



**INSTITUTE OF
HEALTH ECONOMICS**
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THERAPEUTIC INTRAVENOUS INFUSIONS 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 second 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, therapeutic 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 therapeutic intravenous infusions 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

Randomized controlled trials 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.

Index Intervention

Therapeutic intravenous (IV) infusion of any drug for treating neuropathic pain. Diagnostic IV infusions and IV sympathetic blocks were not included.

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 therapeutic IV infusions 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. 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 IV infusion 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-two studies were identified that potentially met the inclusion criteria. On closer examination of the full text article, 35 of these studies were excluded and the reasons documented (Appendix B). Five SRs and one CPG were included (Table 1). Eleven 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.

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			
Forouzanfar et al. ²¹	2002	Average (4/6)	Complex regional pain syndrome type I or reflex sympathetic dystrophy
Hempenstall et al. ²²	2005	Good (6/6)	Postherpetic neuralgia
Kalso et al. ²³	1998	Average (4/6)	Peripheral nerve injury Diabetic neuropathy Postherpetic neuralgia
Kalso et al. ²⁴	2004	Poor (3/6)	Postherpetic neuralgia Mixed neuropathic pain Central pain Phantom pain
Kingery ²⁵	1997	Poor (1/6)	Diabetic neuropathy Postherpetic neuralgia Nerve injuries
Randomized Controlled Trials			
Attal et al. ²⁶	2004	<i>Internal validity</i> Good (9/9) <i>External validity</i> Moderate (4/6)	Postherpetic neuralgia or traumatic nerve injury Crossover trial (n=22): lidocaine vs saline
Brill et al. ²⁷	2002	<i>Internal validity</i> Good (7/9) <i>External validity</i> Moderate (4/6)	Postherpetic neuralgia Crossover trial (n=7): magnesium vs saline
Eichenberger et al. ²⁸	2008	<i>Internal validity</i> Good (8/9) <i>External validity</i> Moderate (4/6)	Phantom limb pain Crossover trial: calcitonin (n=20) vs ketamine (n=10) vs calcitonin plus ketamine (n=20) vs saline (n=20)
Finnerup et al. ²⁹	2005	<i>Internal validity</i> Good (8/9) <i>External validity</i> Good (5/6)	Spinal cord injury Crossover trial (n=24): lidocaine vs saline
Gottrup et al. ³⁰	2006	<i>Internal validity</i> Poor (3/9) <i>External validity</i> Good (5/6)	Nerve injury Crossover trial (n=20): lidocaine vs ketamine vs saline

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

Study	Year	Quality Rating	Pain Condition/Treatment Comparisons
Randomized Controlled Trials (cont'd)			
Kvarnström et al. ³¹	2003	<i>Internal validity</i> Moderate (6/9) <i>External validity</i> Good (5/6)	Peripheral nerve or root lesions of traumatic origin Crossover trial (n=12): lidocaine vs ketamine vs saline
Kvarnström et al. ³²	2004	<i>Internal validity</i> Moderate (6/9) <i>External validity</i> Good (5/6)	Traumatic spinal cord injury Crossover trial (n=10): lidocaine vs ketamine vs saline
Medrik-Goldberg et al. ³³	1999	<i>Internal validity</i> Moderate (5/9) <i>External validity</i> Moderate (4/6)	Lumbar radicular pain Crossover trial (n=30): lidocaine vs amantadine vs saline
Robinson et al. ³⁴	2004	<i>Internal validity</i> Moderate (6/9) <i>External validity</i> Moderate (3/6)	Complex regional pain syndrome type I Pamidronate (n=14) vs saline (n=13)
Tremont-Lukats et al. ³⁵	2004	<i>Internal validity</i> Good (7/9) <i>External validity</i> Moderate (4/6)	Peripheral neuropathic pain Lidocaine 1 mg/kg/hour (n=7) vs lidocaine 3 mg/kg/hour (n=9) vs lidocaine 5 mg/kg/hour (n=8) vs saline (n=7)
Viola et al. ³⁶	2006	<i>Internal validity</i> Moderate (4/9) <i>External validity</i> Good (5/6)	Diabetic neuropathy Crossover trial (n=15): lidocaine 5 mg/kg vs lidocaine 7.5 mg/kg vs saline
Clinical Practice Guidelines			
North American Spine Society ³⁷	2007	Good (23.5/28)	Degenerative lumbar spinal stenosis

STUDY PROFILES – SYSTEMATIC REVIEWS

Table 2: Study profiles for *systematic reviews* on therapeutic intravenous infusions for neuropathic pain

Systematic Review	Population	Selection Criteria/Outcomes	Methods
<p>Forouzanfar et al. (2002)²¹</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: Intravenous clodronate: n = 32 (one randomized controlled trial (RCT)); Intravenous alendronate: n = 20 (one RCT).</p> <p>Age: Not stated.</p> <p>Included conditions: Complex regional pain syndrome type I or reflect 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)³⁸ 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>

Table 2: Study profiles for systematic reviews on therapeutic intravenous infusions for neuropathic pain (cont'd)

Systematic Review	Population	Selection Criteria/Outcomes	Methods
<p>Hempenstall et al. (2005)²²</p> <p>Objective: To conduct a systematic review and meta-analysis of analgesic therapy for post-herpetic neuralgia.</p> <p>Financial support: No funding received.</p> <p>Conflict of interest: Three of the five authors had received fees for providing services to various pharmaceutical companies.</p>	<p>Total number: Intravenous morphine: n = 19 (one randomized controlled trial (RCT)); Intravenous lidocaine: n = 43 (two RCTs).</p> <p>Age: Adults.</p> <p>Included conditions: Post-herpetic neuralgia (defined as pain persisting for longer than 3 months after the crusting of skin lesions).</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 reporting at least one clinically relevant measure of pain.</p> <p>Study exclusion criteria: Unpublished, letter, abstract-only, and prevention studies. Studies in which fewer than 10 patients were enrolled or the data for post-herpetic neuralgia were not analysed separately from other neuropathic pain syndromes.</p> <p>Outcomes measured: Pain relief outcomes, adverse effects. For efficacy, an outcome was considered clinically relevant if an improvement of 50% or greater in pain relief was achieved.</p>	<p>Literature search: <u>Time period:</u> From January 1966 to October 2004. <u>Limits:</u> Not reported. <u>Databases:</u> PubMed, MEDLINE, EMBASE, CINAHL, <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: Standard list of data extracted independently by two authors.</p> <p>Appraisal of study quality: RCTs assessed independently by at least two reviewers with the Jadad et al. (1996)¹⁶ scale. Studies scoring less than 3 were excluded. Disagreements were resolved by consensus. Unresolved disagreements were referred to a third reviewer.</p> <p>Data analysis: Quantitative where possible.</p> <p>Conclusions supported by results: Yes.</p>
<p>Kalso et al. (1998)²³</p> <p>Objective: To analyse the effectiveness of local anaesthetic-type drugs in chronic pain.</p> <p>Financial support: European Union Biomed 2 contract, National Health Service Research & Development Health Technology Assessment Programme, United Kingdom Overseas Research Students award.</p> <p>Conflict of interest: None.</p>	<p>Total number: Intravenous lidocaine for neuropathic pain: n = 68 (four randomized controlled trials (RCTs)).</p> <p>Age: Not stated.</p> <p>Included conditions: Chronic pain.</p> <p>Excluded conditions: None stated.</p>	<p>Intended comparators: Placebo, any active treatment.</p> <p>Study inclusion criteria: RCTs.</p> <p>Study exclusion criteria: Unpublished reports, abstracts, reviews or reports of experimental pain; trials without randomization or with an inadequate randomization method.</p> <p>Outcomes measured: Pain intensity, pain relief, consumption of supplementary analgesics, adverse effects.</p>	<p>Literature search: <u>Time period:</u> See Databases. <u>Limits:</u> None. <u>Databases:</u> MEDLINE (1981 to 1996), EMBASE (January 1966 to September 1996), The Oxford Pain Relief Database (1950 to 1994). <u>Other sources:</u> Additional reports were identified from reference lists of retrieved studies and review articles.</p> <p>Data extraction: Standard list of data extracted.</p> <p>Appraisal of study quality: RCTs assessed independently by each of the authors with the Jadad et al. (1996)¹⁶ scale. Disagreements were resolved by consensus.</p> <p>Data analysis: Qualitative.</p> <p>Conclusions supported by results: Yes.</p>

Table 2: Study profiles for systematic reviews on therapeutic intravenous infusions for neuropathic pain (cont'd)

Systematic Review	Population	Selection Criteria/Outcomes	Methods
<p>Kalso et al. (2004)²⁴</p> <p>Objective: To analyse the safety and efficacy of opioids in chronic non-cancer pain.</p> <p>Financial support: Helsinki University Central Hospital Research Funds and Pain Research Funds, Oxford.</p> <p>Conflict of interest: Not reported.</p>	<p>Total number: Intravenous opioids for neuropathic pain: n = 115 (four randomized controlled trials (RCTs)).</p> <p>Age: Adults.</p> <p>Included conditions: Chronic non-cancer pain.</p> <p>Excluded conditions: None stated.</p>	<p>Intended comparators: Placebo, any active treatment.</p> <p>Study inclusion criteria: Double-blind RCTs on oral, transdermal, or intravenous fentanyl, hydromorphone, methadone, morphine, oxycodone, or oxymorphone that used a visual analog scale, a numerical rating scale, or a 4-point pain intensity scale to measure pain intensity.</p> <p>Study exclusion criteria: Unpublished reports, abstracts, and reviews; reports with less than 10 patients completing each treatment arm.</p> <p>Outcomes measured: <u>Primary:</u> Pain intensity, pain relief. <u>Secondary:</u> Mood, functional status, quality of life, adverse events.</p>	<p>Literature search: <u>Time period:</u> See Databases. <u>Limits:</u> None. <u>Databases:</u> MEDLINE (January 1966 to September 2003), EMBASE (January 1980 to September 2003), <i>The Cochrane Library</i> (September 2003), The Oxford Pain Relief Database (1950 to 1994). <u>Other sources:</u> Additional reports were identified from reference lists of retrieved studies and review articles.</p> <p>Data extraction: Standard list of data extracted.</p> <p>Appraisal of study quality: RCTs assessed with the Jadad et al. (1996)¹⁶ scale and the Smith et al. (2000) scale³⁹.</p> <p>Data analysis: Quantitative where possible.</p> <p>Conclusions supported by results: Yes.</p>
<p>Kingery (1997)²⁵</p> <p>Objective: To analyse controlled clinical trial data for peripheral neuropathic pain and complex regional pain syndrome.</p> <p>Financial support: Not reported.</p> <p>Conflict of interest: Not reported.</p>	<p>Total number: Intravenous lidocaine: three randomized controlled trials (RCTs) and one non-randomized comparative study; Intravenous ketamine: three RCTs; Intravenous magnesium: one RCT.</p> <p>Data from four trials on intravenous morphine were not summarized because they are included in Hempenstall et al. (2005)²² and Kalso et al. (2004)²⁴.</p> <p>Age: Not stated.</p> <p>Included conditions: Peripheral neuropathic pain and complex regional pain syndrome.</p> <p>Excluded conditions: None stated.</p>	<p>Intended comparators: Placebo, any active treatment.</p> <p>Study inclusion criteria: Controlled clinical trials.</p> <p>Study exclusion criteria: Abstracts, duplicate data, studies in which the results for peripheral neuropathic pain or complex regional pain syndrome patients could not be separated from patients with other disorders.</p> <p>Outcomes measured: Treatment effect.</p>	<p>Literature search: <u>Time period:</u> 1969 to 1996. <u>Limits:</u> Not reported. <u>Databases:</u> Computer search of the literature conducted but details not provided. <u>Other sources:</u> Recent review articles; manual search of the literature conducted but details not provided.</p> <p>Data extraction: Not reported.</p> <p>Appraisal of study quality: RCTs scored according to a methodological criteria list.</p> <p>Data analysis: Quantitative where possible.</p> <p>Conclusions supported by results: Yes.</p>

