

REPORT TO THE MSRB

Intrathecal Drug Delivery Systems

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The Department has prepared this report on intrathecal drug delivery systems in accordance with the guidelines and formats used in the MSRB Charge to its Medications Task Force (October 14, 2004 MSRB meeting). The overall clinical question considered in this review was:

1. What is the proper use of intrathecal drug delivery systems in the treatment of chronic spinal pain and complex regional pain syndrome (reflex sympathetic dystrophy)?

This overall question was addressed by identifying and synthesizing the best available medical data on the following specific issues:

Are intrathecal drug delivery systems *effective* in the treatment of chronic spinal pain and complex regional pain syndrome (reflex sympathetic dystrophy)?

Are intrathecal drug delivery systems *safe*?

What is the appropriate trial period for determining if a patient will have a favorable response to treatment with intrathecal drug delivery systems?

What are the appropriate criteria for judging whether a patient had a favorable response during a trial period?

Department Work Plan

The Department used the same “evidence-based medicine” approach to intrathecal drug delivery systems as had been employed by the MSRB’s Medications Task Force in preparing its report on non-steroidal anti-inflammatory drugs (NSAIDs)¹. Evidence-Based Medicine (EBM) “is the process of systematically reviewing, appraising and using clinical research findings to aid the delivery of optimum clinical care to patients.”² EBM replaces clinical intuition, observations from personal clinical experience, and hypothetical arguments based on pathophysiological principles, as the principle grounds for clinical decision-making. Instead evidence from systematic surveys and critical appraisals of peer-reviewed, methodologically-sound clinical research is gathered, reviewed and synthesized using standardized, objective protocols based on agreed rules of evidence.

Key components of the evidence-based medicine approach used by the Department are:

- a) the systematic search for, and retrieval of, all the relevant medical literature regarding the use of spinal cord stimulators that addresses one or more of the specific issues listed above;
- b) sorting the retrieved literature by level of evidence;
- c) critical appraisal of that literature to systematically examine its validity, results and relevance; and,
- d) synthesis of the findings, with a grade of recommendation.

1 Final Report. MSRB Task Force On Medications. Nonsteroidal Anti-Inflammatory Drugs, July 21, 2005

2 Rosenberg W, Donald A. “Evidence-based medicine: an approach to clinical problem solving” BMJ 1995; 310(6987): 1122–1126

Strauss SE, Richardson WS, Glasziou P, Haynes RB Evidence-based Medicine: How to Practice and Teach EBM Edinburgh; Churchill Livingstone, 2005

The search and retrieval of the medical literature was done using computerized search engines and on-line bibliographical databases of the medical literature. In order to maximize the efficient use of time and resources, the same strategies as used by the MSRB’s Medications Task Force in its analysis on NSAIDs were adopted to target the searches to the best and most recent evidence by using a step-wise search process.

First, the Department searched the medical literature by “level of evidence.” The levels of evidence (Table 1) are a hierarchy representing the strength of the conclusion that can be drawn from a study of that type. Level I evidence is the most compelling, while Level VI evidence is the weakest. The Department restricted the initial search of the medical literature to Level I evidence – systematic reviews and meta-analyses. A systematic review is itself a review of the medical literature conducted using methods (including systematic search and retrieval of all the relevant primary source evidence and critical appraisal of the evidence found using standardized techniques) designed to minimize the likelihood of bias in the results. A meta-analysis is a systematic review in which quantitative methods are used to summarize the results of the review³. Not only are systematic reviews and meta-analyses the strongest evidence available but they have the additional property of representing the other levels of evidence.

Table 1: Levels of Evidence⁴

I	systematic reviews/meta-analyses of multiple randomized, controlled trials
II	randomized, controlled trials
IIIA	controlled studies without randomization
IIIB	other types of quasi-experimental study
IV	non-experimental descriptive studies
V	case series
VI	expert committee reports or opinions/clinical experience of respected authorities, or both

Using Level I evidence means that the Department could review efforts by other researchers who had already searched the medical literature for Level II and higher evidence, retrieved and reviewed these studies to determine their relevance and methodological quality, abstracted and evaluated their findings, and synthesized the results. This allowed the Department to leverage its resources to review a much larger body of evidence.

Second, the Department tried to focus the search on the most recent studies, so as to best represent the most current information.

The Department also searched for any already published, evidence-based guidelines for the use of intrathecal drug delivery systems.

³ Guyatt G, Rennie D Users’ Guides to the Medical Literature. Essentials of Evidence-Based Clinical Practice AMA Press, 2002

FOCUS “Critical Appraisal Tool” at <http://www.focusproject.org.uk/>

⁴ Adapted from Phillips B, Ball C, Sackett D, Badenoch D, Straus S, Haynes B, Dawes M “Levels of Evidence and Grades of Recommendation” Oxford Centre for Evidence-based Medicine, 1998 http://www.cebm.net/levels_of_evidence.asp

Prior to beginning the literature search, the Department adopted a set of guidelines for determining when and how the searches would be extended that were similar to those used by the MSRB's Medications Task Force in its analysis on NSAIDs. If at least 10 valid and unrelated references to systematic reviews were not found, the search would be extended to look for all articles in category II (randomized controlled trials) and for all articles in category I (systematic reviews) in the entire database.

The search for relevant medical literature was in fact extended to all levels of evidence. And the search was extended back in time to encompass all of the available literature in the on-line databases.

The Department conducted the literature searches in two electronic bibliographic databases:

1. Medline through the PubMed portal at <http://www.ncbi.nlm.nih.gov/entrez/query.fcgi> ; and,
2. The Cochrane Library (The Cochrane Database of Systematic Reviews, Database of Abstracts of reviews of Effects, and The Cochrane Central Register of Controlled Trials) through the Lumina portal of the University of Minnesota Libraries at http://tc.liblink.umn.edu/sfx_local/a-z/default.

