p> <p><u>Adverse events:</u> Caudal (n=34): urinary retention that spontaneously resolved (5.9%). NSAIDs (n=30): no serious complications.</p> <p><i>(cont'd next page)</i></p>

Table 6: Summary of relevant data extracted from *randomized controlled trials* on epidural injections for neuropathic pain (cont'd)

Study/Quality Rating	Interventions/Study Population	Relevant Results/Authors' Conclusions
Dincer et al. (2007) ²⁵ (cont'd)		<p>Authors' conclusions Improvement in the caudal epidural group was better and faster than the NSAID group. Caudal epidural injection in the management of subacute/chronic low back pain and radicular pain is preferable because it is simple, cost effective, and carries a low risk of complications. It also reduces the need for NSAIDs, thereby preventing patients from experiencing the potential systemic complications of NSAIDs.</p>

Table 6: Summary of relevant data extracted from *randomized controlled trials* on epidural injections for neuropathic pain (cont'd)

Study/Quality Rating	Interventions/Study Population	Relevant Results/Authors' Conclusions
<p>Owlia et al. (2007)²⁶ Prospective randomized, concurrently controlled trial Quality rating: <i>Internal validity</i> Moderate (6/9) <i>External validity</i> Good (5/6)</p>	<p>Epidural injection (80 mg methylprednisolone); n=43 Epidural injection (40 mg methylprednisolone); n=41 <u>Patient diagnosis:</u> Lumbar radicular pain for more than 2 weeks <u>Mean age:</u> Epidural 80 mg: 38.2 years; Epidural 40 mg: 36.0 years <u>Sex distribution:</u> Epidural 80 mg: M/F = 22 (51.2%)/21 (48.8%) Epidural 40 mg: M/F = 27 (65.9%)/14 (34.1%) <u>Pre-treatment mean visual analog scale pain score:</u> Not reported <u>Mean duration of pain:</u> Epidural 80 mg: 12 weeks; Epidural 40 mg: 9 weeks <u>Disc pathology:</u> Combined patient groups: L5-S1 - 89%; L4-L5 – 11% <u>Patient co-morbidities:</u> Not stated <u>Co-interventions:</u> All patients had rehabilitative management for at least 2 weeks after injection. Patients were allowed to have acetaminophen 500 mg as rescue medication as needed.</p>	<p>Epidural 80 mg versus 40 mg: <u>Lost to follow-up:</u> 0% <u>Outcomes:</u> No statistically significant difference between the two groups with respect to pain intensity at 2 weeks and 3 months after injection. Slightly better results were obtained from patients in the 40 mg group after one month. Proportion of patients with significant improvement (decrement > 2 scales) in visual analog pain score: <u>2 weeks' follow up:</u> epidural 80 mg – 69.8% (30/43); epidural 40 mg – 61.0% (25/41) <u>1 month follow up:</u> epidural 80 mg – 74.4% (32/43); epidural 40 mg – 75.6% (31/41) <u>3 months' follow up:</u> epidural 80 mg – 65.0% (28/43); epidural 40 mg – 51.2% (21/41) <u>Adverse events:</u> Epidural (80 mg) (n=43): major complications (0%); hyperglycaemia (4.6%); flushing (13.9%); post-injection flare (4.6%); cerebrospinal fluid hypotension (2.3%); Epidural (40 mg) (n=41): major complications (0%); hyperglycaemia (0%); flushing (2.4%); post-injection flare (7.3%); cerebrospinal fluid hypotension (7.3%). More patients in the 80 mg group experienced flushing, compared to those in the 40 mg group (P=0.01).</p> <hr/> <p>Authors' conclusions In the case of lumbar radicular pain, epidural steroid injection with low dose (40 mg) methylprednisolone is as effective as high dose (80 mg) with comparable results and fewer adverse effects.</p>

Table 6: Summary of relevant data extracted from *randomized controlled trials* on epidural injections for neuropathic pain (cont'd)

Study/Quality Rating	Interventions/Study Population	Relevant Results/Authors' Conclusions
<p>Pasqualucci et al. (2007)²⁷</p> <p>Prospective randomized, concurrently controlled trial</p> <p>Quality rating: Internal validity Poor (3/9) External validity Good (5/6)</p>	<p>Group A (pain onset 15 to 30 days); n=40 Group B (pain onset 31 to 60 days); n=40 Group C (pain onset 61 to 180 days); n=40 Group D (pain onset >180 days); n=40</p> <p>Patients in each of the four groups were randomly allocated to single epidural injection (n=20) or continuous epidural infusion (n=20)</p> <p><u>Patient diagnosis:</u> Unilateral cervicobrachial pain</p> <p><u>Mean age:</u> Group A: single (S), 62.8 years (standard deviation (SD) 7.19); continuous (C) 65.4 years (SD 6.74); Group B: S, 64.7 years (SD 7.08); C, 64.9 years (SD 5.03); Group C: S, 63.6 years (SD 6.57); C, 63.9 years (SD 7.51); Group D: S, 65.3 years (SD 6.47); C, 65.3 years (SD 6.58)</p> <p><u>Sex distribution:</u> Group A: S, M/F = 12 (60%)/8 (40%); C, M/F = 12 (60%)/8 (40%); Group B: S, M/F = 12 (60%)/8 (40%); C, M/F = 11 (55%)/9 (45%); Group C: S, M/F = 11 (55%)/9 (45%); C, M/F = 10 (50%)/10 (50%); Group D: S, M/F = 9 (45%)/11 (55%); C, M/F = 12 (60%)/8 (40%)</p> <p><u>Pre-treatment mean visual analog scale pain score:</u> Group A: S, 8.0 (SD 1.19); C 8.4 (SD 1.12); Group B: S, 8.1 (SD 1.17); C, 8.1 (SD 1.09); Group C: S, 8.1 (SD 1.04); C, 7.9 (SD 1.13); Group D: S, 8.0 (SD 1.15); C, 8.1 (SD 1.29)</p> <p><u>Mean duration of pain:</u> Data not available for single versus continuous infusion patient groups.</p> <p><u>Disc pathology:</u> Last 4 cervical nerves or first thoracic nerve</p> <p><u>Patient co-morbidities:</u> Not stated</p> <p><u>Co-interventions:</u> None of the patients had surgical interventions during the follow-up period.</p>	<p>Epidural injection versus continuous epidural infusion: Group A (n=36), Group B (n=36); Group C (n=35); Group D (n=34) Single injection (n=69); Continuous infusion (n=72)</p> <p><u>Lost to follow-up:</u> Group A, 10% (4/40); Group B, 10% (4/40); Group C, 12.5% (5/40); Group D, 15% (6/40); Single injection 13.8% (11/80); Continuous infusion 10% (8/80)</p> <p><u>Outcomes:</u> All patients in both single injection and continuous infusion groups achieved a pain control index $\geq 80\%$ 1 week after the end of treatment. At the 1-month and 6-month follow-ups, there were no significant differences between single injection and continuous infusion for patients in Group A, B, or C in terms of pain control and pain-free hours. However, Group D patients receiving continuous epidural had greater pain control and more pain-free hours than those treated with single injection.</p> <p>Median number of single injections required (range): Group A, 4 (3 to 7); Group B, 5 (3 to 9); Group C, 6 (5 to 9); Group D, 7 (5 to 9)</p> <p>Mean duration of continuous epidural in days (SD): Group A, 13.8 (4.33); Group B, 16.9 (5.67); Group C, 22.8 (4.82); Group D, 24.2 (4.64)</p> <p>Pain control index: <i>1 month follow up:</i> Single injection – 59.0 (SD 20.68); Continuous infusion – 75.3 (SD 15.21) (P=0.007) <i>6 months' follow up:</i> Single injection – 58.5 (SD 22.97); Continuous infusion – 73.7 (SD 16.03) (P=0.016)</p> <p>Number of hours of pain-free sleep: <i>1 month follow up:</i> Single injection – 1.7 (SD 1.07); Continuous infusion – 3.0 (SD 1.35) (P=0.0007) <i>6 months' follow up:</i> Single injection – 1.6 (SD 1.11); Continuous infusion – 3.1 (SD 1.35) (P=0.017)</p> <p><u>Adverse events:</u> None of the patients had complications or collateral effects. Three patient withdrawals were due to onset of hypotension and profuse sweating that was probably caused by epidural drug administration.</p> <p>(cont'd next page)</p>

Table 6: Summary of relevant data extracted from *randomized controlled trials* on epidural injections for neuropathic pain (cont'd)

Study/Quality Rating	Interventions/Study Population	Relevant Results/Authors' Conclusions
Pasqualucci et al. (2007) ²⁷ (cont'd)		Authors' conclusions Therapy with continuous epidural local anaesthetic and methylprednisolone provides better control of chronic cervicobrachial pain than single epidural injection.

Table 6: Summary of relevant data extracted from *randomized controlled trials* on epidural injections for neuropathic pain (cont'd)

Study/Quality Rating	Interventions/Study Population	Relevant Results/Authors' Conclusions
<p>Zambello et al. (2006)²⁸</p> <p>Prospective randomized, concurrently controlled trial</p> <p>Quality rating: <i>Internal validity</i> Moderate (6/9) <i>External validity</i> Moderate (3/6)</p>	<p>Epidural steroid injection; n=171 Paravertebral O₂O₃ injection; n=180</p> <p><u>Patient diagnosis:</u> Radiating low back pain over the sciatic nerve for <180 days</p> <p><u>Mean age:</u> Epidural steroid: 48.0 years (standard deviation (SD) 3.2); Epidural O₂O₃: 51.0 years (SD 6.1)</p> <p><u>Sex distribution:</u> Epidural steroid: M/F = 91 (53.2%)/80 (46.8%) Epidural O₂O₃: M/F = 100 (55.6%)/80 (44.4%)</p> <p><u>Pre-treatment mean visual analog scale pain score:</u> Not stated</p> <p><u>Duration of pain:</u> Combined patient groups: <180 days</p> <p><u>Disc pathology:</u> Not stated</p> <p><u>Patient co-morbidities:</u> Not stated</p> <p><u>Co-interventions:</u> Not stated.</p>	<p>Epidural steroid injection versus paravertebral O₂O₃ injection: <u>Lost to follow-up:</u> 0%</p> <p><u>Outcomes:</u> At 3 weeks' follow up, 59% of patients treated with epidural steroid and 88.2% of patients treated with paravertebral O₂O₃ had total or near total remission (50% to 100% reduction) of pain (P<0.05). At 6 months' follow up, 47% of patients treated with epidural steroid and 77% of patients treated with paravertebral O₂O₃ had total or near total remission of pain (P<0.05).</p> <p><u>Crossover outcomes:</u> Epidural steroid injection to O₂O₃ (n=38); O₂O₃ to epidural steroid injection (n=11) At 3 weeks' follow up, 36% of patients treated with epidural steroid and 71% of patients treated with paravertebral O₂O₃ had total or near total remission (50% to 100% reduction) of pain (P<0.05). At 6 months' follow up, 47% of patients treated with epidural steroid and 77% of patients treated with paravertebral O₂O₃ had total or near total remission of pain (P<0.05).</p> <p>Patients opting for surgical treatment: Epidural steroid – 8.8% (15/171); O₂O₃ injection – 1.7% (3/180) (P<0.05)</p> <p><u>Adverse events:</u> Not reported.</p> <hr style="border-top: 1px dashed black;"/> <p>Authors' conclusions Given the relative simplicity of treatment administration, limited contraindications, and lack of side effects, ozone therapy is the first choice treatment in patients refractory to conventional medical management.</p>