STUDY PROFILES – RANDOMIZED CONTROLLED TRIALS

Table 3: Study profiles for *randomized controlled trials* on therapeutic intravenous infusions for neuropathic pain

Authors/Study Details	Intervention/Outcome Measures	Study Design/Execution
<p>Attal et al. (2004)²⁶ France <u>Study design:</u> Prospective randomized, double-blind concurrently controlled crossover trial. <u>Follow-up:</u> 2 hours, 2 weeks. <u>Study period:</u> Not stated. <u>Setting:</u> Pain centre. <u>Financial support:</u> l'Institut UPSA de la Douleur.</p>	<p>Crossover trial (n=22) Lidocaine Intravenous lidocaine (5 mg/kg) in the same volume over a 30-minute period starting at 11:00 am. Saline (placebo) Intravenous saline (0.9% NaCl) in the same volume over a 30-minute period starting at 11:00 am. Lidocaine & saline <u>Washout period:</u> Both treatments were performed in separate sessions 2 weeks apart. <u>Outcome measures:</u> Pain intensity (visual analog scale); average ongoing pain; tactile allodynia; quantitative sensory testing; detection and pain thresholds; thermal sensations; response to suprathreshold stimuli; adverse events. Subsequent treatments Two weeks after the second infusion all patients started oral mexiletine on an open basis at 200 mg/day and titrated upwards every week to the maximal effective dose or to the highest level at which side effects did not interfere with everyday activities.</p>	<p><u>Method of randomization:</u> Computer-generated randomization sequence. <u>Time of randomization:</u> Not reported. <u>Method of allocation concealment:</u> Randomization sequence generated by the study nurse and kept in sealed envelopes until the end of the study. <u>Details of blinding:</u> The study nurse prepared all infusions so that the anaesthesiologists, patients, and outcome assessors were blinded to order of treatment. <u>Participation rate:</u> 91.7% (22/24). <u>Eligibility rate for study:</u> Patients recruited consecutively. <u>Intention-to-treat analysis:</u> By default as all patients received both treatments. <u>Crossovers:</u> All patients received both treatments as part of the study design. <u>Provider:</u> Anaesthesiologists. <u>Assessor details:</u> A single independent assessor evaluated outcomes. <u>Inclusion criteria:</u> Patients with postherpetic neuralgia or traumatic nerve injury who had spontaneous pain of at least moderate severity ($\geq 40/100$ on a visual analog scale) for at least 6 months and no clinical signs of chronic regional pain syndrome. <u>Exclusion criteria:</u> Pain other than peripheral neuropathic pain; severe depression; severe nephropathy; pregnancy; chronic alcoholism or substance abuse; mental disorders preventing an accurate understanding of the tests; contraindications to the use of lidocaine or mexiletine. Patients previously treated with lidocaine or mexiletine, topical local anaesthetics, or other sodium channel blockers. <u>Conclusions supported by results:</u> Yes.</p>

Table 3: Study profiles for *randomized controlled trials* on therapeutic intravenous infusions for neuropathic pain (cont'd)

Authors/Study Details	Intervention/Outcome Measures	Study Design/Execution
<p>Brill et al. (2002)²⁷ United Kingdom <u>Study design:</u> Prospective randomized, double-blind concurrently controlled crossover trial. <u>Follow-up:</u> During infusion, 1 hour, 24 hours. <u>Study period:</u> Not stated. <u>Setting:</u> University hospital. <u>Financial support:</u> Not stated.</p>	<p>Crossover trial (n=7) Magnesium Intravenous magnesium sulphate (30 mg/kg in 100 mL of saline) over a 30-minute period. Saline (placebo) Intravenous saline (100 mL of 0.9% NaCl) over a 30-minute period. Magnesium & saline <u>Washout period:</u> 1 week. <u>Outcome measures:</u> Pain intensity (visual analog scale); degree of pain relief; mechanical dynamic allodynia; adverse events.</p>	<p><u>Method of randomization:</u> Random-number tables. <u>Time of randomization:</u> Not stated. <u>Method of allocation concealment:</u> Not stated. <u>Details of blinding:</u> Not stated. Patients and assessors blinded to treatment allocation. <u>Participation rate:</u> Not stated. <u>Eligibility rate for study:</u> Not stated. <u>Intention-to-treat analysis:</u> By default as all patients received both treatments. <u>Crossovers:</u> All patients received both treatments as part of the study design. <u>Provider:</u> Not stated. <u>Assessor details:</u> Not stated. <u>Inclusion criteria:</u> Patients older than 18 years with postherpetic neuralgia for more than 3 months after healing of the rash and with a pain score of at least 4 on a numerical visual analog scale (range 0 to 10). Patients who had not responded to conventional treatment with anticonvulsants and tricyclic antidepressants. <u>Exclusion criteria:</u> Patients with cardiac failure (New York Heart Association grade III or IV), atrioventricular conduction block (grade II or III), serum creatinine in excess of 110 moles/L, severe liver disease. <u>Conclusions supported by results:</u> Yes.</p>

Table 3: Study profiles for randomized controlled trials on therapeutic intravenous infusions for neuropathic pain (cont'd)

Authors/Study Details	Intervention/Outcome Measures	Study Design/Execution
<p>Eichenberger et al. (2008)²⁸ Denmark, Switzerland <u>Study design:</u> Prospective randomized, double-blind concurrently controlled crossover trial. <u>Follow-up:</u> 48 hours. <u>Study period:</u> Not stated. <u>Setting:</u> University hospital. <u>Financial support:</u> Research Section of the Department of Anesthesiology of the University of Bern (Switzerland) and the Danish Technical Research Council.</p>	<p>Crossover trial (n=20) Calcitonin Intravenous calcitonin (200 IE in 20 mL of 0.9% saline) over a 60-minute period. Ketamine Intravenous ketamine (0.4 mg/kg in 20 mL of 0.9% NaCl) over a 60-minute period. Calcitonin plus ketamine Intravenous calcitonin (200 IE in 20 mL of 0.9% saline) and ketamine (0.4 mg/kg in 20 mL of 0.9% NaCl) over a 60-minute period. Saline (placebo) Intravenous saline (20 mL of 0.9% NaCl) over a 60-minute period. Calcitonin, ketamine, and saline <u>Median washout period:</u> 48 hours (range 48 to 240). <u>Outcome measures:</u> Pain intensity (visual analog scale); sensory assessment (electrical, heat, and pressure stimulation); sedation score.</p>	<p><u>Method of randomization:</u> Lots drawn by a person not involved in the study. <u>Time of randomization:</u> Immediately before the start of the first treatment. <u>Method of allocation concealment:</u> The person who drew lots to determine treatment allocation also prepared the infusion solutions. <u>Details of blinding:</u> Patients and investigators blinded to treatment allocation. <u>Participation rate:</u> Not stated. <u>Eligibility rate for study:</u> Not stated. <u>Intention-to-treat analysis:</u> As-treated analysis as one patient did not come for the last treatment session, which was saline. <u>Crossovers:</u> After analyzing results from 10 patients who received calcitonin, combined calcitonin-ketamine, and saline, a fourth session with ketamine alone was added. Thus, only the last 10 patients received ketamine alone. <u>Provider:</u> Not stated. <u>Assessor details:</u> Not stated. <u>Inclusion criteria:</u> Patients with phantom limb pain for at least 6 months at either the upper or lower extremity due to either surgical or traumatic amputation; mean pain intensity ≥ 3 on a numerical rating scale (range 0 to 10) in the 48 hours prior to recruitment. <u>Exclusion criteria:</u> Episodic pain with pain-free intervals of more than 4 hours, stump pain without phantom limb pain, phantom sensations without phantom limb pain, age < 18 years or > 85 years, any contraindication to calcitonin or ketamine. <u>Conclusions supported by results:</u> Yes.</p>

Table 3: Study profiles for randomized controlled trials on therapeutic intravenous infusions for neuropathic pain (cont'd)

Authors/Study Details	Intervention/Outcome Measures	Study Design/Execution
<p>Finnerup et al. (2005)²⁹ Denmark</p> <p><u>Study design:</u> Prospective randomized, double-blind concurrently controlled crossover trial.</p> <p><u>Follow-up:</u> 35 minutes from start of infusion.</p> <p><u>Study period:</u> September 2002 to August 2003.</p> <p><u>Setting:</u> University pain clinic.</p> <p><u>Financial support:</u> The Ludvig og Sara Elsass' Foundation; The Agnes and Poul Friis Foundation; The Institute of Experimental Clinical Research, Aarhus University; The Sahva Foundation; the Danish Medical Research Council; The Danish Society of Polio and Accident Victims.</p>	<p>Crossover trial (n=24)</p> <p>Lidocaine Intravenous lidocaine (5 mg/kg in 250 mL) over a 30-minute period (n=23). One patient received only 4.75 mg/kg in 28.5 minutes because of adverse effects.</p> <p>Saline (placebo) Intravenous saline (250 mL of 0.9% NaCl) over a 30-minute period.</p> <p>Lidocaine and saline <u>Washout period:</u> At least 6 days.</p> <p><u>Outcome measures:</u> <i>Primary:</i> Spontaneous pain (visual analog scale); number of responders. <i>Secondary:</i> Overall pain relief; median daily pain; effect on brush-evoked allodynia or dysesthesia, cold allodynia, pin-prick hyperalgesia, and pain to repetitive pin-prick; effect on cold detection threshold; adverse events; lidocaine plasma concentrations.</p>	<p><u>Method of randomization:</u> Computer generated randomization list with a block size of four and consecutive allocation of patients.</p> <p><u>Time of randomization:</u> As patients entered the study.</p> <p><u>Method of allocation concealment:</u> One investigator was provided with sealed code envelopes, one for each patient, containing information on the treatment given. The envelopes were returned unopened to the monitor after study termination.</p> <p><u>Details of blinding:</u> Patients and investigators blinded to treatment allocation.</p> <p><u>Participation rate:</u> 96.2% (25/26).</p> <p><u>Eligibility rate for study:</u> 100%.</p> <p><u>Intention-to-treat analysis:</u> By default as all patients received both treatments.</p> <p><u>Crossovers:</u> All patients received both treatments as part of the study design.</p> <p><u>Provider:</u> Not stated.</p> <p><u>Assessor details:</u> Physician.</p> <p><u>Inclusion criteria:</u> Patients aged ≥18 years with neuropathic pain due to trauma or disease of the spinal cord or cauda equina with a median pain intensity ≥3 on a numeric rating scale (range 0 to 10) during a 1-week baseline period.</p> <p><u>Exclusion criteria:</u> Known concomitant cerebral damage or dementia, pregnancy or lactation, alcohol or substance abuse, mental disease, hypersensitivity to lidocaine, cardiac or circulatory disease, severe nephropathy.</p> <p><u>Conclusions supported by results:</u> Yes.</p>