PubMed is a service of the National Library of Medicine (NLM) available via the National Center of Biotechnology's Entrez retrieval system. PubMed is a public access search engine for MEDLINE, NLM's premier bibliographic database for medical literature. MEDLINE contains bibliographic citations and author abstracts from more than 4,800 biomedical journals published in the United States and 70 other countries. The database contains over 12 million citations dating back to mid-1960.

The Cochrane Library consists of a regularly updated collection of evidence-based medicine databases created by the Cochrane Collaboration, an international non-profit independent organization of health care providers and health care researchers. The Cochrane Library is a collection of evidence-based medicine databases, which is up-dated quarterly from the best available information about healthcare interventions found in both published and unpublished medical studies from around the world. The Cochrane Database of Systematic Reviews (CDSR) is the collection of systematic reviews done by Cochrane Collaboration work groups. The Database of Abstracts of Reviews of Effects (DARE) contains summaries of systematic reviews done by others, which have met strict quality criteria established by the Cochrane Collaboration. Included reviews have to be about the effects of interventions. The Cochrane Central Register of Controlled Trials (CENTRAL) includes details of clinical trials found in bibliographic databases (notably MEDLINE and EMBASE), and other published and unpublished sources.

The Department used the same inclusion criteria used by the MSRB's Medications Task Force in its analysis on NSAIDs to determine which of the studies found in the automated searches would be retrieved for further analysis. First, the title of the article was reviewed to confirm that the article was about the therapeutic use of intrathecal drug delivery systems in humans. The abstracts and bibliographical data were then retrieved for articles meeting the first screening and reviewed to determine if:

- the article addressed one of the specific issues of relevance about intrathecal drug delivery systems;
- the article represented a study of the appropriate level of evidence;
- it was a study published during the search time frame;
- the article was published in English; and
- the article was available on-line through the University of Minnesota Bio-Medical Library.

Articles selected for inclusion after a review of the article abstract were retrieved in electronic format from the University of Minnesota Bio-Medical Library through the Lumina portal. An electronic database was created listing the authors, the title of the article, and the journal reference. Each article’s abstract and full text was then hyperlinked to its citation in the database. Retrieved articles were evaluated for their level of evidence and assigned a “relevance” category. Systematic reviews (and/or meta-analyses) and randomized controlled trials were considered to be of “high” relevance. Other types of controlled trials and economic evaluations were considered to be of “medium” relevance. Unsystematic reviews, editorials, case series, case studies and all other types of articles were considered to be of “low” relevance.

An additional computerized search for guidelines, using the key words “pain” and “intrathecal drug delivery systems” was conducted in PubMed and at the websites of organizations known to be active in guideline development, appraisal, or cataloging:

Country	Name of organization	Website
Netherlands	Dutch Institute for Healthcare Improvement	http://www.cbo.nl
New Zealand	New Zealand Guidelines Group Accident Compensation Corporation	http://www.nzgg.org.nz http://www.acc.co.nz/index.htm
Scotland	Scottish Intercollegiate Network	http://www.sign.ac.uk
Sweden	Swedish Council on Technology Assessment in Health Care	http://www.sbu.se
UK	National Library of Guidelines	http://www.library.nhs.uk/guidelinesfinder
USA	National Institutes of Health Consensus Development Program National Guideline Clearinghouse Agency for Healthcare research & Quality	http://consensus.nih.gov http://www.guideline.gov http://www.ahrq.gov/

Finally, the computerized searches were supplemented by hand searches of the bibliographies of key articles (particularly systematic reviews and guidelines) and with any articles submitted by interested parties.

Articles chosen for analysis were then assessed for their quality using criteria that were appropriate to the study type.

For systematic reviews, the quality criteria chosen were:

1. Study Identification	
Multiple electronic databases	
Unbiased explicit searching strategies	
Hand searches	
Attempts to include "gray" literature	
Estimation of potential publication bias	
2. Study selection	
Only randomized controlled trials included	
Explicit inclusion/exclusion criteria	
Selection criteria applied uniformly	
Rationale for excluding studies	
3. Appraisal of studies	
Described in detail	
Uniformly applied to all studies	
Important parameters addressed	
<ul style="list-style-type: none"> • random allocation • double blinding • relevant outcome measures • follow-up of at least 80 per cent of participants • analysis consistent with the study design 	<p>—</p> <p>—</p> <p>—</p> <p>—</p> <p>—</p>
Effect of study quality on conclusions assessed	
4. Data Collection	
Was missing information considered?	
5. Data synthesis	
Assessment for heterogeneity	
All valid studies used	
Sensitivity analysis performed	
Variations between studies considered	

For randomized controlled trials, the quality criteria were:

Random allocation	
Minimal dropouts (< 15%)	
Blinding of patient	
Blinding of the assessor	
Co-treatments have been used in an equivalent manner among treatment groups.	
Assessment of the extent of patient adherence to the prescribed therapy	
No unintended crossovers from one study treatment to the other.	
Adequate consideration of statistical and clinical significance of findings.	
Adequate demographic description of patients, including at least age, gender, and referral source.	
Adequate clinical description, including pain duration, neurologic deficits, sciatica, previous surgery, and other inclusion or exclusion criteria.	
Adequate description of treatment in terms of dosage, duration, frequency, and technique.	
Reporting of all relevant outcomes, which may include symptoms, physiologic changes, functional ability, costs of care, and psychological measures.	

