



**INSTITUTE OF
HEALTH ECONOMICS**
ALBERTA CANADA

INTRAVENOUS DRUG ADMINISTRATION FOR NEUROPATHIC PAIN

ADDENDUM TO SUMMARY OF THE LITERATURE

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

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SCOPE OF THE ADDENDUM

This addendum was prepared in response to a request from the Canadian Pain Society Special Interest Group on Neuropathic Pain (NeP SIG) to broaden the inclusion criteria for clinical practice guidelines, with the aim of making the evidence-base more clinically relevant.

This addendum 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 intravenous drug 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 guidelines.

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METHODS

Modification to the inclusion criteria

Participants

In the original document, data were collected on adult patients (18 years of age or older) with a peripheral or central neuropathic pain condition of any duration. However, given the dearth of clinically useful guidelines on the use of intravenous drug infusions for neuropathic pain, this inclusion criterion was broadened to include patients of any age with a peripheral or central neuropathic pain condition of any duration.

SUMMARY OF ADDITIONAL GUIDELINES

Two additional clinical practice guidelines (CPGs) were included as a result of removing the age limit on patients included in CPGs (Table 1). Study profiles of the included CPGs are summarized in Table 2. The relevant recommendations from each of the included CPGs are provided in Table 3.

Table 1: Summary of additional included guidelines

Study	Year	Quality Rating	Pain Condition
Netherlands Society of Rehabilitation Specialists and the Netherlands Society of Anaesthesiologists ¹	2006	Good (25.5/28)	Complex regional pain syndrome type I
New Zealand Accident Compensation Corporation ²	2005	Good (23.5/28)	Persistent non-cancer pain

STUDY PROFILES – CLINICAL PRACTICE GUIDELINES

Table 2: Study profiles for *clinical practice guidelines* on intravenous drug infusions for neuropathic pain

Guideline	Target Population	Selection Criteria/Outcomes	Methods
<p>Netherlands Society of Rehabilitation Specialists and the Netherlands Society of Anaesthesiologists (2006)¹</p> <p>Objective: To achieve uniformity in the diagnosis and treatment in the various centres and to define the contexts in which multidisciplinary care should be provided to patients with complex regional pain syndrome type I (CRPS-I).</p> <p>Target users: All medical practitioners involved in treating patients with CRPS-I, such as general practitioners, rehabilitation specialists, rheumatologists, anaesthesiologists, neurologists, paediatricians, surgeons, neurosurgeons, plastic surgeons, orthopaedic surgeons, company doctors, insurance doctors, psychologists, physiotherapists, and occupational therapists.</p> <p>Financial support: Order of Medical Specialists in the context of the Evidence-Based Guidelines Development programme.</p> <p>Conflict of interest: None. Files available on request.</p>	<p>Age: Children and adults.</p> <p>Included conditions: CRPS-I.</p> <p>Excluded conditions: Not stated.</p>	<p>Interventions: Medical, interventional, and surgical treatment.</p> <p>Study inclusion/exclusion criteria: Meta-analyses, systematic reviews, randomised controlled trials and controlled trials. When these were not available, comparative cohort, comparative patient control, or non-comparative trials were included. Studies were included if they had adequate size, adequate follow-up, adequate exclusion of selection bias, and the results could be translated to the local context in the Netherlands.</p>	<p>Literature search: <u>Time period:</u> 1980 to June 2004. <u>Limits:</u> English, German, French, Italian, or Dutch language publications. <u>Databases:</u> MEDLINE, EMBASE, the <i>Cochrane Library</i>, CINAHL, and PsycINFO. <u>Other sources:</u> Additional reports were identified from manual searches, recent guidelines on CRPS-I, and the reference lists of retrieved studies.</p> <p>Appraisal of study quality: Members of the project group assessed the quality of the included studies on the basis of Evidence-Based Guidelines Development assessment forms. Articles of moderate or poor quality were excluded. The remaining included studies were then graded according to their evidential strength.</p> <p>Formulation of recommendations: A number of subgroups with representatives of relevant disciplines were set up. A group of core editors was responsible for coordination and consultation between the subgroups. The project group produced texts, either individually or in subgroups, that were discussed at plenary meetings and approved after comments had been taken into account. The plenary project group met ten times to discuss the results of the subgroups. The subgroups' texts were integrated into a single draft guideline by the core editors. These guidelines were presented for comment at a national guidelines meeting. Once the comments had been taken into account, the guidelines were adopted by the full project group and sent to the relevant professional bodies for approval.</p> <p>External review: Peer review by relevant professional bodies.</p> <p>Evidence linked to recommendations: Yes.</p>

Table 2: Study profiles for *clinical practice guidelines* on intravenous drug infusions for neuropathic pain (cont'd)