Table 3: Study profiles for randomized controlled trials on therapeutic intravenous infusions for neuropathic pain (cont'd)

Authors/Study Details	Intervention/Outcome Measures	Study Design/Execution
<p>Gottrup et al. (2006)³⁰ Denmark <u>Study design:</u> Prospective randomized, double-blind concurrently controlled crossover trial. <u>Follow-up:</u> 40 minutes from the start of infusion. <u>Study period:</u> Not stated. <u>Setting:</u> University hospital. <u>Financial support:</u> Danish Medical Research Council; Karen Elise Jensen's Foundation, Denmark; Institute of Clinical Medicine, University of Aarhus, Denmark.</p>	<p>Crossover trial (n=20) Lidocaine Intravenous lidocaine (5 mg/kg in 100 mL of isotonic saline) over a 30-minute period. Mean dose = 377 mg (standard deviation (SD) 78). Ketamine Intravenous ketamine (0.24 mg/kg in 100 mL of isotonic saline) over a 30-minute period. Mean dose = 18.4 mg (SD 3.8). Saline (placebo) Intravenous saline (0.9% NaCl) over a 30-minute period. Lidocaine, ketamine, and saline <u>Washout period:</u> At least 2 days. <u>Outcome measures:</u> Pain thresholds, spontaneous pain (visual analog scale), brush-evoked pain, pinprick-evoked pain, cold allodynia, reaction time, lidocaine and ketamine plasma concentrations, adverse events.</p>	<p><u>Method of randomization:</u> Not stated. <u>Time of randomization:</u> Not stated. <u>Method of allocation concealment:</u> A doctor not involved in the study prepared the bags used for infusion. <u>Details of blinding:</u> Patients and investigators blinded to treatment allocation. <u>Participation rate:</u> Not stated. <u>Eligibility rate for study:</u> Not stated. <u>Intention-to-treat analysis:</u> As-treated analysis as one patient was excluded during the first treatment session (ketamine) because of side effects. <u>Crossovers:</u> All patients received both treatments as part of the study design. <u>Provider:</u> Not stated. <u>Assessor details:</u> Not stated. <u>Inclusion criteria:</u> Patients with verified nerve injury pain and mechanical allodynia and pinprick hyperalgesia lasting more than 3 months. <u>Exclusion criteria:</u> Severe psychiatric disease, polyneuropathy, diabetes mellitus, symptoms reported to originate from the contralateral side, a history of previous cardiac arrhythmia, abnormal 12-lead electrocardiograph. <u>Conclusions supported by results:</u> Yes.</p>

Table 3: Study profiles for randomized controlled trials on therapeutic intravenous infusions for neuropathic pain (cont'd)

Authors/Study Details	Intervention/Outcome Measures	Study Design/Execution
<p>Kvarnström et al. (2003)³¹ Sweden</p> <p><u>Study design:</u> Prospective randomized, double-blind concurrently controlled crossover trial.</p> <p><u>Follow-up:</u> 150 minutes from the start of infusion.</p> <p><u>Study period:</u> Not stated.</p> <p><u>Setting:</u> University hospital pain clinic.</p> <p><u>Financial support:</u> Swedish Medical Research Council; Astra Zeneca R&D, Södertälje, Sweden.</p>	<p>Crossover trial (n=12)</p> <p>Lidocaine Intravenous lidocaine (2.5 mg/kg in saline) over a 40-minute period.</p> <p>Ketamine Intravenous ketamine (0.4 mg/kg in saline) over a 40-minute period.</p> <p>Saline (placebo) Intravenous saline (0.9% NaCl) over a 40-minute period.</p> <p>Lidocaine, ketamine, and saline <u>Washout period:</u> At least 2 days. <u>Outcome measures:</u> Spontaneous pain (visual analog scale), sensibility to mechanical stimuli, thermal sensitivity, lidocaine and ketamine plasma concentrations, adverse events.</p>	<p><u>Method of randomization:</u> Not stated. <u>Time of randomization:</u> Not stated. <u>Method of allocation concealment:</u> Randomization codes were kept in sealed envelopes. <u>Details of blinding:</u> Patients and investigators blinded to treatment allocation. <u>Participation rate:</u> Not stated. <u>Eligibility rate for study:</u> Not stated. <u>Intention-to-treat analysis:</u> By default as all patients received both treatments. <u>Crossovers:</u> All patients received both treatments as part of the study design. <u>Provider:</u> Not stated. <u>Assessor details:</u> Not stated. <u>Inclusion criteria:</u> Patients aged between 20 and 75 years with peripheral nerve or root lesions of traumatic origin with spontaneous and evoked pain in the cutaneous territory supplied by the injured nerve together with clinically demonstrable sensory deficit or sensory hyperfunction. <u>Exclusion criteria:</u> Drug abuse, cardiovascular disease, previous treatment with intravenous ketamine or lidocaine. <u>Conclusions supported by results:</u> Yes.</p>

Table 3: Study profiles for randomized controlled trials on therapeutic intravenous infusions for neuropathic pain (cont'd)

Authors/Study Details	Intervention/Outcome Measures	Study Design/Execution
<p>Kvarnström et al. (2004)³² Sweden</p> <p><u>Study design:</u> Prospective randomized, double-blind concurrently controlled crossover trial.</p> <p><u>Follow-up:</u> 150 minutes from the start of infusion.</p> <p><u>Study period:</u> Not stated.</p> <p><u>Setting:</u> University hospital pain clinic.</p> <p><u>Financial support:</u> Not stated.</p>	<p>Crossover trial (n=10)</p> <p>Lidocaine Intravenous lidocaine (2.5 mg/kg in saline) over a 40-minute period.</p> <p>Ketamine Intravenous ketamine (0.4 mg/kg in saline) over a 40-minute period.</p> <p>Saline (placebo) Intravenous saline (0.9% NaCl) over a 40-minute period.</p> <p>Lidocaine, ketamine, and saline <u>Washout period:</u> At least 4 days. <u>Outcome measures:</u> Spontaneous pain (visual analog scale), sensibility to mechanical stimuli, thermal sensitivity, lidocaine and ketamine plasma concentrations, adverse events.</p>	<p><u>Method of randomization:</u> Not stated. <u>Time of randomization:</u> Not stated.</p> <p><u>Method of allocation concealment:</u> Randomization codes were kept in sealed envelopes. A nurse not involved in the study randomly selected one blank envelope for each experiment and prepared the infusion according the instructions in the envelope.</p> <p><u>Details of blinding:</u> Patients and investigators blinded to treatment allocation. <u>Participation rate:</u> Not stated. <u>Eligibility rate for study:</u> Not stated.</p> <p><u>Intention-to-treat analysis:</u> By default as all patients received both treatments. <u>Crossovers:</u> All patients received both treatments as part of the study design. <u>Provider:</u> Not stated. <u>Assessor details:</u> Not stated.</p> <p><u>Inclusion criteria:</u> Patients with traumatic spinal cord injury who suffered spontaneous pain distally from the level of the lesion. <u>Exclusion criteria:</u> History of chronic pain before the onset of spinal cord injury, drug abuse, cardiovascular disease, previous treatment with ketamine or lidocaine.</p> <p><u>Conclusions supported by results:</u> Yes.</p>

Table 3: Study profiles for *randomized controlled trials* on therapeutic intravenous infusions for neuropathic pain (cont'd)

Authors/Study Details	Intervention/Outcome Measures	Study Design/Execution
<p>Medrik-Goldberg et al. (1999)³³</p> <p>Israel</p> <p><u>Study design:</u> Prospective randomized, double-blind concurrently controlled crossover trial.</p> <p><u>Follow-up:</u> 3 hours from the start of infusion.</p> <p><u>Study period:</u> May 1997 to April 1998.</p> <p><u>Setting:</u> Medical centre.</p> <p><u>Financial support:</u> Not stated.</p>	<p>Crossover trial (n=30)</p> <p>Lidocaine Intravenous lidocaine (5.0 mg/kg in 500 mL) over a 2-hour period.</p> <p>Amantadine Intravenous amantadine (2.5 mg/kg in 500 mL) over a 2-hour period.</p> <p>Saline (placebo) Intravenous saline (0.9% NaCl) over a 2-hour period.</p> <p>Lidocaine, amantadine, and saline <u>Washout period:</u> At least 2 days. <u>Outcome measures:</u> Spontaneous pain, angle of straight leg raise test at which the patient reported an increase in pain; mechanical hyperalgesia, mechanical allodynia, cold allodynia, adverse events.</p>	<p><u>Method of randomization:</u> Not stated.</p> <p><u>Time of randomization:</u> Not stated.</p> <p><u>Method of allocation concealment:</u> Not stated.</p> <p><u>Details of blinding:</u> Patients and investigators blinded to treatment allocation.</p> <p><u>Participation rate:</u> Not stated.</p> <p><u>Eligibility rate for study:</u> Not stated.</p> <p><u>Intention-to-treat analysis:</u> Yes – two patients received only two treatments, but data on drug efficacy referred to all patients.</p> <p><u>Crossovers:</u> Two patients received only two treatments: one patient only received a lidocaine and saline treatment, while another patient only received amantadine and lidocaine.</p> <p><u>Provider:</u> Not stated.</p> <p><u>Assessor details:</u> Not stated.</p> <p><u>Inclusion criteria:</u> Patients aged 18 to 60 years of age with painful lumbar radiculopathy of 3 to 36 months' duration and presence of a herniated disc as demonstrated on imaging studies that correlated with the clinical picture in terms of level and side.</p> <p><u>Exclusion criteria:</u> Patients with pain for more than 3 years who were unlikely to respond to any single intervention; previous back surgery; a history of cardiac disease; epilepsy; impaired renal or liver function.</p> <p><u>Conclusions supported by results:</u> Yes.</p>

Table 3: Study profiles for *randomized controlled trials* on therapeutic intravenous infusions for neuropathic pain (cont'd)

Authors/Study Details	Intervention/Outcome Measures	Study Design/Execution
<p>Robinson et al. (2004)³⁴ New Zealand <u>Study design:</u> Prospective randomized, double-blind concurrently controlled trial. <u>Follow-up:</u> 1 and 3 months. <u>Study period:</u> January 1998 to January 2000. <u>Setting:</u> Multidisciplinary pain management centre. <u>Financial support:</u> Not stated.</p>	<p>Pamidronate; n=14 Saline (placebo); n=13 Pamidronate Intravenous pamidronate (60 mg) as a single infusion. Saline (placebo) Intravenous saline (0.9% NaCl). Pamidronate & saline <u>Outcome measures:</u> Pain (visual analog scale), patient's global assessment of disease severity, functional assessment (SF-36), adverse events.</p>	<p><u>Method of randomization:</u> Not stated. <u>Time of randomization:</u> Not stated. <u>Method of allocation concealment:</u> Not stated. <u>Details of blinding:</u> Patients and investigators blinded to treatment allocation. <u>Participation rate:</u> 67.5% (27/40). <u>Eligibility rate for study:</u> Not stated. <u>Intention-to-treat analysis:</u> By default as there were no dropouts or withdrawals. <u>Crossovers:</u> None occurred. <u>Provider:</u> Not stated. <u>Assessor details:</u> Not stated. <u>Inclusion criteria:</u> Patients who fulfilled the International Association for the Study of Pain criteria for chronic regional pain syndrome type I. <u>Exclusion criteria:</u> Not stated. <u>Conclusions supported by results:</u> Yes.</p>