SUMMARY OF RELEVANT DATA – CLINICAL PRACTICE GUIDELINES

Table 7: Summary of relevant data extracted from *clinical practice guidelines* on epidural injections for neuropathic pain

Guideline/ Quality Rating	Synopsis of Recommendations	Supporting Evidence*						
		SR/MA	NR	RCT	NRCS	CS	G	Other
<p>Boswell et al. (2007)²⁹ (United States)</p> <p>Quality rating: Average (20.5/28)</p>	<p>The evidence for caudal epidural steroid injection is strong for short-term relief and moderate for long-term relief in managing chronic low back and radicular pain. The evidence in post-lumbar laminectomy syndrome and spinal stenosis is limited.</p> <p>The evidence for interlaminar epidural steroid injections in managing lumbar radiculopathy is strong for short-term relief and limited for long-term relief. In managing cervical radiculopathy, the evidence is moderate for short-term and long-term relief. The evidence is indeterminate for the management of neck pain, low back pain, and lumbar spinal stenosis.</p> <p>The evidence for lumbar transforaminal epidural steroid injections in managing lumbar nerve root pain is strong for short-term and moderate for long-term improvement. The evidence for cervical transforaminal epidural steroid injections in managing cervical nerve root pain is moderate for short-term and long-term improvement. The evidence is limited in managing lumbar radicular pain in postlumbar laminectomy syndrome. The evidence is indeterminate in managing axial low back pain, cervical neck pain, and lumbar disc extrusions.</p> <p>Complications of caudal, interlaminar, and transforaminal epidural injections are predominantly of two types: those related to needle placement and those related to drug administration. Reported complications include dural puncture, spinal cord trauma, infection, hematoma formation, abscess formation, subdural injection, intracranial air injection, epidural lipomatosis, pneumothorax, nerve damage, headache, death, brain damage, increased intracranial pressure, intravascular injection, vascular injury, cerebral vascular or pulmonary embolus and effects of steroids. Spinal cord trauma and spinal cord or epidural hematoma formation are catastrophic complications, but are rarely seen following epidural injections.</p>			<p>27 39-51,53-67</p>		<p>14 52,68-80</p> <p>N.B. An additional 75 studies were cited for safety data, but they were not listed in the interests of brevity.</p>		

Table 7: Summary of relevant data extracted from *clinical practice guidelines* on epidural injections for neuropathic pain (cont'd)

Guideline/ Quality Rating	Synopsis of Recommendations	Supporting Evidence*						
		SR/MA	NR	RCT	NRCS	CS	G	Other
Dubinsky et al. (2004) ³⁰ (United States) Quality rating: Average (17/28)	Epidural methylprednisolone and epidural morphine sulphate are not of benefit for patients with postherpetic neuralgia. There is insufficient evidence at this time to make any recommendations on the long-term effects of these treatments.			1 84				
Hunter Integrated Pain Service (2009) ³¹ Quality rating: Poor (10/28)	The place of targeted interventions, such as epidural steroid injection, for spinal and radicular pain remains unclear. Analysis of the place of such interventions within a holistic paradigm is needed. However, it is possible that a time-limited procedural phase may in some cases help the patient progress in broader physical and psychological functioning.	1 21		2 49,85				
North American Spine Society (2007) ³² (United States) Quality rating: Good (23.5/28)	Non-fluoroscopically-guided interlaminar epidural steroid injections can result in short-term (2 to 3 weeks) symptom relief in patients with neurogenic claudication or radiculopathy. There is, however, conflicting evidence concerning long-term efficacy. A single radiographically-guided transforaminal epidural steroid injection can produce short-term relief in patients with radiculopathy from lumbar spinal stenosis. There is, however, conflicting evidence concerning the long-term efficacy of a single injection. A multiple injection regimen of radiographically-guided transforaminal epidural steroid injection or caudal injections can produce long-term relief of pain in patients with radiculopathy or neurogenic intermittent claudication from lumbar spinal stenosis.			4 44,56,60,86		7 68,75,87-91		

*The integers listed in the Supporting Evidence columns represent the total number of discrete studies. Thus, when there are multiple publications for a single study, the integers are less than the number of references listed below them.

APPENDIX A: SEARCH STRATEGY

The literature search was conducted by the IHE Research Librarian from May 5 to 12, 2008. Major electronic databases used included *The Cochrane Library*, the NHS Centre for Reviews and Dissemination (CRD Databases: NHS EED, HTA, DARE), PubMed, EMBASE, and AMED (Allied and Complementary Medicine). In addition, relevant library collections, web sites of practice guideline clearing houses, regulatory agencies, evidence-based resources, and HTA related agency resources were searched (Table A.1). Internet search engines were also used to locate grey literature.

Medical Subject Headings (MeSH) terms relevant to this topic include: Pain; Peripheral nervous system diseases; Neuralgia; Complex regional pain syndromes; Nerve Block; Infusions, Intravenous; Analgesia, Epidural.

Table A.1: Databases and search terms used in the search strategy

Database	Edition/Date Searched	Search Terms
Databases		
<i>The Cochrane Library</i> http://www.thecochranelibrary.com	May 5, 2008	(((neuropath* OR neurogenic) AND pain) OR neuralgia* OR "reflex system dystrophy" Or "reflex sympathetic dystrophy" OR "diabetic neuropathy" OR "peripheral neuropathy" OR radiculopath* or plexopath* or" complex regional pain syndrome" OR causalgia OR ("multiple sclerosis" and pain) OR sciatica OR (("nerve injury" OR "nerve injuries") and pain) OR syringomyelia OR "brachial plexus injury" OR "brachial plexus injuries" OR "phantom limb" OR amputation OR "post mastectomy" OR "post stroke" OR ("spinal cord" and pain) or (sacroiliac and pain)):ti,ab,kw and ("nerve block" or "nerve blocks" or "nerve blockade" or "medial branch block" or "medial branch blocks" or "intravenous infusion" or "intravenous infusions" or "IV infusion" or "IV infusions" or "spinal nerve stimulation" or "spinal cord stimulation" OR "sympathetic block" or "sympathetic blocks" or "sympathetic blockade" or "epidural block" or "epidural blocks" or "epidural blockade" Or "epidural steroid injection" or tfesi or "epidural steroid injections" or "paravertebral block" or "paravertebral blocks" or "paravertebral injection" or "paravertebral injections" or "paraspinal block" or "paraspinal blocks" or "paraspinal injection" or "paraspinal injections" or "stellate ganglion block" or nonpharmacologic* or non-pharmacologic*):ti,ab, from 1997 to 2008
EMBASE –Ovid platform (Licensed resource)	May 5, 2008	See Note 1 for EMBASE search
MEDLINE/PubMed	May 5, 2008	See Note 2 for MEDLINE search PubMed searched for in process citations. (search[tiab] OR medline[tiab] OR systematic review[tiab] OR metaanalys*[tiab] OR randomized[tiab] or clinical trial[ti]) AND (in process[sb] OR pubmednotmedline[sb] OR publisher[sb]) added to textword search

<p>Web of Science – ISI platform (Licensed resource)</p> <p>BIOSIS Previews – ISI platform (licensed resource)</p>	<p>May 5, 2008</p>	<p>neuropath* OR neurogenic OR neuralgia* OR “reflex system dystrophy” OR “reflex sympathetic dystrophy” OR “diabetic neuropathy” OR “peripheral neuropathy” OR radiculopath* OR plexopath* OR “complex regional pain syndrome” OR causalgia OR “multiple sclerosis” OR sciatica OR “nerve injury” OR “nerve injuries” OR syringomyelia OR “brachial plexus injury” OR “brachial plexus injuries” OR “phantom limb” OR amputation OR “post mastectomy” OR “post stroke” OR “spinal cord” OR sacroiliac</p> <p>AND pain</p> <p>AND “nerve block” or “nerve blocks” or “nerve blockade” or “medial branch block” or “medial branch blocks” or “intravenous infusion” or “intravenous infusions” or “IV infusion” or “IV infusions” or “spinal nerve stimulation” or “spinal cord stimulation” OR “sympathetic block” or “sympathetic blocks” or “sympathetic blockade” or “epidural block” or “epidural blocks” or “epidural blockade” Or “epidural steroid injection” or tfesi or “epidural steroid injections” or “paravertebral block” or “paravertebral blocks” or “paravertebral injection” or “paravertebral injections” or “paraspinal block” or “paraspinal blocks” or “paraspinal injection” or “paraspinal injections” or “stellate ganglion block” or nonpharmacologic* or non-pharmacologic*</p> <p>AND random* or "systematic review" or "practice guideline" or search* or "technology assessment" or "clinical trial" or double-blind* or meta-analys* or metaanalys*</p>
<p>CRD Databases (Results from DARE and HTA portions only)</p>	<p>May 5, 2008</p>	<p>neuropath* OR neurogenic OR neuralgia* OR “reflex system dystrophy” OR “reflex sympathetic dystrophy” OR “diabetic neuropathy” OR “peripheral neuropathy” OR radiculopath* OR plexopath* OR “complex regional pain syndrome” OR causalgia OR “multiple sclerosis” OR sciatica OR “nerve injury” OR “nerve injuries” OR syringomyelia OR “brachial plexus injury” OR “brachial plexus injuries” OR “phantom limb” OR amputation OR “post mastectomy” OR “post stroke” OR “spinal cord” OR sacroiliac</p> <p>AND pain</p> <p>AND “nerve block” or “nerve blocks” or “nerve blockade” or “medial branch block” or “medial branch blocks” or “intravenous infusion” or “intravenous infusions” or “IV infusion” or “IV infusions” or “spinal nerve stimulation” or “spinal cord stimulation” OR “sympathetic block” or “sympathetic blocks” or “sympathetic blockade” or “epidural block” or “epidural blocks” or “epidural blockade” Or “epidural steroid injection” or tfesi or “epidural steroid injections” or “paravertebral block” or “paravertebral blocks” or “paravertebral injection” or “paravertebral injections” or “paraspinal block” or “paraspinal blocks” or “paraspinal injection” or “paraspinal injections” or “stellate ganglion block” or nonpharmacologic* or non-pharmacologic*</p> <p>Year published 1997 – 2008 OR Published date 1997 - 2008</p>
<p>AMED</p>	<p>May 5, 2008</p>	<p>See Note 3 for AMED search</p>