These criteria were adapted from recommendations for critical appraisal of systematic reviews and randomized controlled trials found in the peer-reviewed literature and textbooks of evidence-based medicine.⁵

For guidelines, the quality criteria were derived from the instrument developed by The AGREE Collaboration started in 1998 as a research project under the Biomedicine and Health Research (BIOMED 2) Programme, funded by the European Union⁶:

Scope and purpose	
Objective(s) of the guideline are specifically described.	
The clinical question(s) is specifically described.	
The patients to whom the guideline is meant to apply is specifically described.	
Stakeholder involvement	
The guideline development group includes individuals from all the relevant professional groups.	
The patients' views and preferences are sought.	
Rigour of development	
Systematic methods are used to search for evidence.	
The criteria for selecting the evidence are clearly described.	
The methods used for formulating the recommendations are clearly described.	
The health benefits, side effects and risks are considered in formulating the recommendations.	
There is an explicit link between the recommendations and the supporting evidence.	
The guideline was externally reviewed by experts prior to publication.	
A procedure for updating the guideline is provided.	
Clarity and presentation	
The recommendations are specific and unambiguous.	
The different options for diagnosis and/or treatment of the condition are clearly presented.	
Key recommendations are easily identifiable.	
Applicability	
The target users of the guideline are clearly defined.	
The potential organizational barriers in applying the recommendations are discussed.	
The potential cost implications of applying the recommendations were considered.	
The guideline is supported with tools for application.	
The guideline presents key review criteria for monitoring and audit purposes	
The guideline was piloted among end users.	
Editorial independence	
The guideline is editorially independent from the funding body.	
Conflicts of interest of guideline development members are recorded.	

Articles were scored “yes”, “no”, “can’t tell” on each item. A summary score was determined by adding together the “yes” responses, dividing by the total number of criteria. This scoring system is a short hand way of indicating overall study quality and is similar to systems used in many systematic reviews for evaluating primary source literature.

⁵ Oxman AD, Cook DJ, Guyatt GH “Users' guides to the medical literature. VI How to use an overview” Journal of the American Medical Association 1994; 272(17): 1367-1371

Guyatt GH, Sackett DL, Cook DJ “Users' guides to the medical literature. II. How to use an article about therapy or prevention. A. Are the results of the study valid?” Journal of the American Medical Association 1993; 270(21): 2598-601.

Crombie IK The Pocket Guide to Critical Appraisal: A Handbook for Healthcare Professionals London; BMJ Publishing Group, 1996

⁶ <http://www.agreecollaboration.org/>

In addition, the author's conclusions regarding intrathecal drug delivery systems were abstracted, and, in the case of the systematic reviews, the primary literature relied upon by the author(s) in reaching their conclusions was identified and tabulated. The results of the quality review, the author's conclusions, and, if relevant, the bibliography of the primary source literature were entered into a "Summary Sheet" for each article. These Summary Sheets were then also hyperlinked to the Department database.

Finally, the abstracted conclusions from each article were transferred to a separate spreadsheet. There, the conclusions were arranged thematically into columns for comparison across articles.

Results

The first PubMed search used a search string published in the medical literature that has been validated as both sensitive and specific for retrieving systematic reviews.⁷ The search string was combined first with the key words "intrathecal drug delivery" and "pain" while limiting the results to systematic reviews since 1990. Because this search yielded less than 10 unique references, the search for systematic reviews was expanded to the entire Pub Med database. This still yielded less than 10 unique references so the search was expanded to include RCTs since 1990. Finally, since this search yielded only 10 unique references, the search was expanded to include all articles on "intrathecal drug delivery" and "pain" since 1990. The same process was repeated using the search terms "intrathecal medication" and "pain". The results of the searches can be found in the documents "IDD and pain - reviews.doc", "IDD and pain – RCTs.doc", "IDD and pain.doc" "IM and pain - reviews.doc", "IM and pain – RCTs.doc", and "IM and pain.doc". (see Appendix 1).

These searches retrieved 714 titles, some found more than once. Of these, 83 articles were presumed relevant based on their title and retrieved for further review.

The searches of the Cochrane Database of Systematic Reviews (CDSR) of the Database of Abstracts of Reviews of Effects (DARE) were done using the key word "intrathecal drug delivery" and did not yield any references not found in the PubMed search.

The search for guidelines in PubMed and on the World Wide Web found 13 references of which 5 were earlier versions of guidelines whose later versions were included in the analysis.

References for all the articles chosen for further review were combined in an Excel database, [intrathecal drug delivery.xls](#) (see Appendix 2). Of the 96 articles (6 systematic reviews, 6 randomized controlled trials, 13 guidelines, 2 clinical trials, 1 registry study, 2 economic

⁷ " ((meta-analysis [pt] OR meta-analysis [tw] OR metanalysis [tw]) OR ((review [pt] OR guideline [pt] OR consensus [ti] OR guideline* [ti] OR literature [ti] OR overview [ti] OR review [ti]) AND ((Cochrane [tw] OR Medline [tw] OR CINAHL [tw] OR (National [tw] AND Library [tw])) OR (handsearch* [tw] OR search* [tw] OR searching [tw]) AND (hand [tw] OR manual [tw] OR electronic [tw] OR bibliographi* [tw] OR database* OR (Cochrane [tw] OR Medline [tw] OR CINAHL [tw] OR (National [tw] AND Library [tw]))))) OR ((synthesis [ti] OR overview [ti] OR review [ti] OR survey [ti]) AND (systematic [ti] OR critical [ti] OR methodologic [ti] OR quantitative [ti] OR qualitative [ti] OR literature [ti] OR evidence [ti] OR evidence-based [ti]))) BUTNOT (case* [ti] OR report [ti] OR editorial [pt] OR comment [pt] OR letter [pt]) " found in Shojania KG, Bero LA. "Taking advantage of the explosion of systematic reviews: an efficient MEDLINE search strategy" [Eff Clin Pract](#) 2001;4(4): 157-62.

evaluations, 36 unsystematic reviews/editorials, and 30 case series/studies), the full article was available electronically for 70 of them through the Lumina portal at the University of Minnesota (5 systematic reviews, 6 randomized controlled trials, 13 guidelines, 1 registry study, 2 economic evaluations, 16 unsystematic reviews/editorials, and 27 case series/studies). When available, the full article was hyperlinked to the database. The article's abstract was then reviewed to determine level of evidence and the relevance of the article.