Table 3: Study profiles for randomized controlled trials on therapeutic intravenous infusions for neuropathic pain (cont'd)

Authors/Study Details	Intervention/Outcome Measures	Study Design/Execution
<p>Tremont-Lukats et al. (2006)³⁵ United States <u>Study design:</u> Prospective randomized, double-blind concurrently controlled trial. <u>Follow-up:</u> 4 hours after infusion. <u>Study period:</u> Not stated. <u>Setting:</u> General clinical research centre. <u>Financial support:</u> General Clinical Research Centers Program of the National Center for Research Resources, National Institutes of Health.</p>	<p>Lidocaine (1 mg); n=7 Lidocaine (3 mg); n=9 Lidocaine (5 mg); n=8 Saline (placebo); n=8 Lidocaine (1 mg) Intravenous lidocaine (1 mg/kg/hour) over a 6-hour period. Lidocaine (3 mg) Intravenous lidocaine (3 mg/kg/hour) over a 6-hour period. Lidocaine (5 mg) Intravenous lidocaine (5 mg/kg/hour) over a 6-hour period. Saline (placebo) Intravenous saline over a 6-hour period. Lidocaine & saline <u>Outcome measures:</u> Pain (visual analog scale), plasma concentrations of lidocaine and methylethylglycinexylidide, adverse events.</p>	<p><u>Method of randomization:</u> Computer-generated sequences in blocks of four without gender stratification. <u>Time of randomization:</u> Not stated. <u>Method of allocation concealment:</u> Pharmacy staff prepared solutions and gave unlabelled solutions to nursing staff for immediate transfusion. <u>Details of blinding:</u> Patients and investigators blinded to treatment allocation until the time of data analysis. <u>Participation rate:</u> Not stated. <u>Eligibility rate for study:</u> Not stated. <u>Intention-to-treat analysis:</u> All patients completed the study, but data for one patient in the saline group were lost during a computer upgrade, so the results are based on 31 participants only. <u>Crossovers:</u> None occurred. <u>Provider:</u> Not stated. <u>Assessor details:</u> Not stated. <u>Inclusion criteria:</u> Adults with a documented diagnosis of peripheral neuropathic pain of any aetiology for at least 1 year. For patients with pain that was due to multiple coexisting neuropathic and non-neuropathic pain mechanisms, such as radicular low back pain, only patients whose pain was predominantly due to a radicular component were included. Patients with normal liver and renal function, no history of cardiovascular disease, and no known hypersensitivity to lidocaine. <u>Exclusion criteria:</u> Pain from causes that could not be specifically diagnosed; multiple pain complaints that could not be rated specifically; pain in large body areas, such as total body pain; incomplete medical records. <u>Conclusions supported by results:</u> Yes.</p>

Table 3: Study profiles for randomized controlled trials on therapeutic intravenous infusions for neuropathic pain (cont'd)

Authors/Study Details	Intervention/Outcome Measures	Study Design/Execution
<p>Viola et al. (2006)³⁶ Australia <u>Study design:</u> Prospective randomized, double-blind concurrently controlled crossover trial. <u>Follow-up:</u> 28 days. <u>Study period:</u> Not stated. <u>Setting:</u> University hospital. <u>Financial support:</u> NovoNordisk provided part of the funding for the study.</p>	<p>Crossover trial (n=15) Lidocaine 5 mg/kg Intravenous lidocaine (500 mg in 500 mL of 0.9% saline) over a 4-hour period. Lidocaine 7.5 mg/kg Intravenous lidocaine (750 mg in 500 mL of 0.9% saline) over a 4-hour period. Saline (placebo) Intravenous saline (500 mL of 0.9% NaCl) over a 4-hour period. Lidocaine & saline <u>Washout period:</u> 4 weeks. <u>Outcome measures:</u> Pain (McGill Pain Questionnaire), daily pain evaluation via patient journals, hours of sleep, fasting blood glucose, use of other pain relief medication, adverse events.</p>	<p><u>Method of randomization:</u> Not stated. <u>Time of randomization:</u> Not stated. <u>Method of allocation concealment:</u> Identical 500 mL flasks of the solutions were prepared by the hospital pharmacy. <u>Details of blinding:</u> Patients and investigators blinded to treatment allocation. <u>Participation rate:</u> 68.2% (15/22). <u>Eligibility rate for study:</u> 81.5% (22/27). <u>Intention-to-treat analysis:</u> By default as all patients received both treatments. <u>Crossovers:</u> All patients received both treatments as part of the study design. <u>Provider:</u> Not stated. <u>Assessor details:</u> Not stated. <u>Inclusion criteria:</u> Patients with painful diabetic neuropathy who were either inadequately responsive to or were intolerant of conventional therapy (non-steroidal anti-inflammatory drugs, tricyclic antidepressants, anticonvulsant drugs) and were participating in the hospital's lidocaine infusion program after responding to initial treatment and receiving at least four infusions at approximately four weekly intervals; stable diabetes management and neuropathic pain symptoms for at least 12 months. <u>Exclusion criteria:</u> Not stated. <u>Conclusions supported by results:</u> Yes.</p>

STUDY PROFILES – CLINICAL PRACTICE GUIDELINES

Table 4: Study profiles for *clinical practice guidelines* on therapeutic intravenous infusions for neuropathic pain

Guideline	Target Population	Selection Criteria/Outcomes	Methods
<p>North American Spine Society (2007)³⁷</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 therapeutic intravenous infusions for neuropathic pain

Study/ Quality	Patients/ Pain Type	Comparators	Supporting Evidence*							Relevant Results/ Authors' Conclusions	
			SR/MA	NR	RCT	NRCS	CS	G	Other		
Forouzanfar et al. (2002) ²¹ Quality rating: Average (4/6)	Total number: n = 32 for intravenous clodronate (1 RCT); n = 20 for intravenous alendronate (1 RCT). Conditions reviewed: Complex regional pain syndrome type I or reflex sympathetic dystrophy.	Placebo			2 40,41						<p>Efficacy/effectiveness: One high quality RCT found that intravenous clodronate 300 mg given for 10 days resulted in significant improvement in pain compared with placebo. One high quality RCT found that intravenous alendronate 7.5 mg for 3 days resulted in significant improvement in pain compared with placebo.</p> <p>Safety: Not reported.</p> <hr/> <p>Authors' conclusions: There is limited evidence for the efficacy of bisphosphonates in the treatment of complex regional pain syndrome type I or reflex sympathetic dystrophy.</p>
Hempenstall et al. (2005) ²² Quality rating: Good (6/6)	Total number: n = 19 for intravenous morphine (1 RCT); n = 43 for intravenous lidocaine (2 RCTs). Conditions reviewed: Post-herpetic neuralgia.	Placebo			2 42,43 N.B. One trial compared morphine with both lidocaine and placebo.						<p>Efficacy/effectiveness: Intravenous morphine (0.3 mg/kg over 1 hour) provided significant improvement in pain relief compared with placebo. There was no significant difference in pain relief between intravenous lidocaine (1 mg/kg and 5 mg/kg over 1 to 2 hours) and placebo.</p> <p>Safety: Dichotomous data for harms were not available.</p> <hr/> <p>Authors' conclusions: Intravenous administration of lidocaine is not efficacious in the treatment of post-herpetic neuralgia. However, it may be more appropriate to consider this intervention as being "not yet adequately tested" rather than demonstrating "no evidence of efficacy" given the given the small size and low number of trials. (<i>cont'd next page</i>)</p>

Table 5: Summary of relevant data extracted from systematic reviews on therapeutic intravenous infusions 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	
Hempenstall et al. (2005) ²² (cont'd)										Intravenous morphine could be considered as a second-line therapy for postherpetic neuralgia in accordance with recommendations for the use of such drugs in chronic non-cancer pain.
Kalso et al. (1998) ²³ Quality rating: Average (4/6)	Total number: n = 68 for intravenous lidocaine (4 RCTs). Conditions reviewed: Peripheral nerve injury, diabetic neuropathy, postherpetic neuralgia.	Different lidocaine concentrations, morphine, placebo			4 43-46					<p>Efficacy/effectiveness: Intravenous lidocaine (2 mg/kg and 5 mg/kg over 45 minutes) provided significantly better pain relief than placebo in patients with peripheral nerve damage. A dose response was also demonstrated; the minimum effective plasma lidocaine concentration was 1.5 mg/L achieved with doses of 2 to 5 mg/kg infused over 30 to 60 minutes. One study reported that lidocaine (5 mg/kg over 30 minutes) provided significant relief of dysaesthesia in patients with diabetic neuropathy, compared with placebo. The effect lasted for up to 8 days. Lidocaine (5 mg/kg over 60 minutes) was significantly better at lowering pain intensity than placebo, but inferior to morphine, in one study of postherpetic neuralgia. Morphine was significantly better than placebo in relieving pain, but lidocaine was not.</p> <p>Safety: Adverse effects were usually minor and included light-headedness, somnolence, nausea, and perioral numbness.</p> <hr/> <p>Authors' conclusions: In peripheral nerve damage, diabetic neuropathy, and postherpetic neuralgia, intravenous lidocaine was effective at plasma concentrations of 1.5 to 5 mg/L. However, the long-term analgesic effects of intravenous lidocaine have not been systematically studied.</p>

Table 5: Summary of relevant data extracted from systematic reviews on therapeutic intravenous infusions 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	
<p>Kalso et al. (2004)²⁴</p> <p>Quality rating: Poor (3/6)</p>	<p>Total number: n = 115 for intravenous morphine (3 RCTs) and fentanyl (1 RCT).</p> <p>Conditions reviewed: Postherpetic neuralgia, mixed neuropathic pain, central pain, phantom pain</p>	Lidocaine, placebo			<p>4 43,47-49</p>					<p>Efficacy/effectiveness: Mean doses of intravenous morphine were comparable (0.25, 16, and 19 mg/kg); the equianalgesic dose of intravenous fentanyl was 0.873 mg, which was given over 5 hours.</p> <p>All four studies reported a 30% to 60% reduction in pain relief and intensity, compared with a decrease of 25% or an increase of 5% with placebo. Allodynia was reduced by opioids but not lidocaine (two studies).</p> <p>Safety: Adverse effects occurred in most patients and included vomiting and nausea.</p> <hr/> <p>Authors' conclusions: The short-term efficacy of opioids was good in neuropathic pain, but the small number of selected patients and the short follow-ups do not allow conclusions concerning problems such as tolerance and addiction.</p>
<p>Kingery (1997)²⁵</p> <p>Quality rating: Poor (1/6)</p>	<p>Total number: 3 RCTs and 1 NRCS for intravenous lidocaine; 3 RCTs for intravenous ketamine; 1 RCT for intravenous magnesium.</p> <p>Conditions reviewed: Postherpetic neuralgia, diabetic neuropathy, nerve injuries</p>	Placebo			<p>6 43,45,46,50-52</p> <p>N.B. Some trials compared more than one active drug.</p>	<p>1 53</p>			<p>Efficacy/effectiveness: Intravenous lidocaine provided short-term analgesia for patients with diabetic, postherpetic, and peripheral nerve injury. Allodynia can be relieved and analgesia achieved at mean serum levels of between 1.5 and 2.0 µg/mL. No residual analgesia was observed after stopping lidocaine infusion.</p> <p>Intravenous ketamine infusion (100 to 200 µg/kg bolus, 0 to 420 µg/kg/hour infusion) provided analgesia for spontaneous pain and mechanical pain thresholds, mechanical allodynia, and mechanical summated repetitive stimulation.</p> <p>Intravenous magnesium chloride (0.16 mmol/kg bolus, 0.16 mmol/kg/hour infusion) was ineffective in postherpetic neuralgia. (<i>cont'd next page</i>)</p>	