CINAHL	May 5, 2008	<p>(MH "Pain+") or pain</p> <p>AND</p> <p>(MH "Peripheral Nervous System Diseases+") OR (MH "Facial Neuralgia") OR (MH "Trigeminal Neuralgia") OR (MH "Nervous System Diseases+") OR (MH "Reflex Sympathetic Dystrophy") or (MH "Complex Regional Pain Syndromes+") OR (MH "Radiculopathy") or (MH "Polyradiculopathy") or (MH "Polyradiculoneuritis") OR (MH "Multiple Sclerosis") OR (MH "Syringomyelia") OR (MH "Brachial Plexus Neuropathies+") OR (MH "Phantom Limb") or (MH "Phantom Pain") OR (MH "Amputation+") OR (MH "Somatosensory Disorders+") or neuralgia* or neuropath* or neurogenic or "reflex sympathetic dystrophy" or "complex regional pain syndrome" or radiculopath* or plexopath* or polyradiculopath* or causalgia or sciatica</p> <p>AND</p> <p>(MH "Nerve Block") OR (MH "Infusions, Intravenous") or (MH "Infusions, Intraspinal+") OR (MH "Central Nervous System Stimulants") OR (MH "Sympatholytics+") OR (MH "Analgesia, Epidural") or (MH "Infusions, Epidural") or (MH "Injections, Epidural+") OR (MH "Injections, Intraspinal") OR (MH "Ganglionic Blockers") OR "nerve block" or "nerve blocks" or "nerve blockade" or "sympathetic block" or "sympathetic blocks" or "sympathetic blockade" or "intravenous infusion" or "iv infusion" or "intravenous infusions" or "iv infusions" or "spinal nerve stimulation" or "spinal cord stimulation" or "epidural block" or "epidural blocks" or "epidural blockade" or "medial branch block" or "medial branch blocks" or "medical branch blockade" or "epidural steroid injection" or "epidural steroid injections" or tfesi or "paravertebral block" or "paravertebral blocks" or "paraspinal block" or "paraspinal blocks" or "paravertebral infusion" or "paravertebral infusions" or "paraspinal infusion" or "paraspinal infusions" or "ganglion block" or nonpharmacologic* or non-pharmacologic*</p> <p>AND</p> <p>(MH "Meta Analysis") OR (MH "Systematic Review") OR (MH "Practice Guidelines") OR (MH "Clinical Trials") or (MH "Double-Blind Studies") Or random* OR "systematic review" or "practice guideline" or search* or "technology assessment" or "clinical trial" or double-blind* or meta-analys* or metaanalys*</p>
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Theses Canada portal	May 7, 2008	Neuropathic; neuralgia; neuropathy; complex regional; reflex sympathetic; causalgia; radiculopathy; blockade; epidural; nerve block; nerve blocks; spinal cord stimulation Title keyword Pain and nerve and treatment Any keyword
National Library for Health	May 7, 2008	Neuropathic pain; neuralgia; neuropathy; complex regional; reflex sympathetic; causalgia; radiculopathy; nerve block; nerve blockade; nerve blocks; epidural block(s,ade); spinal cord stimulation; iv infusion(s); intravenous infusions(s)
Proquest Dissertations and Theses	May 7, 2008	TITLE(neuropathic pain) TITLE(neuralgia or neuropathy or causalgia) AND (treat* or therap*) TITLE(complex regional) OR TITLE (reflex sympathetic) TITLE (nerve block or nerve blocks or nerve blockade) TITLE(epidural block or epidural blocks or epidural blockade) TITLE(iv infusion or iv infusions or intravenous infusion or intravenous infusions)
Guidelines		
AMA Clinical Practice Guidelines http://www.topalbertadoctors.org/TOP/CPG/CPGTopics.htm	May 7, 2008	Browsed list of guidelines
CMA Infobase http://mdm.ca/cpgsnew/cpgs/index.asp	May 7, 2008	Neuropathic; neuropathy; neurogenic; neuralgia; pain; nerve; nerves; intravenous; block; stimulation; epidural
National Guideline Clearinghouse http://www.ngc.gov	May 7, 2008	"neuropathic pain"; "complex regional pain syndrome"; nerve block; nerve blocks; intravenous infusion; spinal nerve stimulation; spinal cord stimulation; sympathetic block; sympathetic blocks; epidural Clinical specialty; neurology
Guidelines International Network	May 7, 2008	Neuropathic pain; neuralgia; neuropathy; nerve block; nerve blockade; blockade; epidural; infusion; stimulation; complex regional; reflex; causalgia; radiculopathy; polyradiculopathy
New Zealand Guidelines Group http://www.nzgg.org.nz	May 7, 2008	Browsed list of guidelines.
SIGN http://www.sign.ac.uk	May 7, 2008	Browsed list of guidelines.
Clinical Trials		
ClinicalTrials.gov (US) http://clinicaltrials.gov/	May 7, 2008	Neuropathic pain and nerve block; Epidural block; Neuralgia pain block; Causalgia pain block Spinal cord stimulation Iv infusions pain; intravenous infusions pain Complex regional pain syndrome Reflex sympathetic dystrophy Radiculopathy
CenterWatch Clinical	May 7, 2008	Neuropathic pain

Trials Listing Service http://www.centerwatch.com/		Nerve block (s/ade) Epidural block (s/ade) Spinal cord stimulation Intravenous (IV) infusion pain CRPS Reflex sympathetic
metaRegister of Controlled Trials (mRCT) http://www.controlled-trials.com/mrct/	May 12, 2008	Neuropathic pain and block Neuralgia Nerve block (s/ade) and pain Epidural block (s/ade) pain Epidural nerve pain Spinal cord stimulation Complex Regional pain syndrome Reflex sympathetic Iv infusion and pain; intravenous infusion and pain
HTA resources		
AETMIS http://www.aetmis.gouv.qc.ca	May 12, 2008	Neuropathic pain; neuralgia; causalgia; neuropathy; nerve; epidural; stimulation; pain syndrome; sympathetic; intravenous
CADTH http://www.cadth.ca	May 12, 2008	Neuropathic; neuralgia; causalgia; neuropathy; nerve; epidural; stimulation; pain syndrome; sympathetic; intravenous
Institute for Clinical and Evaluative Sciences (ICES), Ontario http://www.ices.on.ca/	May 12, 2008	Browsed list of reports
Health Technology Assessment Unit At McGill http://www.mcgill.ca/tau/	May 12, 2008	Browsed list of reports
Medical Advisory Secretariat http://www.health.gov.on.ca/english/providers/program/mas/mas_mn.html	May 12, 2008	Browsed list of analyses and recommendations
CCE http://www.med.monash.edu.au/healthservices/cce/	May 12, 2008	Browsed list of current evidence reviews
ASERNIP-S http://www.surgeons.org/asernip-s/	May 12, 2008	Browsed list of publications
WorksafeBC http://www.worksafebc.com/health_care_providers/related_information/evidence_based_medicine/default.asp	May 12, 2008	Browsed list of systematic reviews

NIHR Health Technology Assessment Programme http://www.ncchta.org	May 12, 2008	Browsed HTA research
NZHTA http://nzhta.chmeds.ac.nz/publications.htm	May 12, 2008	Browsed list of publications
NICE (UK) http://www.nice.org.uk/	May 12, 2008	Neuropathic; neuralgia; causalgia; neuropathy; nerve; block; epidural; stimulation; pain; sympathetic; intravenous
MSAC http://www.msac.gov.au/	May 12, 2008	Browsed lists of current and completed assessments
National Horizon Scanning Centre http://www.pcpoh.bham.ac.uk/publichealth/horizon	May 12, 2008	Browsed lists of publications and technology briefings
AHRQ http://www.ahrq.gov	May 12, 2008	Browsed lists of technology assessments and evidence reports
California Technology Assessment Forum (CTAF) http://www.ctaf.org	May 12, 2008	Browsed list of assessments
Euroscan	May 12, 2008	Browsed list of technology reports

“*” is a truncation character that retrieves all possible suffix variations of the root word e.g. surg* retrieves surgery, surgical, surgeon, etc.

; separates search terms that were searched separately

Note 1: EMBASE Search Strategy

1. pain.mp. or POSTOPERATIVE PAIN/ or exp PAIN/
2. exp Neuropathic pain/
3. 1 or 2
4. exp NEURALGIA/
5. exp Neuropathy/
6. (neuropath\$ or neurogenic or neuralgia\$).mp.
7. reflex sympathetic dystrophy.mp.
8. complex regional pain syndrome\$.mp.
9. exp Radiculopathy/
10. (radiculopath\$ or plexopath\$).mp.
11. exp Nervous System Injury/
12. post stroke.mp.
13. causalgia.mp.
14. Multiple Sclerosis/
15. exp Spinal Cord Disease/
16. sciatic nerve/
17. peripheral nerve/
18. peripheral nerve injur\$.mp.
19. brachial plexus/
20. (sciatica or ischialgia).mp.
21. exp spinal cord/
22. exp Nervous System Tumor/
23. exp Agnosia/

24. exp amputation/
25. post mastectomy.mp.
26. exp Somatosensory Disorder/
27. or/4-25
28. 3 and 27
29. (non-pharmacologic\$ adj2 (treatment\$ or intervention\$ or therap\$)).mp.
30. exp nerve block/
31. nerve block\$.mp.
32. medial branch block\$.mp.
33. intravenous drug administration/
34. ((intravenous or iv) adj1 infusion\$).mp.
35. spinal cord stimulation/
36. ((spinal cord or spinal nerve) adj1 stimulat\$).mp.
37. sympathetic blocking/
38. sympathetic block\$.mp.
39. exp epidural anesthesia/
40. epidural block\$.mp.
41. (epidural steroid injection\$ or tfesi).mp.
42. epidural drug administration/
43. ((paravertebral or paraspinal) adj1 (block\$ or injection\$)).mp.
44. stellate ganglion block\$.mp.
45. or/29-44
46. 28 and 45
47. meta-analysis.mp.
48. (medline or pubmed or search\$).mp.
49. systematic\$ review\$.mp.
50. (technology assessment\$ or hta).mp.
51. practice guideline.mp.
52. clinical pathway/
53. consensus development.mp. or consensus statement.ti.
54. or/47-53
55. 46 and 54
56. random\$.tw. or placebo\$.mp. or double-blind\$.tw. or trial.ti.
57. controlled clinical trial/ or randomized controlled trial/
58. 56 or 57
59. 46 and 58
60. 55 or 59
61. limit 60 to yr="1997 - 2008"

Note 2: MEDLINE Search Strategy

1. pain.mp. or exp Pain/ or Pain, Postoperative/
2. neuropath\$.mp.
3. neurogenic.mp.
4. exp peripheral nervous system diseases/ or brachial plexus neuropathies/ or complex regional pain syndromes/ or diabetic neuropathies/ or neuralgia/ or sciatica/
5. Facial Neuralgia/
6. Trigeminal Neuralgia/
7. neuralgia\$.mp.
8. reflex sympathetic dystrophy.mp.
9. exp polyradiculopathy/
10. (radiculopath\$ or plexopath\$).mp.
11. complex regional pain syndromes/ or causalgia/ or reflex sympathetic dystrophy/
12. thalamic.mp.
13. post stroke.mp.
14. exp Multiple Sclerosis/