In all, 21 articles met all of the inclusion criteria and were not versions of other references (5 systematic reviews, 5 randomized controlled trials, 8 guidelines, 1 registry study, and 2 economic evaluations) and were entered into a second Excel database, [intrathecal drug delivery - review.xls](#) (see Appendix 3). When more than one version of a study was available, the most complete and most recent version was used. In addition, two references available only as abstracts were included as they represented high quality studies (1 systematic review and 1 clinical trial). A quality review was then performed for each article. One clinical trial available as an abstract only was omitted as it was an earlier version of the one included.

The retrieved articles varied in quality. The RCTs had relatively high summary quality scores ranging from 10/12 to 12/12. Four of the systematic reviews had poor summary quality scores ranging from 1/22 to 5/22; the fifth had a moderate score of 11/23. The guidelines had the most variation in summary quality scores, ranging from 9/23 to 20/23; 2 had high scores, while four had scores of 11/23 or less.

The systematic reviews and guidelines referenced a combined total of 426 primary studies. These are listed on the summary sheet for individual systematic reviews and guidelines and for all of the systematic reviews and guidelines in an Excel database [intrathecal drug delivery – primary sources.xls](#) (see Appendix 5) with a listing for each primary study of the systematic reviews and guidelines in which it is referenced as data.

Quality review was not done for the registry study, the two economic evaluations, or the two studies only available as abstracts.

Overall, all of the systematic reviews and 4 of the RCTs addressed the question of effectiveness. Two of the systematic reviews and four of the RCTs addressed issues of safety. Only one of the systematic reviews reported on the appropriate trial period and the criteria used for judging whether a patient had a favorable response during a trial period.

The evidence used in developing the recommendations in the guidelines analyzed was referenced in the available text for 7 of the 8 guidelines. Those guidelines relied, at least in part, on systematic reviews and RCTs. Four of the 7 with references used at least one systematic review; 6 of 7 used at least one RCT; and 4 of 7 referenced other guidelines or previous versions of the guideline being analyzed. In some cases those systematic reviews, RCTs, and guidelines were the same ones identified in the searches done for this report (as noted in columns J, K, and M of [intrathecal drug delivery - review.xls](#)).

The findings made by the article's author(s) were then abstracted and entered into a third database, [intrathecal drug delivery - analysis.xls](#) (see Appendix 4). There, the findings were

arranged thematically into columns for comparison across articles. Themes were identified inductively from the abstracted conclusions by arranging them into the fewest mutually exclusive categories.

The themes identified were:

<i>theme</i>	<i># articles</i>	<i>summary quality scores</i>
Quantitative results	SysRev: 3 RCT: 5 Guidelines: 1	SysRev: 5/22 – 11/22 RCT: 10/12 – 12/12 Guidelines: 11/23
Reported complications	SysRev: 2 RCT: 4 Guidelines: 4	SysRev: 1/22 – 9/22 RCT: 10/12 – 12/12 Guidelines: 9/23-18/23
Study design issues	SysRev: 3 RCT: 5 Guidelines: 4	SysRev: 2/22 – 10/22 RCT: 10/12 – 12/12 Guidelines: 11/23-20/23
Author's overall conclusions	SysRev: 4 RCT: 5 Guidelines:8	SysRev: 1/22 – 11/22 RCT: 10/12 – 12/12 Guidelines: 9/23 – 20/23
Comments on length of trial period	SysRev: 1 RCT: 0 Guidelines: 4	SysRev: 11/22 Guidelines: 9/23 – 11/23
Comments on judging trial success	SysRev: 1 RCT: 0 Guidelines: 2	SysRev: 11/22 Guidelines: 9/23 – 10/23

Conclusions

The Department found considerable agreement of published opinion on each issue. While the individual articles varied widely in quality, this variation does not significantly affect the conclusions reached by the authors. Articles of higher quality most often reached the same conclusions as those of lower quality.

The conclusions drawn by the Department from the reviewed literature are:

1. There is limited evidence that permanently implanted intrathecal drug delivery systems are effective in the short-term in achieving at least a 50% reduction in pain in some patients with chronic pain conditions who have a positive response during a screening trial period.

Clin J Pain 2007 Feb 23(2) 180-95	SysRev	The studies reviewed found improvement in pain and functioning on average among patients with chronic noncancer pain who received permanent IDDS.
J Pain Symptom Manage 2000 Aug 20(2) S12-36	SysRev	Intrathecal morphine appears to be safe at clinical concentrations, and has favorable efficacy data. Limited information on the other opioid classes also appears favorable, although published literature supporting this is very limited. Based on the currently available literature, both clinical efficacy and toxicology for bupivacaine and clonidine appear favorable. The efficacy of combinations of different drug classes such as opioids/local anesthetics, opioids/clonidine, and opioids/local anesthetics/ clonidine appears favorable, but is based largely on case studies and retrospective analysis.