Table 5: Summary of relevant data extracted from *systematic reviews* on therapeutic intravenous infusions 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	
Kingery (1997) ²⁵ (cont'd)										<p>Safety: The continuous infusion of ketamine is not feasible due to intolerable side effects, including painful indurations at the infusion site, sedation, slowed reaction time, and hallucinations.</p> <p>-----</p> <p>Authors' conclusions: There was consistent (two or more trials) support for intravenous lidocaine and ketamine in patients with neuropathic pain. Intravenous magnesium failed to provide analgesia in a single trial.</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 therapeutic intravenous infusions for neuropathic pain

Study/Quality Rating	Interventions/Study Population	Relevant Results/Authors' Conclusions
<p>Attal et al. (2004)²⁶ Prospective randomized, double-blind concurrently controlled crossover trial</p> <p>Quality rating: <i>Internal validity</i> Good (9/9)</p> <p><i>External validity</i> Moderate (4/6)</p>	<p>Lidocaine; n=22 Saline; n=22</p> <p><u>Patient diagnosis:</u> Postherpetic neuralgia (36.4%) or traumatic nerve injury (63.6%)</p> <p><u>Mean age:</u> 51 years (standard deviation (SD) 16.7)</p> <p><u>Sex distribution:</u> M/F = 15 (68.2%)/7 (31.8%)</p> <p><u>Pre-treatment mean visual analog scale pain score (scale 0 to 100):</u> Before lidocaine: 54 (SD 15.5); Before placebo: 54 (SD 15.4)</p> <p><u>Mean duration of pain:</u> 42 months (SD 51.0)</p> <p><u>Patient co-morbidities:</u> Not stated</p> <p><u>Location of maximal pain:</u> Shoulder – 13.5%; Neck – 4.6%; Foot – 22.6%; Thorax – 27.2%; Forearm – 9.1%; Arm – 4.6%; Leg – 4.6%; Lumbar – 4.6%; Axillary – 4.6%; Hand – 4.6%</p> <p><u>Co-interventions:</u> Patients receiving oral pharmacologic treatment for pain at the time of screening (50%) were permitted to continue at a minimum dose without subsequent modifications throughout the trial.</p>	<p>Lidocaine versus saline (n=22)</p> <p><u>Lost to follow-up:</u> 0%</p> <p><u>Outcomes:</u> <i>Spontaneous pain:</i> Lidocaine significantly improved spontaneous ongoing pain intensity in comparison with saline starting 30 minutes after injection, with a peak between 60 and 120 minutes and lasting for up to 6 hours (P<0.01). The effects were durable for up to 7 days in five patients (22%).</p> <p>Twelve patients (54%) gained at least 33% pain relief with lidocaine, which was considered a meaningful clinical effect. Five patients were pain free with lidocaine, compared with none in the saline group.</p> <p><i>Allodynia and hyperalgesia:</i> Lidocaine significantly reduced the intensity of brush-induced allodynia, compared with saline, from 15 minutes (P<0.05) to 120 minutes (P<0.001) after infusion.</p> <p>Lidocaine improved allodynia by at least 50% in 10 patients (62%) and at least 33% in 11 patients (69%). Allodynia was totally alleviated by lidocaine in 6 patients, compared with none in the saline group.</p> <p>Sixteen patients in the lidocaine group had decreased static mechanical allodynia/hyperalgesia (P=0.01), but no change was observed in thermal allodynia/hyperalgesia.</p> <p><u>Adverse events:</u> Lidocaine (n=22): side effects occurred in 72.7% of patients; mean number of side effects was 1.7 (SD 1.4). Saline (n=22): side effects occurred in 22.7% of patients; mean number of side effects was 0.5 (SD 1.0).</p> <p>The side effects were mainly somnolence, light-headedness, perioral numbness, and garbled speech and were rapidly reversible.</p> <hr/> <p>Authors' conclusions These data indicate modality-specific antihyperalgesic effects of intravenous lidocaine in patients with postherpetic neuralgia and traumatic nerve injury. Patients with mechanical allodynia may be good candidates for treatment with local anaesthetic-like drugs.</p>

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

Study/Quality Rating	Interventions/Study Population	Relevant Results/Authors' Conclusions
<p>Brill et al. (2002)²⁷ Prospective randomized, double-blind concurrently controlled crossover trial</p> <p>Quality score: <i>Internal validity</i> Good (7/9) <i>External validity</i> Moderate (4/6)</p>	<p>Magnesium; n=7 Saline (placebo); n=7</p> <p><u>Patient diagnosis:</u> Postherpetic neuralgia</p> <p><u>Mean age:</u> 71 years (standard deviation (SD) 10.0)</p> <p><u>Sex distribution:</u> M/F = 2 (28.6%)/5 (71.4%)</p> <p><u>Pre-treatment mean visual analog scale pain score (scale 0 to 10):</u> 6.7</p> <p><u>Mean duration of pain:</u> 2 years (SD 1.3)</p> <p><u>Patient co-morbidities:</u> Not stated</p> <p><u>Location of pain:</u> Lumbar – 14.3%; Thoracic – 57.1%; Trigeminal – 14.3%; Cervical – 14.3%</p> <p><u>Co-interventions:</u> Not stated</p>	<p>Magnesium versus saline (n=7)</p> <p><u>Lost to follow-up:</u> 0%</p> <p><u>Outcomes:</u> Magnesium significantly reduced pain scores during infusion at 20 minutes and 30 minutes in comparison with saline (P=0.016). Five out of seven patients (71.4%) reported complete pain relief after magnesium infusion compared with none after the saline infusion. Pain relief lasted up to 1 hour after infusion, although pain returned in all seven patients within 24 hours.</p> <p><u>Adverse events:</u> Magnesium (n=7): No adverse events reported apart from a mild feeling of warmth at the injection site. Saline (n=7): Not stated.</p> <hr/> <p>Authors' conclusions The results show that the physiological action of magnesium can be translated into a viable concept for pain control in some patients with postherpetic neuralgia.</p>

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

Study/Quality Rating	Interventions/Study Population	Relevant Results/Authors' Conclusions
<p>Eichenberger et al. (2008)²⁸</p> <p>Prospective randomized, double-blind concurrently controlled crossover trial</p> <p>Quality score: <i>Internal validity</i> Good (8/9) <i>External validity</i> Moderate (4/6)</p>	<p>Calcitonin; n=20 Ketamine; n=10 Calcitonin and ketamine; n=20 Saline (placebo); n=20</p> <p><u>Patient diagnosis:</u> Phantom limb pain</p> <p><u>Median age:</u> 57.0 years (range 19.3 to 80.9)</p> <p><u>Sex distribution:</u> M/F = 15 (75%)/5 (25%)</p> <p><u>Pre-treatment mean visual analog scale pain score (scale 0 to 10):</u> 3.7</p> <p><u>Median duration of pain:</u> 10.9 years (range 0.9 to 32.3)</p> <p><u>Patient co-morbidities:</u> Not stated</p> <p><u>Location of pain:</u> Lower leg – 30%; Thigh – 45%; Upper arm – 25%</p> <p><u>Co-interventions:</u> Opioids (35%); non-steroidal anti-inflammatory drugs (45%); anticonvulsants (15%); cannabis (5%); tricyclic antidepressants (25%)</p>	<p><u>Lost to follow-up:</u> One patient in the saline group (5%)</p> <p><u>Outcomes:</u> <u>Pain intensity:</u> There were no significant differences in pain intensities preceding the different treatments.</p> <p>There was no difference between calcitonin and saline infusion with respect to pain intensity ($P \geq 0.05$).</p> <p>Ketamine alone and combined calcitonin-ketamine significantly reduced pain intensity, compared with calcitonin alone or saline infusion ($P \leq 0.001$).</p> <p>Patients with at least 50% reduction in pain intensity: calcitonin (10%); ketamine (60%; $P=0.003$ compared with saline); calcitonin-ketamine (60%; $P < 0.001$ compared with saline); saline (5.3%).</p> <p><u>Sensory assessments:</u> Pain thresholds were unaffected by calcitonin. The analgesic effect of combined calcitonin-ketamine was associated with a significant increase in electrical thresholds, but with no change in pressure or heat thresholds.</p> <p><u>Adverse events:</u> Calcitonin (n=20): light sedation (5.0%); facial flushing (10.0%); nausea without vomiting (25.0%); Ketamine (n=10): light sedation (25.0%); heavy sedation (5.0%); light visual hallucination, hearing impairment, impairment of position feeling (25.0%); Calcitonin-ketamine (n=20): light sedation (55.0%); heavy sedation (5.0%); nausea (20.0%); dizziness (45.0%); light visual hallucination, hearing impairment, impairment of position feeling (20.0%); facial flushing (5.0%); Saline (n=19): light sedation (10.5%).</p> <hr/> <p>Authors' conclusions The results show that intravenous infusion of calcitonin is ineffective for treating chronic phantom limb pain. Ketamine appears to be effective in reducing pain intensity in these patients, but adding calcitonin to ketamine does not confer additional benefit.</p>

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

Study/Quality Rating	Interventions/Study Population	Relevant Results/Authors' Conclusions
<p>Finnerup et al. (2005)²⁹ Prospective randomized, double-blind concurrently controlled crossover trial Quality rating: <i>Internal validity</i> Good (8/9) <i>External validity</i> Good (5/6)</p>	<p>Lidocaine; n=24 Saline; n=24 Patients further subdivided into those with evoked pain (n=12) and those without evoked pain (n=12) <u>Patient diagnosis:</u> Spinal cord injury - patients with evoked pain (50%); patients without evoked pain (50%) <u>Median age:</u> With evoked pain: 52 years (range 32 to 61); Without evoked pain: 55 years (range 28 to 66) <u>Sex distribution:</u> With evoked pain: M/F = 10 (83.3%)/2 (16.7%); Without evoked pain: M/F = 7 (58.3%)/5 (41.7%) <u>Pre-treatment median visual analog scale pain score (scale 0 to 10):</u> With evoked pain: 5.5 (range 3.0 to 9.0); Without evoked pain: 8.0 (range 4 to 10) <u>Median duration of pain:</u> With evoked pain: 4.5 years (range 1 to 13); Without evoked pain: 6.5 years (range 2 to 12) <u>Patient co-morbidities:</u> Not stated <u>Location of pain:</u> With evoked pain: at level pain (11/12); below level pain (10/12); Without evoked pain: at level pain (6/12); below level pain (10/12) <u>Co-interventions:</u> With evoked pain: spasmolytics (66.7%); gabapentin (50%); opioids (66.7%); simple analgesics (66.7%); Without evoked pain: spasmolytics (33.3%); gabapentin (33.3%); opioids (25.0%); simple analgesics (41.7%) There was no statistically significant difference between the two groups with respect to duration, location, or description of pain, age, sex distribution, American Spinal Injury Association classification, function, spasticity score, McGill Pain Questionnaire score, or current treatment. However, the intensity of spontaneous pain was higher in the group without evoked pain (P=0.04).</p>	<p>Lidocaine versus saline (n=24) <u>Lost to follow-up:</u> 0% <u>Outcomes:</u> Lidocaine significantly reduced spontaneous pain in all patients (P<0.01) and in each of the two groups with (P<0.01) and without (P=0.048) evoked pain, compared with saline, with no difference in the number of responders (pain reduction ≥ 33%) between patients with (n=6) and without (n=5) evoked pain. Of the twenty patients, 19 reported pain relief during lidocaine treatment and 4 reported pain relief during saline infusion (P<0.01), but there was no difference in median pain intensity the week after each treatment (n=19). Lidocaine significantly relieved at-level and below-level neuropathic pain and decreased brush-evoked dysesthesia, but not cold allodynia, pinprick hyperalgesia, or pain evoked by repetitive pinprick. <u>Adverse events:</u> Lidocaine (n=24): somnolence (45.8%); dizziness (29.2%); dysarthria (29.2%); light-headedness (29.2%); blurred vision (12.5%); other (e.g. unpleasantness, light headache, dry mouth) (62.5%); Saline (n=24): somnolence (4.2%); blurred vision (4.2%).</p> <hr/> <p>Authors' conclusions The trial showed a statistically significant for lidocaine effect on spontaneous neuropathic pain in patients with spinal cord injury independent of the presence or absence of evoked pain.</p>