15. Syringomyelia/
16. Sciatic Nerve/ or Peripheral Nerves/
17. peripheral nerve injur\$.mp.
18. exp Brachial Plexus/ or brachial plexus injury pain syndrome.mp. or exp Brachial Plexus Neuropathies/
19. (sciatica or ischialgia).mp.
20. exp Spinal Cord/
21. exp Spinal Cord Diseases/
22. exp Nervous System Neoplasms/
23. Phantom Limb/
24. amputation/
25. post mastectomy.mp.
26. somatosensory disorders/ or hyperalgia/ or hyperesthesia/ or paresthesia/
27. (complex regional pain syndrome\$ or reflex sympathetic dystrophy\$ or causalgia).mp.
28. or/2-27
29. 1 and 28
30. (non-pharmacologic\$ adj2 (treatment\$ or intervention\$ or therap\$)).mp.
31. exp Nerve Block/
32. nerve block\$.mp.
33. Infusions, Intravenous/
34. ((intravenous or iv) adj1 infusion\$).mp.
35. Anesthetics, Local/
36. spinal nerve stimulat\$.mp.
37. spinal cord stimulat\$.mp.
38. sympathetic block\$.mp.
39. Analgesia, Epidural/
40. Injections, Epidural/
41. epidural block\$.mp.
42. medial branch block\$.mp.
43. (epidural steroid injection\$ or tfesi).mp.
44. ((paravertebral or paraspinal) adj1 (block\$ or injection\$)).mp.
45. stellate ganglion block\$.mp.
46. or/30-45
47. 29 and 46
48. meta-analysis.mp,pt.
49. (medline or pubmed or search\$).mp.
50. systematic\$ review\$.mp.
51. (technology assessment\$ or hta).mp.
52. practice guideline.mp,pt. or guideline.pt.
53. critical pathways/
54. consensus development conference.pt. or consensus statement.ti.
55. or/48-54
56. 47 and 55
57. Clinical trial.pt. or randomized.ab. or placebo.ab. or clinical trials/ or randomly.ab. or trial.ti.
58. 47 and 57
59. 56 or 58
60. limit 59 to yr="1997 - 2008"

Note 3: AMED Search Strategy

1. pain.mp. or exp Pain/
2. (neuropath\$ or neurogenic or neuralgia\$).mp.
3. exp peripheral nervous system disease/
4. (reflex sympathetic dystrophy or complex regional pain syndrome\$).mp.
5. (radiculopath\$ or plexopath\$).mp.
6. causalgia.mp.
7. post stroke.mp.
8. thalamic.mp.
9. multiple sclerosis/
10. exp spinal cord disease/
11. exp spinal cord injuries/
12. exp peripheral nerves/
13. peripheral nerve injur\$.mp.
14. (sciatica or ischialgia).mp.
15. spinal cord/
16. exp nervous system neoplasms/
17. hyperalgesia/ or paresthesia/ or phantom limb/
18. amputation/
19. post mastectomy.mp.
20. or/2-19
21. 1 and 20
22. ((non-pharmacologic\$ or nonpharmacologic\$) adj2 (treatment\$ or intervention\$ or therap\$)).mp.
23. nerve block/
24. nerve block\$.mp.
25. medial branch block\$.mp.
26. ((intravenous or iv) adj1 infusion\$).mp.
27. ((spinal nerve or spinal cord) adj2 stimulat\$).mp.
28. sympathetic block\$.mp.
29. analgesia epidural/
30. epidural block\$.mp.
31. (epidural steroid injection\$ or tfesi).mp.
32. ((paravertebral or paraspinal) adj1 (block\$ or injection\$)).mp.
33. stellate ganglion block\$.mp.
34. or/22-33
35. meta-analys\$.mp. or search\$.tw. or review.pt. or systematic review.mp.
36. random\$.mp.
37. practice guidelines/ or practice guideline\$.mp.
38. or/35-37
39. 21 and 34 and 38
40. limit 39 to yr="1997 - 2008"

APPENDIX B: EXCLUDED STUDIES AND STUDIES NOT RETRIEVED BY THE REPORT DEADLINE

Table B.1: Summary of excluded studies on *epidural injections* (listed in alphabetical order of first author)

Study	Study Type	Reason for Exclusion
Systematic reviews		
Abbasi A. Complications of interlaminar cervical epidural steroid injections: A review of the literature. <i>Spine</i> 2007; 32(19):2144-51.	Quasi-systematic review	Included studies not critically appraised.
Abram SE. Epidural steroid injections for the treatment of lumbosacral radiculopathy. <i>Journal of Back and Musculoskeletal Rehabilitation</i> 1997; 8(2):135-49.	Quasi-systematic review	Included studies not critically appraised.
Agency for Healthcare Research and Quality. Management of chronic central neuropathic pain following traumatic spinal cord injury. Report No. 45. 2001. Available: http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=hstat1.chapter.64890	Systematic review	Included studies on children/adolescents (>13 years of age).
Albazaz R. Complex Regional Pain Syndrome: A Review. <i>Annals of Vascular Surgery</i> 2008; 22(2):297-306.	Quasi-systematic review	Included studies not critically appraised.
Alper BS, Lewis PR. Treatment of postherpetic neuralgia: a systematic review of the literature. <i>The Journal of Family Practice</i> 2002; 51(2):121-8.	Systematic review	Literature searches conducted up to October 2000. Superseded by as Kumar et al. (2004) ²³ .
Argoff CE, Katz N, Backonja M. Treatment of postherpetic neuralgia: A review of therapeutic options. <i>Journal of Pain and Symptom Management</i> 2004; 28(4):396-411.	Narrative review	Not a systematic review.
Armon C, Argoff CE, Samuels J, Backonja MM; Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Assessment: Use of epidural steroid injections to treat radicular lumbosacral pain: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. <i>Neurology</i> 2007; 68(10):723-9.	Systematic review	Literature searches conducted up to February 2005. Superseded by Abdi et al. (2007) ²¹ .
Attal N. Pharmacologic treatment of neuropathic pain. <i>Acta Neurologica Belgica</i> 2001; 101(1):53-64.	Narrative review	Not a systematic review.
Awad JN, Moskovich R. Lumbar disc herniations: Surgical versus nonsurgical treatment. <i>Clinical Orthopaedics and Related Research</i> 2006; 443:183-97.	Quasi-systematic review	Included studies not critically appraised.
Bernstein RM. Injections and surgical therapy in chronic pain. <i>Clinical Journal of Pain</i> 2001; 17(4 Suppl):S94-S104.	Quasi-systematic review	Included studies not critically appraised.
Bhargava A, DePalma MJ, Ludwig S, Gelb D, Slipman CW. Injection therapy for lumbar radiculopathy. <i>Current Opinion in Orthopaedics</i> 2005; 16(3):152-7.	Systematic review	Literature searches conducted from December 2003 to January 2005. Superseded by Abdi et al. (2007) ²¹ .
Boswell MV, Hansen HC, Trescot AM, Hirsch JA. Epidural steroids in the management of chronic spinal pain and radiculopathy. <i>Pain Physician</i> 2003; 6(3):319-34.	Systematic review	Literature searches conducted up to March, 2003. Superseded by Abdi et al. (2007) ²¹ .

Carragee EJ, Hurwitz EL, Cheng I, Carroll LJ, Nordin M, Guzman J, et al. Treatment of neck pain: injections and surgical interventions: results of the Bone and Joint Decade 2000-2010 Task Force on Neck Pain and Its Associated Disorders. <i>Spine</i> 2008; 33(4 Suppl):S153-69.	Systematic review	Literature searches conducted up to 2005; additional key articles included that were published in 2006 and early 2007. All of the relevant studies were also included in Abdi et al. (2007) ²¹ , but Abdi et al. (2007) had broader inclusion criteria and consequently included more studies than Carragee et al. (2008).
Chan PSL, Clark AJ. Postherpetic neuralgia: Review of treatment modalities. <i>Pain Research and Management</i> 2000; 5(1):69-74.	Quasi-systematic review	Included studies not critically appraised.
DePalma MJ, Bhargava A, Slipman CW. A critical appraisal of the evidence for selective nerve root injection in the treatment of lumbosacral radiculopathy. <i>Archives of Physical Medicine and Rehabilitation</i> 2005; 86(7):1477-83.	Systematic review	Literature searches conducted up to 2003. Superseded by Abdi et al. (2007) ²¹ .
Halbert J, Crotty M, Cameron ID. Evidence for the optimal management of acute and chronic phantom pain: A systematic review. <i>The Clinical Journal of Pain</i> 2002; 18(2):84-92.	Systematic review	Does not include epidural injections for pain lasting more than 2 weeks after limb amputation.
Harden RN. Pharmacotherapy of complex regional pain syndrome. <i>American Journal of Physical Medicine & Rehabilitation</i> 2005; 84(3 Suppl):S17-S28.	Narrative review	Search strategy not described. Included studies not critically appraised.
Hempenstall K, Nurmikko TJ, Johnson RW, A'Hern RP, Rice ASC. Analgesic therapy in postherpetic neuralgia: A quantitative systematic review. <i>PLoS Medicine</i> 2005; 2(7):e164.	Systematic review	Included the same studies as Kumar et al. (2004) ²³ . Kumar et al. (2004) ²³ had broader inclusion criteria and consequently included more studies than Hempenstall et al. (2005). Also, the epidural steroid injection results in Hempenstall et al. (2005) were reported only as the comparator intervention for intrathecal injections.
Institute for Clinical Systems Improvement (ICSI). Fluoroscopically guided transforaminal epidural steroid injections for lumbar radicular pain. Bloomington (MN): Institute for Clinical Systems Improvement (ICSI); 2004. Available: http://www.icsi.org/technology_assessment_reports_-_active/ta_fluoroscopically_guided_transforaminal_epidural_steroid_injections_for_lumbar_radicular_pain.html	Systematic review	Search strategy date limits not reported, included the same studies as Abdi et al. (2007) ²¹ .
Kalso E, Edwards JE, Moore RA, McQuay HJ. Opioids in chronic non-cancer pain: systematic review of efficacy and safety. <i>Pain</i> 2004; 112(3):372-80.	Systematic review	Does not include epidural injections.
Kemler MA. Complex regional pain syndrome type I. <i>Pain Reviews</i> 2001; 8(1):35-45.	Quasi-systematic review	Included studies not critically appraised.
Kindler CH, Seeberger MD, Staender SE. Epidural abscess complicating epidural anesthesia and analgesia. An analysis of the literature. <i>Acta Anaesthesiologica Scandinavica</i> 1998; 42(6):614-20.	Quasi-systematic review	Included studies not critically appraised. Does not include studies on epidural injections for neuropathic pain.