Health Technology Assessment 2000; Vol. 4; No. 32	SysRev	Such data as are available indicate a generally positive effect of the therapy, with side effects and complications occurring in about a quarter of the recipients, but it is difficult to draw definite conclusions because the quality of the data is so poor.
Anesth Analg 2000 Dec 91(6) 1493-8	RCT	The combination of morphine and clonidine produced significantly more pain relief than placebo 4 h after administration; either morphine or clonidine alone did not produce as much pain relief.
J Clin Oncol 2002 Oct 1 20(19) 4040-9	RCT	IDDSs improved clinical success in pain control, reduced pain, and significantly relieved common drug toxicities in patients with refractory cancer pain.
J Pain Symptom Manage 2006 May 31(5) 393-406	RCT	Slow titration of ziconotide, a nonopioid analgesic, to a low maximum dose resulted in significant improvement in pain and was better tolerated than in two previous controlled trials that used a faster titration to a higher mean dose.
JAMA 2004; 291:63-70	RCT	Intrathecal ziconotide provided clinically and statistically significant analgesia in patients with pain from cancer or AIDS.
Pain Physician. 2007 Jan;10(1):7-111	Guide	The evidence for implantable intrathecal infusion systems is strong for short-term improvement in pain of malignancy or neuropathic pain.
Guidelines For Longterm Intrathecal Infusions (PM6)	Guide	A range of non-opioid spinal analgesic agents are utilized for long-term therapy, some of which are supported by low levels of evidence and for which safety has not been fully established. There is level II evidence for efficacy in treating neuropathic pain with intrathecal clonidine; neuropathic pain following spinal cord injury with morphine and clonidine combined; neuropathic pain with ziconotide. Intrathecal administration of opioids and local anaesthetics and / or clonidine could be considered as an alternative agent in patients with poorly controlled neuropathic pain ... following spinal cord injury. Many of these combinations are ... "off label" ...
Assessment and management of chronic pain.	Guide	Intrathecal Medication Delivery Systems can provide an excellent therapeutic effect for nonmalignant and cancer pain. However, it should be reserved only for patients who have failed other conservative approaches for the treatment of pain, and should be used cautiously. The best candidates are patients who respond well to oral opioids but who cannot tolerate the side effects (e.g., sedation, nausea, constipation).
Complex Regional Pain Syndrome type I Guidelines	Guide	Intrathecal baclofen has no place in the treatment of patients with CRPS-I. Intrathecal baclofen can only be considered for patients with CRPS-I if dystonia is a major problem and conventional therapy has proven ineffective. This treatment must be administered in the context of a trial.
Treatment in Workers' Compensation 2006	Guide	Recommended only as an end-stage treatment alternative for selected patients. This treatment should only be used relatively late in the treatment continuum, when there is little hope for effective management of chronic intractable pain from other therapies. The specific criteria in these cases include the failure of at least 6 months of other conservative treatment modalities, intractable pain secondary to a disease state with objective documentation of pathology, further surgical intervention is not indicated, psychological evaluation unequivocally states that the pain is not psychological in origin, and a temporary trial has been successful prior to permanent implantation as defined by a 50-70% reduction in pain.
Evidence-based clinical practice guideline for interdisciplinary rehabilitation of chronic non-malignant pain syndrome patients	Guide	Given the continued absence of quality research, however, the current guidelines do not recommend using implantable infusion pumps or spinal cord stimulators with chronic non-malignant pain syndrome patients.
Intrathecal drug delivery for the management of pain and spasticity in adults; recommendations for best clinical practice	Guide	Intrathecal drug delivery can be an effective method of pain control. Patient selection is important, particularly when used for CNMP. It must be carried out by a multi-professional team with a comprehensive understanding of the physical, psychological and rehabilitation aspects of the patient's condition.
Pain Med 2004 5 6-13.	Registry	Current clinical practices related to trialing of drug-delivery systems resulted in the majority of patients successfully trialed. At 12-month follow-ups, implanted patients experienced reductions in numeric back and leg pain ratings, improved Oswestry scores, and high satisfaction with the therapy.

2. There is no reliable evidence that permanently implanted intrathecal drug delivery systems are effective in the long-term in achieving at least a 50% reduction in pain in patients with chronic pain conditions who have a positive response during a screening trial period.

Clin J Pain 2007 Feb 23(2) 180-95	SysRev	Methodologic limitations preclude conclusions concerning the effectiveness of this technology long-term and as compared with other treatments.
J Pain Symptom Manage 2000 Aug 20(2) S12-36	SysRev	No information is available on the long-term compatibility of these combinations.
Pain Physician. 2007 Jan;10(1):7-111	Guide	The evidence is moderate for long-term management of chronic pain.

3. Economic models indicate that permanently implanted intrathecal drug delivery systems are cost-effective in treating patients who have had at least a 50% reduction in pain during a screening trial period.

CLIN THER 1997 19(1) 96-112	CE	When both costs and adverse event rates were set at base case values, the expected cost (discounted at 5%) of IMT over 60 months was \$82,893 (\$1382 per month). With costs and adverse event rates at the best case values, the expected 60-month total cost was \$53,468 (\$891 per month), and when all the values were set at the worst case, the projected total cost rose to \$125,102 (\$2085 per month). By comparison, the cumulative 60-month total cost for medical management was \$85,186.
Neuromodulation 1999; 2:77-84	CE	Decision Analysis: "For the base case and the best case, the cumulative cost with an implanted, programmable pump is less than the cost of medical management after 22 months and 11 months, respectively." Cost Analysis: "...intrathecal drug delivery becomes more cost effective than oral therapy after 4-6 months have elapsed."

4. There is no reliable evidence that permanently implanted intrathecal drug delivery systems are more effective than alternative treatment options.