Guideline	Target Population	Selection Criteria/Outcomes	Methods
<p>New Zealand Accident Compensation Corporation (2005)²</p> <p>Objective: To assist health practitioners and consumers make informed decisions in the management of persistent non-cancer pain.</p> <p>Target users: Health practitioners and consumers.</p> <p>Financial support: Not reported.</p> <p>Conflict of interest: Some members of the advisory group who are in clinical practice receive payments from the New Zealand Accident Compensation Corporation for the use of interventional pain management procedures. Some members of the advisory group received fees for providing services to various pharmaceutical companies.</p>	<p>Age: People over the age of 12 years.</p> <p>Included conditions: Persistent non-cancer pain.</p> <p>Excluded conditions: Pain due to malignancy; acute resolving pain such as postoperative pain; childbirth; dysmenorrhoea; dental pain; infection such as postherpetic neuralgia; systemic inflammatory conditions; migraine; angina; other visceral pain; peripheral vascular disease; haematological disorders.</p>	<p>Interventions: Infusions, injections, intradiscal electrothermal therapy, nerve blocking procedures, neuroablation, neuromodulation.</p> <p>Study inclusion criteria: Systematic reviews; guidelines; randomized controlled trials; quasi-randomized controlled trials; concurrent control and case-control studies with at least 10 participants; case series and cohort studies with at least 50 participants. Case series and cohort studies with fewer than 50 participants were included if they reported on adverse events or safety concerns associated with the intervention in question.</p> <p>Study exclusion criteria: Studies that: reported on healthy volunteers or involved experimentally induced pain; did not report pain control or pain relief as a primary outcome; were graded as low quality.</p>	<p>Literature search: <u>Time period:</u> See databases. <u>Limits:</u> English language publications. <u>Databases:</u> MEDLINE (1966 to April 2004), EMBASE (1988 to April 2004), PsycINFO (1974 to April 2004), the <i>Cochrane Database of Systematic Reviews</i>, the American College of Physicians Journal Club, the Database of Abstracts of Reviews of Effects, the Cochrane Central Register of Controlled Trials, and the TRIP database. <u>Other sources:</u> Additional reports were identified from manual searches of five journals (January 2003 to April 2004): <i>Spine</i>, <i>The Spine Journal</i>, <i>Clinical Journal of Pain</i>, <i>Regional Anaesthesia and Pain Medicine</i>, and <i>Pain Research and Management</i>. The <i>Journal of Negative Results in Biomedicine</i> and the proceedings of the International Association for the Study of Pain 9th and 10th world conferences were searched for relevant material, as were the reference lists of retrieved studies.</p> <p>Appraisal of study quality: Researchers from the New Zealand Health Technology Assessment unit appraised all eligible experimental studies, guidelines, systematic reviews, and health technology assessments using the Generic Appraisal Tool for Epidemiology (GATE) checklists.³ Observational studies were assessed with an alternative rating system.⁴</p> <p>Formulation of recommendations: The whole body of evidence for each intervention was considered by the advisory group and clinical practice recommendations were made using a considered judgement form.</p> <p>External review: Not reported.</p> <p>Evidence linked to recommendations: Yes, for most recommendations.</p>

SUMMARY OF RELEVANT DATA – CLINICAL PRACTICE GUIDELINES

Table 3: Summary of relevant data extracted from *clinical practice guidelines* on intravenous drug infusions for neuropathic pain

Guideline/ Quality Rating	Synopsis of Recommendations	Supporting Evidence*						
		SR/MA	NR	RCT	NRCS	CS	G	Other
Netherlands Society of Rehabilitation Specialists and the Netherlands Society of Anaesthesiologists (2006) ¹ (The Netherlands) Quality rating: Good (25.5/28)	<i>Ketamine</i> An intravenous sub-anaesthetic dose of ketamine should be considered for patients with complex regional pain syndrome type I (CRPS-I) who are experiencing pain symptoms.					1 5		
	<i>Opioids</i> Strong opioids should not be administered to this patient group.					1 6		
	<i>Bisphosphonates</i> As there is little experience with the use of bisphosphonates in patients with CRPS-I, it is currently advised that these drugs should only be considered in the context of a trial. Intravenous bisphosphonates cause relatively few side effects, but the dosage, frequency, and duration are unclear. Consideration can be given to 40 mg of alendronate a day for eight weeks, especially for patients with elevated bone metabolism.	2 7,8						
	<i>Mannitol</i> There is no evidence that intravenous mannitol is effective in treating patients with CRPS-I.					1 9		

Table 3: Summary of relevant data extracted from *clinical practice guidelines* on intravenous drug infusions for neuropathic pain (cont'd)