Kingery WS. A critical review of controlled clinical trials for peripheral neuropathic pain and complex regional pain syndromes. <i>Pain</i> 1997; 73(2):123-39.	Systematic review	Does not include studies on epidural injections for neuropathic pain.
Koes BW. Epidural steroid injections for low back pain and sciatica: An updated systematic review of randomized clinical trials. <i>Pain Digest</i> 1999; 9(4):241-7.	Systematic review	Literature searches conducted up to 1998. Superseded by Abdi et al. (2007) ²¹ .
Luijsterburg PA, Verhagen AP, Ostelo RW, Van Os TA, Peul WC, Koes BW. Effectiveness of conservative treatments for the lumbosacral radicular syndrome: a systematic review. <i>European Spine Journal</i> 2007; 16(7):881-99.	Systematic review	Literature searches conducted up to May 2004. Superseded by Abdi et al. (2007) ²¹ .
Manchikanti L, Singh V. Managing phantom pain. <i>Pain Physician</i> 2004; 7(3):365-75.	Narrative review	Search strategy not described. Included studies not critically appraised.
McQuay HJ, Moore RA, Eccleston C, Morley S, De C Williams AC. Systematic review of outpatient services for chronic pain control. <i>Health Technology Assessment</i> 1997; 1(6):1-137. Available: http://www.ncchta.org/execsumm/summ106.htm	Systematic review	Literature searches conducted up to May 1993. Superseded by Abdi et al. (2007) ²¹ .
Middleton WJ. Lumbar sympathetic block: A review of complications. <i>Techniques in Regional Anesthesia and Pain Management</i> 1998; 2(3):137-46.	Narrative review	Search strategy not described. Included studies not critically appraised.
Nelemans PJ, deBie RA, deVet HC, Sturmans F. Injection therapy for subacute and chronic benign low back pain. <i>Spine</i> 2001; 26(5):501-15.	Systematic review	Literature searches conducted up to 1998. Superseded by Abdi et al. (2007) ²¹ .
Nelson DV, Stacey BR. Interventional therapies in the management of complex regional pain syndrome. <i>Clinical Journal of Pain</i> 2006; 22(5):438-42.	Narrative review	Search strategy not described. Included studies not critically appraised.
Novak S, Nemeth WC. The basis for recommending repeating epidural steroid injections for radicular low back pain: a literature review. <i>Archives of Physical Medicine and Rehabilitation</i> 2008; 89(3):543-52.	Systematic review	Literature searches conducted up to December 2005. Superseded by Abdi et al. (2007) ²¹ .
Peloso PMJ, Gross A, Haines T, Trinh K, Goldsmith CH, Burnie SJ, Cervical Overview Group. Medicinal and injection therapies for mechanical neck disorders. <i>Cochrane Database of Systematic Reviews</i> 2007, Issue 3. Art. No.: CD000319. DOI: 10.1002/14651858.CD000319.pub4	Systematic review	The only two relevant studies were also included in Abdi et al. (2007) ²¹ . Abdi et al. (2007) ²¹ had broader inclusion criteria and consequently included more studies than Peloso et al. (2007).
Perez RS, Kwakkel G, Zuurmond WW, de Lange JJ. Treatment of reflex sympathetic dystrophy (CRPS type 1): a research synthesis of 21 randomized clinical trials. <i>Journal of Pain and Symptom Management</i> 2001; 21(6):511-26.	Systematic review	Literature searches conducted up to 2000. Superseded by Forouzanfar et al. (2002) ²² .
Rowbotham MC. Pharmacologic management of complex regional pain syndrome. <i>Clinical Journal of Pain</i> 2006; 22(5):425-29.	Narrative review	Search strategy not described. Included studies not critically appraised.
Rozenberg S, Dubourg G, Khalifa P, Paolozzi L, Maheu E, Ravaud P, and the Critical Analysis Group of the French Society for Rheumatology. Efficacy of epidural steroids in low back pain and sciatica. A critical appraisal by a French Task Force of Randomized Trials. <i>Revue du Rhumatisme</i> 1999; 66(2):79-85.	Quasi-systematic review	Included studies not critically appraised.

Stafford MA, Peng P, Hill DA. Sciatica: a review of history, epidemiology, pathogenesis, and the role of epidural steroid injection in management. <i>British Journal of Anaesthesia</i> 2007; 99(4):461-73.	Quasi-systematic review	Included studies not critically appraised.
Van Zundert J, Harney D, Joosten EAJ, Durieux ME, Patijn J, Prins MH, Van Kleef M. The role of the dorsal root ganglion in cervical radicular pain: Diagnosis, pathophysiology, and rationale for treatment. <i>Regional Anesthesia and Pain Medicine</i> 2006; 31(2):152-67.	Systematic review	Literature searches conducted up December 2004. Superseded by Abdi et al. (2007) ²¹ .
Vroomen PC, de Krom MC, Slofstra PD, Knottnerus JA. Conservative treatment of sciatica: a systematic review. <i>Journal of Spinal Disorders</i> 2000; 13(6):463-9.	Systematic review	Literature searches conducted up to 1998. Superseded by Abdi et al. (2007) ²¹ .
Wunderlich RP. Pathophysiology and treatment of painful diabetic neuropathy of the lower extremity. <i>Southern Medical Journal</i> 1998; 91(10):894-98.	Quasi-systematic review	Included studies not critically appraised.
Randomized controlled trials		
Aldrete JA. Epidural injections of indomethacin for postlaminectomy syndrome: a preliminary report. <i>Anesthesia and Analgesia</i> 2003; 96(2):463-8.	Randomized controlled trial	Indication not described in the included systematic reviews.
Arakawa M, Aoyama Y, Ohe Y. Epidural bolus injection with alkalized lidocaine improves blockade of the first sacral segment--a brief report. <i>Canadian Journal of Anaesthesia</i> 2002; 49(6):566-70.	Randomized controlled trial	Only included surgical patients.
Jeong HS, Lee JW, Kim SH, Myung JS, Kim JH, Kang HS. Effectiveness of transforaminal epidural steroid injection by using a preganglionic approach: a prospective randomized controlled study. <i>Radiology</i> 2007; 245(2):584-90.	Randomized controlled trial	Technical paper.
Lee IS, Kim SH, Lee JW, Hong SH, Choi J-Y, Kang HS, et al. Comparison of the temporary diagnostic relief of transforaminal epidural steroid injection approaches: conventional versus posterolateral technique. <i>AJNR: American Journal of Neuroradiology</i> 2007; 28(2):204-8.	Non-randomized comparative study	Not a randomized or quasi-randomized controlled trial.
Guidelines		
Airaksinen O, Brox JI, Cedraschi C, Hildebrandt J, Klaber-Moffett J, Kovacs F, et al. on behalf of the COST B13 Working Group on Guidelines for Chronic Low Back Pain. European guidelines for the management of chronic non-specific low back pain. 2004. Available: http://www.kovacs.org/Imagenes/EuropeanGuidelinesCHRONIC.LBP.pdf	Guideline	Non-specific chronic low back pain only. Radicular pain not included.
Ambrosio F, Finco G, Mattia C, Mediati R, Paoletti F, Coluzzi F, et al. SIAARTI recommendations for chronic non-cancer pain. <i>Minerva Anestesiologica</i> 2006; 72(11):859-80.	Guideline	Does not specifically address epidural injections for neuropathic pain.
American Society of Anesthesiologists. Practice guidelines for chronic pain management. A report by the American Society of Anesthesiologists Task Force on Pain Management, Chronic Pain Section. <i>Anesthesiology</i> 1997; 86(4):995-1004.	Guideline	Does not include epidural injections.
Bennett G, Burchiel K, Buchser E, Classen A, Deer T, De Pen S, et al. Clinical guidelines for intraspinal infusion: report of an expert panel. <i>Journal of Pain and Symptom Management</i> 2000; 20(2):S37-S43.	Consensus statement	Not an evidence-based guideline.

Bogduk N. Epidural steroids for low back pain and sciatica: Executive summary and recommendations of the working party of the National Health and Medical Research Council. <i>Pain Digest</i> 1999; 9(4):226-34.	Guideline	Document is a summary of the recommendations made in a clinical practice guideline that was published in 1994. Since the original document was published earlier than the date limits for this summary, it was not included.
Dworkin RH, Backonja M, Rowbotham MC, Allen RR, Argoff CR, Bennett GJ, et al. Advances in neuropathic pain: diagnosis, mechanisms, and treatment recommendations. <i>Archives of Neurology</i> 2003; 60(11):1524-34.	Guideline	Does not include epidural injections.
Institute for Clinical Systems Improvement (ICSI). Assessment and management of chronic pain. Bloomington (MN): Institute for Clinical Systems Improvement (ICSI); 2007. Available: http://www.ngc.gov/summary/summary.aspx?doc_id=10724&nbr=005586&string=%22neuropathic+pain%22	Guideline	Does not specifically address neuropathic pain.
Netherlands Society of Rehabilitation Specialists and the Netherlands Society of Anaesthesiologists. Guideline: Complex regional pain syndrome type I. 2006. Available: http://www.cbo.nl/product/richtlijnen/folder20021023121843/rl_crps_eng_07.pdf	Guideline	Included studies on children.
New Zealand Accident Compensation Corporation. Caudal/sacral epidural injection of steroid (with/without local anaesthetic). 2005. Available: http://www.acc.co.nz/for-providers/interventional-pain-management/interventions/intervention-index/WCM1_033805	Guideline	Included studies on children/adolescents (>12 years of age).
New Zealand Accident Compensation Corporation. Lumbar epidural steroid injection (with/without local anaesthetic). 2005. Available: http://www.acc.co.nz/for-providers/interventional-pain-management/interventions/intervention-index/WCM1_033801	Guideline	Included studies on children/adolescents (>12 years of age).
New Zealand Accident Compensation Corporation. Transforaminal epidural injection of steroid (with/without local anaesthetic). 2005. Available: http://www.acc.co.nz/for-providers/interventional-pain-management/interventions/intervention-index/WCM1_033825	Guideline	Included studies on children/adolescents (>12 years of age).
New Zealand Accident Compensation Corporation. Cervical epidural steroid and local anaesthetic injection. 2005. Available: http://www.acc.co.nz/for-providers/interventional-pain-management/interventions/intervention-index/WCM1_033866	Guideline	Included studies on children/adolescents (>12 years of age).
Sanders SH, Harden RN, Vicente PJ. Evidence-based clinical practice guidelines for interdisciplinary rehabilitation of chronic non-malignant pain syndrome patients. <i>Pain Practice</i> 2005; 5(4):303-15.	Guideline	Does not specifically address neuropathic pain.
Stanton-Hicks M, Baron R, Boas R, Gordh T, Harden N, Hendler N, et al. Complex Regional Pain Syndromes: guidelines for therapy. <i>Clinical Journal of Pain</i> 1998; 14(2):155-66.	Consensus statement	Not an evidence-based guideline.
The College of Physicians and Surgeons of Ontario. Evidence-Based Recommendations for Medical Management of Chronic Non-malignant Pain. 2000. Available: https://www.cpso.on.ca/uploadedFiles/policies/guidelines/met_hadone/MedicalManagementPain.pdf	Guideline	Does not include epidural injections.