J Clin Oncol 2002 Oct 1 20(19) 4040-9	RCT	Sixty of 71 IDDS patients (84.5%) achieved clinical success compared with 51 of 72 CMM patients (70.8%, P = .05). IDDS patients more often achieved >20% reduction in both pain VAS and toxicity (57.7% [41 of 71] v 37.5% [27 of 72], P = .02). The mean CMM VAS score fell from 7.81 to 4.76 (39% reduction); for the IDDS group, the scores fell from 7.57 to 3.67 (52% reduction, P = .055). The mean CMM toxicity scores fell from 6.36 to 5.27 (17% reduction); for the IDDS group, the toxicity scores fell from 7.22 to 3.59 (50% reduction, P = .004). The IDDS group had significant reductions in fatigue and depressed level of consciousness (P < .05).
Guidelines For Longterm Intrathecal Infusions (PM6)	Guide	A range of non-opioid spinal analgesic agents are utilized for long-term therapy, some of which are supported by low levels of evidence and for which safety has not been fully established. There is level II evidence for efficacy in treating neuropathic pain with intrathecal clonidine; neuropathic pain following spinal cord injury with morphine and clonidine combined; neuropathic pain with ziconotide. Intrathecal administration of opioids and local anaesthetics and / or clonidine could be considered as an alternative agent in patients with poorly controlled neuropathic pain ... following spinal cord injury. Many of these combinations are ... "off label" ...
Assessment and management of chronic pain.	Guide	Intrathecal Medication Delivery Systems can provide an excellent therapeutic effect for nonmalignant and cancer pain. However, it should be reserved only for patients who have failed other conservative approaches for the treatment of pain, and should be used cautiously. The best candidates are patients who respond well to oral opioids but who cannot tolerate the side effects (e.g., sedation, nausea, constipation).

Treatment in Workers' Compensation 2006	Guide	Recommended only as an end-stage treatment alternative for selected patients. This treatment should only be used relatively late in the treatment continuum, when there is little hope for effective management of chronic intractable pain from other therapies. The specific criteria in these cases include the failure of at least 6 months of other conservative treatment modalities, intractable pain secondary to a disease state with objective documentation of pathology, further surgical intervention is not indicated, psychological evaluation unequivocally states that the pain is not psychological in origin, and a temporary trial has been successful prior to permanent implantation as defined by a 50-70% reduction in pain.
Evidence-based clinical practice guideline for interdisciplinary rehabilitation of chronic non-malignant pain syndrome patients	Guide	Given the continued absence of quality research, however, the current guidelines do not recommend using implantable infusion pumps or spinal cord stimulators with chronic non-malignant pain syndrome patients.
Intrathecal drug delivery for the management of pain and spasticity in adults; recommendations for best clinical practice	Guide	Intrathecal drug delivery can be an effective method of pain control. Patient selection is important, particularly when used for CNMP. It must be carried out by a multi-professional team with a comprehensive understanding of the physical, psychological and rehabilitation aspects of the patient's condition.

5. Complications occur in 1/3 or more of cases. Most are side effects of the medication delivered by the system, are dose-dependent, and sometimes improve with continued administration. Catheter, procedure and device related complications are relatively uncommon.

Clin J Pain 2007 Feb 23(2) 180-95	SysRev	The most commonly reported permanent IDDS drug side effects were nausea/vomiting (mean rate weighted by sample size=33%), urinary retention (24%), and pruritus (26%). Catheter problems were also reported commonly. Rare but serious complications included intrathecal catheter tip granulomas.
Pain Physician 2007 Mar 10(2) 357-66	SysRev	Most side effects of intrathecal morphine therapy are dose dependent and mediated by opioid receptors. Common ones include nausea, vomiting, pruritus, urinary retention, constipation, sexual dysfunction, and edema. Less common ones include respiratory depression, and hyperalgesia. Catheter tip inflammatory mass formation is a less common complication that may not be mediated by opioid receptors. Treatment usually involves the utilization of opioid receptor antagonist, such as naloxone.
Eur J Anaesthesiol 2006 Jul 23(7) 605-10	RCT	The incidence of nausea and vomiting was higher at 2- and 4-h observation times, and decreased 24 h after intrathecal injection. No urinary retention was observed in the control group, while 2 h after intrathecal injection urinary retention was observed in 20–40% of cases, and decreased to less than 10% 24 h after spinal injection without differences among the four doses.
Anesth Analg 2000 Dec 91(6) 1493-8	RCT	The most common side effects after morphine administration in those with SCI were pruritus, oxygen desaturation, sedation, nausea, and hypotension (>15% decrease in blood pressure). The most common side effects after clonidine administration were hypotension, nausea, sedation, oxygen desaturation, and dry mouth. Of those who received saline, 13% experienced sedation and 13% had oxygen desaturation. The most common side effects after the administration of the mixture were hypotension, oxygen desaturation, pruritus, dry mouth, and sedation. Using the mixture did not result in a marked reduction in the incidence of side effects.
J Pain Symptom Manage 2006 May 31(5) 393-406	RCT	Significant adverse events reported in the ziconotide group were dizziness, confusion, ataxia, abnormal gait, and memory impairment. Discontinuation rates for AEs and serious AEs were comparable for both groups.
JAMA 2004; 291:63-70	RCT	Nine types of adverse events (fever, hypotension, nausea, vomiting, confusion, dizziness, somnolence, abnormal gait, and urinary retention) occurred with significantly greater frequency in the ziconotide group compared with the placebo group, but starting at the lower dosage, using smaller dose increments, and increasing the