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

Study/Quality Rating	Interventions/Study Population	Relevant Results/Authors' Conclusions
<p>Gottrup et al. (2006)³⁰ Prospective randomized, double-blind concurrently controlled crossover trial Quality score: <i>Internal validity</i> Poor (3/9) <i>External validity</i> Good (5/6)</p>	<p>Lidocaine; n=20 Ketamine; n=20 Saline (placebo); n=20 <u>Patient diagnosis:</u> Nerve injury pain <u>Mean age:</u> 49 years (range 29 to 73) <u>Sex distribution:</u> M/F = 13 (65%)/7 (35%) <u>Pre-treatment mean visual analog scale pain score (scale 0 to 100):</u> 50 (standard deviation 19) <u>Duration of pain:</u> Range 3 to 300 months <u>Patient co-morbidities:</u> Not stated <u>Location of pain:</u> Arm – 40%; Lower leg – 30%; Upper leg – 5%; Back – 5%; Axillary – 15%; Abdominal – 5% <u>Co-interventions:</u> Analgesics (65%). Patients were allowed to continue present analgesic treatment provided that it was kept stable and unchanged for at least a week before study entry and during the entire study period.</p>	<p><u>Lost to follow-up:</u> One patient (5%) <u>Outcomes:</u> There were no significant differences in pain intensities preceding the different treatments. Ketamine significantly reduced ongoing pain ($P<0.01$) and evoked pain to brush ($P<0.05$) and pinprick ($P<0.001$), compared with saline, whereas lidocaine only reduced evoked pain to repetitive pinprick stimuli ($P=0.03$). In the lidocaine group, 21% of patients (4/19) were responders (pain reduction $\geq 33\%$) compared with none in the saline group. In the ketamine group, 42% of patients (8/19) were responders (pain reduction $\geq 33\%$) compared with 5% (1/19) in the saline group. <u>Adverse events:</u> Lidocaine (n=19): tiredness (36.8%); nausea (21.1%); feeling drunk (15.8%); paraesthesia (15.8%); blurred vision (15.8%); dizziness (10.5%); changed taste (15.8%); dysarthria (15.8%); headache (10.5%); dry mouth (10.5%); Ketamine (n=19): tiredness (26.3%); nausea (5.3%); feeling drunk (10.5%); paraesthesia (21.1%); blurred vision (10.5%); dizziness (21.1%); changed taste (10.5%); dysarthria (5.3%); dry mouth (15.8%); euphoria (5.3%); tinnitus (5.3%); Saline (n=19): tiredness (5.3%); nausea (5.3%); paraesthesia (5.3%); dizziness (5.3%); headache (5.3%); dry mouth (5.3%).</p> <hr/> <p>Authors' conclusions Ketamine and lidocaine modulate not only spontaneous pain, but also evoked pain when administered systemically in patients with peripheral nerve injury. The differential effect of ketamine and lidocaine on evoked pain suggested that mechanical hyperalgesia is mediated by different mechanisms. It is not possible to predict the outcome of different treatments from quantitative sensory testing before treatment even in a homogeneous group of patients with nerve injury and mechanical hyperalgesia.</p>

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

Study/Quality Rating	Interventions/Study Population	Relevant Results/Authors' Conclusions
<p>Kvarnström et al. (2003)³¹</p> <p>Prospective randomized, double-blind concurrently controlled crossover trial</p> <p>Quality score: <i>Internal validity</i> Moderate (6/9) <i>External validity</i> Good (5/6)</p>	<p>Lidocaine; n=12 Ketamine; n=12 Saline (placebo); n=12</p> <p><u>Patient diagnosis:</u> Peripheral nerve or root lesions of traumatic origin</p> <p><u>Mean age:</u> 47 years (range 34 to 54)</p> <p><u>Sex distribution:</u> M/F = 3 (25%)/9 (75%)</p> <p><u>Pre-treatment mean visual analog scale pain score (scale 0 to 10):</u> 5.7 (range 3.2 to 8.5)</p> <p><u>Mean duration of pain:</u> 5.5 years (range 1 to 15).</p> <p><u>Patient co-morbidities:</u> Not stated</p> <p><u>Location of pain:</u> Groins bilat – 8.3%; n. radialis superficialis – 16.7%; n. peroneus superficialis – 16.7%; n. intercostalis – 8.3%; n. saphenous – 16.7%; right knee – 8.3%; n. cutaneus antebrachii lat – 8.3%; n. ischiadicus – 8.3%; n. cutaneus antebrachii med – 8.3%</p> <p><u>Co-interventions:</u> Analgesics (83.3%); transcutaneous electrical nerve stimulation (16.7%). The patients continued their regular medication during the test period.</p>	<p><u>Lost to follow-up:</u> 0%</p> <p><u>Outcomes:</u> The mean maximal pain reduction from baseline was 34% for lidocaine, 55% for ketamine, and 22% for saline. The difference in pain reduction was significant between ketamine and saline (P=0.009), but not between lidocaine and saline (P=0.299) or ketamine and lidocaine (P=0.076).</p> <p>Response to treatment (pain reduction > 50%) occurred in 33.3% (4/12) of the lidocaine group, 58.3% (7/12) of the ketamine group, and 16.7% (2/12) of the saline group. The difference was significant for ketamine versus saline (P=0.025), but not for lidocaine versus saline (P=0.32) or lidocaine versus ketamine (P=0.22).</p> <p>Sensibility to thermal stimulation and mechanical stimuli were not changed by infusion of the drugs.</p> <p><u>Adverse events:</u> Lidocaine (n=12): somnolence (75%); light-headedness (42%); out-of-body sensation (34%); hearing changes (17%); vision changes (8%); nausea (25%); itching (17%); unpleasant experience (8%); paraesthesia (17%); Ketamine (n=12): somnolence (100%); light-headedness (75%); out-of-body sensation (67%); hearing changes (42%); vision changes (50%); nausea (33%); itching (17%); unpleasant experience (50%); paraesthesia (83%); Saline (n=12): somnolence (33%); light-headedness (8%); nausea (8%); itching (25%); unpleasant experience (17%).</p> <hr/> <p>Authors' conclusions Ketamine showed a significant analgesic effect in patients with peripheral neuropathic pain, but its clinical usefulness is limited by disturbing side effects.</p>

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

Study/Quality Rating	Interventions/Study Population	Relevant Results/Authors' Conclusions
<p>Kvarnström et al. (2004)³² Prospective randomized, double-blind concurrently controlled crossover trial Quality score: <i>Internal validity</i> Moderate (6/9) <i>External validity</i> Good (5/6)</p>	<p>Lidocaine; n=10 Ketamine; n=10 Saline (placebo); n=10 <u>Patient diagnosis:</u> Traumatic spinal cord injury <u>Mean age:</u> 45 years (range 30 to 60) <u>Sex distribution:</u> M/F = 9 (90%)/1 (10%) <u>Pre-treatment mean visual analog scale pain score (scale 0 to 10):</u> 4.8 (range 1.4 to 9.1) <u>Mean duration of pain:</u> 9 years (range 2 to 35) <u>Patient co-morbidities:</u> Not stated <u>Location of pain:</u> Buttocks, lower legs, feet – 20%; Below injury level – 30%; Back, buttocks, thigh – 10%; Lower leg, feet, hands, forearms – 10%; Buttocks, legs – 10%; Buttocks, back – 10%; Buttocks, trunk – 10% <u>Co-interventions:</u> Analgesics (70%).Patients continued their regular medication with stable doses during the test period.</p>	<p><u>Lost to follow-up:</u> 0% <u>Outcomes:</u> The mean maximal pain reduction from baseline was 10% for lidocaine, 38% for ketamine, and 3% for saline. The difference in pain reduction was significant between ketamine and saline (P=0.01), but not between lidocaine and saline (P=0.60). Response to treatment (pain reduction > 50%) occurred in 10% (1/10) of the lidocaine group, 50% (5/10) of the ketamine group, and 0% of the saline group. The difference was significant for ketamine versus saline (P=0.025), but not for lidocaine versus saline (P=0.31). Sensibility to thermal stimulation and mechanical stimuli was not changed by infusion of the drugs. <u>Adverse events:</u> Lidocaine (n=10): somnolence (50%); dizziness (10%); out-of-body sensation (20%); hearing changes (10%); nausea (10%); unpleasant experience (10%); paraesthesia (20%); Ketamine (n=10): somnolence (70%); dizziness (70%); out-of-body sensation (60%); hearing changes (30%); vision changes (70%); nausea (20%); unpleasant experience (20%); paraesthesia (50%); Saline (n=10): somnolence (10%); dizziness (10%).</p> <hr/> <p>Authors' conclusions Ketamine, but not lidocaine, showed a significant analgesic effect in patients with neuropathic pain after spinal cord injury, but its clinical usefulness is limited by frequent side effects. Pain relief was not associated with altered temperature thresholds or other changes of sensory function.</p>

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

Study/Quality Rating	Interventions/Study Population	Relevant Results/Authors' Conclusions
<p>Medrik-Goldberg et al. (1999)³³ Prospective randomized, double-blind concurrently controlled crossover trial Quality score: <i>Internal validity</i> Moderate (5/9) <i>External validity</i> Moderate (4/6)</p>	<p>Lidocaine; n=30 Amantadine; n=30 Saline (placebo); n=30 <u>Patient diagnosis:</u> Lumbar radicular pain <u>Mean age:</u> 34 years (standard error (SE) 2.0) <u>Sex distribution:</u> M/F = 16 (53.3%)/14 (46.7%) <u>Pre-treatment mean visual analog scale pain score (scale 0 to 100):</u> 52 (SE 5.0) <u>Mean duration of pain:</u> 16 months (SE 2.0) <u>Patient co-morbidities:</u> Not stated <u>Location of disc herniation:</u> L4-L5 – 50%; L5-S1 – 46.7%; L3-L4 – 23.3%; L2-L3 – 6.7% <u>Co-interventions:</u> Not stated</p>	<p><u>Lost to follow-up:</u> 6.7% (one patient from the amantadine group and one patient from the saline group) <u>Outcomes:</u> Lidocaine reduced spontaneous pain compared with amantadine and saline at the 30 (P<0.05), 120 (P<0.01), and 180 (P<0.01) minute time points. Mean maximal pain reduction from baseline was 62% (SE 7) for lidocaine, 43% (SE 7) for amantadine, and 47% (SE 7) for saline. The difference in pain relief between lidocaine and the other two treatments was statistically significant (P≤0.03), whereas there was no statistically significant difference between amantadine and saline. Mean straight leg raise test angle significantly improved with lidocaine from 30° to 37° (P<0.05), compared with amantadine (34° to 36°) and saline (32° to 34°). <u>Adverse events:</u> Lidocaine (n=30): dizziness (40%); nausea (26.7%); drowsiness (20%); paraesthesia (13.3%); weakness (13.3%); headache (6.7%); palpitations (3.5%); Amantadine (n=29): 0%; Saline (n=29): dizziness (3.5%); nausea (3.5%); other (3.5%).</p> <hr/> <p>Authors' conclusions Intravenous lidocaine, but not amantadine or saline, reduced both spontaneous and evoked sciatic pain.</p>