Table B.2: Summary of potentially relevant studies on *epidural injections* that could not be retrieved by the report deadline (listed in alphabetical order of first author)

Study	Abstract
Randomized controlled trials	
<p>Balaban B. The effect of transforaminal and caudal epidural steroid injections in patients with lumbar disk hernia. <i>Journal of Rheumatology and Medical Rehabilitation</i> 2005; 16(3):170-76.</p>	<p>The aim of this study was to investigate the efficacy of epidural steroid injections in patients with back and radicular leg pain due to lumbar disk hernia. Thirty-four patients with discal radicular pain of four or less months were included in the study. The patients were randomized to receive fluoroscopy-guided transforaminal or caudal epidural steroid injections. Clinical assessments were undertaken before treatment and at 2 weeks and 3 months following treatment. At 2 weeks and 3 months, there were significant improvement within both groups compared with pretreatment values ($P < 0.05$). However, at 2 weeks, differences in improvements between the groups were not significant, except for improvement in the Rolland Morris score which was greater in the transforaminal group. After 3 months, the between-group difference was significantly in favour of the transforaminal group with respect to visual analog scale, straight-leg raising test and Roland Morris scale ($P < 0.05$). Transforaminal injection gives an opportunity to use less medication and seems more effective than caudal injection in respect to pain relief and daily activity improvement.</p>

APPENDIX C: QUALITY ASSESSMENT CHECKLIST FOR SYSTEMATIC REVIEWS⁶⁻⁹

Study Question

The research question should be established a priori.

Reported:

The objectives of the review are clearly stated in the abstract, introduction, or methods.

Partially reported:

The objectives of the review are stated in:

- the abstract, introduction, or methods but are vague or unclear; or
- a section of the report other than the abstract, introduction, or methods.

Not reported:

The objectives are not stated in any section of the review.

Inclusion/Exclusion Criteria

The participants, interventions, outcome measures, and types of studies considered for analysis should be established a priori.

Reported:

All four elements (participants, interventions, outcome measures, types of studies) are reported in the abstract, introduction, or methods section of the review.

Partially reported:

Only three of the four elements are reported in the abstract, introduction, or methods section.

Not reported:

Less than three of the four elements are reported in the abstract, introduction, or methods section; or

- The first mention of any of these elements occurs in the results section.

Search Strategy

Electronic databases

Reported:

At least one electronic database was searched and the names of the databases are provided.

Partially reported:

At least one electronic database was searched but the names are not provided.

Not reported:

Electronic databases were not searched or are not mentioned in the review.

Quality subsection 1: At least MEDLINE and EMBASE

Yes:

Both MEDLINE and EMBASE were searched.

Unclear:

It was unclear whether MEDLINE and EMBASE were searched because a complete list of all the electronic databases searched is not provided.

No:

The review stated that neither MEDLINE nor EMBASE was searched;

- Neither MEDLINE nor EMBASE is mentioned in the complete list of electronic databases searched; or
- Only one of the two the databases was searched.

Other sources

Reported:

At least one additional resource or method, other than searching electronic databases, was used to identify relevant literature (e.g. pearling or review of reference lists in retrieved articles, hand searching of journals).

Partially reported:

Other resource or methods were used but details are not provided.

Not reported:

The review did not use other resource or methods to identify relevant literature or does not mention it.

Data Extraction

Data extraction method

Reported:

The data extraction process is described.

Partially reported:

A data extraction process is mentioned but no details are provided.

Not reported:

A data extraction process was not used or described.

Quality subsection 2: Standardized method

Yes:

The data categories extracted are listed or the use of a standardized data extraction form is mentioned.

Unclear:

The review states that a standardized data extraction process was used but does not list the data categories extracted or mention the use of a standardized data extraction form.

No:

The data categories extracted are not listed or the use of a standardized data extraction form is not mentioned.

Quality subsection 3: Independent data extraction by at least two reviewers

Yes:

Data were extracted independently by at least two reviewers.

Unclear:

The number of reviewers who extracted data is not stated.

No:

Data were extracted by:

- only one reviewer; or
- one reviewer and checked by another.

Quality Assessment

Criteria used to assess the validity of included studies

Reported:

A quality assessment tool or checklist was used and details are provided (e.g. name or source).

Partially reported:

A quality assessment tool or checklist was used but no details are provided.

Not reported:

A quality assessment tool or checklist was not used or mentioned; or

- Studies were only categorized according to a level of evidence hierarchy.

Quality subsection 4:

Independent quality assessment by at least two reviewers

Yes:

The quality of the included studies was assessed independently by at least two reviewers.

Unclear:

The number of reviewers who appraised study quality is not stated.

No:

Studies were assessed by:

- only one reviewer; or
- one reviewer and checked by another.

Inter-rater agreement

Reported:

The review provides a statement of the degree of difference/equivalence between the reviewers or a statistical measure of inter-rater agreement.

Partially reported:

The review mentions that inter-rater agreement was measured but does not provide a statement of the degree of difference/equivalence or a statistical measure of inter-rater agreement.

Not reported:

The review does not provide any information on inter-rater agreement.

Data Analysis/Synthesis

Only ONE of the three methods for data analysis/synthesis can be assessed. Select the data analysis type according to the definitions below. Only score the quality subsection that pertains to the particular data analysis method used in the review.

Qualitative review:

A narrative summary of the study results with no statistical analysis or pooling of results.

Quality subsection 5a:

Study quality used in analysis or discussion of study results

Yes:

Results of the included studies are discussed or analyzed in terms of their quality.

Unclear:

- Study quality was assessed but is either not used at all or is only used to analyze some of the included studies.
- The review mentions selective inclusion of 'quality' studies, but without further assessment of their quality (e.g. only RCTs were included but the robustness of their execution was not assessed).

No:

- The results of the included studies are not discussed or analyzed in terms of their quality.
- Study quality was not assessed.

Semi-quantitative review:

Incorporates a statistical analysis of individual studies without pooling the results (e.g. relative risks calculated for individual study outcomes) or pooling of results using only descriptive statistics (e.g. median, mean, mode, frequency).

Quality subsection 5b: Confidence interval/measures of dispersion reported

Yes:

Confidence intervals or measures of dispersion (range, standard deviation, standard error of the mean) are reported for all relevant analyses.

Unclear:

- Confidence intervals or measures of dispersion are only reported for some of the relevant analyses.
- Confidence intervals are reported for all relevant analyses, but the level of confidence is not specified (e.g. unclear if 95% or 99% confidence intervals were calculated).
- Measures of dispersion are reported for all relevant analyses but the type is not specified (e.g. standard deviation or standard error).

No:

Confidence intervals or measures of dispersion are not reported.

Meta-analysis:

A pooled effect estimate is calculated for at least two studies. Reviews that contain a meta-analysis of some studies and a qualitative analysis of the remaining studies are considered a 'meta-analysis'.

Quality subsection 5c: Precision of results reported

Yes:

Confidence intervals are reported for all pooled effect estimates.

Unclear:

- Confidence intervals are reported for some but not all pooled effect estimates.
- Confidence intervals are reported for all pooled effect estimates but the level of confidence is not specified (e.g. unclear if 95% or 99% confidence intervals were calculated).

No:

Confidence intervals are not reported.

Quality subsection 5d: Test of study heterogeneity conducted

Yes:

A statistical analysis of study heterogeneity is reported for all pooled studies.

Unclear:

- A statistical analysis of study heterogeneity is reported for some but not all pooled studies.
- Heterogeneity was examined visually or a statistical analysis of study heterogeneity is reported for all pooled studies, but the type of model used is not specified (e.g. fixed-effect or random-effects).

No:

A statistical analysis of study heterogeneity was not conducted.

Test for publication bias

Reported:

Publication bias was analysed or a reason provided for why it was not.

Partially reported:

- The review mentions analysing publication bias but does not present the results.
- The review states that publication bias was not analysed but does not explain why.

Not reported:

There was no mention of analysing publication bias.

Concluding Section

Potential methodological limitations

Reported:

The methodological limitations or advantages of the review are described in a separate section or paragraph.

Partially reported:

The description of the methodological limitations or advantages of the review is cursory (e.g. single sentence or no separate paragraph or section).

Not reported:

There is no mention of the potential methodological limitations or advantages of the review.

Clinical application of results

The clinical application of results is considered adequate if all of the following four elements are present in the concluding section (includes discussion) or statement of the review: treatment, treatment effect, patient group, and comparator.

Reported:

All four elements are present.

Partially reported:

Only three of the four elements are present.

Not reported:

Less than three of the four elements are present.

Incorporation of methodological quality

The review should take into account the methodological quality of the included studies when formulating the conclusions.

Reported:

The methodological quality of the included studies is mentioned in the concluding section (includes discussion) or statement of the review.

Partially reported:

The study types, as designated by a level of evidence hierarchy category, are mentioned in the concluding section (includes discussion) or statement of the review, but not the quality of the studies.

Not reported:

The methodological quality of the included studies is not mentioned in the concluding section (includes discussion) or statement of the review.

Quality subsection 6: Conclusions supported by results

Yes:

The conclusions drawn by the authors of the review are supported by the evidence presented in the results section.

Unclear:

Some, but not all, of the conclusions drawn by the authors of the review are supported by the evidence presented in the results section.

No:

The conclusions drawn by the authors of the review are not supported by the evidence presented in the results section.

Conflict of Interest and Funding

Conflict of interest

Reported:

A statement of conflict of interest (if any) is provided.

Partially reported:

A conflict of interest is mentioned but details are not provided.

Not reported:

A statement of conflict of interest (if any) is not provided.

Sources of funding

Reported:

- Funding sources are mentioned; or
- The review was developed without external funding (e.g. authors employed by a university or volunteered time to produce a Cochrane Review).

Partially reported:

External funding is mentioned but details are not provided.

Not reported:

Funding sources are not mentioned.

Quality Rating

SRs were rated on how well their methods excluded bias and confounding by examining: the search strategy used; how the data extraction, quality assessment of the included studies, and data analysis/synthesis were conducted; and whether the conclusions of the review matched the results. The SRs were rated with respect to six essential quality criteria (grey boxes above) as follows:

Good – six criteria met (✓✓✓✓✓✓), or five criteria met and one criterion ‘unclear’ (✓✓✓✓✓?).

Average – one criterion not met (✓✓✓✓✓×), or one criterion not met and one criterion ‘unclear’ (✓✓✓✓✓×?), or two criteria ‘unclear’ (✓✓✓✓✓??).

Poor – at least two criteria not met (✓✓✓✓××).

N.B. For a criterion to have been ‘met’, it must be scored as ‘yes’ (✓). For meta-analyses, the two applicable quality subsections (5c and 5d) are counted as a single quality criterion. Therefore, to meet the fifth quality criterion for meta-analyses both 5c and 5d must be scored as ‘yes’ (✓).