		interval between dose titrations tended to reduce this frequency.
Pain Physician. 2007 Jan;10(1):7-111	Guide	The complications include post-dural puncture headache, infection, nausea, urinary retention, pruritus, catheter and pump failure, pedal edema, hormonal changes, granuloma formation, and decreased libido.
Guidelines For Longterm Intrathecal Infusions (PM6)	Guide	Intrathecal drug administration can result in significant undesirable side effects, and has the possibility of morbidity and mortality.
Complex Regional Pain Syndrome type 1 Guidelines	Guide	The main side-effects of the screening process and continuous administration of ITB are post-puncture headache, diminished consciousness and urine retention.
Intrathecal drug delivery for the management of pain and spasticity in adults; recommendations for best clinical practice	Guide	Minor complications are common. In a population of cancer patients, catheter, procedure, device-related and illness-associated adverse incidents occurred at a rate of 0.45 events per patient year. Neurological deficits can occur from the procedure and from inflammatory mass development at catheter tip. There are reports of neurotoxicity and permanent neurologic al damage following intrathecal infusions of local anaesthetics. Possible infections include meningitis, epidural abscess, pump pocket infection or pump reservoir infection. Cerebrospinal fluid leaks, hygromas and post dural puncture headaches have all been reported. Device-related complications include catheter kinking, disconnection, dislodgement or pump failure, program error and overflow or incorrect refill.
Pain Med 2004 5 6-13.	Registry	Adverse events were reported in 23 patients receiving an IDDS implant. Of these, 21 required some surgery to correct the problem. Adverse events included: Infection (2.2%), dislodgment/ migration (1.5%), and cerebrospinal fluid leak (0.7%). The most common adverse event over 12 months was reaction to medication, which occurred in 5.1% of patients. Other, rarely reported events included catheter kinking in 1.5% and catheter fracture in 0.7% of patients.

6. Trial screening periods in the reported case series and clinical trials have lasted from a single injection up to 10 days, with most being 24 hours or less. There is no information to judge whether the length of the trial period influences the reported efficacy of implanted intrathecal drug delivery systems.

Health Technology Assessment 2000; Vol. 4: No. 32	SysRev	In those studies reporting a trial, 23 used a single injection and 7 an infusion for more than 24 hours - of those 6 lasted for more than 48 hours
Guidelines For Longterm Intrathecal Infusions (PM6)	Guide	Prior to the insertion of long term delivery systems ... Intrathecal trials should be undertaken to assess appropriate drugs, doses and efficacy of the drug or drug combinations. Testing with temporary catheter systems allows investigation of the potential side effects of the proposed procedure and medication.
Treatment in Workers' Compensation 2006	Guide	The specific criteria include ... a temporary trial has been successful prior to permanent implantation.
Intrathecal drug delivery for the management of pain and spasticity in adults; recommendations for best clinical practice	Guide	A trial of intrathecal therapy should always be performed. This can be by means of bolus or infusion but the former give limited information. There is no ideal screening method.
Neuromodulation 2007 10(4) 300-328	Guide	The panelists felt that trial procedure should be left up to the physician performing them. The panelists felt that until there are data that suggest that trials are unnecessary, trials should be performed before placing IT delivery agents through an IDDS. Trials can be performed with monotherapy or with polyanalgesia.

Pain Med 2004 5 6-13.	Registry	Trialing methodologies were: Continuous epidural infusion (53%), continuous intrathecal infusion (25%), single intrathecal bolus injection (14%), and multiple intrathecal bolus injections (8%). The majority of patients (81.1%) were trialed with morphine only. The mean duration of the trial was 3.5 ± 5.4 days.
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7. The most common measure of success in the trial period was relief of pain and the most common criteria was pain relief of at least 50%.

Health Technology Assessment 2000; Vol. 4; No. 32	SysRev	Those studies reporting a criteria for judging success used 50% relief of pain.
Guidelines For Longterm Intrathecal Infusions (PM6)	Guide	Base line levels of pain, function and Quality of Life should be recorded.
Treatment in Workers' Compensation 2006	Guide	Defined by a 50-70% reduction in pain

8. There is limited evidence to support the use of morphine, hydromorphone and ziconotide as first line agents in intrathecal drug delivery systems.

(a) There is no evidence to support the use of other medications as first line agents.

(b) There is no reliable evidence on which medications are indicated when morphine, hydromorphone and ziconotide are not effective or become ineffective.

<i>reference</i>	<i>type</i>	<i>author's conclusions</i>
Guidelines For Longterm Intrathecal Infusions (PM6)	Guide	There is level II evidence for efficacy in treating neuropathic pain with intrathecal clonidine; neuropathic pain following spinal cord injury with morphine and clonidine combined; neuropathic pain with ziconotide.
Complex Regional Pain Syndrome type 1 Guidelines	Guide	Intrathecal baclofen has no place in the treatment of patients with CRPS-I.
Neuromodulation 2007 10(4) 300-328	Guide	The first-line agents are morphine, hydromorphone, and ziconotide. Second line agents include 1) the combination of morphine or hydromorphone and bupivacaine or clonidine; 2) the combination of morphine or hydromorphone and ziconotide; or 3) fentanyl alone. Third-line approaches are: 1) clonidine alone; 2) a combination of morphine/ hydromorphone/ fentanyl/ bupivacaine plus clonidine and ziconotide.
J Pain Symptom Manage 2000 Aug 20(2) S12-36	SysRev	Intrathecal morphine appears to be safe at clinical concentrations, and has favorable efficacy data. Limited information on the other opioid classes also appears favorable, although published literature supporting this is very limited. Based on the currently available literature, both clinical efficacy and toxicology for bupivacaine and clonidine appear favorable. The efficacy of combinations of different drug classes such as opioids/local anesthetics, opioids/ clonidine, and opioids/local anesthetics/ clonidine appears favorable, but is based largely on case studies and retrospective analysis. No information is available on the long-term compatibility of these combinations.