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

Study/Quality Rating	Interventions/Study Population	Relevant Results/Authors' Conclusions
<p>Robinson et al. (2004)³⁴ Prospective randomized, double-blind concurrently controlled trial Quality score: <i>Internal validity</i> Moderate (6/9) <i>External validity</i> Moderate (3/6)</p>	<p>Pamidronate; n=14 Saline (placebo); n=13 <u>Patient diagnosis:</u> Complex regional pain syndrome type I <u>Mean age (combined patient groups):</u> 45 years (range 30 to 60) <u>Sex distribution (combined patient groups):</u> M/F = 9 (33.3%)/18 (66.7%) <u>Pre-treatment mean visual analog scale (VAS) pain score (scale 0 to 10):</u> Unable to read from box plot. <u>Mean duration of pain (combined patient groups):</u> 21.6 months (range 3 to 72) <u>Patient co-morbidities:</u> Not stated <u>Location of pain (combined patient groups):</u> Upper limb – 51.9%; Lower limb – 48.1% <u>Co-interventions:</u> Background analgesia continued throughout the treatment period with stable doses. Analgesics included paracetamol, codeine phosphate, and paracetamol/dextropropoxyphene combination. There was no statistically significant difference between the two groups with respect to age, sex distribution, or duration of treatment.</p>	<p>Pamidronate (n=14) versus saline (n=13) <u>Lost to follow-up:</u> 0% <u>Outcomes:</u> The overall VAS pain score was significantly lower (P=0.043) and the percent change in pain score was significantly greater (P=0.048) in the pamidronate group, compared with saline, at the 3-month assessment. The improvement in patient's global assessment of disease severity score was greater in the pamidronate group than in the saline group at 3 months' follow-up (P=0.026). However, there were no significant differences in pain score or global assessment of disease severity score between the two groups 1 month after treatment. Patients in the pamidronate group had higher functional assessment scores than those in the saline group in physical function at 3 months (P=0.047) and in role physical at 1 (P=0.008) and 3 months (P=0.04). <u>Adverse events:</u> Pamidronate (n=30): minor flu-like symptoms (35.7%); mild erythema and discomfort at the infusion site (14.3%); Saline (n=29): minor flu-like symptoms (15.4%).</p> <hr/> <p>Authors' conclusions Pamidronate may be a useful treatment option in the management of patients with chronic regional pain syndrome type I. Although the treatment response was variable, the majority of patients improved. Early administration in tandem with other treatments is recommended.</p>

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

Study/Quality Rating	Interventions/Study Population	Relevant Results/Authors' Conclusions
<p>Tremont-Lukats et al. (2006)³⁵</p> <p>Prospective randomized, double-blind concurrently controlled trial</p> <p>Quality score: <i>Internal validity</i> Good (7/9) <i>External validity</i> Moderate (4/6)</p>	<p>Lidocaine (1 mg/kg/hour); n=7 Lidocaine (3 mg/kg/hour); n=9 Lidocaine (5 mg/kg/hour); n=8 Saline (placebo); n=7</p> <p><u>Patient diagnosis:</u> Peripheral neuropathic pain</p> <p><u>Mean age:</u> Lidocaine (1 mg): 35 years (standard deviation (SD) 9); Lidocaine (3 mg): 43 years (SD 7); Lidocaine (5 mg): 49 years (SD 15); Saline: 32 years (SD 6)</p> <p><u>Sex distribution:</u> Lidocaine (1 mg): M/F = 1 (14.3%)/6 (85.7%); Lidocaine (3 mg): M/F = 5 (55.6%)/4 (44.4%); Lidocaine (5 mg): M/F = 2 (25.0%)/6 (75.0%); Saline: M/F = 1 (14.3%)/6 (85.7%)</p> <p><u>Pre-treatment mean visual analog scale pain score (scale 0 to 100):</u> Lidocaine (1 mg): 66 (SD 25); Lidocaine (3 mg): 52 years (SD 20); Lidocaine (5 mg): 57 years (SD 21); Saline: 62 years (SD 22)</p> <p><u>Mean duration of pain:</u> Lidocaine (1 mg): 2.7 years (SD 1.8); Lidocaine (3 mg): 2.7 years (SD 2.2); Lidocaine (5 mg): 4.8 years (SD 3.5); Saline: 2.6 years (SD 2.0)</p> <p><u>Patient co-morbidities:</u> Not stated</p> <p><u>Type of pain (combined patient groups):</u> Chronic regional pain syndrome type I – 56.3%; Chronic regional pain syndrome type II – 15.6%; Peripheral polyneuropathies – 15.6%; Radicular pain – 9.4%; Brachial plexopathy – 3.1%</p> <p><u>Co-interventions:</u> All patients could take other analgesic drugs except lidocaine or its oral analogs tocainide, mexiletine, or flecainide. Most patients (67%) were taking more than one class of analgesic drug.</p>	<p><u>Lost to follow-up:</u> 3.1% (data for one patient in the saline group were lost).</p> <p><u>Outcomes:</u> The percentage pain intensity difference was significantly greater in the lidocaine 5 mg group, compared with saline (P=0.012). The effect began 4 hours after the onset of treatment and lasted until the end of the study. There was no difference between lidocaine 1 mg and 3 mg and saline with respect to pain relief.</p> <p>At the end of the infusion period (6 hours), response to treatment (percentage pain intensity difference > 30%) occurred in 14.3% (1/7) of the lidocaine 1 mg group, 22.2% (2/9) of the lidocaine 3 mg group, 50% (4/8) of the lidocaine 5 mg group, and 28.6% (2/7) of the saline group. The difference between the groups was not statistically significant.</p> <p>A modest but significant correlation was found between methylethylglycinexylidide levels and pain relief (R²=0.6).</p> <p><u>Adverse events:</u> Lidocaine (1 mg) (n=7): nausea/vomiting (14.3%); light-headedness (42.9%); diplopia (14.3%); tinnitus (28.6%); throat tightness (28.6%); speech disturbance (14.3%); headache (57.1%); muscle twitching (14.3%); scotomata (35.7%); vertigo (14.3%); metallic taste (14.3%); Lidocaine (3 mg) (n=9): nausea/vomiting (11.1%); light-headedness (33.3%); diplopia (11.1%); clumsiness (11.1%); tingling (11.1%); itching (11.1%); speech disturbance (11.1%); perioral numbness (33.3%); muscle twitching (11.1%); Lidocaine (5 mg) (n=8): nausea/vomiting (25.0%); light-headedness (50.0%); diplopia (12.5%); clumsiness (12.5%); tingling (12.5%); throat tightness (12.5%); incoordination (37.5%); itching (12.5%); perioral numbness (37.5%); headache (25%); muscle twitching (12.5%); metallic taste (12.5%); Saline (n=7): light-headedness (14.3%); muscle twitching (14.3%); metallic taste (42.9%).</p> <hr/> <p>Authors' conclusions Ongoing neuropathic pain was relieved during 6 hours of lidocaine infusion at 5 mg/kg/hour. The effect started 4 hours after the infusion began and continued for at least 4 hours after the end of the infusion. The lower infusion rates of lidocaine (1 and 3 mg/kg/hour) were no more effective than saline in relieving pain. The lidocaine infusion was safe and well tolerated.</p>

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

Study/Quality Rating	Interventions/Study Population	Relevant Results/Authors' Conclusions
Tremont-Lukats et al. (2006) ³⁵ (cont'd)	There was no statistically significant difference between the treatment groups with respect to age, duration of pain, pain location, or baseline pain score. However, there were more men in the lidocaine 3 mg group, compared with the other treatment groups (P<0.05). In a multiple regression analysis where age, sex distribution, and duration of pain were covariates and the percentage pain intensity difference was the dependent variable, none of the covariates had a statistically significant effect.	

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

Study/Quality Rating	Interventions/Study Population	Relevant Results/Authors' Conclusions
<p>Viola et al. (2006)³⁶ Prospective randomized, double-blind concurrently controlled crossover trial</p> <p>Quality score: <i>Internal validity</i> Moderate (4/9) <i>External validity</i> Good (5/6)</p>	<p>Lidocaine (5 mg/kg); n=15 Lidocaine (7.5 mg/kg); n=15 Saline (placebo); n=15</p> <p><u>Patient diagnosis:</u> Painful diabetic neuropathy</p> <p><u>Mean age:</u> 64.3 years (standard error (SE) 13.3)</p> <p><u>Sex distribution:</u> M/F = 7 (46.7%)/8 (53.3%)</p> <p><u>Pre-treatment mean visual analog scale pain score:</u> Not stated</p> <p><u>Mean duration of pain:</u> 5.1 years (SE 3.3)</p> <p><u>Patient co-morbidities:</u> Not stated</p> <p><u>Location of pain:</u> Foot/toes – 100%; Leg – 40%; Hand/finger – 20%</p> <p><u>Co-interventions:</u> Patients were permitted to take their usual treatments (principally non-steroidal anti-inflammatory drugs) for pain relief. None of the patients had tricyclic antidepressants or anticonvulsants during the trial.</p>	<p><u>Lost to follow-up:</u> 0%</p> <p><u>Outcomes:</u> The 5 mg (P<0.05) and 7.5 mg (P<0.001) doses of lidocaine significantly reduced the severity of pain compared with saline. This effect was present at both 14 and 28 days after the infusion. The qualitative nature of the pain was also significantly reduced by the 5 mg (P<0.05) and 7.5 mg (P<0.01) doses of lidocaine, compared with saline, for up to 28 days. The preceding dose 4 weeks earlier significantly affected the response to the next dose.</p> <p>There were no significant differences between the treatments with respect to number of pain relieving medications used during the 4 weeks, mean fasting blood glucose levels, mean hours of sleep, or mean daily pain scores recorded in the patient journals.</p> <p><u>Adverse events:</u> Lidocaine 5 mg (n=15): 0%; Lidocaine 7.5 mg (n=15): light-headedness (6.7%); Saline (n=15): 0%.</p> <hr style="border-top: 1px dashed black;"/> <p>Authors' conclusions Intravenous lidocaine ameliorates pain in some diabetic patients with intractable neuropathic pain who have failed to respond to or are intolerant of conventional therapy.</p>

SUMMARY OF RELEVANT DATA – CLINICAL PRACTICE GUIDELINES

Table 7: Summary of relevant data extracted from *clinical practice guidelines* on therapeutic intravenous infusions for neuropathic pain