Table C.1: Quality assessment results for included systematic reviews

Review Characteristic		Abdi et al. (2007) ²¹	Forouzanfar et al. (2002) ²²	Kumar et al. (2004) ²³
Study question established a priori		●	●	●
Inclusion/exclusion criteria		●	●	●
Search strategy	Electronic databases	●	●	●
	<i>1. At least MEDLINE and EMBASE</i>	✓	✓	✓
	Other sources	●	●	●
Data extraction	Data extraction method	●	○	○
	<i>2. Standardized method</i>	✓	X	X
	<i>3. Independent data extraction by at least two reviewers</i>	?	?	?
Quality assessment	Criteria used to assess the validity of included studies	●	●	●
	<i>4. Independent quality assessment by at least two reviewers</i>	?	✓	?
	Inter-rater agreement for quality assessment	○	○	○
Data analysis/synthesis	Qualitative review	●	●	N/A
	<i>5a. Study quality used in analysis or discussion of study results</i>	✓	✓	N/A
	Semi-quantitative review	N/A	N/A	●
	<i>5b. Confidence intervals or measures of dispersion reported</i>	N/A	N/A	✓
	Meta-analysis	N/A	N/A	N/A
	<i>5c. Precision of results reported</i>	N/A	N/A	N/A
	<i>5d. Test of homogeneity conducted</i>	N/A	N/A	N/A
Test for publication bias		○	○	○
Concluding section	Potential methodological limitations/advantages	○	●	●
	Clinical application of results	○	○	○
	Incorporation of methodological quality	●	●	●
	<i>6. Conclusions supported by results</i>	✓	✓	✓
Conflict/funding	Conflict of interest (if any)	●	○	○
	Sources of funding	●	○	●
Quality rating	Six criteria (search at least two databases; standardized data extraction; independent data extraction and quality rating by two reviewers; appropriate data synthesis; conclusions supported by results)	4/6 Average	4/6 Average	3/6 Poor

Key for quality of reporting: Reported: ●; Partially reported: ○; Not reported: ○; Not applicable: N/A

Key for quality of review subsections (grey sections of table): Yes = ✓; Unclear = ?; No = X

APPENDIX D: QUALITY ASSESSMENT CHECKLIST FOR RANDOMIZED CONTROLLED TRIALS

(Adapted from the list recommended in the method guidelines of the Cochrane Back Review Group¹², with additional guidance derived from Downs and Black¹⁸.)

Patient Selection

A. *Were the eligibility criteria specified?*

Inclusion and/or exclusion criteria should be given.

B. *Treatment allocation*

1) *Was a method of randomization performed?*

Studies stating that patients were randomized should be answered 'yes' except where the method of randomization would not ensure random allocation.

Methods of allocation using date of birth, date of admission, hospital numbers, or alternation are not regarded as appropriate.

2) *Was the treatment allocation concealed?*

Assignment generated by an independent person not responsible for determining the eligibility of the patients.

C. *Were the groups similar at baseline regarding the most important prognostic indicators?*

To receive a 'yes', groups must be similar at baseline regarding age, sex distribution, duration of pain, and at least one of the following: patient comorbidities, mobility, health-related quality of life, or pain intensity.

Interventions

D. *Were the index and control interventions explicitly described?*

The description should include (when applicable) type, modality, application technique, intensity, and duration as well as the number and frequency of sessions so that others can replicate the treatment. If any of the treatments are described by name only, with no further detail given, the question should be answered 'no'.

E. *Were co-interventions avoided or comparable?*

Co-interventions should either be avoided in the trial design or comparable between the index and control groups.

F. *Was the patient blinded to the intervention?*

For studies where the patients would have no way of knowing which intervention they received, this should be answered 'yes'. For studies that do not state whether blinding was attempted, the answer should be 'unclear'.

Outcome Measurement

G. *Was the outcome assessor blinded to the intervention?*

For studies where the outcome assessor would have no way of knowing which intervention the patients received, this should be answered 'yes'. For studies that do not state whether blinding was attempted, the answer should be scored as 'unclear'.

H. *Were the outcome measures relevant?*

Outcome measures should be clearly described. Relevant measures for non-malignant chronic pain include changes in pain, mobility, and pain pressure threshold; generic functional status; global measure of improvement; and return to work.

I. *Were adverse effects described?*

Each event should be described and correctly attributed to the allocated treatment. If it was explicitly reported that no adverse events occurred then a 'yes' should be scored. When adverse events are described but not clearly attributed to a particular treatment, the answer should be scored as 'unclear'.

J. *Was the withdrawal/dropout rate described and acceptable?*

Patients included in the study but who did not complete the observation period or were not included in the analysis must be described. If the numbers of patients lost to follow-up were not reported, the question should be answered as 'unclear'. If the proportion lost to follow-up was too small ($\leq 10\%$ in each treatment group for short-term follow-up and $\leq 20\%$ for long-term follow-up) to affect the main findings, the question should be answered 'yes'. (**Note:** These percentages are arbitrary and are not supported by literature).

K. *Timing of follow-up measurements*

1) *Was a short-term follow-up measurement performed?*

Outcome assessment at the end of the intervention period.

2) *Was a long-term follow-up measurement performed?*

Outcome assessment >3 months after randomization.

L. *Was the timing of the outcome assessment comparable in both groups?*

The timing of outcome assessment should be identical for all intervention groups and for all important outcome assessments. Where follow-up was the same for all study patients, the answer should be 'yes'. If the results were adjusted to account for different lengths of follow-up (for example by survival analysis), the answer should be 'yes'. Studies where differences in follow-up were ignored should be answered 'no'.

Statistics

M. *Was the sample size for each group described?*

Simple outcome data (including denominators and numerators) should be reported for all major findings so that the reader can check the major analyses and conclusions.

N. *Did the analysis include an intention-to-treat analysis?*

All randomized patients are reported/analysed for the most important effect measurements (minus missing values) irrespective of non-compliance and co-interventions.

O. *Were point estimates and measures of variability presented for the primary outcome measures?*

Both point estimates and measures of variability should be presented separately for each important outcome. In non-normally distributed data the median and inter-quartile range should be reported. In normally distributed data the mean plus standard error, standard deviation, or confidence interval should be reported. If the distribution of the data is not described, it must be assumed that the estimates used were appropriate and the question should be answered 'yes'.

Quality Rating

For descriptive purposes, the included RCTs were referred to as being good, moderate, or poor quality with respect to internal and external validity according to the total number of criteria met as follows.

- Internal validity (total number of criteria = 9) – good (≥ 7 criteria met), moderate (between 4 and 6 criteria met), poor (< 4 criteria met).
- External validity (total number of criteria = 6) – good (≥ 5 criteria met), moderate (3 or 4 criteria met), poor (< 3 criteria met).

Table D.1: Quality assessment results for included randomized controlled trials

Study Characteristic		Ackerman & Ahmad (2007) ²⁴	Dincer et al. (2007) ²⁵	Owlia et al. (2007) ²⁶	Pasqualucci et al. (2007) ²⁷
Patient Selection	A. Were the eligibility criteria specified?	✓	✓	✓	✓
	B1. Was randomization performed adequately?	✓	?	?	?
	B2. Was treatment allocation concealed?	?	?	?	?
	C. Were the groups similar at baseline?	?	?	✓	?
Interventions	D. Were the index and control interventions explicitly described?	✓	✓	✓	✓
	E. Were co-interventions avoided or comparable?	✓	✓	✓	?
	F. Was the patient blinded to the intervention?	✓	NA	✓	✓
Outcome measurement	G. Was the outcome assessor blinded to the intervention?	✓	✓	?	?
	H. Were the outcome measures relevant?	✓	✓	✓	✓
	I. Were adverse events described?	✓	✓	✓	✓
	J. Was the withdrawal/dropout rate described and acceptable?	✓	✓	✓	×
	K1. Was a short-term follow-up measurement performed?	✓	✓	✓	✓
	K2. Was a long-term follow-up measurement performed?	✓	×	×	✓
	L. Was the timing of the outcome assessment comparable in both groups?	✓	✓	✓	✓
Statistics	M. Was the sample size for each group described?	✓	✓	✓	×
	N. Did the analysis include an intention-to-treat analysis?	✓	✓	✓	×
	O. Were point estimates and measures of variability presented for the primary outcome measures?	✓	✓	×	✓

Key: Yes = ✓; No = ×; Unclear = ?; Not applicable or not possible because of the nature of the intervention = NA

Internal validity criteria: b, e, f, g, h, j, l, n; External validity criteria: a, c, d, i, k; Statistical criteria: m, o

Table D.1: Quality assessment results for included randomized controlled trials (cont'd)

Study Characteristic		Zambello et al. (2006) ²⁸
Patient Selection	A. Were the eligibility criteria specified?	✓
	B1. Was randomization performed adequately?	?
	B2. Was treatment allocation concealed?	?
	C. Were the groups similar at baseline?	?
Interventions	D. Were the index and control interventions explicitly described?	?
	E. Were co-interventions avoided or comparable?	?
	F. Was the patient blinded to the intervention?	✓
Outcome measurement	G. Was the outcome assessor blinded to the intervention?	✓
	H. Were the outcome measures relevant?	✓
	I. Were adverse events described?	x
	J. Was the withdrawal/dropout rate described and acceptable?	✓
	K1. Was a short-term follow-up measurement performed?	✓
	K2. Was a long-term follow-up measurement performed?	✓
	L. Was the timing of the outcome assessment comparable in both groups?	✓
Statistics	M. Was the sample size for each group described?	✓
	N. Did the analysis include an intention-to-treat analysis?	✓
	O. Were point estimates and measures of variability presented for the primary outcome measures?	x

Key: Yes = ✓; No = x; Unclear = ?; Not applicable or not possible because of the nature of the intervention = NA

Internal validity criteria: b, e, f, g, h, j, l, n; External validity criteria: a, c, d, i, k; Statistical criteria: m, o

APPENDIX E: QUALITY ASSESSMENT CHECKLIST FOR CLINICAL PRACTICE GUIDELINES

(Adapted from The Agree Collaboration¹⁹.)

Scope and Purpose (Items 1,2,3)

Item 1 – Guideline objectives

Information about the clinical condition, target population, and expected health benefit should be provided in the objectives statement.

4 – All three elements reported (condition, target population, health benefit).

3 – Two elements reported.

2 – Unclear or only one element reported.

1 – Objectives of the guideline are not provided.

Item 2 – Clinical question

Information about the intervention and clinical condition should be provided.

4 – Two elements reported (intervention, clinical condition).

3 – One element reported.

2 – Unclear.

1 – Information about the clinical question is not provided.

Item 3 – Target population

Information about the age (defined as “adults” or by an age range), comorbidity, and clinical description (if applicable) of the target population should be provided.

4 – All applicable elements reported (age, comorbidity, clinical description). In cases where at least one element is not applicable, the guideline is scored 4 only if all of the remaining applicable elements are present. For example, if comorbidity is not applicable, the guideline will only score 4 if age and clinical description are provided.

3 – One applicable element not reported.

2 – Unclear or two applicable elements not reported.

1 – Information about the target population is not provided.