Anesth Analg 2000 Dec 91(6) 1493-8	RCT	<p>Intrathecal morphine resulted in a mean reduction in pain to 80% of the baseline pain before drug administration. Intrathecal administration of clonidine resulted in a mean reduction in pain levels to 83% of the baseline pain. These reductions in pain levels were not significantly different from the relief obtained after saline administration. Intrathecal administration of the mixture of morphine and clonidine resulted in a mean reduction in pain levels to 63% of the baseline pain. There was a significant difference in the relief obtained with the mixture of morphine and clonidine compared with placebo ($P = 0.0084$).</p>
JAMA 2004; 291:63-70	RCT	<p>Mean VASPI scores improved 53.1% (95% CI, 44.0%-62.2%) in the ziconotide group and 18.1% (95% CI, 4.8%-31.4%) in the placebo group ($P = .001$), with no loss of efficacy of ziconotide in the maintenance phase. Pain relief was moderate to complete in 52.9% of patients in the ziconotide group compared with 17.5% in the placebo group ($P = .001$). Five patients receiving ziconotide achieved complete pain relief, and 50.0% of patients receiving ziconotide responded to therapy compared with 17.5% of those receiving placebo ($P = .001$).</p>
Ann Pharmacother 2006 Jul-Aug 40(7-8) 1293-300	SysRev	<p>In double-blind, placebo-controlled studies, ziconotide significantly improved patient perception of pain from baseline to the end of the study periods, which ranged from 11 to 21 days.</p>

Recommendations

Based on the conclusions derived from the literature the Department proposes the following draft recommendations to the Medical Services Review Board, to be used as the basis for changes to the Permanent Treatment Parameters governing the use of intrathecal drug delivery systems in workers' compensation claims.

I. Intrathecal drug delivery systems can effectively relieve pain in selected patients with chronic pain when other options have failed – at least in the short term.

II. An adequate trial period of 24 hours is needed to determine who might benefit from an intrathecal drug delivery system.

III. Adequate pain relief of at least 50% during the trial period is needed to determine if a patient might benefit from an intrathecal drug delivery system.

Appendix 1

The Word files “IDD and pain - reviews.doc”, “IDD and pain – RCTs.doc”, “IDD and pain.doc” “IM and pain - reviews.doc”, “IM and pain – RCTs.doc”, and “IM and pain.doc” list all of the articles found in the literature searches.

Appendix 2

The Excel workbook [intrathecal drug delivery.xls](#) lists all of the articles that were selected by the Department for further review.

Column A is an ID number

Column B lists the authors of the article.

Column C is the title of the article.

Column D gives the abbreviated citation as found in Medline and is an active link.

Clicking on the journal citation will call up the abstract and/or article

Column E identifies the type of article:

“SysRev” is a systematic review,

“RCT” is a randomized controlled trial

“CCT” is a nonrandomized trial

“Registry” is a registry study

“CE” is an economic evaluation

“SysGuide” is an evidence-based treatment guideline

“Review” is an unsystematic review

“Editorial” is a statement of a single physician’s opinion

“CaseSer” is a case series

“CaseRep” is a single case report

Column F indicates whether the article was determined to be relevant for the purposes of this study based on the levels of evidence hierarchy.

Column G indicates the availability of the article.

Column H is marked with an “X” if the article discusses efficacy.

Column I is marked with an “X” if the article discusses safety.

Column H includes any comments on the article (especially whether it is an alternate version of another article).

Appendix 3

The Excel workbook [intrathecal drug delivery - review.xls](#) lists the results of the quality review of the articles that were selected by the Department for this analysis.

Column A is an ID number

Column B lists the authors of the article.

Column C gives the abbreviated citation as found in Medline and is an active link.

Clicking on the journal citation will call up the abstract and/or article

Column D identifies the type of article:

“SysRev” is a systematic review,

“RCT” is a randomized controlled trial,

“SysGuide” is an evidence-based treatment guideline,

“CCT” is a nonrandomized trial,

“Registry” is a registry study,

“CE” is an economic evaluation.

Column E is marked with an “X” if the article discusses efficacy.

Column F is marked with an “X” if the article discusses safety.

Column G is a hyperlink to the summary sheet for the article.

Column H is a hyperlink to the summary sheet for the article

Column I includes any comments about the article

For guidelines only:

Column J lists the ID# for any systematic reviews included in this analysis that were used by the authors of the guideline.

Column K lists the ID# for any randomized clinical trials included in this analysis that were used by the authors of the guideline.

Column L lists the ID# for any economic evaluations included in this analysis that were used by the authors of the guideline.

Column M lists the ID# for any guidelines included in this analysis that were used by the author's of the guideline.

Appendix 4

The Excel workbook [intrathecal drug delivery -analysis.xls](#) lists the author's findings and conclusions regarding the efficacy and safety of spinal cord stimulators, and any other information relevant to the questions posed for this analysis. Wherever possible, the conclusions are stated in the authors' own words.

Column A gives the abbreviated citation as found in Medline and is an active link. Clicking on the journal citation will call up the abstract and/or article

Column B identifies the type of article:

“SysRev” is a systematic review,

“RCT” is a randomized controlled trial,

“SysGuide” is an evidence-based treatment guideline,

“CCT” is a nonrandomized trial,

“Registry” is a registry study,

“CE” is an economic evaluation.

Column C lists the sources of information used.

Column D lists any comments made by the authors regarding the sources of information.

Column E lists the quantitative results of the study.

Column F lists any information regarding complications.

Column G lists any comments made by the authors regarding the study design or other methodological issues.

Column H lists the authors' overall conclusions on the use of spinal cord stimulation.

Column I is intentionally blank.

Column J lists any information given regarding the conduct of a trial period.

Column K lists any information given regarding the criteria for judging a trial as successful.

Appendix 5

The Excel workbook intrathecal drug delivery –primary sources.xls lists all of the original studies referenced by the authors of systematic reviews and evidence-based guidelines.

Column A gives the ID#(s) ID# of included in this analysis that referenced this primary source

Column B is the citation of the primary source