Guideline/ Quality Rating	Synopsis of Recommendations	Supporting Evidence*						
		SR/MA	NR	RCT	NRCS	CS	G	Other
North American Spine Society (2007) ³⁷ (United States) Quality rating: Good (23.5/28)	There is little evidence that intravenous lipoprostaglandin E(1) provides long-term benefit in patients with lumbar spinal stenosis.					2 54,55		

*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 tfsi 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 tfsi 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.topalbertadors.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 Trials Listing Service http://www.centerwatch.com/	May 7, 2008	Neuropathic pain 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

Table B.1: Summary of excluded studies on *therapeutic intravenous infusions* (listed in alphabetical order of first author)

Study	Study Type	Reason for Exclusion
Systematic reviews		
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	Included the same studies as Hempenstall et al. (2005) ²² .
Challapalli V, Tremont-Lukats IW, McNicol ED, Lau J, Carr DB. Systemic administration of local anesthetic agents to relieve neuropathic pain. <i>Cochrane Database of Systematic Reviews</i> 2005, Issue 4. Art. No.: CD003345. DOI: 10.1002/14651858.CD003345.pub2.	Systematic review	The study population included patients with fibromyalgia, cancer and surgery related pain; the results for other types of neuropathic pain could not be separated from the aggregate data.
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	Included the same studies as Kingery (1997) ²⁵ .
He L, Wu B, Zhou M. Non-antiepileptic drugs for trigeminal neuralgia. <i>Cochrane Database of Systematic Reviews</i> 2006, Issue 3. Art. No.: CD004029. DOI: 10.1002/14651858.CD004029.pub2.	Systematic review	Does not include intravenous infusions.
Hocking G, Cousins MJ. Ketamine in chronic pain management: and evidence-based review. <i>Anesthesia and Analgesia</i> 2003; 97(6):1730-9.	Quasi-systematic review	Included studies not critically appraised.
Kemler MA. Complex regional pain syndrome type I. <i>Pain Reviews</i> 2001; 8:35-45.	Quasi-systematic review	Included studies not critically appraised.
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	Does not include intravenous infusions.
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	Included the same studies as Kalso et al. (1998) ²³ .
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	Included the same studies as Forouzanfar et al. (2002) ²¹ .

Tremont-Lukats IW, Challapalli V, McNicol ED, Lau J, Carr DB. Systemic administration of local anesthetics to relieve neuropathic pain: a systematic review and meta-analysis. <i>Anesthesia and Analgesia</i> 2005; 101(6):1738-49.	Systematic review	Superseded by Challapalli et al. (2005) (listed previously in table).
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	Does not include intravenous infusions.
Randomized controlled trials		
Donovan WH, Halter JA, Graves DE, Blight AR, Calvillo O, McCann MT, et al. Intravenous infusion of 4-AP in chronic spinal cord injured subjects. <i>Spinal Cord</i> 2000; 38(1):7-15.	Randomized controlled trial	Intervention not described in the included systematic reviews.
Finckh A, Zufferey P, Schurch MA, Balagué F, Waldburger M, So AK. Short-term efficacy of intravenous pulse glucocorticoids in acute discogenic sciatica. A randomized controlled trial. <i>Spine</i> 2006; 31(4):377-81.	Randomized controlled trial	Intervention not described in the included systematic reviews.
Kanayama M, Hashimoto T, Shigenobu K, Oha F, Yamane S. New treatment of lumbar disc herniation involving 5-hydroxytryptamine2A receptor inhibitor: a randomized controlled trial. <i>Journal of Neurosurgery. Spine</i> 2005; 2(4):441-6.	Randomized controlled trial	Intervention not described in the included systematic reviews; intervention not administered intravenously.
Khoromi S, Patsalides A, Parada S, Salehi V, Meegan JM, Max MB. Topiramate in chronic lumbar radicular pain. <i>The Journal of Pain</i> 2005; 6(12):829-36.	Randomized controlled crossover trial	Intervention not described in the included systematic reviews; intervention not administered intravenously.
Korhonen T, Karppinen J, Paimela L, Malmivaara A, Lindgren KA, Järvinen S, et al. The treatment of disc herniation-induced sciatica with infliximab: results of a randomized, controlled, 3-month follow-up study. <i>Spine</i> 2005; 30(24):2724-8.	Randomized controlled trial	Intervention not described in the included systematic reviews.
Korhonen T, Karppinen J, Paimela L, Malmivaara A, Lindgren KA, Bowman C, et al. The treatment of disc-herniation-induced sciatica with infliximab: one-year follow-up results of FIRST II, a randomized controlled trial. <i>Spine</i> 2006;31(24):2759-66.	Randomized controlled trial	Intervention not described in the included systematic reviews; follow-up data from Korhonen et al. (2005) (listed previously in table).
Lynch ME, Clark AJ, Sawynok J. Intravenous adenosine alleviates neuropathic pain: a double blind placebo controlled crossover trial using an enriched enrolment design. <i>Pain</i> 2003; 103(1-2):111-7.	Randomized controlled crossover trial	Intervention not described in the included systematic reviews.
McCleane GJ. Intravenous infusion of phenytoin relieves neuropathic pain: a randomized, double-blinded, placebo-controlled, crossover study.[see comment]. <i>Anesthesia and Analgesia</i> 1999; 89(4):985-8.	Randomized controlled crossover trial	Intervention not described in the included systematic reviews.
Reljanovic M, Reichel G, Rett K, Lobisch M, Schuette K, Möller W, et al. Treatment of diabetic polyneuropathy with the antioxidant thioctic acid (alpha-lipoic acid): A two year multicenter randomized double-blind placebo-controlled trial (ALADIN II). <i>Free Radical Research</i> 1999; 31(3):171-9.	Randomized controlled trial	Intervention not described in the included systematic reviews.

Ziegler D, Hanefeld M, Ruhnau KJ, Hasche H, Lobisch M, Schütte K, et al. Treatment of symptomatic diabetic polyneuropathy with the antioxidant alpha-lipoic acid: A 7-month multicenter randomized controlled trial (ALADIN III study). <i>Diabetes Care</i> 1999; 22(8):1296-1301.	Randomized controlled trial	Intervention not described in the included systematic reviews.
Guidelines		
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 include intravenous infusions.
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 intravenous infusions.
Boswell MV, Trescot AM, Datta S, Schultz DM, Hansen HC, Abdi S, et al. Interventional techniques: evidence-based practice guidelines in the management of chronic spinal pain. <i>Pain Physician</i> 2007; 10(1):7-111.	Guideline	Does not include intravenous infusions.
Dubinsky RM, Kabbani H, El-Chami Z, Boutwell C, Ali H. Practice parameter: treatment of postherpetic neuralgia: an evidence-based report of the Quality Standards Subcommittee of the American Academy of Neurology. <i>Neurology</i> 2004; 63(6):959-65.	Guideline	Does not include intravenous infusions.
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 intravenous infusions.
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. Intravenous (IV) infusion of amantadine. 2005. Available: http://www.acc.co.nz/for-providers/interventional-pain-management/interventions/intervention-index/WCM1_033635	Guideline	Included studies on children/adolescents (>12 years of age).
New Zealand Accident Compensation Corporation. Intravenous (IV) infusion of bisphosphonates. 2005. Available: http://www.acc.co.nz/for-providers/interventional-pain-management/interventions/intervention-index/WCM1_033644	Guideline	Included studies on children/adolescents (>12 years of age).
New Zealand Accident Compensation Corporation. Intravenous (IV) infusion of ketamine. 2005. Available: http://www.acc.co.nz/for-providers/interventional-pain-management/interventions/intervention-index/WCM1_033648	Guideline	Included studies on children/adolescents (>12 years of age).

<p>New Zealand Accident Compensation Corporation. Intravenous (IV) infusion of lignocaine. 2005. Available: http://www.acc.co.nz/for-providers/interventional-pain-management/interventions/intervention-index/WCM1_033854</p>	<p>Guideline</p>	<p>Included studies on children/adolescents (>12 years of age).</p>
<p>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; 5:303-15.</p>	<p>Guideline</p>	<p>Does not specifically address neuropathic pain.</p>
<p>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/methadone/MedicalManagementPain.pdf</p>	<p>Guideline</p>	<p>Does not include intravenous infusions.</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		Forouzanfar et al. (2002) ²¹	Hempenstall et al. (2005) ²²	Kalso et al. (1998) 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	✓	✓
	<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	N/A
	<i>5b. Confidence intervals or measures of dispersion reported</i>	N/A	N/A	N/A
	Meta-analysis	N/A	●	N/A
	<i>5c. Precision of results reported</i>	N/A	✓	N/A
	<i>5d. Test of homogeneity conducted</i>	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	6/6 Good	4/6 Average

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

Table C.1: Quality assessment results for included systematic reviews (cont'd)

Review Characteristic		Kalso et al. (2004) ²⁴	Kingery (1997) ²⁵
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
	<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	N/A
	<i>5a. Study quality used in analysis or discussion of study results</i>	N/A	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	●	●
	<i>5c. Precision of results reported</i>	✓	✓
	<i>5d. Test of homogeneity conducted</i>	?	X
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)	3/6 Poor	1/6 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		Attal et al. (2004) ²⁶	Brill et al. (2002) ²⁷	Eichenberger et al. (2008) ²⁸	Finnerup et al. (2005) ²⁹
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?	?	x	✓	✓
	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?	✓	✓	✓	✓
	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?	x	x	x	x
	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?	✓	✓	✓	x
	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

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

Study Characteristic		Gottrup et al. (2006) ³⁰	Kvarnström et al. (2003) ³¹	Kvarnström et al. (2004) ³²	Medrik-Goldberg et al. (1999) ³³
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?	✓	✓	✓	✓
	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		Robinson et al. (2004) ³⁴	Tremont-Lukats et al. (2006) ³⁵	Viola et al. (2006) ³⁶
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?	✓	✓	✓
	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

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		North American Spine Society (2007) ³⁷	
Scope/ purpose	1.Objectives	4	4
	2. Clinical question	4	2
	3. Target population	4	3
Stakeholder involvement	4. Relevant professional groups represented	1	2
	5. Patients' perspectives included	2	1
	6. Target users defined	3	1
	7. Piloted among target users	4	3
Rigour of development	8. Systematic search conducted	4	4
	9. Selection criteria described	4	2
	10. Methods used to formulate recommendations described	4	4
	11. Benefits, side effects, risks considered	3	2
	12. Link between recommendations and evidence	4	4
	13. External review by experts	4	2
	14. Updating procedure described	4	4
Clarity/ presentation	15. Specific, unambiguous recommendations	4	4
	16. Different management options presented	4	2
	17. Key recommendations easily identifiable	4	3
	18. Additional support materials provided	1	1
Applicability	19. Organizational barriers discussed	1	1
	20. Resource implications considered	1	1
	21. Key review criteria presented	3	1
Editorial independ- ence	22. Editorially independent from funder	2	4
	23. Conflicts of interest reported	2	1
Quality Rating	Seven criteria (systematic search, method of formulating recommendations, recommendations-evidence link, external review, clear recommendations, editorial independence, conflict of interest)	23.5 Good	

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

AGREE Domain	North American Spine Society (2007)³⁷
Scope and purpose	83
Stakeholder involvement	38
Rigour of development	83
Clarity and presentation	63
Applicability	11
Editorial independence	42

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