Stakeholder Involvement

Item 4 - Relevant professional groups

Information about the composition of the guideline development group (GDG) and the discipline (job title, university department, etc.) and relevant expertise (particular area of skill, e.g. methodologist, occupational medicine) of its members should be provided.

4 – All three elements (composition of the entire GDG; discipline and expertise of all GDG members) are reported.

3 – Composition of the entire GDG is provided but two elements (discipline and relevant expertise) reported for only some of its members.

2 – Unclear or composition of the entire GDG is provided but only one element (discipline and relevant expertise) reported for all of its members.

1 – Information about the GDG is not provided or composition of the entire GDG is provided but one element (discipline or relevant expertise) reported only for some of its members.

Item 5 - Patients' perspectives

4 – Patient perspectives incorporated and methods reported.

3 – Patient perspectives discussed but methods not reported.

2 – Unclear.

1 – Patient perspectives not incorporated.

Item 6 - Target users defined

4 – Target users explicitly defined by specialty, e.g. general practitioners, neurologists, physiotherapists.

3 – Target users defined in broad terms, e.g. practitioners treating patients with chronic pain.

2 – Unclear.

1 – Target users not defined.

Item 7 - Piloted among target users

4 – Guideline piloted among target users and methods reported.

3 – Guideline piloted among target users but methods not reported.

2 – Unclear.

1 – Guideline not piloted among target users.

Rigour of Development

Item 8 - Systematic methods used to search for evidence

Information about the search terms used, sources consulted, and date limits of the literature searches should be provided.

4 – All three elements reported (search terms, sources, date limits).

3 – Two elements reported.

2 – Unclear or one element reported.

1 – Information about the methods used to search for evidence is not provided.

Item 9 - Selection criteria

4 – Inclusion/exclusion criteria described and reasons for excluding (or including) evidence clearly stated.

3 – Inclusion/exclusion criteria described but reasons for excluding evidence (or including) are not stated.

2 – Unclear.

1 – Inclusion/exclusion criteria not stated.

Item 10 - Methods used to formulate recommendations

Information on the methods used to formulate the recommendations, resolve disagreements, and reach final decisions should be provided.

4 – All three elements reported (formulation of recommendations, resolving disagreements, reaching final decisions).

3 – Two elements reported.

2 – Unclear or only one element reported.

1 – Information about the methods used to formulate the recommendations is not provided.

N.B. In cases where the guideline was written by a single author, the guideline is scored as follows:

4 – The methods used to formulate the recommendations are reported.

2 – Unclear.

1 – Information about the methods used to formulate the recommendations is not provided.

Item 11 - Consideration of benefits, side effects, and risks

Information on the benefits, side effects, and risks of the recommendations should be provided.

4 – All applicable elements reported (benefits, side effects, risks). In cases where at least one element is not applicable, the guideline is scored 4 only if all of the remaining applicable elements are present. For example, if side effects are not applicable, the guideline will only score 4 if benefits and risks are provided.

3 – One applicable element not reported.

2 – Unclear or two applicable elements not reported.

1 – Information about the benefits, side effects, and risks not stated.

Item 12 - Link between recommendations and the supporting evidence

4 – Each recommendation is explicitly linked to the references on which it is based.

3 – Only some of the recommendations are explicitly linked to the references on which they are based.

2 – Unclear.

1 – No explicit link between each recommendation and the references on which it is based.

Item 13 - External review

4 – Externally reviewed by independent clinical and methodological experts and methods reported.

3 – Externally reviewed and one of the following criteria met: methods reported, reviewers included clinical and methodological experts.

2 – Unclear or externally reviewed but none of the following criteria met: methods reported, reviewers included clinical and methodological experts.

1 – Not externally reviewed or no statement about external review.

Item 14 - Procedure for updating the guideline

4 – Statement about updating the guideline and methods reported.

3 – Statement about updating the guideline but methods not reported.

2 – Unclear.

1 – Guideline will not be updated or no statement about updating the guideline.

Clarity and Presentation

Item 15 - Specific, unambiguous recommendations

The recommendations were considered adequate if all of the following three elements were present: management or treatment, patient group, clinical situation.

4 – All three elements reported.

3 – Two elements reported.

2 – Unclear or one element reported.

1 – None of the elements reported.

Item 16 - Different management options presented

4 – Different management options were considered to be adequately presented if the comparators for each intervention were stated in the guideline. For example, massage therapy is more effective than relaxation therapy in patients with chronic low back pain.

3 – The comparators were stated for only some of the interventions.

2 – Unclear.

1 – The comparators for the interventions were not stated.

Item 17 - Key recommendations identifiable

4 – Key recommendations summarized and identifiable.

3 – Key recommendations reported but not summarized or highlighted for easy identification.

2 – Unclear.

1 – Key recommendations not identifiable.

Item 18 - Additional support materials provided

4 – Additional support materials provided.

3 – Additional support materials provided but not easily available e.g. published in a journal that is not open access.

2 – Unclear.

1 – Additional support materials not provided.

Applicability

Item 19 - Organizational barriers discussed

4 – Not applicable or organizational barriers discussed and required changes are outlined.

3 – Organizational barriers mentioned but required changes are not outlined.

2 – Unclear.

1 – Organizational barriers not discussed.

Item 20 - Resource implications considered

4 – Not applicable or resource implications discussed and the effects on resources are outlined.

3 – Resources implications mentioned but the effects on resources are not outlined (or are only outlined for some interventions).

2 – Unclear.

1 – Resource implications not discussed.

Item 21 - Key review criteria presented

4 – Key review criteria presented and specific thresholds provided.

3 – Key review criteria discussed but specific thresholds not provided.

2 – Unclear.

1 – Key review criteria not presented.

Editorial Independence

Item 22 - Editorially independent from funding body

4 – Developed without external funding or details of financial support provided plus an explicit statement that the funding body has not influenced the final recommendations.

3 – Details of financial support provided but no statement about the funding body's influence on guideline development.

2 – Unclear or no details about financial support.

1 – Funding body potentially influenced the final recommendations.

Item 23 - Conflicts of interest reported

4 – Details of the affiliations and conflicts of interest (if any) of the development group are provided.

3 – Details of conflicts of interest (if any) are provided but without a list of the development group’s affiliations.

2 – Unclear or a list of the development group’s affiliations is provided but without details on conflicts of interest (if any).

1 – Details of the affiliations and conflicts of interest (if any) of the development group are not provided.

Quality Rating

Guidelines were rated on how well their methods excluded bias by examining the search strategy used; how the recommendations were formulated and presented; whether the recommendations were directly linked to the evidence; the external review process; and whether conflicts of interest and funding sources were reported. The average quality rating score (maximum possible score is 28 (7 x 4)) for these criteria was derived by dividing the sum of the scores given by each reviewer by the number of reviewers. The guideline was then rated as follows (grey rows in Table E.1).

Good – average score of 22 to 28;

Average – average score of 15 to 21;

Poor – average score 0 to 14.

Standardized Domain Scores

These scores for each of the six domains were combined and converted into standardized domain scores according to the following formula (Table E.2).

$$\text{Standardized domain score (\%)} = \frac{\text{obtained score} - \text{minimum possible score}}{\text{maximum possible score} - \text{minimum possible score}} \times 100$$

Table E.1: AGREE tool quality assessment results for included clinical practice guidelines (two appraisers)

Guideline Characteristic		Boswell et al. (2007) ²⁹		Dubinsky et al. (2004) ³⁰	
Scope/ purpose	1.Objectives	4	4	4	2
	2. Clinical question	4	3	3	4
	3. Target population	3	4	2	2
Stakeholder involvement	4. Relevant professional groups represented	2	3	1	2
	5. Patients' perspectives included	3	2	2	1
	6. Target users defined	4	4	1	1
	7. Piloted among target users	2	2	2	1
Rigour of development	8. Systematic search conducted	2	2	4	4
	9. Selection criteria described	1	2	4	3
	10. Methods used to formulate recommendations described	3	4	1	2
	11. Benefits, side effects, risks considered	4	4	4	3
	12. Link between recommendations and evidence	4	4	4	4
	13. External review by experts	2	2	2	2
	14. Updating procedure described	3	3	1	1
Clarity/ presentation	15. Specific, unambiguous recommendations	3	4	1	3
	16. Different management options presented	1	2	4	3
	17. Key recommendations easily identifiable	3	4	1	4
	18. Additional support materials provided	1	2	1	4
Applicability	19. Organizational barriers discussed	1	1	1	1
	20. Resource implications considered	3	1	1	1
	21. Key review criteria presented	1	1	1	1
Editorial independ- ence	22. Editorially independent from funder	2	4	2	2
	23. Conflicts of interest reported	2	3	2	1
Quality Rating	Seven criteria (systematic search, method of formulating recommendations, recommendations-evidence link, external review, clear recommendations, editorial independence, conflict of interest)	20.5 Average		17 Average	

Table E.1: AGREE tool quality assessment results for included clinical practice guidelines (two appraisers) (cont'd)

Guideline Characteristic		Hunter Integrated Pain Service (2009) ³¹		North American Spine Society (2007) ³²	
Scope/ purpose	1.Objectives	3	2	4	4
	2. Clinical question	4	4	4	2
	3. Target population	2	1	4	3
Stakeholder involvement	4. Relevant professional groups represented	1	1	1	2
	5. Patients' perspectives included	2	1	2	1
	6. Target users defined	3	1	3	1
	7. Piloted among target users	2	1	4	3
Rigour of development	8. Systematic search conducted	1	1	4	4
	9. Selection criteria described	1	1	4	2
	10. Methods used to formulate recommendations described	1	1	4	4
	11. Benefits, side effects, risks considered	3	1	3	2
	12. Link between recommendations and evidence	4	1	4	4
	13. External review by experts	2	1	4	2
	14. Updating procedure described	2	1	4	4
Clarity/ presentation	15. Specific, unambiguous recommendations	1	1	4	4
	16. Different management options presented	1	1	4	2
	17. Key recommendations easily identifiable	1	1	4	3
	18. Additional support materials provided	1	1	1	1
Applicability	19. Organizational barriers discussed	1	1	1	1
	20. Resource implications considered	1	1	1	1
	21. Key review criteria presented	1	1	3	1
Editorial independ- ence	22. Editorially independent from funder	2	1	2	4
	23. Conflicts of interest reported	2	1	2	1
Quality Rating	Seven criteria (systematic search, method of formulating recommendations, recommendations-evidence link, external review, clear recommendations, editorial independence, conflict of interest)	10 Poor		23.5 Good	

Table E.2: AGREE tool standardized domain scores (%) for included clinical practice guidelines (two appraisers)

AGREE Domain	Boswell et al. (2007)²⁹	Dubinsky et al. (2004)³⁰	Hunter Integrated Pain Service (2009)³¹	North American Spine Society (2007)³²
Scope and purpose	89	61	56	83
Stakeholder involvement	58	13	17	38
Rigour of development	62	60	17	83
Clarity and presentation	50	54	0	63
Applicability	11	0	0	11
Editorial independence	58	25	17	42

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