Guideline/ Quality Rating	Synopsis of Recommendations	Supporting Evidence*						
		SR/MA	NR	RCT	NRCS	CS	G	Other
New Zealand Accident Compensation Corporation (2005) ² (New Zealand) Quality rating: Good (23.5/28)	<p><i>Ketamine</i></p> <ul style="list-style-type: none"> • There is medium quality evidence that intravenous infusion of ketamine is effective in the treatment of adults with persistent pain of non-cancer origin in the very short term (up to one week). The clinical relevance of this is questionable. • Side effects reported were many and varied and have been described as 'intolerable'. There is evidence of a high incidence of psychomimetic adverse effects. • Studies did not include long-term therapy or follow up beyond one week. Overall the number of study participants was small. <p>There may be a role for the use of intravenous ketamine in the hospital setting for adults with neuropathic pain, under specialist care. The use of the S+ isomer of ketamine may provide benefits with fewer side effects.</p>	<p>3 10-12</p>		<p>4 13-16</p>				
	<p><i>Lidocaine</i></p> <ul style="list-style-type: none"> • There is conflicting evidence about the effectiveness of intravenous infusion of lidocaine for the treatment of non-cancer pain. Some studies report short term benefit (up to 3 weeks) in the treatment of neuropathic pain; others suggest it is not as effective as ketamine infusion. • Most studies reported short-term follow up (2.5 hours to 5 weeks). There were no studies found reporting long-term follow up. • Lidocaine can have serious side effects, particularly in patients with some cardiac conditions. Central nervous system effects may be expected. <p>Some advisory group members advocate the use of intravenous infusions of lidocaine as an interim intervention for some cases where it is difficult to control acute on chronic pain; however, others suggest intravenous interventions are behaviourally reinforcing.</p> <p><i>(cont'd next page)</i></p>	<p>2 12,17</p>		<p>8 14,15,17-23</p>				

Table 3: Summary of relevant data extracted from *clinical practice guidelines* on intravenous drug infusions for neuropathic pain (cont'd)

Guideline/ Quality Rating	Synopsis of Recommendations	Supporting Evidence*						
		SR/MA	NR	RCT	NRCS	CS	G	Other
New Zealand Accident Compensation Corporation (2005) ² (cont'd)	<p><i>Bisphosphonates</i></p> <ul style="list-style-type: none"> There is medium to high quality evidence that intravenous infusions of bisphosphonates (alendronate or clodronate) are effective in the treatment of adults with CRPS-I. No serious adverse effects were reported. <p>The advisory group suggests that not all bisphosphonates can be assumed to be equally effective or safe and caution is required when extrapolating the results of this review to bisphosphonates other than alendronate or clodronate.</p>			2 24,25				
	<p><i>Amantadine</i></p> <ul style="list-style-type: none"> There is high quality evidence from a single randomized trial (n=30) that intravenous infusion of amantadine is not effective for the treatment of adults with sciatica. The follow-up time reported in this study was only 3 hours; it was unclear whether there was sufficient power to detect a difference between the treatment and control group. No adverse effects were reported. <p>Intravenous infusion of amantadine is not recommended for the treatment of adults with sciatica.</p>			1 21				

*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.

QUALITY ASSESSMENT RESULTS – CLINICAL PRACTICE GUIDELINES

Table 4: AGREE tool quality assessment results for included clinical practice guidelines (two appraisers)

Guideline Characteristic		Netherlands Society of Rehabilitation Specialists & the Netherlands Society of Anaesthesiologists (2006) ¹		NZ Accident Compensation Corporation (2005) ²	
Scope/ purpose	1.Objectives	4	4	3	3
	2. Clinical question	3	4	4	4
	3. Target population	4	3	4	3
Stakeholder involvement	4. Relevant professional groups represented	4	4	2	4
	5. Patients' perspectives included	2	2	2	2
	6. Target users defined	4	4	3	2
	7. Piloted among target users	2	4	2	2
Rigour of development	8. Systematic search conducted	4	4	4	4
	9. Selection criteria described	3	4	4	4
	10. Methods used to formulate recommendations described	2	4	2	4
	11. Benefits, side effects, risks considered	4	4	4	4
	12. Link between recommendations and evidence	4	4	4	4
	13. External review by experts	2	4	1	2
	14. Updating procedure described	4	4	3	3
Clarity/ presentation	15. Specific, unambiguous recommendations	4	4	4	4
	16. Different management options presented	1	4	1	4
	17. Key recommendations easily identifiable	4	4	4	4
	18. Additional support materials provided	4	1	1	1
Applicability	19. Organizational barriers discussed	1	1	1	1
	20. Resource implications considered	1	1	1	1
	21. Key review criteria presented	4	3	1	1
Editorial independ- ence	22. Editorially independent from funder	3	4	2	4
	23. Conflicts of interest reported	4	4	4	4
Quality rating	Seven criteria (systematic search, method of formulating recommendations, recommendations-evidence link, external review, clear recommendations, editorial independence, conflict of interest)	25.5 Good		23.5 Good	

Table 5: AGREE tool standardized domain scores (%) for included clinical practice guidelines (two appraisers)

AGREE Domain	Netherlands Society of Rehabilitation Specialists & the Netherlands Society of Anaesthesiologists (2006)¹	New Zealand Accident Compensation Corporation (2005)²
Scope and purpose	89	83
Stakeholder involvement	75	46
Rigour of development	88	79
Clarity and presentation	75	75
Applicability	28	0
Editorial independence	92	83

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